Bromination of Dipyrromethenes for Porphyrin Synthesis

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5′-Bromo-5-(bromomethyl)-2,2′-dipyrromethenium bromides (**1**) and dimers were prepared in 90% yield from 5′-unsubstituted (**16**), 5′-carboxy- (**15**), or 5′-bromo-5-methyl-2,2′-dipyrromethenium bromides (**17**) by treatment of the latter with bromine and trifluoroacetic acid in chlorocarbon solvents at room temperature. Dipyrromethenes (**1**) are important intermediates in the Johnson regioselective synthesis of porphyrins via biladienes (**3**). Improvements in porphyrin synthetic methodology are exemplified by the preparation of etioporphyrin III (**4a**) and mesoporphyrin II dimethyl ester (**4b**).

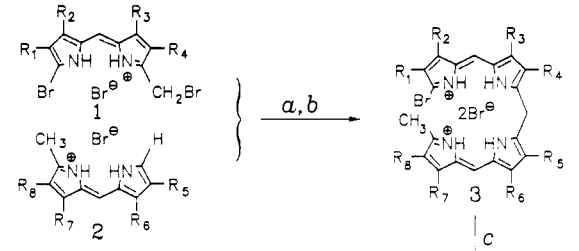
In the course of our research on the synthesis of a wide range of dimeric porphyrins,[2] we have attempted to improve the synthetic methodology for octaalkylporphyrins (**4**) generally. The highest yielding known regioselective synthesis of such porphyrins was discovered by Johnson et al.[3] This entails a stepwise coupling of 5′-(bromomethyl)-5-bromo-2,2′-dipyrromethenium bromide (**1**) with a 5′-unsubstituted 5-methyl-2,2′-dipyrromethenium bromide (**2**) to produce an isolable crystalline 1-bromo-19-methyl-5,15-biladienium dibromide (**3**)—often in yields exceeding 90%. This, when kept for several days dissolved in dimethyl sulfoxide–pyridine, affords the final porphyrin (**4**), also in very high (80–90%) yield (Scheme I). Since these two reactions are so inherently efficient, we have examined methods for improving the access to the obligatory components, **1** and **2**. Here, we present our results relating to the synthesis of **1** by bromination of appropriate precursors.

The traditional preparation[3] of **1** entailed the treatment of **2** with an excess of molecular bromine in hot anhydrous acetic or formic acid. This was a reaction almost impossible to control. A sufficient excess of oxidant needed to be used to ensure against volatility losses as HBr was being expelled from the solution. Losses of yield occurred due not only to under- or overoxidation but to partial hydrolysis as well, and even to partial self-condensation, the brominating conditions being very similar to those employed for actual porphyrin synthesis.[4] Finally, since the products could only be isolated by crystallization, solubility losses were significant. In consequence of all this, a 50% yield was generally considered exceptional.

Our interest in improving this synthetic strategy became critical when we attempted to brominate dimeric dipyrromethenes (**5a,b**) enroute to doubly linked porphyrin dimers[2b,c] (Scheme II). Under the traditional reaction conditions, an intractable mixture of variously brominated products rapidly precipitated from the solvent.

To avoid at least the likelihood of hydrolytic damage, the bromination was investigated in the aprotic chlorocarbon 1,2-dichloroethane,[5,6] a solvent with which we had experienced moderate success in the past (Scheme III). Bromination at C-5′ was rapid in this solvent, but the product (**5c**) crystallized from the reaction mixture as a perbromide salt and reacted no further. When trifluoroacetic acid (TFA), used to dissolve dipyrromethenes for NMR investigation,[7] was added to the boiling mixture, the

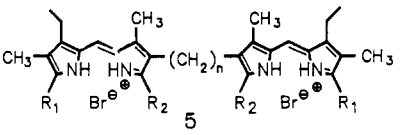
Scheme I



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
3a,4a	Me	Et	Me	Et	Me	Et	Et	Me
3b,4b	Me	Et	Me	P^{Me}	Me	Et	Me	P^{Me}

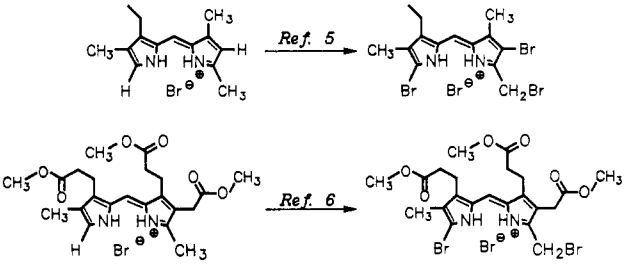
[a] $SnCl_4/CH_2Cl_2$. [b] HBr/CH_3OH. [c] O_2/DMSO, C_5H_5N, room temperature, 7–14 days.

Scheme II



	R_1	R_2	n
a	H	CH_3	8
b	CO_2H	CH_3	8
c	Br	CH_3	8
d	Br	CH_2Br	8
e	CO_2H	CH_3	7
f	H	CH_3	7

Scheme III



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(2) (a) Paine, J. B., III; Dolphin, D. *Can. J. Chem.* **1978**, *56*, 1710–1712. (b) Dolphin, D.; Hiom, J.; Paine, J. B.; III. *Heterocycles* **1981**, *16*, 417–447. (c) Hiom, J.; Paine, J. B., III; Zapf, U.; Dolphin, D. *Can. J. Chem.* **1983**, *61*, 2220–2223.

(3) (a) Harris, R. L. N.; Johnson, A. W.; Kay, I. T. *J. Chem. Soc. C* **1966**, 22–29. (b) Bamfield, P.; Harris, R. L. N.; Johnson, A. W.; Kay, I. T.; Shelton, K. W. *J. Chem. Soc. C* **1966**, 1436–1443.

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(5) Vegh, L.; Dolphin, D., unpublished work.

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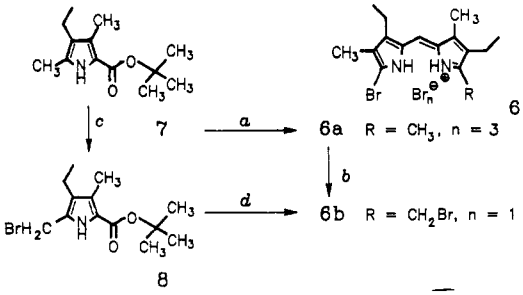
Scheme IV



[a] $3Br_2/CH_3CO_2H$, room temperature. [b] Br_2/CF_3CO_2H, CH_2Cl_2 or $ClCH_2CH_2Cl$, room temperature, 3 days. [c] Br_2/Et_2O. [d] Br_2/Et_2O (inverse addition).

intermediates dissolved promptly. However, now the bromine, taken in considerable excess, was completely consumed within minutes, with the significant formation of the 5-dibromomethyl derivatives (^1H NMR, δ 7.18)[7].

In an effort to achieve greater selectivity, the bromination in the presence of TFA was repeated, again with an excess of bromine, but at room temperature. The reaction mixture gradually changed color over 2–3 days, from an initial yellow-brown to a deep orange (pink in thin layers)—characteristic of the desired product (**5d**). This crystallized readily in near-quantitative yield as a black partial perbromide when the reaction mixture was diluted with diethyl ether. The ^1H NMR spectrum showed the complete absence of either 5-CH_3 (δ 2.72) or 5-$CHBr_2$ (δ 7.18) functionality. The *reaction had gone to completion and stopped!*

The reaction was applied at once to the ubiquitous monomer **6a** derived from the bromination[8] of *tert*-butyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (**7**) in acetic acid (Scheme IV). Pure **6b** was obtained in about 90% yield. This two-step conversion of **7** to **6b** is now the most convenient, reliable, and efficient procedure available, with overall yields ranging from 69 to 77% for the two steps. A wide range of alkyl-substituted dipyrromethenes has now been successfully brominated (see below). Among the various substituents that can be accommodated without injury under the reaction conditions (at least at the 4-position, the most readily accessible point of substitution) are a wide range of esters [(methoxycarbonyl)methyl,[9] 2-(methoxycarbonyl)ethyl, 2-acetoxyethyl,[9] 3-acetoxypropyl[2c]] and substituted alkyls (2-chloroethyl,[9] 2-bromoethyl[9]). The reaction fails altogether[9,10] for dipyrromethenes bearing directly appended ethoxycarbonyl substituents (at least in positions 3′, 4, or 4′), the 5-methyl substituent remaining impervious to oxidation (see below).

