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Syntheses of Oxygen Analogues of Sulfhemes-A and -C

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Abstract: Syntheses of metal-free oxygen analogues of the sulfhemes-A and -C from protoporphyrin-IX dimethyl ester **1** are presented. Oxasulfporphyrin-C dimethyl ester **5** is obtained by intramolecular displacement of a primary tosylate by a tertiary hydroxyl in an appropriately constructed precursor **18**, or by surface-catalyzed rearrangement of the epoxide-bearing oxasulfporphyrin-A dimethyl ester **23**. Compound **23** is in turn prepared by Mitsunobu type internal dehydration of the precursor **12**. The methodology is then successfully extended to more symmetric porphyrin systems. Compounds **23**, **25**, **46**, and **61/62** are the first porphyrin epoxides to be synthesized.

INTRODUCTION

Sulfhemoglobin (SHb) and sulfmyoglobin (SMb) are heme proteins in which the heme prosthetic group has been altered by modification of a pyrrole subunit and incorporation of a sulfur atom into the porphyrin macrocycle. SHb is of considerable medical interest because it is formed *in vivo* under certain pathological conditions, particularly those in which a sulfide source is present[1] or in which there is blood poisoning by certain reducing agents.[2,3] The presence of high dosages of common analgesics[4] or exposure to chemical pollutants[5-7] might also be responsible for initiating onset of the sulfhemoglobinemia disease. The reducing agents serve as catalysts, while the sulfide source is endogenous, probably H_2S from intestinal bacteria.

Hoppe-Seyler,[8] in 1866, was the first to observe a green product formed from the reaction of HbO_2 and H_2S. He called the product "schwefelmethaemoglobin" or sulfhemoglobin. In 1933, Keilin[9] reported that SHb is formed irreversibly only in the presence of O_2. It was also claimed that the characteristic 618 nm band for SHb probably belongs to the ferrous form since it is bleached by $K_3Fe(CN)_6$. In 1938, Michel[10,11] prepared SHb employing a new method, namely the successive addition of dithionite, sulfide and a peroxide to the normal globin. He ruled out the binding of sulfur as distal ligand to the heme since CO bound there. He also prepared analogous spectral species from Mb and from hematoporphyrin-substituted Hb, which lacks vinyl groups. Most later researchers took advantage of Michel's findings and used the simpler protein Mb for their studies. In 1961, Nicholls[12] prepared SMb from the higher oxidation state derivative of Mb, Mb^{IV}, by reacting ferric Mb with H_2O_2. He showed that the addition of 1 mole of H_2S per heme produced ferric SMb, which could then be reduced to the ferrous compound by adding excess H_2S. Morell, Chang and Clezy[4] modified Nicholls' synthesis in 1967 to obtain ferrous SMb in a better yield. Based on the resemblance of ferric and ferrous optical spectra to those of the iron mesochloringlobin compounds, where one of the β-β pyrrolic double bonds is saturated, the authors suggested that in SMb a sulfur atom is added across such a

double bond to form an episulfide bridge. In 1971, Berzofsky *et al.*[13] prepared SMb in higher than 90% purity by reaction of Mb^{IV} with 1.5 fold molar excess of $(NH_4)_2S$ at pH 8. It was soon shown by optical titration with ferricyanide that reduced SMb is in the ferrous state, where it binds oxygen reversibly.[14] It exhibited a rectangular hyperbolic binding curve (Hill coefficient n=1) similar to Mb, but with a $p_{1/2}$ (at 5° and pH 8) of 0.7 atm, which corresponds to an oxygen affinity 2500 times lower than that of Mb at the same temperature, accounting for the apparent inability of SMb to bind oxygen under physiological conditions. Berzofsky then studied the spectra of carboxysulfmyoglobin (SMbCO).[15] The infrared C-O stretching frequency of CO bound to the iron of ferrous SMb appears at 1953 cm^{-1}, about 10 cm^{-1} higher than that of CO bound to Mb. The decrease in O_2 and CO affinity of SMb, as compared to Mb, was attributed primarily to the lowering of electron density at the iron of the prosthetic group. The ferrous form of SMb was isolated as the stable product of the reaction of one mole of inorganic sulfide with one mole of the higher oxidation state derivative of Mb, Mb^{IV}.[16] Using radioactive sulfide, it was shown that exactly 1 g atom of sulfur is incorporated per mole of Mb to form SMb. Almost 90% of the radioactive sulfur is extracted into 2-butanone at pH 3.2, bound to the prosthetic group of SMb. The prosthetic group was called "sulfhemin", and found that it is unstable in organic solvents and undergoes oxidative decomposition to protoheme.

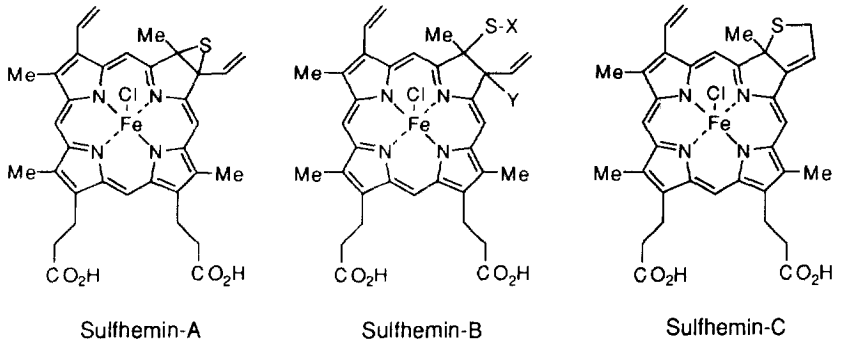


Figure 1: Structures of the sulfhemin pigments according to Chatfield and La Mar.[17,19]

In 1986, Chatfield and La Mar[17] reported evidence that the ^1H NMR spectrum of SMb revealed the presence of three forms, A, B and C, (designated S_AMb, S_BMb, and S_CMb in order of appearance) with different chemical reactivity (Figure 1). The three species cannot be distinguished by optical spectroscopy but provide clearly different NMR spectra. It was found earlier, for intermediates formed during the reconstitution of heme proteins, that high field NMR spectroscopy can be useful in detecting entities that are not differentiated by optical spectroscopy.[18] Chatfield and La Mar suggested that the differences among the three forms involve chemical modifications at the periphery of the porphyrin macrocycle. From one of these three forms of sperm whale SMb, S_CMb, extraction of a green hemin pigment that was stable for many hours at ambient temperatures was possible. The original S_CMb was successfully reconstituted from apoMb and this green "sulfhemin" pigment. Isotopic labeling of the vinyl positions confirmed that it was the 4-vinyl group that reacted in both the extracted "sulfhemin" and S_CMb.[19] This discovery clearly established that there is vinyl group participation in the formation of one of the forms of SMb. For the stable form S_CMb, it was suggested that the multiplet structure of the protons in the ^1H-NMR spectrum of the reacted 4-vinyl is consistent with the

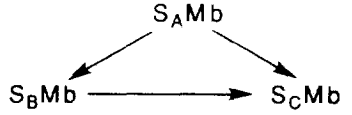


Figure 2: Relationship between SMb species in Mb protein[19]

formation of the dihydrothiophene exocyclic ring. The coupling constants observed were within a small range similar to those of the 3-thiolenes. The proposed mechanism for the formation of S_C involved the process $S_A \rightarrow S_B \rightarrow S_C$ (Figure 2) with the episulfide presumably reacting with the β carbon of the 4-vinyl.

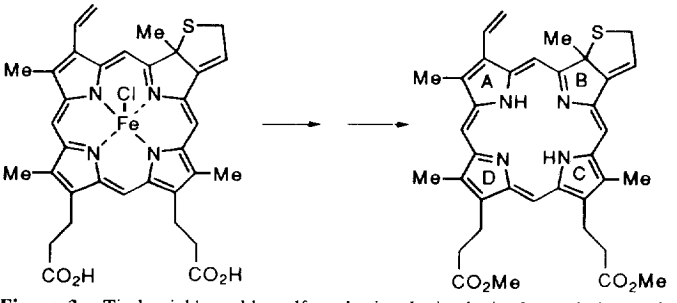
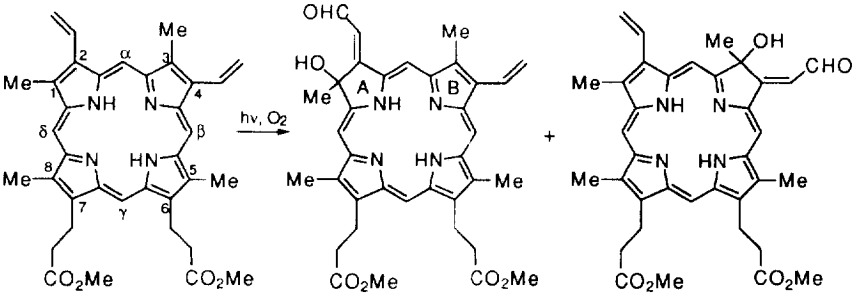


Figure 3: Timkovich's stable sulfporphyrin obtained via demetalation and esterification.[20]

A few months later, Timkovich *et al.*[20] extracted a stable green heme from ferric cyanoSMb, and after removal of iron and conversion to the methyl ester, (Figure 3) the resulting green porphyrin was purified by HPLC. ^{1}H NMR, spectrophotometric and mass spectrometric studies provided confirmatory evidence that rings A, C, and D carried the original proto-porphyrin IX substituents. He suggested that on ring B, the 4-vinyl group had cyclized with one sulfur atom to form an exocyclic ring with a 2,5-dihydrothiophene structure, fully in agreement with the results of La Mar *et al.*[19] achieved using the corresponding iron(III) complexes.

Chatfield and La Mar[21] extensively investigated the formation of SMb from Mb reconstituted with hemins which have hydrogens in place of the vinyl groups. In all cases, green complexes were produced, establishing that vinyl groups are not indispensable for the formation of sulfheme proteins. When the 4-vinyl group is present, three green species are formed, but the most stable of them is not formed in the absence of the 4-vinyl group, as was shown by the ^{1}H NMR spectra of the met-cyano derivatives. This finding established that the 4-vinyl group is reacting in the stable form of sulfmyoglobin.

Recently, Scharberg and LaMar have published their results[22] on the structure of SMb reconstituted with deuterohemin-IX instead of protohemin-IX, but the most significant recent development in this area has been the publication[23] of the three-dimensional crystal structure of a S_CMb, which confirmed ealier structural conclusions based on NMR spectroscopy.

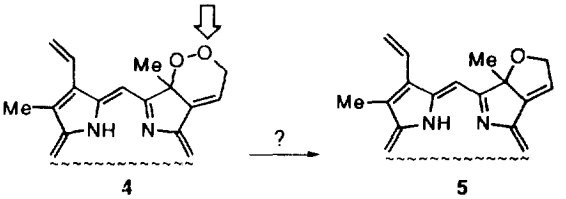


RESULTS AND DISCUSSION

Model Studies

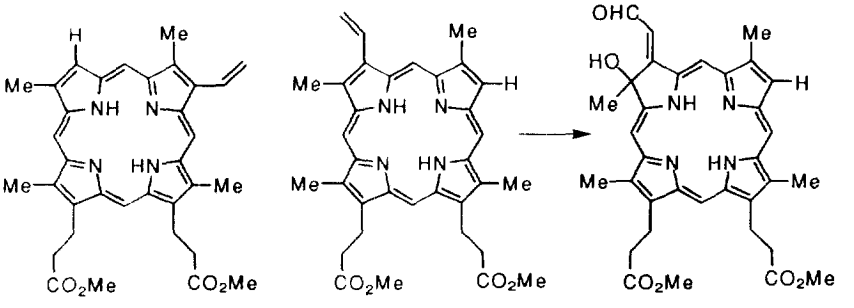
Monovinyl-photoporphyrin Approaches to Oxa-sulfporphyrin-A. Our attempts initially focused on the use of protoporphyrin-IX dimethyl ester **1** for synthesis of the oxygen analogue of the thiolene structure of sulfheme-

C (Figure 1). The latter can be photooxidized to yield the polar regioisomeric photoprotoporphyrin-IX and isophotoprotoporphyrin-IX dimethyl esters (**2** and **3**, respectively). This is a singlet oxygen electrocyclic reaction, whose presumed intermediate is the peroxide **4**.[24] Our objective can be simplistically visualized as the removal of either one of the two oxygen atoms in the peroxide intermediate (e.g. as arrowed in **4**), to produce **5**, the desired metal-free oxygen analogue of sulfheme-C dimethyl ester.

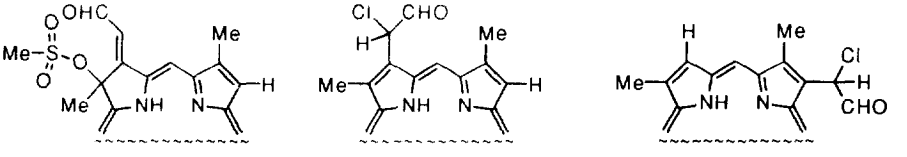


4 **5**

To approach the problem, we initially chose to investigate monovinylporphyrins, allowing us to focus on the chemistry of the single vinyl site of the macrocycle and thereby avoid complications due to isomer formation. Pemptoporphyrin and isopemptoporphyrin dimethyl esters (**6** and **7**, respectively) were the obvious starting materials for the syntheses of these models, as they fulfill that requirement and carry the same peripheral substituents as protoporphyrin-IX dimethyl ester **1** in all but one β-pyrrolic position.



