density difference map. Atomic coordinates for the non-hydrogen atoms are given in Table IV. Additional bond angles, anisotropic thermal parameters, positional parameters for the hydrogen atoms, and a listing of $10|F_o|$ and $10|F_c|$ are available as supplementary material.

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Supplementary Material Available: Tables of anisotropic thermal parameters, hydrogen atomic and triclinic coordinates, additional bond angles, and a listing of $10|F_o|$ and $10|F_c|$ (21 pages). Ordering information is given on any current masthead page.

Meso Substitution of Chlorophyll Derivatives: Direct Route for Transformation of Bacteriopheophorbides *d* into Bacteriopheophorbides *c*

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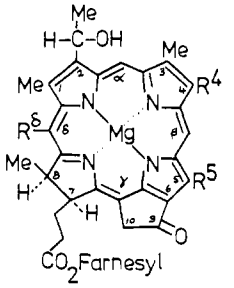
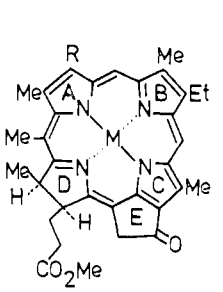
Abstract: In order to develop a procedure for direct methylation of methyl bacteriopheophorbides *d* (Bmph-*d*) to afford methyl bacteriopheophorbides *c* (Bmph-*c*), several reactions involving *meso* substitution of chlorophyll derivatives were investigated. Treatment of zinc(II) methyl mesopyropheophorbide *a* (**7b**) with bromine in chloroform accomplished oxidation, presumably via the π-cation radical, to the corresponding porphyrin, phylloerythrin methyl ester (**16**); *meso* bromination (to give **17**) resulted when metal-free methyl mesopyropheophorbide *a* (**7**) was treated with bromine in chloroform. Friedel–Crafts cyanation (cyanogen bromide/aluminum chloride) of copper(II) methyl mesopyropheophorbide *a* (**7a**) gave 40–50% yields of the *meso*-cyanochlorin **18** after demetalation, but attempts to transform the cyano group into methyl were unsuccessful. Oxidation reactions of **7** using thallium(III) trinitrate resulted in formation of the corresponding *meso*-nitrochlorins **20**. Treatment of copper(II) methyl mesopyropheophorbide *a* (**7a**) with chloromethyl methyl sulfide and titanium tetrachloride afforded the *meso*-methylthiomethyl derivative **19a** (74–77% yields); use of the nickel(II) complex **7d** likewise gave 80–84% yields of **19b**. With Raney nickel, both **19a** and **19b** gave good yields of the required *meso*-methyl metallochlorins **3a** and **3b**, respectively, the former being readily demetalated with HCl gas in dichloromethane to give the *meso*-methylchlorin **3**. Thus, the Bmph-*d* to Bmph-*c* transformation was accomplished by initially protecting the vinyl group in methyl pyropheophorbide *a* (**9**) as the corresponding 2-chloroethyl group; the copper(II) complex **25a** was then methylthiomethylated, treated with Raney nickel (to give **26a**), and finally demetalated with HCl gas to give **27**. Compound **27** has previously been converted into Bmph-*c* [Et, Me] (**4**) by treatment with base (to give the 2-vinyl derivative) followed by hydration of the vinyl with HBr in acetic acid.

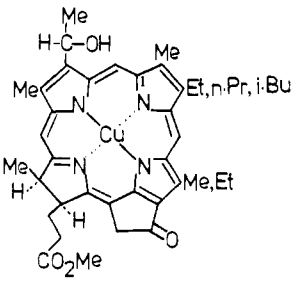
Bacteriochlorophylls *c* (**1**) and *-d* (**2**) (Bchls-*c*, *-d*) are found in various strains of green sulfur bacteria such as *Prosthecochloris aestuarii* (Bchl-*c*) and *Chlorobium vibrioforme* (Bchl-*d*). The pigments produced by such organisms occur as a mixture of homologues (**1a–f**; **2a–h**), and recent work has established the major structural features of these homologues in both the Bchl-*c*[1] and Bchl-*d*[2] series. The major structural difference between the Bchls-*c* and *-d* is the 8-*meso*-methyl substituent found in the former. In our previous synthesis[3] of methyl mesobacteriopheophorbide *c* [Et, Me] (**3**) and methyl bacteriopheophorbide *c* (Bmph-*c*) [Et, Me] (**4**) from copper(II) chlorin e_6 trimethyl ester derivatives, the key *meso*-methyl group was introduced by Vilsmeier formylation and one-step reduction of the resulting *meso*-formyl group. The success of this approach depended on the previously demonstrated fact that aromatic electrophilic substitution occurs adjacent to the reduced D ring in chlorins.[4,5]



	1 R8=Me			2 R8=H		
	R4	R5	Config. at 2'-posn.	R4	R5	Config. at 2'-posn.
a	Et	Me	R	Et	Me	R
b	Et	Et	R	Et	Et	R
c	n-Pr	Et	R	n-Pr	Me	R
d	n-Pr	Et	S	n-Pr	Et	S
e	i-Bu	Et	R	i-Bu	Me	R
f	i-Bu	Et	S	i-Bu	Et	S
g				neo-Pn	Me	R
h				neo-Pn	Et	S



3 R=Et, M=2H
4 R=CH(OH)Me, M=2H
a, M=Cu b, M=Ni



5 M=2H
a, M=Cu

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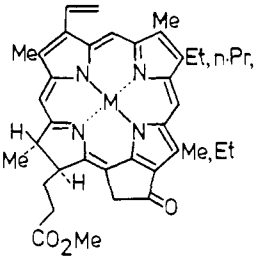
0002-7863/85/1507-4946$01.50/0

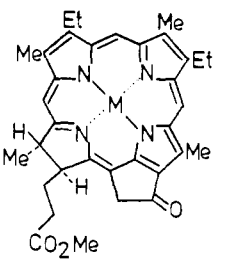
In this paper, we describe attempts to achieve the Bmph-*d* to -*c* transformation more directly by methylation of a Bmph-*d* or suitable derivative in which the isocyclic ring E is already present. The relatively large quantities of the six Bmphs-*d* available to us[2] would enable the previously impossible synthesis of any of the known Bmphs-*c*, plus the as yet unreported [*n*-Pr, Me] and [*i*-Bu, Me] homologues. Furthermore, introduction of a ^{13}C or ^{14}C label into a Bmph-*c* by this route could be useful for biosynthetic studies.

Results and Discussion

Treatment of the copper(II) complex **5a** of a mixture of Bmph-*d* homologues **5** with the Vilsmeier reagent did not give meso-formylated products. It appeared that dehydration of the 2-(1-hydroxyethyl) group to vinyl had occurred cleanly (TLC) to give compounds **6a**; this conclusion is based on the mass spectrum of



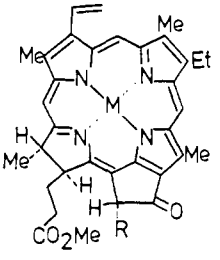
6 M=2H
6a, M=Cu



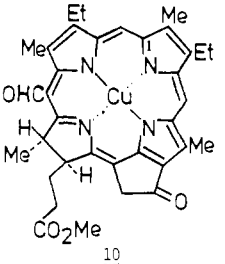
7 M=2H
7a, M=Cu
7b, M=Zn
7c, M=TlX
7d, M=Ni

the crude product, which showed no parent ions corresponding to starting material but instead a peak corresponding to the loss of 18 daltons from each homologue. That these ions were in fact the parent ions of the products produced in the attempted formylation, rather than secondary ions formed by loss of H_2O from each of the homologues in the starting material **5a**, was verified by running the mass spectrum of the starting material under the same conditions. In this case, the parent ions were observed. The greater TLC mobility and a shift in the long wavelength absorption to 654 nm in the products vs. the starting material (646 nm) also supported this conclusion. Similarly, treatment of **5a** with 10% sulfuric acid in TFA, which would be required to remove the copper at the end of the proposed synthetic sequence, gave **6**, the product of dehydration as well as demetalation.

Since it appeared that the stereochemistry at the 2-(1-hydroxyethyl) could not be preserved, it was decided to develop procedures with a less sensitive substrate wherein the 2-(1-hydroxyethyl) group was replaced by ethyl. Methyl mesopyropheophorbide *a* (**7**) fulfilled the necessary requirements and could be obtained in quantity from *Spirulina maxima* algae via methyl pheophorbide *a* (**8**) and methyl pyropheophorbide *a* (**9**). Vilsmeier

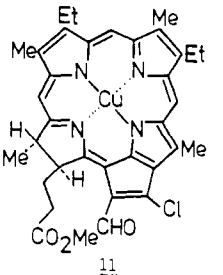


8 M=2H, R=CO_2Me
9 M=2H, R=H
9a, M=Cu
9b, M=Zn
9c, M=Cd
9d, M=Ni

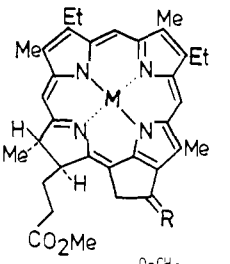


10

formylation of copper(II) methyl mesopyropheophorbide *a* (**7a**) according to the literature,[6] however, gave not the desired δ-*meso*-formylchlorin **10**, but the α,β-unsaturated chloroaldehyde **11**. The structure of this adduct was suggested by its mass



11



12 R=$\begin{matrix}O\text{-}CH_2\\ |\\ O\text{-}CH_2\end{matrix}$, M=2H

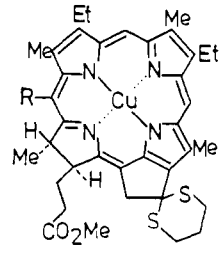
13 R=$\begin{matrix}S\text{-}CH_2\\ \diagdown\\ S\text{-}CH_2\end{matrix}\diagup CH_2$, M=2H

13a, M=Cu

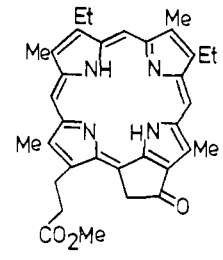
spectrum and elemental analysis as well as by literature precedent for the reaction of the Vilsmeier reagent with enolizable ketones to give α,β-unsaturated chloroaldehydes.[7-9] The infrared spectrum of **11** showed that the 9-carbonyl absorption of the starting material **7a** at 1683 cm^{-1} had been replaced by a new absorption at 1651 cm^{-1}. No attempt was made to obtain an NMR spectrum, since the literature indicated that the necessary demetalation of the copper(II) complex would cause extensive decomposition.[10]

Protection of the carbonyl function to prevent this unwanted side reaction was therefore considered next. Attempts to form the ethylene ketal **12** were less successful than formation of the trimethylene dithioketal **13**, which could readily be formed in high yield by heating **7** with 1,3-propanedithiol in acetic acid with boron trifluoride etherate as the catalyst. Insertion of copper(II) into **13** gave the formylation substrate **13a**.

