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Syntheses and Preliminary *in vivo* Photodynamic Efficacy of Benzoporphyrin Derivatives from Phylloerythrin and Rhodoporphyrin XV Methyl Esters and Aspartyl Amides

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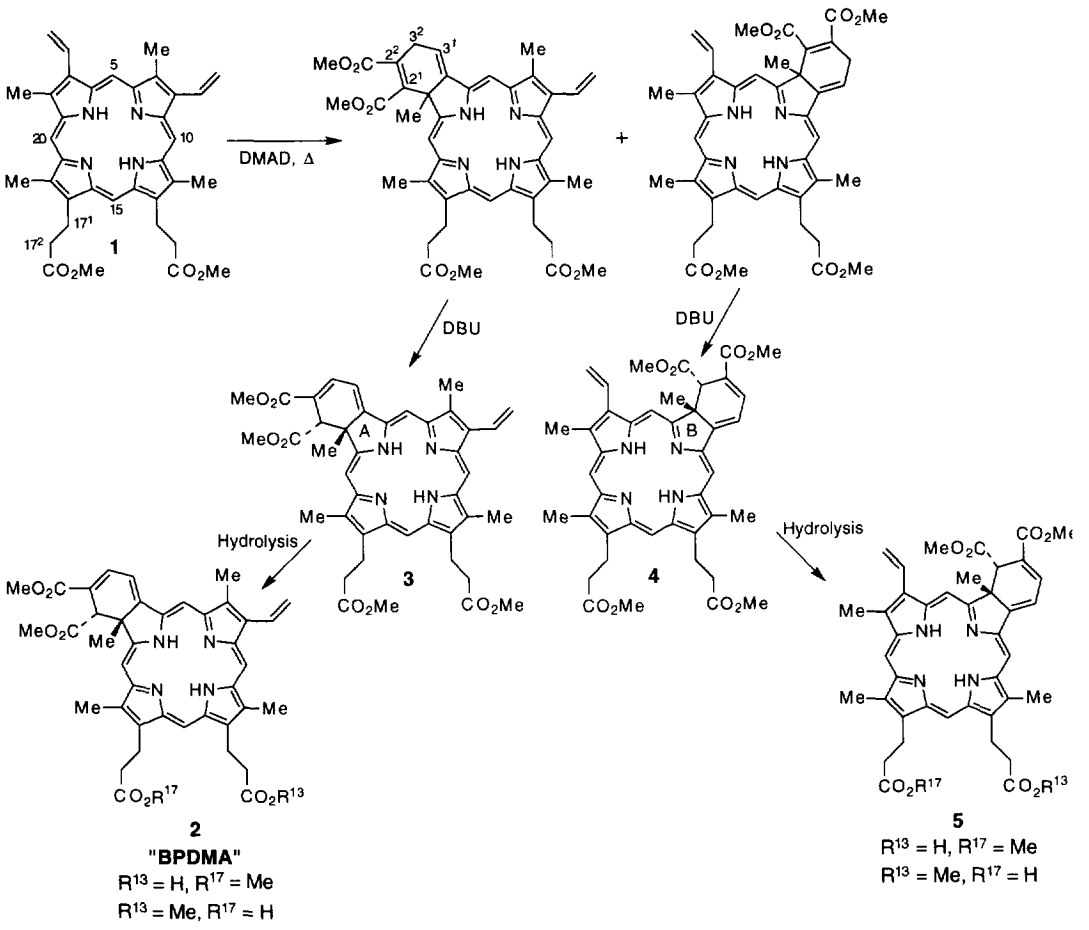
Key words: photosensitizers; photodynamic therapy; Diels-Alder reactions; chlorophyll derivatives

Abstract: Efficient approaches to the synthesis of methyl esters and aspartyl amides of so-called ring 'A'-benzoporphyrin derivatives from rhodoporphyrin XV dimethyl ester **10** and 3-vinylphylloerythrin methyl ester **22** are reported. The benzo-rings in the products are obtained by way of Diels-Alder [4+2] cyclizations which employ a dieneophile and the vinyl and 2,3-double bonds in the starting materials as the diene. In the 3-vinyl-phylloerythrin series, the presence of the 13^1-keto-group in ring E inhibits the Diels-Alder reaction with dimethyl acetylenedicarboxylate, but with more reactive dienophiles, such as tetracyanoethylene, the Diels-Alder adduct was isolated in modest yield. Protection of the 13^1-keto- group as a ketal or thioketal afforded the intermediate benzoporphyrin adducts, which were rearranged to *trans-* and *cis-* isomers on reacting with triethylamine and 1,8-diazabiclo[5,4,0]undec-7-ene, respectively. Among the sensitizers tested so far, the benzoporphyrin derivative (*cis-* isomer) obtained from rhodoporphyrin XV di-*tert-* butyl aspartate showed the best *in vivo* photosensitizing activity in DBA/2 mice transplanted with SMT/F tumors. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Callot et al.[1] showed that protoporphyrin IX dimethyl ester **1** can undergo cycloaddition reactions ([4+2] and [2+2]) with various dienophiles. The products from these reactions were later studied in depth by Morgan, Dolphin, and co-workers.[2,3] Significantly, one of the ring A-benzoporphyrin derivatives obtained from protoporphyrin IX dimethyl ester and dimethyl acetylenedicarboxylate (DMAD), as its monoacid (BPDMA **2**), is currently in phase I and II clinical trials for the treatment of cancer using photodynamic therapy (PDT). Due to the asymmetry associated with protoporphyrin IX dimethyl ester **1**, the reaction with DMAD and subsequent reaction with DBU (to bring the double bond into conjugation, Scheme 1) produces both ring A and ring B isomers **3** and **4**, which are then separated chromatographically, and finally hydrolyzed to give the monoacids **2** and **5**. We recently reported an efficient route for the preparation of such compounds[4] by using 3-acetyl-8-vinyl- **6** and 8-acetyl-3-vinyl-deuteroporphyrin IX dimethyl ester **7** as starting materials.[5] These compounds were then converted into various alkyl ether derivatives.[6,7] Among such alkyl ether derivatives, the 8-(1-hexyloxyethyl)-derivative **8** was found to be more active than the corresponding BPD analogue.[8] Among all the BPD-type derivatives prepared so far, the ring A modified isomer (*cis-* isomer) was found to be most active. Preparation of benzoporphyrin analogues from the isomerically pure, mono-vinyl-

mono-acetyl- intermediates has synthetic advantages, but this methodology still requires the separation of the individual isomers **6** and **7** by preparative HPLC or by Chromatotron chromatography.

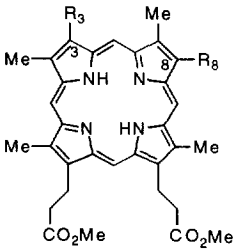


Scheme 1: BPDMA synthesis and isomers

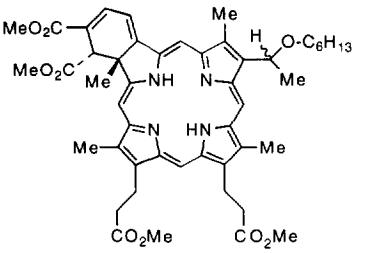
RESULTS AND DISCUSSION

The BPDMA in clinical trials has, as its major structural features, a Diels-Alder modified ring A and a mixed methyl ester and carboxylic acid substituents in the lower half of the molecule. Only this form shows any significant PDT activity in mice treated 3 h post-injection of the drug;[9] under similar treatment conditions, the di-propionic acid analogue was found to be inactive. In order to solve the synthetic problems associated with preparation of biologically active BPDMA, **2**, we decided to use methyl pyropheophorbide-a **9** and rhodoporphyrin XV dimethyl ester **10** as substrates in the Diels-Alder reaction. Both substrates contain only one vinyl group, and this is situated in the more efficacious ring A site; therefore the Diels-Alder product derived from these compounds can only be modified in ring A. Moreover, both molecules **9** and **10** contain

only one propionic ester group; in the example of rhodoporphyrin XV dimethyl ester **10**, there is ample precedent[10] for highly efficient preferential and regiochemical hydrolysis of only one of the two esters, namely the propionic ester. While the present paper was in the review process, Ma and Dolphin[11] published a communication on the syntheses of some related benzoporphyrins.