6 **7** **8**

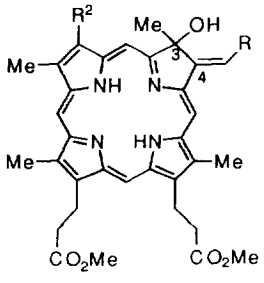


9 **10** **11**

Isopemptoporphyrin dimethyl ester **7** was synthesized from commercial hemin chloride.[25] Photooxygenation[24] yielded the iso*photo*pemptoporphyrin dimethyl ester **8**. Several attempts were made to effect mesylation of the tertiary alcohol at position-1 to afford the methane sulfonate ester **9**. While the use of a small excess of methanesulfonyl chloride showed no reaction even after several hours, a further excess amount turned the color of the solution from green to red-brown. TLC revealed the presence of a red nonpolar band possessing a rhodo-type visible absorption spectrum[26] that was assigned to the 2-α-chloroaldehyde porphyrin **10**.

The reaction was then carried out on isophotopemptoporphyrin dimethyl ester **8** over substantially longer time periods and with the aid of 4-dimethylaminopyridine. After the first 24 hours, only a minor

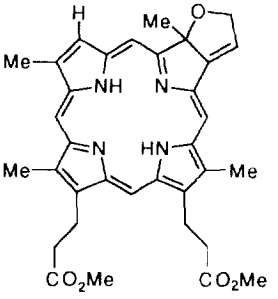
amount of nonpolar porphyrin appeared on the analytical TLC plate. The mixture was then set for reflux in dichloromethane. After an additional three days, there was still no chlorin product formed. Minor amounts of a fast-running porphyrin were isolated after flash chromatography and preparative TLC. This was identified by its proton NMR and mass spectra as the α-chloroaldehyde **11**.



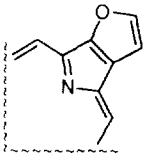
12 R^2 = $CH{=}CH_2$; R = CH_2OH
13 R^2 = H; R = CHO
14 R^2 = H; R = CH_2OH
15 R^2 = H; R = CH_2OTos

Alcohol **12**, obtained by borohydride reduction of isophotoprotoporphyrin-IX dimethyl ester, **3**, presented a different problem. One would expect a primary alcohol at the 4-position to be preferentially mesylated over the tertiary alcohol at position-3. But, after less than two hours at 0°C, most of the starting chlorin (photoporphyrin) **12** had decomposed. Tosylation reactions on similar systems were therefore investigated next. Photopemptoporphyrin dimethyl ester **13** was conveniently obtained from pemptoporphyrin dimethyl ester **6** by photooxidation. Since tosylation of the tertiary alcohol in **13** appeared unlikely (in view of the lack of success with similar less sterically demanding mesylation reactions), we chose to proceed with tosylation of the reduction product, alcohol **14**, hoping to obtain the p-toluenesulfonyl ester **15**. After 15 hours, no product was evident by TLC, so an excess of tosyl chloride was added, along with 10% of 4-DMAP. Within the next several hours, a relatively nonpolar chlorin appeared to be forming. It was isolated in a pure form only after repeated elution on preparative TLC plates. The visible absorption spectrum of the new non-polar compound (not shown) was similar to that of the starting diol **14**, but also bore a striking resemblance to that reported by Timkovich[20] for his so-called S662 sample carrying the novel exocyclic thiolene ring. Our compound showed a λ_{max} at 652 nm, compared with 662 for sulfheme-C, the 10 nm red-shift difference being easily accounted for[27] by the presence of the additional vinyl group in the literature compound.[20] That initial observation raised the possibility that the cyclic oxygen product **16** may have been formed.

This new product was closely examined using ^{1}H-NMR and mass spectroscopies. The low resolution mass spectrum (MS) featured the highest mass peak at m/e 580 (in agreement with the cyclic structure), a weaker one at m/e 564 and extensive fragment ions at lower masses. The m/e 564 peak most likely resulted from the loss of a CH_4 fragment. Such a loss could be driven by the formation of the aromatic furan ring (**17**) and concomitant full aromatic stabilization of the porphyrin. It is supportive that Timkovich *et al.* observed exactly the same pattern (highest mass peak at m/e 622 and a weaker peak at 606) for their extracted sulfheme-C derivative.[20]



16



17
m/e 564

The ^{1}H-NMR spectrum provided strong evidence that the cyclized structure **16** should be assigned to the new product. Two single proton doublet of doublets at 5.37 and 5.60 ppm and a triplet at 7.05 ppm are the resonances of most interest; the first two are assigned to the diastereomeric methylene protons of the exocyclic ring, and the third to the vinylic proton attached to the saturated ring. Timkovich *et al.* reported that the corresponding shifts for the metal free S662 compound (Figure 3),[20] containing sulfur instead of oxygen,

appeared at 4.2, 4.9 and 6.9 ppm. Electronegativity differences (oxygen vs sulfur) can satisfactorily account for the downfield shift observed the methylene in **16**.

Decoupling experiments further verified the validity of the structural assignment for **16**. When the doublet of doublets at 5.60 ppm was irradiated, the second one at 5.37 ppm collapsed to a doublet. When the peak at 7.05 ppm was decoupled, the two dd at 5.37 and 5.60 ppm collapsed to two doublets and their coupling constant was found to be large (J = 14.1 Hz), quite consistent with geminal coupling.

Photoprotoporphyrin Approach to Oxa-sulfheme-A

Once the model compound **16** was characterized, exactly the same conditions were employed with the alcohol **12**. A small amount of the cyclized product **5** was isolated (presumably via **17**) in very low yield after extensive chromatography on silica preparative silica gel TLC plates. The optical spectrum of **5** (Figure 4) exhibited a pattern identical with that of the sulfur containing chlorin, with peaks at 500, 534, and 662 nm. Likewise, the ^{1}H-NMR chemical shifts of the protons of **5** resembled those of the sulfur-containing compound, with only the diastereomeric methylene protons next to the heteroatom having been shifted downfield, as expected (*vide supra*).

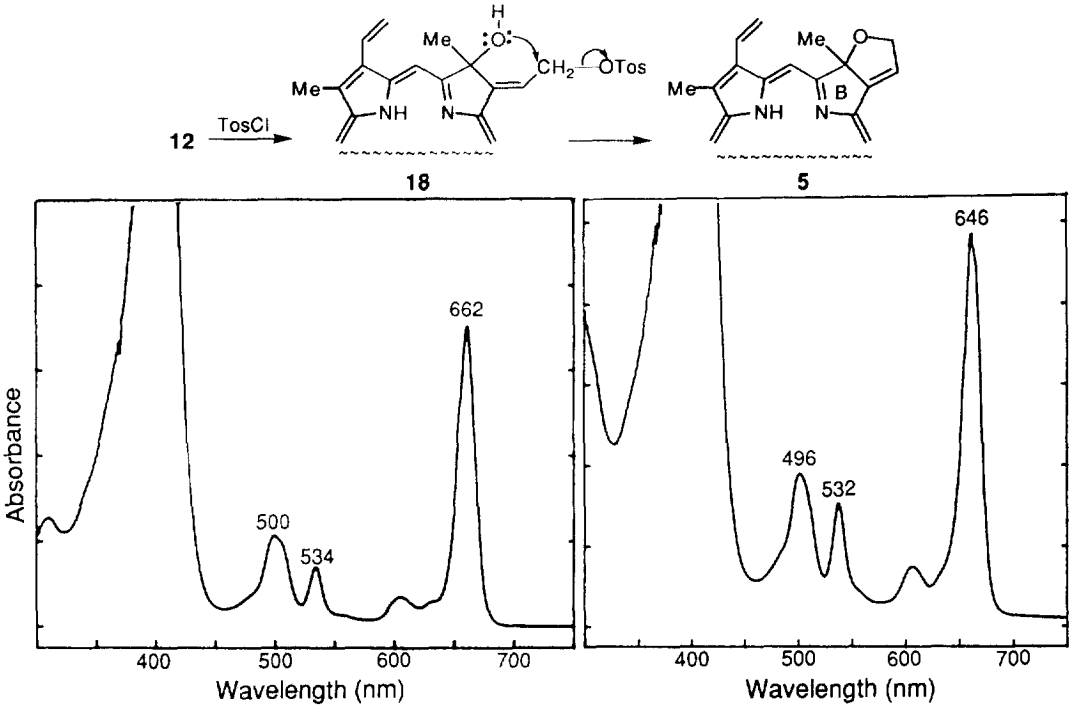


Figure 4: Optical spectrum, in CH_2Cl_2 of compound **5**

Figure 5: Optical spectrum, in CH_2Cl_2 of compound **23**

Attempts to Replace Oxygen with Sulfur. Our next venture was directed towards the search for a method and conditions that would allow successful replacement of oxygen with sulfur into compounds such as **16** and **18**. Obviously, the aforementioned diols **12** and **14**, as well as their ring A isomers, offer a significant advantage based on the fact that the pre-existing substitution pattern matches the desired one of the sulfheme molecule. The first challenge to face is the conversion of the primary alcohol to a thiol or a thiolester. Several methods

for analogous conversion have been reported in the literature.[28-31] However, the majority of them require a series of transformations: (a) initial activation of the hydroxyl function by conversion to a tosylate or halide, (b) displacement with a suitable sulfur-containing nucleophile, and (c) reduction to the desired thiol. The product is usually obtained with inversion of configuration. Unfortunately, the harsh conditions employed in most of these methods, when investigated using **12** for example, resulted in mixtures of products and low yields.

Mitsunobu Approach to Oxa-sulfheme-A. We therefore sought a much milder method, keeping in mind the low stability of diols such as **12** and **14** and their analogues. Volante[32] converted alcohols to thiolesters using a modification of the triphenylphosphine-diethylazodicarboxylate (TPP-DEAD) inversion procedure of Mitsunobu.[33-37] The method consists of first forming the adduct of TPP and diisopropylazodicarboxylate (DIAD), and then treating it at 0°C with a mixture of the alcohol and an appropriate thiolacid. The reaction apparently proceeds through displacement of the alkoxy-phosphonium salt intermediate by the thiolester anion in a regioselective and stereospecific manner. The inverted thiolesters can be isolated in high yield and subsequently reduced to their corresponding thiols by a standard method.

The reaction was carried out on isophotoprotoporphyrin-IX alcohol **12**, using twice the stoichiometrically required amount of TPP-azodicarboxylate and thiolacetic acid. No evidence of alcohol conversion was detected. When a higher excess amount of the TPP-azodicarboxylate and thiolacetic acid reactants was used, a large amount of brown, non-chromatographable material was obtained. Only a trace of chlorin-like product with a λ_{max} at 644 nm was recovered, but it could not be characterized.

This unsuccessful series of reactions served to introduce us into the area of the Mitsunobu[33-37] intermolecular dehydration reactions which generally take place between alcohols and acidic components upon treatment with DEAD and TPP. The mild and neutral conditions, the functional selectivity, the regioselectivity, and the virtually complete inversion of the configuration of the alcoholic hydroxyl group made the reactions extremely attractive to our program.

In its standard form, the reaction proceeds through: (a) addition of TPP to DEAD to give a quaternary phosphonium salt **19**, (b) protonation of this salt, (c) formation of an alkoxy phosphonium salt **20**, and (d) SN_2 type displacement of **20** (Figure 6). In the course of the reaction, TPP is oxidized to TPP oxide and DEAD is reduced to diethyl hydrazinedicarboxylate.

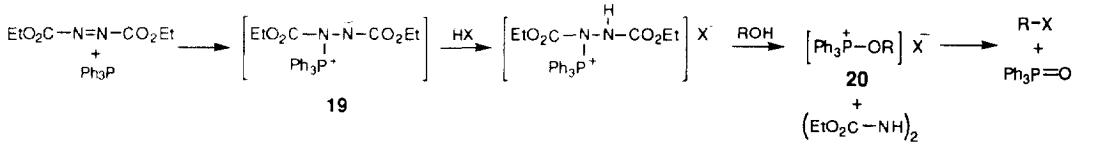


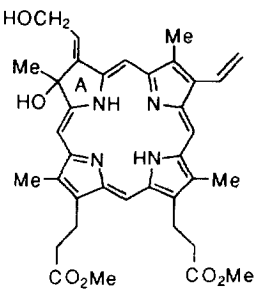
Figure 6: The generalized Mitsunobu intermolecular dehydration reaction.[33-37]

The use of primary-secondary diols in the reaction allows for selective esterification at the primary position in preference to the secondary. This selectivity can be explained in terms of the three bulky phenyl groups attached to the phosphorus atom. If the second hydroxy of the diol, in the case of primary-primary or secondary-secondary diols, is located at a favorable position for the formation of three-, five- and even six-membered cyclic ethers, intramolecular displacement takes place in preference to intramolecular condensation. In 1978, Carlock and Mack[38] reported that when diols were allowed to react with TPP-DEAD

in the absence of an acidic component, a variety of heterocyclic systems could be synthesized. The method afforded a number of oxiranes, oxetanes, oxepanes and aziridines.

The Mitsunobu Approach to Oxa-sulfheme-A

The Mitsunobu reaction was first carried out on a mixture of photoprotoporphyrin-IX and isophotoprotoporphyrin-IX diol dimethyl esters (**21** and **12**, respectively), hoping to obtain some indication of its feasibility. A nonpolar brown band and polar baseline material soon became apparent on the analytical TLC plate. The brown product was recovered by preparative TLC as a single band whose greenish-colored tail indicated the presence of some chlorin. The two regioisomers comprising the brown band (because the starting diols were ring-A and -B isomers) were separated from each other after additional runs on preparative silica gel plates. As expected, they both exhibited identical spectroscopic characteristics. The visible spectra indicated a chlorin with a λ_{max} at 648 nm. The ^{1}H NMR spectra evidenced the presence of two vinyls, one of which was attached to the reduced ring. The two beta protons for the product from **12** appeared at 5.50 and 5.42 ppm and their coupling constants were consistent with *trans* (J = 17.1 Hz) and *cis* (J = 10.2 Hz) couplings. A methyl singlet at 2.21 ppm further confirmed that a methyl group was also attached to the saturated ring. All resonances of the substituents of the unsaturated rings were in agreement with those expected for protoporphyrin-IX dimethyl ester derivatives, indicating that no changes had been affected other than in the reduced site of the porphyrin. After careful examination of the possible mechanistic pathways that could give rise to chlorin products, we narrowed down the field of likely candidates (from **12**) to two isomeric structures, a porphyrinone **22** or a porphyrin epoxide **23**.



