Syntheses and Some Chemistry of 1,2- and 1,1-Bis(2-pyrrolyl)ethenes

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 1996

Impact Factor: 4.72 · DOI: 10.1021/jo961582z

5 AUTHORS, INCLUDING:

Mathias O. Senge
Trinity College Dublin
375 PUBLICATIONS **5,920** CITATIONS

SEE PROFILE

Syntheses and Some Chemistry of 1,2- and 1,1-Bis(2-pyrrolyl)ethenes

Hong Xie, David A. Lee, David M. Wallace, Mathias O. Senge,† and Kevin M. Smith*

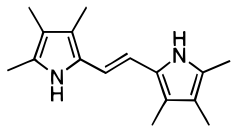
Department of Chemistry, University of California, Davis, California 95616

Received August 14, 1996[⊗]

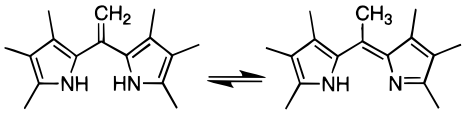
trans-1,2-Bis(2-pyrrolyl)ethenes (e.g. **18**−**20**) are prepared by McMurry-type reductive coupling of the corresponding 2-formylpyrroles. The isomeric 1,1-bis(2-pyrrolyl)ethenes (e.g. **24**) are prepared as a minor byproduct in the reaction of 2-unsubstituted pyrroles (e.g. **22**) with acetic anhydride under Friedel−Crafts conditions; the major product, as expected is the 2-acetylpyrrole **23**. However, 5-(chloromethyl)dipyrromethanes (e.g. **35**) can be obtained in high yield by reaction of 2-unsubstituted pyrroles **22** with chloroacetaldehyde diethyl acetal. Base-catalyzed elimination of HCl from **35** affords the 1,1-bis(2-pyrrolyl)ethene **24** along with the *trans*- and *cis*-1,2-bis(2-pyrrolyl)ethenes **18** and **36**, respectively. Conditions are optimized to afford a 66% yield of the 1,1-bis(2-pyrrolyl)ethene **24**. In neutral organic solvents, 1,1-bis(2-pyrrolyl)ethenes exist in the ethene tautomeric form **2**, rather than as the corresponding 5-methyldipyrromethene isomer **3**; however, under acidic conditions, the 5-methyldipyrromethene salt **38** is observed, and the 5-methyl group undergoes acid-catalyzed exchange in deuterated solvents. 1,1-Bis(2-pyrrolyl)ethenes (e.g. **24**) undergo standard chemistry, such as catalytic hydrogenation (Adams catalyst) of the alkene bond (to give 5-methyldipyrromethane **44**), Vilsmeier formylation [to give 2-formyl-1,1-bis(2-pyrrolyl)-ethene **57**], and reaction with Eschenmoser's salt (*N*,*N*-dimethyl(methylene)ammonium iodide) [to give 2-((*N*,*N*-dimethylamino)methyl)-1,1-bis(2-pyrrolyl)ethene **59**]. Both the 5-methyldipyrromethane-1,9-dicarboxylic acid **45** and the 1,1-bis(5-carboxy-3,4-dimethyl-2-pyrrolyl)ethene **53** react with the 1,9-diformyldipyrromethane **46**, under standard MacDonald conditions, to give 3,5,8-trimethyldeuteroporphyrin IX dimethyl ester **47**.

Introduction

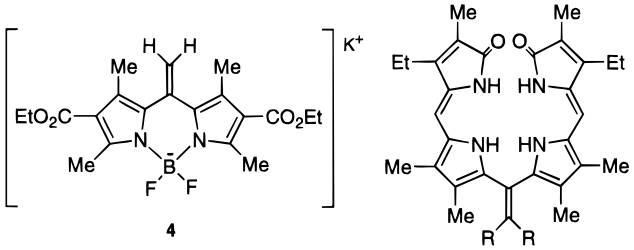
The synthesis, chemistry, and spectroscopy of *trans*-1,2-bis(2-pyrrolyl)ethenes, e.g. **1**, have been described.[1] In contrast, very little has been published[2] on 1,1-bis(2-pyrrolyl)ethenes, e.g. **2**, which are of interest because of the potentially intriguing tautomeric equilibrium with *meso*-5-methyldipyrromethene **3**. One example of a BF_2-stabilized complex **4** was reported by Treibs and Kreuzer[3] in 1968, and two examples of 10-alkylidene-a,c-biladiene-1,19-diones, **5** and **6**, were reported by Falk et al.[4,5] in 1988 and 1989. In 1959, Johnson and co-workers[6] reported the synthesis of 1,2,3,5,7,8,9-heptamethyldipyrromethene **7** and 2,8-bis(2-(methoxycarbonyl)ethyl)-1,3,5,7,9-pentamethyldipyrromethene **8**. They found both compounds to be unstable and they were characterized as zinc(II) complexes by elemental analyses alone. In the present paper we report a new efficient synthesis of 1,2-bis(2-pyrrolyl)ethenes **1** using low-valent titanium condensation methodology, and also describe new syntheses[2] and some chemistry of a number of novel 1,1-bis(2-pyrrolyl)ethenes **2**.



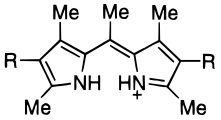
1



2 **3**



4 **5** R = Cl, **6** R = Me



7: R = Me
8: R = $CH_2CH_2CO_2Me$

Results and Discussion

Synthesis of 1,2-Bis(2-pyrrolyl)ethenes via the McMurry Coupling Reaction. Fluorescent 1,2-bis(2-pyrrolyl)ethylenes **9** were first synthesized by Kenner and co-workers[1] in 1965 by the treatment of α-pyridiniummethyl- **10** and α-aminomethyl- **11** pyrroles with 2 N NaOH. Yields were in the range of 10−14%, clearly

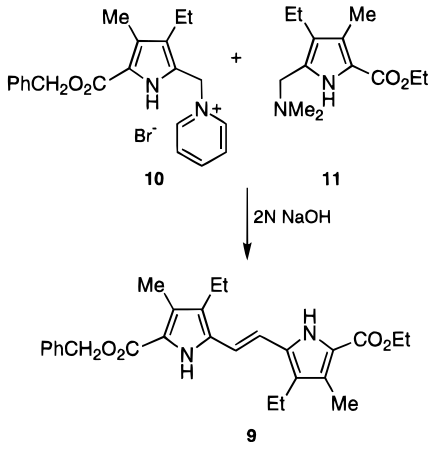
† Present address: Institut für Organische Chemie (WE 02), Fachbereich Chemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany.

⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1996.

(1) Hayes, A.; Jackson, A. H.; Judge, J. M.; Kenner, G. W. *J. Chem. Soc.* **1965**, 4385.
(2) Preliminary communication: Lee, D. A.; Xie, H.; Senge, M. O.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1994**, 791.
(3) Treibs, A.; Kreuzer, F. *Liebigs Ann. Chem.* **1968**, *718*, 208.
(4) Falk, H.; Wöss, H. *Monatsh. Chem.* **1988**, *119*, 1031.
(5) Falk, H.; Müller, N.; Wöss, H. *Monatsh. Chem.* **1989**, *120*, 35.
(6) Johnson, A. W.; Kay, I. T.; Markham, E.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1959**, 3416.

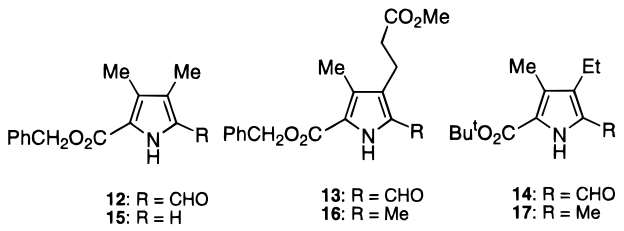
S0022-3263(96)01582-4 CCC: $12.00

leaving much room for improvement. Vogel and coworkers based their syntheses of porphycenes[7] on the McMurry reaction[8] ($TiCl_4$/Zn) of diformylbipyrroles, and



we later adapted a similar McMurry reagent [$TiCl_3$-$(DME)_{1.5}$ in presence of a Zn/Cu couple] for the coupling of 5-formyl- and 5-acroleinyl-porphyrins and -chlorins to give the corresponding pseudo-dimers.[9] We therefore decided to attempt an improvement of the synthesis of 1,2-bis(2-pyrrolyl)ethenes using 2-formylpyrroles and the same McMurry reagent. 1,2-Bis(2-pyrrolyl)ethenes **1** are potentially useful intermediates for the syntheses of expanded porphyrin macrocycles.[10]

For our pyrrole experiments, we chose three different but readily available 2-formylpyrroles, namely **12**−**14**. 2-Formylpyrrole **12** was obtained in high yield by Vilsmeier formylation of the corresponding 2-unsubstituted pyrrole **15**, while pyrroles **13** and **14** were obtained by sulfuryl chloride oxidation of the corresponding, readily available 2-methylpyrroles (**16** and **17**, respectively). For



our first experiment, pyrrole **12** was treated with $TiCl_3$-$(DME)_{1.5}$ and 15 equiv of the Zn−Cu couple in DME. A nonpolar product was characterized by ^{1}H-NMR spectroscopy and high resolution mass spectrometry (HRMS) and found to be the expected alkene **18**, obtained in 81% yield. The unique orientation about the alkene double bond was indicated by overall symmetry in the ^{1}H-NMR spectrum, and a singlet (CH=CH) at 6.60 ppm; the *trans* configuration was confirmed by X-ray crystallography

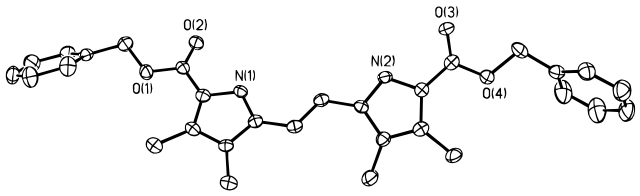
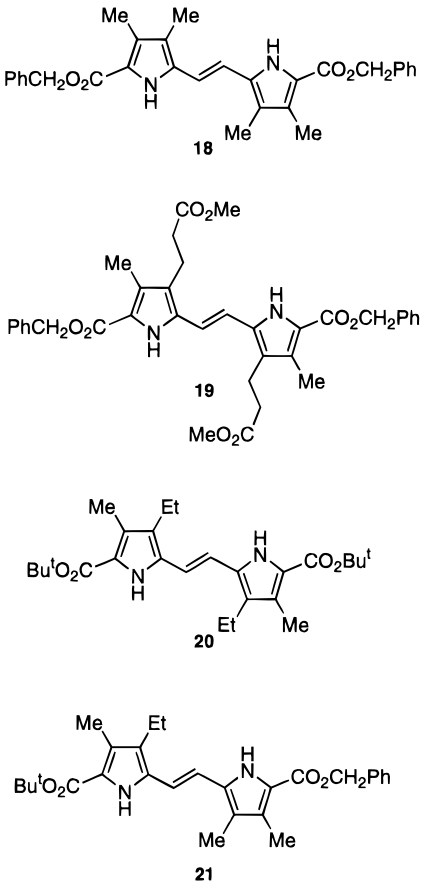


Figure 1. View of the molecular structure of **18** in the crystal. Hydrogen atoms have been omitted for clarity; ellipsoids show 50% occupancy.

