Improved Methods for the Synthesis of Porphyrin Alcohols and Aldehydes from Protoporphyrin IX Dimethyl Ester and Their Further Modification

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Introduction

Organic synthetic transformations involving functional groups attached to the periphery of the porphyrin macrocycle have occupied chemists for the past 65 years since Fischer reported the first total synthesis of protoheme.[1,2] Such transformations have recently taken on added significance through the use of porphyrin alcohols and aldehydes as intermediates in the preparation of compounds with potential uses in binary therapeutic treatments of cancer such as photodynamic therapy (PDT) and boron neutron capture therapy (BNCT)[3,4] and in the treatment of HIV infection.[5] High-yield syntheses of these intermediates from readily available starting materials are especially important in this context since the availability of low-cost intermediates is desirable. Moreover there is continuing interest in organic synthetic methods designed to further probe the functional group chemistry on the porphyrin platform. We report here improved syntheses of four very useful alcoholic and aldehydic porphyrins in which the yields have each been at least doubled over published methods, and on the further elaboration of reactive carbonyl centers with phosphorus and sulfur ylides and with diazomethane.

Results and Discussion

Oxidations of Protoporphyrin IX. Protoporphyrin IX dimethyl ester **1** is readily available by treatment of protohemin from blood with $FeSO_4$ in HCl followed by esterification of the resulting free acid with 5% H_2SO_4/methanol (MeOH) for 18 h at −10 °C in the dark.[2] Even on a large scale (20 g), yields of **1** exceeding 90% are routinely obtained. The bis-glycol **2** has become a very useful starting material in our group, and we have previously found that modifications of the original method of Sparatore and Mauzerall[6] (treatment of **1** with excess osmium tetraoxide (OsO_4) followed by reduction of the osmate esters with sodium sulfite) raised the published yield from 45% to ≥90% even when applied on a 5−10 gram scale. However the expense and toxicity of OsO_4, together with concerns about the proper environmental disposal of the osmium metal byproduct from this stoichiometric reaction, led us to consider other methods for the preparation of bis-glycol **2**. We have recently found that conversion of **1** into the bis-glycol **2** on a large scale is accomplished in ≥97% yield by modification of the osmium-catalyzed dihydroxylation method of Sharpless and co-workers.[7,8] To our knowledge this is the first reported application of this very useful method to porphyrin alkene groups. Treatment of **1** with OsO_4 (0.10 equiv) and *N*-methylmorpholine oxide in carefully argon-sparged aqueous 1,4-dioxane for 24 h at room temperature followed by reduction of the remaining osmate esters with sodium metabisulfite drives the reaction nearly to completion and results in less of the mono-vinyl, mono-glycol byproduct isomers which are difficult to separate from the desired bis-glycol **2**. Careful control of the solution temperature after the ester reduction step and prior to filtration of the solution keeps the product completely soluble and easily separable from the finely divided osmium metal byproduct and unreacted sodium metabisulfite. This method, although not purely catalytic, results in a 90% decrease in the use of OsO_4. The amount of tetraoxide used can be further reduced to 1% and the reaction made truly catalytic by working on a small scale or by allowing the reaction to proceed for longer times. Bis-glycol **2** is a critical intermediate in the synthesis of compounds[9] reported to be potentially useful in boron neutron capture therapy,[3] photodynamic therapy,[4] and treatment of HIV infection[5].

Oxidation of **2** with periodic acid (HIO_4) in THF gives the diformyl product **3** in 80% yield and in a much cleaner manner than the originally published procedure which used sodium periodate in dioxane/water and yielded only about 30% pure diformyl product.[6] Aldehyde **3** has also been prepared in 60% yield by low temperature ozonolysis of **1**,[10] by permanganate oxidation of **1** in 17−22% yield,[11] and in unspecified yield by picryl azide treatment of **1**.[12] Our procedure is simpler, cleaner, and gives better yields with easier isolation of product than any of these methods. Bis-glycol **2** is soluble in dioxane/water, but neither of the mono-formyl, mono-glycol isomeric intermediates nor the dialdehyde product **3** is soluble in this mixture which results in precipitation of the intermediate and a complex product mixture requiring chromatographic separation. Although bis-glycol **2** is poorly soluble in THF, as the reaction proceeds it dissolves with formation of first the mono-formyl, mono-glycol intermediates and then the desired diformyl product **3**, both of which are soluble in THF. Increased yields and cleaner product also appeared to result from using a minimal amount of water to dissolve the HIO_4. By using only 1 equiv of OsO_4 and the HIO_4/THF procedure, it should be possible to synthesize *Spirographis* porphyrin and its isomer in better yields than the published procedure, although we have not attempted to do so.

