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New Amino Acid Porphyrin Derivatives. Part I: Synthesis

Martine Perrée-Fauvet,*[1] Catherine Verchère-Béaur, Eric Tarnaud, Gilles Anneheim-Herbelin, Nathalie Bône and Alain Gaudemer

Laboratoire de Chimie Bioorganique et Bioinorganique associé au CNRS, Institut de Chimie Moléculaire d'Orsay, Université de Paris-Sud, 91405 Orsay, France.

Abstract. In order to obtain molecules that can bind to specific DNA-sequences, several new tri-(N-methyl-4-pyridiniumyl)porphyrins bearing an amino acid or peptide side-chain on the fourth meso aromatic substituent have been synthesized by efficient coupling of a monofunctionalized porphyrin with amino acids or peptides. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Many antitumor agents are designed to target and cleave DNA, in order to inhibit the association of proteins that regulate gene expression. Most of these proteins (restriction enzymes, transcription factors, repressor or activator proteins...) bind to specific DNA-sequences. Structural data on protein-DNA interactions reveal that interactions involved in the DNA-sequence recognition occur mainly via hydrogen bonding between the purine and pyrimidine bases and amino acid side-chains.[1] There is consequently an increasing interest in the design of molecules that can bind specifically to the target sequences of regulatory proteins.

In order to enhance the sequence-selective recognition of DNA, several oligopeptide derivatives of intercalating drugs have been designed and synthesized. The vast majority of molecules in this category involve the linking of netropsin or distamycin to chromophores such as acridine,[2] ellipticine,[3] phenoxazone,[4] oxazolopyridocarbazole,[5] bithiazole,[6] isoalloxazine[7] or cationic porphyrins.[8] In such conjugates, the pseudopeptide entity binds to the minor groove of DNA. Recognition of extended DNA sequences in the major groove remains virtually limited to the category of synthetic antisense oligonucleotides,[9] peptide nucleic acids,[10] oligopeptide dimers[11] and, more recently, peptide complexes of iron terpyridyl[12] and rhodium phenanthroline.[13] The sequences of these oligopeptides, containing as many as 13 residues, are generally[11,12] closely related to those of the active site of the transcriptional activator proteins that they simulate.

[1] E-mail: mperreef@icmo.u-psud.fr Fax: (+33) 01 69 41 72 81

Our approach for DNA-sequence recognition by oligopeptide-intercalator derivatives is a nonconventional one. It involves the use of a cationic porphyrin as an anchoring unit and the extension of its structure by a short peptidyl chain, toward well-defined sites flanking the intercalation site. *Meso*-tetrakis-(N-methyl-4-pyridiniumyl)porphyrin H_2TMPyP-4, is the parent compound of a series of synthetic cationic porphyrins, which have been demonstrated to bind strongly to DNA either by intercalation at C-G sites or via an external mode in a groove,[14] and to cause photochemical[15] or oxidative[16] DNA cleavage. Recently, this porphyrin has been shown to accumulate preferentially in tumors,[17] like the hematoporphyrin derivative HPD.[18] These properties constitute an incentive to reinforcing its DNA-binding affinity and modulate its sequence-selectivities by extending its structure with the help of appropriately-selected short oligopeptides. From this perspective and as a first approach, we have synthesized a large number of mono-, di- and tri-amino acid porphyrin derivatives. The coupled amino acids have been selected according to the target sequence, taking into account the present knowledge on the DNA/protein interactions. For example, a leucine or isoleucine can make van der Waals contacts with a thymine methyl group; a lysine or arginine is known to chelate by H-bonds O_6 and N_7 of guanines in the major groove; and a tyrosine, though less specific, can make H-bonds either with O_4 of thymine or N_7 of purines in the major groove[1]. (Basic amino acids are also involved in ionic interactions with the DNA backbone, but in a non-specific manner). This approach can be related to the work of Gresh *et al.* who have undertaken the design and the synthesis of oligopeptide derivatives of two major groove antitumor intercalators (mitoxantrone and ditercalinium), in order to target well-defined hexameric oligonucleotides sequences.[19, 20]

Several examples of coupling of amino acids to porphyrins have been reported in the literature. The majority of the porphyrin derivatives have been designed as models for the haem protein systems: mono-, di- and tri-peptidyl derivatives of aetioporphyrin,[21] atropisomeric porphyrins coupled to four amino acid derivatives,[22] peptide-sandwiched mesoheme,[23] or for studies in electron transfer reaction: protoporphyrin derivatives linked to a naphthalene ring by a series of sequential peptides,[24] zinc porphyrin derivatives linked to a quinone by a polyglycine chain.[25] Monofunctional tetraphenylporphyrins coupled with the side-chain of extended lysyl and glutamyl peptide derivatives have been also synthesized to be used in magnetic resonance imaging.[26]

We report in the present paper the chemical synthesis and physico-chemical properties of a new series of amino acid porphyrin derivatives. The porphyrin precursors are tripyridylporphyrins bearing at the fourth meso position a phenyl group, substituted by an NH_2 or COOH side-chain to allow the linkage of amino acids. Their syntheses are reported first, then their coupling with individual amino acids or peptides using classical peptide synthesis chemistry is described.

In an attempt to get efficient DNA cleaving molecules, we had also designed a hybrid molecule formed by a tricationic porphyrin linked to a Cu^{II}(GlyGlyHis) complex, a copper complex which has been demonstrated to cleave DNA at specific sites using an oxidative pathway.[27] We report here the synthesis of its amino acid porphyrin precursors.

The synthesis of conjugates involving a porphyrin-netropsin and a porphyrin-bisarginyl connection, respectively designed to target a mixed GC/AT sequence and a specific GC sequence has been described elsewhere.[8, 28]

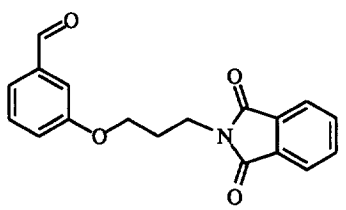
RESULTS AND DISCUSSION

SYNTHESIS OF PORPHYRINS

1) Porphyrin Precursors

We have developed an easy and efficient route for the synthesis of the porphyrin precursors (**1**, **3** and **2**, **4**, Fig.1 and 2).

