the same as that for the preparation of **16b**, **27a** 0.57 g (1.54 mmol) was converted to **16a**, 0.53 g (75%); isolated by chromatography eluting with 1% acetone/CH_2Cl_2. This product was identical with the same product prepared from the synthon.

(2*R*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1-biphenyl]-2-yl)ethenyl]-4-(benzyloxy)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (17a). Using the method substantially the same as that for the preparation of **16b**, 0.45 g (1.21 mmol) of **28a** was converted to **17a**, a clear gum, 0.44 g (80%), R_f 0.41 (1% acetone/CH_2Cl_2): $[\alpha]^{24}_D$ −21.26 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) (360 MHz) δ 1.33 (1 H, ddd, H_{4a}, *J* = 2.9, 11.2, 13.9 Hz), 1.51 (1 H, ddd, H_{2a}, *J* = 3.2, 9.8, 13.2 Hz), 1.69 (1 H, br d, H_{4e}, *J* = 13.4 Hz), 2.07 (1 H, br d, H_{2e}, *J* = 13.4 Hz), 2.28 (3 H, d, CH_3, *J* = 1.7 Hz), 2.33 (3 H, s, CH_3), 2.37 (3 H, s, CH_3), 3.48 (3 H, s, OCH_3), 3.91 (1 H, p, H_3, *J* = 3.2 Hz), 4.34 (1 H, m, H_5), 4.50 (1 H, d, benzyl, *J* = 12 Hz), 4.55 (1 H, d, benzyl, *J* = 12 Hz), 4.73 (1 H, dd, H, *J* = 3.2, 9.5 Hz), 5.46 (1 H, dd, H_6, *J* = 6.4, 16.4 Hz), 6.42 (1 H, d, H_7, *J* = 16.4 Hz), 6.93–7.40 (10 H, m, Ar); exact mass calcd for $C_{30}H_{33}FO_3$ 460.2402, found 460.2410. Anal. Calcd. for $C_{30}H_{33}FO_3$: C, 78.23; H, 7.22. Found: C, 78.39; H, 7.49.

Acknowledgment. We express our sincere appreciation to Dr. M. M. Ponpipom for suggesting **4** as a possible starting point in the synthesis of **2** and to Drs. B. M. Trost and R. L. Smith for helpful discussions.

Registry No. **1a**, 85493-98-7; (±)-**1b**, 86097-37-2; **2**, 82300-44-5; **5**, 63592-79-0; **6**, 64951-98-0; **7**, 82300-39-8; **8**, 82300-40-1; **9**, 82300-41-2; **10**, 82300-42-3; **11**, 82300-43-4; **12**, 80617-38-5; **13**, 90691-40-0; **14** (isomer 1), 100295-44-1; **14** (isomer 2), 100295-45-2; **16a**, 90691-43-3; **16b**, 100189-68-2; **17a**, 100295-49-6; **17b**, 100295-46-3; α-**18a**, 90691-44-4; β-**18a**, 90761-94-7; α-**18b**, 100189-69-3; β-**18b**, 100295-47-4; α-**19a**, 90691-45-5; β-**19a**, 90761-26-5; α-**19b**, 93863-87-7; β-**19b**, 93922-60-2; **20**, 100189-71-7; **21**, 96516-91-5; **22**, 1589-49-7; **23a**, 774-48-1; **23b**, 100-52-7; **23c**, 100189-72-8; **23d**, 93-89-0; **23e**, 100189-73-9; **23f**, 100189-74-0; **23g**, 65-85-0; **27a**, 100189-70-6; **27b**, 93922-58-8; **28a**, 100295-48-5; **28b**, 93863-44-6; 4′-fluoro-2-(hydoroxymethyl)-3,3′,5-trimethyl-1,1′-biphenyl, 90691-37-5; 2-(chloromethyl)-4′-fluoro-3,3′,5-trimethyl-1,1′-biphenyl, 90691-38-6; (4′-fluoro-3,3′,5-trimethyl-[1,1′-biphenyl]-2-yl)methyl phenyl sulfide, 90691-39-7; 1-hydroxy-9-decene, 13019-22-2.

Supplementary Material Available: Detailed results of the GC/MS study of debenzylation products **23a–g** including high resolution, low resolution, chemical ionization, field ionization, capillary GC retention times, and percent area of each of the compounds (1 page). Ordering information is given on any current masthead page.

Syntheses of Some Proposed Biosynthetic Precursors to the Isocyclic Ring in Chlorophyll *a*

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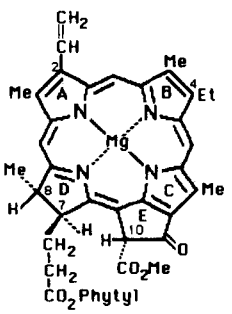
Received July 25, 1985

In connection with studies on the biosynthesis of the isocyclic ring E in chlorophyll *a* (**1**), the magnesium(II) 2,4-divinylporphyrin β-keto ester **8** and hydroxypropionate **6** have been synthesized. The key porphyrin intermediate **36** in these syntheses was obtained most efficiently by cyclization of a 1′-methyl-8′-unsubstituted a,c-biladiene dihydrobromide **31** in hot *o*-dichlorobenzene. An alternative route through copper(II)-promoted cyclization of a 1′,8′-dimethyl-a,c-biladiene hydrobromide, **29**, gave lower yields of porphyrin. The keto ester groups were added by way of the corresponding porphyrin imidazolides **20b** and **39** by using the magnesium(II) complex of methyl hydrogen malonate. Borohydride reduction of the magnesium(II) 2,4-divinylporphyrin β-keto ester **8** gave the corresponding hydroxypropionate porphyrin **6**, but attempts to dehydrate this to give the acrylate **12**, an intermediate also of possible biological significance, were unsuccessful.

The biosynthesis of isocyclic ring E of chlorophyll *a* (**1**) has long been a subject for speculation. In 1948 Granick proposed that the 6-propionic methyl ester side chain of a suitable porphyrin precursor can be oxidized to a β-keto ester as shown in Scheme I.[1] This β-keto ester then undergoes cyclization to form the cyclopentanone ring. In 1968 Ellsworth and Aronoff isolated the magnesium complexes of monovinyl (**2**) and divinyl (**3**) protoporphyrin IX monomethyl esters, mesoporphyrin IX monomethyl ester (**4**), monovinyl (**5**) and divinyl (**6**) 6-β-hydroxypropionate monomethyl esters, monovinyl (**7**) and divinyl (**8**) 6-β-keto methyl esters, and monovinyl (**9**) and divinyl (**10**) pheoporphyrin a_5 monomethyl esters from a mutant of the green algae *Chlorella* in which the synthesis of chlorophyll *a* was blocked.[2,3] The corresponding magnesium monovinyl (**11**) and divinyl (**12**) 6-acrylate monomethyl esters were not isolated, but their presence was inferred from mass spectrometry and oxidative degradation.



1

(1) Granick, S. "The Harvey Lectures"; Thomas: Springfield, IL, 1950; pp 220–245.
(2) Ellsworth, R. K.; Aronoff, S. *Arch. Biochem. Biophys.* **1968**, *125*, 269–277.
(3) Ellsworth, R. K.; Aronoff, S. *Arch. Biochem. Biophys.* **1969**, *130*, 374–383.

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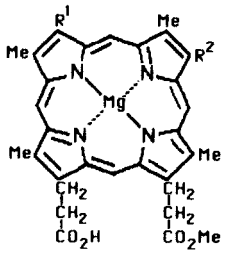
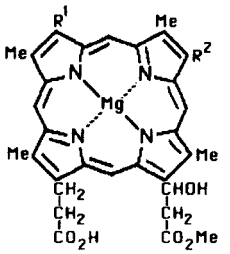


2 R^1 = V, R^2 = Et

3 R^1 = R^2 = V

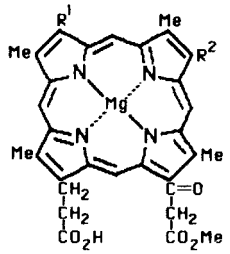
4 R^1 = R^2 = Et



5 R^1 = V, R^2 = Et

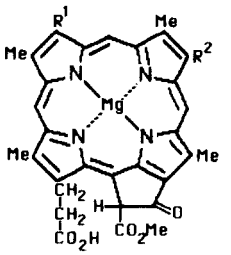
6 R^1 = R^2 = V

V = $CH{=}CH_2$



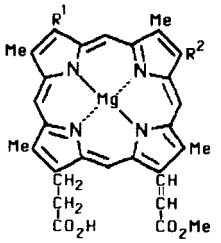
7 R^1 = V, R^2 = Et

8 R^1 = R^2 = V



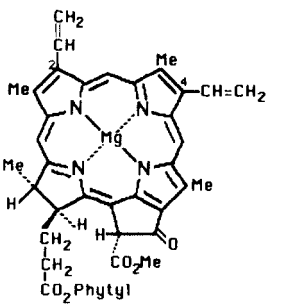
9 R^1 = V, R^2 = Et

10 R^1 = R^2 = V



11 R^1 = V, R^2 = Et

12 R^1 = R^2 = V



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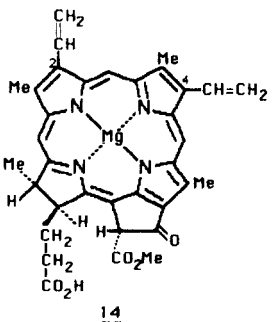
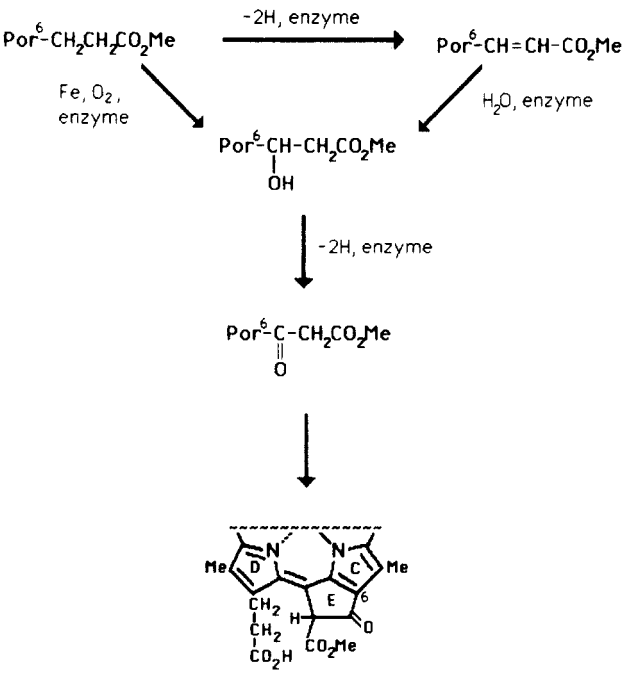


