Selective Synthesis of Monoaryl Substituted Porphyrins

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A synthetic route to meso-monoarylporphyrins using a MacDonald-type 2 + 2 condensation is described. In this method a bisformyl substituted dipyrrylmethane is treated with a biscarboxydipyrrylmethane. The 5-aryldipyrrylmethanes **15**, **25** and **27** were obtained by condensation of the corresponding pyrroles **18**, **28** and **29** respectively with benzaldehyde in presence of *p*-toluenesulfonic acid.

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Horseradish peroxidase (HRP) is a hemoprotein catalyzing the reduction of hydrogen peroxide produced *in vivo* as a byproduct of enzymatic processes [1,2].

The primary HRP sequence is known [3], but efforts to obtain crystals suitable for X-ray analysis have so far proven unsuccessful [4].

Recent heme alkylation experiments employing aryl- and alkylhydrazines have provided substantial data on the structure of the active HRP site. Reaction of phenylhydrazine with myoglobin [5-7], hemoglobin [7-9], catalase [10], cytochrome P_{450} [11] and metalloporphyrins leads to alkylation of the heme iron or nitrogen atoms, whereas with HRP there is partial attachment of the phenyl group to the δ-mesocarbon together with partial conversion of the heme to its 18-hydroxylmethyl derivative. Although the δ-mesocarbon is alkylated by the alkylhydrazine, its hydroxymethyl derivative is not available by this pathway [12]. A complete loss of enzymatic activity results when HRP is treated with phenylhydrazine.

In an attempt to elucidate active site architecture and enzyme-substrate interaction, work is under way in our laboratory to reconstitute HRP with synthetic hemins bearing a phenyl group on a meso carbon to determine whether the substrate binding site is blocked.

The hemins [Fe(III)-porphyrins] derive from porphyrins **1**, **2**, **3** and **4** (Scheme 1).

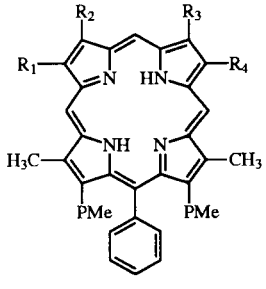
Over the last 50 years, progress has been made to develop synthetic routes to tetraphenyl and natural porphyrins related to heme and chlorophyll, starting with monopyrrole tetramerization, dipyrrylmethane self-condensation in organic acid melts [13], MacDonald's dipyrrylmethane so-called 2 + 2 procedure [14] and Woodward's landmark dipyrrylmethane condensation [15], to reach truly general approaches through unsymmetrically substituted b-bilene and a,c-biladiene [16,18].

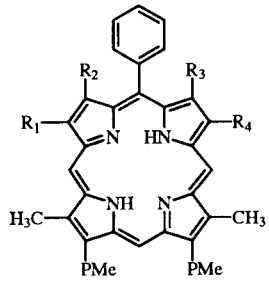
Meso-aryloctaalkyl substituted porphyrins have been obtained either by MacDonald's synthesis [19,20] or by the a,c-biladiene method [20,22].

The present authors found that the most direct approach to obtain the four monoaryl porphyrin isomers in a pure form was to resort to MacDonald's original method [14] in its simplified form [23], consisting in the condensation of a diformyldipyrrylmethane with a dicarboxydipyrrylmethane.

Accordingly, synthesis of **9** and **10** was carried out through condensation of a diformyldipyrrylmethane **13** with the two known dicarboxydipyrrylmethanes **16** and **17** [24,25] bearing ring A and B substituents (Scheme 2).

Scheme 1

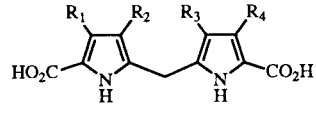




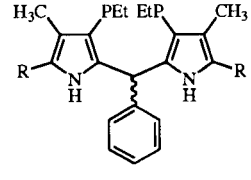
1, R_1, R_4: $-CH_3$; R_2, R_3: $-CH{=}CH_2$
2, R_1, R_4: $-CH{=}CH_2$; R_2, R_3: $-CH_3$
5, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2Cl$
6, R_1, R_4: $-CH_2CH_2Cl$; R_2, R_3: $-CH_3$
9, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OH$
10, R_1, R_4: $-CH_2CH_2OH$; R_2, R_3: $-CH_3$

3, R_1, R_4: $-CH_3$; R_2, R_3: $-CH{=}CH_2$
4, R_1, R_4: $-CH{=}CH_2$; R_2, R_3: $-CH_3$
7, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2Cl$
8, R_1, R_4: $-CH_2CH_2Cl$; R_2, R_3: $-CH_3$
11, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OH$
12, R_1, R_4: $-CH_2CH_2OH$; R_2, R_3: $-CH_3$

Scheme 2



16, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OCOCH_3$
17, R_1, R_4: $-CH_2CH_2OCOCH_3$; R_2, R_3: $-CH_3$

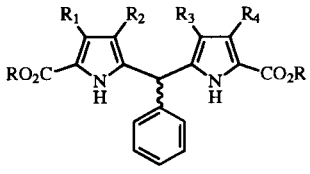


13, R: -CHO
14, R: $-CO_2H$
15, R: $-CO_2CH_2Ph$

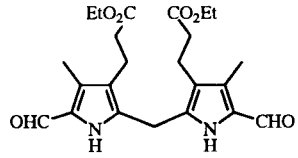
Alternatively, a recent and very convenient method to synthesize dipyrrylmethane **15** is the condensation of the pyrrole **18** [26] with benzaldehyde in the presence of *p*-toluenesulfonic acid. Hydrogenolysis of the benzyl ester group in **15** afforded dicarboxydipyrrylmethane **14** which was formylated with ethyl orthoformate to yield **13**.