In time, the workup procedure was modified to ensure the absence of perbromide and minimize potential solubility losses. The more readily removed and less toxic dichloromethane was found to be as satisfactory as 1,2-dichloroethane. Evaporation of the reaction mixture in vacuo removed most of the excess Br_2 and solubilizing trifluoroacetic acid. The residue, redissolved in CH_2Cl_2, could then be treated with excess cyclohexene to destroy any perbromide. Alcohol-free ethyl acetate was then added, and the mixture was again concentrated by rotary evaporation. Crystalline product was obtained directly in analytical purity. An earlier practice (reflected in several of the procedures in the Experimental Section) of including anhydrous HBr in acetic acid in the workup to guarantee an adequate supply of bromide counterion was found to be unnecessary, as trifluoroacetate was not found to be included in the crystalline product.

With simple alkyl substituents, the bromination was usually found to be complete within 2–3 days. Reaction mixtures needed to be stirred only as long as crystalline perbromide intermediates persisted. Systems of inherently low solubility such as the 3,3′,4,4′-tetramethyl series benefited from the use of higher concentrations of TFA (30–40%) than usual (10–15%). Systems bearing one or more propanoate ester side chains were found to react far more slowly, requiring 1 or 2 weeks for near completion.

The role of CF_3CO_2H is not entirely clear. The improvement of substrate solubility cannot be the whole answer. Since the 5-methyl substituents do not undergo proton exchange in CF_3CO_2D,[9] it is unlikely that core protonation is involved in the oxidation, as by forcing a tautomerization to *exo*-methylene enamines. It may be that the increased concentration of H^+ serves to polarize the molecular bromine (eq 1), increasing the concentration of the more oxidizing Br^+ (Br cation) in the medium.

$$H^+ + Br_2 = Br^+ + HBr \quad (1)$$

The inability of the ester-substituted dipyrromethenes to react may imply a mechanism advanced by Sleiter et al.[11] for the halogenation of simple pyrroles: an oxidation of the aromatic core system, followed by rearrangement. In this case, the presence of directly appended electron-withdrawing substituents must raise the oxidation potential of the aromatic core—perhaps to a level such that Br^+ can no longer initiate the reaction. Also, presumably **1** has an oxidation potential sufficiently high as to discourage further reaction at room temperature, even in the presence of moderate excesses of bromine. This would explain the absence of further oxidation under our conditions, which invariably include an excess of Br_2.

It should be noted that this new bromination procedure is quite general in application with respect to *substitution pattern*, unlike the several ad hoc syntheses,[12,13] which are suitable only for the production of head-to-tail dimers (such as **6b**). Yields of dimeric dipyrromethenes (**5d**), if anything, are higher than those of the monomeric analogues, since the solubility losses are significantly less.

As substrates for the bromination, 5′-unsubstituted (**16**), 5′-bromo-(**17**), and 5′-carboxy-2,2′-dipyrromethenium bromides (**15**) serve equally well (Scheme V). Compounds **15** and **16** react essentially instantly with Br_2, even in the absence of TFA, to give **17**, which then reacts much more slowly to give **1**.

The 5′-carboxy-2,2′-dipyrromethenium bromides (**15**) are often especially convenient, since their precursor 5-formyl-2-pyrrolecarboxylic acids (**13**) lie synthetically close to the 5-methyl-2-pyrrolecarboxylate ester (**9**) starting materials. However, **15** can be beset by problems of either excessive solubility or insufficient stability (or both), although they were found to be well-behaved in both respects with the dimer systems (**5b,e**).

The 5′-carboxy-2,2′-dipyrromethene-4-propionic acid (**15a**), in analogy to materials prepared by Fischer et al.,[14]

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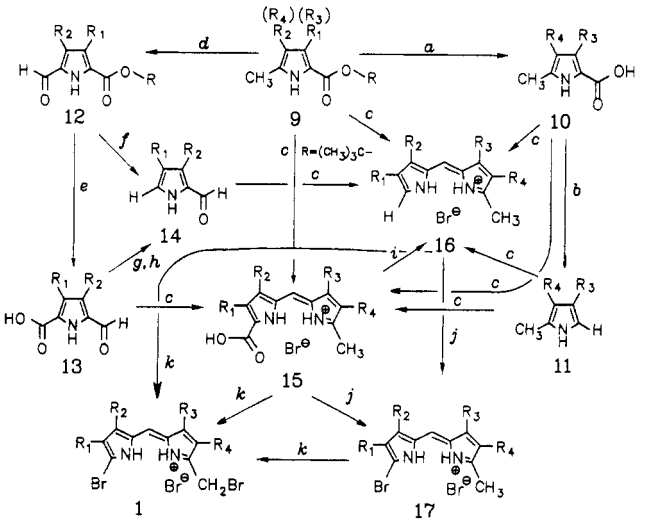
Scheme V



	R_1	R_2	R_3	R_4	R
1a	Me	Me	Me	Me	
1b	Me	Et	Me	Me	
1c	Me	Et	Me	P^{Me}	
9a			Me	P^{Me}	Et
9b			Me	P^{Me}	CH_2Ph
11a			Me	Me	
11b			Et	Me	
11c			Me	P^{H}	
13a	Me	Et			
14a	Me	Et			
15a	Me	Et	Me	P^{H}	
16a	Me	Et	Me	Me	
16b	Me	Et	Et	Me	
16c	Me	Et	Me	P^{H}	
16d	Me	Et	Me	P^{Me}	
17a	Me	Me	Me	Me	
17b	Me	Et	Me	P^{Me}	

P = propanoic acid or ester: $P^{H} = CH_2CH_2CO_2H$, $P^{Me} = CH_2CH_2CO_2CH_3$.

[a] R = Et: NaOH/CH_3OH, reflux; then CH_3CO_2H. R = CH_2Ph: H_2/Pd–C, THF, Et_3N, 1 atm, room temperature. [b] Δ, H^+, or steam distillation. [c] HBr/CH_3OH, CH_3CH_2OH, or CH_3CO_2H. [d] $2SO_2Cl_2/CH_2Cl_2$, then H_2O/THF or $2Pb(OCOCH_3)_4/CH_3CO_2H$. [e] R = Et: NaOH/CH_3OH, reflux; then H^+. R = CH_2Ph: H_2/Pd–C, THF, Et_3N, 1 atm, room temperature. [f] Preceding paper.[15] [g] (Na or K)I_3, $KHCO_3/CHCl_3$, H_2O, 65° C. [h] H_2, MgO/Pd–C, CH_3CH_2OH. [i] CF_3CO_2H, $ClCH_2CH_2Cl$, reflux. [j] $Br_2/ClCH_2CH_2Cl$ or CH_2Cl_2, room temperature, then cyclohexene. [k] Br_2/CF_3CO_2H, CH_2Cl_2 or $ClCH_2CH_2Cl$, room temperature, 3 days.

proved to be especially unstable: the originally prepared magnificent (0.5-cm size) rhombs survived less than a week at room temperature, before degrading to a useless bubbly tar.

We found that the controlled decarboxylation of such dipyrromethenes (**15**) to the stable and useful **16** could be effected in moderate yield (50–60%) in refluxing trifluoroacetic acid (±1,2-dichloroethane). Such product must obviously be destined for use in the Johnson synthesis *as such*, since the *direct* bromination of **15** proceeds in much higher yields than this.

The ^{13}C and ^{1}H NMR chemical shift assignments as reported in the Experimental Section derive from the comparison of the complete set of all sixteen analogues each of **1**, **16**, or **17**, where the 3, 3′, 4, and 4′ substituents were each separately either methyl or ethyl. These analogues were prepared from the appropriate combinations of **11** and **14**, using the above methods. By a brief treatment of **16** with a slight excess of bromine in the absence of trifluoroacetic acid, followed by a workup procedure including cyclohexene, it was possible to intercept **17** in analytically pure form in near-quantitative yield. The 5-unsubstituted 2-pyrrolecarboxaldehydes **14** were prepared as detailed in the preceding paper.[15]

The NMR chemical shift data of these and other dipyrromethenes and of a wide range of porphyrins derived therefrom will be reported elsewhere. Such porphyrins include all of the unnatural isomers of etioporphyrin[16] and a number of ethyl heptaalkylporphyrin-2-carboxylates.

