Novel Macrocycles from Metal-Catalyzed Oxidative Cyclizations of a,c-Biladiene Salts

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From the metal-promoted oxidative cyclization of several 1,19-disubstituted a,c-biladiene dihydrobromide salts, a number of novel macrocycles were prepared. For example, the cyclization of 1,19-bis(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene dihydrobromide salt (**10**) with copper(II) acetate afforded copper(II) 20-((methoxycarbonyl)methyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**13**) (39% yield), which, upon demetalation, yielded the metal-free 20-((methoxycarbonyl)methyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**14**) (48% yield). With the substrate 19-((ethoxycarbonyl)methyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene dihydrobromide (**15**), the metal-catalyzed cyclization process produced copper(II) 20-(ethoxycarbonyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**18**) (27% yield) and copper(II) 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (**23**) (19% yield). Upon demetalation of the copper dihydroporphyrin **18**, 20′-(ethoxycarbonyl)-20-(2-(methoxycarbonyl)ethyl)-2,3,7,8,-12,13,17,18-octamethyl-20′-homoporphyrin (**28**) (16.5% yield) was isolated; demetalation of copper(II) 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (**23**) yielded the free base 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (**25**) (24% yield). Using chromium(III) hydroxy acetate as the oxidant (in place of copper(II)), 1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**5**) (55–62%) was obtained from the 1,2,3,7,8,12,13,17,18,19-decamethyl-a,c-biladiene salt **3**. Mechanisms of macrocycle formation from a,c-biladiene salts, promoted by either copper(II) or chromium(III), appear to proceed via pathways closely resembling the electrochemical cyclization reaction of 1,19-dimethyl-a,c-biladiene salts.

Introduction

Metal-ion-catalyzed cyclizations of a,c-biladiene salts have been at the heart of several approaches to porphyrin synthesis for more than 30 years.[1] In 1961, Johnson and Kay[2] showed that a symmetrical 1,19-dimethyl-a,c-biladiene salt, **1**, could be efficiently cyclized to give a copper(II) porphyrin, **2**, by use of copper(II) acetate. Over a number of years since that time, this basic methodology was advanced and generalized for the synthesis of completely unsymmetrical porphyrins;[3,4] the improvements were related more to the new methodology for synthesis of a,c-biladienes than to the actual metal-catalyzed cyclization conditions. Metals such as nickel(II) and cobalt(II) tended to produce metallotetradehydrocorrins[5] rather than metalloporphyrins, but it was shown, in 1986, that metals other than copper(II) could be used efficiently for the synthesis of porphyrins and metalloporphyrins.[6,7] Most recently, Boschi and co-workers[8] have shown that chromium(III) salts promote very efficient cyclizations of a,c-biladienes (when the 1,19-terminal groups are methyl) to afford metal-free porphyrins, but when the 1,19-groups are, for example, ethyl, then an alternative mechanism dominates and the products from pyrrole ring redistribution reactions predominate entirely.

The mechanism of the a,c-biladiene cyclization reaction has been studied extensively for both electrochemical[9,10] and metal-catalyzed cases.[7,11,12] Similar work has been carried out for the copper(II)-promoted b-bilene cyclizations to give copper(II) porphyrins;[13,14] these authors initially made a structural assignment[13] for a spectroscopically observed "valley" intermediate, which was subsequently corrected,[14] and the identity of an extruded valley group was identified. For the electrochemical cyclizations of a,c-biladienes, it appears[9,10] that the initial product from a,c-biladiene **3** is the fully conjugated species **4**, which then cyclizes to give the macrocycle **5** bearing a valley methyl group which interrupts the conjugated pathway and that this methyl group is lost, either before or after an oxidation step,[10] to give porphyrin **6**. One thing which is certain is that one of the two groups originally present on the 1,19-positions of the a,c-biladiene *must* be lost (or transferred to another site on the macrocycle) for the fully conjugated porphyrin to be produced. Clezy[1b] and Clezy and co-workers[13,14] also observed the production

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(1) For reviews, see: (a) Smith, K. M. In *Porphyrins and Metalloporphyrins*; Elsevier: Amsterdam, 1975; Chapter 2. (b) Clezy, P. S. *Aust. J. Chem.* **1991**, *44*, 1163.

(2) Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1961**, 2418.

(3) Almeida, J. A. P. B.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron* **1976**, *32*, 429.

(4) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302.

(5) Johnson, A. W.; Dolphin, D.; Harris, R. L. N.; Huppatz, J. L.; Kay, I. T. *J. Chem. Soc. C* **1966**, 30.

(6) Smith, K. M.; Minnetian, O. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 277.

(7) Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073.

(8) Boschi, T.; Paolesse, R.; Tagliatesta, P. *Inorg. Chim. Acta* **1990**, *168*, 83.

(9) Jeyakumar, D.; Snow, K. M.; Smith, K. M. *J. Am. Chem. Soc.* **1988**, *110*, 8562.

(10) Swanson, K. L.; Snow, K. M.; Jeyakumar, D.; Smith, K. M. *Tetrahedron* **1991**, *47*, 685.

(11) Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329.

(12) Smith, K. M.; Minnetian, O. M. *Synth. Commun.* **1985**, *15*, 75.

(13) Clezy, P. S.; Ravi, B. N.; Thuc, L. v. *Aust. J. Chem.* **1986**, *39*, 419.

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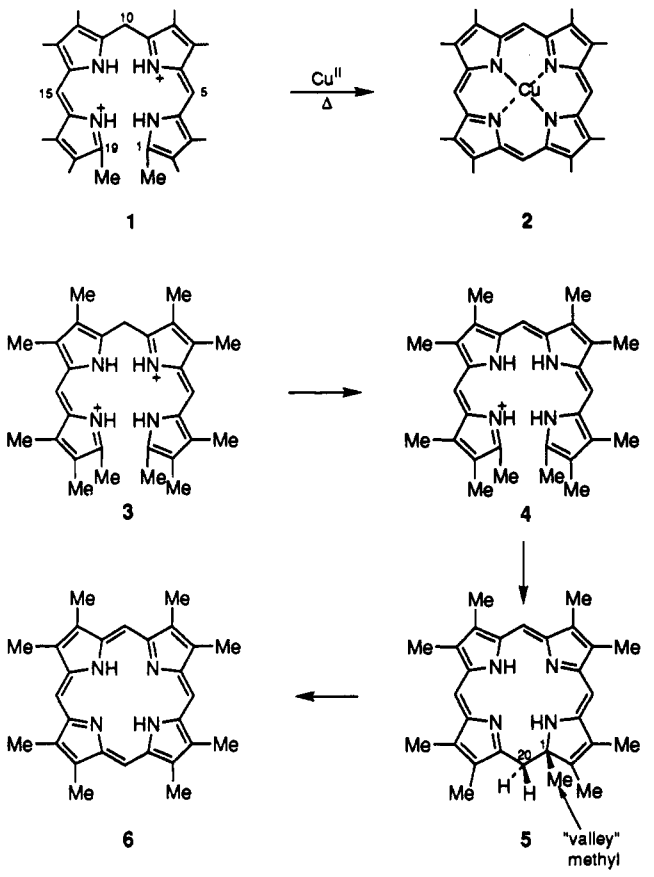
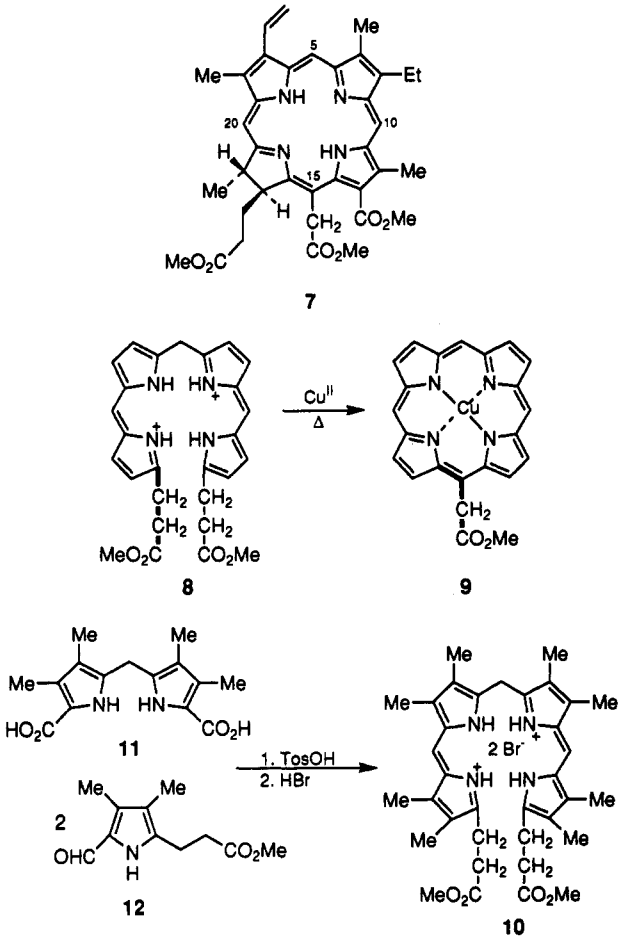


of similar valley-substituted substances in the copper(II) cyclizations of b-bilenes and devised mechanistic interpretations[1b,14] of the pathway for the oxidative cyclization of b-bilenes to porphyrins, which are broadly in agreement with ours for the similar cyclization of a,c-biladienes.

In the present paper, we describe our results on the copper(II)-catalyzed cyclization of a,c-biladiene salts bearing large 1- and 19-substituents. We show that the copper(II) catalyzed approach follows a mechanistic pathway (through valley-substituted intermediates) which is very similar to the electrochemical route. Finally, we show that the chromium(III)-promoted oxidative cyclization of 1,19-dimethyl-a,c-biladiene salts to eventually give metal-free porphyrins likewise proceeds by way of a valley-substituted intermediate.

Results and Discussion

For a number of years, we have been very interested in the ring synthesis, from monopyrroles, of porphyrins bearing a meso (methoxycarbonyl)methyl group.[15] Establishment of this methodology, in our long term view,[16] was essential for the accomplishment of a total synthesis of chlorophyll-*a* and its 3,8-divinyl analogue (IUPAC nomenclature); the 15-(methoxycarbonyl)methyl group is a primary feature in chlorin-e_6 trimethyl ester **7**, which was a key intermediate on the pathway in Woodward's approach to chlorophyll-*a*.[17] We reasoned, by analogy with the 1,19-dimethyl-a,c-biladiene cyclization in which one of the 1- or 19-methyl groups is extruded,[11] that copper(II)-promoted cyclization of a 1,19-bis(2-(methoxycarbonyl)ethyl)-a,c-biladiene (**8**) should lead to a meso ((methoxycarbonyl)methyl)porphyrin, **9**. Thus, we synthesized a model 1,19-bis(2-(methoxycarbonyl)ethyl)-a,c-biladiene dihydrobromide, **10**, in 84% yield from dipyrromethane **11** and 2 molar equiv of formylpyrrole **12**, and we began a study of its oxidative cyclization.[18]



Copper(II)-Promoted Oxidative Cyclizations of a,c-Biladiene Salts. Heating of a,c-biladiene **10** in DMF in the presence of copper(II) acetate at 125 °C for only 5 min gave a deep green solution which, disappointingly,[19] was completely devoid of porphyrin as evidenced by the lack of a Soret absorption band in its optical spectrum. Workup and isolation of the green product in 39% yield from **10** followed by crystallization and single-crystal X-ray studies (not shown, but see Figure 2 in ref 18) revealed that it was the copper(II) complex **13** of the macrocycle bearing a valley 1-propionate group, in which one carbon atom of the other propionate had been used to close the macrocycle. The optical spectrum of **13** showed maxima at 322, 417, 767, and 843 nm.

