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TOTAL SYNTHESIS AND CONFORMATIONAL ANALYSIS OF MONOPHENYL SUBSTITUTED PROTOPORPHYRINS IX

Adriana E. Robinsohn, [#] Marta S. Maier,[##] and Graciela Y. Buldain[#]*

[#]Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, (1113) Buenos Aires, Argentina

[##]Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pabellón 2, (1428) Buenos Aires, Argentina

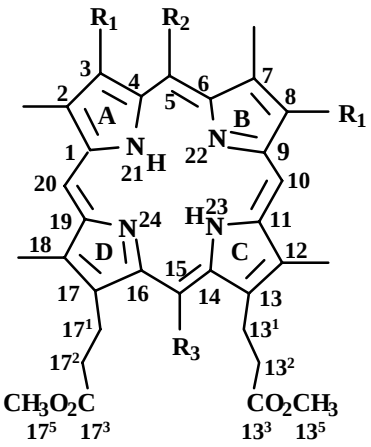
Abstract - The total synthesis of meso-monoaryl protoporphyrins (**1**) and (**2**) using a MacDonald type [2+2] condensation is described. In this method a bisformyl dipyrrylmethane is treated with a biscarboxydipyrrylmethane. Attempts to obtain the δ-meso-monoaryl protoporphyrin (**7**) by the a,c-biladiene method failed as it could not be prepared starting from its tripyrrene precursor. The synthesis of the latter compound is described. Molecular modeling studies allowed us to find the most favorable conformations for compounds (**1**) and (**2**). In both porphyrins, the exocyclic phenyl group adopts a noncoplanar disposition relative to the plane of the macrocycle. In porphyrin (**2)** the macrocycle is nearly planar while nonplanar saddle conformation was obtained for porphyrin (**1**).

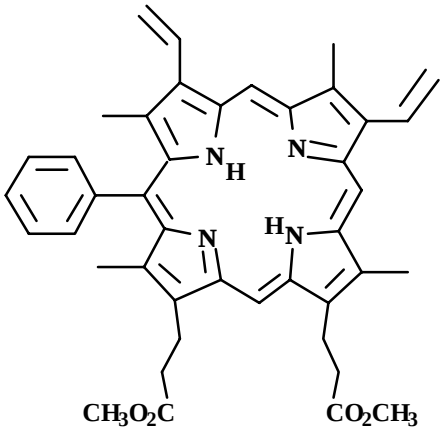
The three general biological functions of the hemoproteins are as follows:

1. electron transport (cytochrome b_5);
2. oxygen transport (hemoglobin); and
3. catalysis of redox reactions (cytochrome P_{450} and peroxidases).

All these hemoproteins share a common Fe-protoporphyrin (hemo) as prosthetic group. Functional differences depend on how the protein interacts with the hemo group and with its potential substrates. When horseradish peroxidase is inactivated during alkylation carried out with phenylhydrazine,[1] a hemin (Fe^{3+}-protoporphyrin IX) is isolated, where the hydrogen atom of 20-meso carbon is replaced by a phenyl group. In order to confirm whether the loss of catalytic activity is only due to selective substitution in such position of the porphyrin macrocycle, total synthesis of the meso phenyl substituted porphyrins (**1**)

and (**2**) was attempted. It was also our aim to prepare 20-phenylprotoporphyrin (**7**), originally isolated from the prosthetic group of the inactive peroxidase and identified by Ortiz de Montellano *et al.*[1] but not yet synthesized, to compare the synthetic product with its biological counterpart.





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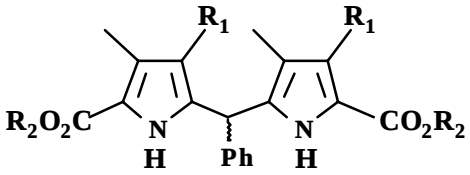
Compound	R_1	R_2	R_3
1	$CH{=}CH_2$	C_6H_5	H
2	$CH{=}CH_2$	H	C_6H_5
3	CH_2CH_2Cl	C_6H_5	H
4	CH_2CH_2Cl	H	C_6H_5
5	CH_2CH_2OH	C_6H_5	H
6	CH_2CH_2OH	H	C_6H_5

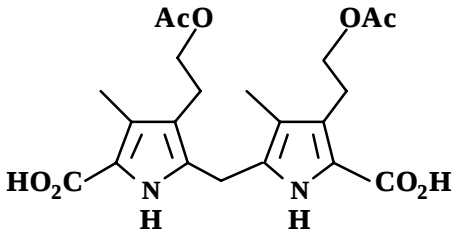
Scheme 1

Computer-assisted conformational analysis of the above porphyrins was performed in order to investigate whether possible conformational variations correlated with spectroscopic properties. In the literature the meso-aryloctaethylporphyrins have been obtained using MacDonald's synthesis[2,3] or the method of oxidative a,c-biladiene cyclization.[4,5]

The present authors found that the most direct approach to monophenylporphyrin isomers (**1**) and (**2**), in a pure form, was to resort to MacDonald's method in its simplified form.[6] For this purpose it was necessary to develop total synthesis of precursor porphyrins (**5**) and (**6**), respectively, which were synthesized by condensation of the corresponding dicarboxydipyrrylmethanes (**8**) and (**12**)[7] with the well-known diformyldipyrrylmethanes (**13**)[8] and **14**,[9] in the presence of *p*-toluenesulfonic acid.[6]

Dicarboxydipyrrylmethane (**8**) was obtained by catalytic hydrogenolysis (10% Pd/C) of **9**, which in turn was prepared by esterification of **10** with acetic anhydride-pyridine. The latter was afforded by reacting dipyrrylmethane (**11**) with diborane in tetrahydrofuran, that transforms the ethoxycarbonylmethyl chains into β-hydroxyethyl groups.





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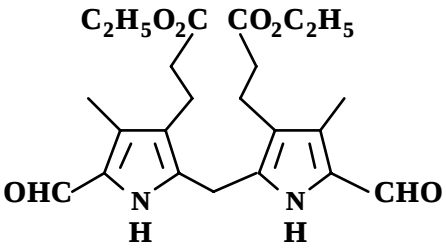
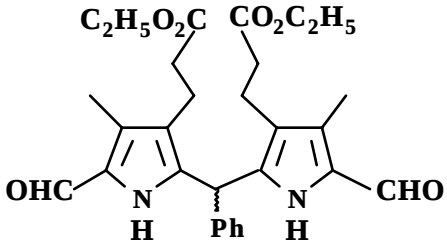
	R_1	R_2
8	$CH_2CH_2OCOCH_3$	H
9	$CH_2CH_2OCOCH_3$	$CH_2C_6H_5$
10	CH_2CH_2OH	$CH_2C_6H_5$
11	$CH_2CO_2C_2H_5$	$CH_2C_6H_5$

