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Synthesis of chlorins possessing a fused naphthalene ring

Dipanjan Sengupta and Byron C. Robinson*

Miravant Pharmaceuticals, Inc., 336 Bollay Drive, Santa Barbara, CA 93117, USA

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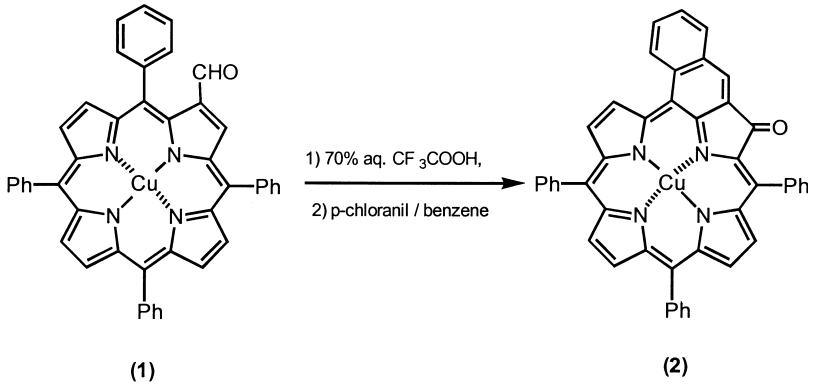
Abstract—Novel chlorins with fused naphthalene ring were synthesized from octaalkyl-20-(2′-hydroxymethylphenyl)porphyrins via acid catalyzed cyclization.

The most commonly used photoselective compounds currently being evaluated as potential drug candidates in the field of photodynamic therapy (PDT)[1] are the tetrapyrrolic macrocyclic compounds called porphyrins.[2a,b] Chlorins[3] are compounds that differ from porphyrins in that one of the pyrrole rings has been reduced. In the field of PDT, compounds that absorb in the red region of visible spectrum are important, as light penetration through tissues has been shown to be greatest for light of long wavelength. For this reason, tetrapyrroles such as chlorins and bacteriochlorins have been evaluated as potential photosensitizers[4] for the treatment of tumors. Our search for potential new photosensitizers has led to the discovery of a relatively simple route to chlorin analogues with a fused naphthalene moiety, namely naphthochlorins. Earlier reports on the synthesis of chlorin ring systems possessing fused aromatic rings, for example, benzochlorins, have been prolific in the literature. Nickel(II) or copper(II) octaethylbenzochlorins have been synthesized via intramolecular cyclization of the *meso*-acrylaldehyde substituted Ni(II) or Cu(II) octaethylporphyrin under acidic conditions.[5] Previously, from our laboratory, cyclization of *meso*-(1-hydroxy-2-propenyl)octaethylporphyrin to octaethylbenzochlorin had been reported[7] on scales up to 100 g. Johnson and Dolphin[8] have reported syntheses of chlorins possessing fused nitrogen containing rings. Smith et al.[9] and Cavaleiro et al.[10] have reported synthesis of naphthalene fused chlorins (naphthochlorins) from tetraphenyl porphyrins. Recently, Ishkov et al.[11a,b] have shown that intramolecular cyclization of copper(II) 5,10,15,20-tetraphenyl-2-formylporphyrin (**1**) followed by oxidation, provided the copper(II) *keto*-naphthochlorin (**2**) in 70% yield (Scheme 1). However, until now, there has been no report on the synthesis of naphthochlorin ring systems from octaalkylporphyrins and consequently their chemical and spectroscopic properties are unknown. We envisioned, quite reasonably, that a variety of functionalized naphthochlorin compounds may be synthesized from *meso*-(2′-hydroxymethylphenyl) octaalkyl-substituted porphyrins. To test this hypothesis we synthesized biladienes (**3**), (**7**) and (**11**) by reaction of appropriate dipyrromethanes and 3,4-diethyl-2-formyl pyrrole following the procedures of Johnson et al.[14] and Grigg et al.,[15]



(1) (2)

Scheme 1.

Keywords: photodynamic therapy; naphthochlorin.

* Corresponding author. Tel.: +1-805-685-9880; fax: +1-805-685-7981; e-mail: brobinson@miravant.com

