The Rational Synthesis of Chlorins via Rearrangement of Porphodimethenes: Influence of β-Substituents on the Regioselectivity and Stereoselectivity of Pyrroline Ring Formation

Dennis H. Burns,* Yue H. Li,† Dong C. Shi,† and Timothy M. Caldwell

Department of Chemistry, Wichita State University, Wichita, Kansas 67260-0051

Dennis.Burns@wichita.edu

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The porphodimethene rearrangement methodology reported in this paper provides for a rational, step-by-step synthesis of chlorins from readily available pyrrole precursors. The intermediate porphodimethenes are furnished directly via the '2 + 2' MacDonald condensation, or by the less symmetry-constrained '3 + 1' condensation of a tripyrrane and bis-formyl pyrrole. The synthetic route is short and highly convergent, especially in the case of the '3 + 1' approach, and furnishes chlorins in good to moderate yields. The synthesis is highly regioselective and appears to be based on the ability of the β-substituent to stabilize excess electron density, with an electron-neutral hydrogen or an electron-withdrawing carbonyl β-substituent demonstrating the greatest influence on the formation of the pyrroline ring. The synthesis is highly stereoselective when epimerization of the pyrroline ring β-carbons is possible, furnishing only the trans-reduced sterioisomer. Finally, there is substantial evidence that a fifth, axial ligand is involved in the transposition of peripheral hydrogens during the rearrangement of the π-system from metalloporphodimethene to metallochlorin.

Introduction

Chlorins (dihydroporphyrins) serve as prosthetic groups for proteins that perform a diverse set of biological functions. Iron chlorins are cofactors for a number of redox proteins, such as the heme in sulfmyoglobin,[1] in the green catalases from Neurospora crassa and *Escherichia coli*,[2] as well as the heme (heme d) in cytochrome d of E. coli.[3] Several dihydroporphyrins have been isolated from marine organisms, such as the sex-differentiating pigment, bonellin, as well as (possible antioxidants) tunichlorin, cyclopheophorbide, and chlorophyllone a.[4] The most abundant chlorins are the magnesium chlorins—chlorophylls a and b, found in the photosynthetic proteins of green plants, and bacteriochlorophylls c, d, and e, found in the green, red, and brown sulfur bacteria[5]—where they are utilized in light-harvesting arrays and electron-transfer reaction centers. Additionally, chlorins have potential medical applications as photosensitizers in photodynamic therapy[6] and material science applications as superior chromophores for use in molecular wires and antenna arrays.[7]

Like the porphyrin ring, the chlorin macrocycle contains four pyrrole rings, but differs in that one pyrrole (pyrroline) ring is saturated at the peripheral (β) macrocyclic positions (Figure 1, chlorin shown with D-ring reduced). The synthesis of an asymmetrically substituted chlorin is no small task, for in the preparation of such a macrocycle it is possible to produce eight isomers: four pyrroline-ring regioisomers each of which could exhibit cis or trans relative stereochemistry at their β-positions. An efficient synthesis of the chlorin ring system requires control over pyrroline ring formation (i.e., regioselective control in the formation of the partially saturated pyrrole ring), control over the stereochemistry of the pyrroline ring, and the ability to create the desired substituent pattern on the β-positions of the macrocyclic ring. Control of the latter feature is imperative for the efficient preparation of chlorins regioselectively functionalized for supramolecular assembly, e.g., antenna arrays or molecular wires, or to model the chlorophylls (indeed, the basic functions of the chlorin protein cofactors are determined not only by the type of metal inserted into the macrocycle, but by the variation of the macrocyclic β-substituents).[4,7] The development of methods to synthesize asymmetric porphyrins from linear tetrapyrroles, and the flexibility these methods have given for isotope labeling, has led to advances in the understanding of structure and function in heme proteins, as well as to new insights in the coordination chemistry of the many metals that bind to

* To whom correspondence should be addressed. Phone: (316) 978−7375. FAX: (316) 978-3431.

† Current address: GlaxoSmithKline.

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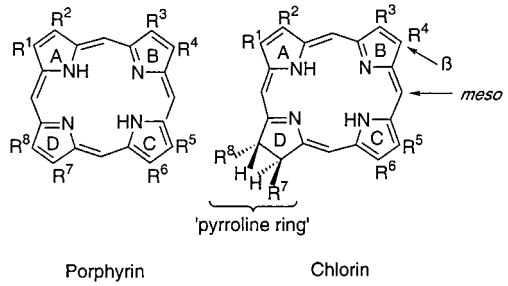

Figure 1. Ring structures of parent porphyrin and chlorin. β- and *meso*-ring positions, as well as the pyrroline ring, are labeled.

the porphyrin core.[8] Likewise, a more complete understanding of the chemistry of chlorins, as well as chlorin-protein systems, will require methods of synthesizing unsymmetrically substituted hydroporphyins in an efficient manner.

The existing methods for the syntheses of hydroporphyrins are almost all variations on the same theme, i.e., the transformation of a parent porphyrin into the corresponding dihydroporphyrin.[4,6,9] The reactions proceed with modest yields, generally involve conditions and reagents that tolerate few functional groups, and are limited to symmetrically substituted porphyrins to avoid structural isomer formation. Besides Woodward's artful synthesis of chlorophyll a,[10] access to the structurally challenging chlorophylls (chlorins with isocyclic rings) is obtained by extraction, an approach limited to those macrocyclic structures that are stable to the extraction conditions and that are found in nature in large quantities. To date, few general methods have been devised in which a chlorin is built in the rational, step-by-step fashion from linear tetrapyrroles as now commonly employed in porphyrin synthesis. The groups of Battersby[11] and Monforts[4,9c] have devised total syntheses of the less common geminally disubstituted chlorins, such as bonellin, Heme d, and Factor I, by utilizing a nonoxidizable *gem*-dialkyl β-substituted reduced ring as one of the four precursor pyrrole rings (Figure 2). Extensions of this elegant, albeit lengthy and not highly convergent, approach have been reported recently by the groups of

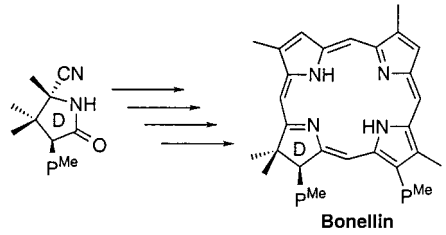

Figure 2. A key feature in the lengthy synthesis of bonellin by the Monfort's group was their utilization of a nonoxidizable *gem*-dialkyl pyrrolidinone ring to construct the chlorin pyrroline ring.

Lindsey[7] and Jacobi.[12] However, this approach is not amenable to the study of the most abundant naturally occurring chlorins, the light-harvesting chlorophylls, whose pyrroline rings are not fixed by *gem*-dialkyl groups.

We have recently communicated the synthesis of chlorins **1** and **2** from the rearrangement of metalated 5,15-porphodimethenes **3** (Scheme 1) in 35−61% yield;[13] the intermediate porphodimethene is the same oxidation state as the chlorin product. Advantages to this method are (1) the reaction conditions are relatively mild, (2) the synthesis is highly regioselective, with only one out of four possible pyrroline ring isomers formed as shown, and (3) the synthesis is short, as the porphodimethene **3** is furnished directly from the '2 + 2' MacDonald condensation[14] of 1,9-diformyldipyrromethane **4** and dipyrromethane **5**, or the '3 + 1' condensation[13a] of tripyrrane **7** and bis-formyl pyrrole **8**.[15] The method, *utilizing readily prepared precursor pyrroles*, allows for a variable chlorin peripheral substituent pattern and does not require the pyrroline ring to be fixed by a *gem*-alkyl group or be prepared prior to macrocyclic ring formation. Thus, we thought that our approach might be a potential route for a rational synthesis of the chlorophylls if we could discover the factors responsible for the selectivity of pyrroline ring formation observed in our initial studies.

The regioselectivity of pyrroline ring formation in chlorins **1** and **2** is truly remarkable. HPLC analysis shows **1** to be 98% of the chlorin mixture, with 1−2% of other unidentified chlorin isomers. Semiempirical calculations (PM3[16]) show this regioisomer *is not* the most thermodynamically stable reduced ring, yet in each case, the only pyrroline ring formed in chlorins **1** and **2** was the one that contained β-hydrogen substituents. These results formed the basis of our hypothesis that the formation of chlorin regioisomers was very sensitive to the type of peripheral substituent on the porphodimethene, and we undertook a project to examine the scope of the rearrangement with regards to different peripheral groups. We now report in full our findings on the influence that β-substituents have on the regioselectivity and stereoselectivity of pyrroline ring formation in the rearrangement of porphodimethene to chlorin.

