chloromethane/hexane to give 25 mg (85%) of the dimethyl acetal **37**, which was dissolved in tetrahydrofuran (10 mL) and water (0.5 mL) and then heated under reflux for 5 min with concentrated hydrochloric acid (0.2 mL). After cooling, dichloromethane (20 mL) and water (5 mL) were added and the porphyrin **38** was extracted into the organic phase, which was dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in dichloromethane (10 mL) and treated with sodium borohydride (10 mg) in ice-cold methanol (2 mL). After stirring for 10 min, analytical TLC determined that the reaction was complete, so acetic acid (0.5 mL) was added. The porphyrin was worked up with dichloromethane and water, as before, and the extracted and evaporated residue was dissolved in 5% concentrated sulfuric acid in methanol (10 mL) and left overnight at 0 °C. After addition of dichloromethane (50 mL), washing with water (3 × 50 mL), drying (Na_2SO_4), and evaporation, the residue was chromatographed on neutral alumina (Brockmann Grade V, elution with 1% methanol in dichloromethane). The red eluates were collected, evaporated to dryness, and crystallization from dichloromethane/hexane gave the required labeled (hydroxyethyl)-porphyrin (20.2 mg, 70%), mp 208–210 °C (lit.[52] mp 210–212 °C, unlabeled). The proton-decoupled carbon-13 NMR spectrum showed a single enhanced peak at 65.0 ppm, which, in the proton-coupled mode, became a triplet with J_{C-H} = 138 Hz.

2-(2-Chloro-[[2-^{13}C]ethyl])deuteroporphyrin IX Dimethyl Ester (40). The foregoing carbon-13-enriched (hydroxyethyl)-porphyrin **39** (12 mg) was dissolved in chloroform (8 mL) and dimethylformamide (1.5 mL) containing potassium carbonate (0.5 g). The mixture was treated with thionyl chloride (0.5 mL) and stirred for 6 h before being poured into water (10 mL). The organic phase was separated, washed with water (2 × 10 mL), and dried (Na_2SO_4). Evaporation gave a residue, which was chromatographed on neutral alumina (Brockmann Grade III, elution with dichloromethane), and the eluates afforded the title compound (8 mg, 70%), mp 196–198 °C (lit.[52] mp 199–201 °C). The proton-decoupled carbon-13 NMR spectrum showed one enhanced signal at 45.1 ppm, which was observed as a triplet (J_{C-H} = 147 Hz) in the proton-coupled mode.

Acknowledgment. This research was supported by grants from the National Institutes of Health (HL 22252) and the National Science Foundation (CHE-78-25557). We are also grateful for financial support (to H.D.T.) from Yarmouk University, Jordan.

Registry No. **2**, 31837-62-4; **2**-^{13}C, 78829-38-6; **3**, 78829-28-4; **4**, 78829-29-5; **4** (unlabeled), 31837-63-5; **6**, 78824-31-4; **6** (undeuterated), 87281-57-0; **8**, 78829-30-8; **8** (unlabeled), 51089-69-1; **9**, 78829-33-1; **10**, 78829-34-2; **11**, 78829-35-3; **11** (undeuterated), 72562-17-5; **12**, 78829-36-4; **13**, 87281-58-1; **17**, 87281-79-6; **18**, 78840-83-2; **19**, 78829-39-7; **20**, 78829-40-0; **21**, 87281-78-5; **21** methyl ester, 87281-71-8; **21** (undeuterated), 62562-76-9; **24**, 62562-74-7; **25**, 87281-55-8; **25** (undeuterated), 87281-66-1; **26**, 87281-68-3; **26** (undeuterated), 87281-67-2; **27**, 87281-63-8; **27** (undeuterated), 87281-62-7; **28**, 87281-65-0; **29**, 87281-80-9; **30**, 87281-64-9; **31**, 87281-81-0; **32**, 87308-15-4; **33**, 87281-69-4; **33** (undeuterated), 62562-77-0; **33** methyl ester, 87281-73-0; **34**, 87281-70-7; **34** methyl ester, 87281-72-9; **35**, 87191-24-0; **36**, 87281-74-1; **37**, 87281-75-2; **38**, 87281-76-3; **39**, 87281-56-9; **40**, 87281-77-4; pyridine, 110-86-1; [1-^{13}C]acetyl chloride, 1520-57-6; carbon tetrabromide, 558-13-4; triphenylphosphine, 603-35-0; thionyl chloride, 7719-09-7; benzyl 3,5-dimethylpyrrole-2-carboxylate, 40236-19-9; 2-(benzyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-5-carboxylic acid, 52091-16-4; benzyl 4-[(methoxycarbonyl)methyl]-3-methyl-5-(trichloromethyl)pyrrole-2-carboxylate, 87281-59-2; benzyl 5-iodo-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate, 87281-60-5; benzyl 4-[(methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate, 87281-61-6; benzyl 4-[1-^{13}C]acetyl-3,5-dimethylpyrrole-2-carboxylate, 78829-37-5.

Porphyrin Synthesis through Tripyrrins: An Alternate Approach

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A new route for synthesis of unsymmetrically substituted porphyrins is described. The route follows the earlier approach through pyrromethanes, tripyrrin hydrobromides, and *a,c*-biladiene dihydrobromides, except that the pyrromethane intermediate is elongated in an initially "clockwise" direction to give a benzyl tripyrrincarboxylate. Various advantages over the *tert*-butyl tripyrrincarboxylates used in the earlier method (Scheme I) are discussed. The new route is demonstrated in the syntheses of five pure porphyrins required for other current studies.