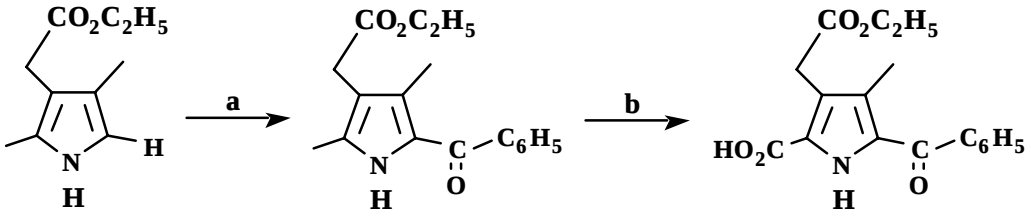




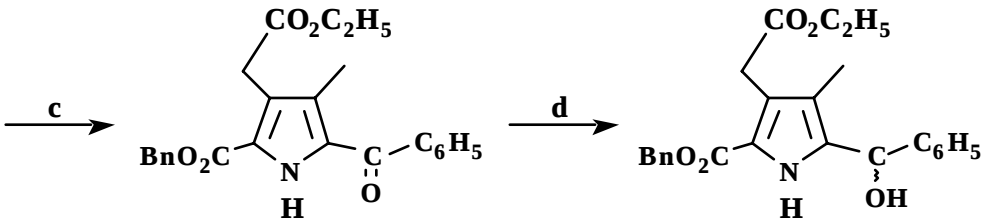
13 **14**

Scheme 2

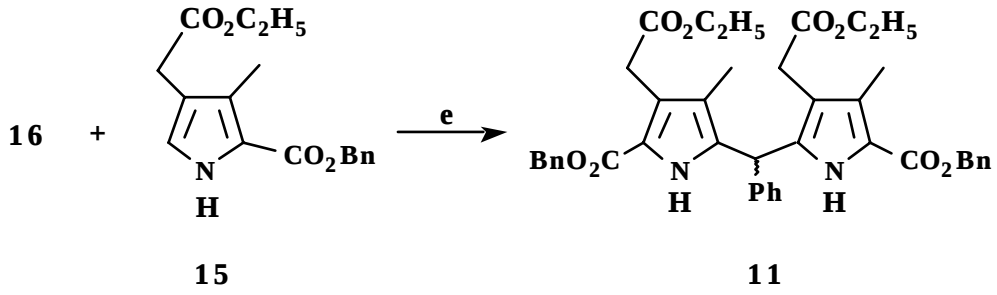
Compound (**11**) was obtained by acid-catalyzed condensation of the well-known α-free pyrrole (**15**)[7] with hydroxybenzylpyrrole (**16**), the latter synthesized starting from pyrrole (**17**)[10] according to Scheme 3.