Porphyrin Synthesis

Several applications of 5′-bromo-5-(bromomethyl)-2,2′-dipyrromethenium bromides (**1**) to porphyrin synthesis [etioporphyrin III (**4a**) and mesoporphyrin II dimethyl ester (**4b**)] are presented in the Experimental Section. These incorporate certain modifications of technique that we have found useful or desirable in improving the convenience and efficiency of the synthesis.

For the workup of the biladiene (**3**), we prefer to quench the excess $SnCl_4$ catalyst with aqueous HBr, before concentrating the solution in vacuo, to spare both product and rotary evaporator from increasing concentrations of $SnCl_4$. By adding the resulting CH_2Cl_2 solution of the biladiene to methanolic HBr and then employing a rotary evaporator, we can readily prepare pure crystalline biladiene. Biladienes may even be recrystallized efficiently in this manner as long as some stabilizing acid is present. (Johnson et al.[3] found many biladienes to be unstable to "standard" recrystallization conditions such as boiling chloroform–methanol.)

For the cyclization of the biladiene (**3**), we find the dimethyl sulfoxide–pyridine method[3b] to be far more reliable and convenient than the refluxing *o*-dichlorobenzene procedure.[3a] Such byproducts as form under the milder procedure are much better behaved, and the product porphyrin generally crystallizes out in pure form directly from the reaction mixture, without need for chromatographic workup.

For best results, however, it is imperative that the biladiene be totally dissolved before addition of pyridine. Otherwise, the undissolved starting material may degrade to a useless resin. Solution may be achieved, if necessary, in CH_2Cl_2 containing some CF_3CO_2H. DMSO could then be added, followed by pyridine in excess. Dichloromethane did not interfere, other than by reducing the partial pressure of O_2 in the vicinity. Attempts to remove CH_2Cl_2 (rotary evaporator) appeared to be detrimental.

Although the reaction has heretofore always been performed in the dark, ostensibly to minimize the possibility of formation of corrinoids,[17] this precaution is only desirable at the initial stages of the reaction. Once the intermediary porphodimethene has formed, corrole formation is no longer possible, and then exposure to light hastens the oxidation of this intermediate.

Oxygen is also required, as evidenced by the fact that the porphyrin usually forms a crystalline scum on the surface of the solution. Since larger scale reactions usually have a proportionally smaller surface area, they usually require a longer time for the reaction to proceed to completion. We usually allow such reactions to proceed for

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at least 2 weeks, rather than the 2–3 days originally recommended.[3b] The initial greenish-brown color fades to a pinkish-purple when the oxidation is complete. The filtrates are always saved for a few days after the recovery of product, just in case any further product decides to form.

Experimental Section

^{1}H NMR spectra were recorded on a Varian HA-100 or an XL-100 instrument. ^{13}C NMR spectra were recorded on a Varian CFT-20 or a Bruker WP-400 instrument. Melting points were generally not determined on dipyrromethenes, since they usually decompose rather than melt cleanly. Microanalyses were performed by Peter Borda at UBC.

5′-Bromo-3′,4-diethyl-3,4′,5-trimethyl-2,2′-dipyrromethenium Bromide/Perbromide (6a).[3a,18] A magnetically stirred solution of *tert*-butyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (**7**)[8] (37.2 g, 0.1668 mol) (prepared via diborane reduction[19] of the corresponding 4-acetylpyrrole[20]) in glacial acetic acid (250 mL) was treated at room temperature over 5 min with a steady stream of a solution of bromine (27.5 mL)[21] in acetic acid (100 mL). The solution warmed, darkened to a greenish-black, and evolved copious fumes (CO_2, HBr). Product began to crystallize about midway through the bromine addition.

The mixture was cooled for an hour (tap water) before being filtered. The solids were rinsed with glacial acetic acid (100 mL), diethyl ether (100 mL), and petroleum ether (200 mL), dried, and stored in a desiccator over KOH in the dark. The yield of steel blue crystals was 36.38 g (77.6% based on the perbromide). The lachrymatory filtrates could be evaporated in vacuo to afford several more grams of product but were usually discarded. This procedure is remarkably reproducible.[21] The product gradually evolves HBr. The solids darken on the surface on standing but remain usable for months.

^{1}H NMR ($CDCl_3$) δ 1.11 (3 H, t, J = 7.5 Hz, 4-Et), 1.20 (3 H, t, J = 7.5 Hz, 3′-Et), 2.06 (3 H, s, 4′-Me), 2.32 (3 H, s, 3-Me), 2.47 (2 H, q, J = 7.5 Hz, 4-Et), 2.72 (3 H, s, 5-Me), 2.72 (2 H, q, J = 7.5 Hz, 3′-Et), 7.07 (1 H, s, meso H), 13.1 (2 H, v br s, NH). Minor peaks at δ 2.09 (3 H, s), 4.90 (2 H, s), and 7.18 (1 H, s) signaled the minor (10–20%) presence of **6b**.

5′-Bromo-5-(bromomethyl)-3′,4-diethyl-3,4′-dimethyl-2,2′-dipyrromethenium Bromide (6b).[3a,12] **Method A.** A suspension of the preceding crude perbromide (**6a**) (22.5 g, 0.04 mol) in a solution of trifluoroacetic acid (31.8 mL), and bromine (8.16 g, 0.051 mol) in 1,2-dichloroethane (153.5 mL) was stirred magnetically at room temperature under moisture exclusion conditions for 3 days. Red crystals of starting material persisted for the first day.

The solvent and excess bromine were removed (rotary evaporator) at 50 °C. The residue was dissolved in 1,2-dichloroethane (50 mL) and transferred to an Erlenmeyer flask with CH_2Cl_2 rinsings. HBr (30%) in acetic acid (15 mL) was added, followed, in a steady stream, by absolute diethyl ether (300 mL) as the mixture was stirred magnetically. The product crystallized from the dark cherry red solution and was recovered by filtration and washed with absolute diethyl ether and then petroleum ether. After drying in a desiccator over KOH, the product weighed 18.18 g (94% nominal yield).

The filtrates were evaporated until only acetic acid remained, affording a second crop of 1.07 g (5.6% nominal). The combined yield of 19.25 g represented an overall yield of 77.5%, based upon the original *tert*-butyl ester (**7**). Subsequent work has shown that a modified procedure (method B) also works well.

Method B. Crude dipyrromethene perbromide (**6a**) (35.7 g, 63.7 mmol), CF_3CO_2H (20.3 mL), and Br_2 (10.7 g, 3.5 mL, 67 mmol) were stirred in CH_2Cl_2 (130 mL) at room temperature. After 3 days, the solvent was removed in vacuo at 40 °C. The residue was dissolved in CH_2Cl_2, treated with cyclohexene (5 mL), and reconcentrated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL) and treated with 30% HBr in acetic acid (25 mL) and then ethyl acetate (158 mL).

The mixture was concentrated in vacuo until a slurry of product resulted. The product was filtered off and rinsed with ethyl acetate until the purple-red color in the filtering solution had faded to pale orange and then with hexane.

The product was dried over KOH in a vacuum desiccator; yield 27.3 g [68.7% based on the *tert*-butyl ester (**7**)] (nominally 89% based on perbromide of fw 562). **6b**, as prepared by method A or method B, is stable indefinitely in the dark.

Anal. Calcd for $C_{16}H_{21}Br_3N_2$: C, 39.95; H, 4.40; N, 5.82; Br, 49.83. Found: C, 39.88; H, 4.37; N, 5.66; Br, 50.05.