(Figure 1).[11] Using the same procedure 1,2-bis(2-pyrrolyl)ethenes **19** (46% yield from 2-formylpyrrole **13**) and **20** (22% yield from **14**) were obtained. The lower yields for the last two compounds are presumably due to lability of the *tert*-butyl and propionic methyl esters in the presence of the titanium reagent. An attempt to cross-couple pyrroles **12** and **14** to form the mixed ethene **21** failed to give any useful product; the alkene **18** was the major product, obtained in 20% yield and once again demonstrating the lability of the *tert*-butyl ester to the McMurry reaction conditions.



Syntheses of 1,1-Bis(2-pyrrolyl)ethenes. 1,1-Bis-(2-pyrrolyl)ethenes were first prepared serendipitously in our laboratory.[2] Treatment of pyrrole **22** with acetic anhydride in the presence of stannic chloride gave the expected 2-acetylpyrrole **23** (87%), along with a minor, less polar product in 6−10% yield. This compound was fully characterized by its ^{1}H and ^{13}C NMR and mass

(7) Vogel, E.; Köcher, M.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 257. Vogel, E.; Balci, M.; Pramod, K.; Koch, P.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 928. Vogel, E.; Grigat, I.; Köcher, M.; Lex, J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1655. Vogel, E.; Köcher, M.; Lex, J.; Ermer, O. *Isr. J. Chem.* **1989**, *29*, 257.

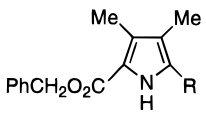
(8) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748.

(9) (a) Smith, K. M.; Vicente, M. G. H. *J. Org. Chem.* **1991**, *56*, 4407. (b) Senge, M. O.; Gerzevske, K. R.; Vicente, M. G. H.; Forsyth, T. P.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 750. (c) Senge, M. O.; Vicente, M. G. H.; Gerzevske, K. R.; Forsyth, T. P.; Smith, K. M. *Inorg. Chem.* **1994**, *33*, 5625.

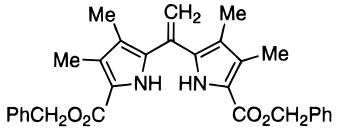
(10) Wallace, D. M. Ph.D. Dissertation, University of California, Davis, **1992**.

(11) The authors have deposited atomic coordinates and a full structure description for compounds **18** and **32** with the Cambridge Crystallographic Data Center. The structures can be obtained, on request, from The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK.

spectra, as well as elemental analysis and X-ray crystallography[2] as 1,1-bis(5-(benzyloxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)ethene **24**. At first, it was thought that the 1,1-bis(pyrrolyl)ethene **24** was formed by nucleophilic



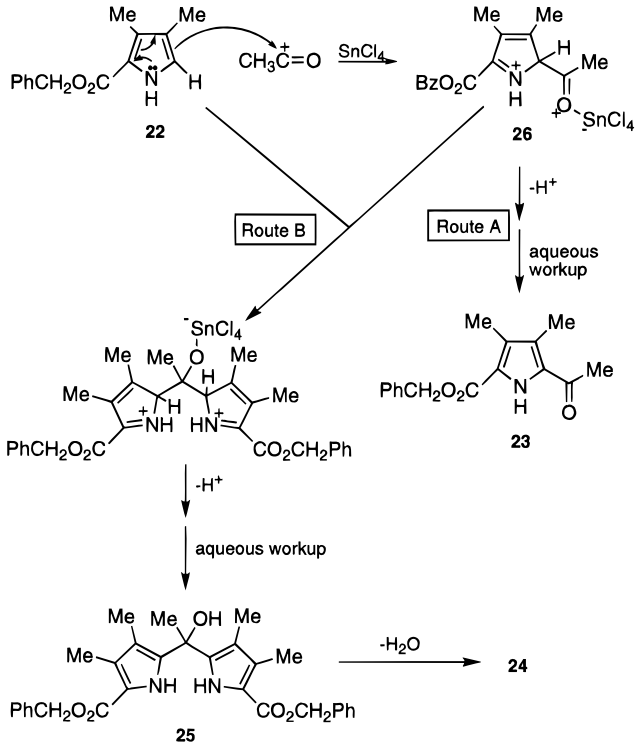
22: R = H
23: R = COMe

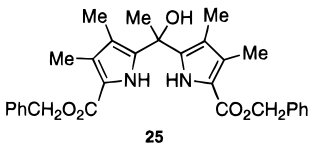


24

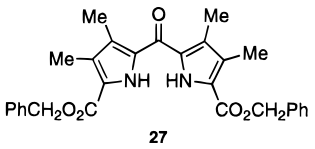
attack of the 2-unsubstituted pyrrole **22** at the carbonyl carbon of the 2-acetylpyrrole **23** followed by dehydration from the intermediate **25**. But when pyrroles **22** and **23** were mixed in the presence of Lewis acids either at 0 °C or at elevated temperatures, no reaction was observed. All attempts to synthesize the bis(pyrrolyl)ethene **24** from 2-H- and 2-acetyl-pyrroles under a variety of conditions failed. These observations suggested that the α-carbonyl group in **23** was not electrophilic enough to react with the 2-unsubstituted pyrrole **22**. Therefore, the formation of **24** might involve an activated intermediate rather than 2-acetylpyrrole **23**. We propose a mechanism for the formation of 2-acetylpyrrole **23** and 1,1-bis(2-pyrrolyl)-ethene **24** as outlined in Scheme 1. An acylium cation is formed by the reaction of acetic anhydride with stannic chloride. Nucleophilic attack of the 2-unsubstituted pyrrole **22** at the acylium ion gives the intermediate **26**, which loses its α-H readily (route A) to give the rearomatized α-acetylpyrrole **23**. The α-carbonyl group in **26** is highly electrophilic because it does experience the deactivating effect from the ring, so it may be attacked by a second molecule of the α-H pyrrole **22** (route B) before it can lose its α-proton. This leads to formation of the intermediate 5-hydroxy-5-methyldipyrromethane **25**. Subsequent dehydration affords the isolated 1,1-bis-(2-pyrrolyl)ethene **24**. Apparently, the rate of the deprotonation (route A) is much greater than that of intermolecular nucleophilic attack (route B), and compound **23** is isolated in greater quantity (80−87%) than is compound **24** (6−10%). When acetyl chloride with 1 equiv of $SnCl_4$ was used instead of acetic anhydride with 2 equiv of $SnCl_4$ for the acylation reaction, no 1,1-bis-(pyrrolyl)ethene was formed. Several attempts to prepare 5-hydroxy-5-methyldipyrromethane **25** were unsuccessful; reduction of dipyrroketone **27** with alkyllithium

Scheme 1. Proposed Mechanism for Formation of 2-Acetylpyrrole 23 and 1,1-Bis(2-pyrrolyl)ethene 24





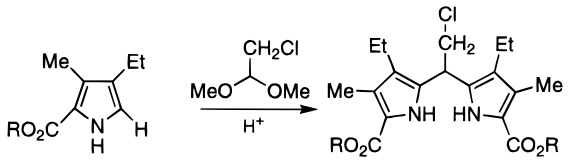
25



27

or alkyl Grignard (MeMgBr) reagents, and attempted condensation of α-metallopyrroles with 2-acetylpyrroles were all unsuccessful.

Using a completely different approach,[12] α-free pyrrole **28** (1 equiv) in toluene was treated with commercially available chloroacetaldehyde diethyl acetal (CADA) (0.6 equiv) and catalytic amounts of TsOH at 100 °C to give the 5-(chloromethyl)dipyrromethane **29** in 91% yield. The ethyl ester variant **30** was likewise prepared in 72% yield



28: R = $PhCH_2$
31: R = Et

29: R = $PhCH_2$
30: R = Et

from pyrrole **31**. 5-(Chloromethyl)dipyrromethanes could also be prepared at room temperature in good to excellent yields (72−91%) by using TFA/K-10 (Montmorillonite) clay as the acid catalyst; the reaction[12] can be performed on a multigram scale, and the products could be directly crystallized from the reaction mixture.