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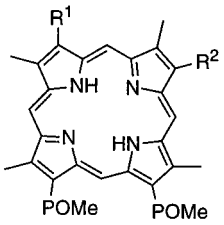
Treatment of **1** with thallium(III) nitrate gives the bis-dimethylacetal of **4** (not shown)[13] which can either be isolated or stirred at room temperature in 88% formic acid to give aldehyde **4** in >90% yield. This very mild, clean method causes no hydrolysis of the ester side chains and produces virtually no side products. Snow and Smith reported that dialdehyde **4** decomposed in solution over time and could not be crystallized,[14] but we found that **4** could be crystallized from hexane/methylene chloride and was stable for at least six weeks on storage at −20 °C. They did not report a yield in their transacetylation of the bis-acetal to give **4**, and the procedure involves chromatographic separation.[14] In all the drawings of this Note, the symbol POMe represents a methyl propionate residue.



1 $R^1 = R^2 =$ vinyl

2 $R^1 = R^2 =$ $CH(OH)CH_2OH$

3 $R^1 = R^2 =$ CHO

4 $R^1 = R^2 =$ CH_2CHO

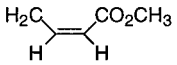
5 $R^1 = R^2 =$ CH_2CH_2OH

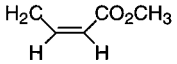
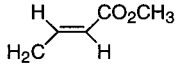
6 $R^1 = R^2 =$ $CH{=}CHCO_2CH_3$

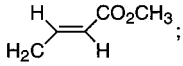
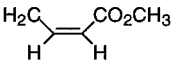
7 $R^1 = R^2 =$ $CH_2CH_2CO_2CH_3$

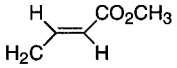
8 $R^1 = R^2 =$ $CH{=}CHCO_2t\text{-}Bu$

9 $R^1 = R^2 =$ $CH_2CH_2CO_2H$

10a $R^1 = R^2 =$ 

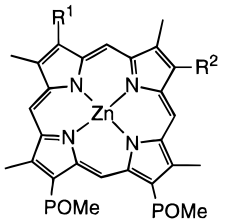
10b $R^1 =$  ; $R^2 =$ 

10c $R^1 =$  ; $R^2 =$ 

10d $R^1 = R^2 =$ 

Direct conversion of **1** to isohematoporphyrin **5** without isolation of **4** is also possible, and the yield of **5** increased considerably, by modifying the procedures of Snow and Smith[14] and Kenner *et al.*[13] After formic acid treatment of the bis-acetal, removal of the solvent, and an aqueous wash, the residue is redissolved in $MeOH/CH_2Cl_2$ and reacted with $NaBH_4$. This procedure avoids ester cleavage and reesterification, is very mild and clean, and provides **5** in 93% overall yield from protoporphyrin, a considerable improvement over the 60% reported in reference 14. Isohematoporphyrin **5** is of considerable interest in the synthesis of compounds for photodynamic therapy[15] and further elaboration of the hydroxyethyl side chain.

When sufficient quantities of **3** and **4** became available through the application of these improvements, it was possible to explore the possibilities of further elaboration at the reactive carbonyl centers. Three reaction types were examined: reactions with Wittig reagents, sulfur ylides, and diazomethane.



11 $R^1 = R^2 =$ CHO

12 $R^1 = R^2 =$ CH_2CHO

13 $R^1 = R^2 =$ $CH_2CH(O)CH_2$

14 $R^1 = R^2 =$ $CH(O)CH_2$

Reactions with Phosphorus Ylides. Reactions between Wittig reagents and formyl-substituted porphyrins have been previously reported, but are surprisingly rare.[16,17] These transformations were limited to simple fluoromethylene or ^{13}C enriched methylene couplings to **3** and/or spirographis/isospirographis porphyrin to yield fluorinated protoporphyrin or ^{13}C-enriched protoporphyrin. We report here the use of more functionalized Wittig reagents with both **3** and **4**. The first reaction sought to produce 2,4-diallyldeuteroporphyrin, a homolog of protoporphyrin, from the Zn(II) complex of the ethanal porphyrin **12** and phosphorane **15**. A variety of bases were used to generate the phosphorane from the phosphonium salt: *n*-butyllithium, LDA, K_2CO_3 in a two-phase system, and potassium *tert*-butoxide. All attempts failed, yielding only uncharacterized degradation products. Indeed potassium *tert*-butoxide caused rapid porphyrin degradation in the absence of phosphonium salt. It seems likely that the phosphorane is basic enough to deprotonate the methylene α to the carbonyl causing rapid side reactions.

