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Synthesis and Study of Chlorin and Porphyrin Dimers with Ether Linkage

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Abstract: *Novel dimers of chlorophyll compounds (pheophorbide a, chlorin p_6) and model porphyrin with ether linkage were synthesized and separated into components A and B (less and more polar). The ratio of these components was the same for all dimers and irrespective of reaction conditions. Method of dimerization through trifluoroacetoxyethylderivative gave higher yields.*

A great number of porphyrin and chlorin dimeric compounds for the modelling of photosynthetic reaction centers have been synthesized and studied.[1-2] Recently, several new dimeric porphyrins with ether linkages have been synthesized to determine the activity of such compounds as photosensitisers for photodynamic therapy[3-6]. Chlorophyll compounds are also promising photosensitisers[7], but their electronic structure differs from that of porphyrins. This has prompted us to study the ability of chlorophyll compounds to form dimers, already described for porphyrins. The present article is devoted to synthetic aspects of the formation of chlorin dimers with an ether linkage, including the comparison of their physicochemical properties with porphyrin analogs.

We studied various methods of dimerization with methylpheophorbide *a* **8c** and chlorin p_6 trimethyl ester **11b**, and with a simpler compound - porphyrin **6b**.

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Results and discussion

The starting porphyrin **6a** was prepared by ring synthesis from the symmetrical dipyrrolylmethane **2c** and the formyl pyrrole **1** to yield 86% of tripyrrene **3** (Scheme 1). Further addition of another formyl pyrrole **4** gave the biladiene-*a,c* **5**, in 88% yield. The biladiene-a,c **5** with methyl and benzyloxycarbonyl groups at positions 1 and 19, was cyclized to the porphyrin **6a** in nitrobenzene under reflux in the presence of bromine and iodine (42% yield). Porphyrin **6a** was then treated with sodium borohydride to give 3-(1-hydroxyethyl)-porphyrin **6b** in 55% yield.

Monomeric chlorins were obtained by the following ways. Pheophorbide *a* **8a** (Scheme 2) was isolated from the blue-green algae *Spirulina platensis* by acidic treatment of the chlorophyll *a* that is the only chlorophyll in this type of algae.[8] The isolation scheme included the following steps: treatment of the frozen biomass (algal suspension) with phosphate buffer to remove water-soluble proteins, extraction of pigments with acetone, acidic hydrolysis followed by separation of carotenoids with petroleum and, lastly, flash chromatography on silica. The overall yield was no less then 65% based on chlorophyll content.

Pheophorbide *a* **8a** was converted into purpurin *18* **10** by alkaline oxidation in pyrinine-ethanol solution followed by acidic treatment.[9] The yield was *ca.* 90%. The addition of KOH solution in methanol cleaved the purpurin lactonic ring to give chlorin p_6 which was converted to its trimethyl ester **11a** by diazomethane treatment.

The treatment of methylpheophorbide *a* **8a** and chlorin p_6 trimethyl ester **11a** with 33% HBr in acetic acid solution gave 3-(1-hydroxyethyl)derivatives of each compound in yields of 52% and 56% respectively. The attempts to increase the yields using a higher concentration of HBr in acetic acid were unsuccessful due to occurence of secondary reactions (decarboxylation, *etc.*).

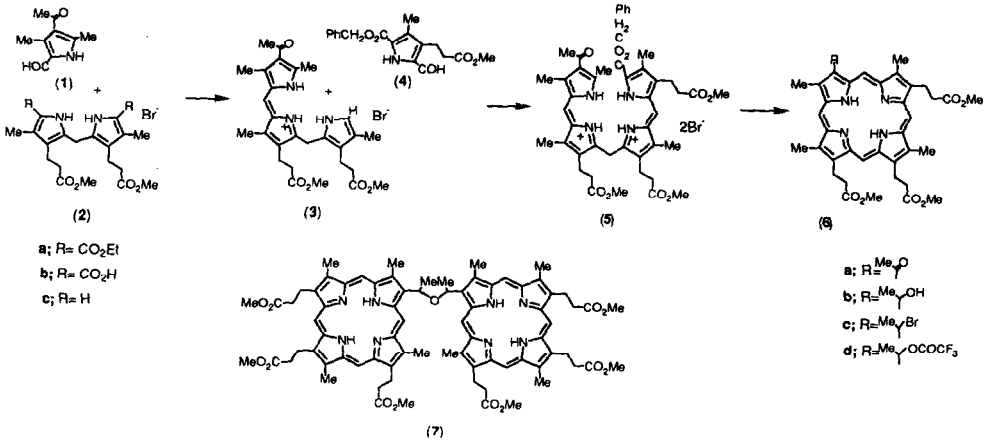
Dimerization of the porphyrin **6b** was achieved in two ways: condensation of **6b** with its 3-(1-bromoethyl) derivative **6c** in 53% yield as well as with 3-(1-trifluoroacetoxyethyl)derivative **6d** in the same yield. Both methods have been developed before.[3,6] Dimeric compounds in the reaction mixture were identified by gel chromatography.[10] In agreement with a recent report[6] we found that the porphyrin dimer **7** consists of two species. Using preparative thin layer chromatography both dimers were isolated and characterized. Surprisingly we found that the more mobile dimer (dimer A) formed in lower amounts than the other dimer (B) and the ratio of dimers was 2/3 (A/B) irrespective of reaction conditions.