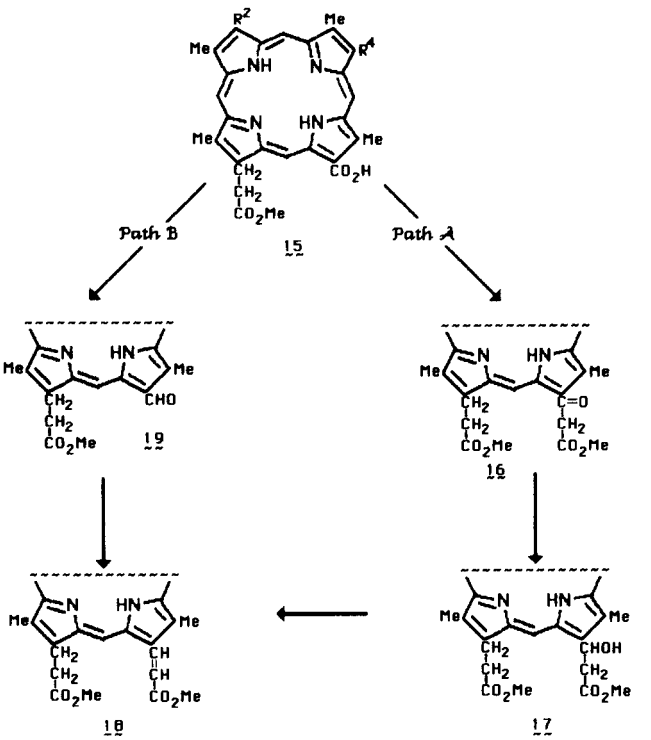
14

For the next decade, this picture remained intact;[4] only monovinyl chlorophyll *a* (**1**) had been found in plants. No 2,4-divinyl- or 2,4-diethylchlorophyll *a* had been observed. Recently, however, the situation has become more complicated. Mutant maize plants have been shown to produce large amounts of 2,4-divinylchlorophyll *a* (**13**).[5] Rebeiz and co-workers have identified numerous chlorophylls and chlorophyll precursors by spectrofluorimetry which differ in their substitution at the 2- and 4-positions and in the pattern of esterification of the 6- and 7-side chains.[6,7] These investigators now postulate six discrete pools of chlorophyll precursors leading to ten species of

Scheme I



Scheme II



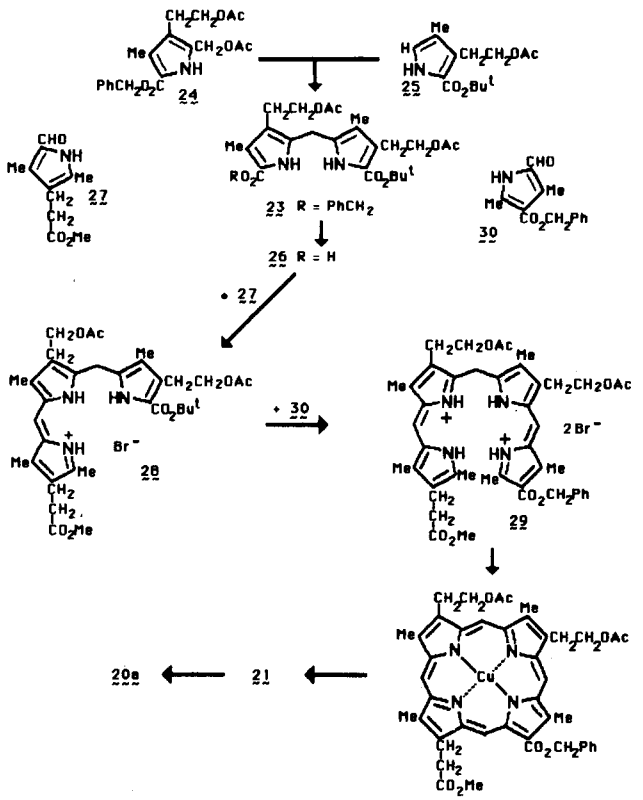
(4) Jones, O. T. G. In "The Porphyrins"; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. VI, p 179.

(5) Bazzaz, M. B.; Brereton, R. G. *FEBS Lett.* **1982**, *138*, 104–108.

(6) Rebeiz, C. A.; Lascelles, J. In "Photosynthesis: Energy Conversion by Plants and Bacteria"; Govindjee, Ed.; Academic Press: New York, 1982; pp 699–780.

(7) Rebeiz, C. A.; Wu, S. M.; Kuhadja, M.; Daniell, H.; Perkins, E. J. "Molecular and Cellular Biochemistry"; Martinus Nijhoff: Boston, 1983; No. 57, p 97.

Scheme III



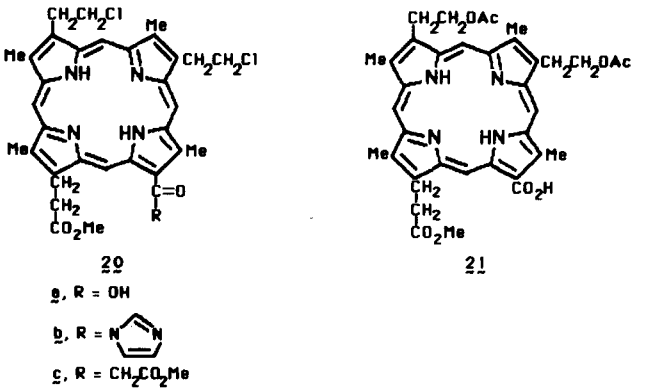
chlorophyll *a* in plants,[7] though results are not universally accepted (see ref 8).

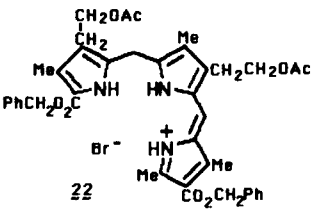
It does appear that cucumber cotyledons grown in the dark accumulate magnesium 2,4-divinylpheoporphyrin a_5 (**10**).[8] Castelfranco et al. have developed a cell-free system from cucumber which converts exogenous magnesium protoporphyrin IX into magnesium 2,4-divinylpheoporphyrin a_5 in the dark.[9-11] The available evidence suggests that the reduction of the 4-vinyl group to ethyl may follow immediately after the light-induced reduction of **10** to 2,4-divinylchlorophyllide *a* (**14**).[10]

We therefore undertook the synthesis of compounds **8**, **6**, and **12** in the divinyl series. Two of these compounds, the keto ester **8** and the hydroxypropionate **6** were successfully synthesized and have subsequently been shown[12,13] to be biosynthetic precursors of 2,4-divinylprotochlorophyllide *a* (**14**) using Castelfranco's cell-free system. Synthesis of a pure sample of the magnesium divinyl acrylate **12** could not be accomplished from the keto ester, and so the problem of whether isocyclic ring formation occurs via acrylate **12** as suggested by Ellsworth and Aronoff[3] or by the more direct β-hydroxylation/oxidation route[9] remains unsolved (see Scheme I).

To our knowledge, there are no published reports of successful incorporation of porphyrin β-keto esters into protochlorophyllide *a* or chlorophyll *a*.[14] However, the Liverpool group synthesized a variety of porphyrins suitable for this purpose, and preliminary feeding experiments of radioactively labeled precursors were made, using plant systems and the photosynthetic bacterium *Rhodospirillum rubrum*.[15] Results were erratic and inconclusive.

The general synthetic plan is shown in Scheme II. It was planned to use the efficient conversion of a suitable derivative of rhodoporphyrin XV **15** into a β-keto ester **16** developed previously,[16] followed by a stepwise conversion to β-hydroxypropionate **17** and then acrylate **18** (Scheme II, path A) with the 2- and 4-vinyl groups to be unmasked at an appropriate point. Path A seemed more economical than path B, which uses a porphyrin carboxylic acid **15** in the synthesis of β-keto esters and a 6-aldehyde **19** for the acrylates.[15,17] It was planned to synthesize the appropriate rhodoporphyrin XV derivative via the a,c-biladiene route rather than by the b-oxobilane method originally used. A third method, the degradation of the chlorophyll *a* derivative, methyl pheophorbide *a*, into rhodoporphyrin derivatives, obviously cannot give entry to the 2,4-divinyl series.[17] The approach therefore hinged on the total synthesis of 2,4-bis(2-chloroethyl)rhodoporphyrin XV (**20a**), which would be obtained by simple transformations of the 2,4-bis(2-acetoxyethyl)rhodoporphyrin XV (**21**).





The synthesis of porphyrin **21** by the 1′,8′-dimethyl-a,c-biladiene route is shown in Scheme III. The pyrrole rings may be assembled in either a clockwise[18] or counterclockwise manner.[19] We settled on the more established counterclockwise route since experiments showed that the yield (27%) of tripyrrene **22** required for the clockwise route was unacceptably low. The known pyrromethane **23** was synthesized by adding 1 equiv of (acetoxymethyl)pyrrole **24** in portions to a solution of α-free pyrrole **25** in acetic acid containing a catalytic amount of *p*-toluenesulfonic acid. Treatment of pyrromethane-5′-carboxylic acid **26** (obtained from **23** by catalytic debenzylation) with 1.05 equiv of formylpyrrole **27** and 2.1 equiv of *p*-toluenesulfonic acid in methanol gave counterclockwise tripyrrene **28** (Scheme III), isolated in 52%

(8) Castelfranco, P. A.; Beale, S. I. *Annu. Rev. Plant Physiol.* **1983**, *34*, 241–277.
(9) Chereskin, B. M.; Wong, Y.-S.; Castelfranco, P. A. *Plant Physiol.* **1982**, *70*, 987–993.
(10) Hanamoto, C. M.; Castelfranco, P. A. *Plant Physiol.* **1983**, *73*, 79–81.
(11) Chereskin, B. M.; Castelfranco, P. A.; Dallas, J. L.; Straub, K. M. *Arch. Biochem. Biophys.* **1983**, *226*, 10–18.
(12) Wong, Y.-S.; Goff, D. A.; Smith, K. M.; Castelfranco, P. A. *Plant Physiol.* **1984**, *75*, S171.
(13) Wong, Y.-S.; Castelfranco, P. A.; Goff, D. A.; Smith, K. M. *Plant Physiol.* **1985**, *79*, 725–729.
(14) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, *32*, 275–283.
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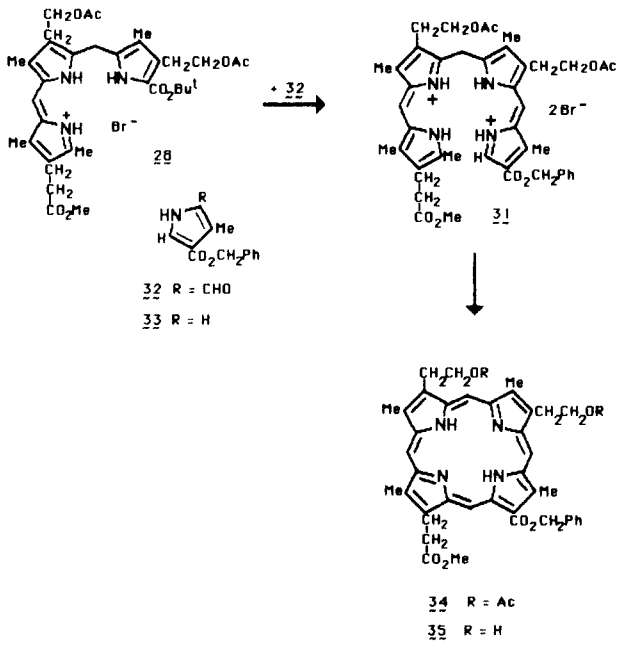
(16) McCombie, S. W. Dissertation, University of Liverpool, 1972.
(17) Sutton, M. J. Dissertation, University of Liverpool, 1974.
(18) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302–4306.
(19) Baptista de Almeida, J. A. P.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron* **1976**, *32*, 1793–1799.

yield as the hydrobromide salt.[20] Tripyrrene hydrobromide **28** was converted straightforwardly into a,c-biladiene dihydrobromide **29** by treatment with formylpyrrole **30**.[19] Yields of 80–90% were consistently obtained. This was cyclized to the fully characterized 2,4-bis(2-acetoxyethyl)rhodoporphyrin 7-methyl ester **21**.