It consists of reacting, by the standard Adler procedure,[29] pyrrole with 4-pyridinecarboxaldehyde and a prefunctionalized benzaldehyde **I** or **II** in a 4/3/1 ratio. The benzaldehydes **I** and **II** were obtained in yields of 72 and 80% respectively, by alkylation of 3-hydroxybenzaldehyde with N-(3-bromopropyl)phthalimide or ethyl 4-bromobutyrate in the presence of K_2CO_3 in refluxing DMF for 2 hours. Condensation of **I** (or **II**) with pyrrole and 4-pyridinecarboxaldehyde was carried out in refluxing propionic acid for 2 hours. Porphyrins **3** and **4** were obtained in 7-8% yields after chromatography of the crude products on a silica gel column. Treatment of **3** with hydrazine in a refluxing ethanol / dichloromethane mixture for 16 hours and saponification of **4** with NaOH in DMF at room temperature for 30 minutes afforded the desired porphyrins **1** and **2** in an overall yield (relative to 3-hydroxybenzaldehyde) of 6%.



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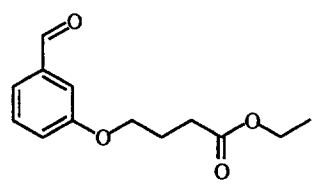
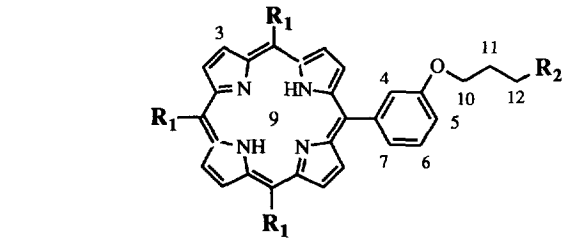


II

2) Amino Acid Porphyrin Derivatives

Two series of amino acid porphyrin derivatives have been synthesized, in which the coupled amino acid has either a terminal NH_2 or a terminal COOH (or methyl ester group).

The first series results from the coupling of **1** with N-protected L-tyrosine, L-lysine, glycine or L-histidine to give mono-amino acid porphyrin derivatives with a protected NH_2 group (Fig.1, **5a**, **6a**, **8a**). Synthesis of a water soluble di-amino acid porphyrin derivative with a terminal NH_2, has also been achieved (Fig.1, **7b**).



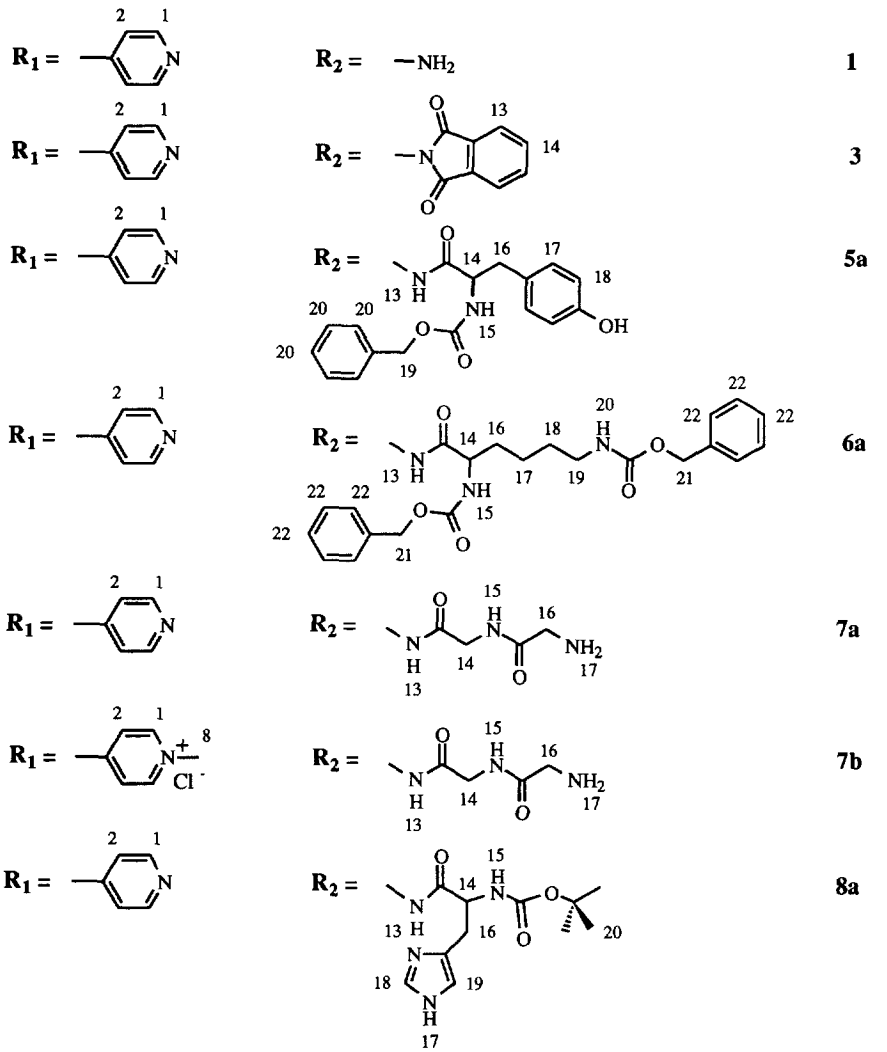
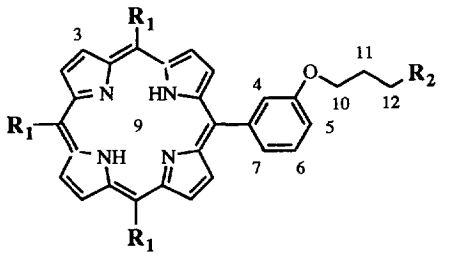
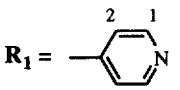
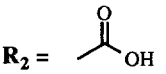


Figure 1: Structures of Porphyrins 1 and 3, and Porphyrin Derivatives







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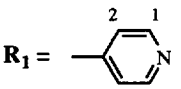

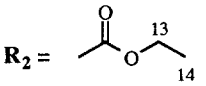

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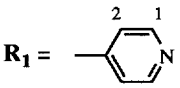
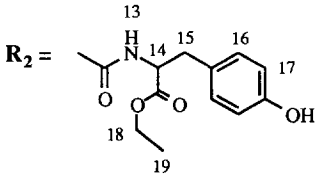
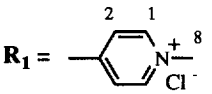
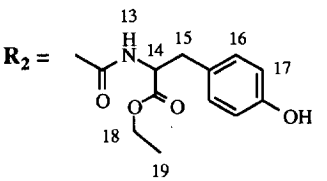




9a





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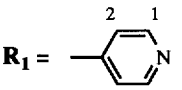
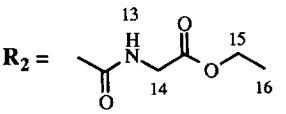
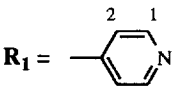
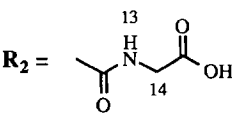