6 R^3 = COMe, R^8 = $CH{=}CH_2$
7 R^3 = $CH{=}CH_2$, R^8 = COMe



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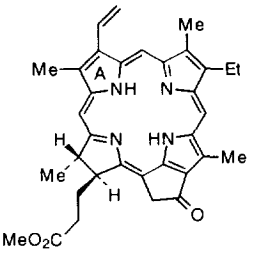

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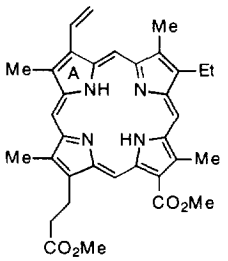

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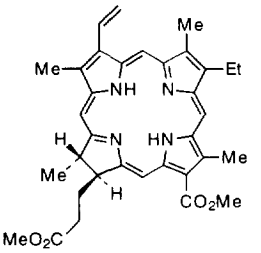

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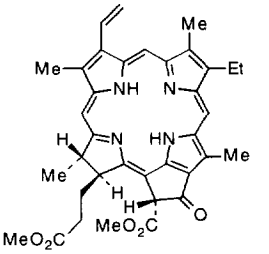


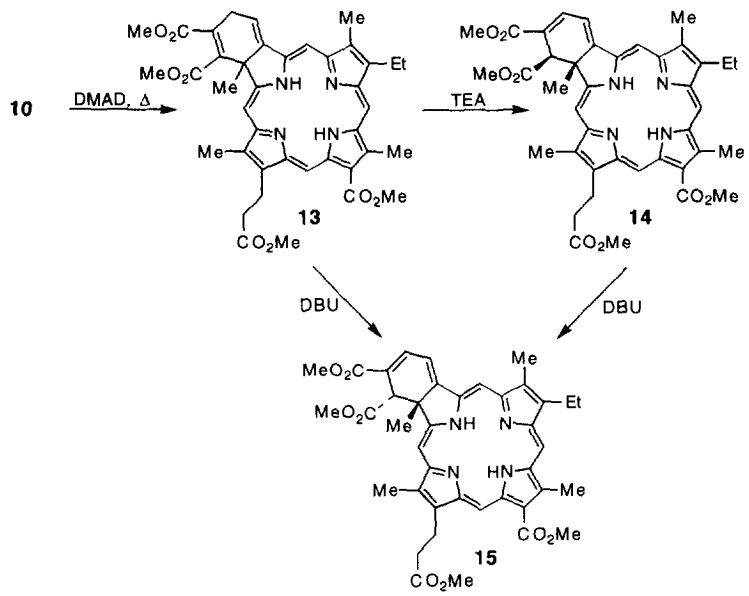
12

Rhodochlorin XV dimethyl ester **11** was obtained from methyl pheophorbide-a **12** by following the literature procedure.[12] Methyl pheophorbide-a **12** was in turn isolated from *Spirulina pacifica* alga by following the procedure developed in our laboratories.[13] Reaction of **11** with DDQ gave rhodoporphyrin XV dimethyl ester **10** in modest yield.[14]

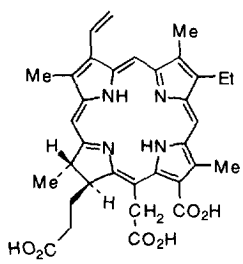
Upon treatment of **10** with DMAD in refluxing toluene, the intermediate Diels-Alder adduct **13** was obtained in 47% yield (Scheme 2). Reaction of **13** with triethylamine (TEA) gave the *trans-* isomer **14**, which upon reaction with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) produced the *cis-* isomer **15**, in quantitative yield. The *cis* isomer **13** can also be obtained directly by reacting the Diels-Alder adduct **13** with DBU. Compound **15** has a long wavelength absorption maximum at 646 nm; however, the TEA and DBU rearranged products demonstrate a considerable red shift in their absorption spectra (to 670 nm) due to the extended conjugation.

A number of chlorophyll a derivatives have been investigated for PDT activity, and the most promising of these, chlorin e_6 **16**, is most active in the form of its mono-aspartyl amide, MACE (**17**).[15,16] For the preparation of aspartyl derivative **18**, the methyl ester **15** was hydrolyzed to the carboxylic acid **19** by treatment with 25% aqueous hydrochloric acid with the dicarboxylic acid **21** being obtained as a by-product;[10] subsequent reaction of **19** with DCC and di-*tert-* butyl aspartic acid[17,18] gave the product, **18**, from which **20** can be obtained if desired, using trifluoroacetic acid.[18] Figure 1 shows the ^{1}H-NMR spectrum of BPD **18**. When the methyl ester derivative **15** was left stirring with 25% HCl gradually increasing amounts of **21** were

observed, in which the unconjugated ester functionalities were also hydrolyzed. Eventually, benzoporphyrin dicarboxylic acid **21** became the major product.



Scheme 2: Regioisomers produced using TEA or DBU



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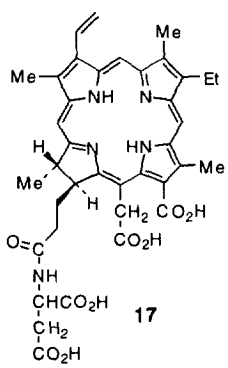

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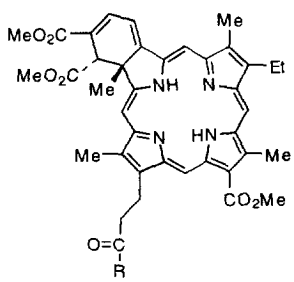
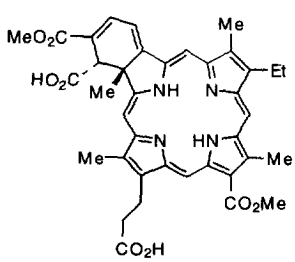


18 R = NHCH(CH_2CO_2But)CO_2But
19 R = OH
20 R = NHCH(CH_2CO_2H)CO_2H



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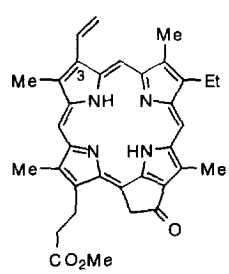

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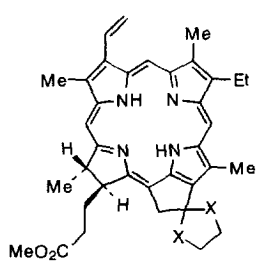


23 X = O
24 X = S

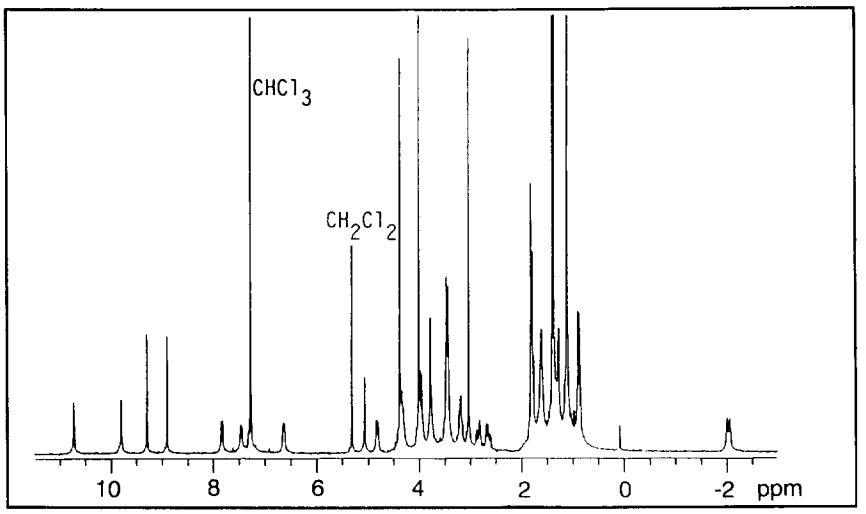
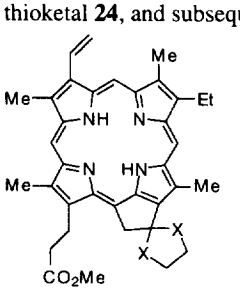
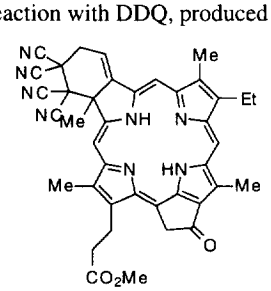


Figure 1: ^{1}H-NMR spectrum (in $CDCl_3$) of aspartyl BPD **18** (tall peaks have been clipped)

