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TETRAPYRROLE PRODUCTS FROM ELECTROCHEMICAL CYCLIZATION OF 1',8'-DISUBSTITUTED-*A,C*-BILADIENE SALTS

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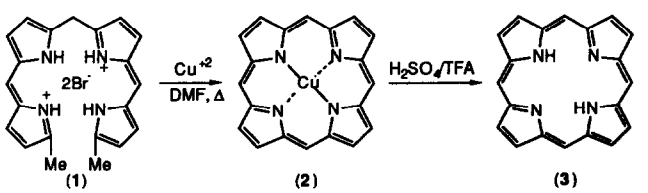
Abstract Anodic oxidation of 1',8'-dimethyl- and other 1',8'-disubstituted *a,c*-biladiene salts affords novel cyclized products. In addition to porphyrin, an unconjugated macrocyclic intermediate product resulting from oxidative cyclization during porphyrin synthesis is isolated, structurally identified, and characterized with regard to its spectroscopy, electrochemical behavior and chemical reactivity. The formation of a novel homoporphyrin from a 1'-ethoxycarbonylmethy-8'-(2-methoxycarbonylethyl)-*a,c*-biladiene salt is also briefly discussed.

Metal-ion promoted oxidative cyclization offers an extremely useful synthetic methodology for preparation of otherwise difficult or impossible to acquire natural porphyrins and synthetic analogues from open-chain tetrapyrrolic intermediates.[1] Scheme 1 shows the most common example of this pathway, involving the copper(II) promoted cyclization of a 1',8'-dimethyl-*a,c*-biladiene hydrobromide (**1**) to give copper(II) porphyrin (**2**). However, the reaction conditions,[2] which usually require refluxing the *a,c*-biladiene with copper(II) acetate in dimethylformamide (DMF), followed by the removal of copper from (**2**) [utilizing H_2SO_4/trifluoroacetic acid (TFA)] to give the metal-free porphyrin (**3**), can greatly reduce the overall yield of porphyrin. To date, all successful oxidative cyclizations of 1',8'-dimethyl-*a,c*-biladiene salts to produce porphyrins have relied on various chemical oxidizing agents.[3] For example, Johnson and Kay[2] first reported the oxidative cyclization of 1',8'-dimethyl-*a,c*-biladiene and 1',8'-dimethyl-*b*-bilene salts with copper(II) acetate in methanol, producing porphyrins in yields of 17-30%. Marked improvements were made in the overall yield of the tetrapyrrole cyclization by briefly refluxing the porphyrin precursor in DMF rather than using prolonged refluxing in methanol;[4] additionally, remarkable improvements were made when the free base *a,c*-biladiene underwent cyclization at room temperature within 2 hours using $CuCl_2$. Similiar treatment of the zinc(II) *a,c*-biladiene chelate with a variety of oxidizing agents[3] also offers yields similar to those obtained by the high temperature cupric salt method. These discoveries, coupled with the development of stepwise syntheses of *a,c*-biladienes via tripyrrenes,[5-7] afforded a general route to the synthesis of unsymmetrical porphyrins.



(1) (2) (3)

Scheme 1

Regardless of the chemical oxidant used for cyclization, it is believed that metal salts play a dual role in orchestrating the oxidative cyclization process. As a chelating agent, Cu(II) can coordinate to the nitrogens of the *a,c*-biladiene ligand forcing it to adopt a planar conformation, thus ensuring that the terminal (1',8') methyl groups are close enough in proximity to effect

macrocyclization. The most important function of Cu(II), however, is as a one-electron oxidizing agent. As mentioned previously, Minnetian and Smith,[3] and Johnson and Kay[2] have shown that Cu(II) is not a uniquely qualified oxidizing agent and many others have also been exploited.

Preparative electrosynthesis has been used by organic chemists for well over 100 years to produce products obtained through either an oxidation or a reduction process. Electrochemical methods often offer advantages over traditional chemical methods since they use mild conditions, can be very selective, and depending on the equivalent chemical reagents, can eliminate the use of toxic inorganic chemicals.[8,9]

Additionally, and particularly in the case of the porphyrin synthesis outlined in Scheme 1, there are interesting mechanistic questions to be addressed; due to paramagnetic problems, the Cu(II) approach eliminates the opportunity to use nuclear magnetic resonance (NMR) methods for monitoring the reaction pathway. Use of anodic oxidation in place of transition metal ions as oxidants offers the opportunity to use spectroscopic techniques to investigate structural issues associated with this intriguing synthetic route (Scheme 1). We have already indirectly addressed the question of the mechanism of *a,c*-biladiene cyclizations to give porphyrins with particular reference to the origin of the newly introduced meso-carbon in (**2**) and (**3**)[10] and the fate of the 1',8'-methyls in (**1**).[3] We have proposed a possible mechanistic pathway[11] for the (**1**) ⇒ (**2**) transformation. Additionally, we have described our work on anodic oxidation of monopyrroles[12] and dipyrroles.[13] In each case we have determined substituent partial potentials for these systems, and have identified a number of novel electrochemical transformations. As an extension of this work, particularly with regard to electrochemical oxidation processes identified for the dipyrroles, we now describe extension of our studies to tetrapyrrole substances which are precursors and intermediates in porphyrin synthesis. To obtain more definitive evidence for the mechanistic pathway from *a,c*-biladienes (**1**) to porphyrins (**3**) (Scheme 1), and to attempt to introduce new synthetic methodology into the porphyrin field, we decided to probe the use of anodic oxidation of open-chain tetrapyrroles for porphyrin synthesis.

ELECTROCHEMICAL ANALYSES

CV (cyclic voltammetry) and SWV (square wave voltammetry) were performed in order to determine the general range of oxidation potentials for the electrolysis of each *a,c*-biladiene substrate. Typically the *a,c*-biladienes were dissolved in a 0.2M tetraethylammonium p-toluenesulfonate (TEA-p-Tos) solution of anhydrous DMF in concentrations ranging between 1.0-1.5 mM. For both CV and SWV measurements a Pt (platinum) button working electrode and Pt wire counter electrode were used and the applied potential was measured with respect to $Ag/AgCl/KCl_{(sat)}$ at room temperature. The solution was vigorously stirred and purged with argon (Ar) prior to analysis. During the experiment a continuous stream of Ar gas was passed over the solution, but the solution remained static. Typically, the *a,c*-biladienes were scanned from 0.0 to 1.5 V, although the oxidation potentials of interest were in the range of 0.0-1.0 V. Since we were primarily interested in behavior towards oxidation, no substrates were investigated for their propensity towards reduction. A typical voltammogram is presented for decamethyl-*a,c*-biladiene (**4**) (Figure 1) but the Zn(II) chelates were also measured; the voltammograms of these are representative of all of the 1',8'-dimethyl-*a,c*-biladienes. There are great differences between the *a,c*-biladiene dihydrobromides and their Zn(II) chelates. The cyclic voltammogram of the zinc complex shows three broad ill-defined oxidations while the dihydrobromide salt (**4**) shows only two sharp and distinct waves. SWV shows the zinc chelates have a weak oxidation at ~0.1 V and two stronger oxidations between 0.7-1.1 V whereas the dihydrobromides have a weak oxidation between 0.2-0.3 V and a stronger oxidation between 0.77-0.82 V. These results indicate two general ranges of oxidation potentials in which to preparatively electrolyze the free base *a,c*-

biladienes, namely 0.2-0.3V and 0.7-0.8V. Results for the zinc(II) chelates were much more difficult to interpret for bulk electrosynthetic use.

