Total Syntheses of 8-Formyl-8-demethylprotoporphyrin IX, 8-(Hydroxymethyl)-8-demethylprotoporphyrin IX, and 8-Fluoromethyl Analogues of Protoporphyrin IX

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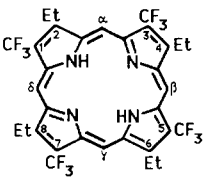
In connection with proposed ^{19}F NMR studies of reconstituted fluorine-substituted heme proteins, synthetic approaches to 8-(fluoromethyl)-8-demethylprotoporphyrin IX dimethyl ester (**6**) and the corresponding 8-(difluoromethyl)-8-demethyl analogue **5** were investigated. After a number of preliminary investigations, the fluorinating agent (diethylamido)sulfur trifluoride (DAST) was chosen as the reagent of choice. With DAST, β-carboxypyrrole **7** gave the acyl fluoride **8**, which could not be further transformed into the trifluoromethyl analogue. (2-Hydroxyethyl)pyrroles, e.g., **13**, reacted with DAST to give the (2-fluoroethyl)pyrrole **14** by way of a cyclopropylpyrrolium ion; corresponding bis(2-hydroxyethyl)porphyrin **36** afforded the bis(2-fluoroethyl) compound **37**, whereas the porphyrindiylbis(acetaldehyde) **34** gave the bis(2,2-difluoroethyl)porphyrin **35**. Formylporphyrins (e.g., **23**) gave difluoromethyl derivatives (e.g., **22**) when treated with DAST, and the corresponding porphyrinyl carbinol **24** gave the fluoromethyl compound **25**. Acetylporphyrins did not react with DAST, but porphyrincarboxylic acid **38** gave the acyl fluoride **39**. A porphyrin (**28**) bearing a β-hydroxypropionate substituent was transformed into the corresponding acrylic porphyrin **29** with DAST, while the related β-keto ester porphyrin **30** gave the fluoroacrylate **31**. As a synthetic approach to **5** and **6**, the 8-unsubstituted porphyrin **54** was prepared by copper(II)-catalyzed 1′,8′-dimethyl-*a*,*c*-biladiene cyclization; one of the byproducts from this cyclization was the required 8-formylporphyrin **42**, obtained by migration of one of the terminal (1′,8′) carbons to the 8-position. The 8-formylporphyrin **42** was also formed from the 8-unsubstituted porphyrin **54** by formylation with a hindered Vilsmeier reagent (using the copper complex **44**) or by a Friedel-Crafts reaction (on the hemin **57**) with tin(IV) chloride and dichloromethyl methyl ether. Vinylation of porphyrin **42** with diazabicycloundecene (after protection of the aldehyde as an acetal) gave the 8-formyl-8-demethylprotoporphyrin ester **62**; sodium borohydride reduction of the formylporphyrin **42**, followed by vinylation (DBU), gave the (hydroxymethyl)porphyrin **65**. The iron complex free acids of these compounds have been isolated (Ator and Ortiz de Montellano *J. Biol. Chem.* **1987**, *262*, 1542) from phenylhydrazine inactivation of horseradish peroxidase. Formylporphyrin **42** was fluorinated with DAST to give the (difluoromethyl)porphyrin **59**, which was vinylated (DBU) to give the required 8-(difluoromethyl)-8-demethylprotoporphyrin **5**. The (hydroxymethyl)porphyrin **65** was similarly fluorinated with DAST to give 8-(fluoromethyl)-8-demethylprotoporphyrin **6**, but this product was extremely easily hydrolyzed and was transformed back to the 8-(hydroxymethyl)porphyrin **65** by simple chromatography.

Introduction

Very few fluorinated porphyrins have been synthesized to date. Billig and Baker[1] were the first to report the synthesis of a mixture of meso-fluorinated porphyrins prepared in low yield by heating the solid meso diazonium tetrafluoroborate of mesoporphyrin IX at 160 °C via Balz-Schiemann-type decomposition.[2] More recently, meso-fluorination of octaethylporphyrin has been accomplished[3] by use of cesium fluoroxysulfate.

Kaesler and LeGoff[4] prepared the first porphyrins bearing perfluorinated side chains by tetramerization of perfluorinated pyrroles. A methylene unit was left between the perfluorinated alkyl chain and the porphyrin macrocycle because it was found[5] that trifluoromethyl groups directly substituted in both the 3- and 4-positions deactivated the pyrrole ring, leaving it completely unreactive toward tetramerization. In 1983, Ogoshi et al.[6] reported a synthesis of β-(trifluoromethyl)pyrroles by a modified Knorr condensation of the oximino derivative of ethyl trifluoroacetoacetate with suitable diones. They utilized[7] the (trifluoromethyl)pyrroles to obtain tetrakis(trifluoromethyl)etioporphyrin (**1**) in 12% yield. Ogoshi and coworkers[8] also tetramerized a β-fluoropyrrole to give a 3% yield of the tetrafluoroporphyrin **2** and then reported[9] the first synthesis of an unsymmetrical mono(trifluoromethyl)porphyrin (**3**) in 1985.



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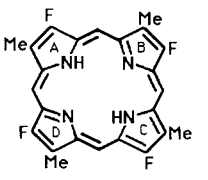

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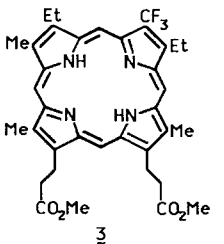

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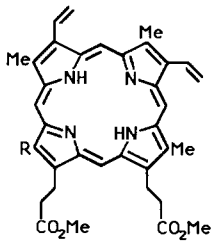
Mesoporphyrin IX is very similar to protoporphyrin IX, the only structural difference being the reduction of the 2,4-vinyl groups to ethyls; however, the most accurate

(1) Billig, M. J.; Baker, E. W. *Chem. Ind. (London)* **1969**, 654.
(2) Balz, G.; Schiemann. G. *Chem. Ber.* **1927**, *60*, 1186. Suschitzky, H. *Adv. Fluorine Chem.* **1965**, *4*, 1.
(3) Andrews, L. E.; Bonnett, R.; Kozyrev. A. N.; Appelman, E. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1735.
(4) Kaesler, R. W.; LeGoff, E. *J. Org. Chem.* **1982**, *47*, 5243.
(5) Leroy, J.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1982**, 313. Kaesler, R. W.; LeGoff, E. *J. Org. Chem.* **1982**, *47*, 4779.
(6) Ogoshi, H.; Homma, M.; Yokota, K.; Toi, H.; Aoyama, Y. *Tetrahedron Lett.* **1983**, *24*, 929.
(7) Homma, M.; Aoyagi, K.; Aoyama, Y.; Ogoshi, H. *Tetrahedron Lett.* **1983**, *24*, 4343.
(8) Onda, H.; Toi, H.; Aoyama, Y.; Ogoshi, H. *Tetrahedron Lett.* **1985**, *26*, 4221.
(9) Toi, H.; Homma, M.; Suzuki, A.; Ogoshi, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1791.

0022-3263/89/1954-3270$01.50/0

probe of heme proteins is the native prosthetic group, protoporphyrin IX. Therefore, if fluorine is to be used in conjunction with ^{19}F NMR as a means of studying heme proteins, synthetic strategies for the preparation of fluorinated protoporphyrin IX must first be devised. It is without question that tetrakis(trifluoromethyl)porphyrins **1** are unsuitable for reconstitutional studies since the four strongly electron withdrawing trifluoromethyl groups severely perturb the molecular orbitals of the macrocycle. A mono(trifluoromethyl)porphyrin **4** is a more reasonable candidate, but the demonstrated electron-withdrawing power of trifluoromethyl would still be expected to perturb the porphyrin at least as much as a nuclear ketone or carboxylic ester functionality. It is self-evident that protoporphyrin IX bearing only one or possibly two fluorine atoms on a methyl group would minimize perturbation effects and be a more authentic probe for the diamagnetic oxygen-bound states of hemoglobin and myoglobin. This paper described our approaches to the synthesis of a (monofluoromethyl)- and (difluoromethyl)porphyrin (**6** and **5**, respectively) designed to produce reconstituted heme proteins that do not show significant electronic perturbational differences from native heme proteins.



4 R = CF_3
5 R = CHF_2
6 R = CFH_2

Protoporphyrin IX dimethyl ester R = Me

Fluorination of Some Model Pyrrolic Systems

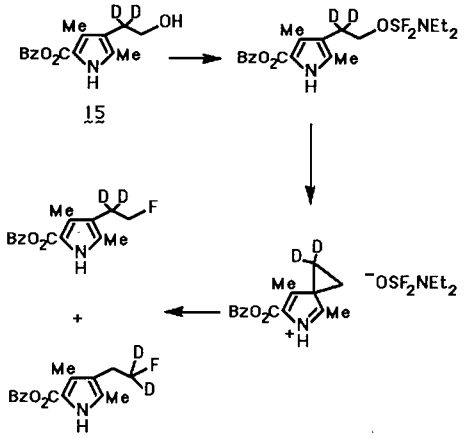
As discussed above, we were specifically interested in synthesizing a fluorinated porphyrin retaining as close as possible the physical, electronic, and spectroscopic properties of protoporphyrin IX. To do this, we felt that protoporphyrin IX regioselectively substituted with as few fluorines as possible was desirable. Moreover, rather than begin our synthesis with fluorinated precursors as Ogoshi and LeGoff have done, we decided a more expedient route would be to introduce fluorine by selective fluorination of a suitable functional group at a late stage in the synthesis. This is a significant deviation from past synthetic strategies for fluorinated porphyrins.

The fluorination potential of a few reagents was qualitatively explored on a variety of pyrroles and porphyrins with some interesting and promising results. The most successful of these were applied toward the synthesis of (monofluoromethyl)- and (difluoromethyl)protoporphyrin IX.

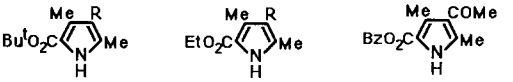
Fluorination of Some Model Pyrroles. The most versatile and easily used fluorinating agent commercially available is (diethylamido)sulfur trifluoride (DAST),[10,11] and most of the pyrrole and porphyrin substrates were chosen or designed with this in mind. We began our investigation by treating the β-carboxypyrrole **7** with DAST. The reagent was added to a solution of the pyrrole in dichloromethane at −78 °C, and after only a few minutes, the presence of a more mobile compound was observed by TLC. ^1H NMR spectra indicated that all the substituents

(10) Middleton, W. J.; Bingham, E. M. *Org. Synth.* **1977**, *57*, 50.
(11) Ibbott, D. G.; Janzen, A. F. *Can. J. Chem.* **1972**, *50*, 2428.

Scheme I. Proposed Mechanism for Anchimerically Assisted Scrambling of Side-Chain Carbons in the DAST-Mediated Fluorination of (Hydroxyethyl)pyrrole 15



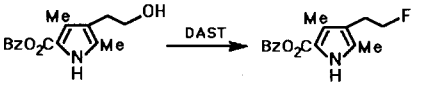
remained unchanged but the carboxylate proton was absent. FT-IR showed two carbonyl stretching frequencies at 1780 and 1670 cm^{-1} suggesting that both carbonyls were still present. Moreover, a singlet at 30.8 ppm (from $CFCl_3$ standard) in the ^{19}F NMR spectrum was consistent with an acyl fluoride **8**.



7 R = CO_2H
8 R = COF
9 R = CF_3
10 R = CHO
12 R = CH_2OH
11

Continued treatment of the acyl fluoride **8** with DAST at elevated temperatures (**CAUTION**! behind a shield) failed to modify the carbonyl group to give the (trifluoromethyl)pyrrole **9**. This apparent reluctance for carbonyl functionalities on pyrroles to be fluorinated with DAST was also borne out on nuclear aldehydes and ketones. Both β-formylpyrrole **10** and β-acylpyrrole **11** were treated with DAST at room temperature and at elevated temperatures with no measurable degree of fluorination. The β-formylpyrrole **10** was reduced to the corresponding β-(hydroxymethyl)pyrrole **12** with sodium borohydride, and the alcohol was treated with DAST at reduced temperature. Surprisingly, a (fluoromethyl)pyrrole was not isolated and TLC indicated that considerable decomposition had occurred. This labile behavior is consistent with what was observed by Middleton and Bingham[10] and Jones et al.[12] for other pyrrolic-type systems.