Clearly, the mechanism of the electrochemical cyclization to porphyrins, which yields **5** as a macrocyclized intermediate, must be very similar to the mechanism of the copper(II)-promoted cyclization of a,c-biladienes. Unlike the valley 1-methyl compound **5**, the copper(II)

(15) Smith, K. M.; Pandey, R. K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1229. Burns, D. H.; Smith, K. M. *J. Chem. Res., Synop.* **1990**, 178; *Miniprint* **1990**, 1349.
(16) Smith, K. M.; Lewis, W. M. *Tetrahedron* **1981**, *37* (Suppl. 1), 399.
(17) Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemenn, A.; Le Goff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *Tetrahedron* **1990**, *46*, 7599.
(18) Liddell, P. A.; Olmstead, M. M.; Smith, K. M. *J. Am. Chem. Soc.* **1990**, *112*, 2038.
(19) However, we did recall that the similar electrochemical cyclization also failed, initially, to yield material possessing a Soret absorption.[9,10]

complex was extremely stable, and the macrocycle even survived demetalation in 1:1 concentrated sulfuric and trifluoroacetic acids. From this acidic demetalation step, a 48% yield of the metal-free macrocycle **14** was obtained, along with minor amounts of side products, including a porphyrin. The identity of **14** was confirmed by single-crystal X-ray studies (see Figure 3 in ref 18), by its optical spectrum which showed maxima at 305, 381, 662 (infl), and 714 nm, and by the proton NMR spectrum with its three methine protons at δ 6.14, 5.28, and 4.82; the chemical shifts compare well with those[9,10] for the three methine protons in the macrocycle **5** (δ 6.26, 5.35, and 5.04). When a,c-biladiene **10** was cyclized at rt over 14 h in DMF containing copper(II) acetate, the green copper(II) complex **13** was again isolated, along with small quantities of a more polar red–brown material. Upon flash chromatography on silica gel, the red–brown material was transformed into the fully characterized green copper(II) macrocycle **13**. This observation does, however, suggest that an intermediate exists which is transformed under relatively mild conditions into the stable final product **13**. In contrast to the chemistry of **5**,[9,10] at no time was it possible to transform the copper(II) macrocycle **13** or its demetalated product **14** into reasonable amounts of porphyrin, suggesting that the methyl group in **5** is more accessible to elimination than the correspondingly sited propionate methylene group in **13** or **14**. When treatments of **14** with hot solutions of nickel(II) acetylacetonate or palladium(II) chloride were attempted, the outcome was usually metalation of the macrocycle, with only minor amounts of nickel or palladium porphyrins being produced.

We next investigated the impact of the nature of the 1- and 19-substituents on the a,c-biladiene during copper(II) cyclization by varying the structure of these terminal groups. a,c-Biladiene **15** (bearing 1-propionic and 19-(ethoxycarbonyl)methyl ester terminal groups) was prepared in 79% yield from tripyrrin **16** and 2-((ethoxycarbonyl)methyl)-5-formyl-3,4-dimethylpyrrole (**17**). When this compound was heated at 130 °C in DMF in the presence of copper(II) acetate, the copper(II) macrocycle **18** was obtained in 27% yield along with a small amount of copper(II) porphyrins and a somewhat larger amount (19% yield) of a copper(II) chlorin. The optical spectrum of **18** (Figure 1) is very similar to that of the analogue **13** (from the 1,19-bis(2-(methoxycarbonyl)ethyl)-a,c-biladiene cyclization). Quite remarkably, the copper(II) macrocycle was identified by single-crystal X-ray studies[18,20] to be uniquely the 1-propionic isomer **18** in which the (ethoxycarbonyl)methyl side chain had provided the macrocyclic bridging carbon. No evidence for the production of the 1-(ethoxycarbonyl)methyl isomer **19** was obtained. Of the copper(II) porphyrins which were present, the major component was tentatively identified as **20**, presumably obtained from the green copper(II) macrocycle **18** by cleavage of the valley propionate group via a six-membered transition state using the enol of **18** (Scheme I); a second copper(II) porphyrin could be **21** since this structure was compatible with the mass spectrum. Again from the mass spectrum, another copper(II) porphyrin appeared to be copper(II) octamethylporphyrin **22**, produced by the complete stripping of the labile substituents. The copper(II) chlorin product from the same reaction was identified (vide infra) as copper(II)

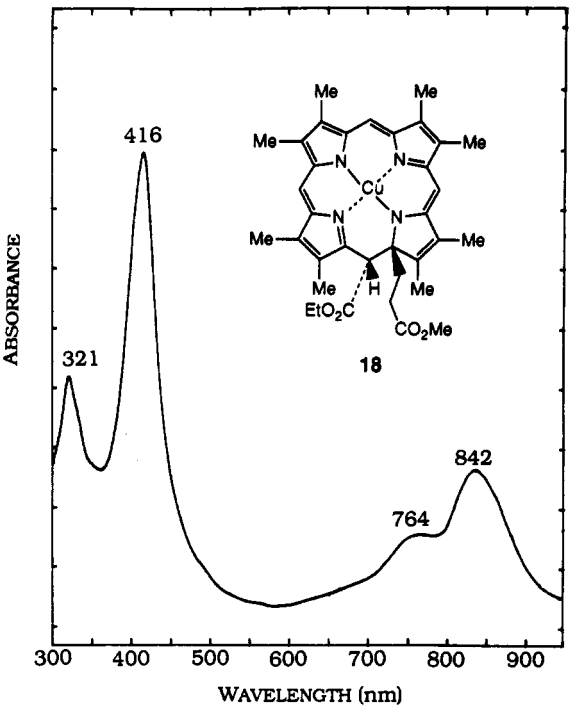
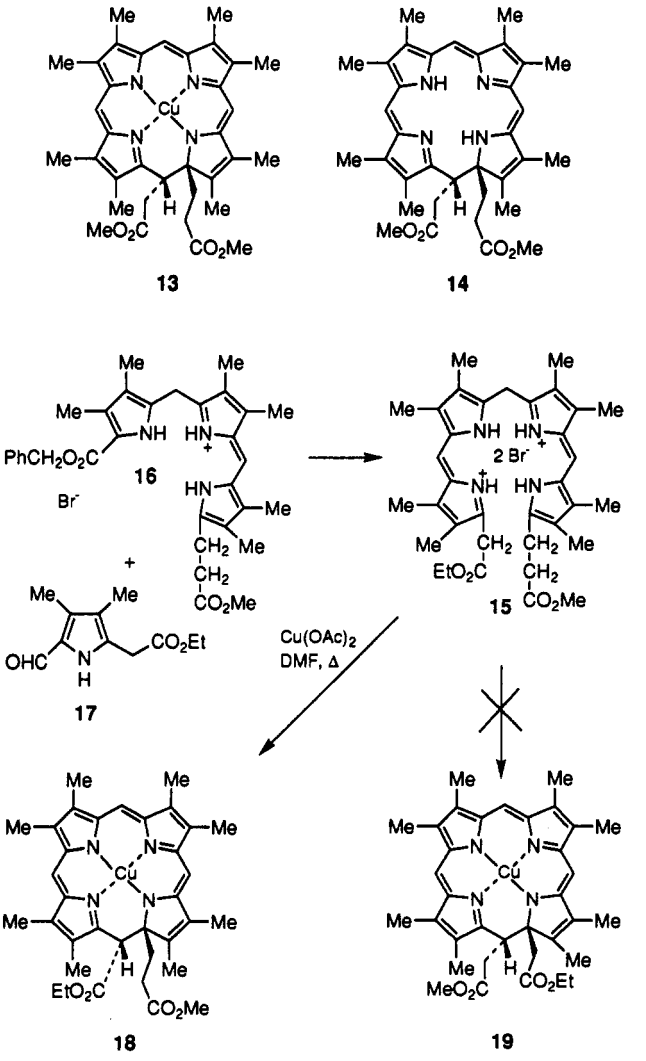


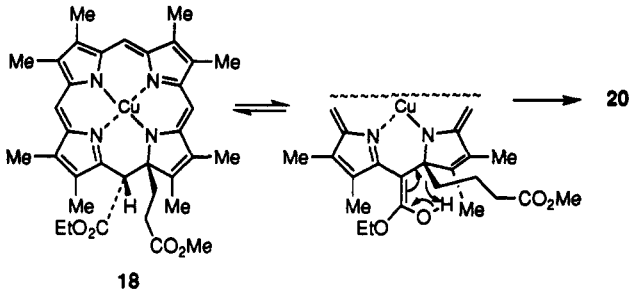
Figure 1. Optical spectrum, in CH_2Cl_2, of the copper(II) complex **18**.



chlorin **23** formed by the migration (rather than by the cleavage) of the valley propionate group; it should be noted,

(20) Though the crystal structure of compound **18** was not displayed in ref 18, it was deposited in the supplementary material for ref 18.

Scheme I. Proposed Mechanism for the Formation of Copper(II) Porphyrin 20 from the Copper(II) Macrocycle 18



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of course, that the green copper(II) macrocycle can aromatize either by loss of the valley group or by placing it somewhere else on the carbon skeleton where it does not interfere so radically with the conjugated pathway in the final product, and the latter outcome is apparent in the formation of **23** from **18**. That such is the case was established by carrying out a rt cyclization of a,c-biladiene **15** in DMF containing copper(II) acetate. From this reaction was isolated only the green copper(II) macrocycle **18**, in 36% yield. This compound, when heated in DMF at 130 °C, was recovered unchanged, but heating at 130 °C for 30 min in DMF containing copper(II) acetate caused **18** to be completely transformed into almost equal amounts of the copper(II) porphyrins described above and copper-(II) chlorin **23** (λ_{max} 410, 512, 552, 580, 626 nm). When attempts were made to take the melting point (>300 °C!) of the copper(II) macrocycle **18**, it was transformed into the paramagnetic copper(II) porphyrin **20**, which was shown still to have a meso (ethoxycarbonyl)methyl group present (by mass spectrometry).

Nominally,[21] the propionic side chain in **18**, when it migrates from the 1-position, could finish up at either the 2-position (to give **23**) or at the 3-position, which would afford the corresponding isomer **24**. We attempted to verify which product had been formed, but we were unable to obtain X-ray-quality crystals of compound **23**; demetalation (TFA/H_2SO_4) of **23** gave the corresponding free-base **25** (λ_{max} 658 nm) which also failed to provide crystals suitable for definitive X-ray analysis. Therefore, the regiochemistry in the copper(II) chlorin product was established by catalytic hydrogenation of the alkene function at the 3-position in the macrocycle to give a 62.5% yield of **26**. This transformation resulted in an 8-nm blue shift of the longest wavelength band (**23** λ_{max} 626 nm; **26** λ_{max} 618 nm) in the optical spectrum, entirely compatible with removal of the exocyclic double bond from conjugation in the chromophore.[22] The X-ray stucture of this material **26** (Figure 2) confirmed that the migrated propionate group is at the 2-position and also that the 3-methylidene double bond was hydrogenated from the face of the molecule opposite to the 2-propionate. A proposal for the mechanism of the formation of copper(II) chlorin **23** from **18** is presented in Scheme II; inherent is an oxidation step which could nominally take place at any point in the pathway to **23**.