Dimers A and B were stable under ordinary conditions, and were not transformed into one another by keeping them in solvents, boiling in chloroform or irradiation with visible light.

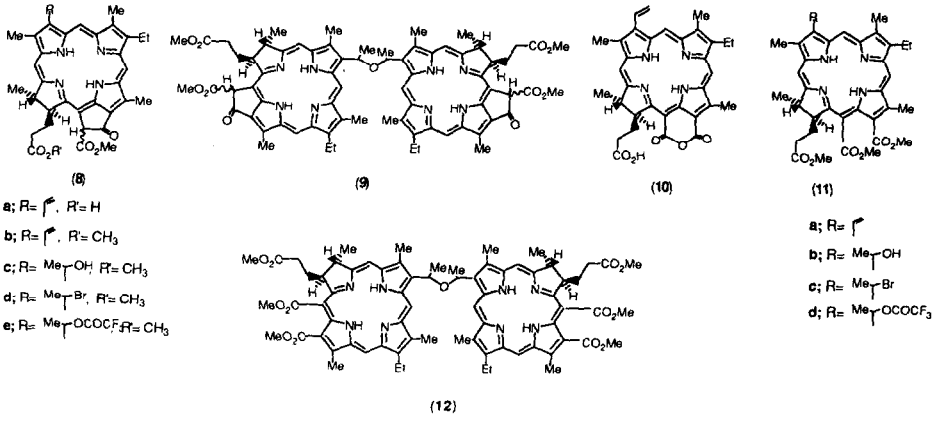
The absorption peaks of the visible spectra for both dimers were broader than those of the monomer. The relationship of the Soret absorption to visible peaks was also decreased for both dimers, but the peak maxima were not changed drastically.

FAB (fast atom bombardment) mass spectra gave molecular ions for dimers A and B and showed identical molecular weights for both isomers. Electron impact mass spectra gave fragmentation only.

The NMR spectra of the dimers exhibited some interesting results. It was found that signals of the methine group in the ether bridge for dimer A were shifted (by 0.3 p.p.m.) to high field compared with the corresponding signals for dimer B. On the other hand, the *meso*-proton signals of dimer A were found at



Scheme 1



Scheme 2

lower field (by 0.2 p.p.m.) with respect to dimer B (Table 1).

The results of fluorescence studies also showed differences between the dimers (Table 2). Both dimers had weaker fluorescence than the monomer (data not showed), but for dimer B it decreased more strongly than for A, suggesting a stronger interaction between macrocycles .

Dimerization of the chlorins was found to be more complicated than the above dimerization of porphyrin **6b**. The yields were lower, the highest being only 30% using trifluoroacetate derivatives **8e** and **11d**. Other methods - catalysis with *p*-toluene sulfonic[11] or trifluoroacetic acid - gave insignificant yields (<5%). Each of the chlorin dimers **9** and **12** consisted of two species as expected from the porphyrin experiments.

Using preparative chromatography on HPTLC-Kieselgel 60H plates each dimer was separated into components A and B (less and more polar). We found that the ratio of these species was the same as for porphyrin dimers - 2/3 (A/B).

All the chlorin dimers synthesized here gave satisfactory mass spectra and showed identical molecular weigths for corresponding isomers.

The NMR spectra of the pheophorbide **9** and the chlorin p_6 **12** dimers (Table 1) exhibited the same trends as those found for the porphyrin dimers A and B. The signals of methine protons at the ether bridge were shifted for dimers A about 0.4 p.p.m. to high field compared to dimers B. In contrast, the *meso*-H signals of dimers A were shifted to the opposite direction by 0.2 p.p.m.. It therefore appears that this is a general trend for both porphyrin and chlorin dimers. Apparently, in spite of conformational flexibility the configuration(s) of the dimers A tends to screen the bridge protons in the magnetic field, while the configuration(s) of dimers B leads presumably toward the screening of macrocycle's protons. At the same time, the analysis of NMR spectra of hydroxyethylchlorins **8c,11b** and their dimers **9,12** was complicated because of the splitting a number of signals. The splitting can be caused by "intermolecular diastereomery", similar to that described for methylpyropheophorbide derivatives,[12] leaving split signals for dimers **9,12** in dilute solution.

