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REGIOSELECTIVE SYNTHESES OF ETHER-LINKED PORPHYRIN DIMERS AND TRIMERS RELATED TO PHOTOFRIN-II®

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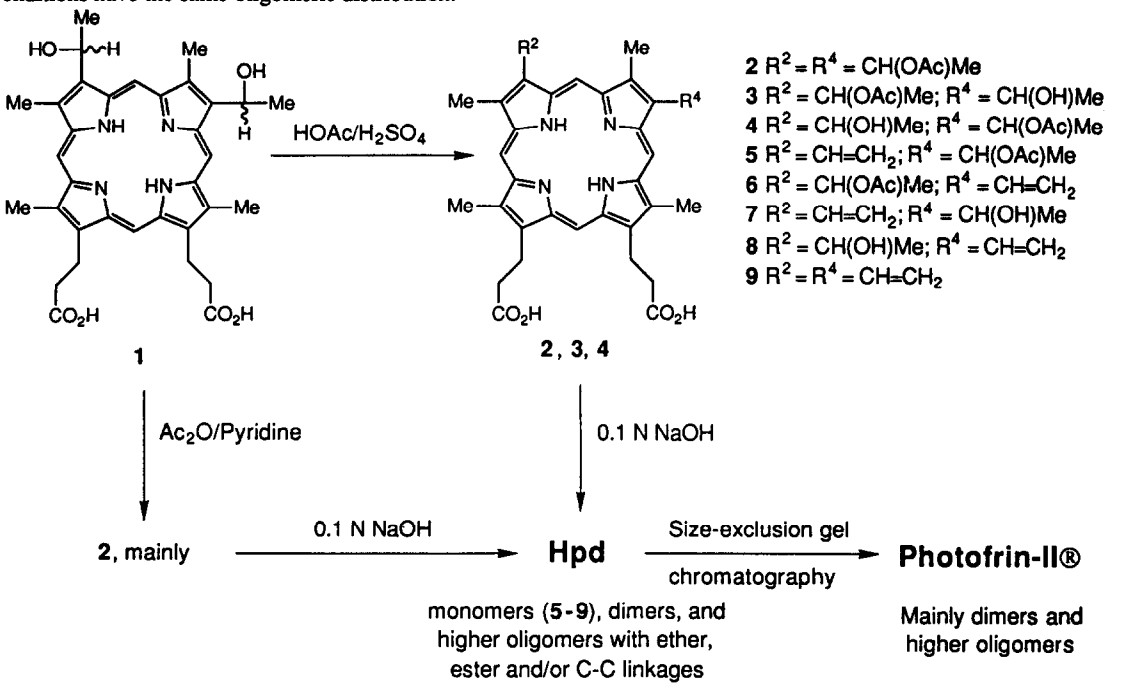
Abstract Using isomerically pure 4-(1-hydroxyethyl)deuteroporphyrin-IX dimethyl ester **10**, 2-(1-hydroxyethyl)deuteroporphyrin-IX dimethyl ester **11**, 2-acetyl-4-(1-hydroxyethyl)deuteroporphyrin-IX dimethyl ester **12** and 4-acetyl-2-(1-hydroxyethyl)deuteroporphyrin-IX dimethyl ester **13** as starting materials, a series of regiochemically pure ether-linked porphyrin dimers **25-41** and trimers **42-47** related to an anticancer drug known as Photofrin-II® were synthesized. Proton NMR nuclear Overhauser enhancement experiments and variable temperature proton NMR spectroscopy were used to characterize the isomers. Some of these compounds were tested for their in vivo photosensitizing ability vis-a-vis Photofrin-II® and the preliminary results are briefly described.

One of the most promising new modalities being explored for use in the control and treatment of tumors is "Photodynamic Therapy" (PDT).[1] This treatment is based on the interaction of a photosensitizer retained in malignant tissue with photons of visible light, resulting in the formation of singlet oxygen, the putative lethal agent.[2] At present, Photofrin-II®, a purified form of hematoporphyrin derivative is the only drug which is being evaluated in Phase-III clinical trials in the United States, specifically for treatment of obstructive endobronchial tumors and superficial bladder tumors.

The commercial method for preparation of Photofrin-II® is depicted in Scheme 1.[3] In brief, hematoporphyrin-IX **1** is first treated with a sulfuric acid/acetic acid mixture to produce mainly hematoporphyrin-IX diacetate **2** and the corresponding mono-acetates **3** and **4**. Treatment of this mixture with aqueous sodium hydroxide (0.1M) causes hydrolysis and elimination to produce compounds **5-9**. Porphyrins **2-9** subsequently couple to provide a gross mixture termed "hematoporphyrin derivative" (Hpd). Hpd contains monomers such as hematoporphyrin-IX **1**, 2- and 4- (1-hydroxyethyl) deuteroporphyrin-IX **7,8** and protoporphyrin-IX **9**, as well as higher oligomers. The aqueous solution thus obtained is separated by size exclusion gel chromatography into two fractions. The higher molecular weight fraction contains the material which is active in vivo (the so-called "Photofrin-II®")[4] and the lower molecular weight fraction contains mainly the monomers, which are either biologically inactive or else promote adverse reactions in the skin.[5] Kessel and co-workers have reported an alternate procedure for Hpd preparation via pure hematoporphyrin diacetate **2** by reacting hematoporphyrin-IX **1** with acetic anhydride/pyridine and then treating the product with dilute aqueous sodium hydroxide,[6] which ultimately resulted in the same complex mixture. As can be seen from the HPLC chromatogram (Figure 1), Photofrin-II® is a complex mixture in all respects. The peaks with retention times 5.0, 15.0, 16.5 and 25.0 min have been characterized as belonging to porphyrin **1**, **7**, **8**, and **9**. The oligomeric fraction with retention times between 19 and 30 min is a complex mixture and it is now accepted that this fraction contains dimers linked with ether,[7-9] ester,[10-12] and/or carbon-carbon linkages.[13,14] The recent data obtained from fast atom bombardment (FAB) mass spectroscopy indicate that the oligomeric components of Photofrin-II®

contain up to nine porphyrin units and the commericial batches of Photofrin-II® prepared under the same controlled conditions have the same oligomeric distribution.[15]



Scheme 1: Commercial Preparation of Photofrin-II®.[3]

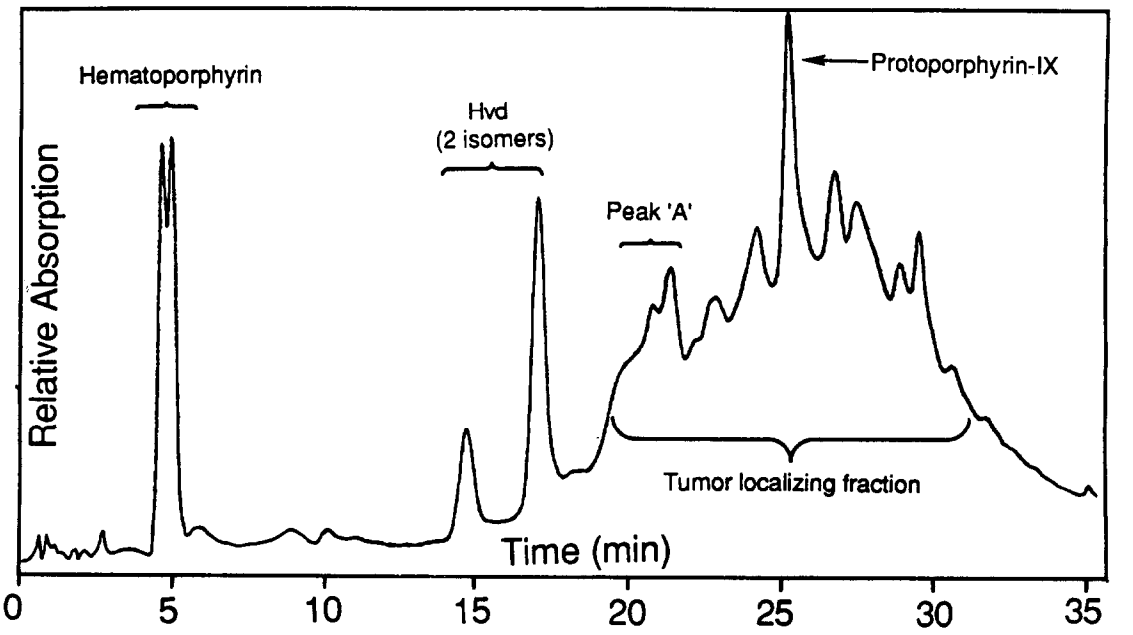
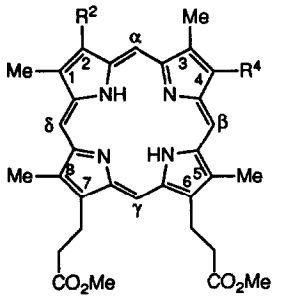


Figure 1: HPLC trace from Photofrin-II® mixture.[17]