17 **18** **19**



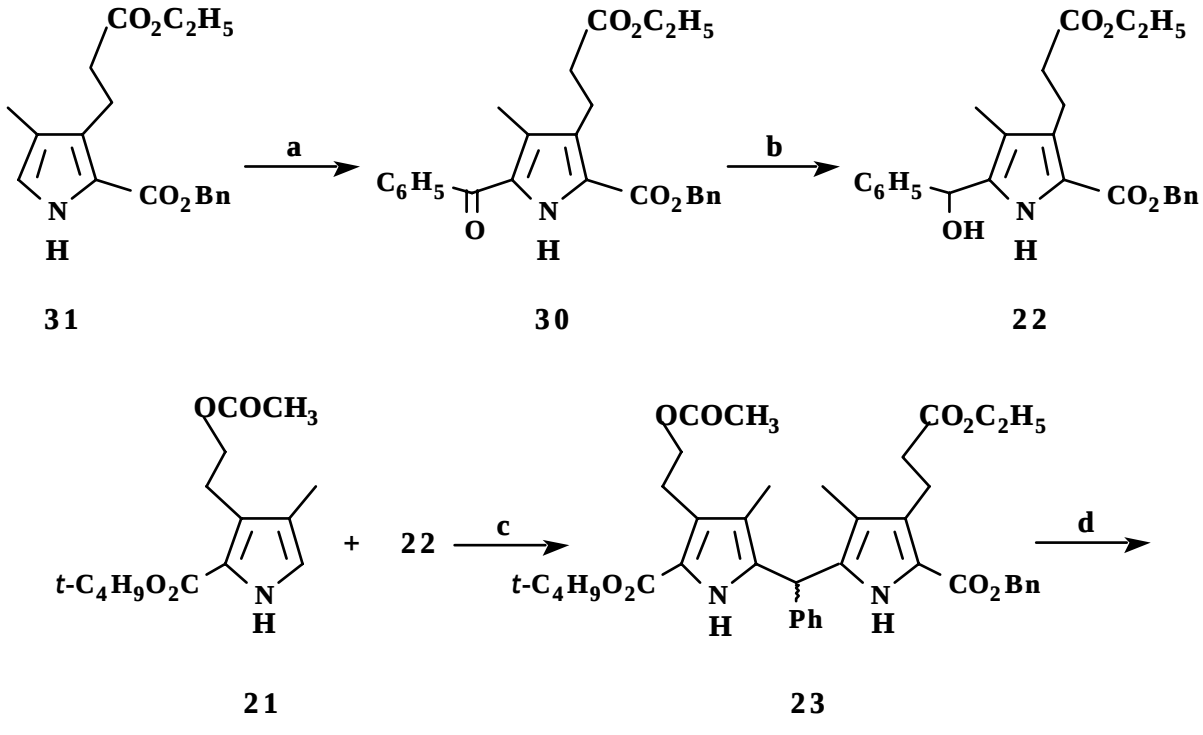
20 **16**

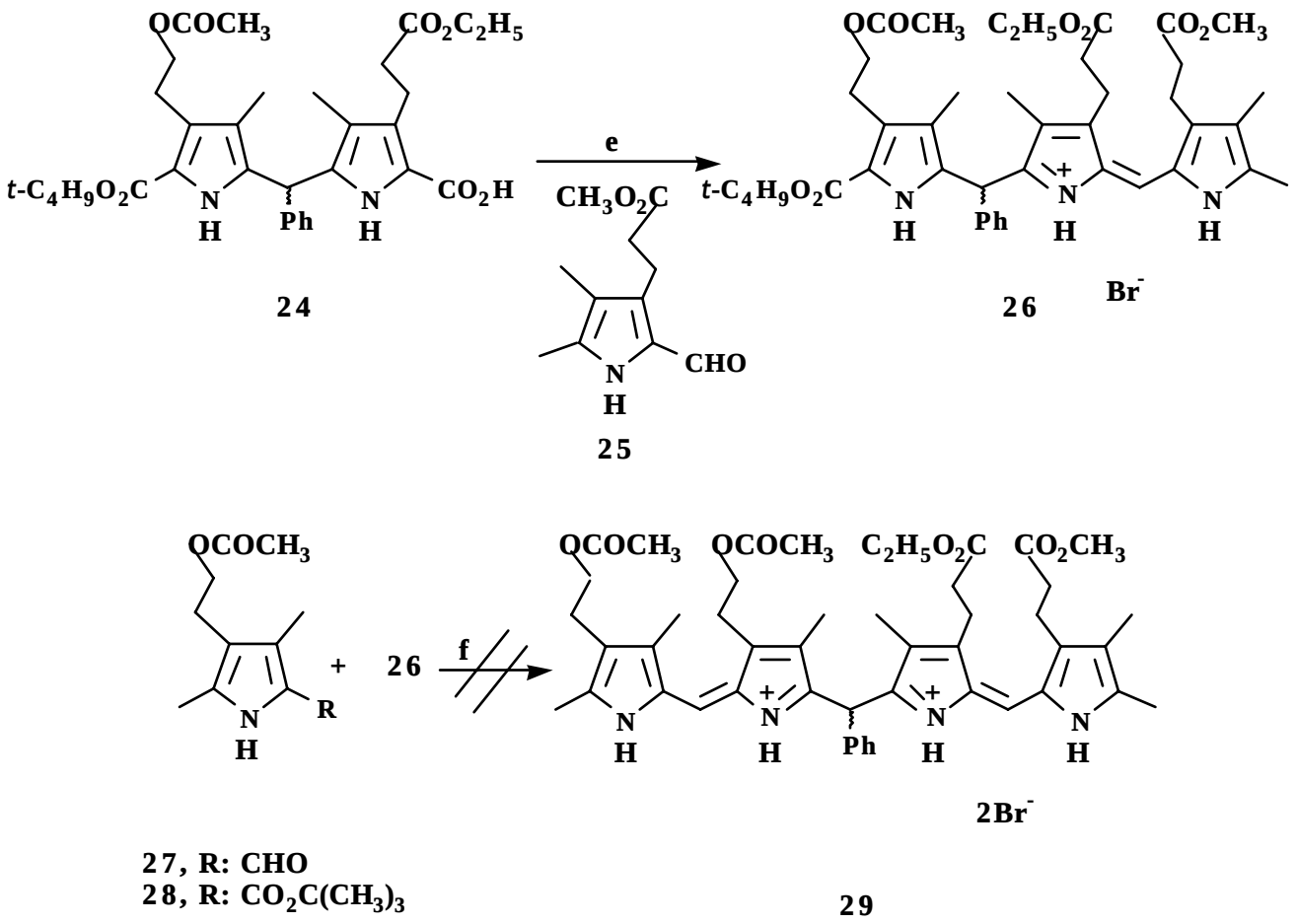


a: ClCOBn, CH_2Cl_2, HCO_3Na; **b**: SO_2Cl_2, CCl_4, AcONa, AcOH; **c**: BnCl, DMF, TEA; **d**: $NaBH_4$, CH_2Cl_2, CH_3OH; **e**: CH_2Cl_2, PTS

Scheme 3

It was necessary to develop this synthetic process to prepare pyrrole (**20**) because direct acylation of the corresponding α-free precursor with two acylating agents [C_6H_5COCl, $(C_6H_5CO)_2O$] and using three Lewis acids [$AlCl_3$, $SnCl_4$ and $TiCl_4$] led to yields below 20%. By treatment with mesyl chloride, the 2-hydroxyethylporphyrins (**5**) and (**6**) were transformed into **3** and **4**, whose vinylation with DBU/DMF afforded the desired porphyrins (**1**) and (**2**), respectively, in good yields.To obtain porphyrin (**7**) it was necessary to develop the total synthesis of a correctly substituted 1,19-dimethyl-a,c-biladiene, isolated as hydrobromide, followed by later ring closure mediated by Cu (II) salts.[11] (Scheme 4).





a: C_6H_5COCl, $SnCl_4$; **b**: $NaBH_4$, CH_2Cl_2, CH_3OH; **c**: CH_2Cl_2, PTS; **d**: H_2, 10% Pd/C; **e**: PTS, CH_2Cl_2, CH_3OH, $HBr_{(g)}$; **f**: TFA, HBr, AcOH, CH_3OH

Scheme 4

The preparation of a,c-biladiene (**29**) required the synthesis of the dipyrrylmethane (**24**), obtained from precursor (**23**) by catalytic hydrogenation. The latter was obtained by acid-catalyzed condensation of α-free pyrrole (**21**)[12] with hydroxybenzylpyrrole (**22**). In turn, this latter pyrrol was synthesized by a benzoylation reaction of α-free pyrrole (**31**)[13] using benzoyl chloride and stannous tetrachloride, to afford benzoyl pyrrole (**30**), which by treatment with sodium borohydride led to the desired pyrrole (**22**). Dipyrrylmethane (**24**) thus obtained was successfully condensed with pyrrole (**25**)[14] to render the hydrobromide of the desired tripyrrin (**26**) whose appearance was monitored by the presence of the characteristic absorption bands of these compounds in the UV-VIS spectrum.[15] Attempts to condense the tripyrrin prepared with formyl pyrrole (**27**), which was synthesized from **28**,[16] failed to afford the a,c-biladiene required for the synthesis of porphyrin (**7**).

Molecular Modeling Studies

Recently, we have reported the energetically favored conformations of four monoaryl-substituted protoporphyrins obtained by molecular mechanics and their correlations with NOE NMR data.[17] In this case we applied the semiempirical molecular orbital method AM1[18] to determine the energetically favored conformations of porphyrins (**1**) and (**2**). This approach based on quantum mechanics but at less computationally demanding level[19] has previously been used to study the structure of porphyrin.[20] The AM1 results provided a good accounting of the geometry and electronic structure of this molecule and were consistent with subsequent *ab initio* molecular orbital calculations.[21]

The presence of a phenyl group at C-5 in porphyrin (**1**) leads to a distorted macrocycle, adopting a nonplanar saddle conformation (Figure 1).

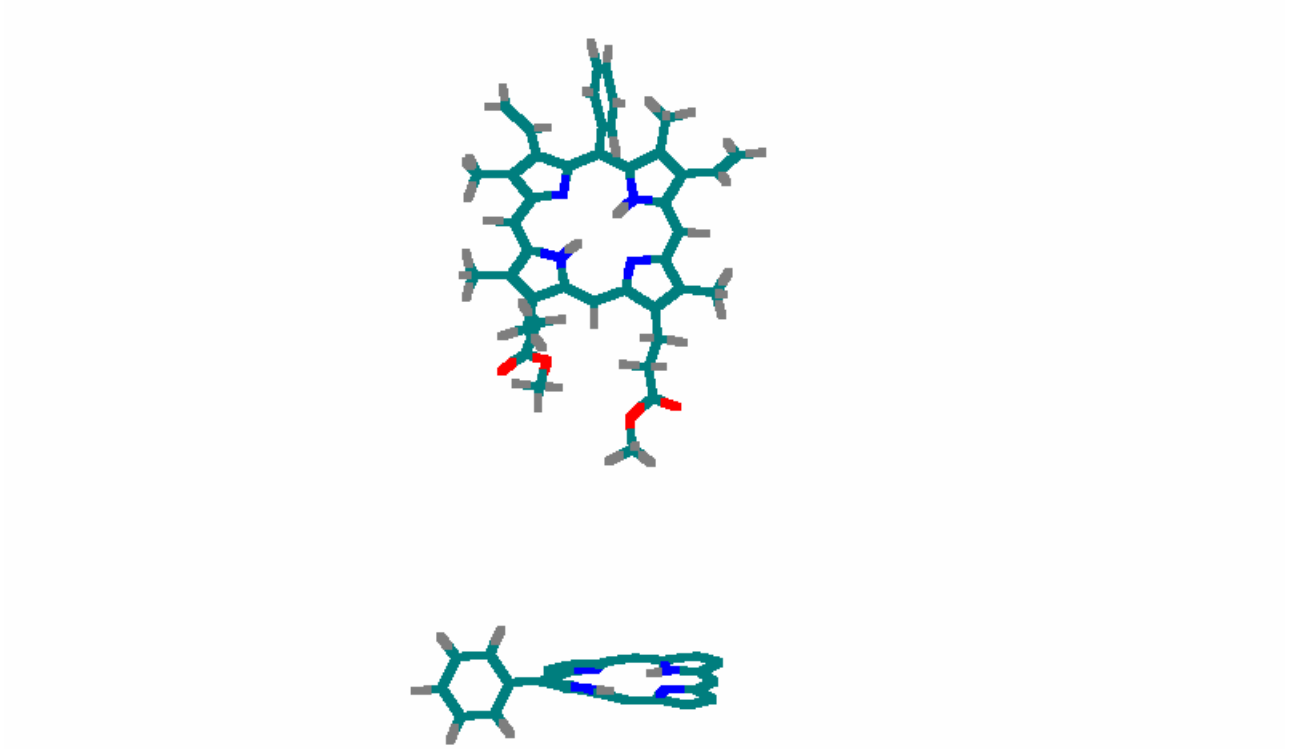


Figure 1. Optimized geometry for porphyrin (**1**). Above: Spatial disposition of the phenyl group respect to the macrocycle, below: Spatial disposition of the macrocycle.