$Ph_3P{=}CH_2$ **15** $Ph_3P{=}CHCOH$ **16**

$Ph_3P{=}CHCO_2CH_3$ **17** $Ph_3P{=}CHCO_2tBu$ **18**

Since it had been previously shown that **3** could be used in a Wittig type reaction, efforts were then focused on this porphyrin. Coproporphyrin, in the form of its tetramethyl ester **7** or as its mixed di-methyl, di-tertiary butyl ester **9**, was a desirable target that potentially could be obtained by this route in higher yield and fewer steps. Coproporphyrin tetramethyl ester **7** has been obtained from **1** in 37% yield[19], in 40% yield[20], and in 36% yield following reduction of **6**.[18] Acrylate ester **6** has previously

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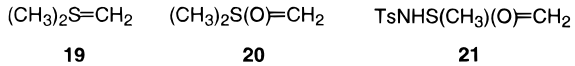
been obtained in 37% yield from deuteroporphyrin dimethyl ester through application of a Heck reaction sequence.[18] We were able to obtain **6** by reaction of diformyl **11** with phosphorane **17** in refluxing CH_2Cl_2 followed by demetalation in 89% yield, 68% yield overall from **1**. The reduction of **6** to **7** is reported to proceed in 96% isolated yield. However, at no time could we reproduce this reduction in more than 63% isolated yield. Modification of the reduction conditions allowed the isolation of an 80% yield, cutting the overall yield of **7** to 54%. Similarly **8** was obtained in 85% yield from **3** and **18** and then subsequently reduced and hydrolyzed to **9** in 78% yield, 50% overall from **1**. This compound is to be selectively modified at the 2,4 positions in ongoing work. Despite the successful use of phosphoranes **17** and **18**, reaction with the phosphorane **16** with **3** failed entirely in either refluxing CH_2Cl_2 or THF.

Unlike the unstable **15**, which is derived by base treatment of the phosphonium salt *in situ*, the phosphoranes **16**−**18** are stable enough to be bottled and stored as the phosphoranes. It was predicted that these reagents might be sufficiently weak bases to allow their use with ethanal **4**. When **4** was treated with **17**, a smooth reaction occurred to yield an isomeric alkene mixture of **10a**−**d**. Flash chromatographic separation of this mixture yielded a trace of the cis/cis isomer **10a**, 17% mixture of cis/trans isomers **10b** and **10c**, 61% percent trans/trans isomer **10d**, and 5% of an unseparated mixture of **10b**−**d**. Total isolated yield of all isomers was 84%. Upon reduction this mixture would yield a homolog of coproporphyrin **7**. Unlike the case with **3**, when **4** was treated with **16** on a small scale in CH_2Cl_2 at room temperature, TLC monitoring showed that reaction did occur albeit at a very slow rate (data not shown). These reactions demonstrate that it is possible to elaborate **4** with certain stabilized phosphoranes if they are sufficiently nonbasic.

Reactions with Sulfur Ylides. Reaction of sulfur ylides with aldehydes is known to give epoxides in good yields,[21,22] but the reaction of sulfur ylides with porphyrins has to our knowledge not been reported. It was proposed to react **12** with sulfur methylides to give the propene oxide **13** which could be further elaborated via nucleophilic substitution. Three ylide reagents **19**−**21** were tried. Use of **19** and **21** failed to yield any characterizable products. However, **20** did yield a small amount of the desired epoxide **13**.



19 **20** **21**

The base used to generate the ylide from the salt influenced the reaction course. When NaH was used to generate the reactive intermediate, either directly or via dimsyl sodium, only rapid degradation of the porphyrin occurred with the formation of almost no desired product as judged by TLC. However, when generated with potassium *tert*-butoxide a small amount of the diepoxide was obtained in 9% isolated yield. It is possible that the poor yields are due to the acidity of the α proton as was the case with the phosphorus ylides.

When porphyrin **11**, which lacks an acidic α proton, was reacted with **20**, reaction occurred at a much slower rate than with **12**, and the reaction required a larger excess of **20** for complete consumption of porphyrin **11** as judged by TLC. It was expected that the desired product **14** would have similar TLC mobility to **13** since the aldehydes **3** and **4** as well as their zinc complexes behave similarly on TLC. However, the crude product mixture gave only nondiscrete streaks on TLC. It is possible that the desired epoxide product did form but was unstable either in solution or on silica gel. No further characterization of the products was attempted.

Reactions with Diazomethane. Treatment of aldehydes with diazomethane (CH_2N_2) can take a number of reaction courses to yield epoxide, homologated ketone, or homologated aldehyde products depending on which group migrates to eliminate nitrogen.[23] Reports of the reaction of CH_2N_2 with porphyrins appears to be limited to a brief personal communication observing that diformyl **3** reacts with CH_2N_2 in ether to form an epoxide which could be hydrolyzed to bis-glycol **2**.[24]

Because of poor solubility in ether, **3** was dissolved in either CH_2Cl_2 or 20% MeOH/CH_2Cl_2 and was treated with ethereal CH_2N_2. No reaction occurred in the absence of MeOH. In the presence of MeOH, complete consumption of **3** required 3−4 days and repeated additions of CH_2N_2. MeOH is known to increase the rate of reaction, to increase epoxide formation relative to ketone formation, but may also promote aryl migration.[23] TLC monitoring of the reaction showed the presence of multiple products which generally appeared as discrete spots. When an aliquot of the crude material was treated with $NaBH_4$ and compared by TLC to an untreated aliquot, it was noted that almost all of the spots shifted to lower R_f, indicating that many of the products contained at least one reducible group (ketone and/or aldehyde) and that epoxide formation was not occurring in high yield. Further characterization was not attempted because of the multiplicity of products.