Despite numerous attempts to formylate **13a** with $POCl_3$/DMF under various conditions, no conclusive evidence for the formation of δ-*meso*-formyl adduct **14** could ever be obtained. Attempts



14 R=CHO
15 R=Me



16

to reduce the crude formylation mixtures directly to the δ-*meso*-methyl derivatives **15** with sodium borohydride in acetic acid did not give recognizable products. Alternative methods for introduction of a *meso*-methyl group were therefore investigated. Smith and co-workers had recently shown that the π-cation radical produced by the oxidation of a metalloporphyrin or metallochlorin can undergo *meso* substitution with various nucleophiles, including cyanide.[11-13] Incorporation of a metal ion, especially magnesi-

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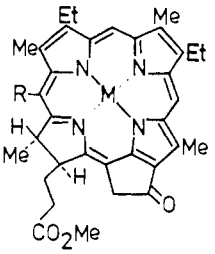
um(II), cadmium(II), or zinc(II), lowers the standard oxidation potential, which for a chlorin is already ca. 0.3 V lower than that of the corresponding porphyrin.[14] Oxidizing agents previously used included tris(*p*-bromophenyl)ammoniumyl hexachloroantimonate ($E°$ = 0.76 V), iodine ($E°$ = 0.54 V), and 1-chlorobenzotriazole.[13,15] For example, zinc(II) octaethylporphyrin was cyanated in 68% yield by this procedure to give zinc(II) *meso*-cyanooctaethylporphyrin.[13] A related electrochemical cyanation of the same porphyrin has also been reported.[16] When zinc(II) (**9b**) or cadmium(II) (**9c**) methyl pyropheophorbide *a* were treated with 3 equiv of iodine in methanol, the green-to-brown change characteristic of π-cation radical formation was not observed. Addition of excess sodium cyanide in methanol gave no reaction, and only starting material was recovered. Reaction of 2.8 equiv of the stronger oxidant, bromine ($E°$ = 1.06 V), with zinc(II) methyl mesopyropheophorbide *a* (**7b**) in methanol gave only starting material and demetalated starting material **7**.

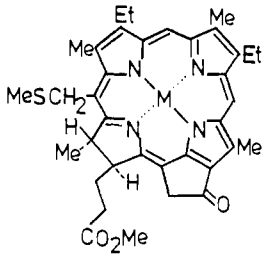
When a solution of bromine (3 equiv) in *chloroform* was added to **7b** in the same solvent, an immediate color change from green to red occurred which was not quenched by the addition of sodium cyanide in methanol. The product of the reaction was identified by its NMR and visible spectra as the corresponding porphyrin, phylloerythrin methyl ester (**16**). Demetalation had also occurred, possibly due to HBr generated in the reaction (no acid was used in the workup). This reaction is clean and proceeds to completion in 10 min or less at room temperature on a 20-mg scale, with or without the addition of cyanide. This experimentally simple procedure may provide a useful alternative to the oxidation of chlorins to porphyrins with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[17]

As expected, the *metal-free* methyl mesopyrophenoporbide *a* (**7**) was not oxidized to phylloerythrin with bromine in chloroform; rather the reaction proceeded cleanly to give a single major product which ran identically on TLC with the starting material. However, the visible spectrum of this compound in dichloromethane (664, 422 nm) was not that of the starting material **7** (656, 408 nm). NMR analysis showed only two meso protons and suggested that the new compound was the δ-bromo derivative **17**, previously prepared by Kenner and co-workers by reaction of **7** with pyridinium bromide perbromide.[18]

Synthesis of the *meso*-cyanochlorin was eventually accomplished by a modification of the Friedel–Crafts cyanation method recently published by Gore and co-workers.[19] These workers synthesized



17 M=2H, R=Br
18 M=2H, R=CN
20 M=2H, R=NO_2
a, M=Cu
b, M=TlX



19 M=2H
a, M=Cu
b, M=Ni

monocyano derivatives of condensed aromatic hydrocarbons such as naphthalene and anthracene in good yields by reaction with cyanogen bromide and aluminum chloride in carbon disulfide.

Prior to the oxidative cyanations discussed here, the only practical method for introducing a *meso*-cyano group onto a chlorin or porphyrin involved Vilsmeier formylation, oxime formation, and dehydration.[20] Thus, reaction of copper(II) methyl mesopyropheophorbide *a* (**7a**) with 11.5 equiv of aluminum chloride and 26 equiv of cyanogen bromide in carbon disulfide at reflux for 7.5 h gave **18a**. The reaction was difficult to monitor by TLC as **18a** runs only slightly faster than **7a** in 97/3 dichloromethane/THF. However, the reaction was conveniently monitored by the change in the long-wavelength visible absorption from 642 to 654 nm as the reaction proceeded to completion. When the copper was removed from **18a** by treatment with 10% sulfuric acid in TFA, no methyl mesopyropheophorbide *a* (**7**) was obtained, indicating that starting material **7a** had been completely consumed. The yield of purified **18** however, was only 16%. When a solution of cyanogen bromide (15 equiv) in chloroform was added to **7a** and $SnCl_4$ (4.6 equiv) in the same solvent and refluxed for 2 h, with monitoring by spectrophotometry, the desired **18** was obtained in 33% yield after demetalation. The cyanation reactions were clean as judged by TLC of the material in solution. However, green solid precipitated out of solution when the $SnCl_4$ was added to the chloroform solution of **7a**. Inverse addition of the $SnCl_4$ to a solution of **7a** and cyanogen bromide in chloroform at room temperature or at 0 °C did not improve the yields or eliminate the green precipitate. Use of $TlCl_4$ as catalyst at lower temperatures (vide infra) might provide an improvement. The best procedure consisted of adding a solution of $SnCl_4$ (3 equiv) and cyanogen bromide (20 equiv) in chloroform to a refluxing suspension of **7a** and potassium carbonate in chloroform. The reaction was usually complete in 7–9 h, considerably less insoluble material was formed, and yields ranged from 40–50% after demetalation of the crude product. Unfortunately, the reaction did not scale-up well; 100 mg of **7a** was the best convenient size.

Rather than expend further effort on optimizing the cyanation, it was decided to establish whether this route was viable, i.e., to determine whether the *meso*-cyano group could be converted into a *meso*-methyl group. There are many methods in the literature for reducing nitriles, but the need for a rapid direct route ruled out any protection deprotection sequences. These considerations eliminated hydride reagents such as $LiAlH_4$ or $LiAl(OEt)_3H$ which would not selectively reduce the cyano function in the presence of the 9-keto and 7-propionic methyl ester groups. Treatment of **1** with borane/THF at 0 °C for 1.5 h gave four products, but all retained the *meso*-cyano function intact. The direct reduction of cyano groups to methyl by catalytic-transfer hydrogenation is well-known.[21] However, refluxing a solution of **18** in THF with the hydrogen-transfer agent *p*-menthene and 10% palladium on carbon[22] or reaction with *p*-menthene as the solvent in the presence of 10% palladium on carbon at 170 °C gave only recovered starting material. Catalytic hydrogenation in a high-boiling inert solvent has also been used to convert a nitrile directly to a methyl group.[23] Bubbling H_2 gas through a refluxing solution of **18** in *p*-cymene in the presence of 10% palladium on carbon for 2 h gave a complex mixture. Brown's mild method for the direct transformation of cyano into methyl (ammonium formate/palladium on carbon/methanol, reflux) gave only recovered **18** and unidentified polar materials.[24]

These negative results led to an investigation of alternative electrophilic substitution reactions. Attempted formylation of **7a** with trimethyl orthoformate either in TFA at 40 °C for 3 h, in chloroform with $AlCl_3$ at reflux for 7 h,[25] or neat with polyphosphoric acid at 100 °C for 2 h[26] gave mostly recovered starting

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(26) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591–7599.

material. Modified Gatterman formylation with zinc cyanide/HCl (g) in diethyl ether gave only demetalated starting material **7**.[27] Direct methylation with methyl iodide in chloroform catalyzed by $AlCl_3$ or $SnCl_4$ failed, as did methylation with methyl fluorosulfonate.[28] Finally, **7a** did not react with 1,3-dithienium tetrafluoroborate in refluxing dichloromethane.[29]

Paterson and co-workers have used chloroalkyl sulfides to alkylate silyl enol ethers and lactones. These sulfides have not been previously used to alkylate aromatic compounds, though a related reaction of α-substituted (methylthio)methyl chlorides has been described in the benzene series.[30] Also *meso*-(phenylthio)methyl groups served as the precursors (via Raney Ni reduction) of the *meso*-methyl groups in Eschenmoser and co-workers' synthesis of cobyric acid.[31] In this case, the (phenylthio)methyl groups were introduced by S_N2 displacement on a *meso*-chloromethyl group with benzenethiol. The *meso*-chloromethyl group was introduced by reaction of the corrin with chloromethyl methyl ether. Thus, a new approach for the meso-Bmph-*d* to -*c* conversion was planned. After some experimentation, it was found that addition of a 1.1 M solution of $TiCl_4$ in dichloromethane (0.9 mol equiv) to a solution of 12 equiv of chloromethyl methyl sulfide and 1 equiv of copper(II) methyl mesopyropheophorbide *a* (**7a**) in dry dichloromethane at −15 °C followed by warming to 40 °C for 1 h gave the desired δ-meso-substituted compound **19a** in 74–77% yield after preparative TLC. The reaction was conveniently monitored by the change in the long-wavelength visible absorption from 642 to 654 nm in dichloromethane solution. Addition of the $TiCl_4$ solution at higher temperatures led to large amounts of dichloromethane-insoluble green material. Other Lewis acids such as $ZnBr_2$ or boron trifluoride etherate led to lower yields, while Me_2AlCl was ineffective as catalyst.

Although **19a** was unsuitable for characterization by NMR as the copper(II) complex, a satisfactory elemental analysis was obtained. The mass spectrum showed the parent ion at *m/e* 671, plus a prominent peak at *m/e* 624 due to loss of −SMe. As will be described later, attempted removal of the copper with acid led to the loss of the *meso* substituent and recovery of methyl mesopyropheophorbide *a* (**7**) (NMR and visible spectroscopy).

The desulfurization of **19a** with Raney Ni was next investigated. Heating **19a** in methanol at 70 °C in a sealed flask with 35 mass equiv of an aqueous pH 10 Raney Ni slurry (Aldrich) for 1 h (conditions similar to those reported by Brockmann and co-workers in the desulfurization of a dithioketal in the Bmph-*e* series) gave a mixture of two products which was purified by silica TLC. The green major product (**3a**) had visible absorptions at 650 and 420 nm, similar to those of starting material **19a** at 654 and 424 nm (dichloromethane). The gray–purple minor product was almost certainly a copper(II) isobacteriochlorin as indicated by its striking visible absorption spectrum [dichloromethane, relative absorbance: 600 nm (0.28), 558 (0.10), 486 (0.06), 418 (0.43), 399 (0.49), 390 (0.49)]. Further discussion of this class of compounds is given in the accompanying paper.[32] The use of milder reduction conditions (40 °C, acetone, 1 h) gave very clean desulfurization without production of the copper(II) isobacteriochlorin. A subsequent NMR study (vide infra) showed that the desulfurization of the nickel complex **19b** with 18 mass equiv of Raney Ni is complete in 20 min or less at room temperature.