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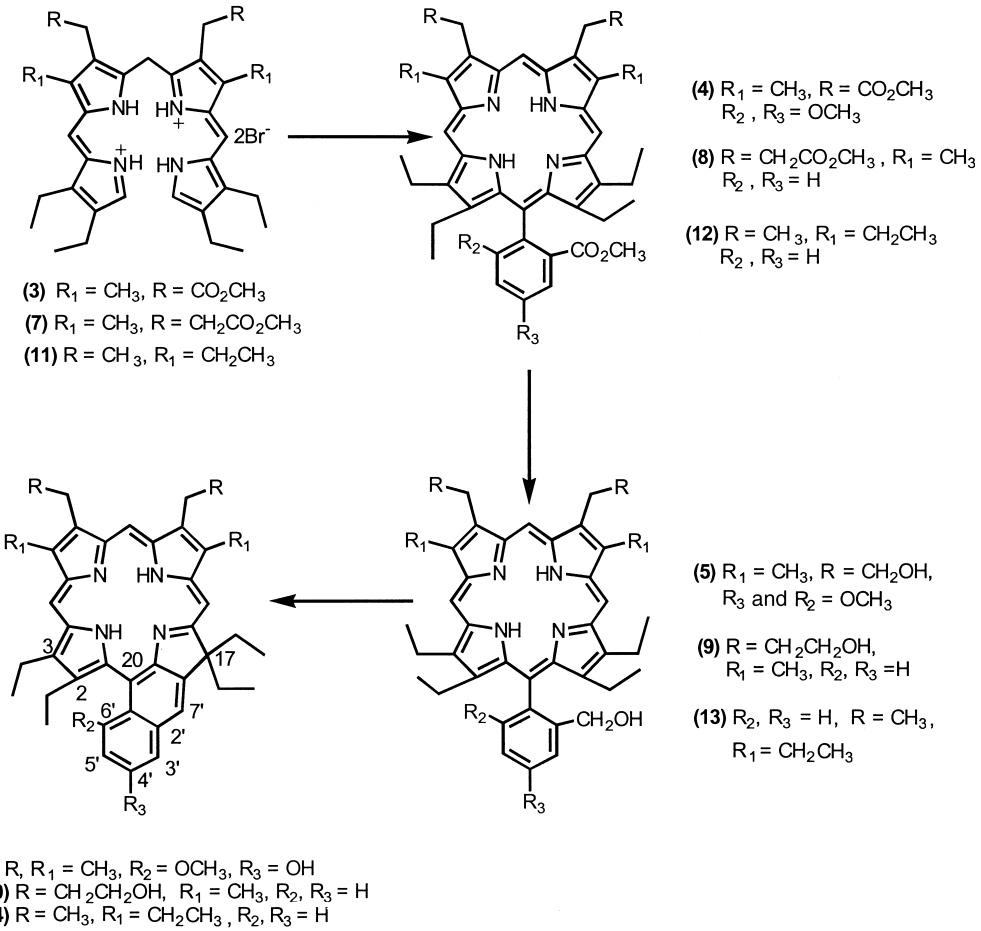


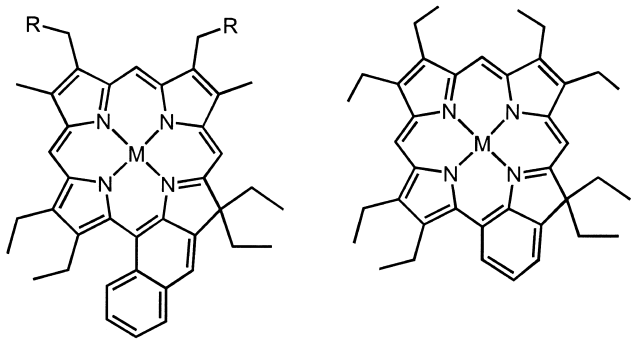
Scheme 2.

respectively. *meso*-(2′-Carbomethoxyphenyl)porphyrin (**4**) was synthesized the treating biladiene (**3**)[12] with methyl 3,5-dimethoxy-2-formylbenzoate (Aldrich) in methanol in the presence of HBr (cat.) (65%) (Scheme 2). Porphyrin (**4**) was converted to (**5**) in 98% via lithium aluminium hydride reduction of the ester groups. Cyclization of compound (**5**) in phosphoric acid at 100°C produced naphthochlorin (**6**) in 30% yield.

A ^{1}H NMR spectrum of (**6**) showed three *meso*-proton singlets at δ 9.28, 8.85 and 8.28 ppm. Two aromatic protons at C-3′ and C-5′ had chemical shifts at δ 7.31 ppm (doublet, J=2.0 Hz) and 6.75 ppm (J=2.0 Hz), respectively. The remaining aromatic proton at C-7′ had a chemical shift at δ 8.30 ppm. It was observed during the cyclization reaction, that demethylation occurred on one of the methoxyl groups on the fused naphthalene moiety. The ^{1}H NMR spectrum showed a one-proton singlet at δ 10.02 ppm, which corresponded to the aromatic hydroxyl group while only one methoxyl singlet was observed at δ 3.71 ppm. The structure of (**6**) was further confirmed by NOE enhancement experiments. Irradiation of the signal at δ 7.31 (C-3′ proton) gave enhancement at the aromatic proton (C-7′) singlet at δ 8.30 ppm and vice versa. This established that the singlet at δ 8.30 ppm was associated with a naphthalene ring proton and not a *meso*-proton. NOE enhancements were observed on the naphthalene ring protons at δ 6.75 (C-5′ proton) and 7.31 ppm (C-3′ proton) when the hydroxy (C-4′) signal at 10.02 ppm was irradiated. Irradiation of the methoxy signal at 3.71 ppm (C-6′) showed enhancement of the aromatic (C-5′) signal at 6.75 ppm. These experiments established unequivocally that the methoxy group at C-4′ had been selectively demethylated during the acid catalyzed cyclization step. Loss of the methyl group was also confirmed by a high resolution electrospray ionization (ESI) mass spectrum which showed *m*/*z* at 673.3763 (M+H).