The cyclization of 1′,8′-dimethyl-a,c-biladiene dihydrobromides with copper(II) salts in solvents such as dimethylformamide or pyridine, followed by the removal of chelated copper with acid, are commonly the final steps in the synthesis of unsymmetrical porphyrins.[21] The yields of porphyrin **21** thus obtained from **29** ranged from 9–28%. The yields in this type of cyclization have been shown[21b,c] to depend not only upon the quality of the a,c-biladiene, but also on the temperature, solvent, and counterion of the copper(II) salt. It should be noted also that treatment of cyclization product (Scheme III) with 10% sulfuric acid in TFA not only removes the chelated copper but cleaves the 6-benzyl ester to give the carboxylic acid **21**.[17]

Due to the disappointingly low yields of porphyrin obtained in the copper(II) cyclization, it was decided to investigate the cyclization of 1′-methyl-8′-unsubstituted a,c-biladienes with iodine and bromine in *o*-dichlorobenzene, as reported by Russian workers.[22,23] They found that the cyclization proceeds best with an electron-withdrawing substituent on the β-position of the 8′-unsubstituted pyrrole ring. a,c-Biladiene **31** met this requirement and could readily be synthesized from tripyrrene **28** and formylpyrrole **32**.



The required formylpyrrole **32** was synthesized from tosylmethyl isocyanide and benzyl crotonate according to the procedure of LeGoff[24] and gave di-α-free pyrrole **33** which was formylated by a modified Gatterman procedure;[25] the triethyl orthoformate/TFA procedure gave only a red intractible tar. Formylpyrrole **32** was condensed with tripyrrene hydrobromide **28** in the usual manner to give a,c-biladiene **31** in reproducible 90–94% yields. The conditions for cyclization of **31** to **34** were next investigated on a small scale (Table I). The Russian workers found that the amount of iodine and/or bromine used was important to the success of the reaction.[22,23] They established that when an electron-withdrawing substituent is located on the *unsubstituted* terminal ring, cyclization proceeds well with 5 equiv of iodine alone (method A). If, however, the electron-withdrawing substituent is located on the 1′-*methyl* substituted terminal ring, much better yields are obtained with 5 equiv of iodine plus 2 equiv of bromine (method B). It was not determined whether method B was superior to method A in the former case.

Table I. Small Scale Cyclizations of a,c-Biladiene 31[a]

run	31, g	mol equiv of I_2	mol equiv of Br_2	yield, %
1	0.20	5	2	35
2	0.20	5		16
3	0.20		5	23

[a] Cyclizations were performed in *o*-dichlorobenzene at reflux for 20 min. The a,c-biladiene used for all three runs was drawn from the same batch.

From this brief examination, method B appeared best for our purposes. A number of large-scale porphyrin cyclizations were therefore carried out with up to 1.6 g of a,c-biladiene **31** and yields of 65–68% of porphyrin could be reproducibly obtained. It was also found that shortening the reaction time from 20 to 10 min did not affect the yield. These results should be compared with those of Johnson and co-workers, who synthesized several rhodoporphyrins by cyclization of 1′-bromo-8′-methyl-a,c-biladienes.[26,27] From their experiments it was concluded that in the initial design of the synthesis of a particular rhodoporphyrin, the nuclear ester group should be remote from the final point of cyclization.[27] In this view the high yields obtained in the cyclization of 1′-methyl-8′-unsubstituted a,c-biladiene **31** to porphyrin **34** represent a worst case. This is intriguing, since a 1′-methyl-8′-bromo-a,c-biladiene analogous to those used by Johnson and coworkers may in fact be an intermediate in the conversion of **31** into **34**. One wonders, therefore, whether yields in the cyclization of 1′-methyl-8′-bromo-a,c-biladiene could be increased by addition of an oxidant such as iodine or bromine[28] and, similarly, whether the yields in the cyclization of 1′-methyl-8′-unsubstituted a,c-biladienes could be further improved by moving the nuclear ester further from the point of cyclization. In any event, the cyclization and purification of the porphyrins prepared by the Russian route is extremely simple experimentally with the further advantage that copper need not be removed from the product. This protocol deserves wider application and, in our view, appears to be the method of choice for the synthesis of rhodoporphyrins when the appropriate a,c-biladiene is available.

The subsequent transformations of 2,4-bis(2-acetoxyethyl)rhodoporphyrin XV **34** firstly involved trans-

(20) Smith, K. M.; Eivazi, F.; Langry, K. C.; Almeida, J. A. P. B.; Kenner, G. W. *Bioorg. Chem.* **1979**, *8*, 485–495.
(21) (a) Smith, K. M. In "Porphyrins and Metalloporphyrins"; Smith, K. M., Ed.; Elsevier: New York, 1975; p 44. (b) Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073–2080. (c) Smith, K. M.; Minnetian, O. M. *J. Chem. Soc., Perkin Trans. 1*, in press.
(22) Mironov, A. F.; Rumyantseva, V. P.; Fleiderman, L. I.; Evstigneeva, R. P. *Zh. Obsch. Khim.* **1975**, *45*, 1150–1153.
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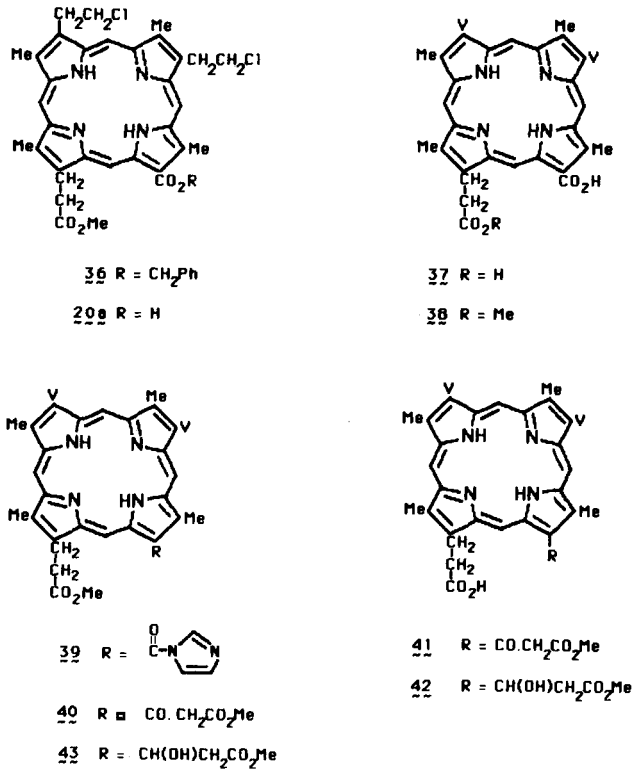
(26) Harris, R. L. N.; Johnson, A. W.; Kay, I. T. *J. Chem. Soc. C* **1966**, 22–29.
(27) Bamfield, P.; Harris, R. L. N.; Johnson, A. W.; Kay, I. T.; Shelton, K. W. *J. Chem. Soc. C* **1966**, *1436*–1443.
(28) Similar improvements in yields of porphyrins from pyrromethene cyclizations have also been documented: Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1471–1475. See also: Eaton, S. S.; Eaton, G. R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 3177–3184.

esterification of the acetate groups with sulfuric acid in methanol.[29] The product **35** was then converted into the 2,4-bis(2-chloroethyl) compound **36** by treatment with thionyl chloride in chloroform/dimethylformamide in the presence of potassium carbonate.[29] The overall yield of **36** from **34** was roughly 90% when **35** was not isolated.

The next step in the sequence was removal of the 6-benzyl ester. It had originally been planned to do this by catalytic hydrogenation. Treatment of **36** with 10% palladium on carbon at 20–28 psi of H_2 in acetone/methanol/tetrahydrofuran or tetrahydrofuran alone gave a mixture of products with a mass recovery of only 41%. In case the low recovery was due to overreduction of the porphyrin nucleus to give porphyrinogen, the zinc(II) complex of **36** was subjected to hydrogenation at 15–30 psi of H_2 in acetone/tetrahydrofuran, but only starting material was recovered, as judged by TLC.

Thus, hydrolysis of the 6-benzyl ester under acidic and basic conditions was investigated. Treatment of **36** with 10% sulfuric acid in TFA gave carboxylic acid **20a** in 77% yield. Though this method worked well on a small (100 mg) scale, it was capricious when scaled-up. Treatment of **36** with pyridine/aqueous potassium hydroxide hydrolyzed the 6-benzyl ester and the 7-propionic methyl ester and dehydrohalogenated the 2- and 4-chloroethyl groups to give **37**. Treatment of **37** with 5% sulfuric acid in methanol afforded selective reesterification of the 7-propionic acid to give **38**. It was more convenient at this point to prepare the imidazolide of **38** rather than to purify the acid itself. Therefore, **38** was refluxed with 1,1'-carbonylimidazole in tetrahydrofuran to give 6-imidazolide **39** which was purified by flash chromatography on silica gel. The overall yield of **39** from **36** was 60–70%.



Imidazolide **39** was then reacted with the magnesium complex of methyl monohydrogen malonate to give the 2,4-divinyl-6-β-keto ester **40**. This key intermediate gave a satisfactory elemental analysis, and its spectral properties were in agreement with those in the literature.[30] The presence of the β-keto ester side chain was confirmed by a pronounced change in the visible absorption spectrum from a "rhodo" to an "etio" type when a base such as methanolic potassium hydroxide was added to a solution of the porphyrin in dichloromethane.[31] The route involving initial basic hydrolysis of the 6-benzyl ester gave compound **40** in an overall yield of 30–35% from **36**, while the yield in the approach involving initial acidic hydrolysis was 18%. In either case, however, more facile hydrolysis might have been achieved with a methyl or ethyl rather than a benzyl ester at the 6-position, the last having been employed to avoid differential deprotection because of the observation that removal of copper form the product in the copper(II)-catalyzed cyclization also selectively removes the 6-benzyl ester (vide supra).