Effects of peak broaden and relative decrease of Soret absorption in the visible spectra and the different weakening of intensity in the fluorescence spectra (Table 2) for chlorin A and B dimers **9** and **12** were very similar to those of the porphyrin dimers **7**.

In general, it is possible to suggest that the chlorin dimers B are the stereoisomers with a configurational tendency to form the "more cofacial" arrangement of the macrocycles in comparison with the "more open" stereoisomers A. The dependence of this phenomenon upon different preferred arrangements of the macrocycles for *R,S (S,R)* isomers at the ether linkage, on the one hand, and for R,R and S,S isomers, on the other hand, will be reported later.

Experimental Section

UV-visible spectra were recorded on a Shimadzu UV-240 spectrophotometer. IR-spectra were recorded on a Shimadzu IR-435 instrument. ^{1}H-NMR spectra were recorded on Bruker-WM 250 (250 MHz) and on Bruker MSL 200 (200MHz) for solutions in deuteriochloroform. Fluorescence spectra were recorded on a Shimadzu PF-540 spectrofluorimeter in air-equilibrated acetone. Acetone was purchased from Merck (HPLC grade). No fluorescence impurities were detected. Mass spectra were recorded on a

Table 1. NMR chemical shifts (δ [p.p.m.] from TMS) of dimers (7), (9) and (12).

(Por= porphyrin dimer, Phb= pheophorbide a dimer, Chn= chlorin p_6 dimer; br= broad, sp= splitting)

Compound		*meso*-H	Bridge's methine	Ester Me-groups	Aromatic Me-groups	Propionic chain groups	17-,18-H, 13^2-H	Bridge's Me-group	NH
Por (7)	A	10.18 10.06 9.86 9.66 (br)	6.28	3.73 13,17 3.69 13,17 3.17 8	3.65 12 3.61 18 3.17 2 2.32 7	4.51 13^1,17^1 3.67 8^1 3.42 13^2,17^2 3.17 8^2	-	2.37	-3.82
	B	10.06 9.85 (br) 9.68 9.44	6.60	3.73 13,17 3.69 3.29 8	3.61 12 3.49 18 3.29 2 2.34 7	4.46 13^1,17^1 3.66 8^1 3.44 13^2,17^2 3.29 8^2	-	2.49	-3.88
Phb (9)	A	9.50 10 9.30 5(br,sp) 8.55 20 (sp)	6.05		1.85 18		6.35 13^2 4.5 18 4.3 17	2.20	
	B	9.25 5,10 8.40 20 (br)	6.43		1.77 18		6.30 13^2 4.4 18 4.2 17	2.35	
Cln (12)	A	9.70 10 (sp) 9.40 5(br,sp) 8.67 20 (sp)	5.97	4.27 13 4.21 15	1.93 18 1.60 8^2		5.25 18 4.42 17	2.18	-1.02
	B	9.50 5,10 (sp) 8.55 20 (br)	6.42	4.27 13 4.21 15	1.84 8^2,18		5.15 18	2.31	-1.05

Table 2. Fluorescence data of the dimers (7),(9) and (12) in acetone.

Compound		λ_{EX}*, nm	λ_{fluor}, nm	Σ_{fluor}	Ratio A:B
(7)	A	397.5	624	124	3.9
	B	395	625	31.5	
(9)	A	405	675	75	1.85
	B	406	675	40.5	
(12)	A	394	672	88	2.0
	B	394	692	43	

*These wavelengths were selected because they correspond to dimer absorbtion maxima.

Varian MAT-731 (electron impact), Kratos MS-50 (FAB), and time-of-flight Selmi mass spectrometer (USSR) (with ^{252}Cf ionization). M.p.s. were determined on a Kofler Boetius apparatus. Preparative scale TLC was performed on Chemapol silica L5-40μ and Merck HPTLC-Kieselgel 60. Analytical gel chromatography was performed on a Laboratorne Pristroje Praha machine with Merck Fractogel HW-40(S) column, eluent toluene-DMSO-acetic acid (1:1:1, v/v/v) with 0.05 ml/min, and bis-(etioporphyrin I -1-yl)propane (M.W. 941) and etioporphyrin I (M.W. 479) as standards.

1,3,7,13-*Tetramethyl-2-acetyl-8,12-di(2-methoxy-carbonylethyl)tripyrrene-a Hydrobromide* **3**. To vigorously stirred formylpyrrole **1** (396 mg, 0.92 mmol) and dipyrrolylmethane **2** (930 mg, 1 mmol) solution in dry ether (150 ml), a mixture of 33% HBr in acetic acid (0.5 ml) and dry ether (30 ml) was added dropwise. After 20 min the precipitate was filtered, washed with ether and dried to give **3** (1.2 g, 86%), m.p. 113-115°C (lit.,[13] 113-114°C), $\lambda_{max}(CHCl_3)$/nm 481.