Using a similar synthetic methodology, we were interested in producing a napthochlorin that had no functionality on the annelated napthalene ring. Porphyrin (**8**) was synthesized from biladiene (**7**) and methyl 2-formylbenzoate[13] in isopropyl alcohol using *p*-toluenesulfonic acid as catalyst. Use of other solvents (e.g. methanol) and HBr as catalyst resulted in low yields of the desired porphyrin. The esters on porphyrin (**8**) were reduced with lithium aluminium hydride to give porphyrin (**9**) (82%). Heating porphyrin (**9**) with phosphoric acid at 95°C resulted in formation of naphthochlorin (**10**) in 63% yield (Scheme 2). A ^{1}H NMR spectrum of (**10**) showed *meso*-protons as singlets at δ 9.22, 8.06 and 8.26 ppm. The naphthalene ring proton resonances were observed at δ 8.82 (d, J=8.1 Hz), 8.30 (d, J=8.1 Hz), 7.98 (s), 7.79 (t, J=6.9 Hz) and 7.66 (t, J=7.2 Hz). The structure was further confirmed by high-resolution ESI mass spectrum that showed a strong peak at *m*/*z* 655.4019 (M+H).

We were interested to synthesize octaethylnaphthochlorin



(15) M= $SnCl_2$, R = CH_2CH_2OH **(17)** M = $SnCl_2$
(16) M= InCl, R = CH_2CH_2OH **(18)** M = InCl

Figure 1.

(**14**), and compare the chemical properties and reactivity of the macrocycle with that of octaethylbenzochlorin.[6,7] Thus, reaction of octaethylbiladiene (**11**)[15] and methyl 2-formylbenzoate[13] in methanol with HBr (cat.) gave (2′-carbomethoxyphenyl) octaethylporphyrin (**12**) (82%) (Scheme 2). Reduction of porphyrin (**12**) with DIBAL in methylene chloride followed by cyclization with phosphoric acid at 100°C gave naphthochlorin (**14**) in 60% yield. The *meso* protons of naphthochlorin (**14**) had chemical shifts at δ 8.61, 8.26 and 8.01 ppm. The naphthalene protons of (**14**) were observed at δ 9.22 (s), 8.84 (d, J=8.1 Hz), 8.30 (d, J=7.2 Hz), 7.81 (t, J=6.9 Hz), 7.69 (t, J=6.9 Hz) ppm.

The UV/visible spectrum of naphthochlorin (**6**) displayed absorbances at λ_{max} (ϵ $M^{-1}\,cm^{-1}$) 436 (73,000), 585 (7700), 627 (9250), 686 (22,800) nm. The band I(Qy) absorption was red shifted 28 nm compared to octaethylbenzochlorin λ_{max} (658 nm). Naphthochlorin (**10**) showed absorption bands at λ_{max} (ϵ $M^{-1}\,cm^{-1}$) 428 (408,000), 533 (7000), 569 (8000), 620 (8000), and 676 (21,000) nm. The band I absorption was red shifted by 18 nm compared to octaethylbenzochlorin. Napthochlorin (**14**) displayed absorption bands at λ_{max} (ϵ $M^{-1}\,cm^{-1}$) 426 (105,000), 534 (6600), 568 (7500), 618 (7800), and 676 (21,100) nm. The longer wavelength absorption observed in napthochlorin (**6**) (λ_{max} 686 nm) compared to naphthochorins (**10**) and (**14**) probably represents distortion of the tetrapyrrolic ring due to the steric hindrance between the naphthalene methoxy group (at C-6′) and the adjacent ethyl group (at C-2) on the pyrrole ring.

Metal free naphthochorins derived from the tetraphenylporphyrin series display band I absorptions[11b] at λ_{max} 683 nm. Metallated derivatives display a blue shift in the band I(Qy) absorptions[11b] to λ_{max} 669 nm. It was of interest to observe whether metallation of the octaalkylnaphthochlorins would result in a blue shift, or a red shift in the band I absorption maxima. Naphthochlorin (**10**) was metallated with tin(IV) and indium(III) to generate the naphthochorins (**15**) and (**16**), respectively (Fig. 1).

Band I absorptions of (**15**) and (**16**) were observed at λ_{max} 688 and 684 nm, respectively. This represented a red shift of 12 and 8 nm over the metal free napthochlorin (**10**) band I absorption (λ_{max} 676 nm). Interestingly however, the indium(III) and tin(IV) octaethylbenzochlorin derivatives (**17**) and (**18**) have band I absorptions at λ_{max} 687 and 691 nm, respectively. Thus, the extension of the chlorin chromophore via annelation to the naphthalene ring red shifts the band I absorption in the metal free series relative to octaalkylbenzochlorins (676 vs. 662 nm), but does not result in a greater red shift on metallation than seen with metallooctaalkylbenzochlorins.

