Synthesis of potential antitumor agents, dimeric and trimeric chlorins, from methylpheophorbide *a*

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A series of dimeric and trimeric chlorins were synthesized from methylpheophorbide *a*. They are potential photosensitizers for photodynamic therapy in oncology. The macrocycles were conjugated due to the formation of ester and amide bonds. The carboxy groups were activated and catalytic transesterification was carried out to form the ester bond. The amide bond was formed using carboxy group activation; in several cases, amidation of the ester group in position 13(2) of the exocycle of methylpheophorbide *a* was carried out, which does not require activation.

Key words: methylpheophorbide *a*, dimers, trimers, chlorin e_6, oligochlorins.

Synthesis of potential photosensitizers (PS) for photodynamic therapy (PDT) in oncology is a topical direction of the chemistry of tetrapyrrole macrocycles. The known drug Photofrin II, which exerts a photocytotoxic effect on cancer cells, is a mixture of porphyrin dimers and trimers.[1] It is reasonable to expect that natural dimeric and trimeric porphyrins possess similar biological activity, and the activity of oligoporphyrin can depend strongly on the mode of conjugation of macrocycles. Dimeric porphyrins are also used for modeling various biological processes.[2,3] In connection with the aforesaid, it seems interesting to develop methods for synthesis of dimers and trimers from chlorophyll derivatives. In the present work, we synthesized a series of chlorin dimers, whose macrocycles are linked by bridges of various length. The macrocycles were conjugated due to the formation of the amide or ester bond. One of the variants of macrocycle conjugation modes during preparation of dimers was used for the synthesis of trimeric chlorins.

Results and Discussion

In Scheme 1, the synthesis based on methylpheophorbide *a* (**1**) of analogs of chlorophyll *a* **2**—**6**, **10**, **11**, and **13** containing carboxy, hydroxy, and amino groups is shown. The latter were used for the preparation of ensembles containing two and three chlorin residues: dimeric and trimeric chlorins. In the synthesis of dimers **14**—**17** (Scheme 2), the macrocycles were conjugated by amide bond formation due to the interaction of the amino group of one chlorin with the activated carboxy group of another chlorin (activation by formation of mixed anhydride).

In the synthesis of dimers **14**—**16**, the methylpropionate substituent of methylpheophorbide *a* (**1**) was hydrolyzed to form the carboxy group, and the corresponding pyro derivative **6** was obtained by reflux of pheophorbide *a* **5** in collidine (see Scheme 1). In the synthesis of dimer **17**, more remote carboxy group was inserted by the treatment of aminochlorin **3** with succinic anhydride. The carboxy group of the synthesized chlorins was activated by the addition of di(*tert*-butyl) dicarbonate.

The ^{1}H NMR spectrum of dimer **15** contains signals of two porphyrin macrocycles. In addition, it exhibits a broadened multiplet corresponding to protons of two amide groups, one of which was formed due to the interaction of pyropheophorbide *a* (**6**) with 5,17-dimethyl chlorin e_6 13-*N*-(6-aminohexyl)amide (**4**). Similar specific features are observed in the spectra of dimers **14** and **16**. The peaks of the corresponding molecular ions are detected in the mass spectra of dimers **14**—**16**.

The MALDI mass spectrum of dimer **17** exhibits peaks attributed to its molecular ion, protonated molecular ion, and the adduct of compound **17** with the sodium cation. In the ^{1}H NMR spectrum of dimer **17**, the signals of two macrocycles in the molecule coincide due to symmetry of its structure.

In several cases, the amide bond was formed without the use of activating agents. It is known that reflux of methylpheophorbide *a* (**1**) with primary and secondary aliphatic amines results in the amidation of the ester group

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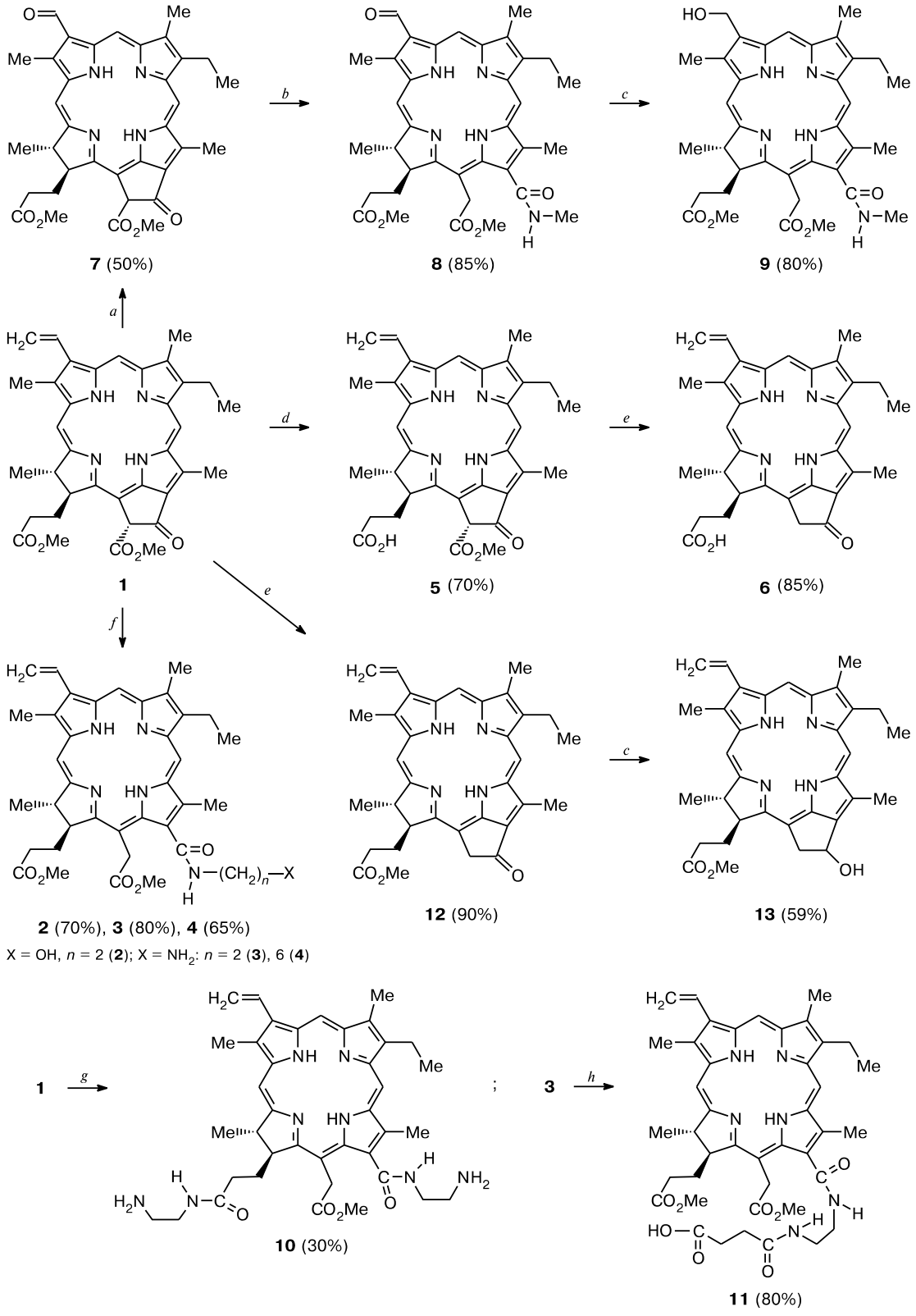
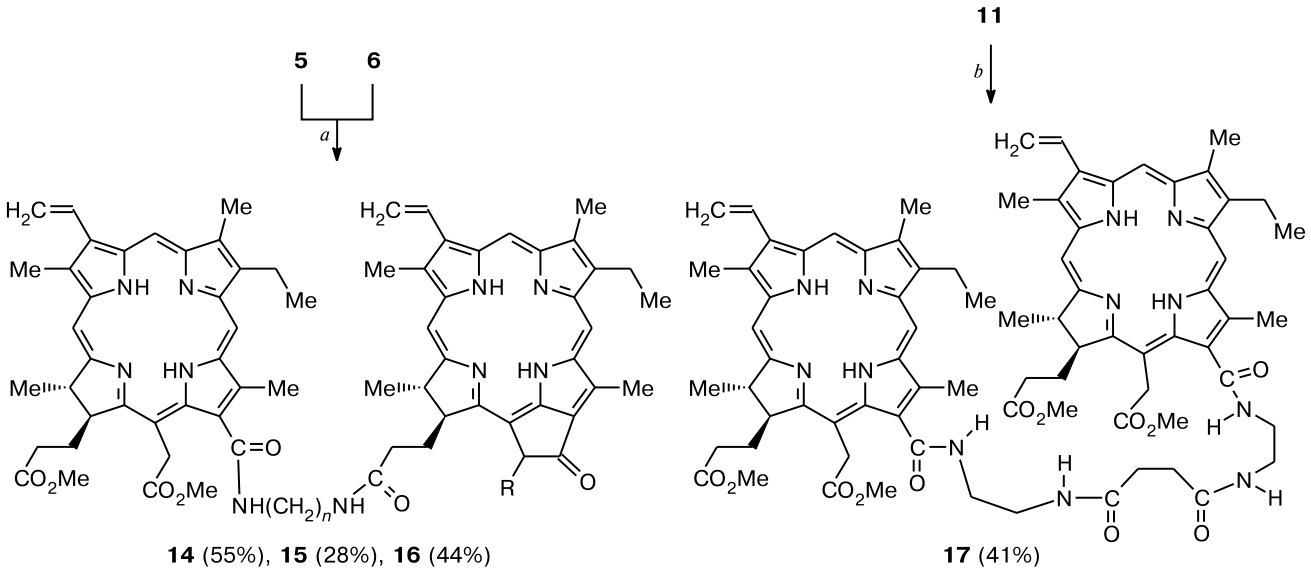
Scheme 1



Reagents and conditions: *a*. $NaIO_4$, OsO_4, 95% AcOH, THF, 3 h, ~20 °C; *b*. $MeNH_2$, THF, 1 h, ~20 °C; *c*. $NaBH_4$, THF, 24 h, ~20 °C; *d*. HCl, H_2O, acetone, 24 h, ~20 °C; *e*. Collidine, reflux, 40 min; *f*. Synthesis of **2**: ethanolamine, chloroform, 4 h, ~20 °C; synthesis of **3**: ethylenediamine, chloroform, 3 h, ~20 °C; synthesis of **4**: hexamethylenediamine, THF, 4 h, ~20 °C; *g*. ethylenediamine (2 mol), 22 h, ~20 °C; *h*. Succinic anhydride, CH_2Cl_2, 2 h, ~20 °C.