The optimized geometry for **1** shows a C(5^2)-C(5^1)-(C5)-C(6) torsional angle of 76.3°. On the other hand, the 24-atom porphyrin core is nearly planar in porphyrin (**2**) with a predominance of the conformer with a C(14)-C(15)-(C15^1)-C(15^2) torsional angle of 88.3° (Figure 2).

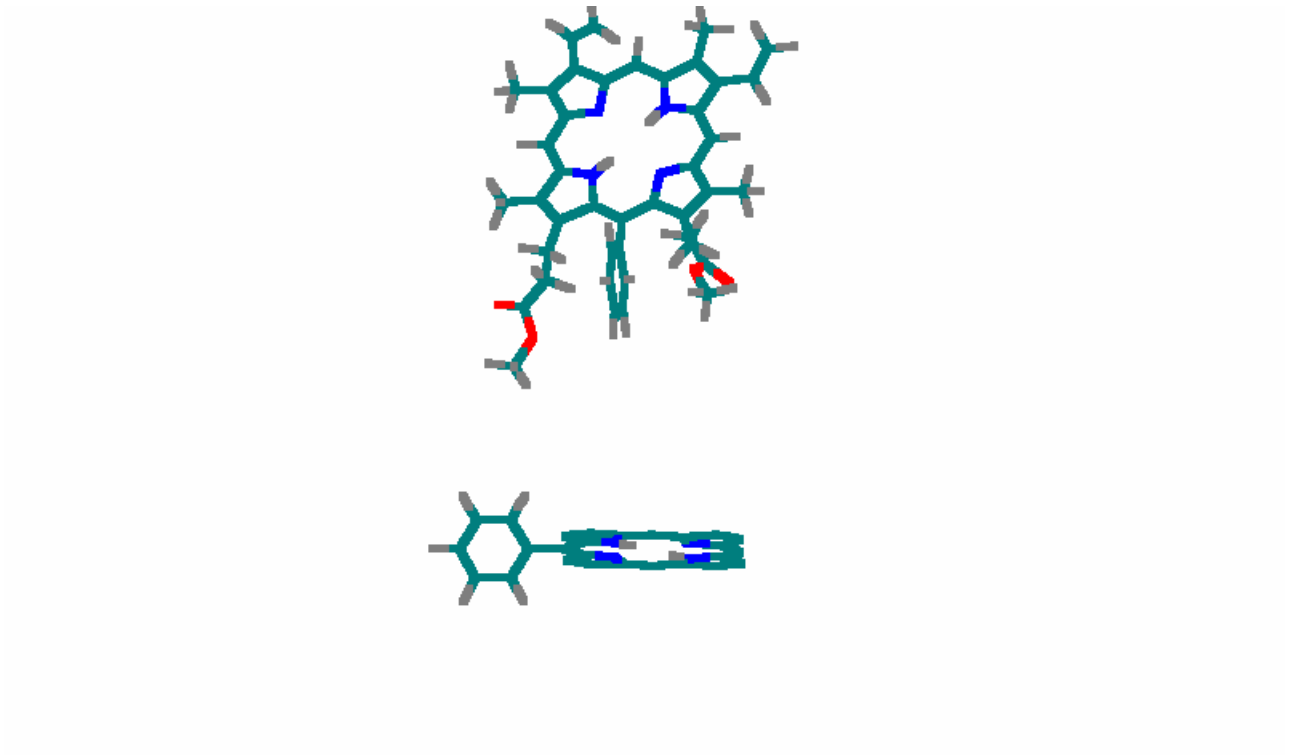


Figure 2. Optimized geometry for porphyrin (**2**). Above: Spatial disposition of the phenyl group respect to the macrocycle, below: Spatial disposition of the macrocycle.

Table1. Dihedral angle Calculated for Porphyrins (**1**) and (**2**) by Molecular Modeling

Torsion angle	**1**	**2**
N(21)-C(1)-C(20)-C(19)	9.07	0.50
N(21)-C(4)-C(5)-C(6)	-5.50	0.80
N(22)-C(6)-C(5)-C(4)	-15.20	1.10
N(22)-C(9)-C(10)-C(11)	14.40	-1.29
N(23)-C(11)-C(10)-C(9)	0.45	0
N(23)-C(14)-C(15)-C(16)	-2.59	-0.13
N(24)-C(16)-C(15)-C(14)	-2.60	0.15
N(24)-C(19)-C(20)-C(1)	1.33	0.30
$C(5^2)$-$C(5^1)$-C(5)-C(6)	76.3^{o}	-
$C(15^2)$-$C(15^1)$-C(15)-C(14)	-	88.3°

The individual pyrrol rings in porphyrin (**1**) are canted with respect to these rings in porphyrin (**2**) (Table 1), reflecting the distorsion of the porphyrin skeleton. This is in accordance with the spatial disposition of

the phenyl group in the four monoarylporphyrins recently studied by us.[18] The methoxycarbonylethyl groups adopt an anti conformation for the substituents of C(13^1) and C(13^2) atoms in both porphyrins.
^{1}H NMR spectra of porphyrins (**1**) and (**2**) showed upfield shifts for those protons near the phenyl group, indicating that this group lies spatially noncoplanar with the macrocycle in coincidence with the AM1 results.

EXPERIMENTAL

General procedures

NMR spectra were determined in deuteriochloroform and recorded by means of a Bruker MSL 300 spectrometer. Chemical shift values are expressed in ppm relative to TMS. 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. Semiempirical calculations were carried out using the AM1 method included in the Hyperchem package.

3-Ethoxycarbonylmethyl-2,4-dimethyl-5-benzoylpyrrole (18).

To a solution of 3-ethoxycarbonylmethyl-2,4-dimethylpyrrole (**17**) (500 mg, 2.8 mmol) in 20 mL of methylene chloride were added 20 mL of saturated aqueous solution of sodium bicarbonate and 0.8 mL (6.9 mmol) of benzoyl chloride. The mixture was stirred overnight at rt and then the organic layer washed with water (20 mL), saturated aqueous solution of sodium bicarbonate (20 mL) and water (20 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated at reduce pressure. The crude product was purified through a silica gel column (3.5 cm x 30 cm) using methylene chloride-methanol (98:2) as solvent.

The residue was crystallized from methanol, 358 mg (45%); mp 101-103ºC; ^{1}H-NMR: δ 1.20[t, J=7.1 Hz, 3, $CH_3(3^5)$], 1.95[s, 3, $CH_3(2)$], 2.30[s, 3, $CH_3(4)$], 3.30[s, 2, $CH_2(3^1)$], 4.10[q, J=7.1 Hz, 2, $CH_2(3^4)$], 7.60[m, 5, CH(Ph)], 9.20 [br s, 1, NH]. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.80; N, 4.80.

3-Ethoxycarbonylmethyl-4-methyl-5-benzoylpyrrole-2-carboxylic Acid (19).