1,3,7,13,18-*Pentamethyl-2-acetyl-8,12,17-tri(2-methoxy-carbonylethyl)-19-benzyloxycarbonylbiladiene-a,c Dihydro-bromide* **5**. — Tripyrrene-*a* **3** (1.25g) and 3,4-dimethyl-2-formyl-5-benzyloxy-carbonylpyrrole **4** (715 mg) were vigorously stirred in acetic acid (10 ml) with 33% HBr in acetic acid (1.3 ml) for 15 min at 20°C. Dry diethyl ether (70 ml) was added and the precipitate was filtered, washed with ether, and dried to yield biladiene **5** (1.85 g, 88%). (Found: C, 60.3; H, 6.0; N, 6.15; Br 17.1. $C_{46}H_{52}N_4O_6{\cdot}2HBr$ requires C, 60.1; H, 5.9; N, 6.1; Br, 17.4%); $\lambda_{max}(CHCl_3)$/nm (relative absorbance) 450 (1.2) and 518 (1.0).

3-*Acetyl* -8-(2-*methoxycarbonylethyl*)*deuteroporphyrin* 13,17-*dimethyl ester* **6a**.—A solution of the foregoing biladiene dihydrobromide **5** (360 mg, 0.37 mmol), bromine (117 mg, 0.72 mmol), and iodine (400 mg, 1.6 mmol) in nitro-benzene (60 ml) was heated under reflux for 10 min. After cooling to room temperature the solution was treated with triethyl amine (1.6 ml), diluted with light petroleum ether (600 ml), and the precipitate was formed. The solution was filtered through a silica column (60 × 20 mm diam.), which was washed with petroleum ether and then with chloroform to elute the product. The precipitate was dissolved in chloroform, combined with eluate, and concentrated by evaporation. The residue was chromatographed on silica column (260 × 30 mm diam.) with chloroform-acetone (98:2, v/v) and then recrystallized from chloroform /methanol to give **6a** (104 mg, 42%), m.p. 179-182°C (lit.,[14] 180-182°C); $\lambda_{max}(CHCl_3)$/nm (relative absorbance) 637 (0.15), 577 (0.83), 550 (1.28), 511 (1.0), 411 (Soret).

3-(1-*Hydroxyethyl*)-8-(2-*methoxycarbonylethyl*)*deuteroporphyrin* 13,17-*dimethyl ester* **6b**.—The sodium borohydride (130 mg), suspended in ethanol (13 ml) was added to the porphyrin **6a** (50 mg) in chloroform (40 ml). The mixture was heated at 35°C for 15 min. Then aqueous 0.01 M HCl solution (70 ml) was added and after that it was neutralized with 5% ammonia in water . The organic solution was washed with water, dried and evaporated. The product was chromatographed on a silica column (150 × 15 mm diam.) with chloroform-acetone (95:5, v/v), and then re-precipitated from chloroform /hexane to give **6b** (28 mg, 55%) (Found: C, 68.0; H, 6.6; N, 8.2 . $C_{38}H_{44}N_4O_7$ requires C, 68.3; H, 6.5; N, 8.4%), λ_{max}(acetone)/nm 621 (ε/$dm^3mol^{-1}cm^{-1}$ 3 600), 567 (5 300), 528.5 (7 200), 497 (10 900), 396 (122 400); δ (CF_3COOD traces) 11.25, 10.88, 10.67, 10.54 (each 1H, s, 5,10,15,20-H), 6.45 (1H, q, 3^1-H), 4.43 (6H, m, 8^1-, 13^1-, 17^1-H), 3.64, 3.52, 3.32 (21H, m, 7 × CH_3), 3.12 (6H, m, 8^2-, 13^2- and 17^2-H), 2.13 (3H, d, 3^2-H); m/z 669 (M^++1).

Bis{1-[8-(2-*methoxycarbonylethyl*)*deuteroporphyrin* 13, 17-*dimethyl ester* -3-*yl*]*ethyl*}*ether* **7**.—Method I. The porphyrin **6b** (10 mg) was dissolved in 33% HBr in acetic acid (3 ml). After 1 h the solvent was distilled off in vacuum. The bromoethylporphyrin **6c** in fresh distilled dry chloroform (3 ml) was mixed with the porphyrin **6b** (10 mg) in equal amount of chloroform. The mixture was stirred at 40°C for 8 h. Then the solution was diluted with chloroform (20 ml), washed with water,