BULK ELECTROLYSES

An electrochemical H cell with a total capacity of 20 ml and with a fritted glass barrier as depicted in Figure 2a was employed as the reaction vessel. A Pt mesh working electrode, a Ag/AgCl reference electrode, and a Pt wire reference electrode were typically used for all bulk electrolysis reactions. The potential was controlled by use of a BAS SP-2 Synthetic Potentiostat.

In our initial experiments we chose to oxidize the chloroethyl-*a*,*c*-biladiene (**5**) in the presence of Zn(II) at 0.50 V in an electrolyte solution of 0.2M TEA-p-Tos/DMF. The Zn(II) chelate, which has a characteristic UV-Vis profile (λ_{max} = 468 nm, 536 nm) as reported by Smith and Minnetian,[3] was electrolyzed for 6 hours yet remained unchanged. However, when the potential was increased to 0.80 V, the solution darkened quickly and dilute sampling aliquots exhibited a faint red tinge. The electrolysis was monitored both by spectrophotometry and thin layer chromatography (TLC); UV-Vis showed the appearance of a Soret absorption band[14] at 406 nm after 1.5 h and the electrolysis was judged to be complete after 6 h. After an aqueous workup the mixture was chromatographed on alumina (Brockmann Grade III), the red porphyrin band eluted with CH_2Cl_2/1%MeOH, and was then dried under vacuum to give a 40% yield of Zn(II) chloroethyl-porphyrin (**6**).

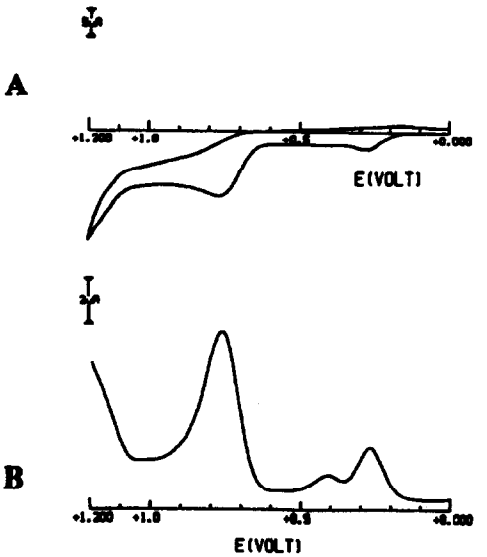


Figure 1. Cyclic voltammogram (A) and square wave voltammogram (B) of decamethyl-a,c-biladiene dihydrobromide salt (4).

Proton NMR spectra and spectrophotometry indicated that only one porphyrin was formed from the electrolysis, thereby demonstrating that a porphyrin can indeed be prepared from a 1',8'-dimethyl-*a*,*c*-biladiene by anodic oxidation (Scheme 2) and without the use of chemical oxidants. Additionally, since this oxidation can be carried out at room temperature to give porphyrin in good yield, the incorporation of acid and heat sensitive substituents into the *a*,*c*-biladiene periphery can be envisioned.

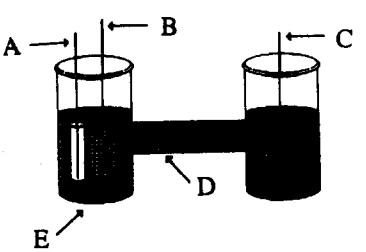


Figure 2a

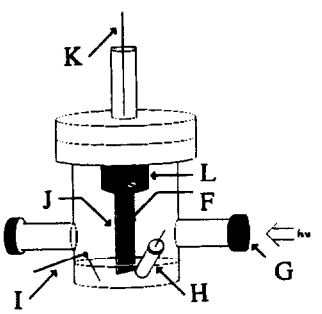
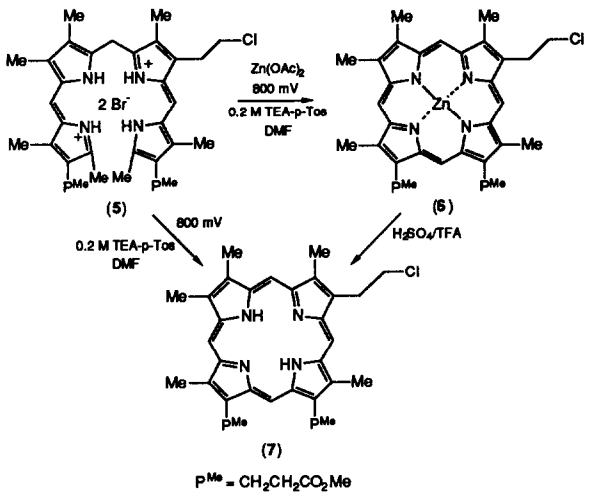


Figure 2b

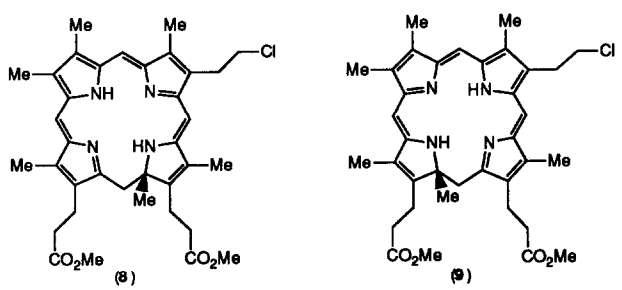
Figure 2a. Electrochemical H cell: A) Ag/AgCl reference electrode, B) Pt mesh working electrode, C) Pt wire auxiliary electrode, D) fritted glass interface, E) magnetic stir bar.

Figure 2b. Spectroelectrochemical apparatus: F) Au mesh working electrode, G) quartz window, H) Ag/AgCl reference electrode, I) Pt wire auxiliary electrode, J) quartz demountable cell- 2 ends open, K) Pt wire connector- to electrochemical analyzer, L) Teflon holder with screw controlled tension.