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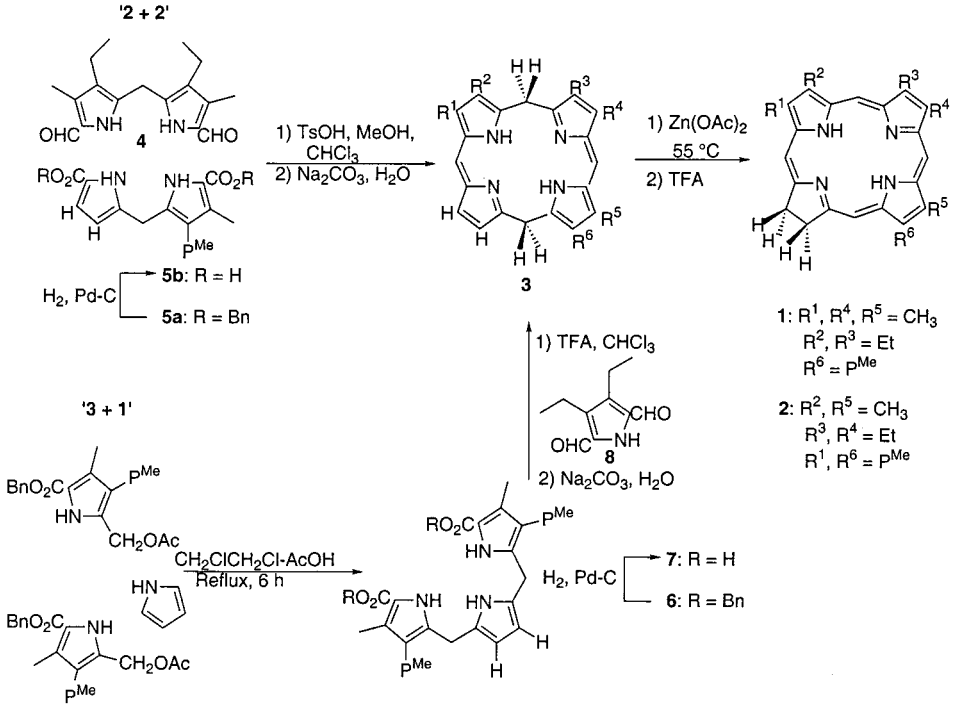
Scheme 1. Examples of the '2 + 2' and '3 + 1' Synthesis of Chlorins via the Rearrangement of Metallated 5,15-porphodimethenes.



Results and Discussion

Regioselectivity of Pyrroline Ring Formation: Electronic versus Steric Effects of Peripheral Substituents. The synthesis of chlorins **1** and **2** demonstrated that pure chlorin isomers could be prepared in good to moderate yield without the need for a porphyrin intermediate, long synthetic schemes, or extensive purification procedures to separate chlorin regioisomers. However, it was not known if the high regioselectivity observed in the rearrangement was limited to only porphodimethenes containing a pyrrole ring with two β-hydrogen substituents. It has been demonstrated that the dissolving metal reduction of iron porphyrins to furnish chlorins does exhibit partial regioselectivtiy in pyrroline ring formation, and the regioselectivity is due to peripheral substituent groups best able to stabilize excess electron density.[17] With this in mind, we initiated an investigation to determine the substituent influence over pyrroline ring formation with the synthesis of porphodimethenes containing β-substituents of different electronic character (i.e., electron withdrawing or electron donating) or a set of substituents with defined steric demands. Results from rearrangements of these types of variously substituted porphodimethenes would outline what kind of substituent is essential for the formation of only one ring-reduced isomer. The purification of chlorin isomers is tedious at best, so to be synthetically useful, the rearrangement must produce (predominantly) one regioisomer. The above studies would thus detail the limitations to chlorin structure efficiently furnished from our rearrangement methodology.

Initially, the variously substituted porphodimethenes were prepared by a '2 + 2' MacDonald approach (a condensation method normally used in the synthesis of porphyrin rings), which required the synthesis of the dipyrromethanes shown in Scheme 2. These dipyrromethanes were precursors to porphodimethenes which would contain a substituent pattern of all alkyl (electron donating) groups, with alkyl groups and one β-hydrogen (electron neutral) substituent, and a porphodimethene with a partial peripheral substitution pattern of β-hydrogen−*meso*-alkyl−β-alkyl. The latter pattern of β-substituents provides a steric effect responsible for the (>95%) formation of one chlorin regioisomer upon dissolving metal reduction of the parent porphyrin (vide infra). Dipyrromethanes **15**−**17** were prepared in typical fashion,[18a] and dipyrromethane **18** was prepared by our reported method,[18e] from pyrroles **9**−**14**.[18]

In general, the '2 + 2" preparation of chlorins was as follows. The bis-formyldipyrromethane **15** was condensed with dipyrromethanes **16**−**18** under anaerobic (glovebox) conditions, furnishing the respective porphodimethenes **19**−**21** (Scheme 3). We modified the MacDonald condensation reaction conditions by utilizing the dilution principle,[19] adding a $CHCl_3$ solution of dipyrromethanes dropwise to a $CHCl_3$/TsOH solution over a 3.5−4 h time period. This modification usually resulted in a 2-fold increase in macrocyclic yield, without apparent scrambling of intermediate porphodimethenes. After being stirred for several more hours, the reaction mixture was neutralized with carbonate and eluted through an alumina gel plug. Subsequent metalation of the porphodimethene with excess $Zn(OAc)_2$ and stirring at 55 °C over a 2 h time period resulted in rearrangement.

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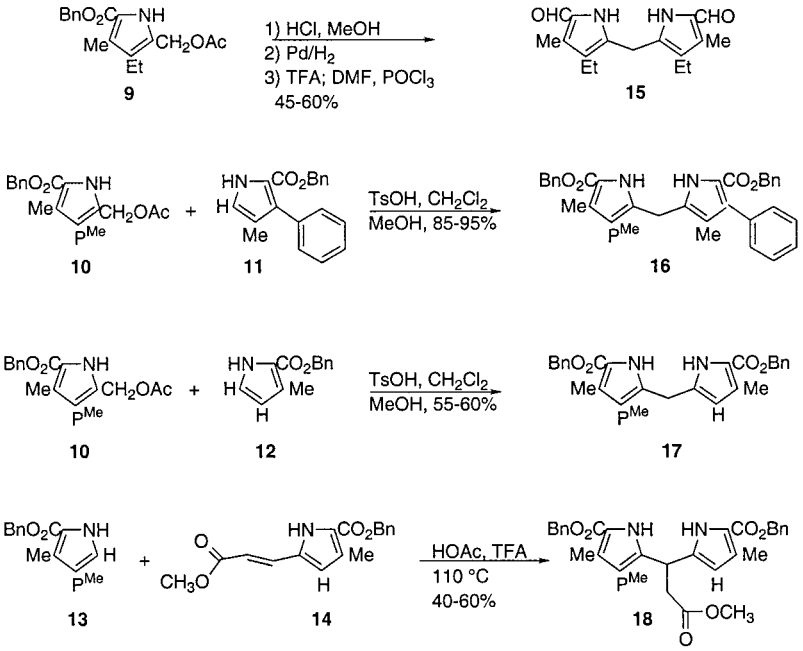
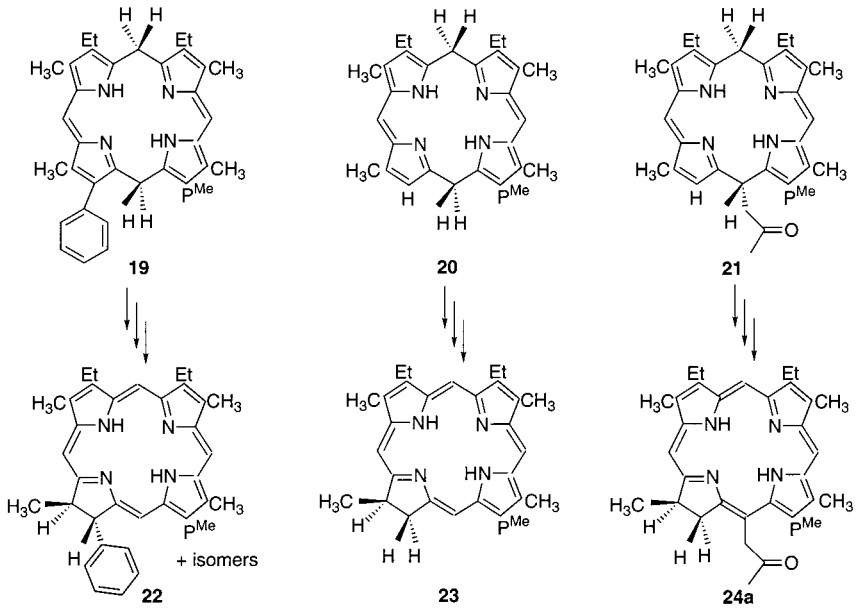
Scheme 2. Synthesis of Dipyrromethanes Utilized in the '2 + 2' Approach to the Preparation of Chlorins.