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(22) Iakovides, P.; Simpson, D. J.; Smith, K. M. *Photochem. Photobiol.* **1991**, *54*, 335.

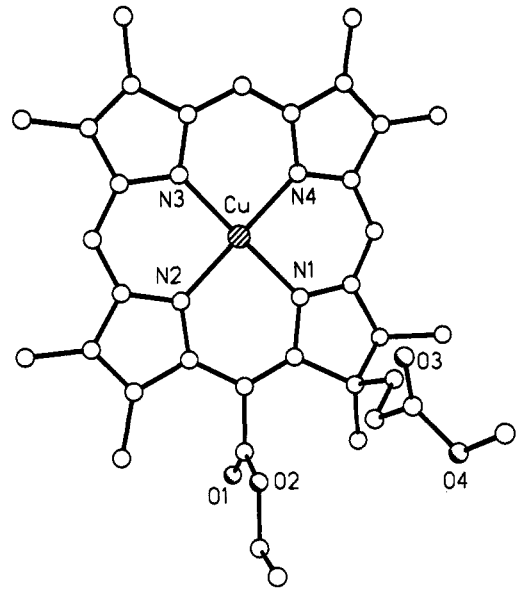
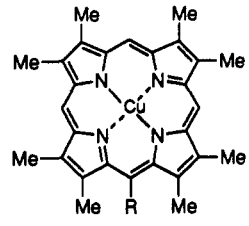
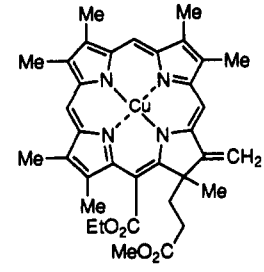


Figure 2. Single crystal X-ray structure of the copper(II) complex **26**.



20 R = CO_2Et
21 R = CH_2CO_2Me
22 R = H



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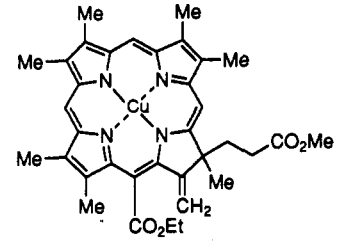

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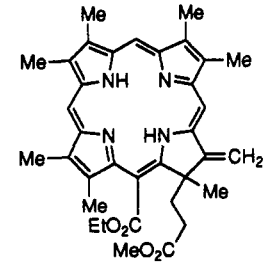

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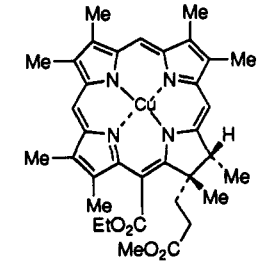

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Demetalation of the copper(II) macrocycle **18** with TFA/H_2SO_4 provided a surprise. It was anticipated that, by analogy with the demetalation of **13** to give **14**, the product would be the metal-free ligand **27**. However, the product from the acid treatment of **18** possessed an optical spectrum (Figure 3; λ_{max} 660 nm) which was quite unlike that of compound **14** (λ_{max} 714 nm). X-ray crystallography[23] revealed that the product from the demetalation reaction of **18** was homoporphyrin **28**.[24] Since we had a

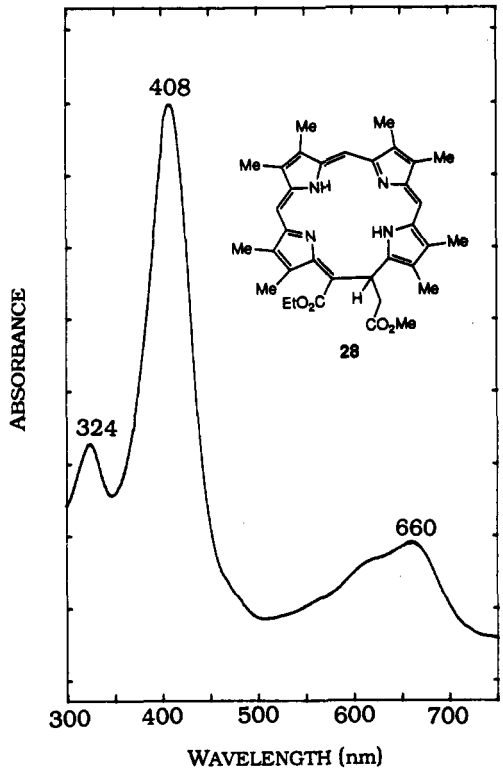
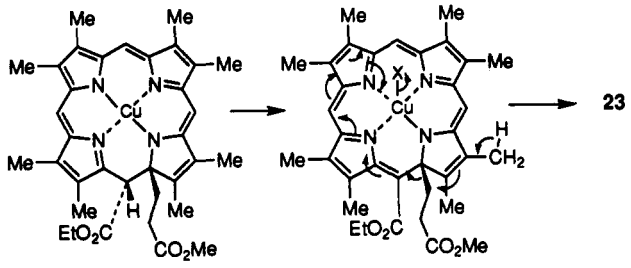


Figure 3. Optical spectrum, in CH_2Cl_2, of homoporphyrin **28**.

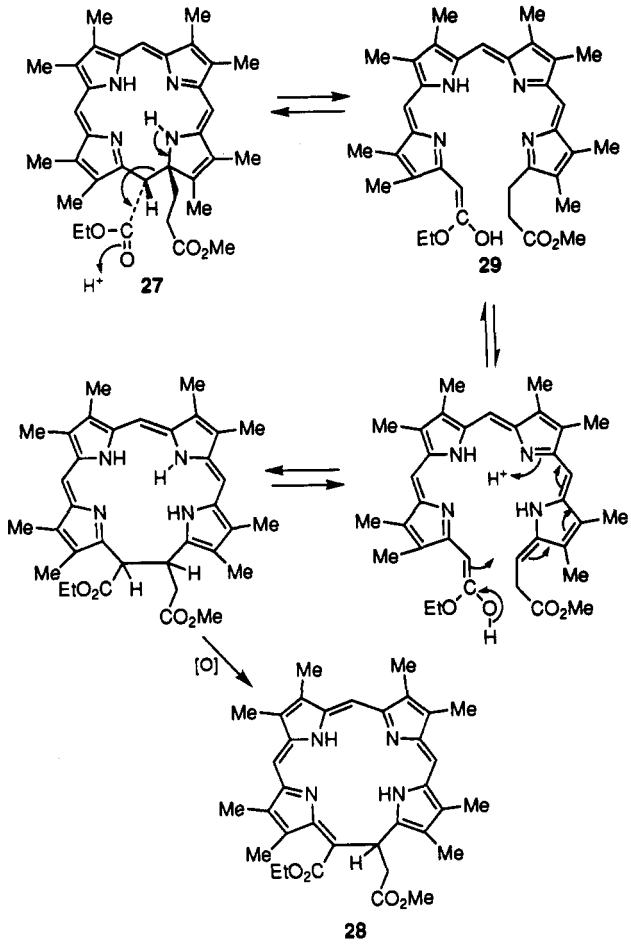
Scheme II. Proposed Mechanism for the Formation of Copper(II) Chlorin 23 from the Copper(II) Macrocycle 18



definitive X-ray structure[18] of the demetalation precursor **18**, the homoporphyrin must have arisen from a ring expansion involving ring opening of **18** or its demetalation product **27** to give **29** (Scheme III) followed by ring closure in the opposite sense and oxidation (or vice versa) to give **28**. The mechanism is dependent upon the presence of the enolizable proton in the terminal (ethoxycarbonyl)-methyl side chain of **29**, thereby accounting for the "normal" demetalation observed in the demetalation **13** → **14**. Interestingly, anodic oxidation of a,c-biladiene dihydrobromide **15** at 800 mV (vs Ag/AgCl, in DMF containing tetraethylammonium toluenesulfonate as electrolyte) leads directly to the same homoporphyrin **28**.[10]

Synthesis of 1,19-bis((ethoxycarbonyl)methyl)-a,c-biladiene **30** was accomplished in 88% yield by condensation of dipyrromethane **11** with 2 molar equiv of formylpyrrole **17**. Treatment of this a,c-biladiene in DMF containing copper(II) acetate afforded a mixture of materials, depending upon the temperature at which the reaction was

Scheme III. Proposed Mechanism for the Formation of Homoporphyrin 28 via 27 During the Demetalation of 18



performed. Typically, at 110 °C, the reaction afforded the pink copper(II) porphyrin **20** and two chromatographically separable yellow–green bands. During chromatography and handling of the products, degradation took place, and the final product was always copper(II) porphyrin **20**. The least polar yellow–green band was shown to be the "normal" copper(II) macrocycle **31**, while the more polar one, which had a λ_{max} at 704 nm, was shown by its X-ray crystal structure (Figure 4) to be copper(II) homoporphyrin **32**. When exposed to fluorescent light, the green copper(II) macrocycle **31** was transformed smoothly (spectrophotometry, with isosbestic points) into a copper(II) porphyrin, and whenever exposed to acid and light, **31** was slowly transformed into **20**. The direct formation of the copper(II) homoporphyrin from the copper(II)-promoted cyclization (rather than after attempted demetalation, as in the case **18** → **28**) indicates further analogy with the electrochemical formation of homoporphyrins; it should also be noted that anodic oxidation of 1,19-bis((ethoxycarbonyl)methyl)-a,c-biladiene **30** results in the direct formation of the metal-free homoporphyrin **33**.[25] Demetalation of the copper(II) macrocycle **31** to give **34** was accomplished in 57% yield.

Reasoning that a valley methyl compound might be preferentially formed and that the methyl would be cleaved easily from the valley 1-position, we hypothesized that oxidative cyclization of an a,c-biladiene, such as **35**, bearing

(23) Not shown, but see Figure 4 in ref 18.

(24) Homoporphyrins have been the subject of extensive studies by Callot and co-workers; see: Callot, H. J.; Tschamber, T. *J. Am. Chem. Soc.* **1975**, *97*, 6175; **1975**, *97*, 6178. Callot, H. J.; Schaeffer, E. *J. Org. Chem.* **1977**, *42*, 1567.

(25) Swanson, K. L. Ph.D. Dissertation, University of California, Davis, CA 1990.