10 R^2 = H; R^4 = CH(OH)Me
11 R^2 = CH(OH)Me; R^4 = H
12 R^2 = COMe; R^4 = CH(OH)Me
13 R^2 = CH(OH)Me; R^4 = COMe
14 R^2 = COMe; R^4 = $CH=CH_2$
15 R^2 = $CH=CH_2$; R^4 = COMe
16 R^2 = R^4 = COMe
17 R^2 = CH(OH)Me; R^4 = $CH=CH_2$
18 R^2 = $CH=CH_2$; R^4 = CH(OH)Me
19 R^2 = COMe; R^4 = CH(Br)Me
20 R^2 = CH(Br)Me; R^4 = COMe
21 R^2 = R^4 = CH(Br)Me
22 R^2 = $CH(OCH_2OCH_2CH_2SiMe_3)Me$; R^4 = COMe
23 R^2 = COMe; R^4 = $CH(OCH_2OCH_2CH_2SiMe_3)Me$
24 R^2 = $CH(OCH_2OCH_2CH_2SiMe_3)Me$ R^4 = CH(OH)Me

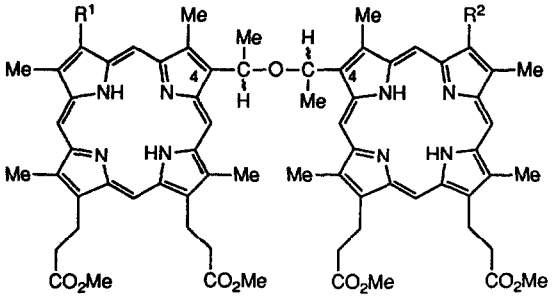
The chemical nature of the tumor localizing fraction of Photofrin-II® has been a subject of discussion for quite some time. Various research groups have made attempts to separate individual components of the oligomeric material in Photofrin-II® by using chromatography, including reversed-phase HPLC, but without much success.[16] We recently reported results on a chromatographically well-separated fraction of the tumor localizing component (Figure 1, peak A),[17] obtained by using a combination of gel filtration chromatography and semi-preparative high performance liquid chromatography. On the basis of mass spectrometric analysis and behavior of the fraction towards base hydrolysis and lithium aluminum hydride reduction, it was deemed to contain ether-linked porphyrin dimers along with a small amount of hematoporphyrin trimer and various dehydration (vinyl) products. The HPLC results suggest that in the oligomeric mixture of Photofrin-II® the retention times of most of the dimers and trimers are very close and they are virtually impossible to separate. Thus, due to the complex nature of Photofrin-II® and the difficulty in separating the individual components, efforts have been made by various groups to synthesize the possible components of this tumor localizing fraction.

Our own work to elucidate the structure of Photofrin-II® started a few years ago; we have previously reported the syntheses of dimers and trimers with ester, ether, and carbon-carbon linkages. Dimers with ester linkages were biologically inactive, while dimers and trimers with ether linkages forged between the 2- and 4- positions of hematoporphyrin-IX showed significant anti-cancer activity. In our initial synthetic studies, we started with a mixture of 2-acetyl-4-(1-hydroxyethyl)- and 4-acetyl-2-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12** and **13**, respectively, which in turn were prepared as a mixture by partial reduction of 2,4-diacetyldeuteroporphyrin-IX dimethyl ester **16**. This resulted in isolation of mixtures of regio- and stereo-isomeric products.[8] Ward et al. have also reported the synthesis of similar mixtures.[18]

In our studies with dimers linked by carbon-carbon linkages,[19] we observed that the dimer prepared from 4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **10** was extremely active as an anticancer agent, while the dimer obtained from 2-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **11** showed little photosensitizing ability. These results prompted us to synthesize regiochemically pure dimers and trimers linked with ether linkages. We anticipate that the biological studies with pure photosensitizers will enable us to know more about structure/activity relationships among the numerous different components of Photofrin-II®.

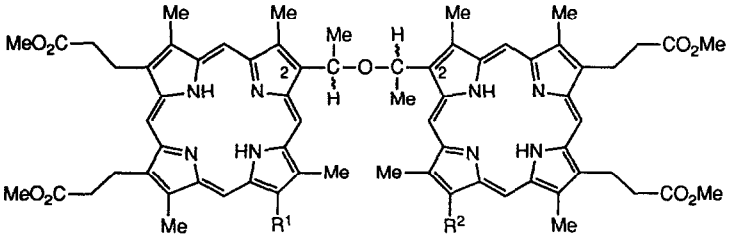
Synthesis of regiochemically pure dimers and trimers requires the ready availability of large quantities of isomerically pure mono-acetyl-mono-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester isomers **12** and **13**. We recently reported[20] an efficient synthesis and characterization of these isomers in a single step from hematoporphyrin-IX dimethyl ester by using tetrapropyl ammoniumperruthenate (TPAP) and 4-methylmorpholine-N-oxide. In our preliminary communication we briefly reported the utility of porphyrins **12** and **13** for the synthesis of porphyrin dimers and trimers. Here, we wish to present the detailed synthesis of porphyrin dimers **25-40** and trimers **41-46**

with various substituents at the peripheral positions, and their characterization by proton NMR, nuclear Overhauser enhancement (NOE) experiments, fast atom bombardment mass spectrometry (FAB), high resolution mass spectrometry (HRMS), and by classical chemical degradation approaches.



25 $R^1 = R^2 = H$
26 $R^1 = R^2 = COMe$
27 $R^1 = R^2 = CH(OH)Me$
28 $R^1 = COMe$; $R^2 = CH{=}CH_2$
29 $R^1 = CH(OH)Me$; $R^2 = CH{=}CH_2$
30 $R^1 = R^2 = CH(OCH_2OCH_2CH_2SiMe_3)Me$

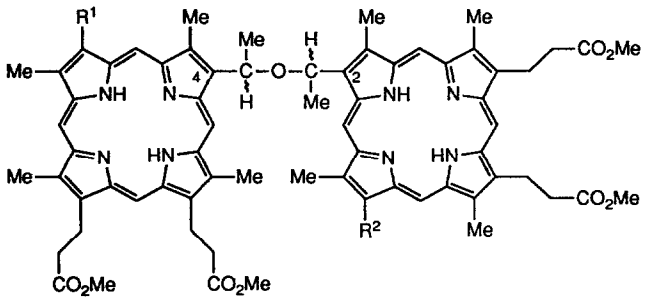
In our initial attempt to simplify and to assess the biological necessity of having two 1-hydroxyethyl substituents at positions 2- and 4- of hematoporphyrin-IX **1**, porphyrin dimers **25** and **31** were prepared starting from 2-(1-hydroxyethyl)- (**11**) and 4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **10**. In brief, for the synthesis of dimer **25**, 4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **10** was converted into the 4-(1-bromoethyl) derivative upon reacting it with either with HBr/acetic acid or HBr gas in dichloromethane. The bromo compound thus obtained was condensed with the porphyrin **10**, and the desired dimer was obtained in good yield. Dimer **31** was obtained in 58% yield from porphyrin **11** following the same approach.



31 $R^1 = R^2 = H$
32 $R^1 = R^2 = COMe$
33 $R^1 = R^2 = CH(OH)Me$
34 $R^1 = COMe$; $R^2 = CH{=}CH_2$
35 $R^1 = CH(OH)Me$; $R^2 = CH{=}CH_2$

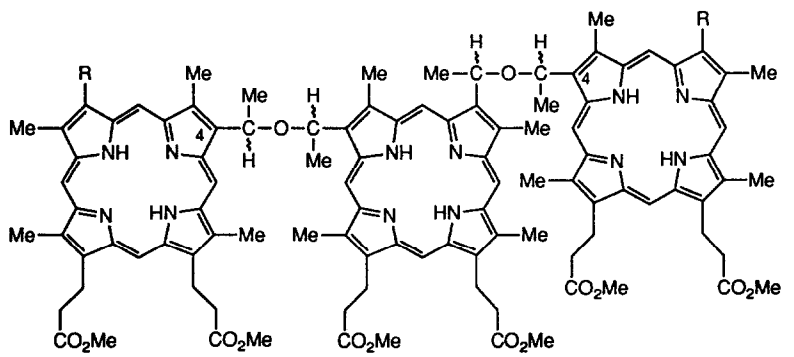
For the synthesis of ether-linked dimers and trimers related to Hpd, and to avoid the prospect of linear polymerization, it was necessary to protect one of the (1-hydroxyethyl) groups so that it can survive the reaction conditions, but can subsequently be deprotected under mild conditions without cleaving the ether linkage joining the porphyrin units. 2-(Trimethylsilyl)-ethoxymethyl chloride has frequently been used for protecting hydroxyl groups, and it can later be cleaved with tetra-n-butylammonium fluoride trihydrate under very mild conditions.[21] We used this strategy and dimer **30** was obtained in 32% yield starting from porphyrin **24**. However, problems were encountered in cleavage of the silyl groups with fluoride ion at room temperature, and at higher temperature the desired product was obtained in poor yield along with a large number of decomposition products. In another approach, porphyrin **12** was treated with methanesulfonyl chloride (at -70°C). The resulting mesylate was treated with lithium bromide and the (1-bromoethyl)porphyrin **19** was immediately condensed with porphyrin **12** and the diacetyl dimer **26** was obtained in 25% yield. Reduction of the acetyl groups in **26** with sodium borohydride afforded the hematoporphyrin dimer **27** in excellent yield. The acetyl dimer **26** was also prepared by converting 2-acetyl-4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12** into the corresponding (1-bromoethyl) analogue by reaction with HBr gas in dichloromethane. The solvent was evaporated under high vacuum

