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SYNTHESES OF WATER-SOLUBLE CATIONIC PORPHYRINS AND CHLORINS†

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Abstract Reactions of vinylchlorins and vinylporphyrins with N,N-dimethylmethyleneammonium iodide ("Eschenmoser's Reagent") gives Mannich adducts in which substitution (with CH_2NMe_2) has taken place on the terminal carbon of the vinyl group to yield a trans-3-(N,N-dimethylaminomethyl)prop-1-enyl derivative. Under no circumstances was meso substitution observed. Use of zinc(II) vinylchlorins or zinc(II) vinylporphyrins afforded the corresponding zinc(II) trans-vinyl adducts at a significantly faster rate than the metal-free substrates. Reaction of Eschenmoser's reagent with deuteroporphyrin-IX dimethyl ester (**29**) (which possesses two peripherally unsubstituted positions) produces the bis-(N,N-dimethylaminomethyl) product (**30**). Treatment of the dimethylamino chlorins and porphyrins with methyl iodide, in all cases, gives an excellent yield of the corresponding quaternary ammonium iodides, and these compounds are highly water-soluble.

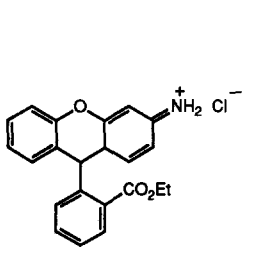
Introduction

Photodynamic therapy (PDT) involves the treatment of malignancies with visible light following the administration of a photosensitizing drug.[1] Tumor cytotoxicity is ascribed to the direct effect of singlet oxygen production as well as to indirect effects related to vascular collapse.[3-5] Currently, Photofrin (a hematoporphyrin derivative), is the only photosensitizer which is being used clinically for photodynamic cancer therapy. While Photofrin has some desirable properties as a photosensitizing agent (namely good efficacy, water solubility, good production of singlet oxygen, and ease of manufacture), it has some disadvantages. It is a complex mixture of porphyrin dimers and higher oligomers[6-9] linked by ether,[10-13] ester[8,14] and/or carbon-carbon bonds;[15,16] thus it is very difficult to study. Besides its chemically complex nature, Photofrin remains in the skin for a long time after administration and shows potential skin phototoxicity in patients for three to four weeks.[17] Due to its relatively weak absorption at 630 nm (a wavelength at which light has poor penetration through tissue) current clinical applications of Photofrin in PDT are limited to the destruction of tumorous tissue less than 4 mm from the source of light used in the therapy. For a compound to be useful as a photosensitizer in PDT, it must be non-toxic in clinically useful doses, it should retained in malignant tissue, and it must be activated by penetrating light. Water solubility is also advantageous, as it avoids the necessity to use additional drug delivery protocols such as Chremophor. Keeping these properties in mind, a variety of long-wavelength absorbing photosensitizers, which absorb in the range of 660 - 780 nm have been reported by various research groups.[18]

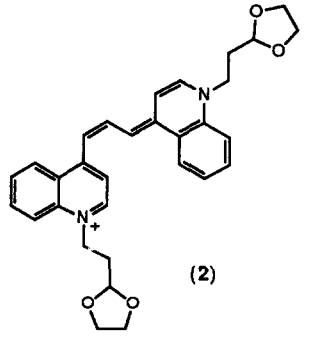
Most of the porphyrin-type photosensitizers investigated so far contain carboxylate functionalities; these are anionic in nature at physiological pH. A few years ago Chen and co-workers demonstrated that carcinoma cells also

† Dedicated to Professor Charles W. Rees, F.R.S., on the occasion of his retirement.

take up cationic molecules such as rhodamine-123 (**1**)[19] which is retained there for longer periods than in normal cells, also showing highly selective light-induced mitochondrial damage and cell killing. Based on these findings, Oseroff et al. recently developed some cationic dyes for PDT. The most effective of these are N,N'-bis(2-ethyl-1,3-dioxolane)kryptocyanine (EDKC; **2**)[20] and its analogues. EDKC was found to be an efficient tumorcidal agent when administered under hypothermic conditions (42°C) together with light. It was one of our objectives to develop simple and efficient procedures for the preparation of new cationic type photosensitizers from readily available porphyrins, chlorins (7,8-dihydroporphyrins), and pheophorbides.[21] We hope that the *in vivo* and *in vitro* results with these compound will help us to understand more about the sites of localization of both cationic and anionic photosensitizers.



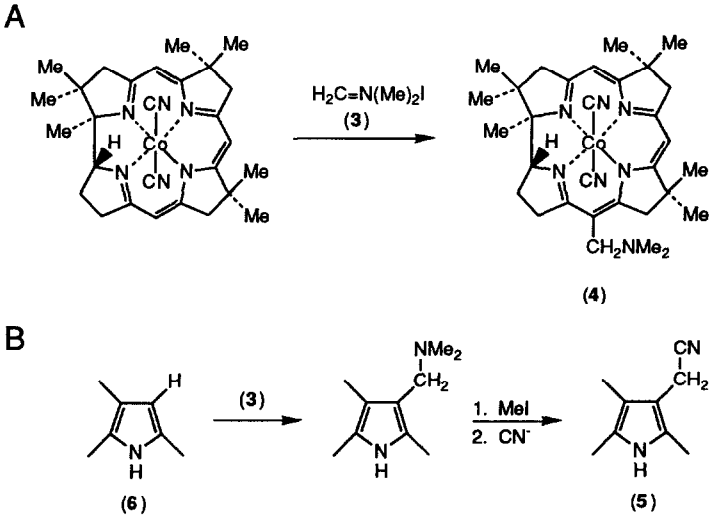
(1)



(2)

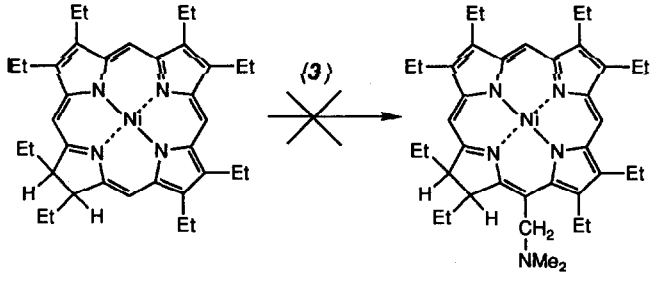
Results and Discussion

Some years ago, Eschenmoser and colleagues[22] demonstrated the utility of the Mannich salt N,N-dimethylmethyleneammonium iodide (**3**) [commercially available under the name "Eschenmoser's Salt" (Aldrich)] as a reagent for the introduction alkyl groups onto corrins (to produce **4**) and of cyanomethyl and β-cyanoethyl side chains (**5**) onto pyrrole units (**6**) (Scheme 1).[23] These reactions involve an electrophilic aromatic substitution reaction to give a Mannich compound followed by quaternization and nucleophilic displacement; thus, we thought it should be possible to perform a similar reaction on chlorin compounds.