Since electron-withdrawing groups α to an aldehyde tend to increase the reactivity toward diazo compounds, the more electron-deficient zinc complex **11** was treated with CH_2N_2 under similar conditions. In this case the overall reaction rate was greater, with the reaction occurring even in the absence of MeOH. However, as in the reaction of unmetalated **3**, many products were formed. Again no isolation or characterization of these products was attempted and efforts in this area were discontinued.

Better results were obtained when either **4** or its zinc complex **12** was treated with ethereal CH_2N_2. Because of the wider range of solvent solubility possessed by **4** and **12**, a number of solvents were examined including: THF, THF/MeOH, CH_2Cl_2, 10% MeOH/CH_2Cl_2, 50% MeOH/CH_2Cl_2, pyridine, dioxane/MeOH, and acetonitrile. As judged by TLC there was very little qualitative difference among the various solvents tried or between the two porphyrins, and the rate of reaction was significantly faster than in the reaction of CH_2N_2 with **3** or its zinc complex. Again, MeOH/CH_2Cl_2 mixtures seemed satisfactory.

In the crude product mixture from the reaction of CH_2N_2 with **4** two main and one minor closely spaced spots were observed by TLC. Attempts to completely separate the products by chromatography were unsuc-

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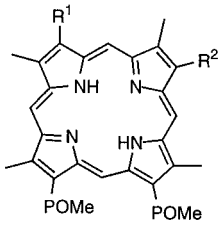

22a $R^1 = R^2 =$ 

22b $R^1 =$  ; $R^2 = CH_2COCH_3$

22c $R^1 = CH_2COCH_3$; $R^2 =$ 

22d $R^1 = R^2 = CH_2COCH_3$

23a $R^1 =$  ; $R^2 = CH_2CH(OH)CH_3$

23b $R^1 = CH_2CH(OH)CH_3$; $R^2 =$ 

23c $R^1 = R^2 = CH_2CH(OH)CH_3$

cessful. However, NMR analysis of the partially separated mixture allowed the structural determination of the products as dihomologated ketone **22d**, mono-epoxide/mono-ketone mixed isomer **22b** and **22c**, and a very small amount of diepoxide **22a**.

When the reaction was repeated and the product mixture subjected to $NaBH_4$ reduction and preparative TLC purification, two major products were obtained. The more mobile product obtained in 18% yield was a mixture of mono-epoxide/mono-alcohol isomers **23a** and **23b**. The less mobile product obtained in 64% yield was identified as the di-2-propanol substituted porphyrin **23c**. These two products differ by only two mass units which can be clearly seen in the mass spectrum. Only a trace of the diepoxide was present and was not isolated.

Conclusion

The Wittig reaction holds potential for the synthesis of more highly functionalized porphyrins. Since neither the sulfur ylides or the diazomethane reaction yielded significant amounts of epoxides, and the ketone products that were obtained were not of great immediate interest to us, further work on these methods has been discontinued.

In summary, improved methods for the synthesis of porphyrin alcohols and aldehydes are reported which are milder, cleaner, and result in significantly improved yields. Further reactions of the porphyrin aldehydes with carbanionoid compounds have been explored, resulting in one case in an improved synthesis of coproporphyrin III. These methods have already had a significant impact on the synthesis of a boronated porphyrin that is close to entering human clinical trials for binary therapies of cancer and are likely to be useful to others interested in porphyrin functional group transformations.

Experimental Section

Protoporphyrin IX was purchased from Porphyrin Products (Logan, Utah) and converted to its dimethyl ester by the method of Smith.[2] Osmium tetraoxide was purchased from Stevens Metallurgical Corp. (New York, NY). All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. Solvents were dried when necessary using standard techniques. Removal of solvents was performed under reduced pressure. Flash chromatography was performed on EM Science silica gel 60 230−240 mesh. Preparative TLC was performed on E. Merk silica gel 60 F_{254}, 1 or 2 mm thickness. High resolution mass spectral data is precise within ±5 ppm, as determined by routine standards evaluation. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, and used TMS as internal standard. Ultraviolet−visible spectra were obtained using a diode array spectrophotometer in methylene chloride at 10−12 μM. Melting points were obtained using a hot stage apparatus and are uncorrected.