An in vitro biological evaluation of compounds (**15**) and (**16**) was performed using a standard V-79 lung fibroblast cells (Chinese Hamster) MTT assay.[16] Final drug concentrations for light treatments were 0.01, 0.05, 0.1, 1.0 and 2.0 μM. Light treatment was performed using a diode laser at a wavelength of 689 nm, with a power setting of 354 mW and a fluence of 1.25 J/cm^2 for 7 min 22 s. After 24 h incubation, plates were read on a plate reader spectrophotometer (Spectra Max 250) at an absorbance of 560 nm. There were six wells/drug dose for new photosensitizer and control wells. Under these conditions compounds (**15**) and (**16**) showed an EC(50) value (drug concentration needed to kill half the cells in the plate following light treatment) of 0.04 μM and 0.08 μM, respectively. Thus, naphthochlorins (**15**) and (**16**) are potent photosensitizers in cell based assays.

With a defined synthetic route to octaalkylnaphthochlorins, we are currently modifying the naphthochlorins to produce other annelated chlorin compounds. A thorough evaluation of naphthochlorins and their derivatives as photosensitizers in the field of PDT is underway and will be reported elsewhere.

1. Experimental

1.1. General

Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise mentioned. All reactions were done under subdued lighting. Silica gel 60 (230–400 mesh) was used for column chromatography. Analytical thin layer chromatography was performed on Merck 60 F254 silica gel (pre-coated on aluminum). ^{1}H NMR spectra were recorded using Unity Innova Varian 500 MHz or Bruker Advance AM-300 spectrometer. Chemical shifts of proton spectra are expressed in parts per million relative to chloroform in deuterated chloroform (set at 7.24 ppm) or DMSO-d_6 (set at 2.5 ppm). Electronic spectra were recorded on a Beckman DU 640 spectrophotometer. Electrospray mass spectra were recorded on PE Sciex-Qstar quadrupole/time of flight mass spectrometer. FAB and EI mass spectra were recorded on VG-70E double focussing magnetic sector mass spectrometer.

1.1.1. 8,12-Di(methoxycarbonylmethyl)-2,3,17,18-tetraethyl-7,13-dimethyl-20-(4′,6′-dimethoxy-2′-methoxycarbonyl) phenyl porphyrin (4). To a stirred solution of biladiene (**3**)[14] (500 mg, 0.67 mmol) in methanol (125 mL) was added methyl 2-formyl-3,5-dimethoxybenzoate (Aldrich) (1.8 g, 8 mmol) followed by 33% HBr (in acetic acid) (500 μL). The reaction mixture was refluxed for 2 h 20 min, cooled to room temperature, poured into water

(200 mL), neutralized with sodium bicarbonate and extracted with methylene chloride (3×100 mL). The combined methylene chloride layer was washed with water (2×100 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by column chromatography (silica: 10% acetone–hexane; 3% acetone–methylene chloride) to get (**4**) 345 mg (65%). UV/visible (methylene chloride/isopropyl alcohol, 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 407 (202,000), 505 (16,000), 539 (7000), 576 (7000), 629 (3000) nm; MS (ESI) *m/z* 789.4 (M+H); HRMS, $C_{46}H_{52}N_4O_8$ 789.3863 (M+H); found 789.3856 (M+H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 2H, *meso*-H), 9.91 (s; 1H, *meso*-H), 7.44 (d, *J*=2.5 Hz, 1H, Ar-H), 6.97 (d, *J*=2.5 Hz, 1H, Ar-H), 5.02 (double doublet, *J*=16 Hz, 4H, –C*H*$_2$–$COOCH_3$), 4.15 (s, 3H, –$COOCH_3$), 3.97 (q, *J*=7.5 Hz, 4H, –C*H*$_2$$CH_3$), 3.76 (s, 6H, –$COOCH_3$), 3.65 (s, 6H, *pyrrolic*-CH_3), 3.54 (s, 3H, –OCH_3), 3.02 (m, 2H, –C*H*$_2$$CH_3$), 2.78 (m, 2H, –C*H*$_2$$CH_3$), 2.29 (s, 3H, –$OCH_3$), 1.82 (t, *J*=7.5 Hz, 6H, –CH_2C*H*$_3$), 1.11 (t, *J*=7.5 Hz, 6H, –CH_2C*H*$_3$), –2.86 (br, 1H, –NH), –2.98 (br, 1H, –NH).

