with an authentic sample by TLC, spectrophotometry, and proton ^1H NMR spectroscopy (in D_2O, as the dicyanoferrihemin).

Acknowledgment. This work was supported by grants from the National Institutes of Health (HL 22252) and the National Science Foundation (CHE 81-20891).

Registry No. **2**, 10589-94-3; **3**, 34713-34-3; **5**, 104834-97-1; **6**, 104834-98-2; **7**, 104834-99-3; **8**, 104848-71-7; **9**, 104848-72-8; **10**, 104848-73-9; **11**, 104835-00-9; **11**–Cu(II) complex, 104835-12-3; **12**, 104835-01-0; **13**, 104835-16-7; **14**, 104835-17-8; **15**, 104835-10-1; **16**, 104835-04-3; **17**, 104835-06-5; **17**–Zn(II) complex, 104835-15-6; **18**, 52091-21-1; **20**, 104835-02-1; **21**, 53751-01-2; **22**, 104835-03-2; **23**, 104835-05-4; **24**, 104835-13-4; **25**, 104835-14-5; **26**, 104835-07-6; **27**, 104835-08-7; **28**, 104835-09-8; **29**, 88055-56-5; **30**, 104848-74-0; **31**, 88059-67-0; *tert*-butyl 4-[2-(methoxycarbonyl)ethyl]-3-methylpyrrole-5-carboxylate, 2199-58-8; 2-formyl-3,5-dimethylpyrrole, 2199-58-8; methyl acrylate, 96-33-3; 2,4-bis(2-hydroxyethyl)-6-(2-carbonylethyl)-7-(2-carbonylvinyl)-1,3,5,8-tetramethylporphyrin, 104835-11-2.

Total Syntheses of Derivatives of Protoporphyrin IX Regioselectively Labeled with Carbon-13 in the Methyls

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Received August 18, 1986

Total syntheses, from monopyrroles via tripyrrenes and *a,c*-biladienes, of the four isomers **2**–**5** of protoporphyrin IX dimethyl ester in which the 1-, 3-, 5-, and 8-methyl groups are individually and regioselectively enriched with carbon-13 are described. The source of labeled carbon was 90% carbon-13-enriched paraformaldehyde, and methyls were inserted at the monopyrrole stage by reductive C-alkylation. The carbon-13-labeled porphyrins, as the corresponding hemes, are of interest as probes in carbon-13 NMR spectroscopic studies of reconstituted heme proteins.

Proton NMR spectroscopy has been extremely productive for studying the electronic structure of paramagnetic porphyrins and heme proteins.[2,3] Significant advances in interpretation of the large isotropic NMR shifts[4–25] in hemes and heme proteins have been made possible by the availability of regioselectively deuterium-labeled hemes.[26–31] Recently, interpretation of resonance Raman spectra of nickel porphyrins,[32] hemes,[33] and heme proteins[33–35] has also been aided by the use of hemes from vinyl-labeled protoporphyrin IX dimethyl ester (**1**). It is to be expected

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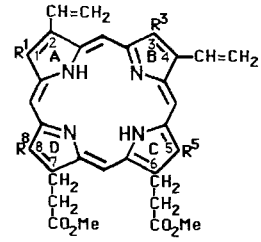
that carbon-13 and deuterium NMR will also contribute significantly to our understanding of the properties particularly of diamagnetic hemes and heme proteins, as well as their paramagnetic counterparts. Labeling of vinyl groups in protoporphyrin IX with carbon-13[36,37] has already been described. On account of the remarkable usefulness of deuterium-labeled methyl derivatives of protoheme, analogues in which the methyl groups at the 1-3-5, and 8-positions are *carbon-13 enriched* should be particularly valuable.



1 R^1, R^3, R^5, R^8 = Me

2 R^1 = $^*CH_3$; R^3, R^5, R^8 = Me

3 R^3 = $^*CH_3$; R^1, R^5, R^8 = Me

4 R^5 = $^*CH_3$; R^1, R^3, R^8 = Me

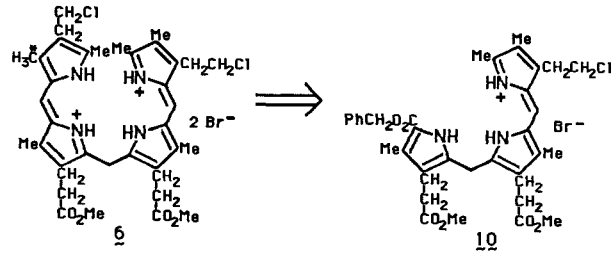
5 R^8 = $^*CH_3$; R^1, R^3, R^5 = Me

(* Denotes carbon-13 enrichment)

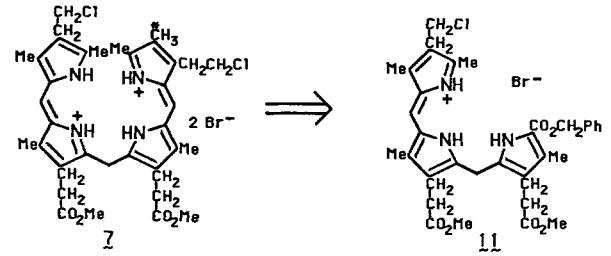
We now report total syntheses of four isomers (2–5) of protoporphyrin IX dimethyl ester in which the methyl groups are individually and regioselectively labeled with carbon-13. The object of the research was to develop synthetic routes to carbon-13-labeled derivatives of protoporphyrin IX and to establish definitive assignments of these peaks in free hemes and heme proteins by carbon-13 NMR spectroscopy. Each of these specifically labeled protoporphyrin IX dimethyl esters can be readily converted into the hemin chloride, which can in turn be reconstituted into a variety of heme proteins, thereby providing a new probe for structure/function relationships in the vitally important biological systems in which heme proteins are found.

In planning synthetic approaches from monopyrroles, a major priority was to accomplish insertion of the expensive carbon-13-labeled pyrroles near the end of the total synthesis. Thus, four different labeled *a,c*-biladienes (6–9) were targeted from four corresponding unlabeled tripyrrenes (10–13).

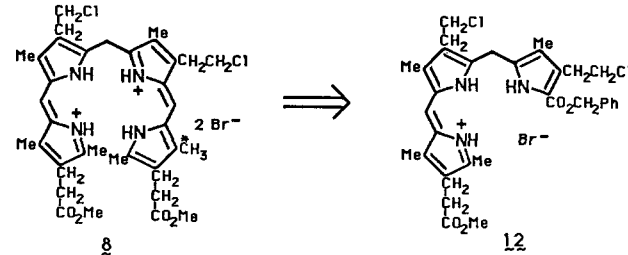
Syntheses of Carbon-13-Enriched Monopyrroles. The first step was to synthesize the necessary carbon-13-labeled pyrroles (14–16) that would eventually be combined with the tripyrrenes. Simple retrosynthetic removal of the carbon-13-enriched methyls and other minor modifications (e.g., visualization of the 2-formyl groups as benzyl esters) yielded the required pyrroles 17–19.



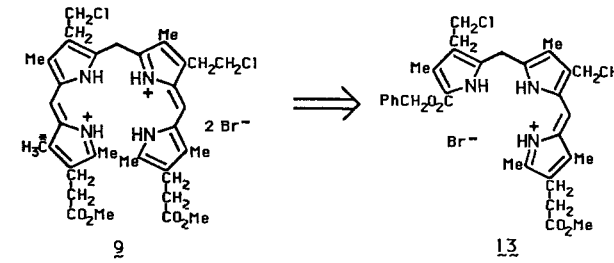
6 → 10



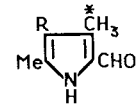
7 → 11



8 → 12

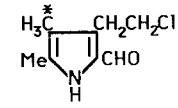


9 → 13

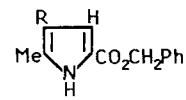


14 R = CH_2CH_2Cl

16 R = $CH_2CH_2CO_2Me$

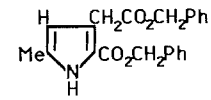


15



17 R = CH_2CO_2Me

19 R = $CH_2CH_2CO_2Me$



18

Pyrrole 17 was prepared as shown in Scheme I. The Fischer–Fink method was used to synthesize the basic pyrrole nucleus **20**, which was regioselectively acetylated (acetic anhydride/boron trifluoride etherate) in the 4-position to give **21** (90%). Thallium(III)-promoted rearrangement[38] gave a 59% yield of the [(methoxycarbonyl)methyl]pyrrole **17**, which was treated with [^{13}C]paraformaldehyde, acetic acid, hydriodic acid, and hypophosphorus acid at 25 °C[39] to give the methyl-labeled

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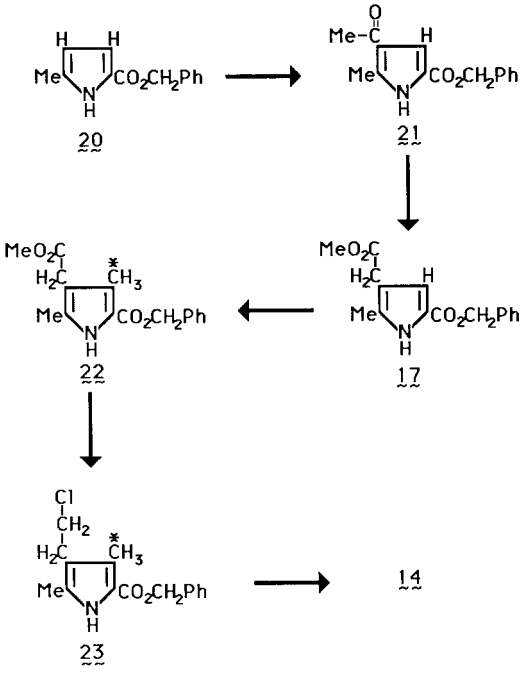
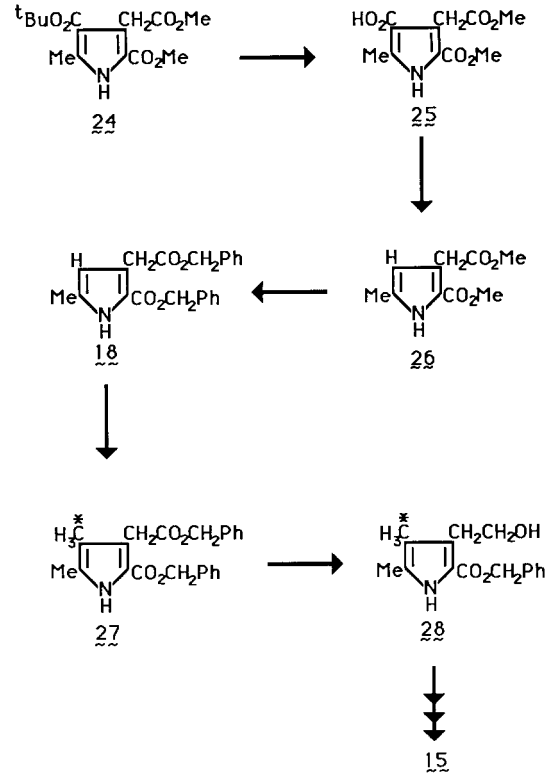
Scheme I