and the (1-bromoethyl) compound was immediately condensed with porphyrin **12** to give the desired dimer **26** in 50% yield. Thus, by using the appropriate starting porphyrins, a series of dimers **25-41** was synthesized. For the preparation of porphyrin trimer **42**, hematoporphyrin-IX dimethyl ester was first converted into its (1-bromoethyl) analogue with HBr gas, and then condensed with two equiv of 2-acetyl-4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12**. The acetyl groups were then reduced with sodium borohydride and the hematoporphyrin trimer **43** was obtained in 75% yield. By following similar chemistry and using the appropriate starting porphyrins, a series of trimers **44-47** was synthesized in 30 to 35% yields.



36 $R^1 = R^2 = COMe$
37 $R^1 = R^2 = CH(OH)Me$
38 $R^1 = COMe$; $R^2 = CH{=}CH_2$
39 $R^1 = CH(OH)Me$; $R^2 = CH{=}CH_2$
40 $R^1 = CH{=}CH_2$; $R^2 = COMe$
41 $R^1 = CH{=}CH_2$; $R^2 = CH(OH)Me$

Diacetyl dimers **26**, **32** and **36**, as individual regioisomers, were prepared as a mixture of three stereoisomers (*d*, *l* and *meso*) and dimers containing one acetyl and one vinyl group (**28**, **34**, **38**, **40**) are individually a mixture of four possible stereoisomers. Proton NMR assignments of the resonances for various groups in diacetyl- and monoacetyl-monovinyl-dimers were easier to make than for the corresponding (1-hydroxyethyl)-derivatives due to addition of two more (in case of dimers **27**, **33** and **37**) or one more (**29**, **35**, **39**, **41**) chiral centers. As shown in Figure 2, in the NMR spectrum of the symmetrical diacetyl dimer **26**, eight meso protons were observed at 9.08, 9.58, 9.92 and 10.38 ppm, each integrating for two protons. The broad peak observed at 9.58 ppm was assigned to two meso (β,β') protons adjacent to the ether bridge [$CH(CH_3)$-O-$CH(CH_3)$]; this was further confirmed by NOE studies in which irradiation of the ether bridge CH_3 protons (d at δ 2.58) resulted in a NOE to the meso protons at β and β'. The C<u>H</u>(CH_3)-O-C<u>H</u>(CH_3) protons were observed as a single quartet at 6.61 ppm.



42 R = COMe
43 R = CH(OH)Me
44 R = $CH{=}CH_2$

Unlike dimers **26** and **32**, the unsymmetrical dimer **36** featured eight meso protons in the range 10.38 to 9.10 ppm. Six of these meso protons were observed as sharp singlets and two as broad peaks. Like the symmetrical diacetyl dimers **26** and **32**, the broad peaks in dimer **36** were assigned to the β,α' meso protons. The $CH(CH_3)$-O-$CH(CH_3)$ were observed as separate quartets at 6.65 and 6.60

ppm, each integrating for one proton. In the diacetyl trimer **42**, sixteen stereoisomers are theoretically possible; twelve meso protons were observed in the range 10.60 to 9.38 ppm (Figure 2). The $CH(CH_3)$-O-$CH(CH_3)$ protons were observed as a multiplet from 6.80 to 5.92 ppm. All four possible regioisomers of mono-acetyl-mono-vinyl dimers **28, 34, 38, 40** were prepared by following an approach similar to described previously for the diacetyl dimer. The NMR spectra of dimers **28** and **40** were similar, but were different from dimers **34** and **38**. The NMR spectrum of dimer **28** shows eight meso protons (six sharp singlets and two broad peaks) in the meso region; the α-vinyl proton was observed as a multiplet at 8.00 ppm and the β-vinyl protons were observed as two doublets at 6.14 and 6.35 ppm, each integrating for one proton. Two CH protons of the bridging $CH(CH_3)$-O-$CH(CH_3)$ moiety were assigned as a multiplet at 6.62 ppm. The meso and vinyl resonances for dimers **34** and **38** display a different pattern, and we did not assign the resonances observed at 5.26 and 5.51 ppm (both are doublets); this work is in progress and will be reported later.

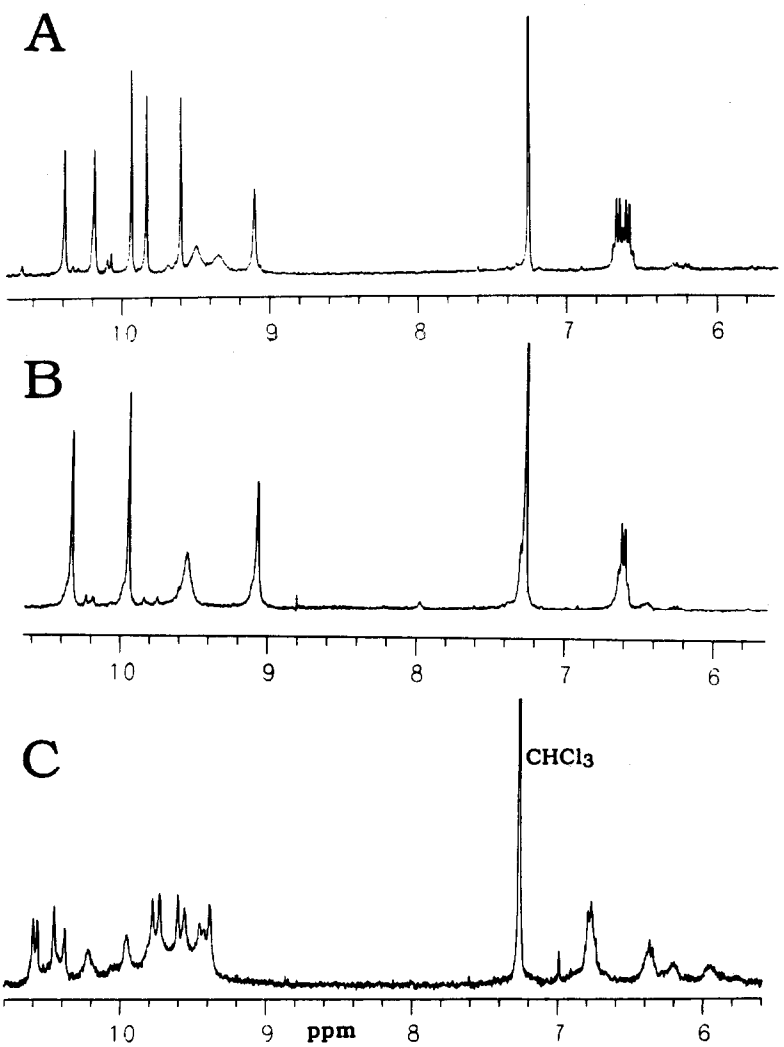
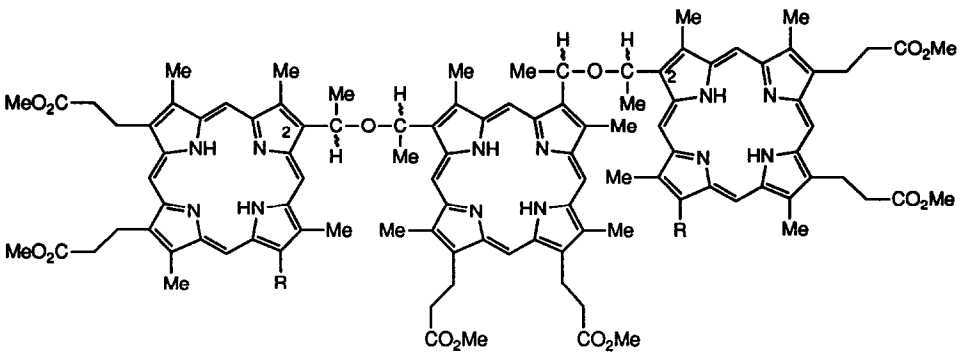
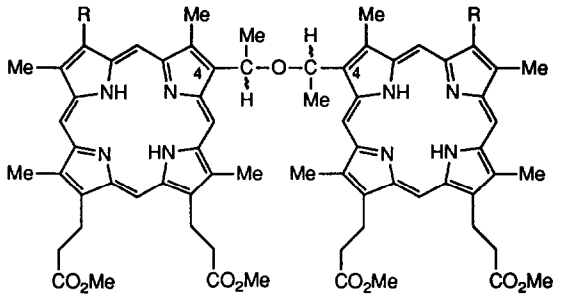