We expected that E2 elimination reactions on 5-(chloromethyl)dipyrromethanes should provide the desired 1,1-bis(2-pyrrolyl)ethenes in improved yields (compared with the Friedel−Crafts route discussed above). 5-(Chloromethyl)dipyrromethane **29** was treated with aqueous NaOH at 50 °C to give two products. ^{1}H-NMR spectroscopy of one product indicated a *trans*-ethylene linkage of *trans*-1,2-di(2-pyrrolyl)ethene **32** (resonance at 6.60 ppm, similar to that observed in compound **18**). The second product featured a resonance at 5.43 ppm, indicative of the desired 1,1-bis(2-pyrrolyl)ethene **33**. In an attempt to minimize formation of **32**, DBU and lower temperature conditions (25 °C) were employed; the 5-(chloromethyl)dipyrromethane **29** was treated with 10 equiv of DBU and gave rise to three products. These were characterized as the *trans*-1,2-bis(2-pyrrolyl)ethene **32**, the 1,1-bis(2-pyrrolyl)ethene **33**, and the *cis*-1,2-bis-(2-pyrrolyl)ethene **34**. X-ray crystallographic analysis of *trans*-1,2-bis(2-pyrrolyl)ethene **32** (Figure 2) further confirmed the structural assignment.[11]

5-(Chloromethyl)dipyrromethane **35** was prepared in 91% yield by condensation of the 2-unsubstituted pyrrole **15** with CADA using the TFA/K-10 clay conditions. A solution of **35** in dichloromethane was then treated with 10 equiv of DBU to again give a mixture of three

(12) Lee, D. A.; Brisson, J. M.; Smith, K. M. *Heterocycles* **1995**, *40*, 131.

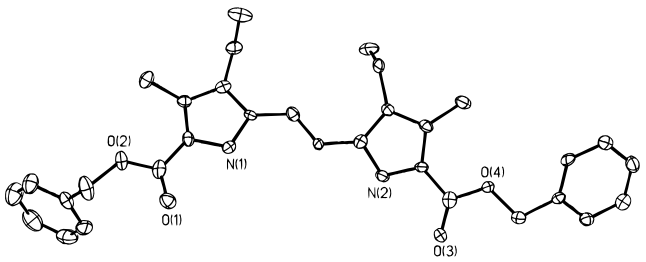
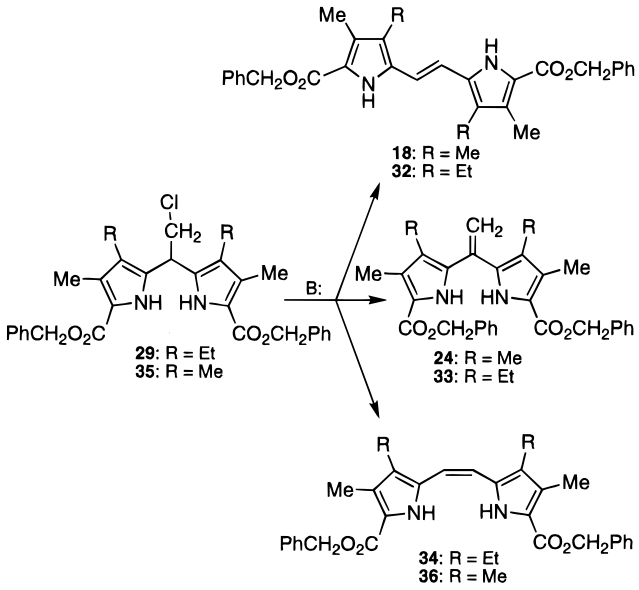


Figure 2. View of the molecular structure of **32** in the crystal. Hydrogen atoms have been omitted for clarity; ellipsoids show 50% occupancy.

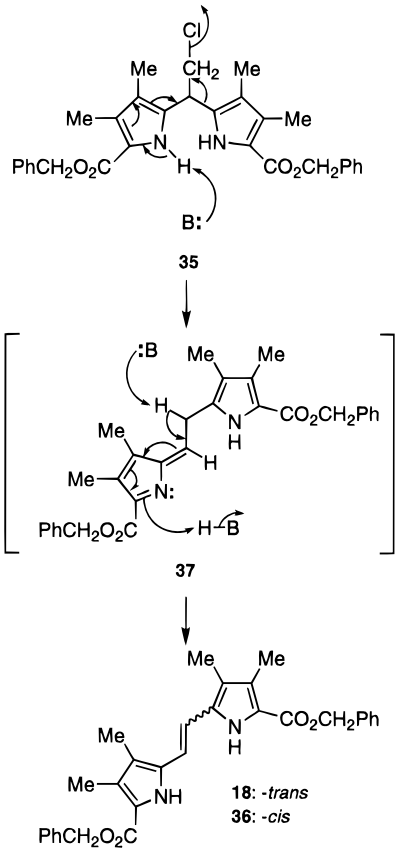
products, in approximately a 2:1:1 ratio; these were structurally assigned as the 1,1-bis(2-pyrrolyl)ethene **24**, the *cis*-1,2-bis(2-pyrrolyl)ethene **36**, and the *trans*-1,2-bis(2-pyrrolyl)ethene **18**. Subsequent purification afforded **24** in 23% yield, a significant (but not yet acceptable) improvement over the earlier Friedel–Crafts approach.



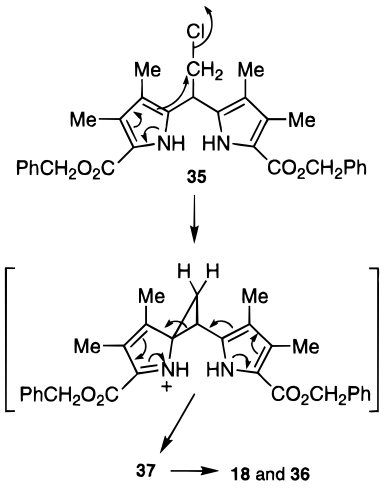
We suspect that the 1,2-bis(pyrrolyl)ethene isomers were formed by some type of base catalyzed migration, as proposed in Scheme 2, involving initial base catalyzed migration followed by base-mediated elimination to afford the 1,2-bis(pyrrolyl)ethenes. There is literature precedent for similar aryl migration reactions, though they are generally catalyzed by strong acids.[13] The *cis* and *trans* isomers are both obtained as a result of the free rotation about the tether of the intermediate **37**. Alternatively, intermediate **37** might be formed via a mechanism (Scheme 3) involving neighboring group participation by the pyrrole nucleus.[14]

On the basis of our mechanistic analyses, we predicted that use of stoichiometric amounts of base, instead of excess, should minimize the formation of the two side products, affording a majority of the 1,1-bis(2-pyrrolyl)-ethene. 5-(Chloromethyl)dipyrromethane **35** was therefore treated initially with 1.3 equiv of DBU to afforded the desired product **24** in 66% yield; the *trans*-1,2-bis-

Scheme 2. Proposed Mechanism for Formation of 1,2-Bis(pyrrolyl)ethene Isomers 18 and 36



Scheme 3. Alternative Mechanistic Proposal for Formation of 1,2-Bis(pyrrolyl)ethene Isomers 18 and 36 Involving Neighboring Group Participation by the Pyrrole Nucleus



(pyrrolyl)ethene **32** was also isolated as a minor product in 9% yield. The *cis*-1,2-bis(pyrrolyl)ethene **36** was also present in small amount but could not be purified. Over a period of time the *cis*-1,2-isomer isomerized to the more thermodynamically stable *trans*-1,2-isomer.

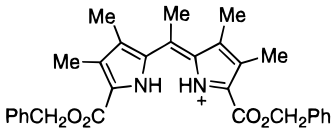
1,1-Bis(2-pyrrolyl)ethene *vs* 5-Methyldipyrromethene Tautomerism. The structure of **24** was confirmed by X-ray crystallography (not shown).[2] This showed the 5-methylidene bond to be 1.333 Å in length, characteristic for a C=C bond. The molecule is not planar, the two pyrrole rings being twisted against each other by 54.9°. We had expected that the fully conjugated, presumably planar tautomer, 5-methyldi-

(13) (a) Becker, K. B. *Synthesis* **1983**, 341 and references therein. (b) Sieber, R. H. *Liebigs Ann. Chem.* **1969**, *730*, 31.

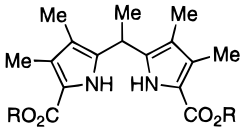
(14) (a) Smith, K. M.; Martynenko, Z.; Pandey, R. K.; Tabba, H. D. *J. Org. Chem.* **1983**, *48*, 4296. (b) We thank a referee for this suggestion.

pyrromethene (e.g. **3**) would be more stable than **2**, based on the fact that 5-unsubstituted dipyrromethenes are quite stable and have been used extensively as intermediates in porphyrin syntheses.[15] However, compound **24** was easily transformed into the 5-methyldipyrromethene salt **38** simply by treatment with an acid; when **24** in dichloromethane was treated with TFA, the solution turned red, as expected for dipyrromethene salts. UV-vis and proton NMR spectra confirmed that the red compound was 5-methyldipyrromethene salt **38**. The 1,1-bis(2-pyrrolyl)ethene **24** has a maximum absorption at 303 nm (ϵ 39 000), while 5-methyldipyrromethene **38** has one at 522 nm (ϵ 79 600); for a figure, see reference 2. The 5-methyl protons in **38** have a chemical shift of 3.05 ppm, and in presence of deuterated TFA the protons resonating at 3.05 ppm were exchanged and concomitantly disappeared from the spectrum. All attempts to crystallize the 5-methyldipyrromethene **38** failed. Upon contact with protic solvents, such as methanol and water, the dipyrromethene reverted to the bis(pyrrolyl)ethene **24** form (UV-vis, ^{1}H-NMR). The 5-methyldipyrromethene could only be observed in aprotic solvents such as CH_2Cl_2 in the presence of excess strong acid, suggesting that 5-substituted dipyrromethene free-bases are not thermodynamically stable, and that their nonplanar 1,1-bis-(2-pyrrolyl)ethene tautomers are the predominant forms under nonacidic conditions. A plausible explanation would be that the periphery of the potentially planar 5-methyldipyrromethenes is heavily laden with substituents so that there is not enough room for all of them without considerable distortion of bond angles or lengths. On the other hand, the steric compressions in these systems are relieved when they adopt the geometry of 1,1-bis(2-pyrrolyl)ethenes in which the two pyrrole rings are tilted against each other.