Scheme 2



R = H: *n* = 2 (**14**), 6 (**15**); R = CO_2Me, *n* = 2 (**16**)

Reagents and conditions: *a*. (1) Di(*tert*-butyl) dicarbonate, dichloromethane—pyridine, 15 min, 0 °C; (2) **3** or **4**, 1 h, ~20 °C; *b*. (1) Di(*tert*-butyl) dicarbonate, dichloromethane—pyridine, 15 min, 0 °C; (2) **3**, 1 h, ~20 °C.

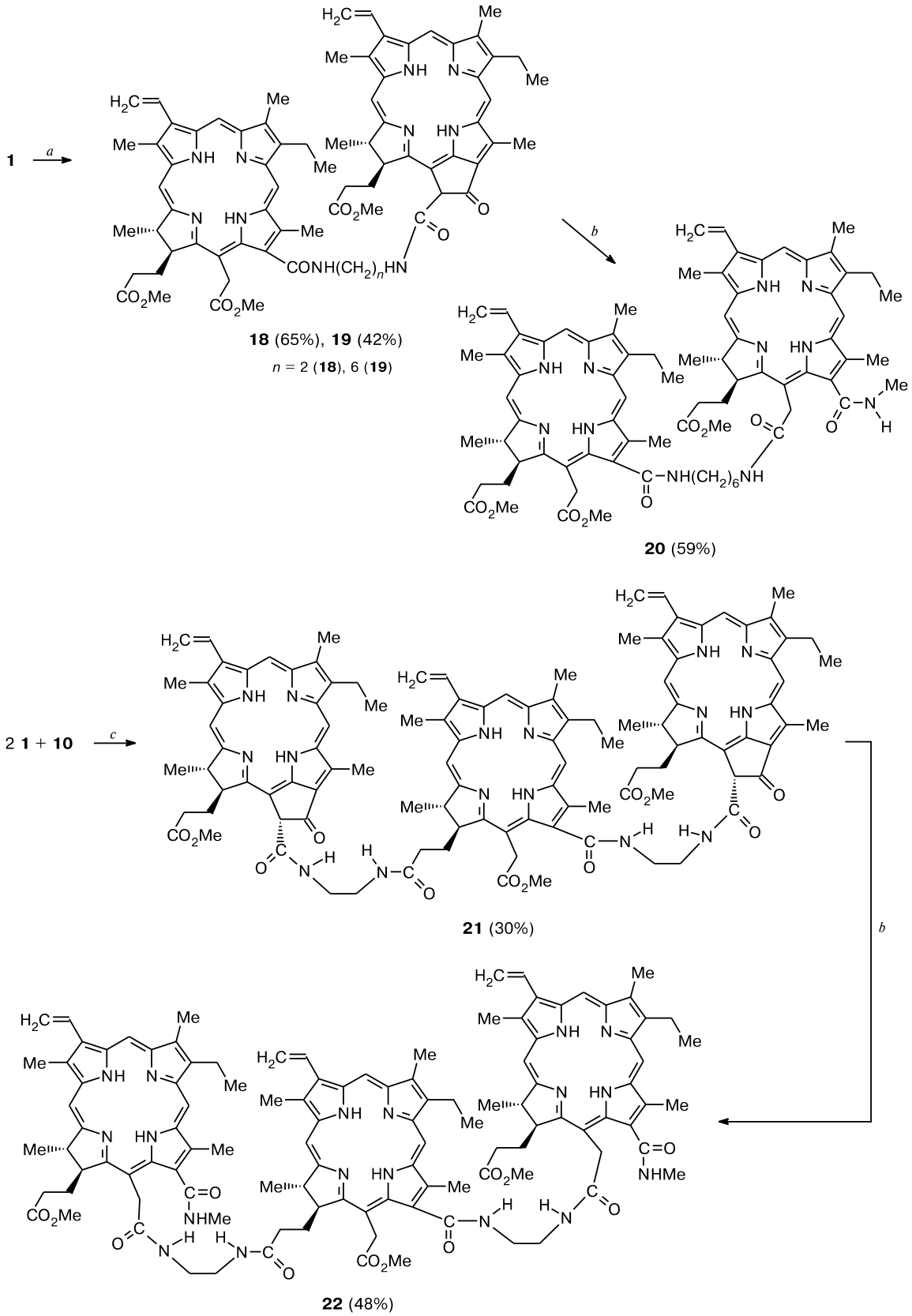
of the exocycle to form the corresponding 13(2)-amides.[4] No activation is required for this reaction to occur but can be used for the conjugation of large fragments.[5] This was accomplished in this work for the synthesis of dimeric and trimeric chlorins (Scheme 3). In the synthesis of dimeric chlorins **18** and **19**, for amidation it is enough to reflux compound **1** in toluene with the corresponding aminochlorins **3** or **4** for 1 h. For the synthesis of trimer **21** by the interaction of diaminochlorin **10** with a twofold molar excess of compound **1**, it is needed to elongate the reaction duration to 10 h. However, despite this, the yield of trimer **21** (30%) can be considered satisfactory.

The structures of the synthesized oligochlorins were confirmed by the data of ^{1}H NMR spectroscopy and mass spectrometry. The mass spectra of dimers **18** and **19** and trimer **21** exhibit peaks of the corresponding molecular ions. The ^{1}H NMR spectrum of chlorin dimer **18** contains signals of two porphyrin macrocycles and an additional broadened triplet appears at δ 7.76, which corresponds to the proton of the amide group formed by the amidation of the ester group of methylpheophorbide *a* (**1**) with aminochlorin **3**. In addition, the singlet signal of the proton in position 13(2) of the exocycle, which is present in the ^{1}H NMR spectrum of the initial methylpheophorbide *a* (δ 6.17), is also observed in the spectrum of the synthesized dimer **18**. This proves that no exocycle opening occurred. No singlet signal at δ 3.80 is observed in the ^{1}H NMR spectrum of dimer **18**, confirming that this was the ester group of the exocycle to which amidation occurred. Similar changes were observed in the ^{1}H NMR spectra of dimer **19** and trimer **21**.

The exocycle of the phorbine fragments of the synthesized dimers and trimers can be opened by the action of amines. This can be used for the transformation of the phorbine fragments into chlorin moieties. We performed this transformation by the action of methylamine in aqueous THF on dimer **19** and trimer **21**. The ^{1}H NMR spectrum of dimer **20** contains an additional (compared to the spectrum of the initial compound **19**) broadened multiplet (δ 6.19—6.13) corresponding to the proton of the amide group, which was formed by opening of the exocycle of dimer **19** by methylamine. In addition, a doublet assigned to protons of the methyl group of the methylamide fragment is observed at δ 3.24. The mass spectrum of the synthesized chlorin—chlorin dimer **20** exhibits peaks corresponding to its molecular ion and the adduct of compound **20** with the sodium cation. The structure of chlorin trimer **22** was similarly confirmed.