Scheme 3. The Regioselective Formation of Chlorins 22 − 24A via the Rearrangement of Metallated Porphodimethenes 19 − 21.



Demetalation with TFA and purification by alumina gel chromatography furnished pure chlorins **22**, **23**, and **24a** in yields between 15 and 49%, with porphyrin byproduct formed in 5−15% yield.

The unsymmetrically substituted chlorin **22** was furnished in 15% yield from the condensation of **15** and **16** followed by rearrangement of porphodimethene **19**. The partial ^{1}H NMR spectrum[20] of chlorin **22** shown in Figure 3 illustrates formation of what appears to be all possible chlorin regioisomers, as well as possible stereoisomers (i.e., cis and trans reduced ring). In the *meso* proton region alone, the spectrum exhibits at least 20 distinct proton resonances between 9.5 and 9.8 ppm and between 8.6 and 9.0 ppm. For each regioisomer of chlorin **22** one would expect a maximum of four *meso* proton resonances (or a maximum of eight for its cis and trans stereoisomers). Clearly, β-alkyl substituents demonstrate no special pyrroline ring directing ability upon rearrangement of the porphodimethene into chlorin. This is in stark contrast to results obtained upon rearrangement of the porphodimethenes which contain a pyrrole ring with two β-hydrogen substituents (vide supra). These two opposite results suggest that formation of the chlorin pyrroline

(20) The ^{1}H NMR spectra of chlorins are quite distinctive, and are quite indicative of their structure. The *meso* protons of chlorins resonate in two separate downfield regions: between 8.5 and 9 ppm for the two *meso* protons adjacent to the pyrroline ring, and between 9.5 and 10 ppm for the other two *meso* protons adjacent to only pyrrole rings. Unsymmetrical chlorins will exhibit four resonances corresponding to each *meso* proton. Protons attached as β-substituents on the chlorin pyrrole rings resonate generally between 8 and 8.5 ppm, while protons attached as β-substituents on the pyrroline ring resonate between 4.3 and 5.0 ppm. Additionally, while protons on carbons attached to the β-position of the chlorin pyrrole rings resonate between 3.4 and 4.2 ppm, the protons on carbons attached to the β-position of the pyrroline ring resonate between 1.8 and 2.5 ppm.

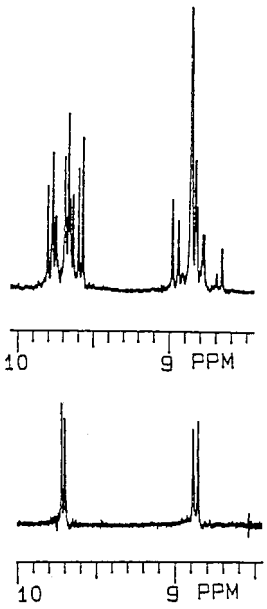


Figure 3. Example of a partial ^{1}H NMR spectrum of chlorins **22** (top) and **23** (bottom), illustrating the difference in the *meso*-proton region of the two spectra due to the difference in the regioselectivity of the porphodimethene rearrangement.

ring during the rearrangement is *extremely sensitive* to electronic effects of the β-substituents, since such markedly different results are observed with electron donating as opposed to electron neutral substituents.

To examine the sensitivity of the rearrangement to β-substituent steric effects, porphodimethenes **20** and **21** were prepared from dipyrromethanes **15**, **17**, and **18** via MacDonald condensation reactions. The rearrangement of porphodimethene **20** into chlorin **23** demonstrates the electronic effect of only one hydrogen β-substituent on pyrroline ring formation, with no obvious steric factors influencing the outcome. On the other hand, the partial peripheral substitution pattern of β-hydrogen−*meso*-ethanoate−β-propanoate of porphodimethene **21** is similar to, if not more sterically congested than, the pattern of β-substituents found on phylloporphyrin: β-hydrogen−*meso*-methyl−β-propanoate. Dissolving metal reduction of phylloporphyrin results in 95% formation of the thermodynamically favored D-ring chlorin regioisomer (Figure 4).[17] Reduction of the phylloporphyrin's D-ring places its β-substituents out of the plane of the macrocyclic ring and eliminates steric compression between the *meso*-methyl substituent and the D-ring β-propanoate group. Indeed, this is the only example of a highly regioselective synthesis of a chlorin by dissolving metal reduction of a porphyrin. In the same manner, if pyrroline ring formation was predominantly influenced by steric effects, one would expect the rearrangement of porphodimethene **21** to largely furnish chlorin isomer **24b**, shown in Figure 4. It was felt that structure of **24b** would lend itself to further elaboration that could furnish a C-ring isocyclic ring, providing for a model synthesis of the chlorophyll macrocycle using our rearrangement methodology. If electronic effects were most important, however, then one would expect the results of the rearrangement to be similar to those observed in the rearrangement of **20**, since both porphodimethenes have one β-hydrogen substituent.

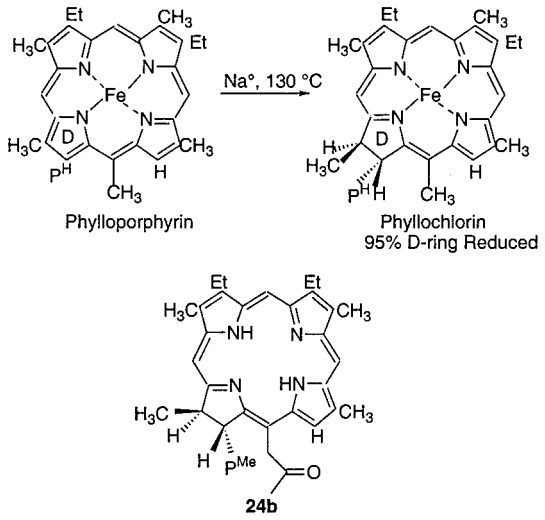
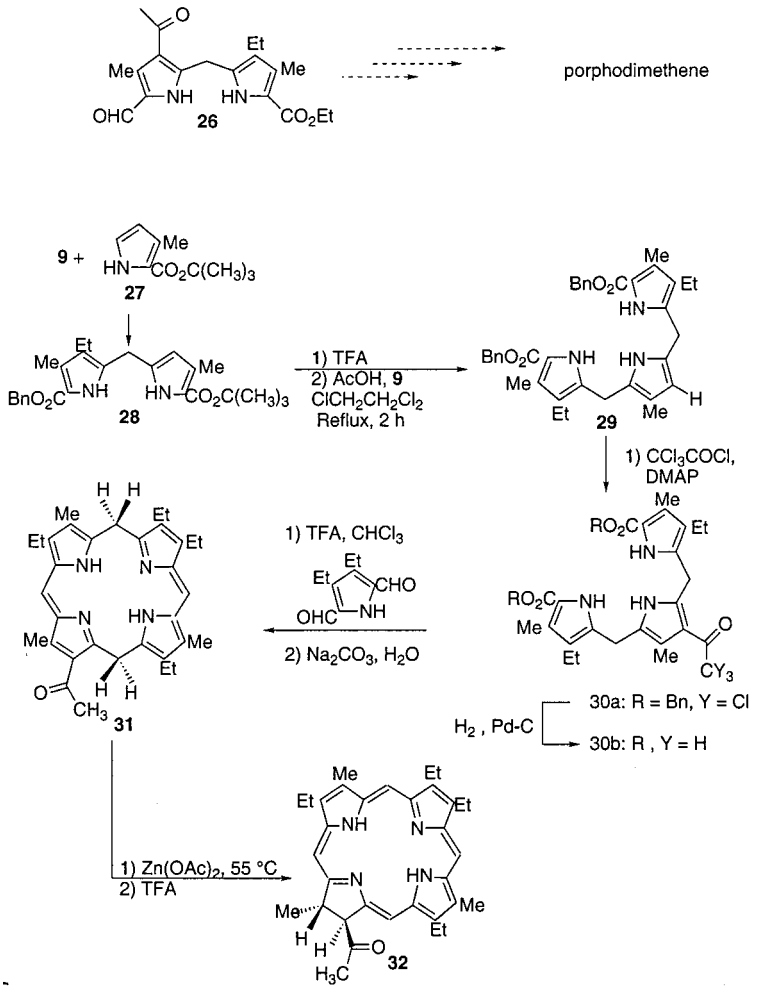


Figure 4. The dissolving metal reduction of metalated phylloporphyrin to furnish metalated phyllochlorin is highly regioselective.