Demetalation of **3a** proved to be more difficult than anticipated. Treatment for up to 30 h with 10–50% sulfuric acid in TFA or 100% sulfuric acid gave demetalated product **3** in a maximum yield of 25%. However, simply bubbling HCl through a solution of **3a** in dichloromethane for 5 min followed by stirring for several hours gave **3** in 55% yield after preparative TLC. This procedure is clearly preferable to sulfuric acid/TFA and with optimization yields should approach 80%, thus satisfying the original goal of a short, efficient synthesis of meso-Bmph-*c* [Et, Me] from methyl mesopyropheophorbide *a* in 50–60% overall yield. The physical properties of the meso-Bmph-*c* [Et, Me] **3** thus obtained agreed well with those of the same compound synthesized from meso-chlorin e_6 trimethyl ester.[3]

The alkylation of the zinc(II), iron(III), and thallium(III) complexes of **7** was also investigated since these metals are considerably easier to remove than copper. These were uniformly worse than with the copper(II) analogue **7a**. The preparation of Tl(III) complex **7c** by reaction of **7** with 1.2 equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in THF at 50 °C for 1.5 h was attempted. The visible spectrum in dichloromethane (660, 424 nm) indicated metalation. This reaction gave two fractions upon chromatographic workup. Fraction 1 (670, 408 nm) had lost thallium during the chromatography. This became obvious when rechromatography of the green, metal-complexed fraction 2 (662, 426 nm) yielded more of the brown, faster-running fraction 1. The brown color and red-shifted long-wavelength visible absorption of fraction 1 suggested the formation of *meso*-nitro-substituted compound **20**. This was confirmed by NMR (loss of the δ-meso resonance) and mass spectrometry, which showed a parent ion at *m/e* 595, with a prominent fragment ion at *m/e* 549 caused by loss of NO_2. Fraction 2 was most likely δ-*meso*-nitro thallium complex **20b**, but this was not further investigated.

Similar transformations had been observed previously.[11-13,15,33] For example, when zinc(II) etioporphyrin I was treated with $Tl(NO_3)_3$, *meso*-nitroetioporphyrin I was obtained in 58% yield after demetalation. The reaction probably proceeds by oxidation of the macrocycle to a π-cation radical, followed by nucleophilic attack, although the nature of the nucleophilic species (NO_2^- or NO_3^-) is not clear.[13,15,33] The reaction with **7** was repeated by using 1.2 mol equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in THF at room temperature for 1 h. The crude product (652, 418 nm, dichloromethane) was then reacted directly with $TiCl_4$/chloromethyl methyl sulfide. The major product (668, 412 nm) appeared to be metal-free. Raney Ni reduction of this again gave a single major product whose NMR and visible spectra were identical with those obtained in the attempted thallation at 50 °C. Thus, the product was again *meso*-nitro adduct **20**. Apparently **20b** was formed during the thallation at room temperature and subsequently demetalated under the conditions of the methylthiomethylation.

Finally, methyl mesopyropheophorbide *a* (**7**) was treated with 1.3 mole equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in THF at 50 °C for 0.5 h (658, 424 nm), followed by treatment with SO_2 (g), and then concentrated HCl and partitioned between dichloromethane and water. The crude product was chromatographed on silica TLC to give a brown band (41%; 670, 406 nm) whose NMR spectrum was identical with that of **20** previously obtained and a greenish-brown band (668, 414 nm). Further treatment of the second band with concentrated HCl in acetone left its visible spectrum unchanged. The NMR spectrum showed three *meso* protons in the 10–11 ppm region, conversion of the usual two-proton AB quartet for the 10-CH_2 into a two-proton singlet, and replacement of the complex multiplets of the 7a,b-CH_2CH_2 with two triplets. This indicates that the minor product was the porphyrin, phylloerythrin methyl ester (**16**). Major brown band **20** was crystallized from dichloromethane/methanol and fully characterized.

The methylthiomethylation of nickel(II) methyl mesopyropheophorbide *a* (**7d**) gave the desired **19b** in 80–84% yield. The NMR spectrum of **19b** showed a three-proton singlet for the −SMe at 2.36 ppm, and the loss of the highest field δ-*meso* proton. The −CH_2SMe protons occur as two one-proton doublets (J = 14.5 Hz) at 4.83 and 4.41 ppm, the latter considerably broadened. The assignment was verified by decoupling experiments. The Raney Ni reduction of **19b** in acetone at *room temperature* was complete in 20 min as judged by NMR spectroscopy. The −SMe peak at

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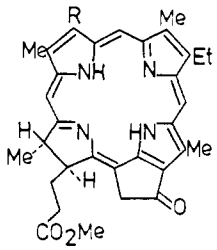
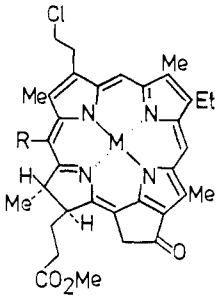
2.36 ppm disappeared, giving rise to a new three-proton singlet for the δ-*meso*-methyl group of **3b** at 3.61 ppm. Though no yield was obtained for the desulfurization, the reaction was very clean by NMR and TLC analysis. Reaction with Raney Ni under more forcing conditions (methanol, 70 °C, or THF, room temperature, 1 atm of H_2) also gave a product similar to that observed with copper(II) complex **19a**, that is, a nickel(II) δ-*meso*-methyl isobacteriochlorin, plus nickel(II) 9-deoxo-Bmph-*c* [Et, Me] and nickel(II) hexahydroporphyrins. These products are described in the accompanying paper.[32]

Attempted demetalation of a small sample of **19a** with 20% concentrated sulfuric acid in TFA for 1 h at 0 °C followed by preparative silica TLC gave methyl mesopyropheophorbide *a* (**7**) as the major product. This assignment is based on the visible spectrum and TLC comparison with an authentic sample. Thus, it appears that the $-CH_2SMe$ group of the copper(II) complex **19a** is easily lost under acidic conditions. One attempt to demetalate **19b** with zinc cyanide and HCl (g) in dichloromethane led to quantitative recovery of starting material. Experience with nickel(II) methyl δ-*meso*-methyl-9-deoxomesopyropheophorbide *a* and nickel(II) methyl 9-deoxomesopyropheophorbide *a* suggested[32] that demetalation would proceed with 1,2-ethanedithiol in TFA,[34] but attempts to carry out this reaction resulted in formation of the dithioketal at the 9-position. Difficulties in removal of the dithioketal eventually required (vide infra) a change to the corresponding copper(II) chelates, this metal being readily removed with HCl gas in dichloromethane.

Direct Partial Synthesis of Bmph-*c* [Et, Me] (4). Two attempts to alkylate nickel(II) methyl pyropheophorbide *a* (**9d**) with $TiCl_4$/chloromethyl methyl sulfide under the standard conditions did not lead to recognizable products. On the assumption that reaction of the alkylating reagent with the 2-vinyl group was causing the problems, the 2-vinyl group was first protected as the 2-(2-chloroethyl) group by using the thallium(III) procedure[35] in the following synthesis of Bmph-*c* [Et, Me] (**4**).

Treatment of methyl pyropheophorbide *a* (**9**) with 2.2 mol equiv of $Tl(NO_3)_3 \cdot 3H_2O$ in methanol and removal of chelated thallium gave the dimethoxyacetal **21**. Aqueous acid treatment then gave





21 R=$CH_2CH(OMe)_2$
22 R=CH_2CHO
23 R=CH_2CH_2OH
24 R=CH_2CH_2Cl
28 R= $CH{=}CH_2$

25 R=H, M=2H
26 R=$MeSCH_2$, M=2H
27 R=Me, M=2H
c, M=Cu
d, M=Ni

the aldehyde **22**, which was immediately reduced with sodium borohydride to give the 2-(2-hydroxyethyl) derivative **23**. This was transformed into the 2-(2-chloroethyl) compound **24** in 72% yield by treatment with benzoyl chloride in dimethylformamide. With the vinyl group adequately protected, nickel(II) was inserted to give **25b** (85%) and this was treated with titanium tetrachloride and chloromethyl methyl sulfide, as discussed previously, to give a 60% yield of the *meso*-substituted nickel(II) complex **26b**. With Raney Ni in acetone, **26b** gave the corresponding *meso*-methyl derivative **27b** in 64% yield. Attempts to remove nickel were unsuccessful under a variety of conditions; in the best procedure developed (using H_2S), less than 10% demetalation of the nickel complex to give **27** was observed. The nickel could be removed by using ethanedithiol and TFA, but the resulting metal-free compound possessed a dithioketal at the 9-carbonyl, and attempts to cleave this in high yield were disappointing. Thus, the entire procedure, from the 2-(2-chloroethyl)pyropheophorbide **24**, was repeated, but by using copper(II) instead of nickel(II) as the chelating metal. The copper(II) 2-(2-chloroethyl) derivative **25a** was treated with titanium tetrachloride and chloromethyl methyl sulfide and gave a 69% yield of the adduct **26a**. Raney Ni reduction of **26a** gave a 59% yield of the copper(II) *meso*-methylchlorin **27a** which was demetalated in 55% yield by using HCl (g) in dichloromethane to give the required metal-free 2-(2-chloroethyl) derivative **27**. Comparison of this material with that previously synthesized by using the longer, alternate route,[6] formally completed the synthesis of Bmph-*c* [Et, Me] (**4**), since treatment of **27** with base, followed by rehydration of the resulting 2-vinyl compound **28** with HBr in acetic acid, gives the chromatographically separable 2-(*R*)- and 2-(*S*)-(1-hydroxyethyl) compounds.

Experimental Section

Melting points, which are uncorrected, were measured on a Thomas/Bristoline microscopic hot-stage apparatus. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer by using solutions in dichloromethane, and mass spectra were measured on a Finnigan 3200 spectrometer (direct insertion probe, 70 eV, 50 μA, source temperature from 200 to 300 °C). Proton NMR spectra were obtained at 360 MHz on a Nicolet NT-360 spectrometer; the chemical shifts are reported relative to $CHCl_3$ at 7.260 ppm. The phrase "dried and evaporated" means drying with sodium sulfate, followed by evacuation with a Buchi rotary evaporator under house or oil pump vacuum. Elemental analyses were determined by the Microchemical Analysis Laboratory at the University of California, Berkeley.