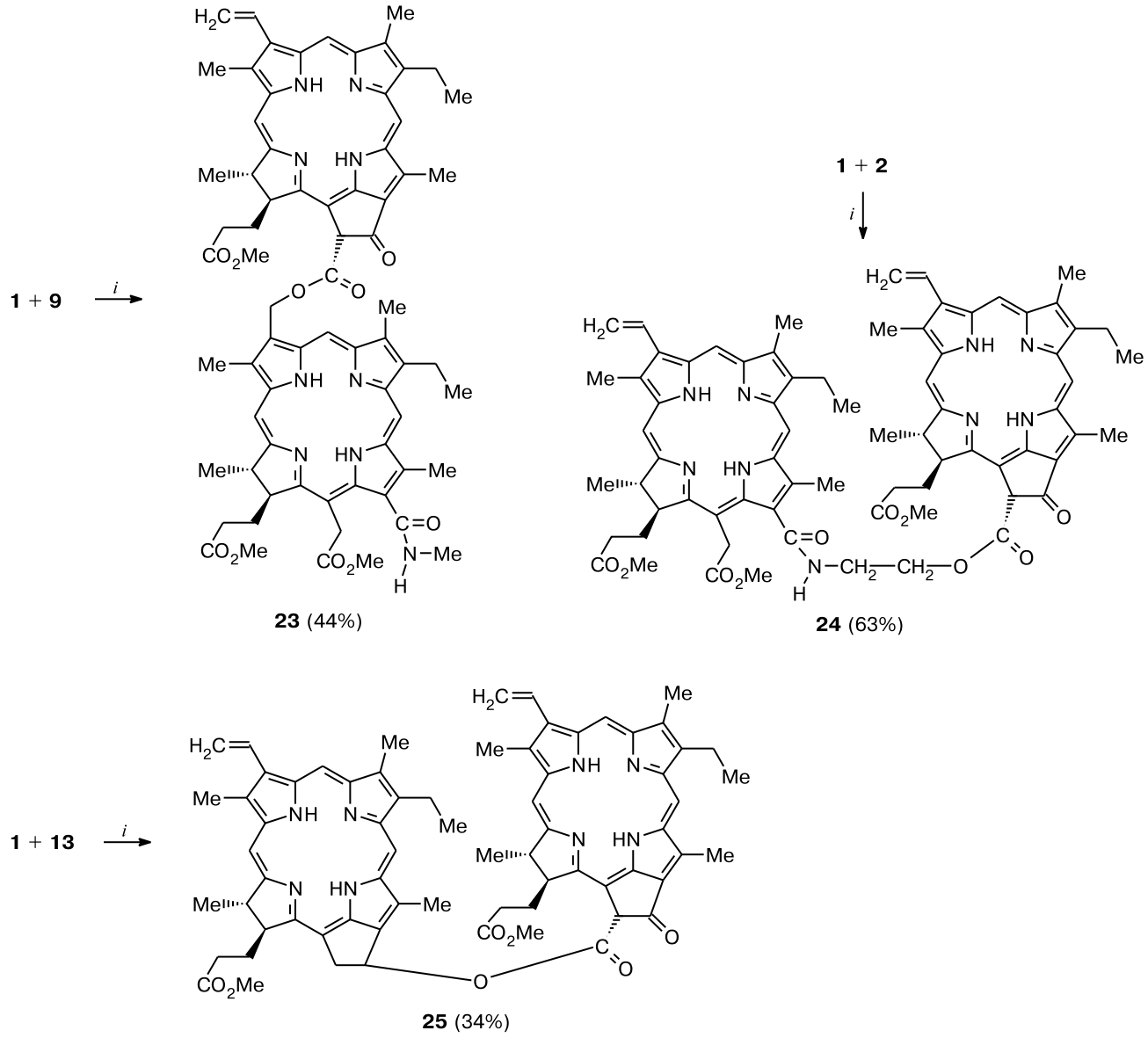
In the synthesis of dimers **23**—**25** (Scheme 4), the ester bond was formed by the catalytic transesterification of the methoxycarbonyl group in position 13(2) of methylpheophorbide *a* (*N*-methyl-2-chloropyridinium iodide in the presence of 4-(dimethylamino)pyridine as a catalyst).[6] The reaction was carried out by reflux in toluene for 3 h. As a result, dimers **23**—**25** were obtained, whose macrocycles are linked by ester bonds (see Scheme 4). The ^{1}H NMR spectrum of product **24** exhibits signals of two macrocycles of the chlorophyll derivatives, indicating

Scheme 3



Reagents and conditions: *a*. **3** or **4**, toluene, reflux, 1 h; *b*. Methylamine, THF, 1 h, ~20 °C; *c*. Toluene, reflux, 10 h.

Scheme 4



i. *N*-Methyl-2-chloropyridinium iodide, DMAP, reflux, toluene, 3 h.

dimer formation. In addition, no singlet signal corresponding to the methyl group in position 13(2) is observed in the ^{1}H NMR spectrum of dimer **24**. This suggests that the reaction proceeded at the ester group in position 13. The mass spectrum of the synthesized compound contains a peak corresponding to the protonated molecular ion of dimer **24**. The structures of dimers **23** and **25** were confirmed analogously.

Thus, we synthesized dimeric and trimeric chlorins **14**—**25**, whose macrocycles are linked by bridges of various length due to the formation of amide and ester bonds. Amide bonds were formed using both carboxy group activation and without activating agents, whereas the formation of ester bonds involved the catalyst. The synthesized individual chlorins can be considered as potential photosensitizers for photodynamic therapy in oncology.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance-300 instrument (300 MHz) in $CDCl_3$ (except for specially marked cases). Mass spectra (MALDI) were obtained on a Vision 2000 mass spectrometer. Silica gel 60 (0.060—0.200 mm,

70—230 mesh) was used for column chromatography. Methylpheophorbide *a* (**1**) was obtained according to the procedure described earlier.[7] 15,17-Dimethyl chlorin e_6 13-*N*-(2-aminoethyl)amide (**3**), 15,17-dimethyl chlorin e_6 13-*N*-(6-aminohexyl)amide (**4**), and 15-methyl chlorin e_6 13,17-*N*,*N*´-(2-aminoethyl)diamide (**10**) were synthesized by the treatment of methylpheophorbide *a* with ethylenediamine and hexamethylenediamine using our earlier developed procedures[8—10]; pheophorbide *a* (**5**), methylpyropheophorbide *a* (**12**), and pyropheophorbide *a* (**6**) were synthesized as described in the literature.[11] 15,17-Dimethyl chlorin e_6 13-*N*-(2-hydroxyethyl)amide (**2**) was synthesized by the action of ethanolamine on methylphephorbide *a* using the procedure described earlier.[8,9] The hydroxy derivative of chlorin e_6 (**11**) was synthesized by the reaction of aminochlorin **3** with succinic anhydride as described earlier.[12] The spectral characteristics of compounds **1**—**7**, **11**, and **12** are analogous to those presented in the literature. Methylpheophorbide *d* (**7**) was obtained by the known procedure.[13] In the assignment of signals of the phorbine macrocycle of dimers **14**—**16**, **18**, **19**, **23**, and **24** and trimer **21** as well as of signals of the methylpheophorbide macrocycle of dimer **25**, the corresponding atoms are marked with trait (´).

15,17-Dimethyl ester of chlorin e_6 3-devinyl-3-formyl-13-*N*-methylamide (8). Methylamine (3 mL) was added to a solution of methylpheophorbide *d* (**7**) (100 mg) in THF (7 mL). The reaction mixture was magnetically stirred at ~20 °C for 50 min (TLC: Sorbfil, CCl_4—acetone (4 : 1) mixture as eluent). The mixture was diluted with chloroform (50 mL), and methylamine excess was washed off with water. The obtained solution was dried over anhydrous Na_2SO_4 and evaporated. The mixture was chromatographed on silica gel (CCl_4—acetone (10 : 1) as eluent). Compound **8** was obtained in a yield of 90 mg (85%). ^{1}H NMR, δ: 11.56 (s, 1 H, C(3)C<u>H</u>=O); 10.30 (s, 1 H, H(10)); 9.65 (s, 1 H, H(5)); 8.98 (s, 1 H, H(20)); 6.42 (q, 1 H, C(13)CON<u>H</u>Me (amide), *J* = 5.14 Hz); 5.58 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.6 Hz); 5.31 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.2 Hz); 4.51 (q, 1 H, H(18), *J* = 7.1 Hz); 4.40 (br.d, 1 H, H(17), *J* = 8.7 Hz); 3.87 (s, 3 H, C(15)CH$_2$CO$_2$<u>Me</u>); 3.81 (s, 3 H, C(12)Me); 3.66 (s, 1 H, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.58 (s, 3 H, C(2)Me); 3.34 (s, 3 H, C(7)Me); 3.77 (q, 2 H, C(8)C<u>H</u>$_2$Me, *J* = 7.7 Hz); 3.32 (d, 3 H, C(13)CONH<u>Me</u>, *J* = 4.5 Hz); 2.68—2.20 (m, 4 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me); 1.74 (d, 3 H, C(18)Me, *J* = 7.2 Hz); 1.73 (t, 3 H, C(8)CH$_2$<u>Me</u>, *J* = 7.5 Hz); −1.44 (br.s, 1 H, I-NH); −1.96 (br.s, 1 H, III-NH).

15,17-Dimethyl ester of chlorin e_6 3-devinyl-3-hydroxymethyl-13-*N*-methylamide (9). $NaBH_4$ (100 mg) was added to a solution of compound **8** (100 mg) in THF (6 mL). The reaction mixture was stored at ~20 °C for 24 h (TLC: CCl_4—acetone (4 : 1) as eluent). The mixture was diluted with chloroform (50 mL), and $NaBH_4$ excess was washed off with water. The obtained solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (5 : 1) as eluent). Product **9** was obtained in a yield of 106 mg (80%). ^{1}H NMR, δ: 9.73 (s, 1 H, H(10)); 9.66 (s, 1 H, H(5)); 8.84 (s, 1 H, H(20)); 6.41—6.31 (br.m, 1 H, C(13)CON<u>H</u>Me); 5.95 (s, 2 H, C(3)C<u>H</u>$_2$OH); 5.56 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.9 Hz); 5.29 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.5 Hz); 4.50 (q, 1 H, H(18), *J* = 7.1 Hz); 4.38 (d, 1 H, H(17), *J* = 8.7 Hz); 3.85 (s, 3 H, C(15)CH$_2$CO$_2$<u>Me</u>); 3.64 (s, 3 H, C(12)Me); 3.59 (s, 1 H, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.50 (s, 3 H, C(2)Me); 3.34 (s, 3 H, C(7)Me); 3.88—3.77 (m, 2 H, C(8)C<u>H</u>$_2$Me); 3.29 (d, 3 H, C(13)CONH<u>Me</u>, *J* = 4.8 Hz); 2.66—2.49 (m, 2 H, C(17)C<u>H</u>$_2$CH$_2$CO$_2$Me); 2.28—2.11 (m, 2 H, C(17)CH$_2$C<u>H</u>$_2$CO$_2$Me); 1.75 (d, 3 H, C(18)Me, *J* = 7.6 Hz); 1.74 (t, 3 H, C(8)CH$_2$<u>Me</u>, *J* = 7.6 Hz); −1.68 (br.s, 1 H, I-NH); −1.93 (br.s, 1 H, III-NH).