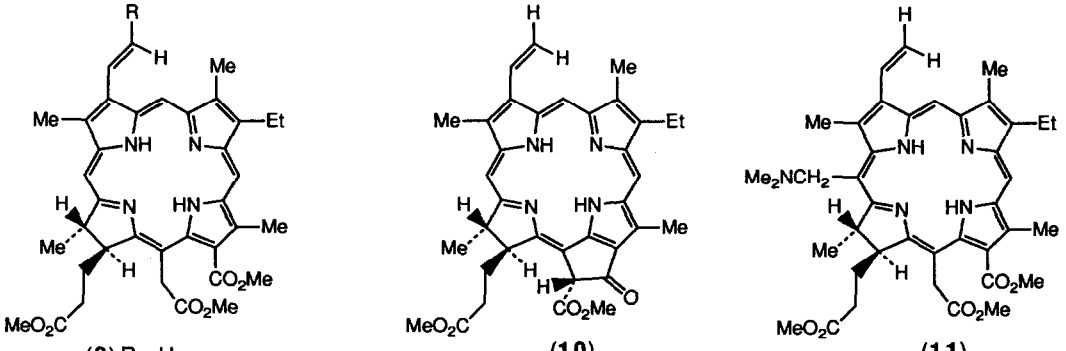
Scheme 1: Use of Eschenmoser's reagent (**3**) in the synthesis of A, substituted corrins (**4**), and B, cyanomethylpyrroles (**5**).

We began a model study by investigating the reaction of nickel(II) octaethylchlorin (NiOEC) (**7**)[24] with Eschenmoser's salt. We expected that the reaction would give the mono-meso-substituted compound (**8**). (In IUPAC nomenclature the *5,10,15,20*-positions are the meso sites). However, dissolving NiOEC and Eschenmoser's salt (20 equiv) in methylene chloride and stirring under nitrogen for 48 h at room temperature, or at reflux, gave no detectable product by thin layer chromatography (TLC). Since it was clear that NiOEC would not undergo the required reaction we turned our attention to chlorin-e_6 trimethyl ester (**9**),[25] which we had used earlier for preparation of the PDT agent, mono-aspartyl chlorin-e_6.[26] Chlorin e_6 trimethyl ester[25] was obtained in 80% yield by treatment of methyl pheophorbide-a (**10**) with sodium methoxide. Methyl pheophorbide-a in turn was extracted either from *Spirulina maxima* or *Spirulina pacifica* alga by following our previously reported method.[27]



(**7**) (**8**)

The chlorin e_6 trimethyl ester (**9**) was dissolved in dry methylene chloride and excess Eschenmoser's salt was added. Monitoring by TLC provided the best evidence for reaction progress. As the reaction proceeded, the TLC spot corresponding to starting material gradually disappeared with simultaneous appearance of two very close, slower-running, spots or streaks. When a few drops of triethylamine were added to the TLC chamber, the less mobile spots not only co-eluted but also ran much faster. This behavior was not unexpected, and indicated that protonation of the tertiary amine product by the silica (to give the ammonium salt) was causing the products to run slowly. After stirring for 48 h (in the case of free base chlorin-e_6 trimethyl ester) the reaction was worked up with water. After chromatography on neutral alumina the purified product was crystallized. It was anticipated that in the reaction with Eschenmoser's salt, electrophilic substitution would take place at the most electron-rich δ-meso carbon to give (**11**).



(**9**) R = H
(**12**) R = CH_2NMe_2
(**13**) R = CH_2NMe_3I

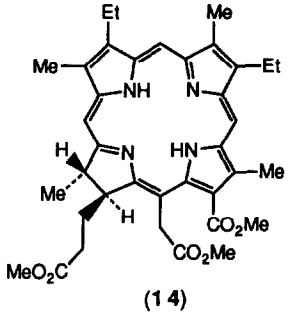
(**10**) (**11**)

However, the proton NMR spectrum gave unexpected results. It showed that there still existed *three* downfield meso protons, indicating that the expected meso-substitution reaction had not occurred. In addition the vinylic region in the proton NMR spectrum had changed from that observed for chlorin-e_6 trimethyl ester. The 2a-H resonance (IUPAC 3a-H) had become a doublet (rather than a doublet of doublets) and the multiplet for the 2b-CH_2

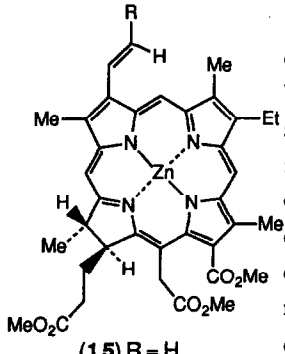
was no longer a doublet of doublets but rather was a doublet of triplets. The J_{HH} value for 2a-H and 2b-H was measured to be 17 Hz, indicative of *trans* coupling; there was no evidence for formation of any *cis* product. Thus, it appeared that the reagent had caused substitution to take place on the terminal carbon of the 2-vinyl group. As expected for such a reaction, the optical spectrum did not change appreciably from that of the starting material; substitution on the δ-meso position (IUPAC 20-position) would most likely have resulted in a bathochromic shift of the long-wavelength absorption maximum by several nanometers. Based on these observations the product was determined to be (**12**) rather than (**11**).

Electrophilic substitution at the terminal carbon of vinyl-porphyrins and -chlorins (to afford acrolein derivatives), rather than at the corresponding meso-positions, has previously been observed by Nichol for iron(III) complexes,[28] and by ourselves [29] for copper(II) and nickel(II) complexes.