Attempts to oxidize methyl pyropheophorbide-a **9** to 3-vinylphylloerythrin methyl ester **22** using various oxidizing agents failed. However, protection of the keto-group (ring E) either as the ketal **23** or the thioketal **24**, and subsequent reaction with DDQ, produced the desired product in excellent yield.[18]



25 X = O
26 X = S



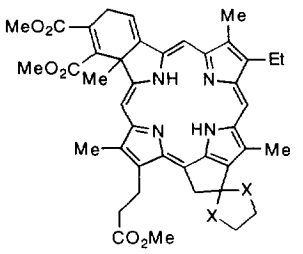
27

The ketal functionality was easily cleaved by stirring **25** or **26** in acidic aqueous acetone, to give 3-vinylphylloerythrin methyl ester **22**. Diels-Alder reaction of 3-vinylphylloerythrin methyl ester **22** with tetracyanoethylene (TCE) in refluxing chloroform under a nitrogen atmosphere gave the desired chlorin **27** in 60% yield. No reaction was observed when the less reactive dienophile, DMAD, was used under similar reaction conditions or even at elevated temperatures. However, the 13^1-glycolketal derivative **25** with DMAD produced the desired Diels-Alder intermediate **28**, which was then rearranged to the *cis*- isomer **29** upon stirring with DBU. Thus, it appears that the presence of the 13^1-keto- group in the isocyclic ring (ring E) of such derivatives inhibits the Diels-Alder reaction. In the phylloerythrin ester **25**, the ketal group tended to cleave slowly during silica column chromatography. In order to avoid this problem, the 13^1-keto- group in **22** was protected as more stable thioketal analog **26** (obtained in 82% yield). Similar to other benzoporphyrin analogues, in this series also the *cis*- isomer **30** obtained by DBU rearrangement of **31** had a longer wavelength absorption (675 nm) than the corresponding *trans*- isomer **32** (663 nm), obtained by TEA rearrangement.

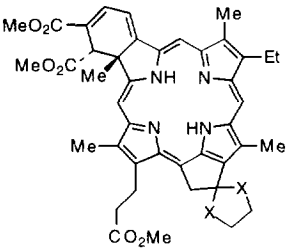
The aspartyl amide derivatives were also prepared in the phylloerythrin series; 3-vinyl phylloerythrin methyl ester **22** was hydrolyzed (aqueous KOH/THF) to give the carboxylic acid **33**, which was reacted with di-tert-butyl aspartic acid and then ketalized by following the method discussed for **25** and **26**. The products

34 and **35** were treated with DMAD and rearranged with DBU, to afford the corresponding Diels-Alder *cis*-isomers **36** and **37** in 42 and 45% yield, respectively.

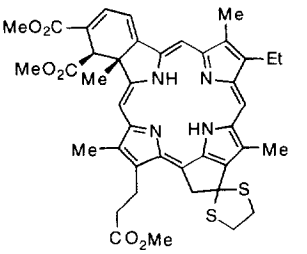
Finally, the ketal BPD **29** was cleaved in acidic acetone to afford the methyl pyropheophorbide BPD **38** in quantitative yield.



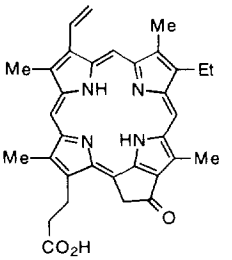
28 X = O
31 X = S



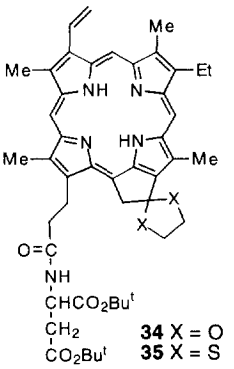
29 X = O
30 X = S



32



33



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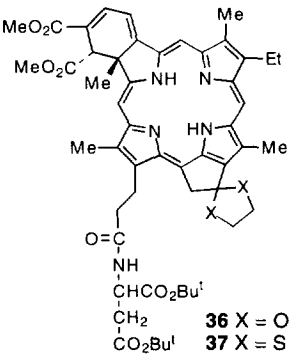
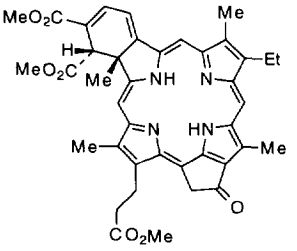
35 X = S



36 X = O
37 X = S



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BIOLOGICAL ACTIVITY

Some of the newly synthesized sensitizers **12, 15, 32, 33** and **34** were tested for *in vivo* photosensitizing activity vis-a-vis BPDMA (**2**) and 4-(1-hexyloxyethyl)-benzoporphyrin derivative dimethyl ester **6**, using the standard screening system of DBA/2 mice bearing transplanted SMT/F tumors.[20] Groups of six mice were used, and treated with light (135 J/cm^2) at 3 h and 24 h post injection of the drug.

In our tumor model, BPDMA is quite effective at a dose of 5.0 mg/kg when the mice were treated 3 h post injection of the drug. However at the same dose, there was no tumor response when the mice were treated 24 h post injection of the drug. Replacement of the vinyl group with a hexyl ether substituent improved photosensitizing efficacy. For example, sensitizer **8**, at a dose of 5 mg/kg gave excellent tumor response at 24 h post injection of the drug (5 out of 6 mice were tumor-free at day 30). The hexyl ether derivative was active even at a dose of 1.0 mg, when treated in 3 h post injection (3 out of 6 mice were tumor free at day 30). Under similar treatment conditions, BPDMA (**2**), did not show any significant photosensitizing efficacy. The ketal- and thioketal analogues as *cis*- and *trans*- isomers (**32, 33** and **34**) were found to be toxic at high doses (2

mg/kg.); at lower doses, tumor regrowth was observed 15 d after the light treatment. In the rhodoporphyrin series, the di-*tert*- butyl aspartic derivative **15** was found to be effective at a dose of 1.0 mg/kg at 3 h post injection of the drug. Under similar dose and treatment conditions, the corresponding methyl ester **12** did not show any significant anti-tumor activity. Skin phototoxicity, mechanistic and other biological studies with these sensitizers are currently in progress.

EXPERIMENTAL

General: Melting points are uncorrected and were measured on a Thomas/Bristoline microscopic hot stage apparatus. Silica gel 60 (70-230 and 230-400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, i.e. deactivated with 6% water) were used for column chromatography. Preparative scale thin layer chromatography was carried out on 20 x 20 cm glass plates coated with Merck G 254 silica gel (2mm thick). Reactions were monitored by thin layer chromatography and spectrophotometry, and were carried out in the nitrogen and in the dark (aluminum foil). ^{1}H NMR spectra were measured in deuterochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to residual chloroform (7.258 ppm). Mass spectra were obtained at the Department of Biophysics, Roswell Park Cancer Institute, Buffalo, and at the University of California, San Francisco, Mass Spectrometry Resource. Elemental analyses were obtained from Mid West Analytical Laboratory, Indianapolis, IN. Electronic absorption spectra were measured in dichloromethane using a Hewlett Packard 8450A spectrophotometer. BPDMA was obtained from QuadraLogic Technologies, Vancouver, Canada.

Rhodoporphyrin XV Dimethyl Ester (10). Rhodochlorin XV dimethyl ester **11** (176 mg, 0.3 mmole) was dissolved in dichloromethane (100 ml). DDQ (40 mg) dissolved in benzene (10 ml) was added, and the reaction mixture was stirred at room temperature for 10 min. It was passed through a short column of alumina (elution with dichloromethane). The eluates were combined, washed with hydrochloric acid (50 ml, 0.1 N), and again with water. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was crystallized from dichloromethane/hexane to give the title compound (120 mg; 69%), mp. 265°C (lit.[14] mp 266-268°C. Uv/vis: λ_{max}: 404 nm (ε 170,000), 512 (11,800), 552 (21,000), 576 (12,700), 636 (3700), 668 (3000). ^{1}H NMR (δ ppm): 10.99, 10.09, 10.04 and 9.91 (each s, 1H, meso H), 8.20 (1H, dd, J = 19.6,12.6 Hz,C<u>H</u>=CH_2), 6.32 (1H, d, J = 19.6 Hz, CH=C<u>H</u>$_2$), 6.16 (1H, d, J = 12.6 Hz, CH=C<u>H</u>$_2$), 4.46, 3.94, 3.70, 3.64, 3.63 and 3.62 (each s, 3H, 3 x Me and 3 x OMe), 4.44 (t, 2H, J = 9 Hz, C<u>H</u>$_2$$CH_2CO$), 4.09 (q, 2H, J = 8 Hz, C<u>H</u>$_2$$CH_3$), 3.37 (2H, t, J = 9 Hz, CH_2C<u>H</u>$_2$CO), 1.86 (3H, t, J = 8 Hz, CH_2C<u>H</u>$_3$), -4.01 (s, 2H, 2NH).

