527 (4.18), 561 (3.72), 604 (3.66), 662 (3.56) nm; ^{1}H NMR ($CDCl_3$) δ −2.17 (2 H, br, NH), 2.30 (8 H, 4 × $CH_2CH_2CH_2$), 3.50 (8 H, 4 × β-CH_2), 4.30 (8 H, 4 × meso-CH_2), 7.5–7.9 (20 H, 4 × Ph); ^{1}H NMR (TFA-*d*–$CDCl_3$) δ 2.41 (8 H, 4 × $CH_2CH_2CH_2$), 3.70 (8 H, 4 × β-CH_2), 4.42 (8 H, 4 × meso-CH_2), 7.4–7.8 (20 H, 4 × Ph).

2,7,12,17-Tetraisopropyl-3,5:8,10:13,15:18,20-tetrapropanoporphyrin (21e). Only trace amounts of porphyrin were obtained from THI **10e**. The product was isolated as an unstable green film: UV (CH_2Cl_2) λ_{max} 432, 532, 574, 610, 672 nm.

2,7,12,17-Tetramethyl-3,5:8,10:13,15:18,20-tetrakis(3-methylpropano)porphyrin (28c). Prepared from **26c** (2.30 g) by the method described for **21a**. Crystallization from dichloromethane–methanol gave the title porphyrin[27] (51 mg; 3%) as purple crystals: mp >300 °C; FAB MS *m/e* 583 ([M + H]$^+$); HR FAB MS calcd for $C_{40}H_{46}N_4$ + H 583.3801, found 583.3781; UV ($CHCl_3$) λ_{max} ($\log_{10}\epsilon$) 422 (5.33), 520 (4.16), 554 (3.69), 595 (3.64), 641 (3.53) nm; ^{1}H NMR ($CDCl_3$) δ −3.05 (2 H, br, 2 × NH), 1.82–1.92 (12 H, m, 4 × $CHCH_3$), 2.77–2.81 (4 H, m), 3.0 (4 H, m) (4 × CH_2CH), 3.54 (12 H, s, 4 × porphyrin-CH_3), 3.7–4.0 (8 H, m, 4 × porphyrin-CH_2), 5.78 (4 H, m, 4 × $CHCH_3$).

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Supplementary Material Available: NMR spectra of the obtained compounds (38 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Porphyrins with Exocyclic Rings. 2.[1] Synthesis of Geochemically Significant Tetrahydrobenzoporphyrins from 4,5,6,7-Tetrahydro-2*H*-isoindoles[2,3]

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Benzo- and tetrahydrobenzoporphyrins are widespread constituents of oil shales and petroleum. Although the origins of these materials are not known, a case is made for divinylchlorophyll a, a widespread pigment in marine algae, being the precursor to many of these geoporphyrins. Total syntheses of four tetrahydrobenzoporphyrins related to etioporphyrin III are described. Tetrahydroisoindoles were prepared by condensation of isocyanoacetates with 1-nitrocyclohexene in the presence of DBU or by reaction of aminomalonates with 2-formylcyclohexanone. Condensation of 3-unsubstituted 4,5,6,7-tetrahydro-2*H*-isoindoles **23c** and **23d** with (acetoxymethyl)pyrroles in the presence of Montmorillonite clay gave dipyrrylmethanes **28a** and **36a** in excellent yield. Hydrogenolysis of the benzyl esters and subsequent acid-catalyzed condensation with pyrrole aldehydes **37a** and/or **37b** gave a series of a,c-biladiene dihydrobromides. Copper(II) mediated cyclization of the a,c-biladienes **32**, **33**, **35**, and **38**, followed by demetallation with 15% sulfuric acid–trifluoroacetic acid, gave four isomeric tetrahydrobenzoporphyrins **10**–**13** in unusually high yield. This work provides a general route for the synthesis of these important porphyrin molecular fossils.

Introduction

Sedimentary deposits, such as oil shales, commonly contain complex mixtures of metalloporphyrins. Initially, there were thought to be two major groups of petroporphyrins: (1) the etioporphyrins, or polyalkyl porphyrins related to etioporphyrin III, and (2) cycloalkanoporphyrins related to deoxophylloerythroetioporphyrin (DPEP; **1**). DPEP is believed to be a degradation product, or molecular fossil, of chlorophyll a (**2a**) and related biological pigments. On the other hand, the etioporphyrins are probably derived from both the hemes (e.g., protoheme (**3**)) and the chlorophylls. However, it is now known that many additional structural types are present in organic-rich sediments, and the origins of these materials is not always clear. In the 1960's, a minor family of petroporphyrins with rhodo-type visible spectra were identified.[4,5] On the basis of mass spectrometry and IR data, Baker et al. suggested[5] that the compounds were benzoporphyrins **4**. This proposal received additional support when synthetic monobenzoporphyrins were shown[6] to have electronic spectra similar to the sedimentary "rhodoporphyrins".

In 1984, Barwise and Roberts isolated[7] a "diDPEP" (porphyrin with two exocyclic rings) from El Lajjun oil shale (Jordan). On the basis of mass spectrometry and partial NOE difference proton NMR data, structure **5** was proposed for this compound. Subsequently, Maxwell and co-workers isolated[8] two benzoDPEP's (**6a** and **6b**) from Boscan oil shale (Venezuela) and unambiguously demonstrated the structures of these petroporphyrins by NOE difference proton NMR spectroscopy. Structures **5** and

(1) Part 1: Lash, T. D.; Bladel, K. A.; Shiner, C. M.; Zajeski, D. L.; Balasubramaniam, R. P. *J. Org. Chem.*, preceding paper in this issue.

(2) Results presented, in part, at the 23rd Midwest Regional ACS Meeting, University of Iowa, Iowa City, IA, Nov 1988; May, D. A., Jr.; Lash, T. D. *Program and Abstracts*, 192. 197th National Meeting of the American Chemical Society, Dallas, TX, April 1989; Lash, T. D.; Balasubramaniam, R. P.; May, D. A., Jr. *Book of Abstracts*, ORGN 257.

(3) Results taken, in part, from: May, D. A., Jr. M.S. Thesis, Illinois State University, 1989.

(4) Howe, W. W. *Anal. Chem.* **1961**, *33*, 255. Thomas, D. W.; Blumer, M. *Geochim. Cosmochim. Acta* **1964**, *28*, 1147. Millson, M. F.; Montgomery, D. S.; Brown, S. R. *Ibid.* **1966**, *30*, 207.

(5) Baker, E. W. *J. Am. Chem. Soc.* **1966**, *88*, 2311. Baker, E. W.; Yen, T. F.; Dickie, J. P.; Rhodes, R. E.; Clark, L. F. *Ibid.* **1967**, *89*, 3631.

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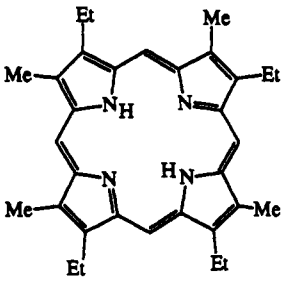
(7) Barwise, A. J. G.; Roberts, I. *Org. Geochem.* **1984**, *6*, 167.

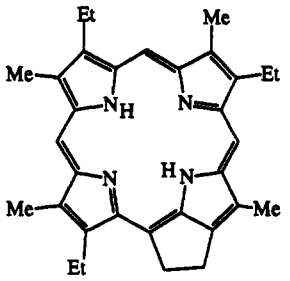
(8) Kaur, S.; Chicarelli, M. I.; Maxwell, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 1347.

0022-3263/92/1957-4820$03.00/0

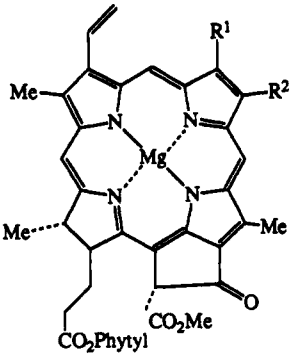
Chart I



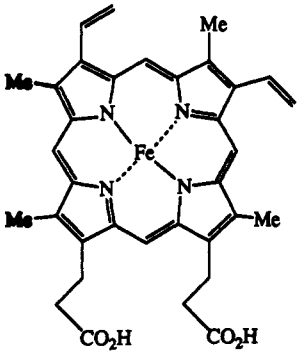
Etioporphyrin-III



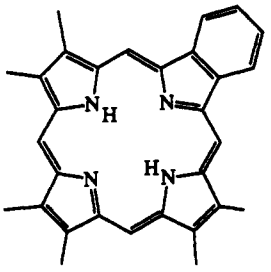
1



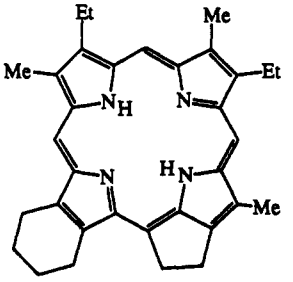
2 a. R^1 = Me; R^2 = Et (Chlorophyll-a)
b. R^1 = CHO; R^2 = Et (Chlorophyll-b)
c. R^1 = Me; R^2 = CH=CH_2