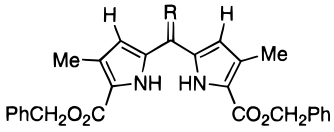
In order to provide more information regarding the equilibrium between 1,1-bis(2-pyrrolyl)ethene **2** and its dipyrromethene tautomer **3**, we synthesized the 3,7-diunsubstituted bis(pyrrolyl)ethene **39**. At the time, our efficient methodology for bis(pyrrolyl)ethene synthesis had not been developed, so we employed the Friedel–Crafts approach by treatment of benzyl 3-methylpyrrole-2-carboxylate **40** with acetic anhydride in the presence of stannic chloride. The 2,3-diunsubstituted pyrrole **40** was prepared following a literature procedure[16] in 39% overall yield from toluene-*p*-sulfonylglycine benzyl ester. Recently, Lash and Hoehner[17] reported an improved synthesis which gave the pyrrole in a 53% overall yield from the same starting materials. When pyrrole **40** was treated with acetic anhydride in the presence of stannic chloride, three compounds were isolated. The two major crystalline products were 3- (**41**, 53%) and 2-acetylpyrroles (**42**, 12%), and the third (minor) product (<1%) was characterized as 1,1-bis(5-(benzyloxycarbonyl)-4-methyl-1*H*-2-pyrrolyl)ethene **39** by its ^{1}H-NMR spectrum and UV-vis spectra. However, like the fully substituted bis(pyrrolyl)ethene **24**, compound **39** turned red in the presence of TFA with a maximum absorption at 522 nm, and the color disappeared when water or methanol was added. Clearly, steric compression is not the only factor involved in the tautomeric equilibria between **2** and **3**, and electronic factors may also play an important role.



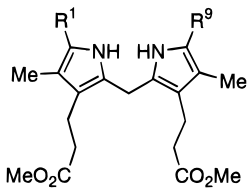
38



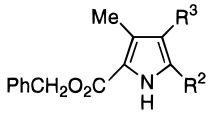
44: R = CH_2Ph
45: R = H



39: R = CH_2
43: R = O



46: $R^1 = R^9$ = CHO
48: $R^1 = R^9 = CO_2CH_2Ph$
49: $R^1 = R^9 = CO_2H$
50: R^1 = CHO; $R^9 = COCF_3$



40: $R^2 = R^3$ = H
41: R^2 = H; R^3 = COMe
42: R^2 = COMe; R^3 = H

Chemistry of 1,1-Dipyrrolylethenes. Oxidation. Although 1,1-bis(5-(benzyloxycarbonyl)-4-methyl-2-pyrrolyl)ethene **39** could be isolated, it was not particularly stable. Attempts to crystallize this oily material yielded crystalline needles which were fully characterized as dipyrroketone **43**, presumably produced by photooxidation of **39**. A characteristic (amide) infrared absorption band at 1600 cm^{-1} was observed for the carbonyl group. In contrast, the fully substituted bis(pyrrolyl)-ethene **24** was much more stable, and its chemistry was therefore investigated.

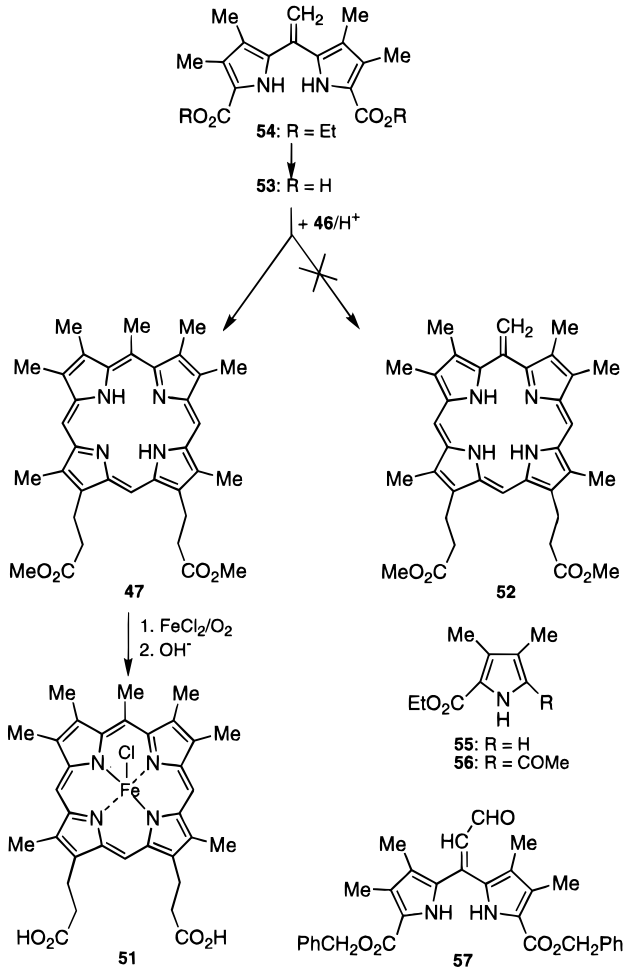
Catalytic Hydrogenation. The external double bond in the 1,1-bis(pyrrolyl)ethene **24** was reduced by catalytic hydrogenation using Adams catalyst, to give dibenzyl 2,3,5,7,8-pentamethyldipyrromethane-1,9-dicarboxylate **44**. Catalytic hydrogenation using palladium on activated carbon gave the corresponding 2,3,5,7,8-pentamethyldipyrromethane-1,9-dicarboxylic acid **45**, which after condensation with 1,9-diformyldipyrromethane **46** in the presence of TsOH afforded the 5-methylporphyrin **47** in 24% yield. The dipyrromethane **46** was prepared from the corresponding 1,9-dibenzyl ester **48**; catalytic hydrogenation gave the 1,9-dicarboxylic acid **49**, and formylation using TFA/trimethyl orthoformate afforded the required 1,9-diformyldipyrromethane **46**, usually along with the 1-formyl-9-(trifluoroacetyl)dipyrromethane **50**. Compound **50** is presumably produced by trifloroacetylation of **49** by the TFA used in the formylation process, and can be avoided by use of the standard $POCl_3$/DMF Vilsmeier approach.[18]

In connection with a separate project involving specificity of heme oxygenase (HO),[19–21] the enzyme which catalyzes the catabolism of heme into biliverdin, the 5-methylporphyrin **47** was transformed into the 5-methylhemin chloride **51** in 81% yield, after treatment of the intermediate Fe(III)-μ-oxo dimer with 2 N HCl. ^{1}H-NMR spectroscopy showed three characteristic singlet β-methyl resonances at 12.12, 11.84, and 11.59 ppm. The

(15) Fischer, H.; Orth, H. *Die Chemie des Pyrrols*; Akademische Verlag.: Leipzig, 1937; Vol. 2, Part 1.
(16) Terry, W. G.; Jackson, A. H.; Kenner, G. W.; Kornis, G. *J. Chem. Soc.* **1965**, 4389.
(17) Lash T. D.; Hoehner, M. C. *J. Heterocycl. Chem.* **1991**, *28*, 1671.
(18) Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229.
(19) Tomaro, M. L.; Frydman, R. B.; Pandey, R. K.; Smith, K. M. *Biochim. Biophys. Acta* **1984**, *791*, 342.
(20) Hernández, G.; Wilks, A.; Paolesse, R.; Smith, K. M.; Ortiz de Montellano, P. R.; La Mar, G. N. *Biochemistry* **1994**, *33*, 6631.
(21) Torpey, J. W.; Ortiz de Montellano, P. R. *J. Org. Chem.* **1995**, *60*, 2195.

resonance for the 5-methyl substituent appeared as a singlet at 46.75 ppm. This extreme deshielding effect is an interesting and unique result. The singlet ^{1}H-NMR resonances for the three meso-protons, two being chemically equivalent, appeared at −11.52 and −18.59 ppm. Novel results using **51** and a recombinant, truncated version of human HO-1[22] will be reported elsewhere.[23]

We were interested to see if a methylidene phlorin **52** would form when 1,1-bis(5-carboxy-3,4-dimethyl-2-pyrrolyl)ethene **53** was condensed with 1,9-diformyldipyrromethane **46** under acid-catalyzed MacDonald conditions.[24,25] The dicarboxylic acid **53** was derived from the corresponding diethyl ester **54** by basic hydrolysis; bis(pyrrolyl)ethene **54** was synthesized from ethyl 3,4-dimethylpyrrole-2-carboxylate **55** in 12% yield (along with the 2-acetylpyrrole byproduct **56**) using the unoptimized Friedel−Crafts approach. Condensation of **53** with 1,9-diformyldipyrromethane **46** in the presence of TsOH gave the 5-methylporphyrin **47** as the only macrocyclic product, indicating that the exocyclic double bond migrated in to the macrocycle after the cyclization occurred.



Vilsmeier Formylation of 1,1-Bis(2-pyrrolyl)-ethenes. The Vilsmeier reaction is used to prepare aldehydes, employing formamides (*N*-methylformanilide, dimethylformamide, etc.) as formylating agents, usually in the presence of $POCl_3$. Although the Vilsmeier reaction was originally designed for aromatic ring formylation, it has been extended to the formylation of olefins.[26] For example, the formylation of styrene and its derivatives was carried out by heating with DMF in the presence of $POCl_3$, producing substituted acroleins.[27] Moreover, vinylporphyrins and chlorins have been shown to formylate preferentially at the terminal carbon of the vinyl group, in preference to the macrocyclic meso-position.[28,29] Like other olefins bearing aryl groups, the vinyl group in 1,1-bis(pyrrolyl)ethene **24** can be easily formylated using the Vilsmeier reagent. Treatment of the bis(pyrrolyl)ethene with $POCl_3$/DMF, followed by basic hydrolysis, afforded 3,3-bis(5-(benzyloxy)carbonyl-3,4-dimethyl-2-pyrrolyl)acrolein **57** in 90% yield. Such compounds may well prove to be valuable as starting materials for the synthesis of novel meso-substituted porphyrins and meso-linked porphyrin dimers.[9,30] Attempts to acylate the vinyl group in **24** using acetic anhydride/$SnCl_4$ failed.

