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Synthesis of a bis-vinylogous chlorin possessing a fused naphthalene ring

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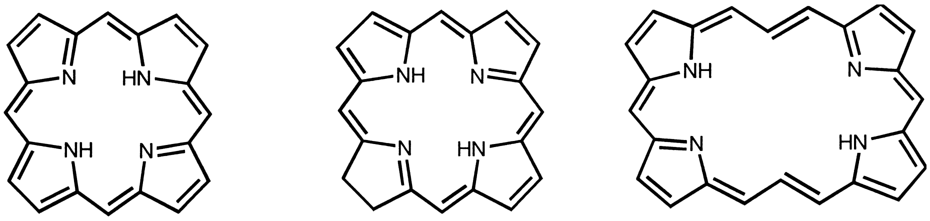
Abstract—A novel expanded chlorin with a fused naphthalene ring was synthesized from an octaalkyl-24-(2′-hydroxymethylphenyl) bis-vinylogous porphyrin via an acid catalyzed cyclization. © 2002 Elsevier Science Ltd. All rights reserved.

Porphyrins (**1**) (Fig. 1) and chlorins (**2**) are a unique class of tetrapyrrolic macrocycles that occur in natural systems, and contribute to various functions in the life process.[1] Due to their interesting biological properties, porphyrins have been widely studied and modified. Such modifications have lead to synthesis of contracted, expanded or isomeric porphyrinic compounds.[2] Frank and co-workers[3a,b] have reported the synthesis of an expanded porphyrin termed a bis-vinylogous porphyrin (**3**). Such macrocycles are of interest to those studying the aromaticity of expanded annulenes. Additionally, such macrocycles have been explored as potential new photosensitizers in the field of photodynamic therapy (PDT).[3–5] The extended conjugation in bis-vinylogous porphyrins produces significant red shifts in the Soret bands when compared to the UV/visible absorption spectra of porphyrins. Unfortunately, there are little significant absorptions greater than 600 nm in these macrocycles. As it is recognized that light penetration through tissues is a significant aspect of photodynamic therapy, especially in regard to oncological applications, compounds absorbing strongly at wavelengths greater than 630 nm offer the hope of better therapeutic outcomes for deeply situated tumors. Toward this goal, we were interested in exploring chemistries that would modify bis-vinylogous porphyrins such that longer wavelength derivatives may be produced. In the field of porphyrin chemistry, reduction of one pyrrolic ring system on the macrocycle generally results in a red shift in the lowest energy Qy absorption band, with a simultaneous increase in the molar absorptivity of the Qy absorption band. As there is no example in the literature of reduced derivatives of bis-vinylogous porphyrins, i.e. bis-vinylogous chlorins, it was of interest to us to explore the synthesis and chemical properties of these ring systems. We envisioned that a bis-vinylogous naphthochlorin (**11**) (Scheme 2) may be synthesized from *meso*-(2′-hydroxymethylphenyl) substituted bis-vinylogous octaalkylporphyrins following a similar synthetic procedure outlined for the synthesis of octaalkylnaphthochlorins.[6] In this instance, naphthochlorins have been produced via an acid catalyzed cyclization of a *meso*-(2-hydroxymethyl)phenyl moiety with the pyrrolic ring system. Herein, we describe the synthesis and characterization of a bis-vinylogous naphthochlorin (**11**).

The synthesis of the bis-vinylogous naphthochlorin was envisaged to proceed through the bis-vinylogous biladiene



(1) **(2)** **(3)**

Figure 1.

Keywords: expanded porphyrin; bis-vinylogous naphthochlorin; chlorin; photodynamic therapy.