13(1)-Deoxo-13(1)-hydroxymethylpyropheophorbide *a* (13). $NaBH_4$ (300 mg) was added to a solution of methylpyropheophorbide *a* (**12**) (210 mg) in THF (20 mL). The reaction mixture was stirred at ~20 °C for 48 h (TLC: Sorbfil, CCl_4—acetone (4 : 1) as eluent). The mixture was diluted with chloroform (50 mL), and $NaBH_4$ excess with washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (20 : 1) as eluent). Compound **13** was obtained as a mixture of diastereomers in a yield of 123 mg (59%). ^{1}H NMR, δ: 9.90 (s, 1 H, H(10)); 9.67 (s, 1 H, H(5)); 8.93 (s, 1 H, H(20)); 8.26 (dd, 1 H, C(3)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 12.0 Hz); 6.49, 6.52 (both d, 1 H each, C(13)C(1)H, *J* = 6.6 Hz); 6.13 (d, 1 H, C(3)CH=CH<u>H</u> (*cis*), *J* = 11.1 Hz); 6.09 (d, 1 H, C(3)CH=CH<u>H</u> (*cis*), *J* = 17.7 Hz); 5.27, 5.38 (both dd, 1 H each, *J* = 18.0 Hz, *J* = 6.0 Hz)*; 4.72, 4.59 (both d, 1 H each, C(13)C(2)CH$_2$, *J* = 18.0 Hz)*; 4.68 (m, 1 H, H(18)); 4.49, 4.49 (both d, 1 H each, H(17), *J* = 6.2 Hz)*; 3.88 (q, 2 H, C(8)C<u>H</u>$_2$Me, *J* = 6.5 Hz); 3.65 (s, 3 H, C(2)Me); 3.59 (s, 3 H, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.46 (s, 3 H, C(12)Me); 3.44 (s, 3 H, C(7)Me); 2.88—2.50 (m, 4 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me); 1.88, 1.89 (both d, 3 H each, C(18)Me, *J* = 6.0 Hz)*; 1.79 (t, 3 H, C(8)CH$_2$<u>Me</u>, *J* = 9.0 Hz); −1.31 (br.s, 1 H, I-NH); −3.18 (br.s, 1 H, III-NH).

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[2-(*N*-17(3)-pyropheophorbidyl)aminoethyl]amide (14). Di(*tert*-butyl) dicarbonate (22 mg, 0.093 mmol) was added to a solution of pyropheophorbide *a* (**6**) (50 mg, 0.093 mmol) in a pyridine—CH_2Cl_2 (5 : 10) mixture, and the reaction mixture was stirred at 0 °C for 15 min. Aminochlorin **3** (62 mg, 0.093 mmol) was added, and the mixture was stirred at ~20 °C for 1 h (TLC: Sorbfil, CCl_4—acetone (2 : 1) as eluent). The reaction mixture was diluted with chloroform (50 mL), pyridine was washed off with 7% HCl, and the acid was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (10 : 1) as eluent). Dimer **14** was obtained in a yield of 61 mg (55%). ^{1}H NMR, δ: 9.29 (s, 1 H, H(10)); 8.69 (s, 1 H, H(5)); 8.86 (s, 1 H, H(10´)); 8.45 (s, 1 H, H(5´)); 8.16 (s, 1 H, H(20)); 7.79 (s, 1 H, H(20´)); 7.90 (dd, 1 H, C(3)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 11.7 Hz); 7.89 (dd, 1 H, C(3´)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 11.6 Hz); 7.18 (br.m, 1 H, chlorin-C(13)CON<u>H</u>CH$_2$CH$_2$NHCOC(17)-phorbine (bridge)); 6.76 (br.m, 1 H, C(13)CONHCH$_2$CH$_2$N<u>H</u>CO (bridge)); 6.25 (d, 2 H, C(3)CH=CH<u>H</u> (*trans*), C(3´)CH=CH<u>H</u> (*trans*), *J* = 18.0 Hz); 6.13 (d, 1 H, C(3)CH=C<u>H</u>$_2$ (*trans*), *J* = 11.1 Hz); 6.09 (d, 1 H, C(3´)CH=C<u>H</u>$_2$ (*trans*), *J* = 11.7 Hz); 5.30 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.9 Hz); 5.15 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.5 Hz); 4.62 (d, 1 H, C(13)(C(2´))CH$_2$, *J* = 19.8 Hz); 4.02 (m, 1 H, C(13)C(2´)CH$_2$); 4.37 (q, 1 H, H(18), *J* = 7.2 Hz); 4.21 (br.d, 1 H, H(17), *J* = 8.7 Hz); 3.72—3.05 (m, 10 H, H(18´), H(17´), C(8)C<u>H</u>$_2$Me, C(8´)CH$_2$Me, C(13)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCO (bridge)); 3.60

* Signals of diastereomers differed in chemical shifts are marked with asterisk (*).

(s, 3 H), 3.45 (s, 3 H), 3.42 (s, 3 H), 3.31 (s, 6 H), 3.26 (s, 3 H), 3.08 (br.s, 3 H), 3.03 (s, 3 H), 2.33 (br.s, 6 H) (C(15)CH_2CO_2Me, C(17)$CH_2CH_2CO_2$Me, C(2)Me, C(7)Me, C(12)Me, C(17)Me, C(2´)Me, C(7´)Me, C(12´)Me); 2.39—2.26 (m, 4 H, C(17)CH_2CH_2CO_2Me, C(17´)CH_2CH_2); 2.25—2.10 (m, 4 H, C(17)CH_2CH_2CO_2Me, C(17´)CH_2CH_2); 1.84—1.69 (m, 6 H, C(18´)Me, C(8´)CH_2Me); 1.44 (d, 3 H, C(18)Me, J = 6.9 Hz); 1.34 (t, 3 H, C(8)CH_2Me, J = 7.5 Hz); –0.25 (br.s, 1 H, I´-NH); –1.94 (br.s, 1 H, III´-NH); –2.06 (br.s, 1 H, I-NH); –2.33 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1183.1602. $C_{71}H_{78}N_{10}O_7$. For $[M]^+$ calculated: 1182.6055.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[6-(*N*-17(3)-pyropheophorbidyl)aminohexyl]amide (15). Di(*tert*-butyl) dicarbonate (22 mg, 0.093 mmol) was added to a solution of pyropheophorbide *a* (**6**) (50 mg, 0.093 mmol) in a pyridine—CH_2Cl_2 (1 : 2) mixture, and the reaction mixture was stirred at 0 °C for 15 min. Aminochlorin **4** (68 mg, 0.093 mmol) was added, and the mixture was stirred at ~20 °C for 1 h (TLC: Sorbfil, CCl_4—acetone (2 : 1) as eluent). The reaction mixture was diluted with chloroform (50 mL), pyridine was washed off with 7% HCl, and the acid was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (3 : 1) as eluent). Dimer **15** was obtained in a yield of 33 mg (28%). ^{1}H NMR, δ: 9.43 (s, 2 H, H(10), H(10´)); 9.41 (s, 1 H, H(5)); 9.10 (s, 1 H, H(5´)); 8.80 (s, 1 H, H(20)); 8.49 (s, 1 H, H(20´)); 8.01 (dd, 2 H, C(3)CH=CH_2, C(3´)CH=CH_2, J = 11.9 Hz, J = 17.9 Hz); 6.68—6.57 (br.m, 1 H, chlorin-C(13)CO$NH$$(CH_2)_6$NHCOC(17)-phorbine (bridge)); 5.27—5.18 (br.m, 1 H, chlorin-C(13)CONH$(CH_2)_6$NHCOC(17)-phorbine (bridge)); 6.34 (d, 1 H, C(3)CH=CHH (*trans*), J = 18.0 Hz); 6.29 (d, 1 H, C(3´)CH=CHH (*trans*), J = 18.0 Hz); 6.18 (d, 1 H, C(3)CH=CHH (*cis*), J = 11.7 Hz); 6.14 (d, 1 H, C(3´)CH=CHH (*cis*), J = 11.7 Hz); 5.51 (d, 1 H, C(15)CH_2CO_2Me, J = 18.9 Hz); 5.21 (d, 1 H, C(15)CH_2CO_2Me, J = 18.9 Hz); 5.03 (d, 1 H, C(13´)C(2)CH_2, J = 19.8 Hz); 4.91 (d, 1 H, C(13´)C(2)CH_2, J = 20.1 Hz); 4.50—4.33 (m, 2 H, C(18)H, H(18´)); 4.34 (d, 1 H, H(17), J = 9.6 Hz); 4.19 (d, 1 H, H(17´)); 3.86—3.75 (m, 4 H, C(8)CH_2Me, C(8´)CH_2Me); 3.54—3.41 (m, 4, chlorin-C(13)CONHC$H_2$$(CH_2)_4CH_2$NHCOC(17)-phorbine (bridge)); 3.78 (s, 3 H), 3.58 (s, 3 H), 3.49 (s, 3 H), 3.48 (s, 3 H), 3.38 (s, 3 H), 3.27 (s, 3 H), 3.21 (s, 3 H), 3.07 (s, 3 H) (C(15)CH_2CO_2Me, C(17)$CH_2CH_2CO_2$Me, C(2)Me, C(7)Me, C(12)Me, C(17)Me, C(2´)Me, C(7´)Me, C(12´)Me); 2.55—2.30 (m, 4 H), 2.27—2.15 (m, 4 H) (C(17)CH_2CH_2CO_2Me, C(17´)CH_2CH_2); 1.73 (t, 6 H, C(8´)CH_2Me, C(8)CH_2Me, J = 7.4 Hz); 1.64 (d, 3 H, C(18´)Me, J = 7.5 Hz); 1.52 (d, 3 H, C(18)Me, J = 7.5 Hz); 0.96—0.81 (m, 8 H, chlorin-C(13)CONHC$H_2$$(CH_2)_4$$CH_2$NHCOC(17)-phorbine (bridge)); 0.2 (br.s, 1 H, I´-NH); –1.77 (br.s, 1 H, III´-NH); –1.8 (br.s, 1 H, I-NH); –1.97 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1238.8230. $C_{75}H_{86}N_{10}O_7$. For $[M]^+$ calculated: 1238.6680. Found: 1239.8325. $C_{75}H_{87}N_{10}O_7$. For $[MH]^+$ calculated: 1239.6759.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[2-(*N*-17(3)-pheophorbidyl)aminoethyl]amide (16). Di(*tert*-butyl) dicarbonate (20 mg, 0.084 mmol) was added to a solution of pheophorbide *a* (**5**) (50 mg, 0.084 mmol) in a pyridine—CH_2Cl_2 (1 : 2) mixture, and the reaction mixture was stirred at 0 °C for 15 min. Then aminochlorin **3** (57 mg, 0.084 mmol) was added, and the mixture was stirred at ~20 °C for 1 h (TLC: Sorbfil, CCl_4—acetone (2 : 1) as eluent). The reaction mixture was diluted with chloroform (50 mL), pyridine was washed off with 7% HCl, and the acid was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (7 : 1) as eluent). Dimer **16** was obtained in a yield of 46 mg (44%). ^{1}H NMR (DMF-d_7), δ: 9.86 (s, 1 H, H(10)); 9.83 (s, 1 H, H(5)); 9.76 (s, 1 H, H(10´)); 9.48 (s, 1 H, H(5´)); 9.22 (s, 1 H, H(20)); 8.99 (s, 1 H, H(20´)); 8.83 (br.t, 1 H, chlorin-C(13)CO$NH$$CH_2CH_2$NHCOC(17)-phorbine (bridge), J = 5.0 Hz); 8.38 (dd, 1 H, C(3)CH=CH_2, J = 11.6 Hz, J = 18.0 Hz); 8.18 (dd, 1 H, C(3´)CH=CH_2, J = 11.6 Hz, J = 18.0 Hz); 7.98 (br.t, 1 H, chlorin-C(13)CONHCH_2CH_2-NHCOC(17)-phorbine (bridge), J = 5.6 Hz); 6.51 (s, 1 H, C(13)C(2´)H); 6.49 (d, 1 H, C(3)CH=CHH (*trans*), J = 18.6 Hz); 6.34 (d, 1 H, C(3´)CH=CHH (*trans*), J = 17.8 Hz); 6.19 (d, 1 H, C(3)CH=CHH (*cis*), J = 11.8 Hz); 6.16 (d, 1 H, C(3´)CH=CHH (*cis*), J = 11.6 Hz); 5.62 (d, 1 H, C(15)CH_2CO_2Me, J = 18.8 Hz); 5.35 (d, 1 H, C(15)CH_2CO_2Me, J = 19.2 Hz); 4.74—4.65 (m, 2 H, C(18)H, H(18´)); 4.50 (br.d, 1 H, H(17), J = 10.4 Hz); 4.26 (br.d, 1 H, H(17´), J = 7.6 Hz); 3.80 (q, 4 H, C(8)CH_2Me, C(8´)CH_2Me, J = 7.6 Hz); 3.76—3.65 (m, 4 H, chlorin-C(13)CONHCH_2CH_2NHCOC(17)-phorbine (bridge)); 3.93 (s, 3 H), 3.67 (s, 3 H), 3.62 (s, 3 H), 3.58 (s, 3 H), 3.57 (s, 3 H), 3.44 (s, 3 H), 3.42 (s, 3 H), 3.36 (s, 3 H), 3.22 (s, 3 H) (C(15)CH_2CO_2Me, C(15´)CH_2CO_2Me, C(17)$CH_2CH_2CO_2$Me, C(2)Me, C(7)Me, C(12)Me, C(7)Me, C(2´)Me, C(7´)Me, C(12´)Me); 2.82—2.67 (m, 2 H), 2.58—2.48 (m, 2 H), 2.37—2.20 (m, 4 H) (C(17)CH_2CH_2CO_2Me, C(17)C$H´_2$C$H´_2$); 1.88 (d, 3 H, C(18)Me, J = 7.2); 1.69 (d, 3 H, C(18´)Me, J = 6.8 Hz); 1.65 (t, 3 H, C(8)CH_2Me, J = 7.6 Hz); 1.62 (t, 3 H, C(8´)CH_2Me, J = 7.4 Hz); 0.55 (br.s, 1 H, I´-NH); –1.67 (br.s, 1 H, I-NH); –1.69 (br.s, 1 H, III´-NH); –2.00 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1241.4301. $C_{73}H_{81}N_{10}O_9$. For $[MH]^+$ calculated: 1241.6188.