Chlorin **23** was furnished in 49% yield from the condensation of dipyrromethanes **15** and **17** followed by the rearrangement of porphodimethene **20**. Its ^{1}H NMR spectrum clearly shows formation of only the one ring-reduced isomer (Figure 3). Only four *meso* proton resonances are present (9.65, 9.63, 8.81, 8.78 ppm), no pyrrole β-hydrogen resonance is observed, and a doublet at 1.97 ppm is due to the β-methyl group attached to the pyrroline ring. The proton resonances of the methyl propanoate and ethyl groups are observed only on the fully aromatic pyrrole rings of the chlorin. The multiplets at 4.89−4.93 and 4.38−4.28 ppm, corresponding to pyrroline ring β-hydrogens, integrate to three protons. Overwhelmingly, the ^{1}H NMR data shows the pyrroline ring is formed only from the precursor pyrrole with attached β-hydrogen and β-methyl groups. Consequently, *only one* β-hydrogen is required to selectively direct pyrrole ring-reduction via the rearrangement of the porphodimethene. Porphodimethene **21** rearranged to furnish only one chlorin regioisomer **24a**, but in low yields (4−8%) unless high temperature was employed (refluxing diglyme: 15% yield; sealed tube + chloroform, 90 °C: 24%). The chlorin ^{1}H NMR exhibited only one *meso*-hydrogen resonance (8.69 ppm) adjacent to the reduced ring, no aromatic β-hydrogen resonance, three pyrroline ring hydrogens (multiplet at 4.73−4.82, dd at 4.59, dd at 4.03 ppm), and a methyl doublet at 1.95 ppm, all indicating the chlorin isomer is the one shown in Scheme 3. Once again, the only pyrroline ring formed is from a precursor pyrrole that contains an attached β-hydrogen substituent, *regardless of the opposing steric effect*.[21] This result strongly suggests that the chlorin product is a kinetic product of the rearrangement, and that the highly regioselective porphodimethene rearrangement is extremely sensitive to the nature of the electronic effects of its β-substituents.

Whether the sensitivity of the rearrangement to β-hydrogens was due to their greater ability to stabilize (or at least not destabilize) excess electron density placed in the ring during the transformation of the macrocycle's π-system, or to some unknown factors particular to the mechanism of the rearrangement, was not clear at this point in our study. To illuminate this point in question,

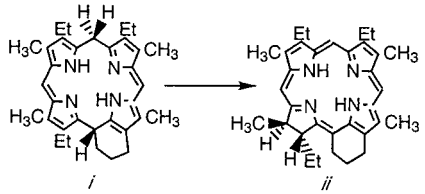
Scheme 4. '3 + 1' Synthesis of Acetylchlorin 32.



porphodimethene **31** (Scheme 4), with an electron-withdrawing β-carbonyl in resonance with the ring's π-system, was targeted for synthesis. The preparation of this porphodimethene proved much more difficult than anticipated via a 2 + 2 condensation approach. While we were able to construct the 1-formyl-3-acetyldipyrromethane **26**[22] (Scheme 4), the preparation of an acetylporphodimethene using this dipyrromethane proved problematic.[23]

We have communicated a model study which demonstrated that the recently developed '3 + 1' approach for the construction of the porphyrin macrocycle could also be used for the synthesis of chlorins via the porphodimethene rearrangement.[13a] The advantage of this approach to the construction of an acetyl porphodimethene is that the carbonyl group, attached to the middle pyrrole of the tripyrrane, would not retard the end pyrroles ability to undergo aromatic electrophilic addition with the bisformyl pyrrole **8**. Tripyrranes **29** and **30** (Scheme 4) were therefore targeted for synthesis, and the challenge to their preparation was several-fold. Tripyrrane **29** is not symmetric and required more that the usual one-pot reaction to prepare it. Tripyrranes are extremely sensitive to even slightly acidic conditions, and their reported syntheses commonly use acetic acid as the proton source, and ethanol as the solvent.[24] In ethanol, the tripyrrane usually precipitates out of solution when it is formed, removing it from the mild acid conditions and obviating the need for further deleterious purification procedures. The filtered tripyrranes are then used without further elaboration to condense with a bisformyl pyrrole. Our strategy dictated the delicate tripyrrane be modified with an acetyl group, and there-

(21) The only time a steric effect promoting regioselectivity was observed occurred in the rearrangement of porphodimethene **i** where no β-hydrogen substituents were present. In this case, the all alkyl-substituted **i** rearranged to > 70% chlorin regioisomer **ii** (determined by ^{1}H NMR) presumably due to the relief of steric compression between the isocyclic hexyl ring and the now out-of-the-plane reduced-ring ethyl group. This results suggest that with an appropriate isocyclic ring placed in a precursor porphodimethene, our rearrangement method could furnish a chlorophyll macrocycle in an efficient manner. Additionally, this result begs the question, does the isocyclic ring in protochlorophyllide play a part in the regioselectivity of D-ring reduction in the biosynthesis of the chlorophyll precursor chlorophyllide by protochlorophyllide reductase, or is the regioselectivity of D-ring reduction solely a result of protein regiochemical control?



(22) Burns, D. H.; Burden, M. W.; Li, Y. H. *J. Porphyrins Phthalocyanines* **1998**, *2*, 295−304.

(23) Porphyrin macrocycles that contain electron-withdrawing β-substituents are typically synthesized from the ring closure of β-bilenes and not from MacDonald condensations. See Clezy, P. S. *Aust. J. Chem.* **1991**, *44*, 1163−1193.

(24) For an overview, see ref 15, and (a) Lash, T. D. *Chem. Eur. J.* **1996**, *2*, 1197−1200. (b) Boudif, A.; Momenteau, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1235−1242.

fore both tripyrranes **29** and **30** would require purification routines.

The synthetic route for **30** and chlorin **32** is detailed in Scheme 4. Dipyrromethane **28** was made from pyrroles **9** and **27**[25] in 85% yield. Selective removal of the *tert*-butyl ester, decarboxylation, and reaction with pyrrole **9** furnished tripyrrane **29** in 30% overall yield. Best yields of tripyrrane **29** were afforded with the use of 1,2-dichloroethane as solvent rather than ethanol or 2-propanol. It was necessary to purify the crude reaction material by chromatography, and the best resolution with the least amount of carnage was attained with Florisil. Acetylation of tripyrrane **29** in the usual manner (acetyl chloride or acetic anhydride and $SnCl_4$, BF_3−etherate, $AlCl_3$, in various solvents) furnished only decomposition products. Addition of various bases to the reaction mixture to neutralize the acid byproduct proved fruitless. Acetylation succeeded only with the use of the reactive electrophile CCl_3COCl and 3 equiv of DMAP, as an activator and *strong base*. Purification of the crude reaction material by Florisil furnished the tripyrrane **30a** in 87% yield. Hydrogenation removed the benzyl groups and also resulted in complete dehalohydrogenolysis to produce tripyrrane **30b** in 79% yield. Decarboxylation of **30b** and condensation with bisformyl **8**, followed by our rearrangement protocol, furnished chlorin **32** in 46% yield. The ^{1}H NMR spectrum of the acetyl chlorin shows only four *meso* proton resonances (9.76, 9.74, 8.89, and 8.85 ppm), and that the pyrroline ring contains two hydrogens with a splitting pattern of a doublet and a doublet of quartets, along with a β-methyl doublet at 2.02 ppm. All the NMR data is consistent with the production of the one chlorin regioisomer wherein the pyrroline ring contains the acetyl group. This result, coupled with our previous ones, further corroborates our hypothesis that the high regioselectivity observed in the rearrangement of porphodimethene to chlorin is due to the ability of β-substituents to accommodate excess electron density that builds up in the macrocyclic ring during the transformation of its π-system.

