Intramolecular Ligation of Carbonyl Oxygen to Central Zinc in Synthetic Oligopeptide-Linked Zinc-Porphyrins

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Oligopeptide-linked zinc-porphyrins were prepared (oligopeptide=–Phe$_m$–Ala$_n$–OMe and porphyrin=5,15-diaryl-2,3,7,8,12,13,17,18-octaethylporphyrin). ^{1}H NMR, IR, visible, and CD spectra of the synthetic molecule in a chlorinated methane ($CDCl_3$ or CH_2Cl_2) showed that the carbonyl oxygen of the *N*-terminal amino acid of the linked peptide should ligate the central zinc metal in the molecule as the axial ligand to form a pentacoordinated zinc-porphyrin. The coordination of the zinc with the peptide framework changed the optical and electrical properties, indicating that such ligation might control the reactivity in biological metallotetrapyrrole–protein systems as well as the coordination to the peptide residue.

Metallotetrapyrroles such as metalloporphyrins and chlorines coordinate proteins to form biologically important complexes.[1] Typically, proteins with metallotetrapyrrole(s) as a cofactor play roles of oxygen carrier in hemoglobin, oxidation catalyst in cytochrome P-450, energy mediator in sunlight-harvesting antenna, and electron mediator in cytochrome *c* and photosynthetic reaction center. Many models are available for synthetic peptide-linked metalloporphyrins as the biological model.[2—4] In almost all the models with linked peptides as an axial ligand to the central metal of metalloporphyrin,[2,3] to our best knowledge, the intramolecular interaction of the metal with the residue of linked peptides has been discussed. In this paper, to investigate the intramolecular interaction of the metal with the amide bond of linked peptide, we report on preparation of oligopeptide-linked zinc-porphyrins, elucidation of the conformation of the basis of the spectroscopic data, and relationship between the conformation and the optical and electrical properties. To clarify the interaction of metalloporphyrin with the peptide framework, L-alanine and L-phenylalanine with uncoordinatable hydrocarbons as the residue (X=Me and $CH_2C_6H_5$ as shown in Fig. 1) were used in the synthetic peptide-linked zinc-porphyrins.

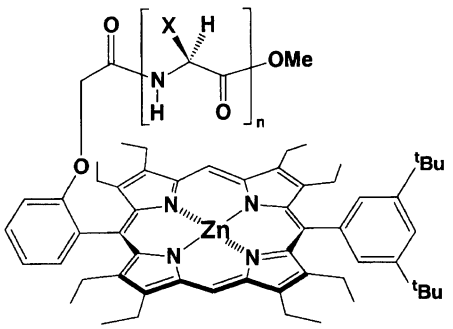

Fig. 1. Synthetic oligopeptide-linked zinc-porphyrins.

Results and Discussion

5,15-Diaryl-2,3,7,8,12,13,17,18-octaethylporphyrins were synthesized by condensation of two pyrroles and an aldehyde (Scheme 1) and successive coupling of dipyrrolylmethanes (Scheme 2) and then oligopeptide-linked zinc-porphyrins were prepared with modification on the side chain of an aryl group and insertion of zinc metal (Schemes 2 and 3). For improvement of solubility of the synthetic porphyrins in almost organic solvents, two *t*-butyl groups were introduced on the other aryl group. We have already reported these groups are good substituents for enhancement of the solubility.[6] For restriction of the conformations of the porphyrin, ethyl groups were substituted on all the eight β-positions of pyrrole ring. In such a molecule, both 5- and 15-aryl plains are fixed to be perpendicular to the porphyrin ring by steric repulsion between the aryl group and the neighboring ethyl groups, which is supported by comparison with similar well-defined molecules by the X-ray crystallography.[7] Protected di- and tripeptides with L-configurations were prepared by use of standard methods for peptide synthesis (see Scheme 3).[8] During all the procedures, no racemization could be observed. After carboxyl-porphyrin (H_2P–OH) was bonded with oligopeptide methyl ester (H–AA–OMe=H–R), zinc-metellation gave desired peptide-linked zinc(II)-porphyrins (ZnP–R).

^{1}H NMR spectra of ZnP–Ala$_n$–OMe (n=1—3) in $CDCl_3$ were measured at 25 °C (ca. 10^{-3} mol dm^{-3}). The chemical shifts (δ) which were determined by ^{1}H–^{1}H decoupling measurements, are listed in Table 1. These values were compared with the corresponding δ in Ac–Ala$_n$–OMe (n=1—3). These differences are indicated in the parenthesis in Table 1. Table 1 shows that all the δ of –Ala$_n$–OMe are high-field shifted and that the chemical shifts of terminal methyl ester (δ_{OMe}) in ZnP–Ala–OMe and of the proton (δ_{CH}) at the same position ($-^1$Ala–Y–C<u>H</u>–) on the α-carbon of the second alanine (^{2}Ala) in ZnP–Ala$_n$–OMe (n=2 and 3) are

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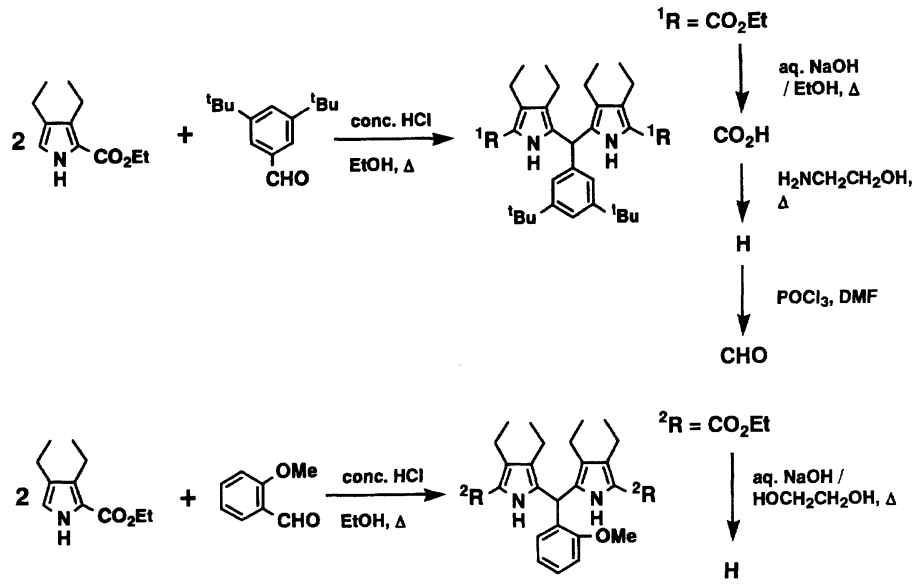
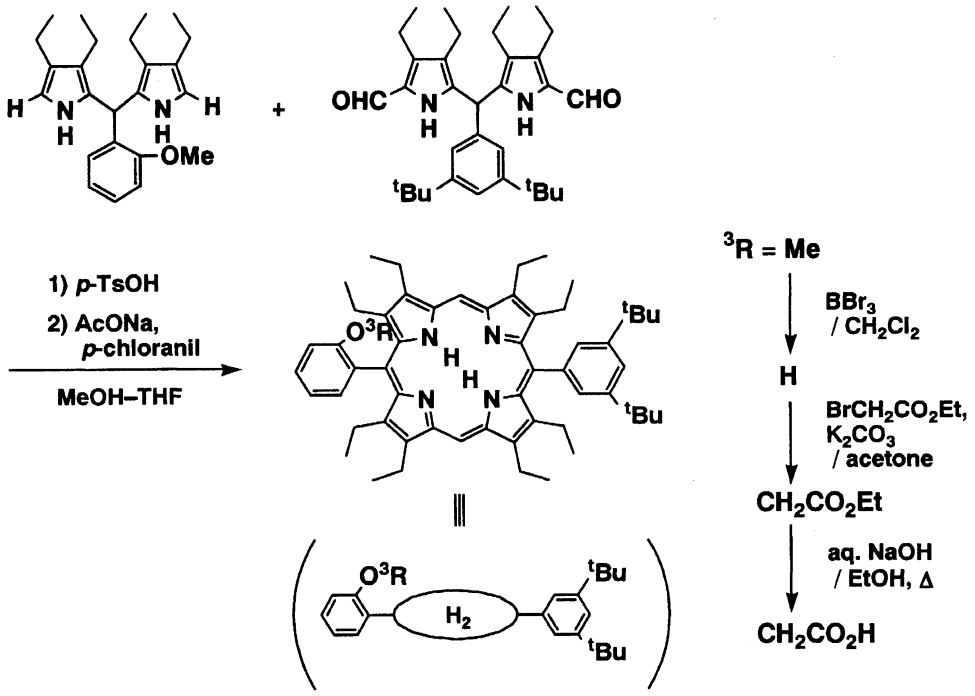


Scheme 1. Synthesis of dipyrrolylmethanes with an aryl group.