dried and evaporated. The dimer fraction was chromatographed on a silica column (150 × 15 mm diam.) with chloroform to give 7 (10 mg, 53%). Method II. The porphyrin 7 (10 mg) was dissolved in trifluoroacetic anhydride (3 ml). After 15 min the solvent was evaporated in vacuum. Product **6d** in fresh distilled dry chloroform (3 ml) was mixed with the porphyrin **6b** (10 mg) in an equal amount of chloroform. The mixture was stirred at room temperature for 8 h. Then the solution was diluted with chloroform (20 ml) and worked up as in Method I to give the same **7** (10 mg, 53%) (Found C, 69.5; H, 6.7; N, 8.8. $C_{76}H_{86}N_8O_{13}$ requires C, 69.2; H, 6.5; N, 8.5%).

The dimer fraction (10 mg) was chromatographed by preparative TLC on a silica (Chemapol) (plates 20 × 20 cm adsorbent 0.75 mm), eluted with carbon tetrachloride-acetone (15:1, v/v). Two substances were collected, and then re-precipitited from chloroform/hexane to give dimer A (3.5 mg) and dimer B (5.5 mg). Dimer A: λ_{max}(acetone)/nm 622.5 (ε/dm^{3}mol^{-1}cm^{-1} 3 100), 569 (5 400), 531 (7 300), 498 (11 500), 397.5 (110 000); δ 10.18, 10.06, 9.86, 9.66 (br) (each 1H, s, 5,10,15,20-H), 6.28 (1H, q, 3^1-H), 4.51 (4H, m, 13^1- and 17^1-H), 3.73, 3.69 (each 3H, s, 13^3- and 17^3-OCH_3), 3.67 (2H, m, 8^1-H), 3.65 (3H, s, 12^1-H), 3.61 (3H, s, 18^1-H), 3.42 (4H, m, 13^2-and 17^2-H), 3.17 (8H, m, 8^2-H, 2^1-H and 8^3-OCH_3), 2.37 (3H, d, 3^2-H), 2.32 (3H, s, 7^1-H), -3.82 (2H, s, N-H); m/z 1319 (M^++1). Dimer B: λ_{max}(acetone)/nm 622.5 (ε/dm^{3}mol^{-1}cm^{-1} 3 300), 570 (3 800), 531 (7 600), 499 (11 600), 395 (113 000); δ 10.06, 9.85 (br), 9.68, 9.44 (each 1H, s, 5,10,15,20-H), 6.60 (1H, q, 3^1-H), 4.46 (4H, m, 13^1- and 17^1-H), 3.73, 3.69 (each 3H, s, 13^3-and 17^3-OCH_3), 3.66 (2H, m, 8^1-H), 3.61 (3H, s, 12^1-H), 3.49 (3H, s, 18^1-H), 3.44 (4H, m, 13^2- and 17^2-H), 3.29 (8H, m, 8^2-H, 2^1-H and 8^3-OCH_3), 2.49 (3H, d, 3^2-H), 2.34 (3H, s, 7^1-H), -3.88 (2H, s, N-H); m/z 1319 (M^++1).

Pheophorbide a **8a**.—Frozen biomass of *Sp. platensis* algae (dry weight 17%) (600 g) was thawed out at room temperature , mixed with phosphate buffer pH 6.0 (6 l) and centrifuged (3000 rpm, 35 min). The supernatant was separated, and the residue was stirred with acetone (900 ml). The suspension was filtered through filter paper under vacuum.The chlorophyll extract was vigorously shaken with petroleum ether (1 l). The petroleum phase which contained chlorophyll was collected and evaporated. The residue was re-dissolved in acetone (0.5 l), concentrated hydrochloric acid (0.75 l) was added and the mixture was stirred for 1.5 h. Then water (1 l) was added and carotenoids were extracted with petroleum ether (3 × 1 l). The water phase was collected, neutralized with 10% aqueous NaOH to pH 6.0 and pheophorbide *a* was extracted with dichloromethane (600 ml). Pheophorbide was purified by flash chromatography on silica, and then recrystallized from ethanol to give **8a** (0.95 g, 67%), m.p. 190-195°C (lit.,[15] 190-195°C); λ_{max} (acetone)/nm 667 (ε/dm^{3}mol^{-1}cm^{-1} 55 700), 610 (7 980), 535 (9 500), 507 (12 000), 408.5 (119 500) (lit.,[15] 667 (55 200), 409 (119 200)); δ 9.53 (1H, s, 10-H), 9.38 (1H, s, 5-H), 8.59 (1H, s, 20-H), 7.98 (1H, m, 3^1-H_X), 6.28 and 6.21 (2H, dd, 3^2-H_{AB}), 6.25 (1H, s, 13^2-H), 4.46 (1H, m, 18-H), 4.23 (1H, m, 17-H), 3.87 (3H, s, 13^2-OCH_3), 3.68 (3H, s, 12^1-H), 3.66 (2H, q, 8^1-H), 3.42 (3H, s, 2^1-H), 3.23 (3H, s, 7^1-H), 2.50 (2H, m, 17^1-H), 2.27 (2H, m, 17^2-H), 1.82 (3H, d, 18^1-H), 1.68 (3H, t, 8^2-H) and epimer *a*' signals 9.48 (s, 10-H), 9.32 (s, 5-H), 8.50 (s, 20-H), 3.79 (s, 13^2-OCH_3). Treatment **8a** with diazomethane gave pheophorbide *a* methyl ester **8b**; m.p. 205-206°C (from chloroform/methanol) (lit.,[16] 205-206°C); λ_{max} (CH_2Cl_2)/nm 668 (ε/dm^{3}mol^{-1}cm^{-1} 46 100), 610 (6 900), 535.5 (9 700), 505.5 (11 200), 409 (116 100) (lit.,[16] 666 (45 000), 406 (118 000)) nm.

