917-54-4; Se, 7782-49-2; MeSeLi, 50491-55-9; MeSNa, 5188-07-8; o-C_6H_4PhSeMe, 87137-13-1; m-C_6H_4PhSeMe, 87137-14-2; p-C_6H_4PhSeMe, 75480-68-1; 2-$C_{10}H_7$SeMe, 20613-84-7; 4-C_9H_6NSeMe, 87137-15-3; p-C_6H_4PhSeCN, 87137-16-4; 2-$C_{10}H_7$SeCN, 87137-17-5; p-$C_6H_4ClS^-$, 35337-68-9; o-C_6H_4PhCl, 2051-60-7; m-C_6H_4PhBr, 2113-57-7; p-C_6H_4PhBr, 92-66-0; 2-$C_{10}H_7$Bu, 580-13-2; 4-C_9H_6NCl, 611-35-8; MeI, 74-88-4; EtI, 75-03-6; Me_2CHI, 75-30-9; ICN, 506-78-5.

Neighboring Group Participation in the Pyrrole Series[1]

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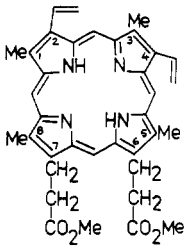
With use of proton and carbon-13 NMR spectroscopy of deuterium- and carbon-13-labeled substrates, the transformation of certain (2-hydroxyethyl)pyrroles (**4**, **18**, **21**) into the corresponding (2-haloethyl)pyrroles (using thionyl chloride/pyridine or triphenylphosphine/carbon tetrabromide) is shown to proceed with scrambling of the two carbons in the side chain. The mechanism is proposed to involve neighboring group participation by the pyrrole nucleus to give an ethylenepyrrolonium ion, **17**. When a nuclear ester is conjugated with the carbon bearing the hydroxyethyl side chain and the adjacent peripheral β position is unsubstituted (e.g., pyrrole **25**), the transformation into (2-chloroethyl)pyrrole **26** proceeds without scrambling. In contrast, the β-methylpyrrole **21** was transformed into a mixture of (2-chloroethyl)pyrroles (**33** and **34**) when treated with thionyl chloride/pyridine. Using carbon-13-enriched porphyrins, conversion of (2-hydroxyethyl)porphyrins into the corresponding 2-chloroethyl derivatives is shown to take place without scrambling of the side-chain carbons and therefore without anchimeric assistance by the porphyrin nucleus.

Several different types of strategy have been employed in synthetic approaches[2-8] to regioselectively labeled derivatives of protoporphyrin IX dimethyl ester (**1**). As the



corresponding iron(III) porphyrindicarboxylic acids (hemins), these compounds have been used successfully in a series of high-resolution NMR[9-22] and resonance Raman[23-25] studies of hemes, hemoproteins, and of various structure–activity relationships. It was anticipated[1] that a simple sequence of reactions (**2** → **7**) could be used to accomplish regioselective deuterium labeling of the α methylene groups in pyrrole **7** and that this could be built into the corresponding labeled protoporphyrin IX dimethyl ester (**1**).[26,27] In this paper we report on our attempts to

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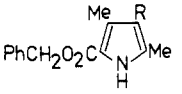
accomplish this chemistry and analyze an unexpected rearrangement process that provides the first example of neighboring group participation by monocyclic pyrroles.

Results and Discussion

The [(methoxycarbonyl)methyl]pyrrole **2** was successfully deuterated (to give **3**) without transesterification of the benzyl ester by treatment in MeOD with a catalytic amount of NaOMe. The proton NMR spectrum of the



2	R = CH_2CO_2Me	**10**	R = CH_2CD_2CN
3	R = CD_2CO_2Me	**11**	R = CD_2CH_2Br
4	R = CD_2CH_2OH	**12**	R = CH_2CD_2Br
5	R = CD_2CH_2X	**13**	R = CD_2CH_2OAc
6	R = CD_2CH_2CN	**14**	R = CD_2CH_2OMes
7	R = $CD_2CH_2CO_2Me$	**18**	R = $CH_2\dot{C}H_2OH$
8	R = CD_2CH_2Cl	**19**	R = $CH_2\dot{C}H_2Cl$
9	R = CH_2CD_2Cl	**20**	R = $\dot{C}H_2CH_2Cl$

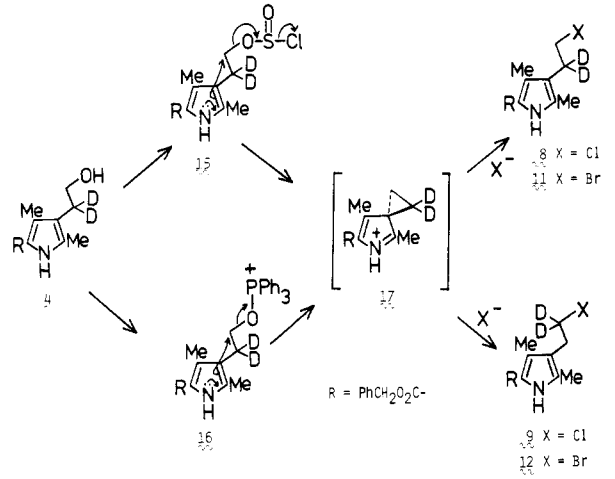
• Indicates 99% carbon-13 enrichment.

crude product showed no evidence of a singlet a 3.37 ppm due to the methylene, so the product was reduced with diborane to give a quantitative yield of the labeled 4-(2-hydroxyethyl)pyrrole **4**, which lacked the requisite methylene protons (and coupling) in its proton NMR spectrum.[1] The diborane reduction step effectively "locked-in" the hydroxyethyl labels, such that no special conditions appeared necessary to protect them from loss through subsequent adventitious exchange. Pyrrole **4** was treated with thionyl chloride and pyridine and afforded a 74% yield of 4-(2-chloroethyl)pyrrole. The NMR spectrum[1] indicated[28] approximately 1:1 formation of **8** and its isomer **9**. Integration of the spectrum suggested that the required pyrrole was in a very slight excess over its unwanted isomer **9**. The mixture of deuterated pyrroles, **8** and **9**, was treated with sodium cyanide in dimethyl sulfoxide and gave a 91% yield of 4-(2-cyanoethyl)pyrrole, which again (NMR analysis) consisted of two isomers, **6** and **10**. Integration of the methylene singlets at 2.44 and 2.76 ppm indicated exactly a 1:1 mixture. When bromination of pyrrole **4** was attempted with carbon tetrabromide and triphenylphosphine, a mixture of isomers **11** and **12** was again observed. With acetic anhydride in pyridine, the labeled hydroxyethylpyrrole **4** gave (NMR analysis) a single 4-(2-acetoxyethyl)pyrrole (**13**). Likewise, treatment of pyrrole **4** with mesyl chloride/pyridine gave the pure, unrearranged pyrrole **14**. Treatment of **13** with sodium cyanide in dimethyl sulfoxide or *N*-methylpyrrolidone failed to accomplish nucleophilic displacement of the acetate function, and only starting material was recovered, but similar treatment of **14** gave a mixture of the two possible (cyanoethyl)pyrroles **6** and **10**.