15,17-Dimethyl ester of *N*,*N*´-bis[13(3)-e_6-chlorinyl-13-*N*-ethylaminosuccine]diamide (17). Di(*tert*-butyl) dicarbonate (15 mg, 0.065 mmol) was added to carboxychlorin **11** (50 mg, 0.065 mmol) in a pyridine—CH_2Cl_2 (1 : 2) mixture. The reaction mixture was stirred at 0 °C for 15 min. Aminochlorin **3** (44 mg, 0.065 mmol) was added, and the reaction mixture was stirred at ~20 °C for 1 h (TLC: Sorbfil, chloroform—methanol (9 : 1) as eluent). The mixture was diluted with chloroform (50 mL), pyridine was washed off with 7% HCl, and the acid was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. After evaporation the residue was chromatographed (CCl_4—acetone (3 : 1) as eluent). Dimer **17** was obtained in a yield of 37 mg (41%). ^{1}H NMR, δ: 9.46 (s, 2 H, H(10)); 9.32 (s, 2 H, H(5)); 8.82 (s, 2 H, H(20)); 7.74 (dd, 2 H, C(3)CH=CH_2, J = 11.6 Hz, J = 17.3 Hz); 6.20—6.05 (br.m, 2 H, NH (amide)); 5.72—5.44 (br.m, 2 H, NH (amide)); 5.99 (d, 2 H, C(3)CH=CHH (*trans*), J = 17.7 Hz); 5.82 (d, 1 H, C(3)CH=CHH (*cis*), J = 11.4 Hz); 4.99 (d, 2 H, C(15)CH_2CO_2Me, J = 19.8 Hz); 4.87 (d, 2 H, C(15)CH_2CO_2Me, J = 19.4 Hz); 4.54 (q, 2 H, H(18), J = 7.1 Hz); 4.40 (d, 2 H, H(17), J = 9.3 Hz); 3.84—3.70 (m, 4 H, C(8)CH_2Me); 3.68 (s, 6 H), 3.55 (s, 6 H), 3.27 (s, 6 H), 2.85 (s, 6 H), 2.65 (s, 6 H) (C(15)CH_2CO_2Me, C(17)$CH_2CH_2CO_2$Me, C(2)Me, C(7)Me, C(12)Me); 3.65—3.44 (m, 6 H, chlorin-C(13)CONH$(CH_2)_2$-NHCO$(CH_2)_2$CONH$(CH_2)_2$NHOCC(13)CH_2-chlorin (bridge)); 2.44—2.24 (m, 8 H, C(17)CH_2CH_2CO_2Me,