Porphyrins **11** and **12** were prepared by condensing dicarboxydipyrrylmethanes **20** and **22** with the diformyldipyrrylmethane **23** [27] (Scheme 3).

Scheme 3



19, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OCOCH_3$; R: $-CH_2Ph$
20, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OCOCH_3$; R: -H
21, R_1, R_4: $-CH_2CH_2OCOCH_3$; R_2, R_3: $-CH_3$; R: $-CH_2Ph$
22, R_1, R_4: $-CH_2CH_2OCOCH_3$; R_2, R_3: $-CH_3$; R: -H
24, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CH_2OH$; R: $-CH_2Ph$
25, R_1, R_4: $-CH_3$; R_2, R_3: $-CH_2CO_2CH_2CH_3$; R: $-CH_2Ph$
26, R_1, R_4: $-CH_2CH_2OH$; R_2, R_3: $-CH_3$; R: $-CH_2Ph$
27, R_1, R_4: $-CH_2CO_2CH_2CH_3$; R_2, R_3: $-CH_3$; R: $-CH_2Ph$



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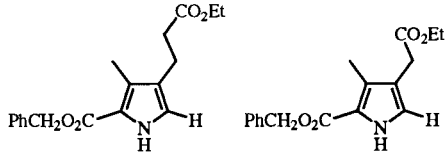
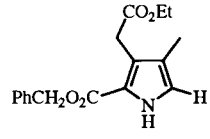
Dipyrrylmethanes **27** and **25** were synthetized by condensation of the respective α-unsubstituted pyrroles **28** and **29** following the method described for the preparation of **15** (Scheme 4).

Scheme 4



18 **28**



29

Treatment of **25** and **27** with diborane resulted in the reduction of the side-chain esters to yield dipyrrylmethanes **24** and **26**, whose esterification with acetic anhydride-pyridine led to **19** and **21**. Hydrogenolysis of the latter resulted in dipyrrylmethanes **20** and **22**.

By treatment with mesyl chloride, the 2-hydroxyethyl-porphyrins were transformed into **5**, **6**, **7** and **8**, whose vinylation with DBU/DMF afforded the desired porphyrins **1**, **2**, **3** and **4**, respectively, in good yields.

EXPERIMENTAL

General Procedures.

The nmr spectra were obtained in deuteriochloroform and recorded by means of a Bruker MSL-300 spectrometer. Chemical shift values are expressed in ppm relative to TMS. High-resolution mass spectra were obtained on a ZAB spectrometer. Electronic spectra were recorded on a Hitachi V-2000 instrument.

Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Column chromatography was carried out with Riedel de Haen Kieselgel DG for thin layer chromatography.

Dibenzyl 2,8-Dimethyl-3,7-di[2-(ethoxycarbonyl)ethyl]-5-phenyldipyrrylmethane-1,9-dicarboxylate **15**.

Pyrrole **18** (500 mg) was dissolved in chloroform (40 ml), and 1 ml benzaldehyde and 125 mg *p*-toluenesulphonic acid were added to this solution. The mixture was heated for 2 hours and then diluted with water (50 ml). The organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate (20 ml) and then with water (20 ml). The organic solution was dried with anhydrous sodium sulfate, filtered and evaporated at reduced pressure. The desired product was obtained as an amber oil after purifying it through a silica gel column (2.5 cm x 15 cm). Excess benzaldehyde was washed out with methylene chloride and the product eluted with methylene chloride-methanol (99:1), yield 90% (530 mg); ^{1}H nmr: δ 1.05 [t, 6, CH_3 (3^6, 7^6)], 2.15 [s, 6, CH_3 (2^1, 8^1)], 2.10, 2.45 [m, m, 8, CH_2 (3^2, 7^2, 3^1, 7^1)], 3.95 [q, 4, CH_2 (3^5, 7^5)], 5.15 [s, 4, CH_2 (1^3, 9^3)], 5.75 [s, 1, CH (5)], 7.05, 7.30 [m, m, 15, CH (Ph)], 8.45 [bs, 2, NH (10, 11)]; ms: Calcd. for $C_{43}H_{46}N_2O_8$: 718.3254. Found: hrms 718.3261.

Dibenzyl 3,7-Dimethyl-2,8-di[2-(ethoxycarbonylmethyl]-5-phenyldipyrrylmethane-1,9-dicarboxylate **27**.