^{1}H NMR[7] ($CDCl_3$) δ 1.19 (3 H, t, J = 7.5 Hz, 4-Et), 1.21 (3 H, t, J = 7.5 Hz, 3′-Et), 2.05 (3 H, s, 4′-Me), 2.34 (3 H, s, 3-Me), 2.53 (2 H, q, J = 7.5 Hz, 4-Et), 2.78 (2 H, q, J = 7.5 Hz, 3′-Et), 4.84 (2 H, s, CH_2Br), 7.20 (1 H, s, meso), 13.33 (2 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.17) δ 151.40 (5), 149.82 (3′), 143.60 (3), 132.81 (5′), 132.03 (4), 128.34 (2′), 127.61 (2), 126.17 (4′), 120.76 (meso), 19.75 (CH_2Br), 19.06 (3′-CH_3CH_2), 17.23 (4-CH_3CH_2), 16.07 (3′-CH_3CH_2), 14.09 (4-CH_3CH_2), 10.37 (3-CH_3), 9.71 (4′-CH_3).

5′-Bromo-5-(bromomethyl)-3,3′,4,4′-tetramethyl-2,2′-dipyrromethenium Bromide (1a).[12a] A suspension of crude 5′-bromo-3,3′,4,4′,5-pentamethyl-2,2′-dipyrromethenium bromide/perbromide (**17a**) (7.70 g, 14.4 mmol) (prepared analogously from *tert*-butyl 3,4,5-trimethyl-2-pyrrolecarboxylate[22]) in a solution of bromine (4.11 g, 25.7 mmol), and trifluoroacetic acid (24.8 mL) in CH_2Cl_2 (100 mL) was stirred magnetically until the solids had dissolved (2 days).

The solvent was removed in vacuo. The residue was suspended in CH_2Cl_2 (100 mL), dissolving when cyclohexene (5 mL) was added. Ethyl acetate (100 mL) was added and the mixture concentrated in vacuo. The solids were filtered off, washed with ethyl acetate, and dried. Yield 5.28 g (80.8% nominal). The purple filtrates were discarded.

The compound was analyzed as such. Anal. Calcd for $C_{14}H_{17}Br_3N_2$: C, 37.12; H, 3.78; N, 6.18; Br, 52.92. Found: C, 36.86; H, 3.62; N, 5.92; Br, 53.20. Found for another batch: C, 36.94; H, 3.75; N, 6.10; Br, 53.11.

^{1}H NMR ($CDCl_3$) δ 2.07 (3 H, s, 4′-Me), 2.10 (3 H, s, 4-Me), 2.30 (3 H, s, 3-Me), 2.36 (3 H, s, 3′-Me), 4.92 (2 H, s, CH_2Br), 7.19 (1 H, s, meso), 13.85 (2 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.05) δ 152.08 (5), 143.49 (3), 143.05 (3′), 132.89 (5′), 128.62 (2′), 127.54 (2), 127.02 (4′), 126.01 (4), 120.58 (meso), 19.91 (CH_2Br), 10.79 (3′-CH_3), 10.29 (3-CH_3), 9.85 (4′-CH_3), 8.82 (4-CH_3).

3′-Ethyl-3,4,4′,5-tetramethyl-2,2′-dipyrromethenium Bromide (16a). This compound was prepared from 3-ethyl-4-methyl-2-pyrrolecarboxaldehyde (**14a**)[15] (2.80 g, 20.4 mmol), 2,3,4-trimethylpyrrole (**11a**)[23] (2.25 g, 20.6 mmol), and concentrated HBr (5.0 mL, 48%) in ethanol (20 mL) as for **16b**. Yield 5.87 g (92.9%).

Anal. Calcd for $C_{15}H_{21}BrN_2$: C, 58.26; H, 6.84; N, 9.06; Br, 25.84. Found: C, 58.08; H, 6.83; N, 9.06; Br, 25.91.

^{1}H NMR ($CDCl_3$) δ 1.16 (3 H, t, J = 7.5 Hz, 3′-Et), 1.96 (3 H, s, 4-Me), 2.04 (3 H, s, 4′-Me), 2.26 (3 H, s, 3-Me), 2.62 (3 H, s, 5-Me), 2.66 (2 H, q, J = 7.5 Hz, 3′-Et), 7.09 (1 H, s, meso), 7.41 (1 H, d, J = 3.5 Hz, 5′-H), 12.90 (1 H, v br s, NH), 13.11 (1 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.27) δ 158.20 (5), 147.16 (3′), 144.31 (3), 138.40 (5′), 127.78 (2), 125.62 (2 C, 2′, 4), 123.44 (4′), 120.58 (meso), 18.31 (3′-CH_3CH_2), 16.14 (3′-CH_3CH_2), 13.17 (5-CH_3), 10.52 (3-CH_3), 9.83 (4′-CH_3), 8.93 (4-CH_3).

5′-Bromo-5-(bromomethyl)-3′-ethyl-3,4,4′-trimethyl-2,2′-dipyrromethenium Bromide (1b). 3′-Ethyl-3,4,4′,5-tetramethyl-2,2′-dipyrromethenium bromide (**16a**) (1.57 g, 5.08 mmol),

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(19) Whitlock, H. W.; Hanauer, R. *J. Org. Chem.* **1968**, *33*, 2169–2171.
(20) Treibs, A.; Hintermeier, K. *Chem. Ber.* **1954**, *87*, 1167–1174.
(21) This procedure derives its higher yields than those previously published[8,18] from the use of a *sufficient* excess of bromine to react with the isobutylene formed and still provide a suitable level of perbromide counterion.
(22) Bullock, E.; Johnson, A. W.; Markham, E.; Shaw, K. B. *J. Chem. Soc.* **1958**, 1430–1440.
(23) 2,3,4-Trimethylpyrrole (**11a**) and 4-ethyl-2,3-dimethylpyrrole (**11c**) were prepared from the corresponding 5-(ethoxycarbonyl)pyrroles[24] by saponification with excess NaOH, exact neutralization with CH_3CO_2H, and subsequent steam distillation in exact analogy with 3-ethyl-2,4-dimethylpyrrole (cryptopyrrole).[25]

trifluoroacetic acid (4.0 mL), bromine (2.11 g, 13.18 mmol), and CH_2Cl_2 (21 mL) were kept at room temperature for 3 days protected from atmospheric moisture with stirring until the intermediary perbromide had dissolved.

The solvent was removed in vacuo. The residue was taken into CH_2Cl_2, treated with cyclohexene (1 mL) and then ethyl acetate (10 mL), and concentrated (rotary evaporator) until the product had crystallized in bulk. It was filtered off, rinsed with ethyl acetate, and dried. Yield 2.18 g (91.8%) as dark brown-maroon dense sparkling granules, with blue-gray reflex.

Anal. Calcd for $C_{15}H_{19}Br_3N_2$: C, 38.57; H, 4.10; N, 6.00; Br, 51.33. Found: C, 38.80; H, 4.09; N, 5.70; Br, 51.22.

^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.5 Hz, 3′-Et), 2.08 (3 H, s, 4-Me), 2.09 (3 H, s, 4-Me), 2.30 (3 H, s, 3-Me), 2.76 (2 H, q, J = 7.5 Hz, 3′-Et), 4.91 (2 H, s, CH_2Br), 7.18 (1 H, s, meso), 13.81 (2 H, br s, NH).

^{13}C NMR ($CDCl_3$ at 77.08) δ 152.09 (5), 149.42 (3′), 143.67 (3), 132.91 (5′), 127.64 (2 C, 2, 2′), 126.20 (4′), 126.05 (4), 120.55 (meso), 19.91 (CH_2Br), 18.98 (3′-CH_3CH_2), 15.95 (3′-CH_3CH_2), 10.36 (3-CH_3), 9.67 (4′-CH_3), 8.83 (4-CH_3).

3,3′-Diethyl-4,4′,5-trimethyl-2,2′-dipyrromethenium Bromide (16b). 3-Ethyl-4-methyl-2-pyrrolecarboxaldehyde (**14a**))[15] (13.7 g, 0.1 mol) and 4-ethyl-2,3-dimethylpyrrole (**11b**)[23] (12.5 g, 0.1 mol) (freshly steam distilled) in ethanol (250 mL) were stirred magnetically and treated *all at once* with concentrated HBr (43.5 g, 30.0 mL, 48.3%).

The solution darkened at once, and product soon crystallized. After 20 min, the solids were filtered off and washed with ethanol, ethyl acetate, and finally hexane. Yield 24.4 g (75.5%); second crop, 5.1 g (15.7%); third crop, 0.7 g (2.2%); total 30.2 g (93.4%).