The most likely explanation for the formation of the pairs of isomers **8**/**9** and **11**/**12** is shown in Scheme I. The mechanism proposes neighboring group participation on the part of the electron-rich pyrrole nucleus, such that the initially formed species **15** ($SOCl_2$) or **16** (PPh_3/CBr_4) reacts intramolecularly to give the ethylenepyrrolonium ion **17**. Subsequent attack by the chloride or bromide counterion can then take place at either cyclopropyl methylene to give the isomeric products. The slight excess

(28) Two *uncoupled* singlets at the chemical shifts of the methylene triplets in the proton NMR spectrum of the unlabeled compound clearly indicated the formation of two isomeric molecules.

Scheme I



of the isomers **8** and **11** indicates that though the majority of the reaction proceeds through the intermediate **17**, some small amount of direct displacement is taking place. The proposals in Scheme I are precedented in the literature, though not specifically for the case of anchimeric assistance by pyrroles. For example, neighboring group participation by the phenyl ring[29-39] was documented as early as 1949 by Cram. Neighboring group participation has also been observed in the indole series, and several investigations have clearly established that the electron-rich indole nucleus is a potent neighboring group.[40-46]

A clearer picture of the carbon-based rearrangement processes inherent in Scheme I can be obtained by using carbon-13 NMR spectroscopy. The carbon-13 NMR spectrum of the enriched hydroxyethylpyrrole **18** showed a singlet at 62.68 ppm. Treatment of **18** with thionyl chloride gave the carbon-13-enriched 4-(2-chloroethyl)-pyrroles **19** and **20**, with resonances in the carbon-13 NMR spectrum at 44.32 (CH_2Cl) and 27.87 ppm (CH_2CH_2Cl). This observation fully confirmed the proposals outlined in Scheme I.

In a separate proton NMR experiment, the ethylene-pyrrolonium ion **17** was observed during the chlorination reaction of **4**. The deuterated 4-(2-hydroxyethyl)pyrrole **4** was dissolved, in an NMR tube, in $CDCl_3$; the spectrum showed the methylene singlet at 3.8 ppm. To this solution was added an excess of thionyl chloride, and proton

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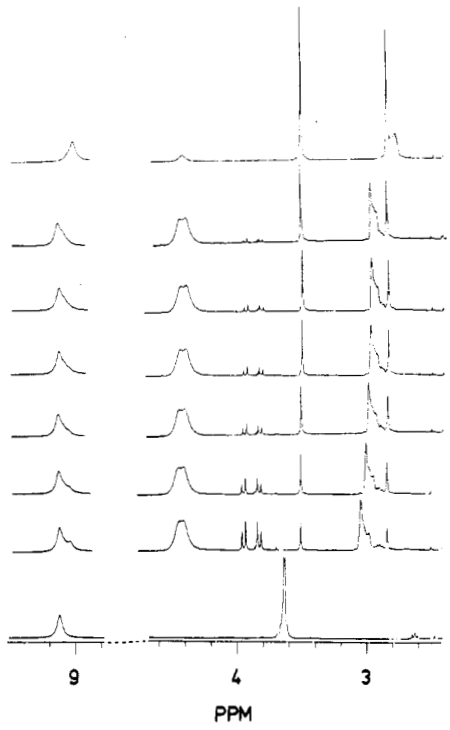
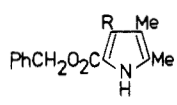
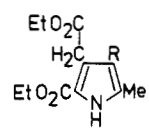


Figure 1. Direct NMR observation (360 MHz, in $CDCl_3$) of the ethylenepyrrolonium ion **17** during the transformation of labeled pyrrole **4** into **8** and **9**. The bottom scan represents the starting material and the top one the products. The resonances from the methylenes in the ethylenepyrrolonium ion **17** are assigned to the transient quartet at 3.8–3.9 ppm. The cyclopropane protons in the ethylene-*p*-anisonium ion (in SbF_5/SO_2) resonate at 3.47 ppm.[38]

FTNMR spectra were recorded at intervals (determined in preliminary work) of 1.2 min. The reaction was complete after 30 min, and Figure 1 shows stack-plotted spectra indicating changes in spectrum with time. A gradual disappearance of the methylene protons in **4** can be seen with time, and the α and β methylene resonances of the products **8** and **9** appear. At an intermediate stage, the spectrum shows the β-methylene protons of the thionyl chloride activated species **15** in conjunction with two transient sets of doublets at 3.8 and 3.9 ppm, which we assign to the methylene signals in the cyclopropylpyrrolium ion **17**. Much more complicated spectra were observed, as expected, for the unlabeled 4-(2-hydroxyethyl)pyrrole.

Since the intramolecular interaction responsible for formation of the ethylenepyrrolonium ions depends upon an electron-rich pyrrole nucleus undergoing nucleophilic displacement of a good leaving group on the terminus of the two-carbon side chain, the dependence of the position of electron-withdrawing substituents on the pyrrole nucleus was next examined. In pyrrole **21**, an isomer of **4**, the

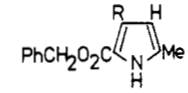


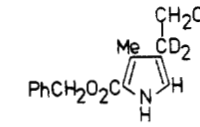


21 R = CD_2CH_2OH
33 R = CD_2CH_2Cl
34 R = CH_2CD_2Cl

22 R = CO_2t-Bu
23 R = H

nuclear benzyl ester group is conjugated with the β-pyrrole position from which nucleophilic displacement of the side-chain leaving group takes place. One might therefore expect that the cyclopropylpyrrolium ion would not be as favored in the case of **21** as it appeared to be for **4**. Pyrrole **21** was transformed into **24** by way of **22** and **23** by using standard conditions;[27] the methylene in **24** was then exchanged as previously, and the product was reduced with diborane to give **25**, which was treated with thionyl chloride

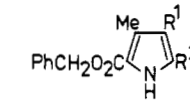


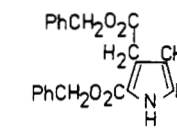


24 R = $CH_2CO_2CH_2Ph$
25 R = CD_2CH_2OH
26 R = CD_2CH_2Cl

27

and pyridine to give the corresponding 4-(2-chloroethyl)-pyrrole. Proton NMR spectroscopy indicated that the only product obtained was **26** and that no rearrangement had taken place, presumably owing to deactivation at the 4-position by the conjugated 5-ester. The yield of pyrrole obtained by the "direct" route was lower than that of the 2-chloroethylpyrroles produced by way of the ethylene-pyrrolonium ion **17**. In case the noninvolvement of the ethylenepyrrolonium ion in the chlorination of **25** was due to protonation equilibria involving the free β position, the isomer **27** was likewise chlorinated. In this case the product was obtained as a mixture of **28** and **29**. Also