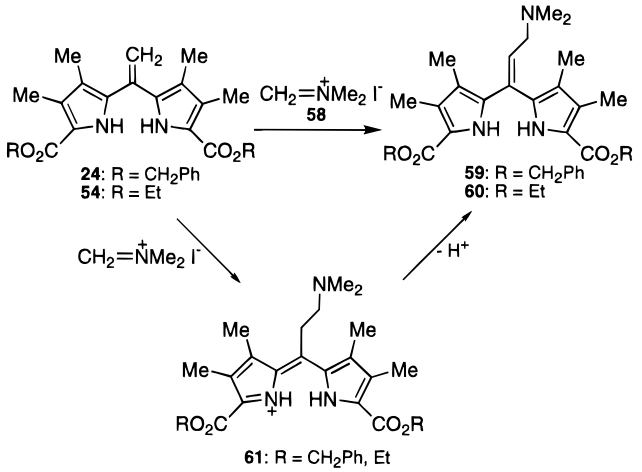
Reaction of 1,1-Dipyrrolylethenes with Eschenmoser's Salt. Eschenmoser's salt,[31,32] dimethyl(methylene)ammonium iodide $CH_2{=}NMe_2{}^+I^-$, **58**, is highly electrophilic, and has found applications in pyrrole[33] and porphyrin/chlorin[34] chemistry. It is commercially available from Aldrich. There is no report on the reaction of Eschenmoser's salt with C=C double bonds in olefins and aromatic systems. When 1,1-bis(pyrrolyl)ethene **24** or **54** was treated with a large excess of Eschenmoser's salt **58** the novel compounds 1,1-bis(5-(benzyloxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)-3-(dimethylamino)propene **59** or 1,1-bis(5-(ethoxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)-3-(dimethylamino)propene **60**, respectively, were isolated in almost quantitative yield. We suspect that these products were formed via the dipyrromethene intermediate **61**. Quaternization of **59** or **60**, followed by reactions with nucleophiles, should provide access to a number of interesting dipyrrole species, and well as potential porphyrin precursors.

Experimental Section

General details are as previously described.[35] Mass spectra were measured at the Mass Spectrometry Facility, University of California, San Francisco.

Crystal Structure Determinations: For techniques and programs used, see reference 9c.

(22) Wilks, A.; Black, S, M.; Miller, W. L.; Ortiz de Montellano, P. R. *Biochemistry* **1995**, *34*, 4421.
(23) Torpey, J. W.; Lee, D. A.; Smith, K. M.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 9172.
(24) Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.
(25) Cavaleiro, J. A. S.; Gonsalves, A. M. d'A. R.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771.
(26) Olah, G. A.; Kuhn, S. J. In *Friedel−Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York; 1964; Vol. 3, part 2, pp 1214−19.
(27) Schmidle, C. J.; Barnett, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 3209.
(28) Nichol, A. W. *J. Chem. Soc. (C)* **1970**, 903.
(29) Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* **1980**, *45*, 2218.
(30) Paolesse, R.; Pandey, R. K.; Forsyth, T. P.; Jaquinod, L.; Gerzevske, K. R.; Nurco, D. J.; Senge, M. O.; Liccocia, S.; Boschi, T.; Smith, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3869.
(31) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.
(32) Bryson, T. A.; Bonitz, G. H.; Reichel, C. J.; Dardis, R. E. *J. Org. Chem.* **1980**, *45*, 524.
(33) Nguyen, L. T.; Senge, M. O.; Smith, K. M. *Tetrahedron Lett.* **1994**, *35*, 7581; *J. Org. Chem.* **1996**, *61*, 998.
(34) Pandey, R. K.; Smith, N. W.; Shiau, F.-Y.; Dougherty, T. J.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1637. Pandey, R. K.; Shiau, F.-Y.; Smith, N. W.; Dougherty T. J.; Smith, K. M. *Tetrahedron* **1992**, *48*, 7591.
(35) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245.



(**18**) $C_{30}H_{30}N_2O_4$, at 130 K, (Mo Kα radiation $\lambda = 0.71069$Å, $2\theta_{max} = 48°$), monoclinic, space group $P2/c$, $a = 19.987(11)$, $b = 10.117(7)$, $c = 13.423(8)$ Å, $\beta = 107.94(4)°$, $V = 2582(2)$ Å^3, $Z = 4$, $R = 0.059$, $wR = 0.076$, $s = 1.06$ for 2457 reflections with $F > 4.0\sigma(F)$ and 325 parameters.

(**32**) $C_{32}H_{34}N_2O_4$, at 130 K, (Mo Kα radiation $\lambda = 0.71069$Å, $2\theta_{max} = 55°$), monoclinic, space group $P2_1/c$, $a = 12.720(8)$, $b = 17.94(3)$, $c = 12.145(8)$ Å, $\beta = 103.27(5)$, $V = 2697(4)$ Å^3, $Z = 4$, $R = 0.087$, $wR = 0.065$, $s = 1.49$ for 2441 reflections with $F > 4.0\sigma(F)$ and 343 parameters.

***trans*-1,2-Bis(5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene (18).** $TiCl_3(DME)_{1.5}$ (5.2 g; 17.9 mmol) and Zn−Cu couple (4.9 g; 69 mmol) were added to a dry nitrogen-filled flask in a dry box. DME (100 mL) was added to the reaction flask, and the resulting mixture was refluxed for 2 h under an atmosphere of N_2 to yield a black suspension. Formylpyrrole **12** (1.12 g; 4.36 mmol) in dry DME (10 mL) was added, and the mixture was refluxed for 8 h. After being cooled to rt, the reaction mixture was filtered through a bed of neutral alumina (CH_2Cl_2 elution). The filtrate was evaporated, yielding 0.853 g (81%) of the title ethene, mp 208−210 °C. λ_{max}: 268 nm (ϵ 14 100) and 389 (27 500); ^{1}H-NMR: δ, ppm, 2.06 (s, 6H), 2.27 (s, 6H), 5.33 (s, 4H), 6.60 (s, 2H), 7.38 (m, 10H), 8.79 (bs, 2H); ^{13}C-NMR: δ, ppm, 9.2, 10.6, 65.8, 114.3, 128.1, 128.6, 161.4. LRMS: m/z (%) 482 (70), 359 (30), 256 (10), 211 (13), 91 (100). HRMS: Calcd for $C_{30}H_{30}N_2O_4$: 482.2205. Found 482.2184. Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.65; H, 6.27; N, 5.81. Found: C, 74.64; H, 6.17; N, 5.71.

***trans*-1,2-Bis(5-(benzyloxycarbonyl)-4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl)ethene (19).** $TiCl_3(DME)_{1.5}$ (4.31 g; 14.9 mmol), Zn-Cu couple (4.0 g; 56.7 mmol), dry DME (100 mL), and formylpyrrole **13**[36] (1.20 g; 3.63 mmol) in dry DME (10 mL) were mixed as described above and then refluxed for 8 h. After workup as above, the title compound was obtained as bright yellow crystals (0.521 g, 45.8%), mp 186−188 °C. ^{1}H-NMR: δ, ppm, 2.29 (s, 6H), 2.46 (t, 4H), 2.85 (t, 4H), 3.62 (s, 6H), 5.34 (s, 4H), 6.68 (s, 2H), 7.38 (m, 10H), 9.00 (bs, 2H). LRMS: m/z (%) 626 (16), 448 (9), 151 (19), 113 (20), 91 (100). HRMS: Calcd for $C_{36}H_{38}N_2O_8$: 626.2628. Found 626.2618. Anal. Calcd for $C_{36}H_{38}N_2O_8$: C, 68.98; H, 6.12; N, 4.47. Found: C, 69.28; H, 6.03; N, 4.29.

1,2-Bis(5-(*tert*-butoxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene (20). $TiCl_3(DME)_{1.5}$ (5.5 g; 19.1 mmol), Zn−Cu couple (5.2 g; 72.8 mmol), dry DME (100 mL), and formylpyrrole **14**[37] (1.04 g; 4.66 mmol) in dry DME (10 mL) were mixed as described above and then refluxed for 8 h. After workup, as above, 0.210 g (21.7%) of the title ethene, mp (unobserved due to slow decomposition). ^{1}H-NMR: δ, ppm, 1.01 (s, 18H), 1.51 (s, 6H), 1.62 (s, 6H), 6.55 (s, 2H), 10.13 (bs, 2H). LRMS: m/z (%) 414 (22), 358 (14), 302 (100), 284 (25), 269 (34). HRMS: Calcd for $C_{24}H_{34}N_2O_4$: 414.2518. Found 414.2497. Anal. Calcd for $C_{24}H_{34}N_2O_4 \cdot {}^1/_2H_2O$: C, 68.08; H, 8.33; N, 6.62. Found: C, 68.57; H, 8.22; N, 6.52.

Benzyl 5-Acetyl-3,4-dimethylpyrrole-2-carboxylate (23) and 1,1-Bis(5-(benzyloxycarbonyl)-3,4-dimethyl-1H-2-pyrrolyl)ethene (24) (Friedel−Crafts Approach). A stirred solution of pyrrole **22** (3.42 g; 14.9 mmol), in dichloromethane (56 mL) and acetic anhydride (2.0 mL; 21.1 mmol) was cooled to 0 °C under nitrogen, and stannic chloride (3.5 mL; 30.0 mmol) was added dropwise over 3 min. The mixture was stirred at 0 °C for 10 min. The cherry red solution was poured into a mixture of ice−water and dichloromethane; the organic layer was separated and washed with cold water. It was then washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation and chromatography on silica gel (elution with 1:3 ethyl acetate/cyclohexane) afforded 3.49 g (12.9 mmol, 87%) of the 5-acetylpyrrole **23** as the major product, mp 101.5−103 °C (lit.[38] mp 103 °C); ^{1}H-NMR: δ, ppm, 2.28 (s, 6H), 2.49 (s, 3H), 5.32 (s, 2H, 7.4 (m, 5H), 9.5 (bs, 1H); LRMS: m/z (%) 271 (20), 91 (100). 1,1-Bis-(2-pyrrolyl)ethene **24** was isolated in 6−10% yield, mp 135−136 °C; λ_{max}: 251 nm (ϵ 17 000), 303 (39 000); ^{1}H-NMR: δ, ppm, 1.98, 2.27 (each s, 6H), 5.19 (s, 4H), 5.46 (s, 2H), 7.3−7.4 (m, 10H), 9.34 (bs, 2H). ^{13}C-NMR: δ, ppm, 10.6, 10.9, 65.6, 116.0, 118.2, 119.6, 127.5, 127.8, 128.2, 128.6, 130.7, 132.5, 136.2, 161.6. LRMS: m/z (%) 482.2 (100). Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.52; H, 6.30; N, 5.87. HRMS: Calcd for $C_{30}H_{30}N_2O_4$: 482.2205; Found 482.2201. Dipyrrolylethene **24** was converted into the 5-methyldipyrromethene **38** when treated with excess TFA, resulting in a red solution; λ_{max}: 522 nm (ϵ 79 600); ^{1}H-NMR: δ, ppm, ($CDCl_3$ + TFA) 2.23, 2.34 (each s, 6H), 3.05 (s, 3H), 5.50 (s, 4H), 7.43 (s, 10H), 10.87 (bs, 2H). When deuterated TFA was used, **38** was formed but the 5-methyl peak at 3.05 ppm was either partially or completely absent.