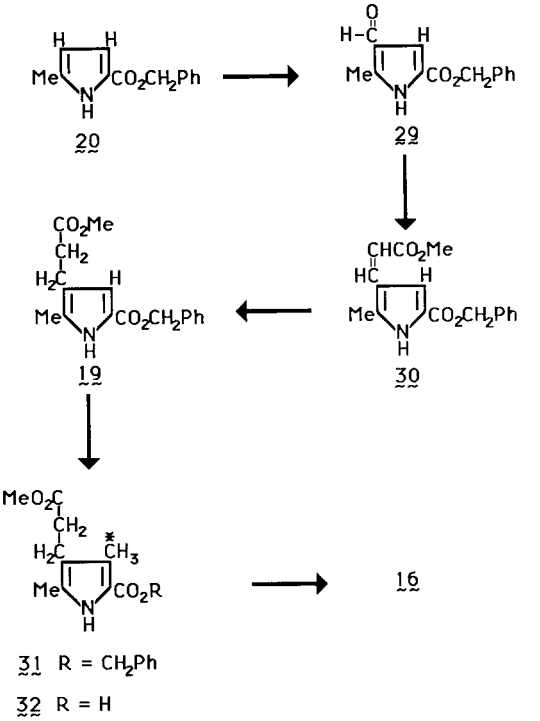
Scheme II



pyrrole **22** in 81% yield. Presence of the carbon-13 label was readily apparent in the proton NMR spectrum (d, J = 127 Hz, 2.29 ppm). Diborane reduction of **22** followed by thionyl chloride treatment gave the (2-chloroethyl)-pyrrole **23** (80%), which was catalytically debenzylated and then formylated with trimethyl orthoformate in trifluoroacetic acid to give the key formylpyrrole **14** in 60% yield.

Pyrrole **18** was synthesized as shown in Scheme II. Pyrrole **24** was obtained from dimethyl oximinoacetone-dicarboxylate and *tert*-butyl acetoacetate and was then treated with trifluoroacetic acid to give the pyrrole-carboxylic acid **25**, which was decarboxylated to give **26** by heating in quinoline in the presence of copper(II) acetate. Transesterification of **26** with benzyl alcohol and sodium metal gave the desired pyrrole **18** in 81% yield from **26**. Reductive C-alkylation of **26** with [^{13}C]para-formaldehyde as before gave **27**, which was reduced with diborane (to give **28**) and then transformed into the (chloroethyl)formylpyrrole as described in Scheme I.

Scheme III



Scheme III shows the route adopted for synthesis of pyrrole **19**. Pyrrole **20** was treated with trimethyl ortho-formate and trifluoroacetic acid to give a 62% yield of the regioselectively formylated pyrrole **29**. This was subjected to a Knoevenagel reaction (methyl hydrogen malonate, piperidine) to give the acrylate pyrrole **30** (85%), which was reduced with hydrogen and Adam's catalyst to give the propionic pyrrole **19**. Reductive C-alkylation with carbon-13-enriched paraformaldehyde gave pyrrole **31**, which was catalytically debenzylated (to give **32**) and formylated with trimethyl orthoformate to give the required labeled pyrrole **16**.

Porphyrin Syntheses. The four *a,c*-biladienes (**6**–**9**) can be synthesized from three pyrromethanes (**33**–**35**). Pyrromethane **33**, a new compound, was the source of both the 1- and the 3-labeled porphyrins while pyrromethane **34** was the source of the 5-methyl-labeled porphyrin. Pyrromethane **35**, which has been synthesized previously, is the source of the 8-methyl-labeled porphyrin. Scheme IV shows the syntheses of the 1- and 3- methyl-labeled porphyrins **2** and **3**. Pyrromethane **33** was obtained from the (acetoxymethyl)pyrrole **36** and the 2-unsubstituted pyrrole **37**, in 90% yield. This pyrromethane was elongated[40] to give the benzyl tripyrrene salt **10** by reaction with formylpyrrole **38**. The desired *a,c*-biladiene **6** was obtained in 77.5% yield by further treatment with formylpyrrole **14**. Cyclization, promoted by copper(II) chloride, in boiling dimethylformamide gave the porphyrin **39** after demetalation, and this afforded the vinylporphyrin

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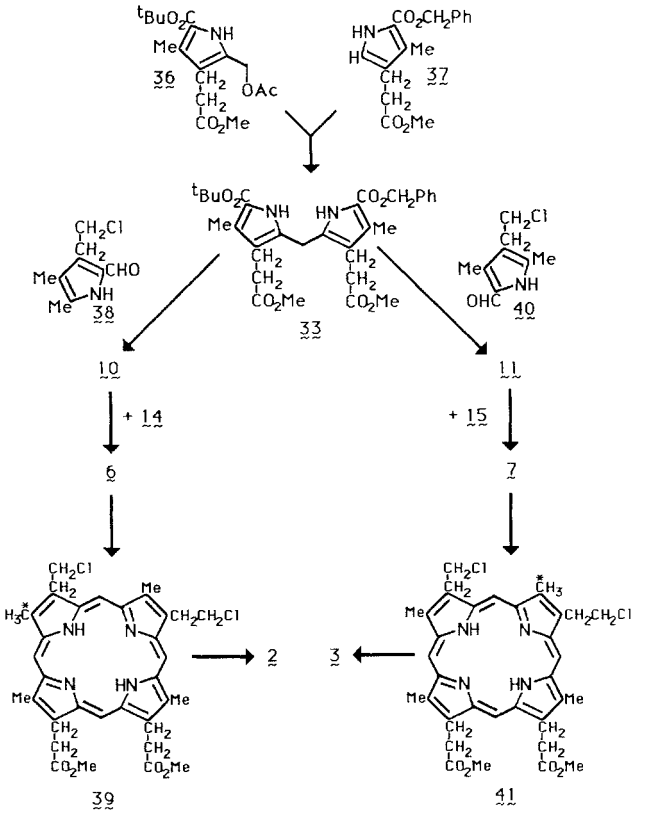
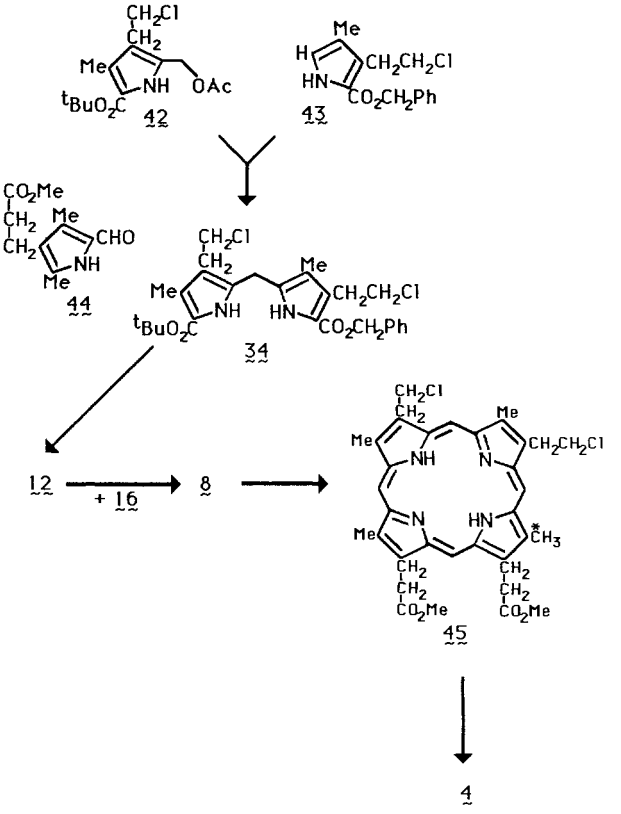
(40) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302–4306.

Scheme IV



Scheme V



2 after treatment with base.

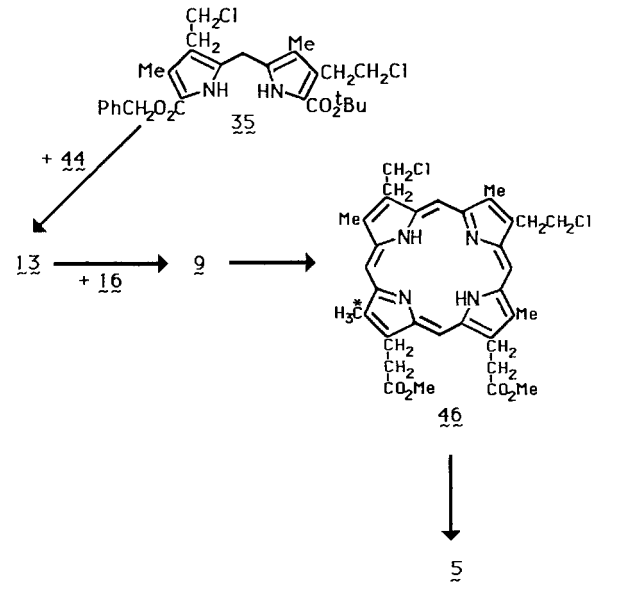
As shown also shown in Scheme IV, the 3-methyl-enriched porphyrin **3** was obtained from the same pyrromethane **33**. Treatment with trifluoroacetic acid followed by unlabeled formylpyrrole **40** gave the tripyrrene hydrobromide **11**. With the labeled formylpyrrole **15**, an 81% yield of the *a,c*-biladiene **7** was obtained, and this was cyclized (to give **41**) and vinylated as described above to give the 3-methyl-labeled porphyrin **3**.

The ring C-labeled porphyrin (Scheme V) was synthesized from the (chloroethyl)pyrromethane **34**. This was prepared in 84% yield from the 2-unsubstituted pyrrole **42** and the (acetoxymethyl)pyrrole **43**. The *tert*-butyl group of pyrromethane **34** was first cleaved with trifluoroacetic acid, and this was followed by addition of the formylpyrrole **44** to give a 33% yield of the tripyrrene salt **12**. Reaction with the ^{13}C-labeled formylpyrrole **16** gave the *a,c*-biladiene **8**. Following copper(II) cyclization, demetalation (to give **45**), and dehydrohalogenation, the desired carbon-13-labeled protoporphyrin IX dimethyl ester **4** was obtained.

Tripyrrene **13** was obtained by the reaction of the known pyrromethane **35** and unlabeled formylpyrrole **46** (Scheme VI). The final ^{13}C-labeled *a,c*-biladiene **9** was synthesized by reacting the tripyrrene salt **13** with the [^{13}C]formylpyrrole **16**. Copper(II)-promoted cyclization, demetalation (to give **47**), and dehydrohalogenation resulted in the formation of the carbon-13-labeled protoporphyrin IX dimethyl ester **5**.