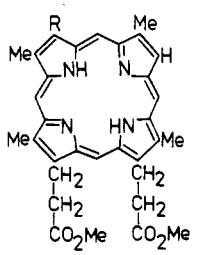


28 R^1 = CD_2CH_2Cl; R^2 = H
29 R^1 = CH_2CD_2Cl; R^2 = H
30 R^1 = CD_2CH_2Cl; R^2 = Cl
31 R^1 = CH_2CD_2Cl; R^2 = Cl

32

obtained from this reaction were the corresponding 5-chloropyrroles **30** and **31**, which also had suffered rearrangement during the chlorination. The precise analogue, **21**, of the 4-(2-hydroxyethyl)pyrrole **4** was prepared from the dibenzyl ester pyrrole **24** by Vilsmeier formylation (to give **32**) prior to diborane reduction, which gave **21** by concomitant reduction of the 3-formyl group and 4-ester. Treatment of labeled pyrrole **21** with thionyl chloride and pyridine resulted in formation of both pyrroles **33** and **34**. Thus, there appears to be a fine line of differentiation between the electronics of systems that permit the direct displacement to take place (e.g., **25**/**26**) compared with those that proceed by way of the ethylenepyrrolonium ion **17** (e.g., **4**/**8**,**9** and **21**/**33**,**34**). Apparently, introduction of the methyl group into pyrrole **25** (to give **21**) provides enough additional electron density to alter the mechanistic pathway.

Having established the intermediacy of the ethylene-pyrrolonium ion in the above reactions, and the dependence of its formation upon the electronic features of the substituents, the ability of the porphyrin nucleus to behave as a neighboring group was next investigated. For the purposes of this study, a porphyrin bearing a 2-hydroxyethyl substituent was required, and this was accessible by making use of quantities of 2-[[1-^{13}C]acetyl]deuteroporphyrin IX dimethyl ester (**35**), which was available as a by product from another, unconnected, study.[7] The acetylporphyrin **35** was reduced with sodium borohydride and then dehydrated, by using *p*-toluene sulfonic acid in *o*-dichlorobenzene, to give vinyl-labeled isopemptoporphyrin dimethyl ester (**36**). The proton-coupled carbon-13 NMR spectrum showed one doublet centered at 130.2 ppm. With thallium(III) nitrate in methanol, compound **36** was transformed into the corresponding dimethyl



35 R = $\overset{*}{C}O_2Me$
36 R = $\overset{*}{C}H{=}CH_2$
37 R = $CH_2\overset{*}{C}H(OMe)_2$
38 R = $CH_2\overset{*}{C}HO$
39 R = $CH_2\overset{*}{C}H_2OH$
40 R = $CH_2\overset{*}{C}H_2Cl$

acetal **37**, which was hydrolyzed (to give **38**) and then reduced by using sodium borohydride to give the required labeled 2-(2-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**39**). The proton-decoupled carbon-13 NMR spectrum of porphyrin **39** showed a single absorption at 65.0 ppm; after treatment with thionyl chloride and pyridine, the resulting 2-(2-chloroethyl)porphyrin (**40**) showed only one enriched carbon signal at 45.1 ppm, which split into a triplet (J_{C-H} = 147 Hz) when run in the proton-coupled mode. Thus, chlorination of (2-hydroxyethyl)porphyrins does not proceed through a spirocyclopropyl ion due to neighboring group participation by the porphyrin nucleus. The carbon-13 NMR spectra, however, did confirm that aryl migration takes place in the thallium(III) reaction of the vinylporphyrin **36** to give the dimethyl acetal **37**.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. Neutral alumina 90 (Merck, 70–230 mesh) was used for column chromatography, and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1-mm thick). Analytical TLC was performed on Merck silica gel 60 F 254 precoated sheets (0.2 mm). Electronic absorption spectra were measured on a Cary 17 spectrophotometer (solutions in dichloromethane), proton NMR spectra were measured at 360 MHz on a Nicolet NT-360 spectrometer, and carbon-13 NMR spectra were measured at 50.3 Mz on a Nicolet NT-200 instrument (solutions in $CDCl_3$). Mass spectra were measured (direct insertion probe, 70 eV, 50 μA, source temperature ca. 200 °C) on a Finnegan 3200 mass spectrometer. Elemental analyses were performed at the Berkeley Microanalytical Laboratory, Department of Chemistry, UC, Berkeley.

Benzyl 4-(2-Hydroxy-1,1-dideuterioethyl)-3,5-dimethylpyrrole-2-carboxylate (4). Benzyl 4-[(methoxycarbonyl)methyl]-3,5-dimethylpyrrole-2-carboxylate (**2**)[47] (15.6 g) and sodium methoxide (560 mg) were stirred at room temperature in MeOD (100 g) for 24 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (200 mL) and quickly washed with water (2 × 200 mL), dried (Na_2SO_4), and evaporated to dryness. The methylene peak at 3.35 ppm in the proton NMR spectrum of the unlabeled compound was absent, indicating >95% deuteration. The deuterated pyrrole was reduced with diborane[48] and gave 14.1 g (97%) of pyrrole **4**, mp 117–118 °C (lit.[48] mp 120–121 °C, undeuterated). The 4-α-methylene was not observed in the proton NMR spectrum, and the 4-β-methylene appeared as a singlet of integrated intensity two protons.

Benzyl 4-(2-Chloro-1,1-dideuterioethyl)-3,5-dimethylpyrrole-2-carboxylate (8) and Benzyl 4-(2-Chloro-2,2-dideuterioethyl)-3,5-dimethylpyrrole-2-carboxylate (9). The foregoing labeled hydroxyethylpyrrole **4** (11.3 g) in dry dichloromethane (280 mL) and pyridine (2.1 mL) was heated at 50 °C with stirring during dropwise addition of thionyl chloride (3 mL); nitrogen gas was then passed through the solution for 2 h, more dichloromethane being added at 30-min intervals to substitute for loss by evaporation, and after this time the reaction was determined to be complete by analytical TLC. The solvent was evaporated under vacuum, and the brown oily residue was reevaporated several times with toluene (as a chaser for thionyl chloride and pyridine). The residue was then chromatographed on a short column of silica gel (elution with dichloromethane) and then on a similar column of neutral alumina (Brockmann Grade III, elution with dichloromethane). The eluates were evaporated, and the residue was crystallized from dichloromethane/hexane to give the chloroethylpyrroles **8** and **9** (8.6 g, 74%): mp 118–119 °C, (lit.[49] mp 121–122 °C); ^{1}H NMR 2.21, 2.30 (each s, 3 H, 3,5-Me), 2.84, 3.50 (each br s, ca. 1 H, approximately 1:1 CH_2CD_2Cl and CD_2CH_2Cl, 5.32 (s, 2 H, CH_2Ph), 7.34–7.45 (m, 5 H, Ph), 8.90 ppm (br s, 1 H, NH); MS, *m/e* (relative intensity) 296 (4), 295 (26), 294 (20), 293 (44, M^+, ^{35}Cl), 292 (28), 281 (29), 256 (27), 244 (40), 242 (53), 221 (37), 207 (100).