1,1-Bis(5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)-ethene (24) (Elimination Approach). To a solution of dipyrromethane **35** (1.004 g, 1.934 mmol) in freshly distilled dichloromethane (240 mL), under argon, was added DBU (0.350 mL, 2.321 mmol, 1.2 equiv). The reaction mixture was stirred at rt in the dark for 7 h, after which time additional DBU (0.040 mL, 0.268 mmol) was added. After 25 h all the starting material was consumed (TLC analysis). The solvent was evaporated to afford a yellow oil that was purified by silica gel flash chromatography (elution with 1% methanol/dichloromethane), to afford the title ethene **24** (611 mg, 66%) as a crystalline yellow solid, mp 133−135 °C, identical in all respects with the material obtained using the Friedel−Crafts approach. A minor product *trans*-1,2-bis(5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene **18** (88 mg, 9%) was isolated as yellow crystals (mp 210−212 °C; identical in all respects with the material described above, synthesized using the McMurry approach.). A very minor product *cis*-1,2-bis(5-(benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene **36** was not quantified, [^{1}H-NMR: δ, ppm, 1.90 (s, 6H), 2.25 (s, 6H), 5.26 (s, 4H), 6.30 (s, 2H), 7.30−7.43 (m, 10H), 8.78 (bs, 2H). HRMS: Calcd for $C_{30}H_{30}N_2O_4$: 482.2205. Found 482.2224].

Dibenzyl 5-(Chloromethyl)-3,7-diethyl-2,8-dimethyl-dipyrromethane-1,9-dicarboxylate (29). To a rt solution of pyrrole **28** (1.035 g, 4.256 mmol) and TsOH (0.201 g, 1.057 mmol) in freshly distilled toluene (25.0 mL), under argon, was added 2-chloroacetaldehyde diethyl acetal (0.395 mL, 2.639 mmol). The reaction mixture was heated at 100 °C for 40 min, after which time water and dichloromethane were added. The organic layer was separated, the aqueous layer was extracted with dichloromethane, and the combined organic layer was washed with brine and then dried over anhydrous sodium sulfate. Evaporation gave a deep brown oil which was purified by silica gel flash column chromatography (elution with 1% methanol/dichloromethane) to give the title product (1.06 g, 91%) as a light brown foam, which was recrystallized from dichloromethane/*n*-hexane to give a tan powder, mp 178−180 °C. ^{1}H-NMR: δ, ppm, 1.03 (t, $J = 7.5$ Hz, 6H), 2.26 (s, 6H), 2.43 (q, $J = 7.5$ Hz, 4H), 4.01 (d, $J = 7.5$ Hz, 2H), 4.59 (t, $J =$

(36) Clezy, P. S.; Liepa, A. J.; Nichol, A. W.; Smythe, G. A. *Aust. J. Chem.* **1970**, *23*, 589.

(37) Paine, J. B., III; Woodward, R. B.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 2826.

(38) Smith, K. M.; Miura, M.; Tabba, H. D. *J. Org. Chem.* **1983**, *48*, 4779.

7.5 Hz, 1H), 5.22 (s, 4H), 7.20−7.35 (m, 10H), 9.61 (bs, 2H). HRMS: Calcd for $C_{32}H_{35}ClN_2O_4$: 546.2285. Found 546.2307. Anal. Calcd for $C_{32}H_{35}ClN_2O_4$: C, 70.30; H, 6.46; N, 5.13. Found: C, 70.12; H, 6.42; N, 4.96.

Diethyl 5-(Chloromethyl)-3,7-diethyl-2,8-dimethyldipyrromethane-1,9-dicarboxylate (30). Pyrrole **31** (1.397 g, 7.708 mmol), TsOH (0.367 g, 1.927 mmol), toluene (30.0 mL), and 2-chloroacetaldehyde diethylacetal (0.715 mL, 4.779 mmol) were mixed as above and heated at 100 °C for 75 min, after which time water and dichloromethane were added. After workup as above, the solid was purified by successive silica gel flash columns, the first column being eluted with 1% methanol/dichloromethane, and the second with 0.5% methanol/dichloromethane, to give the title compound (1.18 g, 72%) as a tan/brown foam. Recrystallization from dichloromethane/*n*-hexane gave colorless prisms, mp 151−152 °C. ^{1}H-NMR: δ, ppm, 1.02 (t, J = 7.5 Hz, 6H), 1.27 (t, J = 7.5 Hz, 6H), 2.27 (s, 6H), 2.42 (q, J = 7.5 Hz, 4H), 4.06 (d, J = 7.2 Hz, 2H), 4.24 (q, J = 7.5 Hz, 4H), 4.59 (t, J = 7.2 Hz, 1H), 9.39 (bs, 2H). HRMS: Calcd for $C_{22}H_{31}ClN_2O_4$: 422.1972. Found 422.1977. Anal. Calcd for $C_{22}H_{31}ClN_2O_4$: C, 62.53; H, 7.40; N, 6.63. Found: C, 62.34; H, 7.37; N, 6.52.

1,1-Bis(5-(benzyloxycarbonyl)-3-ethyl-4-methyl-2-pyrrolyl)ethene (33). To a solution of 5-(chloromethyl)-dipyrromethane **29** (503 mg, 0.919 mmol) in freshly distilled dichloromethane (35 mL), under argon, was added DBU (0.185 mL, 1.241 mmol, 1.35 equiv). The reaction mixture was stirred at rt in the dark for 22 h, after which time additional DBU (0.040 mL, 0.268 mmol, 0.29 equiv) was added. After 24 h (46 h total) all the starting material was consumed (TLC analysis), so the mixture was purified using a silica gel plug column (elution with 1% methanol/dichloromethane) to afford a mixture of products (**33**, **32**, **34**) (412 mg, 88%) as a yellow foam, which was recrystallized from dichloromethane/*n*-hexane to give a crystalline yellow powder. Yield data is approximated, based on the ^{1}H-NMR spectrum of the chromatographed product mixture [approximately 2.5 parts **33** (187 mg, 40%) to 2 parts **32** (87 mg, 19%) to 1 part **34** (137 mg, 29%)]. [Title compound, **33**: ^{1}H-NMR: δ, ppm, 0.99 (s, 6H), 2.30 (q, J = 7.5 Hz, 4H), 2.31 (s, 6H), 5.26 (s, 4H), 5.43 (s, 2H), 7.35−7.45 (m, 10H), 9.10 (bs, 2H). HRMS: Calcd for $C_{32}H_{34}N_2O_4$: 510.2518. Found 510.2512. *trans*-1,2-Bis(5-(benzyloxycarbonyl)-3-ethyl-4-methyl-2-pyrrolyl)ethene (**32**): ^{1}H-NMR: δ, ppm, 1.10 (t, J = 7.5 Hz, 6H), 2.30 (s, 6H), 2.52 (q, J = 7.5 Hz, 4H), 5.35 (s, 4H), 6.60 (s, 2H), 7.35−7.45 (m, 10H), 8.84 (bs, 2H). HRMS: Calcd for $C_{32}H_{34}N_2O_4$: 510.2518. Found 510.2502. *cis*-1,2-Bis(5-(benzyloxycarbonyl)-3-ethyl-4-methyl-2-pyrrolyl)ethene (**34**): ^{1}H-NMR: δ, ppm, 1.06 (t, J = 7.5 Hz, 6H), 2.28 (s, 6H), 2.44 (q, J = 7.5 Hz, 4H), 5.20(s, 4H), 6.31 (s, 2H), 7.32 (s, 10H), 8.75 (bs, 2H). HRMS: Calcd for $C_{32}H_{34}N_2O_4$: 510.2518; Found 510.2517].

Dibenzyl 5-(Chloromethyl)-2,3,7,8-tetramethyldipyrromethane-1,9-dicarboxylate (35). To a rt solution of pyrrole **22** (2.075 g, 9.050 mmol) and a suspension of Montmorillonite K-10 clay (15.0 g) in dichloromethane (150 mL), under argon, were added 2-chloroacetaldehyde diethyl acetal (0.865 mL, 5.792 mmol), and then TFA (5.35 mL, 69.685 mmol, 15.4 equiv). This solution was stirred at rt for 90 min, after which time the solids were filtered off and rinsed several times with dichloromethane. The combined organic layer was poured into saturated aqueous sodium bicarbonate and shaken carefully until effervescence ceased. The aqueous layer was extracted with dichloromethane, and the combined organic layer was washed with brine and then dried over anhydrous sodium sulfate. Evaporation gave a crude product which was crystallized from dichloromethane/*n*-hexane to give the title dipyrromethane (1.69 g, 72%) as a crystalline tan solid. The mother liquor from the crystallization, after silica gel flash column chromatography (elution with 1% methanol/dichloromethane), afforded another 0.435 g (18.5%), to give an overall yield of 91% (2.13 g), mp 158−162 °C. ^{1}H-NMR: δ, ppm, 1.94 (s, 6H), 2.24 (s, 6H), 4.01 (d, J = 6.9 Hz, 2H), 4.58 (t, J = 6.9 Hz, 1H), 5.25 (s, 4H), 7.25−7.40 (m, 10H), 9.25 (bs, 2H). HRMS: Calcd for $C_{30}H_{31}ClN_2O_4$: 518.1972. Found 518.1967. Anal. Calcd for $C_{30}H_{31}ClN_2O_4$: C, 69.47; H, 6.03; N, 5.40. Found: C, 69.40; H, 6.13; N, 5.40.