However, not all pyrrole alcohols were destroyed during fluorination. The (2-hydroxyethyl)pyrrole **13** was converted with DAST into the (2-fluoroethyl)pyrrole **14** in good yield. An anchimeric assisted mechanism (Scheme

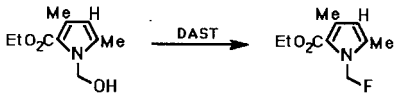


13 **14**

I), similar to that seen for the chlorination of (hydroxyethyl)pyrroles with thionyl chloride,[13] was demonstrated when DAST was treated with (1,1-dideuterio-2-hydroxyethyl)pyrrole **15**. Instead of the label remaining on the 1-carbon of the 2-fluoroethyl side chain, deuterium was

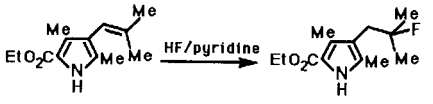
(12) Jones, R. A.; Rustidge, D. C.; Cushman, S. M. *Synth. Commun.* **1984**, *14*, 575.
(13) Smith, K. M.; Martynenko, Z.; Pandey, R. K.; Tabba, H. D. *J. Org. Chem.* **1983**, *48*, 4296.

found to scramble to both the 1- and 2-carbons, indicating the formation of a cyclopropylpyrrolium ion. An *N*-(hydroxymethyl)pyrrole **16** was successfully fluorinated to give the *N*-(fluoromethyl)pyrrole **17** with DAST, confirming that forming a stable fluoromethyl group on pyrroles is not dependent on DAST or the hydroxymethyl group but rather on the location of the alcohol.

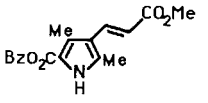


16 17

A β-(2,2-dimethylvinyl)pyrrole **18** was treated in dichloromethane with a solution of 70% HF/pyridine (Olah's reagent) to afford the addition product, (2-fluoro-2,2-dimethylethyl)pyrrole **19**. A β-acrylate pyrrole **20** did not add HF across the double bond under similar conditions. When β-(hydroxymethyl)pyrrole **12** was treated with Olah's reagent, the main product was the β,β′-pyrromethane **21**; the structure of the pyrromethane was confirmed by comparison with an authentic sample formed by treatment of the β-(hydroxymethyl)pyrrole **12** with dilute acetic acid.



18 19



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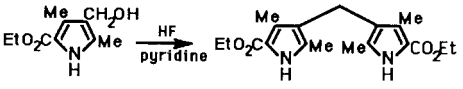
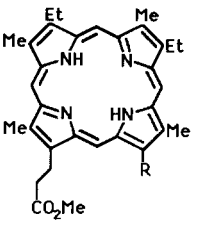


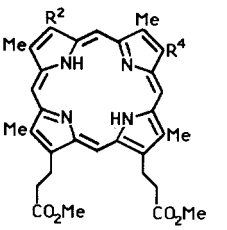
12 21

Fluorination of Some Model Porphyrins. Despite our inability to fluorinate β-(hydroxymethyl)- and β-formylpyrrole substituents with DAST, we performed the same series of experiments on a variety of porphyrins. Surprisingly, β-formylporphyrins can be readily fluorinated with DAST. A 67% yield of the (difluoromethyl)porphyrin **22** was isolated after treatment of the aldehyde **23**[14] with DAST over a period of 8–10 h at room temperature. If the solution was stirred for longer than 10 h, decomposition to uncharacterized byproducts occurred. When the mixture was warmed, fluorination was retarded and decomposition occurred at a faster rate. The product **22** is stable to both silica gel and alumina column chromatography; however, if spotted on a TLC plate, decomposition to the aldehyde (from red to green) is observed if the material is left in stationary contact with the medium for only a moderate period of time.

The characteristic coupling of fluorine to hydrogen (J_{HF} = 55.1 Hz) in the difluoromethyl group of **22** is observed by ^{1}H NMR as a downfield triplet. Although ^{19}F NMR spectroscopy provides unequivocal proof for the presence of fluorine, ^{1}H NMR was routinely used to assess the efficiency of fluorination. Both the characteristic coupling constants and an unobstructed chemical shift "window"



22 R = CF_2H
23 R = CHO
24 R = CH_2OH
25 R = CH_2F



26a R^2 = COMe; R^4 = H
26b R^2 = H; R^4 = COMe
27 R^2 = R^4 = COMe

made evaluation using ^{1}H NMR a simple and routine matter. Both ^{19}F NMR and EI mass spectroscopy assisted in identifying the product. The optical spectrum provided much salient information. The absorbance maxima for both the Soret and satellite bands are red-shifted (λ_{max} = 402, 502, 538, 568, 622 nm) relative to that of an electro-"neutral" system like deuteroporphyrin (λ_{max} = 399, 496, 528, 566, 620 nm), with their values closely resembling that of a porphyrin bearing only one vinyl substituent (λ_I = 624 nm; etio type).[15] The mildly perturbed etio absorption profile of **22** is a further testament to the minimal electronic effect of the difluoromethyl group on the porphyrin electronic structure.

The β-formyl substituent in **23** was reduced with sodium borohydride to afford the β-(hydroxymethyl)porphyrin **24** in quantitative yield. This was treated with DAST at reduced temperature in dichloromethane, and TLC indicated that the starting material was rapidly consumed. The optical spectrum (etio type: λ_{max} = 400, 498, 536, 568, 622 nm) of the organic phase following aqueous workup was very similar to that of deuteroporphyrin IX, but after chromatography on either silica gel or alumina, the spectrum returned to that of the hydroxymethyl starting material (λ_{max} = 400, 498, 532, 566, 622 nm). ^{1}H NMR spectra of the chromatographed sample did not contain the expected downfield doublet of the fluoromethyl group. However, if chromatography was avoided, ^{1}H NMR spectroscopy showed the presence of the H–F doublet (J_{HF} = 49.3 Hz, δ 6.86 ppm), indicating a near quantitative yield of (monofluoromethyl)porphyrin **25**.

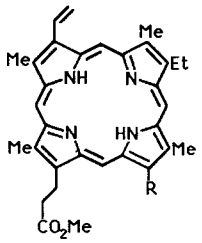
Whereas formylporphyrins could be fluorinated with DAST, acetylporphyrins could not. Both mono- and diacetyldeuteroporphyrin IX **26a,b** and **27**, respectively, were mixed with an excess of DAST. No reaction was observed in either case. This lack of reactivity is not too surprising in light of the fact that hydroxylamine, hydrazine, and bisulfite react readily with formylporphyrins but not with acetylporphyrins.[16]

An interesting reaction occurred when a methyl β-hydroxypropionate porphyrin was treated with DAST. Upon treatment of the porphyrin **28** at reduced temperature with DAST, the optical spectrum (λ_{max} = 410, 504, 542, 570, 626 nm) of the mixture was red-shifted, resembling that of an acrylate. After chromatography, ^{1}H NMR spectroscopy clearly featured the trans-H,H coupling (J_{HH} = 16.2 Hz) of the acrylate side chain in **29**. Apparently, after reaction with the hydroxyl group, a concerted loss of diethylsulfamoyl fluoride and hydrogen fluoride generates the acrylate (Scheme II). When the methyl β-ketopropionate porphyrin **30** was treated with DAST at room temperature, a similar result was observed. Instead of two doublets, the ^{1}H NMR spectrum of the product showed only one doublet

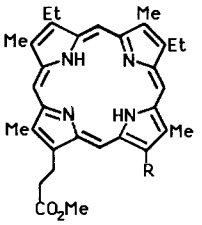
(14) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, *32*, 275.

(15) Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam; 1975, Chapter 1.

(16) Reference 15, Chapter 19.



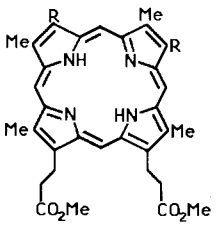
28 R = $CH(OH)CH_2CO_2Me$
29 R = $CH{=}CHCO_2Me$



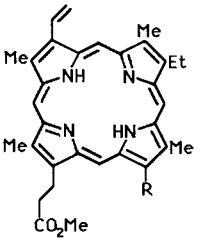
30 R = $CO.CH_2CO_2Me$
31 R = $CF{=}CHCO_2Me$

at 6.74 ppm (J = 16.9 Hz). The coupling constant is consistent with trans-H,F coupling, and a concerted elimination similar to that invoked for the previous example can be used to illustrate how a β-fluoroacrylate side chain **31** can form (Scheme III). It is quite clear that the methyl ester functionality is required for this transformation to occur since no reaction was observed for the acetylporphyrins **26** and **27**.

As expected, acetaldehyde and 2-hydroxyethyl side chains, whose functional groups are separated from the porphyrin by a methylene unit, were readily fluorinated with DAST and produced perfectly stable products. Protoporphyrin IX dimethyl ester (**32**) was treated with thallium(III) nitrate in methanol to produce bis(2,2-dimethoxyethyl)deuteroporphyrin IX (**33**).[17] The bis(dimethyl acetal) was trans-acetalated in acetone with *p*-toluenesulfonic acid to give the bis(acetaldehyde) **34**. Once isolated, the bis(acetaldehyde) was fluorinated with DAST to give a 27% yield of the corresponding bis(2,2-difluoroethyl)deuteroporphyrin IX **35**. Reduction of the aldehyde in **34** with sodium borohydride produced the bis(2-hydroxyethyl)deuteroporphyrin IX **36**, which in turn was fluorinated to give the bis(2-fluoroethyl)deuteroporphyrin IX **37** in 26% yield.



32 R = $CH{=}CH_2$
33 R = $CH_2CH(OMe)_2$
34 R = CH_2CHO
35 R = CH_2CHF_2
36 R = CH_2CH_2OH
37 R = CH_2CH_2F



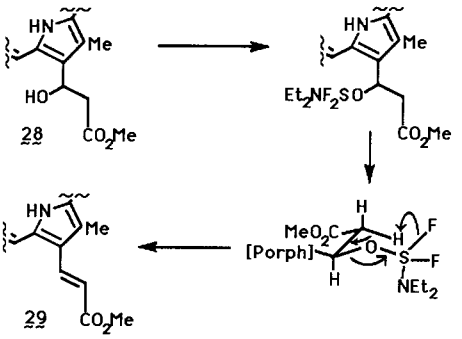
38 R = CO_2H
39 R = CO.F
40 R = CF_3

DAST also rapidly converted a β-carboxyporphyrin **38** into the acyl fluoride **39** at reduced temperature. However, as was observed for the pyrrole, continued heating with DAST failed to give the (trifluoromethyl)porphyrin **40**.

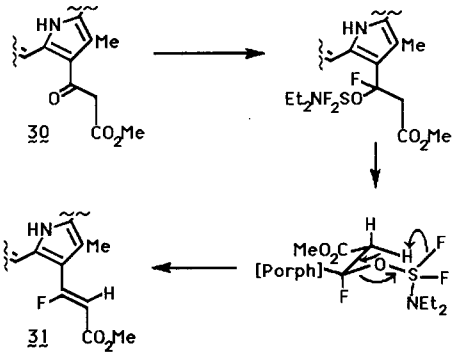
Total Synthesis and Fluorination of a Protoporphyrin IX Analogue

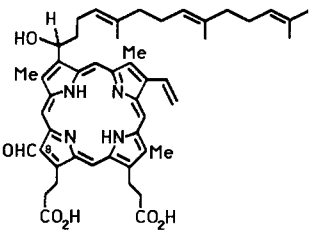
After establishing that porphyrin aldehyde and hydroxymethyl groups could be fluorinated with DAST to give the corresponding (difluoromethyl)- and (monofluoromethyl)porphyrins respectively, our next objective was the design and execution of a synthesis of an analogue of protoporphyrin IX that could be easily fluorinated. The problem then simplified to designing a synthesis of protoporphyrin IX with a formyl group in place of one of the methyl groups. Rather than try to carry an aldehyde functionality through a multistep tetrapyrrole synthesis, it was decided to introduce the aldehyde by formylation of an unsubstituted position on the preformed porphyrin. Since protoporphyrin IX contains four methyl groups, one on each pyrrole ring, the synthetic strategy revolved around choosing the one pyrrole, having an unsubstituted position ordinarily occupied by a methyl group, that would be the simplest to synthesize. It was decided that the pyrrole common to both the C and D rings would be the easiest to prepare. Either pyrrole would have provided the necessary β-unsubstituted position after cyclization of the tetrapyrrole, but we recognized an opportunity to prepare, by total synthesis, a structural analogue of porphyrin a (**41**). On paper, it looked as though our proposed synthesis would be equally as efficient, and more efficient in some cases, as those carried out over the past 20 years.