1.1.2. 8,12-Di(hydroxyethyl)-2,3,17,18-tetraethyl-7,13-dimethyl-20-(4′,6′-dimethoxy-2′-hydroxymethyl) phenyl porphyrin (5). A solution of porphyrin (**4**) (327 mg, 0.41 mmol) in anhydrous THF (7 mL) was added (in drops) to a stirred slurry of LAH (129 mg, 3.4 mmol) in anhydrous THF (5 mL) at room temperature. Stirring was continued for 50 min. The excess LAH was decomposed by dropwise addition of 0.2N HCl to the cooled reaction mixture (15°C). The reaction mixture was diluted with water (50 mL) and extracted with methylene chloride (3×25 mL). The combined methylene chloride layer was washed with water (2×30 mL), dried (Na_2SO_4) and the solvent removed to give the reduced product (**5**), 286 mg (98%); UV/visible (methylene chloride: isopropyl alcohol, 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 405 (188,000), 504 (14,600), 538 (7000), 573 (7000), 626 (2400) nm; MS (ESI) *m/z* 705.4 ($M+H^+$); HRMS, $C_{43}H_{52}N_4O_5$ 705.4016 (M+H)); found: 705.4003 (M+H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.18 (s, 2H, *meso*-H), 10.11(s, 1H, *meso*-H), 7.16 (d, *J*=2.5 Hz, 1H, Ar-H), 6.92 (d, *J*=2.5 Hz, 1H, Ar-H), 5.19 (t, *J*=5 Hz, 2H, –CH_2), 4.9 (t, *J*=5.5 Hz, 2H, –OH), 4.24 (m, 8H, –CH_2–CH_2–), 4.07 (s, 3H, –OCH_3), 4.03 (q, *J*=7.5 Hz, 4H, –CH_2), 3.65 (s, 6H, *pyrrolic*-CH_3), 3.57 (s, 3H, –OCH_3), 3.12 (m, 2H, –CH_2), 2.8 (m, 2H, –CH_2), 1.82 (t, *J*=7.5 Hz, 6H, –CH_3), 1.162 (t, *J*=7.5 Hz, 6H, –CH_3), −3.14 (s, 1H, –NH), −3.28 (s, 1H, –NH).

1.1.3. Naphthochlorin (6). A solution of (**5**) (230 mg, 0.3 mmol) in phosphoric acid (85% solution) (20 mL) was heated with stirring under nitrogen at 100°C for 5 h. The solution was cooled to room temperature, poured into ice water (75 mL), neutralized with 20% aqueous NaOH and extracted with a chloroform–pyridine mixture (3:2) (2×40 mL). The combined organic layer was washed with water (2×30 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by column chromatography (silica: with increasing polarity of mobile phase: 3% methanol–methylene chloride; 5% methanol–methylene chloride; 8% methanol–methylene chloride) to give (**6**) 65 mg (30%). UV/visible (chloroform: isopropyl alcohol, 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 436 (73,000), 583 (7700), 627 (9250), 686 (22,800) nm; MS (ESI) *m/z* 673.3 (M+H); HRMS, $C_{42}H_{48}N_4O_4$ 673.3753 (M+H); found: 673.3763 (M+H); Calc. C:H:N; C, 72.90; H, 7.18; N, 8.30; Found C, 72.8; H, 7.1; N, 8.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.02 (s, 1H, Ar-OH), 9.28 (s, 1H, *meso*-H), 8.85 (s, 1H, *meso*-H), 8.30 (s, 1H, Ar-H), 8.28 (s, 1H, *meso*-H), 7.31 (d, *J*=2 Hz, 1H, Ar-H), 6.75 (d, *J*=2 Hz, 1H, Ar-H), 5.08 (t, *J*=5.5 Hz, 1H, –OH), 5.02 (t, *J*=5.5 Hz, 1H, –OH), 4.07 (q, *J*=7 Hz, 2H, –CH_2–), 3.97 (q, *J*=6 Hz, 2H, –CH_2–), 3.83 (m, 2H, –CH_2–), 3.71 (s, 3H, –OCH_3), 3.62–3.53 (m, 2H, –CH_2–), 3.42 (m, 1H, –CH_2–), 3.19 (s, 3H, *pyrrolic*-CH_3), 3.16 (s, 3H, *pyrrolic*-CH_3), 2.92 (m, 2H, –CH_2–), 2.64 (m, 2H, –CH_2–), 2.55 (m, 1H, –CH_2–) 1.53 (t, *J*=7.5 Hz, 3H, –CH_2–C*H*$_3$), 0.39 (t, *J*=7.5 Hz, 3H, –CH_2–C*H*$_3$), 0.09 (t, *J*=7.5 Hz, 3H, –CH_2–C*H*$_3$), −0.08 (t, *J*=7.5 Hz, 3H, –CH_2–C*H*$_3$).