Ethylene Ketal (23) of Methyl Pyropheophorbide a (9). Methyl pyropheophorbide-a **9** (2.5 g) in dry dichloromethane (500 ml) was stirred under nitrogen and ethylene glycol (2 ml) and trimethylsilyl chloride (2 ml) were added. The reaction mixtrure was stirred for 12 h. It was cooled by using a dry ice/isopropyl alcohol bath (-27°C) and then poured into a 1N NH_4OH solution which had some residual ice in it (at ≈ -6°C). This mixture was diluted with dichloromethane, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The bright green residue dissolved in dichloromethane and eluted through an alumina column. The lighter green fraction was recrystallized from dichloromethane/MeOH to give the title compound (2.35 g, 88%) as bright green crystals, mp: 173-176°C. Uv/vis λ_{max}:400 nm (ε 163,300), 500 (19,800), 550 (6600), 598 (9350), 652 (49,700). ^{1}H NMR (δ ppm): 9.70, 9.65 (each s, 1H, 5 and 10 meso H), 8.75 (s, 1H, 20 meso H), 8.00 (dd J = 18,12 Hz, 1H, C<u>H</u>=CH_2), 6.28 (d J = 18 Hz, 1H, CH=C<u>H</u>$_2$), 6.17 (d J = 12 Hz, 1H, CH=C<u>H</u>$_2$), 5.00-5.18 (m, 2H, 13^2-CH_2), 4.70-4.40 (m, 5H, 18-H and 13^1 -OCH_2CH_2O-), 4.35 (m, 1H, 17-H), 4.00 (q, 2H, C<u>H</u>$_2$$CH_3$), 3.60, 3.54, 3.44, 3.40 (each s, 3H, Me and OMe), 2.80-2.20 (m, 4H, 17-CH_2CH_2), 1.80 (d, 3H, 18-Me), 1.69 (t, 3H, CH_2C<u>H</u>$_3$),-1.12, -3.09 (each br s, 1H, NH). Anal. Calcd for $C_{36}H_{40}N_4O_4 \cdot H_2O$: C, 70.80; H, 6.93; N, 9.17. Found: C, 71.09; H, 6.67; N, 9.02.

Thioketal (24) of Methyl Pyropheophorbide a (9). Methyl pyropheophorbide-a **9** (1.45 g) was dissolved in dichloromethane (200 ml) and 1,2-ethanedithiol (1.5 ml) and TMSiCl (1.5 ml) were added. Water (10 drops) was added and the mixture was stirred for 24 h. This mixture was poured into 5% ammonia solution, washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude mixture was heated with isopropyl alcohol, which only partially dissolved the porphyrin, but served to leach out the 1,2-ethanedithiol (which tends to interfere with the subsequent column chromatography purification). After heating to boiling while scraping the sides of the flask to loosen the solid, the flask was cooled and the solid was filtered off. This was then heated with petroleum ether in a similar manner, cooled and filtered. The crystals were dissolved in dichloromethane and eluted through an alumina column (Brockmann Grade III, elution with 0.25% methanol/2% THF in dichloromethane). The fastest-running light green product was collected, evaporated to dryness, and crystallized from dichloromethane/isopropyl alcohol by slowly evaporating off the dichloromethane from the solvent mixture at room temperature under vacuum. The solid was filtered and rinsed with petroleum ether to remove excess isopropyl alcohol, affording the title compound as blue-green powder (1.12 g, 76%), mp: 121-123°C. Uv/vis λ_{max}: 408 nm (ε 78,700), 506 (10,500), 600 (4600), 652 (22,100). ^{1}H NMR (δ ppm): 9.88, 9.67 (each s, 1H, 5 and 10 meso H), 8.91 (s, 1H, 20 meso H), 8.23 (dd J = 12,18 Hz, 1H, C$\underline{H}$=CH$_2$), 6.39 (d J = 18 Hz, 1H, CH=C$\underline{H_2}$), 6.20 (d J = 12 Hz, 1H, CH=C$\underline{H_2}$), 5.55-5.75 (m, 2H, 13^2-CH$_2$), 4.84 (q, 2H, C$\underline{H_2}$CH$_3$), 4.67 (m, 1H, 18-H), 4.42 (m, 1H, 17-H), 3.97 (m, 4H, 13^1 -SCH$_2$CH$_2$S-), 3.67, 3.63, 3.58, 3.42 (each s, 3H, Me and OMe), 2.8-2.2 (m, 4H, 17-CH$_2$CH$_2$), 1.86 (d, 3H, 18-Me), 1.77 (t, 3H, CH$_2$C$\underline{H_3}$), -1.26, -3.19 (each br s, 1H, NH). Anal. Calcd for $C_{36}H_{40}N_4O_2S_2$: C, 69.42; H, 6.15; N, 9.00. Found: C, 67.50; H, 6.35; N, 8.80.

Ethylene Ketal (25) of 3-Vinylphylloerythrin Methyl Ester (22). The ketal **23** of methyl pyropheophorbide a (51 mg) was stirred in dichloromethane (30 ml) at 0°C while DDQ (220 mg) was added. After 3 min the mixture was passed through a small pad of alumina, using dichloromethane for complete elution. After evaporation of the solvent, the solid residue was recrystallized from dichloromethane/n-hexane to give the title compound (42 mg, 82%) as a pink dust, mp: >300°C. Uv/vis λ_{max}: 406 nm (ε 224,500), 508 (20,800), 544 (16,600), 570 (15,400), 622 (9600). ^{1}H NMR (δ ppm): 10.01, 9.94, 9.87 (each s, 1H, 5, 10 and 20 meso H), 8.17 (dd J = 12,18 Hz, 1H, C$\underline{H}$=CH$_2$), 6.26 (d J = 18 Hz, 1H, CH=C$\underline{H_2}$), 6.07 (d J = 12 Hz, 1H, CH=C$\underline{H_2}$), 5.69 (s, 2H, 13^2-CH$_2$), 4.68 (m, 4H, 13^1 -OCH$_2$CH$_2$O-), 4.28 (t, 2H, 17^1-CH$_2$), 4.05 (q, 2H, C$\underline{H_2}$CH$_3$), 3.73, 3.68, 3.57, 3.56, 3.54 (each s, 3H, Me and OMe), 3.1 (t, 2H, 17^2-CH$_2$), 1.82 (t, 3H, CH$_2$C$\underline{H_3}$), -3.03, -3.85 (each br s, 1H, NH). Anal. Calcd for $C_{36}H_{38}N_4O_4 \cdot H_2O$: C, 71.03; H, 6.62; N, 9.20. Found: C, 71.28; H, 6.47; N 9.22.

Thioketal (26) of 3-Vinylphylloerythrin Methyl Ester (22). The thioketal **24** of methyl pyropheophorbide a (1.0 g) was stirred in dichloromethane (50 ml) at 0°C while DDQ (350 mg) in benzene (20 ml) was added. After 3 min the reaction mixture was filtered through a small pad of alumina, eluting with 1% MeOH/dichloromethane. After evaporation to dryness, the red solid was recrystallized from dichloromethane/MeOH to give the title compound (0.93 g, 93%) as a pink-red powder, mp: 120-121°C. Uv/vis λ_{max}: 408 nm (ε 224,100), 508 (22,900), 546 (17,600), 570 (16,350), 620 (10,300). ^{1}H NMR (δ ppm): 10.03, 9.97, 9.92 (each s, 1H, 5, 10 and 20 meso H), 8.20 (dd J = 12,18 Hz, 1H, C$\underline{H}$=CH$_2$), 6.25 (d J = 18 Hz, 1H, CH=C$\underline{H_2}$), 6.10 (d J = 12 Hz, 1H, CH=C$\underline{H_2}$), 6.25 (s, 2H, 13^2-CH$_2$), 4.37 (t, 2H, 17^1-CH$_2$) 4.1-4.0 (m, 6H, C$\underline{H_2}$CH$_3$ and 13^1 -SCH$_2$CH$_2$S-), 3.59, 3.59, 3.59, 3.73, 3.76 (each s, 3H, Me and OMe), 3.10 (t, 4H, 17^2-CH$_2$), 1.84 (t, 3H, CH$_2$C$\underline{H_3}$), -3.01, -3.85 (each br s, 1H, NH).

