Anomalous Double Cyclization Reactions of β-Formylporphyrins

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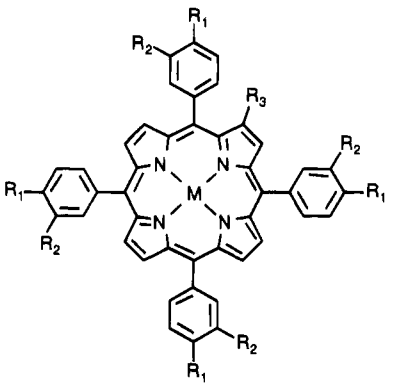
Treatment of nickel(II) and copper(II) complexes of 2(β)-formyl-*meso*-tetraphenylporphyrins with strong acid results in intramolecular cyclization involving the carbonyl carbon and the *ortho*-phenyl position leading to naphthoporphyrin derivatives. However, when electron-releasing groups are present at the *m*-phenyl positions, a second cyclization occurs involving the 3(β) position and the ortho position of the adjacent phenyl ring to give an additional fused ring.

Introduction

Peripheral functionalization of porphyrins in order to introduce biologically significant substituents has been achieved most commonly via a formyl group. Vilsmeier formylation, in which phosphorus oxychloride and *N,N*-dimethylformamide are used to form an iminium complex which is subsequently hydrolyzed, is undoubtedly the most convenient method for the introduction of this functional group.[1-3] With porphyrins, formylation is commonly carried out on Cu(II) or Ni(II) complexes although the effect of other coordinated metals has been investigated.[4] However, demetalation of Cu and Ni complexes of β-formyl-*meso*-tetraphenylporphyrins in strong acid has been shown to result in unusual intramolecular cyclizations involving the carbonyl group and the *ortho* position of the adjacent phenyl moiety to yield naphthoporphyrin derivatives containing an additional fused ring.[4-6] We report here some unexpected observations where a second cyclization, resulting in a fused naphthoindenyl pyrrole as part of the porphyrin skeleton, occurs when methoxyl substituents are present in the meta position. The utilization of the results in developing potential new photosensitizers for photodynamic cancer therapy (PDT) is noted.[7,8]

Results and Discussion

Extending work on stable synthetic bacteriochlorins[9] (with absorption maxima around 800 nm) as effective sensitizers for PDT, we directed our attention toward the synthesis of hydroporphyrins (chlorins and bacteriochlorins) by diimide reduction[10,11] of easily accessible *meso*-tetraphenylporphyrins. By manipulating the substituents at both the phenyl and pyrrolic position it was thought possible to bring about a bathochromic shift of the 740 nm absorption characteristic of bacteriochlorins and at the same time alter the hydrophobicity of the molecule. Toward this goal, we prepared *meso*-tetrakis(*m*-methoxyphenyl)porphyrin (the electron-donating *m*-methoxy group increases the rate of the diimide reduction and improves the yield of the bacteriochlorin product). Formylation of the Cu complex and attempted demetalation of the β-formyl copper porphyrin **1a** at room temperature using 15% H_2SO_4–TFA gave after neutralization, workup, and chromatography, in order of increasing polarity, a brown fraction (A) and two red fractions B and C, the latter being a minor component.



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a: R_1=H, R_2=OCH_3, M=Cu, R_3=CHO
b: R_1=OCH_3, R_2=H, M=Cu, R_3=CHO
c: R_1=H, R_2=OCH_3, M=Ni, R_3=CHO
d: R_1=OCH_3, R_2=H, M=Ni, R_3=CHO
e: R_1=H, R_2=OCH_3, M=2H, R_3=CHO

None of these fractions corresponded to **1e**, the anticipated product. B and C are isomeric and exhibited a parent ion at *m/z* = 758 and a high resolution mass corresponding to a molecular formula $C_{49}H_{34}N_4O_5$ (*four* hydrogen atoms less than the expected demetalated β-formylporphyrin **1e**) indicating two additional rings or unsaturations in the molecule. Based on the previous reports of intramolecular cyclizations of β-formyl-*meso*-

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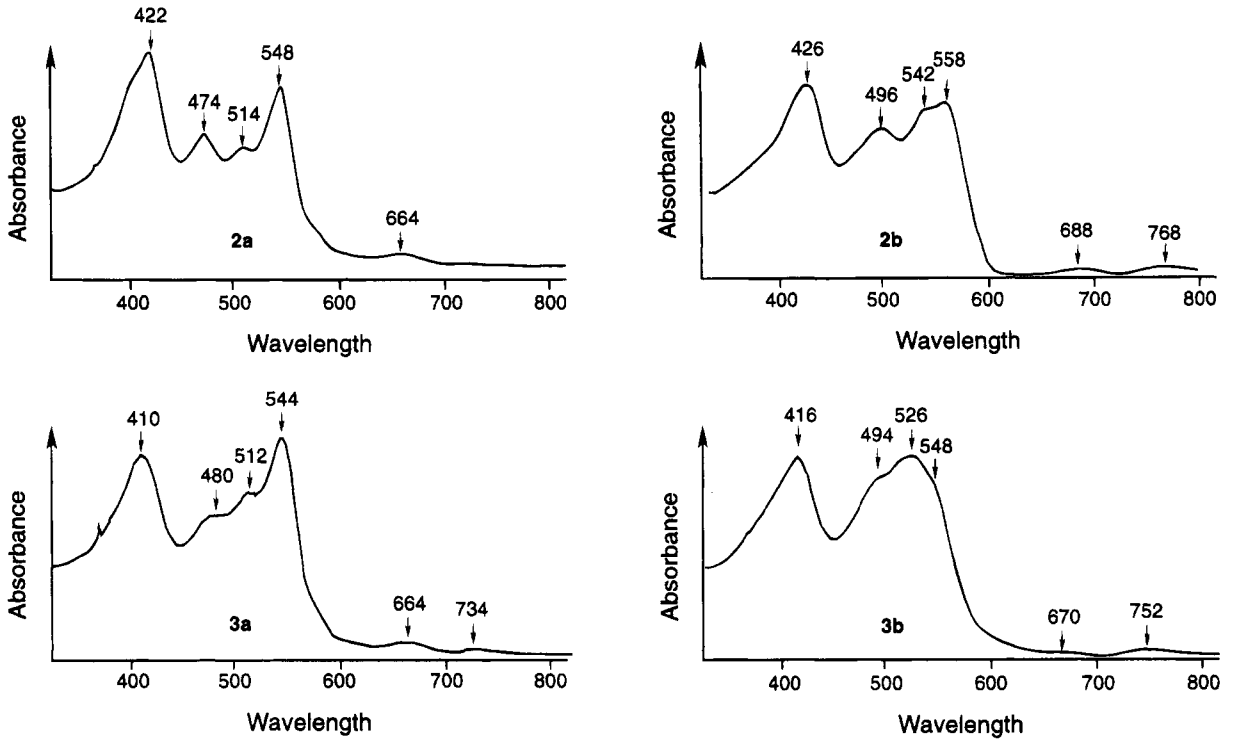
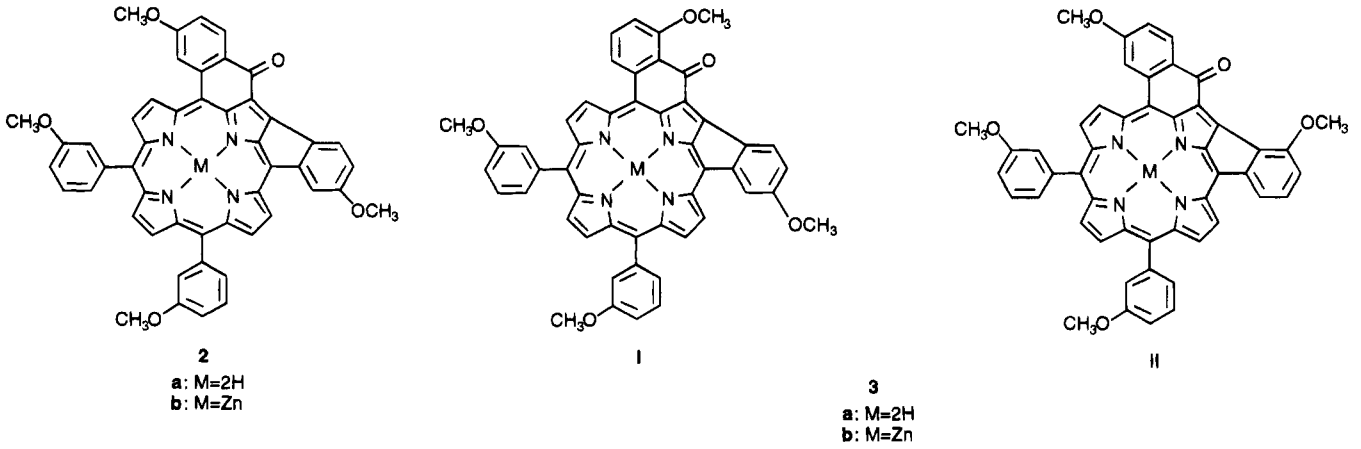


Figure 1. Optical spectra of compounds **2a**, **2b**, **3a**, and **3b** measured in CH_2Cl_2.



tetraphenylporphyrins,[6] the doubly cyclized structures **2** and **3** were postulated with the major fraction (B) corresponding to **2** (M = 2H in each case). The similarity of the UV-visible spectra of **2** and **3** (Figure 1) is consistent with their isomeric nature.