1.1.4. 8,12-Di(methoxycarbonylethyl)-2,3,17,18-tetraethyl-7,13-dimethyl-20-(2′-methoxycarbonylphenyl) porphyrin (8). To a solution of biladiene (**7**)[15] (10.0 g, 12.9 mmol) in isopropyl alcohol (1.2 L) was added methyl 2-formyl benzoate[13] (34.3 g, 0.13 mol) followed by *p*-toluenesulfonic acid (6.0 g). The reaction mixture was refluxed for 1 h 45 min, cooled to room temperature. The volume of the reaction was reduced to approximately 750 mL by rotoevaporation and the resulting solution poured into water (1.5 L), neutralized with sodium bicarbonate and extracted with methylene chloride (3×500 mL). The combined methylene chloride layers were washed with water (2×750 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by column chromatography (silica: 10% acetone–hexane; 2% acetone–methylene chloride) to give (**8**) 4.3 g (44%); UV/visible (methylene chloride: isopropyl alcohol, 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 398 (155,000), 497 (13,000), 530 (9000), 567 (6000), 620 (4000) nm; MS (EI) *m/z* 756 (M^-); HRMS, $C_{46}H_{52}N_4O_6$ 756.388 (M^+); Found 756.3893 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) d 10.11 (s, 2H, *meso*-H), 9.86 (s, 1H, *meso*-H), 8.39 (d, *J*=7.5 Hz, 1H, Ar-H), 8.27 (d, *J*=7.5 Hz, 1H, Ar-H), 7.9 (t, *J*=7.5 Hz, 1H, Ar-H), 7.8 (t, *J*=7.5 Hz, 1H, Ar-H), 4.37 (t, *J*=7.5 Hz, 4H, –CH2–), 3.96 (m, 4H, –C*H*$_2$$CH_3$), 3.65 (s, 6H, –$COOCH_3$), 3.63 (s, 6H, *pyrrolic*-CH_3), 3.27 (t, *J*=7.5 Hz, 4H, –CH_2–), 2.68 (m, 4H, –C*H*$_2$$CH_3$), 2.59 (s, 3H, Ar-$COOCH_3$) 1.82 (t, *J*=7.5 Hz, 6H, –CH_2C*H*$_3$), 1.05 (t, *J*=7.5 Hz, 6H, 6H, –CH_2C*H*$_3$), −2.91(br, 1H, –NH), −3.04 (br, 1H, –NH).

1.1.5. Naphthochlorin (10). A solution of (**8**) (4.6 g, 6 mmol) in anhydrous THF (200 mL) was added in drops to a stirred slurry of LAH (1.36 g, 36 mmol) in anhydrous THF (110 mL). The mixture was stirred in room temperature for 10 min. Excess LAH was decomposed with slow addition of 0.2N aqueous HCl to the cooled reaction mixture (15°C). The reaction mixture was poured into water (500 mL) and extracted with methylene chloride (3×250 mL). The combined methylene chloride layers were washed with water (1×300 mL), dried (Na_2SO_4) and the solvent removed to get (**9**) 3/3 g (82%). The crude product was used directly for the next step without further purification.

A solution of porphyrin (**9**) (386 mg, 0.5 mmol) in phosphoric acid (50 mL) was heated with stirring under nitrogen

at 95–110°C for 1 h and 10 min. The reaction was monitored by analyzing the UV/visible spectrum of reaction aliquots at regular intervals (absorption at 675 nm appeared and the Soret band appeared at 421 nm). The solution was cooled to room temperature, poured into ice-water (150 mL), neutralized with 25% aqueous sodium hydroxide solution and extracted with methylene chloride (3×50 mL). The combined methylene chloride layers were washed with water (2×75 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by column chromatography (silica: with increasing polarity of mobile phase: 10% acetone–CH_2Cl_2; 30% acetone–CH_2Cl_2; 5% methanol–CH_2Cl_2) to give naphthochlorin (**10**), which was crystallized from a mixture of methylene chloride–isopropyl alcohol–hexane (235 mg, 63%). UV/visible (chloroform: isopropyl alcohol, 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 428 (108,000), 533 (7000), 569 (8000), 620 (8000), 676 (21,000) nm; MS (ESI) *m/z* 655.4 (M+H); HRMS, $C_{43}H_{50}N_4O_2$ 655.4011 (M+H); found: 655.4019 (M+H); Calc. C:H:N; C, 78.86; H, 7.69; N, 8.55%; Found C, 78.8; H, 7.6; N, 8.4%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H, *meso*-H), 8.82 (d, *J*=8.1 Hz, 1H, Ar-H), 8.8 (s, 1H, *meso*-H), 8.29 (d, 1H, *J*=8.1 Hz, Ar-H), 8.26 (s, 1H, *meso*-H), 7.98 (s, 1H, Ar-H), 7.79 (t, *J*=7 Hz, Ar-H), 7.64 (t, *J*=7.2 Hz, Ar-H), 3.86 (q, *J*=5.7 Hz, 4H, –CH_2–), 3.72 (t, *J*=7.2 Hz, 2H, –CH_2–), 3.61 (m, 4H, –CH_2–), 3.49 (m, 1H, non-equivalent-CH_2–), 3.27 (m, 1H, non-equivalent-CH2–), 3.12 (s, 3H, *pyrrolic*-CH_3), 3.11 (s, 3H, *pyrrolic*-CH_3), 2.65 (m, 4H, –CH_2–), 2.25 (m, 4H, –CH_2–), 1.53 (t, *J*=7.5 Hz, 3H, –CH_2–CH_3), 0.59 (t, *J*=7.5 Hz, 3H, –CH_2–CH_3), 0.24 (t, *J*=7.2 Hz, 3H, –CH_2–CH_3), 0.03 (t, *J*=7.2 Hz, 3H, –CH_2–CH_3).