Figure 2: Proton NMR spectra (low field region only, at 300 MHz) in $CDCl_3$ of A, dimer **36**; B, dimer **26**; C, trimer, **42**

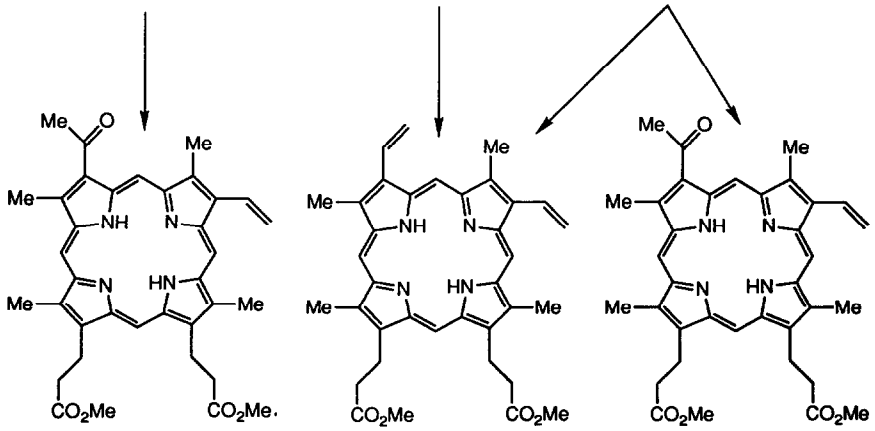


45 R = COMe
46 R = CH(OH)Me
47 R = CH=CH$_2$

Classical chemical degradation approaches were also used to confirm the structures of all dimers and trimers. For example, treating dimers **25**, **26** or **27** with aqueous sulfuric acid produced the related monomers such as protoporphyrin-IX **9** and the corresponding mono-acetyl-monovinyl-porphyrin **14**, due to cleavage of the ether linkage and subsequent dehydration of the (1-hydroxyethyl) analogue. Diacetyl trimers **42** and **45** produced the corresponding monomers which were characterized by proton NMR spectroscopy. Hematoporphyrin trimers **43** and



25 R^1 = R^2 = COMe **26** R^1 = R^2 = CH(OH)Me **27** R^1 = COMe; R^2 = CH=CH$_2$



14 **9** (dimethyl ester) **14**

46 and divinyl trimers **44** and **47**, upon similar treatment (after diazomethane treatment) produced protoporphyrin-IX dimethyl ester as the sole product. Acid treatment of these dimers afforded protoporphyrin-IX **9** as the sole product. The structures of all these dimers and trimers were also confirmed by use of FAB mass spectrometry and HRMS.

In recent years there has been much discussion about the stability of Photofrin-II® components. In our hands, porphyrin dimers with ester linkages were found to be unstable and were readily cleaved by leaving a solution at room temperature even for a short time. In our preliminary communication we showed, by variable temperature NMR spectroscopy, that ether linked dimers and trimers are stable at high temperature, but were cleaved easily even under slightly acidic conditions (pH, 6.2). From this study it is quite possible that the ether linked oligomer of Photofrin-II® might be cleaving in the tumor (at pH 6.4) at body temperature (37°C). Further model work as well as in vivo NMR studies with these components are in progress.

All the synthetic dimers and trimers are being tested for in vivo photosensitizing activity, vis-a-vis Photofrin-II®. The tumor system (subcutaneously implanted SMT-f tumors in DBA/2 mice) and the biological testing procedure were followed as described by Dougherty et al.[22] Normal tissue response was tested by exposing the mouse foot to light in a manner identical with the tumor response test. These photosensitizers were tested, either as methyl esters or as the corresponding carboxylic , and identical results were obtained in either case. In brief, hematoporphyrin dimers with ether linkages (**27**, **33**, and **37**) were found to be less active than Photofrin-II®. Replacement of one of the (1-hydroxyethyl) groups with a vinyl group (as in dimer **29**) was found to introduce moderate activity. When both heat (43-44°C) and light were used, dimer **29** was found to be extremely active, even at doses lower than used with Photofrin-II®. Under similar conditions, hematoporphyrin dimers **27**, **33**, and **37** did not show any significant increase in their photosensitizing activity. Dimers **25** and **31**, in which the (1-hydroxyethyl) groups have been replaced by a hydrogen, were found to be almost as active as Photofrin-II®. Amongst the trimers, so far only hematoporphyrin trimer **43** and divinyl trimer **44** have been tested. Preliminary results show that divinyl trimer **44** is more active than trimer **43**, which is much more active than the hematoporphyrin dimers **27**, **33**, and **37**.

Our preliminary data indicate that hydrophilicity/hydrophobicity are one of the factors which play an important role in localization of photosensitizers in tumors. For example in hematoporphyrin dimers **27**, **33**, and **37**, two (1-hydroxyethyl) groups make them more hydrophilic than the mono-(1-hydroxyethyl)-mono-vinylporphyrin dimer **29**, and **29** was found to have poor photosensitizing ability. Presumably due to the hydrophobic nature of dimers **25** and **31**, these dimers were found to be almost as active as Photofrin-II®. Similar tumorcidal results were obtained in the trimer series. Moan and coworkers have also reported similar results in simple ether derivatives (with variable carbon length chains) of hematoporphyrin dicarboxylic acids.[23] Our own studies with different ether derivatives of chlorins and methyl pheophorbides have also shown that hydrophilicity/hydrophobicity characteristics play an important role for a photosensitizer to show a significant photosensitizing efficacy.[24] Detailed biological studies with photosensitizers discussed herein are in progress and will be reported later.

Experimental

Melting points were measured on a Thomas/Bristoline microscopic hot stage apparatus and were uncorrected. Silica gel 60 (70-230 and 230-400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, i.e. deactivated with 6% water) were used for column chromatography. Preparative 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 was performed using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by thin layer chromatography and spectrophotometry and were carried out under nitrogen and in the dark. Proton and carbon-13 NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.258 ppm). FAB mass spectra were

recorded independently at SUNY Buffalo or at Lederle Laboratories, Pearl River, New York. At Buffalo, mass spectra were obtained with an Ion-Tech fast atom gun using xenon gas on a Kratos MS80RFA instrument equipped with a Kratos DS90 data system. Compounds were dissolved in dichloromethane and 3-nitrobenzyl alcohol mixture, which served as the FAB matrix, and the solution was deposited on a stainless steel FAB probe tip. When a copper probe tip was used, protonated as well as copper-containing molecular ion species were produced. The instrument was typically operated at 1000 resolution and calibrated with sodium and cesium iodide depending on the mass range required. The samples studied at Lederle Laboratories were run on a VG ZAB-SE high performance mass spectrometer, equipped with VG11-250 data system. The instrument was calibrated with cesium iodide and scanned from m/z 350 to 2500 for low- mass samples, and from m/z 2000 to 4500 for high-mass samples. The matrix used was a 50:50:0.5 (v/v/v) thioglycerol/glycerol/TFA FAB matrix, and this was stable for the duration of the FAB experiments. Elemental analyses were obtained from Galbraith Laboratories, Knoxville,TN, USA. Electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer.

2-(1-Hydroxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphyrin (11). 2-Acetyldeuteroporphyrin-IX dimethyl ester (150 mg) was dissolved in dichloromethane (100 ml). Sodium borohydride (380 mg) in methanol was added and the reaction mixture was stirred at room temperature for 30 min; glacial acetic acid (2 ml) was added to decompose the excess of sodium borohydride and the reaction mixture was poured into water, extracted with dichloromethane, washed with aqueous sodium bicarbonate and again with water, and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column eluted with 2% methanol in dichloromethane. The appropriate eluates were collected and evaporation of the solvent, followed by crystallization from dichloromethane/hexane gave the title compound in 90% yield (135 mg). UV-Vis λmax, 400 nm (ε 169,100), 498 (13,500), 531 (8,170), 566 (6,100), 620 (3,800). NMR (ppm): 10.20, 10.00, 9.98, 9.96 (s, 1H, 4 meso-H), 9.02 (s, 1H, β-H), 6.25 [q, 1H, C<u>H</u>(OH)CH_3], 4.40 (m, 4H, 2C<u>H_2</u>CH_2CO_2), 3.72 (s, 6H, 2 OCH_3), 3.70, 3.68, 3.64, 3.60 (s, 3H, 4 CH_3), 3.26 (t, 4H, CH_2C<u>H_2</u>CO_2), 2.10 [d, 3H, CH(OH)C<u>H</u>$_3$], -4.0 (s, 2H, 2NH). Analysis Calcd for $C_{34}H_{38}N_4O_5$: C, 70.09; H, 6.49; N, 9.43. Found: C, 69.91; H, 6.45; N, 9.39.