Functionalization of porphyrin and chlorin vinyl groups in this manner with dimethylaminomethylene, followed by quaternization of the tertiary amine with methyl iodide appeared to us to be a useful approach for use in syntheses of water soluble PDT agents which might also target tumor sites other than those accessible to normal anionic porphyrin sensitizers. In order to obtain the desired cationic species, treatment of (**12**) with methyl iodide in acetone gave the quaternary ammonium salt (**13**). Proton NMR analysis of this compound was complicated somewhat by broad signals, but it was possible to assign nearly all of the peaks. The mass spectrum did not match the calculated molecular formula, but the accurate mass of the largest fragment corresponded, not unexpectedly, to loss of the $-N(CH_3)_3$ fragment. It was interesting to note that upon quaternization of the amine, the absorption maximum of the longest wavelength peak underwent a bathochromic shift of 16nm. This is a useful observation since one of the primary objectives of current research in PDT is to obtain compounds which have long-wavelength absorption maxima. Mesochlorin-e_6 trimethyl ester (**14**), which has a 2-ethyl in place of the 2-vinyl in (**9**), did not react with Eschenmoser's reagent even after several days of stirring at room temperature or at reflux.



(**14**)

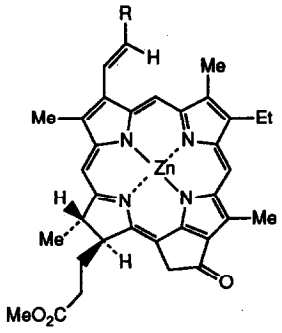


(**15**) R = H
(**16**) R = CH_2NMe_2
(**17**) R = CH_2NMe_3I

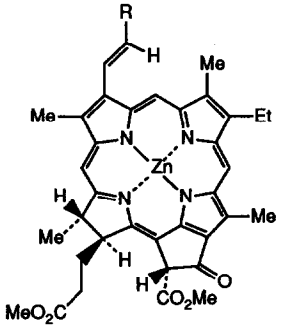
We next investigated the reaction of zinc(II) chlorin-e_6 trimethyl ester (**15**) with Eschenmoser's salt. We hypothesized that this reaction might direct substitution toward the meso-position due to insertion of zinc(II), which would make the chlorin ring more electron-rich than the metal-free derivative. The zinc(II) complex was prepared by refluxing (**9**) in dichloromethane with excess saturated zinc(II) acetate in methanol. The Eschenmoser's salt reaction was set up as described for the free base, but the reaction took place in only 2.5 h (instead of 24 h). After workup and purification, the proton NMR spectrum again showed vinyl-substitution, as it had previously for the free base compound. There was no substitution on the meso-positions and the reaction was cleanly restricted to the vinyl substituent, to give (**16**), again in a strictly *trans* configuration. Stirring for longer periods gave no additional products (i.e. no meso-substitution). In addition, the 78% yield observed represented a considerable improvement over the yield obtained using the free base compound. The effect of the zinc(II), therefore, is to increase the yield and the rate of the reaction without affecting regioselectivity in the substitution. In a similar fashion to that above, the quaternary salt (**17**) was obtained by briefly stirring (**16**) with methyl iodide. The proton NMR spectrum was again complicated by broad signals and the high resolution mass

spectrum once again showed cleavage of the trimethylamine fragment. Quaternization caused a now predictable red-shift of the long-wavelength absorption maximum.

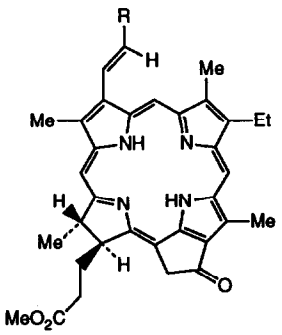
In recent years, among long-wavelength absorbing photosensitizers, methyl pheophorbide-a, methyl pyropheophorbide-a, and their derivatives have generated considerable attention due to their excellent photosensitizing properties.[30-33] To better understand the structure/activity relationships among anionic and cationic photosensitizers in this particular series of compounds, we extended the Eschenmoser salt substitution reaction into the pheophorbide series; the tertiary amines [(**18**) and (**19**)] from zinc(II) methyl pyropheophorbide (**20**) and zinc(II) methyl pheophorbide (**21**), respectively, were isolated in good yield. In all of these reactions, the conditions were the same as described above, except the time required for each individual reaction to go to completion was variable. After removal of the zinc(II) from (**18**) and (**19**) with acid, the resulting free bases (**22**) and (**23**) were treated with methyl iodide and afforded high yields of the corresponding quaternary ammonium iodides (**24**) and (**25**), respectively.



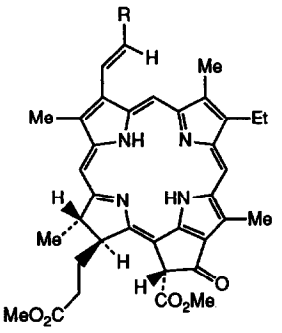
(**18**) R = CH_2NMe_2
(**20**) R = H



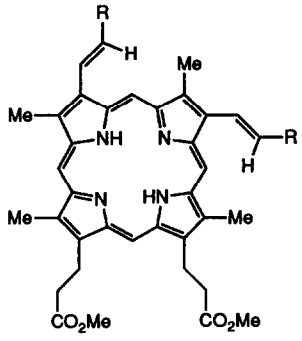
(**19**) R = CH_2NMe_2
(**21**) R = H



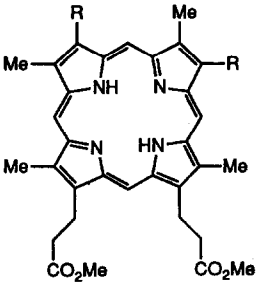
(**22**) R = CH_2NMe_2
(**24**) R = CH_2NMe_3I



(**23**) R = CH_2NMe_2
(**25**) R = CH_2NMe_3I



(**26**) R = H
(**27**) R = CH_2NMe_2
(**28**) R = CH_2NMe_3I



(**29**) R = H
(**30**) R = CH_2NMe_2
(**31**) R = CH_2Me_3I

By following a similar approach, protoporphyrin-IX dimethyl ester (**26**) gave the adduct (**27**). Deuteroporphyrin-IX dimethyl ester (**29**) [lacking the 2- and 4-vinyl groups(IUPAC 3- and 8-vinyl groups)] afforded (**30**) in quantitative yield. In both the porphyrin and chlorin series, the rate of reaction was significantly faster when the corresponding zinc complexes [e.g. (**Zn-26**), (**Zn-29**)] were used as starting materials, as expected from the results described above. Removal of the chelated zinc(II), for example from (**Zn-30**), by acid treatment afforded the same metal-free products.