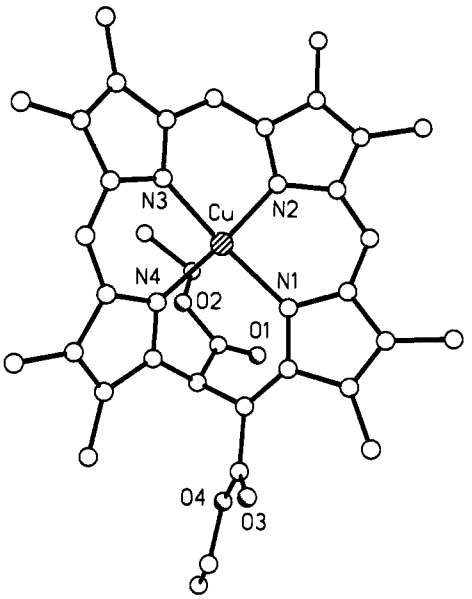
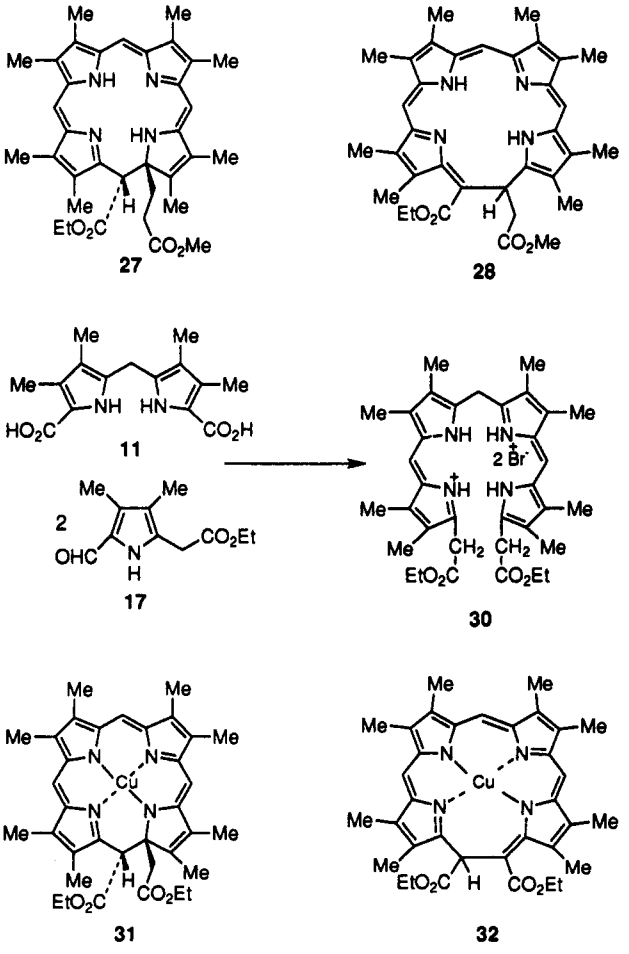
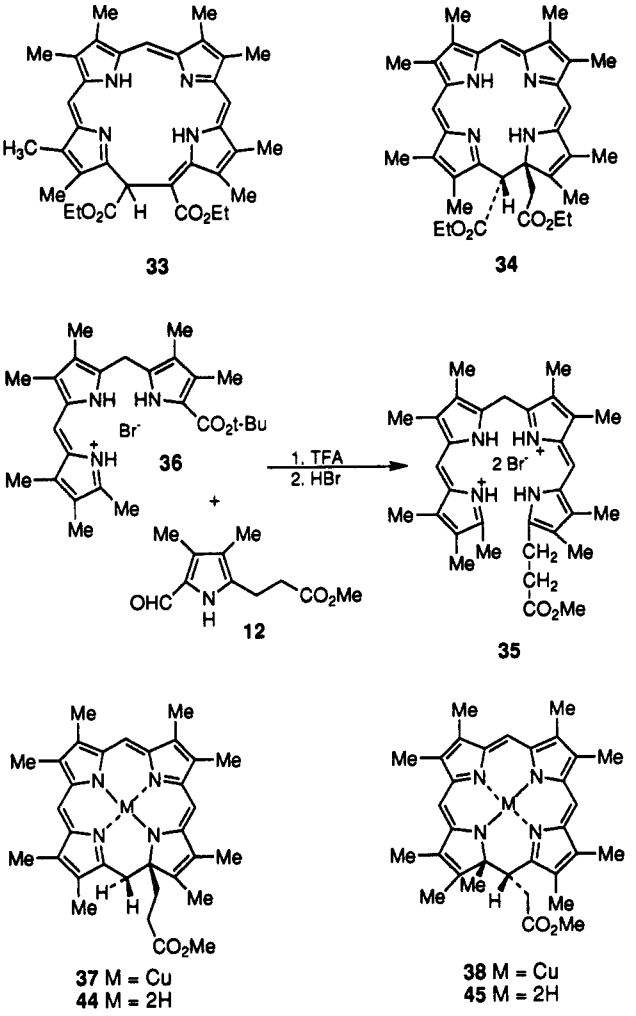


Figure 4. Single-crystal X-ray structure of copper(II) homoporphyrin **32**.



a 1-methyl and a 19-(2-(methoxycarbonyl)ethyl) group might well yield the type of meso ((methoxycarbonyl)-methyl)porphyrin which we had sought at the onset of our studies. Thus, a,c-biladiene **35** was synthesized in 84% yield from tripyrrin **36** and formylpyrrole **12**. Copper-(II)-promoted cyclization at 120 °C in DMF for 2 min gave mostly decomposition products, but a small amount of an unidentified green copper(II) macrocycle (**37** or **38**) was obtained, along with at least three copper(II) porphyrins. Demetalation of the macrocycle (**37** or **38**) gave only decomposition products and therefore was not further investigated.

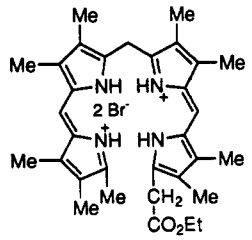


1-((Ethoxycarbonyl)methyl)-19-methyl-a,c-biladiene **39** was next synthesized from tripyrrin **36** and formylpyrrole **17** and obtained in 82% yield. Cyclization in DMF containing copper(II) acetate at 100 °C for 2 min gave a trace amount of copper(II) octamethylporphyrin **22** (identified spectrophotometrically; λ_{max} 398, 524, 560 nm) together with a 47% yield of the copper(II) macrocycle **40**. Demetalation (TFA/H_2SO_4) of this macrocycle resulted in a large amount of decomposition products, but it was possible to isolate small quantities (8%) of the metal-free macrocycle **41**, along with traces of a metal-free homoporphyrin (presumably **42**).

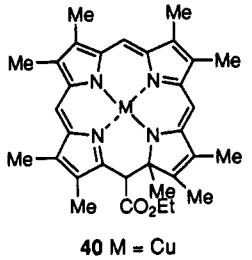
Chromium(III)-Promoted Oxidative Cyclizations of a,c-Biladiene Salts. Boschi and co-workers[8] recently showed that metal-free porphyrins result from the cyclization of a,c-biladienes using chromium(III) acetate in hot buffered EtOH. We began with the model decamethyl-a,c-biladiene dihydrobromide **3** which Boschi and co-workers had shown[8] could be converted directly into octamethylporphyrin **6** using chromium(III) acetate. We chose $Cr_3(OAc)_7(OH)_2$ as our chromium(III) reagent (the nearest commercially available substance to "chromium-(III) acetate" which could be purchased from Aldrich). To our surprise, treatment of **3** with $Cr_3(OAc)_7(OH)_2$ in hot EtOH buffered with sodium acetate gave an excellent (62%) yield of the metal-free valley 1-methyl intermediate **5**. However, with the hot EtOH method, we found the

yields to be erratic and difficult to reproduce. Yields ranged from 40% to greater than 70%, with 60% as a median. We therefore decided to pursue a different solvent in the hope of introducing more reproducibility to the procedure. Previous experience brought us to DMF. Upon attempting the reaction at 100 °C, we were able to obtain the desired intermediate **5** in a yield of 55%. We found this method to be more reproducible and typical. It is worth mentioning that we had never previously obtained the valley methyl compound from *any* metal-ion-promoted 1,19-dimethyl-a,c-biladiene cyclization reaction.

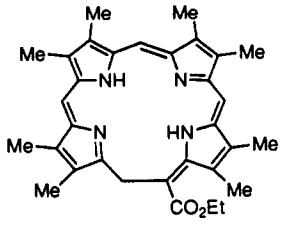
We then applied the new chromium(III) methodology to the oxidative cyclization of the 1,19-substituted a,c-biladienes **35** and **39**, which had shown only limited applicability using the copper(II) methodology, with the intention of providing direct access to metal-free macrocycles such as **41** and **44** (or **45**), which by analogy would provide us with compounds previously unavailable due to decomposition during copper demetalation. First of all, we attempted to cyclize **39** using the EtOH method (before the discovery of the DMF method). The reaction was performed similiarly to that in the case of the decamethyl-a,c-biladiene, except that the reaction was found to be complete in 5 min (spectrophotometry). After typical workup and column chromotograpy, several bands were isolated; most were relatively unstable and uncharacterizable except for the major product, identified as the valley 1-methyl intermediate **41** and obtained in 30% yield. The reaction was also performed at rt and gave a 67% yield of the same product. Using the DMF method, the cyclization of **39** was attempted at 140 °C to see if any changes occurred. To our surprise, a 30% yield of the 1-(ethoxycarbonyl)methyl compound **43**, the isomer of **41**, was obtained. We suggest that the compound **41** is the kinetic product in this cyclization reaction due to the stabilization of the intermediate radical next to the ester group (for the proposed mechanism, see Scheme IV), whereas the isomer **43** is the thermodynamic product due to the steric considerations and release of strain by placing the ester in the valley 1-position. Our hypothesis was verified by heating **41** in DMF for 5 min to provide exclusively **43** as the valley-substituted component. With the above observation, we can conclude that the copper(II) method gives the kinetic copper intermediate when the reaction is performed at 100 °C.



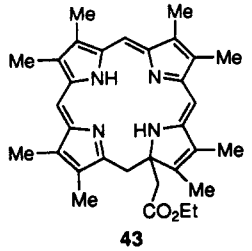
39



40 M = Cu
41 M = 2H

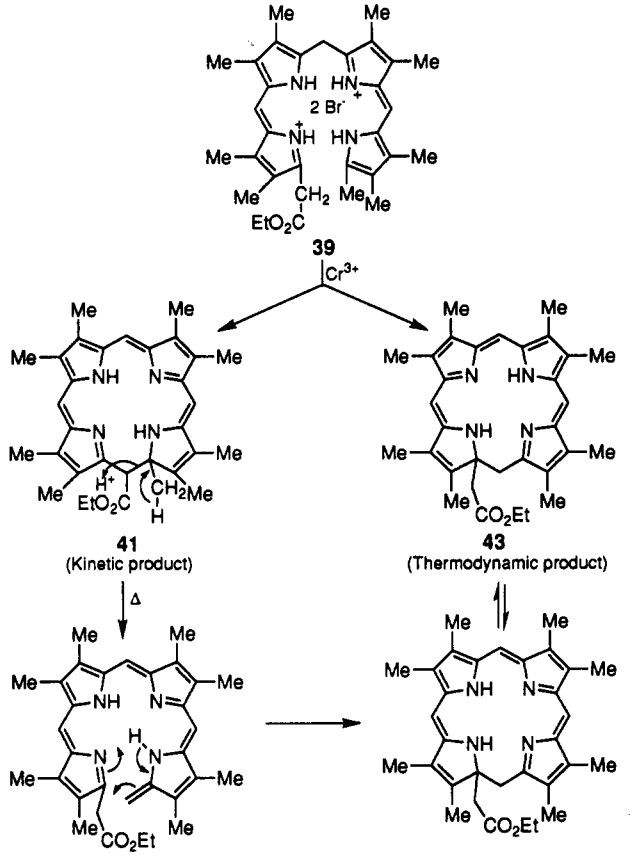


42



43

Scheme IV. Proposed Mechanism for the Formation of the Kinetic Product 41 and the Thermodynamic Product 43 from a,c-Biladiene Dihydrobromide 39



Our attention then turned to 19-(2-(methoxycarbonyl)-ethyl)-1-methyl- a,c-biladiene **35**. At this point, the DMF method had become our method of choice. Heating **35** at 140 °C in DMF with chromium acetate hydroxide gave exclusively the 1-propionic ester valley intermediate **44** in 14% yield. In comparison with the copper(II) methodology, the chomium(III) method is superior for the preparation of this product, and further, it can be concluded that the copper valley intermediate formed in this reaction is the compound **37** and not **38**. These observations add further definitive proof to our proposal[18] with regard to the similarity of the mechanisms for the electrochemical and metal-ion-promoted oxidative cyclization reactions of a,c-biladienes.