4-(1-Hydroxyethyl)-6,7-bis(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphyrin (10). 4-Acetyl-deuteroporphyrin-IX dimethyl ester (150 mg) was treated with sodium borohydride (380 mg) by following the procedure as described for the foregoing porphyrin and was isolated in 85% yield (128 mg), m.p. 216-218°C. UV-Vis λmax, 400 nm (ε 173,400), 498 (14,000), 531 (8,500), 566 (6,300), 620 (3,900). NMR (ppm): 10.25, 10.00, 9.98, 9.90 (s, 1H, 4 meso-H), 9.05 (s, 1H, β-H), 6.25 [q, 1H, C<u>H</u>(OH)CH_3], 4.40 (m, 4H, C<u>H_2</u>CH_2CO_2), 3.75 (s, 6H, 2, OCH_3), 3.70, 3.52, 3.50, 3.45 (s, 3H, 4 CH_3), 3.30 (t, 4H, CH_2C<u>H_2</u>CO_2), 2.10 [d, 3H, CH(OH)C<u>H</u>$_3$], -4.0 (s, 2H, 2 NH). Analysis Calcd for $C_{34}H_{38}N_4O_5$: C, 70.09; H, 6.49; N, 9.43. Found: C, 69.97; H, 6.54; N, 9.49.

Porphyrin Dimer (31). 2-(1-Hydroxyethyl)-6,7-bis-(2 methoxycarbonylethyl)-1,3,5,8-tetramethylporphyrin **11** (25 mg) was stirred with 30 % HBr/acetic acid in a stoppered flask for 2 h at room temperature. The solvent was evaporated under high vacuum (1 mm Hg). The resulting (1-bromoethyl) derivative was not isolated and was immediately treated with porphyrin **11** (25 mg) dissolved in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 10 min under a nitrogen atmosphere, diluted with dichloromethane, and then poured into cold water (200 ml). The dichloromethane layer was washed with water (4x100 ml), dilute aqueous sodium bicarbonate solution, and then with water again. The organic layer was dried over anhydrous sodium sulfate and evaporation of the solvent gave a residue which was purified on preparative silica gel thick layer plates (developed with 5% methanol in dichloromethane). Three main bands were isolated. The most labile band was identified as 2-vinyl deuteroporphyrin-IX dimethyl ester (m.p. 211-212°C), most likely formed due to dehydration of the starting porphyrin. The least polar band was identified as the starting porphyrin **11**. The central band was characterized as the desired dimer **31**. The product was isolated by washing the appropriate silica gel band with 5% methanol in dichloromethane, which was then washed with water before drying over anhydrous sodium sulfate. Evaporation of the solvent and crystallization with dichloromethane/hexane gave the title dimer in 58% yield (28.5 mg). The yield was >75% if calculated on the basis of the consumed starting porphyrin. M.p. 108-112°C. UV-Vis λmax: 398 nm (ε 218,600), 497 (24,350), 529 (13,750), 568 (10,520) and 622 (7,100). NMR: (ppm), 10.40, 10.05 (s, 1H, 2 meso-H); 9.98, 9.65, 9.60 (s, 2H, 6 meso-H); 8.40 (s, 2H, β-pyrrolic H), 6.70 [m, 2H, 2 C<u>H</u>(CH_3)-O-]; 4.45 (m, 8H, 4 C<u>H_2</u>CH_2CO_2); 3.70, 3.68 (s, 6H, 4-OCH_3); 3.60 (s, 6H, CH_3); 3.39 (s, 6H, 2 CH_3); 3.30 (m, 8H, CH_2C<u>H_2</u>CO_2); 2.53 (s, 6H, 2 CH_3); 2.51 [d, 6H, 2 CH(OH)C<u>H</u>$_3$]; -4.35 (s, 4H, 4 NH). HRMS Calcd for $C_{68}H_{74}N_8O_9$; 1147. 5660 (M+1). Found: 1147.5682.

Porphyrin Dimer (25). 4-(1-Hydroxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphyrin **10** (25 mg) was converted into the corresponding (1-bromoethyl) derivative and then condensed with porphyrin **10** following the method described for the foregoing porphyrin. The title compound was isolated in 48% yield. M.p. 100-102°C. UV-Vis λmax: 400 nm (ε 190,000), 498 (20,500), 528 (13,000), 565 (10,000) and 622 (6,500). NMR (ppm): 10.10, 9.75 (s, 3H, 6-meso H); 9.52 (s, 2H, 2 meso-H); 8.98 (s, 2H, β-pyrrolic H); 6.70 [q, 2H, 2 C<u>H</u>(CH_3)-O-]; 4.40 (m, 8H, C<u>H_2</u>CH_2CO_2); 3.80, 3.40 (s, 3H, 2 CH_3); 3.72, 3.45 (s, 9H, 3 CH_3); 3.70 (s, 12H, 4-

OCH_3); 3.32 (m, 8H, $CH_2C\underline{H}_2CO_2$); 2.50 [d, 6H, 2 CH(OH)C$\underline{H}_3$]; -4.40 (s, 4H, 4 NH). HRMS Calcd for $C_{68}H_{74}N_8O_9$; 1147.5660 (M+1). Found: 1147.5678.

Diacetylporphyrin Dimer (26).
Method 1: 2-Acetyl-4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12** (25 mg) was dissolved in dry dichloromethane (10 ml). The reaction mixture was stirred at -70°C under a nitrogen atmosphere. Freshly distilled methane sulfonyl chloride (100 µl) was added and the mixture was stirred for 2 h. Lithium bromide (20 mg) dissolved in dry THF (5 ml) was added to the reaction mixture and it was stirred for a further 1 h. Porphyrin **12** (25 mg) dissolved in dry dichloromethane (15 ml) was added to the reaction mixture, which was stirred at room temperature for an additional 15 min. It was then diluted with dichloromethane (100 ml), washed with water, aqueous sodium bicarbonate, and again with water. Evaporation of the solvent gave a residue which was found to be a mixture of three components by analytical TLC. The most labile fraction was identified as 2-acetyl-4-vinyl-deuteroporphyrin-IX dimethyl ester. The second fraction was identified as the diacetyl dimer **26** and the most polar band was found to be the starting material **12**. The diacetyl dimer was crystallized from dichloromethane/hexane and was obtained in 25% yield (13 mg) yield. M.p. 222-224°C. UV-Vis λmax: 406 nm (ε 184,900), 510 (14,700), 548 (14,100), 578 (10,600), 636 (3,100). NMR (ppm): 10.38, 9.92, 9.08 (s, 2H, 6 meso-H), 9.58 (bs, 2H, 2 meso-H), 6.60 [q, 2H, 2C$\underline{H}$(CH_3)-O-], 4.32 (m, 8H, 4 $C\underline{H}_2CH_2CO_2$), 3.90, 3.75, 3.72, 3.60, 3.58, 3.50 (s, 36 H, 8 ring CH_3 and 4 OCH_3), 3.20 (s, 6H, 2 $COCH_3$), 3.18 (m, 8H, 4 $CH_2C\underline{H}_2CO_2$), 2.58 [d, 6H, 2 CH(C$\underline{H}_3$)-O-], -4.92 (s, 4H, 4 NH). HRMS Calcd for $C_{72}H_{78}N_8O_{11}$, 1231.5868 (M+1). Found: 1231.5854.
Method 2: Porphyrin **12** (12 mg) was dissolved in dry dichloromethane (10 ml) and HBr gas was slowly bubbled through the solution for 5 min; the reaction mixture was then stirred for **15** min. The solvent was evaporated under high vacuum at 30°C. The residue was redissolved in dichloromethane (10 ml) and porphyrin **12** (12 mg) dissolved in dichloromethane (10 ml) was added and the reaction mixture was stirred at room temperature for 10 min. The mixture was diluted with dichloromethane (100 ml), washed with water, aqueous sodium bicarbonate and again with water. Evaporation of the solvent gave a residue and the title compound was purified by preparative TLC as described above, and was obtained in 50% yield (12 mg). The dimer was identical in every respect with the diacetyl dimer **12** obtained by Method 1. Method 2 was more convenient than the mesylate method, so all other dimers and trimers were prepared by following this approach.

Diacetylporphyrin Dimer (32). The (1-bromoethyl) derivative **20** prepared from corresponding (1-hydroxyethyl) analogue **13** (25 mg), was condensed with the starting porphyrin **13** (25 mg), and dimer **32** was obtained in 48 % yield (24 mg). M.p.146-147°C. UV-Vis λmax: 406 nm (ε 218,000), 512 (18,700), 548 (17,000), 636 (3,350). NMR (ppm): 10.28, 9.92, 9.64 (s, 2H, 6 meso-H), 9.50 (bs, 2H, 2 meso-H), 6.65 [q, 2H, 2 C$\underline{H}$(CH_3)-O-], 4.48, 4.31 (t, 4H, $C\underline{H}_2CH_2CO_2$), 3.75, 3.67, 3.50 (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.30 (s, 6H, 2 $COCH_3$), 3.25 (m, 4H, $CH_2C\underline{H}_2CO_2$), 2.55 [d, 6H, CH(C$\underline{H}_3$)-O-], -4.07 (s, 4H, 4NH). HRMS Calcd for $C_{72}H_{78}N_8O_{11}$; 1231.5868 (M+1). Found: 1231.5858.