1.1.6. 2,3,7,8,12,13,17,18-Octaethyl-20-(2′-carbomethoxyphenyl) porphyrin (12). To a stirred solution of octaethylbiladiene (**11**)[15] (500 mg, 0.7 mmol) in methanol (125 mL) was added methyl 2-formylbenzoate (1.8 g, 11 mmol) followed by 31% HBr (in acetic acid) (500 μL). The solution was refluxed for 3 h, cooled to room temperature, poured into water (200 mL) and neutralized with sodium bicarbonate. The aqueous mixture was extracted with methylene chloride (3×100 mL). The combined methylene chloride layer was washed with water (2×100 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by column chromatography (silica: 5% ethyl acetate–methylene chloride) to give porphyrin (**12**) 400 mg (82%). UV/visible (methylene chloride–isopropyl alcohol; 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 407 (186,000), 505 (15,000), 539 (7000), 575 (7000), 628 (2500) nm; MS (ESI) *m/z* 669.4 (M+H); HRMS, $C_{44}H_{52}N_4O_2$ 668.4168 (M+H); Found 669.4137 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 2H, *meso*-H), 9.91 (s, 1H, *meso*-H), 8.42 (d, *J*=7.8 Hz, 1H, Ar-H), 8.31 (d, *J*=7.5 Hz, Ar-H), 7.93 (t, *J*=7.8 Hz, 1H, Ar-H), 7.83 (t, *J*=7.5 Hz, 1H, Ar-H), 4.14–4.3.91 (m, 12H, –CH_2–), 2.82 (m, 4H, –CH_2–), 2.59 (s, 3H, –$COOCH_3$), 1.95 (t, *J*=7.5 Hz, 6H, –$CH_2C H_3$), 1.92 (t, *J*=7.5 Hz, 6H, –$CH_2C H_3$), 1.86 (t, *J*=7.5 Hz, 6H, –$CH_2C H_3$), 1.09 (t, *J*=7.2 Hz, 6H, –$CH_2C H_3$), −2.79 (brs, 1H, –NH), 2.98 (brs, 1H, –NH).

1.1.7. Octaethylnaphthochlorin (14). A solution of porphyrin (**12**) (111 mg, 0.16 mmol) in methylene chloride (25 mL) was added dropwise to a solution of DIBAL (1.42 g, 10 mmol, 5 mL of 2 M solution) in THF in room temperature and the resulting solution was stirred for 50 min. Excess DIBAL was decomposed by the slow addition of ethyl acetate (10 mL). Phosphoric acid (80% solution, 15 mL) was added and organic solvents were removed by rotoevaporation under reduced pressure. The phosphoric acid solution was stirred and heated at 100°C for 2 h. Water (50 mL) was added to the reaction mixture, which was then cooled to room temperature and the solid precipitate filtered. The solid residue was purified by column chromatography (silica: 1% acetone–methylene chloride) to give naphthochlorin (**14**) 60 mg (58%). UV/visible (methylene chloride–isopropyl alcohol; 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 426 (105,000), 534 (6600), 568 (7500), 618 (7800), 676 (21,100) nm; MS (ESI) *m/z* 623.4 (M+H); HRMS, $C_{43}H_{50}N_4$ 623.4113 (M+H): Found 623.4085 (M+H); Calc. C:H:N; C, 82.91; H, 8.09; N, 8.99%; Found C, 82.8; H, 7.9; N, 8.8%. ^{1}H NMR (300 MHz, $CDCl_3$) d 9.22 (s, 1H, Ar-H), 8.84 (d, *J*=8.1 Hz, 1H, Ar-H), 8.61 (s, 1H, *meso*-H), 8.30 (d, *J*=7.2 Hz, 1H, Ar-H), 8.27 (s, 1H, *meso*-H), 8.02 (s, 1H, *meso*-H), 7.81 (t, *J*=6.9 Hz, 1H, Ar-H), 7.69 (t, *J*=6.9 Hz, Ar-H), 3.6 (m, 11H, –CH_2–), 3.28 (m, 1H, CH–), 2.8–2.55 (m, 4H, –CH_2–), 1.66 (m, 12H, –$CH_2C H_3$), 1.54 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$), 0.63 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$), 0.29 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$), 0.06 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$).