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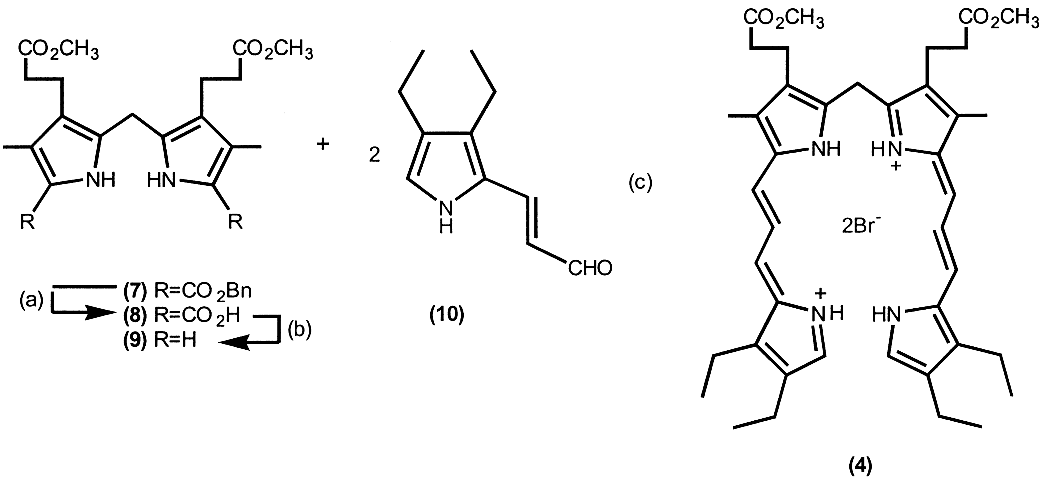
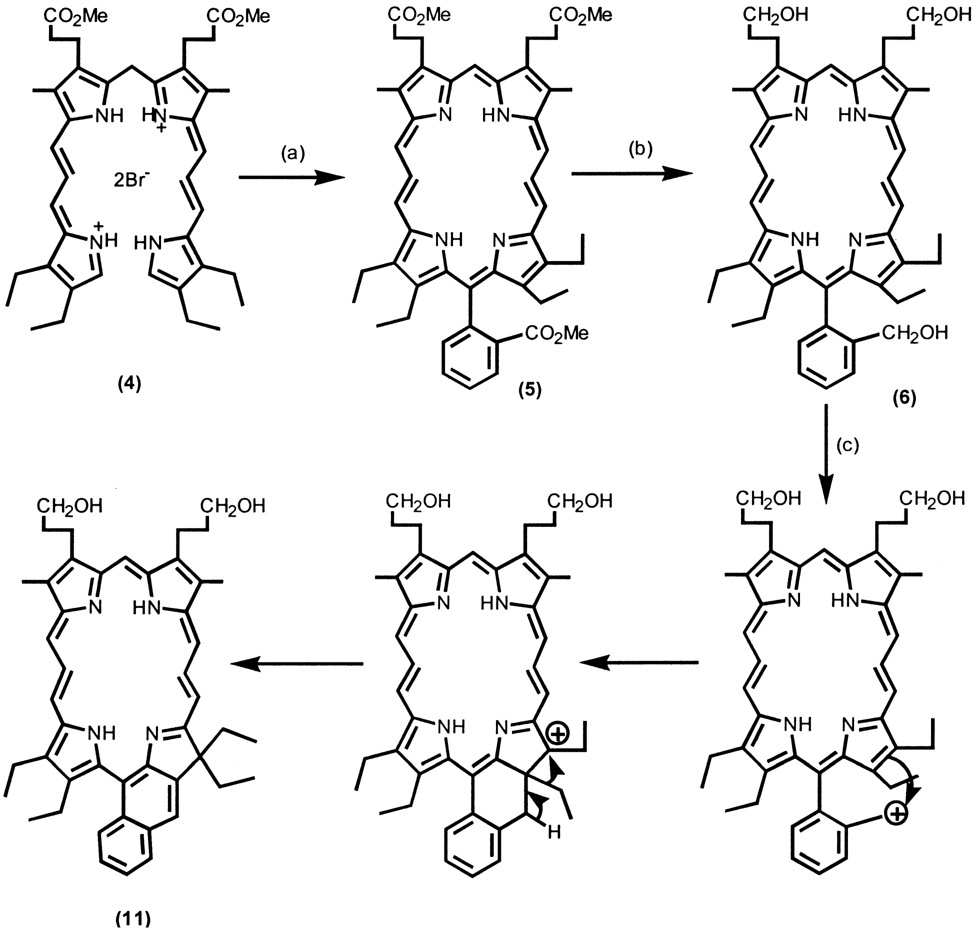


Scheme 1. *Reagents and conditions*: (a) H_2–5%Pd/C–THF; (b) DMF, reflux, 2 h; (c) methanol, 33% HBr (in acetic acid), −78°C to −10°C.