Depending upon the complexity of the target molecule, porphyrin syntheses can be approached from a variety of directions.[1,2] If laborious separations of mixtures are to be avoided, totally unsymmetrical porphyrins must usually be synthesized by cyclization of a preformed open chain tetrapyrrole such as an *a,c*-biladiene or a *b*-bilene. Over the years, a particularly useful synthesis of completely unsymmetrical porphyrins has been the stepwise approach through tripyrrins.[3] In this procedure (Scheme I), an unsymmetrically substituted and differentially protected benzyl *tert*-butyl pyrromethane-5,5′-dicarboxylate, **1**, is catalytically debenzylated to give the pyrromethane-5-carboxylic acid, **2**; in an initially "anticlockwise" manner, the dipyrrole **2** is transformed into a tripyrrin salt, **3**, by condensation under acidic conditions with a 2-formylpyrrole, **4**. Condensation with a second formylpyrrole **5** gives an *a,c*-biladiene salt, **6**. Finally, the 1′,8′-dimethyl-*a,c*-biladiene salt is cyclized to give porphyrin by brief treatment with copper(II) chloride in dimethylformamide.[3]

Several technical problems arise in the "anticlockwise" approach outlined in Scheme I. The first is that the formylpyrrole **4** requires an acid (*p*-toluenesulfonic acid) to accomplish its reaction with the pyrromethane-5-carboxylic acid, **2**. The presence of the 5′-*tert*-butyl ester, which is itself labile to cleavage by acids, poses a definite problem, particularly when the formation of the tripyrrin salt is slow

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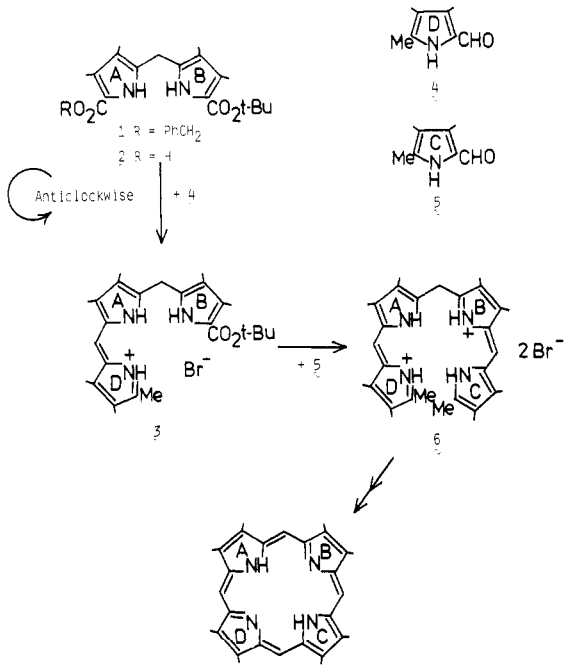
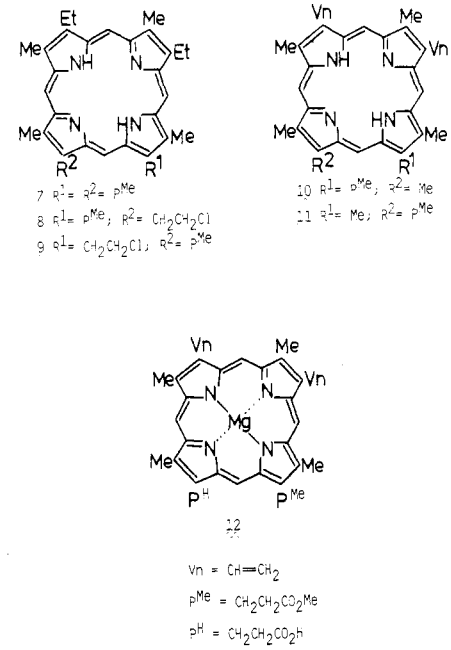
Scheme I



(for example when bulky substituents overhang the site of condensation). Moreover, since the *p*-toluenesulfonate salt of the tripyrrin is rarely crystalline, it is necessary to treat the tripyrrin briefly with hydrogen bromide gas in order to form the more crystalline hydrobromide, **3**. On occasion, because this is an erratic procedure, the *tert*-butyl ester is cleaved, or partially cleaved, and this causes problems with side reactions and also in the full characterization of the tripyrrin. In this paper we describe a modification to the existing procedure. In this new route a tripyrrin is prepared by an alternative "clockwise" elongation of the pyrromethane **1**, and the resulting tripyrrin, which bears a benzyl (rather than *tert*-butyl) ester, is efficiently transformed into *a,c*-biladiene and porphyrin. The "clockwise" method has the advantage that the tripyrrin benzyl ester is very much more stable to acid than its *tert*-butyl counterpart, **3**, and it also provides a complementary pathway wherein, by judicious choice of either route, one can add labeled or otherwise valuable pyrroles as the last step in the tripyrrin to *a,c*-biladiene conversion.