Scheme 2. Synthesis of octaethylporphyrins with two aryl groups on the *meso*-position.

highest-field shifted in each molecule. Considering the ring-current effect by a porphyrin moiety,[9] these results mean that $-Ala_n-OMe$ should be on the π-plane of the porphyrin ring and the proton in $-^1Ala-Y-C\underline{H}-$ (Y=NH or O) should be situated close to the central zinc metal.

Infrared spectra of $ZnP-Ala_n-OMe$ ($n=1$—3) in CH_2Cl_2 were measured at 25 °C (ca. 10^{-4} mol dm^{-3}). The vibrational bands (ν) are listed in the upper three rows of Table 2, showing the followings; i) the sole vibrational peaks in the amide NH region (ν_{NH}) are almost the same, ca. 3380 cm^{-1}; ii) $\nu_{esterC=O}$ in ZnP–Ala–OMe is about 15 cm^{-1} smaller than those in $ZnP-Ala_n-OMe$ ($n=2$ and 3); iii) a 1660-cm^{-1} band ($\nu_{amideC=O}$) appears in $ZnP-Ala_n-OMe$ ($n=2$ and 3) besides 1680—1690 cm^{-1} bands but not in ZnP–Ala–OMe. These results indicate weakening of an ester carbonyl bonding in ZnP–Ala–OMe and of an amide C=O bonding in $ZnP-Ala_n-OMe$ ($n=2$ and 3). These carbonyl oxygens should be coordinated with an oxygen-acceptor, not with an amide hydrogen.

From the above ^{1}H NMR and IR-measurements in a chlorinated methane solution, the carbonyl oxygen of the *N*-terminal alanine (^{1}Ala) should ligate the central zinc metal in the molecule as the axial ligand to form a pentacoordinated zinc-porphyrin.

Visible spectra of ZnP–R in CH_2Cl_2 at 25 °C (ca.

Table 1. ^{1}H NMR Spectral Data of ZnP–Ala$_n$–OMe[a)]

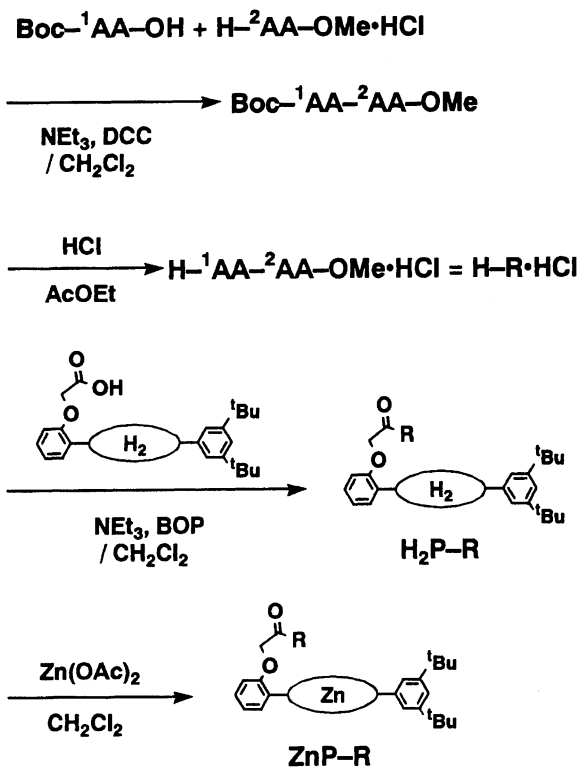
	^{1}Ala			^{2}Ala			^{3}Ala			OMe
ZnP–Ala$_n$–OMe	NH	CH	Me	NH	CH	Me	NH	CH	Me	
n=1	3.60	2.73	−0.57							0.44
	(−3.04)	(−1.88)	(−1.98)							(−3.30)
n=2	3.53	2.75	−0.93	4.45	0.11	−0.86				3.35
	(−3.08)	(−1.82)	(−2.33)	(−2.43)	(−4.48)	(−2.22)				(−0.39)
n=3	4.04	2.85	−0.66	4.22	0.60	−0.59	4.48	3.14	0.84	3.59
	(−2.46)	(−1.72)	(−2.04)	(−2.74)	(−3.99)	(−1.94)	(−2.48)	(−1.38)	(−0.55)	(−0.14)

a) In $CDCl_3$, ca. 10^{-3} mol dm^{-3} at 298 K. These values show the chemical shift δ in ppm. The errors of δ were within ±0.01 ppm. Parenthesis indicates the δ [in ZnP–Ala$_n$–OMe] − the corresponding δ [in Ac–Ala$_n$–OMe].

Table 2. IR Spectral Data of *N*-Protected–Ala$_n$–OMe[a)]

	Amide NH	Ester C=O	Amide C=O	
ZnP–Ala$_n$–OMe				
n=1	3381	1724	1680 (br)	
n=2	3374	1739	1680 (sh)	1660
n=3	3376	1741	1686	1658
Ac–Ala$_n$–OMe				
n=1	3330	1743	1680	
n=2	3340	1745	1680	
n=3	3320	1747	1684	

a) In CH_2Cl_2, ca. 10^{-4} mol dm^{-3} at 298 K. These values show the vibrational band peak ν in cm^{-1}. The errors of ν were within ±2 cm^{-1}.



Scheme 3. Synthesis of oligopeptide-linked porphyrins (^{1}AA=L-amino acid, ^{2}AA=L-amino acid or L,L-dipeptide, see Ref. 5 for abbreviations).

10^{-6} mol dm^{-3}) were dependent upon the linked R. Table 3 lists their spectroscopic data, the absorption maxima λ_{max} and the intensity ratios $\varepsilon_\alpha/\varepsilon_\beta$. The λ_{max} in B (Soret)- and Q (α and β)-bands are red-shifted, –OEt < –Ala–OMe < –Ala$_2$–OMe≈–AA$_3$–OMe. The $\varepsilon_\alpha/\varepsilon_\beta$ decrease as well, –OEt > –Ala–OMe > –Ala$_2$–OMe≈–AA$_3$–OMe. From the previously reported red shift and decrease in the intensity of zinc-octaethylporphyrin with an axial ligand,[10] these changes support the conformation that linked peptides should be coordinated with central zinc in the molecule. Moreover, no change of λ_{max} and of $\varepsilon_\alpha/\varepsilon_\beta$ in coordinatable THF, in which an unambiguously pentacoordinated zinc(II)-porphyrin with a THF as the axial ligand were formed,[10] supports the above intramolecular ligation in CH_2Cl_2.

Steady-state fluorescence spectra of ZnP–R show the similar behavior with their visible spectra (see Table 3). Red shift of maxima α' and β' (–OEt < –Ala–OMe < –Ala$_2$–OMe≈–AA$_3$–OMe) and decrease in the intensity ratio $I_{\alpha'}/I_{\beta'}$ (–OEt > –Ala–OMe > –Ala$_2$–OMe≈–AA$_3$–OMe) were observed in CH_2Cl_2 and neither shift of the maxima nor change of the ratio in THF.

Circular dichroism spectra of ZnP–Ala$_n$–OMe were measured under the same conditions as visible measurement (see Fig. 2). In CH_2Cl_2, the peaks were observed in the Soret region. The Cotton effect indicates that the chiral linked oligopeptide should be close to the zinc-porphyrin ring.[11] In THF, the spectrum of ZnP–Ala$_3$–

Table 3. Visible and Fluorescence Spectral Data of ZnP–R[a)]

	CH_2Cl_2							THF						
	Visible				Fluorescence			Visible				Fluorescence		
R	Soret	β	α	$\varepsilon_\alpha/\varepsilon_\beta$	α'	β'	$I_{\alpha'}/I_{\beta'}$	Soret	β	α	$\varepsilon_\alpha/\varepsilon_\beta$	α'	β'	$I_{\alpha'}/I_{\beta'}$
–OEt	413	541	576	0.53	584	640	1.56	420	548	580	0.37	593	648	0.84
–Ala–OMe	416	543	578	0.43	586	643	1.30	420	549	579	0.38	592	649	0.85
$-Ala_2-OMe$	419	545	579	0.36	589	645	1.11	420	549	580	0.36	589	649	0.84
$-Ala_3-OMe$	419	546	580	0.36	590	646	1.05	420	549	581	0.36	592	650	0.85
–Phe–Ala_2–OMe	419	546	579	0.34	589	645	1.14	420	550	580	0.37	592	649	0.85
$-Phe_2-Ala-OMe$	419	546	579	0.33	589	645	1.16	420	550	582	0.34	591	649	0.83
$-Phe_3-OMe$	419	546	580	0.36	589	645	1.14	421	550	582	0.34	592	649	0.83

a) Visible and fluorescence (excitation at the Soret band) were measured in ca. 10^{-6} mol dm^{-3} at 298 K. These values show the band peak λ_{max} in nm. The errors of λ_{max} were within ±1 nm. The $\varepsilon_\alpha/\varepsilon_\beta$ and $I_{\alpha'}/I_{\beta'}$ represent the intensity ratio of the each peak of visible and fluorescence spectra, respectively. The errors of the ratios were within ±10%.