To a solution of 670 mg, (2.4 mmol) of **18** in 50 mL of carbon tetrachloride was added 0.61 mL (7.5 mmol) of freshly distilled sulfuryl chloride. The mixture was kept at 45ºC for 4 h, then evaporated to dryness. The residue was dissolved in a mixture of sodium acetate (6 g), water (30 mL) and 1,4-dioxane (30 mL). Heated to reflux for 2 h and then poured over 200 mL of ice-water, the solution was adjusted to

pH 2 with concentrated hydrochloric acid. The mixture was extracted with ether (2 x 100 mL), the organic layer washed with water (50 mL) and extracted with 5% aqueous solution of sodium bicarbonate (2 x 25 mL). A stream of nitrogen was bubbed through the above alkaline solution during 1 h and then the acid (**19**) was precipitated with 50% aqueous solution of acetic acid. It was filtered and the residue was crystallized from methanol, 300 mg (41%); mp 148-151ºC; ^{1}H-NMR: δ 1.25[t, J=7.2 Hz, 3, $CH_3(3^5)$], 2.10 [s, 3, $CH_3(4)$], 3.90[s, 2, $CH_2(3^1)$], 4.20[q, J=7.2 Hz, 2, $CH_2(3^4)$], 7.50[m, 5, CH(Ph)], 9.00[br s, 1, NH], 9.90[br s, 1, COOH]. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.86; H, 5.38; N, 4.36.

Benzyl 3-Ethoxycarbonylmethyl-4-methyl-5-benzoylpyrrole-2-carboxylate (20).

Pyrrole (**19)** (300 mg, 0.9 mmol) was dissolved in a mixture of 7.7 mL of DMF, 4.4 mL (38.2 mmol) of benzyl chloride and 4.4 mL (31.6 mmol) of TEA. The solution was stirred at rt for 48 h, then evaporated to dryness and the residue dissolved in 50 mL of methylene chloride. The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and water (20 mL). The organic solution was dried with anhydrous sodium sulfate and evaporated at reduced pressure. The crude product was purified through a silica gel column (3 cm x 30 cm) using methylene chloride-methanol (98:2) as solvent, to obtain a white solid from methylene chloride-hexane, 192 mg (50%); mp 99-100ºC; ^{1}H-NMR: δ 1.20[t, J=7.1 Hz, 3, $CH_3(3^5)$], 2.10[s, 3, $CH_3(4)$], 3.85[s, 2, $CH_2(3^1)$], 4.10[q, J=7.1 Hz, 2, $CH_2(3^4)$], 5.30[s, 2, $CH_2(2^3)$], 7.35-7.50[m, 7, CH(Ph,5^4,$5^{4'}$)], 7.55[t, J=7.6 Hz, 1, CH(5^5)], 7.70[dd, J=7.6 Hz and 1.9 Hz, 2, CH(5^3,$5^{3'}$)], 9.70[br s, 1, NH]. Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.20; H, 5.70; N, 3.56.

Benzyl 3-(Ethoxycarbonylmethyl)-4-methyl-5-(1-hydroxybenzyl)pyrrole-2-carboxylate (16).

Sodium borohydride (150 mg, 3.9 mmol) was added to a solution of pyrrole (**20**) (150 mg, 0.4 mmol) in a mixture of 4 mL of dry methanol and 4 mL of dry methylene chloride. The mixture was stirred at 20ºC during 30 min, then poured over water (20 mL) and the solution adjusted to pH 6 with 1 N hydrochloric acid. The organic layer was separated and the aqueous solution extracted with methylene chloride (3 x 20 mL). The pooled organic layers were evaporated to dryness and the residue dissolved in a small volume of methylene chloride and chromatographed on a silica gel column (3 x 30 cm) using the same solvent. Fractions containing **16** were pooled and evaporated to dryness; the residue was crystallized from methylene chloride-hexane: 141 mg (93%); mp 87-89ºC; ^{1}H-NMR: δ 1.20[t, J=7.0 Hz, 3, $CH_3(3^5)$], 1.80[s, 3, $CH_3(4)$], 3.20[br s, 1, OH], 3.80[s, 2, $CH_2(3^1)$], 4.10[q, J=7.0 Hz, 2, $CH_2(3^4)$], 5.20[s, 2, $CH_2(2^3)$], 5.80[s, 1, CH(5^1)], 7.40[m, 10, CH(Ph)], 9.35[br s, 1, NH]. Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.68; H, 6.25; N, 3.50.

Dibenzyl 2,7-Bisethoxycarbonylmethyl-5-phenyl-3,8-dimethyldipyrrylmethane-1,9-dicarboxylate (11).

Pyrrole (**15**) (167 mg, 0.53 mmol) and 64 mg (0.4 mmol) of *p*-toluenesulfonic acid were dissolved in 20 mL of methylene chloride under nitrogen. A solution of pyrrole (**16**) (232 mg, 0.55 mmol) dissolved in 20 mL of the same solvent was then added dropwise. The solution was stirred for 1 h at 20ºC, then poured onto a saturated aqueous solution of sodium acetate (100 mL) and extracted with methylene chloride (3 x 50 mL). The organic layers were combined, 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 crude product was purified through a silica gel column (3 cm x 30 cm) using methylene chloride-methanol (99:1) as solvent, to obtain a light brownish oil, yield 79% (300 mg); ^{1}H-NMR: δ 1.15[t, J=7.1 Hz, 3 ,$CH_3(7^5)$], 1.20[t, J=7.2 Hz, 3, $CH_3(2^5)$], 1.80[s, 3, $CH_3(3)$], 2.25[s, 3, $CH_3(8)$], 3.20[d, J=1.8 Hz, 2, $CH_2(7^1)$], 3.80[d, J=1.3 Hz, 2, $CH_2(2^1)$], 4.10[m, 4, $CH_2(2^4,7^4)$], 5.20[m, 4, $CH_2(1^3,9^3)$], 5.70[s, 1, CH(5)], 7.35[m, 15, CH(Ph)], 8.85, 8.90[br s, br s, 1, 1, NH]. Anal. Calcd for $C_{41}H_{42}N_2O_8$: C, 71.29; H, 6.13; N, 4.06. Found: C, 71.44; H, 6.05; N, 3.96.

Dibenzyl 2,7-Bis(2-hydroxyethyl)-5-phenyl-3,8-dimethyldipyrrylmethane -1,9-dicarboxylate (10).

Diborane generated by the addition of boron trifluoride diethyl ether (6 mL) to sodium borohydride (2 g, 52.9 mmol) in diglyme (10 mL) was passed in a slow stream of nitrogen through a solution of dipyrrylmethane (**11**) (300 mg, 0.4 mmol) in tetrahydrofuran (50 mL). The solution was left overnight at rt 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 through a silica gel column (3.5 cm x 30 cm) and eluted with methylene chloride-methanol (99:1). A yellow oil was obtained, yield 87% (227 mg); ^{1}H-NMR: δ 1.80[s, 3, $CH_3(3)$], 2.25[s, 3, $CH_3(8)$], 2.90[m, 2, $CH_2(7^1)$], 2.40[m, 2, $CH_2(2^1)$], 3.70[m, 4, $CH_2(2^2,7^2)$], 5.25[s, 4, $CH_2(1^3,9^3)$], 5.60[s, 1, CH(5)], 7.10-7.40[m, 15, CH(Ph)], 8.75, 8.95[br s, br s, 1, 1, NH]. Anal. Calcd for $C_{37}H_{38}N_2O_6$: C, 73.25; H, 6.31; N, 4.62. Found: C, 73.38; H, 6.28; N, 4.54.

Dibenzyl 2,7-Bis(2-acetoxyethyl)-5-phenyl-3,8-dimethyldipyrrylmethane-1,9-dicarboxylate (9).