Anal. Calcd for $C_{16}H_{23}BrN_2$: C, 59.45; H, 7.17; N, 8.67; Br, 24.72. Found: C, 59.45; H, 7.05; N, 8.40; Br, 24.88.

^1H NMR ($CDCl_3$) δ 1.18 (6 H, t, J = 7 Hz, 3,3′-Et), 1.98 (3 H, s, 4-Me), 2.04 (3 H, s, 4′-Me), 2.62 (3 H, s, 5-Me), 2.71 (4 H, q, J = 7 Hz, 3,3′-Et), 7.13 (1 H, s, meso), 7.39 (1 H, d, J = 3.5 Hz, 5′-H), 12.86 (H, br s, 1′-NH), 13.04 (1 H, br s, 1-NH).

^{13}C NMR ($CDCl_3$ at 77.52) δ 158.25 (5), 150.48 (3), 147.23 (3′), 138.28 (5′), 126.69 (2), 125.59 (2′), 124.94 (4), 123.39 (4′), 120.48 (meso), 18.43 (2 C, 3,3′-CH_3CH_2), 16.10 (2 C, 3,3′-CH_3CH_2), 13.13 (5-CH_3), 9.80 (4′-CH_3), 8.72 (4-CH_3).

Etioporphyrin III (4a).[26a] **(A) Synthesis of 1-Bromo-3,8,13,17-tetraethyl-2,7,12,18,19-pentamethyl-5,15-biladienium Dibromide (3a).** 5′-Bromo-5-(bromomethyl)-3′,4-diethyl-3,4′-dimethyl-2,2′-dipyrromethenium bromide (**6b**) (15.0 g, 31.2 mmol) and 3,3′-diethyl-4,4′,5-trimethyl-2,2′-dipyrromethenium bromide (**16b**) (9.7 g, 30.1 mmol) in CH_2Cl_2 (500 mL, distilled from CaH_2) were treated with $SnCl_4$ (34.5 mL). After 100 min at room temperature, the solution was treated with 48% HBr (55 mL) in H_2O (260 mL), and the mixture was swirled until the organic phase cleared. Any separated third bottom $SnCl_4$ hydrate phase was dissolved in the remaining (top) aqueous phase, before the organic phase was isolated, and added to a solution of 48% HBr (23 mL) in CH_3OH (200 mL).

The resulting solution was concentrated at 40 °C on a rotary evaporator until a thick slurry of product resulted . An initial cherry red phase recrystallized as brick red metallic flakes. These were filtered off and rinsed with 2% (v/v) 48% HBr in CH_3OH (55 mL) and then ethyl acetate. Yield 20.8 g (95.5%).

Anal. Calcd for $C_{32}H_{43}Br_3N_4$: C, 53.15; H, 5.99; N, 7.74; Br, 33.14. Found: C, 53.36; H, 6.19; N, 7.60; Br, 32.91.

^1H NMR ($CF_3CO_2H/CDCl_3$; $CHCl_3$ at 7.28, CF_3CO_2H at 10.88) δ 1.08 (3 H, t, J = 7.6 Hz), 1.19 (3 H, t, J = 7.6 Hz), 1.20 (3 H, t, J = 7.6 Hz), 1.22 (3 H, t, J = 7.6 Hz), 2.05 (3 H, s), 2.10 (3 H, s), 2.17 (3 H, s), 2.34 (3 H, s), 2.58 (2 H, q, J = 7.6 Hz), 2.70 (3 H, s), 2.71 (2 H, q, J = 7.6 Hz), 2.73 (2 H, q, J = 7.6 Hz), 2.77 (2 H, q, J = 7.6 Hz), 4.45 (2 H, s), 7.19 (1 H, s), 7.26 (1 H, s), 11.79 (1 H, br s), 11.87 (1 H, br s), 12.28 (1 H, br s), 12.32 (1 H, br s).

^{13}C NMR (10% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.27; CF_3CO_2H at 114.86, 158.72) δ 159.76 (19), 152.14 (17), 151.15 (9), 150.77 (3), 149.10 (13), 146.09 (11), 144.48 (7), 132.45 (8), 131.43 (1), 128.32 (6), 127.54 (2 C, 4, 16), 126.69 (2), 126.31 (18), 125.60 (14), 123.13 (12), 120.87 (5), 119.85 (15), 23.90 (10), 19.04 (3-C-H_3CH_2), 18.60 (2 C, 13,17-CH_3CH_2), 17.45 (8-CH_3CH_2), 15.88 (3 C, 3,13,17-CH_3CH_2), 14.31 (8-CH_3CH_2), 13.52 (19-CH_3), 10.44 (7-CH_3), 9.64 (2-CH_3), 9.04 (12-CH_3), 8.69 (18-CH_3).

(B) Cyclization of the Biladiene 3a to Etioporphyrin III (4a). Biladiene (**3a**) (20.1 g, 27.8 mmol) was dissolved in CH_2Cl_2 (500 mL) in a 4-L Erlenmeyer flask. Dimethyl sulfoxide (1000 mL) and pyridine (25 mL) were added, and the mixture was kept for 8 days in the dark. The reaction mixture was then exposed to daylight near a window for another 6 days. The resulting purple needles were filtered off, washed with methanol, and dried. Yield 11.05 g (83.2%) (79.4% based on the dipyrromethenes).

^1H NMR (10% CF_3CO_2H in $CDCl_3$) δ −4.16 (4 H, s, NH, dication), 1.73 (3 H, t, J = 7.5 Hz, Et), 1.74 (9 H, t, J = 7.8 Hz, Et), 3.68 (12 H, s, Me), 4.16 (8 H, q, J = 7.8 Hz, Et), 10.71 (4 H, s, meso); 9.74 (s, TFA).

^{13}C NMR (100.6 MHz) (10% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.14; CF_3CO_2H at 113.90, 156.89) δ 143.78, 143.75 (2 C), 143.67, 142.43 (2 C), 142.40, 142.36, 141.63 (2 C), 141.60, 141.56, 137.12 (3 C), 137.09, 98.55, 98.35, 98.17, 97.96, 20.12 (4 C), 16.33 (4 C), 11.68 (2 C), 11.66 (2 C).

2,4-Dimethyl-3-pyrrolepropanoic Acid (11c).[27] A solution of ethyl 4-(2-(methoxycarbonyl)ethyl)-3,5-dimethyl-2-pyrrolecarboxylate (**9a**)[24] (53.6 g, 0.21 mol) in ethanol (300 mL) was treated with a solution of NaOH (33.2 g, 0.83 mol) in H_2O (200 mL) and heated (steam bath) for 2.5 h. Acetic acid (100 mL) was added to the hot solution, which effervesced vigorously. The solution was concentrated in vacuo to a thick slurry. The light tan needles of product were filtered off, washed with H_2O, and dried in air. Yield 24.08 g (68%). Other preparations afforded yields as high as 79%. The product was unstable and best used within a few weeks.

^{13}C NMR ($CDCl_3$ at 77.05) δ 179.84 (CO), 124.30 (2), 117.90 (4), 116.53 (3), 113.16 (5), 35.43 ($CH_2CH_2CO_2H$), 19.79 ($CH_2C-H_2CO_2H$), 11.26 (2-CH_3), 10.32 (4-CH_3).

5′-Carboxy-4-(2-carboxyethyl)-3′-ethyl-3,4′,5-trimethyl-2,2′-dipyrromethenium Bromide (15a). 4-Ethyl-5-formyl-3-methyl-2-pyrrolecarboxylic acid (**13a**)[28] (3.63 g, 20.1 mmol) and 2,4-dimethyl-3-pyrrolepropanoic acid (**11c**) (3.35 g, 20.1 mmol) were suspended in acetic acid (22.4 mL) and treated with 48% HBr (25 mL). When the reaction subsided, further 48% HBr (15 mL) was added and the mixture kept overnight in a freezer. Some ice crystallized, along with large rhombs of product. These were filtered off, washed with H_2O, and dried.

Yield 6.35 g. This material is unstable; after a few weeks at room temperature, the original sample was found to have decayed to an intractable bubbly tar. It was therefore used promptly for the following reaction.