Diacetylporphyrin Dimer (36). This dimer was prepared by condensing 2-acetyl-4-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **19**, obtained from 4-(1-hydroxyethyl) analogue **12** (20 mg) with 2-(1-hydroxyethyl)-4-acetyldeuteroporphyrin-IX dimethyl ester **13** (20 mg) and was isolated in 52% yield (26 mg). M.p. 180-182°C. UV-Vis λmax: 406 nm (ε 218,000), 510 (21,200), 548 (19,250), 580 (14,600), 636 (5,300). NMR (ppm): 10.38, 10.18, 9.90, 9.80, 9.60, 9.10 (s, 1H, 6 meso-H), 9.50, 9.35 (bs, 1H, 2 meso-H), 6.65 and 6.60 [q (merged), 2H, 2 C$\underline{H}$(CH_3)-O-), 4.50, 4.38 (t, 4H, 4 $C\underline{H}_2CH_2CO_2$), 9.82, 9.78, 9.77, 9.76, 9.73, 9.72, 9.70, 9.55, 9.52 (s, total 36H, 8 CH_3 and 4 OCH_3), 2.55, 2.45 [d, 3H, 2 CH(C$\underline{H}_3$)-O], -2.70 and -2.71 [s (merged), 2H, 4 NH]. HRMS calculated for $C_{72}H_{78}N_8O_{11}$; 1231.5868 (M+1). Found: 1231.5815.

Mono-acetyl-mono-vinylporphyrin Dimer (28). 2-Acetyl-4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12** (22 mg) was converted to (1-bromoethyl) analogue **19** and condensed with 4-(1-hydroxyethyl)-2-vinyldeuteroporphyrin-IX dimethyl ester **18**[25] (22 mg) and the title dimer was obtained in 50% yield (22 mg). M.p. 212-214°C. UV-Vis λmax: 402 nm (ε 200,900), 506 (14,400), 540 (11,000), 576 (8,700), 628 (2,200). NMR (ppm): 10.32, 9.99, 9.92, 9.58, 9.20, 9.17 (s, 1H, 6 meso-H), 9.80, 9.50 (bs, 1H, 2 meso-H), 8.00 (m, 1H, C$\underline{H}$=CH_2), 6.62 [m, 2H, 2 C$\underline{H}$(CH_3)-O-], 6.14 and 6.35 (d, 2H, CH=C$\underline{H}_2$), 4.37 (m, 8H, 4 $C\underline{H}_2CH_2CO_2$), 3.90, 3.76, 3.70, 3.67, 3.65, 3.55, 3.47, 3.37 (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.21(s, 3H, $COCH_3$), 3.20 [m (merged with acetyl protons), 8H, 4 $CH_2C\underline{H}_2CO_2$], 2.58 [m (2 d merged), 6H, 2 CH(C$\underline{H}_3$)-O-], -4.80 and -5.00 (s, 2H, 4 NH); HRMS Calcd for $C_{72}H_{78}N_8O_{10}$; 1215.5919 (M+1). Found:1215.5902.

Mono-acetyl-mono-vinylporphyrin Dimer (34). 4-Acetyl-2-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **20** obtained from **13** (15 mg) was treated with 2-(1-hydroxyethyl)-4-vinyldeuteroporphyrin-IX dimethyl ester **17** [25] (15 mg) and the title dimer **34** was obtained in 33% yield (10 mg). M.p.198-200°C. UV-Vis λmax: 402 nm (ε 208,000), 506 (15,100), 540 (11,000), 578 (9,100), 626 (4,000). NMR (ppm): 10.34, 10.24, 10.08, 9.92, 9.86, 9.85, 9.63, 9.56, 9.49 (s, total 8H, 8 meso-H), 8.29-8.19 (m, 1H, C$\underline{H}$=CH_2), 6.66 [m, 1H, C$\underline{H}$(CH_3)-O-], 6.38-

6.19 [m, 3H, CH=C$\underline{H}_2$ and C$\underline{H}$(CH_3)-O-], 4.47-4.30 (m, 8H, 4 C$\underline{H}_2CH_2CO_2$), 3.73-3.46 [multiple s, 36 H, 8 CH_3 and 4 OCH_3), 3.40-3.20 (m, 8H, $CH_2C\underline{H}_2CO_2$), 2.54, 2.49 (1d and 1s merged, 6H, $COCH_3$ and CH(C$\underline{H}_3$)-O-], 2.11 [d, 3H, CH(C$\underline{H}_3$)-O-], -4.13, -4.15, -4.21 and -4.36 (s, 1H, 4 NH). HRMS Calcd for $C_{72}H_{78}N_8O_{11}$; 1215.5916 (M+1). Found: 1215.5902.

Mono-acetyl-mono-vinylporphyrin Dimer (38). 2-Acetyl-4-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **19** prepared from **12** (15 mg) upon condensation with 2-(1-hydroxyethyl)-4-vinyldeuteroporphyrin-IX dimethyl ester **17** (15 mg) gave dimer **38** in 23 % yield (7 mg). M.p. 170-172°C. UV-Vis λmax: 402 nm (ε 255,000), 504 (22,750), 538 (17,400),626 (6,700). NMR (ppm): 10.27, 10.18, 10.05, 9.86, 9.84, 9.68, 9.50, 9.43, 9.24 (s, total 8 H, 8 meso-H), 8.24 (m, 1H, C$\underline{H}$=CH_2), 6.69 [m, 1H, C$\underline{H}$(CH_3)-O-], 6.37-6.14 [m, 3H, CH=C$\underline{H}$2 and C$\underline{H}$(CH_3)-O-], 4.38-4.29 (m, 8H, 4 C$\underline{H}_2CH_2CO_2$), 3.73-3.38 (multiple s, 36 H, 8 CH_3 and 4 OCH_3), 3.25 (m, 8H, 4 $CH_2C\underline{H}_2CO_2$), 3.18 (s, 3H, $COCH_3$), 2.58, 2.38, 2.08 (m, m, d [total 6 H, 2 CH(C$\underline{H}_3$)-O-], -4.08 (s, 2H, 2 NH), -4.65 and -4.80 (s, 1H, 2NH). HRMS Calcd for $C_{72}H_{78}N_8O_{11}$; 1215.5916 (M+1). Found: 1215.5881.

Mono-acetyl-mono-vinylporphyrin Dimer (40). 4-Acetyl-2-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **13** was converted into its (1-bromoethyl) analogue **20** and was condensed with 4-(1-hydroxyethyl)-2-vinyldeuteroporphyrin-IX dimethyl ester **18** (15 mg) and dimer **40** was obtained in 40 % yield (12 mg). M.p. 205-207°C. UV-Vis λmax: 402 nm (ε 245,000), 504 (21,100), 538 (16,200), 574 (12,800), 626 (5,800). NMR (ppm): 10.32, 10.00, 9.90, 9.72 (s 1H, 4 meso-H), 9.70,(s, 2H, 2 meso-H), 9.32 (bs, 2H, 2 meso H), 7.95 (m, 1H, C$\underline{H}$=CH_2), 6.65 [m, 2H, 2 C$\underline{H}$(CH_3)-O-], 6.10-6.22 (m,2H,CH=C$\underline{H}_2$); 4.50, 4.30 (t, 4H, 4 C$\underline{H}_2CH_2CO_2$), 3.75, 3.74, 3.72, 3.71, 3.62, 3.58, (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.26 (m, 8H, 4 $CH_2C\underline{H}_2CO_2$); 3.20 (s, 3H, $COCH_3$), 2.60, 2.40 [d, 3H, 2CH(C$\underline{H}_3$)-O-], -4.30 and -4.40 (s, 2H, 4NH). HRMS Calcd for $C_{72}H_{78}N_8O_{11}$; 1215.5919 (M+1). Found: 1215.5946.