Stereoselectivity of Pyrroline Ring Formation. To examine the stereoselectivity of the rearrangement, octaethylchlorin was prepared in 19% yield utilizing our rearrangement protocol. Only one chlorin regioisomer can be furnished because of the symmetrical structure of the ring, making it easy to distinguish the formation of both cis and trans stereoisomers by ^{1}H NMR. The octaethylchlorin furnished from our rearrangement protocol exhibits a 60−40 cis−trans stereoisomer ratio as determined from integration of *meso* proton resonances in its ^{1}H NMR spectrum. Metalation of an authentic sample of *cis*-octaethylchlorin (*p*-toluenesulfonhdrazide reduction of octaethylporphyrin[26]) with excess $Zn(OAc)_2$ and heating the reaction mixture at 55 °C for 2 h results in no epimerization of the chlorin. Both stereoisomers are therefore formed during the rearrangement.

On the other hand, acetyl chlorin **32** is produced with high diastereoselectivity upon rearrangement of the precursor porphodimethene **31**. Only one diastereoisomer is observed in its ^{1}H NMR spectrum, as indicated by only four *meso* proton resonances, only one set of pyrroline

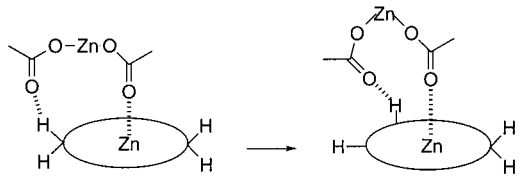


Figure 5. A schematic drawing of the hypothetical mechanism for the rearrangement of metalated 5,15-porphodimethene into metalated chlorin.

β-proton resonances, and only one pyrroline β-methyl resonance (vide supra). NOE experiments carried out on the two pyrroline β-hydrogens and β-methyl group show that the diastereoisomer is in the trans configuration. However, when crude material from the rearrangement is not subject to demetalation or alumina gel chromatography, the ^{1}H NMR spectrum of the chlorin indicates both trans and cis stereoisomers are present in approximately a 4:1 ratio, respectively (a second doublet at 5.80 ppm corresponds to the pyrroline β-proton on the same carbon as the β-acetyl group in the cis-reduced ring). The conditions of the reaction, demetalation, and purification allow for the epimerization of the pyrroline ring to selectively form the most thermodynamically stable stereoisomer, presumably due to the reactive β-carbonyl group. Consequently, while the rearrangement is not intrinsically stereoselective, a chlorin stereoisomer can be selectively produced if epimerization of the pyrroline β-carbons is possible.

Mechanism of Porphodimethene Rearrangement. We have shown with UV/Visible spectrophotometry that both the '2 + 2' and '3 + 1' condensation reactions lead to an equilibrium mixture of phlorin and 5,15-porphodimethene, and that metalation shifts the equilibrium to the metalated 5,15-porphodimethene.[13] The porphodimethene does not undergo rearrangement without metalation, and only a small amount of chlorin is produced if the reaction is not heated after metalation of the porphodimethene. When excess $Zn(acac)_2$[27] (with a more basic ligand than acetate) was added to the neutralized reaction mixture, metalation was immediate but no rearrangement took place upon heating. Further experiments demonstrated that the formation of chlorin was slow to nonexistent when 1−1.5 equiv of $Zn(OAc)_2$ were used, but rearrangement was essentially complete within a 1 h time frame when more than 2 equiv were used. Additionally, when the saturated $Zn(OAc)_2$/methanol solution was removed (water wash) and the metalated porphodimethene in chloroform was heated to 55 °C, rearrangement occurred in a normal manner. In a heated anaerobic cuvette, no chlorin was produced from metalated porphodimethene when the cuvette solution was made slightly basic with triethylamine, nor was rearrangement observed when the cuvette solution was made slightly acidic with acetic acid.

The above data is consistent with the possibility that a second equivalent of $Zn(OAc)_2$, bound as a fifth, axial ligand to the metalloporphodimethene via an acetate, uses its other acetate to shuttle protons about the periphery of the ring while the whole group rotates about the metal, as depicted in Figure 5.[28] Triethylamine is a

(25) (a) Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664−7665. (b) Jackson, A. H.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. (C)* **1971**, 502 -509.

(26) Whitlock, H. W.; Hanauer, R.; Oester, M. Y.; Bower, B. K. *J. Am. Chem. Soc.* **1969**, *91*, 7485−7489.

(27) Lahiri, G.; Summers, J. *Inorg. Chem.* **1991**, *30*, 5049−5052.

(28) For a similar rearrangement in the synthesis of porphyrinogen to corphin, see Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 5−39.

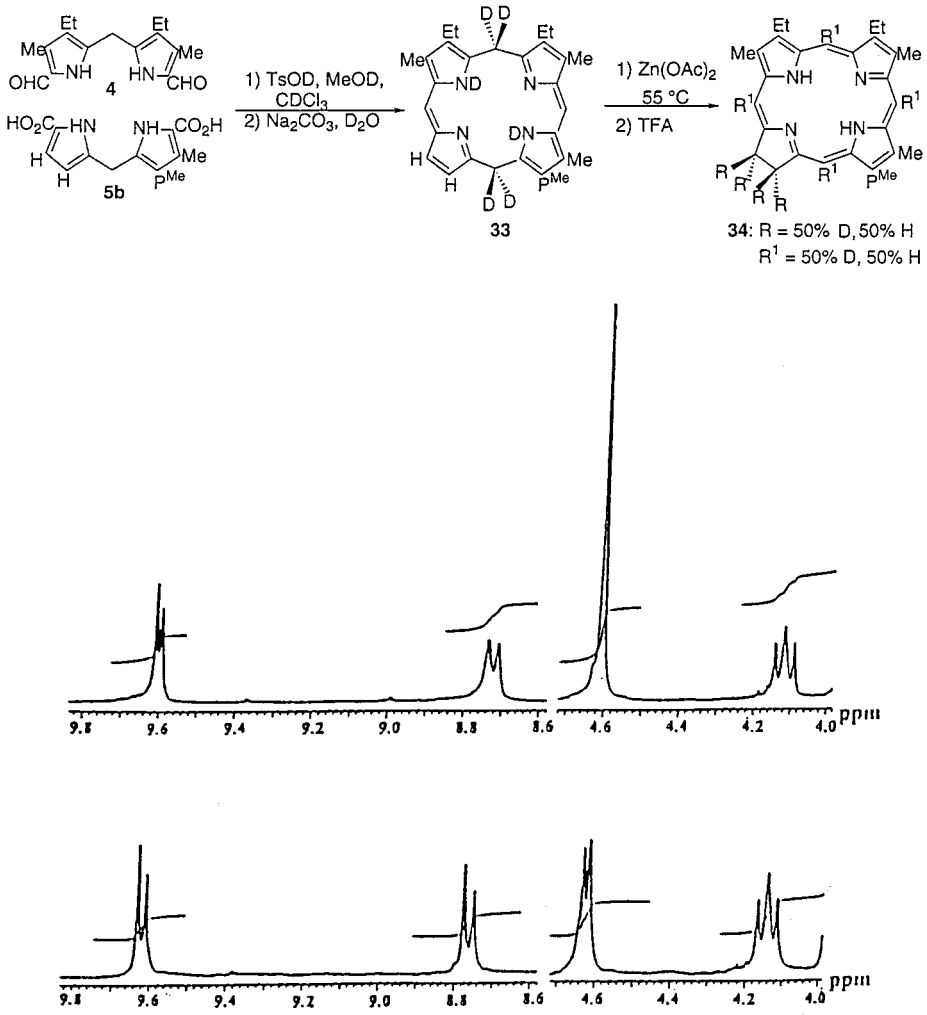


Figure 6. Synthesis of deuterated chlorin **34**, and partial ^{1}H NMR spectra of chlorins **1** (top) and **34** (bottom).

better ligand for Zn(II) than acetate, and acetic acid could hydrogen bond to the acetate ligands. In either case, the added reagent would act to displace the acetate from the metalloporphodimethene, not allowing it to participate in any shifting of ring peripheral protons. Metalation of the porphodimethene with $Zn(acac)_2$ and heating did not furnish chlorin, corroborating the need for more than simple metalation for the rearrangement to proceed. The need for a minimum of 2 equiv of $Zn(OAc)_2$ for a facile preparation of chlorin suggests that a second $Zn(OAc)_2$ is involved in the rearrangement. Additionally, removal of excess $Zn(OAc)_2$ with concomitant rearrangement suggests the shifting of hydrogens is intramolecular in origin.