4-(2-Carboxyethyl)-3′-ethyl-3,4′,5-trimethyl-2,2′-dipyrromethenium Bromide (16c). Method A. The preceding 5′-carboxydipyrromethene (**15a**) (6.35 g, 15.5 mmol if anhydrous) was dissolved in CF_3CO_2H (25 mL), and the solution was refluxed for 2 h. The solvent was removed in vacuo and chased with acetic acid (30 mL).

The residue was dissolved in CH_3CO_2H (30 mL) and treated with 48% HBr (30 mL) and then H_2O (2 × 100 mL). Black tars separated and were filtered off. The filtrates were diluted to 500 mL with H_2O and treated with further 48% HBr (40 mL). After standing overnight, the orange-brown needles of product were filtered off, washed with H_2O, and dried. Yield 3.08 g (54.4%).

Method B. 2,4-Dimethyl-3-pyrrolepropanoic acid (**11c**) (8.47 g, 50.7 mmol) and 3-ethyl-4-methyl-2-pyrrolecarboxaldehyde (**14a**)[15] (6.90 g, 50.3 mmol) were suspended in acetic acid (100 mL) and treated with 48% HBr (10 mL). The mixture was warmed (steam bath) until homogeneous and then evaporated in vacuo to dryness. The solids were recrystallized from ethanol–H_2O–HBr. Yield 13.56 g (73.3%). (Part of the loss may have been due to partial esterification during recrystallization.)

Anal. Calcd for $C_{17}H_{23}BrN_2O_2$: C, 55.59; H, 6.31; N, 7.63; Br, 21.76. Calcd for $C_{17}H_{23}BrN_2O_2 \cdot 0.5\ H_2O$: C, 54.26; H, 6.43; N, 7.44;

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(26) Fischer, H.; Orth, H. *Die Chemie des Pyrrols*; Johnson Reprint Corp., N.Y. 1968 Vol. 2, Part 1, (a) p. 199-201, (b) p. 436-437.
(27) Fischer, H.; Orth, H, "Die Chemie des Pyrrols" Johnson Reprint Co: New York, 1968; Vol. 1, pp 284–286.
(28) (a) Jackson, A. H.; Kenner, G. W.; Sach, G. S. *J. Chem. Soc. C* **1967**, 2045–2059. (b) Fischer, H.; Sturm, G.; Friedrich, H. *Liebigs Ann. Chem.* **1928**, *461*, 244–277.

Br, 21.24. Found: C, 54.35; H, 6.38; N, 6.99; Br, 21.11.

^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, t, J = 7.5 Hz, 3′-Et), 2.02 (3 H, s, 4′-Me), 2.29 (3 H, s, 3-Me), 2.49–2.71 (6 H, m), 2.59 (3 H, s, 5-Me), 7.13 (1 H, s, meso), 7.48 (1 H, s, 5-H), 12.80 (2 H, v br s, NH) (broad humps at ca. δ 6.1 and 10.3 presumably due to hydration and CO_2H, respectively).

^{13}C NMR ($CDCl_3$ at 77.20) δ 176.34 (CO_2H), 157.34 (5), 147.99 (3′), 144.64 (3), 139.81 (5′), 128.10 (4), 127.78 (2), 126.17 (2′), 124.06 (4′), 121.00 (meso), 33.69 ($CH_2CH_2CO_2H$), 19.15 ($CH_2CH_2CO_2H$), 18.27 (3′-CH_3CH_2), 16.08 (3′-CH_3CH_2), 13.04 (5-CH_3), 10.40 (3-CH_3), 9.77 (4′-CH_3).

3′-Ethyl-4-(2-(methoxycarbonyl)ethyl)-3,4′,5-trimethyl-2,2′-dipyrromethenium Bromide (16d). Method A. Benzyl 4-(2-(methoxycarbonyl)ethyl)-3,5-dimethyl-2-pyrrolecarboxylate (**9b**)[29] (15.8 g, 50.3 mmol) was hydrogenated to completion in tetrahydrofuran (250 mL) containing triethylamine (10 drops) and 10% Pd–C (1.20 g) at 1 atm and room temperature.

3-Ethyl-4-methyl-2-pyrrolecarboxaldehyde (**14a**)[15] (6.91 g, 50.4 mmol) was added to the mixture, which was warmed (steam bath) to dissolve the solids and then filtered to remove the catalyst. Methanol (100 mL) was added to the filtrate, followed by 48% HBr (10.1 mL). After 3 min, trimethyl orthoformate (105 mL) was added, and the mixture was warmed briefly (steam bath). The solvent was removed in vacuo, and the residue was taken into methanol (50 mL). After seeding, the product was allowed to crystallize undisturbed for several hours. It was filtered off, rinsed with ethyl acetate, diethyl ether, and finally petroleum ether (bp 30–60 °C), and dried. Yield 11.5 g (59.8%).

Method B. 2,4-Dimethyl-3-pyrrolepropanoic acid (**11c**) (8.42 g, 50.4 mmol) and 3-ethyl-4-methyl-2-pyrrolecarboxaldehyde (**14a**)[15] (6.86 g, 50.0 mmol) were dissolved in CH_3OH (50 mL) (steam bath) and treated with 48% HBr (10 mL). Trimethyl orthoformate (101 mL) was added over several minutes through the reflux condenser, reacting vigorously. After 2 h of reflux, the solvent was removed in vacuo. The residue was recrystallized from CH_3OH (50 mL) at 0 °C. The solids were filtered off, rinsed with ethyl acetate and then petroleum ether (bp 60–115 °C), and dried. Yield 12.1 g (63.6%).

Anal. Calcd for $C_{18}H_{25}BrN_2O_2$: C, 56.70; H, 6.61; N, 7.35; Br, 20.96. Found: C, 56.78; H, 6.72; N, 7.11; Br, 20.75.

^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 7.5 Hz, 3′-Et), 2.09 (3 H, s, 4′-Me), 2.39 (3 H, s, 3-Me), 2.55 (2 H, q, J = 7.5 Hz, 3′-Et), 2.71 (3 H, s, 5-Me), 2.74± (4 H, m, CH_2CH_2), 3.69 (3 H, s, CH_3O), 7.25 (1 H, s, meso), 7.52 (1 H, d, J = 3.5 Hz, 5′-H), 13.01 (1 H, v br s, 1′-NH), 13.15 (1 H, br s, 1-NH).

^{13}C NMR ($CDCl_3$ at 77.48) δ 172.51 (CO), 157.22 (5), 147.91 (3′), 144.61 (3), 139.26 (5′), 128.11 (4), 127.52 (2), 125.85 (2′), 123.79 (4′), 121.07 (meso), 51.78 (CH_3O), 33.59 (CH_2CH_2CO), 19.25 (CH_2CH_2CO), 18.32 (3′-CH_3CH_2), 16.15 (3′-CH_3CH_2), 13.09 (5-CH_3), 10.52 (3-CH_3), 9.83 (4′-CH_3).

5′-Bromo-5-(bromomethyl)-3′-ethyl-4-(2-(methoxycarbonyl)ethyl)-3,4′-dimethyl-2,2′-dipyrromethenium Bromide (1c). 3′-Ethyl-4-(2-(methoxycarbonyl)ethyl)-3,4′,5-trimethyl-2,2′-dipyrromethenium bromide (**16d**) (7.64 g, 20 mmol) in CH_2Cl_2 (85 mL) was treated with CF_3CO_2H (15.6 mL) and Br_2 (7.15 g, 44.7 mmol) for 3 days, protected from atmospheric moisture. The solvent was removed in vacuo (40 °C). The residue was triturated with diethyl ether containing cyclohexene (1 mL) until it crystallized. The solids were filtered off, rinsed with Et_2O and then petroleum ether (bp 65–100 °C), and dried. Yield 10.15 g (nominally 94%). When ^{13}C NMR showed a CH_2Br:CH_3 ratio of ca. 2:1 due to unreacted **17b**, the solids were redissolved in CH_2Cl_2 (69 mL) and treated with CF_3CO_2H (32 mL) and Br_2 (3.25 g, 20.3 mmol). After 4 days, the solvent was evaporated as before.