Experimental Section

General conditions are as described previously.[7]

Pyrroles. Benzyl 5-((Ethoxycarbonyl)methyl)-3,4-dimethylpyrrole-2-carboxylate. This reaction was performed four times for preparative scale amounts, and the products were combined. Benzyl 3,4-dimethylpyrrole-2-carboxylate[11] (7.00 g, 0.029 mol; three times 4.89 g, 0.0203 mol) was dissolved in dry cyclohexane (50 mL; three times 40 mL) under N_2, and copper bronze (0.7 g; three times 0.49 g) was added. The suspension was heated to 80 °C, and ethyl diazoacetate (14 mL, 0.133 mol; three times 10 mL, 0.095 mol) was slowly added at a rate of 1.2 mL/h. After 24 h, TLC indicated starting material and several products. The reaction mixture was cooled, filtered to remove the copper metal which was rinsed several times with CH_2Cl_2, and concentrated to obtain a green oil. The crude mixtures of the four reactions were combined for purification. It was subjected to flash silica gel column chromatography, eluting with a 3:2 mixture of CH_2Cl_2 and cyclohexane. After another flash silica gel column, eluting with a 1:9 mixture of ethyl acetate in cyclohexane,

recrystallization from CH_2Cl_2 and cyclohexane gave long, hair-like crystals (11.73 g, 43%), mp 98–99 °C. ^1H NMR: δ 9.26 (br s, 1H), 7.40 (m, 5H), 5.30 (s, 2H), 4.17 (q, 2H), 3.57 (s, 2H), 2.27, 1.93 (each s, 3H), 1.26 (t, 3H). HRMS: calcd for $C_{11}H_{15}NO_3$ 315.1468, found 315.1475. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.63; H, 6.73; N, 4.50.

2-((Ethoxycarbonyl)methyl)-5-formyl-3,4-dimethylpyrrole (17). The foregoing pyrrole (6.31 g, 0.02 mol) in dry THF (200 mL) containing 10% Pd–C (0.5 g) was hydrogenated at rt and atmospheric pressure for 12 h; TLC then indicated that no starting material remained. The catalyst was filtered off through a pad of Celite and evaporated to give a white solid. It was subjected to high vacuum for several hours before being dissolved in DMF (40 mL) and heated to 154 °C under N_2 for 4.25 h. The clear solution was cooled to 0–5 °C before Vilsmeier reagent ($POCl_3$ (5.60 mL, 0.06 mol) added to dry DMF (7.75 mL, 0.10 mol), kept at <10 °C over a 5-min period) was added via cannula. Stirring was continued at 0–5 °C for 20 min, and the mixture was warmed to rt and then stirred for 1 h. CH_2Cl_2 (150 mL) was added followed by saturated $NaHCO_3$ (400 mL), and the solution was refluxed for 40 min before being cooled. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, concentrated, and diluted with ether and then washed with water (5 × 120 mL), dried (Na_2SO_4), and concentrated. The crude mixture was chromatographed on silica gel, eluting with 40% ethyl acetate in cyclohexane. Recrystallization from CH_2Cl_2/hexane gave 4.08 g (97%) as yellow needles, mp 92–93 °C. ^1H NMR: δ 9.65 (br s, 1H), 9.54 (s, 1H), 4.18 (q, 2H), 3.62 (s, 2H), 2.25, 1.93 (each s, 3H), 1.27, (t, 3H). HRMS, calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1039. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.09; H, 7.23; N, 6.73.

2-Formyl-5-(2-(methoxycarbonyl)ethyl)-3,4-dimethylpyrrole (12). This pyrrole was similarly prepared from benzyl 5-(2-(methoxycarbonyl)vinyl)-3,4-dimethylpyrrole-2-carboxylate[8] (15.76 g, 0.05 mol) by hydrogenation in THF (400 mL) containing 10% Pd–C (1.6 g) for 12 h. The solid was decarboxylated in DMF (100 mL) at 154 °C under N_2 for 4.0 h and then treated at 0–5 °C with Vilsmeier reagent ($POCl_3$ (17.4 mL, 0.186 mol) added to dry DMF (19.4 mL, 0.25 mol), kept at <10 °C over a 5-min period). Column chromatography on silica gel, eluting with 25% ethyl acetate in cyclohexane, and recrystallization from CH_2Cl_2/hexane gave the title pyrrole (7.41 g, 71%) as pale yellow plates, mp 89–91 °C (lit.[8] mp 88–90 °C). ^1H NMR: δ 9.75 (br s, 1H), 9.48 (s, 1H), 3.68 (s, 3H), 2.90, 2.62 (each t, 2H), 2.22, 1.92 (each s, 3H). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.27; N, 6.74.

***tert*-Butyl 9-((Benzyloxy)carbonyl)-2,3,7,8-tetramethyldipyrromethane-1-carboxylate.** Benzyl 5-(acetoxymethyl)-3,4-dimethylpyrrole-2-carboxylate[26] (9.06 g, 30.0 mmol) under N_2 in deoxygenated HOAc (250 mL) was treated with *tert*-butyl 3,4-dimethylpyrrole[26] (7.03 g, 36.0 mmol), and the mixture was stirred under N_2 at 65 °C for 8 h. Evaporation under high vacuum gave a residue which was flash-chromatographed on silica gel, eluting with cyclohexane/4% ethyl acetate, to give 10.0 g (76% yield) of a white crystalline solid, mp 134–136 °C (lit.[26] mp 132.5–134 °C). ^1H NMR: δ 8.86, 8.61 (each br s, 1H), 7.34 (m, 5H), 5.27 (s, 2H), 3.81 (s, 2H), 2.26, 2.22, 1.94, 1.93 (each s, 3H), 1.52 (s, 9H). Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.60; H, 7.40; N, 6.46.

Tripyrrins. Benzyl 1-(2-(Methoxycarbonyl)ethyl)-2,3,7,8,-12,13-hexamethyl-5-tripyrrin-14-carboxylate Hydrobromide (16). *tert*-Butyl 9-((benzyloxy)carbonyl)-2,3,7,8-tetramethyldipyrromethane-1-carboxylate (3.00 g, 6.87 mmol) in TFA (20 mL) was stirred for 5 min at rt during gas evolution. It was then cooled to 0 °C before addition, as rapidly as possible, of 2-formyl-5-(2-(methoxycarbonyl)ethyl)-3,4-dimethylpyrrole[8] (12) (1.73 g, 8.25 mmol) in MeOH (10 mL). Stirring was continued at rt under N_2 for 2 h, after which a solution of 30% HBr in HOAc (1 mL) in ether (130 mL) was added. The mixture was kept at −40 °C for 2 d and then filtered, and the orange crystalline material was washed with cold ether and then dried under vacuum at 50 °C to give 2.55 g of the title tripyrrin hydrobromide. A second crop of crystals (750 mg) was obtained by evaporation of the filtrate, giving 3.30 g (79% yield) overall, with mp 116–121 °C. ^1H NMR: δ 13.23, 12.96, 10.52 (each br s, 1H), 7.50 (d, 1H), 7.29 (m, 4H), 7.08 (s, 1H), 5.31 (s, 2H), 4.31 (s, 2H), 3.63 (s, 3H), 4.25, 2.98 (each t, J = 7.2 Hz, 2H), 2.26, 2.24, 2.21, 2.04, 2.03, 2.00 (each s, 3H). UV–visSPCLN λ_{max} 279 nm (ε 22 200), 379 (6800), 494 (83 100). Anal. Calcd for $C_{32}H_{38}BrN_3O_4$: C, 63.16; H, 6.29; N, 6.90. Found: C, 63.88; H, 6.07: N, 6.71.

***tert*-Butyl 1,2,3,7,8,12,13-Heptamethyl-5-tripyrrin-14-carboxylate Hydrobromide (36).** *tert*-Butyl 9-((benzyloxy)carbonyl)-2,3,7,8-tetramethyldipyrromethane-1-carboxylate (6.00 g, 13.74 mmol) was dissolved in dry THF (100 mL) containing 10% Pd–C (600 mg), and the mixture was hydrogenated at rt and atmospheric pressure for 10 h. The catalyst was filtered off using a pad of Celite, and the filtrate was evaporated to give a white solid which was dissolved in CH_2Cl_2 (200 mL) and treated with 2-formyl-3,4,5-trimethylpyrrole[27] (2.07 g, 15.12 mmol) followed by *p*-toluenesulfonic acid (5.75 g, 30.21 mmol) in MeOH (20 mL) over a 15-min period. After 45 min, the mixture was diluted with CH_2Cl_2 (60 mL) and washed with aqueous $NaHCO_3$. After drying (anhy Na_2SO_4), the filtrate was concentrated and residual MeOH and water were removed azeotropically using evaporation of aliquots of benzene. The dark residue was dried under high vacuum for several hours, dissolved in CH_2Cl_2 (40 mL), and then subjected to a stream of HBr(g) for about 5 s. The deep red solution was immediately evaporated to dryness, and the residue was taken up in toluene which was then quickly azeotropically evaporated. CH_2Cl_2 (30 mL) and MeOH (10 mL) were added, and then, ether (200 mL) was added dropwise. The mixture was then kept at -40 °C for several hours before the precipitate was filtered off, washed with ether, and then dried to give 5.28 g (76% yield), mp 206–212 °C dec. ^1H NMR: δ 13.15 (br s, 2H), 10.39 (br s, 1H), 7.03 (s, 1H), 4.25 (s, 2H), 2.64, 2.25, 2.202, 2.215, 2.02, 2.01, 1.98 (each s, 3H), 1.56 (s, 9H). UV-vis: λ_{max} 276 nm (ε 38 700), 376 (7500), 494 (83 200). Anal. Calcd for $C_{26}H_{36}BrN_3O_2$: C, 62.15; H, 7.22; N, 8.36. Found: C, 62.14; H, 7.22; N, 8.36.

a,c-Biladiene Salts. 1,19-Bis(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene Dihydrobromide (10). Dibenzyl 2,3,7,8-tetramethyldipyrromethane-1,9-dicarboxylate[28] (4.09 g, 8.69 mmol) in dry THF (200 mL) containing 10% Pd–C (400 mg) was hydrogenated at rt and atmospheric pressure for 14 h. Shortly after the hydrogenation had begun, a white precipitate (of dicarboxylic acid 11) began to appear in the flask, so DMF (20 mL) was added to redissolve the precipitate. The catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated to give a white solid which was dried under high vacuum at 35 °C for several hours to remove traces of residual DMF. The resulting dicarboxylic acid 11 in TFA (25 mL) was stirred for 30 min before cooling to 0 °C, and as rapidly as possible, formylpyrrole[8] 12 (4.0 g, 19.12 mmol) in MeOH (30 mL) was added. After several minutes, the mixture was a deep red color and so HBr(g) was bubbled into it for 1 min. Stirring was continued for a further 1 h, and then ether (200 mL) was added dropwise to precipitate the a,c-biladiene dihydrobromide; it was filtered off after the flask had been set aside for 2 h in a refrigerator, and the precipitate was washed with cold ether. The yield was 84% (5.46 g), mp 222–227 °C dec. ^1H NMR: δ 13.53, 13.16 (each br s, 2H), 7.12 (s, 2H), 4.86 (s, 2H), 3.66 (s, 6H), 3.18 (t, J = 7.4 Hz, 4H), 2.83 (t, J = 7.4 Hz, 4H), 2.27, 2.21, 2.04, 1.80 (each s, 6H). UV–vis: λ_{max} 452 nm (ε 123 000), 526 (82 700). Anal. Calcd for $C_{35}H_{46}Br_2N_4O_4$: C, 56.31; H, 6.21; N, 7.50. Found: C, 56.28; H, 6.17; N, 7.59.