Scheme 2

Since the data from the CV and SWV experiments showed that the oxidations of the dihydrobromide salts of *a,c*-biladienes were far cleaner and more distinct than those of the Zn(II) chelates, there was good indication that the presence of Zn(II) may not be necessary to cyclize *a,c*-biladienes. To test this hypothesis, the chloroethyl-*a,c*-biladiene (**5**) was oxidized at 0.80 V under exactly the same conditions as the previous experiment, but the Zn(II) acetate was omitted (Scheme 2). Within 3 hours TLC showed a predominant red band with a high R_f and a minor quantity of blue-green material with a slightly lower R_f. Spectrophotometry also indicated that a considerable amount of porphyrin had formed. TLC showed the blue-green band had completely disappeared after 5 hours and UV-Vis indicated the reaction to be complete after 8 hours of electrolysis. Aqueous workup and chromatography on alumina (Brockmann Grade III) afforded a 42% yield of free base porphyrin (**7**); no attempt was made to optimize the yield. The optical spectrum of the porphyrin (λ_{max}=399 nm, 498, 532, 568, 622; etio-type[14]) and the proton NMR spectrum were consistent with those reported for the identical free base chloroethyl-porphyrin (**7**) prepared previously.[15] This is the first example of an oxidative cyclization of 1',8'-dimethyl-*a,c*-biladiene to give porphyrin without the use of a chelating agent. To illustrate that application of an electrochemical potential is essential for the cyclization, a control experiment was run by stirring the same amount of *a,c*-biladiene in 0.2M TEA-p-Tos/DMF with an immersed platinum electrode at room temperature for 8 hours; no change was observed in the solution during this period.



The quantity of chloroethyl-*a,c*-biladiene (**5**) was increased ten-fold (to 53 mg) and placed into the anodic compartment of a larger H cell (total capacity 50 ml) containing 0.2M TEA-p-Tos/DMF. A 1.25 cm x 5.0 inch cylindrical platinum cage was combined with the Pt gauze anode which was fed within to effectively triple the electrode surface area. As one might expect, increasing the quantity of substrate by an order of magnitude while only doubling the volume and tripling the electrode surface area would considerably retard the rate of oxidation. This was borne out by experiment as TLC showed only a minute amount of porphyrin had formed after 9 hours of electrolysis at 0.80 V. However, a large quantity of a blue-green compound was now apparent. The oxidation was run overnight and after 25 h TLC indicated that considerably more porphyrin had been produced but the blue-green compound was still predominant; oxidation was therefore terminated. Following workup the mixture was chromatographed. A mobile blue-green band (9 mg) eluted quickly, followed by the desired porphyrin in 9% yield.

The optical spectrum of the blue-green compound (**8,9**) (λ_{max}= 305, 380, 650, 704 nm) [Figure 3; UV-Vis spectrum of (**16**) shown; chloroethyl-intermediate (**8,9**) is identical] appeared similar to that of a phlorin (λ_{max}= 387, 620 nm)[16] and also bore a resemblance to the optical spectrum of a supposed oxidized *a,b,c*-bilatriene [λ_{max}= 305 nm (ε 19,950), 385 (53,700), 705 (12,000), with an inflection at 605 nm (ε 10,500)] reported by Johnson.[17]

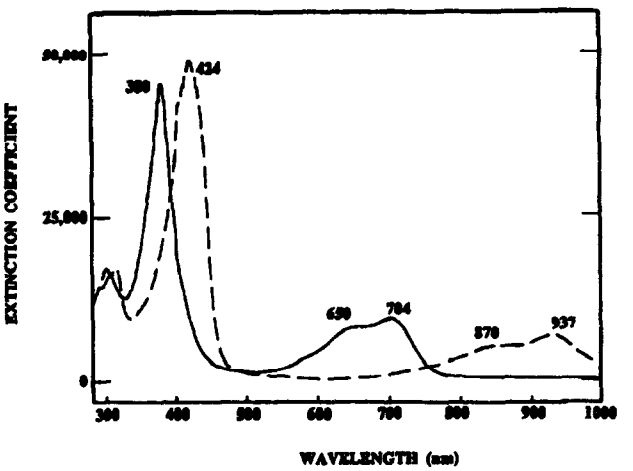
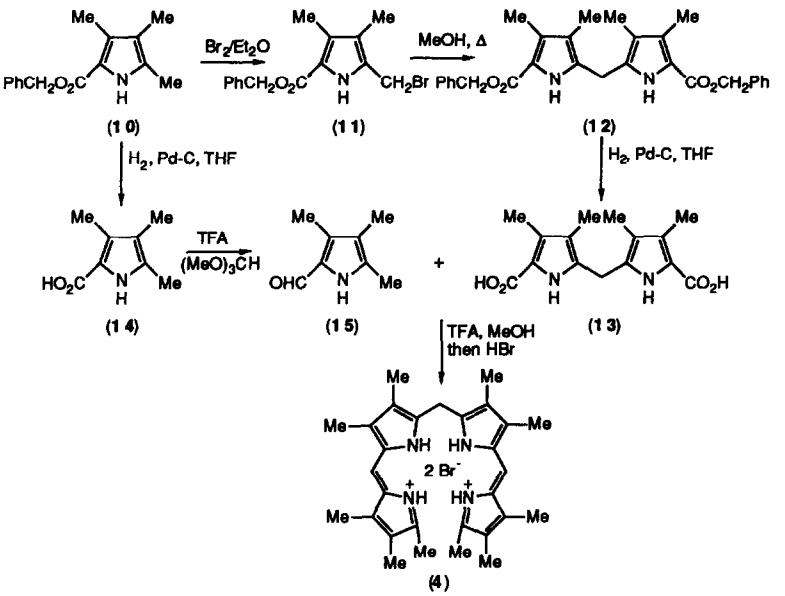


Figure 3. Optical spectrum of the cyclized nonamethyl intermediate (**16**) in dichloromethane (solid line) and after the addition of TFA (dashed line).

The proton NMR spectrum was complex. Based on the multiplicity of peaks in the spectrum, it was quite apparent that the blue-green compound was a mixture of two structurally similar compounds, present in slightly unequal proportions. Also, based on the appearance and disappearance of this blue-green compound detected by TLC in the initial smaller scale experiment, we assumed that this was an intermediate along the oxidative pathway to porphyrin from *a,c*-biladiene. This was confirmed by simply electrolyzing a small portion of the pure blue-green substance under identical conditions for 30 min, whereupon a considerable quantity of porphyrin formed. The isolated porphyrin has the same spectral properties as (**7**) formed from the previous small scale electrochemical experiment.