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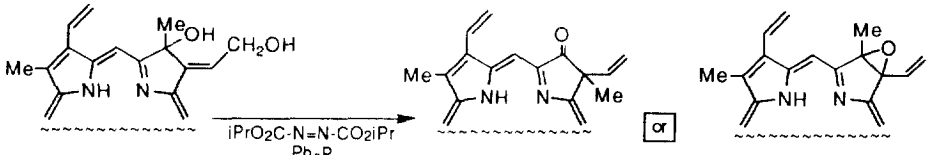


12 **22** **23**

The primary allylic alcohol is expected to be preferentially alkylated to form the alkoxyphosphonium salt intermediate (Figure 6). The driving force for the displacement of this salt is the formation of triphenylphosphine oxide, allowing the ethylidene double bond to move over to generate a vinyl group and thus create a positively charged center at position 4. The electronic imbalance can be restored by two distinct routes. Either the negatively charged oxygen of the 3-hydroxyl can react at the 3-carbon atom with concomitant migration of the methyl group to the four position to yield the porphyrinone **22**, or it can directly attack the 4-carbon to form an epoxide ring, as in **23**. Both structures can fit the ^{1}H NMR data very well, they both possess the same substituents on all sites of the porphyrin periphery and are isomers of each other.

A relatively large number of fully characterized porphyrinones have been previously reported in the literature, as opposed to virtually none for porphyrin epoxides. After consideration of the available information, it was decided that the porphyrinone structure **22** should be assigned to the product. Three facts contributed towards this assignment: First, the ^{1}H NMR spectrum exhibited a three and one pattern in the

meso proton region - very typical of virtually all porphyrinones; the one meso proton resonance usually appears at a relatively high field, probably due to the deshielding effect of the carbonyl group. Second, the visible absorption spectrum (not shown) perfectly matched the typical pattern for a ketochlorin, characterized by the presence of a shoulder on the left side of the 510 nm satellite band. Finally, and quite conclusively, the presence of a carbonyl group was evidenced by infrared spectroscopy.

Porphyrinones were first reported in 1930 by Fischer and coworkers.[39] They claimed that mesoporphyrin-IX , when treated with hydrogen peroxide in concentrated sulfuric acid, yielded a "dioxy-mesoporphyrin" derivative. It was originally thought that this was a mesodihydroxyporphyrin or even a vicinal dihydroxyporphyrin. They next concluded that the product was actually a monooxy derivative, and later an epoxide added across a ββ double bond.[40] In the 1960s, Bonnett,[41] Johnson,[41,42] Inhoffen[43,44] and their coworkers reinvestigated the oxidation reaction using octaethylporphyrin and etioporphyrin and definitively concluded that the true structure of the product of the hydrogen peroxide/sulfuric acid treatment is a ketochlorin formed by a pinacol rearrangement of the intermediate diol. The most substantial evidence for a conjugated carbonyl group was found in the IR spectrum [ν(CO)= 1708 cm^{-1}]. Diketones and even triketones can be formed under the reaction conditions.[43-45] Porphyrinones can also be synthesized in two steps by first treating porphyrins with osmium tetroxide[46] to produce a vic-dihydroxy chlorin, which then undergoes pinacol-pinacolone rearrangement in acidic media.

In recent years, the chemistry of porphyrinones came under full scrutiny, mainly through Chang's elucidation of the structure of heme d_1, the non-covalently bound heme prosthetic group of the bacterial nitrite reductase-cytochrome oxidase from *Pseudomonas aeruginosa*. He first suggested[47] and later demonstrated,[48] that heme d_1 is not an iron chlorin, as was originally proposed, but an iron dioxo-isobacteriochlorin. In the process, various aspects of the chemistry of these compounds were examined in detail. Migratory aptitudes of common porphyrin substituents on the saturated site of vic-dihydroxychlorins that undergo pinacol-pinacolone rearrangement reactions were shown to follow the order: alkyl groups, propionates, hydrogen > methyl group > acetates.[49] It was also discovered that zinc porphyrinones react with osmium tetroxide to generate exclusively diketo-isobacteriochlorins without any of the diketo-bacteriochlorins that are normally formed from such a reaction with free base porphyrinones.[50] These conclusions may be of significant help in determining possible biosynthetic precursors and devising methods for chlorin syntheses.

Recently, Bonnett *et al.*[51] reported that a number of octaethylporphyrin derived porphyrinones as well as some polyhydroxy precursors had been tested *in vivo* as tumor photosensitizers and found to be more effective in tumor photonecrosis than Photofrin II®, the commercial photosensitizer used almost universally in clinical research. The osmium tetroxide reaction has also been used to prepare a number of chlorin and bacteriochlorin[52-55] vicinal diols and so-called[44] geminiketones (porphyrinones and chlorinones) from chlorophyll degradation products, which are showing promise as "second generation" PDT sensitizers.

To the best of our knowledge, porphyrinone **22** is the first to be obtained in a way other than the hydrogen peroxide/sulfuric acid or the osmium tetroxide oxidation. It is also the first protoporphyrin-IX derived ketochlorin, since it has retained its vinyl group substituents on both reduced and non-reduced rings. Methods used by earlier researchers are too harsh to allow the vinyl groups to remain intact under the reaction conditions.

Unanswered questions still remained regarding the identity and the role of the green mobile band that was formed along with the porphyrinone, but which seemed to gradually disappear during purification. It

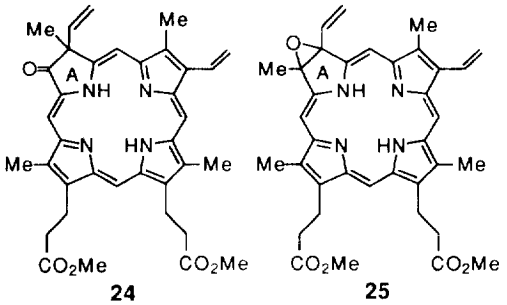
appeared that it might be a reaction intermediate. Both Fischer and Bonnett had previously suggested that an epoxide type intermediate might be involved in the porphyrinone formation process but any tentative assignments they made proved unsuccessful. The reaction was therefore performed using the pure ring A and B photoprotoporphyrin diol isomers so as to attempt to monitor it closely, both chromatographically and spectroscopically.

Five minutes after the addition of DIAD to the cooled mixture of isophotoprotoporphyrin-IX alcohol **12** and TPP, TLC clearly indicated the appearance of a green mobile band following the highly mobile porphyrinone; a brown baseline was the only other band shown on the TLC plate. Over the next two-hour period no change in the composition of the reaction mixture was evident. The mixture was purified on an alumina column (early attempts suggested that the green product was degraded on silica gel). The desired product, which could not survive temperatures greater than 40°C, was reproducibly recovered in 11% yield, and free of porphyrinone **22**; its visible absorption spectrum (Figure 5) featured a chlorin λ_{max} at 646 nm. The ^{1}H NMR spectrum showed two sets of meso protons, indicative of a chlorin. Interestingly, the one meso proton resonance of the upfield set appeared shorter and broader than the other three. Similar to what was encountered with the porphyrinone, the presence of two vinyls was confirmed, one of them apparently being attached to the saturated site. The chemical shifts of the beta vinyl protons of this aliphatic vinyl appeared at 6.10 (*cis* β) and 6.25 ppm (*trans* β), an approximately 0.7 ppm downfield shift compared to the analogous resonances in the porphyrinone molecule **22**. The alpha proton of the same vinyl group appeared at 6.74 ppm, a 0.4 ppm downfield shift from the similar porphyrinone resonance. Irradiation at 6.25 ppm caused the collapse of the 6.74 peak to a doublet with a coupling constant J = 10.59 Hz, consistent with *cis* coupling. When the 6.10 ppm peak was decoupled, a doublet with J = 17.13 Hz (*trans*) emerged at 6.25 ppm. The NH split resonance at -2.88 and -2.87 is diagnostic of a chlorin, as are the resolvable propionate triplets at 4.37 and 4.23 ppm. Finally, the methyl singlet at 2.53 ppm is assigned to a methyl attached to the reduced ring. A chlorin **23** with an epoxide ring attached to the β pyrrolic positions of the reduced ring perfectly matched all of the above data. The carbon edited spectrum of **23** (not shown) clearly showed the presence of six methine carbon atoms, two of which are vinyl, verifying our assignment in ring B. Low-resolution MS (electron impact) showed the highest ion mass peak at m/e 608, in agreement with the epoxide structure **23**.

The meso proton chemical shifts of **23** are 9.18, 9.34, 9.86 and 9.89 ppm. The highest upfield of these is both shorter and broader than the other three. In order to assign this peak, the α and β vinyl protons of position-4 were first decoupled. Assuming that the peak at 9.18 ppm is due to the β meso proton, such decoupling should result in a nuclear Overhauser enhancement (NOE). However, decoupling at both 6.74 ppm (4a proton) and 6.10 ppm (4b proton) had no effect on the meso-proton at 9.18 ppm. Decoupling of the 3-Me singlet at 2.53 ppm, however, yielded an enhancement of the 9.34 ppm resonance. This result accordingly assigns the 9.34 ppm peak to the α-meso proton and the broader and more upfield shifted 9.18 ppm resonance to the β-meso proton (for nomenclature, see structure **1**).

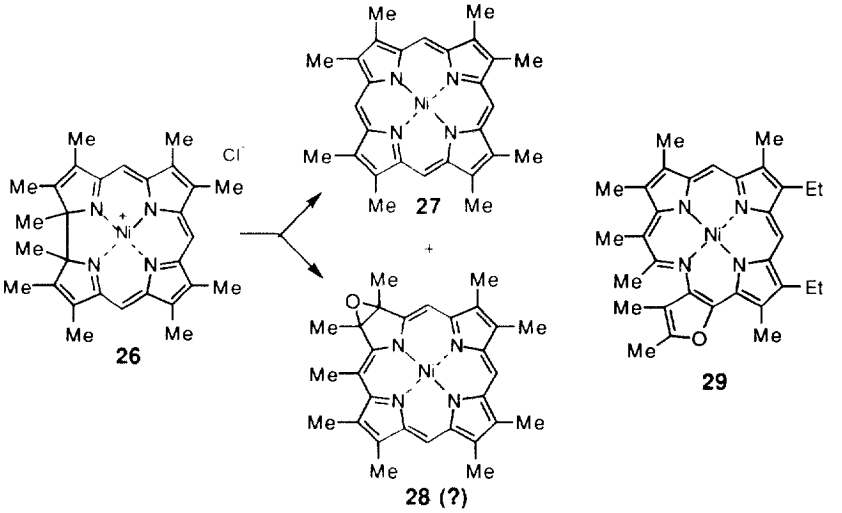
The ring-A isomers **24** and **25** were also successfully synthesized and showed the expected spectroscopic correspondence with the ring-B derivatives (see experimental section).

We believe the novel synthesis of a protoporphyrin epoxide to be significant. The methodology should provide us with access to a new class of porphyrin compounds, which through epoxide ring-opening can potentially be utilized as intermediates for various transformations at the chlorin level. In the porphyrin literature there is only one case of an epoxide reported. In 1969, Johnson and coworkers[56] proposed a method



24 25

of preparation of meso-alkyl porphyrins via thermolysis of nickel 19-alkyl-1-methyltetradehydrocorrin perchlorates. It is the carbon of the original 1-methyl substituent which becomes the meso-carbon of the porphyrin. There is a single exception to the method; in the case of nickel(II) decamethyltetradehydrocorrin chloride **26**, the main products were the meso-unsubstituted porphyrin **27** and, quite remarkably, the purported epoxide **28** of a nickel(II) meso-methylporphyrin.



26 27 29 28 (?)

In an attempt to clarify the unique chemistry of the above process for formation of **28**, we repeated the reaction on the nickel(II) tetradehydrocorrin chloride in refluxing o-dichlorobenzene. After work-up, the blue nickel(II) chlorin was isolated and its ^{1}H-NMR, visible and MS data were in agreement with the literature reported values. However, in our hands, **28** could not be converted into the isomeric ketochlorin upon treatment with acid, the primary basis for the structural assignment of **28**. In 1992, Chang and coworkers repeated[57] the Johnson work and showed their conclusions regarding the porphyrin epoxide to be incorrect; X-ray crystallography showed the proposed epoxide to possess structure **29** (diethyl series).

Synthesis of Oxa-sulfheme-C

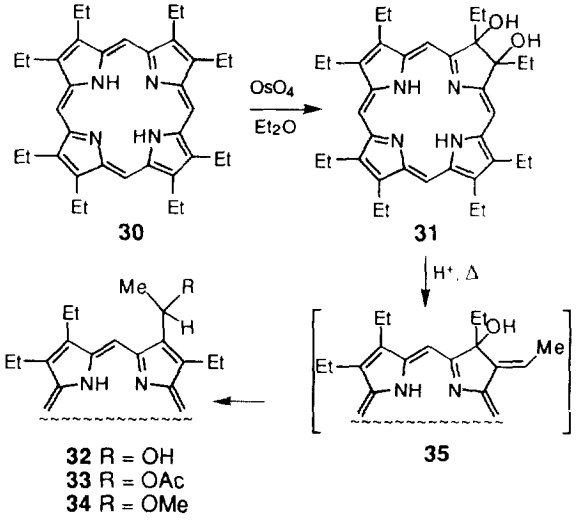
The ring-B protoporphyrin-IX epoxide **23** is indeed the dimethyl ester of the iron-free oxygen analogue form of sulfheme-A (Figure 1), and is also the proposed precursor of the terminal stable form of the prosthetic group of SMb, sulfheme-C. This relationship prompted us to investigate the possible protocols which might promote the transformation of the three-membered epoxide ring (in **23**) into the five-membered thiolene ring. That would require initial opening of the epoxy functionality and subsequent recyclization with incorporation of the vinyl moiety. A plethora of methods related to opening of epoxide rings can be found in the literature.[58-60] Two substantial limitations were apparent: (a) the high sensitivity associated with the porphyrin epoxide that virtually eliminated most standard methods employing acid catalysis or alkoxide

nucleophiles, and (b) the fact that introduction of certain functionalities might not contribute towards favorable recyclization pathways.