In a separate series of reactions, the keto ester **40** was also synthesized by formation of the imidazole **20b** from **20a** (44% yield), followed by treatment with magnesium(II) methyl hydrogen malonate to give **20c** (77%) and dehydrohalogenation to give the divinyl keto ester **40** (78%).

The further elaboration of **40** to the desired precursors **8**, **6**, and **12** was determined by two factors: (1) the conditions under which magnesium could be inserted and, (2) the necessity of selectively hydrolyzing the 7-propionic methyl ester to the acid in the presence of a methyl ester on the 6-side chain. Previous work had established that the 7-propionic methyl ester could be selectively hydrolyzed if the β-keto-ester side chain at the 6-position was *intact*,[14] presumably because removal of the acidic 6b-hydrogen prevents attack of hydroxide on the adjacent ester. Therefore, **40** (in tetrahydrofuran) was hydrolyzed to **41** with methanol/water/potassium hydroxide in 85–100% yield.

The question of magnesium insertion was next considered. The most elegant procedure is undoubtedly that of Eschenmoser,[32] which uses a reagent formed from ethyl magnesium iodide and 4-methyl-2,6-di-*tert*-butylphenol (BHT) in diethyl ether/dichloromethane. Unfortunately, while **41** is soluble in tetrahydrofuran or pyridine, it is very poorly soluble in diethyl ether or chlorinated hydrocarbons, the solvents of choice for the Eschenmoser procedure. Thus we were unable to use the mild Eschenmoser procedure, which otherwise would have been ideal, particularly to protect a 6-β-hydroxypropionate side chain which could easily undergo β-elimination to give the acrylate. Therefore older procedures which all involve more vigorous conditions such as prolonged reflux in pyridine with a large excess of magnesiating reagent were examined. The large excess of magnesiating reagent can hinder scale-up and makes workup tedious. The two simplest procedures were magnesium perchlorate/pyridine[33] and methoxymagnesium bromide/pyridine.[17] Treatment of **41** with magnesium perchlorate in pyridine at 100 °C gave the magnesium complex **8**. Treatment of a small portion of this with TFA removed the magnesium. The resulting porphyrin gave a positive spectroscopic test (vide supra) when a solution in dichloromethane was treated with methanolic potassium hydroxide. Thus, the β-keto ester side chain had survived the magnesiation intact. Unfortunately, the reaction did not scale-up well, and during the

(29) Carr, R. P.; Jackson, A. H.; Kenner, G. W.; Sach, G. S. *J. Chem. Soc. C* **1971**, 487–502.

(30) Cox, M. T.; Jackson, A. H.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 516–527.

(31) Reference 21a, p 21.

(32) Isenring, H. P.; Zass, E.; Smith, K.; Falk, H.; Luisier, J. L.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 2357–2367.

(33) Baum, S. J.; Burnham, B. F.; Plane, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1964**, *52*, 1439.

prolonged reflux time necessary to insert magnesium into 20 mg of **41** the material suffered extensive decomposition. The methoxymagnesium bromide method also required a lengthy reflux in pyridine, and, following the literature, a huge excess of the reagent was used.[17]

Since it was doubted that a 6-β-hydroxypropionate side chain could withstand 3 h of reflux in pyridine, **41** was first converted into its magnesium complex **8**, and then the β-keto ester was reduced to a β-hydroxypropionate with sodium borohydride in methanol/tetrahydrofuran.[14] We had previously performed this reaction on metal-free **41** in order to obtain an NMR spectrum of the product **42**. The spectrum obtained revealed the presence of a single porphyrin and is consistent with the formation of the desired β-hydroxypropionate. The 6a-methine proton is reasonably assigned to the multiplet at 6.7 ppm in **42**. Unfortunately, the 6b-methylene cannot be seen in the spectrum, although integration suggests that it is located under the triplet for the 7a-CH_2 at ca. 4.2 ppm. It is clear that the β-keto ester moiety is no longer present in **42** since the *meso* protons occur as one set of four resonance rather than the two sets of four resonances caused by keto–enol tautomerism in the β-keto ester. The product of the sodium borohydride reduction of magnesium(II) 6-β-keto ester 7-propionic acid porphyrin **8** was poorly soluble even in Me_2SO-d_6, and consequently a good NMR spectrum could not be obtained. The visible spectrum of the sodium borohydride reduction product showed the expected absorptions at 590 and 552 nm, and its identity was confirmed by demetalation and treatment with diazomethane to give the dimethyl ester **43**, also obtained by sodium borohydride reduction of the 2,4-divinyl β-keto ester **40**.

Several attempts were made to synthesize 6-acrylate porphyrin **12** from 6-β-hydroxypropionate **6** by treatment with $POCl_3$ in pyridine at 50 °C. However, it proved practically impossible to extract the porphyrin products of these reactions from the aqueous layer during workup. Thus the synthesis of 6-acrylate porphyrin **12** failed, principally owing to the requirement to carry out transformations on the magnesium(II) complex of the monomethyl ester. Current studies are aimed at synthesis of optically resolved hydroxypropionate porphyrins and an entirely different approach to selectively protected acrylate porphyrins via palladium-catalyzed coupling of mercurated porphyrins with methyl acrylate, and this work will be described elsewhere.

Experimental Section

Melting points, which are uncorrected, were measured on a Thomas/Bristoline microscopic hot stage apparatus. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer using solutions in dichloromethane, and mass spectra were measured on a Finnigan 3200 spectrometer (direct insertion probe, 70 eV, 50 μA, source temperature from 200 to 300 °C). Proton NMR spectra were obtained at 360 MHz on a Nicolet NT-360 spectrometer or at 500 MHz on a Nicolet NT-500 spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ at 7.260 ppm (360 and 500 MHz). The phrase "dried and evaporated" means drying with sodium sulfate, followed by evacuation with a Büchi rotary evaporator under house or oil pump vacuum. Elemental analyses were determined by the Microanalytical Laboratory at the University of California, Berkeley. Monitoring of reactions by thin-layer chromatography (TLC) was performed on cut strips (approximately 2 cm by 6 cm) of E. Merck silica gel 60 F254 precoated (0.25-mm thickness) plastic-backed sheets. Preparative TLC was performed on freshly prepared 20 cm by 20 cm TLC plates of ca. 1 mm thick E. Merck silica gel GF 254 and 60 G. Plates were activated prior to use by heating at 150 °C for at least 8 h. Two types of packing material were employed in column chromatography; E. Merck neutral alumina (70–230 mesh) and Merck silica gel 60. The alumina was deactivated with either 6% H_2O (Brockmann Grade III) or 15% H_2O (Brockmann Grade V) before use. A 250 mL J.T. Baker column was used for flash chromatography. Medium-pressure liquid chromatography utilized an FMI Model RPG150 pump, an Altex rotary injection valve, and a 1000-mm Altex glass chromatography column.

***tert*-Butyl 3-(2-Acetoxyethyl)-4-methylpyrrole-2-carboxylate (25).** *tert*-Butyl 4-(2-acetoxyethyl)-2-iodo-3-methylpyrrole-5-carboxylate (11.89 g) was dissolved in 100 mL of methanol, and then 12 g of $NaOAc{\cdot}3H_2O$ and 0.25 g of PtO_2 were added. Hydrogenation was performed for 18 h at 31 psi on a Parr apparatus. The catalyst was filtered off and the solvent concentrated. Dichloromethane was added and the solution rinsed with water. The organic layer was dried, evaporated, and recrystallized from dichloromethane/*n*-hexane to give 7.82 g (97%) of fine, colorless needles: mp 75 °C; NMR (90 MHz, $CDCl_3$) 8.90 (br s, NH), 6.66 (d, 1 H, J = 3 Hz, α-H), 4.18 (t, 2 H, J = 7.5 Hz, CH_2CH_2OAc), 3.02 (t, 2 H, J = 7.5 Hz, CH_2CH_2OAc), 2.02, 2.03 (2 s, 3 H each, OAc and 4-Me); 1.58 (s, 9 H, CO_2-*t*-Bu). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.80; H, 7.85; N, 5.11.

Benzyl 3-Methylpyrrole-4-carboxylate (33). Benzyl *trans*-2-butenoate (benzyl crotonate) (10.92 g; 62 mmol) and 12.11 g (62 mmol) of tosylmethyl isocyanide were dissolved in a mixture of 170 mL of anhydrous diethyl ether and 80 mL of dry dimethyl sulfoxide in a 300-mL round-bottom flask. This solution was cannulated under nitrogen into an addition funnel and then added dropwise over 60 min to a suspension of 4.25 g (106 mmol) of 60% sodium hydride in mineral oil and 20 mL of dry diethyl ether at room temperature with stirring under nitrogen. Copious evolution of hydrogen was observed. The brownish suspension was stirred an additional 0.5 h at room temperature. Then 200 mL of water was added cautiously, and the reaction mixture was poured into an additional 300 mL of water. The solution was then extracted 8 × 100 mL with diethyl ether. The organic layers were dried and evaporated. The resulting brown oil was triturated with toluene, and the solvents were evaporated under oil pump vacuum. The product was purified by flash chromatography on silica, eluting with 85/15 *n*-hexane/ethyl acetate. The resulting oil was put under high vacuum (0.02 mmHg) at room temperature overnight, whereupon a pale yellow crystalline solid formed. The solid as rinsed with cold *n*-hexane to give 9.07 g (68%) of **33**; mp 75–76 °C; NMR (90 MHz, $CDCl_3$) 9.0 (br s, NH), 7.40 (m, 5 H, Ar), 7.25 and 6.50 (2 m, 1 H each, α-H), 5.28 (s, 2 H, CH_2Ph), 2.28 (s, 4-Me). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; 6.09; N, 6.51. Found: C, 72.32; H, 6.09; N, 6.49.

Benzyl 2-Formyl-3-methylpyrrole-4-carboxylate (32).[25,34] Benzyl 4-methylpyrrole-3-carboxylate (**33**) (4.0 g; 18.6 mmol) and 3.27 g (28 mmol) of zinc cyanide were placed in a three-neck 250-mL round-bottom flask equipped with thermometer and gas outlet connected to an aqueous KOH trap. Then ca. 100 mL of dry diethyl ether was cannulated into the flask under nitrogen. The suspension was cooled to 0 °C on an ice–sodium chloride bath. Then HCl (gas) was slowly bubbled through the vigorously stirred suspension for 1 h at a rate such that the temperature did not exceed 20 °C. As the HCl was bubbled in, the solid material dissolved to give a clear solution, which then turned yellow. Gradually, a voluminous yellow precipitate formed. At the end of 1 h this solid was filtered off and washed with 50 mL of cold diethyl ether. It was then dissolved in methanol (70 mL). Water (70 mL) was added and the suspension heated at 70 °C bath temperature under nitrogen for 20 min. During this time all the solid dissolved. The reaction mixture was poured into 200 mL of ice–water to precipitate the product, which was then filtered, redissolved in dichloromethane, separated from residual water in a separatory funnel, dried, and evaporated. Flash chromatography on silica, eluting with 75/25 *n*-hexane/ethyl acetate, followed by recrystallization from dichloromethane/*n*-hexane, gave **32** as white crystals: 3.46 g (76%); mp 104–105 °C; NMR (90 MHz, $CDCl_3$) 10.38 (br s, NH), 9.75 (s, CHO), 7.68 (d, 1 H, α-H), 7.40 (m, 5 H, Ar), 5.30 (s, 2 H, CH_2Ph), 2.60 (s, 3-Me). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.91; H, 5.46; N, 5.73.