3



4



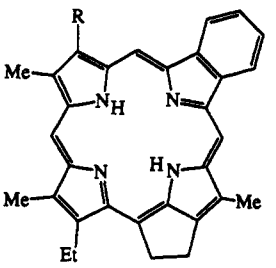
5

6 both bear five-membered exocyclic rings, and this indicates that they are probably derived from the chlorophylls. However, the origin of the six-membered ring or benzo unit is unclear. Maxwell et al. have reinvestigated[9] the El Lajjun oil shale and have isolated and characterized two fused ring "diDPEPs" **7a** and **7b**. However, the tetrahydrobenzoDPEP **5** could not be detected, and it seems likely that Barwise and Roberts were in fact handling **7a**. French workers[10] have isolated tetrahydrobenzoporphyrins **8a**, **8b**, and **9** from the Moroccan Timahdit oil shale, and complex mixtures of benzoporphyrins have been shown to be present in a variety of organic-rich sediments.[11]

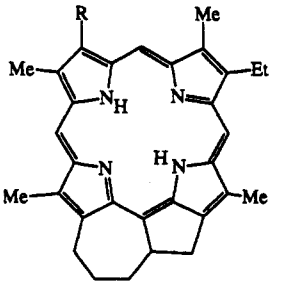
Origins of Sedimentary Benzo- and Tetrahydrobenzoporphyrins

The origins of sedimentary benzo- and tetrahydrobenzoporphyrins are obscure. Benzoporphyrins have been detected in relatively immature sediments[12] and must, therefore, have been formed under mild conditions. A number of proposals for the origin of the benzo unit have appeared in the literature. The cyclization of the alkyl units in bacteriochlorophylls d has been suggested,[8] but this seems somewhat improbable. The cyclization of propionic acid (or ester) side chains with adjacent methyl substituents has been proposed,[6b,7] but again there is little evidence to support such a pathway. Cycloadditions involving a tautomer of chlorophyll b (**2b**) has also been put forward[12b] to explain the formation of the benzo unit at the B ring, and while this is an imaginative proposal, there

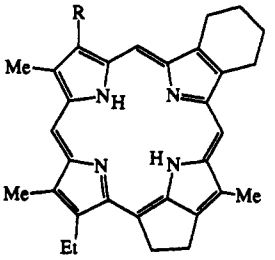
Chart II



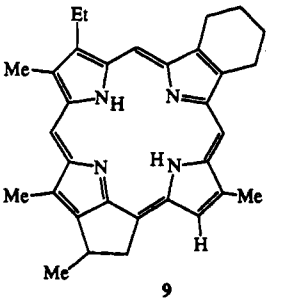
6 a. R = Et
b. R = Me



7 a. R = Et
b. R = Me



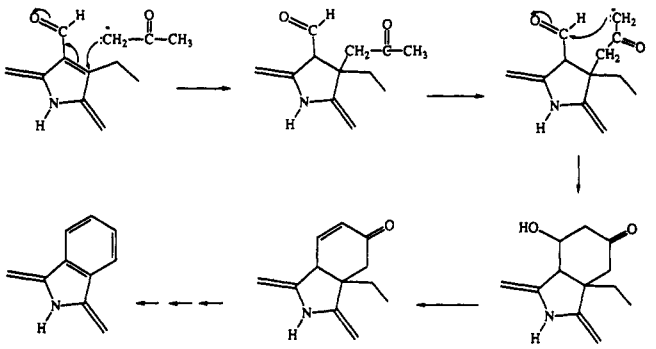
8 a. R = Et
b. R = Me



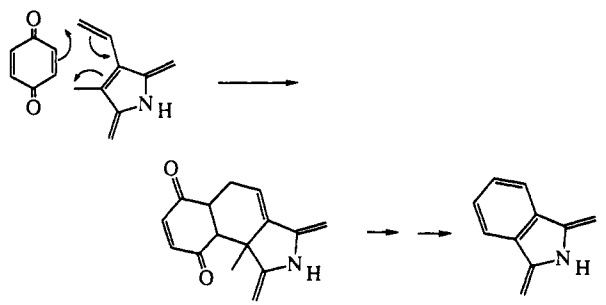
9

(9) Prowse, W. G.; Chicarelli, M. I.; Keely, B. J.; Kaur, S.; Maxwell, J. R. *Geochim. Cosmochim. Acta* **1987**, *51*, 2875.
(10) Verne-Mismer, J.; Ocampo, R.; Callot, H. J.; Albrecht, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1581.
(11) Kaur, S.; Gill, J. P.; Evershed, R. P.; Eglinton, G.; Maxwell, J. R. *J. Chromatogr.* **1989**, *473*, 135.
(12) (a) Baker, E. W.; Louda, J. W. *Org. Geochem.* **1986**, *10*, 905. (b) Quirke, J. M. E.; Dale, T.; Britton, E. D.; Yost, R. A.; Trichet, J.; Belayoumi, H. *Ibid.* **1990**, *15*, 169.

Scheme I



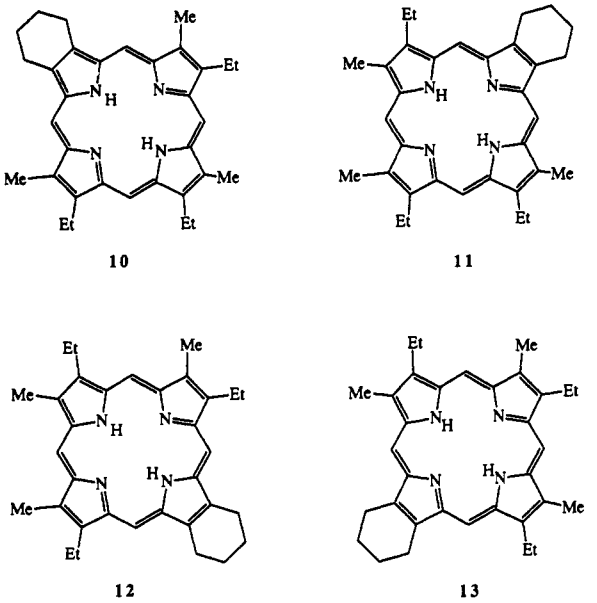
Scheme II



is no evidence for reactions of this type at the present time. It has also been suggested[6b,13] that the chlorophylls associated with ancient organisms may have retained an acetate and propionate group on the B ring (these moieties are present in the biosynthetic precursor uroporphyrinogen III) and that the six-membered ring structure arose via a Dieckmann cyclization. Chemistry of this type was utilized in the synthesis of benzoporphyrins,[6] but the likelyhood that such divergent chlorophyll structures were common constituents of photosynthetic organisms in past geological ages must be considered highly speculative at best. Another possibility, which has not been proposed previously, is that chlorophyll b undergoes a conjugative addition with an enolate ion (Scheme I, using acetone as an example), followed by cyclization onto the formyl moiety to give the six-membered ring.

Baker and Palmer have proposed[14] that the benzo unit arises by way of a Diels–Alder cycloaddition between naturally occurring quinones and chlorophyll a (Scheme II). Diels–Alder reactions of this type have been studied in detail,[15,16] primarily with protoporphyrin IX, and in certain cases the adducts have been converted[17] into the related benzoporphyrins. Hence, the proposed chemistry in Scheme II has solid support from these model studies. In addition, plastoquinones are present in substantial quantities in photosynthetic organisms. It was anticipated that Diels–Alder cycloadditions of chlorophyll a (**2a**) would lead to the formation of geoporphyrins with benzo-ring fusion at the A ring. As structures of this type have never been observed in organic sediments, the Diels–Alder hypothesis has fallen from favor. We would like to point out that divinyl chlorophyll a (**2c**) is a common constituent of marine algae.[18] Cycloaddition reactions with **2c** are likely to take place regioselectively at the B ring, rather than the A ring, since this would lead to the more favorable bacteriochlorin chromophore.[16] Hence, we favor divinyl chlorophyll a as the biological precursor to many of the benzo- and tetrahydrobenzoporphyrins from oil shales and petroleum. Chlorophyll c_2 is more likely to be the precursor to tetrahydrobenzoporphyrin **9**.[10]

Chart III



10 **11** **12** **13**

Synthesis of Tetrahydrobenzoporphyrins Related to Etioporphyrin III

Given the complexity of the porphyrin structures present in organic sediments, synthetic standards are needed in the analysis of these materials. Our research group is developing new synthetic routes to geochemically significant porphyrins.[19,20] In the present paper, we report new syntheses of tetrahydrobenzoporphyrins. We selected structures **10–13** as target molecules for the present work, as they correspond to the four tetrahydrobenzoporphyrins related to etioporphyrin III. Porphyrins **10** and **11** might arise from Diels–Alder adducts of protoheme (**3**). On the other hand, cyclization of the propionic acid side chains onto the adjacent methyl substituents, as proposed by Clezy and Mirza,[6b] would be expected to give the isomeric tetrahydrobenzoporphyrins **12** and **13**. Hence, the isolation of tetrahydrobenzoetioporphyrins of this type would provide valuable information about the origins of these structures.