Posner and Rogers[61] showed that commercially available neutral chromatographic alumina can be used as a mild catalyst in the nucleophilic opening of epoxides by alcohols, thiols, amines, acetic acid, and benzeneselenol. The authors suggested a concerted mechanism that involved simultaneous polarization of the C-O epoxide bond and activation of the nucleophile by the alumina. Water was chosen as the nucleophile for our reaction. After forming a slurry of alumina, the "doping" agent was added followed by the substrate dissolved in a small amount of dichloromethane. The slurry was stirred for 20 hours at room temperature by which time no starting epoxide remained. The optical spectrum of the product proved to be identical with that of Timkovich's S662 sulfheme-C, with a λ_{max} at 662 nm and satellite bands at 502, 538 and 606 nm. Analytical TLC excluded the possibility of the regeneration of the original precursor of the epoxide, photoprotoporphyrin-IX alcohol dimethyl ester **12**. After purification on a single preparative plate, ^{1}H-NMR data unequivocally supported the conversion of the oxasulfporphyrin-A dimethyl ester **23** into the oxasulfporphyrin-C dimethyl ester **5**.

Further Model Studies

The same methodology was then applied to a number of symmetrical porphyrins carrying no functional groups. Octaethylporphyrin (OEP, **30**) is, next to meso-tetraphenylporphyrin, the most widely used porphyrin as a model for natural systems.[62] Our route required that the starting porphyrin carry one vinyl group substituent on its periphery and, preferably, no other functionalities. Only recently have methods of functionalizing the ethyl chain of octaethylporphyrin been reported. Chang and Sotiriou[63] discovered that the vicinal dihydroxychlorin **31**, obtained from osmium tetroxide oxidation of OEP, when treated with acidic media, is converted to mono-(1-hydroxyethyl)- **32**, mono-(1-acetoxyethyl)- **33** and mono-(1-methoxyethyl)- **34** heptaethylporphyrins. These compounds are presumably derived from an ethylenylhydroxychlorin intermediate **35**. When the dihydroxychlorin **31** was heated in benzene containing concentrated hydrochloric acid, the monovinylheptaethylporphyrin **36** was obtained in a very high yield. In our hands a fair amount of the porphyrinone **37** was also obtained, along with the expected monovinylporphyrin **36**. The two products were separated by flash chromatography. The porphyrinone is apparently the result of a pinacolone-type rearrangement of the dihydroxychlorin. Interestingly, the acid treatment of **31** is not necessary for conversion to the vinylporphyrin. As was accidentally discovered during the drying process, **31** can be transformed into **36** just by heating in a vacuum oven at 60°C. In an analogous manner, the dihydroxyetiochlorin **38** afforded the vinyletioporphyrin **39** and the ketochlorin **40**.

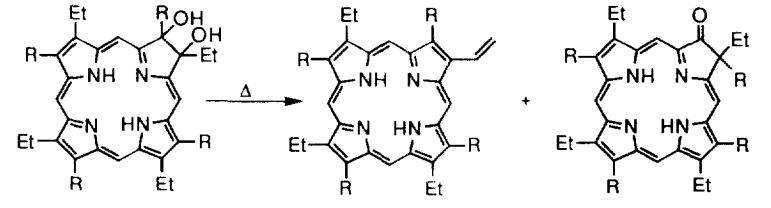


30 **31**

32 R = OH
33 R = OAc
34 R = OMe

35

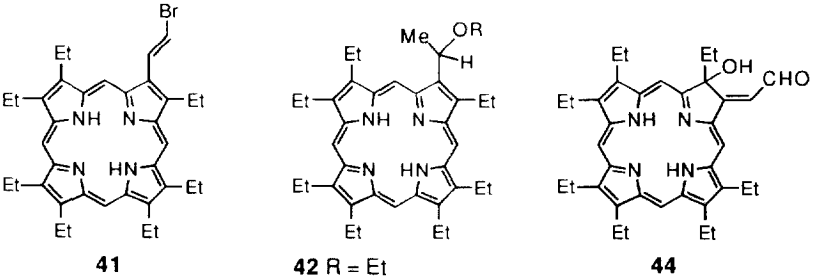
Recent work[64,65] offers a potential method for functionalizing the side chains of a number of symmetrically substituted alkylporphyrins. In the case of octaethylporphyrin, treatment with N-bromosuccinimide (NBS) and AIBN resulted in high yield of the *trans*-(2-bromovinyl) compound **41**. When the reaction was carried out in the presence of primary and secondary alcohols, the bromoethyl intermediate reacted to give the corresponding ether derivatives. The ethoxyethyl derivative **42** can be converted into monovinylporphyrin **36** by refluxing in toluene. Similarly, the trimethylsilylethoxy derivative **43** can afford the desired monovinyl compound by treatment with trimethylsilyliodide, followed by heating in toluene.



31 R = Et
38 R = Me

36 R = Et
39 R = Me

37 R = Et
40 R = Me

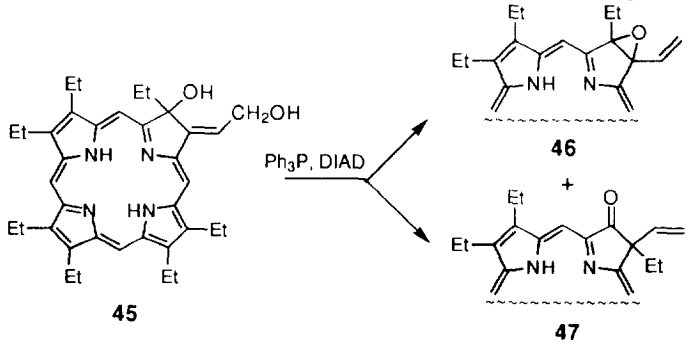


41

42 R = Et
43 R = $CH_2CH_2Si(Me)_3$

44

The monovinylheptaethylporphyrin **36**, obtained by either of the above methods, can then react with singlet oxygen in a Diels-Alder fashion to give the photoproduct **44** via the corresponding endoperoxide. The absence of regioisomers greatly facilitated the chromatographic purification of this chlorin. Borohydride reduction of the aldehyde group produced the diol **45**, and this was subjected to the conditions of the modified Mitsunobu reaction, as worked out earlier. The model porphyrin epoxide **46** and porphyrinone **47** were formed as expected, and isolated after chromatography on an alumina column. Both compounds showed excellent spectroscopic correspondence with the analogous protoporphyrin-IX compounds. The presence of only one vinyl group simplified the ^{1}H-NMR spectrum of the epoxide **46**. All three vinyl proton resonances (6.14, 6.36 ppm for the *cis* and *trans* beta protons and 6.93 ppm for the alpha proton) were appropriately shifted upfield, since they are two carbons away from the nearest aromatic site. The multiplet at 2.96 ppm and the triplet at 0.74 ppm were assigned to the methylene and methyl protons of the ethyl group attached to



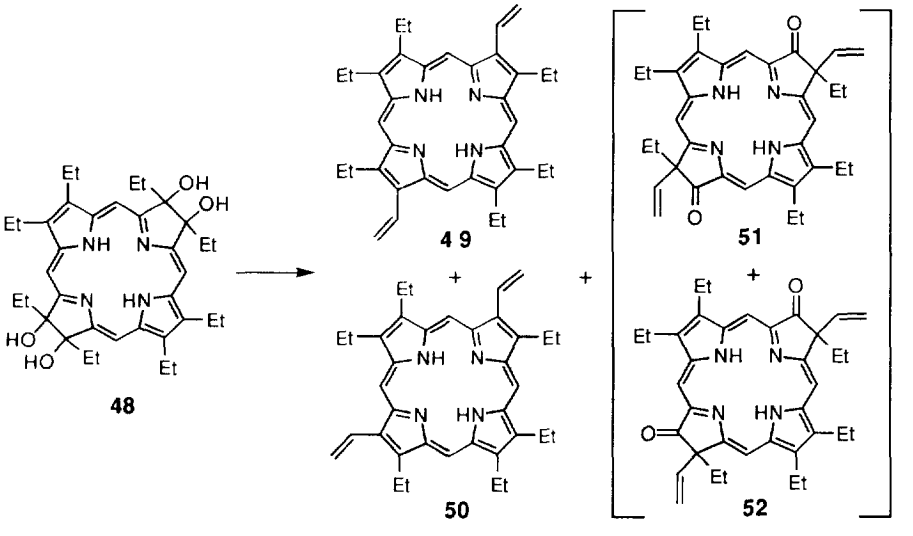
45

46

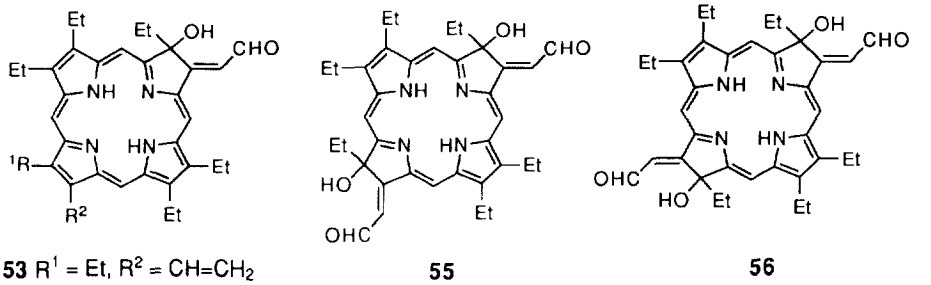
47

the reduced ring. The meso proton pattern exhibited the peculiarity encountered in the protoporphyrin-IX series, with one of the upfield peaks being shorter and broader than the others. The chemical shifts of the vinylic protons in the ^{1}H-NMR spectrum of the isomeric porphyrinone **47** were shifted upfield (by 0.46 ppm the alpha and by 1 ppm the *cis* and *trans* beta) compared to the corresponding resonances in the epoxide compound, in accordance with the relation seen in the protoporphyrin-IX series. The optical spectrum of the epoxide **46** showed the same pattern as the compounds in the corresponding protoporphyrin-IX, but with the chlorin λ_{max} blue shifted by 10 nm.

Prolonged osmium tetroxide oxidation of octaethylporphyrin produced a substantial amount of the tetrahydroxybacteriochlorin **48** which could be obtained free of the dihydroxy chlorin (**3.26**) after chromatography on silica gel. Acid treatment of **48** resulted in the mixture of 1,5- and 1,6-divinylhexaethyl-porphyrins **49** and **50** as the major products. In addition to that, a small amount of a ketochlorin mixture was formed, apparently consisting of the diketobacteriochlorins **51** and **52** as well as a mixture of monovinyl-monohydroxyethyl-porphyrins. The divinyl mixture could be separated by normal phase HPLC. No attempt was made to separate the various isomers of the minor products.



48 **49** **50** **51** **52**

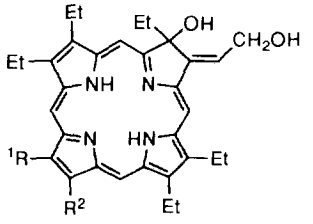


53 R^1 = Et, R^2 = CH=CH_2
54 R^1 = CH=CH_2, R^2 = Et

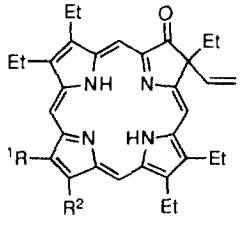
55 **56**

The mixture of divinyl compounds **49** and **50** was subjected to photooxidation to give the photoproducts **53** and **54**. A minor amount of a polar product was eluted from the silica gel column and its visible absorption spectrum showed a λ_{max} at 732 nm. Although it was not fully characterized, it is believed to be one of the

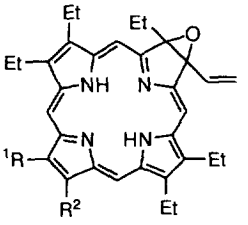
isomeric photobacteriochlorins **55** or **56**. Borohydride reduction of the mixture of **53** and **54** afforded the diols **57** and **58**. The mixture of the two underwent dehydration upon treatment with triphenylphosphine/DIAD providing the ketochlorin mixture **59/60**, and the epoxide mixture **61/62**.



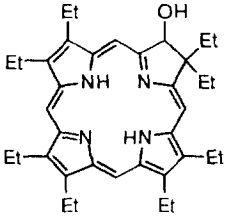
57 R^1 = Et, R^2 = CH=CH_2
58 R^1 = CH=CH_2, R^2 = Et



59 R^1 = Et, R^2 = CH=CH_2
60 R^1 = CH=CH_2, R^2 = Et



61 R^1 = Et, R^2 = CH=CH_2
62 R^1 = CH=CH_2, R^2 = Et



63

Porphyrinones derived from octaethylporphyrin have drawn attention as potential sensitizers in photodynamic therapy (PDT) research.[66] Efforts are being made by various groups towards the isolation of a single substance that will show higher selectivity for tumor tissue than Photofrin®, the current "first generation" industry standard. Photofrin® consists of a mixture of porphyrin dimers and higher oligomers linked with ether, ester, and carbon-carbon bonds.[67-75] Bonnett *et al.*[51] have reported that the OEP ketochlorin **37** can easily be functionalized through its reduced form **63** to give a number of second generation tumor photosensitizers. Some of them have already been shown to be several times as effective as Photofrin® in tumor photonecrosis. Other vicinal diols and ketochlorins in the chlorin and bacteriochlorin series[52-55] are also showing promise in preliminary animal studies. Since the ketochlorins synthesized in the present work carry additional (one or two) vinyl groups, their obvious advantage for further derivatization to afford systems possessing more advantageous amphiphilic properties can be utilized.