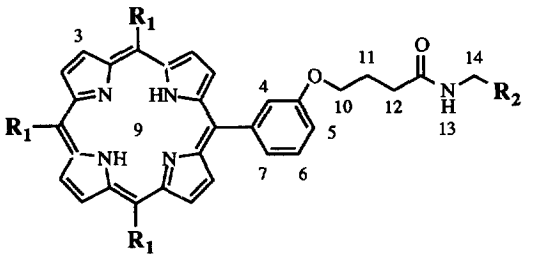
10a





10b

Figure 2: Structures of Porphyrins 2 and 4, and Mono-Amino Acid Porphyrin Derivatives



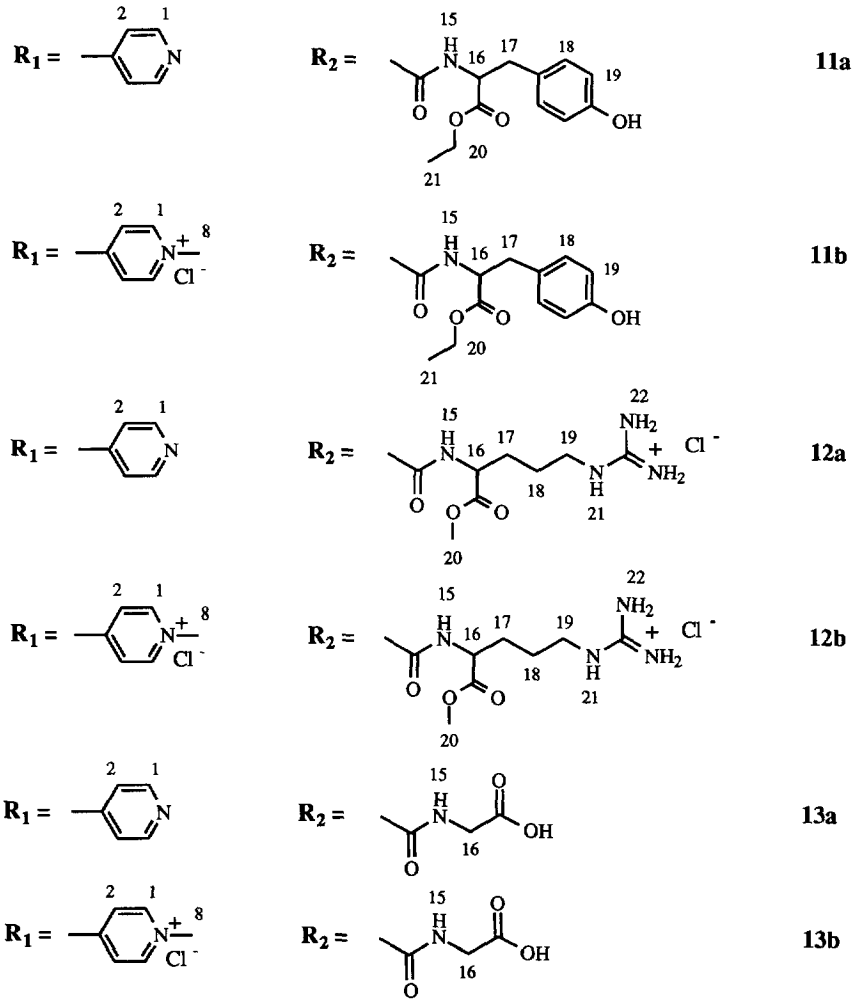
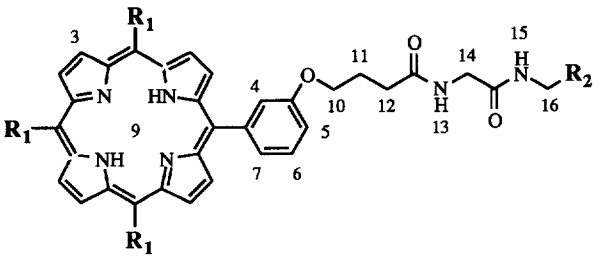


Figure 3: Structures of the Di-Amino Acid Porphyrin Derivatives (C-terminal)



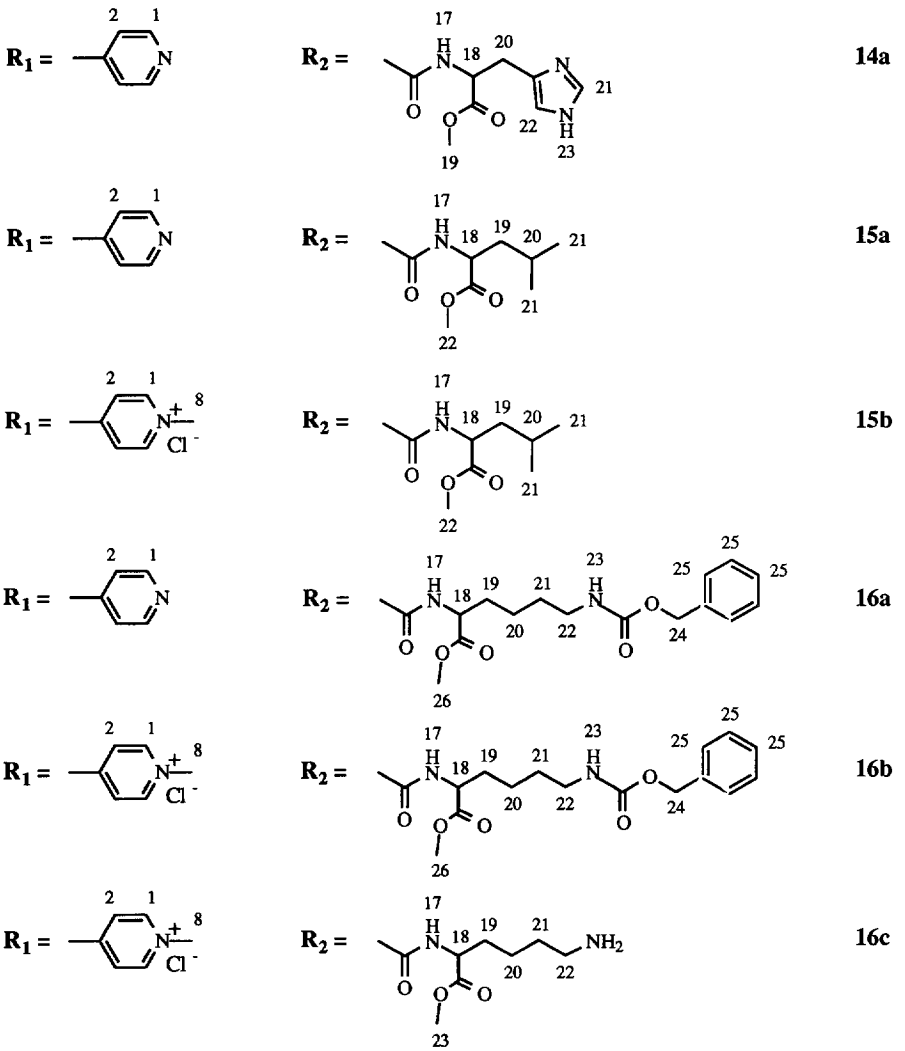


Figure 4: Structures of the Tri-Amino Acid Porphyrin Derivatives (C-terminal)