$31,32$-Didehydrorhodochlorin-15-carboxylic acid-δ-lacton **10** (purpurin 18).—To pheophorbide *a* (60 mg) in pyridine (5 ml) were added diethyl ether (40 ml) and 30% KOH in methanol (30 ml). The solution was stirred with for 30 min while air was bubbled through it, and then diluted with water (500 ml) and neutralized. Pigments were extracted with chloroform , washed with water and evaporated. The precipitate was re-dissolved in acetone-diethyl ether (1:1,v/v) and evaporated again. These operations were repeated until purpurin 18 was completely formed (using TLC control). The product was chromatographed on a silica column (100 × 20 mm diam.) with chloroform-acetone (6:1, v/v) and recrystallized from chloroform /hexane to yield **10** (51 mg,

90%), m.p. >300°C (lit.,[17] 270-280°C) (Found C, 68.8; H, 5.6; N, 8.8. $C_{33}H_{32}N_4O_5$, calc. C, 70.2; H, 5.7; N, 8.8%); ν_{max}(KBr)/cm^{-1} 3300 (NH), 1740 and 1700 (CO); λ_{max} (acetone)/nm 696 (ε/dm^{3}mol^{-1}cm^{-1} 46 200), 646.5 (9 800), 544 (22 700), 506.5 (6 300), 479 (4 200), 407 (116 000), 361 (45 400) (lit.,[9] 695 (41 800), 407 (104 000)); δ 9.58 (1H, s, 10-H), 9.35 (1H, s, 5-H), 8.56 (1H, s, 20-H), 7.86 (1H, m, 3^1-H_X), 6.27 and 6.19 (2H, dd, 3^2-H_{AB}), 5.18 (1H, m, 18-H), 4.38 (1H, m, 17-H), 3.77 (3H, s, 12^1-H), 3.67 (2H, q, 8^1-H), 3.33 (3H, s, 2^1-H), 3.15 (3H, s, 7^1-H), 2.78 (2H, m, 17^1-H), 2.47 (2H, m, 17^2-H), 1.72 (3H, d, 18^1-H), 1.65 (3H, t, 8^2-H), -0.76 (2H, s, N-H); m/z (relative intensity) 564 (M^+, 100%), 538 (M^+—CH=CH, 35), 519 (M^+—CO_2H, 26), 506 (M^+—$CHCO_2H$, 35), 491 (M^+—$CH_2CH_2CO_2H$, 61).

$31,32$-Didehydrorhodochlorin-15-carboxylic acid 13,15,17-tri-methyl ester **11a** (chlorin p_6 trimethyl ester).—Purpurin 18 **10** (50 mg) in tetrahydrofuran (30 ml) was stirred with 5% aqueous KOH (20 ml) for 10 min, and water (200 ml) was added. The solution was neutralized with HCl and the product was extracted with chloroform. The organic phase was washed with water, dried and treated with diazomethane. After chromatography on a silica column (100 × 20 mm diam.) with chloroform-acetone (9:1, v/v) and re-precipitation from chloroform /petroleum ether **11a** was obtained (47 mg, 87%), m.p. 236-238°C (lit.,[17] 236°C); λ_{max} ($CHCl_3$) 670 (ε/ dm^{3}mol^{-1}cm^{-1} 41 000), 615 (4 600), 564 (1 800), 529 (5 300), 499 (11 000), 403.5 (143 000); δ 9.65 (1H, s, 10-H), 9.38 (1H, s, 5-H), 8.63 (1H, s, 20-H), 7.88 (1H, m, 3^1-H_X), 6.15 and 6.05 (2H, dd, 3^2-H_{AB}), 5.14 (1H, m, 18-H), 4.44 (1H, m, 17-H), 4.16 and 4.11 (6H, d, 13^1- and 15^1–OCH_3), 3.60 (2H, q, 8^1-CH_2), 3.57 (3H, s, 17^3-OCH_3), 3.47 (3H, s, 12^1-H), 3.31 (3H, s, 2^1-H), 3.12 (3H, s, 7^1-H), 2.20 (4H, m, 17^1- and 17^2-H), 1.81 (3H, d, 18^1-H), 1.63 (3H, t, 8^2-H), -1.40 (2H, s, N-H).