C(17)C<u>H</u>´$_2$C<u>H</u>´$_2$); 1.75 (t, 6 H, C(8)CH$_2$<u>Me</u>, *J* = 7.2 Hz); 1.76 (d, 6 H, C(18)Me, *J* = 7.2 Hz); −1.75 (br.s, 2 H, I-NH); −2.06 (br.s, 2 H, III-NH). MS (MALDI), *m/z*: found: 1414.8993. $C_{80}H_{94}N_{12}O_{12}$. For $[M]^+$ calculated: 1414.7114. Found: 1415.8577. $C_{80}H_{95}N_{12}O_{12}$. For $[MH]^+$ calculated: 1415.7192. Found: 1437.8702. $C_{80}H_{94}N_{12}O_{12}Na$. For $[MNa]^+$ calculated: 1437.7011.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[2-(*N*-13(2)-methylpheophorbidyl)aminoethylamide] (18). Aminochlorin **3** (55 mg, 0.082 mmol) was added to a solution of methylpheophorbide *a* (**1**) (50 mg, 0.082 mmol) in toluene (10 mL). The mixture was refluxed for 1 h (TLC: Sorbfil, CCl_4—acetone (2 : 1) as eluent) and then chromatographed (CCl_4—acetone (5 : 1) as eluent). Dimer **18** was obtained in a yield of 63 mg (65%). ^{1}H NMR, δ: 9.67 (s, 1 H, H(10)); 9.63 (s, 1 H, H(5)); 9.39 (s, 1 H, H(10´)); 9.36 (s, 1 H, H(5´)); 8.80 (s, 1 H, H(20)); 8.45 (s, 1 H, H(20´)); 8.13 (dd, 1 H, C(3)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 11.4 Hz); 7.99 (dd, 1 H, C(3´)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 11.7 Hz); 7.82 (br.t, 1 H, chlorin-C(13)CO<u>NH</u>CH$_2$CH$_2$NHCOC(17)-phorbine (bridge), *J* = 4.8 Hz); 7.76 (br.t, 1 H, chlorin-C(13)CONHCH$_2$CH$_2$<u>NH</u>COC(17)-phorbine (bridge), *J* = 4.5 Hz); 6.39 (d, 1 H, C(3)CH=CH<u>H</u> (*trans*), *J* = 17.6 Hz); 6.28 (d, 1 H, C(3´)CH=CH<u>H</u> (*trans*), *J* = 17.6 Hz); 6.18 (d, 2 H, C(3)CH=CH<u>H</u> (*cis*), C(3´)CH=CH<u>H</u> (*cis*), *J* = 11.0 Hz); 6.17 (s, 1 H, C(13)C(2´)H); 5.73 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.8 Hz); 5.31 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.4 Hz); 4.55—4.34 (m, 2 H, H(18), H(18´)); 4.20—3.98 (m, 2 H, H(17), H(17´)); 3.77—3.43 (m, 4 H, C(8)C<u>H</u>$_2$Me, C(8´)C<u>H</u>$_2$Me); 3.70 (s, 3 H), 3.57 (s, 3 H), 3.52 (s, 6 H), 3.46 (s, 3 H), 3.34 (s, 6 H), 3.24 (s, 3 H), 3.17 (s, 3 H) (C(15)CH$_2$CO$_2$<u>Me</u>, C(2)Me, C(7)Me, C(12)Me, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>, C(2´)Me, C(7´)Me, C(12´)Me, C(17´)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.50—3.28 (m, 4 H, chlorin-C(13)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCOC(17)-phorbine (bridge)); 2.70—1.92 (m, 8 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me, C(17´)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me); 1.73—1.62 (m, 12 H, C(8)CH$_2$<u>Me</u>, C(8´)CH$_2$<u>Me</u>, C(18)Me, C(18´)Me); 0.58 (br.s, 1 H, I´-NH); −1.57 (br.s, 1 H, III´-NH); −1.52 (br.s, 1 H, I-NH); −1.79 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1240.6321. $C_{73}H_{80}N_{10}O_9$. For $[M]^+$ calculated: 1240.6109. Found 1241.6357. $C_{73}H_{81}N_{10}O_9$. For $[MH]^+$ calculated: 1241.6188. Found: 1264.6571. $C_{73}H_{80}N_{10}O_9Na$. For $[MNa]^+$ calculated: 1264.6007.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[6-(*N*-13(2)-methylpheophorbidyl)aminohexylamide] (19). Aminochlorin **4** (59 mg, 0.082 mmol) was added to a solution of methylpheophorbide *a* (**1**) (50 mg, 0.082 mmol) in toluene (10 mL). The reaction mixture was refluxed for 1 h (TLC: Sorbfil, CCl_4—acetone (2 : 1) as eluent). The mixture was chromatographed on silica gel (CCl_4—acetone (4 : 1) as eluent). Dimer **19** was obtained in a yield of 36 mg (42%). ^{1}H NMR, δ: 9.51 (s, 1 H, H(10)); 9.39 (s, 1 H, H(5)); 9.38 (s, 1 H, H(10´)); 9.20 (s, 1 H, H(5´)); 8.82 (s, 1 H, H(20)); 8.52 (s, 1 H, H(20´)); 8.02 (dd, 2 H, C(3)C<u>H</u>=CH$_2$, C(3´)C<u>H</u>=CH$_2$, *J* = 17.2 Hz, *J* = 11.4 Hz); 7.05 (br.t, 1 H, chlorin-C(13)CO<u>NH</u>CH$_2$CH$_2$NHCOC(17)-phorbine (bridge), *J* = 5.0 Hz); 6.68 (br.t, 1 H, chlorin-C(13)CONH(CH$_2$)$_6$N<u>H</u>-COC(17)-phorbine (bridge), *J* = 5.0 Hz); 6.44—6.05 (m, 4 H, C(3)CH=C<u>H</u>$_2$, C(3´)CH=C<u>H</u>$_2$); 5.94 (s, 1 H, C(13)C(2´)H); 5.61 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.4 Hz); 5.26 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.1 Hz); 4.56—4.42 (m, 2 H, H(18), H(18´)); 4.42—4.32 (m, 2 H, H(17), H(17´)); 4.01—3.68 (m, 4 H, C(8)C<u>H</u>$_2$Me, C(8´)C<u>H</u>$_2$Me); 3.83 (s, 3 H), 3.60 (s, 3 H), 3.55 (s, 3 H), 3.53 (s, 3 H), 3.52 (s, 3 H), 3.42 (s, 3 H), 3.41 (s, 3 H), 3.22 (s, 3 H), 3.00 (s, 3 H) (C(15)CH$_2$CO$_2$<u>Me</u>, C(2)Me, C(7)Me, C(12)Me, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>, C(2´)Me, C(7´)Me, C(12´)Me, C(17´)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.55—3.26 (m, 4 H, chlorin-C(13)CONHC<u>H</u>$_2$(CH$_2$)$_4$C<u>H</u>$_2$NHCOC(17)-phorbine (bridge)); 2.66—1.99 (m, 8 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me, C(17´)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me); 1.97—1.69 (m, 12 H, C(8)CH$_2$<u>Me</u>, C(8´)CH$_2$<u>Me</u>, C(18)Me, C(18´)Me); 0.35 (br.s, 1 H, I-NH´); −1.64 (br.s, 1 H, III-NH´); −1.69 (br.s, 1 H, I-NH); −1.91 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1296.8458. $C_{77}H_{88}N_{10}O_9$. For $[M]^+$ calculated: 1296.6736. Found: 1297.8123. $C_{77}H_{89}N_{10}O_9$. For $[MH]^+$ calculated: 1297.6814. Found: 1319.8784. $C_{73}H_{80}N_{10}O_9Na$. For $[MNa]^+$ calculated: 1319.6634.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[6-(*N*-15(2)-e_6-chlorinyl-13-*N*´-methylamide-17-methyl ester)aminohexylamide] (20). A 33% aqueous solution of methylamine (1 mL) was added to a solution of dimer **19** (30 mg) in THF (7 mL), and the reaction mixture was stirred at ~20 °C for 2 h. The reaction mixture was diluted with chloroform (50 mL), and methylamine was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (1 : 1) as eluent). The purity of the product was monitored by TLC (Sorbfil, $CHCl_3$—methanol (9 : 1) as eluent). Product **20** was obtained in a yield of 20 mg (59%). ^{1}H NMR, δ: 9.67 (s, 1 H, H(10)); 9.66 (s, 1 H, H(5)); 9.61 (s, 1 H, H(10´)); 9.56 (s, 1 H, H(5´)); 8.84 (s, 1 H, H(20)); 8.83 (s, 1 H, H(20´)); 8.12 (dd, 1 H, C(3)C<u>H</u>=CH$_2$, *J* = 18.0 Hz, *J* = 11.4 Hz); 7.94 (dd, 1 H, C(3´)C<u>H</u>=CH$_2$, *J* = 17.9 Hz, *J* = 11.6 Hz); 6.84 (m, 1 H, C(13´)CO<u>NH</u>Me); 6.77 (m, 1 H, chlorin-C(13)CO<u>NH</u>(CH$_2$)$_6$NHCOCH$_2$C(15´)-chlorin (bridge)); 6.39 (d, 1 H, C(3)CH=CH<u>H</u> (*trans*), *J* = 18.3 Hz); 6.24 (d, 1 H, C(3´)CH=CH<u>H</u> (*trans*), *J* = 18.0 Hz); 6.17 (d, 1 H, C(3)CH=CH<u>H</u> (*cis*), *J* = 10.8 Hz); 6.01 (d, 1 H, C(3´)CH=CH<u>H</u> (*cis*), *J* = 11.4 Hz); 6.17 (m, 1 H, chlorin-C(13)CO<u>NH</u>(CH$_2$)$_6$-NHCOCH$_2$C(15´)-chlorin (bridge)); 5.43 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 18.9 Hz); 5.18 (d, 1 H, C(15)C<u>H</u>$_2$CO$_2$Me, *J* = 19.2 Hz); 5.35 (d, 1 H, C(15´)C<u>H</u>$_2$CO$_2$Me, *J* = 17.1 Hz); 5.11 (d, 1 H, C(15´)C<u>H</u>$_2$CO$_2$Me, *J* = 17.7 Hz); 4.69 (d, 1 H, H(17), *J* = 9.6 Hz); 4.46 (q, 2 H, H(18), H(18´), *J* = 7.1 Hz); 4.39 (d, 1 H, H(17´), *J* = 9.0 Hz); 3.84—3.70 (m, 4 H, C(8)C<u>H</u>$_2$Me, C(8´)C<u>H</u>$_2$Me); 3.68 (s, 3 H), 3.61 (s, 3 H), 3.59 (s, 3 H), 3.52 (s, 3 H), 3.43 (s, 3 H), 3.44 (s, 3 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.19 (s, 3 H) (C(15)CH$_2$CO$_2$<u>Me</u>, C(15´)CH$_2$CO$_2$<u>Me</u>, C(2)Me, C(7)Me, C(12)Me, C(17)CH$_2$CH$_2$CO$_2$<u>Me</u>, C(2´)Me, C(7´)Me, C(12´)Me, C(17´)CH$_2$CH$_2$CO$_2$<u>Me</u>); 3.37—3.26 (m, 4 H, chlorin-C(13)CONHC<u>H</u>$_2$(CH$_2$)$_4$C<u>H</u>$_2$NHCOCH$_2$C(15´)-chlorin (bridge)); 3.24 (d, 3 H, C(13´)CO<u>NH</u>Me, *J* = 4.8 Hz); 2.56—2.06 (m, 6 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me, C(17´)C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$Me); 1.78—1.62 (m, 12 H, C(18)Me, C(8)CH$_2$<u>Me</u>, C(18´)Me, C(8´)CH$_2$<u>Me</u>); 1.63—1.40 (m, 4 H, chlorin-C(13)CONH-CH$_2$(C<u>H</u>$_2$)$_4$CH$_2$NHCOCH$_2$C(15´)-chlorin (bridge)); −1.61 (br.s, 2 H, I-NH, I´-NH); −1.86 (br.s, 1 H), −1.91 (br.s, 1 H) (III-NH, III´-NH). MS (MALDI), *m/z*: found: 1327.6744. $C_{78}H_{93}N_{11}O_9$. For $[M]^+$ calculated: 1327.5178. Found: 1328.6770. $C_{78}H_{94}N_{11}O_9$. For $[MH]^+$ calculated: 1328.7236. Found: 1350.6978. $C_{78}H_{93}N_{11}O_9Na$. For $[MNa]^+$ calculated: 1350.7055.

15-Methyl ester of 13,17-bis-*N*,*N*´-[2-(*N*-13(2)-methylpheophorbidyl)aminoethylamide]diamide-e_6-chlorin (21). Methylpheophorbide *a* (**1**) (92 mg, 0.150 mmol) was added to a solution of diaminochlorin **10** (50 mg, 0.075 mmol), and the mixture was refluxed for 10 h (TLC: Sorbfil, $CHCl_3$—MeOH (9 : 1) as eluent).