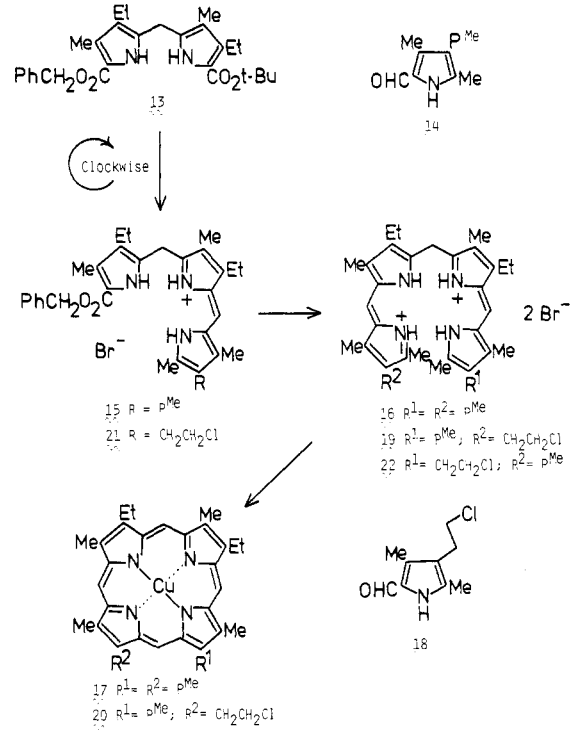
The new approach is demonstrated initially in the synthesis of mesoporphyrin IX dimethyl ester (**7**) (a degradation product from heme) and then in synthesis of the pairs of porphyrin isomers **8**/**9** and **10**/**11**. These synthetic targets are important in connection with ongoing studies in this laboratory of heme orientational heterogeneity in hemoproteins[4-12] and in the total synthesis of magnesium protoporphyrin IX monomethyl ester, a key intermediate[13]



in the biosynthesis of chlorophyll a.

Synthesis of Mesoporphyrin IX Dimethyl Ester (7). In the past, mesoporphyrin IX dimethyl ester (**7**) has been a common synthetic objective for testing of new approaches in porphyrin synthesis.[1] This is because it possesses ester functions on two of its four subunits, and any unexpected problems causing randomization of subunits during the synthetic steps can readily be detected due to formation of porphyrins bearing variable numbers of ester groups (0 → 4), and these can be instantly detected by TLC.

The benzyl *tert*-butyl pyrromethane-5,5′-dicarboxylate **13** was treated with the formylpyrrole **14** in TFA and



methanol, and following addition of HBr in acetic acid, the tripyrrin hydrobromide **15** was isolated crystalline in 83% yield. The tripyrrin **15** was treated for 6 h in 30% HBr

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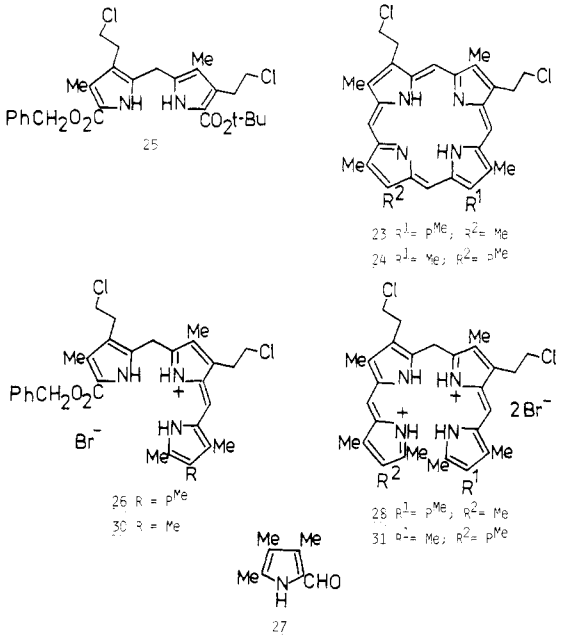
in acetic acid and TFA followed by addition of a second equivalent of the formylpyrrole **14**. The *a,c*-biladiene dihydrobromide **16** was produced in 65% yield. When treated briefly with copper(II) chloride in hot dimethylformamide, the copper(II) complex **17** was obtained, and this was demetalated in 15% sulfuric acid in TFA to give a 38% yield (from **16**) of mesoporphyrin IX dimethyl ester (**7**). Analysis by 360-MHz NMR spectroscopy and melting point data established that the product was pure, and that no randomization of the subunits had taken place at any of the individual synthetic steps.

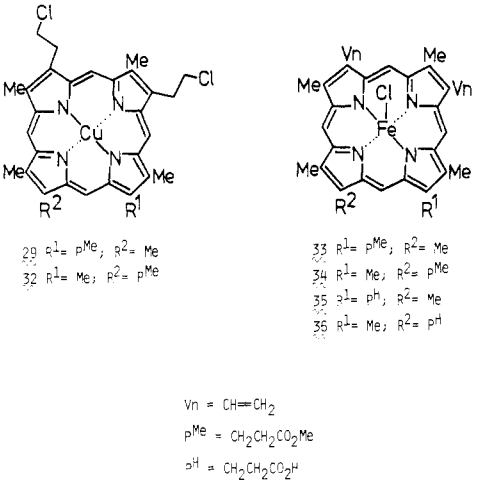
Synthesis of the Porphyrins 8 and 9. Synthesis of these porphyrins required stepwise addition of two different formylpyrroles. Thus, for the synthesis of **8**, the tripyrrin hydrobromide **15** was dissolved in HBr in acetic acid and TFA (1:4) for 6 h. Addition of formylpyrrole **18** in methanol resulted in the formation of the *a,c*-biladiene dihydrobromide **19** as a crystalline solid in 72% yield. Treatment of this intermediate with copper(II) chloride in dimethylformamide at 160 °C for 4 min gave the copper(II) porphyrin **20** which was subsequently demetalated with 15% sulfuric acid in TFA to yield the porphyrin **8** in 28% yield from the *a,c*-biladiene salt. Synthesis of the isomeric porphyrin **9** in a similar stepwise manner involved addition first of the formylpyrrole **18** to pyrromethane **13** to afford the tripyrrin hydrobromide **21**, and then formylpyrrole **14** to give the *a,c*-biladiene **22**, eventually affording the porphyrin **9**; the yield in the final step was 32%. Comparison of 360-MHz NMR spectra, melting point, and analytical data confirmed the absence of pyrrole scrambling in the crucial stages of the condensation steps and clearly indicated the formation of pure **8** and **9** in each case.