The ease with which the trimethylammonium moiety leaves when the Mannich bases are treated with a variety of nucleophiles[22,23] should provide several new compounds, outside of the immediate PDT objectives discussed here, which could be subjected to further elaboration. Thus, this methodology for preparing the quaternary ammonium salts is not limited to preparation only of water soluble photosensitizers, but can also be used for synthesizing a variety of porphyrins and chlorins with variable substituents. Applications of the work reported herein to other tetrapyrroles of biological significance are in progress.

Detailed *in vivo* studies with the title compounds are in progress and will be reported elsewhere.

Experimental

Melting points were measured on a Thomas/Bristoline microscopic hot stage apparatus and were uncorrected. 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 (2 mm thick). Analytical thin layer chromatography was performed using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by thin layer chromatography (solvents usually mixtures of dichlormethane/methanol or hexane/ethyl acetate) and spectrophotometry and were carried out under nitrogen and in the dark (aluminum foil). Proton and carbon-13 NMR spectra were obtained in deuteriochloroform 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 UC San Francisco Mass Spectrometry Resource. Elemental analyses were obtained from MidWest Analytical Laboratory. Electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer.

Chlorin-e_6 Trimethyl Ester (9): Methyl pheophorbide-a (**10**) (617 mg) was dissolved in dry THF (20 ml) and stirred at room temperature under N_2. Sodium metal (190 mg) was dissolved in dry methanol (20 ml) under N_2 and after the reaction subsided, was transferred to the pheophorbide solution via a syringe. After stirring for 1 h, the reaction mixture was poured into water (200 ml) and extracted with CH_2Cl_2 until the organic layers were colorless. Acidification of the aqueous layer helped to settle emulsions. The combined organic layers were washed four times with water and then dried (Na_2SO_4) and evaporated. The residue was purified on alumina (Brockmann Grade III) eluting with 1:1 toluene/CH_2Cl_2. The main (bright-green) band was collected and evaporated to dryness. This residue was recrystallized from CH_2Cl_2/hexane to give 347 mg (53% yield) of the title compound. Mp: 208-209°C (Lit.[25] 211°C). λ_{max}: 402 nm (ε 150,000), 500 (11,600), 530 (4800), 608 (5300), 664 (45,500). ^{1}HNMR: 9.68,9.56 (α and β meso H), 8.73 (δ meso H), 8.06 (dd, 1H, 2a-H, J_{cis}=12, J_{trans}=18), 6.35 (dd, 1H, 2b-H trans to 2a-H, J_{trans}=18, J_{gem}=3), 6.14 (dd, 1H, 2b-H cis to 2a-H, J_{cis}=12, J_{gem}=3), 5.30 (ABq, 2H, γa-CH_2, J=18, J=24), 4.41 (m, 2H, 7-H and 8-H), 4.25 (s, 3H, 6-CO_2Me), 3.79 (q, 2H, 4a-CH_2), 3.76, 3.62, 3.57, 3.46, 3.29 (each s, 5 x 3H, 1,3,5 ring Me and γ-OMe and 7-OMe), 2.55, 2.20 (each m, 2 x 2H, 7-CH_2CH_2), 1.76 (d, 3H, 8-CH_3), 1.73 (t, 3H, 4b-CH_3),1.31,1.47 (each br s, 2 x 1H, NH).

2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-chlorin-e_6 Trimethyl Ester (12): Chlorin-e_6 trimethyl ester (**9**) (38.2 mg) (0.060 mmole) was dissolved in dry CH_2Cl_2 and 203.3 mg (1.10 mmole, 18 equiv) of Eschenmoser's salt were added. After stirring the reaction mixture under N_2 at room temperature for 48 h, it was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and evaporated to dryness. The product was purified on alumina (Grade III, eluting with 0.5%MeOH/CH_2Cl_2), and crystallization from CH_2Cl_2/hexane gave 23.9 mg (57% yield) of the title compound. Mp: 142-145°C. λ_{max}: 402 nm (ε 236,000), 500 (19,500), 530 (7500), 608 (7490), 662 (67,800). ^{1}HNMR: 9.67, 9.52 (each s, 2 x H, α and β meso H), 8.71 (s, 1H, δ meso H), 7.86 (d, 1H, 2a-H, J=17 Hz), 6.86 (dt, 1H, 2b-H, J=17, J=7 Hz), 5.27 (AB q, 2H, γa-CH_2), 4.42 (q, 1H, 8H), 4.37 (m, 1H, 7H), 4.24 (s, 3H, 6-CO_2Me), 3.75, 3.62, 3.56, 3.45, 3.29 (each s, 5 x 3H, 1-, 3-, 5-Me, γb-Me, 7-OMe), 3.78 (q, 2H, 4a-CH_2), 3.57 (d, 2H, 2c-CH_2), 2.57 (s, 6H, NMe_2), 2.52, 2.19 m, 7-CH_2CH_2), 1.73 (d, 3H, 8-Me), 1.70 (t, 3H, 4b-Me), -1.30, -1.45 (each br s, NH). HRMS: Calcd for $C_{40}H_{49}N_5O_6$ minus $N(CH_3)_2$ = 650.3104; Found: 651.3118. Anal Calcd. for $C_{40}H_{49}N_5O_6$.1.5 H_2O: C, 66.47; H, 7.25; N, 9.69. Found: C, 66.68; H, 6.94; N, 9.64.