A deuteration study was undertaken to shed more light on the mechanism of the rearrangement and to provide direct evidence for the intramolecular shifting of protons about the ring. MacDonald condensation of **4** and **5** with *p*-toluenesulfonic acid-*d*·*x*D_2O in $CDCl_3$, followed by a D_2O/bicarbonate wash, produced 5,15-tetradeuterioporphodimethene **33** (Figure 6).[29] Metalation of **33** with a saturated solution of $Zn(OAc)_2$·*x*D_2O in CH_3OD, followed by a second D_2O wash, removal of all solvent, reintroduction of chloroform and use of typical rearrangement and purification protocols, furnished chlorin **34**. The rearrangement of **33** resulted in the deuteration of 50% of the β-carbons in the reduced ring and *50% of all meso-carbons*, as determined from its ^{1}H NMR spectrum (Figure 6). The experiment firmly establishes that during the rearrangement of the π-system, protons are shifted about the periphery of the macrocyclic ring. This result is certainly consistent with the view that a fifth ligand is involved in aiding the movement of protons about the ring.

The high regioselectivity of the rearrangement is consistent with a fifth, axial ligand shuttling protons about the ring. As protons are removed from the ring, excess electron density will build up in the π-system. The shifted protons find final placement on the carbons where the excess electron densitiy is stabilized the most, i.e., those carbons with attached electron stabilizing or neutral β-substituents. That the rearrangement to chlorin **24a** works best with high temperatures may be ascribed to differing conformational stability of the intermediates, and its affect on the axial fifth ligand's ability to shift protons about the ring. Porphodimethenes are relatively flexible, and take on angled rooflike conformations, where the *meso*-methylene carbons have substituents in axial- and equatorial-like conformations. CPK models of **21** show the methine hydrogen to be buried between the

(29) Our procedure for the tetradeuteration of both methylene positions of a porphodimethene was a modification of a reported method. Cavalairo, J.; Gonsalves, A.; Kenner, G.; Smith, K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771−1781.

meso-acetic and β-propanoic substituents when it is in the "equatorial" position, which force field calculations[30] show to be the most stable conformation. This conformation is similar to the bis-methylated porphodimethenes of Buchler, whose *meso*-methyl groups are both in the "axial" position.[31] In porphodimethene **21**, the "equatorial" hydrogen cannot be readily reached by the acetate ligand. Rearrangement is slowed, and high temperatures are needed to place the porphodimethene in its higher energy conformation with an "axial" methine hydrogen, which is then accessible to removal via the acetate ligand.

The stereochemical outcome of the rearrangement is not as easily rationalized using the fifth, axial ligand model. Both cis and trans stereoisomers are formed during the rearrangement. While production of the cis isomer is consistent with the model (proton shifts all on one side of the ring), production of the trans isomer needs additional explanation. One possibility is that the Zn(II)porphodimethene is six-coordinate, allowing the shifting of protons on either side of the ring (resulting in the trans-reduced pyrroline ring). This scenario seems unlikely since the metal prefers to be five-coordinate over six-coordinate, and the porphodimethene conformation is angled, not flat, such that a sixth ligand would face steric repulsion from the angled ring. As peripheral protons are shifted about the ring, and the π-system is being transformed, it is likely that the ring becomes less angular and more flat. Since the acetate ligand is kinetically labile, ligand exchange could occur on opposite sides of the incipient chlorin ring, and in that way, a trans chlorin could be produced.

Conclusion

The porphodimethene rearrangement methodology provides for a rational, step-by-step synthesis of chlorins from readily available pyrrole precursors. The intermediate porphodimethenes are furnished directly via the '2 + 2' MacDonald condensation, or by the '3 + 1' condensation of a tripyrrane and bis-formyl pyrrole. The synthetic route is short and highly convergent, and furnishes chlorins in good to moderate yields. The reaction conditions are relatively mild, so many types of substituent functional groups are expected to be tolerated. The synthesis is highly regioselective, and appears to be based on the ability of the β-substituent to stabilize excess electron density, with an electron-neutral hydrogen or an electron-withdrawing carbonyl β-substituent demonstrating the greatest influence on the formation of the chlorin's pyrroline ring. The synthesis is highly stereoselective when epimerization of the pyrroline ring β-carbons is possible, furnishing only the trans-reduced sterioisomer. Finally, there is substantial evidence that a fifth, axial ligand is involved in the intramolecular transposition of peripheral hydrogens during the rearrangement of the π-system from metalloporphodimethene to metallochlorin.

Experimental Section

Materials and Procedures. The following chemicals were used as indicated: benzoyl chloride and oxalyl chloride were distilled just before use; silica gel (Davisil 633) (Silica Gel 60) was used for column chromatography, and analytical thin-layer chromatography was performed using precoated silica gel GF plates. Alumina (60−325 mesh) and Florosil (100−200 mesh) were also used for column chromatography. Some samples that underwent spectral and analytical analysis were purified by radial chromatography using a Chromatotron. Analytical samples were dried under vacuum in a drying pistol at 112 °C for a minimum of 2 days. All oxygen-sensitive reactions (i.e., the '2 + 2' or '3 + 1' synthesis of chlorins) were preformed in a glovebox.

Solvents were dried and purified according to literature methods.[32] Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone; dichloromethane was distilled first from phosphorus pentoxide and then from calcium hydride; dimethylformamide (DMF) and acetonitrile were distilled from calcium hydride; 1,2-dichloroethane was distilled from phosphorus pentoxide, (dimethylamino)pyridine (DMAP) was sublimed at 80−85 °C under vacuum before use. Solvents were degassed either by bubbling argon through the solvent overnight (methanol, chloroform, water, hexane, and ethyl acetate) or bubbling argon using Teflon tubing for 6 h (TFA). All solvents used in the glovebox were first degassed by the methods mentioned above followed by sonication for 30 min in the glovebox before use.

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at either 400 MHz or 300 MHz in $CDCl_3$ or DMSO-d_6 as solvent and Me_4Si as an internal standard (0 ppm) unless otherwise specified. Elemental analyses were done by MHW Laboratories, Phoenix, AZ.

'2 + 2' Approach to the Chlorin Macrocycle. 3,7-Diethyl-2,8,12,18-tetramethyl-13-(2-methoxycarbonylethyl)-17,18-dihydroporphyrin (23). All reactants and reagents were exposed to the atmosphere of the glovebox for 24 h before the experiment was started. A solution of dipyrromethane **17** (0.23 g, 0.65 mmol) and dipyrromethane **15** (0.20 g, 0.71 mmol) in CH_3Cl (27 mL) and CH_3OH (14 mL) was added dropwise over the course of 3.5 h to *para*-toluenesulfonic acid monohydrate (0.54 g, 2.8 mmol) dissolved in $CHCl_3$ (90 mL) and CH_3OH (20 mL). The reaction mixture was stirred an additional 4 h, and then quenched with aqueous Na_2CO_3 (1.3 g in 50 mL water). The organic layer was separated and the aqueous phase was extracted by chloroform. The combined organic phases were run through a alumina plug (10 cm) and the column was washed with CH_3Cl until the eluent was clear. A saturated solution of zinc acetate in CH_3OH (10 mL) was added to the CH_3Cl solution, and the mixture was stirred at 65 °C for 2 h, and then allowed to stir at ambient temperature overnight. The solvent was removed under vacuum, and degassed TFA (10 mL) was added and the solution stirred for 10 min under nitrogen at 0 °C. The demetalation reaction was quenched with 5% ammonium hydroxide, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, and the solvent was removed under vacuum. The crude dark solid was chromatographed on alumina gel (grade III) eluting with benzene/CH_2Cl_2 (99/1) to yield the title chorin (0.1632 g, 0.32 mmol, 49.3%). mp: 183−185 °C; UV/Visible: CH_2Cl_2 λ_{max} nm (ϵ): 390 nm (7.44×10^4), 488 nm (1.02×10^4), 496 nm (9.83×10^3), 646 nm (1.55×10^4); ^{1}H NMR ($CDCl_3$, 400M Hz): δ 9.66, 9.65 (s, 2H), 8.83, 8.80 (s, 2H), 4.96−4.86 (m, 2H), 4.37−4.24 (m, 1H), 4.18 (t, 2H, J = 8.01 Hz), 3.97 (q, 2H, J = 7.64 Hz), 3.84 (q, 2H, J = 7.64 Hz), 3.69, 3.50, 3.39, 3.37 (s, 12H), 3.13 (t, 2H, J = 8.01 Hz), 1.97 (d, 3H, J = 6.62 Hz), 1.77 (t, 3H, J = 7.64 Hz), 1.75 (t, 3H, J = 7.64 Hz), −2.38 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.53, 170.70, 163.58, 150.36, 149.78, 143.00, 139.94, 138.60, 136.76, 135.82, 133.44, 132.74, 132.48, 130.40, 127.86, 99.14, 98.69, 92.45, 92.10, 51.69, 44.39, 41.70, 36.66, 23.64, 21.47, 19.79, 19.54, 17.77, 17.34, 11.43, 11.23, 10.94; LRMS *m*/*z* (relative intensity) 510 (M+, 30), 495 (3), 437 (2). Anal. Calcd for $C_{32}H_{38}N_4O_2$: C, 75.26; H, 7.50; N, 10.96. Found: C, 75.19; H, 7.53; N, 10.55.