Dipyrrylmethane (**10**) (227 mg, 0.4mmol), anhydrous pyridine (10 mL, 124.1 mmol) and acetic anhydride (2 mL, 21.2 mmol) were mixed. The solution was stirred for 2 h, then poured onto 200 mL of water and extracted three time with methylene chloride (3 x 50 mL). The organic layers were combined, washed with water (40 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 (3.5 cm x 40 cm) using methylene chloride as solvent, when the dipyrrylmethane was obtained as a yellow oil, yield 96% (231

mg); ^{1}H-NMR: δ 1.80[s, 6, $CH_3(2^5,7^5)$], 1.95[s, 3, $CH_3(3)$], 2.15[s, 3, $CH_3(8)$], 2.40[t, J=7.2 Hz, 2, $CH_2(7^1)$], 3.05[t, J=7.1 Hz, 2, $CH_2(2^1)$], 3.80[t, J=7.1 Hz, 2, $CH_2(7^2)$], 4.10[t, J=7.1 Hz, 2, $CH_2(2^2)$], 5.20, 5.25[s, 4, $CH_2(1^3,9^3)$], 5,55[s, 1, CH(5)], 7.10-7.30[m, 15, CH(Ph)], 8.40[br s, 2, NH]. Anal. Calcd for $C_{41}H_{42}N_2O_8$: C, 71.29; H, 6.13; N, 4.06. Found: C, 71.48; H, 6.04; N, 3.96.

2,7,12,18-Tetramethyl-3,8-bis(2-hydroxyethyl)-5-phenyl-13,17-bis(2-methoxycarbonylethyl)-porphine (5).

A solution of dipyrrylmethane (**9**) (420 mg, 0.6 mmol) in ethanol (100 mL) was reduced with hydrogen at 40 psi over 300 mg of 10% Pd on charcoal during 3 h. The catalyst was filtered, the solvent evaporated to dryness at reduced pressure. The crude product was purified through a silica gel column (3 x 10 cm) using methylene chloride-methanol (90:10) as solvent, to obtain a pink oil, yield 88% (269 mg). Anal. Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92; N, 5.49. Found: C, 63.40; H, 6.00; N, 5.62.

Acid (**8**) (200 mg, 0.4 mmol) thus obtained was dissolved in a mixture of 150 mL of dry methylene chloride and 24 mL of methanol containing 172 mg (0.4 mmol) of diformyldipyrrylmethane (**13**) and 450 mg (2.6 mmol) of *p*-toluenesulfonic acid were added. The mixture was kept in the dark at 20ºC for 24 h, then 32 mL of methanol saturated with zinc acetate dihydrate was added. After a further period of 72 h at 20ºC in the dark the solution was evaporated to dryness at 40ºC, and the residue was dissolved in 90 mL of a 5% sulfuric acid in methanol solution. The mixture was kept during 16 h at 20ºC in the dark, diluted with 100 mL of chloroform, and washed with water (40 mL), 5% aqueous sodium bicarbonate solution (40 mL) and water (40 mL), dried (sodium sulfate) and evaporated to dryness at 40ºC. 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 (**5**) was crystallized from methylene chloride-hexane, 84 mg (30%); mp 262-264ºC; ^{1}H-NMR: δ -3.30, -3.18[br s, br s, 1, 1, NH], 2.41[s, 3, $CH_3(7)$], 2.92[t, J=7.5 Hz, 2, $CH_2(3^1)$], 3.26[t, J=7.6 Hz, 4, $CH_2(13^2,17^2)$], 3.65[m, 15, $CH_3(2,12,18,13^5,17^5)$], 4.22[t, J=7.5 Hz, 2, $CH_2(3^2)$], 4.30-4.40[m, 8, $CH_2(8^2,8^1,13^1,17^1)$], 7.67[t, J=7.4 Hz, 2, $CH(5^3,5^{3'})$], 7.85[t, J=7.4 Hz, 1, $CH(5^4)$], 8.00[d, J=7.4 Hz, 2, $CH(5^2,5^{2'})$], 9.97[s, 1, CH(15)], 10.11[s, 2, CH(10,20)]. Anal. Calcd for $C_{42}H_{46}N_4O_6$: C, 71.77; H, 6.60; N, 7.97. Found: C, 71.85; H, 6.52; N, 7.92.

2,7,12,18-Tetramethyl-3,8-bis(2-chloroethyl)-5-phenyl-13,17-bis(2-methoxycarbonylethyl)porphine (3).

To a solution of porphyrin (**5**) (72 mg, 0.1 mmol) in 7 mL of dry DMF was added 0.91 mL (11.8 mmol) of mesyl chloride, and the mixture was heated at 75º for 5 h under nitrogen. The cooled solution was then

diluted with 100 mL of water and extracted with methylene chloride (4 x 50 mL). Extracts were dried (sodium sulfate) and evaporated to dryness *in vacuo* at 40ºC. The residue was dissolved in methylene chloride and filtered through a TLC silica gel column as described above. Bischloroethylporphyrin (**3**) was crystallized from methylene chloride-hexane: 42 mg (56%); mp 265-267ºC; ^{1}H-NMR: δ -3.10,-3.05[br s, br s, NH], 2.44[s, 3, CH_3(7)], 3.16[t, J=7.9 Hz, 2, CH_2(3^1)], 3.26[m, 4, CH_2(13^2,17^2)], 3.60[m, 17, CH_2(3^2), CH_3(2,12,18,13^5,17^5)], 4.17[t, J=7.6 Hz, 2, CH_2(8^1)], 4.30[m, 4, CH_2(13^1,17^1)], 4.47[m, 2, CH_2(8^2)], 7.76[t, J=7.4 Hz, 2, CH(5^3,$5^{3'}$)], 7.97[t, J=7.4 Hz, 1, CH(5^4)], 8.04[m, 2, CH(5^2,$5^{2'}$)], 9.94[s, 1, CH(15)], 10.17[s, 2, CH(10,20)]. Anal. Calcd for $C_{42}H_{44}N_4O_4Cl_2$: C, 68.19; H, 6.00; N, 7.57. Found: C, 68.27; H, 6.05; N, 7.68.

2,7,12,18-Tetramethyl-3,8-divinyl-5-phenyl-13,17-bis(2-methoxycarbonylethyl)porphine (1).

To a solution of porphine (**3**) (40 mg, 0.05 mmol) in 50 mL of dry DMF was added 1.5 mL (10.0 mmol) of 1,5-diazobicyclo[5.4.0]-5-undecene (DBU), and the mixture was heated for 20 h at 100ºC in the dark. The cooled solution was then diluted with 100 mL of water and extracted with methylene chloride (4 x 50 mL). Extracts were dried (sodium sulfate) and evaporated to dryness *in vacuo* at 40ºC. The residue was dissolved in methylene chloride and filtered through a column as described above. Porphyrin (**1**) was crystallized from methylene chloride-hexane: 18.4 mg (51%); mp 223-225ºC; visible spectrum (dichloromethane): λ max. 406nm (ε131200), 505(12500), 539(6600), 575(5800). ^{1}H-NMR: δ -3.20, -3.06[br s, br s, 1, 1, NH], 2.55[s, 3, CH_3(7)], 3.29[t, J=7.4 Hz, 4, CH_2(13^2,17^2)], 3.62[s, 3, CH_3(2)], 3.66[s, 6, CH_3(12,18)], 3.68[s, 6, CH_3(13^5,17^5)], 4.37[t, J=7.4 Hz, 4, CH_2(13^1,17^1)], 5.31[dd, J=2.3 Hz and 10.8 Hz; 1, CH($3^{2'}$)], 5.41[dd, J=2.3 Hz and 17.5 Hz, 1, CH(3^2)], 6.15[dd, J=2.0 Hz and 11.4 Hz; 1, CH($8^{2'}$)], 6.21[dd, J=2.0 Hz and 17.7 Hz, 1, CH(8^2)], 6.39[dd, J=10.8 Hz and 17.5 Hz, 1, CH(3^1)], 7.69[t, J=7.4 Hz, 2, CH(5^3,$5^{3'}$)], 7.77[m, 1, CH(5^4)], 7.98[d, J=7.4 Hz, 2, CH(5^2,$5^{2'}$)], 8.09[dd, J=11.4 Hz and 17.7 Hz, 1, CH(8^1)], 9.94[s, 1, CH(15)], 10.19[s, 1, CH(20)], 10.28[s, 1, CH(10)]. Anal. Calcd for $C_{42}H_{42}N_4O_4$: C, 75.65; H, 6.35; N, 8.40. Found: C, 75.54; H, 6.26; N, 8.51.