(34) Rimmer, J. Dissertation, University of Liverpool, 1977, p 121.

3,4'-Bis(2-acetoxyethyl)-5'-(*tert*-butoxycarbonyl)-3',4-dimethylpyrromethane-5-carboxylic Acid (26). *tert*-Butyl 3-(2-acetoxyethyl)-4-methylpyrrole-2-carboxylate (**25**) (2.0 g, 7.5 mmol) was dissolved in 10 mL of acetic acid and heated at 40 °C bath temperature under nitrogen. Then 246 mg of *p*-toluenesulfonic acid monohydrate was introduced, followed by the dropwise addition over 10 min of 1.94 g (5.2 mmol) of benzyl 4-(2-acetoxyethyl)-5-(acetoxymethyl)-3-methylpyrrole-2-carboxylate (**24**) dissolved in 50 mL of acetic acid. The solution was stirred a further 20 min, whereupon TLC appeared to show no (acetoxymethyl)pyrrole **24** remaining. The reaction was poured into a mixture of dichloromethane and water and shaken. The organic layer was removed, diluted with water, and neutralized carefully with solid sodium bicarbonate. The organic layer was separated, dried, and evaporated. Flash chromatography on a 19-cm bed of silica, eluting with 90/10 *n*-hexane/ethyl acetate, under nitrogen gave recovered α-free pyrrole **25**. Elution with 70/30 *n*-hexane/ethyl acetate then yielded the crude pyrromethane **23**. The oily, light brown pyrromethane 5-benzyl ester **23** was immediately hydrogenated on a Parr apparatus in acetone with 700 mg of 10% palladium on carbon for 19 h at 35 psi. TLC (70/30 *n*-hexane/ethyl acetate) showed only baseline material, which did not give a positive orange bromine test. The catalyst was filtered off, the solvent evaporated, and the product precipitated from dichloromethane with *n*-hexane to give 1.08 g (45%) of a faintly pinkish white solid: mp 143–145 °C; NMR (360 MHz, $CDCl_3$) 11.59, 10.90 (2 br s, NH), 4.01, 4.13 (2 t, 2 H each, J = 7.2 Hz, CH_2CH_2OAc), 3.90 (s, 2 H, methylene bridge), 2.78, 2.99 (2 t, 2 H each, J = 7.2 Hz, CH_2CH_2OAc), 2.13, 2.33 (2 s, 3 H each, 3'-,4-Me), 2.04, 2.05 (2 s, 3 H each, OAc), 1.56 (s, 9 H, CO_2-*t*-Bu). Anal. Calcd for $C_{25}H_{35}N_2O_8$: C, 61.09; H, 7.18; N, 5.70. Found: C, 61.31; H, 7.03; N, 5.70.

***tert*-Butyl 4,6-Bis(2-acetoxyethyl)-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5-tetramethyltripyrrene-a-6'-carboxylate Hydrobromide (28).** 3,4'-Bis(2-acetoxyethyl)-5'-*tert*-(butoxycarbonyl)-3',4-dimethylpyrromethane-5-carboxylic acid (**26**) (0.94 g; 2.0 mmol) and 0.42 g (2.0 mmol) of 2-formyl-4-[2-(methoxycarbonyl)ethyl]-3,5-dimethylpyrrole (**27**) were dissolved in 25 mL of dry dichloromethane. Then 415 mg of *p*-toluenesulfonic acid monohydrate in 6 mL of dry methanol was added. The solution was stirred at room temperature under nitrogen for 75 min and then rinsed with water and saturated aqueous sodium bicarbonate. (The color of the organic layer should change from red-orange to dark green with the bicarbonate wash.) The organic layer was dried and evaporated and the residue redissolved in the *minimum* volume of *dry* dichloromethane. After cooling on an ice bath (possible *tert*-butyl ester cleavage at higher temperatures), HBr (gas) was bubbled vigorously through the solution for 5–8 s. The tripyrrene hydrobromide was then precipitated by addition of *dry* diethyl ether (filtered through sodium sulfate directly into the flask) and refrigeration. Contamination by water should be avoided at any stage. The product was filtered to give 748 mg (52%) of a brick-red solid: mp 172–174 °C; NMR (360 MHz, $CDCl_3$) 13.30, 13.21, 10.35 (3 br s, NH), 7.10 (s, methine bridge), 4.35 (s, 2 H, methylene bridge), 4.13, 3.99 (2 t, J = 7.2 Hz, CH_2CH_2OAc), 3.67 (s, CO_2Me), 3.02 (s, 2 H, $CH_2CH_2CO_2Me$), 2.75–2.77 (m, 4 H, CH_2CH_2OAc), 2.72, 2.32, 2.29 (3 s, 3 × Me), 2.49 (t, 2 H, $CH_2CH_2CO_2Me$), 2.07, 2.04, 2.01 (3 s, 1 × Me, 2 × OAc); UV–vis (2% v/v TFA/CH_2Cl_2) 484 nm (ϵ 8.94 × 10^4). Anal. Calcd for $C_{35}H_{48}BrN_3O_8$: C, 58.49; H, 6.73; N, 5.85. Found: C, 58.17; H, 6.40; N, 5.84.

4,6-Bis(2-acetoxyethyl)-8-[(benzyloxy)carbonyl]-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5,7,8'-hexamethyl-a,c-biladiene Dihydrobromide, (29). *tert*-Butyl 4,6-bis(2-acetoxyethyl)-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5-tetramethyltripyrrene-a-6'-carboxylate hydrobromide (**28**) (721 mg, 1.0 mmol) was dissolved in 10 mL of TFA and allowed to stir for 5 min at room temperature. Then 283 mg (1.1 mmol) of benzyl 2-formyl-3,5-dimethylpyrrole-4-carboxylate (**30**)[35] in a mixture of 5 mL of dichloromethane and 5 mL of methanol was added and the solution stirred for 75 min. The reaction mixture was then diluted with dichloromethane and washed with water and saturated aqueous sodium bicarbonate (red dication is converted to the green free base). The organic layer was dried and evaporated at *room temperature*, and then the residue was dissolved in the minimum volume of dry dichloromethane and bubbled with HBr (gas) for 8 s. The a,c-biladiene dihydrobromide was precipitated by addition of *dry* diethyl ether (filtered through sodium sulfate directly into the flask) and refrigeration. The brick-red solid, 683 mg (72%) was then filtered off. A second crop of 127 mg (13%) was also obtained. If the reaction is performed carefully, the first crop will yield 85–95% and the second crop, if obtained, is usually of very poor quality. The product had mp 135–137 °C: UV–vis (2% v/v TFA/CH_2Cl_2) 446 nm (ϵ 1.46 × 10^5), 518 (3.63 × 10^4); NMR (360 MHz, $CDCl_3$ 14.11, 13.49 (2 H), 13.35 (3 br s, NH), 7.47, 7.15 (2 s, a,c-methane bridges), 7.25–7.42 (m, 5 H, Ar), 5.34 (s, CH_2Ph), 5.31 (s, b-methylene bridge), 4.09, 3.55 (2 t, CH_2CH_2OAc), 3.68 (s, CO_2Me), 2.97, 2.74, 2.67, 2.34, 2.29 (5 s, ring Me); 2.01, 2.00 (2 s, OAc); 1.86 (s, ring Me). A satisfactory elemental analysis for this compound could not be obtained.

2,4-Bis(2-acetoxyethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin-6-carboxylic Acid (21). Anhydrous copper(II) chloride (1.76 g, 13.1 mmol) in 50 mL of DMF was heated at 150 °C bath temperature under nitrogen for 5 min to give a brown solution. Then 0.69 g (0.74 mmol) of 4,6-bis(2-acetoxyethyl)-8-[(benzyloxy)carbonyl]-1-[2-(methoxycarbonyl)-ethyl]-1',2,3,5,7,8'-hexamethyl-a,c-biladiene dihydrobromide (**29**) was added as a solid. The mixture was heated 5 min at 150 °C. The visible spectrum showed the presence of a Soret band. The reaction mixture was cooled, diluted with dichloromethane, and rinsed with water. The organic layer was dried, evaporated, and subjected to flash chromatography on a 6-cm bed of Grade V neutral alumina to remove excess copper salts. The eluate was evaporated, dissolved in 17 mL of TFA, and cooled to 0 °C, whereupon 3 mL of concentrated sulfuric acid was added dropwise with stirring. The solution was stirred for 15 min under nitrogen at 0 °C until solid began to precipitate. The ice bath was then removed and stirring continued for 15 min further. The reaction mixture was diluted with dichloromethane and rinsed with water. The organic layer was removed, carefully neutralized with solid sodium bicarbonate, rinsed with water, dried, and evaporated. The crude porphyrin was purified by preparative silica TLC, eluting with 80/20 dichloromethane/THF. The major band, R_f 0.25, was recrystallized from dichloromethane/*n*-hexane to give 77 mg (16%) of **21**: mp 261 °C; UV–vis (CH_2Cl_2) 634 nm (ϵ 1.32 × 10^3), 576 (6.75 × 10^3), 548 (1.11 × 10^4), 508 (8.08 × 10^3), 404 (1.80 × 10^5); MS, *m/e* (relative intensity) 668 (79.3, M^+), 624 (100, base peak, $M^+ - CO_2$), 608 (14.9, $M^+ - CH_3CO_2H$, McLafferty rearrangement of OAc); NMR (360 MHz, $CDCl_3$/TFA) 11.57, 10.93, 10.72, 10.57 (4 s, *meso*-H), 4.82 (m, 4 H, 2 CH_2CH_2OAc), 4.45 (m, 6 H, 2 CH_2CH_2OAc plus CH_2CH_2Me), 4.05 (s, 3 H, 7d-OMe), 3.69, 3.67, 3.66, 3.62 (4 s, 3 H each, 1-,3-,5-,8-Me), 3.21 (t, 2 H, $CH_2CH_2CO_2Me$), 2.04, 2.03 (2 s, 3 H each, OAc). Anal. Calcd for $C_{37}H_{40}N_4O_8$: C, 66.45; H, 6.03; N, 8.38. Found: C, 66.18; H, 6.06; N, 8.36.