2-Devinyl-2-[3-(N,N,N-trimethylammonium)prop-1-enyl]-chlorin-e_6 Iodide Trimethyl Ester (13): 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-chlorin-e_6 trimethyl ester (**12**) (9.5 mg) was dissolved in 8 ml of acetone. Methyl iodide (20 drops) was added and the mixture was swirled at room temperature for 5 min. The acetone and methyl iodide were removed by evaporation and the residue was precipitated from CH_2Cl_2/hexane to give 10.7 mg (93% yield) of product. Mp: >300°C. λ_{max}: 406 nm (ε 125,000), 506 (11,700), 536 (7400), 622 (5000), 676 (49,000). ^{1}HNMR: 9.70, 8.58, 7.94 (each s, 3 x 1H, α,β,δ-meso H),7.28 (d, 1H, 2a-H), 6.40 (d, 1H, 2b-H), 5.30 (AB q,γ-a H),4.45 (q, 1H, 8H), 4.38 (m, 1H, 7H), 4.30, 3.93, 3.66, 3.61, 2.87, 2.62 (each s, 6 x 3H, 1-Me, 3-Me, 5-Me, 6-OMe, γ-OMe, and 7-OMe), 2.66 (s, 6H, NMe_2), 2.40 and 2.22 (m, 4H, 7-CH_2CH_2),1.86 (d, 3H, 8-Me), 1.67 (t, 3H, 4b-CH_3), -1.69, -1.89 (each br s, 1H, NH). (The 2c-CH_2 and the 4a-CH_2 signals for this compound were obscured). HRMS: Calcd for $C_{41}H_{52}N_5O_6$ minus $N(CH_3)_3$ = 650.3104; Found: 650.3140. Anal Calcd. for $C_{41}H_{52}IN_5O_6$.1.5 H_2O: C, 56.95; H, 6.41; N, 8.09. Found: C, 57.05; H, 5.98; N, 7.90.

Zinc(II) Chlorin-e_6 Trimethyl Ester (15): Chlorin e_6 trimethyl ester (**9**) (115.3 mg) was dissolved in CH_2Cl_2 and refluxed with excess saturated zinc(II) acetate in MeOH. After UV-Vis and TLC indicated complete reaction, the mixture was poured into water and extracted with more CH_2Cl_2. The organic layer was washed twice with water, then dried (Na_2SO_4) and evaporated. The residue was purified on a short alumina (Brockmann Grade III) column, eluting

with 1% MeOH/CH_2Cl_2. The solvent was removed and the residue was crystallized from CH_2Cl_2/hexane to give 128.1 mg (100%) of zinc(II) chlorin-e_6 trimethyl ester. Mp: 224-227°C. λ_{max}: 410 nm (ε 139,000), 510 (5300), 548 (3100), 592 (9600), 638 (60,000). ^{1}HNMR: 9.53, 9.49 (each s, 2 x 1H, α and β meso H), 8.55 (s, 1H, δ meso H), 8.01 (dd, 1H, 2a-H, J_{trans}=18, J_{cis}=12 Hz), 6.17 (dd, 1H, 2b-H trans to 2a-H, J_{trans}=18, J_{gem}=2 Hz), 6.02 (dd, 1H, 2b-H cis to 2a-H, J_{cis}=12, J_{gem}=2 Hz), 5.15 (ABq, 2H, γa-CH_2, J=21, J=30 Hz), 4.33 (m, 1H, 8-H), 4.28 (m, 1H, 7-H), 4.18 (s, 3H, 6-OMe), 3.75 (q, 2H, 4a-CH_2), 3.81, 3.58, 3.44, 3.34, 3.29 (each t, 5 x 3H, 1,3,5 ring Me, and γ-OMe and 7-OMe), 2.51, 2.17 (each m, 2 x 2H, 7-CH_2CH_2), 1.71 [m , 5H, 4b-CH_3 and 8-Me (overlapping t and d)].

Zinc(II) 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-chlorin-e_6 Trimethyl Ester (16): Zinc(II) chlorin-e_6 trimethyl ester (**15**) (128.1 mg) was dissolved in 25 ml of dry CH_2Cl_2 and Eschenmoser's salt (341.3 mg) was added. The mixture was stirred at room temperature under N_2 for 2.5 h. After that time, TLC showed no starting material to be present, so the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water two more times, then dried (Na_2SO_4) and evaporated. The residue was purified on alumina (Brockmann Grade III, eluting with 2% MeOH/CH_2Cl_2). After removal of solvents the residue was crystallized from CH_2Cl_2/hexane to give 88.0 mg of product initially (64%) and an additional 11.6 mg were obtained from the mother liquor for a total yield of 99.6 mg (78%). Mp: >300°C. λ_{max}: 414 nm (ε 128,000), 518 (4200), 598 (9200), 638 (52,500). ^{1}HNMR: ($CDCl_3$ + pyridine-d_5) 9.48, 9.43 (each s, 2 x 1H, α and β mesoH), 8.37 (s, 1H, δ meso H), 7.85 (d, 1H, 2a-CH, J=15 Hz), 6.69 (dt, 1H, 2b-CH, J=15, J=7 Hz), 5.21 (s, 2H, γ-CH_2), 4.22 (m, 2H, 8-H and 7-H), 4.19 (s, 3H, 6-OMe), 3.76 (m, 2H, 4a-CH_2, partially obscured), 3.74, 3.60, 3.43, 3.32, 3.30 (each s, 5 x 3H, 1, 3, and 5 ring CH_3, γ-OMe, and 7-OMe), 3.50 (d, 2H, 2c-CH_2, J=7 Hz), 2.50 (s, 6H, NMe_2), 2.40 and 2.00 (m, 7-CH_2CH_2), 1.65 (t, 3H, 4b-Me), 1.54 (d, 3H, 8-Me). HRMS: Calcd. for $C_{40}H_{47}N_5O_6Zn$ minus NMe_2 = 713.2311; Found; 713.2318. Anal Calcd. for $C_{40}H_{47}N_5O_6Zn.H_2O$: C, 61.81; H, 6.35; N, 9.01. Found: C, 61.82; H, 6.43; N, 8.78.