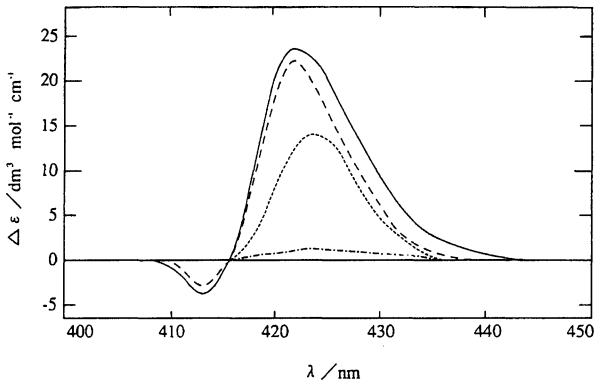


Fig. 2. CD spectra of ZnP–Ala_n–OMe (ca. 10^{-6} mol dm^{-3}, at 25 °C). ····: n=1 (CH_2Cl_2), ---: n=2 (CH_2Cl_2), ——: n=3 (CH_2Cl_2), and –·–: n=3 (THF).

OMe was almost flat at the same region and the chiral link was further from zinc-porphyrin than in CH_2Cl_2.

Fluorescence lifetimes τ_f of ZnP–R were measured and all the fluorescence decay followed a single exponential curve. The lifetime τ_f of ZnP–R in CH_2Cl_2 were dependent upon the linked R. Table 4 shows τ_f (R=–OEt)=1.3, τ_f (R=–Ala_n–OMe; n=1—3)=1.6, and τ_f (R=–Phe_m–Ala_{3-m}–OMe; m=1—3)=1.8 ns. The τ_f values in CH_2Cl_2 depend upon the coordination number (4 or 5) of zinc as well as the visible and fluorescence spectra and such a coordination effect on the τ_f is also supported by little change of the τ_f in THF (always pentacoordinated). In addition, the τ_f in CH_2Cl_2 was dependent upon the *N*-terminal amino acid (^{1}AA) residue (–Me and $-CH_2C_6H_5$).

First and second oxidation potentials $E^1_{1/2}$ and $E^2_{1/2}$ of ZnP–R (one by one-electron oxidation of the peripheral porphyrin π-system[12)] in CH_2Cl_2 (ca. 10^{-4} mol dm^{-3}) changed by the linked R (see Table 4). In spite of the presence of 1000 equivalents of a salt ($Bu_4N^+ClO_4^-$), the fluctuation of $E_{1/2}$ was observed, indicating that fairly tight intramolecular coordination occurred under the measurement conditions. As expected, $E_{1/2}$ in THF were the same within error, $E^1_{1/2}$ (Zn(II)P–R→Zn(II)P$^+$–R)=0.77±0.02 V and $E^2_{1/2}$ (Zn(II)P$^+$–R→Zn(II)P^{2+}–R)=0.90±0.01 V.

In conclusion, the coordination of the central zinc with an amide carbonyl oxygen in CH_2Cl_2[13)] changed the optical (visible and fluorescence) and electrical (oxidation potential) properties, indicating that ligation of the peptide framework with the central metal might be the additional factor for fine-tuning the reactivity in biological metallotetrapyrrole-protein systems besides coordination of the metal with the peptide residue[1—3)] to be the well-known major factor.

Experimental

Apparatus. All melting points were measured with a Yanagimoto micro melting point apparatus and were uncorrected. Ultraviolet and visible spectra were measured with a Shimadzu UV-3000 spectrometer. Circular dichroism spectra were measured with a JASCO J-600 spectropolarimeter. Fluorescence spectra were recorded with a Shimadzu RF-502A spectrometer. Fluorescence lifetimes were measured with a Horiba NAES-1100 time-resolved spectrofluorometer. Infrared spectra were measured with a Horiba FT-300 spectrometer in 0.5 nm-cell of CaF_2. ^{1}H NMR spectra were recorded on a JEOL JMN-FX 400 instrument in $CDCl_3$ with $CHCl_3$ (δ=7.26) as an internal standard. FAB mass spectra were measured with a JEOL JMS-DX-300 spectrometer; samples were dissolved in chloroform and *m*-nitrobenzyl alcohol was used as the matrix. Cyclic voltanometry was performed with a PAR Model 174.

Materials. All solvents and chemicals were of reagent grade quality, purchased commercially and used without further purification except as noted below. CH_2Cl_2 used in the demethylation and peptide formation was distilled before use from P_2O_5 followed by K_2CO_3. THF was pre-dried over KOH and distilled from benzophenone ketyl. Flash column chromatography was carried out using Wakogel FC-40. Dipyrrolylmethanes and porphyrins were synthesized in similar procedures as reported (see Schemes 1 and 2).[14)] Peptides and peptide-linked porphyrins were synthesized as the following procedures (see Scheme 3). The full synthetic procedures were already reported in the master thesis of Kiyomori in Kyoto University.[15)]

Ethyl 3,4-Diethyl-2-pyrrolecarboxylate. According to the reported procedures,[16)] the titled compound was

Table 4. Fluorescence Lifetimes τ_f and Oxidation Potentials $E_{1/2}$ of ZnP–R[a)]

R	CH_2Cl_2			THF		
	τ_f	$E_{1/2}{}^1$	$E_{1/2}{}^2$	τ_f	$E_{1/2}{}^1$	$E_{1/2}{}^2$
–OEt	1.32	0.59	0.73	1.20	0.75	0.90
–Ala–OMe	1.60	0.64	0.77	1.23	0.78	0.89
–Ala_2–OMe	1.62	0.56	0.85	1.27	0.76	0.91
–Ala_3–OMe	1.59	0.56	0.81	1.24	0.76	0.90
–Phe–Ala_2–OMe	1.74	0.59	0.81	1.26	0.77	0.90
–Phe_2–Ala–OMe	1.79	0.61	0.81	1.29	0.77	0.90
–Phe_3–OMe	1.75	0.61	0.80	1.28	0.77	0.91

a) Fluorescence lifetimes τ_f (ns) were measured in ca. 10^{-6} mol dm^{-3} at 298 K (excitation at Soret band and detection of β'-band at 640 and 649±15 nm in CH_2Cl_2 and THF, respectively). The errors of τ_f were within ±0.05 ns. Oxidation potentials $E_{1/2}$ (V, vs. SCE) were recorded in ca. 10^{-4} mol dm^{-3} at 298 K with 10^{-1} mol dm^{-3} tetrabutylammonium perchlorate as a supporting electrolyte (sweep rate=0.1 V s^{-1}). The errors of $E_{1/2}$ were within ±0.02 V.

synthesized and purified by distillation instead of column chromatography; 95%, pale yellow solids; mp≈15 °C, bp 102—103 °C/0.6 mmHg (1 mmHg=133.322 Pa); ^{1}H NMR ($CDCl_3$) δ=1.14+1.19 (3 H+3 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.35 (3 H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.45+2.75 (2 H+2 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.31 (2 H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 6.67 (1 H, d, J=2 Hz, 5-H), and 8.72 (1 H, br, NH).

1-[Bis[5-(ethoxycarbonyl)-3,4-diethyl-2-pyrrolyl]-methyl]-3,5-di-*t*-butylbenzene. 72%, white crystals; mp 146—147 °C; ^{1}H NMR ($CDCl_3$) δ=0.85+1.15 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.27 (18 H, s, *t*-Bu), 1.31 (6 H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.28+2.72 (4 H+4 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.26 (4 H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.48 (1 H, s, methyne), 6.92 (2 H, d, J=1.5 Hz, 2,6-H), 7.32 (1 H, t, J=1.5 Hz, 4-H), and 8.27 (2 H, br, NH).