The second series has been more intensively studied in the laboratory and encompass:

- mono-amino acid porphyrin derivatives resulting from the coupling of **2** with L-tyrosine or glycine (Fig.2, **9**, **10**),
- di-amino acid porphyrin derivatives resulting from the coupling of **10** with L-tyrosine, L-arginine or glycine (Fig.3, **11**, **12**, **13**),
- tri-amino acid porphyrin derivatives resulting from the coupling of **13** with L-histidine, L-leucine or L-lysine (Fig.4, **14**, **15**, **16**)

1) Coupling Methods

Two different coupling methods have been used in the synthesis of the porphyrins of the first series:

- the first one which involves the activation of N-protected amino acids by formation of a mixed anhydride with an alkyl chloroformate in the presence of a tertiary amine[30] has been used in the synthesis of porphyrins **5a** and **6a** which were obtained in 90% yields.

- the synthesis of porphyrins **7a** and **8a** has been performed using a coupling method which is more widely used in peptide synthesis and involves the formation of an activated ester by benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent) as coupling agent. It was also used in the synthesis of the porphyrins **9** - **16** of the second series, involving in that case, the formation of a reactive porphyrin ester intermediate. Coupling yields were over 90%.

This second coupling method was preferred over others attempted,[21-26] because it proceeds at very mild conditions: all the reagents are added at room temperature and the reaction mixture is allowed to stand at ambient temperature for several hours until reaction is complete. Other methods have to be performed either at low temperature (mixed anhydride method and ref.[24]), or in refluxing solvent (use of NN'-carbonyldiimidazole as coupling reagent, in refluxing THF).[21]

2) Deprotection of the Amino Acid Moiety

- Removal of the NH_2 protecting group

Porphyrin **7a** was obtained by hydrogenolysis of the N-tert-butoxycarbonyl (Boc) protecting group of the GlyGly moiety, using H_2, Pd/C.

Several attempts to remove the N-tert-butoxycarbonyl protecting group of the histidine-porphyrin **8a** (hydrogenolysis (H_2, Pd/C), trifluoroacetic acid) resulted in a degradation of the imidazole ring. In the NMR spectrum of the crude product, the signals of the imidazole H_{18} and H_{19} protons were not detected. This suggests a photooxydation of the imidazole by singlet oxygen produced by photosensitization of the nearby porphyrin. Similar results were obtained by Smith and Milgrom[21] who were unsuccessful in their attempts to synthesize unprotected histidyl porphyrins. In contrast, iron porphyrins which are not photosensitizers are easily linked to a histidine moiety.[23]

The deprotected ε-NH_2 porphyrin **16c** was obtained by hydrogenolysis of the N-benzyloxycarbonyl group of porphyrin **16b**. The highest yields (>95%) were obtained using catalytic hydrogen transfer with 1,4-cyclohexadiene, 10% palladium on carbon, in dry methanol at room temperature.[31]

- Removal of the ester group

The amino acid porphyrin derivatives **10b** and **13a** have been obtained by saponification of the corresponding ester with a large excess of NaOH in DMF for 15 min at room temperature. After addition of water and neutralization by HCl, the porphyrin acid was obtained pure in 90% yield.

Attempts to saponify **14a** resulted in the loss of the imidazole group of the amino acid chain, probably due to a photooxidation reaction promoted by the porphyrin.

3) Methylation of the Pyridine Nitrogens

The water-soluble porphyrins **7b, 9b, 11b, 12b, 13b, 15b** and **16b** were obtained in 90% yield by treatment of the corresponding porphyrins **7a, 9a**, ... with a large excess of CH_3I in DMF (50°C, 3h), followed by ion exchange with a Cl^- Dowex resin, precipitation in a water-acetone mixture and lyophilization.

CHARACTERIZATION OF THE AMINO ACID PORPHYRIN DERIVATIVES

All the synthesized porphyrins were characterized by their ^1H NMR spectrum. Their NMR data (chemical shifts and coupling constants) are given on tables 1-4. Their UV-visible data are collected on table 5. Mass spectrum and elemental analyses are given for several of the porphyrins as representative species (see experimental section).

CONCLUSION

Synthesis of several new water-soluble porphyrins with amino acid or peptide side-chains has been achieved. The synthetic methods which involve conventional reactions both in porphyrin and peptide chemistry, give the desired products in reasonable yields and in a high degree of purity. The major exception concerns the synthesis of histidine-substituted porphyrins: though the protected precursors could be obtained, several attempts to remove the protecting groups either by saponification or hydrogenolysis failed to give a pure compound. A possible explanation lies in the close proximity of the porphyrin chromophore, acting as a good sensitizer for singlet oxygen production, and the imidazole ring, which is known for its $^1O_2$ quenching properties. A similar instability of a free base cationic porphyrin has been observed with a netropsin-porphyrin species and was tentatively explained in a similar way.

Table 1: ^{1}H NMR chemical shifts (ppm) and coupling constants (herz, *ital.*) of the amine porphyrin precursors and of their mono- and di-amino acid porphyrin derivatives; (a): undetected signal.