Benzyl 4-(2-Cyanoethyl)-3,5-dimethylpyrrole-2-carboxylate (6/10, Undeuterated). A stirred mixture of benzyl 4-(2-chloroethyl)-3,5-dimethylpyrrole-2-carboxylate (**8/9** unlabeled, 1.10 g), dry sodium cyanide (2.0 g), and dry dimethyl sulfoxide (250 mL) was heated at 80 °C for 3 h. The mixture was cooled and poured into water (1 L), whereupon white, needle-like crystals formed. After the suspension was allowed to stand at room temperature overnight in an ice bath, the solid was collected by filtration and was washed with water (200 mL). After drying overnight, under vacuum, at 60 °C, the product was crystallized from methanol as long needles (0.95 g, 89%): mp 119–119.5 °C; ^{1}H NMR 2.24, 2.30 (each s, 3 H, 3,5-Me), 2.44, 2.76 (each t, 2 H, CH_2CH_2CN), 5.32 (s, 2H, CH_2Ph), 7.30–7.45 (m, 5 H, Ph), 9.03 ppm (br s, 1 H, NH); MS, *m/e* (relative intensity) 282 (78, M^+), 281 (48), 242 (100), 207 (8), 191 (21), 175 (34), 148 (25), 134 (40), 108 (29); IR ν_{max} (Nujol) 2280, 1660 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 72.30; H, 6.43; N, 9.93. Found: C, 72.22; H, 6.43; N, 9.88.

For the synthesis of the deuterium-labeled analogues (**6** and **10**) the same procedure was followed, except that the labeled (chloroethyl)pyrrole mixture **8/9** was used; a 91% yield of the mixture of deuterated isomers was obtained; mp 118.5–119.5 °C. The ^{1}H NMR spectrum was identical with that described above, except that the (cyanoethyl)methylenes appeared as 1:1 single-proton singlets at 2.44 and 2.76 ppm.

Benzyl 4-(2-Bromoethyl)-3,5-dimethylpyrrole-2-carboxylate (11, Undeuterated). Benzyl 4-(2-hydroxyethyl)-3,5-dimethylpyrrole-2-carboxylate (**4** unlabeled, 5.53 g) was dissolved in dichloromethane (150 mL), and a solution of carbon tetrabromide (13.4 g) and triphenylphosphine (10.5 g) in dichloromethane (20 mL) was added. The mixture was refluxed overnight, but there appeared, by TLC analysis, to be no change in the 40:60 product–starting material ratio after the first 2 h. The solvent was evaporated under vacuum, and the residue was chromatographed on a short column of neutral alumina (Brockmann Grade II, eluction with dichloromethane). The required product was obtained, after a further chromatography (Brockmann Grade III, elution with dichloromethane), as long needles from dichloromethane/hexane (2.55 g, 38%, with the mass balance being unchanged polar starting material, separated on the first alumina chromatography). Bromoethylpyrrole **11**: mp 120.5–121.5 °C; ^{1}H NMR 2.23, 2.29 (each s, 3,5-Me), 2.95, 3.38 (each t, 2 H, CH_2CH_2Br), 5.29 (s, 2 H, CH_2Ph), 7.41 (m, 5 H, Ph), 8.78 ppm (br s, 1 H, NH); MS, *m/e* (relative intensity) 338 (16), 337 (68), 336 (40), 335 (66, M^+, ^{79}Br), 334 (26), 256 (52), 242 (100). Anal. Calcd for $C_{16}H_{18}BrNO_2$: C, 57.16; H, 5.40; N, 4.17. Found: C, 57.25; H, 5.48; N, 4.13.

The preparation of the deuterated analogues **11** and **12** was carried out in an identical manner and gave a 23% yield of the labeled (bromoethyl)pyrroles; mp 119–120.5 °C. The α- and β-methylenes were each observed as broad singlets at 2.95 ppm (0.8 H, CH_2CD_2Br) and 3.38 ppm (1.2 H, CD_2CH_2Br), indicating an approximately 60:40 mixture of **15** and **16**: MS, *m/e* (relative intensity) 340 (18%), 339 (87), 338 (82), 337 (100, M^+, ^{79}Br), 336 (73), 279 (70), 258 (60), 244 (90).

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Benzyl 4-(2-Acetoxy-1,1-dideuterioethyl)-3,5-dimethylpyrrole-2-carboxylate (13). Acetic anhydride (1.1 mL) was added to a solution of the deuterated 4-(2-hydroxyethyl)pyrrole 4 (1.02 g) in pyridine (10 mL), and the mixture was stirred at room temperature for 4 h, after which time the reaction was determined to be complete by analytical TLC. The mixture was slowly added to water but oiled out rather than precipitated, so the solution was extracted with chloroform (2 × 100 mL), and the combined organic fractions were washed with water (150 mL), dried (Na_2SO_4), and evaporated to dryness under vacuum. The residue was chromatographed on 1-mm-thick 20 × 20 cm silica gel preparative TLC plates (elution with dichloromethane), and the major band was collected to afford 946 mg (80%) of the labeled (acetoxyethyl)pyrrole: mp 72–73 °C (lit.[49] mp 73.5–74.5 °C, unlabeled); ^{1}H NMR 1.98 (s, 3 H, OCOMe), 2.18, 2.29 (each s, 3 H, 3,5-Me), 4.09 (br s, 2 H, 4-CD_2CH_2O), 5.28 (s, 2 H, CH_2Ph), 7.33 (m, 5 H, Ph), 9.50 ppm (br s, 1 H, NH).