(**4**). Bis-vinylogous biladiene (**4**) was synthesized[3a,9] by condensation of 2 equiv. of vinylogous aldehyde (**10**)[3a,7] and the dipyrromethane (**9**)[8] in 77% yield (Scheme 1).

The *meso*-(2-carbomethoxyphenyl)bis-vinylogous porphyrin (**5**) (Scheme 2) was obtained by reacting biladiene (**4**) with methyl 2-formyl benzoate[10] in the presence of 33% HBr (in acetic acid) in methanol, followed by in situ oxidation with chloranil (53%). As was observed previously in the naphthochlorin series,[6] the reaction required periodic additions of fresh methyl 2-formyl benzoate and HBr to progress. This most likely is due to the decomposition of the aldehyde under the acidic conditions, as the aldehyde is sensitive to acids.[11] The reaction progress was monitored by TLC until no further starting biladiene was observed.

Reduction of the bis-vinylogous porphyrin esters in (**5**) proceeded smoothly using lithium aluminum hydride to give the tri-alcohol bis-vinylogous porphyrin (**6**) (30%). This molecule displayed a UV/visible spectra consistent



Scheme 2. *Reagents and conditions*: (a) (i) methyl 2-formylbenzoate, HBr (cat), methanol, reflux; (ii) chloranil; (b) LAH, THF; (c) H_3PO_4, 75°C.