1,19-Bis((ethoxycarbonyl)methyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene Dihydrobromide (30). This compound was similarly prepared in 88% yield via 11 and formylpyrrole 17 (3.00 g, 14.3 mmol), starting from dibenzyl 2,3,7,8-tetramethyldipyrromethane-1,9-dicarboxylate[28] (3.07 g, 6.52 mmol). Precipitation with ether gave 4.31 g, mp 209–214 °C dec. ^1H NMR: δ 13.46, 13.26 (each br s, 2H), 7.16 (s, 2H), 5.17 (s, 2H), 4.24 (s,

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4H), 4.21 (q, 4H), 2.29, 2.22, 1.98, 1.89 (each s, 6H), 1.28 (t, 6H). UV-vis: λ_{max} 452 nm (ϵ 102 600), 528 (113 400). HRMS: calcd for $[C_{35}H_{45}N_4O_4]^+$ 585.3440, found 585.3465. Anal. Calcd for $C_{35}H_{46}Br_2N_4O_4$: C, 56.31; H, 6.21; N, 7.50. Found: C, 56.01; H, 6.26; N, 7.57.

19-((Ethoxycarbonyl)methyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene Dihydrobromide (15). Compound **16** (1.217 g, 2.00 mmol) was suspended in 40% HBr/HOAc (12 mL) and cooled to 0 °C under N_2. TFA (24 mL) was added, and the resulting mixture was stirred at 0 °C for 1 h and then for 1 h at rt. After the solution had cooled to 0 °C, pyrrole **17** (502 mg, 2.40 mmol) in MeOH (25 mL) was added (color changed from yellow-green to red-orange). Stirring at 0 °C was continued for 1 h, and the mixture was kept under N_2 for 48 h at −40 °C. The a,c-biladiene (1.33 g, 89%) was filtered off, washed with cold ether, and dried under vacuum at 50 °C, mp >300 °C. ^{1}H NMR: δ 13.43 (br s, 2H), 13.23, 13.08 (each br s, 1H), 7.16, 7.12 (each s, 1H), 5.19 (s, 2H), 4.23 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 3.27 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.29, 2.28, 2.23, 2.21, 2.05, 1.98, 1.90, 1.88 (each s, 3H), 1.28 (t, 3H). UV-vis: λ_{max} 452 nm (ϵ 104 200), 528 (105 800). HRMS: calcd for $[C_{35}H_{46}BrN_4O_4]^+$ 665.2702, found 665.2714. Anal. Calcd for $C_{35}H_{46}Br_2N_4O_4 \cdot H_2O$: C, 54.98; H, 6.33; N, 7.33. Found: C, 55.06; H, 6.32; N, 7.31.

1-((Methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (35). Tripyrrin hydrobromide **36** (2.50 g, 4.98 mmol) in TFA (40 mL) was stirred at rt under N_2 for 5 min before addition of formylpyrrole[8] **12** (1.25 g, 5.97 mmol) in MeOH (15 mL). After 5 min of stirring, HBr(g) was bubbled into the solution for 1 min and stirring was continued under N_2 at rt for 1.5 h. Ether (200 mL) was then added dropwise to the stirred solution, and the mixture was placed in a refrigerator for 8 h. The orange solid was filtered off and recrystallized from CH_2Cl_2/MeOH/ether (2:1:8) to afford 2.82 g (84%), mp 209–216 °C dec. ^{1}H NMR: δ 13.46, 13.29, 13.18, 13.11 (each br s, 1H), 7.11, 7.08 (each s, 1H), 5.14 (s, 2H), 3.67 (s, 3H), 3.28 (t, 2H), 3.00 (t, 2H), 2.67, 2.05, 2.00 (each s, 3H), 2.28, 2.21, 1.89 (each s, 6H). UV-vis: λ_{max} 452 nm (ϵ 125 00), 528 (91 500). HRMS: calcd for $C_{32}H_{40}N_4O_2$ 512.3146, found 512.3133. Anal. Calcd for $C_{32}H_{42}Br_2N_4O_2 \cdot 0.5H_2O$: C, 56.23; H, 6.34; N, 8.20. Found: C, 56.30; H, 6.15; N, 8.14.

1-((Ethoxycarbonyl)methyl)-2,3,7,8,12,13,17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (39). This a,c-biladiene was synthesized in 82% yield (2.77 g) (as for compound **35**) from tripyrrin **36** (2.50 g, 4.98 mmol) and formylpyrrole **17** (1.25 g, 5.97 mmol), mp 214–220 °C dec. ^{1}H NMR: δ 13.43, 13.29, 13.24, 13.16 (each br s, 1H), 7.15, 7.08 (each s, 1H), 5.18 (s, 2H), 4.24 (s, 2H), 4.20 (q, 2H), 2.68, 2.29, 2.27, 2.22, 2.21, 1.98, 1.96, 1.91, 1.90, 1.28 (t, 3H). UV-vis: λ_{max} 452 nm (ϵ 110 000), 528 (103 000). Anal. Calcd for $C_{32}H_{42}Br_2N_4O_2$: C, 56.98; H, 6.28; N, 8.31. Found: C, 56.90; H, 6.28; N, 8.31.

Cyclization of a,c-Biladienes with Copper(II) Acetate. Cyclization of 1,19-Bis(2-(methoxycarbonyl)ethyl)-2,3,7,8,-13,14,17,18-octamethyl-a,c-biladiene Dihydrobromide (10). Copper(II) acetate (4.14 g, 22.77 mmol) and dry DMF (50 mL) under N_2 were heated to 125 °C; a,c-biladiene **10** (1.00 g, 1.339 mmol) was added in one portion. Heating and stirring under N_2 were continued for 5 min; the mixture was allowed to cool for 5 min before being poured into ice water. CH_2Cl_2 (100 mL) was added, and after shaking, the organic layer was run off. More CH_2Cl_2 (2 × 100 mL) was used, and the organic phases were combined. Evaporation of the volatile organics gave a dark residue which was dissolved in ether and washed several times with water to remove residual DMF. Evaporation gave a residue which was flash-chromatographed on silica gel, eluting with CH_2Cl_2 containing 10% cyclohexane. Crystallization from CH_2Cl_2/hexane gave 668 mg (39% yield) of copper(II) 1-(2-(methoxycarbonyl)ethyl)-20-((methoxycarbonyl)methyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**13**), mp >300 °C dec (to porphyrin/chlorin). UV-vis: λ_{max} 322 nm (ϵ 20 900), 417 (41 800), 767 (6600), 843 (17 100). Anal. Calcd for $C_{35}H_{40}CuN_4O_4$: C, 65.25; H, 6.25; N, 8.70. Found: C, 65.22; H, 6.05; N, 8.65. The structure was confirmed by single-crystal X-ray analysis.[29] Compound **13** (400 mg, 0.621 mmol) was demetalated by dissolving it under N_2 in TFA (45 mL) containing concd H_2SO_4 (30 mL). The mixture was stirred for 2 h at rt before being poured into water and ice containing CH_2Cl_2. The lower layer was run off, and the aqueous layer was extracted with more CH_2Cl_2 until colorless. The combined organic phases were washed with aqueous $NaHCO_3$ and then water and finally dried over anhy Na_2SO_4. Evaporation gave a residue which was flash-chromatographed on a silica gel column, eluting with CH_2Cl_2 containing 0.5% MeOH. The major colored band gave a residue which was crystallized from CH_2Cl_2/hexane to give 174 mg (48%) of compound **14**, mp 225–228 °C. ^{1}H NMR: δ 14.14, 13.60 (each br s, 1H), 6.14, 5.24, 4.85 (each s, 1H), 3.61, 3.56 (each s, 3H), 3.42 (d of d, J = 9.6, 15.9 Hz, 1H), 3.05, 2.21 (each m, 2H), 2.95 (d of d, J = 9.6, 3.5 Hz, 1H), 2.34 (d of d, J = 16.1, 3.5 Hz, 1H), 1.96, 1.94, 1.87, 1.81, 1.71, 1.67 (each s, 3H), 1.84 (s, 6H). UV-vis: λ_{max} 305 nm (ϵ 19 500), 381 (55 100), 662 (8500), 714 (9600). HRMS: calcd for $C_{35}H_{42}N_4O_4$ 582.3206, found: 582.3206. Anal. Calcd for $C_{35}H_{42}N_4O_4$: C, 72.14; H, 7.26; N, 9.61. Found: C, 71.99; H, 7.16; N, 9.61. The structure was confirmed by X-ray analysis.[30]

Cyclization of 19-((Ethoxycarbonyl)methyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-a,c-biladiene Dihydrobromide (15). This reaction was performed at 130 °C for 5 min as described for compound **10**, using 375 mg (0.50 mmol) of a,c-biladiene **15** in DMF (20 mL) containing copper(II) acetate (1.51 g, 8.50 mmol). After flash chromatography on silica gel, eluting with CH_2Cl_2/15% cyclohexane, three bands were isolated. The very minor least polar pink band was composed of as many as three copper(II) porphyrins; the most predominant copper porphyrin was either **20** or **21** (LRMS: calcd for $C_{31}H_{32}CuN_4O_2$ 555.18, found 555). Since only a very small quantity of the copper(II) porphyrins were obtained, they were not further investigated. A band of medium polarity contained uniquely the yellow-green macrocycle copper(II) 20-(ethoxycarbonyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**18**), (86 mg, 27% yield), mp >300 °C dec (to porphyrin **20**). UV-vis: λ_{max} 321 nm (ϵ 23 500), 416 (45 000), 764 (7300), 842 (14 600). HRMS: calcd for $C_{35}H_{40}CuN_4O_4$ 643.2345, found: 643.2296. Anal. Calcd for $C_{35}H_{40}CuN_4O_4$: C, 65.25; H, 6.26; N, 8.70. Found: C, 65.29; H, 6.32; N, 8.69. The structure was confirmed by single-crystal X-ray analysis.[18,20] The most polar band (blue) gave 62 mg (19% yield) of copper(II) 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (**23**), mp 218–220 °C. UV-vis: λ_{max} 308 nm (ϵ 12 100), 410 (156 000), 512 (5500), 552 (10 000), 580 (7700), 626 (42 800). HRMS: calcd for $C_{35}H_{38}CuN_4O_4$ 641.2189, found 641.2222. Anal. Calcd for $C_{35}H_{38}CuN_4O_4$: C, 65.45; H, 5.96; N, 8.72. Found: C, 65.49; H, 5.97; N, 8.75. When the cyclization of a,c-biladiene **15** (373 mg) was carried out at rt with copper(II) acetate (1.54 g) in DMF (20 mL) for 12 h, only the copper(II) macrocycle **18** (115 mg, 36% yield) was isolated. Heating of the macrocycle **18** (5 mg) in DMF (15 mL) containing copper(II) acetate (100 mg) afforded either copper(II) porphyrin **20** or **21** (vide infra) (2 mg) and copper(II) chlorin **23** (1.5 mg) after workup and flash chromatography on silica gel.