2-(Benzyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-5-carboxylic Acid. The 5-methylpyrrole **2** (20 g) was suspended with stirring in carbon tetrachloride (200 mL) and treated with freshly distilled sulfuryl chloride (17 mL) dropwise during 3 h. After this time the mixture was stirred for a further 16 h before NMR analysis (neat reaction mixture) showed complete disappearance of the CH_2Cl and $CHCl_2$ peaks at 4.6 and 6.6 ppm, respectively. The solvent was evaporated, and dioxane (700 mL) and sodium acetate (105 g) in water (500 mL) were added. The mixture was heated with stirring on a boiling water bath for 2 h and was then left overnight at room temperature. Then, the mixture was extracted with ether (3 × 500 mL), which was in turn extracted with aqueous sodium bicarbonate solution and then aqueous sodium carbonate. The combined aqueous layers were then flushed with a rapid stream of air (to remove ether and dioxane) and then adjusted to pH 6 with acetic acid initially to pH 8 and finally with sulfur dioxide gas. The precipitated pyrrole carboxylic acid was filtered, washed with water, and then dried to give 12 g (55 %): mp 187–192 °C; ^{1}H NMR 2.28 (s, 3 H, Me), 3.70 (s, 3 H, OMe), 3.85 (s, 2 H, CH_2), 5.32 (s, 2 H, CH_2Ph), 7.41 (s, 5 H, Ph), 9.68 ppm (br s, 1 H, NH). Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.41; H, 5.00; N, 4.08.

Benzyl 5-Iodo-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate. The foregoing pyrrole carboxylic acid (12 g) in methanol (98 mL) and water (98 mL) containing sodium bicarbonate (9.8 g) was stirred at 60 °C and treated dropwise with potassium iodide (15.8 g) and iodine (10 g) in methanol (120 mL) and water (30 mL). After complete addition, the mixture was kept for 1 h at 60 °C and then treated slowly with water (120 mL). After cooling, the solid product was collected by filtration, washed with ice cold water, and then recrystallized from ether/hexane to give 10 g (67 %): mp 118–119 °C; ^{1}H NMR 2.25 (s, 3 H, Me), 3.35 (s, 2 H, CH_2), 3.62 (s, 3 H, OMe), 5.25 (s, 2 H, CH_2Ph), 7.32 (s, 5 H, Ph), 9.15 ppm (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{16}INO_4$: C, 46.48; H, 3.87; N, 3.38. Found: C, 46.56; H, 3.90; N, 3.29.

Benzyl 4-[(Methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate. The foregoing pyrrole (10 g) in methanol (200 mL) containing sodium acetate trihydrate (10 g) and Adams catalyst (100 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased (5 h). The catalyst was filtered off (Celite), and the solution was concentrated to 50 mL before being diluted with dichloromethane (100 mL). The organic phase was washed with water (50 mL), dried (Na_2SO_4), and evaporated to dryness to give a residue, which was passed through a short column of silica (elution with ethyl acetate/cyclohexane, 1:4). Evaporation of the eluates gave 5.93 g (85.5 %) of the 5-unsubstituted pyrrole: mp 80 °C; ^{1}H NMR 2.30 (s, 3 H, Me), 3.42 (s, 2 H, CH_2), 3.68 (s, 3 H, OMe), 5.30 (s, 2 H, CH_2Ph), 6.82 (d, 1 H, 5-H), 7.40 (s, 5 H, Ph), 8.85 ppm (br s, 1 H, NH). (This pyrrole was deuterated at the methylene position by using the general procedure described earlier for pyrrole **3**. The product was identical with that described above, except that the methylene at 3.42 ppm was absent in the ^{1}H NMR spectrum.) Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.85. Found: C, 66.83; H, 5.81; N, 4.85.

Benzyl 4-(2-Hydroxyethyl)-3-methylpyrrole-2-carboxylate (27, Undeuterated). The foregoing pyrrole (5 g) in tetrahydrofuran (50 mL) was treated with 1 M BH_3·THF complex (35 mL) at a temperature <10 °C, and the mixture was stirred overnight at room temperature. TLC monitoring then indicated that the reaction was complete, so it was worked up in the usual way after addition of methanol to decompose excess borane. The product was chromatographed on silica (elution with 30% ethyl acetate in cyclohexane) and, after recrystallization from dichloromethane/hexane gave 3.60 g (80%) isolated as an oil: ^{1}H NMR 2.25 (s, 5 H, Ph), 2.62, 3.68 (each t, 2 H, CH_2), 5.25 (s, 2 H, CH_2Ph), 6.65 (d, 1 H, 5-H), 7.30 (s, 5 H, Ph), 9.00 ppm (br s, 1 H, NH). (The corresponding deuterated material **27** was prepared in a similar manner and was identical, except for absence of the peak at 2.62 ppm and the appearance of the other side-chain methylene as a singlet at 3.70 ppm.)

Benzyl 5-Chloro-4-(2-chloro-1,1-dideuterioethyl)-3-methylpyrrole-2-carboxylate (30) and Benzyl 5-Chloro-4-(2-chloro-2,2-dideuterioethyl)-3-methylpyrrole-2-carboxylate (31). The foregoing deuterated pyrrole **27** (1 g) in dichloromethane (10 mL) and pyridine (3 mL) was treated with thionyl chloride (0.3 mL). The mixture was stirred at 50 °C for 2 h, after which time TLC analysis indicated the reaction to be complete. The reaction was worked up as described earlier for other (chloroethyl)pyrroles, and the crude product was chromatographed on silica (elution with dichloromethane) to give 155 mg (10 %) of the 5-chloropyrrole: mp 120–121 °C; ^{1}H NMR 2.32 (s, 3 H, Me), 2.85 (s, 1 H, CH_2CD_2Cl), 3.52 (s, 1 H, CD_2CH_2Cl), 5.30 (s, 2 H, CH_2Ph), 7.40 (s, 5 H, Ph), 9.20 ppm (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{15}Cl_2NO_2$ (undeuterated): C, 57.70; H, 4.84; N, 4.49. Found: C, 57.74; H, 4.85; N, 4.32.

Further purification steps using silica gel preparative plates afforded a 25% (268 mg) yield of deuterated **benzyl 4-(2-chloroethyl)-3-methylpyrrole-2-carboxylates (28 and 29)** as an oily liquid: ^{1}H NMR 2.28 (s, 3 H, Me), 2.82, 3.50 (each s, 1 H, CD_2CH_2Cl and CH_2CD_2Cl), 5.30 (s, 2 H, CH_2Ph), 6.70 (d J = 3 Hz, 1 H, 5-H), 7.40 (s, 5 H, Ph), 9.05 ppm (br s, 1 H, NH).

Benzyl 4-(2-Hydroxyethyl)-2-methylpyrrole-5-carboxylate (25, Undeuterated). Benzyl 4-[[(benzyloxy)carbonyl]-methyl]-2-methylpyrrole-5-carboxylate (**24**)[50] (2 g) was treated as described above with BH_3·THF complex and afforded 990 mg (70%) of the required pyrrole: mp 80–84 °C; ^{1}H NMR 2.20 (s, 3 H, Me), 2.85 and 3.80 (each t, 2 H, CH_2CH_2OH), 5.25 (s, 2 H, CH_2Ph), 5.90 (s, 1 H, 3-H), 6.70 (d, J = 3 Hz, 1 H, 5-H), 7.40 (s, 5 H, Ph), 8.90 ppm (br s, 1 H, NH). (The deuterated analogue **25** was prepared in a similar manner, and the product was identical except for the absence of the resonance at 2.85 ppm and the appearance of the peak at 3.80 ppm as a singlet.) Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.29; H, 6.57; N, 5.25.