1-[Bis(3,4-diethyl-2-pyrrolyl)methyl]-3,5-di-*t*-butylbenzene. 87%, pale yellow crystals; mp 93—94 °C; ^{1}H NMR ($CDCl_3$) δ=0.86+1.18 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.25 (18 H, s, *t*-Bu), 2.27+2.45 (4 H+4 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 5.47 (1 H, s, methyne), 6.36 (2 H, d, J=3 Hz, pyrrole 5-H), 6.94 (2 H, d, J=2 Hz, 2,6-H), 7.34 (2 H, br, NH), and 7.35 (1 H, t, J=2 Hz, 4-H).

1-[Bis(3,4-diethyl-5-formyl-2-pyrrolyl)methyl]-3,5-di-*t*-butylbenzene. 91%, pale brown crystals; mp 165—166 °C; ^{1}H NMR ($CDCl_3$) δ=0.89+1.24 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.25 (18 H, s, *t*-Bu), 2.32+2.72 (4 H+4 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 5.54 (1 H, s, methyne), 6.86 (2 H, d, J=2 Hz, 2,6-H), 7.33 (1 H, t, J=1.5 Hz, 4-H), 8.81 (2 H, br, NH), and 9.52 (2 H, s, CHO).

1-[Bis[5-(ethoxycarbonyl)-3,4-diethyl-2-pyrrolyl]-methyl]-2-methyoxybenzene. 86%, viscous orange oil; ^{1}H NMR ($CDCl_3$) δ=0.89+1.13 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.31 (6 H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.28+2.70 (4 H+4 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 3.77 (3 H, s, OCH_3), 4.26 (4 H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.79 (1 H, s, methyne), 6.91 (1 H, d, J=7.5 Hz, 3-H), 6.92 (1 H, t, J=7.5 Hz, 5-H), 6.99 (1 H, dd, J=2 and 7.5 Hz, 6-H), 7.26 (1 H, dt, J=2 and 7.5 Hz, 4-H), and 8.43 (2 H, br, NH).

1-[Bis(3,4-diethyl-2-pyrrolyl)methyl]-2-methoxybenzene. 72%, pale brown solids; mp 63—65 °C; ^{1}H NMR ($CDCl_3$) δ=0.90+1.18 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.28+2.44 (4 H+4 H, q+q, J=7.5 Hz, $C\underline{H}_2CH_3$), 3.73 (3 H, s, OCH_3), 5.83 (1 H, s, methyne), 6.34 (2 H, d, J=2 Hz, pyrrole 5-H), 6.87 (1 H, dd, J=1 and 7.5 Hz, 3-H), 6.88 (1 H, dt, J=1 and 7.5 Hz, 5-H), 7.03 (1 H, dd, J=2 and 7.5 Hz, 6-H), 7.15 (1 H, dt, J=2 and 7.5 Hz, 4-H), and 7.50 (2 H, br, NH).

5-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-15-(2-methoxyphenyl)porphyrin. 47%, purple powder; mp 278—280 °C; UV (CH_2Cl_2) λ_{max} 411 (ε 215000), 510(18000), 544 (4900), 577(7200), 628(1100), and 657 nm (200); ^{1}H NMR ($CDCl_3$) δ=−1.96 (2 H, br, NH), 1.12+1.19 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.49+1.51 (9 H+9 H, s+s, *t*-Bu), 1.86 (12 H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.79—3.03 (8 H, m, $C\underline{H}_2CH_3$), 3.65 (3 H, s, OCH_3), 4.01 (8 H, br-q, J=7.5 Hz, $C\underline{H}_2CH_3$), 7.25 (1 H, d, J=7.5 Hz, 15-phenyl 3-H), 7.30 (1 H, t, J=7.5 Hz, 15-phenyl 5-H), 7.79 (1 H, dt, J=1.5 and 7.5 Hz, 15-phenyl 4-H), 7.83 (1 H, t, J=1.5 Hz, 5-phenyl 4-H), 7.94 (1 H, dd, J=1.5 and 7.5 Hz, 15-phenyl 6-H), 8.00+8.05 (1 H+1 H, t+t, J=1.5 Hz, 5-phenyl 2,6-H), and 10.21 (2 H, *meso*-H); MS m/z 829 (MH^+).

5-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-15-(2-hydroxyphenyl)porphyrin. 99%, purple solids; mp 230—232 °C; ^{1}H NMR ($CDCl_3$) δ=−1.90 (2 H, br, NH), 1.11+1.24 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.50 (18 H, s, *t*-Bu), 1.86 (12 H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.82+3.00+4.02 (4 H+4 H+8 H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 5.03 (1 H, br-s, OH), 7.30 (1 H, dt, J=1.5 and 7.5 Hz, 15-phenyl 3-H), 7.31 (1 H, dd, J=1.5 and 7.5 Hz, 15-phenyl 5-H), 7.74 (1 H, dt, J=1.5 and 7.5 Hz, 15-phenyl 4-H), 7.84 (1 H, t, J=1.5 Hz, 5-phenyl 4-H), 8.00+8.02 (1 H+1 H, t+t, J=1.5 Hz, 5-phenyl 2,6-H), 8.04 (1 H, dd, J=1.5 and 7.5 Hz, 15-phenyl 6-H), and 10.25 (2 H, s, *meso*-H); MS m/z 815 (MH^+).

Ethyl 2-[15-(3,5-Di-*t*-butylphenyl-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetate (H_2P–OEt). 86%, purple powder; mp 204—206 °C; UV (CH_2Cl_2) λ_{max} 412 (ε 235000), 510(18000), 544 (5200), 576(7300), 629(1100), and 663 nm (200); Fluorescence (CH_2Cl_2) λ_{max} 632 and 697 nm; ^{1}H NMR ($CDCl_3$) δ=

−1.97 (2 H, br, NH), 1.02 (3 H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.12+1.19 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.50+1.51 (9 H+9 H, s+s, *t*-Bu), 1.87 (12 H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.82 (4 H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 2.98 (4 H, m, $C\underline{H}_2CH_3$), 4.02 (8 H+2 H, m, $C\underline{H}_2CH_3+CO_2C\underline{H}_2CH_3$), 4.37 (2 H, s, $OC\underline{H}_2CO_2Et$), 7.11 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.36 (1 H, t, J=8 Hz, 5-phenyl 5-H), 7.77 (1 H, dt, J=1.5 and 8 Hz, 5-phenyl 4-H), 7.84 (1 H, t, J=2 Hz, 15-phenyl 4-H), 8.02 (2 H, t, J=1.5 Hz, 15-phenyl 2,6-H), 8.09 (1 H, dd, J=2 and 8 Hz, 5-phenyl 6-H), and 10.21 (2 H, s, *meso*-H); MS m/z 901 (MH^+).

Ethyl 2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetate Zinc Complex (ZnP–OEt). 86%, purple crystals; mp 143—145 °C; ^{1}H NMR ($CDCl_3$) δ=1.03 (3 H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.04+1.13 (6 H+6 H, t+t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.49+1.50 (9 H+9 H, s+s, *t*-Bu), 1.85 (12 H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.72 (4 H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 2.82—2.96 (4 H, m, $C\underline{H}_2CH_3$), 3.97—4.04 (8 H, m, $C\underline{H}_2CH_3$), 4.03 (2 H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.35 (2 H, s, $OC\underline{H}_2CO_2Et$), 7.10 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.36 (1 H, t, J=8 Hz, 5-phenyl 5-H), 7.77 (1 H, dt, J=1.5 and 8 Hz, 5-phenyl 4-H), 7.83 (1 H, t, J=2 Hz, 15-phenyl 4-H), 8.02+8.06 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.11 (1 H, dd, J=1.5 and 8 Hz, 5-phenyl 6-H), and 10.14 (2 H, s, *meso*-H); MS m/z 964 (MH^++1, for ^{64}Zn).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetic Acid (H_2P–OH). 100%, purple solids; mp 192—197 °C; MS m/z 873 (MH^+).

General Procedure for the Synthesis of Peptides and Peptide-Linked Porphyrins. (a) Deprotection of *N*-Boc Group: 4 mol dm^{-3} HCl–AcOEt solution (10 ml) of *N*-Boc protected peptide (Boc–AA–OMe, 1 mmol) was stirred at 0 °C for 2 h without moisture. After evaporation, the residue was washed with Et_2O twice by decantation, dried in vacuo to give the hydrogen chloride salt (H–AA–OMe·HCl) quantitatively.