Scheme 3

In order to simplify the proton NMR data we decided to electrolyze decamethyl-*a,c*-biladiene (**4**). The synthesis is straightforward (Scheme 3). The pyrrole (**10**) was prepared in a Kleinspehn-type method;[18] a portion of this was self-condensed via treatment with Br_2/ether followed by refluxing of the resultant bromomethyl-pyrrole (**11**) to afford the symmetrical pyrromethane (**12**). This was hydrogenated over Pd-C followed by decarboxylation to form (**13**). Hydrogenation of pyrrole (**10**) to form the carboxylic acid pyrrole (**14**) followed by decarboxylation and formylation (by treatment with triethyl orthoformate in TFA) gave the required

formylpyrrole (**15**). This pyrrole (**15**) and pyrromethane (**13**) were condensed together in the presence of TFA to give, after brief treatment with HBr/HOAc and crystallization from ether, the decamethyl-*a,c*-biladiene (**4**).

Oxidation of the substrate (**4**) for only 3-6 hours (depending on the concentration of *a,c*-biladiene) at 0.80V provided the blue-green intermediate, after workup and chromatography, in a yield of 71%. This intermediate (**16**) shared nearly identical UV-Vis spectral properties with the blue-green intermediate (**8,9**) obtained in the chloroethyl-*a,c*-biladiene electrolysis. However, the proton NMR spectrum (Figure 4) was very simple and unambiguously pointed to the identity of the blue-green intermediate as structure (**16**). Three methine peaks at 5.00, 5.35, and 6.26 ppm and eight methyl peaks from 1.77-2.03 ppm were present. The region from 2.3-3.6 ppm, previously obscured by a multitude of methylene triplets, clearly revealed an AB-quartet with J_{AB}=15.3 Hz for each doublet at 2.52 and 2.98 ppm. A single peak at 1.4 ppm represented the "valley" α-methyl group. Decoupling of the doublet at 2.98 ppm caused the the doublet at 2.52 ppm to collapse to a singlet, illustrating the connectivity of the bridging methylene protons.

Definitive proof of the identity and location of the "valley" α-methyl group came from a nuclear Overhauser enhancement (NOE) experiment. The peak at 1.40 ppm, attributed to the α-methyl group, was irradiated and the resulting difference spectrum showed an NOE at the doublet at 2.52 ppm and also one at one of the two methyl groups represented by the chemical shift at 1.77 ppm. Enhancement at 2.52 ppm and not at 2.98 ppm suggests that the hydrogen of the bridging methylene cis to the α-methyl group is at 2.52 ppm and therefore that the trans hydrogen is at 2.98 ppm.

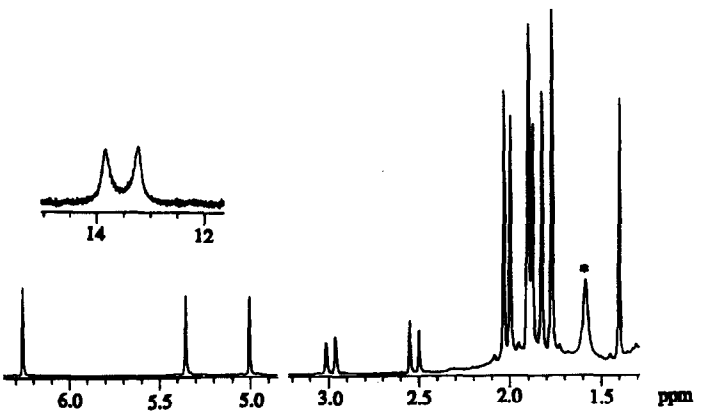
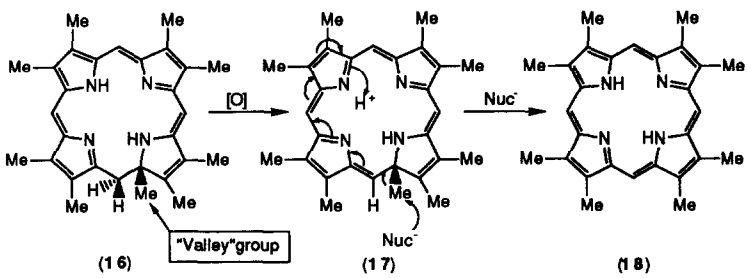


Figure 4. Proton NMR spectrum of the cyclized nonamethyl intermediate (**16**) in deuterochloroform. Region 14-12 ppm not drawn to scale. * = water.



Scheme 4

A potential problem arises with electrolyses at high voltages since bromide can potentially be oxidized to bromine [$Br_{2(aq)}$ + 2e⁻ = 2Br⁻, E=1.087 V vs. NHE; E=0.890 V vs. Ag/AgCl/$KCl_{(sat)}$]. As a control, the oxidation potential of tetraethyl-ammonium bromide in 0.2M TEA-p-Tos/DMF was measured by CV and revealed an irreversible oxidation wave at 0.87 V. This value is significantly higher than the applied potential and it was therefore assumed that Br_2 formation, and its use, do not play a role in the oxidation process. Additional experiments conclusively confirmed this assertion since the cyclization of the dihydrochloride

a,c-biladiene salt and the free-base *a,c*-biladiene formed the intermediary green products (**8**,**9**,**16**) in yields comparable with those of the *a,c*-biladiene dihydrobromide salts.

Our interest next turned to the mechanism of porphyrin formation from the intermediate products (**8**,**9**,**16**). The transformation of the intermediate to porphyrin can theoretically be explained in two steps by (1) the loss of the α-methyl substituent, and (2) oxidation of the tetrapyrrole to yield a fully oxidized 22 π-electron macrocycle. In an attempt to test our hypothesis regarding this mechanism, a number of experiments were pursued. Attempts to react (**16**) with various nucleophiles, e.g. methoxide, triethylamine, pyridine, and cyanide, proved unsuccessful. Even after heating the reaction mixture of intermediate and nucleophile to elevated temperatures, the starting material could be recovered in nearly quantitative yield.

Electrochemical oxidation of (**16**) at 0.8 V in 50mM TEA-p-Tos/DMF afforded the desired porphyrin in high yield (determined by spectrophotometry), and seems to be the best method for transforming the intermediate into porphyrin (**18**). Interestingly enough, by combining (**16**) with various oxidizing agents, e.g. DDQ, TCQ, and THQ, formation of porphyrin was accomplished (monitored by spectrophotometry) (Scheme 4). Any attempts to isolate (**17**), the presumed intermediate, were unsuccessful. This result is not surprising since nucleophilic attack on the "valley" methyl group, involving some kind of S_N2 process, would result in loss of the aromatic porphyrin as leaving group and provide a highly favorable driving force. These results suggested that immediately following the formation of (**16**), subsequent oxidation of the intermediate to (**17**) is feasible and loss of the methyl group is then facile. On the other hand, nucleophilic displacement of the macrocycle in (**16**) is a less favorable process because there is no thermodynamic gain from porphyrin formation in this step.