The residue, in CH_2Cl_2 (10 mL), was treated with cyclohexene (2.5 mL) and then diethyl ether (60 mL). The resulting crystals were filtered off, washed as before, and dried. Yield 8.48 g (78.4%). By ^{13}C NMR, this was 95% pure.

^{13}C NMR ($CDCl_3$ at 77.31) δ 172.57 (CO), 151.15 (5), 150.36 (3′), 144.07 (3), 133.62 (5′), 128.17 (4), 127.71 (2), 127.33 (2), 126.46 (4′), 121.02 (meso), 51.85 (CH_3O), 33.24 (CH_2CH_2CO), 19.98 (CH_2Br), 19.09 (2 C, CH_2CH_2CO and 3′-CH_3CH_2), 16.06 (3′-CH_3CH_2), 10.62 (3-CH_3), 9.73 (4′-CH_3).

(29) Johnson, A. W.; Markham, E.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1958**, 4254–4257.

Mesoporphyrin II Dimethyl Ester (4b).[26b] **(A) 1-Bromo-3,13-diethyl-8,18-bis(2-(methoxycarbonyl)ethyl)-2,7,12,17,19-pentamethyl-5,15-biladienium Dibromide (3b).** 3′-Ethyl-4-(2-(methoxycarbonyl)ethyl)-3,4′,5-trimethyl-2,2′-dipyrromethenium bromide (**16d**) (5.60 g, 14.7 mmol) and 5′-bromo-5-(bromomethyl)-3′-ethyl-4-(2-(methoxycarbonyl)ethyl)-3,4′-dimethyl-2,2′-dipyrromethenium bromide (**1c**) (7.92 g, 14.7 mmol) in CH_2Cl_2 (250 mL, distilled from CaH_2) were treated with $SnCl_4$ (22 mL). After 75 min at room temperature, the mixture was quenched with 48% HBr (37 mL)–H_2O (211 mL) and shaken until the organic phase cleared.

The organic phase was isolated and added to 48% HBr (12.3 mL) in CH_3OH (102 mL). The solvent was removed at 40 °C (rotary evaporator) until a thick slurry of product resulted. The slurry was thinned to a filterable consistency with methanol, ethyl acetate, and diethyl ether. The solids were filtered off, washed with ether (20 mL), and finally petroleum ether (bp 30–60 °C). Yield 10.72 g (87%).

Anal. Calcd for $C_{36}H_{47}Br_3N_4O_4$: C, 51.51; H, 5.64; N, 6.67; Br, 28.55. Found: C, 51.81; H, 5.77; N, 6.42; Br, 28.18.

^{1}H NMR (CF_3CO_2H in $CDCl_3$) δ 1.19 (3 H, t, J = 7.5 Hz), 1.23 (3 H, t, J = 7.5 Hz), 2.12 (3 H, s), 2.16 (3 H, s), 2.37 (6 H, s), 2.52–2.99 (12 H, m), 2.75 (3 H, s), 3.75 (3 H, s), 3.77 (3 H, s), 4.66 (2 H, s), 7.29 (1 H, s), 7.34 (1 H, s), 12.02 (2 H, br s), 12.52 (2 H, br s) (TFA at 10.53).

^{13}C NMR (10% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.29, CF_3CO_2H at 114.84, 158.89) δ 175.59 (CO); 175.16 (CO); 158.28 (19); 151.52, 150.41, 150.16 (2 C) (3, 9, 11, 13); 146.10 (2 C, 7, 17); 133.20 (1); 128.69, 128.28, 128.09 (2 C), 127.98, 127.24, 126.01 (2, 4, 6, 8, 14, 16, 18); 123.80 (12); 121.16 (5); 120.75 (15); 52.94 (2 C, CH_3O); 33.96 (2 C, $CH_2CH_2CO_2Me$); 24.01 (10); 19.38 (2 C, $CH_2CH_2CO_2Me$); 19.08 (3-CH_3CH_2); 18.63 (13-CH_3CH_2); 15.86 (2 C, 3,13-CH_3CH_2); 13.36 (19-CH_3); 10.55 (17-CH_3); 10.33 (7-CH_3); 9.65 (2-CH_3); 9.13 (12-CH_3).

(B) Cyclization of the Biladiene 3b to Mesoporphyrin II Dimethyl Ester (4b). The biladiene (**3b**) (9.96 g, 11.9 mmol) was dissolved in dimethyl sulfoxide (505 mL) and then treated with pyridine (24 mL). After 4 days in the dark at room temperature in an open Erlenmeyer flask (3 L), the reaction mixture was exposed to daylight in a window for 6 days longer.

The resulting purple satiny flakes were filtered off, rinsed with methanol, and then dried. Yield 4.54 g (64.5%). After 2 days of further standing, the filtrates had finally gone reddish and were refiltered. Second crop, 0.82 g (11.7%); total 5.36 g (76.2%).

^{13}C NMR ($CDCl_3$, CF_3CO_2H) ($CDCl_3$ at 77.18; CF_3CO_2H at 113.91, 157.38) δ 174.06 (CO), 144.42, 142.64, 142.06, 141.76, 141.37, 140.00, 138.61, 138.03, 99.01, 98.58, 52.28 (CH_3O), 35.60 (CH_2CH_2CO), 21.80 (CH_2CH_2CO), 20.16 (CH_3CH_2), 16.35 (CH_3CH_2), 11.99 (CH_3), 11.81 (CH_3). (Each peak represents two carbons.)

1,7-Bis(5′-carboxy-3′-ethyl-3,4′,5-trimethyl-2,2′-dipyrromethen-4-yl)heptane Dihydrobromide Trihydrate (5e). 1,7-Bis(5-(benzyloxycarbonyl)-2,4-dimethylpyrrol-3-yl)heptane[2a] [**9**: R = CH_2Ph; R_3 = Me; R_4 = $-(CH_2)_7-$] (11.1 g, 20.1 mmol) was hydrogenated to completion in tetrahydrofuran (250 mL) containing triethylamine (20 drops) and 30% Pd–C (0.8 g) at 1 atm and room temperature. The catalyst was filtered off and rinsed with THF. 4-Ethyl-5-formyl-3-methyl-2-pyrrolecarboxylic acid (**13a**)[28] (7.45 g, 41.2 mmol) was added to the filtrates, which were then concentrated in vacuo to an oil. This was dissolved in acetic acid (100 mL), treated with concentrated HBr (42.5 mL, 48%), and then diluted with H_2O (110 mL). The mixture was seeded, and after crystallization was well established, further H_2O (100 mL) was added. After cooling in ice, the mixture was filtered, and the orange fluffy solids were rinsed with slightly acidified (HBr) H_2O until the rinsings were colorless and then allowed to dry in air. Yield 15.84 g (95.3%). The first crop was analyzed several years later, having maintained both its stability and hydration in the interim.

Anal. Calcd for $C_{37}H_{50}Br_2N_2O_4 \cdot 3H_2O$: C, 53.63; H, 6.81; N, 6.76; Br, 19.29. Found: C, 53.70; H, 6.77; N, 6.68; Br, 19.15.

^{1}H NMR (30% CF_3CO_2H in $CDCl_3$) δ 1.18 (6 H, t, J = 7.5 Hz, 3′-Et), 1.36 (6 H, s, chain), 1.48 (4 H, br s, chain), 2.32 (6 H, s, 4′-Me), 2.37 (6 H, s, 3-Me), 2.49 (4 H, t, J = 7.4 Hz, chain termini), 2.64 (6 H, s, 5-Me), 2.72 (4 H, q, J = 7.6 Hz, 3′-Et), 7.35 (2 H, s, meso), 10.54 (2 H, s, 1′-NH), 11.88 (2 H, s, 1-NH), CO_2H not observed; 9.64 (s, TFA).

^{13}C NMR (20% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.31, CF_3CO_2H at 114.86, 160.35) δ 169.40 (2 C, 5), 165.31 (2 C, C=O), 149.14 (2 C, 3'), 145.63 (2 C, 3), 135.90 (2 C), 134.07 (2 C), 130.74 (2 C), 130.64 (2 C), 127.45 (2 C), 121.80 (2 C, meso), 29.59 (5 C, 2'', 3'', 4'', 5'', 6''), 24.26 (2 C, 1'', 7''), 18.35 (2 C, 3'-CH_3CH_2), 15.92 (2 C, 3'-CH_3CH_2), 14.29 (2 C, 5-CH_3), 10.47 (2 C, 3-CH_3), 10.08 (2 C, 4'-CH_3).