The synthesis of tetrahydrobenzoporphyrins **10–13** required the intermediacy of tetrahydroisoindole intermediates. Initially, we elected to prepare this system from 2-acetylcyclohexanone **14** (Scheme II) using Knorr-type chemistry. Oximes of malonate esters are well-known to

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(18) Bidigare, R. R.; Kennicutt, M. C., II; Ondrusek, M. E.; Keller, M. D.; Guillard, R. R. L. *Energy Fuels* **1990**, *4*, 653.
(19) Lash, T. D. *Org. Geochem.* **1989**, *14*, 213. Lash, T. D.; Balasubramaniam, R. P.; Catarello, J. J.; Johnson, M. C.; May, D. A., Jr.; Bladel, K. A.; Feeley, J. M.; Hoehner, M. C.; Marron, T. G.; Nguyen, T. H.; Perun, T. J., Jr.; Quizon, D. M.; Shiner, C. M.; Watson, A. *Energy Fuels* **1990**, *4*, 668.
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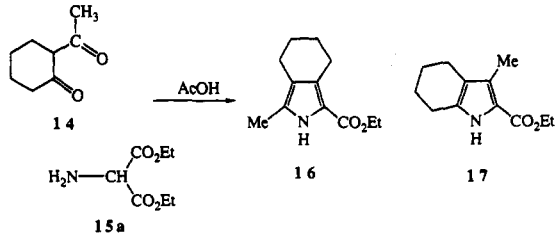
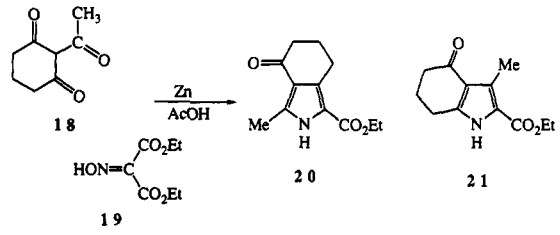
Scheme III



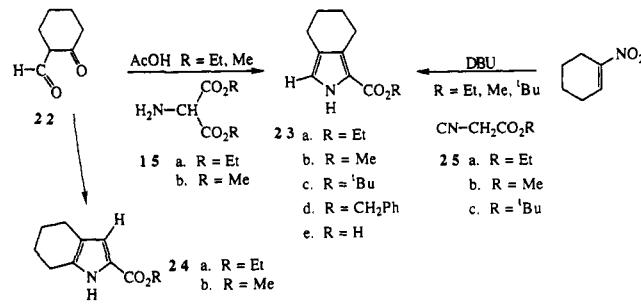
Scheme IV



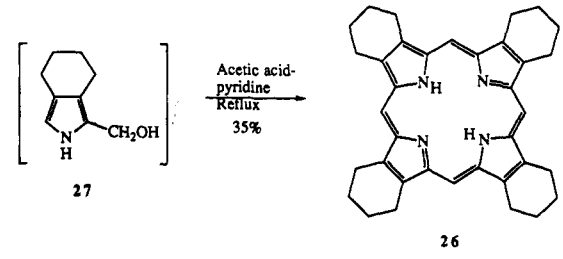
condense[21] with β-diketones in the presence of zinc dust and acetic acid to give pyrroles. The oxime is initially reduced to the corresponding amine **15**, and subsequent reaction leads to pyrrole formation. Dolphin and Paine have shown[22] that yields are considerably improved when the oxime is first reduced by hydrogenation over palladium–charcoal, and the amine is isolated. Condensations between diethyl aminomalonate **15a** and asymmetrical β-diketones usually takes place with initial nucleophilic attack at the less sterically hindered carbonyl group,[22,23] and we anticipated that **15a** and **14** would condense to yield the required tetrahydroisoindole **16** rather than the isomeric tetrahydroindole **17** (Scheme III). In the event, when **14** and **15a** were heated under reflux in acetic acid solution, tetrahydroindole **17** was the sole isolated product. Shortly after we had carried out this study, Paine and co-workers reported[24] a more detailed study on this chemistry. Their work also showed that **17** was formed preferentially from **14**, although 2-acetylcyclopentanone showed the opposite regioselectivity. Interestingly, 2-acetyl-1,3-cyclohexanedione **18** (Scheme IV) was shown[6a] to react with oxime **19** in the presence of zinc dust and acetic acid to give the 5-oxotetrahydroisoindole **20**, albeit in low yield, and the isomeric 4-oxotetrahydroindole **21** was not observed. The factors effecting the regioselectivity of these reactions remain obscure.

In order to form the tetrahydroisoindole system, we needed to direct the initial nucleophilic attack away from the ring carbonyl grouping. We reasoned that aldehydes are more susceptible to nucleophilic attack and that 2-formylcyclohexanone **22** would be more likely to form tetrahydroisoindole **23** (Scheme V). The sodium salt of **22** was prepared by condensation of methyl formate with cyclohexanone in the presence of sodium ethoxide; reaction with diethyl aminomalonate (**15a**) in refluxing acetic acid afforded the required tetrahydroisoindole **23a** in moderate yield (Scheme V), although the isomer **24a** was evident in the carbon-13 NMR spectrum of the crude product (ratio of **23a**:**24a** estimated as 3.6:1). Condensation of **22** with dimethyl aminomalonate (**15b**) similarly gave a mixture

Scheme V



Scheme VI



of **23b** and **24b**. In the latter case, a sample of **24b** was isolated and fully characterized.

We also considered an alternative approach which involved the use of a new pyrrole synthesis developed by Barton and Zard.[25] Condensation of 1-nitrocyclohexene[26] with ethyl isocyanoacetate (**25a**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded **23a** in good yield (Scheme V). The related methyl and *tert*-butyl esters **23b** and **23c** were prepared similarly from methyl isocyanoacetate (**25b**) and *tert*-butyl isocyanoacetate (**25c**), respectively. Transesterification of **23a**, or **23b**, with benzyl alcohol containing trace amounts of sodium benzyl oxide gave the benzyl ester **23d**. Attempts to prepare **23d** directly by condensing dibenzyl oximinomalonate with **22** in the presence of zinc dust and buffered acetic acid resulted in the formation of only trace amounts of pyrrolic products.

Now that the tetrahydroisoindoles **23a–d** were in hand, we decided to investigate the synthesis of the symmetrical porphyrin **26** (Scheme VI). This structure had been previously synthesized by Fuhrhop and Hosseinpour[27] using an entirely different approach. Initially, we converted **23a** to the corresponding carboxylic acid **23e** and attempted to condense this compound with formaldehyde in refluxing pyridine–acetic acid. These experiments only produced trace amounts of porphyrin. However, when the pyrrole ester was first reduced with lithium aluminum hydride to give the labile (hydroxymethyl)pyrrole **27** and further treated with refluxing pyridine–acetic acid, the symmetrical porphyrin **26** (Scheme VI) was formed in excellent yield. When these studies were first reported,[2,3] this latter approach represented a new route for the synthesis of symmetrical porphyrins. However, Ono and co-workers have now independently developed this methodology for the synthesis of a wide selection of symmetrical porphyrins.[28]

Now that the utility of the tetrahydroisoindole intermediates had been demonstrated in a model study, we

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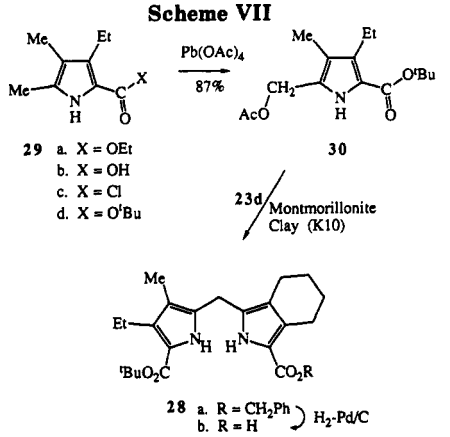
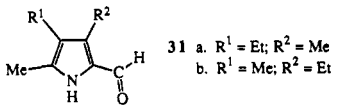
Scheme VII



turned our attention to the synthesis of porphyrins **10–13**. Three of these porphyrins could be synthesized from the dipyrrylmethane **28a** (Scheme VII), and this compound was prepared by the following approach. Saponification of the pyrrole ethyl ester **29a** with sodium hydroxide in methanol–water, followed by careful neutralization at 0 °C, gave the carboxylic acid **29b**. Reaction with 1 equiv of sodium hydroxide afforded the corresponding sodium salt, and further reaction with oxalyl chloride gave the acyl chloride **29c**. Treatment of **29c** with a mixture of *tert*-butyl alcohol and triethylamine yielded the *tert*-butyl ester **29d**. Further reaction with lead tetraacetate in acetic acid gave the corresponding (acetoxymethyl)pyrrole **30**. Condensation of **30** with tetrahydroisoindole **23d** in the presence of Montmorillonite clay[29] gave the desired dipyrrylmethane **28a** in quantitative yield (Scheme VII). Hydrogenolysis over palladium–charcoal gave the related carboxylic acid **28b**.