Hematoporphyrin Dimer (27). Diacetyl dimer **26** (25 mg) was dissolved in dichloromethane (20 ml). An ice chilled solution of methanol (10 ml) containing sodium borohydride (50 mg) was added and the reaction mixture was stirred at >5°C until completion of the reaction was determined by analytical TLC and spectrophotometry (etio- to rhodo- and back to etio-type). The reaction mixture was cooled to 0°C and dilute aqueous acetic acid was added to quench any excess of sodium borohydride. The mixture was extracted with dichloromethane, washed with water (3 x 200 ml), then dried over anhydrous sodium sulfate, and the solvent was removed under high vacuum at 30°C. The residue was purified by preparative TLC on silica gel, eluting with 5% methanol in dichloromethane. The major band was collected. Evaporation of the solvent and crystallization with dichloromethane/hexane afforded the title porphyrin dimer in 80% yield (20 mg). M.p. 235-237°C. UV-Vis λmax: 394 nm (ε 200,800), 504 (20,000), 534 (12,400), 470 (11,400), 622 (5,200). NMR (ppm): 9.97, 9.95, 9.92, 9.80, 9.48, 9.38 (all s), 9.70, 9.20 [(both b) (total 8 H, 8 meso-H)], 6.65, 6.58, 6.50, 6.10, 5.50, 5.70 [bm, total 4H, 2 C$\underline{H}$(OH)CH_3 and 2 C$\underline{H}$(CH3)-O-], 4.43 (m, 8H, 4 C$\underline{H}_2CH_2CO_2$), 3.75-3.52 (10 s, 36H, 8 ring CH_3 and 4 OCH_3), 3.30, 3.10 (m, total 8H, 4 $CH_2C\underline{H}_2CO_2$), 2.58 [m, 6H, CH(C$\underline{H}_3$)-O-], 1.96 [m, 6H, CH(OH)C$\underline{H}_3$], -4.76 (s, 1H, NH), -4.83 (s, 2H, NH), -4.92 (s, 1H, NH). HRMS Calcd for $C_{72}H_{82}N_8O_{11}$; 1235.6181 (M+1). Found: 1235.6152.

The other diacetyl- and mono-acetyl-dimers were reduced to the corresponding (1-hydroxyethyl) dimers upon treatment with sodium borohydride and were obtained in excellent yield. Their spectral details (UV-Vis and NMR) and physical constants are as follows:

Hematoporphyrin Dimer (33). This dimer was obtained from diacetyl dimer **32** in 82% yield. M.p.185-187°C. UV-Vis λmax: 396 nm (ε 210,000), 504 (20,800), 534 (13,300), 570 (12,100), 622 (5,200). NMR (ppm): 10.28, 10.22, 10.10, 10.00, 9.32 (all bs), 10.22, 10.20, 10.18, 10.13 [(s) (total 8H, meso-H)], 6.60 [m, 2H, C$\underline{H}$(OH)CH_3], 6.40 [m, 2H, C$\underline{H}$(CH_3)-O-], 4.58 (m, 8H, 4 C$\underline{H}_2CH_2CO_2$), 3.80-3.52(s merged, 36 H, 8 CH_3 and 4 OCH_3), 3.50 (m, 8H, $CH_2C\underline{H}_2CO_2$), 2.50 [m, 6H, 2 CH(C$\underline{H}_3$)-O-], 2.35 (m, 6H, CH(OH)C$\underline{H}_3$), -4.02, -4.50 (s, 2H, 4 NH). HRMS Calcd for $C_{72}H_{82}N_8O_{11}$; 1235.6181 (M+1). Found: 1235.6193.

Hematoporphyrin Dimer (37). Diacetyl dimer **36** (25 mg) was reduced following similar approach and the title dimer was obtained in 80% yield. M.p. 180-182°C. UV-Vis λmax: 406 nm (ε 218,000), 510 (21,200), 548 (14,700), 626 (5,300). NMR: 10.04-8.70 (multiple s, 8H, 8 meso-H), 6.32-6.10 [m, 4H, 2 C$\underline{H}$(OH)CH_3 and 2 C$\underline{H}$(CH_3)-O-], 4.50 (m, 8H, 4 C$\underline{H}_2CH_2CO_2$), 3.80, 3.78, 3.73, 3.64, 3.62, 3.60, 3.58, 3.56, 3.42 (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.25 (m, 8H, 4 $CH_2CH_2CO_2$), 2.52 [m, 6H, CH(C$\underline{H}_3$)-O-], 0.90 [m, 6H, CH(OH)C$\underline{H}_3$], -4.70, -4.82, -4.90, -5.00 (s, 1H, 4 NH). HRMS Calcd for $C_{72}H_{82}N_8O_{11}$; 1235.6181 (M+1). Found: 1235.6155.

Mono-(1-hydroxyethyl)-mono-vinyl Dimer (29). Mono-acetyl-mono-vinyl dimer **28** (10 mg) was treated with sodium borohydride (20 mg) in methanol (10 ml) and the title dimer **29** was afforded in 80% yield. M.p.135-137°C. UV-Vis λmax: 404 nm (ε 257,000), 502 (22,550), 572 (16,800), 624 (9,300). NMR (ppm): 10.25-9.20 (multiple s, 8H, 8 meso-H), 8.36-8.22 (m, 1H, C$\underline{H}$=CH2), 6.68-5.60 [m, 4H, 2C$\underline{H}$(CH_3)-O- and CH=C$\underline{H}_2$], 4.50-4.30 (m, 8H, C$\underline{H}_2CH_2CO_2$), 3.78-3.40 (multiple s, 36 H, 8 CH_3 and 4 OCH_3), 3.22-3.25 (m, 8H,

$CH_2C\underline{H}_2CO_2$),2.60 [m, 6H, 2CH($C\underline{H}_3$)-O-], -3.88 (s, 2H, 2NH), -4.62 and -4.70 (s, 1H, 2NH). HRMS Calcd for $C_{72}H_{80}N_8O_{10}$; 1217.6075 (M+1). Found: 1217.6002.

Mono-(1-hydroxyethyl)-mono-vinyl Dimer (35). This dimer was obtained in 82% yield from the corresponding acetyl analogue **34** (20 mg) M.p. 127-129°C. UV-Vis λmax: 404 nm (ε 239,000), 504 (17,600), 538 (13,200), 574 (10,000), 626 (3000). NMR (ppm): 10.25-9.45 (multiple s, 8H, 8 meso-H), 8.25 (m, 1H, C$\underline{H}$=CH2), 6.63-6.50 [m, 2H,C$\underline{H}$(OH)CH_3], 6.40-6.17 (m, 2H, CH=C$\underline{H}_2$), 4.52-4.25 (m, 8H, 4 $C\underline{H}_2CH_2CO_2$), 3.79, 3.66, 3.65, 3.64, 3.63, 3.62, 3.61, 3.60, 3.58, 3.53, 3.50 (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.40-3.20 (m, 8H, $CH_2C\underline{H}_2CO_2$), 2.58, 2.43 [m, 3H, 2 CH($C\underline{H}_3$) -O-], 2.12 [d, 3H, CH(OH)$C\underline{H}_3$], -4.15 (s, 2H, 2 NH), -4.42 and -4.58 (bs, 1H, 2 NH). HRMS Calcd for $C_{72}H_{80}N_8O_{11}$; 1217.6075 (M+1). Found: 1217.6068.

Mono-(1-hydroxyethyl)-mono-vinyl Dimer (39). The acetyl group of dimer **38** (30 mg) was reduced to the corresponding (1-hydroxyethyl) and the title dimer was produced in 84% yield (25 mg). M.p.134-138°C. UV-Vis λmax: 402 nm (ε 240,000), 504 (20,000), 536 (16,500), 572 (12,000), 624 (7,500). NMR (ppm): 10.32, 10.22, 9.94, 9.87, 9.85, 9.60, 9.40, 9.12 (s, total 8H, 8 meso-H), 8.28 (m, 1H, C$\underline{H}$=CH2), 6.30-5.62 [m, 4H 2 C$\underline{H}$(OH)CH_3 and CH=C$\underline{H}_2$), 4.40 (m, 8H, 4 $C\underline{H}_2CH_2CO_2$), 3.75, 3.70, 3.65 3.60, 3.57, 3.50, 3.44 (s, total 36 H, 8 CH_3 and 4 OCH_3), 3.30-3.20 (m, 8H, $CH_2C\underline{H}_2CO_2$), 2.57 [m, 6H, 2 CH($C\underline{H}_3$)-O-], 2.18 [d, 3H, CH(OH)$C\underline{H}_3$], -3.85 (s, 2H, 2 NH), -3.70 and -3.85 (s, 1H, 2 NH). HRMS Calcd for $C_{72}H_{80}N_8O_{11}$; 1217.6075 (M+1). Found: 1217.6086.

Mono-(1-hydroxyethyl)-mono-vinyl Dimer (41). Dimer **40** (15 mg) was converted into the corresponding (1-hydroxyethyl) derivative upon treatment with sodium borohydride, and the title product was obtained in 85% yield. M.p.128-131°C. UV-Vis λmax: 406 nm (ε 238,500), 504 (21,000), 536 (17,500), 570 (13,000), 626 (8,000). NMR (ppm): 10.35-9.15 (multiple s, total 8 H, 8 meso-H), 8.26 (m, 1H, C$\underline{H}$=CH2), 6.32-6.12 [m, 4H, 2 C$\underline{H}$(OH)CH_3 and CH=C$\underline{H}_2$], 4.35-4.32 (m, 8H, 4 $C\underline{H}_2CH_2CO_2$), 3.75-3.38 (multiple s, 36 H, 8 CH_3 and 4 OCH_3), 3.28-3.20 (m, 8H, 4 $CH_2C\underline{H}_2CO_2$), 2.20 [d, 3H, CH(OH)$C\underline{H}_3$], -3.85 to -4.60 (3 bs, 4 H, 4 NH). HRMS Calcd for $C_{72}H_{80}N_8O_{11}$; 1217.6075 (M+1). Found: 1217.6074.