2,4-Bis(1,2-dihydroxyethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (2). Protoporphyrin IX dimethyl ester (**1**) (4.88 g; 8.26 mmol) was dissolved in a mixture of dioxane (2.0 L) and water (200 mL) which had previously been vigorously sparged with argon. OsO_4 (0.45 g; 1.77 mmol) and 4-methylmorpholine *N*-oxide (2.98 g; 25.4 mmol) were added to the dioxane solution. The reaction was stirred under argon in the dark for 24 h and monitored continuously by TLC (10% MeOH/CH_2Cl_2). Sodium metabisulfite (30.0 g; 158 mmol) was added to the reaction mixture in a single portion at room temperature. After 1 h of stirring, the reaction flask was placed in a room temperature water bath whose temperature was then raised to 65 °C. After 15 min at this temperature, the water bath was removed and the solution allowed to cool to 53 °C. The reaction mixture was then filtered through a 1.5 L fritted funnel (10−20 μm) and the filtered solid washed with 1,4-dioxane (∼200 mL) until the filtrate became colorless. The filtrate was evaporated *in vacuo* until ∼ 200 mL remained. To this solution was added water (∼20 mL) slowly, and the suspension gradually became a homogenous solution. Water (1.5 L) was added slowly with stirring to crystallize the porphyrin. The solids were collected by filtration through a 1.5 L fritted funnel (10−20 μm), giving a green filtrate. The collected solids were washed slowly with water (∼1.0 L) to remove any remaining water-soluble impurities. The air-dried solid was suspended with stirring in 10% MeOH/CH_2Cl_2 (450 mL) and hexanes (550 mL) slowly added with stirring to complete the crystallization. The solids were filtered and washed with hexanes. The above crystallization procedure was repeated twice more to completely remove any remaining monoglycol−monovinyl byproduct and yielded 5.30 g (8.05 mmol; 97.5%) of the desired bis-glycol product (mp 225−229 °C; lit. 238−240 °C)[6]. This material appears pure by thin layer chromatography and is suitable for most further transformations, but can be recrystallized in the manner of Sparatore and Mauzerall[6] to yield analytically pure material if desired. The mass spectrum ($MH^{+\bullet}$ = 658) was consistent with **2** as was the ^{1}H NMR spectrum.

2,4-Diformyl-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (3). Bis-glycol **2** (101 mg; 0.153 mmol) was suspended in THF (100 mL). Periodic acid (205 mg; 5.8 equiv) dissolved in water (4 mL) was then added. Within a few minutes the solution became homogenous. At 1 h the once again heterogenous solution was reduced in volume *in vacuo*, diluted with chloroform, and washed three times with water. The solvent was removed and the crude porphyrin was dissolved in hot $CHCl_3$ and precipitated with hexane to obtain 72 mg, 80%: mp 283−286 °C (lit.[11,14] 284−286 °C). The ^{1}H NMR spectra match the published values.[6] The mass spectrum ($MH^{+\bullet}$ = 596) was also consistent with **3**. **3** can be quatitatively converted to the zinc complex **11** using the zinc acetate method.[24]

2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (4). Protoporphyrin IX dimethyl ester **1** (250 mg; 0.423 mmol) was brought to reflux in a mixture of CH_2Cl_2 (60 mL) and MeOH (10 mL). Thallium(III) nitrate trihydrate (670 mg; 1.50 mmol) was dissolved in MeOH (22 mL) and added rapidly. The solution was refluxed 10 min and then cooled. SO_2 was bubbled through, and concd HCl (1.3 mL) was added. The white thallium(I) salts were filtered off, and the solution was diluted with CH_2Cl_2 (50 mL) and washed three times with water. The solvent was removed, the residue redissolved in CH_2Cl_2, and the solvent removed again. The solid was dissolved in 88% formic acid (20 mL) and after 2 h the solvent was removed under vacuum. The residue was redissolved in CH_2Cl_2, washed three times with water, and

(24) See reference 2, p 798.

removed. The crude porphyrin was crystallized from CH_2Cl_2/hexane. Obtained 240 mg, 91%. No satisfactory melting point could be obtained for this compound. The ^1H NMR matched published values.[13,14] The mass specrum ($MH^{+\bullet} = 582$) was also consistent with **4**. Anal. Calcd for $C_{36}H_{38}N_4O_6$: C, 69.44; H, 6.15; N, 9.00. Found: C, 69.16; H, 6.33; N, 8.75. **4** could be quatitatively converted to the zinc complex **12** using the zinc acetate method.[24]

2,4-Bis(2-hydroxyethyl)-6,7-bis[2-(methoxycarbonyl)-ethyl]-1,3,5,8 tetramethylporphyrin (5). Starting with 200 mg of **1** the above procedure for the synthesis of **4** was followed but without isolation of **4**. **4** was redissolved in 50% MeOH/CH_2Cl_2, and $NaBH_4$ was added. After 10 min, reaction was quenched with glacial acetic acid, the porphyrin washed three times with water, and solvent removed. The crude porphyrin was recrystallized from MeOH/CH_2Cl_2/hexane and dried under high vacuum to obtain 197 mg, 93%: mp 224−226 °C (lit.[14] mp 222−226 °C); ^1H NMR matched published values.[13,14] The mass spectrum ($MH^{+\bullet} = 624$) was also consistent with **5**.