Scheme II. Proposed Mechanism for DAST-Mediated Acrylate Formation from Hydroxypropionate Porphyrin 28



Scheme III. Proposed Mechanism for DAST-Mediated Fluoroacrylate Formation from β-Keto Ester Porphyrin 30





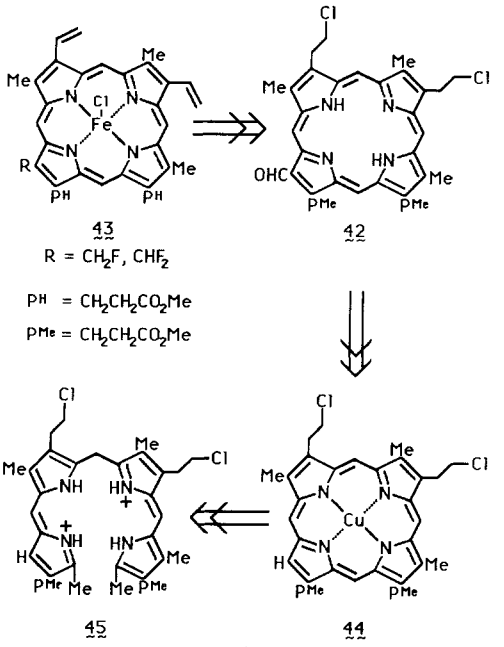
41

Heme a is the prosthetic group of the cytochromes a and a_3, known collectively as cytochrome oxidase.[18,19] The fine details of the structure of the heme with its lipid-soluble side chain are now established.[20] The total synthesis of

(17) Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Justus Liebigs Ann. Chem.* **1973**, 1329.

(18) Lemberg, M. R. *Nature (London)* **1953**, *172*, 619.
(19) Lemberg, M. R. *Physiol. Rev.* **1969**, *49*, 48.
(20) Caughey, W. S.; Smythe, G. A.; O'Keefe, D. H.; Maskasky, J. E. Smith, M. L. *J. Biol. Chem.* **1975**, *250*, 7602.

Scheme IV. Retrosynthetic Analysis of Approach to 8-(Fluoromethyl)protohemins 43



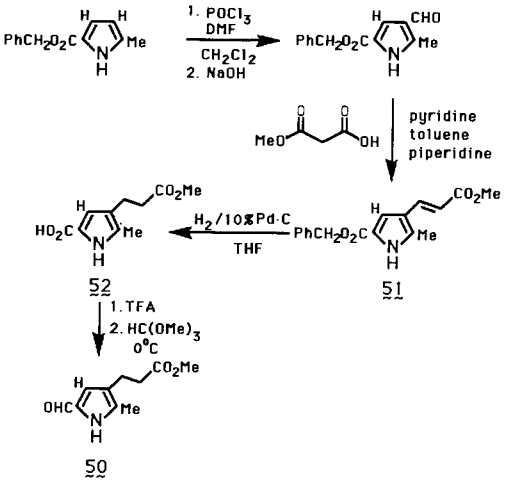
43 42 45 44

heme a has been approached by a number of groups,[21] but a complete and unequivocal total synthesis has only recently been reported.[22]

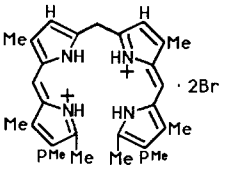
Synthesis of a Porphyrin a Analogue

A retrosynthetic analysis of the target fluoromethyl protoporphyrin IX (Scheme IV) illustrates the straightforward nature of our proposed synthesis. We envisioned a routine series of transformations to get from the target 8-formylporphyrin **42** to the fluoromethylhemins **43**. Although we were uncertain of the precise order in which we would carry out dehydrochlorination, saponification, fluorination, and iron insertion, we felt confident that the necessary steps could be carried out. A variety of formylation reactions are available for electrophilic aromatic formylation of β-unsubstituted porphyrins, and on paper, this posed no immediate concern for converting the cyclized 8-β-free-porphyrin **44** to the 8-formylporphyrin **42**. The 8-β-free-porphyrin **44** was to be oxidatively cyclized from the corresponding 1′,8′-dimethyl-*a*,*c*-biladiene **45** by refluxing with copper(II) salts in dimethylformamide. Although cyclization of 1-unsubstituted 1′,8′-dimethyl-*a*,*c*-biladienes has been demonstrated to give low yields of porphyrins, in light of Mironov's experiments showing that a 4,5-diunsubstituted 1′,8′-dimethyl-*a*,*c*-biladiene **46** was cyclized in good yield (27%), it was not clear to us that 2-unsubstituted *a*,*c*-biladienes would suffer the same inherent problem. Following routine synthesis of the pyrroles, the A and B rings would be coupled, forming the differentially protected northern half of the porphyrin. Proceeding in a clockwise fashion, ring C would be condensed with the pyrromethane, and ring D with the resultant tripyrrene.

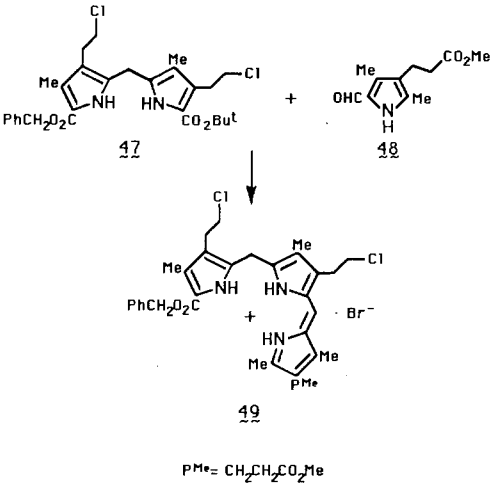
Scheme V. Synthetic Scheme for Formation of Ring-D Pyrrole 50



52 51 50



46



47 48 49

The known[23] pyrromethane **47** can be sequentially deprotected in one of two ways. The most common "counter-clockwise" approach[24] is to hydrogenolyze the benzyl ester, decarboxylate the resultant carboxylic acid with *p*-toluenesulfonic acid, and condense ring D with the pyrromethane. Ring C is then condensed with the tripyrrene after deprotection and decarboxylation of the *tert*-butyl ester. An alternative method involves[25] the facile acid-catalyzed deprotection and decarboxylation of the *tert*-butyl ester and condensation with ring C in the "clockwise" direction followed by removal of the benzyl ester with HBr/acetic acid and condensation with the final pyrrole. This approach eliminates the problems associated with treating *tert*-butyl ester pyrromethanes with *p*-toluenesulfonic acid.

(21) (a) Kulish, M. A.; Mironov, A. F.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Obshch. Khim.* **1971**, *41*, 2743. (b) Mironov, A. F.; Kulish, M. A.; Kobak, V. V.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Obshch. Khim.* **1974**, *44*, 1407. (c) Kulish, M. A.; Mironov, A. F.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Obshch. Khim.* **1971**, *41*, 2743. (d) Nizhnik, A. N.; Kozyrev, A. N.; Mironov, A. F. *Bioorg. Khim.* **1985**, *11*, 692. (e) Clezy, P. S.; Diakiw, V. *Aust. J. Chem.* **1975**, *28*, 2703. (f) Clezy, P. S.; Fookes, C. J. R. *Aust. J. Chem.* **1981**, *34*, 871.

(22) Thompson, M.; Barrett, J.; McDonald, E.; Battersby, A. R.; Fookes, C. J. R.; Chaudhry, I. A.; Clezy, P. S. *J. Chem. Soc., Chem. Commun.* **1977**, 278. Battersby, A. R.; McDonald, E.; Thompson, M.; Chaudhry, I. A.; Clezy, P. S.; Fookes, C. J. R.; Hai, T. T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 135.

(23) Caveleiro, J. A. S.; Rocha Gonsalves, A. M. d'A.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2471; **1974**, 1771.

(24) de Almeida, J. A. P. B.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron* **1976**, *32*, 1793.

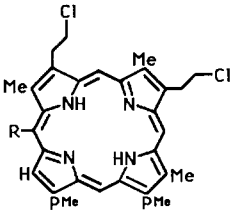
(25) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302.

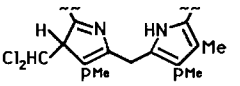
Construction of ring C (**48**) proceeded uneventfully.[23-25] This was condensed with the pyrromethane **47** under acid catalysis (to cleave the *tert*-butyl ester) and gave the tripyrrene hydrobromide **49** in good yield. Ring D (**50**) was assembled by a more circuitous route (Scheme V). The oximino complex of benzyl acetoacetate was prepared and added, in the presence of zinc, to a solution of the dimethyl acetal of acetylacetaldehyde (Fischer–Fink approach). The resulting di-β-unsubstituted pyrrole was modified by attachment of a methyl propionate side chain, achieved by regioselectively formylating the di-β-unsubstituted pyrrole at the position nonconjugated with the ester, by Vilsmeier formylation. Knoevenagel condensation of the formylpyrrole with the mono(methyl ester) of malonic acid gave the corresponding methyl acrylate pyrrole **51**, which in turn was reduced over Pd/C to give the β-unsubstituted pyrrole **52**. The pyrrole was treated with trifluoroacetic acid, and the α-position was formylated in situ with trimethyl orthoformate to give **50**.

It was reported[25] that 6–8 h is required for complete deprotection of the benzyl ester of tripyrrenes [with commercially available HBr/acetic acid (31% HBr) in trifluoroacetic acid]. However, more concentrated, freshly prepared HBr/acetic acid solution (43%) deprotects the ester much more rapidly. During one study, small aliquots were removed from the acidic tripyrrene solution every 5 min and mixed with an excess of the β-unsubstituted pyrrole in methanol for 1 min before measuring the optical spectrum. After only 20 min, the single tripyrrene absorption band in **49** at 494 nm disappeared and was replaced by the characteristic two-peak absorbance of the *a,c*-biladiene at 450, 524 nm. In practice, however, the tripyrrene was stirred in the acidic solution for a full hour before treatment with the ring-D pyrrole in methanol followed by crystallization of the *a,c*-biladiene dihydrobromide **45** in 85% yield from ether.

Oxidative cyclization of the *a,c*-biladiene dihydrobromide **45** was carried out with both copper(II) chloride and copper(II) acetate. As a rule of thumb, copper(II) chloride mediated cyclization generally provides higher yields of porphyrin but can also result in unexpected[21a,26] porphyrin side products. Copper(II) acetate on the other hand produces fewer side products, but the yield of porphyrin is frequently lower.

As chance would have it, oxidative cyclization of the *a,c*-biladiene **45** with copper(II) chloride provided us with unexpected results. The first experiments followed standard procedure: the *a,c*-biladiene was refluxed with 20 equiv of anhydrous copper(II) chloride in dimethylformamide for 5 min before the mixture was poured onto ice water. Aqueous workup, demetalation with H_2SO_4/trifluoroacetic acid, and chromatography afforded only one porphyrin. To our surprise, the optical spectrum was of the phyllo type [λ_{max} = 406 (ϵ = 197 000), 504 (15 500), 538 (5530), 576 (6010), 630 nm (1290)], and the material was subsequently shown[27] to be meso-chlorinated (**53**). After several trial experiments, the quantity of δ-*meso*-chloroporphyrin **59** gradually accumulated and a method was sought for the conversion of **53** into **54**. *meso*-Acetoxyporphyrins can be deacetoxylated[28] by first reducing the porphyrin over Pd/C and then oxidizing the porphyrinogen back to porphyrin with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Upon reoxidation, the acetoxy group is lost. This methodology was applied to a 2:3 mixture of **53** and **54**, and after chromatography on alumina, the desired porphyrin **54** was exclusively obtained from the mixture in a 78% yield. Although we were pleased with this conversion, the route to porphyrin was far too indirect for practical purposes.