Benzyl 4-Acetyl-3-methylpyrrole-2-carboxylate (41), Benzyl 5-Acetyl-3-methylpyrrole-2-carboxylate (42), and 1,1-Bis(5-(benzyloxycarbonyl)-4-methyl-2-pyrrolyl)-ethene (39). Stannic chloride (10 mL, 85.6 mmol) was added over 5−6 min to a well stirred mixture of pyrrole **40**[16] (11.63 g, 54.0 mmol), dichloromethane (100 mL), and acetic anhydride (5.6 mL, 59.2 mmol) at 0 °C, under N_2. The resulting brick red suspension was kept at 0 °C for 6 min before being poured into ice−water/dichloromethane. The organic layer was separated, washed with water several times, with aqueous sodium bicarbonate twice, and then once with brine. The yellow solution was dried with anhydrous sodium sulfate and evaporated, and the orange-yellow oily residue was crystallized from 25% ethyl acetate/cyclohexane to give benzyl 4-acetyl-3-methylpyrrole-2-carboxylate **41** as the major product in 53% yield, mp 110−113 °C, ^{1}H-NMR: δ, ppm, 2.39, 2.63 (each s, Me), 5.33 (s, 2H), 7.3 (m, 5H), 7.40 (s, 1H), 9.8 (bs, 1H). A second crystallization of the mother liquor from 25% ethyl acetate/cyclohexane gave benzyl 5-acetyl-3-methylpyrrole-2-carboxylate **42** in ca. 12% yield, mp 86−88 °C; ^{1}H-NMR: δ, ppm, 2.35, 2.42 (each s, 3H), 5.32 (s, 2H), 6.65 (d, 1H), 7.4 (m, 5H), 9.6 (bs, 1H). Chromatography of the final mother liquor on silica gel (elution with 25% ethyl acetate/cyclohexane) gave the desired 1,1-bis(pyrrolyl)ethene **39** as an oil (<1%). λ_{max}: 298 nm; λ_{max}: (CH_2Cl_2 + TFA) 522 nm; ^{1}H-NMR: δ, ppm, 2.29 (s, 6H), 5.12 (s, 4H), 5.47 (s, 2H), 6.32 (s, 2H), 7.3−7.4 (m, 10H), 10.64 (bs, 2H).

Dibenzyl 2,8-Dimethyldipyrroketone-1,9-dicarboxylate (43). Attempts to crystallize the foregoing oily 1,1-bis-(2-pyrrolyl)ethene from ethyl acetate/cyclohexane yielded the title dipyrroketone as needles, mp 203−205 °C; ^{1}H-NMR: δ, ppm, 2.39 (s, 6H), 5.35 (s, 4H), 6.88 (d, 2H), 7.3−7.5 (m, 10H), 9.81 (bs, 2H). HRMS: Calcd for $C_{27}H_{24}N_2O_5$: 456.16852. Found 456.16789. Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found C, 70.99; H, 5.33; N, 6.17.

Dibenzyl 2,3,5,7,8-Pentamethyldipyrromethane-1,9-dicarboxylate (44). 1,1-Dipyrrolylethene **24** (1.13 g, 2.34 mmol) in THF (2l mL) was hydrogenated over Adams catalyst (39 mg; 7 mol%) using a hydrogen balloon at rt. The reaction was monitored by ^{1}H-NMR spectroscopy. After 17 h, the reaction was only about 30% completed, so more Adams catalyst (ca. 12 mg) was added. When the total reaction time reached 5 days, ^{1}H-NMR spectra indicated negligible starting material to be present, so the catalyst was filtered off and the solvent was evaporated under reduced pressure. The brownish residue was chromatographed on silica gel (elution with 1:3 ethyl acetate/cyclohexane) to remove debenzylated product and base line material. Recrystallization of the residue from ethyl acetate/cyclohexane afforded 0.82 g (1.69 mmol, 72%) of the title product as a white solid, mp 159.5−161.5 °C; ^{1}H-NMR: δ, ppm, 1.56 (d, 3H), 1.86 (s, 6H), 2.24 (s, 6H), 4.27 (q, 1H), 5.28 (s, 4H), 7.3 (m, 10H), 8.69 (bs, 2H); LRMS: m/z (%) 484.2 (66), 91.0 (100). Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78. Found: C, 74.31; H, 6.56; N, 5.71.

1,9-Diformyl-3,7-bis(2-(methoxycarbonyl)ethyl)-2,8-dimethyldipyrromethane (46) and 3,7-Bis(2-(methoxycarbonyl)ethyl)-2,8-dimethyl-1-formyl-9-(trifluoroacetyl)-dipyrromethane (50). Dipyrromethane **48**[18] (1.0 g; 1.63 mmol), in THF (56 mL), triethylamine (0.1 mL), and absolute ethanol (20 mL) was hydrogenated over 10% Pd−C (100 mg) at rt overnight, before being filtered through Celite to remove the catalyst. The solvent was evaporated to give the dicarboxylic acid **49** as a yellow solid, which was dissolved in TFA (46 mL) under N_2 and stirred for 45 min. The mixture was cooled to −5 °C (ice water/NaCl) while separately and simultaneously triethyl orthoformate (28 mL) was also cooled. The triethyl orthoformate was added to the cold mixture and stirred for 8 min before removing the ice/NaCl bath and stirring for another 2 min. The mixture was poured into aqueous sodium bicarbonate/CH_2Cl_2 mixture, and the organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give a dark orange oil. The oil was chromatographed on a silica gel flash column [elution with cyclohexane/ethyl acetate (70/30)]. The appropriate fractions were combined and the solvent was evaporated to give the title dipyrromethane as a white solid (311.7 mg, 48%), mp 179−

181 °C (lit.[18] 180−181 °C). ^{1}H-NMR: δ, ppm, 2.28 (s, 6H), 2.50 (t, 4H), 2.78 (t, 4H), 3.68 (s, 6H), 4.04 (s, 2H), 9.42 (s, 2H), 10.46 (bs 2H). The 9-(trifluoroacetyl)dipyrromethane **50** was also isolated from the column as a light tan solid (27%), mp 136−138 °C. ^{1}H-NMR: δ, ppm, 2.30 (s, 3H), 2.32 (s, 3H), 2.56 (m, 4H), 2.80 (m, 4H), 3.69 (s, 3H), 3.70 (s, 3H), 4.11 (s, 2H), 9.48 (s, 1H), 10.21 (bs, 1H), 10.34 (bs, 1H). ^{13}C-NMR: δ, ppm, 8.9, 11.2, 18.9, 19.0, 22.7, 34.0, 34.2, 51.8, 117.0 (C_aF_3 [J_{19F-a} = 285.26 Hz]), 121.5, 128.9, 133.0, 133.2 (5α-C_c [J_{19F-c} = 6.29 Hz]), 135.7, 136.6, 168.3 (-C_bOCF_3 [J_{19F-b} = 35.73 Hz]), 173.4, 173.5, 177.0. LRMS: *m*/*z* (%) 470 (100), 441 (33), 395 (42), 321 (28), 113 (50). HRMS: Calcd for $C_{22}H_{25}F_3N_2O_6$: 470.1665. Found 470.1679. Anal. Calcd for $C_{22}H_{25}F_3N_2O_6$: C, 56.17; H, 5.36; N, 5.95. Found: C, 55.55; H, 5.24; N, 5.90.

13,17-Bis(2-(methoxycarbonyl)ethyl)-2,3,5,7,8,12,18-heptamethylporphyrin (47). Method A: A mixture of 1,1-bis(pyrrolyl)ethene **24** (224.5 mg, 0.465 mmol), THF (5.8 mL), and 10% Pd−C (44 mg, 9 mol %) was stirred under hydrogen (under a balloon) at rt for 3.5 h. The catalyst was filtered off and washed with MeOH/THF (1:1). The filtrate was evaporated under vacuum at 40−50 °C to give 2,3,5,7,8-pentamethyldipyrromethane-1,9-dicarboxylic acid **45**, which was immediately treated with TFA (2 mL) and stirred at rt under nitrogen for 30 min. A solution of 1,9-diformyldipyrromethane **46** (183.5 mg, 0.456 mmol) in dry dichloromethane (30 mL) was added and rinsed with more dichloromethane (15 mL). The red reaction mixture was stirred at rt under oxygen (via a balloon) for 42 h. It was then poured into dichloromethane/water. The organic layer was separated and washed successively with water, saturated sodium bicarbonate solution, and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography (neutral alumina, Brockmann Grade III; elution with 1% MeOH/dichloromethane) to provide the 5-substituted porphyrin **47** as the fastest-running band. Crystallization from CH_2Cl_2/hexane afforded 74 mg (0.127 mmol, 28%) of the title porphyrin, mp > 300 °C; λ_{max}: 404 nm (ϵ 174 000), 504 (14 000), 538 (5800), 576 (5800), 628 (1900); ^{1}H-NMR: δ, ppm, −3.14 (bs, 2H), 3.27 (t, 4H), 3.46, 3.53 (each s, 6H), 3.60, 3.68 (each s, 6H), 4.35 (s and overlapping t, 7H), 9.82 (s, 1H), 9.98 (s, 2H). LRMS: *m*/*z* (%) 580.3 (100). HRMS: Calcd for $C_{35}H_{40}N_4O_4$: 580.3049. Found 580.3037. Anal. Calcd for $C_{35}H_{40}N_4O_4$: C, 72.39; H, 6.94; N, 9.65. Found: C, 72.28; H, 6.89; N, 9.28.