Synthesis of the Pentamethylporphyrinmonopropionic Esters 10 and 11. As previously, only the order in which the third and fourth pyrroles were condensed differed between these two syntheses, and this resulted in comparable yields of the chloroethylporphyrin isomers (**23** and **24**). Synthesis of the C7-methyl porphyrin isomer



10 involved deprotection of the pyrromethane **25** with TFA followed by condensation of the formylpyrrole **14** in methanol for 30 min. Crystallization from ether afforded the desired tripyrrin hydrobromide **26** in 90% yield. Treatment of this tripyrrin for 6 h under the usual acidic conditions followed by addition of the formylpyrrole **27**, gave the *a,c*-biladiene **28** in 71% yield. Subsequent cyclization with copper(II) chloride in dimethylformamide for 4 min at 145 °C gave a good yield of the copper(II) porphyrin **29**. Demetalation with 15% sulfuric acid in TFA afforded the product **23** in 28% yield. Dehydrochlorination in pyridine and sodium hydroxide under an inert atmosphere and protected from light led to the divinylporphyrin isomer **10** in 72% yield following reesterification with 5% sulfuric acid–methanol. Analysis by 360-MHz NMR spectroscopy was consistent for the single pure product. In a similar sequence, the pyrromethane **25** was deprotected with TFA and condensed with the formylpyrrole **27** to afford the tripyrrin hydrobromide **30** in 73% yield. Deprotection of the benzyl ester with 30% HBr in acetic acid and TFA, followed by condensation with the formylpyrrole **14** gave the *a,c*-biladiene **31** in 60% yield. Cyclization of this compound in hot dimethylformamide containing copper(II) chloride gave the copper(II) porphyrin **32**. Demetalation, as before, with 15% sulfuric acid in TFA gave the porphyrin **24** in 58% yield. Dehydrochlorination afforded the divinylporphyrin **11** in 73% yield. The 360-MHz NMR spectrum was consistent with the formation of a single pure product.

In preparation for reconstitution into apoproteins, the porphyrins **10** and **11** were converted into the corresponding hemin dimethyl esters (**33** and **34**, respectively)



by using iron insertion with ferrous chloride in acetonitrile.[14] These esters were hydrolyzed to give the corresponding hemins, **35** and **36**, by using KOH in aqueous methanol.[14] Results of reconstitution experiments into several hemoproteins will be described elsewhere.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. Neutral alumina (Merck) was used for column chromatography, and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical TLC was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm). Electronic absorption spectra were measured on a Hewlett Packard 8450 spectrophotometer (solutions in methylene chloride), and proton NMR spectra were measured at 360 MHz with a Nicolet NT-360 spectrometer (solutions in $CDCl_3$). Elemental analyses were performed at the Berkeley Microanalytical Laboratory, Department of Chemistry, UC Berkeley, CA.

Benzyl 3,5-Diethyl-1-(2-(methoxycarbonyl)ethyl)-1′,2,4,6-tetramethyltripyrrin-*a*-6′-carboxylate Hydrobromide (15). The pyrromethane **13**[15] (400 mg, 0.86 mmol) was treated with TFA

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(3 mL) with stirring under nitrogen atmosphere at ambient temperature for 5 min. Then, the formylpyrrole **14**[16] (180 mg, 0.87 mmol) previously dissolved in methanol (20 mL) was added all at once. The red solution was stirred an additional 90 min followed by the addition of 30% HBr in acetic acid (3 drops) and ether (25 mL). Continued stirring for 15 min resulted in the formation of reddish-orange crystals. Collection by filtration and washing thoroughly with ether gave the product (461 mg, 0.72 mmol) in 83% yield, mp 115–116 °C; ^{1}H NMR δ ppm, 13.10, 13.20, 10.60 (NH, each s, 1 H), 7.40 (ArH, m, 5 H), 7.25 (methine bridge, s), 5.25 ($ArCH_2$, s), 4.45 (meso CH_2, s, 2 H), 3.75 (CO_2Me, s), 2.75, 2.60, 2.50 ($CH_2CH_2CO_2Me$ and CH_2CH_3, t, t, q, each 2 H), 2.25, 2.23, 2.10 (CH_3, each s, 6 H, 3 H, 3 H), 1.10, 1.00 (CH_2CH_3, each t, 3 H); λ_{max} 494 nm (ε 67 800).