53 R = Cl
54 R = H

PMe = $CH_2CH_2CO_2Me$

55

Room-temperature cyclization with copper(II) chloride provided even more surprises. Following the previously developed protocol,[29] the *a,c*-biladiene **45** was stirred for 2 h at room temperature in DMF with 20 equiv of copper(II) chloride. After demetalation, TLC indicated that two main products were present in the mixture: a highly mobile, red porphyrin and a less mobile, green porphyrin. The two bands were easily separated by column chromatography, and the optical spectrum of the red band seemed to be a composite of phyllo and etio profiles, suggesting the red band to be a mixture of porphyrins. Neither alumina nor silica gel TLC offered any hope of separating these compounds by normal chromatographic methods. ^{1}H NMR confirmed that the red band is a mixture of two porphyrins. Nine singlets are present in the downfield meso region, and two sets of N–H protons are upfield. We concluded that the mixture is composed of δ-*meso*-chloroporphyrin **53** and the desired β-unsubstituted porphyrin **54** in a 2:3 ratio, respectively. The yield of porphyrin in the red band was 30%. The rhodo spectrum (λ_{max} = 412, 516, 556, 580, 640 nm) of the less mobile green band from the same reaction clearly indicated the presence of an electron-withdrawing substituent on the porphyrin. ^{1}H NMR spectroscopy showed that the green compound is composed of only one porphyrin. Structural information about the nature of the electron-withdrawing substituent was obtained from the meso region of the spectrum. The five singlets at 11.56, 11.00, 10.32, 9.96, and 9.95 ppm could account for the four meso protons and one β-proton that are expected from the desired porphyrin **54**; however, considering the optical spectrum, the NMR spectrum is best explained if a formyl group is present on the ring. The chemical shift (11.56 ppm) of the furthest downfield proton is consistent with that of a β-formyl group, and the furthest upfield singlet in the meso region is far downfield from the region normally occupied by β-protons (δ 9–9.3). From this evidence we have concluded that the green porphyrin is the 8-formylporphyrin **42**. An authentic sample of 8-formylporphyrin **42** was prepared (vide infra), and the product was identical in every way with the porphyrin formed by oxidative cyclization. Moreover, a mixture melting point showed no depression. Based on our assignment, the yield of 8-formylporphyrin **42** from the room-temperature cyclization is only 1.5%.

This is the first reported example of an aldehyde that has formed upon cyclization of a 1′,8′-dimethyl-*a,c*-bila-

(26) Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073.
(27) The general subject of meso- and β-halogenation in unsymmetrical porphyrins will be the subject of a forthcoming paper (Snow, K. M.; Smith, K. M. In preparation. Snow, K. M. Ph.D. Dissertation, University of California, Davis, 1988).
(28) Jackson, A. H.; Kenner, G. W.; McGillivray, G.; Smith, K. M. *J. Chem. Soc. C* **1968**, 294.
(29) Smith, K. M.; Minnetian, O. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 277.

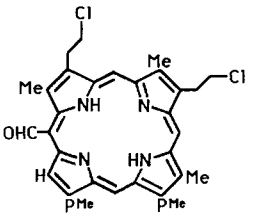
diene having a 2-unsubstituted position; formylporphyrins arising from the cyclization of 1-unsubstituted 1′,8′-dimethyl-*a*,*c*-biladienes have been reported.[21b,c,26] It has been shown that the aldehyde is not derived from dimethylformamide. Assuming that the aldehyde is derived from an oxidized form of one of the terminal methyl groups, most likely the 1′-methyl group, a simple mechanism to explain the result is difficult to invoke. It seems most likely that rearrangement of a dichloromethyl group occurs either by two sequential [1,2] migrations or by a concerted [1,3] migration. Either way, the phlorin tautomer **55** must oxidize to the porphyrin and the dichloromethyl group hydrolyze to the aldehyde. The first of the sequential [1,2] migrations would leave the dichloromethyl group and propionate side chain on the same carbon atom.

Oxidative cyclization of the *a*,*c*-biladiene **45** with copper(II) acetate proceeded in the expected manner providing the desired porphyrin **54** in 14–21% yield.

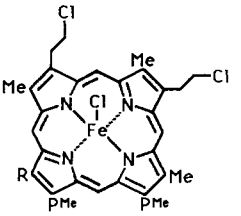
Formylation of the 8-unsubstituted porphyrin **54** was a more complex problem than originally thought. A sterically hindered Vilsmeier complex, diisobutylformamide (DIBF) and phosphoryl chloride ($POCl_3$), predominantly formylates the β-unsubstituted position of copper(II) porphyrins.[30] The meso carbons of copper(II) porphyrins are considered to be more nucleophilic (higher electron density) than the β-carbons, and formylation of porphyrins with dimethylformamide/$POCl_3$ has been shown to give primarily the *meso*-formyl product.[30,31] By increasing the size of the formylating agent, the sterically congested meso positions become less accessible and β-formylation predominates.[30]

The copper(II) complex **44** of the 8-unsubstituted porphyrin **54** was prepared by refluxing the porphyrin in methanol with copper(II) acetate. Treatment of the copper(II) porphyrin in dichloromethane with preformed DIBF/$POCl_3$ over a period of 22 h produced a green solution. The reaction was sluggish, probably due to a bulky methyl propionate side chain adjacent to the unsubstituted position. The mixture was treated with H_2SO_4/TFA to remove the chelated copper(II). TLC indicated the presence of two slower running green spots of roughly equal intensity and a great deal of the more mobile starting material. After separation of the starting material from the two green spots by chromatography, NMR spectroscopy of the green mixture indicated the presence of the desired 8-formyl product **42** and the δ-*meso*-formylporphyrin **56** in the proportion 3:4 respectively (as measured by NMR integration); the chemical yield of formyl product (both isomers) was only 56%. The low yield and unsatisfactory proportion of β to meso products must be due to the steric constraints imposed by the neighboring propionate side chain.

Our focus was drawn to another proven method of formylation. In 1934, Fischer and Swartz[32] described the formylation of the iron(III) complex of a β-unsubstituted porphyrin with dichloromethyl methyl ether and tin(IV) chloride; only the β-aldehyde is formed. Iron(II) was inserted into the 8-unsubstituted porphyrin **54** by a literature method,[33] and this was oxidized to give the iron(III) chloride complex **57** in nearly quantitative overall yield. Formylation of the iron(III) complex **57** by Fischer's method afforded a 60% yield of formylated product **58**.



56



57 R = H
58 R = CHO

Demetalation afforded predominantly the β-formylated product **42** in an overall yield of 40% from **57**. It is interesting to note that treatment of the copper(II) complex **44** with dichloromethyl methyl ether/tin(IV) chloride gave a similar mixture as before of β- and *meso*-formylporphyrins (**42** and **56**), illustrating that the result is dependent on the nature of the chelated metal and not on the formylating agent.

Fluorination of a Porphyrin a Analogue

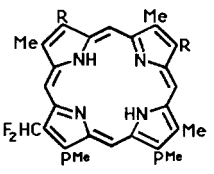
With the porphyrin a analogue in hand, it appeared a simple matter to prepare the desired 8-(difluoromethyl)- and 8-(monofluoromethyl)protoporphyrin IX. Kenner and co-workers[34] had previously found that β-formyl groups are sensitive to base and are lost upon saponification. To circumvent this problem, the aldehyde was protected as a cyclic acetal before reforming the aldehyde by acid-catalyzed hyrolysis of the acetal after appropriate manipulations of the chloroethyl substituents. We felt this process might be avoided and conducted a study of dehydrochlorination with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU).

DBU and DBN have been shown to be gentle, effective dehydrohalogenating agents.[35] We have found[36] that DBU could be applied to porphyrin systems, but experienced difficulty in obtaining a completely converted vinylporphyrin in refluxing THF. By switching to the more polar and higher boiling dimethylformamide, we found that dehydrohalogenation occurred rapidly and quantitatively with an excess of DBU at ≥100 °C without saponification of the propionate esters. Utilizing a model mono(2-chloroethyl)porphyrin, we determined that the reaction temperature could be reduced to as low as 50 °C while maintaining the efficiency of dehydrochlorination (complete after 3 h as measured by spectrophotometry). Unfortunately, these conditions were not mild enough to prevent the loss of the aldehyde, and an alternate route was sought. We discovered that the (difluoromethyl)porphyrin **22**, prepared during our preliminary investigation, lost fluorine upon treatment with 3% KOH in pyridine at 80 °C. Fortunately, the conditions described above for dehydrochlorination with DBU are mild enough to prevent the loss of fluorine. The model (monofluoromethyl)porphyrin **25** was labile to both KOH and DBU.

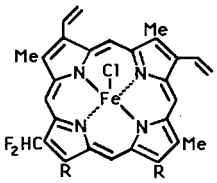
With the methodology laid out, 8-formylporphyin **42** was fluorinated at room temperature with DAST, providing the corresponding 8-(difluoromethyl)porphyrin **59** in a 60% yield; the 8-(difluoromethyl)porphyrin **59** was subsequently treated with DBU, affording a 60% yield of the target 8-(difluoromethyl)protoporphyrin IX dimethyl ester **5**. Iron was inserted into **5** with iron(II) chloride in acetonitrile/chloroform to afford the target 8-(difluoro-

(30) Smith, K. M.; Langry, K. C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 439.
(31) Brockmann, H., Jr.; Bliesener, K.-M.; Inhoffen, H. H. *Justus Liebigs Ann. Chem.* **1968**, *718*, 148.
(32) Fischer, H.; Swartz, A. *Justus Liebigs Ann. Chem.* **1934**, *512*, 239.
(33) Smith, K. M.; Fujinari, E. M.; Langry, K. C.; Parish, D. W.; Tabba, H. D. *J. Am. Chem. Soc.* **1983**, *105*, 6638.
(34) Jackson, A. H.; Kenner, G. W.; Wass, J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1475; **1974**, 480.
(35) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.
(36) Smith, K. M.; Morris, I. K. *J. Chem. Res. Synop.* **1988**, 16; *J. Chem. Res., Miniprint* **1988**, 224.

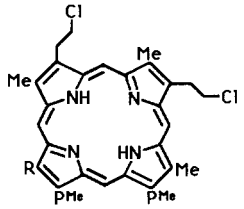
methyl)hemin IX **60**, and the methyl esters were hydrolyzed in $HCl/H_2O/THF$ to give the corresponding dicarboxylic acid **61**.



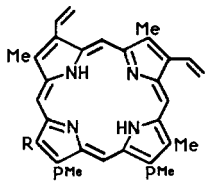
5 R = $CH{=}CH_2$
59 R = CH_2CH_2Cl



60 R = $CH_2CH_2CO_2Me$
61 R = $CH_2CH_2CO_2H$



42 R = CHO
63 R = 
64 R = CH_2OH



6 R = CH_2F
62 R = CHO
65 R = CH_2OH

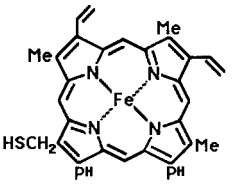
Formylporphyrins are known to be labile toward basic reagents,[34] so the 8-formylporphyrin **42** was transformed into the corresponding 2,4-divinylporphyrin **62** in one sequence by protection of the 8-formyl group as the acetal **63**, followed by vinylation with DBU and then cleavage of the acetal protecting group to give **62**.

Problems associated with dehydrochlorination of the (monofluoromethyl)porphyrins were avoided by dehydrochlorinating prior to fluorination. 8-Formylporphyrin **42** was reduced to the corresponding alcohol **64** by brief treatment with sodium borohydride in dichloromethane/methanol. 8-(Hydroxymethyl)porphyrin **64** was treated at 75 °C for 1.5 h with DBU/dimethylformamide to give 8-(hydroxymethyl)protoporphyrin IX dimethyl ester **65**. The target 8-(monofluoromethyl)protoporphyrin IX dimethyl ester **6** was prepared with DAST at −78 °C in dichloromethane. Due to the lability of the monofluoromethyl group, purification and conversion of **6** to hemin has not yet been efficiently accomplished.