Method B: A mixture of 1,9-dicarboxylic acid **53** (made from 231 mg, 0.644 mmol, of the corresponding diethyl ester) and 1,9-diformyldipyrromethane **46** (284 mg, 0.706 mmol) was stirred in the presence of TsOH (436 mg, 2.29 mmol) for 20 h at rt under nitrogen. The reaction was monitored by spectrophotometry. An absorption around λ_{max} 618 nm was observed shortly after the reaction was initiated and its intensity decreased with time. After being exposed to air, a Soret absorption around λ_{max} 404 nm was observed and its intensity increased with time. The final reaction mixture was washed with aqueous sodium bicarbonate and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated and the residue was chromatographed (neutral alumina, Brockmann Grade III; elution with 1% MeOH in dichloromethane) to give the 5-methylporphyrin **47** as the major product in low yield. ^{1}H-NMR and analytical TLC indicated that this product was identical to that obtained by the method A.

13,17-Bis(2-carboxyethyl)-2,3,5,7,8,12,18-heptamethylhemin Chloride (51). A solution of porphyrin **47** (33 mg, 0.057 mmol) in chloroform (20 mL) was degassed with a nitrogen purge for 30 min. Iron(II) chloride (525 mg, 2.709 mmol) was added to degassed methanol (10 mL), which was degassed an additional 30 min, after which time the solution of **47** in chloroform was added. The mixture was heated at 50 °C for 80 min in the dark under argon and then poured into water; dichloromethane was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane, and the combined organic layer was washed with water and with brine and then dried over anhydrous sodium sulfate. The solvent was evaporated to afford a deep brown solid [Fe(III) μ-oxo-dimer] which was used for the next step without further purification [λ_{max} (rel absorbance) 394 nm (17.43), 501 (2.10), 533 (1.67), 638 (1.00).] To a solution of the above product in THF (28 mL) and methanol (15 mL), under argon, was added 1 N potassium hydroxide (6 mL). The mixture was stirred vigorously at rt in the dark for 24 h. The reaction mixture was poured into water, chloroform was added, and the aqueous layer was separated. The aqueous layer was acidified with 2 N HCl (2−3 mL) to pH 3, and the resulting flocculant precipitate was extracted with 30% THF in diethyl ether. The solvent was evaporated to afford the crude product which was recrystallized from THF/*n*-hexane to afford the desired product 3,7-bis(2-carboxyethyl)-2,3,5,7,8,12,18-heptamethylhemin chloride **51** (30 mg, 81%) as a brown precipitate. The purity of the hemin chloride dicarboxylic acid was confirmed by low-spin ^{1}H-NMR spectroscopy. [^{1}H-NMR: δ, ppm, (D_2O) 46.75 (bs, 3H), 12.12 (s, 6H), 11.84 (s, 6H), 11.59 (s, 6H), 6.87 (s, 4H), 4.02 (s, 4H) −11.52 (s, 1H), −18.59 (s, 2H)]. This material has been used[23] in studies of biliverdin formation by a recombinant, truncated human HO-1.[21]

1,1-Bis(5-(ethoxycarbonyl)-3,4-dimethyl-2-pyrrolyl)-ethene (54). Stannic chloride (10 mL, 85.6 mol) was added over 10 min to a well-stirred mixture of pyrrole **55** (9.97 g, 59.6 mmol), dichloromethane (120 mL), and acetic anhydride (4.0 mL, 42.3 mmol) at 0 °C under nitrogen. After the addition was complete, the dark red solution was stirred at 0 °C under nitrogen for an additional 5 min. An additional 1.6 mL of acetic anhydride (total amount: 59.2 mmol) was added dropwise. The mixture was stirred for a further 10 min before it was poured in ice water. The organic layer was separated, washed with cold water, aqueous sodium bicarbonate, and brine, and then dried over anhydrous sodium sulfate. Evaporation and chromatography on silica gel (elution with 25% ethyl acetate/cyclohexane) gave 1.28 g (12%) of the title 1,1-bis(pyrrolyl)ethene **54** from the minor, fast running band, mp 154−156 °C; ^{1}H-NMR: δ, ppm, 1.28 (t, 6H), 2.06, 2.26 (each s, 6H), 4.06 (q, 4H), 5.44 (s, 2H), 9.99 (bs, 2H). HRMS: Calcd for $C_{20}H_{26}N_2O_4$; 358.1893. Found 358.1888. Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.00; H, 7.32; N, 7.82. Found C, 67.03; H, 7.37; N, 7.83. Ethyl 5-acetyl-3,4-dimethylpyrrole-2-carboxylate **56** was isolated as the major product (slow running band), but the yield was not determined, mp 102−104 °C, (lit.[39] mp 106 °C and 106−108 °C); ^{1}H-NMR: δ, ppm, 1.30 (t, 3H), 2.21, 2.22, 2.42 (each s, 3H), 4.26 (q, 2H), 9.5 (s, 1H).

2,3,7,8-Tetramethyl-5-methylenedipyrromethane-1,9-dicarboxylic Acid (53). A solution of KOH (0.879 g; 15.7 mmol, 4 equiv) in 95% ethanol (16 mL) was added to a mixture of **54** (0.728 g; 2.03 mmol) in 95% ethanol (30 mL). The suspension turned into a solution upon heating. The resulting orange-red solution was refluxed for 4 h. Most of the solvent was removed at reduced pressure. The solid residue was dissolved in enough water to give a yellow-brown solution which, after extraction with dichloromethane, was acidified to pH 2 with 1 N HCl. An olive green precipitate was collected, washed with water several times, and dried in vacuum oven at 70 °C overnight, to afford 0.460 g (1.52 mmol; 75%) of the title product, mp >180 °C dec; ^{1}H-NMR: δ, ppm, ($CDCl_3$ + DMSO-d_6) 1.56, 1.98 (each s, 6H), 5.15 (s, 2H), 9.12 (bs, 2H).

3,3-Bis(5-(benzyloxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)acrolein (57). Vilsmeier reagent was prepared by mixing dry DMF (0.46 mL; 5.94 mmol) and $POCl_3$ (0.35 mL; 3.75 mmol) at 0 °C under nitrogen. The mixture was kept at 0 °C for 5 min before addition of **34** (573.7 mg; 1.19 mmol) in dry carbon tetrachloride (26 mL) over 10 min. The mixture was warmed to 50 °C and maintained at this temperature for 3 h before being cooled slightly and addition of saturated sodium acetate solution (40 mL). The two-phase mixture was stirred at rt for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane, which was washed successively with sodium bicarbonate solution, water, and then brine. It was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was chromatographed on silica gel (elution with 25% ethyl acetate/cyclohexane). The desired product was collected

(39) Fisher, H.; Höfelmann, H. *Liebigs Ann. Chem.* **1938**, *533*, 216. Moon, M. W.; Wade, R. A. *J. Org. Chem.* **1984**, *49*, 2663.

and crystallized from dichloromethane/hexane to give 547 mg (1.07 mmol, 90%) of the title compound as a yellow solid, mp 178.5−180.5 °C; ^{1}H-NMR: δ, ppm, 2.08, 2.18, 2.27, 2.30 (each s, 3H), 5.07, 5.09 (each s, 2H), 6.35 (d, 1H), 7.33 (bd, 10H), 9.44 (d, 1H), 10.18, 10.70 (each bs, 1H,); ^{13}C-NMR: δ, ppm, 10.8, 10.9, 11.8, 66.3, 121.7, 121.9, 124.4, 125.6, 126.0, 127.2, 127.6, 128.0, 128.2, 128.5, 131.2, 135.3, 135.3, 139.9, 161.4, 161.9, 192.6. LRMS: *m*/*z* (%) 511.1 (100, MH^+), 91.0 (71). Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49. Found: C, 72.81; H, 5.83; N, 5.37.

1,1-Bis(5-(benzyloxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)-3-dimethylaminopropene (59). A mixture of 1,1-bis-(pyrrolyl)ethene **24** (215 mg; 0.446 mmol) and Eschhenmoser's salt **58** (670 mg; 3.62 mmol, 8 equiv) in dry dichloromethane (50 mL) was stirred at rt for 20 h. The yellow suspension was diluted with dichloromethane, washed with water and then with brine, and then dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed (neutral alumina, Brockmann Grade III; elution with 0−2% MeOH/dichloromethane) to afford 215 mg (0.398 mmol, 90%) of the title product as pale flaky solid, mp 57−59 °C; ^{1}H-NMR: δ, ppm, 1.51, 1.94, 2.32, 2.34 (each s, 3H), 2.19 (s, 6H), 2.86 (d, 2H), 5.31, 5.33 (each s, 2H), 5.87 (t, 1H), 7.4 (m, 10H), 8.77, 12.80 (each bs, 1H); ^{13}C-NMR: δ, ppm, 9.0, 9.5, 10.31, 10.6, 44.0, 56.2, 65.4, 65.5, 117.6, 118.9, 119.1, 120.5, 126.1, 127.9, 128.2, 128.4, 128.4, 129.5, 130.7, 132.6, 136.4, 136.5, 161.3. LRMS: *m*/*z* (%) 539.3 (18, M^+), 495.2 (100), 91.1 (31). Anal. Calcd for $C_{33}H_{37}N_3O_4$: C, 73.44; H, 6.91; N, 7.79. Found: C, 73.20; H, 6.82; N, 7.63.

1,1-Bis(5-(ethoxycarbonyl)-3,4-dimethyl-1*H*-2-pyrrolyl)-3-(dimethylamino)propene (60). 1,1-Dipyrrolylethene **54** (232 mg; 0.647 mmol) and Eschenmoser's salt (946 mg; 5.11 mmol, 8 equiv) was stirred at rt for 20 h, as described above. Chromatography gave 255 mg (95%) of the title product as pale flaky solid, mp 101−103 °C; ^{1}H-NMR: δ, ppm, 1.28 (t, 6H), 1.71, 1.80, 2.17, 2.20 (each s, 3H), 2.67 (s, 6H), 2.59 (d, 2H), 4.14 (q, 4H), 6.25 (t, 1H), 9.71, 10.49 (each bs, 1H). Anal. Calcd for $C_{23}H_{33}N_3O_4$: C, 66.48; H, 8.00; N, 10.11. Found: C, 66.44; H, 8.03; N, 10.00.

Acknowledgment. This work was supported by grants from National Institutes of Health (HL 22252), the National Science Foundation (CHE 93−05577), the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. Mass spectrometric analyses were performed by the UCSF Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

JO961582Z