This compound was prepared and purified as described above from pyrrole **29** (300 mg), chloroform (24 ml), benzaldehyde (0.6 ml) and *p*-toluenesulfonic acid (75 mg). An amber oil was obtained, yield 90% (320 mg); ^{1}H nmr: δ 1.17 [t, 6, CH_3 (2^5, 8^5)], 1.77 [s, 6, CH_3 (3, 7)], 3.79 [s, 4, CH_2 (2^1, 8^1)], 4.05 [q, 4, CH_2 (2^4, 8^4)], 5.22 [s, 4, CH_2 (1^3, 9^3)], 5.53 [s, 1, CH (5)], 7.12, 7.33 [m, m, 15, CH (Ph)], 8.65 [bs, 2, NH (10, 11)]; ms: Calcd. for $C_{41}H_{42}N_2O_8$: 690.2941. Found: hrms 690.2953.

Dibenzyl 2,8-Dimethyl-3,7-di[2-(ethoxycarbonyl)methyl]-5-phenyldipyrrylmethane-1,9-dicarboxylate **25**.

This compound was prepared and purified as described above from pyrrole **28** (500 mg), chloroform (40 ml), benzaldehyde (1 ml) and *p*-toluenesulfonic acid (125 mg). An amber oil was obtained, yield 85% (500 mg); ^{1}H nmr: δ 1.00 [t, 6, CH_3 (3^5, 7^5)], 2.25 [s, 6, CH_3 (2, 8)], 3.00, 3.05 [s, s, 4, CH_2 (3^1, 7^1)], 3.90 [q, 4, CH_2 (3^4, 7^4)], 5.25 [s, 4, CH_2 (1^3, 9^3)], 5.80 [s, 1, CH (5)], 7.30 [m, 15, CH (Ph)], 9.40 [bs, 2, NH (10, 11)]; ms: Calcd.

for $C_{41}H_{42}N_2O_8$: 690.2941. Found: hrms 690.2934.

2,8-Dimethyl-3,7-di[2-(ethoxycarbonyl)ethyl]-5-phenyldipyrrylmethane-1,9-dicarboxylic Acid **14**.

A solution of diprrylmethane **15** (530 mg) in ethanol (100 ml) was reduced with hydrogen at 50 psi over 250 mg of 10% Pd on charcoal during 3 hours. The catalyst was filtered, the solvent evaporated to dryness at reduced pressure, and the acid **14** thus obtained was recrystallized from methanol-water, yield 90% (375 mg), mp 121-122°; ^{1}H nmr: δ 1.05 [t, 6, CH_3 (3^6, 7^6)], 1.95, 2.55 [m, m, 8, CH_2 (3^2, 7^2, 3^1, 7^1)], 2.25 [s, 6, CH_3 (2^1, 8^1)], 3.95 (q, 4, CH_2 (3^5, 7^5)], 5.75 [s, 1, CH (5)], 7.10 [m, 5, CH (Ph)], 9.35 [bs, 2, NH (10, 11)].

Anal. Calcd. for $C_{29}H_{34}N_2O_8$: C, 64.68; H, 6.32; N, 5.20. Found: C, 64.71; H, 6.29; N, 5.24.

2,8-Dimethyl-3,7-di[2-(ethoxycarbonyl)ethyl]-5-phenyl-1,9-diformyldipyrrylmethane **13**.

A solution of dipyrrylmethane **14** (400 mg) in trifluoroacetic acid (6.3 ml) was maintained at 25° for 10 minutes, cooled to 0°, and trimethyl orthoformate (2.1 ml) was added. The mixture was kept at 0° for 5 minutes, water (30 ml) was added and was stirred for 30 minutes. The aqueous mixture was extracted three times with methylene chloride (3 x 20 ml). The organic layer was washed with aqueous saturated sodium acetate (20 ml), aqueous saturated sodium bicarbonate (20 ml), water (20 ml), dried over sodium sulfate and then evaporated under vacuum. The crude product was purified on a silica gel column, and eluted with methylene chloride-methanol (97.5:2.5). The dipyrrylmethane thus obtained was recrystallized from methylene chloride-hexane, yield 71% (265 mg), mp 160-161°; ^{1}H nmr: δ 1.05 [t, 6, CH_3 (3^6, 7^6)], 2.15 [m, 10, CH_2 (3^2, 7^2), CH_3 (2^1, 8^1)], 2.50 [m, 4, CH_2 (3^1, 7^1)], 4.00 [q, 4, CH_2 (3^5, 7^5)], 5.85 [s, 1, CH (5)], 7.00 and 7.30 [m, m, 5, CH (Ph)], 9.45 [bs, 4, NH (10, 11), CHO (1^1, 9^1)].

Anal. Calcd. for $C_{29}H_{34}N_2O_6$: C, 68.77; H, 6.72; N, 5.53. Found: C, 68.79; H, 6.73; N, 5.51.

Dibenzyl 2,8-Dimethyl-3,7-di(2-hydroxyethyl)-5-phenyldipyrrylmethane-1,9-dicarboxylate **24**.