(b) Coupling by DCC: To a CH_2Cl_2 (10 ml) suspension of the above salt (H–^{2}AA–OMe·HCl, 1 mmol) were added Et_3N (140 ml, 1 mmol) and an acid (Boc–^{1}AA–OH, 1 mmol). To the ice-chilled clear solution was added DCC (227 mg, 1.1 mmol) under nitrogen. After stirring the ice-chilled clear solution was added DCC (227 mg, 1.1 mmol) under nitrogen. After stirring overnight (0°C→room temperature), the solution was evaporated and AcOEt (100 ml) was added to the residue. After filtration of insoluble DCU on celite, the filtrate was washed with aq 5% $KHSO_4$, aq 10% $NaHCO_3$, and brine, dried over Na_2SO_4 and then evaporated. The residue was recrystallized from AcOEt and hexane to give the pure amide (Boc–^{1}AA–^{2}AA–OMe).

(c) Coupling by BOP: To a CH_2Cl_2 (10 ml) suspension of the salt (H–R·HCl, 40 μmol) were added Et_3N (40 μmol) and an acid (H_2P–OH, 26.5 μmol). To the resulting clear solution were added BOP reagent (30 μmol) and Et_3N (30 μmol) under nitrogen at 0 °C in the dark. After stirring for 15 h, the solvent was evaporated and the residue was dissolved in AcOEt (30 ml), which was washed with aq 5% $KHSO_4$, aq 10% $NaHCO_3$, and brine, dried over Na_2SO_4 and then evaporated. The residue was purified by flash column chromatography on silica gel ($CHCl_3$–0—1% MeOH) to give the pure amide (H_2P–R).

(d) Zinc Metallation: To a CH_2Cl_2 solution of free-base porphyrin (H_2P–R) was added a MeOH solution of $Zn(OAc)_2\cdot 2H_2O$ at room temperature under nitrogen in the dark. After checking disappearance of the free-base by TLC, the solution was washed with brine, dried over Na_2SO_4 and then evaporated. The residue was purified by flash column chromatography on silica gel ($CHCl_3$–0—1% MeOH) to give the pure zinc complex (ZnP–R).

Boc–Ala$_2$–OMe: 88%, white needles; mp 112—113 °C; ^{1}H NMR ($CDCl_3$) δ=1.36 (3 H, d, J=7 Hz, ^{1}Ala Me), 1.40 (3 H, d, J=7 Hz, ^{2}Ala Me), 1.45 (9 H, s, *t*-Bu), 3.74 (3 H, s, OMe), 4.16 (1 H, br, ^{1}Ala α-H), 4.57 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 4.99 (1 H, br, ^{1}Ala NH), and 6.61 (1 H, br, ^{2}Ala NH). Found: m/z 275.1573. Calcd for $C_{12}H_{23}N_2O_5$: MH^+, 275.1607.

Boc–Ala$_3$–OMe: 89%, white crystals; mp 194—196 °C; ^{1}H NMR ($CDCl_3$) δ=1.36 (3 H, d, J=7 Hz, ^{1}Ala Me), 1.38 (3 H, d, J=7 Hz, ^{2}Ala Me), 1.40 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.44 (9 H, s, *t*-Bu), 3.74 (3 H, s, OMe), 4.16 (1 H, br, ^{1}Ala α-H), 4.49 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 4.53 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 5.02 (1 H, br, ^{1}Ala NH), and 6.76 (2 H, br, ^{2}Ala+^{3}Ala NH). Found: m/z 346.1930. Calcd for $C_{15}H_{28}N_3O_6$: MH^+, 346.1978.

Boc–Phe–Ala$_2$–OMe: 93%, white crystals; mp 162—164 °C; ^{1}H NMR ($CDCl_3$) δ=1.33 (3 H, d, J=7 Hz, ^{2}Ala Me), 1.38 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.39 (9 H, s, *t*-Bu), 3.01—3.15 (2 H, m, Phe β-H), 3.74 (3 H, s, OMe), 4.37 (1 H, br, Phe α-H), 4.47 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 4.50 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 5.01 (1 H, br, Phe NH), 6.58 (1 H, br-d, J=7 Hz, ^{2}Ala NH), 6.76 (1 H, br-d, J=7 Hz, ^{3}Ala NH), and 7.17—7.30 (5 H, m, Ph). Found: m/z 422.2301. Calcd for $C_{21}H_{32}N_3O_6$: MH^+, 422.2291.

Boc–Phe–Ala–OMe: 84%, white crystals; mp 107—109 °C; ^{1}H NMR ($CDCl_3$) δ=1.35 (3 H, d, J=7 Hz, Ala Me), 1.41 (9 H, s, *t*-Bu), 3.02—3.09 (2 H, m, Phe β-H), 3.71 (3 H, s, OMe), 4.34 (1 H, br, Phe α-H), 4.52 (1 H, quintet, J=7 Hz, Ala α-H), 4.96 (1 H, br, Phe NH), 6.37 (1 H, br-d, J=7.5 Hz, Ala NH), and 7.20—7.36 (5 H, m, Ph). Found: m/z 351.2038. Calcd for $C_{18}H_{17}N_2O_5$: MH^+, 351.1920.

Boc–Phe$_2$–Ala–OMe: 84%, white crystals; mp 153—155 °C; ^{1}H NMR ($CDCl_3$) δ=1.31 (3 H, d, J=7 Hz, Ala Me), 1.38 (9 H, s, *t*-Bu), 2.88—3.17 (4 H, m, Phe β-H), 3.71 (3 H, s, OMe), 4.30 (1 H, br, ^{1}Phe α-H), 4.45 (1 H, quintet, J=7 Hz, Ala α-H), 4.62 (1 H, br, ^{2}Phe α-H), 4.80 (1 H, br, ^{1}Phe NH), 6.39 (2 H, br, ^{2}Phe+Ala NH), and 7.08—7.31 (10 H, m, Ph). Found: m/z 498.2682. Calcd for $C_{27}H_{36}N_3O_6$: MH^+, 498.2604.

Boc–Phe$_2$–OMe: 92%, white crystals; mp 124—125 °C; ^{1}H NMR ($CDCl_3$) δ=1.40 (9 H, s, *t*-Bu), 2.99—3.10 (4 H, m, Phe β-H), 3.67 (3 H, s, OMe), 4.31 (1 H, br, ^{1}Phe α-H), 4.78 (1 H, dt, J=6 and 7 Hz, ^{2}Phe α-H), 4.92 (1 H, br, ^{1}Phe NH), 6.26 (1 H, br, ^{2}Phe NH), and 6.97—7.30 (10 H, m, Ph). Found: m/z 427.2284. Calcd for $C_{24}H_{31}N_2O_5$: MH^+, 427.2233.

Boc–Phe$_3$–OMe: 94%, white crystals; mp 174—177 °C; ^{1}H NMR ($CDCl_3$) δ=1.37 (9 H, s, *t*-Bu), 2.90—3.08 (6 H, m, Phe β-H), 3.66 (3 H, s, OMe), 4.29 (1 H, br, ^{1}Phe α-H), 4.53 (1 H, dt, J=6 and 7.5 Hz, ^{3}Phe α-H), 4.55 (1 H, dt, J=6.5 and 7.5 Hz, ^{2}Phe α-H), 4.83 (1 H, br, ^{1}Phe NH), 6.20 (1 H, br, ^{2}Phe NH), 6.76 (1 H, br, ^{3}Phe NH), and 6.97—7.30 (15 H, m, Ph). Found: m/z 574.3056. Calcd for $C_{33}H_{40}N_3O_6$: MH^+, 574.2917.