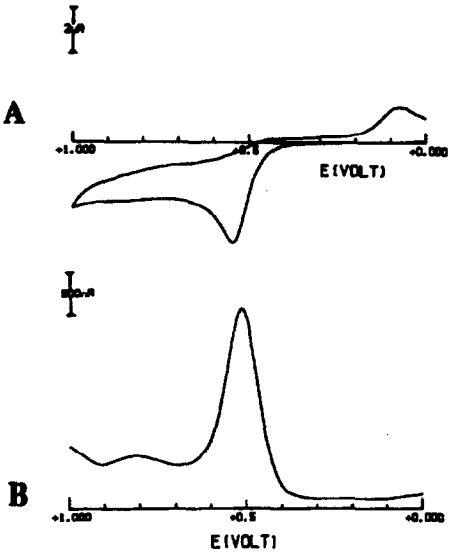


Figure 5. Cyclic voltammogram (A) and square wave voltammogram (B) of the cyclized nonamethyl-intermediate (**16**).

Typically, depending on the length of the electrolysis, a mixture of both intermediate and porphyrin were isolated. Analyses of the electrochemical properties of the intermediate compound were consistent with the theory that further oxidation of the intermediate is required before the nucleophilic displacement step to form porphyrin. The cyclic voltammogram of the intermediate product displayed a single oxidation wave when scanned from 0.0 through 1.6 V. Figure 5 shows the CV and SWV in which SWV provides evidence of a non-reversable oxidation potential is at 0.512 V relative to Ag/AgCl. Further oxidation of the intermediate product would be expected and is in fact observed in the oxidation process of *a,c*-biladienes. By using a spectroelectrochemical apparatus (Figure 2b) we were able to observe the changes in the visible absorption spectrum as the transformation of (**16**) into octamethylporphyrin (**18**) progressed (Figure 6).

Immediately after the potential of 0.8 V was applied, the major peak at 380 nm, the minor peak (λ_{max}=700 nm) and its shoulder peak (λ_{max}=658 nm) began to disappear. The formation of three new peaks became apparent at λ_{max} 422, 500, and 730 nm. Observation of this bathochromic shift suggests the initial oxidation of the

methylene bridge in (**16**), presumably to form (**17**), thus increasing the length of the conjugated π system. The formation of this product was observed within the first 6 min. Within the next 14 min the disappearance of the inter-

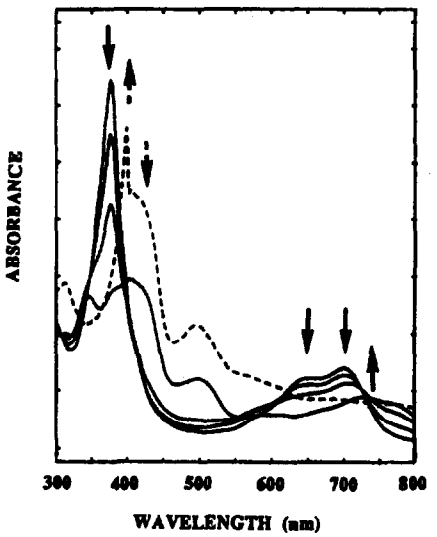
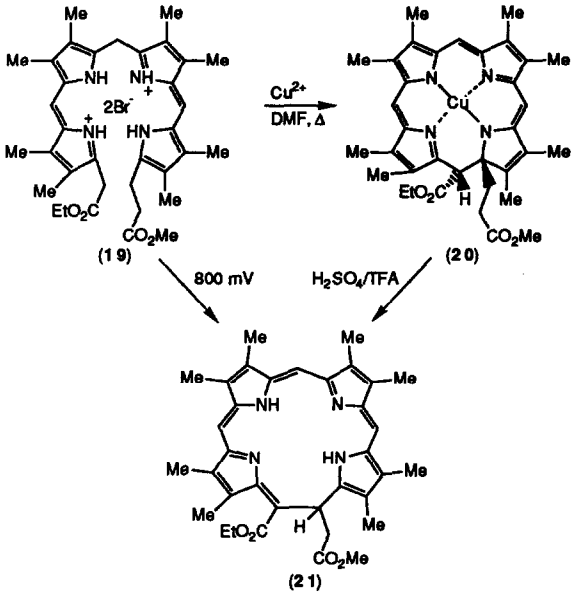


Figure 6. Spectroelectrochemical data from the anodic oxidation of cyclized nonamethyl intermediate (**16**). Time = 0.0 min, 2.0 min, 4.0 min, 6.0 min (solid lines) demonstrating the disappearance of absorbances at 380 nm, 704 nm and its shoulder peak at 650 nm, and the formation of the absorbance at 420nm and 730 nm demonstrating the formation of an increased π-system, presumably (**15**). The electronic absorbance of the oxidation reaction after 30 min showing the beginning of the formation of porphyrin and the disappearance of the absorbance at 422 nm.

mediate (**16**) was complete. The final 70 min of the spectroelectrochemical experiment involved the formation of a Soret absorption band at 400 nm in addition to the disappearance of the absorbances noted for the transitional compound (λ_{max} 422, 500, and 730 nm). The final visible absorption spectrum had the major Soret absorbance at 400 nm. An absorbance at 500 nm persisted, in addition to the appearance of one at 562 nm; both peaks were assumed to represent either side-products or decomposition products. This experiment provides strong evidence for formation of a fully oxidized tetrapyrrole such as (**17**) prior to the loss of the "valley" methyl group. If the initial step were to be loss of the methyl group due to nucleophilic attack, one would not expect to observe a bathochromic shift in the visible absorption spectrum .