EXPERIMENTAL

M.p.s 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 thin layer chromatography was carried out on 20 x 20 cm glass plates coated with Merck G 254 silica gel (1 mm thick). Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark (aluminum foil). ^{1}H-NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.258 ppm). Elemental analyses were performed at the Midwest Microlab., Inc., Indianapolis, IN. Unless stated otherwise, electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. In many cases, amounts of final products were insufficient for elemental analyses, or amounts of intermediates were sufficient only for completion of the reaction sequence; therefore, elemental composition was verified using high resolution mass spectroscopy (HRMS), after obtaining evidence of

homogeneity using proton NMR spectroscopy. Mass spectra, both HRMS and low resolution (LRMS), were obtained at the Mass Spectrometry Facility, University of California, San Francisco, CA.

Photooxidation of Protoporphyrin-IX Dimethyl Ester (1). Protoporphyrin-IX dimethyl ester **1** (1 g, 1.69 mmol) prepared from hemin using the Grinstein method[76] was dissolved in dichloromethane (400 mL) in an Erlenmeyer flask and pyridine (20 mL) was added. The unstoppered flask was placed inside a Rayonet photochemical drum fitted with 24 "cool white" 20 watt fluorescent tubes. The mixture was irradiated for 24 h. The progress of the reaction was monitored by analytical TLC (1.5% methanol in dichloromethane) and spectrophotometry (judged by the appearance of a chlorin λ_{max} at 670 nm). The green solution was washed with water (3 x 250 mL) to remove the pyridine and the remaining traces of solvents were removed under high vacuum (oil pump). The separation of the photoproto- and isophotoprotoporphyrin dimethyl ester mixture was carried out by either flash chromatography on silica gel or on a Chromatotron (Harrison Research Inc., Palo Alto, CA; 2 mm thickness plate). Unreacted protoporphyrin-IX dimethyl ester **1** (110 mg, 11%) was first recovered with 1% tetrahydrofuran in dichloromethane. The solvent was then changed to 2% tetrahydrofuran in dichloromethane to obtain the isomeric chlorins photoprotoporphyrin-IX dimethyl ester **2** (268 mg, 25%) and isophotoprotoporphyrin-IX dimethyl ester **3** (295 mg, 28%), while a substantial amount of the mixture of **2** and **3** was also recovered (170 mg, 16%). The purity of the fractions was determined by analytical normal phase HPLC (elution with 3% tetrahydrofuran in dichloromethane). The unseparated chlorin mixture was rechromatographed until total resolution was achieved. Interestingly, an even more polar chlorin mixture was recovered with 3-4% tetrahydrofuran in dichloromethane, this being characterized[77] as a mixture of hydroxyethyl-photoporphyrins.

Photoprotoporphyrin-IX Dimethyl Ester (**2**), mp 244°C (lit.[24] mp 244°C). ^{1}H-NMR: δ, ppm, -4.21 (br s, 1H, NH), -3.71 (br s, 1H, NH), 1.33 (s, 3H, 1-CH_3, aliphatic), 3.21 (m, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 2.61 (s, 3H, ring Me), 3.29 (s, 3H, ring Me), 3.38 (s, 3H, ring Me), 3.71 (s, 6H, 2 x CO_2CH_3), 4.19 (m, 4H, 2 x $\underline{CH_2}CH_2CO_2Me$), 5.70 (d, 1H, 2a olefinic-H), 6.11 (dd, 1H, 4b-*cis* -H), 6.03 (dd, 1H, 4b-*trans* -H), 7.85 (dd, 1H, 4a-H), 7.23, 8.18, 9.49, 9.64 (each s, 1H, meso-H), 10.01 (d, 1H, CHO). UV-vis: λ_{max}, nm = 422, 500, 566, 608, 670. HRMS (FAB), Calcd for $C_{36}H_{38}N_4O_6$: 623.2869; found 623.2865.

Isophotoprotoporphyrin-IX Dimethyl Ester (**3**), mp 224°C (lit.[24] mp 222-223°C). ^{1}H-NMR: δ, ppm, -4.18 (br s, 1H, NH), -3.76 (br s, 1H, NH), 1.03 (s, 3H, 3-CH_3, aliphatic), 3.25 (m, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.33 (s, 3H, ring Me), 3.41 (s, 3H, ring Me), 3.59 (s, 3H, ring Me), 3.69 (s, 3H, CO_2CH_3), 3.71 (s, 3H, CO_2CH_3), 4.23 (m, 4H, 2 x $\underline{CH_2}CH_2CO_2Me$), 6.35 (d, 1H, 4a olefinic-H), 6.05 (dd, 1H, 2b-*cis* -H), 6.10 (dd, 1H, 2b-*trans* -H), 7.48 (dd, 1H, 2a-H), 7.38, 8.26, 9.63, 9.74 (each s, 1H, meso-H), 9.83 (d, 1H, CHO). UV-vis : λ_{max}, nm = 436, 500, 566, 612, 670.

Photoprotoporphyrin-IX Alcohol Dimethyl Ester (21). Photoprotoporphyrin-IX dimethyl ester **2** (106 mg, 0.17 mmol) dissolved in dichloromethane (40 mL) was added to an ice-chilled solution of sodium borohydride (100 mg, 2.63 mmol) in absolute ethanol. The mixture was stirred under nitrogen for 20 min and analytical TLC indicated that the reduction was completed. The excess of borohydride was neutralized with acetic acid (1 mL). The solution was diluted with dichloromethane (40 mL), washed with water (3 x 100 mL), dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with 1% methanol in dichloromethane. The main product was recrystallized from dichloromethane/n-hexane to give the title porphyrin (96 mg, 90%), mp 175-177°C. ^{1}H-NMR: δ, ppm, -3.80 (br s, 2H, NH), 1.45 (s, 3H, 1-CH_3, aliphatic), 2.86 (s, 3H, ring Me), 3.10 (q, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.17 (s, 3H, ring Me), 3.19 (s, 3H, ring Me), 3.66 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.97 (q, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.08 (m, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.32 (dd, 1H, 2b-$CH_2$), 4.47 (dd, 1H, 2b-$CH_2$), 6.01 (dd, 1H, 4b-*cis* -H), 6.16 (dd, 1H, 4b-*trans* -H), 6.27 (t, 1H, 2a-H, olefinic), 7.81 (dd, 1H, 4a-H), 8.00, 8.21 (each s, 1H, α- or δ-meso-H), 9.33, 9.40 (each s, 1H, β- or γ-meso-H). UV-vis: λ_{max}, nm, 404 (ε 146 600), 500 (17 900), 534 (15 100), 604 (11 400), 660 (41 300). LRMS (EI+): m/e (%), 624 (34), 606 (100), 281

(19), 255 (38). HRMS (FAB), Calcd for $C_{36}H_{40}N_4O_6$: 625.3026 (M+1); found 625.3026.

Isophotoprotoporphyrin-IX Alcohol Dimethyl Ester (12). The title chlorin was obtained in high yield (>90%) from isophotoprotoporphyrin-IX dimethyl ester **3** in a manner similar to that described above for the photoprotoporphyrin-IX alcohol dimethyl ester **21**. Mp 202-204°C. ^{1}H-NMR: δ, ppm, -3.50 (br s, 2H, NH), 1.49 (s, 3H, 3-CH_3, aliphatic), 3.05 (q, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.12 (s, 3H, ring Me), 3.20 (s, 3H, ring Me), 3.39 (s, 3H, ring Me) 3.65 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.00 (m, 4H, 2 x $C\underline{H}_2CH_2CO_2Me$), 4.51 (dd, 1H, 4b-$CH_2$), 4.65 (dd, 1H, 4b-$CH_2$), 6.71 (t, 1H, 4a-H, olefinic), 5.98 (dd, 1H, 2b-*cis* -H), 6.13 (dd, 1H, 2b-*trans* -H), 7.76 (dd, 1H, 2a-H), 8.23, 8.43 (each s, 1H, α- or β-meso-H), 9.31, 9.36 (each s, 1H, γ- or δ-meso-H). UV-vis: λ_{max}, nm, 404 (ε 168 800), 500 (21 000), 534 (16 800), 606 (12 500), 660 (50 700). LRMS (FAB): m/e (%) 625 (100), 607 (26), 595 (20), 577 (14). HRMS (FAB), Calcd for $C_{36}H_{40}N_4O_6$: 625.3026 (M+1); found 625.3025.

Oxa-sulfpemptoporphyrin-C Dimethyl Ester (16). *(A) Photopemptoporphyrin Dimethyl Ester* (**13**). Pemptoporphyrin dimethyl ester[78] **6** (40 mg, 0.070 mmol) was dissolved in dichloromethane (30 mL) in an Erlenmeyer flask. The mixture was placed inside the light drum and stirred while subjected to irradiation for 16 h. Analytical TLC and spectrophotometry (chlorin λ_{max} 662 nm) indicated the formation of the photooxidized product. The mixture was washed with water (3 x 50 mL), dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The residue was purified on a silica gel column, eluting first with 0.5% tetrahydrofuran in dichloromethane to recover the unreacted pemptoporphyrin dimethyl ester (12 mg, 30%), and then with 3% tetrahydrofuran in dichloromethane to obtain the title compound **13** (22 mg, 53%). [^{1}H-NMR: δ, ppm, -3.6 (br d, 2H, NH), 1.41 (s, 3H, 3-CH_3, aliphatic), 3.18 (q, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.28 (s, 3H, ring Me), 3.38 (s, 3H, ring Me), 3.59 (s, 3H, ring Me), 3.62 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 4.19 (m, 4H, 2 x $C\underline{H}_2CH_2CO_2Me$), 6.66 (d, 1H, 4a-H, olefinic), 7.89 (s, 1H, meso-H), 8.44 (s, 1H, 2-H), 8.48, 9.65, 9.70 (each s, 1H, meso-H), 10.11 (d, 1H, aldehyde-H). UV-vis: λ_{max} , nm, 384 (ε 33 200), 424 (35 400), 568 (17 000), 602 (15 900), 662 (23 100). LRMS (FAB): m/e (%) 597 (100), 580 (38), 568 (29), 551 (18). HRMS (FAB), Calcd for $C_{34}H_{36}N_4O_6$: 597.2713 (M+1); found 597.2709]. *(B) Photopemptoporphyrin Alcohol Dimethyl Ester* (**14**). The title porphyrin was prepared in high yields (>90%) from **13** by the standard reduction procedure described earlier for **12**. [^{1}H-NMR: δ, ppm, -3.40 (br s, 2H, NH), 1.68 (s, 3H, 3-CH_3, aliphatic), 3.06 (t, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.08 (s, 3H, ring Me), 3.24 (s, 3H, ring Me), 3.53 (s, 3H, ring Me), 3.62 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.98 (m, 4H, 2 x $C\underline{H}_2CH_2CO_2Me$), 4.68 (dd, 1H, 4b-$CH_2$), 4.57 (dd, 1H, 4b-$CH_2$), 6.74 (t, 1H, 4a-H, olefinic), 8.39, 8.44 (each s, 1H, meso-H), 8.44 (s, 1H, 2-H), 9.31, 9.51 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 418, 496, 530, 568, 596, 622, 654. LRMS (FAB): m/e (%) 599 (100), 581 (27), 569 (23), 551 (20). HRMS (FAB), Calcd for $C_{34}H_{38}N_4O_6$: 599.2869 (M+1); found 599.2873]. *(C) Oxa-sulfpemptoporphyrin-C Dimethyl Ester* (**16**). The foregoing diol **14** (25 mg, 0.0418 mmol) was dissolved in dichloromethane (15 mL), triethylamine (10 mL) was added and the solution was cooled down to 0°C. Tosyl chloride (9.55 mg, 0.0502 mmol) was added and the mixture stirred under nitrogen. Analytical TLC showed no ester formation after 15 h, so more tosyl chloride (9 mg, 0.047 mmol) as well as 4-N,N-dimethylaminopyridine (2 mg, 0.018 mmol) were added (to obtain **15**). Within 2 h, a relatively mobile green band appeared on analytical TLC. After a total of 48 h, the reaction was stopped, the solution diluted with dichloromethane (30 mL), poured over ice-water (50 mL) and washed with dilute acid (2 x 50 mL, 0.1 M HCl), saturated solution of sodium bicarbonate (2 x 50 mL) and water (2 x 50 mL). The desired product (4 mg, 16%), mp 168°C, was obtained in pure form after several runs on preparative TLC plates (2% methanol in dichloromethane). ^{1}H-NMR: δ, ppm, -3.08 (br s, 1H, NH), -3.01 (br s, 1H, NH), 1.94 (s, 3H, 3-CH_3, aliphatic), 3.16 (m, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.33 (s, 3H, ring Me), 3.41 (s, 3H, ring Me), 3.54 (s, 3H, ring Me), 3.65 (s, 6H, 2 x CO_2CH_3), 4.11 (m, 2H, $C\underline{H}_2CH_2CO_2Me$), 4.22 (m, 2H, $C\underline{H}_2CH_2CO_2Me$), 5.37 (dd, 1H, 4b-$CH_2$), 5.60 (dd, 1H, 4b'-$CH_2$, $J_{4b\text{-}H:4b'\text{-}H}$ = 14.10 Hz), 7.05 (t, 1H, 4a-H), 8.65 (s, 1H, 2-H), 8.79, 9.00,

9.60, 9.66 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 400 (ε 104 200), 496 (20 100), 530 (18 300), 594 (15 500), 652 (30 400). LRMS (FAB): m/e (%) 581.4 (65), 580.5 (100), 564 (31), 507.4 (19). HRMS (FAB), Calcd for $C_{34}H_{36}N_4O_5$: 581.2764 (M+1); found 581.2765.