3-*Desvinyl*-3-(1-*hydroxyethyl*)*pheophorbide a* 17-*methyl ester* **8c**.—Methylpheophorbide *a* **8b** was disolved in 33% HBr in acetic acid (15 ml) and the mixture was kept in the dark for 12 h. Then water was added (50 ml), and 2 h later the mixture was neutralized with 30% aqueous NaOH. The precipitate was extracted with chloroform, washed with water, dried and treated with diazomethane in ether . The product was chromatographed on a silica column (150 × 15 mm diam.) with chloroform-acetone (7:1, v/v) and re-precipitated from chloroform/hexane to give **8c** (27 mg, 52%) (Found C, 68.3; H, 6.0; N, 8.8. $C_{36}H_{40}N_4O_6$ requires C, 69.2; H, 6.4; N, 9.0%); λ_{max} ($CHCl_3$)/nm 657 (ε/dm^{3}mol^{-1}cm^{-1} 44 800), 600.5 (6 600), 532 (8 400), 501 (9 800), 471 (3 600), 405 (104 200); δ 9.66 (1H, s, 10-H), 9.52 (1H, s, 5-H), 8.54 (1H, s, 20-H), 6.41 (1H, q, 3^1-H), 6.26 (1H, s, 13^2-H), 4.40 (1H, m, 18-H), 4.28 (1H, m, 17-H), 3.92 (3H, s, 13^2-OCH_3), 3.68 (3H, s, 17^3-OCH_3), 3.65 (2H, q, 8^1-H), 3.63 (3H, s, 12^1-H), 3.45 (3H, s, 2^1-H), 3.23 (3H, s, 7^1-H), 2.50 (2H, m, 17^1-H), 2.20 (2H, m, 17^2-H), 2.11 (3H, d, 3^2-H), 1.77 (3H, d, 18^1-H), 1.67 (3H, t, 8^2-H); m/z (relative intensity) 625 (M^++1, 85%), 567 (M^++1—CO_2CH_3, 100).

3-(1-Hydroxyethyl)rhodochlorin-15-carboxylic acid 13,15, 17-trimethyl ester **11b** (hydroxyethylchlorin p_6 t.m.e.).—Chlorin p_6 t.m.e. **11a** (50 mg) was treated as described for **8c** to yield **11b** (25 mg, 52%) (Found: C, 66.7; H, 6.8; N, 8.4. $C_{36}H_{42}N_4O_7$ requires C, 67.3; H, 6.5; N, 8.7%); λ_{max} ($CHCl_3$)/nm 662 (ε/dm^{3}mol^{-1}cm^{-1} 38 100), 609 (5 200), 560 (9 100), 527 (4 900), 497 (9 900), 399 (94 500); δ 9.66 (1H, s, 10-H), 9.60 (1H, s, 5-H), 8.74 (1H, s, 20-H), 6.12 (1H, q, 3^1-H), 5.17 (1H, m, 18-H), 4.41 (1H, m, 17-H), 4.25 (3H, s, 13^1-OCH_3), 4.18 (3H, s, 15^1-OCH_3), 3.67 (2H, q, 8^1-H), 3.63 (3H, s, 12^1-H), 3.55 (3H, s, 17^3-OCH_3), 3.30 (3H, s, 2^1-H), 3.18 (3H, s, 7^1-H), 2.41 (2H, m, 17^1-H), 2.08 (2H, m, 17^2-H), 2.00 (3H, d, 3^2-H),1.86 (3H, d, 18^1-H), 1.67 (3H, t, 8^2-H), 0.07 (2H, s, N-H); m/z 643 (M^++1).