CYCLIZATION OF ADDITIONAL *A,C*-BILADIENES

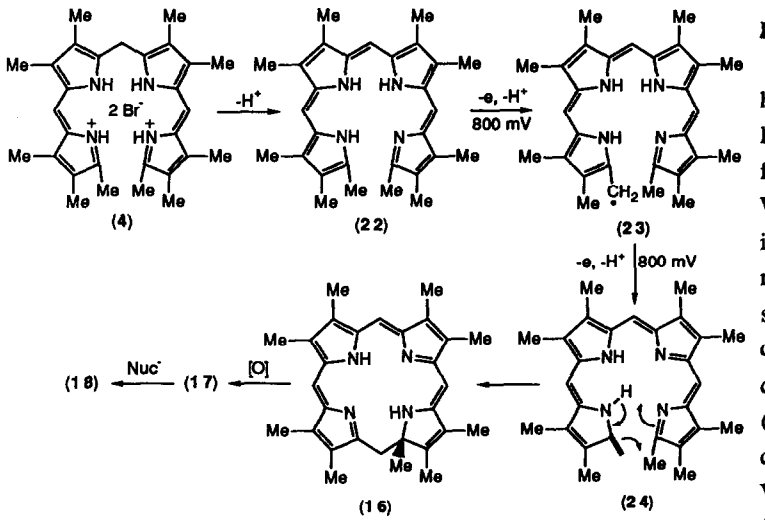
Various other *a,c*-biladiene substrates were analyzed for their electrochemical reactivity. In addition to a number of other disubstituted *a,c*-biladienes, the CV and SWV results for 8'-ethoxycarbonylmethyl-1'-(2-methoxycarbonylethyl)-1,2,3,4,5,6,7,8-decamethyl-*a,c*-biladiene (**19**) demonstrated marked differences from the electrochemical results obtained from the 1',8'-dimethyl-*a,c*-biladienes. Treatment of (**19**) with Cu(II) salts at less than reflux temperatures afforded (**20**).[19] This result is consistent with those obtained from the electrochemical oxidation of (**4**) which formed the blue-green free base intermediate (**16**). We therefore assumed that the electrolysis of (**19**) would yield comparable results.



Scheme 5

Anodic oxidation of (**19**) at 0.8 V accomplished a very interesting transformation. The progress of the reaction, which was monitored spectrophotometrically, showed that within 30 min no starting material remained in the reaction vessel. Routine work-up/purification of the products afforded (**21**), isolated in 42% yield. Interestingly enough as we have previously reported,[19] treatment of (**20**) with TFA/H_2SO_4 in order to potentially demetalate the product also affords (**21**) as the major product in 30% yield (Scheme 5).

Additional compounds also containing more complex substitution patterns are currently being studied in our laboratory, demonstrating their potential as starting materials for electrosynthesis of porphyrins, homoporphyrins, and other novel systems. Details of these studies, including experimental procedures, will be published elsewhere.



Scheme 6

DISCUSSION

The intermediates that we have isolated and characterized have long been thought to be elusive and far too unstable for isolation.[20-24] While we have observed some instability in the macrocycle toward rearrangement which may be due to steric strain imposed by the quaternary α-methyl group, the cyclized porphyrin intermediate (**16**) can readily be isolated using common laboratory procedures. We propose a mechanism of formation of the intermediate and porphyrin as outlined in Scheme 6. Initial deprotonation of the *a,c*-biladiene (**4**) affords the conjugated molecule (**22**); this is oxidized anodically to produce the α-methyl radical (**23**) from which another electron and proton are lost to give an intermediate (**24**) bearing an exocyclic double bond. This then cyclizes to form the isolated α-methyl intermediate (**16**) which undergoes oxidation to give (**17**) followed by nucleophilic displacement of the α-methyl group to give porphyrin (**18**).

Work remains to be done to permit a complete understanding of the chemistry of the α-methyl intermediate and how it is transformed into porphyrin. Hopefully this new electrochemical method will offer a superior route above and beyond established methods for porphyrin synthesis[1] which fall short in the synthesis of more sensitive and labile porphyrins (e.g. some meso- and N-substituted porphyrins and porphyrins bearing labile side chains). We have thus far been successful in obtaining good yields of porphyrin from only 10-50 mg of *a,c*-biladiene; we therefore intend to determine what types of electrodes or modifications in our cell design can make the transformation more efficient. In addition to studying the oxidative cyclization of dimethyl-*a,c*-biladienes, we are also interested in the potential that this methodology has for construction of extended tetrapyrrole type compounds.

EXPERIMENTAL

Electrochemical analyses were performed on a BAS 100A Electrochemical Analyzer with a BAS Auto Cell Stand attachment; bulk electrolyses were carried out with a BAS SP-2 Synthetic Potentiostat. Both chemical and electrochemical reactions were carried out under argon, in the dark, and were monitored by thin layer chromatography and spectrophotometry. Melting points were measured on a hot stage apparatus and were uncorrected. Silica gel 60 (70-230 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, i.e. deactivated with 6% water) were used for column chromatography. Preparative thick 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). Proton NMR spectra were obtained in deuterochloroform 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 Microchemical Analysis Laboratory, U.C. Berkeley. Electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained on a VG Analytical ZAB-HS instrument.

ZINC(II) 4-(2-CHLOROETHYL)-6,7-BIS-(2-METHOXYCARBONYLETHYL)-1,2,3,5,8-PENTAMETHYL PORPHYRIN, (6)

The *a,c*-biladiene (**5**)[10] (8.4 mg) and zinc(II) acetate (10 mg) were dissolved in 10 ml of a solution of TEA-p-Tos (0.2M) in DMF and an oxidation potential of 0.8 V (vs. Ag/AgCl) was applied to the substrate for a period of 6 h. The mixture was poured from the anode compartment and diluted with dichloromethane before washing twice with aqueous $NaHCO_3$, four times with water, and once with brine; the organic phase was dried (Na_2SO_4) before removing the solvent by rotoevaporation. The residue was chromatographed using a 1 x 10 cm alumina column (Brockmann Grade III) eluting with 99:1 dichloromethane/methanol. The most mobile pink zinc(II) porphyrin band was collected to give 2.9 mg (40% yield) of the title porphyrin. ^{1}H-NMR: ($CDCl_3$) δ 3.22 (m, 4H, $CH_2C\underline{H_2}CO_2Me$), 3.45 (s, 3H, ring Me), 3.47 (s, 3H, ring Me), 3.50 (s, 3H, ring Me), 3.54 (s, 3H, ring Me), 3.59 (s, 3H, ring Me), 3.68 (s, 3H, Me ester), 3.69 (s, 3H, Me ester), 4.20-4.40 (m, 8H, 2 x $C\underline{H_2}CH_2CO_2Me$, 2 x $C\underline{H_2}CH_2Cl$, and 2 x $CH_2C\underline{H_2}Cl$), 9.66 (s, 1H, meso-H), 9.68 (s, 1H, meso-H), 9.73 (s, 1H, meso-H), 9.81 (s, 1H, meso-H). UV-Vis (CH_2Cl_2): λ_{max}=400 nm (ε 208,800), 532 (14,600), 568 (17,800).