3-Vinylphylloerythrin Methyl Ester (22). The ketal **25** of 3-vinylphylloerythrin methyl ester **22** (350 mg) was dissolved in THF (100 ml) and acetone (50 ml) and 1M HCl (20 ml) was added while the flask was warmed. This mixture was stirred for 10 min before dichloromethane was added and the organic layer was

washed, dried over anhydrous Na_2SO_4, and evaporated to dryness. The red residue was recrystallized from dichloromethane/MeOH to give the title compound (318 mg, 92%) as a red powder, mp: 279-281°C (lit.[21] mp 278°C). Uv/vis λ_{max}: 406 nm (ε 194,000), 508 (19,400), 544 (15,700), 570 (15,000), 622 (9500). ^{1}H NMR (δ ppm): 9.90, 9.83, 9.52 (each s, 3x1H, 5, 10 and 15 meso H), 8.18 (dd, 1H, 3^1-CH, J = 18,12 Hz), 6.30 (d, 1H, 3^2-CH *trans* to 3^1-CH, J = 18 Hz), 6.19 (d, 1H, 3^2-CH *cis* to 3^1-CH, J = 12 Hz), 5.47 (s, 2H, 13^2-CH_2), 4.05 (q, 2H, 8^1-CH_2), 3.96 (t, 2H, 17^1-CH_2), 3.73, 3.80, 3.61, 3.58, 3.42 (each s, 5x3H, 2-Me, 7-Me, 12-Me, 17^3-OMe, and 18-Me), 2.90 (t, 2H, 17^2-CH_2), 1.86 (t, 3H, 8^2-Me), -3.1, -3.3 (each br s, 2x1H, NH).

3-Vinylphylloerythrin (33). 3-Vinylphylloerythrin methyl ester **22** (300 mg) was dissolved in THF (300 ml) and was treated with 1M KOH (40 ml). The mixture was refluxed for 1 h. After cooling the reaction mixture it was slowly poured into ice cold 0.1N HCl. The pH was adjusted to about 5 and the resulting precipitate was collected by suction filtration. If precipitation failed to occur, the water was extracted with dichloromethane which was dried over anhydrous Na_2SO_4, evaporated to dryness, and the product was then crystallized from dichloromethane/hexane in 96% yield (290 mg), mp > 300°C. It was used as such with out further purification in subsequent reactions. Uv/vis λ_{max} (relative intensities) in pyridine/dichloromethane: 420 nm (100), 476 (9.2), 524 (10.0), 566 (15.4), 590 (13.1), 640 (7.3). ^{1}H NMR (pyridine) (δ ppm): 10.25, 10.09, 9.84 (each s, 1H, 5, 10, and 20 meso H), 8.20 (dd, 1H, C<u>H</u>=CH_2), 6.30, 6.19 (each d, 1H, CH=C<u>H</u>$_2$), 5.76 (s, 2H, 13^2-CH_2), 4.10-3.99 (t, 2H, 17^1-CH_2, and q, 2H, 8-C<u>H</u>$_2$$CH_3$), 3.85, 3.54, 3.49, 3.43 (each s, 3H, Me), 3.20 (t, 2H, 17^2-CH_2), 1.88 (t, 3H, 8-CH_2C<u>H</u>$_3$), -2.40, -3.65 (each br s, 1H, NH).

General Method for Synthesis of Di-tert-butyl Aspartyl Amide Derivatives of Porphyrin Acids. Porphyrin carboxylic acid (50 mg), DCC (50 mg), di-tert-butyl aspartate (50 mg), and DMAP (5 mg) were placed into a oven dried 100 ml round bottom flask equipped with a magnetic stir bar. Dry dichloromethane (15 ml) was added and the mixture was stirred overnight under an atmosphere of nitrogen. The reaction was then diluted with water (50 ml) and extracted with dichloromethane. The organic phases were combined, evaporated, and the product was crystallized (as reported below).

3-Vinylphylloerythrin Di-tert-butyl Aspartyl Amide. 3-Vinylphylloerythrin **33** (252 mg), DCC (250 mg), di-tert-butyl aspartic acid (250 mg), and DMAP (25 mg) were placed into a oven dried 100 ml round bottom flask equipped with a magnetic stir bar. Dry dichloromethane (75 ml) was added and the reaction mixture was stirred overnight under a nitrogen atmosphere. It was then diluted with water (250 ml) and dichloromethane (200 ml), washed with more water and the organic phase was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the product was passed through a short column of alumina (Brockmann Grade III, elution with 2% MeOH in dichloromethane). The filtrate was evaporated to dryness and the product was recrystallized from dichloromethane/MeOH to give the title compound (185 mg, 70 %) as a red dust, mp: 221-223°C. Uv/vis λ_{max}: 418 nm (ε 208,300), 534 (19,600), 566 (28,400), 588 (23,500), 640 (12,300). ^{1}H NMR (δ ppm): 9.90, 9.83, 9.52 (each s, 1H, meso H), 8.18 (dd J = 12,18 Hz, 1H, C<u>H</u>=CH_2), 6.45 (bs, 1H, Asp N-H), 6.30 (d, J = 18 Hz, 1H, CH=C<u>H</u>$_2$), 6.15 (d, J = 12 Hz, 1H, CH=C<u>H</u>$_2$), 5.14 (s, 2H, 13^2-CH_2), 3.96 (t, 2H, 17^1-CH_2), 3.80, 3.73, 3.61 (each s, 3H, Me), 2.60 (t, 2H, 17^2-CH_2), 2.68-2.35 (m, 2H, Asp-CH_2), 1.86 (t, 3H, CH_2C<u>H</u>$_3$), 1.42, 1.17 (each s, 9H, t-Bu), -3.10 , -3.30 (each br s, 1H, NH). Anal. Calcd for $C_{45}H_{57}N_5O_6$: C, 70.75; H, 7.22; N, 9.17. Found: C, 70.44; H, 6.97; N, 9.17.

Thioketal (35) of 3-Vinylphylloerythrin Di-tert-butyl Aspartyl Amide. 3-Vinylphylloerythrin methyl ester thioketal **26** (255 mg) was dissolved in THF (200 ml), KOH (1M, 10 ml) was added and the mixture was refluxed for 3 h. The reaction mixture was cooled in an ice bath before the addition of 2M HCl (20 ml). The precipitate so obtained was filtered and dried under vacuum. It was directly converted into the aspartyl derivative by reacting aspartic acid di-tert butyl ester (200 mg), DCC (200 mg), DMAP (20 mg), and dichloromethane (50 ml). After work-up, the solid was recrystallized from dichloromethane/MeOH to give the

title compound as a green dust (210 mg, 76%), mp: > 300°C. Uv/vis λ_{max}: 408 nm (ε 220,000), 508 (22,000), 546 (17,000), 570 (16,000), 620 (10,000). ^{1}H NMR (δ ppm): 10.30, 10.10, 10.07 (each s, 1H, 5, 10 and 20 meso H), 8.23 (dd J = 12,18 Hz, 1H, C<u>H</u>=CH$_2$), 6.62 (bs, 1H, Asp N-H), 6.32 (d J = 18 Hz, 1H, CH=C<u>H$_2$</u>), 6.07 (d J = 12 Hz, 1H, CH=C<u>H$_2$</u>), 6.26 (s, 2H, 13^2-CH$_2$), 4.90 (X of ABX, 1H, Asp-CH), 4.40 (t, 2H, 17^1-CH$_2$), 4.15 (q, 2H, C<u>H$_2$</u>CH$_3$), 4.04 (m, 4H, 13^1 -SCH$_2$CH$_2$S-), 3.78, 3.75, 3.68, 3.66 (each s, 3H, Me), 3.20 (t, 2H, 17^2-CH$_2$), 2.80-2.60 (m, 2H, Asp-CH$_2$), 1.82 (t, 3H, CH$_2$C<u>H$_3$</u>), 1.42, 1.17 (each s, 9H , t-Bu), -3.00, -3.85 (each br s,1H, NH). Anal. Calcd for $C_{47}H_{61}N_5O_5S_2$: C, 67.19; H, 7.31; N, 8.33. Found: C, 67.29; H, 7.28; N, 8.29.