The preparation for reconstitution with apoproteins (to be published elsewhere), the labeled protoporphyrin IX dimethyl ester samples were chelated with iron and hydrolyzed to the hemins as described in the preceding paper.[41]

Scheme VI



Experimental Section

General directions are as described in the preceding paper in this issue.[41]

Benzyl 5-Methylpyrrole-2-carboxylate (20). To a three-necked flask with a mechanical stirrer and a 500-mL dropping funnel were added benzyl acetoacetate (305 g) and glacial acetic acid (400 mL) and the resultant mixture stirred at 0 °C. Sodium nitrite (115 g) in water (400 mL) was then added dropwise. The reaction temperature was maintained below 10 °C. The mixture was stirred for an additional 1 h at 5 °C and stored overnight at 0 °C to give the oxime as an orange-red solution. This solution was added to a mixture of acetoacetaldehyde dimethyl acetal (210 g) and glacial acetic acid (350 mL), previously warmed to 60 °C. An admixture of zinc dust (300 g) and sodium acetate (300 g) was

(41) Smith, K. M.; Miura, M.; Morris, I. K., preceding paper in this issue.

simultaneously added to the reaction vessel. After the addition, the reaction temperature was raised to 78 °C and the mixture was stirred for an additional 2 h. The mixture was poured into ice–water (3 L) to give a precipitate. Filtration and recrystallization from methanol/water yielded 207 g (62%) as cream-colored needles: Mp 96–97 °C. IR ($CHCl_3$, NaCl cell) 3461 (m, br, NH), 1688 (s, br, C=O) cm^{-1}. NMR (ppm) 2.22 (s, 3 H, Me), 5.30 (s, 2 H, $PhCH_2$), 5.87 (dd, 1 H), 6.85 (dd, 1 H), 7.37 (m, 5 H, Ph), 9.99 (br s, 1 H, NH). MS, *m/e* (%) 215 (97), 108 (72), 91 (100). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.50. Found: C, 72.54; H, 6.09; N, 6.34.

Methyl 3-[(Methoxycarbonyl)methyl]-4-(*tert*-butoxycarbonyl)-5-methylpyrrole-2-carboxylate (24). Dimethyl 1,3-acetonedicarboxylate (320 g) was treated with concentrated HCl (3.2 mL) at 0 °C. Freshly distilled amyl nitrite (224 mL) was added during 1 h while the reaction temperature was maintained below 10 °C. The resulting oxime was left to stand overnight at 25 °C. *tert*-Butyl acetoacetate (251 g) in glacial acetic acid (960 mL) was heated to 65 °C. The freshly prepared oxime was simultaneously added with zinc dust (320 g) and ammonium acetate (224 g) with rapid stirring over a 1-h period. The mixture was then stirred vigorously for 4 h at 60 °C and poured into ice–water (4 L). The precipitate was collected by filtration and recrystallized from methanol/water to yield 116 g (20.3%) of the title compound as white crytals: Mp 127–129 °C. IR ($CHCl_3$, NaCl cell), 3440 (m, br, NH), 1730, 1678 (s, br, C=O) cm^{-1}. NMR (ppm) 1.53 (s, 9 H, *t*-Bu H), 2.43 (s, 3 H, Me), 3.70 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.20 (s, 2 H, CH_2), 9.40 (br s, 1 H, NH). MS, *m/e* (%) 147 (15), 164 (33), 178 (20), 196 (79), 209 (42), 223 (100), 237 (66), 255 (28), 311 (36), 312 (5). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.89; H, 6.81; N, 4.47.

Benzyl 3-(2-Chloroethyl)-4-methylpyrrole-2-carboxylate (43). Benzyl 3-(2-chloroethyl)-5-iodo-4-methylpyrrole-2-carboxylate (next compound) (1.01 g) in 50 mL of a methanolic solution containing sodium acetate trihydrate (1.00 g) was hydrogenated for 15 h (at 1 atm, 25 °C) over Adams catalyst (11.1 mg). The solution was filtered and evaporated to dryness. The residue was dissolved in dichloromethane (200 mL) and washed three times with water (200 mL). The solvent was evaporated, and the residue was chromatographed on a silica gel column (elution with 25% ethyl acetate in cyclohexane). Concentration of the solution, followed by recrystallization from dichloromethane/hexane, gave 390 mg (56%) of pale pink prisms: Mp 89–90 °C. IR ($CHCl_3$, NaCl cell) 3455 (m, br, NH), 1680 (s, br, C=O) cm^{-1}. NMR (ppm) 2.06 (s, 3 H, Me), 3.16 (t, 2 H, CH_2CH_2Cl), 3.60 (t, 2 H, CH_2CH_2Cl), 5.30 (s, 2 H, $PhCH_2$), 6.64 (d, 1 H, J = 2.7 Hz), 7.40 (s, 5 H, Ph), 8.93 (br s, 1 H, NH). MS, *m/e* (%) 277 (100), 241 (8), 228 (36). Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.85; H, 5.81; N, 5.04. Found: C, 64.62; H, 5.81; N, 4.98.

Benzyl 3-(2-Chloroethyl)-5-iodo-4-methylpyrrole-2-carboxylate. 2-[(Benzyloxy)carbonyl]-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylic acid (next compound) (1.33 g) was added to methanol (11 mL) and 11 mL of an aqueous solution containing sodium bicarbonate (104 mg), and the resultant mixture was warmed to 60 °C. A solution of iodine (167.7 mg) in methanol (15 mL) and water (4 mL) was added dropwise at 60 °C over a period of 7.5 h. To the orange reaction mixture was added water (15 mL) dropwise, and the mixture was stirred for an additional 1 h at the same temperature. The precipitate was filtered, washed with water (100 mL), and dried under vacuum to afforded 1.55 g (94%) of the title compound as off-white crystals: Mp 139–140 °C. IR ($CHCl_3$, NaCl cell) 3440 (m, br, NH), 1682 (s, br, C=O) cm^{-1}. NMR (ppm) 2.01 (s, 3 H, Me), 3.18 (t, 2 H, CH_2CH_2Cl), 3.58 (t, 2 H, CH_2CH_2Cl), 5.31 (s, 2 H, $PhCH_2$), 7.43 (s, 5 H, Ph), 9.10 (br s, 1 H, NH). MS, *m/e* (%) 403 (100), 276 (17). Anal. Calcd for $C_{15}H_{15}ClINO_2$: C, 44.64; H, 3.75; N, 3.47. Found: C, 44.53; H, 3.79; N, 3.64.

2-[(Benzyloxy)carbonyl]-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylic Acid. *tert*-Butyl 3-(2-chloroethyl)-4-methylpyrrole-5-carboxylate[42] (2 g) was dissolved in trifluoroacetic acid (10 mL) at 50 °C with stirring. Upon obtaining homogeneity, immediate solidification occurred. Additional trifluoroacetic acid (10 mL) was added, and the reaction mixture was stirred for 1 h at 50 °C. The mixture was poured into cold water (100 mL) and filtered. The solid was air-dried and washed with petroleum ether (50 mL). Recrystallization from acetone/dichloromethane yielded 1.4 g (82%) of the title compound: Mp 190 °C dec. IR (KBr wafer) 3291 (m, br, NH), 3581–2276 (m, br, CO_2H), 1680, 1675 (s, br C=O) cm^{-1}. NMR (ppm; acetone-d_6) 2.31 (s, 3 H, Me), 3.16 (t, 2 H, CH_2CH_2Cl), 3.64 (t, 2 H, CH_2CH_2Cl), 5.32 (s, 2 H, $PhCH_2$), 7.38 (m, 5 H, Ph). MS, *m/e* (%) 321 (61), 272 (13), 91 (100). Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.35. Found: C, 59.73; H, 5.10; N, 4.44.

Benzyl 4-Acetyl-5-methylpyrrole-2-carboxylate (21). Acetic anhydride (6.5 mL) was stirred for 2 min at 0 °C under dry nitrogen. To this mixture was added boron trifluoride etherate (11 mL), and the resultant solution was stirred; addition of benzyl 5-methylpyrrole-2-carboxylate (**20**) (10 g) followed. The resulting orange solution was stirred at 0 °C for 15 min (generating a suspension), at 25 °C for 1 h, and finally at 40 °C for 1.5 h. The solution was diluted with dichloromethane (700 mL) and warmed to 50 °C to dissolve the residue. The dichloromethane phase was washed four times with water (500 mL), twice with saturated sodium bicarbonate (500 mL), and finally twice with water (500 mL). The organic phase was evaporated, and the residue was chromatographed on a silica gel column (elution with 30% ethyl acetate in cyclohexane). Recrystallization from methanol/water gave 10.8 g (90%) of the title compound, as white crystals: Mp 131–132.5 °C. IR ($CHCl_3$, NaCl cell) 3430 (m, br, NH), 1667, 1698 (s, br, C=O) cm^{-1}. NMR (ppm) 2.40 (s, 3 H, Me), 2.57 (s, 3 H, Me), 5.30 (s, 2 H, $PhCH_2$), 7.26 (d, J = 2 Hz, 1 H, β-H), 7.40 (s, 5 H, Ph), 9.56 (br s, 1 H, NH). MS, *m/e* (%) 257 (88), 242 (43), 150 (40), 134 (15), 91 (100). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88 N, 5.44. Found: C, 69.99; H, 5.98; N, 5.44.

Benzyl 4-[(Methoxycarbonyl)methyl]-5-methylpyrrole-2-carboxylate (17). The foregoing pyrrole **21** (10.8 g) was dissolved in dry methanol (100 mL). To this mixture was added a methanolic solution (150 mL) of thallium(III) nitrate trihydrate (21.6 g), and this was stirred at 30 °C for 1 h. Concentrated nitric acid (0.1 mL) was added and stirred at the same temperature for an additional 17 h. Sulfur dioxide gas was then bubbled through the solution for 5 min, and the methanolic solution was decanted and filtered. The thallium(I) salts were washed with dichloromethane (500 mL), and the combined organic phase was washed with brine (3 × 150 mL), a 50:50 mixture of saturated sodium bicarbonate and brine (3 × 200 mL), brine (3 × 150 mL), and finally water (2 × 150 mL). The organic phase was dried (Na_2SO_4) and concentrated to an oil. The brown oil was dissolved in dichloromethane and chromatographed on a silica column (elution with 1% methanol in dichloromethane). After solvent removal under vacuum, 7.1 g (59%) of product was recovered as off-white crystals: Mp 55–56 °C. IR ($CHCl_3$, NaCl cell) 3445 (m, br, NH), 1728, 1685 (s, br, C=O) cm^{-1}. NMR (ppm) 2.23 (s, 3 H, Me), 3.40 (s, 2 H, CH_2CO), 3.69 (s, 3 H, OMe), 5.30 (s, 2 H, $PhCH_2$), 6.86 (d, 1 H, β-H), 7.40 (s, 5 H, Ph), 9.70 (br s, 1 H, NH). MS, *m/e* (%) 287 (90), 228 (70), 180 (20), 91 (100). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.68; H, 6.12; N, 4.96.