4-(2-CHLOROETHYL)-6,7-BIS-(2-METHOXYCARBONYLETHYL)-1,2,3,5,8-PENTAMETHYLPORPHYRIN, (7)

The *a,c*-biladiene (**5**) (5.0 mg) was dissolved in 10 ml of a solution of TEA-p-Tos (0.2M) in DMF and an oxidation potential of 0.8 V (vs. Ag/AgCl) was applied to the mixture for a period of 8 h. The solution was poured from the anode compartment and worked-up as described above. Product yield was 42% (1.6 mg). ^{1}H-NMR: ($CDCl_3$) δ -3.75 (s, 2H, NH), 3.29 (t, 2H, $CH_2C\underline{H_2}CO_2Me$), 3.30 (t, 2H, $CH_2C\underline{H_2}CO_2Me$), 3.63 (s, 6H, 2 x Me), 3.66 (s, 12H, 4 x Me), 3.68 (s, 3H, Me), 4.30-4.53 (m, 8H, 2 x $C\underline{H_2}CH_2CO_2Me$, 2 x $C\underline{H_2}CH_2Cl$, and 2 x $CH_2C\underline{H_2}Cl$), 10.03 (s, 1H, meso-H), 10.09 (s, 1H, meso-H), 10.10 (s, 1H, meso-H), 10.11 (s, 1H, meso-H). UV-Vis (CH_2Cl_2): λ_{max}=399 nm (ε 165,000), 498 (16,500), 532 (12,900), 568 (10,000), 622 (16,500).

"CHLOROETHYL INTERMEDIATES", OR *δ,δ*-DIHYDRO-6-(2-CHLOROETHYL)-1,8-BIS-(2-METHOXYCARBONYLETHYL)-2,3,4,5,7,8'-OCTAMETHYL-*A,B,C*-SMITHERENE AND *δ,δ*-DIHYDRO-6-(2-CHLOROETHYL)-1,8-BIS-(2-METHOXYCARBONYLETHYL)-2,3,4,5,7,1'-OCTAMETHYL-*A,B,C*-SMITHERENE, (8,9)

The "chloroethyl-*a,c*-biladiene" (**5**) (53.0 mg) was dissolved in 25 ml of a solution of tetraethylammonium p-toluenesulfonate (0.2M) in DMF and an oxidation potential of 0.8 V (vs. Ag/AgCl) was applied to the substrate for a period of 25 h. Whereas porphyrin was obtained from the small scale reaction (above), in this instance, a blue-green material was formed first followed by the slow but steady generation of porphyrin from it as detected by silica gel TLC. It appeared by TLC that no changes were occurring after 25 h. The solution was poured from the

anode compartment and worked up as described above. The residue was chromatographed on a 1.5 x 15 cm alumina column (Brockmann Grade III) eluting with dichloromethane, with porphyrin eluting first followed by the blue-green compound. UV-Vis and NMR spectra verified that the porphyrin was indeed (**7**) (3.5 mg, 9%). The yield of the blue-green intermediate was 9 mg. ^{1}H-NMR: ($CDCl_3$) δ 1.43 (s, 3H, α-Me), 1.46 (s, 3H, α-Me) [α-Me groups in ratio of $42_{(\delta 1.46)}$:$58_{(\delta 1.43)}$], 1.82 (s, 6H, 2 x ring Me), 1.89 (s, 3H, ring Me), 1.90 (s, 3H, ring Me), 1.91 (s, 3H, ring Me), 1.95 (s, 3H, ring Me), 1.92 (s, 3H, ring Me), 1.99 (s, 3H, ring Me), 2.06 (s, 3H, ring Me), 2.07 (s, 3H, ring Me), 2.35-3.01 (m, 4H, 2 x $CH_2CH_2CO_2Me$, 2 x $CH_2CH_2CO_2Me$, 2 x CH_2CH_2Cl, 2 x *d*-CH_2), 3.46-3.58 (m, 4H, 2 x CH_2CH_2Cl), 3.65 (s, 6H, 2 x Me ester), 3.70 (s, 6H, 2 x Me ester), 4.97 (s, 1H, methine-H) and 5.04 (s, 1H, methine-H) in a ratio of 42:58 respectively, 5.36 (s, 1H, methine-H) and 5.48 (s, 1H, methine-H) in a ratio of 58:42 respectively, 6.20 (s, 1H, methine-H) and 6.28 (s, 1H, methine-H) in a ratio of 58:42 respectively, 13.15 ($s_{(broad)}$, 2H, NH), 13.75 ($s_{(broad)}$, 2H, NH). UV-Vis (CH_2Cl_2): λ_{max}= 305 nm (ε 16,600), 380 (45,110), 650 (9,070), 704 (10,510). LR mass spectrum: *m/e* 630 (100%), 615 (8). HR mass spectrum (FAB) for $C_{36}H_{43}ClN_4O_4$ requires: 630.2970; Found: 630.2993

DIBENZYL 3,3',4,4'-TETRAMETHYLPYRROMETHANE-5,5'-DICARBOXYLATE, (12)

Benzyl 3,4,5-trimethylpyrrole-2-carboxylate (**10**) (2.0 g) was dissolved in anhydrous ether (45 ml) and with stirring was treated with bromine (0.5 ml). The bromomethylpyrrole (**11**) immediately precipitated from the solution, but the mixture was stirred for an additional 1.5 h before evaporation of the ether (CAUTION: HBr gas) to give an orange residue of (**11**). The solid was dissolved in methanol (25 ml) and heated under reflux for 4 h, before being set aside at room temperature overnight. The product was collected by filtration and recrystallized from dichloromethane/petroleum ether to afford the title compound (1.1 g, 56 %), Mp 178-179°C. ^{1}H-NMR: ($CDCl_3$) δ 1.95 (s, 6H, 2 x ring Me), 2.25 (s, 6H, 2 x ring Me), 3.77 (s, 2H, CH_2), 5.23 (s, 4H, 2 x benzyl CH_2), 7.28 (m, 10 H, 2 x C_6H_5), 9.24 ($s_{(broad)}$, 2H, NH). Anal. Calcd. for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.42; N, 5.95. Found: C, 74.10; H, 6.38; N, 5.97.

2-FORMYL-3,4,5-TRIMETHYLPYRROLE, (15)

Benzyl 3,4,5-trimethylpyrrole-2-carboxylate (**10**) (5.0 g) in THF (200 ml) containing Pd-C (500 mg) and triethylamine (0.1 ml) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased (3 h). The solution was filtered through a bed of Celite, which was washed with THF (50 ml) and the combined filtrates were evaporated to dryness to give 3,4,5-trimethylpyrrole-2-carboxylic acid (**14**) (2.66 g) [^{1}H-NMR: ($CDCl_3$) δ 1.98 (s, 3H, ring Me), 2.24 (s, 3H, ring Me), 2.36 (s, 3H, ring Me), 9.51 ($s_{(broad)}$, 1H, NH), 11.98 ($s_{(broad)}$, 1H, CO_2H)]. This material (1.92 g) was dissolved under nitrogen in DMF (6 ml) and heated under reflux for 3 h before cooling to 0°C and addition of benzoyl chloride (3 ml). The mixture was stirred an additional 2 h after which benzene (15 ml) was added and the solution was stirred for 30 min at room temperature. A brown-yellow precipitate was collected by flitration, air dried, and suspended in a saturated solution of sodium carbonate (100 ml). The mixture was stirred for 3 h at 60°C, and a yellow precipitate was collected. The product was recrystallized from dichloromethane/hexane to give the title pyrrole (**15**) (1.42 g; 82% yield), Mp 102-104°C. ^{1}H-NMR: ($CDCl_3$) δ 1.91 (s, 6H, ring Me), 2.24 (s, 6H, 2 x ring Me), 9.10 ($s_{(broad)}$, 1H, NH), 9.43 (s, 1H, CHO). Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.09; H, 8.11; N, 10.19.