(30) CAChe 3.9 MM2, CAChe Scientific (Oxford Molecular), Beaverton, OR 97076.

(31) (a) Buchler, J. W.; Puppe, L.; Rohbock, K.; Schneehage, H. H. *Ann. N. Y. Acad. Sci.* **1973**, *206*, 116−137. (b) Dwyer, P. N.; Buchler, J. W.; Scheidt, W. R. *J. Am. Chem. Soc.* **1974**, *96*, 2789−2795.

(32) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.

3,7-Diethyl-2,8,12,18-tetramethyl-13-(2-methoxycarbonylethyl)-15-(2-methoxycarbonylmethyl)-17,18-dihydroporphyrin (24a). All reactants and reagents were exposed to the atmosphere of the glovebox for 24 h before the experiment was started. A solution of dipyrromethane **18** (0.198 g, 0.47 mmol) and dipyrromethane **15** (0.123 g, 0.43 mmol) in CH_3Cl (16.4 mL) and CH_3OH (8.5 mL) was added dropwise over the course of 2 h to *p*-toluenesulfonic acid monohydrate (0.82 g, 4.3 mmol) dissolved in $CHCl_3$ (7.2 mL) and CH_3OH (12 mL). The reaction mixture was stirred an additional 20 h, and then quenched with aqueous Na_2CO_3 (1.0 g in 30 mL water). The organic layer was separated, and the aqueous phase was extracted with chloroform. The organic phases were combined and run through a alumina column (3 cm), and the column was washed with $CHCl_3$ until the eluent was clear (2 mL of CH_3OH was used at the end of elution). The eluent was collected in a 500 mL pressure bottle with stir bar, and a saturated solution of zinc acetate in CH_3OH (5 mL) was added into the pressure bottle. The pressure bottle was sealed inside the glovebox and then taken out of the box and stirred at 98 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature and stir for an additional 24 h, at which time the solvent was removed under vacuum. Degassed TFA (7 mL) was added to the crude mixture and the solution stirred for 10 min under nitrogen at 0 °C. The demetalation reaction was quenched with 5% NH_4OH, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and water and dried with sodium sulfate, and the solvent was removed under vacuum. The crude dark solid was chromatographed on alumina gel (grade III) eluting with cyclohexane/ethyl acetate (80/20) to yield the title chorin (0.061 g, 0.11 mmol, 24.3%). mp:172−174 °C; UV/Visible: CH_2Cl_2 λ_{max} nm (ϵ): 394 (7.82×10^4), 498 (1.17×10^4), 656 (2.65×10^4); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.73, 9.48 (s, 2H), 8.76 (s, H), 5.19−5.07 (m, 2H), 4.82−4.73 (m, 1H, 8-H**)**, 4.56 (dd, 1H, J = 16.04 Hz and J = 9.3 Hz**)**, 4.11 (t, 2H, J = 6.71 Hz), 4.03 (dd, 1H, J = 16.04 Hz and J = 3.96 Hz**)**, 3.86 (q, 2H, J = 7.52 Hz), 3.79 (q, 2H, J = 7.52 Hz), 3.79 (s, 6H), 3.53, 3.39, 3.38 (s, 9H), 3.01−2.97 (m, 2H), 1.97 (d, 3H, J = 3.9 Hz), 1.79−1.71 (m, 6H), −1.69 (br s, 1H). −2.05 (br s, 1H); ^{13}C NMR: 173.19, 173.11, 170.26, 164.52, 151.73, 149.17, 142.55, 139.97, 138.57, 136.83, 136.63, 135.90, 134.43, 130.17, 128.92, 100.80, 100.31, 97.80, 92.29, 92.21, 52.33, 52.19, 51.90, 51.76, 43.46, 41.88, 41.77, 38.83, 36.32, 23.89, 19.70, 19.46, 17.66, 17.25, 11.64, 11.54, 11.48, 11.41, 10.99; HRMS (FAB) Calcd for $C_{35}H_{42}N_4O_4$ 583.3284, found 583.3275. Anal. Calcd for $C_{35}H_{42}N_4O_4$: C, 72.14, H, 7.26, N, 9.61. Found: C, 71.81, H, 6.98, N, 9.37.

'3 + 1' Approach to the Chlorin Macrocycle. Benzyl 9-(*tert*-Butoxycarbonyl)-3-ethyl-2,8-dimethyldipyrromethane-1-carboxylate (28). *tert*-Butyl 3-methylpyrrole-2-carboxylate (**27**) (0.1156 g, 0.638 mmol) and Benzyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (**9**) (0.100 g, 0.319 mmol) were dissolved in 1,2-dichloroethane (1.19 mL), and glacial acetic acid (0.1 mL) was added to the reaction mixture. After being refluxed under a N_2 atmosphere for 36 h, the reaction mixture was cooled to room temperature and diluted with $CHCl_3$, and the organic phase was washed sequentially with water, 5% aqueous $NaHCO_3$ solution, and water and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the crude material was purified by column chromatography (silica gel, hexane/ethyl acetate, 85/15) and recrystallized using hexane/ethyl acetate (85/15) to yield orange crystals (0.117 g, 0.270 mmol, 85%), mp: 189−190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.18 (br s, 1H), 8.96 (br s, 1H), 7.25−7.37 (m, 5H), 5.80 (s, 1H), 5.26 (s, 2H), 3.83 (s, 2H), 2.4 (q, 2H, J = 7.32 Hz), 2.28 (s, 3H), 2.25 (s, 3H), 1.51 (s, 9H), 1.03 (t, 3H, J = 7.32 Hz); ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 161.62, 161.29, 136.51, 131.69, 129.32, 128.59, 128.48, 127.98, 124.48, 120.03, 117.58, 111.25, 80.48, 65.62, 28.47, 24.67, 17.17, 15.47, 12.89, 10.58; LRMS (electrospray): *m*/*z* (relative intensity) 435 (M − 1, 100), 367(20), 319 (18). Anal. Calcd for $C_{26}H_{32}O_4N_2$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.18; H, 7.27; N, 6.41.

Dibenzyl 3,12-Diethyl-2,7,13-trimethyltripyrrane-1,14-dicarboxylate (29). TFA (3.0 mL) was added to benzyl 9-(*tert*-butoxycarbony)-3-ethyl-2,8-dimethyldipyrromethane-1-carboxylate **28** (0.500 g, 1.15 mmol) and the solution stirred for 20 min at the ambient temperature under N_2. The reaction mixture was diluted with CH_2Cl_2, and neutralized by a saturated solution of $NaHCO_3$ and washed with water. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude product mixture, pyrrole **9** (1.08 g, 3.45 mmol), and glacial acetic acid (0.27 mL) were dissolved in 1,2-dichloromethane (5.3 mL), and the reaction mixture was allowed to reflux for 2 h under N_2. The reaction mixture was cooled to room temperature, washed with water, 5% aqueous $NaHCO_3$ solution, and water, and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the crude product material was purified by column chromatography (Florisil, hexane/ethyl acetate, 85/15) and recrystallized using hexane/ethyl acetate to yield a yellow powder (0.2089 g, 0.352 mmol, 30%). mp: 209 °C (decomposed); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.00 (br s, 2H), 8.88 (br s, 1H), 7.29−7.02 (m, 10H), 5.73 (d, 1H, J = 2.4 Hz), 4.39 (s, 4H), 3.57 (s, 2H), 3.49 (s, 2H), 2.38−2.28 (m, 4H), 2.23, 2.06 (s, 9H), 0.95 (t, 6H, J = 7.81 Hz); ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 162.69, 136.99, 132.86, 132.76, 128.14, 127.24, 126.82, 126.63, 123.89, 123.24, 117.30, 117.15, 112.86, 106.77, 65.30, 24.27, 22.04, 17.17, 17.09, 15.69, 15.65, 10.98; LRMS (electrospray): *m*/*z* (relative intensity) 590 (M-1, 85), 335 (20). Anal. Calcd for $C_{37}H_{41}N_3O_4$: C, 75.10; H, 6.98; N, 7.10. Found: C, 75.36; H, 6.68; N, 7.28.