Benzyl 4-[(Methoxycarbonyl)methyl]-3,5-[3-^{13}C]dimethylpyrrole-2-carboxylate (22). The foregoing pyrrole **17** (2.0 g) and [^{13}C]paraformaldehyde (90 atom % enriched; 208 mg) in glacial acetic acid (25 mL) was treated with hydriodic acid (4.25 mL) and hypophosphorus acid (1.0 mL) and stirred for 30 min under nitrogen at 25 °C. Dry Celite (2 g) was immediately added, and the mixture was stirred for an additional 18 h at room temperature. The suspension was carefully poured into saturated sodium bicarbonate solution (100 mL) and further diluted to 750 mL with the same solution. After stirring for 1 h at 25 °C, the mixture was filtered under vacuum and the Celite was washed with water (100 mL). After suction, the powder was washed with dichloromethane (700 mL). The combined mixture was shaken with brine (100 mL), and the organic phase containing pyrrole **22** was set aside for further isolation. The bicarbonate solution was acidified to pH 4 with concentrated hydrochloric acid to afford a precipitate (acid analogue of **22**) that was stirred at 25 °C for 3 h. The precipitate was filtered, washed with water (100 mL) and then with petroleum ether (100 mL), and dried under vaccum. The residue was then dissolved in tetrahydrofuran (200 mL) and

(42) Smith, K. M.; Pandey, R. K. *Tetrahedron* **1984**, *40*, 1749–1754.

treated briefly with ethereal diazomethane. After solvent removal, the desired product **22** was combined with the previously saved dichloromethane phase, which was washed with 600 mL of water containing brine (50 mL) and then twice with water (600 mL). The organic phase was dried (Na_2SO_4) and evaporated under vacuum to give an oil. The combined product was then chromatographed on silica gel (elution with a 50:50 mixture of 1% methanol in dichloromethane and 25% ethyl acetate in cyclohexane) to afford cream-colored crystals in 81% (1.7 g) yield after solvent removal: Mp 88–89.5 °C (lit.[43] mp 93–94 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3447 (m, br, NH), 1718, 1670 (s, br, C=O) cm^{-1}. NMR (ppm) 2.23 (s, 3 H, Me), 2.29 (d, J = 127.2 Hz, 3 H, $^{13}CH_3$), 3.38 (s, 2 H, CH_2CO), 3.67 (s, 3 H, OMe), 5.29 (s, 2 H, $PhCH_2$), 7.39 (s, 5 H, Ph), 8.80 (br s, 1 H, NH).

Benzyl 4-(2-Hydroxyethyl)-3,5-[3-^{13}C]dimethylpyrrole-2-carboxylate. The foregoing pyrrole **22** (7.2 g) was dissolved in dry tetrahydrofuran (100 mL). To this mixture was added borane-tetrahydrofuran (60 mL, 1 M) complex over a 15-min period, and the reaction was left overnight to stir at 25 °C. The excess borane was quenched with dropwise addition of methanol, and the content was evaporated to dryness. Silica gel column chromatography (elution with 5% methanol in dichloromethane) afforded 6.5 g (99.5%) of cream-colored crystals: mp 116.5–118.5 °C (lit.[43] mp 120–121.5 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3445 (m, br, NH), 1665 (s, br, C=O) cm^{-1}. NMR (ppm) 2.22 (s, 3 H, Me), 2.28 (d, J = 127.8 Hz, 3 H, $^{13}CH_3$), 2.64 (t, 2 H, CH_2CH_2OH), 3.64 (t, 2 H, CH_2CH_2OH), 5.29 (s, 2 H, $PhCH_2$), 7.41 (s, 5 H, Ph), 8.68 (br s, 1 H, NH).

Benzyl 4-(2-Chloroethyl)-3,5-[3-^{13}C]dimethylpyrrole-2-carboxylate (23). The foregoing pyrrole (6.5 g) was dissolved in dry dichloromethane (50 mL) and pyridine (2 mL). Freshly distilled thionyl chloride (1.8 mL) was added rapidly and stirred under a nitrogen atmosphere for 3 h at 40 °C. Upon reaction completion as monitored by TLC the mixture was diluted with dichloromethane (300 mL) and washed with 2 N hydrochloric acid (2 × 300 mL), sodium bicarbonate solution (2 × 300 mL), and water (2 × 300 mL). The organic phase was dried (Na_2SO_4) and concentrated to a brown oil. Chromatography on a silica gel column (elution with dichloromethane) gave, after recrystallization from methanol, 5.6 g (80%) of white needles: Mp 116–117 °C (lit.[44] mp 121–122 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3450 (m, br, NH), 1673 (s, br, C=O) cm^{-1}. NMR (ppm) 2.22 (s, 3 H, Me), 2.27 (d, J = 127.8 Hz, 3 H, $^{13}CH_3$), 2.82 (t, 2 H, CH_2CH_2Cl), 3.48 (t, 2 H, CH_2CH_2Cl), 5.28 (s, 2 H, $PhCH_2$), 7.39 (s, 5 H, Ph), 8.71 (br s, 1 H, NH).

4-(2-Chloroethyl)-2-formyl-3,5-[3-^{13}C]dimethylpyrrole (14). The foregoing pyrrole **3** (1.0 g) was dissolved in tetrahydrofuran (25 mL). To this solution was added 10% palladium–carbon (100 mg), and the mixture was hydrogenated (1 equiv of H_2) at 1 atm at ambient temperature. The reaction progress was checked by TLC, and upon completion, the mixture was filtered through Celite (4 g). The Celite was rinsed with tetrahedrofuran (50 mL) and the combined filtrates were evaporated to give an oil that solidified upon flushing with nitrogen. This residue was treated with trifluoroacetic acid (5 mL) at 40 °C for 5 min with stirring. The solution was cooled to 0 °C and trimethyl orthoformate (1.65 mL) was added, again stirring for 5 min at the same temperature. To this mixture was added water (25 mL), and this was stirred for 5 min. The resulting solid was filtered, washed with water (100 mL), and dried under vacuum. The solid was taken up in dichloromethane (200 mL) and carefully added to saturated sodium bicarbonate solution (200 mL). When the effervescence had ceased, the organic phase was gently washed with additional bicarbonate solution (2 × 200 mL) and water (3 × 300 mL) and dried (Na_2SO_4). Solvent was removed under vacuum, and the resulting concentrate was chromatographed on a silica gel column (elution with 30% ethyl acetate in cyclohexane). Recrystallization from dichloromethane/hexane afforded 382 mg (60%) of white crystals: Mp 140–141 °C (lit.[31] mp 143–144 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3445 (m, br, NH), 1624 (s, br, C=O), cm^{-1}. NMR (ppm) 2.27 (d, J = 127.8 Hz, 3 H, $^{13}CH_3$), 2.30 (s, 3 H, Me), 2.86 (t, 2 H, CH_2CH_2Cl), 3.53 (t, 2 H, CH_2CH_2Cl), 9.54 (s, 1 H, CHO), 9.6 (br s, 1 H, NH).

2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-methylpyrrole-4-carboxylic Acid (25). The foregoing pyrrole **24** (10 g) was dissolved in trifluoroacetic acid (50 mL) and the resultant stirred at 50 °C for 1 h. The homogeneous solution was cooled to room temperature and then poured into water, which resulted in a white precipitate. The solid was filtered, washed with water, and vacuum-dried to give 7.8 g (95%) of the desired product. Recrystallization from acetone/dichloromethane afforded white prisms: Mp 224–226 °C dec. IR ($CHCl_3$, NaCl cell) 3255 (m, br, NH), 3600–2267 (br m, CO_2H), 1733, 1688, 1646 (s, br, C=O) cm^{-1}. NMR (ppm; acetone d_6) 2.52 (s, 3 H, Me), 3.57 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 4.18 (s, 2 H, CH_2). Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 52.04; H, 5.28; N, 5.72.

Methyl 3-[(Methoxycarbonyl)methyl]-5-methylpyrrole-2-carboxylate (26). The foregoing pyrrole **25** (10 g), copper(II) acetate (124 mg), and quinoline (90 mL) were placed in a 500-mL round-bottom flask fitted to a 40-cm Vigreux column and a $CaSO_4$ drying tube. The mixture was heated at 160 °C for 30 min. The solution color changed from green to brown during a further 3-h heating at 210 °C. The solution was cooled, diluted with diethyl ether (600 mL), and washed with 2 N hydrochloric acid (2 × 300 mL). The ether phase was set aside, and the combined acid wash was extracted with additional ether (600 mL). The combined organic phase was washed with saturated sodium bicarbonate solution (2 × 300 mL), brine (2 × 300 mL), and water (3 × 300 mL). The ether solution was dried (Na_2SO_4) and evaporated to give a dark brown oil. Silica gel column chromatography (elution with 25% ethyl acetate in cyclohexane) followed by recrystallization from dichloromethane/petroleum ether at −40 °C gave 2.2 g (26.5%) of tan crystals: Mp 61–62 °C. IR ($CHCl_3$, NaCl cell) 3438 (m, br, NH), 1755, 1643 (s, br, C=O) cm^{-1}. NMR (ppm) 2.27 (s, 3 H, Me), 3.71 (s, 3 H, OMe), 3.83 (s, 5 H, CH_2 and OMe), 5.93 (s, J = 2.7 Hz, 1 H, β-H), 9.04 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 57.07; H, 6.42; N, 6.62.

Benzyl 3-[[(Benzyloxy)carbonyl]methyl]-5-methylpyrrole-2-carboxylate (18). The foregoing pyrrole **26** (7.0 g) in benzyl alcohol (100 mL) and sodium metal (150 mg) were heated under vacuum (45 torr) at 120 °C overnight. The excess solvent was carefully evaporated off under vacuum. The resulting oil was then chromatographed on a silica gel column (elution with dichloromethane). Recrystallization from dichloromethane/petroleum ether gave 8.6 g (81%) of the title pyrrole as a light brown powder: Mp 90–91 °C (lit.[45] mp 92–94 °C). IR ($CHCl_3$, NaCl cell) 3450 (m, br, NH), 1724, 1681 (s, br, C=O) cm^{-1}. NMR (ppm) 2.60 (s, 3 H, Me), 4.27 (s, 2 H, CH_2), 5.48, 5.63 (each s, 2 H, $PhCH_2$), 6.30 (d, 1 H, 4-H), 7.71 (s, 10 H, 2 Ph).

Benzyl 3-[[(Benzyloxy)carbonyl]methyl]-4,5-[4-^{13}C]dimethylpyrrole-2-carboxylate (27). Reductive C-methylation of the foregoing pyrrole **18** (1 g) was accomplished with [^{13}C]-paraformaldehyde (100 mg; 90 atom % ^{13}C) by stirring in acetic acid (25 mL), hydriodic acid (2.1 mL), and hypophorphorus acid (0.5 mL) under nitrogen for 30 min. To this mixture was added dry Celite (1 g), and the suspension was stirred at 25 °C for an additional 30 h. A similar workup to that utilized for reductive methylation to give pyrrole **22** afforded the title compound [160 mg (15.4%)] as a yellow-orange oil: IR ($CHCl_3$, NaCl cell) 3450 (m, br, NH), 1695 (s, br, C=O) cm^{-1}. NMR (ppm) 1.87 (d, J = 126.9 Hz, 3 H, $^{13}CH_3$), 2.13 (s, 3 H, Me), 3.82 (s, 2 H, CH_2), 5.06 (s, 2 H, $PhCH_2$), 5.18 (s, 2 H, $PhCH_2$), 7.31 (s, 10 H, 2Ph), 8.9 (br s, 1 H, NH).