1',1,2,3,4,5,6,7,8,8'-DECAMETHYL-*A,C*-BILADIENE DIHYDROBROMIDE, (4)

Dibenzyl 3,3',4,4'-tetramethylpyrromethane-5,5'-dicarboxylate (**12**) (480 mg) and 10% Pd-C (50 mg) were added to THF (100 ml) containing triethylamine (0.1 ml) and the resulting solution was hydrogenated at room temperature and atmospheric pressure for 6 h. Filtration through a 2 cm pad of Celite followed by rotoevaporation of the solvent yielded 3,3',4,4'-tetramethylpyrromethane-5-5'dicarboxylic acid (**13**) (297 mg) as a white solid which was used directly without further purification [^{1}H-NMR: ($CDCl_3$) δ 1.99 (s, 6H, 2 x ring Me), 2.21 (s, 6H, 2 x ring Me), 3.79 (s, 2H, CH_2), 9.28 ($s_{(broad)}$, 2H, NH), 11.20 ($s_{(broad)}$, 2H, CO_2H)]. To (**13**) (297 mg) was added TFA (4 ml) and the resulting mixture was stirred for 5 min before addition of a solution of 2-formyl-3,4,5-trimethylpyrrole (**15**) (297 mg) in methanol (20 ml). Upon addition of (**15**), the solution immediately became orange and to this was added 1 ml of HBr (33%) in acetic acid. Ether (50 ml) was slowly added to the solution and the mixture was left in the refrigerator overnight. The dark-orange crystals were filtered to afford the title compound (473 mg, 76%). Mp >300°C. ^{1}H-NMR: ($CDCl_3$) δ 1.89 (s, 6H, 2 x ring Me), 1.99 (s, 6H, 2 x ring Me), 2.20 (s, 6H, 2 x ring Me), 2.27 (s, 6H, 2 x ring Me), 2.67 (s, 6H, 2 x ring Me), 5.15 (s, 2H, -CH_2-), 7.07 (s, 2H, 2 x methine-H), 13.14 ($s_{(broad)}$, 2H, NH), 13.25 ($s_{(broad)}$, 2H, NH). UV-Vis (CH_2Cl_2): λ_{max}=450 nm (ε 135,000), 526 (70,700). Anal. Calcd. for $C_{29}H_{38}Br_2N_4$: C, 57.82; H, 6.36; N, 9.30. Found: C, 57.95; H, 6.30; N, 9.28.

"DECAMETHYL INTERMEDIATE" OR *δ,δ*-DIHYDRO-1',1,2,3,4,5,6,7,8-NONAMETHYL-*A,B,C*-SMITHERENE, (16)

The same protocol as described above for the preparation (**7**) was applied to the "decamethyl" *a,c*-biladiene (**4**) (13.4 mg). Very little (~2%) of porphyrin was isolated from the mixture and the title compound was isolated in

a 52% yield (5.1 mg). Mp > 300°C, darkened appreciably at 280°C. ^{1}H-NMR: ($CDCl_3$) δ 1.40 (s, 3H, α-Me), 1.77 (s, 6H, 2 x ring Me), 1.83 (s, 3H, ring Me), 1.88 (s, 3H, ring Me), 1.90 (s, 6H, 2 x ring Me), 2.0 (s, 3H, ring Me), 2.03 (s, 3H, ring Me), 2.52 (d, 1H, cis-*d*-CH_2, J_{HH}= 15.3 Hz), 2.98 (d, 1H, trans-*d*-CH_2, J_{HH}= 15.3 Hz), 5.04 (s, 1H, methine-H), 5.35 (s, 1H, methine-H), 6.26 (s, 1H, methine-H), 13.2 ($s_{(broad)}$, 1H, NH), 13.84 ($s_{(broad)}$, 1H, NH). UV-Vis (CH_2Cl_2): λ_{max}=303 nm (ε 15,290), 380 (45,300), 646 (7,980), 704 (9,250). LR mass spectrum: *m/e* 438 (100), 423 (44). HR mass spectrum (FAB) for $C_{29}H_{34}N_4$ requires: 438.2784; Found: 438.2787.

δ'-ETHOXYCARBONYL-δ-HYDRO-δ-METHOXYCARBONYLMETHYL)-1,2,3,4,5,6,7,8-NONAMETHYL-δ-HOMOPORPHYRIN, (21)

The same protocol as that described above for the preparation of (**16**) was applied to *a,c*-biladiene (**19**) (14.6 mg). The title compound was isolated in a 42% yield (4.8 mg). Mp > 300°C, ^{1}H-NMR: ($CDCl_3$) δ 0.94 (d, 2H, ring-CH_2-CO_2Me), 1.54 (t, 3H, $CO_2CH_2CH_3$), 2.40 (s, 3H, ring Me), 2.50 (s, 3H, ring Me), 2.52 (s, 6H, 2 x ring Me), 2.58 (s, 3H, ring Me), 2.64 (s, 3H, ring Me), 2.65 (s, 3H, ring Me), 2.70 (s, 3H, ring Me), 3.12 (s, 3H, -CO_2CH_3), 3.87 ($s_{(broad)}$, 1H, NH), 4.38 (m, 1H, -$CO_2CH_2CH_3$), 4.58 (m, 1H -$CO_2CH_2CH_3$), 5.10 (t, 1H, methine-H), 6.75 ($s_{(broad)}$, 1H, NH), 7.09 (s, 1H, methine-H), 7.83 (s, 1H, methine-H), 7.91 (s, 1H, methine-H). UV-Vis (CH_2Cl_2): λ_{max}=325 nm (ε 25,430), 404 (75,680), 630 (12,000), 662 (13,820). Anal. Calcd. for $C_{34}H_{40}N_4O_4$: C, 72.39; H, 6.94; N, 9.65. Found: C, 72.40; H, 6.88; N, 9.54

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