Detailed analysis of the 400 MHz ^1H NMR and the ^1H–^1H COSY spectra of the Zn complex **2b** (Figure 2) established structure **2** for the major red compound (fraction B). The six pyrrole protons were observed as 4 doublets at δ 8.71, 8.48, 8.20, and 8.08 (1H each) and an AB system at δ = 8.16 and 8.13 (2H). The fourteen phenyl protons were observed between an unusually high range δ 5.8–7.9 ppm, and the four methoxy groups were observed as 3 singlets. The upfield positioning of some of the phenyl protons (compared with corresponding protons of the *meso*-tetraphenylporphyrins) could be at least partly due to the reduced aromaticity of the macrocycle which is subjected to a deformation from the usual planar structure (Figure 3a). This interpretation is also supported by the atypical UV-visible spectra of **2a** and **2b** (Figure 1). The ^{13}C NMR spectrum of the Zn complex **2b** exhibited a carbonyl absorption at δ = 182.5 ppm (TMS = 0) and four resonances for the methoxy carbons at δ = 55.44, 55.33, 55.31, and 55.14, the latter confirming the asymmetric nature of the molecule.

There are three other isomers of **2** depending upon the disposition of the two methoxy groups on the fused portion of the molecule. We have only been able to observe and isolate one of these other isomers (**3**, fraction C). Analysis of ^1H NMR and ^1H–^1H COSY spectra of the zinc complex (**3b**) suggests two possible structures (Figure 4) but we were unable to distinguish between the isomers I and II either of which is consistent with the observed spectra.

Further purification of the brown fraction (**A**) gave a major brown compound which exhibited a broad UV-vis absorption at λ_{max} = 430 nm and a weak absorption at λ_{max} = 740 nm. The low resolution mass spectrum showed a parent ion at *m/z* = 744 with an impurity peak at *m/z* = 805 (M + Cu), which suggested structure **4** for this compound. Although relatively stable in an inert atmosphere, **4** decomposed slowly in solution open to the

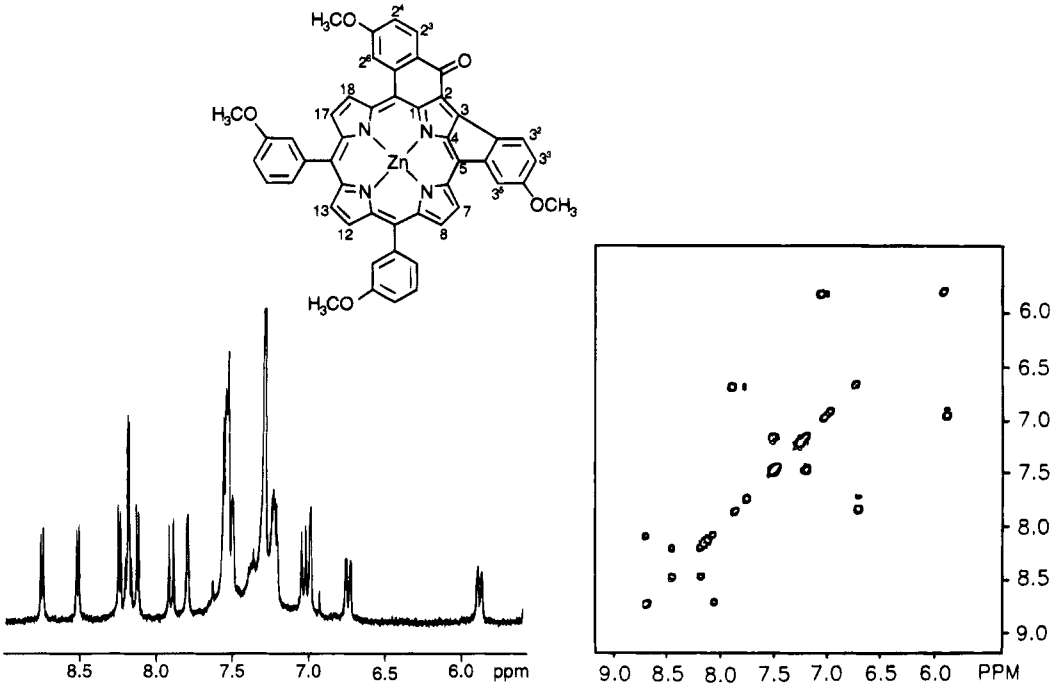


Figure 2. 400 MHz ^1H NMR and $^1H-^1H$ COSY spectra of **2b** measured in $CDCl_3/CD_3OD$.

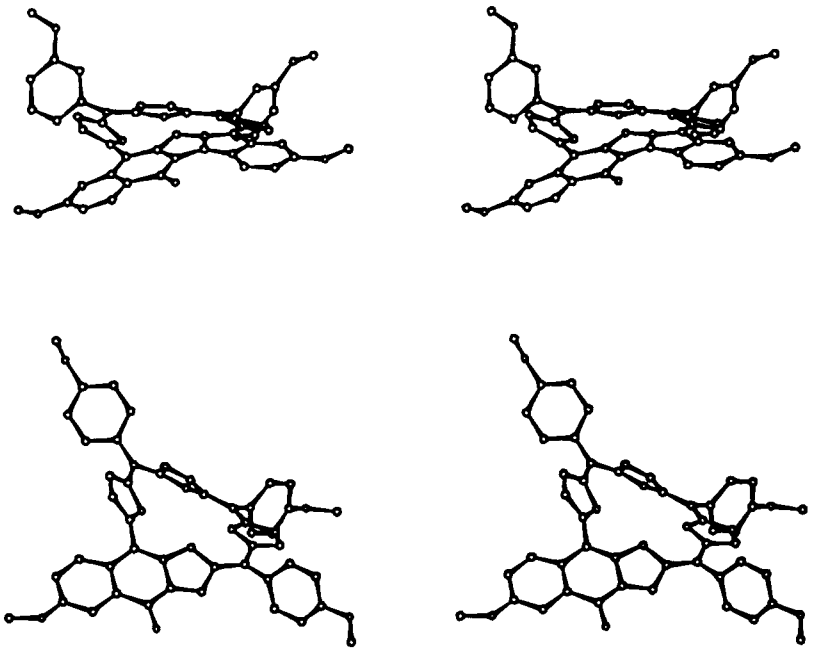


Figure 3. Stereoscopic view of **2a** (upper panel) and **5b** (lower panel). Both structures were minimized using Insight II (Biosym, San Diego).

air to give **2a** and **3a** (as either isomer I or II). The ^1H NMR spectrum of **4** was complex probably due to there being an isomeric mixture as suggested by Callot et al.[6] for analogous monocyclized systems.