Anal. Calcd for $C_{34}H_{42}BrN_3O_4$: C, 64.15; H, 6.60; N, 6.60. Found: C, 63.99; H, 6.60; N, 6.54.

Benzyl 1-(2-Chloroethyl)-3,5-diethyl-1′,2,4,6-tetramethyltripyrrin-*a*-6′-carboxylate Hydrobromide (21). Preparation of this tripyrrin hydrobromide in the same manner utilized the pyrromethane **13** (400 mg, 0.86 mmol) and formylpyrrole **18**[16] (160 mg, 0.87 mmol) and resulted in the desired product (341 mg, 0.56 mmol) in 65% yield, mp 179–181 °C; ^{1}H NMR δ 13.25, 13.20, 10.50 (NH, each s, 1 H), 7.30 (ArH, m, 5 H), 7.20 (methine bridge, s), 5.35 ($ArCH_2$, s), 4.45 (meso CH_2, s, 2 H), 3.65, 2.95 (CH_2CH_2Cl, each t, 2 H), 2.65, 2.50 (CH_2CH_3, each q, 2 H), 1.25, 1.05 (CH_2CH_3, each t, 3 H); λ_{max} 494 nm (ε 88 100).

Anal. Calcd for $C_{32}H_{39}BrN_3O_2 \cdot 0.5\ H_2O$: C, 61.83; H, 6.37; N, 6.76. Found: C, 61.80; H, 6.28; N, 6.56.

Benzyl 3,5-Bis(2-chloroethyl)-1-(2-(methoxycarbonyl)ethyl)-1′,2,4,6-tetramethyltripyrrin-*a*-6′-carboxylate Hydrobromide (26). Preparation of this tripyrrin utilized the pyrromethane **25**[17] (996 mg, 1.87 mmol) and formylpyrrole **14**[16] (402 mg, 1.92 mmol) resulting in formation of the desired product (1.187 g, 1.68 mmol) in 90% yield, mp 162–163 °C; ^{1}H NMR δ 13.29, 10.50 (NH, each s, 2 H, 1 H), 7.30 (ArH, m, 5 H), 7.20 (methine bridge, s), 5.32 ($ArCH_2$, s), 4.35 (meso CH_2, s, 2 H), 3.67 (CO_2Me, s), 3.70, 3.40 (CH_2CH_2Cl, each t, 2 H), 3.20, 2.90 (CH_2CH_2Cl, each t, 2 H), 2.70, 2.50 ($CH_2CH_2CO_2Me$, each t, 2 H), 2.70, 2.31, 2.27, 2.09 (CH_3, each s, 3 H); λ_{max} 494 nm (ε 71 000).

Anal. Calcd for $C_{34}H_{40}BrCl_2N_3O_4 \cdot H_2O$: C, 56.43; H, 5.74; N, 5.83. Found: C, 56.75; H, 5.74; N, 5.83.

Benzyl 3,5-Bis(2-chloroethyl)-1,1′,2,4,6-pentamethyltripyrrin-*a*-6′-carboxylate Hydrobromide (30). Preparation of this tripyrrin utilized the pyrromethane **25** (421 mg, 0.78 mmol) and formylpyrrole **27**[16] (113 mg, 0.80 mmol) resulting in the desired product in 73% yield, mp 155–156 °C; ^{1}H NMR δ 13.25, 13.20, 10.70 (NH, each s, 1 H), 7.40 (ArH, m, 5 H), 7.25 (methine bridge, s), 5.30 ($ArCH_2$, s), 4.30 (meso CH_2, s, 2 H), 3.70, 3.40 (CH_2CH_2Cl, each t, 2 H), 3.15, 2.90 (CH_2CH_2Cl, each t, 2 H), 2.70, 2.30, 2.20, 2.00 (CH_3, each s, 3 H, 6 H, 3 H, 3 H); λ_{max} 494 nm (ε 84 800).

Anal. Calcd for $C_{31}H_{36}BrCl_2N_3O_2$: C, 58.76; H, 5.69; N, 6.63. Found: C, 58.99; H, 5.59; N, 6.58.

8-(2-Chloroethyl)-3,5-diethyl-1-(2-(methoxycarbonyl)ethyl)-1′,2,4,6,7,8′-hexamethyl-*a*,*c*-biladiene Dihydrobromide (19). The tripyrrin hydrobromide **15** (107 mg, 0.17 mmol) was treated with a mixture of 30% HBr in acetic acid (0.5 mL) and TFA (2.5 mL) with stirring under nitrogen atmosphere at ambient temperature for 6 h. Then the formylpyrrole **18**[16] (33 mg, 0.18 mmol), previously dissolved in methanol (10 mL), was added all at once. The orange solution immediately turned dark red in color. After the solution was stirred 30 min, ether (30 mL) was added rapidly but dropwise to form red crystals. Collection by filtration and washing thoroughly with ether gave the product in 72% yield, mp 195–196 °C; ^{1}H NMR δ 13.40, 13.30 (NH, each br s, 2 H), 7.30, 7.10 (methine bridge, each s, 1 H), 5.25 (meso CH_2, s, 2 H), 3.75 (CO_2Me, s), 3.65, 2.50 ($CH_2CH_2CO_2Me$, each t, 2 H), 2.95, 2.60 (CH_2CH_2Cl, each m, 2 H), 2.75 (CH_2CH_3, q, 4 H), 2.70, 2.40, 2.35, 2.20, 1.95 (CH_3, each s, 6 H, 3 H, 3 H, 3 H, 3 H), 1.20, 0.60 (CH_2CH_3, each t, 3 H); λ_{max} 450 nm (ε 67 000), 534 (65 000).