It should be mentioned that the iron complex dicarboxylic acids of porphyrins **62** and **65** have been isolated[37] from phenylhydrazine inactivation of horseradish peroxidase, and the location of the oxidized methyl (at position 8) was used to confirm that the substrate reacts with the heme edge and, moreover, that the δ-meso position and 8-methyl are in the protein exposed sector of horseradish peroxidase. In addition, compounds such as **6** and **65** are potential intermediates in the synthesis of lactoperoxidase heme, recently defined[38] as the corresponding iron(II) thiol derivative **66** of **6** or **65**; work on synthesis of **66**, based on the methodology described herein, is under way.

Experimental Section

Melting points were measured on a hot-stage apparatus and were uncorrected. Silica gel 60 (70–230 mesh, Merck) or neutral alumina (Merck; usually Brockmann grade III, i.e., deactivated with 6% water) were used for column chromatography. Preparative thin-layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck G 254 silica gel (1 mm thick). Analytical thin-layer chromatography was performed by using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by thin-layer chromatography and spectrophotometry and were carried out under nitrogen and in the dark. Proton NMR spectra were obtained in deuteriochloroform solution at 300 MHz by using a General Electric QE300 spectrometer; chemical shifts are expressed in parts per million relative to chloroform (7.258 ppm). Elemental analyses were performed at the Microchemical Analysis Laboratory, U.C. Berkeley. Electronic absorption spectra were measured in dichloromethane solution by using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained on a VG Analytical ZAB-HS instrument.



66
PH = $CH_2CH_2CO_2H$

2,4-Diethyl-6-(difluoromethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (22). The parent formylporphyrin[14] **23** (44 mg, 1 equiv) was dissolved in a minimum quantity of dry dichloromethane, and to it were added sodium fluoride (an HF sponge) (7 mg, 2 equiv) and DAST (350 μL, 30 equiv) under a nitrogen atmosphere. The mixture was stirred at room temperature, and the progress of the reaction was monitored by silica gel TLC. Within 1 h, TLC (5% methanol in dichloromethane) indicated the presence of a more mobile compound (est. 1:4). The reaction was terminated after an additional 7 h; it was found that allowing the reaction to proceed longer than 10 h caused the unreacted starting material and product to become a mobile yellow compound possessing a Soret band but lacking any discernible satellite bands. The reaction mixture was diluted with dichloromethane, and the organic phase was washed four times with water and once with brine; the dichloromethane phase was dried over Na_2SO_4 before removal of the solvent by evaporation. The crude material was chromatographed on a 2 × 50 cm alumina column (Brockmann grade III) eluting with 100% dichloromethane, which afforded 31 mg (67%) of the more mobile (difluoromethyl)porphyrin **22**, followed by 10 mg (24%) of the less mobile starting material **23**; both porphyrins were crystallized from dichloromethane/petroleum ether. Compound **22** had mp 251–253 °C. ^1H NMR ($CDCl_3$): δ −3.79 (s, 2 H, NH), 1.85 (t, 3 H, CH_2CH_3), 1.87 (t, 3 H, CH_2CH_3), 3.31 (t, 2 H, CH_2CH_2CO), 3.55 (s, 3 H, ring methyl), 3.67 (s, 6 H, 2 × ring methyl), 3.68 (s, 3 H, ring methyl), 3.78 (s, 3 H, OMe), 4.01 (q, 2 H, CH_2CH_3), 4.13 (q, 2 H, CH_2CH_3), 4.45 (t, 2 H, CH_2CH_2CO), 8.18 (t, 1 H, CF_2H, J_{HF} = 55.1 Hz), 10.05 (s, 2 H, 2 × meso H), 10.14 (s, 1 H, meso H), 10.27 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 402 (ε 187 000), 502 (11 000), 538 (11 000), 568 (6720), 622 nm (1790). LR mass spectrum: *m/e* 558 (100), 543 (6), 499 (7), 485 (17). HR mass spectrum: $C_{33}H_{36}F_2N_4O_2$ requires 558.2806, found 558.2789. Anal. Calcd for $C_{33}H_{36}F_2N_4O_2$: C, 70.93; H, 6.50; N, 10.03. Found: C, 71.27; H, 6.48; N, 9.64.

2,4-Diethyl-6-(hydroxymethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (24). Within a 25-mL flask was placed dry methanol (5 mL), and the flask was cooled to 0 °C under nitrogen before the addition of sodium borohydride (26 mg). The white slurry was stirred for 5 min at 0 °C before the addition of a solution of formylporphyrin **23**[14] (21 mg) in dichloromethane (5 mL). The green-red hue of the porphyrin solution immediately became redder upon addition to the solution of reducing agent. After 5 min, silica gel TLC (5% methanol in dichloromethane) indicated a nearly quantitative yield of the more mobile (hydroxymethyl)porphyrin **24**. After an additional 5 min of stirring at reduced temperature, the solution was allowed to warm to room temperature (during 5 min), and the mixture was quenched with dichloromethane. The organic layer was washed four times with water and once with brine and dried over Na_2SO_4 before the solvent was stripped off under vacuum. Chromatography of the red residue on alumina (Brockmann grade III) eluting

(37) Ator, M. A.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1987**, *262*, 1542.
(38) Nichol, A. W.; Angel, L. A.; Moon, T.; Clezy, P. S. *Biochem. J.* **1987**, *247*, 147.

with 5% methanol in dichloromethane gave the title compound in quantitative yield. It was recrystallized from dichloromethane/hexane, mp 258–264 °C dec. (lit.[14] mp 260–268 °C dec). ^{1}H NMR ($CDCl_3$): δ −3.70 (s, 2 H, NH), 1.88 (t, 6 H, 2 × CH_2CH_3), 3.28 (t, 2 H, CH_2CH_2CO), 3.53 (s, 3 H, ring methyl), 3.62 (s, 3 H, ring methyl), 3.69 (s, 6 H, 2 × ring methyl), 3.75 (s, 3 H, OMe), 4.07 (q, 2 H, CH_2CH_3), 4.09 (q, 2 H, CH_2CH_3), 4.46 (t, 2 H, CH_2CH_2CO), 6.13 (s, 2 H, CH_2OH), 10.08 (s, 2 H, 2 × meso *H*), 10.11 (s, 1 H, meso *H*), 10.28 (s, 1 H, meso *H*). UV–vis (CH_2Cl_2): λ_{max} 400 (ε 191 000), 498 (13 300), 532 (7800), 566 (5400), 622 nm (3550). LR mass spectrum: *m/e* 538 (100), 522 (7), 479 (3), 466 (13). HR mass spectrum: $C_{33}H_{38}N_4O_2$ requires 538.2944, found 538.2951. Anal. Calcd for $C_{33}H_{38}N_4O_3$: C, 73.57; H, 7.12; N, 10.41. Found: C, 73.27; H, 7.28; N, 10.61.

2,4-Diethyl-6-(fluoromethyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (25). The foregoing porphyrin **24** (5 mg) and NaF (1 mg) in dry dichloromethane were cooled to −78 °C (acetone/dry ice) under a nitrogen atmosphere before the addition of DAST (50 μL) to the solution via a syringe. TLC (silica gel; 5% methanol in dichloromethane) indicated that a majority of the starting material had been consumed after only 1 min. After stirring for 10 min at reduced temperature and another 5 min as the vessel approached room temperature, the mixture was diluted with dichloromethane. The organic phase was washed three times with water and once with brine and then dried over Na_2SO_4 before solvent was stripped off under vacuum. Following workup, both alumina and silica gel TLC indicated that most of the starting material was consumed; however, a significant amount of streaking occurred on the plate. The product mixture was chromatographed on a 0.5 × 15 cm silica gel column, and only one band was collected. Although the change was subtle, the optical spectrum of the product mixture returned to that of the starting material. The ^{1}H NMR spectrum did not show the doublet one would expect from a CH_2F group. However, if chromatography was avoided, the NMR spectrum clearly showed the required doublet. This sensitivity toward chromatographic media was found to be true for alumina as well. On the basis of the NMR spectrum, the yield of **25** was estimated to be 85%, the other major component being starting material. ^{1}H NMR ($CDCl_3$): δ −3.70 (s, 2 H, NH), 1.86 (t, 3 H, CH_2CH_3), 1.88 (t, 3 H, CH_2CH_3), 3.30 (t, 2 H, CH_2CH_2CO), 3.60 (s, 3 H, ring methyl), 3.67 (s, 6 H, 2 × ring methyl), 3.69 (s, 3 H, ring methyl), 3.76 (s, 3 H, OMe), 4.05 (q, 2 H, CH_2CH_3), 4.13 (q, 2 H, CH_2CH_3), 4.46 (t, 2 H, CH_2CH_2CO), 6.86 (d, 2 H, CH_2F, J_{HF} = 49.3 Hz), 10.09 (s, 2 H, 2 × meso *H*), 10.16 (s, 2 H, 2 × meso *H*). UV–vis (CH_2Cl_2): λ_{max} 400, 498, 536, 568, 622 nm. LR mass spectrum: *m/e* 540 (25), 522 (100), 463 (14), 449 (24). The HR mass spectrum for the molecular ion ($C_{33}H_{37}FN_4O_2$) requires 540.2901; however, due to the instability of the parent compound, the molecular weight of the molecular ion could not be measured by high-resolution MS. The most stable daughter ion at 522 [(M^+ − F + H)] was measured, the molecular weight required being 522.2995; found 522.3007.

4-Ethyl-6-[2-(methoxycarbonyl)ethenyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2-vinylporphyrin (29). The title compound was prepared from the parent β-hydroxypropionate porphyrin **28**[39] (3 mg) by addition of DAST (15 μL) via a syringe to a cooled solution of **28** and NaF (1 mg) in dry dichloromethane under an atmosphere of nitrogen. Silica gel TLC (5% methanol in dichloromethane) indicated that after only 5 min of stirring at this temperature a far more mobile major red-green product (est 95% yield) had formed, leaving only a trace of the red starting material near the base line (est 5%). After stirring at reduced temperature for an additional 5 min, the solution was diluted with dichloromethane and washed three times with water and once with brine; this was followed by drying of the organic layer over Na_2SO_4 and removal of the solvent under vacuum. The porphyrinic residue was chromatographed on a 0.5 × 20 cm alumina column (Brockmann grade III) and the product eluted from the column with dichloromethane. Unreacted starting material was flushed from the column with 5% methanol. Due to the paucity of starting material used, the product yield was not measured but is estimated to be ≥95%. ^{1}H NMR ($CDCl_3$): δ −4.09 (s, 2 H, NH), 1.84 (t, 3 H, CH_2CH_3), 3.30 (t, 2 H, CH_2CH_2CO), 3.60 (s, 6 H, 2 × ring methyl), 3.62 (s, 3 H, ring methyl), 3.67 (s, 3 H, ring methyl), 3.71 (s, 3 H, $CH_2CH_2CO_2Me$), 4.06 (q, 2 H, CH_2CH_3), 4.09 (s, 3 H, CH=$CHCO_2Me$), 4.38 (t, 2 H, CH_2CH_2CO), 6.15 (d, H, cis β-vinyl CH, $J_{\alpha\beta}$ = 11.9 Hz), 6.31 (d, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.6 Hz), 7.09 (d, 1 H, CH=$CHCO_2Me$, $J_{\alpha\beta}$ = 16.2 Hz), 8.21 (m, 1 H, α-vinyl CH), 9.30 (d, 1 H, CH=$CHCO_2Me$, $J_{\alpha\beta}$ = 16.2 Hz), 9.92 (s, 1 H, meso H), 9.98 (s, 1 H, meso H), 9.99 (s, 1 H, meso H), 10.05 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 410 (1.00), 504 (0.174), 542 (0.208), 570 (0.133), 626 nm (0.044). LR mass spectrum: *m/e* 590 (100), 517 (19). HR mass spectrum: $C_{36}H_{38}N_4O_4$ requires 590.2893, found 590.2878.