Reactions were monitored by thin-layer chromatography (TLC) by using cut strips (approximately 2 cm by 6 cm) of E. Merck silica gel 60 F254 precoated (0.25-mm thickness) plastic-backed sheets. Preparative TLC was performed on freshly prepared 20 cm by 20 cm TLC plates of ca. 1 mm thick E. Merck silia gel GF 254 and 60 G. Plates were activated prior to use by heating at 150 °C for at least 8 h. Two types of packing material were employed in column chromatography; E. Merck neutral alumina (70–230 mesh) and Merck silica gel 60. The alumina was deactivated with either 6% H_2O (Brockmann Grade III) or 15% H_2O (Brockmann Grade V) before use. A 250-mL J. T. Baker column was used for flash chromatography. Medium-pressure liquid chromatography utilized an FMI Model RPG150 pump, an Altex rotary injection valve, and a 1000-mm Altex glass chromatography column. Analytical high-performance liquid chromatography (HPLC) was performed on a Waters Assoc. instrument equipped with a Model 6000A solvent delivery system, a Valco Model C6U injector, and a Perkin-Elmer LC55B variable wavelength detector. A Waters stainless steel semipreparative μ-Bondapak C-18 column (reverse phase, 7.8 mm × 250 mm, 10 μm particle size) or the Waters Z-Module system equipped with a 10-μm C-18 reverse-phase cartridge was used. The solvent systems used are specified where appropriate. All solvents were reagent grade and were filtered through a 0.45-μm Millipore filter before use. The house deionized water was distilled before use. Preparative HPLC was performed on a Waters Prep-500A chromatograph by using either C-18 reverse-phase or silica cartridges. An ISCO Model 1840 variable wavelength absorbance monitor was used for detection. The samples, but not the solvents, were filtered through 0.45-μm filters before injection.

Methyl Pheophorbide *a* (8) from Spirulina Maxima. Approximately 500 g of dried *Spirulina maxima* alga was slurried in 2 L of acetone and then liquid nitrogen was added to form a frozen slush. This was transferred to a three-neck 5-L round-bottom flask and heated to reflux under nitrogen with mechanical stirring for 2 h. The supernatant was then filtered through Whatman filter paper on a Buchner funnel and more acetone added to the solid. The extraction and filtration process was repeated 2 more times. (Even though the solid remains dark green, the yield of pigment obtained from further extraction was low.) The green filtrate was evaporated and then purified by flash chromatography on Grade V neutral alumina, eluting first with *n*-hexane to remove a fast-running yellow band, with dichloromethane to remove the major blue-gray pheophytin *a* band, and finally with 97/3 dichloromethane/THF to remove some bright-green magnesium containing pigments. Treatment of the pheophytin *a* fraction with 500 mL of 5% sulfuric acid in methanol (degassed by bubbling with nitrogen) for 12.5 h at room temperature in the dark under nitrogen followed by dilution with dichloromethane, rinsing with water and then 10% saturated aqueous sodium

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bicarbonate, drying the organic layer, evaporation, and recrystallization of the reside from dichloromethane/methanol gave methyl pheophorbide *a* (**8**) (1.8 g): mp 206 °C [lit.[36] 228, lit.[18] 224–226 °C]; UV λ_{max} (Et_2O) 666 nm (ϵ 5.84 × 10^4), 610 (7.50 × 10^3), 532 (9.87 × 10^3), 504 (1.23 × 10^4), 406 (1.22 × 10^5) [lit.[37] 667 nm (5.92 × 10^4), 408.5 (1.22 × 10^5)]; UV λ_{max} (CH_2Cl_2) 668 nm (ϵ 4.46 × 10^4), 610 (8.62 × 10^3), 538 (9.71 × 10^3), 506 (1.08 × 10^4), 412 (1.06 × 10^5); NMR (360 MHz, $CDCl_3$) 9.52 (s, β-meso H), 9.40 (s, α-meso H), 8.58 (s, δ-meso H), 8.03 (X of ABX, 2a-H), 6.29, 6.16 (AB of ABX, 2b and 2b′-H), 6.26 (s, 10-CH_2), 4.46 (q, 8-H), 4.20 (d, 7-H), 3.88 (s, 10-CO_2Me), 3.70 (q, J = 7.6 Hz, 4a-CH_2), 3.68 (s, 7d-OMe), 3.57 (s, 5-Me), 3.41 (s, 1-Me), 3.25 (s, 3-Me), 2.64 (7a-H), 2.32 (7a′-H), 2.52 (7b-H), 2.23 (7b′-H), 1.69 (t, J = 7.6 Hz, 4b-Me), 1.81 (d, J = 7.3 Hz, 8-Me), 0.53, −1.67 (each br s, NH).

Alternatively, pheophytin *a* could be selectively hydrolyzed to the 7-propionic acid with degassed TFA/H_2O (80/20) at 0 °C for 1 h without affecting the 10-carbomethoxy group.[38] The acid was then treated with ethereal diazomethane to give methyl pheophorbide *a* (**8**). This procedure worked well on a small scale. If only methylpyropheophorbide *a* (**9**) was desired, it was found simplest to evaporate the acetone algal extract and reflux this in 2,4,6-trimethylpyridine (collidine) for 5–6 h under nitrogen to give pyropheophytin *a*. Evaporation of the collidine on a Kügelrohr apparatus under high vacuum followed by treatment with 5% sulfuric acid/methanol and the standard aqueous basic workup gave crude methyl pyropheophorbide *a* (**9**), which was purified by column chromatography on alumina or silica. This procedure has the advantage that the troublesome β-ketoester functionality of pheophytin *a* which is responsible for the formation of allomerization side products is removed before transesterification and chromatography. On a large scale, it is important to carry out the pyrolysis in collidine for at least 5–6 h, since it is quite difficult to separate unreacted methyl pheophorbide *a* from the desired methyl pyropheophorbide *a* (**9**) on a large scale. The reaction is also difficult to monitor since the visible absorption spectra of **8** and **9** are similar.

Methyl Pyropheophorbide *a* (9). Methyl pheophorbide *a* (**8**) (0.821 g) was dissolved in 80 mL of collidine and stirred at reflux for 1.5 h under nitrogen in the dark. The collidine was removed by Kügelrohr distillation (65 °C bath, 2.5 mmHg). The residue was crystallized from dichloromethane/methanol to give methyl pyropheophorbide *a* (**9**) (0.741 g, 93%): mp 217–219 °C [lit.[39] 220–225 °C]; UV λ_{max} (CH_2Cl_2) 668 nm (ϵ 4.71 × 10^4), 610 (8.53 × 10^3), 538 (9.85 × 10^3), 508 (1.15 × 10^4), 410 (1.13 × 10^5); UV λ_{max} (dioxane) 670 nm (ϵ 5.21 × 10^4), 610 (1.13 × 10^4), 536 (1.29 × 10^4), 508 (1.58 × 10^4), 410 (1.13 × 10^5) [lit.[40] (dioxane) 668 (5.56 × 10^4), 536 (9.9 × 10^3), 507 (1.23 × 10^4), 412 (1.25 × 10^5)]; NMR (360 MHz, $CDCl_3$; 7.1 mmol) 9.52 (s, β-meso H), 9.40 (s, α-meso H), 8.56 (s, δ-meso H), 8.02 (X of ABX, 2a-H), 6.29, 6.18 (AB of ABX, 2b and 2b′-H), 5.27, 5.11 (AB q, 10-CH_2, J = 20.0 Hz), 4.49 (m, 8-H, $J_{7,8}$ = 2.1, $J_{8,8a}$ = 7.3 Hz), 4.30 (m, 7-H), 3.70 (q, J = 7.6 Hz, 4a-CH_2), 3.61 (s, 7d-OMe), 3.68 (s, 5-Me), 3.41 (s, 1-Me), 3.25 (s, 3-Me), 2.70 (7a-H), 2.31 (7a′-H), 2.56 (7b-H), 2.29 (7b′-H), 1.70 (t, J = 7.6 Hz, 4b-Me), 1.81 (d, J = 7.3 Hz, 8-Me), 0.48, −1.67 (each br s, NH).

Methyl Mesopyropheophorbide *a* (7). Methyl pyropheophorbide *a* (**9**) (0.633 g) was dissolved in 70 mL of distilled acetone and hydrogenated at 15 psi of H_2 over 240 mg of 10% palladium on carbon for 1 h at room temperature on a Parr apparatus. Crystallization from dichloromethane/methanol gave **7** (0.500 g, 79%). The mother liquors were evaporated to give a further 75 mg (12%): mp 237–238 °C [lit.[41] 239 °C, lit.[18] 239–242 °C]; UV λ_{max} (CH_2Cl_2) 656 nm (ϵ 5.47 × 10^4), 602 (1.06 × 10^4), 534 (1.19 × 10^4), 502 (1.23 × 10^4), 408 (1.36 × 10^5); UV λ_{max} (dioxane) 656 nm (ϵ 5.27 × 10^4), 602 (8.10 × 10^3), 532 (9.65 × 10^3), 502 (1.10 × 10^4), 408 (1.15 × 10^5) [lit.[40] (dioxane) 655 (5.88 × 10^4), 600 (8.64 × 10^3), 532 (1.02 × 10^4), 502 (1.14 × 10^4), 407 (1.35 × 10^5); NMR (360 MHz, $CDCl_3$) 9.47 (s, β-meso H), 9.20 (s, α-meso H), 8.45 (s, δ-meso H), 5.24, 5.09 (AB q, J = 19.9 Hz, 10-CH_2), 4.45 (d of q, 8-H, $J_{7,8}$ = 2.1 Hz), 4.27 (d of t, 7-H), 3.83 (q, J = 7.6 Hz, 2a-CH_2), 3.68 (q, J = 7.5 Hz, 4a-CH_2), 3.66 (s, 5-Me), 3.61 (s, 7d-OMe), 3.29 (s, 1-Me), 3.25 (s, 3-Me), 2.64–2.74 (m, 2 H), 2.50–2.60 (m, 1 H), 2.22–2.36 (m, 1 H, 7a,b-CH_2CH_2), 1.80 (d, J = 7.3 Hz, 8-Me), 1.73, 1.70 (each t, J = 7.6 Hz, 2b- and 4b-Me), 0.63, −1.60 (each br s, NH).

Copper(II) Methyl 9,10-Didehydro-9-chloro-10-formylmesopyropheophorbide *a* (11). To a two-neck 100-mL round-bottom flask equipped with stir bar and reflux condenser under nitrogen was added 8 mL of dry 1,2-dichloroethane followed by 0.42 mL of $POCl_3$ and then 0.35 mL of DMF. The colorless solution was stirred for 15 min at a 50 °C bath temperature. Then 33 mg of copper(II) methyl mesopyropheophorbide *a* (**7a**) dissolved in 18 mL of 1,2-dichloroethane was added over 10 min. The reaction was then kept at 50 °C for 40 min, whereupon TLC showed no starting material remaining. The reaction mixture was chilled on an ice bath and then added to a stirred solution of 100 mL of ice-cold saturated aqueous sodium acetate. Then solid sodium bicarbonate was added and the two-phase system stirred vigorously for 6.5 h. The organic phase was then separated, rinsed with water, dried, and evaporated. The crude product was purified by preparative TLC (95/5 dichloromethane/THF). Four green bands were obtained; the major, fastest-running band gave the title compound (R_f = 0.58). None of the other bands were starting material, as evidenced by their visible absorption spectra. Compound **11** was recrystallized from dichloromethane/methanol: mp 211–213 °C; UV λ_{max} 626 nm (ϵ 1.46 × 10^4), 440 (6.23 × 10^4), 3.59 (6.70 × 10^4); IR ν_{max} (CH_2Cl_2 solution, cm^{-1}) 1733, 1651, 1633, 1600, 1566. MS, *m/e* (%) 661 (97%), 659 (100), 658 (100), 657 (71), 625 (18), 624 (20), 623 (25). Anal. Calcd for $C_{35}H_{35}ClCuN_4O_3$: C, 63.82; H, 5.36; N, 8.51. Found: C, 63.68; H, 5.42; N, 8.40.