Benzyl 3-(2-Hydroxyethyl)-4,5-[4-^{13}C]dimethylpyrrole-2-carboxylate (28). The foregoing pyrrole **27** (5 g) was dissolved in tetrahydrofuran (100 mL) under nitrogen. The solution was cooled to 0 °C, borane–tetrahydrofuran complex (40 mL, 1 M) was added, and the mixture was stirred for 6 days at 25 °C. Excess borane was then quenched by dropwise addition of methanol (125 mL) until effervescence had ceased. The solution was evaporated to give a yellow oil. Silica gel column chromatography (elution with 3% methanol in dichloromethane) followed by recrystalli-

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zation from benzene/petroleum ether gave 2.8 g (80%) of product as white prisms: Mp 82–83.5 °C (lit.[45] mp 84–85 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3445 (m, br, NH), 1673 (s, br, C=O) cm^{-1}. NMR (ppm) 1.91 (d, J = 127.8 Hz, 3 H, $^{13}CH_3$), 2.15 (s, 3 H, Me), 2.97 (t, 2 H, CH_2CH_2OH), 3.68 (t, 2 H, CH_2CH_2OH), 5.26 (s, 2 H, $PhCH_2$), 7.38 (s, 5 H, Ph), 8.9 (br s, 1 H, NH).

Benzyl 3-(2-Chloroethyl)-4,5-[4-^{13}C]dimethylpyrrole-2-carboxylate. The foregoing pyrrole **28** (1.45 g) was dissolved in dry dichloromethane (50 mL). To this solution was added pyridine (0.4 mL) followed by freshly distilled thionyl chloride (0.4 mL). The reaction mixture was stirred at 40 °C for 3 h. After workup, chromatographic isolation (silica gel), and recrystallization from dichloromethane/petroleum ether, the title compound (1.1 g, 73%) was obtained as cream-colored needles: Mp 111–112 °C (lit.[45] mp 113–115 °C). IR ($CHCl_3$, NaCl cell) 3448 (m, br, NH), 1678 (s, br, C=O) cm^{-1}. NMR (ppm) 2.20 (s, 3 H, Me), 2.94 (d, J = 127.8 Hz, 3 H, $^{13}CH_3$), 3.16 (t, 2 H, CH_2CH_2Cl), 3.60 (t, 2 H, CH_2CH_2Cl), 5.31 (s, 2 H, $PhCH_2$), 7.44 (s, 5 H, Ph, 8.77 (br s, 1 H, NH).

3-(2-Chloroethyl)-2-formyl-4,5-[4-^{13}C]dimethylpyrrole (15). The foregoing pyrrole (1.0 g) was dissolved in tetrahydrofuran (50 mL) and hydrogenated at 1 atm in the presence of 10% palladium–carbon (200 mg) and triethylamine (0.2 mL). After uptake of 1 equiv of hydrogen, the mixture was filtered through Celite under vacuum and evaporated to give an oil. The residue (689 mg) was then treated with trifluoroacetic acid (5 mL) at 40 °C for 5 min. The solution was cooled to 0 °C, trimethyl orthoformate (1.8 mL) was added, and the resultant was stirred for an additional 5 min at this temperature. Addition of water (25 mL) and further stirring for 5 min, followed by similar workup as described for compound **14**, afforded 216 mg (34%) as cream-colored prisms: Mp 99–100.5 °C (lit.[31] mp 101–102 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3441 (m, br, NH), 1625 (s, br, C=O) cm^{-1}. NMR (ppm) 1.93 (d, J = 127.8 Hz, 3 H, $C^{13}CH_3$), 2.23 (s, 3 H, Me), 3.10 (t, 2 H, CH_2CH_2Cl), 3.59 (t, 2 H, CH_2CH_2Cl), 9.2 (br s, 1 H, NH), 9.47 (s, 1 H, CHO).

Benzyl 4-Formyl-5-methylpyrrole-2-carboxylate (29). Pyrrole **20** (2 g) was dissolved in trifluoroacetic acid (10 mL), cooled to 0 °C, and then treated with trimethyl orthoformate (3.3 mL) for 5 min at 0 °C. Cold water (50 mL) was added to the reaction mixture to precipitate out a yellow residue. Workup and silica gel chromatography gave 1.4 g (62%) of cream-colored crystals: Mp 143–144 °C. IR ($CHCl_3$, NaCl cell) 3420 (m, br, NH), 1655 (s, br, C=O) cm^{-1}. NMR (ppm) 2.57 (s, 3 H, Me), 5.30 (s, 2 H, $PhCH_2$), 7.28 (d, J = 2.7 Hz, 1 H, β-H), 7.37 (s, 5 H, Ph), 9.85 (s, 1 H, CHO), 10.0 (br s, 1 H, NH). MS, m/e (%) 243 (90), 136 (85), 109 (37), 91 (100). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.99; N, 5.51; N, 5.64.

Benzyl 4-[2-(Methoxycarbonyl)vinyl]-5-methylpyrrole-2-carboxylate (30). The formylpyrrole **29** (7 g) together with pyridine (50 mL) and toluene (50 mL) were stirred and refluxed under a Dean–Stark trap. After initial traces of water were removed, a solution of piperidine (0.75 mL) in acetic acid (1.5 mL) was added, followed by addition of methyl hydrogen malonate in portions of 3, 1, 1, 0.75, and 0.75 mL while codistilling water with the toluene solvent during a 2-h period. After solvent evaporation with a toluene chaser (2 × 500 mL), the resulting oil was left under vacuum overnight. The residue was dissolved in dichloromethane (500 mL) and washed with 2 N hydrochloric acid (2 × 400 mL) and water (2 × 400 mL). The organic layer was dried (Na_2SO_4) and evaporated to dryness. Recrystallization from methanol gave 7.3 g (85%) of cream-colored prisms: Mp 140–141 °C. IR ($CHCl_3$, NaCl cell) 3430 (m, br, NH), 1691 (s, br, C=O), 1626 (s, br, conjugated vinyl) cm^{-1}. NMR (ppm) 2.37 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 5.30 (s, 2 H, $PhCH_2$), 6.11 (d, J = 16.1 Hz, 1 H, vinyl H), 7.10 (d, J = 2.4 Hz, 1 H, β-H), 7.42 (s, 5 H, Ph), 7.61 (d, J = 16.1 Hz, 1 H, vinyl H), 9.37 (br s, 1 H, NH). MS, m/e (%) 299 (98), 268 (25), 192 (22), 160 (25), 91 (100). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.66; N, 4.64.

Benzyl 4-[2-(Methoxycarbonyl)ethyl]-5-methylpyrrole-2-carboxylate (19). The foregoing pyrrole **30** (6.2 g) was dissolved in tetrahydrofuran (250 mL) and treated with Adams catalyst (626 mg) and triethylamine (0.2 mL) before exposure to 1 equiv of hydrogen at 1 atm and ambient temperature. The catalyst was removed by filtration through Celite, and the filtrate was concentration to an oil. Purification by silica gel chromatography (elution with 50:50 1% methanol in dichloromethane and 25% ethyl acetate in cyclohexane) followed by crystallization from dichloromethane/hexane gave 4.2 g (67%) of cream-colored crystals: Mp 68–69 °C. IR ($CHCl_3$, NaCl cell) 3450 (m, br, NH), 1720, 1683 (s, br, C=O) cm^{-1}. NMR (ppm) 2.25 (s, 3 H, Me), 2.35–2.85 (m, 4 H, CH_2CH_2CO), 3.68 (s, 3 H, OMe), 5.30 (s, 2 H, $PhCH_2$), 6.77 (d, J = 3 Hz, 1 H, β-H), 7.43 (s, 5 H, Ph), 8.93 (br s, 1 H, NH). MS, m/e (%) 301 (95), 228 (87), 194 (30), 167 (13), 91 (100). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.62; H, 6.42; N, 4.70.

Benzyl 4-[2-(Methoxycarbonyl)ethyl]-3,5-[3-^{13}C]dimethylpyrrole-2-carboxylate (31). The foregoing pyrrole **19** (2.77 g) was treated with [^{13}C]paraformaldehyde (277 mg; 90 atom % enriched), acetic acid (25 mL), hydriodic acid (4.5 mL), and hypophosphorus acid (1.25 mL) for 30 min under nitrogen at 25 °C. Dry Celite (2 g) was added to the mixture which was stirred for an additional 24 h. The reaction mixture was carefully worked up with sodium bicarbonate solution (750 mL) and stirred for 1 h at 25 °C. The celite was removed by filtration, and this was washed with water (100 mL) and dichloromethane (700 mL). The aqueous and organic phases were combined and shaken for 1.5 min. The organic phase was saved for further product isolation. The aqueous phase was then acidified to pH 4 with concentrated HCl and stirred for 3 h at 25 °C. The resulting precipitate was filtered and washed with water (100 mL) and petroleum ether (100 mL), and dried under vacuum overnight. The gray residue was dissolved in tetrahydrofuran (100 mL) and briefly treated with ethereal diazomethane at 25 °C. The solution was evaporated to dryness. The dichloromethane phase saved earlier was then concentrated and briefly treated with ethereal diazomethane solution. The two esterified fractions were combined and chromatographed on a silica gel column (elution with 50:50 1% methanol in dichloromethane and 25% ethyl acetate in cyclohexane). Recrystallization from dichloromethane/petroleum ether gave 1.49 g (51%) of white prisms: Mp 95–97 °C (lit.[46] mp 99–101 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3438 (m, br, NH), 1723, 1681 (s, br, carbonyl cm^{-1}. NMR (ppm) 2.20 (s, 3 H, Me), 2.27 (d, J = 127.5 Hz, 3 H, $^{13}CH_3$), 2.33–2.80 (m, 4 H, CH_2CH_2CO), 3.67 (s, 3 H, OMe), 5.29 (s, 2 H, $PhCH_2$), 7.39 (s, 5 H, Ph), 8.90 (br s, 1 H, NH).

2-Formyl-4-[2-(methoxycarbonyl)ethyl]-3,5-[3-^{13}C]dimethylpyrrole (16). The foregoing pyrrole **31** (1.25 g) was hydrogenated at 1 atm in the presence of 10% palladium–carbon (125 mg) and triethylamine (0.1 mL). After filtration through Celite, the pyrrolecarboxylic acid **32** was evaporated and dried under vacuum. To this residue was added trifluoroacetic acid (10 mL) at 0 °C and the mixture stirred for 5 min at 40 °C. Trimethyl orthoformate (2.0 mL) was added at 0 °C and the resultant mixture stirred for 5 min. Water (50 mL) was added, and the mixture was stirred for another 5 min. The usual workup followed by silica gel chromatography and recrystallization from dichloromethane/petroleum ether afforded 382 mg (46%) as cream-colored prisms: Mp 124.5–125.5 °C (lit.[47] mp 128–130 °C, unlabeled). IR ($CHCl_3$, NaCl cell) 3443 (m, br, NH), 1722, 1620 (s, br, C=O) cm^{-1}. NMR (ppm) 2.25 (d, J = 129 Hz, 3 H, $^{13}CH_3$), 2.27 (s, 3 H, Me), 2.43 (t, 2 H, CH_2CO), 2.71 (t, 2 H, CH_2CH_2CO), 3.67 (s, 3 H, OMe), 9.48 (s, 1 H, CHO), 9.52 (br s, 1 H, NH).