Diacetylporphyrin Trimer (42). Hematoporphyrin-IX dimethyl ester (20 mg) in dichloromethane (15 ml) was treated with HBr gas as described for the synthesis of the hematoporphyrin dimer **27**. The 2,4-bis-(1-bromoethyl) porphyrin **21** so obtained was condensed with 2-acetyl-4-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **12** (40 mg) and after the usual work up, the crude product was purified by preparative thick layer chromatography on silica gel and the title trimer was obtained in 31% yield (19 mg) along with starting porphyrins and protoporphyrin-IX and mon-acetyl-mono-vinyl porphyrin esters as a mixture of isomers {m/e 1217 (M+1, 100%)}. The dimeric mixture was not further purified. Diacetyl trimer **42** was crystallized from dichloromethane/hexane as a fine powder. M.p. 185-187°C. UV-Vis λmax: 408 nm (ε 340,000), 506 (30,800), 546 (21,800), 576 (18,200), 624 (4,500). NMR (ppm):10.60-9.38 (12 s, 12 H, 12 meso-H), 6.80, 6.40, 6.20, 5.92 [m, 4H, 4 C$\underline{H}$(CH_3)-O-], 4.40-4.20 (m, 12H, 6 $C\underline{H}_2CH_2CO_2$), 3.80-3.35 (multiple s, 54 H, 12 CH_3 and 6 OCH_3), 3.30 (s, 6H, 2 $COCH_3$), 3.25 (m, 12H, 6 $CH_2C\underline{H}_2CO_2$), 2.50-2.22 [m, 12H, 4 CH($C\underline{H}_3$)-O], -3.80,-3.90, -4.20, -4.38 (bs, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{118}N_{12}O_{16}$; 1839.8667 (M+1). Found 1839.8859.

Diacetylporphyrin Trimer (45). Reaction of 2,4-bis-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **21,** obtained from hematoporphyrin dimethyl ester (20 mg) with 4-acetyl-2-(1-hydroxyethyl)-deuteroporphyrin-IX dimethyl ester **13** afforded dimer **45** in 32 % yield (19.2 mg). M.p.171-173°C. UV-Vis λmax: 408 nm (ε 320,000), 508 (32,200), 548 (23,100), 576 (19,000),624 (5,000). NMR (ppm): 10.55, 10.50, 10.46, 9.97, 9.95, 9.94, 9.82, 9.80, 9.75, 9.71, 9.66, 9.50 (s, 1H, 12 meso-H), 6.70 [m, 2H, 2 C$\underline{H}$(CH_3)-O], 6.22-6.12 [m, 2H, 2 C$\underline{H}$(CH_3)-O-], 4.60-4.20 (m, 12 H, 6 $C\underline{H}_2CH_2CO_2$), 3.80-3.60 (multiple s, 54 H, 12 CH_3 and 6 OCH_3), 3.45, 3.40 (s, 3H, 2 $COCH_3$), 3.28 (m, 12 H, $CH_2C\underline{H}_2CO_2$), 2.50-2.12 [m, 12 H, 4 CH($C\underline{H}_3$)-O-], -3.70 to -4.15 (m, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{118}N_{12}O_{16}$; 1839.8667 (M+1). Found: 1839.8746.

Hematoporphyrin Trimer (43). Diacetylporphyrin trimer **42** (20 mg) dissolved in dichloromethane (10 ml) was treated with sodium borohydride (40 mg) following the method described above for hematoporphyrin dimer **27**. The reaction product after the standard work-up was purified by preparative chromatography (silica gel plates, eluted with 5% methanol in dichloromethane). The major band was isolated and the product was crystallized from dichloromethane/hexane as a dark brown powder. Yield 15 mg (75 %). M.p. 180-183°C. UV-Vis λmax: 402 nm (ε 353,700), 500 (38,000), 532 (24,000), 510 (19,500), 622 (10,600). NMR (ppm): 10.48-9.39 (m, 12 H, 12 meso-H), 6.78-5.82 [m, 4H, C$\underline{H}$(CH_3)-O-], 4.29 (bm, 12 H, 6 $C\underline{H}_2CH_2CO_2$),3.80-3-40 (multiple s, 54 H, 12 CH_3 and 6 OCH_3), 3.23 (m, 12 H, 6 $CH_2C\underline{H}_2CO_2$), 2.50-1.86 [m, 18 H, 2 CH(OH)$C\underline{H}_3$ and 4 CH($C\underline{H}_3$)-O], -4.04-4.30 (bs, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{122}N_{12}O_{16}$: 1843.9160 (M+1). Found: 1843.9146.

Hematoporphyrin Trimer (46). Sodium borohydride reduction of diacetyl trimer **45** (25 mg) gave the title bis-(1-hydroxethyl) trimer in 77% yield (19.2 mg). M.p 183-185°C. UV-Vis λmax: 400 nm (ε 336,000), 502 (40,500),

510 (21,600), 622 (12,000). NMR (ppm): 10.20-9.30 (m, 12 H, 12 meso-H), 6.80-5.80 [m, 4H, 4 C<u>H</u>(CH$_3$)-O-], 4.60-4.30 (m, 12 H, 6 C<u>H$_2$</u>CH$_2$CO$_2$), 3.82-3.40 (multiple s, 54 H, 12 CH$_3$ and 6 OCH$_3$), 3.40-3.20 (m, 12 H, 6 CH$_2$C<u>H$_2$</u>CO$_2$), 2.60-2.10 [m, 18H, 2 CH(OH)C<u>H$_3$</u> and 4 CH(CH$_3$)-O], -3.90 to -4.50 (m, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{122}N_{12}O_{16}$: 1843.9160 (M+1). Found: 1843.9232.

Divinylporphyrin Trimer (44). By following a similar approach, hematoporphyrin dimethyl ester (20 mg) was converted to 2,4-bis-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **21** which on reaction with 4-(1-hydroxyethyl)-2-vinyldeuteroporphyrin-IX dimethyl ester **18** (40 mg) afforded the title trimer in 32% yield (19.5 mg). M.p. 135-137°C. UV-Vis λmax: 402 nm (ε 285,000), 504 (27,500), 538 (20,000), 524 (15,250), 626 (7,400). NMR (ppm): 10.10-9.45 (multiple s, 12 H, 12 meso-H), 8.02-7.90 (m, 2H, 2 C<u>H</u>=CH$_2$), 6.62-5.24 [m, 4H, 4 C<u>H</u>(CH$_3$)-O-], C<u>H</u>=C<u>H$_2$</u>, 4.58-4.38 (m, 12 H, 6 C<u>H$_2$</u>CH$_2$CO$_2$), 3.75-3.20 (multiple s, 54 H, 12 CH$_3$ and 6 OCH$_3$), 3.38-3.20 (m, 12 H, 6 CH$_2$C<u>H$_2$</u>CO$_2$), 2.55-2.12 [m, 12 H, 4 CH(C<u>H$_3$</u>)-O-], - 3.70 to -4.48 (bs, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{118}N_{12}O_{14}$: 1807.8952 (M+1). Found: 1807.8994.

Divinylporphyrin Trimer (47). Reaction of 2,4-bis-(1-bromoethyl)-deuteroporphyrin-IX dimethyl ester **21,** prepared from hematoporphyrin dimethyl ester (20 mg) with 2-(1-hydroxyethyl)-4-vinyldeuteroporphyrin-IX dimethyl ester **17** (40 mg) gave the title divinylporphyrin trimer in 30% yield (18 mg). M.p. 139-141°C. UV-Vis λmax: 404 nm (ε 282,500), 502 (28,100), 538 (21,000), 526 (15,300), 626 (8,000). NMR (ppm): 10.12-9.45 (multiple s, total 12 H, 12 meso-H), 8.01-7.90 (m, 2H, C<u>H</u>=CH$_2$), 6.65 -5.20 [m, 8H, 4 C<u>H</u>(CH$_3$)-O-] and 2 CH=C<u>H$_2$</u>], 4.60-4.35 (m, 12 H, 6 C<u>H$_2$</u>CH$_2$CO$_2$), 3.80-3.30 (multiple s, 54 H, 12 CH$_3$ and 6 OCH$_3$), 2.56-2.25 [m, 12 H, 4 CH(C<u>H$_3$</u>)-O-], -3.70 to -4.50 (bm, 6 H, 6 NH). HRMS Calcd for $C_{108}H_{118}N_{12}O_{14}$: 1807.8952 (M+1). Found: 1807.8970.

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