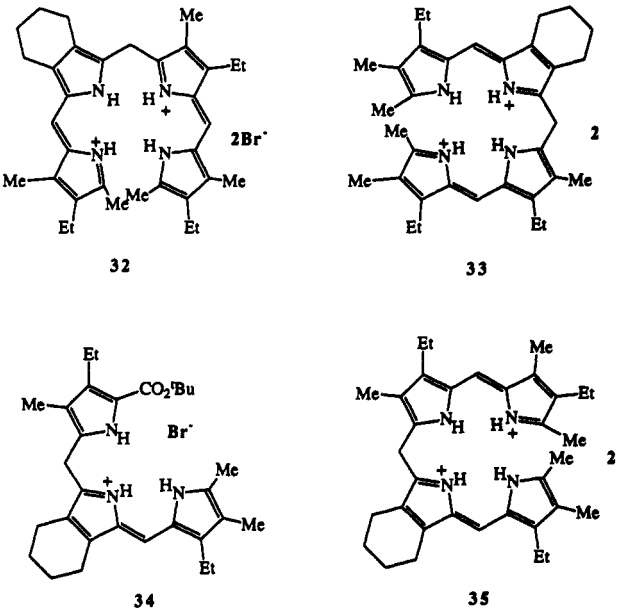
Dipyrrole **28b** was treated with trifluoroacetic acid and further reacted with 2 equiv of the pyrrole aldehyde **31a**



in the presence of hydrobromic acid to give the a,c-biladiene dihydrobromide **32**. Similarly, **28b** and **31b** gave the isomeric a,c-biladiene **33**. Cyclization of the a,c-biladienes in the presence of copper(II) chloride and dimethylformamide at room temperature,[30] and demetalation with 15% sulfuric acid–trifluoroacetic acid, gave the corresponding porphyrins **10** and **11** in excellent yields. The yields for these cyclizations were consistently over 65%, which is substantially higher than is usually obtainable by this procedure.[30] This suggests that the six-membered rings may exert a subtle positive steric interaction during the cyclization process. It is well-known that the peripheral substituents play an essential role in porphyrin formation, and our results suggest that it may be possible to fine tune these interactions to improve the yields of porphyrin products.

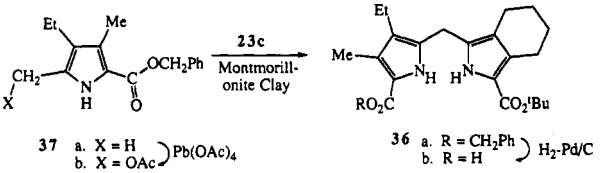
Porphyrin **13** was also prepared from dipyrrylmethane **28b**, although the asymmetry of the target porphyrin forced us to use a slightly different approach. In this synthesis, the stepwise tripyrrene–a,c-biladiene pathway[31] was selected. Condensation of **28b** with **31b** in the presence of *p*-toluenesulfonic acid, followed by brief treatment with HBr, gave the tripyrrene hydrobromide **34**. Further reaction of **34** with **31a** in the presence of hydrobromic acid then yielded the a,c-biladiene **35**. Cyclization of **35** with copper(II) chloride in dimethylformamide gave the related porphyrin **13** in excellent yield.

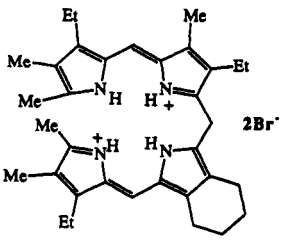
Chart IV



Dipyrrylmethane **36a** (Scheme VIII) was required in the synthesis of the C ring tetrahydrobenzoporphyrin **12**. The pyrrole benzyl ester **37a** reacted with lead tetraacetate in acetic acid to give the (acetoxymethyl)pyrrole **37b**. Subsequent condensation of **37b** with **23c** in the presence of Montmorillonite clay gave the desired dipyrrylmethane **36a** in quantitative yield. Hydrogenolysis over palladium–charcoal afforded the corresponding carboxylic acid **36b**. Treatment with trifluoroacetic acid and condensation with 2 equiv of pyrrole aldehyde **31b** in the presence of hydrobromic acid gave the a,c-biladiene **38**. Copper(II)-mediated cyclization of **38** then gave the tetrahydrobenzoporphyrin **12**, once again in unusually high yield.

Scheme VIII





Conclusion

Efficient syntheses of tetrahydroisoindoles have been developed, and the utility of these compounds in porphyrin synthesis has been explored. Dipyrrylmethanes incorpo-

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rating the tetrahydroisoindole unit have been synthesized and have been further converted into four isomeric a,c-biladienes. Copper(II) chloride mediated cyclization of these a,c-biladienes afforded the tetrahydrobenzoetioporphyrins **10–13** in excellent yield. This work provides a versatile synthetic route to tetrahydrobenzoporphyrin molecular fossils.[32] The availability of synthetic samples may help to provide insights into the origins of these mysterious structures.

Experimental Section

Diethyl malonate, dimethyl malonate, methyl formate, ethyl isocyanoacetate, and methyl isocyanoacetate were purchased from Aldrich Chemical Co.; *tert*-butyl isocyanoacetate was purchased from Fluka Chemie AG. All of these reagents were used without further purification. Chloroform, dichloromethane, and cyclohexanone were distilled prior to use. Hydrogenations were carried out in a Parr hydrogenator at 30–45 psi. Melting points were determined on a Thomas Hoover capillary melting point apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B spectrometer or a Perkin-Elmer 1600 Series FT-IR spectrometer. UV–vis spectra were obtained on a Beckmann DU-40 spectrophotometer. NMR spectra were recorded on a Hitachi-Perkin Elmer R24B 60-MHz NMR spectrometer or a Varian Gemini-300 NMR spectrometer. Mass spectral determinations were made at the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262). Elemental analyses were obtained from Micro-Analysis, Inc., Wilmington, DE 19808.

Diethyl Oximinomalonate (19).[34] Sodium hydroxide pellets (39.0 g) were added to glacial acetic acid (300 mL) in a 2-L three-necked round-bottomed flask. Once the sodium hydroxide had dissolved, a solution of diethyl malonate (232.5 mL) in glacial acetic acid (84 mL) was added. Slow, dropwise addition of sodium nitrite (210 g) in water (375 mL) was initiated immediately. Once the addition was complete (2 h), the resulting mixture was allowed to stir at room temperature overnight. The mixture was extracted twice with equal volumes of ether, and water was added as needed to dissolve any inorganic precipitate. The combined ether extracts were washed first with water and then with 5% sodium bicarbonate solution until the aqueous solutions remained basic. The etherial layer was dried over magnesium sulfate and the solvent removed on a rotary evaporator to give diethyl oximinomalonate (267.9 g; 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (6 H, t, 2 × CH_2CH_3), 4.30 (2 H, q), 4.33 (2 H, q) (2 × OCH_2), 11.0 (1 H, vb, OH).

Dimethyl Oximinomalonate. Prepared from dimethyl malonate (50.0 g) by the procedure given above, except that all of the aqueous solutions were saturated with sodium chloride to diminish losses due to the water solubility of the product. The oxime (50.2 g; 82%) was isolated as a colorless oil that solidified on standing. A sample was recrystallized from chloroform–hexane to give white crystals: mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (3 H, s), 3.89 (3 H, s) (2 × OCH_3), 10.0 (1 H, vb, OH).

Diethyl Aminomalonate (15a).[22] A solution of diethyl oximinomalonate (19; 173.4 g) in ethanol (150 mL) was shaken with 10% palladium–charcoal (5.0 g) under an atmosphere of hydrogen at room temperature and 45 psi for 5 h. The catalyst was filtered off; evaporation of the solvent under reduced pressure afforded diethyl aminomalonate (163.1 g; quantitative) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (6 H, t, 2 × CH_2CH_3), 1.99 (2 H, s, NH_2), 4.00 (1 H, s, CH), 4.15 (4 H, q, 2 × OCH_2).

Dimethyl Aminomalonate (15b). Prepared from dimethyl oximinomalonate (50.0 g) by the method described above. The amine (45.6 g; quantitative) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.02 (2 H, br, NH_2), 3.77 (6 H, s, 2 × OCH_3), 4.20 (1 H, s, CH).

Sodium Salt of 2-Formylcyclohexanone (22).[35] Sodium pellets (23 g) were added to methanol (225 mL) in a 1-L round-bottomed flask, and the mixture was stirred, with cooling to prevent the reaction from becoming too vigorous, until all the sodium had dissolved. A mixture of cyclohexanone (98 g) and methyl formate (60 g) were added to the stirred solution of sodium methoxide over a period of 30 min, and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with ether and the resulting precipitate suction filtered, washed with ether, and dried in vacuo to give the sodium salt of **22** (103 g; 70%) as an amorphous white powder.

Ethyl 4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylate (23a). Method A. Diethyl aminomalonate (94.1 g) was added dropwise over a period of 10 min to a stirred solution of the foregoing sodium salt (**22**; 87.5 g) in glacial acetic acid (500 mL) while the mixture was heated on a boiling water bath. The resulting mixture was heated for an additional 3 h, cooled to 70 °C, and poured into 3 L of ice–water. The water was decanted from the oily product, and the organic material was dissolved in dichloromethane, washed with 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue chromatographed on silica, eluting with toluene. The pyrrolic fractions were combined and crystallized from hexane to give the tetrahydroisoindole **23a** (10.4 g; 10.1%) as fluffy white crystals: mp 77.5–79 °C. An analytical sample was obtained by further crystallization from hexane: mp 79.5–80.5 °C; IR (Nujol mull) ν 3304 (NH str.), 1675 (C=O str.) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.71 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.52 (2 H, t, J = 5.3 Hz, 4-CH_2), 2.79 (2 H, t, J = 5.5 Hz, 7-CH_2), 4.27 (2 H, q, J = 7.2 Hz, OCH_2), 6.61 (1 H, d, J = 2.6 Hz, pyrrole-H), 9.0 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 14.58 (CH_2CH_3), 21.93 (4-CH_2), 23.18, 23.38, 23.43 (5,6,7-CH_2), 59.76 (OCH_2), 117.73 (C-1), 118.77 (C-3), 122.10 (C-3a), 128.15 (C-7a), 161.76 (C=O). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 68.35; H, 7.84; N, 7.25. Found: C, 67.93; H, 7.77; N, 7.20.