9-Trimethylene Dithioketal (13) of Methyl Mesopyropheophorbide *a*. Methyl mesopyropheophorbide *a* (**7**) (1.14 g, 2.11 mmol) was dissolved in 100 mL of acetic acid in a 300-mL round-bottom flask. To this was added 1.3 mL of 1,3-propanedithiol (13.0 mmol) and 1.3 mL of boron trifluoride etherate (13.0 mmol). This solution was stirred under nitrogen at a 50 °C bath temperature in the dark for 4 h. The reaction mixture was then poured into 1 L of iced saturated aqueous sodium bicarbonate. This mixture was divided into two portions and extracted with dichloromethane (1 L). The organic extracts were divided into two portions and each was rinsed 2 × 250 mL with iced saturated aqueous sodium carbonate. The organic layers were dried and evaporated. The residue was recrystallized from dichloromethane/methanol to give an analytically pure green solid, yield 1.18 g (88%): mp 178–182 °C; UV λ_{max} 644 nm (ϵ 4.43 × 10^4), 590 (4.29 × 10^3), 524 (3.25 × 10^3), 496 (1.35 × 10^4), 396 (1.69 × 10^5); MS, *m/e* (%) 641 (89%, M^+), 566 (90), 535, 100, bp, $M^+ - S(CH_2)_3S-$); IR ν_{max} (CH_2Cl_2 solution, cm^{-1}) 1734, 1619; NMR (360 MHz, $CDCl_3$) 9.72, 9.68 (each s, α- and β-meso H), 8.85 (s, δ-meso H), 5.74, 5.68 (AB q, J = 15.7 Hz, 10-CH_2), 4.66 (d of q, $J_{7,8}$ = 2.0 Hz, 8-H), 4.44 (m, 7-H), 4.02 and 3.85 (each q, 2 H each, J = 7.6 Hz, 2a- and 4a-CH_2), 3.63 (s, 7-OMe), 3.76, 3.46, 3.44 (each s, 1-, 3-, and 5-Me), 3.72–3.79, 3.17–3.26, 2.38–2.51 (each m, 2 H each, $S(CH_2)_3S$); 2.77–2.80, 2.51–2.66, 2.29–2.40 (each m, 7a,b CH_2CH_2), 1.85 (d, J = 7.3 Hz, 8-Me), 1.80 and 1.77 (each t, J = 7.6 Hz, 2b- and 4b-Me), −1.31, −3.30 (each br s, NH). Anal. Calcd for $C_{37}H_{44}N_4O_2S_2$: C, 69.34; H, 6.92; N, 8.74. Found: C, 69.09; H, 6.77; N, 8.58.

Copper(II) Trimethylene Dithioketal (13a) of Methyl Mesopyropheophorbide *a*. Dithioketal **13** (160 mg) was dissolved in 10 mL of dichloromethane, and 3 mL of a saturated solution of $Cu(OAc)_2 \cdot H_2O$ in methanol was added. The resulting solution was heated at a 50 °C bath temperature for 1 h under nitrogen. At this point, the reaction was approximately 50% complete (TLC and visible spectrum). $Cu(OAc)_2$ solution (2 mL) was added, and heating continued for 3.5 h, at which point reaction was complete. The solvent was evaporated and the residue crystallized from dichloromethane/methanol, yield 132 mg (75%): TLC (95/5 dichloromethane/THF) **13**, R_f = 0.54, **13a**, R_f = 0.61; mp 205–206 °C; UV λ_{max} (rel absorbance) 618 nm (34.9), 574 (5.2), 530 (1.8), 496 (4.2), 402 (100); IR ν_{max} (CH_2Cl_2 solution, cm^{-1}) 1731 (−CO_2Me), 1640.

Methyl δ-*meso*-Cyanomesopyropheophorbide *a* (18). Copper(II) methyl mesopyropheophorbide *a* (**7a**) (100 mg, 0.16 mmol) and 110 mg of potassium carbonate were placed in a 50-mL two-neck round-bottom flask equipped with a stir bar, addition funnel, and reflux condenser under nitrogen. To this was added 10 mL of chloroform, and the solution was heated to reflux. Then a solution of 60 μL of $SnCl_4$ (0.49 mmol, 3 equiv) and 350 mg of cyanogen bromide (3.3 mmol, 20 equiv) in 5 mL of chloroform was added over 5 min. The solution was then refluxed for 8 h and 45 min. The long-wavelength absorption in the visible spectrum (CH_2Cl_2) went from 642 to 652 nm after 7 h, at which point it did not change further. The cooled reaction mixture was poured into a mixture of dichloromethane and saturated aqueous sodium bicarbonate. After shaking, the organic layer was withdrawn, rinsed with water, dried, and evaporated. The crude reaction mixture was demetalated by treatment with 25 mL of (90/10 v/v) TFA/concentrated sulfuric acid in the dark at room temperature with nitrogen bubbled through the solution for 2

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h. The solution was then poured into 100 mL of ice–water, neutralized with saturated aqueous sodium carbonate, and extracted with dichloromethane. The organic layers were dried and evaporated. TLC showed polar material, so the residue was dissolved in dichloromethane and treated with excess diazomethane. The crude product was purified by preparative TLC on silica, eluting with 97/3 dichloromethane/THF. The major band, $R_f = 0.42$, was recrystallized from dichloromethane/methanol to give the title compound as purple needles, 46 mg (49%). This compound suffered decomposition (loss of the *meso*-cyano group) on prolonged storage at room temperature as judged by NMR spectroscopy: mp 166 °C; UV λ_{max} 672 nm (ϵ 5.91 × 10^4), 614 (1.11 × 10^4), 562 (4.39 × 10^3), 538 (1.74 × 10^4), 504 (1.06 × 10^4), 474 (5.38 × 10^3), 406 (1.38 × 10^5); MS, *m/e* (%) 575 (57%, M^+), 550 (14, $M^+ - CN$), 488 (50, $M^+ - CH_2CH_2CO_2Me$), 460 (17), 251 (100, bp); IR ν_{max} ($CHCl_3$ solution, cm^{-1}) 2251 (s, CN), 1726 (CO_2Me), 1684 (9-C=O); NMR (360 MHz, $CDCl_3$) 9.42, 9.30 (each s, α- and β-meso H), 5.15, 5.09 (AB q, $J = 20.0$ Hz, 10-CH_2), 4.70 (m, 8-H), 4.16 (m, 7-H), 3.82 (q, $J = 7.6$ Hz), and 3.62 (q, part obscured, $J = 7.5$ Hz, 2a- and 4a-CH_2), 3.62 (s, 7d-OMe), 3.59, 3.51, 3.20 (each s, 1-, 3-, 5-Me), 2.62 (7b-H), 2.53 (7a-H), 2.30 (7b′-H), 2.13 (7a′-H), 1.72 (d, $J = 7.0$ Hz, 8-Me), 1.70, 1.66 (each t, 2b- and 4b-Me), −0.65 (br s, NH). Anal. Calcd for $C_{35}H_{37}N_5O_3$: C, 73.02; H, 6.48; N, 12.16. Found: C, 73.08; H, 6.67; N, 11.82.

Methyl δ-*meso*-Nitromesopyropheophorbide *a* (20). Methyl mesopyropheophorbide *a* (**7**) (77 mg) and $Tl(NO_3)_3 \cdot 3H_2O$ (82 mg, 1.3 equiv) were dissolved in 17 mL of dry THF and heated at a 50 °C bath temperature under Ar in dim light for 30 min. At this point, the visible spectrum of an aliquot in dichloromethane showed peaks (absorbance) at 658 (0.71) and 424 (1.78) nm. The reaction was allowed to cool and then bubbled vigorously with SO_2 (g) for 2 min. Then dichloromethane and 15 drops of concentrated HCl were added. The mixture was poured into water and shaken (green turns to brown). The organic layer was removed, rinsed with water, dried, and evaporated. The visible spectrum of the crude product showed peaks at 670 (0.59) and 410 (1.82) nm (CH_2Cl_2). The product was purified by silica TLC, eluting with 97/3 dichloromethane/THF to give two major products. The faster-running brown band [$R_f = 0.4$; 670 nm (0.11), 408 (0.29)] was the desired *meso*-nitro compound **20**. The slower-running greenish-brown band [$R_f = 0.3$; 668 nm (0.18), 416 (1.32)] was dissolved in ca. 20 mL of acetone and treated with 15 drops of concentrated HCl with stirring for 15 min. The reaction mixture was diluted with dichloromethane, rinsed twice with water, dried, evaporated, and chromatographed as before. Some faster-running brown material (670, 406 nm) was obtained, but the major product was still greenish-brown material [668 nm (0.17), 586 (0.08), 562 (0.097), 522 (0.08), 416 (1.25)]. NMR of this material indicated that it was the porphyrin, phylloerythrin methyl ester (**16**) (see text). The major brown band was crystallized from dichloromethane/methanol to give **20**, (27 mg, 32%); mp 145–146 °C; UV λ_{max} 670 nm (ϵ 4.81 × 10^4), 614 (9.29 × 10^3), 540 (1.39 × 10^4), 506 (1.16 × 10^4), 484 (8.06 × 10^3), 476 (8.09 × 10^3), 408 (1.13 × 10^5); MS, *m/e* (%) 595 (100%, bp, M^+), 566 (10), 565 (13), 550 (16, $M^+ - NO_2$); NMR (500 MHz, $CDCl_3$, 38 mM) 9.452, 9.443 (each s, meso H), 5.18, 5.14 (AB q, $J = 19.6$ Hz, 10-CH_2), 4.74 (m, 8-H), 4.24 (m, 7-H), 3.83 (q) and 3.61 (obscured q, 2a- and 4a-CH_2), 3.59 (s, 7d-OMe), 3.60, 3.22, 3.10 (1-, 3-, 5-Me), 2.62 (7-H), 2.53 (7a-H), 2.19 (7a′-H), 2.17 (7b′-H), 1.71 and 1.67 (each t, $J = 7.7$ Hz, 2b- and 4b-Me), 1.53 (b, $J = 7.2$ Hz, 8-Me), 0.89, −1.85 (each br s, NH). Anal. Calcd for $C_{34}H_{37}N_5O_5$: C, 68.55; H, 6.26; N, 11.76. Found: C, 68.16; H, 6.30; N, 11.89.