The reaction mixture was chromatographed on silica gel ($CHCl_3$—MeOH (15 : 1) as eluent). Product **21** was obtained in a yield of 42 mg (30%). ^{1}H NMR, δ: 9.54 (s, 1 H), 9.49 (s, 1 H), 9.31 (s, 1 H), 9.27 (s, 1 H), 9.09 (s, 1 H), 9.07 (s, 1 H), 8.78 (s, 1 H), 8.44 (s, 1 H), 8.42 (s, 1 H) (H(10), H(5), H(10′), H(5′), H(10′), H(5′), H(20), H(20′), H(20′)); 8.00—7.78 (m, 3 H, C(3)C<u>H</u>=CH_2, C(3′)C<u>H</u>=CH_2, C(3′)C<u>H</u>=CH_2); 8.00—7.78 (m, 2 H), 6.90 (m, 1 H), 6.34 (m, 1 H) (C(13)CO<u>NH</u>Me, chlorin-C(13)CO<u>NH</u>CH_2CH_2<u>NH</u>CO-C(13)C(2′)-phorbine (bridge), chlorin-C(17)CO<u>NH</u>CH_2CH_2<u>NH</u>COC(13)C(2′)-phorbine (bridge)); 6.27—6.10 (m, 5 H), 5.93 (br.d, 1 H, *J* = 11.4 Hz) (C(3)CH=C<u>H</u>$_2$, C(3′)CH=C<u>H</u>$_2$, C(3′)CH=C<u>H</u>$_2$); 6.16 (s, 1 H, C(13′)C(2)H); 6.13 (s, 1 H, C(13′)C(2)H); 5.68 (d, 1 H, C(15)C<u>H</u>$_2CO_2$Me, *J* = 18.6 Hz); 5.51—5.47 (m, 1 H, C(15)C<u>H</u>$_2CO_2$Me); 4.54—4.38 (m, 3 H, H(18), H(18′), H(18′)); 3.28—4.11 (m, 3 H, H(17), H(17′), H(17′)); 4.10—3.96 (m, 6 H, C(8)C<u>H</u>$_2$Me, C(8′)C<u>H</u>$_2$Me, C(8′)C<u>H</u>$_2$Me); 3.71 (s, 3 H), 3.52 (s, 3 H), 3.38 (s, 6 H), 3.31 (s, 6 H), 3.29 (s, 3 H), 3.23 (s, 3 H), 3.20 (s, 3 H), 3.17 (s, 6 H), 3.00 (s, 3 H) (C(15)CH_2CO_2<u>Me</u>, C(2)Me, 7-Me, C(12)Me, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>, C(17′)$CH_2CH_2CO_2$<u>Me</u>, C(2′)Me, C(7′)Me, C(12′)Me); 3.65—3.41 (m, 8 H, chlorin-C(17)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCOC(13)C(2′)-phorbine (bridge), chlorin-C(13)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCOC(13)C(2′)-phorbine (bridge)); 2.55—2.02 (m, 12 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me); 1.77—1.51 (m, 18 H, C(18)Me, C(8)CH_2<u>Me</u>, C(18′)Me, C(8′)CH_2<u>Me</u>, C(18′)Me, C(8′)CH_2<u>Me</u>); 0.38 (br.s, 2 H, I′-NH); −1.55 (br.s, 1 H, I-NH); −1.66 (br.s, 1 H, III-NH); −1.70 (br.s, 2 H, III′-NH). MS (MALDI), *m/z*: found: 1844.3300. $C_{109}H_{119}N_{16}O_{12}$. For $[MH]^+$ calculated: 1843.9193.

15,17-Dimethyl ester of 13,17-bis-*N*,*N*′-[2-(*N*-15(2)-e_6-chlorinyl-13-*N*′-methylamide)aminoethylamide]diamide-e_6-chlorin (22). Methylamine (1 mL) was added to a solution of trimer **21** (20 mg) in THF (10 mL), and the reaction mixture was stirred for 3 h (TLC: Sorbfil, $CHCl_3$—MeOH (9 : 1) as eluent). The mixture was diluted with chloroform (50 mL), methylamine was washed off with water, and the residue was chromatographed on silica gel ($CHCl_3$—MeOH (5 : 1) as eluent). Product **22** was obtained in a yield of 12 mg (48%). ^{1}H NMR, δ: 9.64 (s, 1 H), 9.62 (s, 2 H), 9.60 (s, 1 H), 9.53 (s, 1 H), 8.87 (s, 1 H), 8.77 (s, 1 H), 8.75 (s, 1 H), 8.53 (s, 1 H), 8.15 (s, 1 H) (H(10), H(5), H(10′), H(5′), H(10′), H(5′), H(20), H(20′), H(20′)); 8.05 (dd, 3 H, C(3)C<u>H</u>=CH_2, C(3′)C<u>H</u>=CH_2, C(3′)C<u>H</u>=CH_2, *J* = 16.9 Hz, *J* = 11.7 Hz); 6.74—6.46 (m, 3 H), 6.43—6.52 (m, 2 H), 5.79 (m, 1 H) (C(13′)CO<u>NH</u>Me, C(13′)CO<u>NH</u>Me, chlorin-C(13)CO<u>NH</u>CH_2CH_2<u>NH</u>COC(15′)-chlorin (bridge), chlorin-C(17)CO<u>NH</u>CH_2CH_2<u>NH</u>COC(15′)-chlorin (bridge)); 6.33 (br.d, 3 H, C(3)CH=CH<u>H</u> (*trans*), C(3′)CH=CH<u>H</u> (*trans*), C(3′)CH=CH<u>H</u> (*trans*), *J* = 16.2 Hz); 6.13 (br.d, 3 H, C(3)CH=CH<u>H</u> (*cis*), C(3′)CH=CH<u>H</u> (*cis*), C(3′)CH=CH<u>H</u> (*cis*), *J* = 11.4 Hz); 5.27—4.59 (m, 6 H, C(15)C<u>H</u>$_2CO_2$Me, C(15′)C<u>H</u>$_2CO_2$Me, C(15′)C<u>H</u>$_2CO_2$Me); 4.30—4.21 (m, 3 H, H(18), H(18′), H(18′)); 4.50—4.35 (m, 3 H, H(17), H(17′), H(17′)); 3.82—3.66 (m, 6 H, C(8)C<u>H</u>$_2$Me, C(8′)C<u>H</u>$_2$Me, C(8′)C<u>H</u>$_2$Me); 3.47 (s, 6 H), 3.45 (s, 3 H), 3.39 (s, 6 H), 3.36 (s, 6 H), 3.27 (s, 6 H), 3.19 (s, 6 H), 3.14 (s, 3 H) (C(15)CH_2CO_2<u>Me</u>, C(2)Me, C(7)Me, C(12)Me, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>); 3.23—3.20 (m, 6 H, C(13′)CONH<u>Me</u>, C(13′)CONH<u>Me</u>); 3.69—3.46 (m, 8 H, chlorin-C(13)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCOC(15′)-chlorin (bridge), chlorin-C(17)CONHC<u>H</u>$_2$C<u>H</u>$_2$NHCOC(15′)-chlorin (bridge); 2.78—2.58 (m, 12 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me); 1.71—1.60 (m, 18 H, C(18)Me, C(8)CH_2<u>Me</u>, C(18′)Me, C(8′)CH_2<u>Me</u>, C(18′)Me, C(8′)CH_2<u>Me</u>); −1.63 (br.s, 3 H), −1.94 (br.s, 2 H, III′-NH) (I-NH, III-NH, I′-NH, I′-NH, III′-NH, III′-NH); −2.02 (br.s, 1 H, I-NH, III-NH). MS (MALDI), *m/z*: found: 1906.5801. $C_{111}H_{129}N_{18}O_{12}$. For $[MH]^+$ calculated: 1906.0037.