2,4-Bis[2-(methoxycarbonyl)ethenyl]-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (6). To 2,4-diformyldeuteroporphyrin dimethyl ester **3** (282 mg; 0.474 mmol) and methyl (triphenylphosphoranylidene)acetate (**17**) (637 mg; 1.90 mmol) was added dry CH_2Cl_2 (125 mL). The solution was refluxed for 42 h and cooled, the solvent volume was reduced under vacuum, and then hexanes were added to precipitate the porphyrin. The collected porphyrin was recrystallized from CH_2Cl_2/hexanes a second time. Obtained 321 mg, 96%: mp 253−255 °C (lit.[18] mp 259−261 °C); ^1H NMR matched published data; ($MH^{+\bullet} = 707$). Anal. Calcd for $C_{40}H_{42}N_4O_8$: C, 67.97; H, 5.99; N, 7.93. Found: C, 67.83; H, 6.17; N, 7.69.

Coproporphyrin III Tetramethyl Ester (7). 2,4-Bis[2-(methoxycarbonyl)ethenyl]-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**6**) (100 mg; 0.141 mmol) and 10% Pd on activated carbon (100 mg) were added to a 100 mL flask under argon. A 96% formic acid solution (70 mL) was added and the flask placed under a H_2 balloon. At 14 h the solution was filtered and most of the solvent removed. The remaining solution was diluted with CH_2Cl_2 and washed once with water, and then MeOH was added to the organic phase. The solution was briefly treated with ethereal CH_2N_2 and the reaction quenched with acetic acid and then washed twice with water. The solvent was removed, and the porphyrin was purified by preparative TLC on silica gel with 4% MeOH/CH_2Cl_2. Obtained 80 mg, 80%, (77% from diformyl): mp 173−175 °C (lit.[18] mp 175−176 °C); ^1H NMR matched published; ($MH^{+\bullet} = 711$). Anal. Calcd for $C_{40}H_{46}N_4O_8$: C, 67.59; H, 6.52; N, 7.88. Found: C, 67.57; H, 6.72; N, 7.59.

2,4-Bis[2-(*tert*-butoxycarbonyl)ethenyl]-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (8). 2,4-Diformyldeuteroporphyrin dimethyl ester **3** (300 mg; 0.504 mmol) and [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane (**18**) (760 mg; 2.02 mmol) were refluxed in dry CH_2Cl_2 (125 mL) for 42 h. The reaction was cooled and the solvent volume reduced under vacuum. Hexane was added and the precipitate collected. The solid was twice more precipitated from CH_2Cl_2 with hexane and dried. Obtained 339 mg, 85%: mp 226−228 °C; ^1H NMR ($CDCl_3$): δ −4.14 ppm (s, 2H), 1.79 (s, 18H), 3.24 (m, 4H), 3.56−3.67 (overlapping s, 18H), 4.34 (m, 4H), 6.99 (d, 2H, $J = 16$ Hz), 9.17 (d, 2H, $J = 16$ Hz), 9.87 (s, 4H); UV λ_{max} (ϵ) 424 nm (148 000), 516 (17 800), 552 (17 200), 584 (10 000), 638 (8 500); ($MH^{+\bullet} = 791$). Anal. Calcd for $C_{46}H_{54}N_4O_8$: C, 69.85; H, 6.88; N, 7.08. Found: C, 69.88; H, 7.06; N, 6.86.

2,4-Bis(2-carboxyethyl)-6,7-bis[2-(methoxycarbonyl)-ethyl]-1,3,5,8-tetramethylporphyrin (9). To 2,4-Bis[2-(*tert*-butoxycarbonyl)ethenyl]-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**8**) (100 mg; 0.126 mmol) and 10% Pd on activated carbon (100 mg) under argon was added 96% formic acid (60 mL). The reaction was stirred 15 h under a H_2 balloon. The mixture was filtered, the catalyst was washed with 10% MeOH/CH_2Cl_2, and the solvent was removed. The solid was dissolved CH_2Cl_2 and washed twice with water, and the solvent was removed. The crude mixture was purified by flash chromatography using a step gradient of 5, 8, and 10% MeOH/CH_2Cl_2 followed by elution with 10% MeOH/CH_2Cl_2/0.2% glacial acetic acid. The eluted fraction was washed once with water and the solvent removed. Obtained 67 mg, 78%: mp 250−254 °C dec; ^1H NMR ($CDCl_3$): δ 3.27 (m, 8H), 3.66 (s, 18H), 4.43 (broad singlet, 8H), 10.12, 10.14, 10.15, 10.16 (each s, 4H); UV λ_{max} (ϵ) 398 nm (136 000), 498 (14 800), 532 (11 000), 568 (7 400), 622 (6 400); ($MH^{+\bullet} = 683$). Anal. Calcd for $C_{38}H_{42}N_4O_8$: C, 66.85; H, 6.20; N, 8.21. Found: C, 66.82; H, 6.37; N, 8.02.