Anal. Calcd for $C_{35}H_{47}Br_2ClN_4O_2 \cdot H_2O$: C, 54.68; H, 6.53; N, 6.38. Found: C, 54.38; H, 6.26; N, 6.98.

3,5-Diethyl-1,8-bis(2-(methoxycarbonyl)ethyl)-1′,2,4,6,7,8′-hexamethyl-*a*,*c*-biladiene Dihydrobromide (16). Preparation of this *a*,*c*-biladiene dihydrobromide followed the foregoing procedure and utilized the tripyrrin hydrobromide **15** (133 mg, 0.21 mmol) and formylpyrrole **14**[16] (44 mg, 0.21 mmol), resulting in formation of the product (105 mg, 0.14 mmol) in 65% yield, mp 193–194 °C; ^{1}H NMR δ 13.40, 13.30, 13.20, (NH, each s, 1 H, 1 H, 2 H), 7.05, 7.10 (methine bridge, each s, 1 H), 5.25 (meso CH_2, s, 2 H), 3.75, 2.60 ($CH_2CH_2CO_2Me$, each m, 4 H), 3.70 (CO_2Me, s), 2.75, 2.50 (CH_2CH_3, each q, 2 H), 2.70, 2.40, 2.30, 1.90 (CH_3, each s, 6 H, 6 H, 3 H, 6 H, 1.15, 0.70 (CH_2CH_3, each t, 3 H); λ_{max} 450 nm (ε 49 500), 538 (51 000).

Anal. Calcd for $C_{37}H_{50}Br_2N_4O_4 \cdot H_2O$: C, 54.81; H, 6.66; N, 6.91. Found: C, 54.75; H, 6.24; N, 6.80.

1-(2-Chloroethyl)-3,5-diethyl-8-(2-(methoxycarbonyl)ethyl)-1′,2,4,6,7,8′-hexamethyl-*a*,*c*-biladiene Dihydrobromide (22). Preparation of this *a*,*c*-biladiene dihydrobromide followed the foregoing procedure, utilized the tripyrrin hydrobromide salt **21** (100 mg, 0.16 mmol) and formylpyrrole **14**[16] (35 mg, 0.17 mmol), and resulted in isolation of the product (83 mg, 0.24 mmol) in 77% yield, mp 204–206 °C; ^{1}H NMR δ 13.45, 13.30, 13.25, 13.20 (NH, each s, 1 H), 7.15, 7.10 (methine bridge, each s, 2 H), 5.25 (meso CH_2, s, 2 H), 3.75 (CO_2Me, s), 3.65, 2.50 ($CH_2CH_2CO_2Me$, each t, 2 H), 2.75 (CH_2CH_3, q, 2 H), 2.95, 2.60 (CH_2CH_2Cl, each m, 2 H), 2.70, 2.40, 2.35, 2.20, 1.95 (CH_3, each s, 6 H, 3 H, 3 H, 3 H, 3 H), 1.62, 0.60 (CH_2CH_3, each t, 3 H); λ_{max} 450 (ε 46 700), 526 (23 700).

Anal. Calcd for $C_{35}H_{47}Br_2ClN_4O_2 \cdot 0.5\ H_2O$: C, 51.79; H, 5.16; N, 6.17. Found: C, 51.81; H, 5.40; N, 6.27.

3,5-Bis(2-chloroethyl)-1-(2-(methoxycarbonyl)ethyl)-1′,2,4,6,7,8,8′-heptamethyl-*a*,*c*-biladiene Dihydrobromide (28). Preparation of this *a*,*c*-biladiene dihydrobromide followed the foregoing procedure and utilized the tripyrrin **26** (500 mg, 0.71 mmol) and formylpyrrole **27**[16] (102 mg, 0.74 mmol), resulting in isolation of the product (387 mg, 0.51 mmol) in 71% yield, mp > 210 °C; ^{1}H NMR δ 13.48, 13.25, 13.20 (NH, each s, 1 H, 2 H, 1 H), 7.30 (methine bridge, s, 2 H), 5.24 (meso CH_2, s, 2 H), 3.65 (CO_2Me, s), 3.60, 2.50 ($CH_2CH_2CO_2Me$, each t, 2 H), 3.10, 2.75 (CH_2CH_2Cl, each m, 4 H), 2.72, 2.68, 2.40, 2.30, 2.00, 1.95 (CH_3, each s, 3 H, 3 H, 3 H, 6 H, 3 H, 3 H); λ_{max} 448 nm (ε 87 500), 522 (129 600).

Anal. Calcd for $C_{34}H_{44}N_4Br_2Cl_2O_2$: C, 52.92; H, 5.70; N, 7.26. Found: C, 52.66; H, 5.63; N, 7.15.