Copper(II) Methyl δ-*meso*-[(Methylthio)methyl]mesopyropheophorbide *a* (19a). Copper(II) methyl mesopyropheophorbide *a* (**7a**) (207 mg, 0.33 mmol) was dissolved in 20 mL of dry dichloromethane, treated with chloromethyl methyl sulfide (0.3 mL, 4.75 mmol, 14.4 equiv), and cooled to −15 °C on an ethylene glycol/dry ice bath. Then 0.25 mL (0.26 mmol) of a 1.1 M solution of $TiCl_4$ in dichloromethane (Alfa) was added dropwise by syringe. The solution was allowed to warm to room temperature by removing the bath. After 1 h, the Q_y band in the visible spectrum had shifted from 640 to 644 nm. The mixture was then heated on a 40 °C bath for 1 h (656 nm). The reaction mixture was then rinsed with saturated aqueous sodium bicarbonate, and the organic layers were dried and evaporated. The crude product was purified by flash chromatography on silica, eluting with 94/6 dichloromethane/THF. The major product (**19a**) (169 mg, 74%) was isolated: mp (from CH_2Cl_2/*n*-hexane) 114–116 °C; UV λ_{max} 654 nm (ϵ 5.39 × 10^4), 608 (1.20 × 10^4), 560 (6.60 × 10^3), 514 (3.51 × 10^3), 424 (8.80 × 10^4); MS, *m/e* (%) 671 (6.5%, M^+), 624 (29, $M^+ - SMe$), 611 (8, $M^+ - CH_2SMe$). Anal. Calcd for $C_{36}H_{40}CuN_4O_3S$: C, 64.31; H, 6.00; N, 8.33 ($+{}^1/_2H_2O$ requires: C, 63.46; H, 6.06; N, 8.22). Found: C, 63.45; H, 5.97; N, 8.04.

Methyl Mesobacteriopheophorbide *c* [Et, Me] (3). Copper(II) methyl δ-*meso*-[(methylthio)methyl]mesopyropheophorbide (**19a**) (155 mg) was dissolved in acetone and treated with 2.37 g of Raney Ni slurry at 40 °C in a stoppered flask with vigorous stirring for 1 h. The catalyst was filtered off, and the solution was diluted with dichloromethane and rinsed with water. The organic layer was dried and evaporated. The residue was dissolved in a mixture of 40 mL of 1:1 dry diethyl ether/dichloromethane (dichloromethane alone is also satisfactory), and HCl (g) was bubbled vigorously through the solution for 5 min. The reaction mixture was then stirred in the stoppered flask for 1 h at room temperature. The flask was then opened carefully and poured into iced saturated aqueous sodium acetate/dichloromethane. Then saturated aqueous sodium bicarbonate was added to the vigorously stirred solution to neutralize. The organic layer was separated, dried, and evaporated. The crude product was purified by silica TLC, eluting with 95/5 dichloromethane/THF to give **3** (73 mg, 56%). A faster-running brown band (2.7 mg) and two slower-running brown bands (4 and 5 mg) were also collected. The visible spectra of all four bands were similar (666–668, 412–416 nm), but the minor bands were not identified. The major product, **3**, could be precipitated from methanol to give a solid (52 mg): mp 157 °C (lit.[3] 158–165 °C); UV λ_{max} 664 nm (ϵ 4.38 × 10^4), 606 (8.3 × 10^3), 546 (1.14 × 10^4), 532 (8.28 × 10^3), 506 (9.45 × 10^3), 408 (1.28 × 10^5) [lit.[3] 665 nm (ϵ 4.86 × 10^4), 607 (7.7 × 10^3), 547 (1.37 × 10^4), 514 (9.4 × 10^3), 412 (1.14 × 10^5)]; MS, *m/e* (%) 564 (100%, M^+), 550 (35, $M^+ - Me$), 477 (27, $M^+ - CH_2CH_2CO_2Me$), 463 (15); NMR (360 MHz, $CDCl_3$) 9.47, 9.36 (each s, α- and β-meso H), 5.26, 5.21 (AB q, $J = 19.8$ Hz, 10-CH_2), 4.58 (m, 8-H), 4.19 (m, 7-H), 3.90 (s, δ-meso-Me), 3.72 and 3.92 (each q, 2H each, $J = 7.7$ Hz, 2a- and 4a-CH_2), 3.68 (s, 7d-OMe), 3.58, 3.43, 3.30 (each s, 1-, 3-, 5-Me), 2.48–2.53 and 2.15-2.21 (each m, 2 H each, 7a,b-CH_2CH_2), 1.720 and 1.708 (each t, $J = 7.7$ Hz, 2b- and 4b-Me), 1.52 (d, $J = 7.0$ Hz, 8-Me), −1.65 (br s, NH). Anal. Calcd for $C_{35}H_{40}N_4O_3$: C, 74.44; H, 7.14; N, 9.92 ($+H_2O$ requires: C, 73.27; H, 7.20; N, 9.77). Found: C, 73.30; H, 6.92; N, 9.82.

Nickel(II) Methyl δ-*meso*-[(Methylthio)methyl]mesopyropheophorbide *a* (19b). Nickel(II) methyl mesopyropheophorbide *a* (**7d**) (518 mg, 0.85 mmol) was dissolved in 25 mL of dry dichloromethane in a three-neck 100-mL round-bottom flask equipped with a stir bar under Ar. Chloromethyl methyl sulfide (0.81 mL, 11.7 equiv) was introduced, and the solution was cooled to −15 °C on an ethylene glycol/dry ice bath. Then, 0.81 mL (0.88 mmol) of a 1.1 M solution of $TiCl_4$ in dichloromethane was added dropwise. The cooling bath was removed and the solution allowed to warm to room temperature over 1.5 h. The Q_y absorption shifted from 640 to 652 nm during this period. To ensure completion, the reaction was then heated at a 40 °C bath temperature for 0.5 h. The visible spectrum did not change appreciably. TLC (97/3 dichloromethane/THF) showed the desired bright-green **19b**, $R_f = 0.25$, plus two minor green spots at $R_f = 0.1$ and some base-line material. The crude reaction mixture was rinsed with saturated aqueous sodium bicarbonate, dried, evaporated, and purified by flash chromatography on silica, eluting with 97/3 dichloromethane/THF to give **19b** (459 mg, 81%): mp 216–218 °C; UV λ_{max} 654 nm (ϵ 5.84 × 10^4), 570 (7.45 × 10^3), 560 (7.51 × 10^3), 506 (4.05 × 10^3), 422 (7.53 × 10^4), 406 (6.65 × 10^4); MS, *m/e* (%) 668 (7%), 667 (4), 666 (16, M^+), 622 (33), 621 (42), 620 (21), 619 (100, bp, $M^+ - SMe$), 517 (14); NMR (360 MHz, $CDCl_3$) 9.17, 8.84 (each s, α- and β-meso H), 4.87 (q, 8-H), 4.84, 4.63 (AB q, $J = 19.7$ Hz, 10-CH_2), 4.83 (d, 1 H, $J = 12.5$ Hz), and 4.41 (br d, 1 H, CH_2SMe), 3.80 (t, 7-H, $J_{7,7a} = J_{7,7a'} = 7.3$, $J_{7,8} < 1$ Hz), 3.64 (s, 7d-OMe), 3.53–3.57 (each q, 4 H, 2a- and 4a-CH_2), 3.43, 3.38, 3.09 (each s, 1-, 3-, 5-Me), 2.36 (s, 3 H, SMe), 2.39–2.5 (m, 2 H), 2.13–2.19 (m, 1 H), 2.02–2.09 (m, 1 H, 7a,b-CH_2CH_2); 1.57 (each overlapping t, $J = 7.5$ Hz, 2b- and 4b-Me), 1.22 (d, $J = 6.9$ Hz, 8-Me). Anal. Calcd for $C_{36}H_{40}N_4NiO_3S$: C, 64.87; H, 6.05; N, 8.40. Found: C, 64.90; H, 6.09; N, 8.57.

Nickel(II) Methyl Mesobacteriopheophorbide *c* [Et, Me], (3b). Nickel(II) methyl *meso*-[(methylthio)methyl]mesopyropheophorbide *a* (**19b**) (21.4 mg) was dissolved in acetone and treated with 377 mg of Raney Ni slurry at room temperature in a stoppered flask for 95 min. Aliquots were removed at 20, 40, and 95 min. Each aliquot was filtered, diluted with dichloromethane, and rinsed with water. The organic phase was dried and evaporated. NMR spectra of the aliquots showed that the reaction had gone to completion after 20 min: NMR (360 MHz, $CDCl_3$) 9.16, 8.82 (each s, α- and β-meso H), 4.86, 4.63 (AB q, $J = 19.6$ Hz, 10-CH_2), 4.28 (q, 8-H), 3.81 (pseudo-t, 7-H), 3.61 (s, 7d-OMe), 3.54 (each overlapping q, 2 H each, 2a- and 4a-CH_2), 3.44 (s, δ-*meso*-Me), 3.22 (s, 5-Me), 3.10 (s, 6 H, 1- and 3-Me), 2.27–2.43 (m, 2 H, 7b-CH_2), 2.11–2.20 (m, 7a-H), 1.95–2.04 (m, 7a′-H), 1.567, 1.573 (each t, 2b- and 4b-Me), 1.21 (d, $J = 6.9$ Hz, 8-Me).

Compound **3b** was also prepared directly from **7d** without characterization of the intermediate *meso*-methylthiomethyl compound **19b**. In this case, nickel(II) methyl mesopyropheophorbide *a* (**7d**) (61 mg) was dissolved in 25 mL of dry dichloromethane. Then, 0.1 mL of chloromethyl methyl sulfide was added and the solution cooled to −15 °C on an ethylene glycol/dry ice bath. Then, 0.1 mL (0.11 mmol, 1.1 equiv) of a 1.1 M solution of $TiCl_4$ in dichloromethane was added. The solution

was allowed to warm to room temperature by removing the bath. After 1 h, the Q_y band had shifted from 640 to 648 nm (CH_2Cl_2). The mixture was then heated at a 40 °C bath temperature for 0.5 h, whereupon the Q_y absorption increased to 652 nm. The reaction mixture was then rinsed with 50% saturated aqueous sodium bicarbonate solution, dried, and evaporated. Purification by silica TLC, eluting with 97/3 dichloromethane/THF, gave a major green band of **19b** (44 mg, 66%), which was dissolved in ca. 20 mL of acetone and heated at a 40 °C bath temperature in a closed flask with 1.27 g of Raney Ni slurry under vigorous stirring for 1 h. The catalyst was then filtered off on a sintered glass funnel and rinsed well with acetone and dichloromethane. The solution was washed with water, dried, and evaporated to give 37 mg (90%) of **3b** plus 0.4 mg of a nickel(II) isobacteriochlorin mixture. The analytical sample of **3b** was recrystallized from dichloromethane/methanol: mp 206–207 °C; UV λ_{max} 652 nm (ϵ 4.39 × 10^4), 566 (6.78 × 10^3), 484 (2.76 × 10^3), 422 (6.50 × 10^4); MS, *m/e* (%) 623 (30%), 622 (38), 621 (100, bp, M^+, ^{58}Ni), 520 (8), 519 (7), 518 (20), 505 (15), 504 (10), 503 (21); NMR (360 MHz, $CDCl_3$, 5.4 mM) 9.17, 8.83 (each s, α- and β-meso H), 4.86, 4.63 (AB q, J = 19.6 Hz, 10-CH_2), 4.28 (q, 8-H), 3.81 (m, 7-H), 3.61 (s, 7d-OMe), 3.51–3.54 (each overlapping q, 2a- and 4a-CH_2), 3.44 (s, δ-meso-Me), 3.22 (s, 5-Me), 3.10 (s, 6 H, 1-, 3-Me), 2.38 (7b-H), 2.32 (7b′-H), 2.16 (7a-H), 2.01 (7a′-H), 1.58 and 1.57 (each t, J = 7.6 Hz, 2b- and 4b-Me), 1.22 (d, J = 6.9 Hz, 8-Me). Anal. Calcd for $C_{35}H_{38}N_4NiO_3$: C, 67.65; H, 6.16; N, 9.02. Found: C, 67.66; H, 6.17; N, 9.17.