Benzyl 4-(2-Chloroethyl)-2-methylpyrrole-5-carboxylate (26, Undeuterated). The foregoing pyrrole (**25** undeuterated, 1 g) was treated with thionyl chloride and pyridine in exactly the same manner as described above for compound **4**. TLC analysis indicated that the reaction would not go to completion, so it was worked up and gave a mixture of products. Chromatography on silica (elution with dichloromethane) furninshed one fraction that was further purified on thick-layer silica gel plates (elution with dichloromethane). The product was crystallized from dichloromethane/hexane and gave 108 mg (10 %): mp 96–98 °C; ^{1}H NMR 2.25 (s, 3 H, Me), 3.20, 3.65 (each t, 2 H, CH_2CH_2), 5.30 (CH_2Ph), 5.90 (d, 1 H, 3-H), 7.40 (s, 5 H, Ph), 8.90 ppm (br s, 1 H, NH). (When the reaction was carried out on the deuterated analogue **25**, an identical product **26** was obtained, except that in its ^{1}H NMR spectrum the resonance at 3.20 ppm was absent and that at 3.65 ppm was observed as a singlet.) Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.80; N, 5.04. Found: C, 64.88; H, 5.72; N, 4.84.

Benzyl 4-[(Methoxy-[[^{13}C]carbonyl])methyl]-3,5-dimethylpyrrole-2-carboxylate. Benzyl 4-[[1-^{13}C]acetyl]-3,5-dimethylpyrrole-2-carboxylate (340 mg) [obtained[51] from benzyl 3,5-dimethylpyrrole-2-carboxylate by Friedel–Crafts acetylation with [1-^{13}C]acetyl chloride (99% enriched)] was dissolved in

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methanol (10 mL) and treated with thallium(III) nitrate (450 mg) and concentrated nitric acid (0.1 mL) for 24 h at room temperature. The precipitated thallium(I) salts were removed by filtration, and the filtrate was diluted with dichloromethane (40 mL) and then washed with water (100 mL) and dried (Na_2SO_4). The solvent was evaporated to yield an oil, which was crystallized from dichloromethane/hexane to give 342 mg (91%): mp 93–94 °C (lit.[51] mp 93–94 °C); ^1H NMR 2.25, 2.35 (each s, 3 H, 3,5-Me), 3.35 (d, J_{C-C-H} = 7 Hz, 2 H, CH_2CO), 3.62 (d, $J_{C-O-C-H}$ = 4 Hz, 3 H, OMe), 5.25 (s, 2 H, CH_2Ph), 7.25–7.35 (m, 5 H, Ph), 8.80 ppm (br s, 1 H, NH).

Benzyl 4-(2-Hydroxy-[[2-^{13}C]ethyl])-3,5-dimethylpyrrole-2-carboxylate (18). This pyrrole was prepared from the foregoing labeled [(methoxycarbonyl)methyl]pyrrole by diborane reduction.[48] The product had a melting point of 119 °C (lit.[48] mp 120–121 °C), and its carbon-13 NMR spectrum showed an enhanced singlet at 62.68 ppm, which became a triplet of triplets (J_{C-H} = 140 Hz, J_{C-C-H} = 7 Hz) in the proton-coupled mode: ^1H NMR 2.18, 2.27 (each s, 3 H, 3,5-Me), 2.60 (t, 2 H, CH_2CH_2OH), 3.63 (dt, J = 140, 7 Hz, 2 H, CH_2O), 5.28 (CH_2Ph), 7.30–7.45 (m, 5 H, Ph) 8.96 ppm (br s, 1 H, NH).

Benzyl 4-(2-Chloro-[[2-^{12}C]ethyl])-3,5-dimethylpyrrole-2-carboxylate (19) and Benzyl 4-(2-Chloro-[[1-^{13}C]ethyl])-3,5-dimethylpyrrole-2-carboxylate (20). The foregoing carbon-13-enriched (hydroxyethyl)pyrrole **18** was chlorinated with thionyl chloride and conditions identical with those used in the synthesis of pyrroles **8** and **9** and gave a 70% yield of labeled (chloroethyl)pyrroles, mp 119–120 °C (lit.[49] mp 121–122 °C). The carbon-13 NMR spectrum showed two enhanced peaks (of approximately equal intensity) at 27.87 (CH_2CH_2Cl) and 44.32 (CH_2Cl), and in the proton-coupled mode these were split into a triplet of triplets (J_{C-H} = 140 Hz, J_{C-C-H} = 7 Hz) and a triplet (J_{C-H} = 140 Hz), respectively: ^1H NMR 2.12, 2.30 (each s, 3 H, 3,5-Me), 2.52, 2.85, 3.15, 3.50, 3.90 (t, m, q, m, t, total integral 4 H, methylenes), 5.35 (s, 2 H, CH_2Ph), 7.35–7.45 (m, 5 H, Ph), 9.00 ppm (br s, 1 H, NH).

Benzyl 3-[[(Benzyloxy)carbonyl]methyl]-4-formyl-5-methylpyrrole-2-carboxylate (32). Pyrrole **24**[50] (11.6 g) in trifluoroacetic acid (15 mL) was stirred for 5 min before the temperature was raised to 40 °C and trimethyl orthoformate (6 mL) was added. After being stirred for 10 min, the mixture was cooled, treated with water (100 mL), and then stirred for 30 min at room temperature. The precipitated formylpyrrole was collected by filtration, washed well with water, and then recrystallized from aqueous ethanol to give 10.0 g (80%): mp 109–110 °C; ^1H NMR 2.50 (s, 3 H, Me), 4.25 (s, 2 H, CH_2), 5.09 and 5.25 (each s, 2 H, CH_2Ph), 7.32 (s, 10 H, Ph), 9.92 (s, 1 H, CHO), 9.50 ppm (br s, 1 H, NH). (The corresponding deuterated analogue, prepared as described below, showed the peak at 4.25 ppm to be absent in its ^1H NMR spectrum.) Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.37; N, 3.58. Found: C, 70.52; H, 5.41; N, 3.57.