Benzyl 5′-[(*tert*-Butoxycarbonyl)-3,3′-bis[2-(methoxycarbonyl)ethyl]-4,4′-dimethylpyrromethane-5-carboxylate (33). Benzyl 3-[2-(methoxycarbonyl)ethyl]-4-methylpyrrole-5-carboxylate (**37**; 4.61 g) was dissolved in 50 mL of glacial acetic acid at 40 °C under nitrogen, followed by addition of *p*-toluenesulfonic acid monohydrate (145 mg). To this reaction mixture was added a solution of *tert*-butyl 5-(acetoxymethyl)-4-[2-(methoxycarbonyl)ethyl]-3-methylpyrrole-2-carboxylate (**36**; 5.19 g) in acetic acid (50 mL) dropwise during 30 min. The reaction mixture was stirred for an additional 4 h at 40 °C. After cooling, the solution was poured into water (200 mL) and extracted with dichloromethane (300 mL). The organic phase was washed with saturated sodium bicarbonate until the aqueous layer was slightly basic (pH 7–8). The organic phase was dried (Na_2SO_4)

(46) Johnson, A. W.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1958**, 4255–4257.
(47) Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329–2335.

and evaporated to give a brown oil. Column chromatography on silica gel (elution with dichloromethane) gave 8.0 g (89.9%) as a very viscous yellow oil: IR ($CHCl_3$, NaCl cell) 3435 (m, br, NH), 1716, 1670 (s, br, C=O) cm^{-1}. NMR (ppm) 1.55 (s, 9 H, *t*-Bu), 2.24 (s, 3 H, Me), 2.29 (s, 3 H, Me), 2.35–2.87 (m, 8 H, CH_2CH_2CO), 3.58 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.93 (s, 2 H, CH_2), 5.24 (s, 2 H, $PhCH_2$), 7.35 (s, 5 H, Ph), 8.80 (br s, 1 H, NH), 9.10 (br s, 1 H, NH).

***tert*-Butyl 5′-[(Benzyloxy)carbonyl]-3,4′-bis(2-chloroethyl)-3′,4-dimethylpyrromethane-5-carboxylate (34).** Benzyl 3-(2-chloroethyl)-4-methylpyrrole-2-carboxylate (**43**; 3.30 g) in glacial acetic acid (50 mL) in the presence of *p*-toluenesulfonic acid monohydrate (102 mg) was treated dropwise (30 min) with *tert*-butyl 2-(acetoxymethyl)-3-(2-chloroethyl)-4-methyl-5-carboxylate (**42**; 3.76 g) in acetic acid (52 mL). The solution was stirred for 4 h at 40 °C, cooled, then diluted with dichloromethane (300 mL), and washed with sodium bicarbonate solution to between pH 7 and 8, followed by water (3 × 300 mL). The organic phase was dried (Na_2SO_4) and evaporated to give a dark red oil. Purification by silica gel chromatography (elution with dichloromethane) gave 5.3 g (84%) of a viscous brown oil. Recrystallization from methanol afforded cream-colored prisms: Mp 51.5–53 °C. IR ($CHCl_3$, NaCl cell) 3436 (m, br, NH), 1674 (s, br, C=O) cm^{-1}. NMR (ppm) 1.53 (s, 9 H, *t*-Bu), 2.00 (s, 3 H, Me), 2.23 (s, 3 H, Me), 2.70–3.73 (m, 8 H, CH_2CH_2Cl), 3.89 (s, 2 H, CH_2), 5.25 (s, 2 H, $PhCH_2$), 7.36 (s, 5 H, Ph), 9.15 (br s, 1 H, NH), 9.45 (br s, 1 H, NH). Anal. Calcd for $C_{28}H_{34}Cl_2N_2O_4$: C, 63.04; H, 6.42; N, 5.25. Found: C, 63.11; H, 6.41; N, 5.23.

Benzyl 2-(2-Chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1′,1,3,6-tetramethyltripyrrene-*a*-6′-carboxylate (10). The foregoing pyrromethane **33** (2 g) was treated with trifluoroacetic acid (14 mL) with stirring under nitrogen at 35 °C for 10 min. The formylpyrrole **38** (622 mg) in methanol (96 mL) was added at once. The red solution was stirred an additional 90 min, followed by addition of 31% hydrobromic acid solution in acetic acid (0.2 mL) and fresh anhydrous diethyl ether (120 mL). Continued stirring under nitrogen flushing for 10 h resulted in the formation of orange crystals that were filtered off and thoroughly washed with anhydrous ether. Only a small amount of the product was obtained in crystalline form [198 mg (6.6%)], though spectrophotometry indicated very efficient transformation of the pyrromethane to tripyrene: Mp 143–145 °C. IR ($CHCl_3$, NaCl cell) 1724, 1689, 1612 (s, br, C=O) cm^{-1}. NMR (ppm) 2.05 (s, 3 H, Me), 2.29 (s, 6 H, 2 Me), 2.68 (s, 3 H, Me), 2.2–3.4 (m, 12 H, CH_2CH_2Cl and 2 CH_2CH_2CO), 3.69 (s, 6 H, OMe), 5.13 (s, 2 H, CH_2), 5.30 (s, 2 H, $PhCH_2$), 7.10 (s, 1 H, vinyl H), 7.2–7.6 (m, 5 H, Ph), 10.84 (br s, 1 H, NH), 13.85 (br s, 2 H, NH). UV–vis λ_{max} 496 nm (ϵ 82500). Anal. Calcd for $C_{36}H_{42}BrClN_3O_6$: C, 59.39; H, 5.81; N, 5.77. Found: C, 59.49; H, 5.80; N, 5.50.

Benzyl 1-(2-Chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1′,2,3,6-tetramethyltripyrrene-*a*-6′-carboxylate Hydrobromide (11). The foregoing pyrromethane **33** (2.863 g) was stirred for 5 min in trifluoroacetic acid (20 mL) under nitrogen. Previously dissolved formylpyrrole **40**[31] (916 mg) in methanol (120 mL) was added in a single portion. The red-brown solution was stirred for an additional 90 min, followed by the addition of 31% hydrobromic acid in acetic acid (0.5 mL) and diethyl ether (260 mL). The reaction mixture was immediately cooled to 0 °C and stirred for 1 h while flushing with nitrogen which resulted in the formation of reddish orange crystals. Collection by filtration and washing thoroughly with diethyl ether followed by petroleum ether afforded the desired product [1.273 g (35%)] as orange prisms: Mp 100–102 °C. IR ($CHCl_3$, NaCl cell) 1725, 1682, 1616 (s, br, C=O) cm^{-1}. NMR (ppm) 2.31 (s, 6 H, Me), 2.35 (s, 3 H, Me), 2.72 (s, 3 H, Me), 2.18–3.63 (m, 12 H, CH_2CH_2Cl and 2 CH_2CH_2CO), 3.69 (s, 6 H, OMe), 4.45 (s, 2 H, CH_2), 5.31 (s, 2 H, $PhCH_2$), 7.14 (s, 1 H, vinyl H), 7.2–7.6 (m, 5 H, Ph), 10.5 (br s, 1 H, NH), 13.4 (br s, 2 H, 2 NH). UV–vis, λ_{max} 492 nm (ϵ 83500). Anal. Calcd for $C_{36}H_{43}BrClN_3O_6$: C, 59.31; H, 5.94; N, 5.76. Found: C, 59.39; H, 5.92; N, 5.74.

Benzyl 4,6-Bis(2-chloroethyl)-1-[2-(methoxycarbonyl)ethyl]-1′,2,3,5-tetramethyltripyrrene-*a*-6′-carboxylate (12). The foregoing pyrromethane **34** (2.5 g) was treated with trifluoroacetic acid (19 mL) with stirring under nitrogen at room temperature for 5 min. The formylpyrrole **44**[47] (981 mg) previously dissolved in methanol (120 mL) was added all at once. The brownish solution was stirred for 90 min, followed by the addition of 31% hydrobromic acid in acetic acid solution (0.3 mL) and fresh anhydrous diethyl ether (200 mL). Continued stirring for 15 min resulted in the formation of reddish orange crystals. Collection by filtration and washing thoroughly with diethyl ether gave 1.1 g (33.3%) of reddish orange prisms: Mp 188 °C dec. IR ($CHCl_3$, NaCl cell) 1726, 1688, 1615 (s, br, C=O) cm^{-1}. NMR (ppm) 2.09 (s, 3 H, Me), 2.26 (s, 3 H, Me), 2.30 (s, 3 H, Me), 2.69 (s, 3 H, Me), 2.4–3.65 (m, 12 H, 2 CH_2CH_2Cl and CH_2CH_2O), 3.65 (s, 3 H, OMe), 4.33 (s, 2 H, CH_2), 5.27 (s, 2 H, $PhCH_2$), 7.08 (s, 1 H, vinyl H), 7.17–7.57 (m, 5 H, Ph), 10.5 (br s, 1 H, NH), 13.4 (br s, 2 H, 2 NH). UV–vis, λ_{max} 492 nm (ϵ 81000). Anal. Calcd for $C_{34}H_{40}BrCl_2N_3O_4$: C, 57.88; H, 5.71; N, 5.96. Found: C, 57.82; H, 5.66; N, 5.90.

2,8-Bis(2-chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1′,1,3,6,7,8′-[7-^{13}C]hexamethyl-*a*,*c*-biladiene Dihydrobromide (6). The foregoing tripyrrene salt **10** (192 mg) was stirred in trifluoroacetic acid (3.75 mL) at 25 °C for 6 h in the presence of 31% hydrogen bromide in acetic acid solution (0.75 mL). A solution of labeled formylpyrrole **14** (41 mg) in methanol (15 mL) was then added to the reaction mixture that was previously chilled to 5 °C. The resulting red solution was stirred for 30 min before dropwise addition of fresh anhydrous diethyl ether (45 mL). Collection of the resulting crystals and thorough washing with anhydrous ether afforded 162 mg (77.5%) of brick red crystals: Mp >300 °C (lit.[40] mp >300 °C, unlabeled). NMR (ppm) 2.061, 2.269, 2.721, 2.745 (each s, 6 H, 3 H, 3 H, 3 H, Me); 2.348 (d, J = 127.97 Hz, $^{13}CH_3$); 3.443, 3.447 (each s, 3 H, OMe); 2.038, 2.834 (each m, 4 H, CH_2CH_2CO); 2.927, 3.147, 3.594, 3.660 (each t, 2 H, CH_2CH_2Cl); 5.277 (s, 2 H, meso CH_2); 7.130, 7.167 (each s, 1 H, methine bridge CH); 13.38, 13.43, 13.57 (each s, 1 H, 1 H, 2 H, NH). UV–vis, λ_{max} 450 nm (ϵ 90000), 524 (123000).