In order to further investigate these intramolecular cyclizations, **1a** was treated under mildly acid conditions (2.5% TFA in CH_2Cl_2) at room temperature. Upon neutralization and workup, the most polar component exhibited a strong Soret absorption at 460 nm and its mass spectrum had a parent ion at m/z = 821, corresponding to the copper complex of the monocyclized keto compound **5a**. When treated with 15% H_2SO_4–TFA this demetalated quantitatively to give the free base **5b** instead of undergoing a second cyclization to give **2a**, suggesting that **5a** is not an intermediate in the double cyclization to **2a**. The structure of **5b** (Figure 3b) was confirmed by a detailed analysis of the $^1H-^1H$ couplings in its NMR spectrum and the ^{13}C NMR spectrum of the Zn complex **5c**. The stability of this compound coupled with the visible absorption band at 734 nm suggested that this class of compounds may be good candidates for photosensitizers in PDT. Two less polar components from the reaction mixture (**6a**, **6b**) with similar UV-vis spectra exhibited mass spectral parent ions at m/z = 807, corresponding to a reduced product such as **6a**. These results parallel the observations of Callot *et al.* with unsubstituted tetraphenylporphyrins.[6] After demetallation, further characterization by ^1H NMR was not

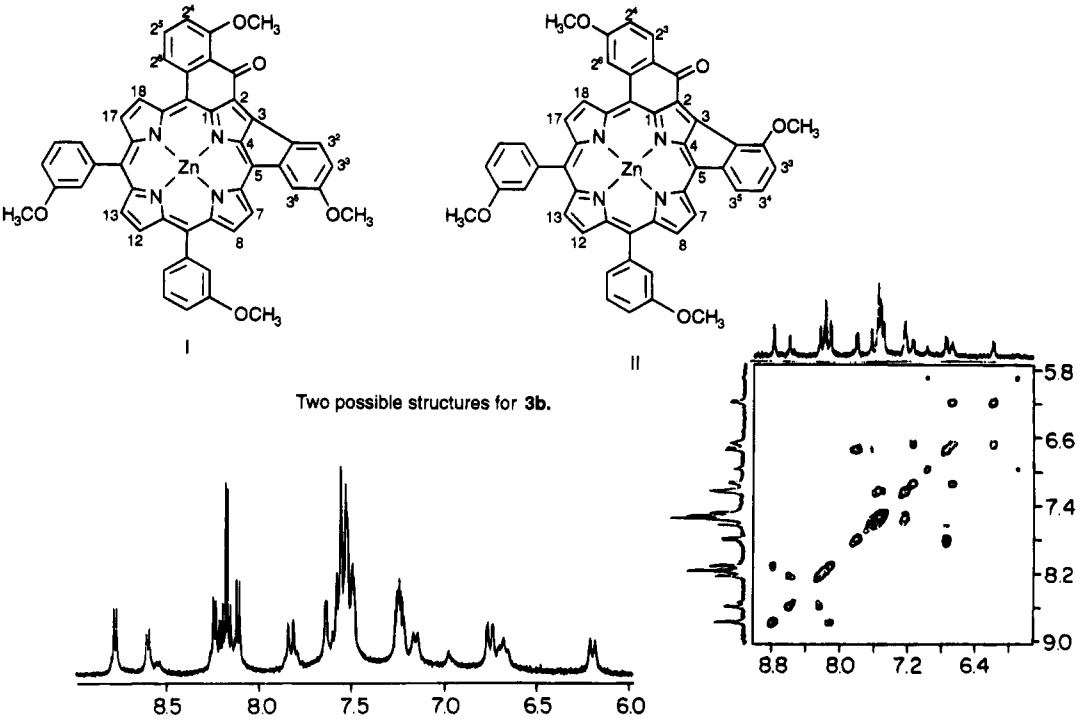
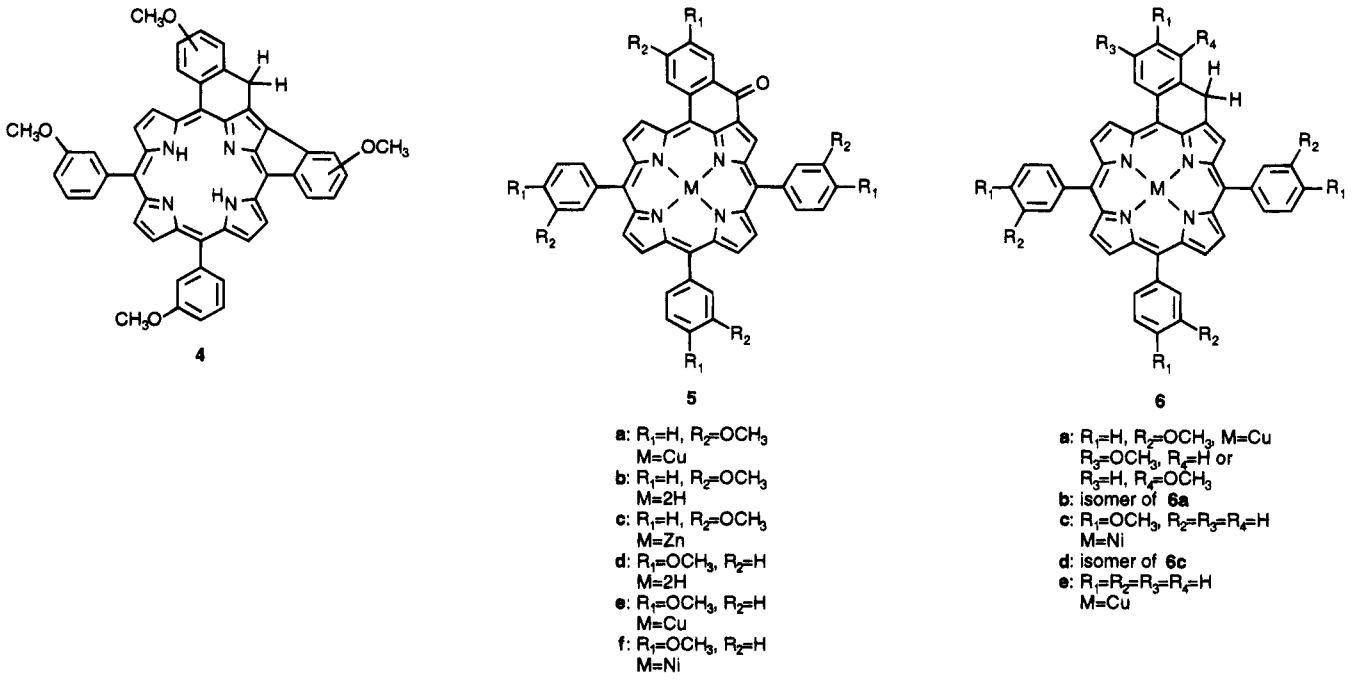


Figure 4. 400 MHz ^1H NMR and $^1H-^1H$ COSY spectra of **3b** measured in CD_2Cl_2/CD_3OD.



possible due to the presence of traces of paramagnetic copper which could not be removed without complete degradation of the compounds.

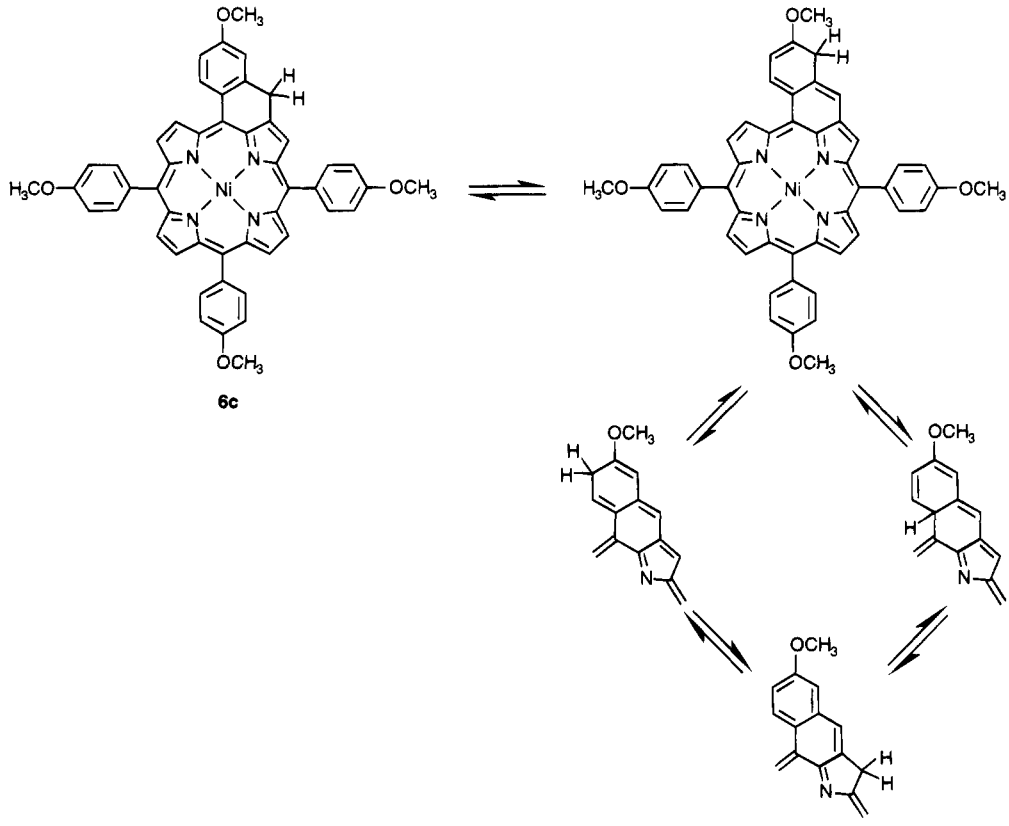
In order to establish that the double cyclization of **1a** in strong acid was the result of activation of the ortho phenyl positions by the electron releasing *m*-methoxy group, the analogous β-formyl-*meso*-(*p*-methoxyphenyl)-porphyrinatocopper complex (**1b**) was prepared and treated with 15% H_2SO_4–TFA. The major product isolated from the reaction mixture was the demetalated monocyclized keto compound **5d**; no dicyclized compounds corresponding to **2**, **3**, or **4** were observed. Although this compound exhibited an optical spectrum similar to that of the meta isomer **5b**, its long wavelength absorption at 768 nm suggested that it will be a better candidate for PDT. The same compound could also be prepared cleanly by treating **1b** with 2% TFA in CH_2Cl_2, isolating the cyclized keto compound as its Cu(II) complex (**5e**) and demetallating with 15% H_2SO_4–TFA. Several *p*-phenyl-substituted analogues were prepared in a similar manner and their UV data are summarized in Table 1.