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alanine Methyl Ester (H_2P–Ala–OMe): 65%, purple powder; mp 70—73 °C; UV (CH_2Cl_2) λ_{max} 412, 510, 544, 576, 629, and 661 nm; Fluorescence (CH_2Cl_2) λ_{max} 634, 670, and 698 nm; ^{1}H NMR ($CDCl_3$) $\delta=-1.97$ (2 H, br, NH), −0.97 (3 H, d, J=7.5 Hz, Ala Me), 1.1—1.2 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.49+1.51 (9 H+9 H, s+s, *t*-Bu), 1.84 (12 H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.18 (3 H, s, OMe), 2.8—3.0 (8 H, m, $C\underline{H}_2CH_3$), 3.26 (1 H, quintet, J=7.5 Hz, Ala α-H), 3.9—4.0 (8 H, m, $C\underline{H}_2CH_3$), 4.36+4.46 (1 H+1 H, d, J=15 Hz, OCH_2CO), 4.72 (1 H, d, J=7.5 Hz, Ala NH), 7.19 (1 H, d, J=7.5 Hz, 5-phenyl 3-H), 7.44 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (1 H, dt, J=1.5 and 7.5 Hz, 5-phenyl 4-H), 7.84 (1 H, t, J=1.5 Hz, 15-phenyl 4-H), 7.98+8.04 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.20 (1 H, dd, J=1.5 and 7.5 Hz, 5-phenyl 6-H), and 10.19+10.20 (1 H+1 H, s+s, *meso*-H); MS m/z 958 (MH^+), 898 (M−CO_2Me), and 797 (898−Ala−OCH_2).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alanine Methyl Ester Zinc Complex (ZnP–Ala–OMe): Reddish purple solids; mp 56—58 °C; CD (CH_2Cl_2) 424 nm (Δε+14); ^{1}H NMR ($CDCl_3$) $\delta=-0.57$ (3 H, d, J=7 Hz, Ala Me), 0.44 (3 H, s, OMe), 0.98+1.04+1.15+1.23 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.49+1.51 (9 H+9 H, s+s, *t*-Bu), 1.79+1.82+1.85+1.88 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.56—2.76 (6 H, m, $C\underline{H}_2CH_3$), 2.73 (1 H, quintet, J=7 Hz, Ala α-H), 3.02—3.11 (2 H, m, $C\underline{H}_2CH_3$), 3.60 (1 H, d, J=7.5 Hz, Ala NH), 3.86—4.04 (8 H, m, $C\underline{H}_2CH_3$), 4.11+4.17 (1 H+1 H, d, J=14 Hz, OCH_2CO), 7.06 (1 H, d, J=7.5 Hz, 5-phenyl 3-H), 7.51 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.79 (1 H, t, J=2 Hz, 15-phenyl 4-H), 7.83 (1 H, dt, J=2 and 8 Hz, 5-phenyl 4-H), 7.84+8.11 (1 H+1 H, t+t, J=2 Hz, 15-phenyl 2,6-H), 8.64 (1 H, dd, J=2 and 8 Hz, 5-phenyl 6-H), and 10.08+10.16 (1 H+1 H, s+s, *meso*-H); MS m/z 1020 (MH^+, for ^{64}Zn).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alaninyl-L-alanine Methyl Ester (H_2P–Ala_2–OMe): 61%, purple powder; mp 73—75 °C; UV (CH_2Cl_2) λ_{max} 412, 510, 544, 577, 628, and 655 nm; Fluorescence (CH_2Cl_2) λ_{max} 632, 663 (sh), and 698 nm; ^{1}H NMR ($CDCl_3$) $\delta=-2.0$ (2 H, br, NH), −1.14 (3 H, d, J=7 Hz, ^{1}Ala Me), 0.49 (3 H, d, J=7 Hz, ^{2}Ala Me), 1.12—1.18 (12 H, m, $CH_2C\underline{H}_3$), 1.49+1.51 (9 H+9 H, s+s, *t*-Bu), 1.85 (12 H, m, $CH_2C\underline{H}_3$), 2.31—3.06 (8 H, m, $C\underline{H}_2CH_3$), 3.18 (1 H, quintet, J=7 Hz, ^{1}Ala α-H), 3.47 (3 H, s, OMe), 3.64 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 3.94—4.09 (8 H, m, $C\underline{H}_2CH_3$), 4.35+4.47 (1 H+1 H, d, J=15 Hz, OCH_2CO), 4.71 (1 H, d, J=7 Hz, ^{1}Ala NH), 5.56 (1 H, d, J=7 Hz, ^{2}Ala NH), 7.20 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.46 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (1 H+1 H, m, 5-phenyl 4-H+15-phenyl 4-H), 7.99+8.05 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.24 (1 H, dd, J=1.5 and 8 Hz, 5-phenyl 6-H), and 10.21 (2 H, s, *meso*-H); MS m/z 1029 (MH^+), 969 (M−CO_2Me), 898 (969−Ala), and 797 (898−Ala−OCH_2).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alaninyl-L-alanine Methyl Ester Zinc Complex (ZnP–Ala_2–OMe): Reddish purple solids; mp 85—87 °C; CD (CH_2Cl_2) 422 nm (Δε+22); ^{1}H NMR ($CDCl_3$) $\delta=-0.93$ (3 H, d, J=7.5 Hz, ^{1}Ala Me), −0.86 (3 H, d, J=7.5 Hz, ^{2}Ala Me), 0.11 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 0.87—1.25 (12 H, m, $CH_2C\underline{H}_3$), 1.41+1.59 (9 H+9 H, s+s, *t*-Bu), 1.70—1.88 (12 H, m, $CH_2C\underline{H}_3$), 2.47—3.25 (8 H, m, $C\underline{H}_2CH_3$), 2.75 (1 H, quintet, J=7 Hz, ^{1}Ala α-H), 3.35 (3 H, s, OMe), 3.53 (1 H, d, J=8 Hz, ^{1}Ala NH), 3.86—4.10 (8 H, m, $C\underline{H}_2CH_3$), 4.13+4.18 (1 H+1 H, d, J=14 Hz, OCH_2CO), 4.45 (1 H, d, J=6 Hz, ^{2}Ala NH), 7.09 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.49 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.74 (1 H, t, J=1.5 Hz, 15-phenyl 4-H), 7.82 (1 H, dt, J=1.5 and 7.5 Hz, 5-phenyl 4-H), 7.82+8.31 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.60 (1 H, dd, J=1.5 and 8 Hz, 5-phenyl 6-H), and 10.05+10.11 (1 H+1 H, s+s, *meso*-H); MS m/z 1091 (MH^+, for ^{64}Zn).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alaninyl-L-alaninyl-L-alanine Methyl Ester (H_2P–Ala_3–OMe): 74%, purple solids; mp 103—105 °C; UV (CH_2Cl_2) λ_{max} 411, 510, 544, 577, 628, and 652 nm; Fluorescence (CH_2Cl_2) λ_{max} 631, 664 (sh), and 698 nm; ^{1}H NMR ($CDCl_3$) $\delta=-2.05+-1.97$ (1 H+1 H, br+br, NH), −1.41 (3 H, d, J=7.5 Hz, ^{1}Ala Me), 0.55 (3 H, d, J=7.5 Hz, ^{2}Ala Me), 1.11—1.20 (12 H, m, $CH_2C\underline{H}_3$), 1.15 (3 H, d, J=7.5 Hz, ^{3}Ala Me), 1.49+1.52 (9 H+9 H, s+s, *t*-Bu), 1.84—1.88 (12 H, m, $CH_2C\underline{H}_3$), 2.77—2.85+2.98—3.06 (8 H+1 H, m, $C\underline{H}_2CH_3$+^{1}Ala α-H), 3.59 (3 H, s, OMe), 3.63 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 3.94—4.07 (8 H, m, $C\underline{H}_2CH_3$), 4.24 (1 H, quintet, J=7.5 Hz, ^{3}Ala α-H), 4.35+4.44 (1 H+1 H, d, J=15 Hz, OCH_2CO), 4.55 (1 H, d, J=7 Hz, ^{1}Ala NH), 5.30 (1 H, d, J=7.5 Hz, ^{2}Ala NH), 6.21 (1 H, d, J=7.5 Hz, ^{3}Ala NH), 7.20 (1 H, d, J=7.5 Hz, 5-phenyl 3-H), 7.48 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.85 (1 H, dt, J=1.5 and 7.5 Hz, 5-phenyl 4-H), 7.85 (1 H, t, J=1.5 Hz, 15-phenyl 4-H), 7.98+8.07 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.26 (1 H, dd, J=1.5 and 7.5 Hz, 5-phenyl 6-H), and 10.21+10.22 (1 H+1 H, s+s, *meso*-H); MS m/z 1100 (MH^+), 1040 (M−CO_2Me), 969 (1040−Ala), 898 (969−Ala), and 797 (898−Ala−OCH_2).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-alaninyl-L-alaninyl-L-alanine Methyl Ester Zinc Complex (ZnP–Ala_3–OMe): Reddish purple solids; mp 117—119 °C; CD (CH_2Cl_2) 413 (Δε−4) and 422 nm (+24); ^{1}H NMR ($CDCl_3$) $\delta=-0.66$ (3 H, d, J=7 Hz, ^{1}Ala Me), −0.59 (3 H, d, J=7 Hz, ^{2}Ala Me), 0.60 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 0.84 (3 H, d, J=7 Hz, ^{3}Ala Me), 0.97—1.13 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.43+1.54 (9 H+9 H, s+s, *t*-Bu), 1.77—1.90 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.52—2.81 (6 H, m $C\underline{H}_2CH_3$), 2.85 (1 H, quintet, J=7 Hz, ^{1}Ala α-H), 2.90—3.06 (2 H, m, $C\underline{H}_2CH_3$), 3.14 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 3.59 (3 H, s, OMe), 3.63—4.05 (8 H, m, $C\underline{H}_2CH_3$), 4.04 (1 H, d, J=7 Hz, ^{1}Ala NH), 4.17+4.32 (1 H+1 H, d, J=14 Hz, OCH_2CO), 4.22 (1 H, d, J=7 Hz, ^{2}Ala NH), 4.48 (1 H, d, J=7 Hz, ^{3}Ala NH), 7.16 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.48 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (2 H, m, 5-phenyl 4-H+15-phenyl 4-H), 7.83+8.13 (1 H+1 H, s+s, 15-phenyl 2,6-H), 8.44 (1 H, dd, J=1.5 and 7.5 Hz, 5-phenyl 6-H), and 10.07+10.11 (1 H+1 H, s+s, *meso*-H); MS m/z 1161 (M^+, for ^{64}Zn).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-alanine Methyl Ester (H_2P–Phe–Ala_2–