2,8-Bis(2-chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1,1′,3,6,7,8′-[1-^{13}C]hexamethyl-*a*,*c*-biladiene Dihydrobromide (7). The foregoing tripyrrene salt **11** (1.02 g) in trifluoroacetic acid (20.5 mL) and 31% hydrobromic acid/acetic acid solution (4.1 mL) was stirred for 7 h under nitrogen at ambient temperature. To this prechilled mixture (5 °C) was added a solution of labeled formylpyrrole **15** (212 mg) in methyl alcohol (50 mL). The mixture was stirred at 25 °C for 30 min before anhydrous diethyl ether (240 mL) was added dropwise. The resulting crystals were filtered and washed with anhydrous ether to give 901 mg (81%) of brick red microprisms: Mp >300 °C (lit.[40] mp >300 °C, unlabeled). NMR (ppm) 2.06 (d, J = 127.52 Hz, 3 H, $^{13}CH_3$); 2.269, 2.272, 2.351, 2.721, 2.744 (each s, 3 H, Me); 3.443, 3.447 (each s, 3 H, OMe); 2.059, 2.834 (each m, 4 H, CH_2CH_2CO); 2.928, 3.148, 3.595, 3.661 (each t, 2 H, CH_2CH_2Cl); 5.276 (s, 2 H, meso CH_2); 7.131, 7.168 (each s, 1 H, methine bridge CH); 13.38, 13.42, 13.55 (each s, 1 H, 1 H, 2 H, NH). UV–vis, λ_{max} 450 nm (ϵ 93000), 524 (125000).

4,6-Bis(2-chloroethyl)-1,8-bis[2-(methoxycarbonyl)ethyl]-1′,2,3,5,7,8-[7-^{13}C]hexamethyl-*a*,*c*-biladiene Dihydrobromide (8). The foregoing benzyl tripyrrene salt **12** (634 mg) was first treated with trifluoroacetic acid (13.2 mL) and 31% HBr/acetic acid solution (2.6 mL) for 6 h under nitrogen at 25 °C. Labeled formylpyrrole **16** (189 mg) dissolved in methanol (25 mL) was added to the precooled (5 °C) reaction mixture. The mixture was stirred at 25 °C for 8 h under nitrogen before dropwise addition of anhydrous diethyl ether (160 mL). The precipitated *a*,*c*-biladiene dihydrobromide salt was filtered off and washed with anhydrous ether. This procedure yielded 548 mg (76.6%) of brick red microcrystals: Mp >300 °C (lit.[31] mp >300 °C, unlabeled). NMR (ppm) 2.00, 2.30, 2.333, 2.745 (each s, 3 H, 3 H, 6 H, 3 H, Me); 2.335 (d, J = 128.08 Hz, 3 H, $^{13}CH_3$); 3.584, 2.488 (each t, 2 H, CH_2CH_2CO); 3.068, 2.778 (each m, 4 H, CH_2CH_2Cl); 3.677 (s, 6 H, OMe); 5.248 (s, 2 H, meso CH_2); 7.138, 7.147 (each s, 1 H, methine bridge CH); 13.55, 13.5, 13.39, 13.32 (each s, 1 H, NH). UV–vis, λ_{max} 450 nm (ϵ 68000), 524 (121000).

4,6-Bis(2-chloroethyl)-1,8-bis[2-(methoxycarbonyl)ethyl]-1′,2,3,5,7,8′-[2-^{13}C]hexamethyl-*a*,*c*-biladiene Dihydrobromide (9). The benzyl tripyrrene salt **13**[40] (585 mg) was added to trifluoroacetic acid (13.2 mL), followed by the addition of 31% hydrogen bromide in acetic acid solution (2.5 mL). The mixture was stirred for 6 h under nitrogen at 25 °C and then cooled to approximately 25 °C before a solution of formylpyrrole **16** (175

mg) in methyl alcohol (25 mL) was added. After stirring for 30 min, dropwise addition of anhydrous diethyl ether (160 mL) caused precipitation of the *a,c*-biladiene salt, which was filtered off and washed with anhydrous ether to give 474 mg (72%) of brick red crystals: Mp >300 °C (lit.[31] mp >300 °C, unlabeled). NMR (ppm) 2.005, 2.303, 2.337, 2.744, 2.747 (each s, 3 H, Me); 2.332 (d, J = 127.96 Hz, 3 H, $^{13}CH_3$); 3.586, 2.489 (each t, 2 H, CH_2CH_2CO); 3.071, 2.779 (each m, 4 H, CH_2CH_2Cl); 3.680 (s, 6 H, OMe); 5.251 (s, 2 H, meso CH_2); 7.139, 7.147 (each s, 1 H, methine bridge CH); 13.58, 13.48, 13.39, 13.30 (each s, 1 H, NH). UV–vis, λ_{max} 448 nm (ϵ 74000), 524 (116000).

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[1-^{13}C]tetramethylporphyrin (39). A solution of anhydrous copper(II) chloride (800 mL) in *N,N*-dimethylformamide (14 mL) was preheated to 150 °C under nitrogen. To this mixture was added *a,c*-biladiene dihydrobromide **6** (153 mg), and the mixture was stirred at this same temperature for 5 min, and an additional 5 min while cooling. The warm solution was poured into water, extracted with dichloromethane (2 × 100 mL), dried (Na_2SO_4), and evaporated to dryness under vacuum: UV–vis, λ_{max} 400 nm, 528, 564. The resulting porphyrin copper complex was demetalated by stirring vigorously for 45 min at 25 °C in 10% sulfuric acid/trifluoroacetic acid (12 mL). The acidic solution was poured into water (100 mL), extracted with chloroform (3 × 100 mL), and washed successively with water (300 mL), sodium bicarbonate solution (200 mL), and water (300 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness under vacuum. Brief treatment of the resulting residue with ethereal diazomethane, followed by evaporation of solvent and column chromatography on neutral alumina (Brockmann grade III, elution with dichloromethane). After recrystallization from dichloromethane/methanol 32 mg (27%) of red crystals [mp 214–216 °C (lit.[48] mp 216–218 °C, unlabeled)] were obtained: NMR (ppm) –3.80 (br s, 2 H, NH); 3.30 (t, 4 H, CH_2CO); 3.655 (s, 3 H, Me); 3.664 (s, sh, 3 H, Me); 3.667 (s, 6 H, OMe); 3.685 (d, J = 127 Hz, 1-[$^{13}CH_3$]); 3.695 (s, 3 H, Me); 4.34 (t, 4 H, CH_2Cl); 4.43 (t, 4 H, CH_2CH_2CO); 4.55 (t, 4 H, CH_2CH_2Cl); 10.04, 10.05, 10.12, 10.13 (each s, 1 H, meso H).

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[3-^{13}C]tetramethylporphyrin (41). The foregoing *a,c*-biladiene salt **7** (883 mg), copper(II) chloride (4.4 g), and dry dimethylformamide (77 mL) were treated in the same manner as described in the previous experiment. The residual copper(II) complex [UV–vis, λ_{max} 400 nm, 526, 562] was demetalated with 10% sulfuric acid/trifluoroacetic acid (65 mL) at 25 °C for 45 min. After workup and chromatographic isolation as mentioned above, 214 mg (31%) of red prisms [mp 216–217 °C (lit.[48] mp 216–218 °C, unlabeled)] were isolated: NMR (ppm) –3.77 (br s, 2 H, NH); 3.29 (t, 4 H, CH_2CO); 3.672 (d, J = 127 Hz, 3 H, 3-[$^{13}CH_3$]); 3.646, 3.651, 3.656, 3.662 (each unresolved s, 15 H, Me and OMe); 4.32 (t, 4 H, CH_2Cl); 4.42 (t, 4 H, CH_2CH_2CO); 4.52 (t, 4 H, CH_2CH_2Cl); 10.02, 10.10 (each s, 2 H, meso H).

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[5-^{13}C]tetramethylporphyrin (45). As described above, *a,c*-biladiene salt **8** (501 mg), copper(II) chloride (2.5 g), and dry dimethylformamide (44 mL) afforded the copper(II) porphyrin: UV–vis, λ_{max} 397 nm, 526, 562. After a similar demetalation procedure using 10% sulfuric acid/trifluoroacetic acid (37 mL) the title porphyrin was obtained (108 mg, 28%) as red crystals: Mp 218–219 °C (lit.[48] mp 216–218 °C, unlabeled). NMR (ppm) –3.80 (br s, 2 H, NH); 3.30 (t, 4 H, CH_2CO); 3.651 (s, 3 H, Me); 3.662 (s, 6 H, OMe); 3.666 (d, J = 126.98 Hz, 3 H, 5-[$^{13}CH_3$]); 3.684 (s, 3 H, Me); 3.692 (s, 3 H, Me); 4.34 (t, 4 H, CH_2Cl); 4.43 (t, 4 H, CH_2CH_2CO); 4.55 (t, 4 H, CH_2CH_2Cl); 10.04, 10.05, 10.12, 10.13 (each s, 1 H, meso H).

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[8-^{13}C]tetramethylporphyrin (46). The foregoing *a,c*-biladiene salt **9** (469 mg), copper(II) chloride (2.3 g), and dry methylformamide (41 mL) were treated in a manner similar to that described above. The copper(II) complex was obtained: UV–vis, λ_{max} 400 nm, 526, 562. Demetalation with 10% sulfuric acid/trifluoroacetic acid (35 mL) afforded 117 mg (32%) as red prisms: Mp 217–218 °C (lit.[48] mp 216–218 °C, unlabeled). NMR (ppm) –3.80 (br s, 2 H, NH); 3.30 (t, 4 H, CH_2CO); 3.660 (d, J = 127 Hz, 3 H, 8-[$^{13}CH_3$]); 3.650, 3.663, 3.668, 3.686 (s, 15 H, Me and OMe); 4.33 (t, 4 H, CH_2Cl); 4.43 (t, 4 H, CH_2CH_2CO); 4.55 (t, 4 H, CH_2CH_2Cl); 10.04, 10.05, 10.12, 10.13 (each s, 1 H, meso H).