In order to characterize the cyclization products and identify any transient intermediates by ^1H NMR spectroscopy, the diamagnetic Ni(II) analogues of **1a** and **1b** were prepared and reacted under appropriate acidic conditions. The *m*-methoxy Ni(II) porphyrin **1c** in 15%

Table 1. UV-Visible Data for Monocyclized Keto Compounds 5

compound	λ_{max} (nm), in CH_2Cl_2						
5a	390	434 sh	460	486 sh	592	644	684 sh
5b	398	436 sh	462	488 sh	576	634	734
5c	396	436	464	488	598	654	696 sh
5d	410	446 sh	472	500 sh	588	654	768
5e	404	444 sh	468	496 sh	598	658	722
5f	396	–	470	–	596 sh	652	698 sh

Scheme 1



H_2SO_4–TFA underwent double cyclization–demetalation to give the identical products **2a**, **3a**, and **4**. When the *p*-methoxy Ni(II) porphyrin **1d** was treated with 10% TFA in dichloromethane at room temperature under nitrogen and worked up as before, the monocyclized keto product **5f**, the methylene analogue **6c**, and its isomeric forms **6d** were obtained in 35, 7, and 41% yields, respectively. The yields, optical and ^1H NMR spectra of these three products were similar to those found by Callot et al. on unsubstituted analogues.[6] Compound **6d** appears to be derived from **6c** which together with **5f** are the primary reaction products; **6c** is unstable in solution and slowly isomerized to **6d** and/or oxidized to **5f**. On the other hand, **6d** is very stable and did not oxidize to the ketone **5f** even when a chloroform solution was refluxed for 6 h open to the air. Although compounds **6c** and **6d** exhibit the same mass spectral parent ion, the proton NMR spectrum of **6d** was too complex to interpret as reported by Callot and co-workers with their unsubstituted analogues.

Several experiments were carried out to shed light on the structures of the isomers **6c**/**6d** which correspond to the monocyclized methylene derivatives. Callot et al. have suggested that for the unsubstituted analogue **6e**, the isomerization processes should involve hydrogen migration similar to that shown in Scheme 1 with participation of the fused phenyl ring. When **6c** was stirred in a mixture of $CH_2Cl_2/D_2O/CF_3COOD$ at room temperature, it isomerized to **6d** and some deuterium was incorporated during the isomerization process, but **6d** also incorporated some deuterium under the same conditions, showing that the isomerization is not an acid-catalyzed prototropic rearrangement. Furthermore, when the monocyclization of **1d** was carried out with CF_3-COOD, no deuterium was incorporated into any of the products. Callot et al. also observed that when their unsubstituted analogue **6e** was treated with triethylamine, a strong absorption was observed at 666 nm which they suggested was due to a delocalized anion. Neither **6c** nor **6d** exhibited any change in the UV-visible spectra under similar conditions due, presumably, to destabilization of such an anion by the electron-releasing methoxy groups.

Since any plausible mechanism for the cyclization reaction should involve a carbonium ion intermediate such as **7** (Figure 5), we attempted to detect and identify such a species in the reaction mixture. For this purpose, the β-formyl-*meso*-tetrakis(*p*-methoxyphenyl)porphyrinatonickel(II) (**1d**) was treated with a 10% solution of CF_3COOD in $CDCl_3$ in an NMR tube and the solution examined without neutralization. The features of the ^1H NMR spectrum of the resulting brown solution are consistent with a delocalized carbocation **7** (Figure 5). In particular, the proton H_3^1 appears as a singlet in the

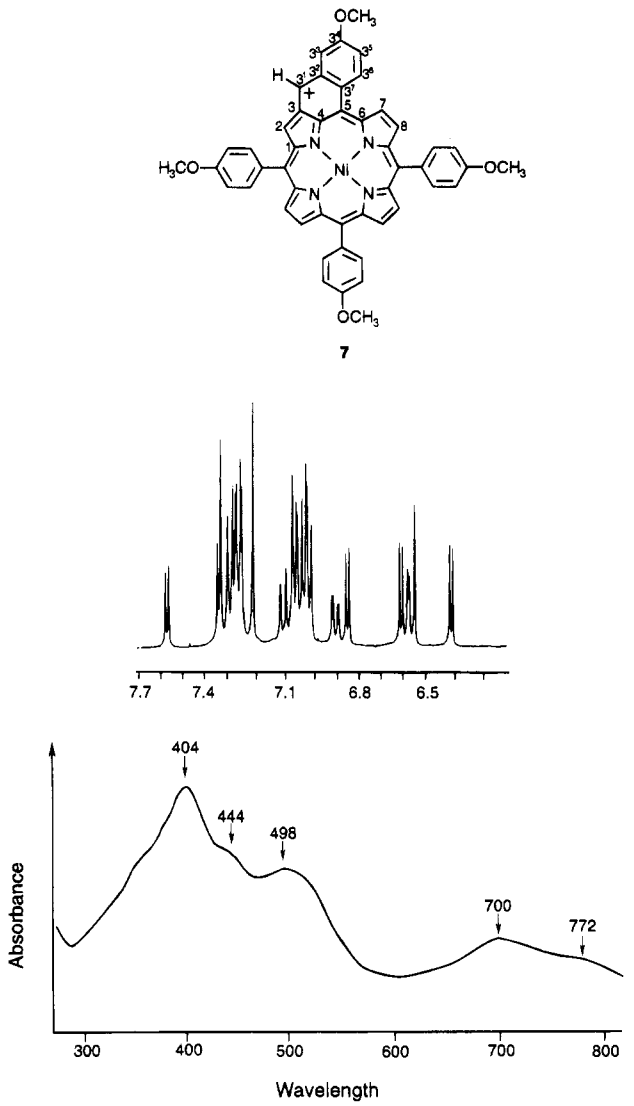


Figure 5. 400 MHz ^{1}H NMR ($CF_3CO_2D/CDCl_3$) and optical spectra ($CHCl_3$/10% TFA) of **7**.

aromatic region (7.37 ppm). This brown solution is stable in an acidic chloroform solution. Dilution with chloroform and attempted precipitation by the addition of methanol/trifluoroacetic acid or neutralization with aqueous bicarbonate resulted in rapid decomposition to give the cyclized keto (**5f**) and methylene derivatives (**6c,d**). The parent ion of the carbonium species could not be observed by mass spectroscopy due to disproportionation under the experimental conditions. However, when the carbonium ion was treated with excess sodium borodeuteride at room temperature, the reaction led to a single product which was shown to be **6c** monodeuteriated on the methylene group, consistent with a carbonium ion structure for **7**.

Callot et al. postulated the existence of a cyclized alcohol as the initial intermediate which subsequently disproportionated to the methylene-bridged and keto-bridged products. When the keto-bridged **5f** in CH_2Cl_2 was reduced with $NaBH_4$ in CH_3OH at room temperature, the secondary alcohol **10** was obtained as the major product together with two minor products **11** and **12** (Scheme 2). The alcohol **10** is unstable and disproportionates to **5f**, **6c**, and **6d** in solution; it is also oxidized rapidly by air in contact with alumina. Although its molecular ion cannot be detected by mass spectroscopy (even in FAB mode) due to disporportionation, the ^{1}H NMR spectrum is consistent with its assigned structure. Furthermore, when the reduction of **5f** was carried out with $NaBD_4$ in $CDCl_3/CD_3OD$ and the resulting alcohol **10** was treated *in situ* with $CF_3COOD/CDCl_3$, it dehydrated to the carbocation **7** as observed by ^{1}H NMR spectroscopy.