2,7,12,18-Tetramethyl-3,8-bis(2-hydroxyethyl)-15-phenyl-13,17-bis(2-methoxycarbonylethyl)-porphine (6).

Dipyrrylmethane diacid (**12**) (280 mg, 0.64 mmol) was condensed with 320 mg (0.64 mmol) of dipyrrylmethane dialdehyde (**14**) following the procedure described for **5**. Final purification of the porphyrin dimethyl ester (**6**) was achieved by means of TLC silica gel column (3 cm x 30 cm) using methylene chloride-methanol (98:2) as a solvent. The porphyrin was crystallized from methylene chloride-hexane, 140 mg (30%); mp 259-261ºC; ^{1}H-NMR: δ -3.20, -3.08 [br s, br s, 1, 1, NH], 2.54[m, 4, CH_2(13^2,17^2)], 3.05[m, 4, CH_2 (13^1,17^1)], 3.50-3.70[m, 18, CH_3(2,7,12,18,13^5,17^5)], 4.35[t, J=7.5 Hz, 4,

$CH_2(3^1,8^1)$], 4.50[t, J=7.5 Hz, 4, $CH_2(3^2,8^2)$], 7.66[t, J=7.5 Hz, 2, $CH(15^3,15^{3'})$], 7.81[t, J=7.5 Hz, 1, $CH(15^4)$], 8.14[d, J=7.5 Hz, 2, $CH(15^2,15^{2'})$], 9.95[s, 1, CH(20)], 10.19[s, 2, CH(5,10)]. Anal. Calcd for $C_{42}H_{46}N_4O_6$: C, 71.77; H, 6.60; N, 7.97. Found: C, 71.69; H, 6.65; N, 7.90.

2,7,12,18-Tetramethyl-3,8-bis(2-chloroethyl)-15-phenyl-13,17-bis(2-methoxycarbonylethyl)porphine (4).

Porphyrin (**6**) (140 mg, 0.2 mmol) was dissolved in 15 mL of dry DMF, 2 mL (25.8 mmol) of mesyl chloride was added and the mixture heated at 70ºC for 5 h. Porphyrin (**4**) was isolated after purification by column chromatography following the procedure described for **3**, 90 mg (61%); mp 257-259ºC (methylene chloride-hexane); ^{1}H-NMR: δ -3.23, -3.08[br s, br s, 1, 1, NH], 2.54[m, 4, $CH_2(13^2,17^2)$], 3.08[m, 4, $CH_2(13^1,17^1)$], 3.50-3.60[m, 18, $CH_3(2,7,12,18,13^5,17^5)$], 4.31[m, 4, $CH_2(3^1,8^1)$], 4.48[m, 4, $CH_2(3^2,8^2)$], 7.68[t, J=7.6 Hz, 2, $CH(15^3,15^{3'})$], 7.82[t, J=7.6 Hz, 1, $CH(15^4)$], 8.15[d, J=7.6 Hz, 2, $CH(15^2,15^{2'})$], 9.85[s, 1, CH(20)], 10.10[s, 2, CH(5,10)]. Anal. Calcd for $C_{42}H_{44}N_4O_4Cl_2$: C, 68.19; H, 6.00; N, 7.57. Found: C, 68.02; H, 6.18; N, 7.43.

2,7,12,18-Tetramethyl-3,8-divinyl-15-phenyl-13,17-bis(2-methoxycarbonylethyl)porphine (2).

To a solution of porphyrin (**4**) (90 mg, 0.1 mmol) in 65 mL of dry DMF was added 2.5 mL (16.7 mmol) of DBU, and the mixture stirred for 2 d at rt in the dark. Porphyrin (**2**) was isolated and purified following the procedure described for **1,** 55 mg (68%); mp 277-279ºC (methylene chloride-hexane); visible spectrum (methylene chloride); λ max 409 nm(ε125300), 508(14200), 543(7700), 579(6700); ^{1}H-NMR: δ -3.12, -2.96[br s, br s, 1, 1, NH], 2.53[t, J=8.6 Hz, 4, $CH_2(13^2,17^2)$], 3.07[m, 4, $CH_2(13^1,17^1)$], 3.56[s, 6, $CH_3(12,18)$], 3.65[s, 6, $CH_3(13^5,17^5)$], 3.68[s, 3, $CH_3(7)$], 3.71[s, 3, $CH_3(2)$], 6.16 and 6.20[dd, dd, J=1.6 Hz and 11.6 Hz, 1, 1, $CH(3^{2'},8^{2'})$], 6.34 and 6.40[dd, dd, J=1.6 Hz and 17.6 Hz, 1, 1, $CH(3^2,8^2)$], 7.67[t, J=7.5 Hz, 2, $CH(15^3,15^{3'})$], 7.79[m, 1, $CH(15^4)$], 8.14[d, J=7.5 Hz, 2, $CH(15^2,15^{2'})$], 8.22 and 8.28 [dd, dd, J=11.6 Hz and 17.6 Hz, 1, 1 ,$CH(3^1,8^1)$], 10.06[s, 1, CH(20)], 10.19[s, 2, CH(5,10)]. Anal. Calcd for $C_{42}H_{42}N_4O_4$: C, 75.65; H, 6.35; N, 8.40. Found: C, 75.73; H, 6.40; N, 8.16.

Benzyl 3-(2-Ethoxycarbonylethyl)-4-methyl-5-benzoylpyrrole-2-carboxylate (30).

To a solution of 700 mg (2.30 mmol) of benzyl 3-(2-ethoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**31**) in 10 mL of methylene chloride were added slowly at 0ºC, 0.12 mL (3.40 mmol) of benzoyl chloride and 4.6 mL (4 mmol) of stannous tetrachloride. The mixture was kept at 0ºC during 45 min, and 3 h at rt, then poured onto 100 mL of water and extracted with methylene chloride (3 x 50 mL). The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and water (20 mL). The organic solution was dried with anhydrous sodium sulfate and evaporated at reduced

pressure. The crude product was purified through a silica gel column (3 cm x 30 cm) using methylene chloride-hexane (98:2) as solvent to obtain a brownish oil, yield 20 % (189 mg); ^{1}H-NMR: δ 1.00[t, J=7.2 Hz, 3, $CH_3(3^6)$], 1.80[s, 3, $CH_3(4)$], 2.35[m, 2, $CH_2(3^1)$], 2.80[m, 2, $CH_2(3^2)$], 3.90[q, J=7.2 Hz, 2, $CH_2(3^5)$], 5.15[s, 2, $CH_2(2^3)$], 7.30[m, 10, CH(PH)], 8.80[br s, 1, NH]; Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.42; H, 6.10; N, 3.46.