Diborane generated by the addition of boron trifluoride diethyl ether (6 ml) to sodium borohydride (2 g) in diglyme (10 ml) was passed in a slow stream of nitrogen through a solution of dipyrrylmethane **25** (490 mg) in tetrahydrofuran (20 ml). The solution was left overnight at room temperature in a closed flask. Methanol was then cautiously added until effervescence ceased. Solvents were evaporated to dryness at reduced pressure. The crude product was purified on a silica gel column (3 cm x 20 cm) and eluted with methylene chloride-methanol (99:1). A yellow oil was obtained, yield 90% (380 mg); ^{1}H nmr: δ 2.15 [s, 6, CH_3 (2, 8)], 2.35 [t, 4, CH_2 (3^1, 7^1)], 3.55 [t, 4, CH_2 (3^2, 7^2)], 5.15 [s, 4, CH_2 (1^3, 9^3)], 5.75 [s, 1, CH (5)], 7.10, 7.30 [m, m, 15, CH (Ph)], 9.45 [bs, 2, NH (10, 11)]; ms: Calcd. for $C_{36}H_{38}N_2O_6$: 594.2730. Found: hrms 594.2746.

Dibenzyl 2,8-Dimethyl-3,7-di(2-acetoxyethyl)-5-phenyldipyrrylmethane-1,9-dicarboxylate **19**.

Dipyrrylmethane **24** (427 mg), anhydrous pyridine (15 ml) and acetic anhydride (3.1 ml) were mixed. The solution was stirred for 2 hours, then poured onto 100 ml of water and extracted three times with methylene chloride (3 x 50 ml). The organic layers were combined, washed with water (20 ml) and dried with anhydrous sodium sulfate. The solution was evaporated to dryness at reduced pressure. The crude product was purified through a silica gel column (3 cm x 20 cm) using methylene chloride-methanol (99:1) as solvent, to obtain a light brownish solid, yield 84% (410 mg), mp 42-43° (methanol-water); ^{1}H nmr: δ 1.8 [s, 6, CH_3 (3^5, 7^5)], 2.15 [s, 6, CH_3 (2, 8)], 2.40 [t, 4, CH_2 (3^1, 7^1)], 3.80 [t, 4, CH_2 (3^2, 7^2)], 5.15 [s, 4, CH_2 (1^3, 9^3)], 5.60 [s, 1, CH (5)], 7.10, 7.30 [m, m, 15, CH (Ph)], 8.50 [bs, 2, NH (10, 11)].

Anal. Calcd. for $C_{40}H_{42}N_2O_8$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.83; H, 6.16; N, 4.17.

2,8-Dimethyl-3,7-di(2-acetoxyethyl)-5-phenyldipyrrylmethane-1,9-dicarboxylic Acid **20**.

A solution of dipyrrylmethane **19** (400 mg) in ethanol (100 ml) was reduced with hydrogen at 45 psi over 300 mg of 10% Pd on charcoal during 3 hours. The catalyst was filtered, the solvent evaporated to dryness at reduced pressure, and the acid **19** thus obtained was recrystallized from methanol-water, yield 90% (375 mg), mp 106-107°; ^{1}H nmr (deuterium oxide/sodium hydroxide): δ 1.65 [s, 6, CH_3 (3^5, 7^5)], 1.95 [s, 6, CH_3 (2, 8)], 2.30 [t, 4, CH_2 (3^1, 7^1)], 3.00 [t, 4, CH_2 (3^2, 7^2)], 5.45 [s, 1, CH (5)], 6.95 [m, 2, CH (5^3, $5^{3'}$], 7.10 [m, 3, CH (5^2, $5^{2'}$, 5^4)].

Anal. Calcd. for $C_{26}H_{30}N_2O_8$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.61; H, 6.04; N, 5.60.

Dibenzyl 2,8-Di(2-hydroxyethyl)-3,7-dimethyl-5-phenyldipyrrylmethane-1,9-dicarboxylate **26**.

Reduction of dipyrrylmethane **27** with diborane was carried out following the procedure described for **24**. From 320 mg of **27** was obtained 248 mg (90%) of dialcohol **26**, mp >300° (methanol-water); ^{1}H nmr: δ 1.70 [s, 6, CH_3 (3, 7)], 2.15 [bs, 2, OH (2^3, 8^3)], 2.85 [t, 4, CH_2 (2^1, 8^1)], 3.50 [t, 4, CH_2 (2^2, 8^2)], 5.10 [s, 4, CH_2 (1^3, 9^3)], 5.45 [s, 1, CH (5)], 7.10, 7.35 [m, m, 15, CH (Ph)], 8.85 [bs, 2, NH (10, 11)].

Anal. Calcd. for $C_{36}H_{38}N_2O_6$: C, 72.73; H, 6.40; N, 4.71. Found: C, 72.70; H, 6.39; N, 4.73.

Dibenzyl 2,8-Di(2-acetoxyethyl)-3,7-dimethyl-5-phenyldipyrrylmethane-1,9-dicarboxylate **21**.

This compound was prepared and purified as described for the synthesis of **19**. From 278 mg of **26**, an amber oil was obtained, yield 70% (220 mg); ^{1}H nmr: δ 1.80 [s, 6, CH_3 (2^5, 8^5)], 1.95 [s, 6, CH_3 (3, 7)], 3.05 [t, 4, CH_2 (2^1, 8^1)], 4.15 [t, 4, CH_2 (2^2, 8^2)], 5.25 [s, 4, CH_2 (1^3, 9^3)], 5.50 [s, 1, CH (5)], 7.10, 7.30 [m, m, 15, CH (Ph)], 8.40 [bs, 2, NH (10, 11)]; ms: Calcd. for $C_{40}H_{42}N_2O_8$: 678.2941. Found: hrms 678.2960.