Compounds		**1**	**3**	**5a**	**6a**	**7a**	**7b**	**8a**
Solvent		$CDCl_3$	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6	DMSO-d_6	$CDCl_3$
Porphyrinic Protons	1	9.05 *5.0*	9.05 *5.5*	8.95	9.00	9.00 *7.5*	9.60	9.00 *7.0*
	2	8.15 *5.0*	8.20 *5.5*	8.10	8.15	8.20 *7.5*	9.00	8.20 *7.0*
	3	8.80	8.85-8.95	8.75-8.85	8.85	8.85-8.95	9.00-9.20	8.85
	4	7.85	7.80	7.80	7.85	7.80	7.70	7.85
	5	7.85	7.80 *7.2*	7.80	7.75 *7.8*	7.75 *7.0*	7.70	7.80 *6.8*
	6	7.65 *8.0*	7.65 *8.0*	7.65	7.60 *7.8*	7.65 *7.0*	7.70	7.70 *6.8*
	7	7.35 *8.0*	7.35 *8.0*	7.70	7.35 *7.8*	7.40 *7.0*	7.35	7.40 *6.8*
	8	-	-	-	-	-	4.75	-
	9	- 2.95	- 2.95	- 2.95	- 3.10	- 3.00	- 3.00	- 3.10
	10	4.15 *7.5*	4.25 *7.5*	4.05	4.20 *7.1*	4.20 *8.0*	4.20	4.20 *7.8*
	11	1.90 *7.5*	2.25 *7.5*	1.95	2.05 *7.1*	2.00 *8.0*	1.25?	2.10 *7.8*
	12	3.00 *7.5*	4.05 *7.5*	2.95	2.95 *7.1*	2.30 *8.0*	3.70	3.55 *7.8*
Side-Chain Protons	13		7.75	6.15	6.60	6.70	8.30	4.50 *5.3*
	14		7.70	4.25	4.10	3.80 *5.8*	3.75	4.35
	15			5.30	5.55	6.60	8.35	6.20 *5.3*
	16			(a)	1.60	3.70 *5.8*	2.95	3.05 *3.5, 11.2*
	17			6.50	1.30	(a)	2.20	> 14
	18			6.90	1.25			8.05
	19			4.90	3.00			7.15
	20			7.10-7.35	4.60			1.40-1.50
	21				4.90			
	22				7.10-7.35			

Table 2 : ^{1}H NMR chemical shifts (ppm) and coupling constants (herz, *ital.*) of the acid and ester porphyrin precursors and of their mono-amino acid porphyrin derivatives.

Compounds		**2**	**4**	**9a**	**9b**	**10a**	**10b**
Solvent		$CDCl_3$	$CDCl_3$	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6
Porphyrinic Protons	1	9.00 *5.2*	9.05 *5.5*	8.95	9.50 *4.8*	9.00	9.00
	2	8.11 *5.2*	8.10 *5.5*	8.05	9.00 *4.8*	8.15	8.25
	3	8.70-8.80	8.90-9.00	8.75-8.80	9.00-9.15	8.35-8.95	8.85-8.95
	4	7.79	7.80	7.75	7.75	7.75	7.75
	5	7.75 *7.2*	7.80 *7.2*	7.75	7.75	7.80 *8.0*	7.80 *7.0*
	6	7.65 *7.2*	7.65 *7.2*	7.60 *7.2*	7.75	7.65 *8.0*	7.70 *7.0*
	7	7.40 *7.2*	7.35 *7.2*	7.30 *7.2*	7.45	7.35 *8.0*	7.45 *7.0*
	8	-	-	-	4.70	-	-
	9	- 2.90	- 3.10	- 3.00	- 3.05	- 2.90	- 3.00
	10	4.35	4.20 *7.5*	4.10	4.10 *7.0*	4.20 *7.0*	4.15 *8.2*
	11	2.30	2.20 *7.5*	2.15	2.00 *7.0*	2.25 *7.0*	2.05 *8.2*
	12	2.75	2.75 *7.5*	2.45 *7.1*	2.30 *7.0*	2.55 *7.0*	2.35 *8.2*
Side-Chain Protons	13		4.10 *7.5*	6.05 *7.0*	8.35	6.20	7.10
	14		1.20 *7.5*	4.80	4.30	4.00	3.30
	15			3.00 *8.0*	2.70, 2.80	4.15 *7.0*	
	16			6.60 *8.0*	6.60 *8.4*	1.20 *7.0*	
	17			6.85 *8.0*	6.90 *8.4*		
	18			4.10	3.90 *7.2*		
	19			1.15 *7.2*	1.05 *7.2*		

Table 3 : ^{1}H NMR chemical shifts (ppm) and coupling constants (herz, *ital.*) of the di-amino acid porphyrin derivatives (C-terminal).

Compounds		**11a**	**11b**	**12a**	**12b**	**13a**	**13b**
Solvent		DMSO-d6	DMSO-d6	DMSO-d6	DMSO-d6	DMSO-d6	DMSO-d6
Porphyrinic Protons	1	9.05	9.50 *7.0*	9.05	9.50 *7.0*	9.00 *7.0*	9.60 *5.0*
	2	8.10	8.95 *7.0*	8.30	9.00 *7.0*	8.25 *7.0*	9.00
	3	8.80-8.95	9.00-9.15	8.85-8.95	9.00-9.15	8.85-8.95	9.00-9.15
	4	7.75	7.80	7.80	7.80	7.80	7.90
	5	7.80 *7.3*	7.80	7.80	7.80	7.70 *7.0*	7.90
	6	7.60 *7.3*	7.75 *7.0*	7.70 *7.3*	7.75 *7.0*	7.60 *7.0*	7.78 *7.0*
	7	7.30 *7.3*	7.45 *7.0*	7.55 *7.3*	7.45 *7.0*	7.30 *7.0*	7.45 *7.0*
	8	-	4.75	-	4.70	-	4.75
	9	- 3.05	- 3.05	- 3.00	- 3.05	- 2.95	- 3.05
	10	4.10 *6.0*	4.20 *6.7*	4.20 *6.7*	4.20 *7.0*	4.20 *7.8*	4.20 *7.0*
	11	2.20 *6.0*	2.00 *6.7*	2.00 *6.7*	2.00 *7.0*	2.20 *7.8*	2.05 *7.0*
	12	2.55 *6.0*	2.35 *6.7*	2.35 *6.7*	2.35 *7.0*	2.50 *7.8*	2.40 *7.0*
Amino Acid Protons	13	6.40 *6.0*	8.15 *6.0*	8.15 *6.0*	8.20 *6.0*	6.95 *5.8*	8.40 *7.0*
	14	3.90 *6.0*	3.75 *6.0*	3.65 *6.0*	3.75 *6.0*	3.95 *5.7*	3.75 *5.0*
	15	6.35	8.20 *7.0*	8.30 *7.0*	8.40 *7.0*	6.65 *5.8*	8.30 *7.0*
	16	4.75	4.25	4.25	4.15	3.85 *5.7*	3.70 *5.0*
	17	3.05	2.70	1.70	1.55-1.65		
	18	6.70	6.60 *7.0*	1.60	1.45		
	19	6.90	6.85 *7.0*	3.05	3.05 *6.0*		
	20	4.20 *7.0*	3.95 *6.7*	3.55	3.55		
	21	1.20 *7.0*	1.00 *6.7*	7.30	7.85 *6.0*		
	22			6.70-7.20	6.85-7.55		

Table 4 : ^1H NMR chemical shifts (ppm) and coupling constants (herz, *ital.*) of the tri-amino acid porphyrin derivatives (C-terminal); (a): undetected signal.