Ketal (34) of 3-Vinylphylloerythrin Di-tert-butyl Aspartyl Amide. The di-tert-butyl aspartyl derivative of 3-vinylphylloerythrin (108 mg), dichloromethane (50 ml), chlorotrimethylsilane (0.5 ml), and ethylene glycol (0.5 ml) were stirred under nitrogen for 2 h. The standard work up and then direct recrystallization from dichloromethane/MeOH gave the title ketal (82 mg, 72%) as a red powder, mp: > 300°C. Uv/vis λ_{max}: 400 nm (ε 165,000), 500 (20,000), 550 (6500), 598 (9300), 652 (49,500). ^{1}H NMR (δ ppm): 9.95, 9.90, 9.75 (each s, 1H, 5, 10 and 15 meso H), 8.17 (dd J = 12,18 Hz, 1H, C<u>H</u>=CH$_2$), 6.62 (bs, 1H, Asp N-H), 6.26 (d J = 18 Hz, 1H, CH=C<u>H$_2$</u>), 6.07 (d J = 12 Hz, 1H, CH=C<u>H$_2$</u>), 5.75 (s, 2H, 13^2-CH$_2$), 4.90 (X of ABX, 1H, Asp-CH), 4.70-4.55 (m, 4H, 13^1 -OCH$_2$CH$_2$O-), 4.28 (t, 2H, 17^1-CH$_2$), 4.05 (q, 2H, C<u>H$_2$</u>CH$_3$), 3.68, 3.54, 3.51, 3.49, (each s, 3H, Me), 3.1 (t, 2H, 17^2-CH$_2$), 2.80-2.60 (ABX, 2H, Asp-CH$_2$), 1.82 (t, 3H, CH$_2$C<u>H$_3$</u>), 1.42, 1.17 (each s, 9H, t-Bu), -3.20, -4.05 (each br s, 1H, NH). Anal. Calcd. for $C_{47}H_{61}N_5O_7$: C, 69.86; H, 7.61; N, 8.67. Found: C, 69.90; H, 7.54; N, 8.68.

DMAD Adduct (28) of Ketal of 3-Vinylphylloerythrin Methyl Ester (25). 3-Vinylphylloerythrin methyl ester ketal **25** (100 mg) and DMAD (1.0 ml) were dissolved in toluene (50 ml) and the reaction mixture was refluxed for 5 d under a nitrogen atmosphere. After evaporation of the solvent under high vacuum, the residue was purified on preparative silica gel plates, eluting with 2%MeOH/dichloromethane. The major band was collected, and after the standard work up, the residue was crystallized from dichloromethane/hexane to give 65 mg (52%) of the DMAD adduct, mp: 254-256°C. Uv/vis λ_{max}: 408 nm (ε 200,700), 514 (17,200), 542 (14,900), 592 (11,400), 646 (36,100). ^{1}H NMR (δ ppm): 9.57 (s, 1H, 10 meso H), 9.17, 8.94 (each s, 1H, 5 and 20 meso H), 7.38 (t, 1H, 3^1-CH), 5.50 (s, 2H, 13^2-CH$_2$), 4.6-4.5 (m, 4H, 13^1 -OCH$_2$CH$_2$O-), 4.25 (t, 2H, 17^1-CH$_2$), 3.85 (q, 2H, C<u>H$_2$</u>CH$_3$), 3.98, 3.88, 3.76, 3.52, 3.45, 3.42 (each s, 3H, Me and OMe), 3.02 (t, 2H, 17^2-CH$_2$), 2.15 (s, 3H, 2-Me), 1.74 (t, 3H, CH$_2$C<u>H$_3$</u>), -1.38, -2.25 (each br s, 1H, NH). LRMS (%), (EI): 732.3 (12), 716.3 (15.), 688.3 (12), 673.3 (45), 672.3 (100). HRMS: Calcd for $C_{42}H_{44}N_4O_8$: 732.3159. Found: 732.3174.

DBU Rearranged Product (29). The foregoing Diels-Alder adduct **28** (40 mg) was dissolved in dichloromethane (10 ml) and DBU (5 drops) was added. The reaction mixture was stirred at room temperature for 10 min under a nitrogen atmosphere. After evaporating the solvent, the residue was chromatographed on a column of alumina (Brockmann Grade III, eluting with dichloromethane). The solvent was evaporated, and the residue was crystallized from dichloromethane/hexane to give a quantitative yield (39 mg), mp: > 300°C. Uv/vis λ_{max}: 358 nm (ε 48,900), 444 (102,300), 514 (17,400), 584 (26,100), 614 (20,800), 674 (37,900). ^{1}H NMR (δ ppm): 9.60 (s, 1H, 10 meso H), 9.35, 8.90 (each s, 1H, 5 and 20 meso H), 7.85, 7.38 (each d, 1H, 3^1-H and 3^2-H), 5.50 (s, 2H, 13^2-CH$_2$), 4.6-4.5 (m, 4H, 13^1 -OCH$_2$CH$_2$O-), 4.45 (t, 2H, 17^1-CH$_2$) 3.85 (q, 2H, C<u>H$_2$</u>CH$_3$), 3.98, 3.98, 3.60, 3.50, 3.45, 3.00 (each s, 3H, Me and OMe), 3.20 (t, 2H, 17^2-CH$_2$), 1.85 (s, 3H, 2-Me), 1.64 (t, 3H, CH$_2$C<u>H$_3$</u>), -1.25, -2.10 (each br s, 1H, NH). HRMS: Calcd for $C_{42}H_{44}N_4O_8$: 732.3159. Found: 732.3050.

DMAD Adduct (38) of 3-Vinylphylloerythrin. The foregoing DBU rearranged product **29** (20 mg) was dissolved in acetone (10 ml) and 1M HCl (4 drops) was added. The reaction mixture was stirred at room

temperature for 5 min. The organic layer was then washed with water until pH 7. The organic layer was dried over anhydrous Na_2SO_4, and evaporation of the solvent gave a residue which was crystallized from dichloromethane/methanol affording 10 mg (53%), mp: >300°C. Uv/vis λ_{max}: 442 nm (ε 120,000), 616 (41,000), 664 (16, 00), 680 (26,900). ^{1}H NMR (δ ppm): 9.62, 9.30, 8.90 (each s, 1H, meso H), 7.82, 7.42 (each d, 1H, 3^1-H and 3^2-H), 5.50 (q, 2H, 13^1-CH_2), 5.02 (s, 1H, 2^1-C<u>H</u>CO_2Me), 4.45 (t, 2H, 17^1-CH_2), 3.85 (q, 2H, C<u>H</u>$_2CH_3$), 3.98, 3.97. 3.58. 3.52. 3.50, 2.98 (each s, Me and OMe), 3.20 (t, 2H, 17^2-CH_2), 2.38 (s, 3H, 2-Me), 1.78 (t, 3H, CH_2C<u>H</u>$_3$), -1.45 and -2.38 (each bs, 1H, NH). Anal. Calcd for $C_{40}H_{40}N_4O_7$: C, 69.73; H, 5.85; N, 8.13. Found: C, 69.72; H, 5.88; N, 8.10.

DMAD Adduct (31) of Thioketal from 3-Vinylphylloerythrin Methyl Ester (22). 3-Vinylphylloerythrin thioketal methyl ester **26** (100 mg) was reacted with DMAD as described above. The intermediate DMAD adduct was isolated (62 mg) in 50% yield after recrystallization from dichloromethane/hexane, mp: 224-225°C. Uv/vis λ_{max}: 410 nm (ε 245,400), 508 (25,100), 542 (22,300), 594 (18,000), 646 (43,100). ^{1}H NMR (δ ppm): 9.57 (s, 1H, 10 meso H), 9.28, 8.96 (each s, 1H, 5 and 20 meso H), 7.35 (t, 1H, 3^1-CH), 6.00 (s, 2H, 13^2-CH_2), 4.37 (t, 2H, 17^1-CH_2) 4.0-3.9 (m, 6H, 3^2-CH_2 and 13^1 -SCH_2CH_2S-), 3.75 (q, 2H, C<u>H</u>$_2CH_3$), 3.98, 3.88, 3.76, 3.52, 3.45, 3.42 (each s, Me and OMe), 3.10 (t, 2H, 17^2-CH_2), 2.15 (s, 3H, 2-Me), 1.74 (t, 3H, CH_2C<u>H</u>$_3$), -1.41, -2.31 (each br s, 1H, NH). MS (%), (EI): 764.3 (33.5), 704.3 (35.5), 688.2 (100). HRMS: Calcd for $C_{42}H_{44}N_4O_6S_2$: 764.27023 Found: 764.26816.