Method B. DBU (7.0 g) in 2-propanol (50 mL) was added to a solution of ethyl isocyanoacetate (**25a**; 5.00 g) and 1-nitrocyclohexene (5.62 g) in tetrahydrofuran (50 mL) and the resulting mixture stirred at room temperature overnight. The mixture was successively washed with 2 M hydrochloric acid (100 mL), water (100 mL), 5% sodium bicarbonate solution (100 mL), and water (100 mL). The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was chromatographed on a silica column, eluting with dichloromethane. Crystallization from hexane gave **23a** (5.58 g; 65%) as white crystals: mp 79–80 °C.

Methyl 4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylate (23b). Prepared from methyl isocyanoacetate (**25b**; 5.00 g) and 1-nitrocyclohexene (6.42 g) by the procedure described for **23a** (method B). Recrystallization from ethanol–water gave **23b** (6.15 g; 68%) as small colorless needles: mp 93–94 °C; IR (Nujol mull) ν 3300 (NH str.), 1665 (C=O str.) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.54 (2 H, t, J = 5.3 Hz, 4-CH_2), 2.80 (2 H, t, J = 5.5 Hz, 7-CH_2), 3.82 (3 H, s, OCH_3), 6.64 (1 H, d, J = 2.6 Hz, 3-H), 9.0 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 21.90 (4-CH_2), 23.14, 23.34, 23.41 (5,6,7-CH_2), 50.99 (OCH_3), 117.49 (C-1), 118.98 (C-3), 122.12 (C-3a), 128.36 (C-7a), 162.14 (C=O). Anal. Calcd for $C_{10}H_{13}NO_2 \cdot {}^1/_{10}H_2O$: C, 66.35; H, 7.29; N, 7.74. Found: C, 66.51; H, 7.18; N, 7.61.

Condensation of Dimethyl Aminomalonate with the Sodium Salt of 22. Dimethyl aminomalonate (**15b**; 10.0 g) was added to a solution of the sodium salt of 2-formylcyclohexanone (**22**; 10.2 g) in acetic acid (120 mL) while the solution was heated on a boiling water bath. The mixture was heated at 100 °C for 3 h, cooled to 70 °C, and poured into ice–water (500 mL). Crystallization from dichloromethane–hexane gave **24b** (0.58 g; 4.8%) as off-white crystals: mp 150–152 °C; IR (Nujol mull) ν 3297 (NH str.), 1673 (C=O str.) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.49 (2 H, t, J = 5.8 Hz, 4-CH_2), 2.61 (2 H, t, J = 6.0 Hz, 7-CH_2), 3.82 (3 H, s, OCH_3), 6.64 (1 H, d, J = 2.1 Hz, 3-H), 9.5 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 22.72, 22.88, 22.97, 23.54 (4 × ring-CH_2), 51.17 (OCH_3), 114.43 (C-3), 119.64, 120.03 (C-2,3a), 133.95 (C-7a), 162.24 (C=O). Anal. Calcd for

(32) After these studies were underway, a synthesis of the tetrahydrobenzoDPEP **8a** was reported.[10,33]

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(34) Cerchez, V. *Bull. Soc. Chim. Fr.* **1930**, *47*, 1279. Shaw, K. N. F.; Nolan, C. *J. Org. Chem.* **1957**, *22*, 1668.

(35) Ainsworth, C. *Organic Synthesis*; Wiley: New York, 1963; Coll. Vol. IV, p 536.

$C_{10}H_{13}NO_2 \cdot {}^1/_3H_2O$: C, 64.85; H, 7.44; N, 7.56. Found: C, 64.96; H, 7.08; N, 7.43.

***tert*-Butyl 4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylate (23c).** Prepared from *tert*-butyl isocyanoacetate (**25c**; 4.85 g) and 1-nitrocyclohexene (4.37 g) by the procedure given for **23a** (method B). Recrystallization from ethanol–water gave the tetrahydroisoindole (5.10 g; 67%) as a pale brown solid: mp 123–126 °C. Further recrystallization from ethanol–water gave white crystals: mp 131–132 °C; IR (Nujol mull) ν 3312 (NH str.), 1672 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (9 H, s, ^{t}Bu), 1.73 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.53 (2 H, t, J = 5.4 Hz, 4-CH_2), 2.78 (2 H, t, J = 5.6 Hz, 7-CH_2), 6.61 (1 H, d, J = 2.2 Hz, 3-H), 9.1 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 21.99 (4-CH_2), 23.27, 23.47 (5,6,7-CH_2), 28.55 (^{t}Bu), 80.24 (OC), 118.13 (C-3), 119.01 (C-1), 121.95 (C-3a), 127.22 (C-7a), 161.40 (C=O). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.27; H, 8.34; N, 6.31.

Benzyl 4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylate (23d). Sodium (0.336 g) was added to benzyl alcohol in a 1-L round-bottomed flask. Once all the sodium had reacted, pyrrole **23a** (5.63 g) was added and the resulting mixture heated on a boiling water bath for 6 h. The mixture was allowed to stand at room temperature overnight, and 1 equiv of acetic acid was added to neutralize the sodium benzyloxide. The benzyl alcohol was evaporated under reduced pressure, and the residue, which solidified on standing, was dissolved in dichloromethane, washed with water, and treated with decolorizing charcoal. The organic solution was filtered through Celite, dried over magnesium sulfate, and evaporated to dryness on a rotary evaporator. Crystallization from hexane gave the benzyl ester (4.01 g; 60%) as off-white crystals: mp 88–90 °C; IR (Nujol mull) ν 3293 (NH str.), 1662 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.54 (2 H, t, J = 5.3 Hz, 4-CH_2), 2.83 (2 H, t, J = 5.4 Hz, 7-CH_2), 5.30 (2 H, s, CH_2Ph), 6.65 (1 H, d, J = 2.6 Hz, pyrrole-H), 7.3–7.45 (5 H, m, Ph), 8.8 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 21.89 (4-CH_2), 23.19, 23.31, 23.34 (5,6,7-CH_2), 65.52 (OCH_2), 117.39 (C-1), 118.96 (C-3), 122.32 (C-3a), 128.00 (C-7a, *o*- and *p*-Ph), 128.52 (*m*-Ph), 136.55 (Ph C_{att}), 161.25 (C=O). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.72; N, 5.49. Found: C, 74.87; H, 6.90; N, 5.46.

***tert*-Butyl 3-Ethyl-4,5-dimethylpyrrole-2-carboxylate (29d).** Ethyl 3-ethyl-4,5-dimethylpyrrole-2-carboxylate[22,36] (**29a**; 10.0 g) in methanol (150 mL) was added to a solution of sodium hydroxide (14.4 g) in water (75 mL) and the resulting mixture heated under reflux for 4 h. The solution was cooled to room temperature and washed with several portions of ether and the aqueous solution heated on a steam bath for several minutes to remove traces of ether. The solution was cooled to 0 °C in an ice–salt bath and carefully acidified to Congo red with 10% hydrochloric acid while the temperature of the mixture was maintained below 5 °C. The resulting precipitate was filtered off, washed with liberal amounts of water to remove traces of acid, and dried in vacuo overnight to give the carboxylic acid **29b** as a light beige solid (5.87 g; 69%). The carboxylic acid was dissolved in methanol (60 mL) and added to a solution of sodium hydroxide (1 equiv; 1.41 g) in methanol. The solvent was removed under reduced pressure and the resulting sodium salt vacuum dried overnight. The solid (6.61 g) was taken up in dry benzene (150 mL), and a solution of oxalyl chloride (1 equiv; 4.44 g) in anhydrous benzene (50 mL) was added to the stirred mixture over a period of 15 min while the reaction flask was cooled in an ice bath. The resulting mixture was stirred at room temperature for 1 h. A mixture of *tert*-butyl alcohol (13.0 g) and triethylamine (17.8 g) was added over 15 min and the mixture stirred for an additional 30 min. The solution was diluted with an equal volume of chloroform and washed successively with equal volumes of 2% hydrochloric acid, water, 5% sodium bicarbonate, and water. The chloroform layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica, using toluene as the eluent. Crystallization from hexane gave the title pyrrole (4.76 g; 61%) as fluffy white crystals: mp 133–134.5 °C; IR (Nujol mull) ν 3318 (NH str.), 1652 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.56 (9 H, s, ^{t}Bu), 1.92 (3 H, s, 4-CH_3), 2.18 (3 H, s, 5-CH_3), 2.69 (2 H, q, J = 7.5 Hz, pyrrole-CH_2), 8.85 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 8.55 (4-Me), 11.40 (5-Me), 15.27 (CH_2CH_3), 18.61 (CH_2CH_3), 28.51 (^{t}Bu), 79.96 (OC), 115.99 (C-2), 117.32 (C-4), 129.05 (C-5), 133.09 (C-3), 161.41 (C=O). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.90; H, 9.50; N, 6.27. Found: C, 69.86; H, 9.30; N, 6.28.