Compounds		**14a**	**15a**	**15b**	**16a**	**16b**	**16c**
Solvent		DMSO-d6	$CDCl_3$	DMSO-d6	$CDCl_3$	DMSO-d6	DMSO-d6
Porphyrinic Protons	1	9.00 *7.0*	9.05 *7.0*	9.60 *6.4*	9.05 *7.2*	9.60 *6.4*	9.60 *6.4*
	2	8.25 *7.0*	8.15 *7.0*	9.00	8.10 *7.2*	9.00	9.00
	3	8.85-8.95	8.85	9.00-9.15	8.85	9.00-9.20	9.00-9.20
	4	7.80	7.80	7.75	7.80	7.70	7.70
	5	7.78	7.75 *7.8*	7.75	7.70 *7.8*	7.70	7.70
	6	7.70 *7.0*	7.60	7.75	7.60 *7.8*	7.70	7.70
	7	7.40 *7.0*	7.30	7.45 *8.0*	7.30	7.45 *7.3*	7.45 *7.3*
	8	-	-	4.75	-	4.80	4.80
	9	- 3.05	- 3.00	- 3.10	- 2.95	- 3.05	- 3.05
	10	4.20 *7.8*	4.20 *8.0*	4.25 *7.8*	4.20 *7.8*	4.20 *7.8*	4.20 *7.8*
	11	2.00 *7.8*	2.20 *8.0*	2.00 *7.8*	2.20 *7.8*	2.00 *7.8*	2.00 *7.8*
	12	2.35 *7.8*	2.50 *8.0*	2.35 *7.8*	2.50 *7.8*	2.60 *7.8*	2.60 *7.8*
Amino Acid Protons	13	(a)	6.85 *5.7*	8.30 *5.3*	6.60 *5.5*	8.35 *5.4*	8.35 *5.4*
	14	3.70 *5.2*	3.90 *5.7*	3.75 *5.3*	3.95 *5.5*	3.80 *5.4*	3.80 *5.4*
	15	(a)	6.45 *5.7*	7.20 *5.7*	(a)	8.20 *5.4*	8.25 *5.4*
	16	3.65 *5.2*	3.90 *5.7*	3.70 *5.3*	3.85 *5.5*	3.70 *5.4*	3.70 *5.4*
	17	(a)	6.70 *5.7*	8.40 *5.2*	6.95 *5.5*	7.45 *7.3*	7.45 *7.2*
	18	4.55	4.55	4.30	4.45	4.40	4.35
	19	3.50	1.60 *8.0*	1.50 *7.8*	1.85	1.60	1.55
	20	3.00 *3.5*	1.55	1.40	1.40	1.45	1.40
	21	8.15	0.90 *5.2*	0.80 *5.2*	1.30	1.25	1.20
	22	7.15	3.60	3.50	3.15	3.10	3.10
	23	(a)			5.15 *5.8*	(a)	3.60
	24				5.00	4.90	
	25				7.30	7.3	
	26				3.60	3.60	

Table 5 : Visible absorption bands of the synthesized porphyrins

Porphyrin	Solvent	Wavelength in nm (Optical density % or molar extinction coefficient in L $mmol^{-1}$ cm^{-1})
1	CH_2Cl_2	416 (100), 512 (7.2), 545 (4.1), 586 (4.3), 648 (0.2)
2	CH_2Cl_2	416 (100), 512 (5.9), 546 (2.8), 587 (2.6), 643 (0.2)
3	CH_2Cl_2	416 (100), 512 (6.4), 545 (2.5), 586 (2.2), 642 (0.3)
4	CH_2Cl_2	417 (492), 513 (24.6), 547 (8.4), 587 (8.4), 643 (3.9)
5a	CH_2Cl_2	416 (100), 513 (8.7), 547 (1.3), 588 (1.3), 644 (0.9)
7a	CH_2Cl_2	417 (100), 513 (6.0), 550 (1.5), 600 (1.4), 650 (0.1)
8a	CH_2Cl_2	415 (100), 511 (6.8), 545 (3.7), 588 (3.6), 643 (0.2)
9a	CH_2Cl_2	425 (100), 521 (7.7), 560 (3.9), 585 (3.7), 645 (2.2)
9b	H_2O	424 (100), 520 (7.0), 559 (3.6), 589 (3.6), 647 (1.6)
10a	CH_2Cl_2	417 (273), 513 (15.3), 546 (6.0), 589 (5.7), 643 (3.3)
10b	CH_2Cl_2	417 (260), 513 (14.0), 546 (6.2), 590 (6.0), 644 (3.6)
11a	CH_2Cl_2	417 (100), 513 (5.1), 547 (1.6), 587 (1.6), 643 (0.9)
11b	H_2O	429 (100), 527 (6.9), 561 (3.8), 592 (3.4)
12a	CH_3OH	413 (100), 510 (7.5), 544 (3.9), 587 (3.8), 643 (2.5)
12b	H_2O	424 (100), 523 (8.5), 562 (4.8), 590 (4.8)
13a	CH_2Cl_2	413 (100), 510 (5.1), 544 (1.1), 588 (1.0), 645 (0.3)
13b	H_2O	422 (100), 519 (6.1), 555 (3.2), 583 (2.8)
14a	CH_2Cl_2	420 (100), 514 (6.2), 552 (4.9), 590 (3.7), 648 (3.6)
15a	CH_2Cl_2	414 (100), 512 (6.8), 543 (3.4), 586 (3.2), 644 (0.2)
15b	H_2O	424 (166), 520 (12.5), 558 (7.0), 584 (6.6)
16a	CH_2Cl_2	412 (100), 511 (7.3), 545 (3.9), 587 (3.7), 644 (0.2)
16b	H_2O	423 (100), 519 (5.9), 556 (2.4), 585 (2.3)
16c	H_2O	424 (238), 524 (17.9), 563 (10.7), 589 (10.0), 645 (5.5)

EXPERIMENTAL SECTION

General methods

All the syntheses were performed under argon, in dry solvents and usually in the dark (aluminium foil). Electronic absorption spectra were measured in CH_2Cl_2, CH_3OH or H_2O using a Safas 190 DES spectrophotometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AC 250 spectrometer at 250 MHz. Mass spectra were run on a ^{252}Cf time-of-flight mass spectrometer constructed at the Institut de Physique Nucléaire in Orsay. The flight distance was either 40 or 90 cm and the acceleration voltages were +15 and -15kV. About 10 to 20 μL of the solutions (1 mg of product in 1 mL of CH_2Cl_2, CH_3OH or DMF) were electrosprayed on aluminized Mylar targets.[32] Elemental analyses were performed by the Laboratoire de Microanalyse du CNRS in Gif sur Yvette.