2,4-Bis[3-(methoxycarbonyl)-2-propenyl]-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin Isomers 10a−d. To 2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)-ethyl]-1,3,5,8-tetramethylporphyrin **4** (100 mg; 0.161 mmol) and methyl (triphenylphosphoranylidene)acetate (**17**) (215 mg; 0.643 mmol) was added dry CH_2Cl_2 (10 mL). After 4 h stirring at room temperature, the volume was reduced under vacuum and hexane added to precipitate the porphyrin. After a second recrystallization the crude mixture was purified by flash chromatography using a step gradient of 0, 0.2, 0.3, 0.4% MeOH/CH_2Cl_2. Obtained a trace (<1 mg) of putative cic/cis isomer **10a**: mp 182−184 °C; ^1H NMR ($CDCl_3$): δ −3.75 (s, 2H), 3.29 (m, 4H), 3.62−3.66 (overlaping s, 18H), 4.04 (s, 6H), 4.42 (m, 4H), 5.52 (d, 4H), 6.06 (d, 2H, $J = 11.3$ Hz), 6.85 (m, 2H, $J = 11.3$ Hz), 10.09, 10.10, 10.21, 10.22 (each s, 4H); insuficient material was available to measure UV-vis extinction coefficients accurately or to perform elemental analysis ($MH^{+\bullet} = 735$).

Next was obtained the putative mixed mono cis/mono trans isomers **10b** and **10c**, 20 mg, 17%: mp 161−166 °C; ^1H NMR ($CDCl_3$): δ −3.74 (s, 2H), 3.28 (m, 4H), 3.56−3.65 (overlaping s, 18H), 4.04 (s, 6H), 4.42 (m, 4H), 4.95 (d, 2H), 5.53 (d, 2H), 5.95 (d, 1H, $J = 15.7$ Hz), 6.07 (d, 1H, $J = 11.3$ Hz), 6.84 (m, 1H, $J = 11.3$ Hz), 7.74 (m, 1H, $J = 15.7$ Hz), 9.95, 10.10, 10.21, 10.24 (s, 4H); UV λ_{max} (ϵ) 400 nm (159 000), 498 (15 300), 532 (10 800), 568 (6 300), 572 (6 500), 622 (6 300); ($MH^{+\bullet} = 735$). Anal. Calcd for $C_{42}H_{46}N_4O_8$: C, 68.65; H, 6.31; N, 7.62. Found: C, 68.61; H, 6.38; N, 7.50.

After the elution of an impure fraction composed of mixed mono cis/mono trans isomers and trans/trans isomer **10b**, **10c**, and **10d** (6 mg, 5%) was obtained pure putative trans/trans isomer **10d** 73 mg (61%): mp 190−192 °C; ^1H NMR ($CDCl_3$): δ −3.87 (s, 2H), 3.25 (t, 4H), 3.39, 3.40 (each s, 6H), 3.52−3.58 (singlets, 12H), 3.64 (s, 6H), 4.33 (m, 4H), 4.70 (m, 4H), 5.87 (overlapping d, 2 H, $J = 15.7$ Hz), 7.64 (m, 2H, $J = 15.7$ Hz), 9.40−10.10 (singlets, 4H); UV λ_{max} (ϵ) 400 nm (178 000), 498 (17 500), 532 (12 300), 572 (7 400), 622 (6 600); ($MH^{+\bullet} = 735$). Anal. Calcd for $C_{42}H_{46}N_4O_8$: C, 68.65; H, 6.31; N, 7.62. Found: C, 68.64; H, 6.45; N, 7.42.

Zn−2,4-Bis(oxiranylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (13). To the zinc complex of 2,4-bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)-ethyl]-1,3,5,8-tetramethylporphyrin (**12**) (100 mg; 0.147 mmol) in dry DMSO (10 mL) was added a solution of dimethyloxosulfonium methylide (**20**) (1.9 mL of an ~0.160 M solution in DMSO, ~0.304 mmol). After 45 min the solution was diluted with CH_2Cl_2, washed three times with water and the solvent removed. The crude mixture was purified by flash chromatography using a step gradient of 0, 0.5, 0.6, 0.8% MeOH/CH_2Cl_2. The compound was unstable to TFA-demetalation conditions and was characterized as the zinc complex. Obtained 9 mg, 8.6%: mp 223−225 °C; ^1H NMR ($CDCl_3$): δ 2.51−2.67 (m, 4H), 3.17 (m, 4H), 3.24−3.32 (overlaping s and m, 8H), 3.47 (s, 6H), 3.67 (s, 6H), 3.87−3.99 (m, 4H), 4.27 (m, 4H), 9.32, 9.47, 9.54, 9.62 (each s, 4H); ^{13}C NMR ($CDCl_3$): δ 11.33, 11.47, 21.27, 29.07, 36.97, 47.33, 51.69, 52.90, 96.13−96.76, 134.1−147.2, 173.6; UV λ_{max} (ϵ) 398 (140 000), 532 (13 900), 568 (18 700); ($MH^{+\bullet} = 712$). Anal. Calcd for $C_{38}H_{40}N_4O_6Zn$: C, 63.91; H, 5.65; N, 7.85. Found: C, 63.53; H, 5.75; N, 7.55.