Zinc(II) 2-Devinyl-2-[3-(N,N,N-trimethylammonium)prop-1-enyl]-chlorin-e_6 Iodide Trimethyl Ester (17): Zinc(II) 2-devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-chlorin-e_6 trimethyl ester (**16**) (69.5 mg) was dissolved in 15 ml of acetone; 2 ml of methyl iodide were added and the mixture was stirred for 10 min under nitrogen at room temperature. The acetone and excess methyl iodide were removed by evaporation, and the residue was crystallized from CH_2Cl_2/hexane to give 80.4 mg of product (97% yield). Mp: 201-206°C. λ_{max}: 412 nm (ε 99,900), 514 (5600), 558 (4200), 604 (11,500), 650 (45,000). ^{1}HNMR: 9.65 (s, 1H, meso H), 8.40, 7.66 (each br s, 2 x 1H, meso H), 7.34 (m, 1H, 2a-H), 5.68 (m, 1H, 2b-H), 5.24 (AB q, 2H, γa-CH_2), 4.20-4.35 (m, 2H, 7-H and 8-H), 4.27, 3.93, 3.68, 3.55, 2,94, 2.36 (each s, 6 x 3H, 1-Me, 3-Me, 5-Me, 6-OMe, γ-OMe and 7-OMe), 2.39 (s, 9H, NMe_3), 1.78 (d, 3H, 8-Me). (The 2c-CH_2, 4a-CH_2 and 4b-CH_3 signals for this compound were obscured). HRMS Calcd for $C_{41}H_{50}IN_5O_6Zn$ minus NMe_3I = 713.2311; Found; 713.2334.

Zinc(II) Methyl 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-pyropheophorbide-a (18): Zinc(II) methyl pyropheophorbide-a (**20**) (50 mg) and Eschenmoser's salt (130 mg) were dissolved in dry CH_2Cl_2 (25 ml), and then stirred at room temperature under N_2 in the dark for 20 h. The mixture was poured in water and extracted with dichloromethane. The dichloromethane layer was washed with water, the organic phase was separated, dried (Na_2SO_4) and evaporated to give a residue which was chromatographed on alumina (Brockmann Grade III), eluting first with CH_2Cl_2 to remove the starting material. Further elution with 2% MeOH/CH_2Cl_2, gave a major green fraction. The solvent was evaporated and the residue was crystallized from THF/n-hexane to give 30 mg (55%) of the title compound. Mp: >300°C. λ_{max} 428 nm (ε 98,000), 530 (3200), 582 (5900), 612 (11,400), 658 (63,000). ^{1}HNMR: 9.48, 9.18, 8.27 (s, 1H, meso H), 7.72 (d, 1H, 2a-H, J=16 Hz). 6.60 (dt, 1H, 2b-H, J =15 Hz, 7Hz), 5.14-4.93 (ABq, 2H, 10-CH_2), 4.32 (q, 1H, 8-H), 4.12 (m, 2H, 7-H), 3.70 (q, 2H, 4 x CH_2), 3.61, 3.48, 3.26, 3.17 (s, 3H, ring Me and OMe), 2.43 (s, 6H, NMe_2), 2.40-2.10 (m, 4 H, 7 CH_2CH_2), 1.64 (d, 3H, 8-Me), 1.19 (t, 3H, $CH_2C\underline{H}_3$). HRMS Calcd for $C_{37}H_{41}N_5O_3Zn$ minus $N(CH_3)_2$ = 623.1995; Found: 623.1998. Anal Calcd. for $C_{37}H_{41}N_5O_3Zn$: C, 66.41; H, 6.18; N, 10.47. Found: C, 66.27; H, 6.31; N, 10.26.

Methyl 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-pyropheophorbide-a (22): The Zn complex (**18**) (10 mg) was treated with TFA (0.5 ml) stirred at room temperature under N_2 for 10 min. It was then diluted with CH_2Cl_2, washed with water, aqueous $NaHCO_3$ and then again with water. The organic phase was dried (Na_2SO_4). Evaporation of the solvent gave a residue which was crystallized from THF/n-hexane to give (**22**) in quantitative yield (9 mg). Mp: 130-132°C. λ_{max} 412 nm (ε 89, 000), 474 (3700), 508 (8,500), 540 (8000), 666 (34,700). ^{1}HNMR: 9.47 (s, 1H, meso H), 9.33 (s, 1H, meso H), 8.52 (s, 1H, meso H), 7.81, 7.75 (d, 1H, 2a-H), 6.80 (m, 1H, 2b-H), 5.27-5.03 (q, 2H, 10-H), 4.45 (m, 1H, 8-H), 4.26 (m, 1H, 7-H), 3.68 (q, 2H, $C\underline{H}_2CH_3$), 3.64 (s, 3H, OMe), 3.58 (s, 3H, ring Me), 3.56 (d, 2H, $C\underline{H}_2NMe_2$), 3.37 (s, 3H, ring Me), 3.22 (s, 3H, ring Me), 2.55 (s, 6H, $N\underline{Me}_2$), 2.27 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 1.80 (d, 3H, 8-Me), 1.67 (t, 3H, $CH_2C\underline{H}_3$), 0.43 (s, 1H, NH), -1.71 (s, 1H, NH). HRMS Calcd for $C_{37}H_{43}N_5O_3$ minus $N(Me)_2$ = 561.2860; Found; 561.2890. Anal Calcd. for $C_{37}H_{43}N_5O_3.H_2O$: C, 71.24; H, 7.24; N, 11.23. Found: C, 70.94; H, 7.16; N, 10.44.