Benzyl 3-(2-Hydroxyethyl)-4,5-dimethylpyrrole-2-carboxylate (21, Undeuterated). BH_3·THF complex (180 mL of 1.0 M solution in THF) was added dropwise to the foregoing pyrrole **32** (9.0 g) in THF at a temperature below 10 °C (ice bath) and under an atmosphere of nitrogen. The mixture was then stirred at room temperature for 36 h, after which time the reaction was determined to be complete by analytical TLC. Methanol (50 mL) was carefully added to the mixture, and it was then evaporated to dryness. The residue was chromatographed on silica gel (elution with 20% ethyl acetate in cyclohexane), the appropriate eluates were evaporated, and the residue was crystallized from benzene/hexane to give 4.27 g (68%) of the required pyrrole: mp 83–85 °C (lit.[50] mp 84–85 °C); ^1H NMR 1.90, 2.15 (each s, 3 H, Me), 2.95 (t, 2 H, CH_2CH_2OH), 3.75 (t, 2 H, CH_2OH), 4.60 (br s, 1 H, OH), 5.25 (s, CH_2Ph), 7.41 (s, 5 H, Ph), 8.68 ppm (br s, 1 H, NH). The corresponding methylene-deuterated pyrrole **21** was prepared by treating **32** (5.0 g) with sodium methoxide (200 mg) in methanol-d_1 (50 mL) for 24 h at room temperature. The solvent was removed by evaporation, and the residue, in dichloromethane (50 mL), was quickly washed with water (50 mL). The organic phase was separated, dried (Na_2SO_4), and then evaporated to dryness to give a crude oil, which was shown by proton NMR spectroscopy to be a mixture of the required deuteriated pyrrole dibenzyl ester, the corresponding pyrrole dimethyl ester (produced by transesterification), monobenzyl monomethyl pyrrole diester (transesterified only in the aliphatic side chain), and benzyl alcohol. All pyrrolic products lacked the methylene singlet aroung 4.25 ppm, indicating complete exchange of the side-chain methylene. The benzyl alcohol was removed under high vacuum, and the residue was treated with BH_3·THF complex as indicated above. The product was found to be a mixture of the required benzyl ester **21** and the corresponding deuteriated methyl ester pyrrole, in what appeared to be an equal mixture. The total yield was 2.20 g (63%), and this mixture was separated by using preparative thick-layer silica gel plates, affording compound **21**, mp 83–85 °C, in which the proton NMR spectrum showed only a singlet at 3.75 ppm, indicating complete deuteration of the methylene adjacent to the pyrrole nucleus. The corresponding deuteriated methyl ester, mp 108–109 °C, also lacked the methylene group in its NMR spectrum, (1.85, 2.20 (each s, 3 H, Me), 3.70 (s, 2 H, CD_2CH_2O), 3.85 ppm (s, 3 H, OMe)).

Benzyl 3-(2-Chloroethyl)-4,5-dimethylpyrrole-2-carboxylate (33/34, Undeuterated). The (2-hydroxyethyl)-pyrrole **21** undeuterated (3.5 g) in dichloromethane (30 mL) and pyridine (1.2 mL) was treated with freshly distilled thionyl chloride (1.1 mL) and then heated under reflux for 2 h, after which time the reaction was determined by analytical TLC to be complete. Dichloromethane (100 mL) was added, and the organic phase was washed with 2 N hydrochloric acid (100 mL and then water (100 mL) and aqueous sodium bicarbonate (100 mL) and then dried (Na_2SO_4). After evaporation to dryness, the residue was chromatographed on silica gel (elution with dichloromethane), and the appropriate eluates were evaporated to give a residue, which was crystallized from dichloromethane/hexane to give 1.80 g (47%) of the (2-chloroethyl)pyrrole, mp 113–114 °C (lit.[50] mp 113–115 °C). The deuteriated (2-chloroethyl)pyrroles **33/34** were synthesized in exactly the same manner, and the proton NMR spectrum indicated randomization of the two-carbon side chain: 1.92, 2.20 (each s, 3 H, Me), 3.10, 3.55 (each s, 1 H, CH_2CD_2 and CD_2CH_2), 5.25 (s, 2 H, CH_2Ph), 7.35 ppm (s, 5H, Ph).

When the corresponding methyl (2-hydroxyethyl)pyrrole-2-carboxylate was chlorinated under identical conditions, a similar yield of the rearranged (2-chloroethyl)pyrroles was obtained: NMR 1.95, 2.20 (each s, 3 H, Me), 3.18, 3.62 (each s, 1 H, CH_2CD_2 and CD_2CH_2), 3.83 ppm (s, 3H, OMe).

2-[[1-^{13}C]Vinyl]deuteroporphyrin IX Dimethyl Ester (36). 2-[[1-^{13}C]Acetyl]deuteroporphyrin IX dimethyl ester (**35**,[7] 40.6 mg) in dichloromethane (20 mL) was treated with an ice-cold solution of sodium borohydride (100 mg) in methanol (6 mL). The mixture was stirred for 10 min, after which time the reaction was determined to be complete by analytical TLC and acetic acid (2 mL) was added. The solution was diluted with dichloromethane (50 mL) and washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in *o*-dichlorobenzene (25 mL) containing *p*-toluene sulfonic acid hydrate (125 mg) and heated at 145 °C for 40 min as a stream of nitrogen gas was passed through the mixture. The cooled mixture was diluted with dichloromethane (75 mL), washed with water (3 × 75 mL), dried (Na_2SO_4), and evaporated to dryness to give a residue, which was chromatographed on 1-mm-thick 20 × 20 cm silica gel preparative TLC plates (elution with 2% methanol in dichloromethane). The major band afforded the required labeled isopemptoporphyrin dimethyl ester, 30 mg (76%), mp 218.5 °C (lit.[52] mp 220–221 °C, unlabeled), after crystallization from dichloromethane/hexane. The proton-decoupled carbon-13 NMR spectrum showed a single enhanced peak at 130.2 ppm, and the proton-coupled spectrum showed a doublet with J_{C-H} = 152.9 Hz.