Benzyl 3-(2-Ethoxycarbonylethyl)-4-methyl-5-(1-hydroxybenzyl)pyrrole-2-carboxylate (22).
Sodium borohydride (130 mg, 3.4 mmol) was added to a solution of 130 mg (0.3 mmol) of pyrrole (**30**) in a mixture of 3 mL of dry methanol and 3 mL of dry methylene chloride. The mixture was stirred at 20ºC during 30 min, then poured over water (20 mL), and the mixture adjusted to pH 6 with 1 N hydrochloric acid. The organic layer was separated and the aqueous solution was extracted with methylene chloride (3 x 20 mL). The pooled organic layers were evaporated to dryness and the residue was dissolved in a small volume of methylene chloride-methanol (99:1) and chromatographed through a silica gel column (3 cm x 30 cm) using the same solvent, to obtain a brownish oil, yield 79 % (103 mg); ^{1}H-NMR: δ 1.00[t, J=7.2 Hz, 3, $CH_3(3^6)$], 1.70[s, 3, $CH_3(4)$], 2.30[m, 2, $CH_2(3^1)$], 2.80[m, 2, $CH_2(3^2)$], 3.90[q, J=7.2 Hz, 2, $CH_2(3^5)$], 5.10[s, 2, $CH_2(2^3)$], 5.70[s, 1, $CH(5^1)$], 7.30[m, 10, CH(Ph)], 9.20[br s, 1, NH]; Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.32; H, 6.38; N, 3.43.

Benzyl *tert*-Butyl 2-(2-Ethoxycarbonylethyl)-3,7-dimethyl-8-(2-acetoxyethyl)-5-phenyldipyrryl-methane-1,9-dicarboxylate (23).
Pyrrole (**21**) (42.3 mg, 0.16 mmol) and 32 mg (0.19 mmol) of *p*-toluenesulfonic acid were dissolved in 6 mL of methylene chloride under nitrogen. A solution of pyrrole (**22**) (64 mg, 0.15 mmol) dissolved in 6 mL of the same solvent was then added dropwise. The solution was stirred for 1 h at 20ºC, then poured onto a aqueous sodium acetate (40 mL) and extracted with methylene chloride (3 x 20 mL). The organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (15 mL) and then with water (15 mL). The organic solution was dried with anhydrous sodium sulfate, filtered and evaporated at reduced pressure. The crude product was purified through a silica gel column (2 x 30 cm) using methylene chloride-methanol (99.5:0.5) as solvent, to obtain a colorless oil, yield 99 % (110 mg); ^{1}H-NMR: δ 1.05[t, J=7.2 Hz, 3, $CH_3(2^6)$], 1.35[s, 9, $CH_3(9^4)$], 1.65 and 1.85[s, s, 6, 3, $CH_3(3,7,8^5)$], 2.30[m, 2, $CH_2(2^1)$], 2.85[m, 4, $CH_2(2^2,8^1)$], 3.95[m, 4, $CH_2(8^2,2^5)$], 5.10[s, 2, $CH_2(1^3)$], 5.30[s, 1, CH(5)], 7.05 and 7.35[m, m, 5, 5, CH(Ph)], 8.23 and 8.45[s, s, 1, 1, NH]; Anal. Calcd for $C_{39}H_{46}N_2O_8$: C, 69.83; H, 6.91; N, 4.18. Found: C, 69.91; H, 6.86; N, 4.26.

2-(2-Ethoxycarbonylethyl)-3,7-dimethyl-8-(2-acetoxyethyl)-5-phenyl-9-*tert*-butoxycarbonyldipy-rrylmethane-1-carboxylic Acid (24).

A solution of dipyrrylmethane (**23**) (110 mg, 0.16 mmol) in ethanol (150 mL) was reduced with hydrogen at 50 psi over 100 mg of 10% Pd on charcoal during 3 h. The catalyst was filtered, the solvent evaporated to dryness at reduced pressure and the acid (**24**) purified through a silica gel column (2 x 30 cm) using methylene chloride-methanol (97:3) as solvent to obtain a pink oil, 66% (59.5 mg); ^{1}H-NMR: δ 1.05[t, J=7.2 Hz, 3, $CH_3(2^6)$], 1.40[s, 9, $CH_3(9^4)$], 1.85, 1.90[s, s, 6, 3, $CH_3(3,7,8^5)$], 2.35[m, 2, $CH_2(2^1)$], 2.85[m, 4, $CH_2(2^2,8^1)$], 3.95[m, 4, $CH_2(8^2,2^5)$], 5.30[s, 1, CH(5)], 7.05[m, 5, CH(Ph)], 9.95 and 10.95[s, s, 1, 1, NH]; Anal. Calcd for $C_{32}H_{40}N_2O_8$: C, 66.19; H, 6.94; N, 4.82. Found: C, 66.30; H, 6.87; N, 4.90.

2-(2-Acetoxyethyl)-8-(2-ethoxycarbonylethyl]-3,7,13,14-tetramethyl-12-(2-methoxycarbonylethyl)-1-*tert*-butoxycarbonyl-5-phenyl-5,17-dihydrotripyrrin Hydrobromide (26).

Dipyrrylmethane (**24**) (44.2 mg, 0.07 mmol) was dissolved in 4 mL of methylene chloride under nitrogen. A solution of 16.21 mg (0.07 mmol) of pyrrole (**25**) and 90 mg (0.5 mmol) of *p*- toluenesulfonic acid in 1 mL of methanol was then added dropwise. The solution was stirred for 1 h at rt under nitrogen and then poured onto water (40 mL) and extracted with methylene chloride (3 x 20 mL). The organic layers were combined, washed with aqueous solution of sodium bicarbonate (15 mL) and then with water (15 mL). The organic solution was dried with anhydrous sodium sulfate and evaporated at reduced pressure. The residue was dissolved in dry methylene chloride and hydrogen bromide passed through the solution during 10 sec, then the latter cooled in ice water. The solution was evaporated to dryness to obtain an orange oil, yield 94% (58.3 mg); visible spectrum (dichloromethane): λ max. 489 nm; ^{1}H-NMR: δ 1.00[t, J=7.2 Hz, 3, $CH_3(8^6)$], 1.30[s, 9, $CH_3(1^4)$], 1.65, 1.75, 1.80, 1.90 and 1.95[s, s, s, s, s, 3, 3, 3, 3, 3, $CH_3(3,7,13,14,2^5)$], 2.30[m, 4, $CH_2(8^1,12^1)$], 2.75[m, 6, $CH_2(8^2,12^2,2^1)$], 3.50[s, 3, $CH_3(12^5)$], 3.95[m, 4, $CH_2(2^2,8^5)$], 5.30[s, 1, CH(5)], 6.75[s, 1, CH(10)], 7.30[m, 5, CH(Ph)]; Anal. Calcd for $C_{42}H_{54}N_3O_8Br$: C, 62.37; H, 6.73; N, 5.20. Found: C, 62.51; H, 6.60; N, 5.34.

3,5-Dimethyl-4-(2-acetoxyethyl)-2-formylpyrrole (27).

A solution of pyrrole (**28**) (400 mg, 1.4 mmol) in trifluoroacetic acid (10 mL) was maintained at 25ºC for 30 min, cooled to 0ºC and trimethyl orthoformate (3.5 mL, 31.9 mmol) was added. The mixture was kept at 0ºC for 8 min, water (50 mL) was added and mixture was stirred for 30 min. 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 (98:2). The pyrrole (**27**) thus obtained was recrystallized from methanol, yield (52%) 154.7 mg; mp 152-154ºC; ^{1}H-NMR: δ 1.85[s, 3, $CH_3(3)$], 2.10[s, 6, $CH_3(5,4^5)$], 2.60[t, J=7.2 Hz, 2, $CH_2(4^1)$], 3.95[t, J=7.2 Hz, 2, $CH_2(4^2)$], 9.50[br s, 1, CH(2)].

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.29; H, 7.15; N, 6.51.

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