4,6-Bis(2-acetoxyethyl)-8-[(benzyloxy)carbonyl]-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5,7-pentamethyl-a,c-biladiene Dihydrobromide (31). *tert*-Butyl 4,6-bis(2-acetoxyethyl)-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5-tetramethyltripyrrene-a-6'-carboxylate hydrobromide (**28**) (0.793 g, 1.10 mmol) was treated with 6 mL of TFA for 5 min at room temperature under nitrogen. Then 0.281 g (1.16 mmol) of benzyl 2-formyl-3-methylpyrrole-4-carboxylate (**32**) in a mixture of 3 mL of dichloromethane and 3 mL of methanol was added and the reaction stirred for 60 min at room temperature under nitrogen. The reaction mixture was then diluted with dichloromethane, followed by rinsing with water and saturated aqueous sodium bicarbonate. The organic layer was dried and evaporated at *room temperature*. The residue was dissolved in dry dichloromethane and HBr (gas) was bubbled in for 10 s, followed by the addition of dry diethyl ether and refrigeration. The precipitate was filtered to give **31** as a brick-red solid: 0.947 g (93%); mp 154–155 °C; UV–vis (2% v/v TFA/CH_2Cl_2) 442 nm (ϵ 1.35 × 10^5), 516 (2.93 × 10^4); NMR (360 MHz, $CDCl_3$) 14.18, 13.75, 13.49, 13.35 (4 br s, NH), 8.24 (d, J = 3.7 Hz, 8'-H); 7.40 (m, 5 H, Ar), 7.58, 7.15 (2 s, 1 H each, a,c-methine H), 5.33 (s, 2 H, CH_2Ph), 5.13 (s, 2 H, b-methylene bridge), 4.13 (t, 2 H, $CH_2CH_2CO_2Me$), 3.68 (s, 7d-OMe), 3.57 (t, 2 H, $CH_2CH_2CO_2Me$), 3.02, 2.90 (2 t, 2 H each, CH_2CH_2OAc), 2.79 (obscured t), 2.49 (t) (2 H each, CH_2CH_2OAc), 2.75, 2.72, 2.34,

(35) Clezy, P. S.; Fookes, C. J. R.; Liepa, A. J. *Aust. J. Chem.* **1972**, *25*, 1979–1990.

2.29, 1.84 (5 s, 1'-,2-,3-,5-,7-Me), 2.00, 2.04 (2 s, 3 H each, OAc). Anal. Calcd for $C_{44}H_{52}Br_2N_4O_8$: C, 57.15; H, 5.67; N, 6.06. Found: C, 56.88; H, 5.75; N, 6.20.

2,4-Bis(2-acetoxyethyl)-6-[(benzyloxy)carbonyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (34). 4,6-Bis(2-acetoxyethyl)-8-[(benzyloxy)carbonyl]-1-[2-(methoxycarbonyl)ethyl]-1',2,3,5,7-pentamethyl-a,c-biladiene dihydrobromide (**31**) (1.60 g, 1.73 mmol) was dissolved in 600 mL of *o*-dichlorobenzene. Then 2.20 g (8.65 mmol, 5 mol equiv) of iodine and 0.553 g (2 mol equiv) of bromine were added. The reaction flask was placed in an oil bath preheated to 200 °C and refluxed for 20 min under air. The reaction mixture was cooled, treated with 2 mL of triethylamine, and divided into three portions. Each portion was poured directly onto a bed of Grade V neutral alumina in a flash chromatography column. The *o*-dichlorobenzene was forced off, and the column was developed first with *n*-hexane to remove traces of *o*-dichlorobenzene and iodine and then with dichloromethane to obtain the porphyrin. The entire porphyrin fraction was then subjected to flash chromatography on silica, eluting with 97/3 dichloromethane/THF. The first fraction contained two minor porphyrin products. The second, major, band contained the desired **34**. A final fraction contained mostly porphyrin band 3. The first and last fractions were rechromatographed on the flash column as before to obtain more **34**. The remaining mixed fractions were then purified by TLC on silica and combined accordingly. Recrystallization from dichloromethane/*n*-hexane gave **34** as a solid, 1.78 g (68%), as well as band 1 (0.14 g) and band 3 (0.40 g, oil). Band 1 was subsequently repurified by TLC, eluting with 97/3 dichloromethane/THF to give band 1A and band 1B (in order of elution). Band 3 was also repurified by silica TLC to give bands 3A (4.4 mg) and 3B (66 mg). NMR showed that bands 1A, 1B, and 3B were each a mixture of two compounds, and further purification was not attempted. The mass spectra of the three bands did not show parent ions. The unusual visible spectrum of band 1B suggests that it is a mixture of *meso*-halogen-substituted porphyrins. Bands 1A and 3B are probably also halogen substituted, either by displacement of an OAc group by halide or halogen substitution as in $OCOCH_2X$.

Compound 34: mp 183 °C; UV–vis (CH_2Cl_2) 634 nm (ϵ 2.10×10^3), 574 (9.12×10^3), 548 (1.59×10^4), 508 (1.23×10^4), 406 (2.31×10^5); NMR (360 MHz, $CDCl_3$ 11.08, 10.30, 10.11, 10.03 (4 s, *meso*-H), 7.83 (d, 2 H, ortho Ar), 7.46–7.58 (m, 3 H, meta and para Ar), 5.90 (s, 2 H, CH_2Ph), 4.87 (m, 4 H, CH_2CH_2OAc), 4.46 (t, 2 H, $CH_2CH_2CO_2Me$), 4.33 (m, 4 H, CH_2CH_2OAc), 4.00 (s, 3 H, 7d-OMe), 3.72, 3.67, 3.60, 3.59 (4 s, 3 H each, 1-,3-,5-,8-Me), 3.15 (t, 2 H, $CH_2CH_2CO_2Me$), 2.04, 2.09 (2 s, 3 H each, OAc), −4.0 (br s, 2 H, NH). Anal. Calcd for $C_{44}H_{46}N_4O_8$: C, 69.64; H, 6.11; N, 7.38. Found: C, 69.70; H, 6.26; N, 7.35.

Band 1A: UV–vis (CH_2Cl_2, relative absorbance) 634 nm (12.0), 576 (59.0), 548 (100), 508 (72.4).

Band IB: UV–vis (CH_2Cl_2, relative absorbance) 644 nm (43.7), 586 (48.2), 548 (62.5), 512 (100).

Band 3B: UV–vis (CH_2Cl_2, relative absorbance) 632 nm (14.4), 574 (58.9), 546 (100), 508 (78.7).

6-[(Benzyloxy)carbonyl]-2,4-bis(2-hydroxyethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (35). 2,4-Bis(2-acetoxyethyl)-6-[(benzyloxy)carbonyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**34**) (338 mg) was dissolved in 100 mL of 95/5 v/v methanol/concentrated sulfuric acid and stirred at room temperature in the dark under nitrogen for 1 h, whereupon TLC showed reaction was complete: starting material, R_f 0.5; product, R_f 0.16 (95/5 dichloromethane/methanol). The reaction mixture was poured into a mixture of dichloromethane and water and shaken. The organic layer was removed, rinsed with saturated aqueous sodium bicarbonate, dried, and evaporated. The crude product was purified by flash chromatography on Grade V neutral alumina eluting with 95/5 dichloromethane/methanol to remove a trace of base line. The product was precipitated from dichloromethane with *n*-hexane to give 282 mg (94%): mp 266 °C; UV–vis (CH_2Cl_2) 634 nm (ϵ 2.60×10^3), 574 (1.06×10^4), 548 (1.83×10^4), 508 (1.41×10^4), 406 (2.42×10^5); NMR (360 MHz, $CDCl_3$ + Me_2SO-d_6) 10.69, 9.97, 9.76, 9.68 (4 s, *meso*-H), 7.55 (d, 2 H, J = 7.3 Hz, ortho Ar), 7.26 (m, 3 H, meta and para Ar), 5.61 (s, 2 H, CH_2Ph), 4.0–4.1 (m, 8 H) and 3.93 (t, 2 H) (2a,b- and 4a,b-CH_2CH_2 and 7a-CH_2), 3.67 (s, 3 H, 7d-OMe), 3.40, 3.36, 3.33, 3.28 (4 s, 3 H each, 1-,3-,5-,8-Me), 2.89 (t, 2 H, 7b-CH_2), −4.12 (br s, NH). Anal. Calcd for $C_{40}H_{42}N_4O_6 \cdot H_2O$: C, 69.35; H, 6.40; N, 8.08. Found: C, 69.05; H, 6.26; N, 8.12.

6-[(Benzyloxy)carbonyl]-2,4-bis(2-chloroethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (36). 6-[(Benzyloxy)carbonyl]-2,4-bis(2-hydroxyethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**35**) (265 mg) was dissolved in a mixture of 65 mL of chloroform and 32 mL of DMF. Potassium carbonate (6 g) was added, followed by addition of 5 mL of thionyl chloride. The reaction was stirred at room temperature under nitrogen in the dark for 1 h. The reaction was complete by TLC (95/5 dichloromethane/methanol): **36** runs with the solvent front, while **35** has R_f 0.16. The reaction mixture was carefully poured into water. The organic layer was removed, neutralized with saturated aqueous sodium bicarbonate, dried, and evaporated. The product was purified on a silica gel column, eluting with 98/2 dichloromethane/THF. The major product was recrystallized from dichloromethane/*n*-hexane to give 253 mg (90%): mp 203 °C; UV–vis (CH_2Cl_2 634 nm (ϵ 2.71×10^3), 576 (1.12×10^4), 548 (1.95×10^4), 510 (1.64×10^4), 406 (2.87×10^5); NMR (360 MHz, $CDCl_3$) 11.06, 10.13, 10.00, 9.92 (4 s, *meso*-H), 7.83 (d, 2 H, J = 7.3 Hz, ortho Ar), 7.55 (m, 3 H, meta and para Ar), 5.90 (s, 2 H, CH_2Ph), 4.55 (t, 2 H), 4.42 (t, 2 H), 4.33 (m, 6 H) (2a,b- and 4a,b-CH_2CH_2 and 7a-CH_2), 3.96 (s, 3 H, 7d-OMe), 3.69, 3.65, 3.59, 3.58 (4 s, 3 H each, 1-,3-,5-,8-Me), 3.19 (t, 7b-CH_2), −3.71 (br s, NH). Anal. Calcd for $C_{40}H_{40}Cl_2N_4O_4$: C, 67.51; H, 5.66; N, 7.87. Found: C, 67.22; H, 5.75; N, 7.93.

2,4-Bis(2-chloroethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin-6-carboxylic Acid, (20a). 6-[(Benzyloxy)carbonyl]-2,4-bis(2-chloroethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**36**) (130 mg) was dissolved in a solution of 2 mL of concentrated sulfuric acid diluted to 20 mL with TFA and allowed to stir at room temperature under nitrogen for 45 min. Neutralization of an aliquot and TLC (95/5 dichloromethane/methanol) showed complete consumption of **36** and the production of acid porphyrin **20a**, R_f 0.1. The reaction mixture was poured into a mixture of iced aqueous sodium acetate solution and dichloromethane and shaken. The organic layer was removed, rinsed with saturated aqueous sodium bicarbonate, dried, and evaporated. The crude **20a** was too insoluble in THF, methanol, dichloromethane, or acetone to be chromatographed effectively, although it was passed through a silica column (flash) with 85/15 dichloromethane/methanol. The "eluates" were evaporated to give 88 mg (77%): mp >300 °C; UV–vis (CH_2Cl_2) 634 nm (ϵ 1.98×10^3), 574 (7.07×10^3), 544 (1.17×10^4), 506 (1.10×10^4), 404 (1.90×10^5); NMR (360 mHz, $CDCl_3$/TFA) 11.58, 10.80, 10.60, 10.54 (4 s, *meso*-H), 4.54 and 4.18 (2 m, 4 H each, 2a,b- and 4a,b-CH_2CH_2), 4.41 (t, 2 H, 7a-CH_2), 4.02 (s, 3 H, 7d-OMe), 3.68, 3.67, 3.65, 3.58 (4 s, 3 H each, 1-,3-,5-,8-Me), 3.18 (t, 2 H, 7b-CH_2). Anal. Calcd for $C_{33}H_{34}Cl_2N_4O_4$: C, 63.77; H, 5.51; N, 9.01. Found: C, 63.55; H, 5.54; N, 8.77.