2,8-Di(2-acetoxyethyl)-3,7-dimethyl-5-phenyldipyrrylmethane-1,9-dicarboxylic Acid **22**.

This compound was prepared as described above for the synthesis of **20**. From 220 mg of **21**, an oil was obtained, 142 mg (88%) of the diacid **22**; ^{1}H nmr: δ 1.75 [s, 12, CH_3 (2^5, 3, 7, 8^5)], 2.85 [t, 4, CH_2 (2^1, 8^1)], 4.00 [t, 4, CH_2 (2^2, 8^2)], 5.45 [s, 1, CH (5)], 7.05 [m, 5, CH (Ph)], 8.55 [bs, 2, NH (10, 11)], 9.85 (bs, 2, OH); ms: Calcd. for $C_{26}H_{30}N_2O_8$: 498.2002. Found: hrms 498.2015.

2,8,12,18-Tetramethyl-3,7-di(2-hydroxyethyl)-13,17-di[2-(methoxycarbonyl)ethyl]-15-phenylporphine **9**.

Acid **16** (135 mg, 0.32 mmole) was dissolved in a mixture of 150 ml of dry methylene chloride, and 24 ml of methanol con-

taining 160 mg (0.32 mmole) of diformyldipyrrylmethane **13** and 450 mg of *p*-toluenesulfonic acid were added. Mixtures were kept in the dark at 20° for 24 hours, when 32 ml of methanol saturated with zinc acetate dihydrate was added. After a further period of 72 hours at 30° in the dark the solution was evaporated to dryness at 40°, and the residue was dissolved in 90 ml of a 5% sulfuric acid in methanol solution. The mixture was kept during 16 hours at 20° in the dark, it was then diluted with 200 ml of chloroform, and washed with water (80 ml), then with a 5% sodium bicarbonate solution (80 ml), dried (sodium sulfate), and evaporated to dryness at 40°. The residue was dissolved in methylene chloride-methanol (98:2) and filtered through a column (3.5 cm x 30 cm) of tlc silica gel, packed and prewashed with the same solvent. Eluates containing the main porphyrin band (monitored by its fluorescence) were collected and evaporated to dryness, and the residue of porphyrin **9** was crystallized from methylene chloride-hexane, 90 mg (39%), mp 279-281°; ^{1}H nmr: δ -3.2, -3.1 [bs, bs, 1, 1, NH (21, 23)], 2.54 [m, 4, CH_2 (13^2, 17^2)], 3.06 [m, 4, CH_2 (13^1, 17^1)], 3.56 [s, 6, CH_3 (12, 18)], 3.65 [s, 6, CH_3 (2, 8)], 3.69 [s, 6, CH_3 (13^5, 17^5)], 4.28 [t, 4, CH_2 (3^1, 7^1)], 4.44 [t, 4, CH_2 (3^2, 7^2)], 7.67 [t, 2, CH (15^3, $15^{3'}$)], 7.81 [t, 1, CH (15^4)], 8.15 [d, 2, CH (15^2, $15^{2'}$)], 9.95 [s, 1, CH (5)], 10.19 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{46}N_4O_6$: C, 71.80; H, 6.55; N, 7.98. Found: C, 71.81; H, 6.52; N, 7.99.

2,8,12,18-Tetramethyl-3,7-di(2-chloroethyl)-13,17-di[2-(methoxycarbonyl)ethyl]-15-phenylporphine **5**.

To a solution of porphyrin **9** (77.8 mg) in 10.5 ml of pyridine was added 3.5 ml of mesyl chloride, and the mixture heated at 75° for 35 minutes under nitrogen. The cooled solution was then diluted with 50 ml of water and extracted with methylene chloride (4 x 25 ml). Extracts were dried (sodium sulfate) and evaporated to dryness *in vacuo* at 40°. The residue was dissolved in methylene chloride-methanol (99.5:0.5) and was filtered through a tlc silica gel column as described above. Bischloroethylporphyrin **5** was crystallized from methylene chloride-hexane, 52.6 mg (64%), mp 266-268°; ^{1}H nmr: δ -3.20, -3.10 [bs, bs, 1, 1, NH (21, 23)], 2.55 [m, 4, CH_2 (13^2, 17^2)], 3.05 [m, 4, CH_2 (13^1, 17^1)], 3.55 [s, 6, CH_3 (12, 18)], 3.64 [s, 6, CH_3 (2, 8)], 3.70 [s, 6, CH_3 (13^5, 17^5)], 4.33 [t, 4, CH_2 (3^1, 7^1)], 4.45 [t, 4, CH_2 (3^2, 7^2)], 7.65 [t, 2, CH (15^3, $15^{3'}$)], 7.80 [t, 1, CH (15^4)], 8.15 [d, 2, CH (15^2, $15^{2'}$)], 9.88 [s, 1, CH (5)], 10.19 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{44}N_4Cl_2O_4$: C, 68.20; H, 5.95; N, 7.58. Found: C, 68.23; H, 5.97; N, 7.61.