***tert*-Butyl 5-(Acetoxymethyl)-3-ethyl-4-methylpyrrole-2-carboxylate (30).** Lead tetraacetate (11.1 g) was added in portions to a stirred solution of the foregoing pyrrole (**29d**; 5.32 g) in glacial acetic acid (100 mL). The mixture was stirred for 2 h and poured into ice–water (300 mL). After 3 h, (CH_2CH_3), resulting precipitate was filtered off, dried under vacuum, and recrystallized from chloroform–hexane to give the (acetoxymethyl)pyrrole **30** (5.87 g; 87%) as fluffy white crystals: mp 137.5–139 °C; IR (Nujol mull) ν 3305 (NH str.), 1740 (acetoxy C=O str.), 1652 (pyrrole C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.56 (9 H, s, ^{t}Bu), 2.02 (3 H, s), 2.07 (3 H, s) (acetoxy-CH_3 and pyrrole-CH_3), 2.70 (2 H, q, J = 7.5 Hz, pyrrole-CH_2), 5.01 (2 H, s, CH_2OAc), 8.9 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 8.43 (4-Me), 15.15 (CH_2CH_3), 18.36 (CH_2CH_3), 20.94 ($COCH_3$), 28.42 (^{t}Bu), 57.09 (CH_2OAc), 80.67 (OC), 119.24, 119.91 (C-2,4), 126.36 (C-5), 132.23 (C-3), 161.03 (pyrrole C=O), 171.53 (acetoxy C=O). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.02; H, 8.25; N, 4.98. Found: C, 63.78; H, 8.25; N, 4.95.

Benzyl 5-(Acetoxymethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (37b). Prepared from benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (20.0 g) by the procedure described above. Recrystallization from dichloromethane–hexane gave **37b** (20.5 g; 84%) as fluffy white crystals: mp 120–121 °C (lit.[37] mp 122 °C); IR (Nujol mull) ν 3313 (NH str.), 1734 (acetoxy C=O str.), 1668 (pyrrole C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.05 (3 H, s, $OCOCH_3$), 2.29 (3 H, s, pyrrole-CH_3), 2.46 (2 H, q, J = 7.5 Hz, CH_2CH_3), 5.01 (2 H, s, CH_2OAc), 5.30 (2 H, s, OCH_2Ph), 7.3–7.45 (5 H, m, Ph), 9.1 (1 H, br, NH); ^{13}C NMR ($CDCl_3$) δ 10.33 (3-Me), 15.96 (CH_2CH_3), 17.09 (CH_2CH_3), 20.93 ($COCH_3$), 56.93 (CH_2OAc), 65.69 (OCH_2Ph), 118.90 (C-2), 126.50, 126.83, 127.00 (C-3,4,5), 128.11 (*o*- and *p*-Ph), 128.54 (*m*-Ph), 136.37 (Ph C_{att}), 161.17 (pyrrole C=O), 171.49 (acetoxy C=O).

Benzyl 3,4-Butano-5′-(*tert*-butoxycarbonyl)-4′-ethyl-3′-methyl-2,2′-dipyrrylmethane-5-carboxylate (28a). Montmorillonite clay (K10; 27.1 g) was added to a stirred solution of benzyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**23d**; 4.85 g) and *tert*-butyl 5-(acetoxymethyl)-3-ethyl-4-methylpyrrole-2-carboxylate (**30**; 5.34 g). The resulting mixture was stirred vigorously for 1 h, although TLC indicated that the reaction was complete after 20 min. The clay catalyst was filtered off and washed with dichloromethane and the solvent removed on a rotary evaporator. The residual orange oil was chromatographed on Grade III alumina, eluting with toluene. The title dipyrrylmethane (9.03 g; quantitative) was isolated as a gum; upon drying in vacuo a brittle orange foam resulted, mp 74–76 °C. However, all attempts to recrystallize this compound were unsuccessful: IR (Nujol mull) ν 3314 (NH str.), 1682 (C=O str.), 1654 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3 H, t, CH_2CH_3), 1.51 (9 H, s, ^{t}Bu), 1.71 (4 H, m, $CH_2(CH_2)_2CH_2$), 1.95 (3 H, s, pyrrole-CH_3), 2.40 (2 H, m, 3-CH_2), 2.68 (2 H, q, CH_2CH_3), 2.78 (2 H, m, 4-CH_2), 3.76 (2 H, s, bridge CH_2), 5.27 (2 H, s, OCH_2Ph), 7.31 (5 H, m, Ph), 9.0 (1 H, br), 9.5 (1 H, br) (2 × NH); ^{13}C NMR ($CDCl_3$) δ 8.64 (3′-Me), 15.20 (CH_2CH_3), 18.54 (CH_2CH_3), 21.20 (3-CH_2), 22.88 (bridge-CH_2), 23.15, 23.20, 23.45 (3 × CH_2), 28.43 (^{t}Bu), 65.64 (OCH_2Ph), 80.18 (OC), 116.04, 116.18 (C-3,5), 118.37, 119.30 (C-3′,5′), 127.67 (*o*-Ph), 127.83 (*p*-Ph), 128.42 (*m*-Ph), 128.52, 129.68, 129.89 (C-2,2′,4), 133.01 (C-4′), 136.50 (Ph C_{att}), 161.24, 161.99 (2 × C=O). Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 72.52; H, 7.55; N, 5.71.

***tert*-Butyl 3,4-Butano-5′-(benzyloxycarbonyl)-3′-ethyl-4′-methyl-2,2′-dipyrrylmethane-5-carboxylate (36a).** Prepared from benzyl 5-(acetoxymethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (**37b**; 0.80 g) and *tert*-butyl-4,5,6,7-tetrahydroindole-2*H*-isoindole-1-carboxylate (**23c**; 0.58 g) by the procedure described above. The dipyrrylmethane **36a** (1.20 g; 99%) was obtained as a pale yellow gum. A sample was crystallized from hexane to give small off-white nodules: mp 107–108 °C; IR (Nujol

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mull) ν 3346 (NH str.), 1678, 1641 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.52 (9 H, s, ^{t}Bu), 1.71 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.29 (3 H, s, 4'-Me), 2.38 (2 H, m, 3-CH_2), 2.39 (2 H, q, CH_2CH_3), 2.75 (2 H, m, 4-CH_2), 3.79 (2 H, s, bridge CH_2), 5.27 (2 H, s, OCH_2Ph), 7.3–7.4 (5 H, m, Ph), 8.5 (1 H, br), 8.64 (1 H, br) (2 × NH); ^{13}C NMR ($CDCl_3$) δ 10.60 (4'-CH_3), 15.45 (CH_2CH_3), 17.21 (CH_2CH_3), 21.27 (3-CH_2), 22.99 (bridge-CH_2), 23.28 (3 × CH_2), 28.54 (^{t}Bu), 65.58 (OCH_2Ph), 80.19 (OC), 117.58, 117.95 (C-3,5), 119.10 (C-5'), 124.48, 127.20, 127.46 (C-2',3',4'), 128.00 (*o*- and *p*-Ph), 128.50 (*m*-Ph), 128.21, 128.98 (C-2,4), 136.50 (Ph C_{att}), 161.21, 161.45 (2 × C=O). Anal. Calcd for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 73.47; H, 7.48; N, 5.75.

3,4-Butano-5'-(*tert*-butoxycarbonyl)-4'-ethyl-3'-methyl-2,2'-dipyrrylmethane-5-carboxylic Acid (28b). A solution of dipyrrylmethane **28a** (3.00 g) in acetone (200 mL) containing 35 drops of triethylamine was shaken with 10% palladium/charcoal (0.375 g) an atmosphere of hydrogen at room temperature and 30 psi for 18 h. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was taken up in 5% aqueous ammonia (160 mL) and cooled to 0 °C in an ice–salt bath. The mixture was carefully neutralized with glacial acetic acid, maintaining the temperature throughout below 5 °C, and the resulting precipitate was filtered off, washed with liberal quantities of water to remove traces of acid, and dried in vacuo overnight. The dipyrrylmethane carboxylic acid **28b** (2.276 g; 93%) was obtained as a pale pink powder: mp 177 °C dec; ^1H NMR ($CDCl_3$) δ 1.08 (3 H, t, CH_2CH_3), 1.53 (9 H, s, ^{t}Bu), 1.72 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.05 (3 H, s, pyrrole-CH_3), 2.4–2.9 (6 H, m, 3 × pyrrole-CH_2), 3.78 (2 H, s, bridge CH_2), 10.67 (1 H, br), 11.22 (1 H, br) (2 × NH). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 8.03; N, 7.03.

3',4'-Butano-5'-(*tert*-butoxycarbonyl)-3-ethyl-4-methyl-2,2'-dipyrrylmethane-5-carboxylic Acid (36b). Prepared from dipyrrylmethane **36a** (0.90 g) by the procedure described above for **28b**. The carboxylic acid **36b** (0.69 g; 94%) was isolated as a pink powder; mp 118–119 °C dec; ^1H NMR ($CDCl_3$) δ 1.02 (3 H, t, CH_2CH_3), 1.53 (9 H, s, ^{t}Bu), 1.73 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.29 (3 H, s, pyrrole-CH_3), 2.4–2.8 (6 H, m, 3 × pyrrole-CH_2), 3.78 (2 H, s, bridge-CH_2), 10.62 (1 H, br), 10.87 (1 H, br) (2 × NH). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: 68.26; H, 7.67; N, 7.05.