Photoisopemptoporphyrin Dimethyl Ester (8). The title photoporphyrin was prepared in yields ranging from 42-50%, by the method described above for the chlorin **13**. ^{1}H-NMR: δ, ppm, -3.40 (br s, 1H, NH), -3.30 (br s, 1H, NH), 1.45 (s, 3H, 1-CH_3, aliphatic), 3.23 (q, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.42 (s, 3H, ring Me), 3.47 (s, 3H, ring Me), 3.49 (s, 3H, ring Me), 3.70 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.22 (m, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.33 (m, 2H, $\underline{CH_2}CH_2CO_2Me$) 6.65 (d, 1H, 2a-H, olefinic), 8.61 (s, 1H, 4-H), 8.90 , 8.95 , 9.75, 9.77 (each s, 1H, meso-H), 10.44 (d, 1H, aldehyde-H). UV-vis: λ_{max} , nm, 386 (ε 45 200), 399 (42 900), 406 (38 400), 430 (34 800), 560 (17 000), 604 (15 900), 662 (23 100). LRMS (FAB): m/e (%) 597 (100), 578 (29), 569 (22)

Oxa-sulfprotoporphyrin-C Dimethyl Ester (5). The title chlorin was prepared from **12** by the method described above for the model chlorin **16** but in a lower yield (4%). ^{1}H-NMR: δ, ppm, -3.20 (br s, 2H, NH), 2.25 (s, 3H, 3-CH_3, aliphatic), 3.10 (t, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.27 (s, 3H, ring Me), 3.31 (s, 3H, ring Me), 3.56 (s, 3H, ring Me), 3.65 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.13 (m, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.82 (dd, 1H, 4b-$CH_2$), 4.91 (dd, 1H, 4b'-$CH_2$), 6.08 (dd, 1H, 2b-*cis* -H), 6.22 (dd, 1H, 2b-*trans* -H), 6.96 (t, 1H, 4a-H), 7.88 (dd, 1H, 2a-H), 8.51, 8.72, 9.47, 9.58 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 398 (ε 165 000), 500 (22 100), 534 (17 400), 608 (11 900), 662 (52 000). LRMS (EI+): m/e (%) 606 (100), 592 (40), 578 (28), 535 (19), 256 (63). HRMS (EI+), Calcd for $C_{36}H_{38}N_4O_5$: 606.2842; found 606.2846.

Intramolecular Dehydration of Isophotoprotoporphyrin-IX Alcohol Dimethyl Ester (12). The diol **12** (50 mg, 0.080 mmol) was dissolved in dry tetrahydrofuran (8 mL) in a two-neck round bottom flask. Triphenylphosphine (21 mg, 0.080 mmol) was added and the solution was chilled to 0°C in an ice-water bath. Diisopropylazodicarboxylate (21 mL, 0.1068 mmol) was added to the mixture dropwise using a syringe and stirring at the same time. After only 2 min, analytical TLC indicated two highly mobile bands, one brown-red and the other green. A substantial amount of green baseline material was also present on the TLC. The composition of the mixture did not seem to be affected when the reaction times were longer. The solvent was removed and the crude product was purified on a short alumina (Grade III) column, eluting with dichloromethane to obtain the porphyrinone **22** (6 mg, 12.5%) followed by the epoxide **23** (5 mg, 11%). The polar baseline material was recovered by elution with 1% methanol in dichloromethane and its was shown to contain the starting diol. However, several attempts to further separate this chlorin from its impurities (mainly triphenylphosphine oxide) were unsuccessful.

6,7-Bis-[(2-methoxycarbonyl)ethyl]-1,4,5,8-tetramethyl-2,4-divinyl-3-oxochlorin (**22**). Mp 179-180°C. ^{1}H-NMR: δ, ppm, -2.92 (s, 1H, NH), -2.81 (s, 1H, NH), 2.21 (s, 3H, 4-CH_3, aliphatic), 3.23 (q, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.45 (s, 3H, ring Me), 3.57 (s, 3H, ring Me), 3.64 (s, 1H, ring Me), 3.67 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2Me), 4.22 (t, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.37 (t, 2H, $\underline{CH_2}CH_2CO_2Me$), 5.42 (dd, 1H, 4b-*cis* -H), 5.50 (dd, 1H, 4b-*trans* -H), 6.18 (dd, 1H, 2b-*cis* -H), 6.34 (dd, 1H, 2b-*trans* -H), 6.40 (dd, 1H, 4a-H), 8.13 (dd, 1H, 2a-H), 9.23, 9.81, 9.86, 9.90 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 408 (ε 150 300), 510 (16 000), 550 (16 300), 592 (11 700), 648 (33 800). LRMS (FAB): m/e (%) 607 (100), 591 (32), 576 (32), 562 (21). HRMS (FAB), Calcd for $C_{36}H_{38}N_4O_5$: 607.2920 (M+1); found 607.2922.

6,7-Bis-[(2-methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinyl-3,4-epoxychlorin (**23**). Mp 90-91°C. ^{1}H-NMR: δ, ppm, -2.88 (s, 1H, NH), -2.87 (s, 1H, NH), 2.53 (s, 3H, 3-CH_3, aliphatic), 3.23 (q, 4H, 2 x $CH_2\underline{CH_2}CO_2Me$), 3.47 (s, 3H, ring Me), 3.49 (s, 3H, ring Me), 3.64 (s, 1H, ring Me), 3.66 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2Me), 4.23 (t, 2H, $\underline{CH_2}CH_2CO_2Me$), 4.37 (t, 2H, $\underline{CH_2}CH_2CO_2Me$), 6.10 (dd, 1H, 4b-*cis* -H), 6.25 (dd, 1H, 4b-*trans* -H), 6.14 (dd, 1H, 2b-*cis* -H), 6.37 (dd, 1H, 2b-*trans* -H), 6.74 (dd, 1H, 4a-H), 8.11 (dd, 1H, 2a-H), 9.18, 9.34, 9.86, 9.89 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 395 (ε 91 100), 496 (20 600), 532

(15 300), 592 (16 800), 646 (30 200). LRMS (FAB): m/e (%) 607 (18), 591 (100), 576 (26), 562 (19). HRMS (FAB), Calcd for $C_{36}H_{38}N_4O_5$: 607.2920 (M+1); found 607.2921.

Intramolecular Dehydration of Photoprotoporphyrin-IX Alcohol Dimethyl Ester (21). The same modified Mitsunobu reaction conditions were employed as for the porphyrin **12**. The products obtained were the ring-A regioisomers **24** and **25**. The relatively polar (starting) material recovered from the alumina column with 1% methanol in dichloromethane could not be purified.

6,7-Bis-[(2-methoxycarbonyl)ethyl]-2,3,5,8-tetramethyl-2,4-divinyl-1-oxochlorin (**24**). Mp 197-198°C. ^{1}H-NMR: δ, ppm, -2.96 (s, 1H, NH), -2.81 (s, 1H, NH), 2.23 (s, 3H, 2-CH_3, aliphatic), 3.23 (q, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.46 (s, 3H, ring Me), 3.58 (s, 3H, ring Me), 3.61 (s, 1H, ring Me), 3.64 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2Me), 4.24 (t, 2H, $C\underline{H}_2CH_2CO_2Me$), 4.39 (t, 2H, $C\underline{H}_2CH_2CO_2Me$), 5.42 (dd, 1H, 2b-*cis* -H), 5.50 (dd, 1H, 2b-*trans* -H), 6.29 (dd, 1H, 4b-*cis* -H), 6.41 (dd, 1H, 4b-*trans* -H), 6.38 (dd, 1H, 2a-H), 8.21 (dd, 1H, 4a-H), 9.15, 9.83 , 9.94, 9.98 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 410 (ε 109 300), 510 (14 700), 548 (13 800), 594 (11 000), 650 (26 700). LRMS (FAB): m/e (%) 607 (100), 591 (12), 561 (15), 547 (10), 486 (19). HRMS (FAB), Calcd for $C_{36}H_{38}N_4O_5$: 607.2920 (M+1); found 607.2922.

6,7-Bis-[(2-methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinyl-1,2-epoxychlorin (**25**). ^{1}H-NMR: δ, ppm, -2.94 (br s, 1H, NH), -2.90 (br s, 1H, NH), 2.50 (s, 3H, 1-CH_3, aliphatic), 3.22 (q, 4H, 2 x $CH_2C\underline{H}_2CO_2Me$), 3.44 (s, 3H, ring Me), 3.51 (s, 3H, ring Me), 3.57 (s, 1H, ring Me), 3.64 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2Me), 4.22 (t, 2H, $C\underline{H}_2CH_2CO_2Me$), 4.36 (t, 2H, $C\underline{H}_2CH_2CO_2Me$), 6.09 (dd, 1H, 2b-*cis* -H), 6.25 (dd, 1H, 2b-*trans* -H), 6.18 (dd, 1H, 4b-*cis* -H), 6.38 (dd, 1H, 4b-*trans* -H), 6.73 (dd, 1H, 2a-H), 8.24 (dd, 1H, 4a-H), 9.16, 9.24, 9.81, 10.01 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 396 (ε 108 000), 496 (24 700), 532 (17 900), 592 (19 000), 648 (32 700). LRMS (FAB): m/e (%) 607 (17), 590 (100), 575 (31), 561 (18). HRMS (FAB), Calcd for $C_{36}H_{38}N_4O_5$: 607.2920 (M+1); found 607.2920.

Conversion of Oxa-sulfprotoporphyrin-A Dimethyl Ester (23) to Oxa-sulfprotoporphyrin-C Dimethyl Ester (5). Neutral chromatographic alumina (40 mg) was transferred to a round bottom flask equipped with a magnetic stir bar. Dichloromethane was added (8 mL) to form the slurry. To the stirred slurry was added one drop of water as the doping agent. After 5 min, the sulfporphyrin-A substrate **23** (5 mg, 0.008 mmol) dissolved in dichloromethane (3 mL) was added. The slurry was stirred for 24 h (analytical TLC indicated conversion to a less mobile chlorin) and poured into methanol (20 mL), where it was allowed to stand for 1.5 h. It was then filtered through a Celite pad and washed well with methanol. The major product after purification on an alumina column was shown by proton NMR, spectrophotometry and mass spectroscopy to be the oxa-sulf-protoporphyrin-C **5** (2 mg, 40%).

Nickel(II) Decamethyltetradehydrocorrin Chloride (26).[56] 1',1,2,3,4,5,6,7,8,8'-Decamethyl-a,c-biladiene dihydrobromide[56] (1.5 g, 3,4 mmol) suspended in methanol (200 mL) containing nickel acetate (1.9 g) was refluxed for 3 h. The volume of the solvent was reduced (100 mL), chloroform (50 mL) was added and the solution poured into water (400 mL). The chloroform layer was collected and dried over anhydrous sodium sulfate, the solvent was removed and the residue was chromatographed on alumina (Grade III). The column was first eluted with chloroform, but the two minor fractions (brown-red color) collected were not identified. The solvent was then changed to 10% methanol in chloroform and the purple fraction collected was shaken with dilute hydrochloric acid (2 x 50 mL, 5%) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was crystallized from chloroform (1.2 g, 71%), mp > 300°C (lit.[56] mp >300°C). ^{1}H-NMR: δ, ppm, -0.60 (s, 6H, 2 x methyl attached to the α-pyrrolic position), 2.48 (s, 6H, 2 x ring Me), 2.51 (s, 6H, 2 x ring Me), 2.56 (s, 12H, 4 x ring Me), 7.25, 7.39, 7.47 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 281, 356, 552. LRMS (FAB): m/e (%) 564 (43), 548 (36), 520 (30), 504 (29), 495 (100), 481 (26), 460 (25).

Thermal Rearrangement[56] of the Nickel(II) Tetradehydrocorrin Salt (26). The foregoing nickel(II) tetradehydrocorrin chloride **26** (188 mg, 0.379 mmol) was dissolved in o-dichlorobenzene (150 mL), heated under reflux for 70 min and then evaporated to dryness with the aid of a vacuum pump. The residue was

dissolved in chloroform and chromatographed on alumina (Grade III), eluting with chloroform. A green band was rapidly eluted and the first fraction collected showed a λ_{max} at 686 nm. Proton NMR data of this product are in agreement with the corresponding values provided by Johnson[56] for the subsequently discredited[57] epoxide **28** (33 mg, 17%). The subsequent fractions contained increasing amounts of nickel(II) octamethylporphyrin **27**. They were combined and run twice through a silica gel flash column for further purification. Interestingly, contact with silica seemed to cause some decomposition and/or rearrangement of the proposed epoxide. No "epoxide" was recovered from the recolumning.

"Nickel 1,2,3,4,5,6,7,8,δ-meso-Nonamethyl-1,2-epoxychlorin (**28**)" (subsequently shown[57] to be **29**). Mp 240-242°C, (lit.[56] mp 244-247°C). ^{1}H-NMR: δ, ppm, 2.20 (s, 3H, methyl, aliphatic), 2.47 (s, 3H, methyl, aliphatic), 2.86 (s, 3H, ring Me), 2.90 (s, 3H, ring Me), 2.98 (s, 6H, 2 x ring Me), 3.01 (s, 3H, ring Me), 3.05 (s, 3H, ring Me), 3.12 (s, 3H, δ-meso-methyl), 7.18 (s, 1H, α-meso-H), 8.54, 8.71 (each s, 1H, β- and γ-meso-H). UV-vis : λ_{max}, nm, 430, 518, 552, 684. LRMS (EI+): m/e (%) 511 (13), 510 (47.5), 508 (100), 506 (23), 494 (25), 492 (44.), 478 (37), 464 (11). HRMS (EI+) Calcd for $C_{29}H_{30}N_4NiO$: 508.17729; found 508.17703.