6,7-Bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[1-^{13}C]tetramethyl-2,4-divinylporphyrin [[1-^{13}C]Protoporphyrin IX Dimethyl Ester] (2). The foregoing (chloroethyl)porphyrin **39** (32 mg) was dissolved in freshly distilled pyridine (25 mL) and the resultant mixture refluxed under nitrogen for 30 min. To this mixture was added water (4 mL), and the solution was stirred at 105 °C under nitrogen; after 5 min 3% aqueous potassium hydroxide (4.5 mL) was added. The reaction mixture was stirred for an additional 2.5 h at the same temperature before cooling and diluting with dichloromethane (200 mL) and tetrahydrofuran (200 mL). The organic layer was washed with 2 M hydrochloric acid solution (3 × 300 mL), filtered through filter paper, and evaporated to dryness. After brief treatment with excess ethereal diazomethane, the solution was evaporated under reduced pressure and the residue was chromatographed on neutral alumina (Brockmann grade III, elution with 20% toluene in dichloromethane). Recrystallization from dichloromethane/*n*-hexane gave 7 mg (25%) of the desired carbon-13-labeled protoporphyrin IX dimethyl ester as purple prisms: Mp 227–228 °C (lit.[43] mp 224–225 °C, unlabeled). ^{1}H NMR (ppm) –3.80 (br s, 2 H, NH); 3.28 (t, 4 H, CH_2CO); 3.628 (s, 3 H, Me); 3.643 (s, 3 H, Me); 3.662 (s, 6 H, OMe); 3.716 (s, 3 H, Me); 3.727 (d, J = 127 Hz, 3 H, 1-[$^{13}CH_3$]); 4.41 (t, 4 H, CH_2CH_2CO); 6.20, 6.38 (each d, 2 H, 2 H, β-vinyl H); 8.28 (m, 2 H, α-vinyl H); 10.07, 10.13, 10.21, 10.27 (each s, 1 H, meso H). ^{13}C NMR (ppm) 12.77 (s, split into a quartet, J = 127 Hz, in the proton-coupled mode). UV–vis, λ_{max} 406 nm (ϵ 145000), 506 (13500), 540 (11000), 576 (6300), 630 (4500), 654 (500).

6,7-Bis[2-(methoxycarbonyl)methyl]-1,3,5,8-[3-^{13}C]tetramethyl-2,4-divinylporphyrin [[3-^{13}C]Protoporphyrin IX Dimethyl Ester] (3). As described above, treatment of the (chloroethyl)porphyrin **41** (214 mg) with pyridine (120 mL), water (30 mL), and 3% aqueous potassium hydroxide (30 mL) resulted in 118 mg (62%) of the carbon-13-labeled product as purple crystals: Mp 226–228 °C (lit.[43] mp 224–225 °C, unlabeled). ^{1}H NMR (ppm) –3.60 (br s, 2 H, NH); 3.29 (t, 4 H, CH_2CO); 3.639 (s, 3 H, Me); 3.64 (s, sh, 3 H, Me); 3.664 (s, 6 H, OMe); 3.733 (d, J = 127 Hz, 3 H, 3-[$^{13}CH_3$]); 3.745 (s, 3 H, Me); 4.42 (t, 4 H, CH_2CH_2CO); 6.20, 6.40 (each d, 2 H, 2 H, β-vinyl H); 8.28 (m, 2 H, α-vinyl H); 10.07, 10.13, 10.21, 10.27 (each s, 1 H, meso H). ^{13}C NMR (ppm) 12.731 (s, split into a quartet, J = 127 Hz, in the proton-coupled mode). UV–vis, λ_{max} 404 nm (ϵ 145000), 506 (13000), 540 (10000), 576 (6000), 630 (4000), 654 (500).

6,7-Bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[5-^{13}C]tetramethyl-2,4-divinylporphyrin [[5-^{13}C]Protoporphyrin IX Dimethyl Ester] (4). A similar reaction with (chloroethyl)porphyrin **45** (108 mg), pyridine (60 mL), water (15 mL), and 3% aqueous potassium hydroxide solution (15 mL) gave the carbon-13-labeled porphyrin [38 mg (40%)] as purple prisms: Mp 227–228 °C (lit.[43] mp 224–225 °C, unlabeled). ^{1}H NMR (ppm) –3.64 (br s, 2 H, NH); 3.29 (t, 4 H, CH_2CO); 3.632 (d, J = 126.89 Hz, 3 H, 5-[$^{13}CH_3$]); 3.651 (s, 3 H, Me); 3.664 (s, 6 H, OMe); 3.725 (s, 3 H, Me); 3.736 (s, 3 H, Me); 4.42 (t, 4 H, CH_2CH_2CO); 6.20 6.38 (each d, 2 H, 2 H, β-vinyl H); 8.28 (m, 2 H, α-vinyl H); 10.06, 10.11, 10.19, 10.25 (each s, 1 H, meso H). ^{13}C NMR (ppm) 11.662 (s, split into a quartet, J = 127 Hz in the proton-coupled mode). UV–vis λ_{max} 404 nm (ϵ 145000), 504 (12800), 540 (9750), 576 (5700), 630 (4000), 654 (900).

6,7-Bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-[8-^{13}C]tetramethyl-2,4-divinylporphyrin [[8-^{13}C]Protoporphyrin IX Dimethyl Ester] (5). In a similar procedure (chloroethyl)porphyrin **45** (117 mg), pyridine (60 mL), water (15 mL), and 3% aqueous potassium hydroxide (15 mL) afforded the title carbon-13-labeled protoporphyrin IX dimethyl ester [60 mg (58%)] as purple crystals: Mp 228–229 °C (lit.[43] mp 224–225 °C, unlabeled). ^{1}H NMR (ppm) –3.65 (br s, 2 H, NH); 3.29 (t, 4 H, CH_2CO); 3.630 (s, 3 H, Me); 3.645 (d, J = 126.93 Hz, 3 H, 8-[$^{13}CH_3$]); 3.662 (s, 6 H, OMe); 3.720 (s, 3 H, Me); 3.731 (s, 3 H, Me), 4.41 (t, 4 H, CH_2CH_2CO); 6.20, 6.38 (each d, 2 H, 2 H, β-vinyl H); 8.26 (m, 2 H, α-vinyl H); 10.05, 10.10, 10.18, 10.24 (each s, 1 H, meso H). ^{13}C NMR (ppm) 11.608 (s, split into a quartet in

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the proton-coupled mode). UV-vis, λ_{max} 408 nm (ϵ 142 000), 506 (13 700), 540 (10 500), 576 (6200), 630 (4400), 654 (700).

Acknowledgment. This research was supported by grants from the National Institutes of Health (HL 22252) and the National Science Foundation (CHE-81-20891). We are pleased to acknowledge financial assistance (to H.D.T.) from Yarmouk University, Jordan.

Registry No. **2**, 104834-69-7; **3**, 104834-70-0; **4**, 104834-71-1; **5**, 104834-72-2; **6**, 104848-65-9; **7**, 104834-62-0; **8**, 104834-63-1; **9**, 104834-65-3; **10**, 104848-64-8; **11**, 104834-60-8; **12**, 104834-61-9; **13**, 104834-64-2; **14**, 104834-50-6; **15**, 104834-54-0; **16**, 104834-58-4; **17**, 89909-45-5; **18**, 62562-74-7; **19**, 89909-44-4; **20**, 87462-15-5; **21**, 87462-14-4; **22**, 104834-47-1; **23**, 104834-49-3; **24**, 60024-79-5; **25**, 50622-71-4; **26**, 50622-73-6; **27**, 104834-51-7; **28**, 104834-52-8; **29**, 89909-50-2; **30**, 104834-55-1; **31**, 104834-56-2; **32**, 104834-57-3; **33**, 32725-82-9; **34**, 104834-59-5; **36**, 30089-44-2; **37**, 31896-88-5; **38**, 88055-46-3; **39**, 104848-66-0; **39** (Cu(II) complex), 104834-73-3; **40**, 87434-71-7; **41**, 104834-66-4; **41** (Cu(II) complex), 104834-74-4; **42**, 92735-21-2; **43**, 104834-45-9; **44**, 18818-25-2; **45**, 104834-67-5; **45** (Cu(II) complex), 104848-67-1; **46**, 104834-68-6; **46** (Cu(II) complex), 104834-75-5; benzyl acetoacetate, 5396-89-4; acetoacetaldehyde dimethyl acetal, 5436-21-5; dimethyl 1,3-acetonedicarboxylate, 1830-54-2; dimethyl 1,3-acetonedicarboxylate (oxime), 73870-13-0; *tert*-butyl acetoacetate, 1694-31-1; benzyl 3-(2-chloroethyl)-5-iodo-4-methylpyrrole-2-carboxylate, 104834-44-8; 2-[(benzyloxy)carbonyl]-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylic acid, 104834-46-0; *tert*-butyl 2-[(benzyloxy)carbonyl]-3-(2-chloroethyl)-4-methylpyrrole-5-carboxylate, 89909-57-9; benzyl 4-(2-hydroxyethyl)-3,5-[3-^{13}C]dimethylpyrrole-2-carboxylate, 104834-48-2; benzyl 3-(2-chloroethyl)-4,5-[4-^{13}C]dimethylpyrrole-2-carboxylate, 104834-53-9; methyl hydrogen malonate, 16695-14-0.

Photochemistry of Polyfunctional Molecules. Intramolecular Aryl to Ketone Singlet Energy Transfer in the *trans*- and *cis*-Decalins, 7-Keto-13β-methyl-5,6,7,8,9,10,13β,14α-octahydrophenanthrene, and Its 14β Isomer[1a]

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Received June 23, 1986

The photochemistry and photophysics of the title compounds are reported. The trans fused aryldecalone (TAK), upon excitation with 254-nm light in methanol, undergoes typical ketone photochemistry to give products of reduction (1) and α cleavage (**2**–**4**) with ϕ_{loss} = 0.27. The cis fused aryldecalone (CAK) also gives ketone photochemistry upon 254-nm excitation; ϕ_{loss} = 0.17. Both isomers show greatly reduced aryl fluorescence and appreciable ketone emission upon excitation of the aryl functionality, and it is proposed that their photochemistry derives from intramolecular (exchange) singlet energy transfer from the aryl to the keto chromophore. Rate constants for this energy transfer in CAK and TAK, in isopropyl alcohol, are estimated at $\geq 5 \times 10^9$ and 2.7×10^9 s^{-1}, respectively, in good agreement with literature estimates for such rates in other aryl ketones.

The photochemistry and photophysics associated with polyfunctional organic molecules has evolved into an area of broad interest to synthetic and physical organic chemists concerned with the consequences of intramolecular interactions in the excited states of complex substrates.[2] Despite the extensive activity in this field, nonconjugated aryl ketones have been relatively neglected when one considers that (1) the coexistence of these moieties is quite common, as for example among the steroids, (2) this functional group pair has the potential for several significant interactions including exothermic singlet and triplet aryl to ketone energy transfer, as well as exciplex quenching of the ketone excited state by the aryl group,[3,4] and (3) intramolecular energy transfer could by synthetically useful if one could selectively sensitize (i.e., "activate") a particular keto group in an aryl polyketone (by capitalizing on a ketone's propitious location relative to the sensitizing chromophore). It was within the latter context that we decided to study the 254-nm initiated photochemistry of two prototypical aryl ketones, the trans and cis fused decalins, 7-keto-13β-methyl-5,6,7,8,9,10,13β,14α-octahydrophenanthrene (TAK) and its 14β isomer CAK.

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