2,4-Diethyl-6-[1-fluoro-2-(methoxycarbonyl)ethenyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (31). The title compound was prepared from the parent β-ketopropionate porphyrin[40] **30** (2 mg) by addition of DAST (15 μL) to a solution of **30** in dry dichloromethane (2.0 mL) at room temperature under nitrogen. Upon addition of DAST, the solution immediately turned from red to a greenish-brown color. After 0.5 h, alumina TLC (dichloromethane) indicated that a considerable amount of a more mobile red product had formed. The reaction was allowed to proceed for another 2 h at ambient temperature, but TLC indicated little change in the composition of reaction during this time. The solution was diluted with dichloromethane and washed three times with water and once with brine; this was followed by drying of the organic layer over Na_2SO_4 and removal of the solvent under vacuum. The porphyrinic residue was chromatographed on a 0.5 × 15 cm alumina column (Brockmann grade III) and the product eluted from the column with dichloromethane. Due to the paucity of starting material used, the product yield was not measured. ^{1}H NMR ($CDCl_3$): δ −3.65 (s, 2 H, NH), 1.86 (t, 3 H, CH_2CH_3), 1.89 (t, 3 H, CH_2CH_3), 3.29 (t, 2 H, CH_2CH_2CO), 3.45 (s, 3 H, ring methyl), 3.58 (s, 3 H, ring methyl), 3.65 (s, 3 H, ring methyl), 3.68 (s, 3 H, ring methyl), 3.70 (s, 6 H, 2 × OMe), 4.02 (q, 2 H, CH_2CH_3), 4.17 (q, 2 H, CH_2CH_3), 4.44 (t, 2 H, CH_2CH_2CO), 6.74 (d, 1 H, CF=$CHCO_2Me$, J_{HF} = 16.9 Hz), 10.02 (s, 1 H, meso H), 10.07 (s, 1 H, meso H), 10.08 (s, 1 H, meso H), 10.21 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 404 (1.00), 504 (0.107), 542 (0.114), 570 (0.086), 624 nm (0.051). LR mass spectrum: *m/e* 610 (100), 595 (8), 579 (3), 537 (19). HR mass spectrum: $C_{36}H_{39}FN_4O_4$ requires 610.2955, found 610.2964.

2,4-Bis(2,2-dimethoxyethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (33). The title porphyrin was prepared by treatment of protoporphyrin IX dimethyl ester (**32**) with thallium(III) nitrate in methanol according to the literature method.[17] Product yield was 65%, mp >210 °C dec. ^{1}H NMR ($CDCl_3$): δ −3.70 (s, 2 H, NH), 3.29 (t, 2 H, CH_2CH_2CO), 3.30 (t, 2 H, CH_2CH_2CO, 3.47 (s, 6 H, 2 × ring methyl), 3.48 (s, 6 H, 2 × ring methyl), [3.65 (s, 3 H), 3.66 (s, 6 H), 3.69 (s, 3 H), 3.70 (s, 6 H); 2 × CO_2Me and 4 × OMe], 4.38 (d, 2 H, $CH_2CH(OMe)_2$, J_{HH} = 5.4 Hz), 4.43 (t, 2 H, CH_2CH_2CO), 4.46 (t, 2 H, CH_2CH_2CO), 5.17 (t, 1 H, $CH_2CH(OMe)_2$, J_{HH} = 5.4 Hz), 10.10 (s, 1 H, meso H), 10.13 (s, 1 H, meso H), 10.19 (s, 1 H, meso H), 10.20 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 400 (1.00), 498 (0.098), 532 (0.071), 568 (0.055), 622 nm (0.042).

2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (34). Transacetalation of the foregoing porphyrin **33** was carried out by dissolving the bis(acetal) porphyrin (87 mg, 1 equiv) in anhydrous acetone (15 mL) containing *p*-toluenesulfonic acid (24 mg, 10 equiv) at room temperature under an atmosphere of nitrogen. After only 5 min, the less mobile product was detected by silica gel TLC (5% methanol in dichloromethane; the aliquot was quenched with triethylamine before spotting on the silica gel plate), and after 2 h, TLC indicated the reaction to be nearly complete. After an additional 1 h, the mixture was diluted with dichloromethane and

(39) Prepared by sodium borohydride reduction of the corresponding β-keto ester: Mansfield, K. E. Ph.D. Dissertation, University of California, Davis, 1988.

(40) (a) Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 527. (b) Cox, M. T.; Jackson, A. H.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 516. Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2517.

(41) This footnote was deleted on revision.

washed with water, saturated sodium bicarbonate, then twice with water, and once with brine; the organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was chromatographed on a 3 × 30 cm alumina column (Brockmann grade III) eluting off the more mobile porphyrinic bands with 1% methanol in dichloromethane; the title compound **34** was eluted from the column with 3% methanol in dichloromethane. All attempts to crystallize the product failed, and decomposition occurred if the material was left in solution for a protracted period. The following reactions, for which this porphyrin was prepared, were carried out with haste. ^{1}H NMR ($CDCl_3$): δ −3.88 (s, 2 H, NH), 3.26 (t, 2 H, CH_2CH_2CO), 3.27 (t, 2 H, CH_2CH_2CO), 3.54 (s, 3 H, ring methyl), 3.55 (s, 3 H, ring methyl), 3.57 (s, 3 H, ring methyl), 3.59 (s, 3 H, ring methyl), 3.66 (s, 6 H, 2 × OMe), 4.37 (t, 4 H, 2 × CH_2CH_2CO), 4.97 (m, 4 H, CH_2CHO), 9.80 (s, 1 H, meso H), 9.81 (s, 1 H, meso H), 10.01 (s, 1 H, meso H), 10.05 (s, 1 H, meso H), 10.20, (br s, 2 H, CH_2CHO).

2,4-Bis(2-hydroxyethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (36). The title porphyrin was prepared by treatment of the foregoing bis(acetaldehyde) porphyrin **34** with sodium borohydride according to the literature method.[17] Product yield was 60%, mp 222–226 °C (lit.[17] mp 225–226 °C). ^{1}H NMR ($CDCl_3$): δ −3.74 (s, 2 H, NH), 3.30 (t, 4 H, CH_2CH_2CO), 3.66 (s, 6 H, 2 × ring methyl), 3.66 (s, 6 H, 2 × ring methyl), 3.69 (s, 6 H, 2 × CO_2Me), 4.34–4.50 (m, 12 H, 2 × $CH_2CH_2CO_2Me$, 2 × CH_2CH_2OH, 2 × CH_2CH_2OH), 10.11 (s, 1 H, meso H), 10.12 (s, 2 H, 2 × meso H), 10.13 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 400 (1.00), 498 (0.106), 530 (0.077), 566 (0.059), 620 nm (0.047).

2,4-Bis(2,2-difluoroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (35). The bis(acetaldehyde) porphyrin **34** (used immediately following chromatography as in protocol described above) was dissolved in freshly distilled dichloromethane, and the resulting solution was cooled to 0 °C. To this solution under an atmosphere of nitrogen was added DAST (200 μL). After 5 min, alumina TLC (dichloromethane) indicated that a large quantity of red, nonpolar porphyrinic material had been produced. The reaction was terminated after 30 min by diluting the mixture with dichloromethane, and the organic phase was washed three times with water and once with brine; the organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum. The residue was chromatographed on a 2 × 15 cm alumina column (Brockmann grade III), and the product (most mobile) was eluted from the column with 100% dichloromethane. The title porphyrin was crystallized from dichloromethane/petroleum ether to afford a 27% yield (based on bis(acetal) porphyrin **33**) of **35**, mp 205–207.5 °C. ^{1}H NMR ($CDCl_3$): δ −3.92 (s, 2 H, NH), 3.27 (t, 4 H, CH_2CH_2CO), 3.56 (s, 3 H, ring methyl), 3.59 (s, 6 H, 2 × ring methyl), 3.60 (s, 3 H, ring methyl), 3.66 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 4.36 (t, 4 H, 2 × CH_2CH_2CO), 4.46 (dt, 2 H, CH_2CHF_2, J_{HF} = 16.5 Hz, J_{HH} 4.5 Hz), 4.50 (dt, 2 H, CH_2CHF_2, J_{HF} = 16.5 Hz, J_{HH} = 4.5 Hz), 6.51 (tt, 1 H, CH_2CHF_2, J_{HF} = 56.4 Hz, J_{HH} = 4.5 Hz), 6.53 (tt, 1 H, CH_2CHF_2, J_{HF} = 56.4 Hz, J_{HH} = 4.5 Hz), 9.89 (s, 1 H, meso H), 9.895 (s, 1 H, meso H), 10.00 (s, 1 H, meso H), 10.03 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 400 (ε 167 000), 498 (12 600), 530 (7720), 568 (5390), 622 nm (3390). LR mass spectrum: *m/e* 666 (100), 647 (4), 628 (14), 607 (15), 593 (72). HR mass spectrum: $C_{36}H_{38}F_4N_4O_4$ requires 666.2829, found 666.2837.

2,4-Bis(2-fluoroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (37). The bis(2-hydroxyethyl)porphyrin **36** (51 mg) was dissolved in dry dichloromethane (20 mL) under a nitrogen atmosphere, and to the solution was added NaF (10 mg). The mixture was cooled to −78 °C (acetone/dry ice), and to it was slowly added DAST (250 μL) via a syringe. The mixture was stirred at reduced temperature for 15 min and for an additional 5 min during the course of warming to room temperature. The mixture was quenched with dichloromethane, and the organic phase was washed four times with water and once with brine; the organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum. The crude residue was chromatographed on a 1 × 20 cm alumina column (Brockmann grade III), and the product (most mobile) was eluted from the column with 100% dichloromethane. The title porphyrin was crystallized from dichloromethane/petroleum ether, affording a 26% yield, mp 214–218 °C. ^{1}H NMR ($CDCl_3$): δ −3.84 (s, 2 H, NH), 3.29 (t, 4 H, CH_2CH_2CO), 3.62 (s, 3 H, ring methyl), 3.62 (s, 6 H, 2 × ring methyl), 3.63 (s, 3 H, ring methyl), 3.66 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 4.40 (t, 4 H, CH_2CH_2CO), 4.40–4.51 (m, 4 H, CH_2CH_2F), 5.19 (dt, 2 H, CH_2CH_2F, J_{HF} = 46.8 Hz), 5.19 (dt, 2 H, CH_2CH_2F, J_{HF} = 46.8 Hz), 9.99 (s, 1 H, meso H), 10.00 (s, 1 H, meso H), 10.06 (s, 1 H, meso H), 10.07 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 399 (ε 167 000), 498 (13 500), 530 (8800), 568 (6200), 622 nm (4180). LR mass spectrum: *m/e* 630 (100), 599 (4), 571 (3), 557 (23). HR mass spectrum: $C_{36}H_{40}F_2N_4O_4$ requires 630.3018, found 630.3017.

4-Ethyl-6-(fluorocarbonyl)-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2-vinylporphyrin (39). 2-Vinylrhodoporphyrin XV 7-methyl ester[40] **38** (12 mg) was dissolved in freshly distilled dichloromethane (2.5 mL), and to this was added NaF (1 mg). The resulting mixture was cooled to −78 °C (acetone/dry ice), and under a nitrogen atmosphere was added DAST (6.0 μL) via a syringe. After 5 min, TLC (alumina; dichloromethane) indicated that nearly all the starting material had been consumed, resulting in the production of a more mobile porphyrin product. After an additional 30 min of stirring at reduced temperature, the mixture was quenched with dichloromethane and the organic phase washed four times with water and once with brine; the organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum. The crude residue was chromatographed on a 1 × 20 cm alumina column (Brockmann grade III), and the product (most mobile) was eluted from the column with 100% dichloromethane. The product yield was 4.6 mg (37%). The optical spectrum was slightly red-shifted from that of the starting material [2-vinylrhodoporphyrin XV methyl ester: λ_{max} 406 (1.00), 512 (0.078), 554 (0.126), 578 (0.086), 638 nm (0.039)] and does not change when treated with triethylamine whereas rhodoporphyrin **38** changes from rhodo to etio type. ^{1}H NMR ($CDCl_3$): δ −3.93 (s, 2 H, NH), 1.85 (t, 3 H, CH_2CH_3), 3.30 (t, 2 H, CH_2CH_2CO), 3.62 (s, 3 H, ring methyl), 3.64 (s, 3 H, ring methyl), 3.65 (s, 3 H, ring methyl), 3.68 (s, 3 H, ring methyl), 3.94 (s, 3 H, OMe), 4.10 (q, 2 H, CH_2CH_3), 4.43 (t, 2 H, CH_2CH_2CO), 6.16 (d, 1 H, cis β-vinyl CH, $J_{\alpha\beta}$ = 11.1 Hz), 6.31 (d, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.7 Hz), 8.19 (dd, 1 H, α-vinyl CH), 9.91 (s, 1 H, meso H), 10.04 (s, 1 H, meso H), 10.09 (s, 1 H, meso H), 10.74 (s, 1 H, meso H). ^{19}F NMR ($CFCl_3$): δ 37.5. UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 408 (1.00), 516 (0.068), 560 (0.124), 580 (0.092), 636 nm (0.035). LR mass spectrum: *m/e* 552 (100), 537 (4), 479 (16). HR mass spectrum: $C_{33}H_{33}FN_4O_3$ requires 552.2537, found 552.2536.