TEA Rearranged Product (30) from (31). The above Diels-Alder adduct **31** (20 mg) was treated with triethylamine (1 ml) and left stirring overnight. The desired product was isolated (19.5 mg) in quantitative yield. Mp: 256-259°°C. Uv/vis λ_{max}: 356 (ε 43,200), 438 (112,000), 512 (16,000), 574 (24,600), 608 (16,700), 664 (32,350), 668 (32,000). ^{1}H NMR (δ ppm): 9.61 (s, 1H, 10 meso H), 9.23, 9.15 (each s, 1H, 5 and 20 meso H), 7.73, 7.35 (each d, 1H, 3^1-CH and 3^2-CH), 6.00 (s, 2H, 13^2-CH_2), 4.78 (s, 1H, 2^1-CH), 4.37 (t, 2H, 17^1-CH_2) 4.0-3.9 (m, 4H, 13^1 -SCH_2CH_2S-), 4.23 (q, 2H, C<u>H</u>$_2CH_3$), 4.24, 3.95, 3.77, 3.52, 3.50, 3.45 (each s, 3H, Me and OMe), 3.10 (t, 2H, 17^2-CH_2), 2.15 (s, 3H, 2-Me), 1.74 (t, 3H, CH_2C<u>H</u>$_3$), -1.53, -2.40 (each br s, 1H, NH). Anal. Calcd for $C_{42}H_{44}N_4O_6S_2$: C, 65.94; H, 5.80; N, 7.32. Found: C, 65.88; H, 5.86; N, 7.30.

DBU Rearranged Product (32) from (30). The above DMAD product **30** (18 mg) was dissolved in dichloromethane (10 ml), and was treated with DBU (8 drops) as described for the preparation of **29**; the title compound (16.4 mg) was isolated in 91% yield, mp: 266-268°C. Uv/vis λ_{max}: 359 nm (ε 46,900), 444 (92,400), 514 (12,900), 584 (21,900), 616 (15,500), 674 (35,300). ^{1}H NMR (δ ppm): 9.60, 9.28, 8.90 (each s, 1H, meso H), 7.80 and 7.42 (each d, 3^1-H and 3^2-H), 6.00 (s, 2H, 13^1-CH_2), 5.02 (s, 1H, 2^1-C<u>H</u>CO_2Me), 4.20 (t, 2H, 17^1-CH_2), 3.95 (m, 6H, 8-C<u>H</u>$_2CH_3$ and -SCH_2CH_2S-), 3.98, 3.78, 3.52. 3.46, 3.44, 2.98 (each s, 3H, Me and OMe), 3.20 (t, 2H, 17^2-CH_2), 2.15 (s, 3H, ring 2-Me), 1.78 (t, 3H, CH_2C<u>H</u>$_3$), -1.35 and -2.20 (each bs, 1H, 2 x NH). Anal. Calcd for $C_{42}H_{44}N_4O_6S_2$: C, 65.94; H, 5.80; N, 7.32. Found: C, 65.92; H, 5.86; N, 7.28.

DMAD Adduct (36) of Ketal from 3-Vinylphylloerythrin Di-tert-butyl Aspartyl Amide (34). The di-tert-butyl aspartyl amide ketal **34** from 3-vinylphylloerythrin (60 mg) and DMAD (0.5 ml) were dissolved in toluene (50 ml) and refluxed for 5 d. After the standard work up, the intermediate adduct was dissolved in dichloromethane (5 ml) and treated with DBU (3 drops). The residue obtained after purification was crystallized from dichloromethane/hexane to give 25 mg (45%), mp. 250-252°C. Uv/vis λ_{max}: 408 nm (ε 200,700), 514 (17,200), 542 (14,900), 592 (11,400), 646 (36,800). ^{1}H NMR (δ ppm): 9.52, 9.45 and 8.89 (each s, 1H, meso H), 7.85, 7.40 (each d, 1H, 3^1-H and 3^2-H), 6.60 (bs, 1H, Asp-NH), 5.45 (s, 2H, 13^2-CH_2), 5.05 (s, 1H, 2^1-C<u>H</u>CO_2Me), 4.52 (m, 1H, Asp-CH), 4.50 (t, 2H, 17^1-CH_2), 4.15 (q, 2H, C<u>H</u>$_2CH_3$), 3.98, 3.50, 3.40, 3.38, 3.00 (each s, Me and OMe), 3.36-3.38 (m, 4H, 13^1 -OCH_2CH_2O-), 3.20 (t, 2H, 17^2-CH_2), 2.60-

2.80 (m, 2H, Asp-CH_2), 2.15 (s, 3H, 2^1-Me), 1.74 (t, 3H, $CH_2C\underline{H}_3$), 1.42 and 1.17 (each s, 9H, t-Bu), -1.38, -2.25 (each b s, 1H, NH). Anal. Calcd for $C_{53}H_{63}N_5O_{11}$: C, 67.26; H, 6.71; N, 7.40. Found: C, 67.22; H, 6.76; N, 7.42.

DMAD Adduct (37) of Thioketal from 3-Vinylphylloerythrin Di-tert-butyl Aspartyl Amide (35). The di-tert-butyl aspartyl amide thioketal **35** from 3-vinylphylloerythrin (60 mg) and DMAD (0.5 ml) were dissolved in toluene (30 ml) and refluxed for 5 d. After the standard work up, the intermediate adduct was purified, and rearranged to the desired BPD derivative on reacting with DBU, to give 29 mg (42 %), mp. 178-182°C. Uv/vis λ_{max}: 408 nm (ε 200,700), 514 (17,200), 542 (14,900), 592 (11,400), 646 (36,100). ^{1}H NMR (δ ppm): 9.42, 9.36, 8.82 (each s, 1H, meso H), 7.65, 7.37 (each d, 1H, 3^1-H and 3^2-H), 6.60 (bs, 1H, Asp-NH), 5. 45 (s, 2H, 13^2-CH_2), 5.05 (s, 1H, 2^1-C$\underline{H}$$CO_2$Me), 4.52 (m, 2H, Asp-$CH_2$), 4.40 (t, 2H, 17^2-CH_2), 4.15 (q, 2H, C$\underline{H}_2CH_3$), 3.98, 3.50, 3.40, 3.38, 3.00 (each s, 3H, Me and OMe), 2.86-3.08 (m, 4H, 13^1 -SCH_2CH_2S-), 3.20 (t, 2H, 17^2-CH_2), 2.15 (s, 3H, 2^1-Me), 1.74 (t, 3H, $CH_2C\underline{H}_3$), 1.42, 1.17 (each s, 9H, t-Bu), -1.18 and -2.01 (each bs, 1H, NH). Anal. Calcd for $C_{53}H_{63}N_5O_9S_2$: C, 65.07; H, 6.49; N, 7.16. Found: C, 65.00; H, 6.54; N, 7.14.