Compound **11** exhibits a characteristic chlorin-like UV-visible spectrum and was characterized by ^{1}H NMR and FAB MS. Although **11** is more stable than **10**, it too slowly disproportionates when left in solution.

Reduction of the copper keto porphyrin **5a** to the corresponding alcohol followed by treatment with 15% H_2SO_4 in TFA at room temperature gave, as shown by UV-vis, TLC, and MS analysis, the doubly cyclized free bases **2a** and **4** in significant yield, although neither could be observed when **5a** was treated directly with 15% H_2SO_4/TFA, suggesting that a monocyclized carbonium ion is an intermediate in the double cyclization process of **1a**.

Conclusion

The results presented here are in agreement with Callot's hypothesis that under moderately strong acidic conditions, nickel and copper β-formylporphyrins **1a–d** undergo intramolecular cyclization to give, initially, a cyclic alcohol (e.g. **10**). However, this unstable alcohol undergoes protonation and loss of water to yield a stable delocalized carbocation **7**. We have shown that the alcohol **10**, though too unstable for isolation, can be characterized spectroscopically. Neutralization of **7** with aqueous sodium bicarbonate produces the alcohol which disproportionates (via intermolecular hydride transfer) to give the cyclized keto **5f** and the methylene compounds **6c** and **6d** as products (Scheme 3). The fact that no deuterium incorporation is observed when **1** is cyclized in CF_3COOD further confirms an intermolecular hydride shift during this disproportionation. Analogous carbonium ion formation and/or subsequent disproportionation have previously been described for benzhydrol and its derivatives.[14] Welch and Smith[14b] obtained a brown benzhydryl carbocation when benzhydrol was treated with 100% H_2SO_4, which yielded the methyl ether when reacted with methanol. However, we were unable to isolate the analogous methyl ether after treating **7** with methanol. Bartlett and McCollum[14c] obtained dimethoxybenzophenone and dianisylmethane on treatment of *p,p'*-dimethoxybenzhydrol with trichloroacetic acid (followed by neutralization); no deuterium incorporation was observed on treatment with CCl_3COOD. These results, which are similar to those observed in the present work, have also been used to argue in favor of an intermolecular hydride transfer in the formation of the products.

The mechanism of double cyclization may also involve the initial formation of an unstable alcohol (e.g. **10**) and a stable delocalized carbocation (e.g. **7**). However, activation by an electron-releasing *m*-methoxy group on the

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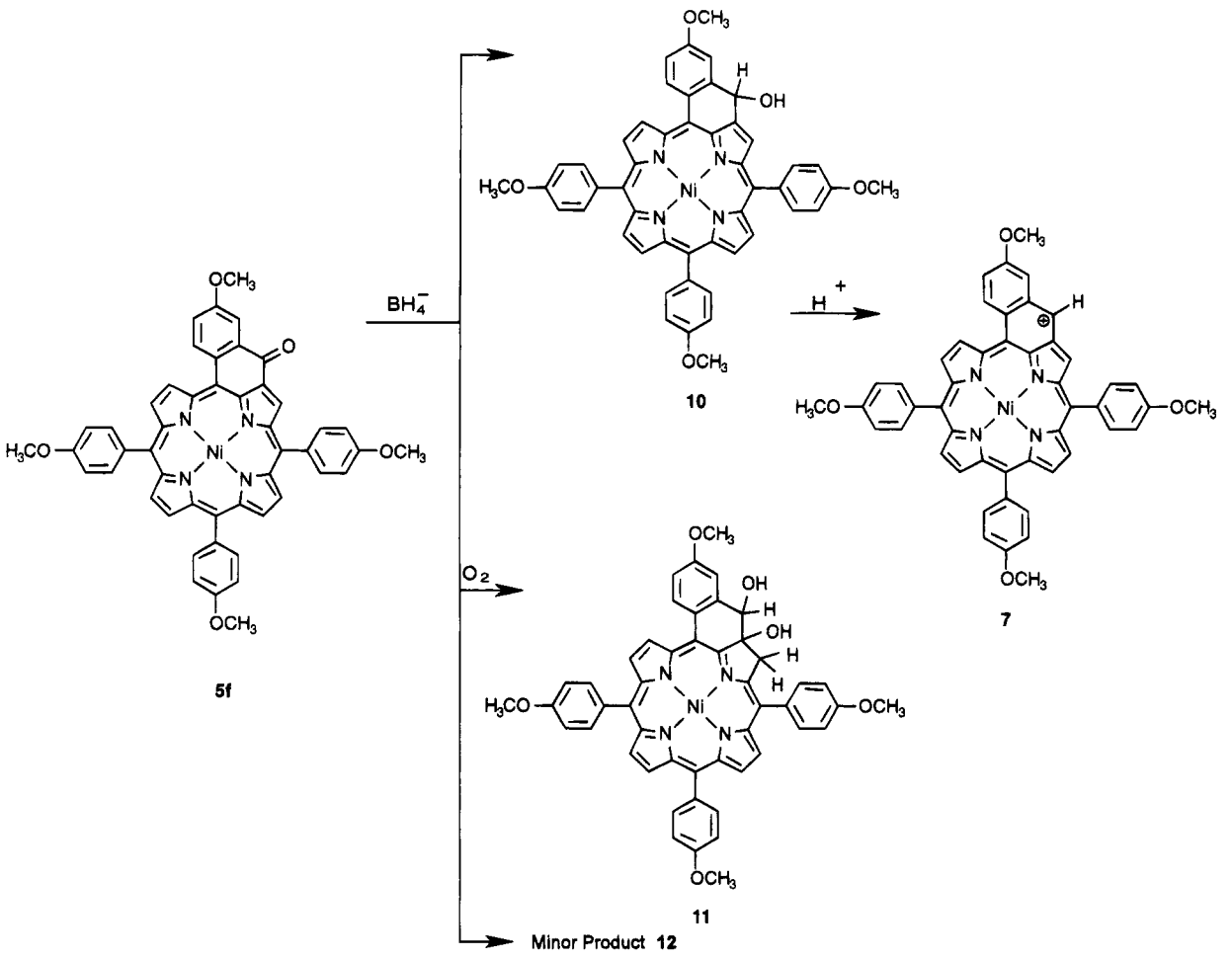
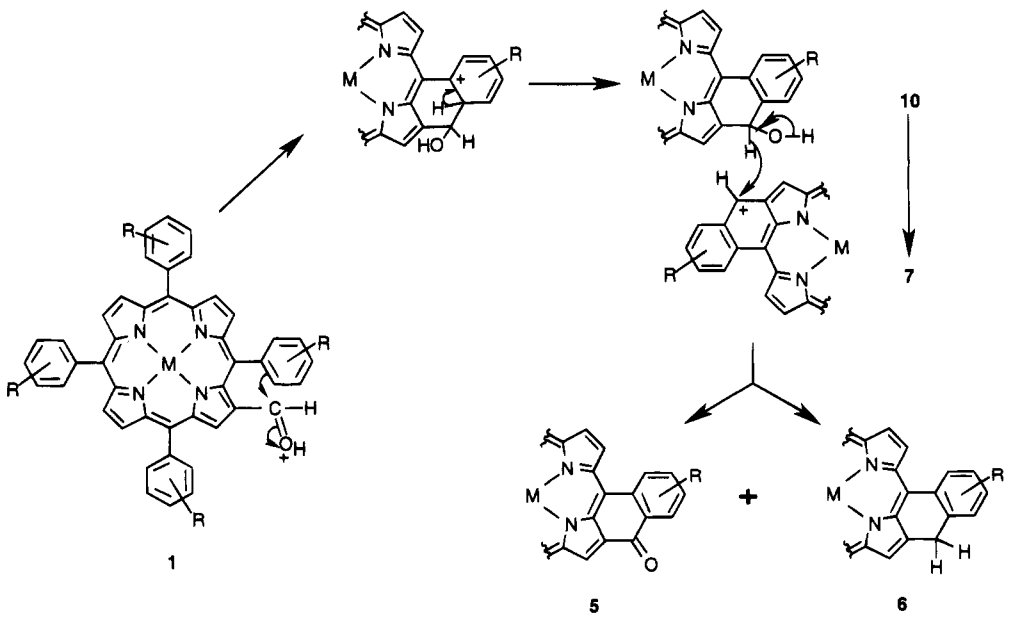
Scheme 2