3,5-Bis(2-chloroethyl)-8-(2-(methoxycarbonyl)ethyl)-1,1′,2,4,5,6,8′-heptamethyl-*a*,*c*-biladiene Dihydrobromide (31). The preparation of this *a*,*c*-biladiene dihydrobromide followed the foregoing procedure and utilized the tripyrrin hydrobromide **30** (1.01 mmol) and the formylpyrrole **14**[16] (215 mg, 1.02 mmol), resulting in the product (460 mg, 0.59 mmol) being obtained in 60% yield, mp 219–220 °C; ^{1}H NMR δ 13.48, 13.35 (NH, each br s, 2 H), 7.15 (methine bridge, s, 2 H), 5.25 (meso CH_2, s, 2 H), 3.65 (CO_2Me, s), 3.55, 2.50 ($CH_2CH_2CO_2Me$, each t, 2 H), 3.15, 2.70 (CH_2CH_2Cl, each m, 4 H), 3.00, 2.70, 2.25, 2.00 (CH_3, each s, 3 H, 6 H, 6 H, 6 H); λ_{max} 448 nm (ε 56 700), 528 (112 000).

Anal. Calcd for $C_{34}H_{44}Br_2Cl_2N_4O_2$: C, 52.92; H, 5.70; N, 7.26. Found: C, 53.13; H, 5.63; N, 7.06.

7-(2-Chloroethyl)-2,4-diethyl-6-(2-(methoxycarbonyl)ethyl)-1,3,5,8-tetramethylporphyrin (8). The *a*,*c*-biladiene dihydrobromide **19** (180 mg, 0.24 mmol) was dissolved in dry dimethylformamide (19 mL) containing copper(II) chloride (1.07 g). The solution was stirred for 4 min at 145 °C under nitrogen atmosphere. After cooling the solution was poured into water and extracted with methylene chloride. After the organic layer was dried over anhydrous sodium sulfate, the solution was evaporated to dryness followed by column chromatography on Brockmann Grade III alumina (methylene chloride elution). The red eluants were evaporated to dryness and the residue (compound **20**) was treated with 15% sulfuric acid in TFA (15 mL) for 45 min. This mixture was again partitioned between methylene chloride and aqueous sodium bicarbonate and the separated organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent gave a solid which was further purified by silica TLC (2% methanol in methylene chloride development). Extraction of the red major band from the silica plate gave the desired porphyrin (44 mg, 0.08 mmol) in 28% yield, mp 246–247 °C; ^{1}H NMR δ 10.01, 9.99, 9.98, 9.92 (meso H, each s,

(16) Prepared from the corresponding benzyl pyrrole-2-carboxylate by catalytic debenzylation followed by Vilsmeier formylation; see ref 3.

(17) Cavaleiro, J. A. S.; Rocha Gonsalves, A. M. d'A.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771–1781.

1 H), 4.40 ($CH_2CH_2CO_2Me$ and CH_2CH_2Cl, m, 4 H), 4.10 (CH_2CH_3 and CH_2CH_2Cl, m, 6 H), 3.55 (CO_2Me, s), 3.50, 3.45, 3.40 (CH_3, each s, 3 H, 3 H, 6 H), 3.25 ($CH_2CH_2CO_2Me$, t, 2 H), 1.95 (CH_2CH_3, m, 6 H); λ_{max} 400 nm (ϵ 166 000), 500 (13 400), 532 (8600), 568 (6400), 620 (3600).

Anal. Calcd for $C_{34}H_{39}ClN_4O_2$: C, 71.58; H, 6.83; N, 9.80. Found: C, 71.62; H, 6.79; N, 9.81.

6-(2-Chloroethyl)-2,4-diethyl-7-(2-(methoxycarbonyl)ethyl)-1,3,5,8-tetramethylporphyrin (9). Preparation of this porphyrin followed the previously described procedure utilizing the *a,c*-biladiene dihydrobromide **22** (180 mg, 0.24 mmol) and resulted in a 32% yield, mp 194–196 °C; ^1H NMR δ 10.75, 10.50 (meso H, each s, 1 H, 3 H), 4.50, 3.25 ($CH_2CH_2CO_2Me$, each m, 2 H), 4.40, 3.50 (CH_2CH_2Cl, each m, 2 H), 4.00 (CH_2CH_3, m, 4 H), 3.64, 3.62, 3.60 (CH_3 and CO_2Me, each s, 3 H, 3 H, 9 H), 3.25 (CH_2CH_2Cl, t, 2 H), 1.95 (CH_2CH_3, m, 6 H), −2.52 (NH, br s, 2 H); λ_{max} 400 nm (ϵ 161 000), 498 (11 900), 532 (9500), 568 (6800), 622 (3600).

Anal. Calcd for $C_{34}H_{39}ClN_4O_2$: C, 71.58; H, 6.83; N, 9.80. Found: C, 71.71; H, 6.80; N, 9.75.

2,4-Diethyl-6,7-bis(2-(methoxycarbonyl)ethyl)-1,3,5,8-tetramethylporphyrin (7) (Mesoporphyrin IX Dimethyl Ester). Preparation of this porphyrin followed the previously described procedure utilizing the *a,c*-biladiene dihydrobromide **16** (170 mg, 0.22 mmol) and the copper(II) porphyrin **17** and resulted in isolation of the product (49 mg, 0.08 mmol) in 38% yield, mp 210–212 °C (lit.[18] mp 212 °C); ^1H NMR δ 10.02 (meso H, s, 4 H), 4.40, 3.25 ($CH_2CH_2CO_2Me$, each m, 4 H), 4.10 (CH_2CH_3, m, 4 H), 1.95 (CH_2CH_3, m, 6 H), 3.80, 3.70, 3.60, 3.50 (CH_3, each s, 3 H), −3.95 (NH, br s, 2 H).