1.1.8. Tin(IV) Naphthochlorin dichloride (15). To a solution of naphthochlorin (**10**) (100 mg, 0.15 mmol) in acetic acid (10 mL) was added $SnCl_2$ (60 mg, 0.3 mmol) followed by sodium acetate (86 mg, 1 mmol) and the mixture was refluxed for 1.5 h. After cooling to room temperature water (50 mL) was added and the solution was extracted with methylene chloride (2×25 mL). The combined methylene chloride layer was washed with 1N HCl (2×25 mL), dried (Na_2SO_4) and the solvent removed. The residue was dissolved in methanol (3 mL) and potassium carbonate (40 mg, 0.27 mmol) was added and the solution was stirred at room temperature for 17 h. The resulting solution was poured into water (20 mL), neutralized with dilute HCl (6N) and extracted with methylene chloride (3×10 mL). The combined methylene chloride layers were washed with water (2×10 mL) followed by 1N HCl (2×10 mL), dried (Na_2SO_4) and the solvent removed. The residue was crystallized from methylene chloride–hexane to give (**15**) 58 mg. UV/visible (methylene chloride–isopropyl alcohol; 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 434 (76,000), 453 (82,000), 633 (10,000), 688 (33,000) nm; $C_{43}Cl_2H_{48}N_4O_2Sn$ *m/z*=842, MS (LR-FAB) *m/z* 842 (M^+); Calc. C:H:N; C, 61.30; H, 5.74; N, 6.65%; Found C, 61.2; H, 5.6; N, 6.5%. ^{1}H NMR (300 Hz, $CDCl_3$) δ 9.62 (s, 1H, *meso*-H), 9.46 (s, 1H, *meso*-H), 8.82 (d, *J*=8 Hz, 1H, Ar-H), 8.50 (s, 1H, *meso*-H), 8.40 (d, *J*=7 Hz, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 7.90 (t, *J*=7 Hz, 1H, Ar-H), 7.78 (t, *J*=7.2 Hz, 1H, Ar-H), 3.94 (m, 4H, –CH_2–), 3.81 (m, 4H, –CH_2–), 3.67–3.51 (m, 2H, –CH_2–), 3.31 (s, 3H, *pyrrolic*-CH_3), 3.19 (s, 3H, *pyrrolic*-CH_3), 2.95–2.83 (m, 2H, –CH_2–), 2.71 (m, 2H, –CH_2–), 2.35 (m, 6H, –CH_2–),1.80 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$), 0.82 (t, *J*=7.5 Hz, 3H, –$CH_2C H_3$), 0.34 (2t, *J*=7.5 Hz, 6H, –$CH_2C H_3$).

1.1.9. In(III) Naphthochlorin chloride (16). To a solution

of naphthochlorin (**10**) (200 mg, 0.3 mmol) in acetic acid (10 mL) was added $InCl_3$ (101 mg, 0.45 mmol) and sodium acetate (123 mg, 1.5 mmol) and the mixture was refluxed under nitrogen for 2 h. After cooling to room temperature, water was added dropwise with stirring. The precipitated solid was filtered and dried, dissolved in methylene chloride (50 mL) and washed with 1N HCl (2×25 mL), dried (Na_2SO_4) and the solvent removed. The residue was dissolved in methanol (5 mL) and potassium carbonate (63 mg, 0.45 mmol) was added. The mixture was stirred at room temperature for 5 h. and poured into water (20 mL). The precipitated solid was filtered, dried and purified by column chromatography (silica: 5% methanol–methylene chloride; methanol–methylene chloride–acetic acid: (10:90: 0.04) and the major fraction collected. The crude product was dissolved in methylene chloride (50 mL) and washed with 1N HCl (2×25 mL), dried (Na_2SO_4) and the solvent removed to give (**16**). The residue was dissolved in dichloromethane and precipitated from hexane to give a dark green powder (90 mg). UV/visible (chloroform: isopropyl alcohol; 1:1) λ_{max} (ϵ M^{-1} cm^{-1}) 447 (98,000), 601 (6800), 630 (10,200), 684 (35,900) nm; MS (FAB) *m/z* 767 (M−Cl); HRMS, $C_{43}H_{48}N_4O_2InCl$ 767.2813 (M−Cl); Found 767.2822 (M−Cl); Calc. C:H:N; C, 64.30; H, 6.02; N, 6.97%; Found C, 64.2; H, 5.9; N, 6.8%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H, *meso*-H), 9.16 (s, 1H, *meso*-H), 8.91 (d, *J*=8.1 Hz, 1H, Ar-H), 8.35 (s, 1H, *meso*-H), 8.33 (d, *J*=8 Hz, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.83 (t, *J*=7.2 Hz, 1H, Ar-H), 7.71 (t, *J*=7 Hz, 1H, Ar-H), 3.81 (m, 6H, $-CH_2-$), 3.57 (m, 6H, $-CH_2-$), 3.22 (s, 3H, *pyrrolic*-CH_3), 3.08 (s, 3H, *pyrrolic*-CH_3), 2.89–2.69 (m, 2H, $-CH_2-$), 2.54 (m, 2H, $-CH_2-$), 2.24 (m, 4H, $-CH_2-$), 1.56 (t, *J*=7.5 Hz, 3H, $-CH_2CH_3$), 0.39 (m, 6H, $-CH_2CH_3$), 0.05 (t, *J*=7.5 Hz, 3H, $-CH_2CH_3$).

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