Chemicals

Dichloromethane (CH_2Cl_2) was dried over $CaCl_2$ and distilled prior to use. Dimethylformamide (DMF) was dried on barium oxide at 110°C for 2h, distilled under reduced pressure and stored under argon over molecular sieves. Pyrrole was distilled under reduced pressure and used immediately. The other reagents and the amino acids (all in L configuration) were from commercial sources and used without further purification. TLC were carried out using Merck silica gel $60F_{254}$ or neutral alumina $60F_{254}$ precoated plates. Merck silica gel type 60 (70-230 mesh) was used for column chromatography.

Syntheses

Benzaldehyde I

A mixture of 3-hydroxybenzaldehyde (3.66 g, 30 mmol), N-(3-bromopropyl)phthalimide (9.65 g, 36 mmol) and K_2CO_3 (4.98 g, 36 mmol) was dissolved in DMF (30 mL) and refluxed for 1.5 h. After cooling, the reaction product was precipitated by addition of water (30 mL), filtered and washed several times with water. It was purified by chromatography on silica with a CH_2Cl_2/ethyl acetate (90/10 v/v) eluent (6.7 g, 72%). ^1H NMR ($CDCl_3$) δ(ppm) 9.80 (s, 1H, C<u>H</u>O), 7.85 (m, 2H, phthalimide), 7.65 (m, 2H, phthalimide), 7.45 (m, 2H, phenyl), 7.40 (s, 1H, phenyl), 7.05 (t, 1H, phenyl), 4.10 (t, 2H, O-C<u>H</u>$_2$-CH$_2$), 3.95 (t, 2H, N-C<u>H</u>$_2$-CH$_2$), 2.15 (q, 2H, CH$_2$-C<u>H</u>$_2$-CH$_2$).

Benzaldehyde II

A mixture of 3-hydroxybenzaldehyde (3.66 g, 30 mmol) and K_2CO_3 (4.98 g, 36 mmol) was stirred in anhydrous DMF (30 mL). Ethyl 4-bromobutyrate (7.02 g, 36 mmol) was added dropwise and the mixture was heated at 70°C for 2 h, then refluxed for 1 h. After cooling, the salts were filtered. DMF was evaporated to dryness and the reaction mixture was redissolved in CH_2Cl_2 (20 mL) and washed with 2 x 10 mL distilled water. After drying on sodium sulfate, filtration and evaporation of the solvent, the reaction product was purified by chromatography on silica with a CH_2Cl_2/heptane (70/30 v/v) eluent (5.7 g, 80%). ^1H NMR ($CDCl_3$) δ(ppm): 9.95 (s, 1H, C<u>H</u>O), 7.40 (s, 1H, phenyl), 7.38 (d, 1H, phenyl), 7.30 (d, 1H, phenyl), 7.10 (t,

1H, phenyl), 4.13 (q, 2H, O-C<u>H</u>$_2$-CH$_3$), 4.05 (t, 2H, O-C<u>H</u>$_2$-CH$_2$), 2.50 (t, 2H, C<u>H</u>$_2$-CO), 2.15 (q, 2H, CH$_2$-C<u>H</u>$_2$-CH$_2$), 1.25 (t, 3H, O-CH$_2$-C<u>H</u>$_3$). IR ν(cm^{-1}): 2980, 2830-2730 (O=C-H), 1732 (O-C=O), 1698 (H-C=O).

Porphyrins 3 and 4

Porphyrins **3** and **4** were synthesized according to the same following procedure: benzaldehyde I (4.02 g, 13 mmol) or benzaldehyde II (3.07 g, 13 mmol) and 4-pyridinecarboxaldehyde (4.17 g, 39 mmol) were poured into refluxing propionic acid (250 mL) and pyrrole (3.49 g, 52 mmol) was added dropwise. The reflux was maintained for 2 h, then the crude product was evaporated to dryness under vacuum. A first chromatography on silica gel with a CH_2Cl_2/EtOH (92/8, v/v) eluent was performed to remove the tar. A second one performed with CH_2Cl_2 and increasing amounts of ethanol (0 to 8%) allowed separation of the six porphyrins. The tripyridylphenylporphyrins **3** and **4** were eluted as the fifth fraction with CH_2Cl_2/EtOH (94/6, v/v) and obtained in 8% yield. Porphyrin **3**: Anal: found: 72.70 C, 4.67 H; calcd. for $C_{52}H_{36}N_8O_3$, 2 H_2O = 856.9 g/mol: 72.88 C, 4.70 H. Porphyrin **4**: Anal: found: 73.70 C, 5.01 H, 12.80 N, 8.40 O; calcd. for $C_{47}H_{37}N_7O_3$, 1 H_2O = 765.9 g/mol: 73.71 C, 5.13 H, 12.80 N, 8.36 O.

Porphyrin 1

A mixture of porphyrin **3** (0.20 g, 0.25 mmol) and hydrazine monohydrate (0.125 g, 2.5 mmol) was dissolved in CH_2Cl_2/EtOH (1/2, v/v) (5 mL), refluxed for 16 h, then stirred at room temperature for 24 h. Phthalhydrazide was precipitated by addition of HCl (10% solution) and filtered. The solution was neutralized by addition of NaOH (10% solution) and the porphyrin was extracted from the aqueous layer with a CH_2Cl_2/EtOH (95/5, v/v) mixture. After drying over sodium sulfate and evaporation of the solvents, the porphyrin **1** (0.14 g) was obtained pure in 80% yield. Anal: found: 72.24 C, 5.38 H, 6.47 O; calcd. for $C_{44}H_{34}N_8O$, 2 H_2O = 726.8 g/mol: 72.71 C, 5.27 H, 6.60 O. MS (PDMS ^{252}Cf, positive ionization) *m/z* = 691.67 $[M+H]^+$.

Porphyrin 2

A mixture of porphyrin **4** (0.30 g, 0.40 mmol) and NaOH (0.32 g, 4.0 mmol) in fine powder was stirred in DMF (5 mL) at room temperature for 30 min. The reaction was controlled by TLC. At the end of the reaction, water (20 mL) was added and the solution was neutralized by HCl (10% solution). The porphyrin was extracted from the aqueous layer with a CH_2Cl_2/EtOH (95/5, v/v) mixture. The organic phase was washed with water, dried over sodium sulfate and evaporated to dryness. The porphyrin **2** (0.23 g) was obtained pure in 80% yield. Anal: found: 71.53 C, 4.87 H, 12.81 N, 9.56 O; calcd. for $C_{45}H_{33}N_7O_3$, 2 H_2O = 755.8 g/mol: 71.51 C, 4.93 H, 12.97 N, 10.58 O.