Demetalation of Copper(II) 20-(Ethoxycarbonyl)-1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,-20-dihydroporphyrin (18). The copper(II) macrocycle **18** (450 mg, 0.698 mmol) in TFA (60 mL) at 0 °C was stirred during the dropwise addition of concentrated sulfuric acid (30 mL). Stirring was continued at 0 °C for 2 h and then at rt for 30 min before the mixture was poured carefully into a water/ice/CH_2Cl_2 mixture. The organic phase was run off, and the aqueous phase was washed with additional CH_2Cl_2 until colorless. The organic phases were combined, washed with aqueous $NaHCO_3$, washed with water, dried over anhy Na_2SO_4, and evaporated to dryness. The residue was flash-chromatographed on silica gel, eluting with CH_2Cl_2 containing 1% MeOH, to give 67 mg (16.5% yield) of 20′-(ethoxycarbonyl)-20-((methoxycarbonyl)methyl)-2,3,7,8,12,13,-17,18-octamethyl-20′-homoporphyrin (**28**), mp >300 °C dec. ^{1}H NMR: δ 7.91, 7.83, 7.09 (each s, 1H), 6.74 (br s, 1H), 5.11 (t, J = 7.5 Hz, 1H), 4.60, 4.39 (each m, J = 7.2 Hz, 1H), 3.89 (br s, 1H), 3.12 (s, 3H), 2.69, 2.65, 2.64, 2.58, 2.51, 2.41 (each s, 3H), 2.52 (s,

(29) Not shown, but see Figure 2 in ref 18.

(30) Not shown, but see Figure 3 in ref 18.

6H), 1.44 (t, J = 7.0Hz, 3H), 0.96 (d, J = 7.2 Hz, 2H). Assignments were confirmed by decoupling experiments. UV–vis: λ_{max} (Figure 3) 324 nm (ϵ 25 500), 408 (75 800), 630 (11 900), 660 (13 700). HRMS: calcd for $C_{35}H_{40}N_4O_4$ 580.3050, found 580.3056. Anal. Calcd for $C_{35}H_{40}N_4O_4$: C, 72.39; H, 6.94; N, 9.64. Found: C, 72.40; H, 6.88; N, 9.54. The structure was confirmed by single-crystal X-ray analysis.[23]

Demetalation of Copper(II) 20-(Ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (23). Chlorin **23** (70 mg) was demetalated in TFA (6 mL) and concd H_2SO_4 (4 mL) under N_2 at rt for 12 h, as described for homoporphyrin **28**. Flash chromatography on silica gel, eluting with CH_2Cl_2 containing 1% acetone, separated many bands; the major ones were the recovered copper(II) chlorin **23** (8 mg) and 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,7,8,12,13,17,18-heptamethyl-3-methylidene-2,3-dihydroporphyrin (**25**) (15 mg, 24%), mp 218–220 °C. ^{1}H NMR: δ 9.76, 9.55, 8.82 (each s, 1H), 6.43, 5.84 (each d, J = 1Hz, 1H), 4.88 (q, J = 7.5 Hz, 2H), 3.49, 3.44, 3.43, 3.40, 3.32, 3.29 (each s, 3H), 3.33 (s, 3H), 3.00, 2.66, 2.22, 1.20 (each m, 1H), 2.10 (s, 3H), 1.62 (t, J = 7.2 Hz, 3H), −2.08, −2.49 (each br s, 1H). UV–vis: λ_{max} 400 nm (ϵ 178 000), 498 (10 300), 532 (8400), 602 (3300), 658 (35 300). HRMS: calcd for $C_{35}H_{40}N_4O_4$ 580.3050, found 580.3073. Anal. Calcd for $C_{35}H_{40}N_4O_4$: C, 72.39; H, 6.94; N, 9.65. Found: C, 72.30; H, 6.97; N, 9.64. X-ray-quality crystals of this material were not obtained, so its copper(II) complex **23** was subjected to catalytic hydrogenation as follows: **23** (14 mg, 0.0218 mmol) in THF (5 mL) containing 10% Pd–C (3 mg) was hydrogenated at rt and atmospheric pressure until the uptake of hydrogen ceased (24 h). The catalyst was filtered off using a pad of Celite, and after washing with more THF, the combined filtrates were evaporated to dryness to give a residue which was flash-chromatographed on silica gel, eluting with CH_2Cl_2 containing 15% cyclohexane. The blue eluates were collected; evaporation followed by crystallization from CH_2Cl_2/hexane afforded copper(II) 20-(ethoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-*trans*-chlorin (**26**) (9 mg, 62.5% yield). UV–vis: λ_{max} (rel. intenstities) 400 nm (1.00), 496 (0.027), 532 (0.013), 580 (infl, (0.047), 618 (0.313). HRMS: calcd for $C_{35}H_{40}CuO_4N_4$ 643.2345, found 643.2348. All of the remaining material was crystallized from CH_2Cl_2/hexane and afforded X-ray-quality crystals; the X-ray structure (Figure 2) confirmed our proposal and, by inference, the structure of **23**.

Cyclization of 1,19-Bis((ethoxycarbonyl)methyl)-2,3,7,8,-12,13,17,18-octamethyl-a,c-biladiene Dihydrobromide (30). This reaction was performed at 110 °C for 2.5 min as described above for compound **10**, using 747 mg (1.00 mmol) of **30** in DMF (40 mL) containing copper(II) acetate (3.10 g, 17.0 mmol). After flash chromatography on silica gel, three bands were isolated. The fastest running band was pink and provided 10 mg (2%) of copper(II) porphyrin **20** (HRMS: calcd 555.1821, found 555.1836). The major band of medium polarity gave copper(II) 20-(ethoxycarbonyl)-1-((ethoxycarbonyl)methyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**31**) (130 mg, 20% yield), mp 232–235 °C dec (some, to porphyrin). UV–vis: λ_{max} 320 nm (ϵ 23 500), 415 (45 800), 759 (8200), 833 (15 300). HRMS: calcd for $C_{35}H_{40}CuN_4O_4$ 644.2346, found: 644.2422. Anal. Calcd for $C_{35}H_{40}CuN_4O_4$: C, 65.25; H, 6.26; N, 8.70. Found: C, 65.25; H, 6.21; N, 8.66. The most polar major band yielded copper(II) 20,20′-bis-(ethoxycarbonyl)-2,3,7,8,12,13,17,18-octamethyl-20′-homoporphyrin (**32**) (41 mg, 6.4%), mp 300 °C dec (to copper(II) porphyrin). UV–vis: λ_{max} 341 nm (ϵ 17 300), 444 (76 900), 558 (4200), 704 (15 100). Anal. Calcd for $C_{35}H_{38}CuN_4O_4$: C, 65.45; H, 5.96; N, 8.72. Anal. Calcd for $C_{35}H_{38}CuN_4O_4 \cdot H_2O$: C, 63.67; H, 6.11; N, 8.48. Found: C, 63.79, 63.85; H, 5.90, 5.91; N, 8.26, 8.24. The structure was confirmed by an X-ray crystal structure (Figure 4).

Demetalation of Copper(II) 20-(Ethoxycarbonyl)-1-((ethoxycarbonyl)methyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (31). Compound **31** (100 mg, 0.155 mmol) was demetalated as described above for compound **28** using TFA (12.0 mL) and concd H_2SO_4 (8.0 mL). After chromatography, 20-(ethoxycarbonyl)-1-((ethoxycarbonyl)methyl)-2,3,7,8,12,13,-17,18-octamethyl-1,20-dihydroporphyrin (**34**) (51 mg, 57%) was isolated, mp 170–180 °C dec. ^{1}H NMR: δ 14.35, 13.71 (each br s, 1H), 6.14, 5.22, 4.86 (each s, 1H), 4.16 (m, 1H), 4.01 (m, 3H), 3.67 (s, 1H), 3.26, 2.99 (each d, J = 14.1 Hz, 1H), 1.98, 1.95, 1.860, 1.858, 1.851, 1.68 (each s, 3H), 1.82 (s, 6H), 1.19, 1.13 (each t, J = 7.2 Hz, 3H). UV–vis: λ_{max} 378 nm (44 600), 656 (7300), 708 (8500). HRMS: calcd for $C_{35}H_{42}N_4O_4$ 582.3206, found: 582.3211. Anal. Calcd for $C_{35}H_{42}N_4O_4$: C, 72.14; H, 7.26; N, 9.61. Found: C, 72.11; H, 7.24; N, 9.64. This material was discarded. An unstable polar green compound (40 mg) was also isolated and discarded.

Cyclization of 1-(2-(Methoxycarbonyl)ethyl)-2,3,7,8,12,-13,17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (35). This reaction was performed twice (once at 120 °C for 2 min and once at rt for 2 h) in DMF (40 mL) containing copper(II) acetate (3.10 g, 17 mmol) and a,c-biladiene **35** (675 mg, 1.00 mmol), as described above for a,c-biladiene **10**, but with limited success. The crude products from both reaction mixtures were combined, and numerous minor chromatographic bands were isolated. The major fractions (with increasing polarity) consisted of several unidentified copper(II) porphyrins (42 mg, <3%). Only a trace (5 mg, <1%) of the expected copper(II) macrocycle was obtained, and it was not possible to confirm whether this was copper(II) 1-(2-(methoxycarbonyl)ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,-20-dihydroporphyrin (**37**) or copper(II) 20-((methoxycarbonyl)-methyl)-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**38**). Demetalation of either **37** or **38** met with little success due to decomposition. Subsequent reactions using the chromium acetate hydroxide method (vide infra) allowed us to postulate the product to have been copper(II) 1-(2-(methoxycarbonyl)-ethyl)-2,3,7,8,12,13,17,18-octamethyl-1,20-dihydroporphyrin (**37**).