Scheme 3

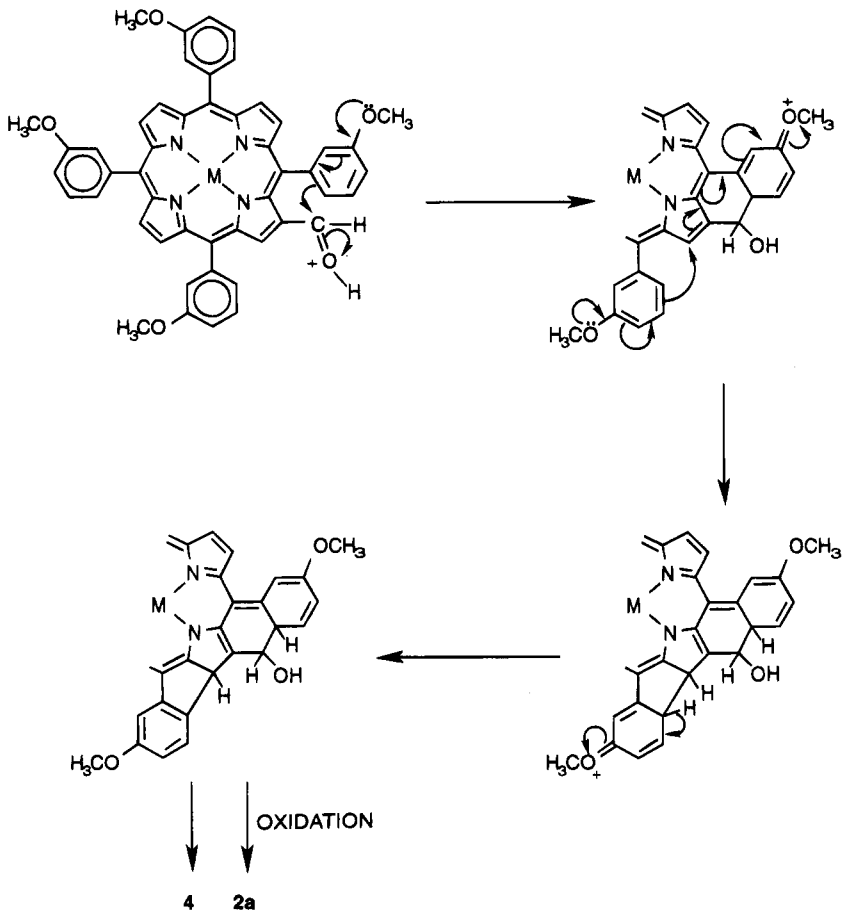


phenyl ring is required for the second cyclization which then occurs under strongly acidic conditions. Under the same conditions the copper complex of the analogous *p*-methoxyphenylporphyrin **1b** did not result in a second cyclization, probably due to the lack of sufficient activation at the ortho phenyl position. A proposed mechanism for the double cyclization based on these observations, is given in Scheme 4. This parallels the mechanism proposed for the cyclization of 7-phenyl-7-hydroxy-7,12-dihydropleiadene to a fluorene derivative through a carbonium ion intermediate.[15]

Experimental Section

NMR spectra were obtained at 300 and 400 MHz on Varian XL-300 and Bruker WH-400 spectrometers. UV-visible spectra were recorded on a Hewlett-Packard 8452A diode array

Scheme 4



spectrophotometer in CH_2Cl_2, except for **2b**, which was dissolved in 10% CH_3OH in CH_2Cl_2 (λ_{max} are given in nm and extinction coefficients (ϵ) in mol^{-1} mL cm^{-1}). Porphyrins and especially metalloporphyrins frequently give irreproducible results upon combustion analysis. This proved to be the case with this series of compounds, and the new compounds reported here were characterized by mass spectral and NMR analysis; the NMR spectra have been deposited as supplementary material. Mass spectra were obtained on a Kratos MS 50 spectrometer (EI, 70eV) and a AEI MS 9 spectrometer (FAB). Chromatographic separations were performed either using columns (Merck 60, 70–230 mesh silica gel, Fisher Florisil 100–200 mesh, or Fisher neutral alumina, Brockmann activity I, 80–200 mesh deactivated with 4% water w:w) or a Chromatotron (Harrison) (Merck 60 PF_{254} silica gel containing gypsum). Reactions were followed by thin layer chromatography (TLC) using Merck 60 F_{254} silica gel plates (0.2 mm thickness).

meso-Tetrakis(methoxyphenyl)porphyrins were prepared following Adler's procedure[16] and were metalated with copper(II) or nickel(II) acetate in DMF also according to literature procedures.[17]

2-Formyl-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrinatocopper(II) (1a). 5,10,15,20-Tetrakis(3-methoxyphenyl)porphyrinatocopper(II) (120 mg, 0.15 mmol) in 1,2-dichloroethane (60 mL) was added within 10 min to a warm solution (50 °C) of a Vilsmeier reagent prepared from *N,N*-dimethylformamide (5 mL, 0.07 mol) and phosphorus oxychloride (7 mL, 0.08 mol). The solution was stirred at 70 °C for 3 h, added to sufficient aqueous sodium bicarbonate solution, and warmed to complete neutralization. The organic phase was isolated, washed with water, and dried (Na_2SO_4) and the product (**1a**) isolated by chromatography followed by recrystallization. Yield 62 mg (50%). UV-vis: λ_{max} (ϵ) 428 (310), 516 (6), 550 (19), 590 (13). EI HRMS *m/z* calcd for $^{63}CuC_{49}H_{36}N_4O_5$, 823.1982, found: 823.1985.

2-Formyl-5,10,15,20-tetrakis(4-methoxyphenyl)porphyrinatocopper(II) (1b). Compound **1b** was prepared according to the procedure described above and obtained in 67% yield. UV-vis: λ_{max} (ϵ) 432 (373), 520 (6), 554 (19), 594 (14). EI HRMS *m/z* calcd for $^{63}CuC_{49}H_{36}N_4O_5$, 823.1982; found: 823.1977.

2-Formyl-5,10,15,20-tetrakis(4-methoxyphenyl)porphyrinatonickel(II) (1d). The Vilsmeier reagent was prepared as described above from DMF (21 mL, 0.27 mol) and $POCl_3$ (30 mL, 0.33 mol). Tetrakis(4-methoxyphenyl)porphyrinatonickel(II) (500 mg, 0.63 mmol) was suspended/dissolved in $CHCl_3$ (250 mL) and added dropwise to the Vilsmeier reagent over 10 min. The porphyrin then completely dissolved in the reaction medium to give a green solution which was refluxed for 18 h. The solution was cooled and worked up as described above, to give 475 mg of **1d** (92% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.32 (2H, 2s), 8.63 (6H, m), 7.90 (8H, m), 7.21 (8H, m), 4.03 and 4.05 (2s). UV-vis: λ_{max}(ϵ): 434 (219), 510sh (6), 544 (14), 582 (11). EI HRMS *m/z* calcd for $^{58}NiC_{49}H_{36}N_4O_5$, 818.2038; found: 818.2031.

2-Formyl-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrinatonickel(II) (1c). Compound **1c** was prepared according to the procedure used for **1d** above. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.32 and 9.24 (2H, 2s), 8.73 (6H, m), 7.56 and 7.25, 3.92, 3.91, 3.91, and 3.89 (12H, 4s). UV-vis: λ_{max} (ϵ) 430 (208), 508 sh (6), 540 (13), 580 (10). EI HRMS *m/z* calcd for $^{58}NiC_{49}H_{36}N_4O_5$, 818.2038; found: 818.2054.

Double Cyclization/Demetalation of 1a. 1a (150 mg, 0.18 mmol) was stirred with 15% H_2SO_4 in TFA (v/v; 13 mL) for 1 h at room temperature. The resulting dark green solution was poured onto ice, extracted with CH_2Cl_2, and washed with

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saturated aqueous $NaHCO_3$, followed by water. The dried organic layer was concentrated and chromatographed on alumina using CH_2Cl_2 as eluent to give a green compound **5b** (2.5 mg, 2% yield), followed by brown **4** (33 mg, 24% yield) and red **2a** (58 mg, 42% yield). Increasing the polarity of the eluent to 0.5% CH_3OH eluted **3a** (5 mg, 4% yield). Further purification using a Chromatotron was necessary to obtain pure products.