Bis[1-(3-*desvinylpheophorbide a* 17-*methyl ester* -3-*yl*)*ethyl*] *ether* **9**.—Pheophorbide **8c** was condensed as described for porphyrin **7** using method II to yield dimer **9** (14 mg, 28%) (Found C, 69.95; H, 6.15; N, 9.0. $C_{72}H_{78}N_8O_{11}$ requires C, 70.2;

H, 6.3; N, 9.1%). The product was chromatographed on plates with HPTLC-Kieselgel 60 (10 × 20 cm) with chloroform-carbon tetrachloride-acetone (7:7:1, v/v/v) to give dimer A (5.0 mg) and dimer B (7.5 mg). Dimer A: λ_{max} (acetone)/nm 663 (ε/dm^{3}mol^{-1}cm^{-1} 41 400), 606.5 (6 400), 533 (8 000), 504 (8 800), 469 (3 800), 405 (79 800); δ 9.50 (1H, s, 10-H), 9.30 (1H, br s, 5-H), 8.55 (1H, s, 20-H), 6.35 (1H, s, 13^2-H), 6.05 (1H, q, 3^1-H), 4.5 (1H, m, 18-H), 4.3 (1H, m, 17-H), 2.20 (3H, d, 3^2-CH_3), 1.85 (3H, d, 18^1-H); m/z (relative intensity) 1230.6 (M^++1, 90%), 1172.7 (M^+—CO_2CH_3, 100), 1114.3 (16), 609.7 (M^+_{8c}—OH, 47), 550.8 (40). Dimer B: λ_{max} (acetone)/nm 661.5 (ε/dm^{3}mol^{-1}cm^{-1} 42 100), 605 (7 500), 533 (9 800), 504 (10 100), 467.5 (4 700), 406 (91 600); δ 9.25 (2H, m, 10-H and 5-H), 8.40 (1H, br s, 20-H), 6.43 (1H, m, 3^1-H), 6.30 (1H, s, 13^2-H), 4.4 (1H, m, 18-H), 4.2 (1H, m, 17-H), 2.35 (3H, d, 3^2-H),1.77 (3H, d, 18^1-H); m/z (relative intensity) 1231.0 (M^++1, 100%), 1173.0 (M^+—CO_2CH_3, 70), 608.1 (M^+_{8c}—OH, 40), 549.7 (19).

Bis[1-(*rhodochlorin*-15-*carboxylic acid* 13,15,17-*tri-methyl ester* -3-*yl*)*ethyl*]*ether* **12**.—Chlorin **11b** (50 mg) was condensed as described for porphyrin **7** using method II to yield dimer **12** (15 mg, 30%) (Found C, 68.0; H, 6.45; N, 8.9 . $C_{36}H_{82}N_8O_{14}$ requires C, 68.2; H, 6.5; N, 8.8%). The product was chromatographed on plates with HPTLC-Kieselgel 60 (10 × 20 cm) with chloroform-carbon tetrachloride-acetone (7:9:1, v/v/v) to give dimer A (5.0 mg) and dimer B (7.5 mg). Dimer A: λ_{max} (acetone)/nm 663 (ε/dm^{3}mol^{-1}cm^{-1} 36 700), 609 (4 400), 526 (4 800), 496 (10 300), 394 (108 700); δ 9.70 (1H, s, 10-H), 9.40 (1H, br s, 5-H), 8.67 (1H, s, 20-H), 5.97 (1H, q, 3^1-H), 5.25 (1H, m, 18-H), 4.42 (1H, m, 17-H), 4.27 (3H, s, 13^1-OCH_3), 4.21 (3H, s, 15-OCH_3), 2.18 (3H, d, 3^2-H),1.93 (3H, d, 18^1-H), 1.60 (3H, t, 8^2-H), -1.02 (2H, s, N-H); m/z (relative intensity) 1267.0 (M^++1, 100%), 1236.5 (M^++1—OCH_3, 9), 1222.4 (M^+—CO_2H, 4), 1209.0 (M^+—CO_2CH_3, 5), 1179.4 (M^+—$CH_2CH_2CO_2CH_3$, 2), 641.0 (M^+_{11b}—H, 3), 633.1, 625.7 (M^+_{11b}—OH, 13). Dimer B: λ_{max} (acetone)/nm 661.5 (ε/dm^{3}mol^{-1}cm^{-1} 38 000), 609 (4 900), 525.5 (5 300), 496 (10 900), 394 (121 300); δ 9.50 (2H, m, 10-H and 5-H), 8.55 (1H, br s, 20-H), 6.42 (1H, q, 3^1-H), 5.15 (1H, m, 18-H), 4.35 (1H, m, 17-H), 4.27 (3H, s, 13^1-OCH_3), 4.21 (3H, s, 15^1-OCH_3), 2.31 (3H, d, 3^2-H),1.84 (6H, m, 18^1-H and 8^2-H), -1.05 (2H, s, N-H); m/z (relative intensity) 1266.8 (M^++1, 100%), 1236.0 (M^++1—OCH_3, 6), 1229.9 (M^+—CO_2H, 4), 1209.5 (M^+— CO_2CH_3, 2), 1179.9 (M^+—$CH_2CH_2CO_2CH_3$, 2), 640.5 (M^+_{11b}—H, 13), 625.5 (M^+_{11b}—OH, 18).

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