Methyl 2-(2,2-Dimethoxyethyl)-2-devinylpyropheophorbide *a* (21). Methyl pyropheophorbide *a* (**9**) (400 mg) was dissolved in dry dichloromethane (85 mL) and stirred at 40 °C while thallium(III) trinitrate trihydrate (720 mg) was added in dry methanol (30 mL). The mixture was stirred for 30 min before sulfur dioxide gas was bubbled through the solution during 30 s and then concentrated hydrochloric acid (0.5 mL) was added and the solution was poured into water and diluted with dichloromethane. The organic layer was washed with water, dried, and evaporated to dryness. A small portion was purified by preparative silica gel TLC (elution with 5% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/methanol: mp 221–223 °C; NMR (360 MHz, $CDCl_3$) 8.50, 9.28, 9.48 (each s, 1 H, δ-, α-, β-meso-H), 5.17 (ABq, J = 20 Hz, 2 H, 10-CH_2), 5.03 (t, 1 H, 2-$CH_2CH(OMe)_2$), 4.48 (q, 1 H, 8-H), 4.28 (d, 1 H, 7-H), 4.11 (d, 2 H, $CH_2CH(OMe)_2$), 3.69 (q, 2 H, 4a-CH_2), 3.61, 3.66 (each s, 3 H, 5-Me, 7d-OMe), 3.46 (s, 6 H, 2-$CH_2CH(OCH_3)_2$), 3.23, 3.25 (each s, 3 H 3-, 1-Me), 2.22–2.38, 2.50–2.70 (each m, 2 H, 7a,b-CH_2CH_2), 1.81 (d, 3 H, 8-Me), 1.70 (t, 3 H, 4b-Me), −1.67 (br s, 2 H, NH); UV λ_{max} 408 nm (ϵ 9.3 × 10^4), 504 (6.8 × 10^3), 534 (6.4 × 10^3), 602 (6.1 × 10^3), 660 (4.0 × 10^4). Anal. Calcd for $C_{36}H_{42}N_4O_5$: C, 70.80; H, 6.93; N, 9.17. Found: C, 70.84; H, 6.92; N, 9.09.

Methyl 2-(2-Hydroxyethyl)-2-devinylpyropheophorbide *a* (23). Crude methyl 2-(2,2-dimethoxyethyl)-2-devinylpyropheophorbide *a* (**21**) was dissolved in dichloromethane (15 mL) and tetrahydrofuran (85 mL), to which was added concentrated hydrochloric acid (1.7 mL) in water (2.6 mL). The mixture was heated under reflux for 45 min and then diluted with dichloromethane and water. The organic layer was washed with water, dried, and evaporated to dryness. TLC monitoring showed the ester to be hydrolyzed, so the residue was dissolved in dry dichloromethane (35 mL) and stirred at 0 °C while sodium borohydride (50 mg) in dry methanol (2 mL) was added. The mixture was stirred for 30 min before glacial acetic acid (0.5 mL) was added and the solution was poured into water. After the aqueous phase was extracted with dichloromethane, the organic layers were combined, washed with saturated aqueous sodium chloride, dried, and evaporated to dryness. The product was treated with excess ethereal diazomethane, and after being allowed to stand for a few minutes, the solution was evaporated to dryness. The product was purified by flash column chromatography on silica gel (elution with 5% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/hexane, giving 160 mg (51% yield based on recovery of 95 mg of unreacted methyl pyropheophorbide *a*): mp 196–198 °C (lit.[6] mp 196–197 °C); NMR (360 MHz, $CDCl_3$) 8.49, 9.23, 9.43 (each s, 1 H, δ-, α-, β-meso-H); 5.17 (ABq, J = 20 Hz, 2 H, 10-CH_2), 4.42 (q, 1 H, 8-H), 4.21 (d, 1 H, 7-H), 4.08, 4.33 (each t, 2 H, 2a,b-CH_2), 3.68 (q, 2 H, 4a-CH_2), 3.24, 3.32, 3.59, 3.61 (each s, 3 H, 3-, 1-, 5-Me, 7d-OMe), 2.20–2.23, 2.26–2.53 (each m, 2 H, 7a,b-CH_2CH_2), 1.79 (d, 3 H, 8-Me), 1.68 (t, 3 H, 4b-Me), −1.71 (br s, 2 H, NH); UV λ_{max} 408 nm (ϵ 1.15 × 10^5), 472 (3.8 × 10^3), 504 (1.03 × 10^4), 534 (9.7 × 10^3), 602 (8.6 × 10^3), 660 (5.01 × 10^4).

Methyl 2-(2-Chloroethyl)-2-devinylpyropheophorbide *a* (24). Methyl 2-(2-hydroxyethyl)-2-devinylpyropheophorbide *a* (**23**) (75 mg) was dissolved in dry dimethylformamide (8.0 mL) and then cooled to 0 °C. Benzoyl chloride (0.5 mL) was added dropwise under nitrogen, and this mixture was stirred for 30 min at 0 °C. The solution was warmed to room temperature and then heated at 60 °C for 15 min. The mixture was diluted with dichloromethane (100 mL) and washed with 10% aqueous sodium hydroxide (75 mL), water (2 × 75 mL), and dried. Solvents were removed under vacuum, and the residue was purified by flash column chromatography on silica gel (elution with 3% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/methanol to give 56 mg (72% yield): mp 199–200 °C; NMR (360 MHz, $CDCl_3$) 8.53, 9.20, 9.52 (each s, 1 H, δ-, α-, and β-meso-H), 5.18 (ABq, J = 20 Hz, 2 H, 10-CH_2), 4.50 (q, 1 H, 8-H), 4.33 (m, 3 H, 2b-CH_2, 7-H), 4.22 (t, 2 H, 2a-CH_2), 3.70 (q, 2 H, 4a-CH_2), 3.26, 3.36, 3.61, 3.68 (each s, 3 H 3-, 1-, 5-Me, 7d-OMe), 2.24–2.38, 2.51–2.78 (each m, 2 H, 7a,b-CH_2CH_2), 1.81 (d, 3 H, 8-Me), 1.70 (t, 3 H, 4b-Me), −1.71 (br s, 2 H, NH); UV λ_{max} 408 nm (ϵ 1.08 × 10^5), 5.04 (5.5 × 10^3), 534 (4.9 × 10^3), 604 (4.7 × 10^3), 660 (4.95 × 10^4). Anal. Calcd for $C_{34}H_{37}ClN_4O_3 \cdot H_2O$: C, 67.71; H, 6.52; N, 9.29. Found: C, 67.91; H, 6.36; N, 9.58.

Nickel(II) Methyl 2-(2-Chloroethyl)-2-devinylpyropheophorbide *a* (25b). Methyl 2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (**24**) (60 mg) was dissolved in dichloromethane (10 mL). Saturated nickel(II) acetate in methanol (10 mL) and 2 drops of acetic acid were added, and this mixture was refluxed for 24 h. The reaction mixture was diluted with dichloromethane, washed with water, dried, and evaporated. The product was purified by preparative TLC (elution with 3% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/methanol, giving 55 mg (85%) and mp 177–179 °C: NMR (360 MHz, $CDCl_3$) 8.15, 8.90, 9.32 (each s, 1 H, δ-, α-, and β-meso-H), 4.82 (ABq, J = 19.7 Hz, 2 H, 10-CH_2), 4.28 (q, 1 H, 8-H), 4.00–4.10 (m, 5 H, 2a,b-CH_2CH_2, 7-H), 3.60–3.62 (m, 5 H, 4a-CH_2, 7d-OMe), 3.09, 3.15, 3.48 (each s, 3 H 3-, 1-, 5-Me), 2.1–2.3, 2.4–2.5 (each m, 2 H, 7a,b-CH_2CH_2), 1.61 (t, 3 H, 4b-Me), 1.54 (d, 3 H, 8-Me); UV λ_{max} 395 nm (ϵ 4.8 × 10^4), 416 (5.9 × 10^4), 642 (5.8 × 10^4). Anal. Calcd for $C_{34}H_{35}ClN_4NiO_3$: C, 63.63; H, 5.50; N, 8.73. Found: C, 63.41; H, 5.49; N, 8.47.

Nickel(II) Methyl δ-*meso*-[(Methylthio)methyl]-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (26b). Nickel(II) methyl 2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (**25b**) (40 mg) was dissolved in dry dichloromethane (10 mL); chloromethyl methyl sulfide (80 μL) was added, and the solution was cooled to −15 °C. $TiCl_4$ (80 μL of 1.1 M solution in dichloromethane) was added dropwise via a syringe, and after 15 min, the mixture was allowed to warm to room temperature. After 2 h, the reaction was determined by spectrophotometry to be incomplete so the mixture was cooled to −15 °C and an additional 75 μL of $TiCl_4$ solution was added. After 2 h at room temperature, the reaction mixture was diluted with dichloromethane (75 mL), washed with aqueous saturated $NaHCO_3$ (50 mL), water (2 × 50 mL), dried, and evaporated. The product was purified by preparative TLC on silica gel (elution with 3% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/methanol, giving 26 mg, (60%) mp 206–208 °C: NMR (360 MHz, $CDCl_3$) 8.85, 9.21 (each s, 1 H, α- and β-meso-H), 4.90 (q, 1 H, 8-H), 4.75 (ABq, J = 19.4 Hz, 10-CH_2), 4.40 and 4.85 (br d and d, each 1 H, CH_2SMe), 4.00–4.04 (m, 4 H, 2a,b-CH_2CH_2), 3.83 (t, 1 H 7-H), 3.64 (s, 3 H, 7d-OMe), 3.57 (q, 2 H, 4a-CH_2), 3.44 (overlapping s, 6 H, 1-, 5-Me), 2.37, 3.11 (each s, 3 H, S-Me), 2.06–2.09, 2.16–2.19 (each m, 1 H), and 2.42–2.51 (m, 2 H, 7a,b-CH_2CH_2), 1.58 (t, 3 H, 4b-Me), 1.23 (d, 3 H, 8-Me); UV λ_{max} 424 nm (ϵ 6.14 × 10^4), 656 (4.7 × 10^4). Anal. Calcd for $C_{36}H_{39}ClN_4NiO_3S$: C, 61.60; H, 5.60; N, 7.98. Found: C, 61.31; H, 5.40; N, 7.97.