5b: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.35 (1H, d, J = 4.7 Hz), 9.26, (1H, s), 8.70 (1H, d, J = 4.8 Hz), 8.65, 8.62, 8.60, and 8.55 (4H, 4d, J = 4.8 Hz), 8.50 (1H, d, J = 8.6 Hz), 7.86 (1H, d, J = 2.2 Hz), 7.65 (9H, m), 7.32 (3H, m), 7.02 (1H, dd, J = 8.5 Hz, J = 2.2 Hz), 4.09, 4.00, 3.98, and 3.97 (12H, 4s), −0.76 (2H, s). UV-vis: λ_{max} (ϵ) 398 (47), 436 sh (52), 462 (137), 488 sh (42), 576 (7), 634 (10), 734 (9). EI HRMS m/z calcd for $C_{49}H_{36}N_4O_5$, 760.2685; found: 760.2677.

4: UV-vis: λ_{max} (rel int) 430 (1), 740 (0.09). EI HRMS m/z calcd for $C_{49}H_{36}N_4O_4$, 744.2737; found: 744.2740.

2a: UV-vis: λ_{max} (ϵ) 410 sh (78), 422 (85), 474 (53), 514 (48), 548 (71), 580 sh (18), 664 (7).

3a: UV-vis: λ_{max} (rel int) 410 (0.93), 480 (0.66), 512 (0.76), 544 (1), 664 (0.09), 734 (0.05).

Metalation of 2a and 3a with Zn(II). Compound **2a** (14 mg, 0.018 mmol) dissolved in CH_2Cl_2 (25 mL), was stirred with $Zn(OAc)_2{\cdot}2H_2O$ (20 mg, 0.092 mmol) in CH_3OH (5 mL) for 15 h at room temperature. CH_3OH (20 mL) was added and the product **2b** precipitated by evaporation of CH_2Cl_2 under reduced pressure, filtered, washed with water and methanol, and dried under vacuum. It was subsequently lyophilized from a benzene solution containing a few drops of methanol and dried for 15 h at 100 °C under vacuum (12 mg, 79% yield).

Metalation of **3a** with Zn^{2+} was performed in a similar way.

2b: ^1H NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ (ppm): 8.71, 8.48, 8.20, 8.08 (4H, 4d, H_7, H_{18}, H_{17}, H_8 respectively, or H_{18}, H_7, H_8, H_{17} respectively; J = 4.8 Hz), 8.16, 8.13 (2H, 2d, H_{12} and H_{13}; J = 4.8 Hz), 7.86 (1H, d, H_{3^2} or H_{2^3}, J = 8.5 Hz), 7.75 (1H, d, H_{3^5} or H_{2^6}, J = 1.8 Hz), 7.48, 7.19 (6H, 2H respectively, 2m, H phenyl), 6.99 (1H, d, H_{2^3} or H_{3^2}, J = 8.5 Hz), 6.95 (1H, d, H_{2^6} or H_{3^5}, J = 1.8 Hz), 6.70 (1H, dd, H_{3^3} or H_{2^4}, J = 8.5 Hz, J = 1.8 Hz), 5.83 (1H, dd, H_{2^4} or H_{3^3}, J = 8.5 Hz, J = 1.8 Hz), 4.01, 3.97, 3.77 (3H, 6H, and 3H respectively, 3s, OCH_3) (Figure 2). UV-vis: λ_{max} (ϵ) 426 (73), 496 (57), 542 (64), 558 (66), 690 (6), 768 (7). EI HRMS m/z calcd for $^{64}ZnC_{49}H_{32}N_4O_5$, 820.1664; found: 820.1659.

3b: ^1H NMR (CD_2Cl_2 + CD_3OD, 400 MHz) δ (ppm): For structure I the NMR spectrum can be interpreted as follows. Structure I (Figure 4): 8.77, 8.60, 8.23, 8.11 (4H, 4d, H_7, H_{18}, H_{17}, H_8 respectively, or H_{18}, H_7, H_8, H_{17} respectively; J = 4.8 Hz), 8.18, 8.15 (2H, 2d, H_{12} and H_{13}; J = 4.8 Hz), 7.82 (1H, d, H_{3^2}, J = 8.5 Hz), 7.63 (1H, d, H_{3^5}, J = 1.8 Hz), 7.54, 7.24 (6H, 2H respectively, 2m, H phenyl), 7.15 (1H, d (meta coupling not detected), H_{2^4} or H_{2^6}, J = 7.5 Hz), 6.75 (1H, dd, H_{3^3}, J = 8.5 Hz, J = 1.8 Hz), 6.68 (1H, t, H_{2^5}), 6.19 (1H, d (meta coupling not detected), H_{2^6} or H_{2^4}, J = 7.5 Hz), 3.97, 3.95, 3.93, 3.73 (12H, 4s, OCH_3).

However for structure II the ^1H NMR spectrum can be interpreted as follows. Structure II (Figure 4): 8.77, 8.60, 8.23, 8.11 (4H, 4d, H_7, H_{18}, H_{17}, H_8 respectively, or H_{18}, H_7, H_8, H_{17} respectively; J = 4.8 Hz), 8.18, 8.15 (2H, 2d, H_{12} and H_{13}; J = 4.8 Hz), 7.82 (1H, d, H_{2^3}, J = 8.5 Hz), 7.63 (1H, d, H_{2^6}, J = 1.8 Hz), 7.54, 7.24 (6H, 2H respectively, 2m, H phenyl), 7.15 (1H, d (meta coupling not detected), H_{3^3} or H_{3^5}, J = 7.5 Hz), 6.75 (1H, dd, H_{2^4}, J = 8.5 Hz, J = 1.8 Hz), 6.68 (1H, t, H_{3^4}), 6.19 (1H, d (meta coupling not detected), H_{3^5} or H_{3^3}, J = 7.5 Hz), 3.97, 3.95, 3.93, 3.73 (12H, 4s, OCH_3). UV-vis: λ_{max} (rel int): 416 (0.99), 494 sh (0.89), 526 (1), 548 sh (0.87), 670 (0.10), 752 (0.11). EI HRMS m/z calcd for $^{64}ZnC_{49}H_{32}N_4O_5$, 820.1664; found: 820.1660.

Monocyclization of 1a. To compound **1a** (50 mg, 6.1 × 10^{-5} mol) dissolved in CH_2Cl_2 (5 mL) was added TFA (1 mL) and the mixture was stirred for 30 min at room temperature and washed with aqueous $NaHCO_3$ and then with water. After drying with Na_2SO_4, a preparative TLC (SiO_2 2 mm thickness, CH_2Cl_2 as eluent) allowed the recovery of a trace of compound **6b** (R_f = 0.8, which appears to be an isomer of **6a**), followed by two major components: the green **6a** (R_f = 0.6), which was lyophilized from a benzene solution (6 mg, 12% yield), and the green **5a** (R_f = 0.3), subsequently precipitated from CH_2Cl_2/hexane (18.5 mg, 37% yield).

6b: UV-vis: λ_{max} (rel int) 446 (1), 600 sh (0.08), 622 (0.09), 680 (0.21), 686 sh (0.17). EI LRMS: 807 (M^+).

6a: UV-vis: λ_{max} (ϵ) 428 (137), 572 (10), 610 (9), 686 (7). EI HRMS m/z calcd for $^{63}CuC_{49}H_{36}N_4O_4$, 807.2033; found: 807.2033.

5a: UV-vis: λ_{max} (ϵ) 390 (47), 434 sh (50), 460 (175), 486 sh (45), 550 (5), 592 (7), 644 (17), 684 sh (11). EI HRMS m/z calcd for $^{63}CuC_{49}H_{34}N_4O_5$, 821.1825; found: 821.1838.

Preparation of 5c. 5a (13 mg, 1.58 × 10^{-5} mol) was treated with a solution of 15% H_2SO_4 in TFA (5 mL, v/v) for 1 h and the workup was performed as indicated above (double cyclization of **1a**). The product was purified by chromatography on silica; the free base **5b** was eluted using 0.5% of CH_3OH in CH_2Cl_2 and then precipitated from CH_2CL_2/hexane (7.2 mg, 9.46 × 10^{-6} mol, yield = 60%). The spectral data of **5b** are given under "Double cyclization/demetalation of **1a**", above. The compound was then metalated with Zn according to the procedure used for **2a** above. ^{13}C NMR: ($CDCl_3$ + CD_3OD, 100 MHz, decoupled spectrum) δ (ppm) 184.0, 163.0, 157.9, 157.8, 157.6, 152.7, 152.1, 152.0, 150.6, 150.3, 149.9, 148.4, 146.6, 145.4, 143.7, 143.4, 142.9, 133.8, 132.9, 132.6, 132.5, 132.4, 131.9, 131.5, 131.4, 130.5, 127.5, 127.4, 127.2, 127.1, 127.0, 126.7, 123.3, 123.1, 121.3, 120.5, 120.4, 120.0, 113.2, 113.1, 113.0, 111.6, 110.6, 55.6, 55.4, 55.36, and 55.34. UV-vis: λ_{max} (rel int) 396 (0.26), 438 sh (0.24), 464 (1), 488 (0.24), 598 (0.03), 652 (0.08), 694 (0.06). EI HRMS m/z calcd for $^{64}ZnC_{49}H_{34}N_4O_5$, 822.1821; found: 822.1823.