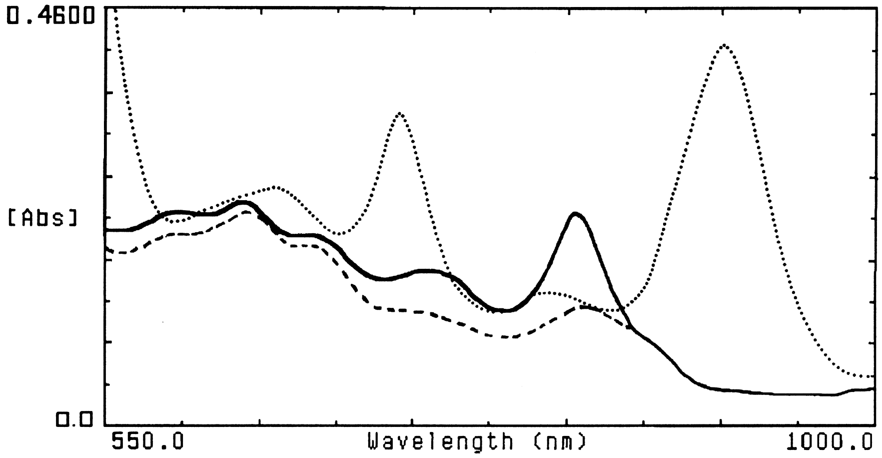


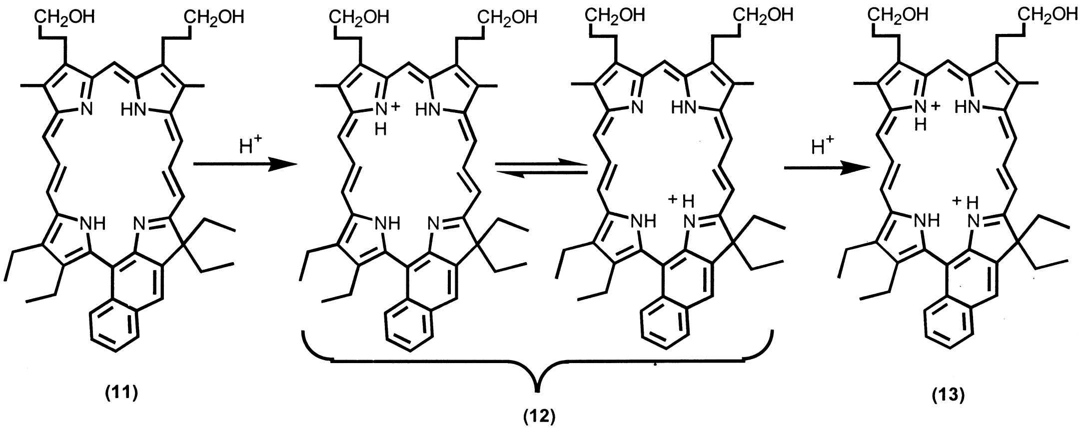
Figure 2. Electronic spectra of the Q band region of (**11**) in different solvents; CH_2Cl_2/TFA (excess) (···) (i.e. (**13**)); CH_2Cl_2 (stabilized (i.e. (**12**)) (—); CH_2Cl_2/Et_3N (excess) (- - -).

with other aryl substituted bis-vinyologous porphyrins (i.e. (**5**)) and was not further characterized, but used directly in the acid cyclization step. The acid catalyzed rearrangement (phosphoric acid, 75°C, 30 min) of porphyrin (**6**) afforded bis-vinylogous naphthochlorin (**11**) in 56% yield. A high-resolution mass spectra showed a molecular ion at *m*/*z* 707.4328 (M+H) consistent with the structure.

The UV/visible spectrum of (**11**) (Fig. 2) showed absorption peaks that were highly dependent on the dissolution solvent, perhaps indicating that the molecule is readily protonated to different degrees in different solvents. In dichloromethane/isopropyl alcohol (1:1), for example, (**11**) displayed a Soret absorption at 471 (ε=94600 M^{-1} cm^{-1}) nm as well as small Q band absorptions at 633 (ε=13700 M^{-1} cm^{-1}), 669 (ε=12330 M^{-1} cm^{-1}), 743 (ε=11240 M^{-1} cm^{-1}) and 831 (ε=12610 M^{-1} cm^{-1}) nm. In dichloromethane containing triethylamine (excess), a similar but not identical absorption spectra to that seen in dichloromethane/isopropyl alcohol occurs, with the Soret band absorbing at 469 nm, while weak Q band absorptions occurred at 591, 631, 669, 720 and 831 nm (relative intensities: 23.6:2:2.4:1.8:1:1). In a newly opened bottle of stabilized reagent grade dichloromethane, the compound displayed a broad absorption band at 485 nm and three Q bands at 675, 749 and 829 nm (relative intensities: 8:1:1.4:3). In this case, it is assumed that the observed electronic spectra arises from the monocationic bis-vinylogous naphthochlorin(s) (**12**) (Scheme 3), produced by sequestering available protons in the solvent. In dichloromethane containing an excess of TFA, peaks were observed at 398, 505 (Soret), 648, 719, 810, 909 nm (relative intensities: 8:36.2:2.5:4:1:5) which presumably arises from the dicationic bis-vinylogous napthochlorin (**13**).

A ^1H NMR spectrum of (**11**) in deuterated chloroform revealed that the inner vinylogous protons H-6, H-18 resonated at δ −1.22 and −0.73 (as two triplets, *J*=14.4, 13.2 Hz, respectively) consistent with significant shielding. The external macrocycle protons had chemical shift resonances between δ ~9.8 and 9.0. The difference of chemical shifts of 'internal' and 'external' protons is about 10 ppm. Franck and co-workers[3b] have shown for bis-vinylogous porphyrins the difference in chemical shift of internal and external protons of the macrocycle is about 18–20 ppm. The aromatic protons of the annelated naphthalene group of (**11**) resonated at δ 7.70 (triplet, *J*=7.6 Hz), 7.85 (triplet, *J*=7.2 Hz), 8.32 (doublet, *J*=7.2 Hz) and 8.33 (doublet, *J*=7.2 Hz).