Cyclization of 1-((Ethoxycarbonyl)methyl)-2,3,7,8,12,13,-17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (39). This reaction was performed at 100 °C for 2 min in DMF (40 mL) containing copper(II) acetate (3.10 g, 17 mmol) and a,c-biladiene **39** (675 mg, 1.00 mmol), as described for a,c-biladiene **10**. It afforded two bands upon flash chromatography on silica gel, eluting with 60:40 CH_2Cl_2/cyclohexane. A small quantity of the product from the least polar band was copper(II) porphyrin **22** (UV–vis: λ_{max} 398 nm, 524, 560). The major band contained copper(II) 20-(ethoxycarbonyl)-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**40**) (255 mg, 45%), mp 265–268 °C dec (to porphyrin). UV–vis: λ_{max} 319 nm (21 700), 414 (44 000), 756 (7250), 830 (17 000). Anal. Calcd for $C_{32}H_{36}CuN_4O_2$: C, 67.17; H, 6.34; N, 9.79. Found: C, 67.11; H, 6.38; N, 9.91. Demetalation of copper(II) 20-(ethoxycarbonyl)-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**40**) (40 mg) was carried out using TFA (9 mL) and concd H_2SO_4 (6 mL). Flash chromatography on silia gel, eluting with cyclohexane containing 8% ethyl acetate, afforded three bands, with much decomposition. Of the two identifiable compounds from the chromatography, the least polar band (3 mg, 8%) was the metal-free compound 20-(ethoxycarbonyl)-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**41**). Analytical data matched those of the kinetic product prepared in the chromium acetate hydroxide method (vide infra). A trace amount of a yellow band of medium polarity was not characterized, and the most polar band (1 mg, 3% yield) was identified as 20-(ethoxycarbonyl)-2,3,7,8,12,13,17,18-octamethyl-20′-homoporphyrin (**42**).

Cyclizations of a,c-Biladienes with Chromium(III) Acetate Hydroxide. Cyclization of 1,2,3,7,8,12,13,17,18,19-Decamethyl-a,c-biladiene Dihydrobromide (3). DMF Method. Dry DMF (50 mL) was purged of oxygen by bubbling with N_2 for 5 min before being heated at 100 °C. After 5 min, a,c-biladiene **3** (55.4 mg, 0.920 mmol) and $Cr_3(OAc)_7(OH)_2$ (76 mg, 0.126 mmol) were added simultaneously. Dry triethylamine (0.5 mL) was then quickly added via a syringe. The gas above the solvent was N_2-purged three times with a large (50-mL) syringe. The reaction mixture was protected from light. After 23 h, the reaction was complete (spectrophotometry), the mixture was cooled, diluted with CH_2Cl_2 (100 mL) and water (100 mL), and extracted, and the organic phases were combined and concentrated to give a green oil which was taken up in ether (100 mL) and washed with water (7 × 100 mL) and then brine (100 mL) to drive off residual DMF. After being dried over Na_2SO_4, the solution was concentrated and chromatographed on alumina (Brockmann, Grade III), eluting with 1:1 CH_2Cl_2/petroleum ether, to provide the blue–green compound 1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**5**) (22.2 mg, 55% yield). Ana-

lytical data were identical with those for the same compound produced using the electrochemical cyclization techniques.[9,10]

Ethanol Method. Aqueous EtOH (95% 200 mL) was degassed for 5 min by bubbling with N_2 gas. Chromium acetate hydroxide (206 mg, 0.341 mmol) and NaOAc (1.0 g, 12.2 mmol) were added simultaneously followed by an additional 5 min of N_2 purging. a,c-Biladiene **3** (199 mg, 0.330 mmol) was added all at once, and the mixture was heated at 65 °C for 17 h before being cooled and diluted with CH_2Cl_2 (200 mL) and water (200 mL). The organic layer was washed with water (2 × 200 mL) and then brine (200 mL) to remove residual EtOH. Evaporation gave a solid which was chromatographed on alumina (Brockmann, Grade III; elution with 4:1 CH_2Cl_2/petroleum ether) to give the compound **5** (90 mg, 62%), identical with the material obtained from the DMF method.

Cyclization of 1-((Ethoxycarbonyl)methyl)-2,3,7,8,13,14,-17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (39). At 70 °C. a,c-Biladiene dihydrobromide **39** (49.4 mg, 0.073 mmol) was similarly cyclized following the EtOH method, using NaOAc (250 mg, 3.05 mmol) and chromium acetate hydroxide (103 mg, 0.171 mmol) in EtOH (25 mL) heated at 70 °C for 10 min. Alumina column chromatography (Brockmann, Grade III; elution with 1:1 CH_2Cl_2/ petroleum ether) gave a nonpolar orange band which was not characterized due to its complexity and instability. A blue–green band of medium polarity yielded 20-(ethoxycarbonyl)-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**41**) (11 mg, 30% yield), mp >150 °C dec (to porphyrin). ^{1}H NMR: δ 14.44, 13.85 (each br s, 1H), 6.13, 5.19, 4.87 (each s, 1H), 4.17, 4.05 (each m, 1H), 3.35 (s, 1H), 1.98, 1.94, 1.85, 1.84, 1.80, 1.68, 1.53 (each s, 3H), 1.82 (s, 6H), 1.21 (t, J = 7.2 Hz, 3 H). The ^{1}H NMR spectrum of a dried sample also showed a peak at 5.30 ppm (CH_2Cl_2; see combustion analysis). UV–vis: λ_{max} 304 nm (ε 19 700), 378 (48 700), 656 (8800), 703 (9800). HRMS: calcd for $C_{32}H_{38}N_4O_2$ 510.2995, found 510.2974. Anal. Calcd for $C_{32}H_{38}N_4O_2 \cdot 0.5CH_2Cl_2$: C, 70.57; H, 7.11; N, 10.12. Found: C, 70.57; H, 6.95; N, 9.92. A trace amount of the material isolated from a polar band was tentatively identified as homoporphyrin **42** (HRMS: calcd for $C_{32}H_{36}N_4O_2$ 508.2833, found: 508.2843).

At 140 °C. a,c-Biladiene dihydrobromide **39** (52 mg, 0.077 mmol) was cyclized following the DMF method, using chromium acetate hydroxide (108 mg, 0.179 mmol) in dry degassed DMF (50 mL) at 140 °C for 5 min. Alumina column chromatography (Brockmann, Grade III; elution with 1:1 CH_2Cl_2/petroleum ether) gave compound **43** (12 mg, 30% yield; identical with the thermodynamic product isomer of **41**) in a 13:1 ratio with its kinetic isomer, **41**. **Characterization of 43**: mp 214–217 °C dec (to porphyrin). ^{1}H NMR: δ 13.73, 13.10 (each br s, 1H), 6.28, 5.37, 5.01 (each s, 1H), 3.95 (m, 2H), 3.20, 2.80 (each d, J = 14.0 Hz, 1H), 2.97, 2.76 (each d, J = 15.3 Hz, 1H), 2.03, 2.01, 1.88, 1.84, 1.81, 1.78 (each s, 3H), 1.90 (s, 6H, Me), 1.09 (t, 3H). UV–vis: λ_{max} 305 nm (ε 18 300), 379 (52 700), 652 (9600), 702 (10 900). HRMS: calcd for $C_{32}H_{38}N_4O_2$ 510.2995, found 510.2977. Anal. Calcd for $C_{32}H_{38}N_4O_2$: C, 75.26; H, 7.50; N, 10.97. Found: C, 75.15; H, 7.44; N, 10.84.

At RT. Aqueous EtOH (95%, 25 mL) was degassed for 5 min with bubbling N_2. NaOAc (245 mg, 2.98 mmol) and chromium acetate hydroxide (102 mg, 0.169 mmol) were added all at once, and the mixture was degassed for a further 10 min. a,c-Biladiene dihydrobromide **39** (51.7 mg, 0.077 mmol) was then added, and the mixture was stirred, protected from light, at rt. After 11.5 h, the reaction was complete, CH_2Cl_2 (50 mL) and water (50 mL) were added to the flask, and the green organic layer was separated from the aqueous layer and further extracted until no green color remained. The organic layer was washed with water (4 × 100 mL) and then brine (100 mL) to drive off residual EtOH. After being dried over Na_2SO_4, the solution was concentrated and chromatographed on alumina (Brockmann, Grade III), eluting with 20% CH_2Cl_2 in petroleum ether. A fast moving orange band was again obtained but only in trace amounts. The blue–green band of medium polarity afforded 26.3 mg (67% yield) of compound **41**. The NMR data matched that of the same compound obtained at 70 °C. Again, a trace of a polar band was obtained but was discarded.

Cyclization of 1-(2-(Methoxycarbonyl)ethyl)-2,3,7,8,13,-14,17,18,19-nonamethyl-a,c-biladiene Dihydrobromide (35). This reaction was also carried out using the DMF method from chromium acetate hydroxide (148 mg, 0.245 mmol) and a,c-biladiene **35** (48 mg, 0.070 mmol) in dry degassed DMF (50 mL) heated at 140 °C for 37 min. After flash silica gel column chromatography (eluting with 1% MeOH and 3% acetone in CH_2Cl_2), the least polar band contained a trace (>1 mg) of at least three porphyrins (spectrophotometry), which were discarded. A final green band of slightly greater polarity was rechromatographed on an alumina column (Brockmann, Grade III; elution with CH_2Cl_2) to give **44** (5.0 mg, 14% yield), mp >225 °C dec (to porphyrin). ^{1}H NMR: δ 13.84, 13.23 (each br s, 1H), 6.24, 5.33, 4.96 (each s, 1H), 3.58 (s, 3H), 3.07, 2.54 (each d, J = 15.5 Hz, 1H), 3.00, 2.13 (each m, 2H), 2.01, 1.99, 1.90, 1.88, 1.87, 1.81, 1.77, 1.71 (each s, 3H). UV–vis: λ_{max} 305 nm (ε 18 100), 380 (52 200), 650 (8900), 708 (10 400). HRMS: calcd for $C_{32}H_{38}N_4O_2$ 510.2995, found 510.2990. Anal. Calcd for $C_{32}H_{38}N_4O_2$: C, 75.26; H, 7.50; N, 10.97. Found: C, 75.43; H, 7.64; N, 10.81.

Crystal Structure Analyses.[31] Dark blue plates of **26** were obtained by slow diffusion of hexane into a concentrated solution of the compound in CH_2Cl_2. Crystal data at 130 K: triclinic, space group $P\bar{1}$, a = 10.806(2) Å, b = 10.902(3) Å, c = 13.894(5) Å, α = 76.47(2)°, β = 74.12(2)°, γ = 78.01(2)°, V = 1512.4(7) Å^3, Z = 2, R = 0.066, R_w = 0.086 for 3556 reflections with $F > 4\sigma(F)$ and 387 parameters. The structure showed considerable disorder in one of the propionic ester side chains. Dark blue plates of **32** were obtained by slow diffusion of hexane into a concentrated solution of the compound in CH_2Cl_2. Crystal data at 130 K: triclinic, space group $P\bar{1}$, a = 7.632(3) Å, b = 14.376(7) Å, c = 15.743(14) Å, α = 114.48(3)°, β = 95.78(3)°, γ = 102.02(3)°, V = 1508.2(16) Å^3, Z = 2, R = 0.040, R_w = 0.043 for 3534 reflections with $F > 4\sigma(F)$ and 397 parameters.[32]

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(31) Programs used in this study include the following: Hope, H.; Moezzi, B. XABS, program for absorption correction; University of California: Davis, CA, 1989. Sheldrick, G. M. SHELXTL PLUS, program for crystal structure solution; Universität Göttingen: Germany, 1989. All calculations were performed on a Vax-station 3200. For full details of experimental techniques and methods used, see: Hope, H. *ACS Symp. Ser.* **1987**, *357*, 257. Senge, M. O.; Ruhlandt-Senge, K.; Smith, K. M. *Acta Crystallogr.* **1992**, *C48*, 1810.

(32) The author has deposited atomic coordinates for structures **26** and **32** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1E2, UK.