Benzyl 3,5-Bis(2-chloroethyl)-1-[2-(methoxycarbonyl)ethyl]-1′,2,4,6-tetramethyltripyrrene-*a*-6′-carboxylate Hydrobromide (49). The title tripyrene was prepared from the pyrromethane **47** and formylpyrrole **48** according to the method previously described in detail;[25] mp 162–163 °C. ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3 H, ring methyl), 2.26 (s, 3 H, ring methyl), 2.31 (s, 3 H, ring methyl), 2.46 (s, 3 H, ring methyl), 2.47 (t, 2 H, CH_2CH_2CO), 2.76 (t, 2 H, CH_2CH_2CO), 2.86 (t, 2 H, CH_2CH_2Cl), 3.11 (t, 2 H, CH_2CH_2Cl), 3.26 (t, 2 H, CH_2CH_2Cl), 3.63 (t, 2 H, CH_2CH_2Cl), 3.67 (s, 3 H, OMe), 4.17 (s, 2 H, bridging methylene CH_2), 5.29 (s, 2 H, $PhCH_2$), 7.29–7.45 (m, 5 H, Ph), 11.06 (br s, 1 H, NH), 13.16 (br s, 1 H, NH), 13.28 (br s, 1 H, NH). UV–vis (CH_2Cl_2): λ_{max} 494 nm (ε 71 000). Anal. Calcd for $C_{34}H_{40}BrCl_2N_3O_4 \cdot 2H_2O$: C, 55.07; H, 5.98; N, 5.67. Found: C, 55.33; H, 6.30; N, 5.36.

2-Formyl-4-[2-(methoxycarbonyl)ethyl]-5-methylpyrrole (50). Benzyl 4-[2-(methoxycarbonyl)ethyl]-5-methylpyrrole-2-carboxylate[42] (530 mg) was dissolved in dry tetrahydrofuran (20 mL) and hydrogenolyzed over 10% Pd/C (20 mg) in the presence of a drop of triethylamine. Cleavage of the benzyl ester was judged to be complete after 5 h. The solution was passed through a bed of Celite, and the solvent was removed under vacuum. The resulting pyrrole was treated with trifluoroacetic acid (7.0 mL) for 5 min at room temperature before cooling to 0 °C. After 5 min of stirring at reduced temperature, trimethyl orthoformate (11 mL) was slowly added to the pyrrolic solution. The solution was stirred for 5 min at 0 °C and for an additional 5 min at room temperature before being diluted with dichloromethane and poured onto iced water. The organic layer was washed three times

(42) Smith, K. M.; Fujinari, E. M.; Pandey, R. K.; Tabba, H. D. *J. Org. Chem.* **1986**, *51*, 4667.

with water and once with brine before drying over Na_2SO_4 and evaporation to dryness. The residual solid was recrystallized from dichloromethane/petroleum ether to afford 340 mg (86%) of the title pyrrole as white crystals, mp 76–80 °C. ^1H NMR ($CDCl_3$): δ 2.29 (s, 3 H, ring methyl), 2.59 (t, 2 H, CH_2CH_2CO), 2.74 (t, 2 H, CH_2CH_2CO), 3.67 (s, 3 H, OMe), 6.75 (s, 1 H, 3-H), 9.30 (s, 1 H, CHO), 9.50 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 71.71; H, 6.02; N, 10.14. Found: C, 71.70; H, 6.19; N, 10.11.

4,6-Bis(2-chloroethyl)-1,8-bis[2-(methoxycarbonyl)ethyl]-1′,3,5,7,8′-pentamethyl-*a*,*c*-biladiene Dihydrobromide (45). The title *a*,*c*-biladiene was prepared from the tripyrrene **49** and the formylpyrrole **50** by the method previously described in detail.[25] A more concentrated solution of HBr/HOAc (43%) was used to cleave the benzyl ester, which occurred with ease after 1 h. The product was crystallized from ether in 85% yield, mp >300 °C dec. ^1H NMR ($CDCl_3$): δ 2.01 (s, 3 H, ring methyl), 2.28 (s, 3 H, ring methyl), 2.34 (s, 3 H, ring methyl), 2.49 (t, 2 H, CH_2CH_2CO), 2.61 (t, 2 H, CH_2CH_2CO), 2.74 (s, 3 H, α-ring methyl), 2.745 (s, 3 H, α-ring methyl), 2.78 (m, 4 H, 2 × CH_2CH_2Cl), 3.05 (m, 6 H, 2 × CH_2CH_2Cl and CH_2CH_2CO), 3.59 (t, 2 H, CH_2CH_2CO), 3.68 (s, 3 H, OMe), 3.69 (s, 3 H, OMe), 5.26 (s, 2 H, methylene bridge CH_2), 6.98 (s, 1 H, β-H), 7.10 (s, 1 H, methine H), 7.15 (s, 1 H, methine H), 13.36 (br s, 1 H, NH), 13.53 (br s, 1 H, NH), 13.57 (br s, 1 H, NH), 13.60 (br s, 1 H, NH). UV–vis (CH_2Cl_2): λ_{max} 450 (ε 85 600), 524 (111 000). Anal. Calcd for $C_{36}H_{46}Br_2Cl_2N_4O_4$: C, 52.13; H, 5.59; N, 6.75. Found: C, 51.95; H, 5.47; N, 6.69.

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (54). Method A. The title porphyrin was prepared, in yields ranging from 14–21%, by the oxidative cyclization of the β-unsubstituted *a*,*c*-biladiene **45** with $Cu(OAc)_2$ by the standard cyclization method as previously described.[25]

Method B. The title porphyrin was obtained from the room-temperature cyclization using $CuCl_2$ as described elsewhere.[29] Two clear chromatographic bands were separated, the most polar red band being shown to consist of a mixture of the δ-*meso*-chloroporphyrin **53** and the title porphyrin **54** in a 2:3 ratio and a combined yield of 30%. A less mobile green material was obtained from the second chromatographic band and possessed a rhodo-type spectrum (λ_{max} 412, 516, 556, 580, 640 nm). It was shown by ^1H NMR and mass spectroscopy to be the 8-formylporphyrin **42**; the yield was only 1.5%, and the material was fully characterized by comparison with an authentic sample prepared (vide infra) by Friedel–Crafts formylation of the hemin **57**, followed by demetalation.

Method C. Oxidation of the *a*,*c*-biladiene **45** with $CuCl_2$ and demetalation of the resulting copper(II) porphyrin with trifluoroacetic/sulfuric acids (85:15) was carried out by standard methods previously described.[25] The resultant mixture of *meso*-chloroporphyrin[26] **53** and the desired β-unsubstituted porphyrin **54** (94.1 mg total) was dissolved in tetrahydrofuran (50 mL) containing triethylamine (0.05 mL), and the mixture was hydrogenated over 10% Pd/C (50 mg) for 2 days until the solution became nearly colorless. The porphyrinogen solution was immediately filtered through a bed of Celite, and the solvent was evaporated to near dryness. To a stirring solution of this in dichloromethane (20 mL) was added dichlorodicyanobenzoquinone (85 mg) in dichloromethane (5 mL) whereupon the solution immediately became red. The solution was chromatographed on a 2 × 20 cm alumina column (Brockmann grade III), and the porphyrin was eluted from the column with dichloromethane; 71 mg of the title porphyrin was recovered (78% recovery) after crystallization from dichloromethane/petroleum ether; mp 168–174 °C. ^1H NMR ($CDCl_3$): δ −3.77 (s, 2 H, NH), 3.30 (t, 2 H, CH_2CH_2CO), 3.49 (t, 2 H, CH_2CH_2CO), 3.66 (s, 3 H, ring methyl), 3.67 (s, 3 H, ring methyl), 3.68 (s, 3 H, ring methyl), 3.69 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.31–4.59 (m, 12 H, 2 × CH_2CH_2CO, 2 × CH_2CH_2Cl, 2 × CH_2CH_2Cl), 9.12 (s, 1 H, 8β-H), 10.05 (s, 2 H, 2 × meso H), 10.09 (s, 1 H, meso H), 10.17 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 399 (ε 185 000), 498 (12 200), 532 (7200), 568 (5050), 620 nm (2330). LR mass spectrum: *m*/*e* 648 (100), 614 (64), 599 (12), 580 (15), 575 (10). HR mass spectrum: $C_{35}H_{38}Cl_2N_4O_4$ requires 648.2270, found 648.2285. Anal. Calcd for $C_{35}H_{38}Cl_2N_4O_4$: C, 64.71; H, 5.90; N, 8.63. Found: C, 64.67; H, 5.98; N, 8.58.

Iron(III) 2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin Chloride (57). This iron complex of **54** was prepared according to the literature method,[33] using ferrous chloride in acetonitrile. It was obtained in quantitative yield. LR mass spectrum: *m*/*e* 705 (14), 703 (13), 669 (59), 635 (100). Anal. Calcd for $C_{35}H_{36}Cl_3FeN_4O_4$: C, 56.89; H, 4.91; N, 7.58. Found: C, 57.03; H, 4.95; N, 7.56.

2,4-Bis(2-chloroethyl)-8-formyl-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (42). The β-unsubstituted hemin **57** (61 mg) was dissolved in freshly distilled dichloromethane (10 mL) and dichloromethyl methyl ether (4.0 mL) (**CAUTION! reagent is a known carcinogen**), and the solution was cooled to 0 °C. To this solution under nitrogen was slowly added tin(IV) chloride (1.0 mL) by syringe. After 20 min, the green solution was diluted with dichloromethane and poured into water; the organic phase was washed with saturated Na_2CO_3, three times with water, and once with brine. The solution was dried over Na_2SO_4 and the solvent removed by evaporation to give 38 mg (60%) of the formylhemin **58**. This was dissolved in glacial acetic acid (25 mL), purged with nitrogen gas (30 min), and while nitrogen was still bubbling through the mixture, a solution of ferrous sulfate heptahydrate in concentrated HCl [2.0 mL; prepared by adding ferrous sulfate (1.1 g) to concentrated HCl (10 mL) and stirring under nitrogen for 5 min] was added. The mixture was stirred for 5 min before being poured into dichloromethane (100 mL), washed with saturated sodium acetate, then saturated sodium carbonate, and finally washed twice with water and once with brine. The organic phase was dried over Na_2SO_4 and then evaporated to dryness to give a green residue, which was flash chromatographed with a 1 × 30 cm silica gel column and elution with 0.5% methanol in dichloromethane. A minor, slightly more mobile porphyrin was collected first, followed by the title compound. The minor compound is believed to be the δ-*meso*-formyl product (λ_{max} 412, 514, 556, 578, 644 nm and δ_{CHO} ~12.5 ppm). The title porphyrin (23 mg, 41%) was isolated following crystallization from dichloromethane/petroleum ether, mp 223–229 °C (uncorrected), 233–239 °C (corrected) (lit.[21f] mp 234–237 °C). ^1H NMR ($CDCl_3$): β −3.48 (s, 2 H, NH), 3.31 (t, 2 H, CH_2CH_2CO), 3.40 (t, 2 H, CH_2CH_2CO), 3.59 (s, 3 H, ring methyl), 3.61 (s, 3 H, ring methyl), 3.63 (s, 3 H, ring methyl), 3.70 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 4.28–4.75 (m, 12 H, 2 × CH_2CH_2CO, 2 × CH_2CH_2Cl, 2 × CH_2CH_2Cl), 9.95 (s, 1 H, meso H), 9.96 (s, 1 H, meso H), 10.32 (s, 1 H, meso H), 11.00 (s, 1 H, meso H), 11.56 (s, 1 H, CHO). UV–vis (CH_2Cl_2): λ_{max} 412 (172 000), 516 (11 900), 556 (19 400), 580 (13 000), 640 nm (5400). LR mass spectrum: *m*/*e* 676 (92), 642 (100). HR mass spectrum: $C_{36}H_{38}Cl_2N_4O_5$ requires 676.2219, found 676.2205. When the copper(II) complex **44** of the 8-unsubstituted porphyrin **54** was treated under Vilsmeier conditions with DIBF/$POCl_3$, followed by demetalation with H_2SO_4/trifluoroacetic acid, a 56% yield of formylporphyrins was obtained. However, TLC and ^1H NMR analysis showed this to be a 3:4 mixture of the 8-formylporphyrin **42** and the δ-*meso*-formylporphyrin **56**, respectively.