Methyl 2-Devinyl-2-[3-(N,N,N-trimethylammonium)prop-1-enyl]-pyropheophorbide-a Iodide (24): Methyl 2-[3-(N,N-dimethylamino)prop-1-enyl]-pyropheophorbide-a (**22**) (10 mg) was dissolved in acetone (5 ml), treated with methyl iodide (0.5 ml) and the reaction mixture was then stirred at room temperature for 10 min. The precipitate so obtained was filtered and dried under vacuum. Mp: 210-212°C. λ_{max} 416 nm (ε 80,300), 510 (8700), 542 (7900), 616 (7000), 678 (32,100). ^{1}HNMR: 9.04 (s, 1H, meso H), 8.97 (s, 1H, meso H), 8.55 (s,1 H, meso H), 7.52 (d, 1H, 2a-H), 6.49 (m, 1H, 2b-H), 5.02 (d, 2H, $C\underline{H}_2NMe_2$), 5.00 (q, 2H, 10-H), 4.24 (m, 1H, 8-H), 4.09 (m, 1H, 7-H), 3.56 (s, 3H, OMe), 3.54 (s, 9H, NMe_3), 3.40 (q, 2H, $C\underline{H}_2CH_3$), 3.36 (s, 3H, ring Me), 3.26 (s, 3H, ring Me), 3.02 (s, 3H, ring Me), 2.49-2.20 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 1.64 (d, 3H, 8-Me), 1.42 (t, 3H, $CH_2C\underline{H}_3$), -0.48 (s, 1H, NH), -2.46 (s, 1H, NH). HRMS: Calcd for $C_{38}H_{46}IN_5O_3$ minus $N(Me_3)I$ = 561.2861; Found; 561.2852. Anal Calcd. for $C_{38}H_{46}IN_5O_3.2\,H_2O$: C, 58.22; H, 6.43; N, 8.94. Found: C, 57.78; H, 6.18; N, 8.83.

Zinc(II) Methyl 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-pheophorbide-a (19): Zinc(II) methyl pheophorbide-a (**21**) (35 mg) was dissolved in dichloromethane (15 ml) and reacted with Eschenmoser's salt as described for the preparation of the methyl pyropheophorbide-a derivative (**22**) and the desired product was isolated in 58 % yield (23 mg). Mp: 142-145°C. λ_{max} 426 nm (ε 94,000), 530 (3300), 574 (3200), 612 (11,200), 658 (62,500). ^{1}HNMR: 9.60, 9.30, 8.38 (each s, 1 meso H), 7.79 (d, 1H, 2a-H, J=16 Hz), 6.68 (m, 1H, 2b-H, J = 16, 7 Hz), 6.18 (s, 1H, 10-H), 4.20 (m, 1H, 8H), 4.02 (m, 1H, 7-H), 3.80 (m, 2H, 4-$C\underline{H}_2CH_3$), 3.65-3.15 (singlets, 15H, 3 x Me and 2 x OMe), 2.56 (s, 6H, NMe_2), 2.38-1.89 (m, 4H, $CH_2CH_2CO_2$), 1.65 (t, 3H, $CH_2C\underline{H}_3$), 1.41 (m, 3H, 8-Me). Anal Calcd. for $C_{39}H_{43}N_5O_5Zn$: C, 64.42; H, 5.96; N, 9.63. Found: C, 64.28; H, 6.11; N, 9.41.

Methyl 2-Devinyl-2-[3-(N,N-dimethylamino)prop-1-enyl]-pheophorbide-a (23): The Zn complex (**19**) (30 mg) was treated with TFA (10 ml) stirred at room temperature under N_2 for 10 min. It was then diluted with CH_2Cl_2, washed with water, aqueous $NaHCO_3$ and then again with water. The organic phase was dried (Na_2SO_4). Evaporation of the solvent gave a residue which was crystallized from THF/n-hexane to give (**23**) in quantitative yield (27 mg). Mp: 135-136°C. λ_{max} 410 nm (ε 92,000), 476 (3800), 508 (8600), 540 (8100), 666 (34,800). ^{1}HNMR: 9.53 (s, 1H, meso H), 9.42 (s, 1H, meso H), 8.63 (s, 1H, meso H), 7.84 (d, 1H, 2a-H), 6.83 (dt, 1H, 2b-H), 5.25 (ABq, 2H, γa-CH_2), 4.38 (q, 1H, 8-H), 4.26 (m, 1H, 7-H), 4.23 (s, 3H, 6-OMe), 3.78, 3.66, 3.58, 3.47, 3.30 (each s, 3H, ring Me, γb-OMe, 7-OMe), 3.75 (q, 2H, $C\underline{H}_2CH_3$), 3.57 (d, 2H, 2c-Me), 2.59 (s, 6H, NMe_2), 2.50, 2.20 (each m, 2H, $C\underline{H}_2C\underline{H}_2$), 1.80 (d, 3H, 8-Me), 1.73 (t, 3H, $CH_2C\underline{H}_3$), -1.40 (s, 1H, NH), -1.51 (s, 1H, NH). Anal Calcd. for $C_{39}H_{45}N_5O_5$: C, 70.35; H, 7.12; N, 10.52. Found: C, 70.64; H, 7.02; N, 11.12.

Methyl 2-Devinyl-2-[3-(N,N,N-trimethylammonium)prop-1-enyl]-pheophorbide-a Iodide (25): Methyl 2-[3-(N,N-dimethylamino)prop-1-enyl]-pyropheophorbide-a (**23**) (20 mg) was dissolved in acetone (10 ml), treated with methyl iodide (0.5 ml) and the reaction mixture was then stirred at room temperature for 10 min. The precipitate so obtained was filtered and dried under vacuum. Mp: > 300°C. λ_{max} 414 nm (ε 90,000), 508 (8900), 544 (8000), 618 (6900), 678 (32,500). Anal Calcd. for $C_{40}H_{48}IN_5O_5.H_2O$: C, 57.07; H, 6.23; N, 8.32. Found: C, 56.83; H, 5.96; N, 8.14.

2,4-Bis[3-(N,N-dimethylamino)prop-1-enyl]-deuteroporphyrin-IX Dimethyl Ester (27): Protoporphyrin-IX dimethyl ester (**26**) (250 mg) and Eschenmoser's salt (640 mg) were dissolved in dry CH_2Cl_2 (150 ml) then stirred at room temperature under N_2 for 20 h before being poured into water, extracted with CH_2Cl_2, washed with water three times, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade III) eluted with 2%MeOH/CH_2Cl_2. The major fraction was collected, the solvent removed, and the residue was crystallized from CH_2Cl_2/n-hexane to give 150 mg (50%) of the title compound. Mp: 125-126°C. λ_{max} 404 nm (ε 71, 000), 504 (5100) 540 (4100), 576 (2800), 628 (1000). ^{1}HNMR: 10.15 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.03 (s, 1H, meso H), 10.00 (s, 1H, meso H),8.08, 8.02 (d, d, 1H, 1H, 2a-H), 6.98 (m, 2H, 2b-H), 4.41-4.36 (m, 4H, $C\underline{H}_2CH_2CO_2$), 3.69, 3.68 (m, 10-H, 2 x ring Me, 2 x $C\underline{H}_2NMe_2$), 3.66 (s, 6H, 2 x OMe), 3.61 (s, 3H, ring Me), 3.60 (s, 3H, ring Me), 3.30-3.25 (m, 4H, 2 x $CH_2C\underline{H}_2CO_2$), 2.62 (s, 12H, NMe_2), -3.74 (s, 2H, NH). HRMS: Calcd for $C_{42}H_{52}N_6O_4$ minus 2 $N(CH_3)_2$ = 616.3044; Found: 616.3058. Anal Calcd. for $C_{42}H_{52}N_6O_4.H_2O$: C, 69.78; H, 7.53; N, 11.07. Found: C, 69.81; H, 6.82; N, 11.24.