2,8,12,18-Tetramethyl-3,7-divinyl-13,17-di[2-(methoxycarbonyl)ethyl)]-15-phenylporphine **1**.

To a solution of porphyrin **5** (44.2 mg) in 20 ml of dry DMF was added 1 ml of 1,5-diazabicyclo[5.4.0]-5-undecene (DBU), and the mixture heated for 40 hours at 20° in the dark. The solution was evaporated to dryness and the residue was dissolved with water (3 x 20 ml), dried (sodium sulfate) and evaporated. The residue was dissolved in methylene chloride-methanol (99.5:0.5) and filtered through a column as described above. Porphyrin **1** was crystallized from methylene chloride-hexane: 26.4 mg (66%); mp >300°; visible spectrum (dichloromethane): λ_{max} 408 nm (ε 141300), 508 (13800), 543 (7800), 579 (6600); ^{1}H nmr: δ -3.07, -2.94 [bs, bs, 1, 1, NH (21, 23)], 2.54 [m, 4, CH_2 (13^2, 17^2)], 3.07 [m, 4, CH_2 (13^1, 17^1)], 3.55 [s, 6, CH_3 (12, 18)], 3.68 [s, 6, CH_3 (2, 8)], 3.70 [s, 6, CH_3 (13^5, 17^5)], 6.17, 6.39 [dd, J = 1.5 Hz and 11.5 Hz, dd, J = 1.5 Hz and 17.8 Hz, 2, 2, CH_2 (3^2, 7^2)], 7.67 [t, 2, CH (15^3, $15^{3'}$)], 7.81 [t, 1, CH (15^4)], 8.19 [m, 4, CH (3^1, 7^1, 15^2, $15^{2'}$)], 10.19 [s, 3, CH (5, 10, 20)].

Anal. Calcd. for $C_{42}H_{42}N_4O_4$: C, 75.68; H, 6.31; N, 8.41. Found: C, 75.65; H, 6.28; N, 8.45.

3,7,12,18-Tetramethyl-2,8-di(2-hydroxyethyl)-13,17-di[2-(methoxycarbonyl)ethyl]-15-phenylporphine **10**.

Dipyrrylmethane diacid **22** (135 mg, 0.32 mmole) was condensed with 160 mg (0.32 mmole) of dipyrrylmethane dialdehyde **13** following the procedure described for **9**. Final purification of the dimethyl ester **10** was achieved by means of a tlc silica gel column (3.5 cm x 30 cm) using methylene chloride-methanol (98:2). The porphyrin was crystallized from methylene chloride-hexane, 62 mg (28%), mp 266-268°; ^{1}H nmr: δ -3.26, -3.10 [bs, bs, 1, 1, NH (21, 23)], 2.50 [m, 4, CH_2 (13^2, 17^2)], 3.05 [m, 4, CH_2 (13^1, 17^1)], 3.53 [s, 6, CH_3 (12, 18)], 3.59 [s, 6, CH_3 (3, 7)], 3.69 [s, 6, CH_3 (13^5, 17^5)], 4.28 [m, 4, CH_2 (2^1, 8^1)], 4.44 [m, 4, CH_2 (2^2, 8^2)], 7.65 [t, 2, CH (15^3, $15^{3'}$)], 7.80 [t, 1, CH (15^4)], 8.11 [m, 2, CH (15^2, $15^{2'}$)], 9.94 [s, 1, CH (5)], 10.14 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{46}N_4O_6$: C, 71.80; H, 6.55; N, 7.98. Found: C, 71.83; H, 6.58; N, 7.96.

3,7,12,18-Tetramethyl-2,8-di(2-chloroethyl)-13,17-di[2-(methoxycarbonyl)ethyl]-15-phenylporphine **6**.

Porphyrin **10** (50 mg) dissolved in 5 ml of dry DMF was heated at 70° for 5 minutes and then was treated with 0.65 ml of mesyl chloride, and the mixture heated at 70° for 5 hours. Porphyrin **6** was isolated after purification by column chromatography following the procedure described for **5**, 43 mg (82%), mp 253-254° (methylene chloride-hexane); ^{1}H nmr: δ -3.25, -3.08 [bs, bs, 1, 1, NH (21, 23)], 2.54 [m, 4, CH_2 (13^2, 17^2)], 3.08 [m, 4, CH_2 (13^2, 17^2)], 3.57 [s, 6, CH_3 (12, 18)], 3.61 [s, 6, CH_3 (3, 7)], 3.70 [s, 6, CH_3 (13^5, 17^5)], 4.31 [m, 4, CH_2 (2^1, 8^1)], 4.50 [m, 4, CH_2 (2^2, 8^2)], 7.69 [t, 2, CH ($15^{3'}$)], 7.82 [t, 1, CH (15^4)], 8.17 [d, 2, CH (15^2, $15^{2'}$)], 9.95 [s, 1, CH (5)], 10.09 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{44}N_4Cl_2O_4$: C, 68.20; H, 5.95; N, 7.58. Found: C, 68.19; H, 5.96; N, 7.55.