7,8-Butano-2,13,18-triethyl-1,3,12,17,19-pentamethyl-10,23-dihydrobilin Dihydrobromide (32). Dipyrrylmethane **28b** (0.800 g) was dissolved in trifluoroacetic acid and the resulting mixture stirred for 10 min at room temperature. A solution of 4-ethyl-3,5-dimethylpyrrole-2-carboxaldehyde (**31a**; 0.626 g) in methanol was added, followed immediately by a solution of hydrobromic acid in acetic acid (30%; 3.2 mL). The deep red solution was stirred at room temperature for 30 min, anhydrous ether (68 mL) was added dropwise, and the resulting mixture was stirred for an additional 2 h. The red/brown precipitate was filtered off and washed well with ether. After vacuum drying the sample overnight, the a,c-biladiene dihydrobromide (1.036 g; 75%) was obtained as a red/brown crystals: mp 244–245 °C; UV (CH_2Cl_2) λ_{max} ($\log_{10}\epsilon_{max}$) 451 (5.07), 527 (4.93); ^1H NMR ($CDCl_3$) δ 1.11 (6 H, t), 1.17 (3 H, t) (3 × CH_2CH_3), 1.67 (4 H, m, $CH_2(CH_2)_2CH_2$), 1.93 (3 H, s, 12-Me), 2.2–2.3 (2 H, m, 8-CH_2), 2.26 (3 H, s), 2.29 (3 H, s) (3,17-CH_3), 2.44 (2 H, q), 2.45 (2 H, q) (2,18-CH_2), 2.58 (2 H, q, 13-CH_2CH_3), 2.65–2.7 (2 H, m, 7-CH_2), 2.70 (3 H, s), 2.71 (3 H, s) (1,19-CH_3), 5.15 (2 H, s, bridge CH_2), 6.98 (1 H, s), 7.07 (1 H, s) (2 × methine-H), 13.04 (1 H, s), 13.14 (1 H, s), 13.25 (1 H, s), 13.30 (1 H, s) (4 × NH). Anal. Calcd for $C_{34}H_{46}N_4Br_2$: C, 60.88; H, 6.93; N, 8.35. Found: C, 61.05; H, 7.22; N, 8.14.

7,8-Butano-3,13,17-triethyl-1,2,12,18,19-pentamethyl-10,23-dihydrobilin Dihydrobromide (33). Prepared from dipyrrylmethane **28b** (0.800 g) and 3-ethyl-4,5-dimethylpyrrole-2-carboxaldehyde (**31b**; 0.626 g) by the procedure described above. The product (1.01 g; 73%) was isolated as a green/brown crystals: mp 239–240 °C; UV (CH_2Cl_2) λ_{max} ($\log_{10}\epsilon_{max}$) 452 (5.07), 526 (4.96); ^1H NMR ($CDCl_3$) δ 1.14 (3 H, t), 1.18 (3 H, t), 1.20 (3 H, t) (3 × CH_2CH_3), 1.7 (4 H, m, $CH_2(CH_2)_2CH_2$), 1.93 (3 H, s, 12-CH_3), 2.00 (3 H, s), 2.01 (3 H, s) (2,18-CH_3), 2.27 (2 H, m, 8-CH_2), 2.59–2.70 (8 H, m, 4 × pyrrole-CH_2), 2.68 (3 H, s), 2.69 (3 H, s) (1,19-CH_3), 5.14 (2 H, s, bridge CH_2), 6.96 (1 H, s), 7.05 (1 H, s) (2 × methine-H), 13.01 (1 H, s), 13.15 (1 H, s), 13.27 (1 H, s), 13.31 (1 H, s) (4 × NH). Anal. Calcd for $C_{34}H_{46}N_4Br_2$: C, 60.88; H, 6.93; N, 8.35. Found: C, 60.60; H, 7.17; N, 7.98.

7,8-Butano-3,12,17-triethyl-1,2,13,18,19-pentamethyl-10,23-dihydrobilin Dihydrobromide (38). Prepared from dipyrrylmethane **36b** (585 mg) and pyrrole aldehyde **31b** (442 mg) by the method detailed for **32**. The a,c-biladiene **38** (878 mg; 87%) was obtained as brown crystals: mp 239–240 °C; UV ($CHCl_3$) λ_{max} ($\log_{10}\epsilon_{max}$) 457 (4.11), 528 (4.95); ^1H NMR ($CDCl_3$) δ 0.71 (3 H, t, 12-CH_2CH_3), 1.18 (3 H, t), 1.20 (3 H, t) (3,17-CH_2CH_3), 1.7 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.00 (3 H, s), 2.01 (3 H, s) (2,18-CH_3), 2.26 (3 H, s, 13-CH_3), 2.30 (2 H, m, 8-CH_2), 2.46 (2 H, q, 12-CH_2CH_3), 2.6–2.7 (6 H, m, 3,7,17-CH_2), 2.68 (3 H, s), 2.69 (3 H, s) (1,19-CH_3), 5.15 (2 H, s, bridge CH_2), 6.96 (1 H, s), 7.07 (1 H, s) (2 × methine-H), 13.07 (1 H, s), 13.15 (1 H, s), 13.25 (1 H, s), 13.35 (1 H, s) (4 × NH). Anal. Calcd for $C_{34}H_{46}N_4Br_2$: C, 60.88; H, 6.93; N, 8.35. Found: C, 60.48; H, 6.83; N, 8.20.

7,8-Butano-1-(*tert*-butoxycarbonyl)-2,12-diethyl-3,13,14-trimethyl-5,16-dihydrotripyrrin Hydrobromide (34). *p*-Toluenesulfonic acid (1.30 g) in methanol (15 mL) was added in one portion to a stirred solution of dipyrrylmethane **28b** (1.000 g) and 3-ethyl-4,5-dimethylpyrrole-2-carboxaldehyde (**31b**; 0.391 g) in dichloromethane (130 mL) and the resulting solution stirred at room temperature for 40 min. The orange solution was washed successively with water, saturated sodium bicarbonate solution, and water. The organic layer was dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was taken up in dichloromethane, and hydrogen bromide gas bubbled through the solution for 5 s. The solvent was immediately removed on a rotary evaporator, and toluene (80 mL) was added and then evaporated under reduced pressure to azeotrope out trace amounts of water and hydrobromic acid. A second portion of toluene (80 mL) was added and the solvent removed as before. Ether (50 mL) was added and evaporated under reduced pressure. The residue was then taken up in a minimal volume of ether and the solution cooled in ice to induce crystallization. The precipitate was filtered off and washed with ether to give the tripyrrene hydrobromide (0.750 g; 52%) as an orange powder with a green sheen: mp 200–201 °C, darkening at 195 °C; UV ($CHCl_3$) λ_{max} ($\log_{10}\epsilon$) 499 nm (4.92); ^1H NMR ($CDCl_3$) δ 1.08 (3 H, t), 1.16 (3 H, t) (2 × CH_2CH_3), 1.58 (9 H, s, ^{t}Bu), 1.78 (4 H, m, $CH_2(CH_2)_2CH_2$), 2.00 (3 H, s), 2.03 (3 H, s) (3,13-CH_3), 2.43 (2 H, m, 7-CH_2), 2.57–2.72 (6 H, m, 3 × pyrrole-CH_2), 2.65 (3 H, s, 14-CH_3), 4.26 (2 H, s, bridge CH_2), 6.93 (1 H, s, methine H), 10.27 (1 H, br, pyrrole NH), 12.90 (1 H, br), 13.20 (1 H, br) (2 × pyrromethene NH). Anal. Calcd for $C_{30}H_{42}N_3O_2Br \cdot {}^1/_2H_2O$: C, 63.71; H, 7.66; N, 7.43. Found: 63.91; H, 7.46; N, 7.36.

7,8-Butano-3,13,18-triethyl-1,2,12,17,19-pentamethyl-10,23-dihydrobilin Dihydrobromide (35). The foregoing tripyrrene **34** (570 mg) was dissolved in trifluoroacetic acid (3.3 mL) and stirred at room temperature for 15 min. A solution of 4-ethyl-3,5-dimethylpyrrole-2-carboxaldehyde (154 mg) in methanol (13.8 mL) was then added, immediately followed by a 30% solution of hydrobromic acid in acetic acid (2.8 mL). The mixture was stirred at room temperature for 40 min. Ether (80 mL) was added dropwise and the resulting mixture allowed to stir for an additional 2 h. The dark precipitate was filtered and washed with ether to give the a,c-biladiene **35** (605 mg; 89%) as a dark green crystals: mp 236–237 °C; UV ($CHCl_3$) λ_{max} ($\log_{10}\epsilon_{max}$) 456 (4.13), 528 (4.97); ^1H NMR ($CDCl_3$) δ 1.08 (3 H, t), 1.14 (3 H, t), 1.18 (3 H, t) (3 × CH_2CH_3), 1.6–1.7 (4 H, m, $CH_2(CH_2)_2CH_2$), 1.93 (3 H, s, 12-CH_3), 2.00 (3 H, s, 2-CH_3), 2.26 (2 H, m, 8-CH_2), 2.29 (3 H, s, 17-CH_3), 2.45 (2 H, q, 18-CH_2CH_3), 2.56–2.72 (6 H, m, 3 × pyrrole-CH_2), 2.69 (3 H, s), 2.70 (3 H, s) (1,19-CH_3), 5.15 (2 H, s, bridge CH_2), 6.95 (1 H, s), 7.07 (1 H, s) (2 × methine H), 13.03 (1 H, s), 13.13 (1 H, s), 13.25 (1 H, s), 13.31 (1 H, s) (4 × NH). Anal. Calcd for $C_{34}H_{46}N_4Br_2 \cdot H_2O$: C, 59.29; H, 7.04; N, 8.14. Found: C, 59.61; H, 6.82; N, 8.13.