Nickel(II) Methyl δ-*meso*-Methyl-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (27b). Nickel(II) methyl δ-*meso*-[(methylthio)-methyl]-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (**26b**) (25 mg) was dissolved in acetone (10 mL). Raney Ni (pH 10 slurry) (500 mg) was added, and the solution was stirred for 20 min. The Raney Ni was then filtered off, and the product was purified by preparative TLC on silica gel (elution with 3% tetrahydrofuran in dichloromethane). After chromatography, the product was crystallized from dichloromethane/hexane, giving 15 mg (64%), mp 120–123 °C: NMR (360 MHz, $CDCl_3$) 8.83, 9.20 (each s, 1 H, α- and β-meso-H), 4.75 (ABq, J = 19.6 Hz, 10-CH_2), 4.31 (q, 1 H, 8-H), 4.00-4.10 (m, 4 H, 2a,b-CH_2CH_2), 3.87 (t, 1 H, 7-H), 3.60 (s, 3 H, 7d-OMe), 3.57 (q, 2 H, 4a-CH_2), 3.12, 3.16, 3.24, 3.45 (each s, 3 H, 3-, 1-, 5-, δ-meso-Me); 1.9–2.25, 2.3–2.4 (each m, 2 H, 7a,b-CH_2CH_2), 1.60 (t, 3 H, 4b-Me), 1.23 (d, 3 H, 8-Me); UV λ_{max} 422 nm (ϵ 5.56 × 10^4), 570 (4.7 × 10^3), 656 (3.62 × 10^4). Anal. Calcd for $C_{35}H_{37}ClN_4NiO_3$: C, 64.10; H, 5.69; N, 8.54. Found: C, 64.06; H, 5.91; N, 8.65.

Attempts to remove the nickel from this compound were largely unsuccessful. In the most successful procedure, nickel(II) methyl δ-*meso*-methyl-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (10 mg) was dissolved in trifluoroacetic acid (3 mL) in a Carius tube, and H_2S gas was bubbled in for 2 min before the tube was sealed. The solution was

allowed to stir for 7 days at room temperature before being diluted with dichloromethane, neutralized with aqueous saturated sodium bicarbonate, washed with water, and dried (Na_2SO_4). The product was purified by preparative TLC on silica gel (elution with 3% tetrahydrofuran in dichloromethane), giving less than 1 mg of demetalated product (**27**) and mostly unreacted nickel(II) complex (**27b**).

Copper(II) Methyl δ-*meso*-[(Methylthio)methyl]-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (26a). Methyl 2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (**24**) (55 mg) was dissolved in dichloromethane (6 mL), and saturated copper(II) acetate hydrate in methanol (3 mL) was added. The resulting solution was refluxed under nitrogen for 6.5 h before being diluted with dichloromethane, washed with water, dried, and evaporated. The resulting copper(II) complex (**25a**) was crystallized from dichloromethane/hexane and had mp 186-190 °C: UV λ_{max} 400 nm (ϵ 6.4 × 10^4), 420 (9.6 × 10^4), 504 (4.1 × 10^3), 548 (5.1 × 10^3), 598 (1.2 × 10^4), 646 (6.15 × 10^4). This material, without further purification, was dissolved in dry dichloromethane (10 mL), and chloromethyl methyl sulfide (80 μL) was added under nitrogen before the solution was cooled to −15 °C. $TiCl_4$ (80 μL; 1.1 M solution in dichloromethane) was added dropwise via a syringe, and after 15 min, the mixture was allowed to warm to room temperature. After 2 h, the reaction was determined by spectrophotometry to be incomplete so the mixture was cooled to −15 °C and an additional 80 μL of $TiCl_4$ solution was added. After 1 h at room temperature, the mixture was heated to 40 °C for 1 h, after which the reaction was determined by spectrophotometry to be complete. The reaction mixture was then diluted with dichloromethane (75 mL), washed with aqueous saturated sodium bicarbonate (50 mL) and water (2 × 50 mL), dried, and evaporated. The product was purified by flash column chromatography on silica gel (elution with 3% tetrahydrofuran in dichloromethane), giving 45 mg (68% yield from methyl 2-(2-chloroethyl)-2-devinylpyropheophorbide *a*), mp 117-121 °C: UV λ_{max} 424 nm (ϵ 6.1 × 10^4), 610 (4.2 × 10^3), 658 (3.6 × 10^4).

Copper(II) Methyl δ-*meso*-Methyl-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (27a). Copper(II) methyl δ-*meso*-[(methylthio)methyl]-2-(2-chloroethyl)-2-devinylpyropheophoride *a* (**26a**) (40 mg) was dissolved in acetone (15 mL); Raney Ni (pH 10 slurry; 700 mg) was added, and the stoppered flask was stirred for 1 h at 40 °C. The Raney Ni was then filtered off and the product was purified by preparative TLC on silica gel (elution with 3% tetrahydrofuran in dichloromethane), giving 20 mg (59%) of the required *meso*-methylchlorin, mp 113-117 °C: UV λ_{max} 424 nm (ϵ 5.9 × 10^4), 612 (1.2 × 10^3), 658 (3.5 × 10^4).

Methyl δ-*meso*-Methyl-2-(2-chloroethyl)-2-devinylpyropheophorbide *a* (27). Copper(II) methyl δ-*meso*-methyl-2-(2-chloroethyl)-2-devinylpyropheophorbide (**27a**) (20 mg) was dissolved in dichloromethane (5 mL), and HCl (g) was bubbled through the solution for 5 min. The reaction mixture was then stirred in a stoppered flask for 30 min at room temperature before being opened carefully and the contents poured into iced saturated aqueous sodium acetate/dichloromethane. Then, saturated aqueous sodium bicarbonate was added to the vigorously stirred solution to pH 7. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give a residue which was purified by silica gel TLC (elution with 3% tetrahydrofuran in dichloromethane), and the product was crystallized from dichloromethane/methanol, giving 10 mg (55% yield). [This material was identical with an authentic sample which had previously been converted into the corresponding Bmph-*c* [Et, Me] (**4**)]: mp 211-212 C [lit.[6] mp 212-213 °C]: NMR (500 MHz, $CDCl_3$) 9.34, 9.52 (each s, 1 H, α- and β-meso-H), 5.25 (ABq, J = 19.5 Hz, 10-CH_2), 4.60 (q, 1 H, 8-H), 4.18-4.23, 4.40 (m, t, 5 H, 2a,b-CH_2CH_2, 7-H), 3.92 (s, 3 H, δ-meso-Me), 3.73 (q, 2 H, 4a-CH_2), 3.31, 3.49, 3.58, 3.70 (each s, 3 H, 3-, 1-, 5-Me, 7d-OMe), 2.10-2.23, 2.50-2.55 (each m, 2 H, 7a,b-CH_2CH_2), 1.72 (t, 3 H, 4b-Me), 1.53 (d, 3 H, 8-Me), −1.72 (br s, 2 H, NH); UV λ_{max} 412 nm (ϵ 1.12 × 10^5), 484 (3.5 × 10^3), 516 (9.4 × 10^3), 550 (1.3 × 10^4), 612 (6.8 × $1/^3$), 670 (5.04 × 10^4).

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Registry No. 3, 68464-68-6; **3a**, 96806-69-8; **3b**, 96806-63-2; **4** (isomer 1), 59924-02-6; **4** (isomer 2), 73365-61-4; **7**, 36151-62-9; **7a**, 96806-58-5; **7d**, 15634-17-0; **8**, 5594-30-9; **9**, 6453-67-4; **11**, 96806-59-6; **13**, 96806-70-1; **13a**, 96806-60-9; **16**, 33719-95-8; **17**, 51742-45-1; **18**, 96806-71-2; **18a**, 96825-30-8; **19a**, 96806-61-0; **19b**, 96806-62-1; **20**, 96806-72-3; **21**, 66229-98-9; **22**, 66229-99-0; **23**, 66230-00-0; **23** (acid), 66230-01-1; **24**, 96806-73-4; **25a**, 96806-67-6; **25b**, 96806-64-3; **26a**, 96825-31-9; **26b**, 96806-65-4; **27**, 73333-66-1; **27a**, 96806-68-7; **27b**, 96806-66-5; pheophytin *a*, 603-17-8; pheophytin *a* (7-propionic acid), 57458-59-0; pyropheophytin *a*, 14409-87-1.

Synthesis of Nickel(II) Isobacteriochlorins from Nickel(II) Complexes of Chlorophyll Derivatives

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Abstract: Treatment of nickel(II) methyl δ-*meso*-[(methylthio)methyl]mesopyropheophorbide *a* (**1c**) with Raney Ni gives the expected nickel(II) δ-*meso*-methyl compound **5** as well as byproducts, which are shown to be the nickel(II) isobacteriochlorin **2b**, nickel(II) hexahydroporphyrin **4**, and methyl nickel(II) δ-*meso*-methyldeoxomesopyropheophorbide *a* **3c**. The nickel(II) isobacteriochlorin is shown to consist substantially of one isomer (**2b**, "tcc") by using HPLC and high-field NMR spectroscopy. When the same reaction is carried out with the δ-meso-unsubstituted nickel(II) compound **9b**, similar isobacteriochlorin **11a**, hexahydroporphyrin **12**, and deoxo compound **10b** are obtained. In this case, the isobacteriochlorin is separated by HPLC into approximately equal amounts of two isomers. On the basis of extensive NMR experiments, structures for the two isomeric nickel(II) isobacteriochlorins are proposed. Variation of the solvent used in the Raney Ni reduction allows preferential formation of either the isobacteriochlorins **11a** or the deoxo compound **10b**, but under no circumstances are materials formed in which both the 9-ketocarbonyl and the ring A pyrrole subunit have been reduced. The presence of the δ-*meso*-methyl substituent (e.g., in **1c**) also has an effect on the Raney Ni reaction such that significantly higher yields of nickel(II) isobacteriochlorin **2b** are obtained (compared with reduction of **9b** to give **11a**).

The recent discovery of the nitrite and sulfite reductases containing the isobacteriochlorin prosthetic group, siroheme,[1a] and the structure elucidation of the nickel-containing factor 430 from methanogenic bacteria[1b] have sparked a resurgence of interest in highly reduced porphyrin systems. As mentioned in the preceding paper[2] Raney Ni desulfurization of copper(II) methyl δ-*meso*-[(methylthio)methyl]mesopyropheophorbide *a* (**1b**) in methanol at 70 °C gave rise to a major side product tentatively identified

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