Porphyrins 5a and 6a

A mixture of N-(carbobenzyloxy)-L-tyrosine (95 mg, 0.30 mmol) and triethylamine (21 µL, 0.15 mmol) was dissolved in anhydrous DMF (6 mL) and the solution was cooled at -18°C. Isobutyl chloroformate (20 µL, 0.15 mmol) was added, then a solution of porphyrin **1** (110 mg, 0.15 mmol) in triethylamine (21 µL). The mixture was stirred for 3 hours at -18°C, and 2 hours at room temperature. After addition of water, the precipitate was filtered, washed with water and ether and dried in a dessicator at 50°C under vacuum. The

porphyrin **5a** (139 mg) was obtained in 90% yield. The porphyrin **6a** was obtained by the same way in 90% yield.

Porphyrins 7a and 8a

The following procedure of coupling was applied for the synthesis of porphyrins **7a**, **8a**: triethylamine (63 μL, 0.45 mmol) and BOP reagent (100 mg, 0.225 mmol) were added to a solution of N-tert-butoxycarbonyl amino acid (0.15 mmol) (diglycine or L-histidine). The mixture was stirred for 10 min to allow the formation of the activated ester, then 0.075 mmol of porphyrin **1** was added and the solution was stirred overnight. After addition of water, the precipitate was collected and washed with water and ether. After purification on a silica gel column using CH_2Cl_2 as eluent and removal of the N-tert-butoxycarbonyl protecting group by hydrogenolysis 12 h in methanol using H_2, Pd/C, the porphyrin **7a** was obtained in 70% yield. Attempts to remove the protecting group of **8a** failed and resulted in a decomposition of the amino acid porphyrin.

Porphyrins 9a and 10a

A mixture of porphyrin **2** (0.15 mmol), triethylamine (63 μL, 0.45 mmol) and BOP reagent (100 mg, 0.225 mmol) was dissolved in anhydrous DMF (10mL) and the solution was stirred at room temperature for 10 min. Then the L-tyrosine (or glycine) ethyl ester (0.30 mmol) was added and the solution was stirred at room temperature overnight in the dark. The reaction was controlled by TLC. The corresponding amino acid porphyrins **9a** and **10a** were precipitated by addition of water, filtered, washed several times with water and dried in a dessicator at 50°C under vacuum. Yields ranged from 90 to 98%. Porphyrin **10a**: Anal: found: 68.45 C, 5.20 H, 13.11 N; calcd. for $C_{49}H_{40}N_8O_4$, 3 H_2O = 858.3 g/mol: 68.50 C, 5.40 H, 13.05 N.

Porphyrin 10b

Porphyrin **10a** (90 mg, 0.11mmol) was stirred at room temperature with a solution 1M KOH-MeOH (35 mL). At the end of the reaction (controlled by TLC), water was added, then HCl (10% solution) until pH = 7. The porphyrin was extracted from the aqueous layer with a CH_2Cl_2/EtOH (90/10, v/v) mixture. After drying over sodium sulfate and evaporation of the solvents, the porphyrin **10b** (84 mg) was obtained pure in 98% yield.

Porphyrins 11a and 12a

Porphyrins **11a** and **12a** were synthesized according to the procedure used in the synthesis of porphyrins **9a** and **10a**, by coupling of porphyrin **10b** (78 mg, 0.10 mmol) respectively with L-tyrosine ethyl ester hydrochloride (74 mg, 0.30 mmol) (82% yield) and L-arginine methyl ester dihydrochloride (78 mg, 0.30 mmol) (87% yield).

Porphyrin 13a

The same procedure was applied for the synthesis of porphyrin **13a**, by coupling of porphyrin **2** (110 mg, 0.15 mmol), with the dipeptide Gly-Gly ethyl ester hydrochloride (88 mg, 0.45 mmol). The porphyrin ester was precipitated by addition of water, filtered and washed several times with water. Then it was redissolved in dichloromethane, dried over sodium sulfate and purified by column chromatography on silica

gel with a CH_2Cl_2/EtOH (99/1, v/v) eluent. Finally, it was precipitated from a mixture of dichloromethane-hexane and obtained pure in 86% yield (113 mg). The saponification, carried out on 105 mg (0.12 mmol) (see synthesis of porphyrin **10b**) gave porphyrin **13a** (95 mg) in a 93% yield.

Porphyrins 14a, 15a and 16a

The same method of coupling was used for the synthesis of these porphyrins, obtained in 90% yield, by coupling of porphyrin **13a** (85 mg, 0.10 mmol) with the corresponding L-amino acid methyl ester (0.30 mmol).

GENERAL PROCEDURE FOR THE METHYLATION OF THE PORPHYRINS

Porphyrins 7b, 9b, 11b, 12b, 13b, 15b, 16b

Porphyrin **15a** (or **7a**, **9a**, **11a**, **12a**, **13a**, **16a**) (0.060 mmol) was dissolved in anhydrous DMF (4 mL). A large excess of CH_3I (380 µl, 6 mmol) was added and the mixture was heated at 50°C for 3h. The porphyrin was precipitated by addition of acetone, filtered and washed with cold water. It was then dissolved in hot water, passed over a Cl^- Dowex exchange resin and lyophilized. Yields ranged from 75% (porphyrin **9b**, **11b**) to 95-97% (porphyrins **7b**, **12b**, **13b**, **15b**, **16b**). Porphyrin **11b**: Anal: found: 56.90 C, 6.08 H, 9.34 N, 14.76 O; calcd. for $C_{61}H_{58}N_9O_6Cl_3$, 6 H_2O, 1 NaCl = 1286.1 g/mol: 56.97 C, 5.49 H, 9.80 N, 14.93 O. Porphyrin **15b**: Anal: found: 55.27 C, 5.98 H, 10.37 N, 16.89 O; calcd. for $C_{59}H_{61}N_{10}O_6Cl_3$, 7 H_2O, 1 NaCl = 1297.1g/mol: 54.63 C, 5.83 H, 10.80 N, 16.03 O. MS (PDMS ^{252}Cf, positive ionization) *m/z* = 1006 $[M\text{-}3Cl]^+$.

Porphyrin 16c

Porphyrin **16b** (0.100 g, 0.078 mmol) was dissolved in anhydrous methanol. 1,4-cyclohexadiene (75 µl, 0.78 mmol) and one equivalent Pd on activated carbon (10%, 83 mg) were added and the mixture was stirred at room temperature for 3h. The reaction was controlled by TLC. The catalyst was filtered and the solution evaporated to dryness. The porphyrin was dried in a dessicator at 50°C under vacuum and obtained in 98% yield. Anal: found: 51.89 C, 5.23 H, 17.55 O; calcd. for $C_{59}H_{62}N_{11}O_6Cl_3$, 9 H_2O, 1.5 NaCl = 1377.4 g/mol: 51.45 C, 5.85 H, 17.42 O. MS (PDMS ^{252}Cf, positive ionization) *m/z* = 1021 $[M\text{-}3Cl]^+$.

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