2,4-Bis(2-chloroethyl)-6-(2-(methoxycarbonyl)ethyl)-1,3,5,7,8-pentamethylporphyrin (23). Preparation of this porphyrin followed the previously described procedure utilizing the *a,c*-biladiene dihydrobromide **28** (352 mg, 0.45 mmol) and the copper(II) porphyrin **29** to give the desired product in 28% yield, mp 228–229 °C; ^1H NMR δ 9.98, 9.96, 9.95 (meso H, each s, 2 H, 1 H, 1 H), 4.52 ($CH_2CH_2CO_2Me$ and CH_2CH_2Cl, m, 6 H), 4.30 (CH_2CH_2Cl, t, 4 H), 3.25 ($CH_2CH_2CO_2Me$, t, 2 H), 3.75, 3.65, 3.60, 3.50 (CH_3 and CO_2Me, each s, 3 H, 3 H, 3 H, 9 H); −4.02 (NH, br s, 2 H); λ_{max} 400 nm (ϵ 162 000), 498 (12 900), 532 (9700), 568 (7300), 622 (3900).

Anal. Calcd for $C_{33}H_{36}Cl_2N_4O_2$: C, 67.00; H, 6.13; N, 9.47. Found: C, 67.23; H, 6.11; N, 9.57.

2,4-Bis(2-chloroethyl)-7-(2-(methoxycarbonyl)ethyl)-1,3,5,6,8-pentamethylporphyrin (24). Preparation of this porphyrin followed the previously described procedure utilizing the *a,c*-biladiene dihydrobromide **31** (450 mg, 0.58 mmol) and the copper(II) porphyrin **32** to give the desired product in 58% yield, mp 249–250 °C; ^1H NMR δ 10.20, 10.10, 10.00 (meso H, each s, 1 H, 2 H, 1 H), 4.55 ($CH_2CH_2CO_2Me$ and CH_2CH_2Cl, m, 6 H), 4.30 (CH_2CH_2Cl, m, 4 H), 3.25 ($CH_2CH_2CO_2Me$, t, 2 H), 3.60, 3.55 (CH_3 and CO_2Me, each s, 9 H), −3.70 (NH, s, 2 H); λ_{max} 400 nm (ϵ 183 800), 500 (15 200), 532 (10 800), 568 (7200), 622 (4000).

Anal. Calcd for $C_{33}H_{36}Cl_2N_4O_2$: C, 67.00; H, 6.13; N, 9.47. Found: C, 66.84; H, 6.00; N, 9.34.

6-(2-(Methoxycarbonyl)ethyl)-1,3,5,7,8-pentamethyl-2,4-divinylporphyrin (10). The porphyrin **23** (60 mg, 0.10 mmol) was dissolved in pyridine (7 mL) containing 3% aqueous sodium hydroxide (5 mL) followed by heating at reflux for 2.5 h. The cooled mixture was treated with dilute aqueous acetic acid and then evaporated to dryness followed by addition of water. The mixture was filtered onto Celite and washed twice with water. The precipitate was dissolved in methanol and methylene chloride and then evaporated to dryness. The residue was treated with 5% sulfuric acid in methanol (50 mL) for 8 h in the dark. The mixture was partitioned between methylene chloride and aqueous sodium carbonate followed by drying over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the residue was purified by silica TLC (2% methanol–methylene chloride). Extraction from silica and evaporation gave the desired product (37 mg, 0.07 mmol) in 72% yield, mp 244–245 °C; ^1H NMR δ 10.18, 10.15, 9.90, 9.87 (meso H, each s, 1 H), 8.50, 6.40, 6.20 (vinyl H, each m, 2 H), 4.40, 3.25 ($CH_2CH_2CO_2Me$, each t, 2 H), 3.70, 3.65, 3.60, 3.50 (CH_3 and CO_2Me, each s, 3 H, 3 H, 3 H, 9 H), −3.95 (NH, s, 2 H); λ_{max} 404 nm (ϵ 183 200), 504 (13 400), 540 (10 500), 574 (6300), 630 (5100).

Anal. Calcd for $C_{33}H_{34}N_4O_2$: C, 76.38; H, 6.56; N, 10.81. Found: C, 75.95; H, 6.52; N, 10.61.

7-(2-(Methoxycarbonyl)ethyl)-1,3,5,6,8-pentamethyl-2,4-divinylporphyrin (11). Preparation of this porphyrin followed the previously described procedure for porphyrin **10** but utilized the foregoing porphyrin **24** (160 mg, 0.27 mmol) to give the product in 73% yield, mp 259–260 °C; ^1H NMR δ 10.30, 10.20, 10.15, 10.05 (meso H, each s, 1 H), 8.30, 6.40, 6.25 (vinyl H, each m, 2 H), 4.40, 3.25 ($CH_2CH_2CO_2Me$, each t, 2 H), 3.75, 3.73, 3.70, 3.54, 3.52 (CH_3 and CO_2Me, each s, 3 H, 3 H, 3 H, 6 H); λ_{max} 404 nm (ϵ 172 000), 504 (13 300), 540 (10 600), 576 (6300), 630 (4600).

Anal. Calcd for $C_{33}H_{34}N_4O_2$: C, 76.38; H, 6.56; N, 10.81. Found: C, 76.69; H, 6.69; N, 10.75.

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