1,2-Dihydroxy-octaethylchlorin (31). Osmium tetroxide (128 mg, 0.505 mmol) in diethylether (3 mL) was added to a solution of octaethylporphyrin **30** (150 mg, 0.280 mmol) in dichloromethane (80 mL) and pyridine (1 mL). The mixture was allowed to stir at room temperature in the dark for 48 h. It was then diluted with methanol (20 mL) and hydrogen sulfide gas was bubbled through for 25 min. The precipitated osmium sulfide was removed by filtration (twice) and the solvent removed under vacuum. The product was purified on a silica gel column, eluting first with dichloromethane (a minor amount of unreacted octaethylporphyrin was recovered) and then with 1% methanol in dichloromethane to obtain the desired product (95 mg, 60%). Mp 212-215°C (dec.), [lit.[79] mp 213°C (dec.), lit.[80] mp 219-220°C]. ^{1}H-NMR: δ, ppm, -2.41 (br s, 2H, NH), 1.02 (t, 6H, 2 x $CH_2C\underline{H}_3$, aliphatic), 1.86 (t, 18 H, 6 x $CH_2C\underline{H}_3$, aromatic), 2.64 (q, 4H, 2 x $C\underline{H}_2CH_3$, aliphatic), 3.92 (m, 12H, 6 x $C\underline{H}_2CH_3$, aromatic), 9.06 (s, 2H, α- and β-meso-H), 9.76 (s, 2H, γ- and δ-meso-H). UV-vis: λ_{max}, nm, 410 (ε 192 000), 494 (18 000), 524 (7500), 590 (9000), 642 (55 000).

1,2-Dihydroxy-etiochlorin-I (38).[81] The title chlorin was prepared from etioporphyrin-I by the method described above for the chlorin **31**. ^{1}H-NMR: δ, ppm, 0.86 (t, 3H, 2-$CH_2C\underline{H}_3$, aliphatic), 1.26 (s, 3H, 1-CH_3, aliphatic), 1.76 (m, 9H, 3 x $CH_2C\underline{H}_3$, aromatic), 2.45 (q, 2H, 2-$C\underline{H}_2CH_3$, aliphatic), 3.43 (s, 3H, ring Me), 3.45 (s, 3H, ring Me), 3.50 (s, 3H, ring Me), 3.89 (q, 4H, 2 x $C\underline{H}_2CH_3$, aromatic), 3.95 (q, 2H, CH_2CH_3, aromatic), 9.02, 9.08, 9.72, 9.74 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 406 (ε 186 000), 496 (17 700), 522 (7000), 588 (9900), 640 (52 300). LRMS (FAB): m/e (%) 512 (100), 495 (115), 465 (12). HRMS (EI+), Calcd for $C_{32}H_{40}N_4O_2$: 512.3151; found 512.3137.

1,2,5,6-Tetrahydroxyoctaethylbacteriochlorin (48). The same method as in the preparation of **31** was used, but the reaction time was prolonged to three days. After work-up, the mixture of dihydroxy- and tetrahydroxy-compounds was separated by flash chromatography on silica gel, eluting with 2% tetrahydrofuran in dichloromethane. The title bacteriochlorin was obtained in yields ranging from 15-20%. Mp 165-167°C (dec.), [lit.[79] mp 170-172°C (dec.)]. ^{1}H-NMR: δ, ppm, -2.25 (s, 2H, NH), 1.09 (t, 12H, 4 x $CH_2C\underline{H}_3$, aliphatic), 1.75 (t, 12H, 4 x $CH_2C\underline{H}_3$, aromatic), 2.60 (q, 8H, 4 x CH_2CH_3, aliphatic), 3.83 (q, 8H, 4 x $C\underline{H}_2CH_3$), 8.89 (s, 4H, α, β, γ, and δ-meso-H). UV-vis: λ_{max}, nm, 380, 470, 500, 714.

1,2,5,6-Tetrahydroxyetiobacteriochlorin-I. The title bacteriochlorin was prepared from etioporphyrin-I in very small scale using the method described above for the analogous bacteriochlorin **48**. ^{1}H-NMR: δ, ppm, -2.34 (br s, 2H, NH), 0.78 (t, 6H, 2 x $CH_2C\underline{H}_3$, aliphatic), 1.70 (t, 6H, 2 x $CH_2C\underline{H}_3$, aromatic), 2.15 (s, 6H, 2 x methyl, aliphatic), 2.40 (q, 4H, 2 x $C\underline{H}_2CH_3$, aliphatic), 3.36 (s, 6H, 2 x ring Me), 3.82 (q, 4H, 2 x $C\underline{H}_2CH_3$, aromatic), 8.87 (s, 2H, 2 meso-H), 8.95 (s, 2H, 2 x meso-H). UV-vis: λ_{max}, nm, 370, 440, 468, 498, 712.

2,3,4,5,6,7,8-Heptaethyl-1-vinylporphyrin (36). The dihydroxychlorin **31** (50 mg, 0.088 mmol) was refluxed in benzene (20 mL) containing five drops of concentrated hydrochloric acid.[11] The reaction was stopped after 4 h, by which time two major and one minor product had been formed. The separation was

carried out on a silica gel column with 20%cyclohexane/dichloromethane to obtain the monovinylporphyrin **36** (26 mg, 55%) and the porphyrinone **37** (7 mg, 14%). A small amount of a relatively polar porphyrin was recovered with 2% tetrahydrofuran in dichloromethane and its visible absorption spectra and proton NMR point to it being the hydroxyethylheptaethylporphyrin. The title porphyrin can also be made (accidentally discovered), by just heating the diol **31** in a vacuum oven for 3 h at 140°C; the yield is much higher (>70%) than in the previous method. The porphyrinone **37** is also formed in approximately 10% yield using the thermal procedure.

2,3,4,5,6,7,8-Heptaethyl-1-vinylporphyrin (**36**), mp 296°C, (lit.[82] mp 296-298°C). ^{1}H-NMR: δ, ppm, -3.70 (br s, 2H, NH), 1.95 (t, 21 H, 7 x $CH_2C\underline{H}_3$), 4.18 (m, 14 H, 7 x $C\underline{H}_2CH_3$), 6.18 (dd, 1H, 1b-*cis* -H, J = 11.5 Hz), 6.40 (dd, 1H, 1b-*trans* -H, J = 18 Hz), 8.29 (dd, 1H, 1a-H), 10.12 (s, 2H, meso-H), 10.18, 10.29 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 400 (ε 179 400), 502 (19 700), 538 (18 400), 570 (13 700), 622 (10 400). LRMS (FAB): m/e (%), 533 (100), 532 (74), 531 (24), 517 (12), 503 (10). HRMS (FAB), Calcd for $C_{36}H_{44}N_4$: 533.36446 (M+1); found 533.36442.

2,2,3,4,5,6,7,8-Octaethyl-1-oxochlorin (**37**), mp 248-249°C, (lit.[83] mp 246-248°C). ^{1}H-NMR: δ, ppm, -2.91 (br s, 1H, NH), -2.82 (br s, 1H, NH), 0.36 (t, 6H, $CH_2C\underline{H}_3$, aliphatic), 1.82 (m, 18H, $CH_2C\underline{H}_3$), 2.73 (q, 4H, $C\underline{H}_2CH_3$, aliphatic), 4.01 (m, 12H, $C\underline{H}_2CH_3$), 9.05, 9.76 , 9.84 , 9.87 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 406 (ε 198 200), 512 (17 500), 552 (22 600), 586 (15 900), 640 (40 600). LRMS (FAB): m/e (%) 551 (100), 535 (20), 521 (29), 505 (18), 491 (14), 477 (12). HRMS (FAB), Calcd for $C_{36}H_{46}N_4O$: 551.3750 (M+1); found 551.3749.

4,6,8-Triethyl-1,3,5,7-tetramethyl-2-vinylporphyrin (39) and 2,4,6,8-Tetraethyl-2,3,5,7-tetramethyl-1-oxochlorin (40). The title chlorins were prepared on a small scale from the dihydroxychlorin **38** by simply heating it in the vacuum oven at 120°C for 3 h. The components of the mixture were separated by silica gel flash chromatography, eluting with dichloromethane.

4,6,8-Triethyl-1,3,5,7-tetramethyl-2-vinylporphyrin (**39**): ^{1}H-NMR: δ, ppm, -3.71 (s, 2H, NH), 1.86 (t, 9H, 3 x $CH_2C\underline{H}_3$), 3.60 (s, 3H, ring Me), 3.64 (s, 3H, ring Me), 3.66 (s, 3H, ring Me), 3.74 (s, 3H, ring Me), 4.12 (m, 6H, 3 x $C\underline{H}_2CH_3$), 6.17 (dd, 1H, 2b-*cis* -H, J_{ab} = 12 Hz), 6.38 (dd, 1H, 2b-*trans* -H, J_{ab} = 18 Hz), 8.35 (dd, 1H, 2a-H), 10.06 (s, 2H, 2 meso-H), 10.13, 10.22 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 400 (ε 139 000), 502 (16 700), 538 (16 300), 570 (12 100), 624 (9700). LRMS (FAB): m/e (%) 477 (100), 461 (17), 351 (21). HRMS (EI+), Calcd for $C_{32}H_{36}N_4$: 476.2939; found 476.2954

2,4,6,8-Tetraethyl-2,3,5,7-tetramethyl-1-oxochlorin (**40**):[84] ^{1}H-NMR: δ, ppm, -2.95 (br s, 1H, NH), -2.81 (br s, 1H, NH), 0.42 (t, 3H, 2-$CH_2C\underline{H}_3$, aliphatic), 1.80 (s, 3H, 2-CH_3, aliphatic), 1.83 (q, 9H, 3 x $CH_2C\underline{H}_3$, aromatic), 2.77 (q, 2H, 2-$C\underline{H}_2CH_3$, aliphatic), 3.46 (s, 3H, ring Me), 3.57 (s, 3H, ring Me), 3.60 (s, 3H, ring Me), 4.02 (m, 6H, 3 x $C\underline{H}_2CH_3$, aromatic), 9.11, 9.82, 9.84, 9.92 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 402 (ε 154 100), 504 (14 800), 544 (16 100), 586 (11 100), 640 (32 200). LRMS (FAB): m/e (%) 495 (100), 474 (31), 465 (33), 439 (22), 395 (30), 386 (31). HRMS (FAB), Calcd for $C_{32}H_{38}N_4O$: 495.3124 (M+1); found 495.3143.

1,3,4,5,6,7,8-Heptaethyl-2-vinyl-1,2-epoxychlorin (46) and 2,3,4,5,6,7,8-Heptaethyl-2-vinyl-1-oxochlorin (47) *(A) Photooctaethylporphyrin* (**44**). The monovinylporphyrin **36** (20 mg, 0.037 mmol) was dissolved in dichloromethane (20 mL) in an Erlenmeyer flask and irradiated for 22 h inside the light drum. The progress of the reaction was monitored by UV-visible spectroscopy (chlorin λ_{max} at 662 nm) and by analytical TLC. The green chlorin was collected after purification on a silica gel column with dichloromethane to recover the unreacted starting porphyrin (5 mg, 25%) and with 2% tetrahydrofuran in dichloromethane to obtain the desired product **44** (12 mg, 57%). [^{1}H-NMR: δ, ppm, -3.07 (br s, 1H, NH), -2.98 (br s, 1H, NH), -0.09 (t, 3H, $CH_2C\underline{H}_3$, aliphatic), 1.80 (m, 18H, 6 x $CH_2C\underline{H}_3$, aromatic), 2.44 (m, 1H, $C\underline{H}_2CH_3$, aliphatic), 2.52 (m, 1H, $C\underline{H}_2CH_3$, aliphatic), 3.87 (m, 8H, 4 x $C\underline{H}_2CH_3$, aromatic), 4.02 (q, 4H, 2 x $C\underline{H}_2CH_3$, aromatic), 7.41 (d, 1H, olefinic C<u>H</u>-CHO), 8.73, 9.15, 9.74, 9.79 (each s, 1H, meso-H), 10.61 (d, 1H, aldehyde-H). UV-vis : λ_{max},

nm, 387 (ε 45 400), 486 (10 700), 496 (10 100), 572 (12 400), 604 (11 200), 662 (20 700). LRMS (FAB): m/e (%) 565 (100), 548 (49), 537 (45), 519 (23), 507 (22). HRMS (FAB), Calcd for $C_{36}H_{44}N_4O_2$: 565.35428 (M+1); found 565.35425]. *(B) Photooctaethylporphyrin Alcohol* (**45**). The chlorin **44** was reduced at the aldehyde group in almost quantitative yield by the method described previously for the reduction of **3** to **12**. [^{1}H-NMR: δ, ppm, -2.85 (br s, 2H, NH), 0.05 (t, 3H, $CH_2C\underline{H}_3$, aliphatic), 1.79 (m, 18H, 6 x $CH_2C\underline{H}_3$, aromatic), 2.36 (q, 1H, $C\underline{H}_2CH_3$, aliphatic), 2.59 (m, 1H, $C\underline{H}_2CH_3$, aliphatic), 3.86 (m, 8H, 4 x $C\underline{H}_2CH_3$, aromatic), 3.98 (m, 4H, 2 x $C\underline{H}_2CH_3$, aromatic), 4.85 (dd, 1H, $C\underline{H}_2OH$), 5.01 (dd, 1H, $C\underline{H}_2OH$), 7.31 (t, 1H, olefinic-H), 8.90, 9.10, 9.72, 9.75 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 391 (ε 122 700), 498 (18 900), 532 (21 000), 596 (14 000), 652 (29 900). LRMS (FAB): m/e (%) 567 (100), 551 (47), 537 (26), 521 (28), 505 (22), 491 (17). HRMS (FAB), Calcd for $C_{36}H_{46}N_4O_2$: 567.3699 (M+1); found 567.3699]. *(C) Intramolecular Dehydration of the Photooctaethylporphyrin Alcohol (45).* The diol **45** (16 mg, 0.028 mmol) was dissolved in dry dichloromethane (6 mL) in a two-neck flask. Triphenylphosphine (7.4 mg, 0.028 mmol) was added, and the solution was chilled down to 0°C in an ice-water bath. Diisopropylazo-dicarboxylate (6 mL, 0.037 mmol) was added to the mixture dropwise using a syringe and stirring at the same time. The reaction was stopped after 10 min when analytical TLC showed the very mobile porphyrinone and epoxide spots, as well as the polar baseline material. Separation of the mixture was carried out on a short alumina column. The epoxide **46** (1.5 mg, 10%) and porphyrinone **47** (2 mg, 13%) were recovered with dichloromethane and the polar starting material with 1% methanol in dichloromethane. In an attempt to improve the yields of the major products, the reaction was run at low temperatures. Surprisingly, at both -15°C (ethylene glycol/carbon dioxide cooling bath) and -78°C, the main product was identified as the aldehyde precursor of **44**. The same amount of the polar band (recovered with 1% methanol in dichloromethane) as with the reactions done at 0°C was formed at both cases.