OMe): 85%, purple solids; mp 94—97 °C; ^{1}H NMR ($CDCl_3$) δ=−2.02+−1.91 (1 H+1 H, br+br, NH), −0.44 (1 H, dd, J=8 and 14 Hz, ^{1}Phe β-H), 0.47 (1 H, dd, J=7 and 14 Hz, ^{1}Phe β-H), 0.83 (3 H, d, J=7 Hz, ^{2}Ala Me), 1.09—1.18 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.13 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.48+1.52 (9 H+9 H, s+s, t-Bu), 1.80—1.89 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.72—3.13 (8 H, m, $C\underline{H}_2CH_3$), 3.19 (1 H, dt, J=8 and 7 Hz, ^{1}Phe α-H), 3.64 (3 H, s, OMe), 3.82 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 3.94—4.16 (8 H, m, $C\underline{H}_2CH_3$), 4.27 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 4.25+4.44 (1 H+1 H, d, J=15 Hz, OCH_2CO), 4.62 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 4.77 (1 H, d, J=7 Hz, ^{1}Phe NH), 5.57 (1 H, d, J=7.5 Hz, ^{2}Ala NH), 5.76 (2 H, t, J=7.5 Hz, ^{1}Phe 3,5-H), 6.24 (1 H, d, J=7.5 Hz, ^{3}Ala NH), 6.28 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 7.16 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.47 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (1 H, t, J=7.5 Hz, 5-phenyl 4-H), 7.83 (1 H, s, 15-phenyl 4-H), 7.94+8.00 (1 H+1 H, s+s, 15-phenyl 2,6-H), 8.25 (1 H, d, J=7.5 Hz, 5-phenyl 6-H), and 10.20+10.26 (1 H+1 H, s+s, *meso*-H); MS m/z 1177 (MH^+), 1116 ($M-CO_2Me$), 1045 (1116−Ala), 974 (1045−Ala), and 797 (974−Phe−OCH_2).

2- [15- (3, 5- Di- *t*- butylphenyl)- 2, 3, 7, 8, 12, 13, 17, 18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-alanyl-L-alanine Methyl Ester Zinc Complex (ZnP−Phe−Ala$_2$−OMe): Reddish purple solids; mp 128—130 °C; CD (CH_2Cl_2) 415 ($\Delta\varepsilon$−12) and 423 nm (+21); ^{1}H NMR ($CDCl_3$) δ=−0.93 (1 H, dd, J=10 and 13 Hz, ^{1}Phe β-H), −0.84 (3 H, d, J=7 Hz, ^{2}Ala Me), 0.00 (1 H, quintet, J=7 Hz, ^{2}Ala α-H), 0.77 (1 H, dd, J=6 and 13 Hz,^{1}Phe β-H), 0.97 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.19 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.49+1.52 (9 H+9 H, s+s, t-Bu), 1.68+1.79+1.87+1.93 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.45—2.65, 2.76—2.88, 3.05—3.20 (8 H, m, $C\underline{H}_2CH_3$), 2.59 (1 H, dt, J=6 and 9 Hz, ^{1}Phe α-H), 3.46 (1 H, d, J=7 Hz, ^{1}Phe NH), 3.59 (3 H, s, OMe), 3.68 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 3.84—4.09 (8 H, m, $C\underline{H}_2CH_3$), 4.10+4.17 (1 H+1 H, d, J=15 Hz, OCH_2CO), 4.25 (1 H, d, J=6.5 Hz, ^{2}Ala NH), 4.47 (1 H, d, J=7 Hz, ^{3}Ala NH), 5.01 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 6.57 (2 H, t, J=7.5 Hz, ^{1}Phe 3,5-H), 6.66 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 7.10 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.52 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (1 H, t, J=7.5 Hz, 5-phenyl 4-H), 7.87 (1 H, s, 15-phenyl 4-H), 7.95+8.05 (1 H+1 H, s+s, 15-phenyl 2,6-H), 8.64 (1 H, d, J=7.5 Hz, 5-phenyl 6-H), and 10.13+10.16 (1 H+1 H, s+s, *meso*-H); MS m/z 1237 (M^+, for ^{64}Zn).

2- [15- (3, 5- Di- *t*- butylphenyl)- 2, 3, 7, 8, 12, 13, 17, 18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-phenylalaninyl-L-alanine Methyl Ester (H_2P−Phe$_2$−Ala−OMe): 92%, purple solids; mp 82—85 °C; ^{1}H NMR ($CDCl_3$) δ=−2.01+−1.89 (1 H+1 H, br+br, NH), −0.36 (1 H, dd, J=8 and 14 Hz, ^{1}Phe β-H), 0.34 (1 H, dd, J=6 and 14 Hz, ^{1}Phe β-H), 1.05—1.17 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.09 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.47+1.51 (9 H+9 H, s+s, t-Bu), 1.80—1.88 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.47 (1 H, dd, J=6 and 14 Hz, ^{2}Phe β-H), 2.55 (1 H, dd, J=7 and 14 Hz, ^{2}Phe β-H), 2.72—2.94, 3.03—3.09 (8 H, m, $C\underline{H}_2CH_3$), 3.22 (1 H, dt, J=8 and 6 Hz, ^{1}Phe α-H), 3.60 (3 H, s, OMe), 3.89—4.14 (8 H, m, $C\underline{H}_2CH_3$), 4.07 (1H, dt, J=7 and 6 Hz, ^{2}Phe α-H), 4.21 (2 H, s, OCH_2CO), 4.25 (1 H, quintet, J=7.5 Hz, ^{3}Ala α-H), 4.45 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 4.76 (1 H, d, J=6 Hz, ^{1}Phe NH), 5.63 (2 H, t, J=7.5 Hz, ^{1}Phe 3,5-H), 5.74 (1 H, d, J=7.5 Hz, ^{2}Phe NH), 6.13 (1 H, d, J=7.5 Hz, ^{3}Ala NH), 6.21 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 6.66 (2 H, d, J=7.5 Hz, ^{2}Phe 2,6-H), 6.97 (2 H, t, J=7.5 Hz, ^{2}Phe 3,5-H), 7.04 (1 H, t, J=7.5 Hz, ^{2}Phe 4-H), 7.13 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.47 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.83 (1 H, t, J=1.5 Hz, 15-phenyl 4-H), 7.85 (1 H, dt, J=1.5 and 8 Hz, 5-phenyl 4-H), 7.93+8.00 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2,6-H), 8.22 (1 H, dd, J=1.5 and 7.5 Hz, 5-phenyl 6-H), and 10.19+10.25 (1 H+1 H, s+s, *meso*-H); MS m/z 1253 (MH^+), 1192 ($M-CO_2Me$), 1121 (1192−Ala), 974 (1121−Phe), and 797 (974−Phe−OCH_2).