1,7-Bis(3'-ethyl-3,4',5-trimethyl-2,2'-dipyrromethen-4-yl)heptane Dihydrobromide (5f). A solution of the heptanediylbis(5'-carboxydipyrromethenium bromide) trihydrate (**5e**) (530 mg, 0.64 mmol) in trifluoroacetic acid (5 mL) was refluxed 2 h. The solvent was removed in vacuo. The residue was dissolved in CH_3OH (5 mL) and treated with 48% HBr (2 mL), and the resulting solution was seeded with authentic **5f**.[2a] Yield 287.7 mg (65.5%). The ^1H NMR was identical with that of authentic **5f**.[2a]

Anal. Calcd for $C_{35}H_{50}Br_2N_4$: C, 61.22; H, 7.34; N, 8.16; Br, 23.28. Found: C, 60.96; H, 7.23; N, 8.21; Br, 23.51.

^1H NMR ($CDCl_3$) δ 1.17 (6 H, t, J = 7 Hz, 3'-Et), 1.33 [10 H, br s, $-(CH_2)_5-$], 2.05 (6 H, s, 4'-Me), 2.27 (6 H, s, 3-Me), 2.39 (4 H, t, J = 7 Hz, chain termini), 2.65 (6 H, s, 5-Me), 2.68 (4 H, q, J = 7 Hz, 3'-Et), 7.12 (2 H, s, meso), 7.48 (2 H, d, J = 4 Hz, 5'-H), 12.96 (2 H, v br s, 1'-NH), 13.16 (2 H, br s, 1-NH).

^{13}C NMR ($CDCl_3$ at 77.06) δ 157.91 (5), 147.31 (3'), 143.72 (3), 139.06 (5'), 130.49 (4), 127.80 (2), 125.81 (2'), 123.67 (4'), 120.57 (meso), 29.77 (2 C, 2'', 6''), 29.38 (1 C, 4''), 29.26 (2 C, 3'', 5''), 23.95 (2 C, 1'', 7''), 18.32 (3'-CH_3CH_2), 16.11 (3-CH_3CH_2), 13.30 (5-Me), 10.34 (3-Me), 9.80 (4'-Me). (All peaks of unmarked multiplicity represent two carbons.)

1,8-Bis(5'-carboxy-3'-ethyl-3,4',5-trimethyl-2,2'-dipyrromethen-4-yl)octane Dihydrobromide Hexahydrate (5b). This compound was prepared similarly to **5e** on a 20.1-mmol scale from 1,8-bis(5-(benzyloxycarbonyl)-2,4-dimethylpyrrol-3-yl)octane[2a] [**9**: R = CH_2Ph; R_3 = Me; R_4 = $-(CH_2)_8-$] and **13a**.[28] The yield, as chocolate brown sparkling granules, was 15.2 g (84.4%).

Anal. Calcd for $C_{38}H_{52}Br_2N_2O_4 \cdot 6H_2O$: C, 50.90; H, 7.19; N, 6.24; Br, 17.82. Found: C, 50.86; H, 7.02; N, 6.10; Br, 17.63.

^1H NMR (30% CF_3CO_2H in $CDCl_3$) δ 1.19 (6 H, t, J = 7.5 Hz, 3'-Et), 1.34 (8 H, s, chain), 1.48 (4 H, br s, chain), 2.33 (6 H, s, 4'-Me), 2.38 (6 H, s, 3-Me), 2.49 (4 H, t, J = 7.5 Hz, chain termini), 2.64 (6 H, s, 5-Me), 2.72 (4 H, q, J = 7.5 Hz, 3'-Et), 7.35 (2 H, s, meso), 10.50 (2 H, s, 1'-NH), 11.81 (2 H, s, 1-NH), CO_2H not observed; 9.54 (s, TFA).

^{13}C NMR (20% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.31; CF_3CO_2H at 114.85, 160.68) δ 169.63 (5), 165.59 (CO), 149.26 (3), 145.61 (3'), 136.16, 134.27, 130.84, 130.56, 127.59, 121.80 (meso), 29.65 (6 C, 2'', 3'', 4'', 5'', 6'', 7''), 24.32 (2 C, 1'', 8''), 18.40 (3'-CH_3CH_2), 15.95 (3'-CH_3CH_2), 14.29 (5-CH_3), 10.53 (3-CH_3), 10.14 (4'-CH_3). (All peaks of unmarked multiplicity represent two carbons.)

1,8-Bis(5'-bromo-5-(bromomethyl)-3'-ethyl-3,4'-dimethyl-2,2'-dipyrromethen-4-yl)octane Dihydrobromide (5d). Octanediylbis(5'-carboxy-2,2'-dipyrromethenium bromide) hexahydrate (**5b**) (3.96 g, 4.41 mmol) was suspended in 1,2-dichloroethane (50 mL). Trifluoroacetic acid (15 mL) was added, causing the solids to clot temporarily.[30] Bromine (4.00 g, 25 mmol) in 1,2-dichloroethane (27 mL) was added, and the mixture was allowed to stand at room temperature, protected from atmospheric moisture. After 2 days further Br_2 (1.1 g, 6.8 mmol) in $ClCH_2CH_2Cl$ (10 mL) was added.

The following day, 30% HBr in glacial acetic acid (10 mL) was added, followed, with magnetic stirring, by absolute diethyl ether (300 mL). The resulting black crystalline solids were filtered off, washed with Et_2O and then petroleum ether (bp 30–60 °C), and dried over KOH. Yield 5.11 g.

Anal. Calcd for $C_{36}H_{48}Br_6N_4$: C, 42.55; H, 4.76; N, 5.51; Br, 47.17. Calcd for $C_{36}H_{48}Br_8N_4$: C, 36.77; H, 4.11; N, 4.76; Br, 54.36. Found: C, 37.97, 37.97, 37.58; H, 4.23, 4.23, 4.35; N, 4.34, 5.02, 4.82; Br, 48.70. The crude material appeared to be a partial perbromide with some solvation, possibly by H_2O (^1H NMR peak at δ 1.78).

^1H NMR ($CDCl_3$) δ 1.21 (6 H, t, J = 7.5 Hz, 3'-Et), 1.36 (12 H, br s, chain), 1.78 (br s, H_2O?), 2.08 (6 H, s, 4'-Me), 2.31 (6 H, s, 3-Me), 2.52 (4 H, t, J = 7 Hz, chain), 2.76 (4 H, q, J = 7.5 Hz, 3'-Et), 4.90 (4 H, s, CH_2Br), 7.17 (2 H, s, meso), 13.78 (4 H, br s, NH).

^{13}C NMR (30% (w/w) CF_3CO_2H in $CDCl_3$) ($CDCl_3$ at 77.45; CF_3CO_2H at 114.89 and 162.06) δ 152.01 (5?); 151.72 (3'?); 145.55 (3); 133.92 (5'); 131.87 (4); 129.04 (2'?); 128.90 (2?); 127.93 (4'?); 121.58 (meso); 30.13, 30.03, 29.79, 24.44 (1'', 8'') (chain); 19.84 (CH_2Br); 19.44 (3'-CH_3CH_2); 16.00 (3'-CH_3CH_2); 10.70 (3-CH_3); 9.81 (4'-CH_3). (All peaks represent two carbons.)

A sample (220.6 mg) in CH_2Cl_2 was treated with cyclohexene (1 mL), and the resulting solution was filtered. HBr (30%) in acetic acid (2 mL) was added, followed by ethyl acetate (50 mL), and the mixture was concentrated with a rotary evaporator. The crystallized solids were filtered off, washed with ethyl acetate and then hexane, and dried. Yield 153.3 mg.

Anal. Calcd for $C_{36}H_{48}Br_6N_4 \cdot C_4H_8O_2$: C, 43.50; H, 5.11; N, 5.07; Br, 43.41. Found: C, 43.22; H, 5.07; N, 5.36; Br, 43.64.

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(30) It is significant that the water of crystallization of **5b** does *not* interfere with the reaction.