2-(2-Hydroxy[[2-^{13}C]ethyl])deuteroporphyrin IX Dimethyl Ester (39). The foregoing carbon-13-enriched isopemptoprophyrin dimethyl ester (**36**, 28 mg) in dichloromethane (10 mL) was treated with thallium(III) nitrate (70 mg) in methanol (3 mL) at 40 °C for 10 min. Sulfur dioxide gas was then passed through the solution for 30 sec, concentrated hydrochloric acid (0.2 mL) was added, and the porphyrin was washed with water (50 mL), dried (Na_2SO_4), and evaporated to dryness to give a residue, which was chromatographed on neutral alumina (Brockmann Grade V, elution with dichloromethane). The red eluates were collected, and after evaporation the residue was crystallized from di-

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chloromethane/hexane to give 25 mg (85%) of the dimethyl acetal **37**, which was dissolved in tetrahydrofuran (10 mL) and water (0.5 mL) and then heated under reflux for 5 min with concentrated hydrochloric acid (0.2 mL). After cooling, dichloromethane (20 mL) and water (5 mL) were added and the porphyrin **38** was extracted into the organic phase, which was dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in dichloromethane (10 mL) and treated with sodium borohydride (10 mg) in ice-cold methanol (2 mL). After stirring for 10 min, analytical TLC determined that the reaction was complete, so acetic acid (0.5 mL) was added. The porphyrin was worked up with dichloromethane and water, as before, and the extracted and evaporated residue was dissolved in 5% concentrated sulfuric acid in methanol (10 mL) and left overnight at 0 °C. After addition of dichloromethane (50 mL), washing with water (3 × 50 mL), drying (Na_2SO_4), and evaporation, the residue was chromatographed on neutral alumina (Brockmann Grade V, elution with 1% methanol in dichloromethane). The red eluates were collected, evaporated to dryness, and crystallization from dichloromethane/hexane gave the required labeled (hydroxyethyl)-porphyrin (20.2 mg, 70%), mp 208–210 °C (lit.[52] mp 210–212 °C, unlabeled). The proton-decoupled carbon-13 NMR spectrum showed a single enhanced peak at 65.0 ppm, which, in the proton-coupled mode, became a triplet with J_{C-H} = 138 Hz.

2-(2-Chloro-[[2-^{13}C]ethyl])deuteroporphyrin IX Dimethyl Ester (40). The foregoing carbon-13-enriched (hydroxyethyl)-porphyrin **39** (12 mg) was dissolved in chloroform (8 mL) and dimethylformamide (1.5 mL) containing potassium carbonate (0.5 g). The mixture was treated with thionyl chloride (0.5 mL) and stirred for 6 h before being poured into water (10 mL). The organic phase was separated, washed with water (2 × 10 mL), and dried (Na_2SO_4). Evaporation gave a residue, which was chromatographed on neutral alumina (Brockmann Grade III, elution with dichloromethane), and the eluates afforded the title compound (8 mg, 70%), mp 196–198 °C (lit.[52] mp 199–201 °C). The proton-decoupled carbon-13 NMR spectrum showed one enhanced signal at 45.1 ppm, which was observed as a triplet (J_{C-H} = 147 Hz) in the proton-coupled mode.

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Registry No. **2**, 31837-62-4; **2**-^{13}C, 78829-38-6; **3**, 78829-28-4; **4**, 78829-29-5; **4** (unlabeled), 31837-63-5; **6**, 78824-31-4; **6** (undeuterated), 87281-57-0; **8**, 78829-30-8; **8** (unlabeled), 51089-69-1; **9**, 78829-33-1; **10**, 78829-34-2; **11**, 78829-35-3; **11** (undeuterated), 72562-17-5; **12**, 78829-36-4; **13**, 87281-58-1; **17**, 87281-79-6; **18**, 78840-83-2; **19**, 78829-39-7; **20**, 78829-40-0; **21**, 87281-78-5; **21** methyl ester, 87281-71-8; **21** (undeuterated), 62562-76-9; **24**, 62562-74-7; **25**, 87281-55-8; **25** (undeuterated), 87281-66-1; **26**, 87281-68-3; **26** (undeuterated), 87281-67-2; **27**, 87281-63-8; **27** (undeuterated), 87281-62-7; **28**, 87281-65-0; **29**, 87281-80-9; **30**, 87281-64-9; **31**, 87281-81-0; **32**, 87308-15-4; **33**, 87281-69-4; **33** (undeuterated), 62562-77-0; **33** methyl ester, 87281-73-0; **34**, 87281-70-7; **34** methyl ester, 87281-72-9; **35**, 87191-24-0; **36**, 87281-74-1; **37**, 87281-75-2; **38**, 87281-76-3; **39**, 87281-56-9; **40**, 87281-77-4; pyridine, 110-86-1; [1-^{13}C]acetyl chloride, 1520-57-6; carbon tetrabromide, 558-13-4; triphenylphosphine, 603-35-0; thionyl chloride, 7719-09-7; benzyl 3,5-dimethylpyrrole-2-carboxylate, 40236-19-9; 2-(benzyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-5-carboxylic acid, 52091-16-4; benzyl 4-[(methoxycarbonyl)methyl]-3-methyl-5-(trichloromethyl)pyrrole-2-carboxylate, 87281-59-2; benzyl 5-iodo-4-[(methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate, 87281-60-5; benzyl 4-[(methoxycarbonyl)methyl]-3-methylpyrrole-2-carboxylate, 87281-61-6; benzyl 4-[1-^{13}C]acetyl-3,5-dimethylpyrrole-2-carboxylate, 78829-37-5.

Porphyrin Synthesis through Tripyrrins: An Alternate Approach

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A new route for synthesis of unsymmetrically substituted porphyrins is described. The route follows the earlier approach through pyrromethanes, tripyrrin hydrobromides, and *a,c*-biladiene dihydrobromides, except that the pyrromethane intermediate is elongated in an initially "clockwise" direction to give a benzyl tripyrrincarboxylate. Various advantages over the *tert*-butyl tripyrrincarboxylates used in the earlier method (Scheme I) are discussed. The new route is demonstrated in the syntheses of five pure porphyrins required for other current studies.

Depending upon the complexity of the target molecule, porphyrin syntheses can be approached from a variety of directions.[1,2] If laborious separations of mixtures are to be avoided, totally unsymmetrical porphyrins must usually be synthesized by cyclization of a preformed open chain tetrapyrrole such as an *a,c*-biladiene or a *b*-bilene. Over the years, a particularly useful synthesis of completely unsymmetrical porphyrins has been the stepwise approach through tripyrrins.[3] In this procedure (Scheme I), an unsymmetrically substituted and differentially protected benzyl *tert*-butyl pyrromethane-5,5′-dicarboxylate, **1**, is catalytically debenzylated to give the pyrromethane-5-carboxylic acid, **2**; in an initially "anticlockwise" manner, the dipyrrole **2** is transformed into a tripyrrin salt, **3**, by condensation under acidic conditions with a 2-formylpyrrole, **4**. Condensation with a second formylpyrrole **5** gives an *a,c*-biladiene salt, **6**. Finally, the 1′,8′-dimethyl-*a,c*-biladiene salt is cyclized to give porphyrin by brief treatment with copper(II) chloride in dimethylformamide.[3]

Several technical problems arise in the "anticlockwise" approach outlined in Scheme I. The first is that the formylpyrrole **4** requires an acid (*p*-toluenesulfonic acid) to accomplish its reaction with the pyrromethane-5-carboxylic acid, **2**. The presence of the 5′-*tert*-butyl ester, which is itself labile to cleavage by acids, poses a definite problem, particularly when the formation of the tripyrrin salt is slow

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