2,8-Divinyl-3,7,12,18-tetramethyl-13,17-di[2-(methoxycarbonyl)ethyl]-15-phenylporphine **2**.

To a solution of porphyrin **6** (30.4 mg) in 20 ml of dry DMF was added 0.1 ml of DBU, and the mixture stirred for 40 hours at 20° in the dark. Porphyrin **2** was isolated and purified following the procedure described for **1**, 20 mg (73%), mp 282-284° (methylene chloride-hexane); visible spectrum (methylene chloride): λ_{max} 409 nm (ε 122300), 508 (16500), 542 (8500), 579 (6900); ^{1}H nmr: δ -3.30, -3.05 [bs, bs, 1, 1, NH (21, 23)], 2.53 [m, 4, CH_2 (13^2, 17^2)], 3.06 [m, 4, CH_2 (13^1, 17^1)], 3.53 [s, 6, CH_3 (12, 18)], 3.57 [s, 6, CH_3 (3, 7)], 3.69 [s, 6, CH_3 (13^5, 17^5)], 6.17, 6.32 [dd, J = 1.5 Hz and 11.5 Hz, dd, J = 1.5 Hz and 17.8 Hz, 2, 2, CH_2 (2^2, 8^2)], 7.67 [t, 2, CH (15^3, $15^{3'}$)], 7.81 [t, 1, CH (15^4)], 8.15 [m, 2, CH (15^2, $15^{2'}$)], 8.22 [dd, J = 11.5 Hz and 17.8 Hz, 2, CH (2^1, 8^1)], 9.83 [s, 1, CH (5)], 10.22 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{42}N_4O_4$: C, 75.68; H, 6.31; N, 8.41. Found: C, 75.65; H, 6.28; N, 8.43.

2,8,12,18-Tetramethyl-3,7-di(2-hydroxyethyl)-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl]porphine **11**.

Dipyrrylmethane diacid **20** (178 mg, 0.35 mmole) was condensed with 150 mg (0.35 mmole) of dipyrrylmethanedialdehyde **23** following the procedure described for **9**. Final purification of dimethyl ester **11** was achieved by purification through tlc silica gel column (3.5 x 20 cm) using methylene chloride-methanol (98:2). The porphyrin was crystallized from methylene chloride-hexane, 105 mg (43%) mp 273-275°; ^{1}H nmr: δ -3.22, -3.06 [bs, bs, 1, 1, NH (21, 23)], 2.98 [t, 4, CH_2 (13^2, 17^2)], 3.29 [t, 4, CH_2 (13^1, 17^1)], 3.64 [m, 22, CH_3 (2, 8, 12, 18, 13^5, 17^5), CH_2 (3^1, 7^1)], 4.37 [t, 4, CH_2 (3^2, 7^2)], 7.74 [m, 2, CH (5^3, $5^{3'}$)], 7.90 [m, 1, CH (5^4)], 8.19 [d, 2, CH (5^2, $5^{2'}$)], 9.94 [s, 1, CH (15)], 10.18 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{46}N_4O_6$: C, 71.80; H, 6.55; N, 7.98. Found: C, 71.85; H, 6.52; N, 8.00.

2,8,12,18-Tetramethyl-3,7-di(2-chloroethyl)-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl]porphine **7**.

This compound was prepared and purified as described for the synthesis of **5**. From 50 mg of **11**, porphyrin **7** was obtained, yield 51% (27 mg), mp 292-294° (methylene chloride-hexane); ^{1}H nmr: δ -3.21, -3.05 [bs, bs, 1, 1, NH (21, 23)], 3.15 [m, 4, CH_2 (13^2, 17^2)], 3.29 [m, 4, CH_2 (13^1, 17^1)], 3.54 [m, 4, CH_2 (3^1, 7^1)], 3.59 [s, 6, CH_3 (2, 8)], 3.64 [s, 6, CH_3 (12, 18)], 3.66 [s, 6, CH_3 (13^5, 17^5)], 4.37 [m, 4, CH_2 (3^2, 7^2)], 7.79 [t, 2, CH (5^3 and $5^{3'}$)], 7.95 [7, 1, CH (5^4)], 8.13 (m, 2, CH (5^2 and $5^{2'}$)], 9.94 [s, 1, CH (15)], 10.18 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{44}N_4Cl_2O_4$: C, 68.20; H, 5.95; N, 7.58. Found: C, 68.17; H, 5.93; N, 7.54.

2,8,12,18-Tetramethyl-3,7-divinyl-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl)porphine **3**.