2- [15- (3, 5- Di- *t*- butylphenyl)- 2, 3, 7, 8, 12, 13, 17, 18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-phenylalaninyl-L-alanine Methyl Ester Zinc Complex (ZnP−Phe$_2$−Ala−OMe): Reddish purple solids; mp 97—100 °C; CD (CH_2Cl_2) 416 ($\Delta\varepsilon$−23) and 424 nm (+15); ^{1}H NMR ($CDCl_3$) δ=−1.03 (1 H, dd, J=10 and 13 Hz, ^{1}Phe β-H), −0.47 (1 H, dd, J=6.5 and 14 Hz, ^{2}Phe β-H), 0.64 (1 H, dd, J=6 and 14 Hz, ^{1}Phe β-H), 0.83 (1 H, dt, J=2.5 and 6.5 Hz, ^{2}Phe α-H), 0.99 (3 H, d, J=7 Hz, ^{3}Ala Me), 1.17—1.25 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.28 (1 H, dd, J=2.5 and 14 Hz, ^{2}Phe β-H), 1.46+1.54 (9 H+9 H, s+s, t-Bu), 1.62+1.66+1.78+1.93 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.45—2.95, 3.05—3.13 (8 H, m, $C\underline{H}_2CH_3$), 2.49 (1 H, dt, J=5.5 and 9.5 Hz, ^{1}Phe α-H), 3.46 (1 H, d, J=9.5 Hz, ^{1}Phe NH), 3.62 (3 H, s, OMe), 3.85 (1 H, quintet, J=7 Hz, ^{3}Ala α-H), 3.80—4.07 (8 H, m, $C\underline{H}_2CH_3$), 4.10+4.15 (1 H+1 H, d+d, J=14 Hz, OCH_2CO), 4.26 (1 H, d, J=6.5 Hz, ^{2}Phe NH), 4.84 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 4.91 (1 H, d, J=7.5 Hz, ^{3}Ala NH), 5.21 (2 H, d, J=7.5 Hz, ^{2}Phe 2,6-H), 6.46 (2 H, t, t=7.5 Hz, ^{1}Phe 3,5-H), 6.59 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 6.61 (2 H, t, J=7.5 Hz, ^{2}Phe 3,5-H), 6.78 (1 H, t, J=7.5 Hz, ^{2}Phe 4-H), 7.12 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.55 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.80 (1 H, s, 15-phenyl 4-H), 7.86 (1 H, dt, J=1.5 and 8 Hz, 5-phenyl 4-H), 7.87+8.23 (1 H+1 H, s+s, 15-phenyl 2,6-H), 8.68 (1 H, dd, J=1.5 and 7.5 Hz, 5-phenyl 6-H), and 10.12+10.16 (1 H+1 H, s+s, *meso*-H); MS m/z 1313 (M^+, for ^{64}Zn).

2- [15- (3, 5- Di- *t*- butylphenyl)- 2, 3, 7, 8, 12, 13, 17, 18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-phenylalaninyl-L-phenylalanine Methyl Ester (H_2P−Phe$_3$−OMe): 87%, purple solids; mp 73—76 °C; ^{1}H NMR ($CDCl_3$) δ=−2.00+−1.89 (1 H+1 H, br+br, NH), −0.31 (1 H, dd, J=8 and 14 Hz, ^{1}Phe β-H), 0.55 (1 H, dd, J=6.5 and 14 Hz, ^{1}Phe β-H), 1.03—1.14 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.47+1.51 (9 H+9 H, s+s, t-Bu), 1.53—1.86 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.53 (2 H, d, J=7 Hz, ^{2}Phe β-H), 2.76 (2 H, d, J=7 Hz, ^{3}Phe β-H), 2.72—2.89, 3.00—3.06 (8 H, m, $C\underline{H}_2CH_3$), 3.24 (1 H, dt, J=8 and 6 Hz, ^{1}Phe α-H), 3.57 (3 H, s, OMe), 3.85—4.15 (8 H, m, $C\underline{H}_2CH_3$), 4.13 (1 H, dt, J=8 and 7 Hz, ^{2}Phe α-H), 4.17 (2 H, s, OCH_2CO), 4.38 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 4.54 (1 H, dt, J=6.5 and 7 Hz, ^{3}Phe α-H), 4.82 (1 H, d, J=6.5 Hz, ^{1}Phe NH), 5.51 (2 H, t, J=7.5 Hz, ^{1}Phe 3, 5-H), 5.92 (1 H, d, J=8 Hz, ^{2}Phe NH), 6.11 (1 H, d, J=7.5 Hz, ^{3}Phe NH), 6.14 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 6.72 (2 H, d, J=7.5 Hz, ^{2}Phe 2,6-H), 6.8+7.0 (2 H+6 H, m, ^{2}Phe 3,4,5-H, ^{3}Phe Ph), 7.11 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.45 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.82 (1 H, t, J=1.5 Hz, 15-phenyl 4-H), 7.84 (1 H, dt, J=2 and 8 Hz, 5-phenyl 4-H), 7.92+8.01 (1 H+1 H, t+t, J=1.5 Hz, 15-phenyl 2, 6-H), 8.18 (1 H, dd, J=2 and 7.5 Hz, 5-phenyl 6-H), and

10.19+10.25 (1 H+1 H, s+s, *meso*-H); MS *m/z* 1329 (MH^+), 1268 (M−CO_2Me), 1121 (1268−Phe), 974 (1121−Phe), and 797 (974−Phe−OCH_2).

2-[15-(3,5-Di-*t*-butylphenyl)-2,3,7,8,12,13,17,18-octaethyl-5-porphyrinyl]phenoxyacetyl-L-phenylalaninyl-L-phenylalaninyl-L-phenylalanine Methyl Ester Zinc Complex (ZnP–Phe$_3$–OMe): Reddish purple solids; mp 77—79 °C; CD (CH_2Cl_2) 415 ($\Delta\varepsilon$ −17) and 423 nm (+11); ^{1}H NMR ($CDCl_3$) δ = −0.51 (1 H, dd, J=9 and 13 Hz, ^{1}Phe β-H), 0.16 (1 H, dd, J=6.5 and 14 Hz, ^{2}Phe β-H), 0.50 (1 H, dd, J=7 and 13 Hz, ^{1}Phe β-H), 1.11+1.13+1.14+1.15 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.18 (1 H, dt, J=4 and 6.5 Hz, ^{2}Phe α-H), 1.49+1.50 (9 H+9 H, s+s, *t*-Bu), 1.57 (1 H, dd, J=4 and 14 Hz, ^{2}Phe β-H), 1.68+1.70+1.78+1.88 (12 H, t×4, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.50 (2 H, dd, J=6.5 and 14 Hz, ^{3}Phe β-H), 2.56—2.89, 2.99—3.05 (8 H, m, $C\underline{H}_2CH_3$), 2.67 (1 H, dt, J=7 and 9 Hz, ^{1}Phe α-H), 3.52 (3 H, s, OMe), 3.80—4.07 (8 H, m, $C\underline{H}_2CH_3$), 3.82 (1 H, d, J=9 Hz, ^{1}Phe NH), 3.98 (1 H, dt, J=8, 7 Hz, ^{3}Phe α-H), 4.14+4.19 (1 H+1 H, d+d, J=14 Hz, OCH_2CO), 4.38 (1 H, d, J=6.5 Hz, ^{2}Phe NH), 4.90 (1 H, d, J=7.5 Hz, ^{3}Ala NH), 4.97 (2 H, d, J=7.5 Hz, ^{1}Phe 2,6-H), 5.59 (2 H, d, J=7.5 Hz, ^{2}Phe 2,6-H), 6.31 (2 H, t, J=7.5 Hz, ^{1}Phe 3,5-H), 6.48 (1 H, t, J=7.5 Hz, ^{1}Phe 4-H), 6.51 (2 H, t, J=7.5 Hz, ^{3}Phe 2,6-H), 6.73 (2 H, t, J=7.5 Hz, ^{2}Phe 3,5-H), 6.86 (1 H, t, J=7.5 Hz, ^{2}Phe 4-H), 6.89 (2 H, t, J=7.5 Hz, ^{3}Phe 3,5-H), 6.97 (1 H, t, J=7.5 Hz, ^{3}Phe 4-H), 7.13 (1 H, d, J=8 Hz, 5-phenyl 3-H), 7.51 (1 H, t, J=7.5 Hz, 5-phenyl 5-H), 7.85 (1 H, s, 15-phenyl 4-H), 7.85 (1 H, t, J=8 Hz, 5-phenyl 4-H), 7.97+8.07 (1 H+1 H, s+s, 15-phenyl 2,6-H), 8.53 (1 H, d, J=7.5 Hz, 5-phenyl 6-H), and 10.12+10.15 (1 H+1 H, s+s, *meso*-H); MS *m/z* 1390 (MH^+, for ^{64}Zn).

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5) The following abbreviations are used in this paper; Boc = *t*-butoxycarbonyl, DCC = dicyclohexylcarbodiimide, BOP = (1-benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate, and AA = amino acid or oligopeptide with L-configuration.

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