2,4-Bis(2-chloroethyl)-6-(imidazol-1-ylcarbonyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin, (20b). Porphyrin-6-carboxylic acid **20a** (494 mg) was dissolved in 50 mL of dry THF and treated with 675 mg 1,1'-carbonyldiimidazole. The solution was refluxed for 2 h under nitrogen. The solvent was evaporated and the crude product purified by flash chromatography on Grade V neutral alumina, eluting with dichloromethane. The product was still contaminated with 1,1'-carbonyldiimidazole, so it was rechromatographed by using a longer bed of alumina. The product (237 mg, 44%) was precipitated from dichloromethane with *n*-hexane: mp 227–229 °C; UV–vis (CH_2Cl_2) 632 nm (ϵ 1.94×10^3), 574 (9.72×10^3), 546 (1.64×10^4), 508 (1.23×10^4), 406 (2.18×10^5); NMR (360 MHz, $CDCl_3$) 10.15, 10.05, 10.01, 10.00 (4 s, *meso*-H); 8.36, 7.94, 7.34 (3 s, 1 H each, imidazolyl ring H); 4.59 (t, 2 H), 4.44 (t, 2 H), 4.3 (m, 6 H) (2a,b- and 4a,b-CH_2CH_2 and 7a-CH_2), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.66 (s, 6 H), 3.58 (s, 3 H) (1-,3-,5-,8-Me and 7d-OMe), 3.21 (t, 2 H, 7b-CH_2), −3.74 (br s, NH). Anal. Calcd for $C_{36}H_{36}Cl_2N_6O_3 \cdot 0.5H_2O$: C, 63.53; H, 5.48; N, 12.34. Found: C, 63.70; H, 5.41; N, 12.19.

2,4-Bis(2-chloroethyl)-6-[(methoxycarbonyl)acetyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin, (20c). A solution of isopropylmagnesium bromide was prepared by heating 0.10 g of Mg turnings (4.1 mmol) with 0.4 mL (4.2

mmol) of isopropyl bromide in ca. 15 mL of dry THF at 60 °C under nitrogen. When all the metal was consumed, the solution was cooled to 0 °C, and 0.26 g of monohydrogen malonate (2.2 mmol) was added. The solution was replaced in the 60 °C bath and heated for 10 min. Then 164 mg (0.26 mmol) of 2,4-bis(2-chloroethyl)-6-(imidazol-1-ylcarbonyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**20b**) in 6 mL of dry dichloromethane was added and the solution heated for 2.5 h at 60 °C under nitrogen. Then 1 mL of acetic acid was added and the reaction heated for a further 10 min. The reaction mixture was then diluted with chloroform and washed with 10% aqueous HCl and then with water. The organic layer was dried and evaporated. TLC showed one major spot, R_f 0.42 (97/3 dichloromethane/THF), which ran much faster than starting material. The crude product was purified immediately by flash chromatography on silica, eluting with 97/3 dichloromethane/THF. Recrystallization from dichloromethane/methanol gave purple needles, 127 mg (77%). The mother liquors contained a further 28 mg (17%): mp 210 °C dec; UV–vis (CH_2Cl_2) 632 nm (ϵ 2.03 × 10^3), 576 (1.12 × 10^4), 546 (1.73 × 10^4), 508 (1.50 × 10^4), 408 (2.40 × 10^5); NMR (360 MHz, $CDCl_3$) [keto form] 10.77, 10.05, 9.98, 9.90 (4 s, *meso*-H), 4.72 (s, 6b-CH_2, relative integral 2.0), 3.69, 3.66, 3.56 (3 s, 1-,3-,5-,8-Me and 6d- and 7d-OMe), −3.72 (br s, NH, relative integral 1.23), [enol form] 13.28 (s, enol OH), 10.52, 10.07, 10.04, 9.95 (4 s, *meso*-H), 6.09 (s, 6b-H, relative integral 0.69), 4.04, 3.93, 3.87, 3.80, 3.68, 3.59 (6 s, 1-,3-,5-,8-Me and 6d- and 7d-OMe), −3.81 (br s, NH, relative integral 0.74), [common resonances] 4.53 (m, 2 H, 7a-CH_2), 4.43 (m, 4 H) and 4.31 (m, 4 H) (2a,b- and 4a,b-CH_2CH_2), 3.31 (m, 2 H, 7b-CH_2). The enol form comprised 37–41% of the mixture based on the relative integrals of the NH peaks and the ratio of 6b-H (enol form) to the 6b-CH_2 (keto form). Anal. Calcd for $C_{36}H_{38}Cl_2N_4O_5 \cdot 0.5H_2O$: C, 62.97; H, 5.72; N, 8.16. Found: C, 63.28; H, 5.68; N, 8.05.

6-(Imidazol-1-ylcarbonyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin (39). 6-[(Benzyloxy)carbonyl]-2,4-bis(2-chloroethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**36**) (418 mg) in 55 mL of pyridine was heated at 100 °C for 5 min before addition of 5 mL of water and then 10 mL of a 6% solution of potassium hydroxide in water. The mixture was heated for 6 h under nitrogen in the dark, and the solvents were then evaporated. The residue was dissolved in 200 mL of 5% sulfuric acid in methanol and stirred in the dark for 17 h. Dichloromethane (100 mL) and aqueous sodium acetate were then added, and the organic phase was washed with aqueous sodium bicarbonate, then water, dried, and evaporated to give a residue, which was dissolved in 50 mL of dry tetrahydrofuran and treated with 498 mg of 1,1′-carbonyldiimidazole. The mixture was refluxed under nitrogen in the dark for 3 h, and then the solvent was evaporated to give a residue, which was flash chromatographed on alumina [Brockmann Grade V, elution with dichloromethane/tetrahydrofuran (97:3)]. The appropriate eluates were evaporated to give a residue, which was recrystallized from dichloromethane-/*n*-hexane to give 281 mg (80%): mp 244–250 °C dec (lit.[30] mp 254–258 °C); UV–vis (CH_2Cl_2) 638 nm (ϵ 1.00 × 10^3), 578 (9.20 × 10^3), 552 (1.44 × 10^4), 514 (9.8 × 10^3), 410 (1.65 × 10^5). This material was used immediately in the following reaction.

6-(2-Methoxycarbonylacetyl)-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (40). A solution of isopropyl magnesium bromide was prepared by heating 0.2 g of Mg turnings (8.3 mmol) with 0.8 mL of isopropyl bromide in ca. 30 mL of dry THF at 60 °C under nitrogen. When the metal was completely consumed, 0.50 g of monohydrogen malonate (4.2 mmol) was added carefully and heating continued for 10 min. Then 6-(imidazol-1-ylcarbonyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin **39** (280 mg, 0.46 mmol) in ca. 12 mL of dry dichloromethane was added and heating continued at reflux for 2.5 h under nitrogen. TLC showed that the starting material was consumed. Acetic acid (2 mL) was added and heating continued for a further 10 min. The reaction mixture was then rinsed with 10% aqueous HCl and then water, and the organic layer was dried and evaporated. Flash chromatography on Grade V neutral alumina, eluting with 97/3 dichloromethane/THF, followed by recrystallization from dichloromethane/methanol gave **40** (90 mg, 31%). This reaction was performed three more times in yields of 57%, 61%, and 100%, respectively. The product had mp >210 °C (lit.[30] mp 179–185 °C): UV–vis (CH_2Cl_2) 640 nm (ϵ 1.63 × 10^3), 582 (8.96 × 10^3), 556 (1.40 × 10^4), 514 (1.10 × 10^4), 412 (1.76 × 10^5); MS, *m/e* (relative intensity) 604 (3.3, M^+), 578 (34.8), 577 (9.4), 576 (14.5), 575 (11.4), 564 (6.6), 563 (6.2), 552 (14.2), 551 (26.1), 550 (29.4), 549 (14.8), 548 (13.1), 523 (17.9), 368 (100, base peak); NMR (360 MHz, $CDCl_3$/TFA) 11.22, 10.70, 10.68, 10.60 (4 s, *meso*-H), 8.11 (2a- and 4a-vinylic H), 6.46 (m, 2b- and 4b-vinylic H), 6.26 (m, 2b′ and 4b′-vinylic H), 6.27 (s, 1 H, 6b-H of enol form, enol OH lost due to exchange), 4.37 (t, 2 H, 7a-CH_2), 3.90 (s, 3 H, 6d-OMe), 3.68, 3.66, 3.62, 3.58, 3.32 (5 s, 3 H each, 1-,3-,5-,8-Me and 7d-OMe), 3.13 (t, 2 H, 7b-CH_2), (in $CDCl_3$) [keto form] 10.72, 10.24, 10.11, 9.98 (4 s, *meso*-H), 4.73 (s, 6b-CH_2), 3.92 (3 H), 3.87 (3 H), 3.73 (3 H), 3.67 (9 H) (1-,3-,5-,8-Me, 6d-OMe, and 7d-OMe), [enol form] 13.26 (s, enol OH), 10.48, 10.26, 10.18, 10.05 (4 s, *meso*-H), 5.30 (s, 6b-H), 4.04, 3.79, 3.70, 3.68, 3.64 (6 s, 1-,3-,5-,8-Me, 6d-OMe, and 7d-OMe), [common resonces] 8.07–8.42 (m, 2a- and 4a-vinylic H), 6.2–6.37 (m, 2b- and 4b-vinylic H), 4.44 (t, 7a-CH_2), 3.33 (t, 7b-CH_2). Integration of the two lowest field *meso* proton resonances gave a keto–enol ratio of 0.99:0.63, or 39% enol form. Anal. Calcd for $C_{36}H_{36}N_4O_5$: C, 71.51; H, 6.00; N, 9.27. Found: C, 71.20; H, 6.17; N, 9.55.