2,4-Bis(2-chloroethyl)-8-(difluoromethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (59). The title compound was prepared according to the method previously described for the formylporphyrin **22**. The product yield was 60% after recrystallization from dichloromethane/hexane, mp 201–204 °C. ^1H NMR ($CDCl_3$): δ −3.86 (s, 2 H, NH), 3.29 (t, 2 H, CH_2CH_2CO), 3.38 (t, 2 H, CH_2CH_2CO), 3.58 (s, 3 H, ring methyl), 3.62 (s, 3 H, ring methyl), 3.65 (s, 3 H, ring methyl), 3.68 (s, 3 H, OMe), 3.69 (s, 3 H, OMe), 4.28–4.55 (m, 12 H, 2 × CH_2CH_2CO, 2 × CH_2CH_2Cl, 2 × CH_2CH_2Cl), 8.20 (t, 1 H, CHF_2, J_{HF} = 54.6 Hz), 9.96 (s, 1 H, meso H), 9.96 (s, 1 H, meso H), 10.02 (s, 1 H, meso H), 10.34 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 400 (ε 201 300), 504 (12 100), 540 (12 400), 568 (7140), 626 nm (1540). LR mass spectrum: *m*/*e* 698 (100), 663 (8), 662 (4), 649 (14). HR mass spectrum: $C_{36}H_{38}Cl_2F_2N_4O_4$ requires 698.2238, found 698.2222. Anal. Calcd for $C_{36}H_{38}Cl_2F_2N_4O_4$: C, 61.87; H, 5.49; N, 8.02. Found: C, 61.59; H, 5.41; N, 8.00.

8-(Difluoromethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethyl-2,4-divinylporphyrin (5). The foregoing porphyrin **59** (38 mg) was dissolved in dry dimethylformamide (8 mL), and to the solution was added DBU (1 mL). The mixture was heated to 55 °C and stirred at this temperature for 1.5 h (reaction judged to be complete by spectrophotometry). The

solution was quenched with dichloromethane and washed five times with 2 N HCl, once with water, and once with brine. After drying of the solution over Na_2SO_4 and stripping off of the solvent by evaporation, the residue was chromatographed on an alumina column (Brockmann grade III) eluting with dichloromethane. The product (34 mg, 60%) was collected as one major band and was recrystallized from dichloromethane/hexane, mp 203–208 °C. ^1H NMR ($CDCl_3$): δ −3.93 (s, 2 H, NH), 3.26 (t, 2 H, CH_2CH_2CO), 3.36 (t, 2 H, CH_2CH_2CO), 3.60 (s, 3 H, ring methyl), 3.61 (s, 3 H, ring methyl), 3.64 (s, 3 H, ring methyl), 3.66 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 4.42 (t, 2 H, CH_2CH_2CO), 4.51 (t, 2 H, CH_2CH_2CO), 6.16 (dd, 1 H, cis β-vinyl CH, $J_{\alpha\beta}$ = 10.8 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.25 (dd, 1 H, cis β-vinyl CH, $J_{\alpha\beta}$ = 10.8 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.30 (dd, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.4 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.43 (dd, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.4 Hz, $J_{\beta\beta}$ = 1.2 Hz), 8.14–8.30 (m, 2 H, 2 × α-vinyl CH), 8.20 (t, 1 H, CHF_2, J_{HF} = 54.9 Hz), 10.06 (s, 1 H, meso H), 10.09 (s, 1 H, meso H), 10.11 (s, 1 H, meso H), 10.31 (s, 1 H, meso H). ^{19}F NMR ($CFCl_3$): δ −102.14. UV–vis (CH_2Cl_2): λ_{max} 406 (ϵ 175 000), 510 (12 400), 546 (13 500), 576 (7730), 632 nm (1890). LR mass spectrum: m/e 626 (100), 607 (30), 553 (23). HR mass spectrum: $C_{36}H_{36}F_2N_4O_4$ requires 626.2705, found 626.2693. Anal. Calcd for $C_{36}H_{36}F_2N_4O_4$: C, 68.98; H, 5.79; N, 8.94. Found: C, 69.02; H, 5.87; N, 8.71.

8-Formyl-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethyl-2,4-divinylporphyrin (62). The 2,4-bis(2-chloroethyl)-8-formylporphyrin **42** (10 mg) in dichloromethane (5 mL) containing several 3 Å molecular sieves was treated with ethylene glycol (1 mL) containing *p*-toluenesulfonic acid (10 mg) at 40 °C for 10 min. After this time, spectrophotometry (λ_{max} 402, 502, 538, 570, 624 nm, in the presence of triethylamine) and TLC showed acetal formation to be complete. The mixture was poured into dichloromethane and water and washed several times with water, then once with sodium bicarbonate solution, and with water one more time. Drying over anhydrous Na_2SO_4 and evaporation to dryness gave a residue, which was dissolved in dimethylformamide (4 mL), DBU (0.5 mL) was added, and the mixture was heated to 55 °C and stirred at this temperature for 2.5 h (reaction was judged to be complete by spectrophotometry). The solution was quenched with dichloromethane and washed five times with 2 N HCl, once with water, and once with brine. After drying of the solution over Na_2SO_4 and stripping off of the solvent by evaporation, the residue was dissolved in dichloromethane (20 mL) and shaken in a separatory funnel with 10 M HCl (5 mL) for 10 s. Water (50 mL) was added, and the aqueous layer was carefully neutralized with aqueous ammonia before the organic layer was separated. The aqueous layer was extracted further with dichloromethane, the combined organic extracts were evaporated to dryness, and the residue was chromatographed on an alumina column (Brockmann grade III) eluting with dichloromethane. The product (7.3 mg, 81%) was collected as one major band and was recrystallized from dichloromethane/hexane, mp 224–226 °C (lit.[21f] mp 228–229 °C). ^1H NMR ($CDCl_3$): δ −4.31 (s, 2 H, NH), 3.23 (t, 2 H, CH_2CH_2CO), 3.30 (t, 2 H, CH_2CH_3CO), 3.58 (s, 3 H, ring methyl), 3.62 (s, 6 H, OMe), 3.64 (s, 6 H, ring methyl), 3.65 (s, 3 H, ring methyl), 4.39 (t, 2 H, CH_2CH_2CO), 4.59 (t, 2 H, CH_2CH_2CO), 6.21 (dd, 1 H, cis β-vinyl CH, $J_{\alpha\beta}$ = 10.7 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.26 (dd, 1 H, cis β-vinyl CH, $J_{\alpha\beta}$ = 10.7 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.32 (dd, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.3 Hz, $J_{\beta\beta}$ = 1.2 Hz), 6.41 (dd, 1 H, trans β-vinyl CH, $J_{\alpha\beta}$ = 17.3 Hz, $J_{\beta\beta}$ = 1.2 Hz), 8.10–8.25 (m, 2 H, 2 × α-vinyl CH), 9.81 (s, 1 H, meso H), 9.84 (s, 2 H, meso H), 10.59 (s, 1 H, meso H), 11.42 (s, 1 H, CHO). UV–vis (CH_2Cl_2): λ_{max} 418 (ϵ 172 000), 518 (10 100), 564 (16 500), 586 (11 500), 648 nm (2100). LR mass spectrum: m/e 604 (100), 589 (8), 545 (4), 539 (28). HR mass spectrum: $C_{36}H_{36}N_4O_5$ requires 604.2686, found 604.2681.

2,4-Bis(2-chloroethyl)-8-(hydroxymethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (64). The title compound was prepared according to the method previously described for the (hydroxymethyl)porphyrin **24**. The product yield was 95% after recrystallization from dichloromethane/petroleum ether. ^1H NMR ($CDCl_3$): δ −3.87 (s, 2 H, NH), 3.26 (t, 4 H, CH_2CH_2CO), 3.47 (s, 3 H, ring methyl), 3.59 (s, 3 H, ring methyl), 3.59 (s, 3 H, ring methyl), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 4.22–4.48 (m, 12 H, 2 × CH_2CH_2CO, 2 × CH_2CH_2Cl 2 × CH_2CH_2Cl), 6.03 (s, 2 H, CH_2OH), 9.91 (s, 1 H, meso H), 9.95 (s, 1 H, meso H), 10.02 (s, 1 H, meso H), 10.12 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 400 (1.00), 500 (0.093), 534 (0.067), 570 (0.053), 624 nm (0.038). LR mass spectrum: m/e 678 (83), 662 (100), 647 (7), 631 (10), 627 (14). HR mass spectrum: requires 678.2376, found 678.2388. Anal. Calcd for $C_{36}H_{40}Cl_2N_4O_5$: C, 63.62; H, 5.93; N, 8.24. Found: C, 63.42; H, 5.97; N, 7.98.

8-(Hydroxymethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethyl-2,4-divinylporphyrin (65). The foregoing porphyrin **64** (14 mg) was dissolved in dry dimethylformamide (5 mL), and to the solution was added DBU (0.25 mL). The mixture was heated to 75 °C and stirred at this temperature for 1.5 h (reaction was judged to be complete by spectrophotometry). The solution was quenched with dichloromethane and washed five times with 2 N HCl, once with water, and once with brine. After drying of the solution over Na_2SO_4 and stripping off of the solvent by evaporation, the residue was chromatographed on an alumina column (Brockmann grade III), eluting with 3% methanol in dichloromethane. The product (12 mg, 90%) was collected as one major band and was recrystallized from dichloromethane/petroleum ether. ^1H NMR ($CDCl_3$): δ −3.93 (s, 2 H, NH), 3.23 (t, 4 H, CH_2CH_2CO), 3.48 (s, 3 H, methyl), 3.59 (s, 3 H, methyl), 3.62 (s, 3 H, methyl), 3.63 (s, 3 H, methyl), 3.66 (s, 3 H, methyl), 4.36 (t, 4 H, CH_2CH_2CO), 6.00 (d, 2 H, CH_2OH, J_{HH} = 4.5 Hz), 6.18 (m, 2 H, 2 × cis β-vinyl CH), 6.34 (m, 2 H, 2 × trans β-vinyl CH), 8.21 (m, 2 H, 2 × α-vinyl CH), 9.90 (s, 1 H, meso H), 10.06 (s, 1 H, meso H), 10.08 (s, 1 H, meso H), 10.12 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} (relative intensities) 406 (1.0), 506 (0.108), 542 (0.092), 576 (0.068), 632 nm (0.054). LR mass spectrum: m/e 606 (100), 591 (2), 547 (4), 533 (24), 516 (4). HR mass spectrum: $C_{36}H_{38}N_4O_5$ requires 606.2842, found 606.2846. Anal. Calcd for $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C, 71.11; H, 5.99; N, 9.15.

8-(Fluoromethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethyl-2,4-divinylporphyrin (6). The title porphyrin was prepared according to the method previously described for the (fluoromethyl)porphyrin **25**. As with the previous example, isolation of this compound in a pure form proved impossible. ^1H NMR (not clean due to inability to chromatograph) ($CDCl_3$): δ −3.50 (s, 2 H, NH), 3.38 (m, 4 H, CH_2CH_2CO), [3.60, 3.73, 3.75, 3.81 (all s, 15 H, 3 × ring methyl and 2 × OMe)], 4.52 (m, 4 H, CH_2CH_2CO), 6.31 (m, 4 H, 2 × β-vinyl H), 6.82 (d, 2 H, CFH_2, J_{HF} = 47.7 Hz), 8.23 (m, 2 H, 2 × α-vinyl H), 10.01 (s, 1 H, meso H), 10.03 (s, 1 H, meso H), 10.04 (s, 1 H, meso H), 10.05 (s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 408, 508, 544, 576, 632 nm. LR mass spectrum: m/e 609 (14), 590 (11), 589 (17), 517 (13).

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