2,3:7,8:12,13:17,18-Tetrabutanoporphyrin (26). A solution of ethyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**23a**; 0.50 g) in anhydrous ether (10 mL) was added dropwise to a stirred mixture of lithium aluminum hydride (0.20 g) in ether (20 mL) over a period of 30 min while the reaction vessel was cooled in an ice bath. The resulting mixture was stirred for a further 1 h. Water (20 mL) was cautiously added dropwise to destroy the excess lithium aluminum hydride. The resulting brown mixture

was then placed in a separatory funnel, the organic layer removed, and the aqueous phase extracted with ether and the organic solutions were combined. The solvent was removed on a rotary evaporator, maintaining the temperature of the water bath between 25–30 °C. The residue was taken up in pyridine (5 mL) and acetic acid (20 mL) and immediately heated under reflux for 1 h. The resulting mixture was allowed to stand at room temperature for several days. The mixture was filtered and the precipitate washed with methanol. The crude porphyrin was chromatographed on Grade III alumina using dichloromethane as the eluent. The red fractions were evaporated to dryness and crystallized from dichloromethane–methanol to give the tetrabutanoporphyrin (120 mg; 35%) as a purple powder: mp >300 °C (lit.[27] mp 320–325 °C; lit.[38] mp 295–300 °C); UV ($CHCl_3$) λ_{max} 395, 497, 532, 567, 620 nm; ^1H NMR ($CDCl_3$) δ −3.9 (2 H, br, 2 × NH), 2.51 (16 H, m, 8 × CH_2), 4.12 (16 H, m, 8 × porphyrin-CH_2), 9.88 (4 H, s, 4 × meso-H); ^{13}C NMR ($CDCl_3$) δ 23.10, 23.85 (16 × CH_2), 95.99 (meso-carbons), 138.63 (β-carbons), 142.0 (α-carbons, very broad due to NH proton exchange).

2,3-Butano-8,13,17-triethyl-7,12,18-trimethylporphyrin (10). The a,c-biladiene **32** (1.000 g) was dissolved in dimethylformamide (500 mL) containing copper(II) chloride (3.008 g) and the resulting mixture stirred for 2 h at room temperature. The solution was diluted with dichloromethane (625 mL) and washed with water (3 × 600 mL). The aqueous solutions were back-extracted with dichloromethane and the organic phases combined. The organic solutions were dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was taken up in 15% sulfuric acid–trifluoroacetic acid (125 mL) and stirred in the dark at room temperature for 45 min. The solution was diluted with dichloromethane (500 mL) and washed with water (500 mL), 5% sodium bicarbonate solution (500 mL), and water (500 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was chromatographed on Grade III alumina, eluting with dichloromethane. Recrystallization from dichloromethane–methanol gave the tetrahydrobenzoporphyrin (425 mg; 68%) as purple crystals: mp >300 °C; FAB MS *m/e* 491 ($[M + H]^+$); HR FAB MS calcd for $C_{33}H_{38}N_4$ + H 491.3175, found 491.3169; UV (CH_2Cl_2) λ_{max} ($\log_{10} \epsilon_{max}$) 396 (5.20), 497 (4.13), 530 (4.02), 564 (3.83), 620 (3.71) nm; ^1H NMR ($CDCl_3$) δ −3.8 (2 H, br, 2 × NH), 1.86 (9 H, m, 3 × CH_2CH_3), 2.50 (4 H, m, $CH_2(CH_2)_2CH_2$), 3.62 (6 H, s), 3.63 (3 H, s) (3 × porphyrin-CH_3), 4.10 (10 H, m, 5 × porphyrin-CH_2), 9.96 (2 H, s), 10.08 (2 H, s) (4 × meso-H). Anal. Calcd for $C_{33}H_{38}N_4 \cdot {}^1/_4H_2O$: C, 80.03; H, 7.85; N, 11.32. Found: C, 80.20; H, 8.11; N, 11.25.

7,8-Butano-3,13,17-triethyl-2,12,18-trimethylporphyrin (11). Prepared from the corresponding a,c-biladiene **33** (0.900 g) by the method described above. Recrystallization from dichloromethane–methanol gave the desired porphyrin (448 mg; 68%) as purple crystals: mp >300 °C; FAB MS *m/e* 491 ($[M + H]^+$); HR FAB MS calcd for $C_{33}H_{38}N_4$ + H 491.3175, found 491.3157; UV (CH_2Cl_2) λ_{max} ($\log_{10} \epsilon_{max}$) 397 (5.20), 497 (4.13), 530 (4.03), 565 (3.83), 620 (3.72) nm; ^1H NMR ($CDCl_3$) δ −3.8 (2 H, br, 2 × NH), 1.87 (9 H, m, 3 × CH_2CH_3), 2.52 (4 H, m, $CH_2(CH_2)_2CH_2$), 3.63 (9 H, s, 3 × porphyrin-CH_3), 4.1 (10 H, m, 5 × porphyrin-CH_2), 9.97 (1 H, s), 9.99 (1 H, s), 10.10 (2 H, s) (4 × meso-H). Anal. Calcd for $C_{33}H_{38}N_4 \cdot {}^1/_4H_2O$: C, 80.03; H, 7.85; N, 11.32. Found: C, 80.35; H, 8.10; N, 11.27.

12,13-Butano-3,8,17-triethyl-2,17,18-trimethylporphyrin (12). Prepared from a,c-butadiene **38** (690 mg) by the procedure described for **10**. Recrystallization from dichloromethane–methanol gave the title porphyrin (339 mg; 67%) as purple crystals: mp >300 °C; EI MS *m/e* (relative intensity) 490 (100) (M^+), 475 (10), 245 (18) (M^{2+}); HR MS calcd for $C_{33}H_{38}N_4$ 490.3099, found 490.3077; UV ($CHCl_3$) λ_{max} ($\log_{10} \epsilon_{max}$) 399 (5.20), 498 (4.11), 532 (4.00), 566 (3.80), 620 (3.69) nm; ^1H NMR ($CDCl_3$) δ −3.8 (2 H, br, NH), 1.86 (6 H, t), 1.87 (3 H, t) (3 × CH_2CH_3), 2.54 (4 H, m, $CH_2(CH_2)_2CH_2$), 3.65 (9 H, s, 3 × porphyrin-CH_3), 4.05–4.12 (6 H, m, 3 × CH_2CH_3), 4.17 (4 H, m, 2 × porphyrin-CH_2CH_2), 9.99 (2 H, s), 10.11 (1 H, s), 10.12 (1 H, s) (4 × meso-H). Anal. Calcd for $C_{33}H_{38}N_4 \cdot {}^1/_4H_2O$: C, 80.03; H, 7.85; N, 11.32. Found: C, 80.08; H, 7.72; N, 11.39.

17,18-Butano-3,8,13-triethyl-2,7,12-trimethylporphyrin (13). Prepared by the method described above for **10** from a,c-biladiene **35** (500 mg). Recrystallization from methanol–dichloromethane gave the tetrahydrobenzoporphyrin **13** (228 mg; 62%) as purple crystals: mp >300 °C; EI MS *m/e* (relative intensity) 490 (100) (M^+), 475 (10), 245 (16) (M^{2+}); HR MS calcd for $C_{33}H_{38}N_4$ 490.3099, found 490.3092; UV ($CHCl_3$) λ_{max} ($\log_{10} \epsilon_{max}$) 398 (5.20), 498 (4.11), 533 (4.01), 566 (3.82), 620 (3.69) nm; ^1H NMR ($CDCl_3$) δ −3.8 (2 H, br, NH), 1.82 (3 H, t), 1.83 (6 H, t) (3 × CH_2CH_3), 2.49 (4 H, m, $CH_2(CH_2)_2CH_2$), 3.58 (3 H, s), 3.61 (6 H, s) (3 × porphyrin-CH_3), 4.1–4.8 (10 H, m, 5 × porphyrin-CH_2), 9.94 (1 H, s), 9.96 (1 H, s), 10.06 (2 H, s) (4 × meso-H). Anal. Calcd for $C_{33}H_{38}N_4 \cdot {}^1/_2H_2O$: C, 79.32; H, 7.87; N, 11.21. Found: C, 79.41; H, 7.83; N, 11.31.

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Supplementary Material Available: NMR spectra for obtained compounds (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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