2,4-Bis[3-(N,N,N-trimethylammonium)prop-1-enyl]-deuteroporphyrin-IX Di-iodide Dimethyl Ester (28): 2,4-Bis[3-(N,N-dimethylamino)prop-1-enyl]-deuteroporphyrin-IX dimethyl ester (**27**) (20 mg) in 10 ml of acetone was stirred with methyl iodide (2 ml) at room temperature for 10 min before removal of the solvent and crystallization of the residue from CH_2Cl_2/n-hexane to give 28 mg (100%) of the title compound. Mp: >300°C. λ_{max} (MeOH) 408 nm (ε 92,700), 506 (5100), 576 (2800), 628(1000). HRMS: Calcd for $C_{44}H_{58}I_2N_6O_4$ minus 2 $N(CH_3)_3I$ = 616.3044; Found; 616.3048. Anal Calcd. for $C_{44}H_{58}I_2N_6O_4$: C, 53.45; H, 5.91; N, 8.50. Found: C, 54.04; H, 5.99; N, 8.14.

Zinc(II) 2,4-Bis[(N,N-dimethylamino)methyl]-deuteroporphyrin-IX Dimethyl Ester (Zn-30): Zinc(II) deuteroporphyrin-IX dimethyl ester (**Zn-29**) (250 mg) and Eschenmoser's salt (670 mg) were dissolved in dry dichloromethane (30 ml) and the reaction mixture was refluxed for 72 h under a nitrogen atmosphere. The reaction was monitored by TLC. The mixture was then diluted with dichloromethane (100 ml), washed with water (3 x 100 ml), the dichloromethane layer was separated, dried (Na_2SO_4), and evaporated to dryness to give a residue which was passed through a short column of alumina (Brockmann Grade III) eluted with 2%MeOH/CH_2Cl_2. Evaporation of the solvent and crystallization from CH_2Cl_2/hexane afforded the title compound in 98% yield (292 mg). Mp: >300°C. λ_{max} 404 nm (ε 253,000), 534 (14,600), 570 (16,800). ^{1}HNMR: 10.15, 10.12, 10.02, 9.95 (each s, 1H, meso H), 4.68 (s, 4H, 2-C$\underline{H_2}$NMe$_2$), 4.35 (t, 4H, C$\underline{H_2}$CH$_2$CO$_2$), 3.61, 3.59, 3.57 (each s, total 18H, 4 Me, 2 OMe), 3.29 (t, 4H, 2 CH$_2$C$\underline{H_2}$CO$_2$), 2.49 (s, 12H, 2-NMe$_2$). HRMS: Calcd for $C_{38}H_{46}N_6O_4Zn$ minus N(CH$_3$)$_2$ = 626.1866; Found; 626.1872. Anal Calcd. for $C_{38}H_{46}N_6O_4Zn$: C, 63.73; H, 6.47; N, 11.73. Found: C, 64.02; H, 6.06; N, 11.51.

2,4-Bis-[(N,N-dimethylamino)methyl]-deuteroporphyrin-IX Dimethyl Ester (30): Zinc(II) 2,4-bis[(N,N-dimethylamino)methyl]-deuteroporphyrin-IX dimethyl ester (**Zn-30**) (50 mg) was treated with trifluoroacetic acid (5 ml) at room temperature and under a nitrogen atmosphere for 5 min. The mixture was poured into water and extracted with dichloromethane which was washed with water, 10% aqueous sodium bicarbonate, and again with water. The organic phase was dried (Na_2SO_4) and evaporated to dryness to give a residue which was crystallized from CH_2Cl_2/hexane to afford the title compound in 100% yield (45 mg). Mp: 128-129°C. λ_{max} 402 nm (ε 138,200), 502 (10,000), 538 (6900), 570 (5500), 622 (2400). ^{1}HNMR: 10.18 (s, 2H, 2 meso H), 10.02, 10.01 (each s, 1H, meso H), 4.85 (s, 4H, C$\underline{H_2}$NMe$_3$),4.39 (m, 4H, 2-C$\underline{H_2}$CH$_2$CO$_2$), 3.65 (s, 6H, 2 OMe), 3.59, 3.58 (each s, 6H, 2 Me), 3.24 (t, 4H, 2 CH$_2$C$\underline{H_2}$CO$_2$), 2.68 (s, 12H, 2NMe$_2$), -3.80 (s, 2H, 2NH). Anal Calcd. for $C_{38}H_{48}N_6O_4$.0.5 H_2O: C, 68.97; H, 7.46; N, 12.70. Found: C, 68.73; H, 6.98; N, 12.32.

2,4-Bis-[(N,N,N-trimethylamino)methyl]-deuteroporphyrin-IX Di-iodide Dimethyl Ester (31): 2,4-Bis[(N,N-dimethylamino)methyl]-deuteroporphyrin-IX dimethyl ester (**30**) (30 mg) was dissolved in acetone (15 ml) and treated with methyl iodide (0.5 ml) and then stirred at room temperature and under a nitrogen atmosphere for 5 min. The precipitate was filtered off to afford the title compound in 100% yield (42 mg). Mp: >300°C. λ_{max} 402 nm (ε 137,000), 502 (11,100), 536 (5700), 572 (4600), 626 (2600). Anal Calcd. for $C_{40}H_{54}I_2N_6O_4$.2 H_2O: C, 49.39; H, 6.01; N, 8.64. Found: C, 49.88; H, 6.09; N, 8.42.

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