Dibenzyl 8-Trichloroacetyl-3,12-diethyl-2,7,13-trimethyltripyrrane-1,14-dicarboxylate (30a). Tripyrrane **29** (0.102 g, 0.172 mmol) and DMAP (0.101 g, 0.827 mmol) were dissolved in 1,2-dichloromethane (10 mL) at ambient temperature under N_2. Three portions of trichloroacetyl chloride (3 × 31.27 mg, 3 × 0.172 mmol) were added dropwise into the reaction mixture every 10 min. After 30 min, the reaction was quenched with ice−water, and the solution was washed with 10% HCl, a saturated solution of Na_2CO_3, and water. The reaction mixture was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude material was purified by column chromatography (Florisil, hexane/ethyl acetate, 85/15) to yield a brown solid (0.1098 g, 0.149 mmol, 87%). mp; 103−104.5 °C; IR (CH_2Cl_2, cm^{-1}) 3289, 2960, 2927, 2868, 1653, 1497, 1450, 1278, 1148, 1084, 751, 693; ^{1}H NMR (DMSO, 400 MHz): δ 11.07 (s, 1H), 11.03 (s, 1H), 10.69 (s, 1H), 7.31−7.43 (m, 10H), 5.24, 5.23 (s, 4H), 4.04, 3.75, (s, 4H), 2.19 (q, 2H, J = 7.33 Hz), 2.10 (q, 2H, J = 7.33 Hz), 2.15, 2.13 (s, 9H), 0.73 (t, 3H, J = 7.33 Hz), 0.72 (t, 3H, J = 7.33 Hz); ^{13}C NMR (DMSO, 100.5 MHz): δ 181.30, 160.56, 160.50, 137.83, 136.87, 136.84, 131.00, 129.75, 128.36, 127.77, 127.71, 127.66, 126.55, 126.19, 126.11, 123.49, 122.88, 116.33, 115.92, 113.24, 113.09, 64.37, 24.40, 21.58, 16.51, 16.39, 14.96, 12.29, 10.26, 10.22; LRMS: *m*/*z* (relative intensity) 736 (M+1, 30), 700 (86), 665 (30); HRMS (FAB): Calcd for $C_{39}H_{39}Cl_3N_3O_5$: 734.1955 (M−H). Found: 734.1925.

8-Acetyl-3,12-diethyl-2,7,13-trimethyltripyrrane-1,14-dicarboxylic Acid (30b). Tripyrrane **30a** (0.187 g, 0.254 mmol), palladium (10% on carbon, 0.0255 g), and triethylamine (0.09 mL) were suspended in THF (19.6 mL), placed under a hydrogen atmosphere, and stirred for 1 h and 40 min at ambient pressure and room temperature. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. The residue was cooled to 0 °C using an ice bath and dissolved using a 5% NH_4OH solution. The solution was washed with CH_2Cl_2 and then acidified by adding glacial acetic acid dropwise until precipitation was complete. The precipitate was filtered, washed with water, and dried over P_2O_5 in a vacuum oven to yield acetyl-tripyrrane diacid (0.0913 g, 0.020 mmol, 79.3%) as a brown powder, mp: 125.5−126.5 °C; ^{1}H NMR (DMSO, 400 MHz): δ 11.83 (s, br, 2H, −COOH), 10.81 (s, 1H), 10.68 (s, 1H), 10.52 (s, 1H), 4.04 (s, 2H), 3.70 (s, 2H), 2.31 (s, 3H), 2.22 (q, 4H, J = 7.81 Hz), 2.14, 2.13, 2.11 (s, 9H), 0.81−0.76 (m, 6H);^{13}C NMR (DMSO, 100.5 MHz): δ 195.12, 162.41, 162.35, 134.20, 130.36, 129.94, 125.03, 124.93, 122.85, 122.23, 120.24, 117.08, 116.89, 113.78, 30.85, 23.90, 21.38, 16.62, 16.44, 15.28, 15.16, 11.78, 10.12, 10.08; LRMS (electrospray): *m*/*z* (relative intensity) 452 (M-1, 30), 436 (50),

408 (48); HRMS (FAB): Calcd for $C_{25}H_{31}N_3O_5$, 453.2264 (M^+). Found: 453.2253.

18-Acetyl-2,7,8,13-tetraethyl-3,12,17-trimethyl-17,18-dihydroporphyrin (32). Tripyrrane **30b** (0.029 g, 0.052 mmol) was stirred with TFA (1.0 mL) under a nitrogen atmosphere in a glovebox for 25 min. The mixture was diluted with $CHCl_3$ (8 mL) followed immediately by the addition of 2,5-diformylpyrrole **8** (0.0085 g, 0.047 mmol), and the resulting mixture was stirred for an additional 2 h. The reaction mixture was placed into a separatory funnel and washed with an aqueous solution of Na_2CO_3 (2.73 g in 100 mL of water), and the separated organic layer was run through an alumina plug. The eluted solution was added to a methanolic saturated solution of zinc acetate (2 mL), and the mixture was stirred at room temperature for 10 min and then heated to 55 °C and stirred for 2 h. The reaction mixture was allowed to cool to ambient temperature and stirred overnight. The crude reaction mixture was then removed from the glovebox, and the solvent was removed under vacuum. The product was cooled on an ice bath and TFA (4 mL) was added and the solution stirred for 10 min under N_2. A 5% aqueous $NaHCO_3$ solution was added to quench the demetalation reaction, and it was then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude chlorin product was purified using column chromatography (alumina, grade III, 60/40, CH_2Cl_2/benzene in glovebox) which furnished a green powder (0.011 g, 0.022 mmol, 46.0%); mp: 165 °C (decomposed); IR 3438, 3343, 2961, 2926, 2866, 1700, 1613; UV/Visible (CH_2Cl_2) λ_{max} nm ($\epsilon \times 10^5$) 388 (1.34), 492 (0.113), 642 (0.354); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.76, 9.74 (s, 2H), 8.89, 8.84 (s, 2H), 5.44 (d, 1H, J = 3.42 Hz), 5.12 (qd, 1H, J = 7.32 and 3.42 Hz), 3.96−3.83 (m, 8H), 3.54, 3.53 (s, 6H), 2.02 (d, 3H, J = 7.32 Hz), 1.94 (s, 3H), 1.82−1.69 (m, 12H), −2.56 (br s, 2H,); ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 206.78, 167.50, 157.94, 150.29, 149.90, 143.04, 142.81, 137.95, 137.00, 135.54, 135.34, 133.67, 133.23, 132.96, 99.75, 99.23, 92.92, 91.79, 71.60, 46.65, 29.70, 25.90, 23.60, 19.69, 19.39, 19.29, 18.63, 18.60, 17.23, 17.09, 11.21, 11.18; LRMS (electrospray): *m*/*z* (relative intensity) 508 (M − 1, 100), 465 (50), 154 (32); HRMS (FAB): Calcd for $C_{33}H_{41}N_4O$, 509.3280 (M + H). Found: 509.3279.

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Supporting Information Available: Copies of ^{1}H NMR spectra of chlorins **1**, **2**, **22**, **23**, **24a**, **32**, ii, the partial ^{1}H NMR spectrum of octaethylchlorin showing cis and trans isomers, the NOE spectrum of chlorin **32** illustrating trans configuration, and experimental details and characterization data of dipyrromethanes **5a**, **16**, **17**, tripyrranes **6** and **7**, chlorins **1**, **2**, and deuterated chlorin **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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