With a defined synthetic route to bis-vinylogous octaalkylnaphthochlorins, we are currently modifying the chemistry



Scheme 3. Protonation of (**11**) in various solvents.

to produce other annelated expanded chlorin compounds. The physical and chemical characterization of these molecules 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 Whatman 60 Å (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 a 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) 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 focusing magnetic sector mass spectrometer.

1.1.1. Bis-vinylogous biladiene (4). A solution of 3,4-diethyl-2-(2-formylvinyl)pyrrole (5.14 g, 29 mmol) and 3,3′-di(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane (5.01 g, 14.5 mmol) in methanol (100 mL) was cooled to −78°C under argon. HBr (7 mL, 33% in AcOH) was added in drops with stirring. The mixture was stirred for 10 min after which the blue solution was warmed to −10°C and the solid filtered. The resulting green solid was washed with a small amount of cold methanol (10 mL) and hexane (30 mL) and dried to give 8.5 g (77%) of crude (**4**). The material was used directly in the next step without further purification. UV/visible (CH_2Cl_2) 537, 645 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.17 (brs, 2H, NH); δ 11.83 (brs, 2H, NH); 8.67 (t, 2H, J=12 Hz, CH=C*H*CH); 7.18–7.30 (m, 6H, CH=CHC*H*, α-H); 4.44 (brs, 2H, methine-CH_2); 3.36 (s, 6H, CO_2CH_3); 2.67 (t, 4H, J=9 Hz, $-CH_2-$); 2.44 (q, 4H, J=9 Hz, CH_2CH_3); 2.27 (q, 4H, J=9 Hz, CH_2CH_3); 2.09 (t, 4H, J=9 Hz, $-CH_2-$); 2.05 (s, 6H, CH_3); 0.99 (t, 6H, J=9 Hz, CH_2CH_3); 0.97 (t, 6H, J=9 Hz, CH_2CH_3).

1.1.2. Bis-vinylogous porphyrin (5). To a solution of vinylogous biladiene (**4**) (200 mg, 0.26 mmol) in methanol (40 mL) was added methyl 2-formylbenzoate (1.5 g, 9.1 mmol) followed by HBr (100 μL, 33% in AcOH). The mixture was refluxed for 6 h and a further amount of methyl 2-formylbenzoate (0.5 g) followed by HBr (50 μL, 33% in AcOH) was added. The solution was refluxed overnight. A further amount of methyl 2-formylbenzoate (0.5 g) and HBr was added (50 μL, 33% in AcOH) and the solution refluxed overnight again. After a total of 45 h reflux time, the solution was cooled to room temperature and chloranil (75 mg) was added. The solution was stirred at room temperature for 1 h, then poured into water and extracted with dichloromethane. The dichloromethane layer was washed again with water, collected and evaporated and the crude residue chromatographed on silica using 2% methanol/CH_2Cl_2 as eluting solvent. The major green fraction was collected and evaporated. The residue was precipitated twice form hexane/CH_2Cl_2 to give the vinylogous porphyrin (**5**), 105 mg (53%). UV/visible (CH_2Cl_2) λ_{max} 468, 499, 603, 743 nm; MS (ESI) *m/z* 809 (M+H); HRMS; theoretical $C_{47}H_{54}N_4O_2$ 809.4278 (M+H); found 809.4248 (M+H); calcd C:H:N 74.23:6.98:6.92; found C74.4: H 7.1; N 7.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.87 (d, 2H, J=15 Hz, CH=CHCH); 11.74 (d, 2H, J=15 Hz, CH=CHCH); 10.20 (s, 1H, *meso*-CH); 8.51 (d, 1H, J=6 Hz, ArH); 8.42 (d, 1H, J=6 Hz, ArH); 8.01 (t, 1H, J=8 Hz, Ar-H); 7.91 (t, 1H, J=8 Hz, Ar-H); 4.59 (t, 4H, J=9 Hz, $-CH_2-$); 4.15–4.45 (m, 4H, CH_2CH_3); 3.95 (s, 6H, CO_2CH_3); 3.77 (s, 6H, CO_2CH_3); 3.45 (t, 4H, J=6 Hz, CH_2); 3.0 (q, 4H, J=6 Hz, CH_2CH_3); 2.89 (s, 3H, CO_2CH_3); 2.07 (t, 6H, J=9 Hz, CH_2CH_3); 1.27 (t, 6H J=9 Hz, CH_2CH_3); −2.1 (vbrs, 2H, NH); −7.87 (t, 1H, J=12 Hz, inner tri-methine bridge-H).