To a solution of porphyrin **7** (25.6 mg) in 20 ml of dry DMF was added 1 ml of DBU and the mixture was heated for 16 hours at 80° in the dark. Porphyrin **3** was isolated and purified following the procedure described for **1**, 11.2 mg (49%), mp 244-246° (methylene chloride-hexane); visible spectrum (methylene chloride): λ_{max} 405 nm (ε 123300), 504 (10200), 538 (5300), 574 (4500); ^{1}H nmr: δ -3.22, -3.10 [bs, bs, 1, 1, NH (21, 23)], 3.30 [t, 4, CH_2 (13^2, 17^2)], 3.62 [s, 6, CH_3 (2, 8)], 3.65 [s, 6, CH_3 (12, 18)], 3.67 [s, 6, CH_3 (13^5, 17^5)], 4.40 [t, 4, CH_2 (13^1, 17^1)], 5.32, 5.42 [dd, J = 2.3 Hz and 11.2 Hz, dd, J = 2.3 Hz and 17.5 Hz, 2, 2, CH_2 (3^2, 7^2)], 6.44 [dd, J = 11.2 Hz and 17.5 Hz, 2, CH (3^1, 7^1)], 7.63 [7, 2, CH (5^3, $5^{3'}$)], 7.73 [t, 1, CH (5^4)], 7.91 [d, 2, CH (5^2 and $5^{2'}$)], 9.96 [s, 1, CH (15)], 10.20 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{42}N_4O_4$: C, 75.68; H, 6.31; N, 8.41. Found: C, 75.65; H, 6.35; N, 8.38.

2,8-Di(2-hydroxyethyl)-3,7,12,18-tetramethyl-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl]porphine **12**.

Dipyrrylmethane diacid **22** (58 mg, 0.12 mmole) was condensed with 50 mg (0.15 mmole) of **23** following the procedure described in the preparation of **9**. After purification by chromatography dimethyl ester **12** was crystallized from methylene chloride-hexane, 35 mg (42%), mp 250-252°; ^{1}H nmr: δ -3.31, -3.17 [bs, bs, 1, 1, NH (21, 23)], 2.49 [3, 6, CH_3 (3, 7)], 3.28 [t, 4, CH_2 (13^2, 17^2)], 3.64 [s, 6, CH_3 (12, 18)], 3.67 [s, 6, CH_3 (13^5, 17^5)], 4.35 [m, 12, CH_2 (2^1, 2^2, 8^1, 8^2)], 7.77 [m, 3, CH (5^3, $5^{3'}$, 5^4)], 8.04 [m, 2, CH (5^2, $5^{2'}$)], 9.95 [s, 1, CH (15)], 10.17 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{46}N_4O_6$: C, 71.80; H, 6.55; N, 7.98. Found: C, 71.78; H, 6.56; N, 7.96.

2,8-Di(2-chloroethyl)-3,7,12,18-tetramethyl-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl]porphine **8**.

To a solution of porphyrin **12** (30 mg) in 5 ml of dry DMF was added 0.4 ml of mesyl chloride, and the mixture heated at 70° for 6 hours under nitrogen. This compound was isolated and purified as described for the synthesis of **5**. Porphyrin **8** was crystallized from methylene chloride-hexane, 18.5 mg (57%), mp 183-184°; ^{1}H nmr: δ -3.26, -3.12 [bs, bs, 1, 1, NH (21, 23)], 2.49 [s, 6, CH_3 (3, 7)], 3.30 [t, 4, CH_2 (13^2, 17^2)], 3.66 [s, 12, CH_3 (12, 18, 13^5, 17^5)], 4.19 [t, 4, CH_2 (2^1, 8^1)], 4.39 [t, 4, CH_2 (13^1, 17^1)], 4.45 [t, 4, CH_2 (2^2, 8^2)], 7.78 [m, 3, CH (5^3, $5^{3'}$, 5^4)], 8.03 [d, 2, CH (5^2, $5^{2'}$)], 9.97 [s, 1, CH (15)], 10.11 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{44}N_4Cl_2O_4$: C, 68.20; H, 5.95; N, 7.58. Found: C, 68.16; H, 5.98; N, 7.55.

2,8-Divinyl-3,7,12,18-tetramethyl-5-phenyl-13,17-di[2-(methoxycarbonyl)ethyl]porphine **4**.

To a solution of porphyrin **8** (16 mg) in 10 ml of dry DMF was added 0.5 ml of DBU and the mixture stirred for 5 days at 20° in the dark. Porphyrin **4** was isolated and purified following the procedure described for **1**, 9 mg (62%), mp 215-217° (methylene chloride-hexane); visible spectrum (methylene chloride): λ_{max} 407 nm (ε 116000), 505 (13300), 539 (5900), 575 (5500); ^{1}H nmr: δ -3.12, -3.00 [bs, bs, 1, 1, NH (21, 23)], 2.52 [s, 6, CH_3 (3, 7)], 3.28 [t, 4, CH_2 (13^2, 17^2)], 3.61 [s, 6, CH_3 (12, 18)], 3.67 [s, 6, CH_3 (13^5, 17^5)], 4.37 [t, 4, CH_2 (13^1, 17^1)], 6.13, 6.21 [dd, J = 1.9 Hz and 17.8 Hz, dd, J = 1.9 Hz and 11.5 Hz, 2, 2, CH_2 (2^2, 8^2)], 7.75 [m, 3, CH (5^3, $5^{3'}$, 5^4)], 8.10 [m, 4, CH (5^2, $5^{2'}$, 2^1, 8^1)], 10.25 [s, 2, CH (10, 20)].

Anal. Calcd. for $C_{42}H_{42}N_4O_4$: C, 75.68; H, 6.31; N, 8.41. Found: C, 75.65; H, 6.38; N, 8.37.

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