1,3,4,5,6,7,8-Heptaethyl-2-vinyl-1,2-epoxychlorin (**46**), mp 127-128°C. ^{1}H-NMR: δ, ppm, -2.98 (br s, 2H, NH), 0.74 (t, 3H, 1-$CH_2C\underline{H}_3$, aliphatic), 1.84 (m, 18H, 6 x $CH_2C\underline{H}_3$, aromatic), 2.96 (m, 2H, 1-$C\underline{H}_2CH_3$, aliphatic), 3.92 (m, 6H, 3 x $C\underline{H}_2CH_3$, aromatic), 4.04 (m, 6H, 3 x $C\underline{H}_2CH_3$, aromatic), 6.14 (dd, 1H, 2b-*cis* -H, J = 10.8 Hz), 6.36 (dd, 1H, 2b-*trans* -H, J = 16.8 Hz), 6.93 (dd, 1H, 2a-H), 9.16, 9.17, 9.84, 9.88 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 394 (ε 66 800), 494 (11 900), 534 (10 100), 582 (9000), 608 (5200), 638 (17 500). LRMS (FAB): m/e (%) 549 (17), 533 (100), 517 (23), 505 (17), 489 (10). HRMS (FAB), Calcd for $C_{36}H_{44}N_4O$: 549.35937 (M+1); found 549.35933.

2,3,4,5,6,7,8-Heptaethyl-2-vinyl-1-oxochlorin (**47**), mp 198-199°C. ^{1}H-NMR: δ, ppm, -2.92 (s, 1H, NH), -2.88 (s, 1H, NH), 0.47 (t, 3H, $CH_2C\underline{H}_3$, aliphatic), 1.82 (m, 18H, 6 x $CH_2C\underline{H}_3$, aromatic), 2.96 (q, 2H, $C\underline{H}_2CH_3$, aliphatic), 3.90 (q, 4H, 2 x $C\underline{H}_2CH_3$, aromatic), 4.05 (m, 8H, 4 x $C\underline{H}_2CH_3$, aromatic), 5.31 (dd, 1H, 2b-*cis* -H), 5.37 (dd, 1H, 2b-*trans* -H), 6.47 (dd, 1H, 2a-H), 9.11, 9.81, 9.84, 9.92 (each s, 1H, meso-H). UV-vis: λ_{max}, nm, 406 (ε 154 000), 510 (13 200), 548 (16 000), 586 (11 100), 640 (36 300). LRMS (FAB): m/e (%) 549 (100), 533 (33), 518 (35), 505 (19), 491 (13), 474 (27). HRMS (FAB), Calcd for $C_{36}H_{44}N_4O$: 549.35937 (M+1); found 549.35933.

2,3,4,6,7,8-Hexaethyl-1,5-divinylporphyrin (49) and 2,3,4,5,7,8-hexaethyl-1,6-divinylporphyrin (50). The tetrahydroxy-bacteriochlorin **48** (100 mg, 0.166 mmol) was dissolved in benzene (25 mL) containing five drops of concentrated hydrochloric acid. The solution was refluxed for 20 min and the solvent removed under vacuum. The product mixture was separated on a silica gel column with dichloromethane. The mixture of divinyl compounds was eluted first (combined yield 30 mg, 34%). The two isomers can be separated by normal-phase HPLC (1.5% tetrahydrofuran in dichloromethane), but the separation was not pursued on a preparative scale. The second band eluted (< 5 mg) seemed to contain the mixture of isomeric diketobacteriochlorins **51** and **52**. Finally, a major band of low mobility was obtained with 2% tetrahydrofuran in dichloromethane as eluent and was shown to be a mixture of several compounds. As the proton NMR: spectra of several of them indicated, the mixture consisted of various combinations of vinyl and hydroxyethyl

groups at positions 1, 5, and 6. ^{1}H-NMR spectrum of **49** or **50**: δ, ppm, -3.66 (s, 2H, NH), 1.95 (t, 18 H, 6 x $CH_2\underline{CH_3}$), 4.17 (m, 12H, 6 x $C\underline{H_2}CH_3$), 6.16 (dd, 2H, 1b-*cis* -H and 5b-*cis* -H or 6b-*cis* -H), 6.36 (dd, 2H, 1b-*trans* -H and 5b-*trans* -H or 6b-*trans* -H), 8.26 (dd, 2H, 1a-H and 5a-H or 6a-H), 10.16, 10.28 (each s, 2H, meso-H). UV-vis: λ_{max}, nm, 400 (ε 112 600), 502 (14 300), 540 (14 100), 570 (11 100), 624 (8700). LRMS (FAB): m/e (%) 548.33 (27), 531.34 (100), 525.31 (17), 504.30 (18). HRMS (FAB), Calcd for $C_{36}H_{42}N_4$: 531.34881 (M+1); found 531.34877.

5-Vinylphotohexaethylporphyrin (53) and 6-Vinylphotohexaethylporphyrin (54).

The foregoing mixture of the isomeric divinylporphyrins **49** and **50** (29 mg, 0.055 mmol) was photooxidized following the standard method described for protoporphyrin-IX dimethyl ester **1**. After purification on a silica gel column (2% tetrahydrofuran in dichloromethane), the mixture of the desired isomeric chlorins **53** and **54** was obtained in a combined yield of 65% (20 mg). A minor amount of the mixture of the bacteriochlorin photoproducts **55** and **56** was eluted from the column with 1.5% methanol in dichloromethane. ^{1}H-NMR (**53** and **54**): δ, ppm, -3.26 (br s, 2H, NH), -3.19 (s, 1H, NH), -3.16 (s, 1H, NH), -0.21 (t, 6H, 2 x $CH_2\underline{CH_3}$, aliphatic), 1.70 (m, 12H, 4 x $CH_2\underline{CH_3}$, aromatic), 1.81 (m, 18H, 6 x $CH_2\underline{CH_3}$, aromatic), 2.35 (m, 2H, 2 x $C\underline{H_2}CH_3$, aliphatic), 2.42 (m, 2H, 2 x $C\underline{H_2}CH_3$, aliphatic), 3.46 (q, 20H, 10 x $C\underline{H_2}CH_3$, aromatic), 6.04 (dd, 2H, 5b- and 6b-*cis* -H), 6.21 (dd, 2H, 5b- and 6b-*trans* -H), 8.08 (dd, 2H, 5a- and 6a-H), 7.10 (d, 1H, C<u>H</u>-CHO), 7.12 (d, 1H, C<u>H</u>-CHO), 8.47, 8.48, 8.79, 8.83, 9.68, 9.72, 9.83 , 9.85 (each s, 1H, meso-H), 10.40 (d, 2H, 2 x aldehyde-H). UV-vis: λ_{max}, nm, 396, 506, 574, 604, 660. LRMS (FAB): m/e (%) 563 (100), 547 (32), 535 (31), 517 (19). HRMS (FAB), Calcd for $C_{36}H_{42}N_4O_2$: 563.3386 (M+1); found 563.3385.

5-Vinylphotohexaethylporphyrin Alcohol (57) and 6-Vinylphotohexaethylporphyrin Alcohol (58). The title porphyrin mixture was obtained in almost quantitative yield from the isomeric mixture of **55** and **56** using the standard method described for the porphyrin **3**. ^{1}H-NMR: δ, ppm, 0.06 (t, 6H, 2 x $CH_2\underline{CH_3}$, aliphatic), 1.75 (m, 12H, 4 x $CH_2\underline{CH_3}$, aromatic), 1.82 (m, 18H, 6 x $CH_2\underline{CH_3}$, aromatic), 2.56 (m, 2H, 2 x $C\underline{H_2}CH_3$, aliphatic), 2.65 (m, 2H, 2 x $C\underline{H_2}CH_3$, aliphatic), 3.84 (m, 8H, 4 x $C\underline{H_2}CH_3$, aromatic), 3.97 (m, 12H, 6 x $C\underline{H_2}CH_3$, aromatic), 4.86 (dd, 2H, 2 x $C\underline{H_2}OH$), 4.99 (dd, 2H, 2 x $C\underline{H_2}OH$), 6.02 (dd, 2H, 5b- and 6b-*cis* -H), 6.18 (dd, 2H, 5b- and 6b-*trans* -H), 7.31 (d, 2H, 2 x C<u>H</u>-CH_2OH), 8.09 (dd, 2H, 5a-H and 6a-H), 9.02, 9.03, 8.84, 8.85 (all s, 4H, 2 α- and 2 β-meso H), 9.70, 9.73, 9.84, 9.88 (all s, 4H, γ- and δ-meso-H). UV-vis: λ_{max}, nm, 404 (ε 115 300), 506 (16 700), 542 (18 700), 594 (13 700), 650 (28 000). LRMS (FAB): m/e (%) 565.6 (100), 547.5 (27), 535.5 (21), 517.5 (22), 505.5 (16). HRMS (FAB), Calcd for $C_{36}H_{44}N_4O_2$: 565.35428 (M+1); found 565.35425.

Intramolecular Dehydration of the Mixture of 5-Vinyl-photohexaethylporphyrin Alcohol (57) and 6-Vinyl-photohexaethylporphyrin Alcohol (58). The mixture of the diols **57** and **58** was subjected to the conditions of the Mitsunobu reaction as previously described for the diol **12**. After purification, the ketochlorin mixture **59/60** and the epoxide mixture **61/62** were obtained.

2,3,4,6,7,8-Hexaethyl-2,5-divinyl-1-oxochlorin (**59**) and *2,3,4,5,7,8-Hexaethyl-2,6-divinyl-1-oxochlorin* (**60**). ^{1}H-NMR: δ, ppm, -2.89 (br s, 2H, NH), -2.81 (br s, 2H, NH), 0.49 (t, 3H, 2-$CH_2\underline{CH_3}$, aliphatic), 0.88 (t, 3H, 2-$CH_2\underline{CH_3}$, aliphatic), 1.82 (m, 15H, 5 x $CH_2\underline{CH_3}$, aromatic), 1.87 (m, 15H, 5 x $CH_2\underline{CH_3}$), 2.97 (m, 4H, 2 x $C\underline{H_2}CH_3$, aliphatic), 4.05 (m, 20H, 10 x $C\underline{H_2}CH_3$, aromatic), 6.06 (dd, 4H, 2 x 2b-*cis* -H + 5b- and 6b-*cis* -H), 6.20 (dd, 4H, 2 x 2b-*trans* -H + 5b- and 6b-*trans* -H), 6.50 (dd, 2H, 2 x 2a-H), 8.13 (dd, 2H, 5a- and 6a-H), 9.11 (s, 2H, 2 x b-meso-H), 9.80 (s, 2H, meso-H), 9.89, 9.97, 10.01, 10.09 (all s, 4H, α-, γ, and δ-meso-H). UV-vis: λ_{max}, nm, 408 (ε 105 200), 514 (8800), 556 (12 000), 586 (8300), 640 (19 400). LRMS (FAB): m/e (%) 563 (26), 546 (100), 533 (27), 521 (34), 503 (22), 489 (23). HRMS (FAB), Calcd for $C_{36}H_{42}N_4O$: 547.34372 (M+1); found 547.34368.

1,3,4,6,7,8-Hexaethyl-2,5-divinyl-1,2-epoxychlorin (**61**) and *1,3,4,5,7,8-Hexaethyl-2,6-divinyl-1,2-epoxychlorin* (**62**). ^{1}H-NMR: δ, ppm, -2.91 (br s, 4H, NH), 0.75 (t, 3H, 1-$CH_2\underline{CH_3}$, aliphatic), 0.85 (t, 3H, 1-

$CH_2C\underline{H}_3$, aliphatic), 1.81 (m, 15H, 5 x $CH_2C\underline{H}_3$, aromatic), 1.85 (m, 15H, 5 x $CH_2C\underline{H}_3$), 2.93 (m, 4H, 2 x $C\underline{H}_2CH_3$, aliphatic), 3.94 (m, 8H, 4 x $C\underline{H}_2CH_3$, aromatic), 4.04 (m, 12H, 6 x $C\underline{H}_2CH_3$, aromatic), 6.04 (dd, 2H, 2 x 2b-*cis* -H), 6.19 (dd, 2H, 2 x 2b-*trans* -H), 6.12 (dd, 2H, 5b- and 6b-*cis* -H), 6.35 (dd, 2H, 5b- and 6b-*trans* -H), 6.91 (dd, 2H, 2 x 2a-H), 8.11 (dd, 2H, 5a- and 6a-H), 9.14 (s, 2H, 2 x α-meso-H), 9.18 (s, 2H, β-meso-H), 9.87, 9.91, 9.99, 10.03 (all s, 4H, 2 γ- and 2 δ-meso-H). UV-vis: λ_{max}, nm, 390, 498, 532, 582, 608, 636. LRMS (FAB): m/e (%) 546 (15), 531 (100), 515 (34), 501 (18), 487 (17). HRMS (FAB), Calcd for $C_{36}H_{42}N_4O$: 547.34372 (M+1); found 547.34368.

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