15,17-Dimethyl ester of e_6-chlorinyl-3-desvinyl-3-(13(2)-methylpheophorbidyloxy)methyl-13-*N*-methylamide (23). Compound **9** (22 mg, 0.033 mmol), 4-dimethylaminopyridine (17 mg, 0.132 mmol), and *N*-methyl-2-chloropyridine iodide (18 mg, 0.066 mmol) were added to a solution of methylpheophorbide *a* (**1**) (20 mg, 0.033 mmol) in toluene (5 mL). The mixture was refluxed for 3 h (TLC: Sorbfil, CCl_4—acetone (10 : 1) as eluent). The mixture was diluted with chloroform (70 mL), pyridine was washed off with 10% HCl, and HCl excess was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (7 : 1) as eluent). Dimer **23** was obtained in a yield of 18 mg (44%). ^{1}H NMR, δ: 9.51 (s, 1 H, H(10)); 9.46 (s, 1 H, H(5)); 9.34 (s, 1 H, H(10′)); 9.31 (s, 1 H, H(5′)); 8.76 (s, 1 H, H(20)); 7.50 (s, 1 H, H(20′)); 7.94 (dd, 1 H, C(3)C<u>H</u>=CH_2, *J* = 11.7 Hz, *J* = 17.7 Hz); 6.72 (d, 1 H, C(3′)CH_2, *J* = 12.9 Hz); 6.61 (d, 1 H, C(3′)CH_2, *J* = 12.3 Hz); 6.52—6.40 (m, 1 H, C(13)CO<u>NH</u>Me); 6.32 (s, 1 H, C(13)C(2′)H); 6.23 (d, 1 H, C(3′)CH=CH<u>H</u> (*trans*), *J* = 18.0 Hz); 6.15 (d, 1 H, C(3′)CH=CH<u>H</u> (*cis*), *J* = 10.5 Hz); 5.58 (d, 1 H, C(15)C<u>H</u>$_2CO_2$Me, *J* = 18.6 Hz); 5.35 (d, 1 H, C(15)C<u>H</u>$_2CO_2$Me, *J* = 18.3 Hz); 4.42 (q, 2 H, H(18), H(18′), *J* = 7.2 Hz); 4.40 (d, 2 H, H(17), H(17′), *J* = 8.1 Hz); 3.92—3.83 (m, 2 H), 3.70—3.64 (m, 2 H) (C(8)C<u>H</u>$_2$Me, C(8′)C<u>H</u>$_2$Me); 3.89 (s, 3 H), 3.72 (s, 6 H), 3.60 (s, 3 H), 3.58 (s, 3 H), 3.44 (s, 3 H), 3.24 (s, 3 H), 3.17 (s, 3 H), 3.02 (s, 3 H) (C(2)Me, C(7)Me, C(12)Me, C(17)$CH_2CH_2CO_2$<u>Me</u>, C(15)CH_2CO_2<u>Me</u>, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>); 3.35 (d, 3 H, C(13)CONH<u>Me</u>, *J* = 4.5 Hz); 2.79—2.70 (m, 1 H), 2.60—2.41 (m, 3 H) (C(17)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me); 2.29—2.02 (m, 4 H, C(17)C<u>H</u>$_2$C<u>H</u>$_2CO_2$Me, C(17′)C<u>H</u>$_2$-C<u>H</u>$_2CO_2$Me); 1.72 (t, 3 H, *J* = 8.1 Hz), 1.42 (t, 3 H, *J* = 7.33 Hz) (C(8′)CH_2<u>Me</u>, C(8)CH_2<u>Me</u>); 1.73 (d, 3 H, *J* = 8.1 Hz), 1.32 (d, 3 H, *J* = 8.3 Hz) (C(18′)Me, C(18)Me); 0.44 (br.s, 1 H, I′-NH); −1.82 (br.s, 1 H, I-NH); −1.97 (br.s, 1 H, III′-NH); −2.06 (br.s, 1 H, III-NH). MS (MALDI), *m/z*: found: 1216.7580. $C_{71}H_{77}N_9O_{10}$. For $[MH]^+$ calculated: 1216.5872.

15,17-Dimethyl ester of e_6-chlorinyl-13-*N*-[2-(13(2)-methylpheophorbidyloxy)ethylamide] (24). 15-17-Dimethyl chlorin e_6 13-*N*-(2-hydroxyethyl)amide (**2**) (60 mg, 0.066 mmol), 4-dimethylaminopyridine (34 mg, 0.264 mmol), and *N*-methyl-2-chloropyridine iodide (35 mg, 0.132 mmol) were added to a solution of methylpheophorbide *a* (**1**) (40 mg, 0.066 mmol) in toluene (10 mL). The reaction mixture was refluxed for 3 h (TLC: Sorbfil, CCl_4—acetone (5 : 1) as eluent). The mixture was diluted with chloroform (70 mL), pyridine was washed off with 10% HCl, and HCl excess was washed with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated, and the residue was chromatographed on silica gel (CCl_4—acetone (7 : 1) as eluent). Dimer **24** was obtained in a yield of 53 mg (63%). ^{1}H NMR, δ: 9.73 (s, 1 H, H(10)); 9.61 (s, 1 H, H(5)); 9.35 (s, 1 H, H(10′)); 9.22 (s, 1 H, H(5′)); 8.85 (s, 1 H, H(20));

8.52 (s, 1 H, H(20′)); 8.17 (dd, 1 H, C(3)C<u>H</u>=CH_2, J = 11.9 Hz, J = 17.9 Hz); 7.98 (dd, 1 H, C(3′)C<u>H</u>=CH_2, J = 12.5 Hz, J = 18.2 Hz); 7.94—7.86 (m, 1 H, chlorin-C(13)CO<u>NH</u>CH_2-CH_2OOCC(13)C(2)-phorbine (bridge)); 6.43 (d, 1 H, C(3)CH=CH<u>H</u> (*trans*), J = 17.7 Hz); 6.32 (s, 1 H, C(13)C(2′)H); 6.29 (d, 1 H, 3′-CH=CH<u>H</u> (*trans*), J = 18.6 Hz); 6.20 (d, 2 H, C(3)CH=CH<u>H</u> (*cis*), C(3′)CH=CH<u>H</u> (*cis*), J = 11.7 Hz); 5.68 (d, 1 H, C(15)C<u>H_2</u>CO_2Me, J = 18.9 Hz); 5.26 (d, 1 H, C(15)C<u>H_2</u>CO_2Me, J = 18.0 Hz); 4.53—4.26 (m, 4 H, H(17), H(17′), H(18), H(18′)); 3.86—3.68 (m, 4 H, C(8)C<u>H_2</u>Me, C(8′)C<u>H_2</u>Me); 3.66—3.50 (m, 4 H, chlorin-C(13)CONH-C<u>H_2</u>C<u>H_2</u>OOCC(13)C(2)-phorbine (bridge)); 3.80 (s, 3 H), 3.56 (s, 6 H), 3.43 (s, 3 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 3.31 (s, 3 H), 3.23 (s, 3 H), 2.93 (s, 3 H) (C(2)Me, C(7)Me, C(12)Me, C(15)CH_2CO_2<u>Me</u>, C(17)$CH_2CH_2CO_2$<u>Me</u>, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>); 2.72—2.37 (m, 4 H), 2.33—1.97 (m, 4 H) (C(17)C<u>H_2</u>C<u>H_2</u>CO_2Me, C(17′)C<u>H_2</u>C<u>H_2</u>CO_2Me); 1.84 (d, 3 H, J = 6.6 Hz), 1.77—1.57 (m, 9 H, J = 7.5 Hz) (C(18)Me, C(18′)Me, C(8)CH_2<u>Me</u>, C(8′)CH_2<u>Me</u>); 0.64 (br.s, 1 H, I′-NH); −1.53 (br.s, 1 H, III′-NH); −1.58 (br.s, 1 H, I-NH); −1.76 (br.s, 1 H, III-NH). MS (MALDI), m/z: found: 1242.6704. $C_{73}H_{80}N_9O_{10}$. For $[MH]^+$ calculated: 1242.6028.

13(1)-Deoxo-13(1)-(13(2)-methylpheophorbidyloxy)methylpyropheophorbide *a* (25). 13(1)-Hydroxymethylpyropheophorbide *a* (**13**) (19 mg, 0.033 mmol), 4-dimethylaminopyridine (17 mg, 0.132 mmol), and *N*-methyl-2-chloropyridine iodide (18 mg, 0.066 mmol) were added to a solution of methylpheophorbide *a* **1** (20 mg, 0.033 mmol) in toluene (5 mL). The reaction mixture was refluxed for 3 h (TLC: Sorbfil, CCl_4—acetone (10 : 1) as eluent). The mixture was diluted with chloroform (70 mL), pyridine was washed off with 10% HCl, and HCl excess was washed off with water. The chloroformic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (CCl_4—acetone (80 : 1) as eluent). Dimer **25** was obtained in a yield of 13 mg (34%). ^{1}H NMR, δ: 9.99 (s, 1 H, H(10′)); 9.66 (s, 1 H, H(10)); 9.64 (s, 1 H, H(5)); 9.35 (s, 1 H, H(5′)); 8.76 (s, 1 H, H(20)); 7.79 (s, 1 H, H(20′)); 8.30 (dd, 1 H, C(3)C<u>H</u>=CH_2, J = 11.6 Hz, J = 17.9 Hz); 7.92 (dd, 1 H, J = 11.6 Hz, C(3′)C<u>H</u>=CH_2, J = 17.9 Hz); 6.54 (s, 1 H, C(13)C(2′)CH); 6.38 (d, 2 H, C(3)CH=CH<u>H</u> (*trans*), C(3′)CH=CH<u>H</u> (*trans*), J = 17.6 Hz); 6.21 (m, 3 H, phorbine-C(13)C(1)C<u>H</u>OCOC(17′)-phorbine, C(13)C(2)CH_2); 6.12 (d, 2 H, C(3)CH=CH<u>H</u> (*cis*), C(3′)CH=CH<u>H</u> (*cis*), J = 11.4 Hz); 4.41 (d, 1 H, J = 17.0 Hz); 4.26 (q, 1 H, J = 7.3 Hz), 3.95—3.85 (m, 3 H) (H(17), H(17′), H(18), H(18′)); 4.00—3.82 (m, 2 H, C(8)C<u>H_2</u>Me, C(8′)C<u>H_2</u>Me); 3.80—3.68 (m, 2 H, C(8)C<u>H_2</u>Me, C(8′)C<u>H_2</u>Me); 3.75 (s, 3 H), 3.54 (s, 3 H), 3.50 (s, 3 H), 3.49 (s, 6 H), 3.30 (s, 3 H), 3.27 (s, 3 H), 3.08 (s, 3 H) (C(2)Me, C(7)Me, C(12)Me, C(17)$CH_2CH_2CO_2$<u>Me</u>, C(2′)Me, C(7′)Me, C(12′)Me, C(17′)$CH_2CH_2CO_2$<u>Me</u>); 2.42—2.28 (m, 4 H), 2.22—2.00 (m, 4 H) (C(17)C<u>H_2</u>C<u>H_2</u>CO_2Me, C(17′)C<u>H_2</u>C<u>H_2</u>CO_2Me); 1.84—1.72 (m, 12 H, C(18)Me, C(18′)Me, C(8)CH_2<u>Me</u>, C(8′)CH_2<u>Me</u>); 0.21 (br.s, 1 H, I′-NH); −1.38 (m, 1 H, I-NH), −1.74 (br.s, 1 H, III-NH′); −3.30 (br.s, 1 H, III-NH). MS (MALDI), m/z: found: 1126.5572. $C_{69}H_{74}N_8O_7$. For $[MH]^+$ calculated: 1126.5681.

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