Compound **40** was also prepared by dehydrohalogenation of 2,4-bis(2-chloroethyl)-6-[2-(methoxycarbonyl)acetyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**20c**). Thus **20c** (121 mg) was dissolved in 40 mL of pyridine and heated at 100 °C bath temperature for 5 min, and then 6 mL of distilled water was added with continued heating for 5 min. Finally 5 mL of an ca. 6% w/w aqueous solution of potassium hydroxide (587 mg potassium hydroxide plus 9.7 mL of water) was added and the solution heated at 100 °C for 5 h. (Adding the aqueous potassium hydroxide at once to **20c** dissolved in pyridine, followed by heating, gave the same result.) The solvent was evaporated and the residue treated with 150 mL of 5% concentrated sulfuric acid in methanol for 17.5 h. The reaction mixture was diluted with dichloromethane and rinsed with water and then with saturated aqueous sodium bicarbonate. The organic layer was dried, evaporated, and purified by flash chromatography on silica, eluting with 97/3 dichloromethane/THF. Recrystallization from dichloromethane/*n*-hexane gave **40** as a solid (62 mg, 57%). The mother liquors were evaporated to give another 23 mg (21%).

6-[(Methoxycarbonyl)acetyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (41). 6-[(Methoxycarbonyl)acetyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin **40** (56 mg) was dissolved in a solution of 165 mg of potassium hydroxide in 10 mL of methanol. Then 0.5 mL of water was added and the solution heated at 50 °C bath temperature under nitrogen in the dark for 2 h. Since there appeared to be undissolved porphyrin in the reaction mixture, 15 mL of THF was added and the reaction continued for a further 2 h. The reaction mixture was then diluted with dichloromethane and rinsed with 10% aqueous HCl. The organic layer was then removed and rinsed with 50% saturated aqueous sodium bicarbonate, but an emulsion resulted which could only be cleared by reacidification with 10% HCl. The organic layer was dried and evaporated. TLC (97/3 dichloromethane/THF) showed nothing but base line material. The product was precipitated from dichloromethane with *n*-hexane and dried at 78 °C in vacuo to give **41** as a red solid: 46.2 mg (84%); mp >310 °C; UV–vis (CH_2Cl_2, relative absorbance) 642 nm (15.3), 580 (68.5), 554 (100), 514 (83.8), [after the addition of methanolic KOH] 630 (29.6), 576 (54.9), 544 (89.4), 508 (100); NMR (360 MHz, $CDCl_3$ + Me_2SO-d_6) 13.16 (s, enol OH), 10.51, 10.34, 10.01, 9.93, 9.90, 9.83, 9.80, 9.75 (8 s, *meso*-H), 8.01–8.11 (m, 2a- and 4a-vinylic H), 5.98–6.32 (m, 2b- and 4b-vinylic H), 6.16 (s, 6b-vinylic H, enol form), 4.63 (s, 6b-CH_2, keto form), 4.30 (t, 7a-CH_2), 3.94, 3.83, 3.69, 3.65, 3.56, 3.55, 3.53, 3.51, 3.48 (ring Me and 7d-OMe), 3.14 (t, 7b-CH_2), −4.22 (br s, NH).

6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin, (42). 6-[(Methoxycarbonyl)acetyl]-7-(carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin **41** (46.7 mg) was dissolved in 15 mL of tetrahydrofuran and a solution of 500 mg of sodium borohydride in 10 mL of ice cold dry methanol was added. The mixture was stirred for 10 min at room temperature before acetone (10 mL) and water were added. Extraction with dichloromethane, followed

by rinsing with water, drying, and evaporation, gave a residue, which was crystallized from dichloromethane/*n*-hexane to give 31.6 mg (68%) of the title porphyrin: mp >300 °C; NMR (360 MHz, $CDCl_3$ + Me_2SO-d_6) 11.70 (br s, CO_2H), 10.29, 10.08, 10.07 (each s, 1 H, 2 H, 1 H, *meso*-H), 8.17, 8.12 (each m, 2- and 4-vinyl α-CH), 6.71 (m, C*H*(OH)), 6.25, 6.07 (each m, 2- and 4-vinyl β-CH_2), 4.28 (m, 7a-CH_2), 3.59, 3.57, 3.54, 3.51 (each s, 3 H, 3 H, 6 H, 3 H, four Me and OMe), 3.09 (t, 7b-CH_2), -3.89 (s, two NH). The 6b-CH_2 resonance was obscured. Anal. Calcd for $C_{35}H_{36}N_4O_5$: C, 70.92; H, 6.12; N, 9.45. Found: C, 71.32; H, 6.24; N, 9.13.

6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin (43). 6-[(Methoxycarbonyl)acetyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin **40** (50 mg) in 25 mL of dry dichloromethane was treated at with a solution of 550 mg of sodium borohydride in 25 mL of ice-cold methanol, and the mixture was stirred at room temperature for 7 min before addition of acetone (10 mL), water, and dichloromethane. The organic phase was washed with water, dried, and evaporated to give a residue, which was flash chromatographed on alumina (Brockmann Grade V, elution with dichloromethane). Evaporation of the appropriate eluates gave a residue, which was recrystallized from methanol to give 18.6 mg (37%): mp >300 °C dec; NMR (360 MHz, $CDCl_3$) 10.49, 10.25, 10.22, 10.10 (each s, *meso*-H), 8.30, 8.29 (each m, 2- and 4-vinyl α-CH), 6.85 (m, C*H*(OH)), 6.39, 6.23 (each m, 2- and 4-vinyl β-CH_2), 4.44 (t, 7a-CH_2), 3.82, 3.74, 3.71, 3.70, 3.66, 3.62 (each s, four Me and two OMe), 3.29 (t, 7b-CH_2), -3.65 (s, two NH). The 6b-CH_2 resonance was obscured. Anal. Calcd for $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C, 71.37; H, 6.29; N, 9.22.

Magnesium 6-[(Methoxycarbonyl)acetyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (8). Metal-free porphyrin **41** (4.86 mg) in 3 mL of dry pyridine was treated with 50 mg of anhydrous $Mg(ClO_4)_2$. The solution was heated to 100 °C under Ar in the dark. After 2 h, metalation was still incomplete, so 65 mg more of $Mg(ClO_4)_2$ was added. After 3.5 h further at 100 °C the reaction was filtered hot through a sintered-glass funnel. No solid $Mg(ClO_4)_2$ was collected. The resulting solution was diluted with dichloromethane and rinsed with water. The organic layer was then rinsed with 25 mL of pH 6.8 phosphate buffer, dried, and evaporated. The residue was dissolved in dichloromethane and precipitated with *n*-hexane. Unfortunately, the precipitate was contaminated with $Mg(ClO_4)_2$. Therefore it was redissolved in dichloromethane, rinsed 5 × H_2O, dried, and evaporated to give a green solid. Some of this solid was treated with TFA in the dark for 75 min, followed by the standard basic aqueous workup. The visible spectrum of the demetalated material in dichloromethane was not a perfect "rhodo" type; however, treatment with methanolic potassium hydroxide gave an obvious spectral change to a clean "etio" type spectrum. Thus the 6-β-keto ester side chain of **8** was judged to be intact: UV-vis (of **8**) (CH_2Cl_2, relative absorbance) 596 nm (81.1), 554 (100), (of **8** after treatment with TFA) (CH_2Cl_2) 630 (30.2), 576 (84.3), 548 (97.1), 510 (100), [after addition of methanolic KOH] 628 (28.7), 574 (62.2), 544 (84.0), 508 (100).

Magnesium 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (6). To 6-[(methoxycarbonyl)acetyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin **41** (4.82 mg) in 10 mL of dry pyridine was added 72 mg of magnesium(II) perchlorate, and the solution was heated at 100 °C under argon in the dark for 3 h to accomplish metalation as described above. The crude product in 5 mL of dry tetrahydrofuran was then added to a solution of 59 mg of sodium borohydride in 2 mL ice-cold methanol. The mixture was stirred at room temperature for 15 min before addition of acetone (5 mL), dichloromethane, and water. The organic phase was dried and evaporated to give a residue: UV-vis (CH_2Cl_2, relative absorbance) 592 nm (13.2), 554 (15.3), 416 (100). Demetalation of this material with trifluoroacetic acid, followed by an aqueous workup, gave compound **42** in high yield. Further treatment with diazomethane gave the hydroxypropionate dimethyl ester **43** (TLC monitoring).

Magnesium 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin. 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin (**43**) (18.6 mg) was dissolved in 4 mL of dry dichloromethane and treated with 4.0 mL of a solution of 175 mg of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in 9 mL of dry dichloromethane and 1.0 mL of 0.080 M ethyl magnesium iodide (freshly prepared and titrated) at room temperature. After 15 min, UV-vis spectrophotometry showed complete metalation [(in CH_2Cl_2, relative absorbance) 592 nm (0.72), 554 (0.912)], so the mixture was poured into water and extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated to give a residue (68 mg) containing excess BHT. This was heated under vacuum at 78 °C to sublime the BHT and afforded 15 mg (77.6%) of the title compound. Treatment of a small amount of this material with trifluoroacetic acid, followed by an aqueous workup, afforded the demetalated starting material (**43**) (TLC analysis) in quantitative yield (spectrophotometry).

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Registry No. **6**, 99898-43-8; **6** (methoxy deriv), 99652-11-6; **8**, 100102-34-9; **20a**, 100046-14-8; **20b**, 100046-15-9; **20c**, 100046-16-0; **21**, 100046-10-4; **23**, 52091-21-1; **24**, 51089-82-8; **25**, 51644-01-0; **25** (iodo deriv), 52460-23-8; **26**, 52091-22-2; **27**, 18818-25-2; **28**, 100046-09-1; **28** (base), 100046-08-0; **29**, 100082-67-5; **29** (base), 100082-66-4; **30**, 37059-18-0; **31**, 100082-69-7; **31** (base), 100082-68-6; **32**, 89909-53-5; **33**, 89909-40-0; **33**·HCl (R = CH=NH), 100046-07-9; **34**, 100046-11-5; **35**, 100046-12-6; **36**, 100046-13-7; **37**, 100046-17-1; **38**, 52559-95-2; **39**, 100046-18-2; **40**, 38220-23-4; **41**, 100046-19-3; **42**, 100046-20-6; **43**, 100046-21-7; (*E*)-H_3CCH=$CHCO_2CH_2Ph$, 71338-71-1; $HO_2CCH_2CO_2CH_3$, 16695-14-0.

Methyl Deuteration Reactions in Vinylporphyrins: Protoporphyrins IX, III, and XIII

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Base-catalyzed deuteration of the methyl groups in protoporphyrin IX dimethyl ester (**1**) proceeds with differential deuteration; rate of deuteration, as measured by NMR spectroscopy of reaction products, follows the order 3-Me > 1-Me > 5-Me > 8-Me. A simple qualitative theory to explain the differential deuteration is discussed, based on primary (vinyl group on subunit bearing the deuteriated methyl) and secondary (vinyl group on adjacent subunits) inductive effects, and this is tested by using the symmetrical porphyrins, protoporphyrin III dimethyl ester (**6**) and protoporphyrin XIII dimethyl ester (**7**). Synthesis of **6** and **7**, from monopyrroles via the a,c-biladiene route, are reported.

In early work[1] with deuterium-labeled porphyrins and hemins, it was discovered that generation of vinyl groups by prolonged treatment of (2-chloroethyl)porphyrins with strong base caused a loss of isotopic label from the methyls

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