Treatment of 2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (4) with Diazomethane to Yield 22a−d. To 2,4-bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**4**) (100 mg; 0.161 mmol) dissolved in 20% MeOH/CH_2Cl_2 (25 mL) was added 5 mL of an ethereal solution of CH_2N_2. Glacial acetic acid (2 drops) was added after 1 h. After another 5 min the solution was diluted with CH_2Cl_2 and washed three times with water. Solvent was removed, and then flash chromatography was performed using a step gradient of 0, 0.2, 0.3, 0.4% MeOH/CH_2Cl_2. Five fractions were obtained all of which contained more than one component. The most mobile fraction was mainly composed of a very small amount of diepoxide **22a** while the least mobile was composed mostly of diketone **22d**. Intermediate fractions contained **22b** and **22c** as well. Comparison of the ^1H NMR of the first and last fractions allowed tentative assign-

ments for the resonances of the ketone and epoxide side chains. For the epoxide side chain ^{1}H NMR ($CDCl_3$): δ 2.95 (d, oxiranyl CH_2), 3.77 (m, oxiranyl C*H*), 4.31−4.45 (m, overlapping with propionate CH_2, CH_2CHOCH_2). For the ketone side chain ^{1}H NMR ($CDCl_3$): δ 2.28 (s, COCH_3), 5.02 (2 s, CH_2COCH_3). Melting points, MS, UV-vis spectra, of elemental analysis were not determined for these mixtures.

Treatment of 2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (4) with Diazomethane Followed by Sodium Borohydride Reduction to Yield 23a−c. 2,4-Bis(formylmethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (**4**) (113 mg, 0.180 mmol) was treated in a manner as for **22**. After workup, the solid was redissolved in 20−30% MeOH/CH_2Cl_2 and treated with $NaBH_4$. After 10 minutes the reaction was quenched with glacial acetic acid and then washed three times with water. Preparative TLC was performed using 10% MeOH/CH_2Cl_2. Two major fractions were isolated from the plate. The more mobile band yielded a mixture of mono epoxide/mono alcohols **23a** and **23b**, 21 mg, 18%: mp 203−205 °C; ^{1}H NMR ($CDCl_3$): δ −3.74 (s, 2H), 1.61 (m, 3H), 2.95 (t, 2H), 3.30 (t, 4H), 3.66 (overlaping s, 18H), 3.77 (m, 1H), 4.24 (m, 2H), 4.32 (m, 2H), 4.43 (m, 4H), 4.77 (m, 1H), 10.11−10.13 (each s, 4H); ^{13}C NMR ($CDCl_3$): δ 11.62, 11.82, 21.74, 23.34, 29.33, 36.22, 36.89, 47.56, 51.74, 53.05, 69.78, 96.14, 96.27, 96.79, 135−145, 173.55; UV λ_{max} (ϵ) 398 (149 000), 498 (14 600), 532 (10 100), 568 (6 100), 622 (5 300); HRMS (EI): obsd mass 652.3287, calcd mass for $C_{38}H_{44}N_4O_6$: 652.3261; fragment obsd mass 607.2922, fragment calcd mass for $C_{36}H_{39}N_4O_5$: 607.2920.

Obtained from the less mobile band the diol **23c**, 76 mg, 64%: mp 205−208 °C; ^{1}H NMR ($CDCl_3$): δ −3.80 (s, 2H), 1.58 (s, 6H), 3.27 (t, 4H), 3.61−3.66 (overlaping s, 18H), 4.16 (m, 4H), 4.38 (m, 4H), 4.73 (m, 2H), 10.04−10.07 (each s, 4H); ^{13}C NMR ($CDCl_3$): δ 11.22, 11.53, 21.50, 22.73, 36.03, 36.67, 51.74, 51.53, 69.46, 95.91, 96.49, 96.79, 96.92, 135−145, 173.72; UV λ_{max} (ϵ) 398 (182 000), 498 (19 100), 532 (13 500), 568 (8 700), 622 (7 000); HRMS (EI): obsd mass 654.3433, calcd mass for $C_{38}H_{46}N_4O_6$: 654.3417; fragment obsd mass 609.3037, fragment calcd mass for $C_{36}H_{41}N_4O_5$: 609.3077.

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Supporting Information Available: Copies of ^{13}C and APT NMR spectra of **23a/b** and **23c** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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