Triethylamine Rearranged DMAD Adduct (14) from Rhodoporphyrin Dimethyl Ester (10). Rhodoporphyrin dimethyl ester **10** (135 mg, 0.24 mmole) was dissolved in toluene (40 ml) and DMAD (1 ml) was added. The reaction mixture was refluxed for 60 h under a nitrogen atmosphere, and was worked up by following the general procedure reported above. After chromatographic separation, the residue was crystallized from dichloromethane/hexane to afford 80 mg (47%) of **13**, mp 130°C. [Uv/vis λ_{max}: 414 nm (ε 148,000), 528 (14,350), 556 (21,850), 590 (13,900), 646 (21,150). ^{1}H NMR (δ ppm): 10.78, 9.81, 9.26, and 9.01 (each s, 1H, meso H), 7.34 (m, 1H, 3^1-CH), 4.36, 4.04, 3.92, 3.79, 3.72, 3.49 and 3.46 (each s, 3H, Me and OMe), 4.34 (t, 2H, 17^1-CH_2), 3.98 (q, 2H, C$\underline{H}_2CH_3$), 3.28 (t, 2H, 17^2-CH_2), 2.10 (s, 3H, 2^1-Me) , 1.81 (t, 3H, $CH_2C\underline{H}_3$), -2.26 (bs, 1H, NH), -2.25 (b s, 1H, NH), 2^3-CH_2 obscured]. The foregoing Diels-Alder adduct **13** (70 mg), was dissolved in dichloromethane (50 ml), triethylamine (1 ml) was added, and the mixture was stirred for 3h. Evaporation of the solvent gave the *trans*- isomer (65 mg, 93 %), mp. 242°C. Uv/vis λ_{max}: 438 nm (ε 42,800), 584 (12,300), 662 (8000). ^{1}H NMR (δ ppm): 10.71, 9.73, 9.13 and 9.10 (each s, 1H, meso H), 7.68 (dd J = 3,6 Hz, 3^2-H), 4.70 (d J = 6 Hz, 1H, 3^1-H), 4.35, 4.24, 3.94. 3.74, 3.70, 3.44 and 3.37 (each s, 3H, Me and OMe, 4.31 (q, 2H, C$\underline{H}_2CH_3$), 3.90 (t, 2H, 17^1-CH_2), 3.25 (t, 2H, 17^2-CH_2), 1.75 (t, 3H, $CH_2C\underline{H}_3$) , 1.58 (s, 3H, 2^1-CH_3), -2.43 (b s, 1H, NH), -2.45 (b s, 1H, NH). Anal. Calcd for $C_{40}H_{42}N_4O_8{\cdot}H_2O$: C, 67.10; H, 6.06; N, 7.83. Found: C, 67.00; H, 6.04; N, 7.89.

DBU Rearranged Product (15). The TEA rearranged product **14** (60 mg) was dissolved in dichloromethane (10 ml) and DBU (10 drops) was added. The mixture was stirred under nitrogen for 20 min. The solvent was evaporated under high vacuum and the residue so obtained was crystallized from dichloromethane/hexane to give *cis*- isomer, 50 mg (83 %), mp. 265°C. Uv/vis λ_{max}: 438 nm (ε 97,800), 592 (31,100), 608 (27,100), 668 (24,300). ^{1}H NMR (δ ppm): 10.75, 9.84, 9.32 and 8.93 (each s, 1H, meso H), 7.86 (d J = 6 Hz, 1H, 3^2-H), 7.48 (d J = 6 Hz, 1H, 3^1-H), 5.10 (s, 1H, 2^1-C$\underline{H}$$CO_2$Me), 4.39, 4.04, 3.81, 3.75, 3.50, 3.47, 3.05 (each s, 3H, Me and OMe), 4.32 (t, 2H, 17^1-CH_2), 4.02 (q, 2H, C$\underline{H}_2CH_3$), 3.90 (t, 2H, 17^2-CH_2), 1.75 (t, 3H, $CH_2C\underline{H}_3$), 1.58 (s, 3H, Me), -2.01, -1.99 (each b s, 1H, NH), Anal. Calcd for $C_{40}H_{42}N_4O_8{\cdot}H_2O$: C, 67.10; H, 6.06; N, 7.83. Found: C, 66.94; H, 6.07; N, 7.91.

Benzoporphyrin Derivative Mono- (19) and Di-carboxylic Acid (21). The DBU rearranged benzoporphyrin **15** (35 mg, 0.05 mmole) was dissolved in tetrahydrofuran (10 ml). 25% Aqueous HCl (10 ml) was added and the mixture was stirred overnight. The reaction was monitored by analytical tlc. It was then diluted with dichloromethane, washed with water until pH 7. Evaporation of the organic eluates after drying over anhydrous Na_2SO_4 gave a residue which was purified on silica gel preparative plates (elution with 5% methanol/dichloromethane). The main band was collected and after the standard work up the product was

crystallized from dichloromethane/hexane to afford 22 mg (64%) of **19**, mp 268°C. Uv/vis λ_{max}: 438 nm (ε 80,800), 592 (23,800), 608 (20,400), 670 (19,000). ^{1}H NMR (δ ppm): 10.72, 9.78, 9.30 and 8.91 (each s, 1H, meso H), 7.84 (d J = 5.6 Hz, 1H, exocyclic ring vinyl CH), 7.46 (d J = 5.6 Hz, 1H, exocyclic ring vinyl CH), 5.08 (s, 1H, exocyclic ring C<u>H</u>CO$_2$Me), 4.33, 4.01, 3.76, 3.48, 3.43, 3.03 (each s, 3H, Me and OMe), 4.26 (t J = 6.7 Hz, 2H, 17^1-CH$_2$), 3.92 (q J = 8 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.31 (t J = 8.6 Hz, 2H, CH$_2$C<u>H</u>$_2$CO), 1.83 (s, 3H, 2-Me), 1.77 (t J = 8 Hz, 3H, CH$_2$C<u>H</u>$_3$), -2.03 (s, 2H, NH). HRMS: Calcd for $C_{39}H_{40}N_4O_8$, 692.2843. Found, 692.2840. A more polar fraction was characterized as benzoporphyrin diacid **21** (10 mg, 23%), mp 165°C: Uv/vis λ_{max}: 440 nm (ε 78,000), 592 (13,000), 608 (20,000), 670 (18,300). ^{1}H NMR (δ ppm): 10.72, 9.79, 9.29, 8.93 (each s, 1H, meso H), 7.94 (d J = 6 Hz, 1H, exocyclic ring vinyl CH), 7.46 (d J = 6 Hz, 1H, exocyclic ring vinyl CH), 5.05 (s, 1H, exocyclic ring C<u>H</u>CO$_2$Me), 4.34, 3.76, 3.48, 3.41, 3.08 (each s, 3H, Me and OMe), 3.94 (q J = 8.3 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.75 (t J = 6.7 Hz, 2H, C<u>H</u>$_2$CH$_2$CO), 3.35 (t J = 6.7 Hz, 2H, CH$_2$C<u>H</u>$_2$CO), 1.82 (s, 3H, 2-Me), 1.76 (t J = 8.3 Hz, 3H, CH$_2$C<u>H</u>$_3$). HRMS: Calcd for $C_{38}H_{38}N_4O_8$, 678.2705. Found: 678.2690.

Benzoporphyrin Derivative Di-tert-butyl Aspartyl Amide (18). Benzoporphyrin monocarboxylic acid **19** (45 mg, 0.065 mmole) DCC (50 mg), DMAP (5 mg) and aspartic acid di-tert-butyl ester (50 mg) were dissolved in dichloromethane (15 ml) and stirred overnight at room temperature under a nitrogen atmosphere. The mixture was then diluted with dichloromethane (100 ml) and washed with water. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was evaporated to give residue which was dissolved in dichloromethane (15 ml) and left in the refrigerator for 2 h. The white solid was filtered off and washed with cold dichloromethane. The residue obtained after evaporating the solvent was purified using silica gel thick layer plates (elution with 5% methanol/dichloromethane). The major band was characterized as the title compound and was obtained in 65% yield (39 mg), mp. 125°C. Uv/vis λ_{max}: 440 nm (ε 85,600), 592 (25,400), 608 (22,400), 670 (20,600). ^{1}H NMR (δ ppm): 10.72, 9.79, 9.29 and 8.99 (each s, 1H, meso H), 7.82 (d J = 6 Hz, 1H, exocyclic vinyl CH), 7.44 (d J = 6 Hz, 1H, exocyclic ring vinyl), 6.62 (bs, 1H, Asp NH), 5.06 (s, 1H, exocyclic ring-C<u>H</u>CO$_2$Me), 4.82 (m, 1H, CH(CO$_2$)), 4.36, 3.99, 3.77, 3.45, 3.42, 3.02 (each s, 3H, Me and OMe), 4.32 (t, 2H, 17^1-CH$_2$), 3.97 (q, 2H, C<u>H</u>$_2$CH$_3$), 3.19 (m, 2H, 17^2-CH$_2$), 2.82 (m 1H, aspartic CH$_2$CO), 2.63 (m, 1H, aspartic CH$_2$CO), 1.80 (s, 3H, 2^1-Me), 1.77 (t, 3H, 8-CH$_2$C<u>H</u>$_3$), 1.60 (s, 3H, 2-Me), 1.38, 1.35, 1.10, 1.09 (each s, diastereomeric t-Bu), -2.01 and -2.07 (each s, 1H, NH). HRMS, (FAB): Calcd for $C_{51}H_{61}N_5O_{11}$: 919.4359 (M+1). Found: 919.4360.

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