1.1.3. Bis-vinylogous porphyrin (6). To a slurry of lithium aluminum hydride (LAH) (43 mg, 1.1 mmol) in dry THF (4 mL) was added a solution of bis-vinylogous porphyrin (**5**) (150 mg, 0.18 mmol) in dry THF (5 mL) dropwise. The mixture was stirred at room temperature for 25 min, then cooled to 0°C in an ice bath. HCl (0.2N, 5 mL) was added to decompose the excess LAH and the solution poured into water. The aqueous solution was extracted with dichloromethane (3×50 mL) and the combined dichloromethane layers washed with water (100 mL). The organic layer was collected and dried over sodium sulfate, filtered and the solvent removed. The residue was chromatographed on silica (10% methanol/CH_2Cl_2) and the dark green fraction collected. The product was precipitated from CH_2Cl_2/hexane to give a dark green powder. Yield=40 mg (30%). UV/visible (CH_2Cl_2) λ_{max} 468, 499, 603, 743 nm. The compound was not further characterized but used directly in the next step.

1.1.4. Bis-vinylogous naphthochlorin (11). A solution of bis-vinylogous porphyrin (**6**) (40 mg) in phosphoric acid (5 mL) was stirred and heated at 75°C for 30 min. The solution was cooled to room temperature, poured into ice-water (15 mL), neutralized with 25% aq. NaOH and extracted with methylene chloride (3×15 mL). The combined methylene chloride layers were washed with water, dried (Na_2SO_4) and filtered. The methylene chloride was removed by roto-evaporation. The residue was crystallized from hexane/methylene chloride to give a dark green powder, 22 mg (56%). UV/visible (methylene chloride/isopropyl alcohol, 1:1) λ_{max} (ε, M^{-1} cm^{-1}) 471 (94600), 633 (13700), 669 (12330), 743 (11240) and 831 (12610) nm; MS (ESI) *m/z* 707 (M+H); HRMS; theoretical $C_{47}H_{54}N_4O_2$ 707.4324 (M+H); found 707.4328 (M+H); calcd C:H:N 79.84:7.70:7.92; found C 79.6:H 7.6:N 7.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (d, 1H, J=14.8 Hz, CH=CHCH); 9.57 (d, 1H, J=12 Hz, CH=CHCH); 9.08 (d, 1H, J=13.6 Hz, CH=CHCH); 9.0 (d, 1H, J=11.2 Hz, CH=CHCH); 8.97 (d, 1H, J=8 Hz, Ar-H); 8.37 (s, 1H, *meso*-CH); 8.33 (d, 1H, J=7.2 Hz, Ar-H); 8.32 (s, 1H, Ar-H); 7.85 (t, 1H, J=7.2 Hz, Ar-H); 7.7 (t, 1H, J=7.6 Hz, Ar-H); 3.88 (q, 2H, J=10 Hz, CH_2CH_3); 3.59 (m, 8H, 4 CH_2s); 3.12 (s, 3H, CH_3-pyrrolic); 3.10 (s, 3H, CH_3-pyrrolic); 2.77 (m, 2H, CH_2CH_3); 2.68 (m, 2H, CH_2CH_3); 2.25 (m, 4H, 2 CH_2s); 1.60 (t, 6H, J=7.6 Hz, CH_2CH_3); 0.84

(t, 6H, J=7.2 Hz, CH_2CH_3); 0.25 (brs, 2H, NH); −0.73 (t, 1H, J=13.2 Hz, inner tri-methine bridge-H); −1.22 (t, 1H, J=14.4 Hz, inner tri-methine bridge-H).

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