Cyclization/Demetalation of 1b. 1b (20.4 mg, 2.48 × 10^{-5} mol), dissolved in 15% H_2SO_4 in TFA (v/v; 10 mL) was stirred for 1 h and the resulting dark green solution treated as with **1a**. Column chromatography on silica gave **5d** using 0.5% to 1% of CH_3OH in CH_2Cl_2 as eluent. The product was recrystallized from CH_2Cl_2/hexane (8 mg, 42% yield). Further purification using Florisil was necessary to obtain a pure product. UV-vis: λ_{max} (ϵ) 408 (64), 446 sh (61), 472 (145), 500 sh (52), 588 (8), 658 (10), 768 (14). EI HRMS m/z calcd for $C_{49}H_{36}N_4O_5$, 760.2685; found: 760.2685.

Double Cyclization/Demetalation of 1c. 1c (2 mg, 2.4 × 10^{-6} mol) was dissolved in 15% H_2SO_4 in TFA (1 mL, v/v) and the solution stirred at room temperature for 6 h. Workup was then performed as described above (double cyclization of **1a**). TLC on silica showed **4** and **2a** as the major products and **3a** as a minor product.

Acid treatment of 1d. 1d (400 mg, 4.9 × 10^{-4} mol) was dissolved in CH_2Cl_2 (80 mL) (red solution) and TFA (8 mL) was added (color turned green). The solution was stirred for 2.5 h at room temperature under N_2 (solution turned brown) and then neutralized with an excess of aqueous $NaHCO_3$. The organic phase was washed with water, dried over Na_2SO_4, and evaporated to dryness. Chromatography on a Chromatotron (eluent CH_2Cl_2 + 1% CH_3OH) afforded, in order of increasing polarity, a red compound **6c** (27 mg, 7% yield), green **6d** (161 mg, 41% yield), and green **5f** (140 mg, 35% yield). All products were recrystallized from CH_2Cl_2/pentane.

6c: ^1H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 9.36 (1H, d, J = 5.0 Hz), 8.78 (1H, d, J = 4.9 Hz), 8.68, 8.67, 8.65 and 8.62 (4H, 4d, J = 5.0 Hz), 8.58 (1H, t, J = 1.7 Hz), 7.99 (1H, d, J = 8.8 Hz), 7.29 (1H, d, J = 2.7 Hz), 7.13 (1H, dd), 7.87 (6H, m), 7.20 (6H, m), 5.06 (2H, br s), 4.03, 4.02, 4.01, 3.95 (12H, 4s). Structure of **6c** and peak assignments were determined by irradiation and differential NOE. ^{13}C NMR ($CDCl_3$, 75 MHz, decoupled spectrum) δ (ppm): 159.3, 159.2, 158.2, 142.6, 142.4, 142.3, 141.0, 139.6, 138.9, 137.8, 137.6, 137.2, 134.7, 134.6, 134.5, 133.9, 133.8, 133.5, 133.1, 133.0, 132.8, 132.3, 132.1, 132.0, 131.9, 131.7, 128.2, 125.9, 118.3, 117.9, 114.7, 113.8, 113.4, 112.6, 112.5, 112.4, 112.3, 110.8, 55.5, 32.0. UV-vis: λ_{max} (rel int) 440 (1), 556 (0.06), 598 (0.05). EI HRMS m/z calcd for $^{58}NiC_{49}H_{36}N_4O_4$, 802.2089; found: 802.2090.

6d: ^1H NMR ($CDCl_3$, 300 MHz): OCH_3 singlet peaks found, δ (ppm) 4.21, 4.19, 4.14, 4.13, 4.10, 4.08, 4.07, 4.05, 4.02, 4.01, 4.00, 3.99, 3.98, 3.97, 3.93 (see ref 6). UV-vis: λ_{max} (rel int): 436 (1), 564 (0.09), 608 (0.11), 672 (0.08). EI HRMS m/z calcd for $^{58}NiC_{49}H_{36}N_4O_4$, 802.2089; found: 802.2082.

5f: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.13 (1H, d, J = 5.1 Hz), 9.10 (1H, s), 8.63 (1H, d, J = 5.1 Hz), 8.48, 8.46, 8.36, and 8.35 (4H, 4d, J = 5.0 Hz), 7.95 (1H, d, J = 2.8 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.80 (6H, m), 7.24 (1H, dd, J = 8.8 Hz, J = 2.8 Hz), 7.19 (6H, m), 4.01, 4.00 and 3.99 (6H, 3H and 3H respectively, 3s). The structure of **5f** and peak assignments were determined by irradiation (H_{3^8}) and differential NOE (H_{3^3}, H_{3^6}). ^{13}C NMR ($CDCl_3$, 75 MHz, decoupled spectrum) δ (ppm): 182.1 (1C, C=O), 159.7, 159.5, 159.4, 159.3, 145.4, 145.3, 144.1, 143.8, 142.9, 140.5, 139.4, 139.1, 136.1, 135.1, 134.7, 134.5, 134.3, 133.9, 133.8, 133.5, 133.4, 133.1, 132.5, 132.2, 132.0, 131.9, 131.5, 131.3, 125.1, 120.8, 120.4, 118.1, 112.7, 112.65, 112.6, 112.2, 109.4, 55.7, 55.6, and 55.5. UV-vis: λ_{max} (ε) 396 (73), 470 (197), 596 sh (10), 652 (23), 698 sh (17). EI HRMS m/z calcd for $^{58}NiC_{49}H_{34}N_4O_5$, 816.1883; found: 816.1874.

In Situ Generation of the Carbonium Ion 7. 1d (5 mg, 6.1×10^{-6} mol) was dissolved in $CDCl_3$ (1 mL) and 0.1 mL of CF_3COOD added. The solution was stirred for 2 h at room temperature under N_2. The brown solution was then filtered and transferred into an NMR tube. For UV-vis analysis the solution was diluted in $CHCl_3$ + 10% TFA. ^{1}H NMR (400 MHz) δ (ppm): 7.59 (1H, d, J = 5.4 Hz), 7.38 (1H, d, J = 5.4 Hz), 7.37 (1H, s), 7.32 (6H, m), 7.12 (1H, d, J = 9.1 Hz), 7.04 (6H, m), 6.90 (1H, dd, J = 9.1 Hz, J = 2.6 Hz), 7.07 and 6.64 (2H, 2d, J = 5.2 Hz), 6.85 and 6.43 (2H, 2d, J = 5.1 Hz), 6.61 (1H, d, J = 2.6 Hz), 6.58 (1H, s), 3.95, 3.93, 3.92, and 3.83 (12H, 4s). ^{13}C NMR ($CDCl_3$, 75 MHz, decoupled spectrum) δ (ppm): 163.0, 161.0, 160.7, 160.4, 159.9, 159.8, 155.9, 152.6, 151.9, 150.5, 148.3, 146.2, 144.3, 144.0, 140.1, 138.9, 137.1, 136.8, 136.6, 135.6, 135.0, 133.5, 133.0, 132.8, 132.7, 132.6, 132.1, 131.5, 130.9, 128.4, 128.0, 127.7, 124.4, 116.0, 115.6, 114.6, 114.5, 113.8, 55.94, 55.87, and 55.79. UV-vis: λ_{max} (rel int) 404 (1), 444 sh (0.74), 498 (0.66), 700 (0.38), 772 sh (0.30).

Quenching of 7 by $NaBD_4$. A solution of **7** in $CDCl_3$–TFA-*d* prepared from 5 mg of **1d** was rapidly poured in a flask (ice bath) containing a large excess of $NaBD_4$ (50 mg, 1.2×10^{-3} mol) partly dissolved in CD_3OD (0.1 mL). The color immediately turned red-green and hydrogen was evolved from the solution which was stirred for 5 min, filtered, and transferred into an NMR tube. TLC and UV-vis spectra of the product in solution were consistent with those of **6c**. ^{1}H NMR spectrum (300 MHz) displayed the characteristic peaks of **6c**, except that integration showed the methylene group was monodeuterated. The broadness of the peak prevented observation of a ^{2}J H–D coupling. The product had a tendency to rapidly isomerize into **6d**. EI HRMS m/z calcd for $^{58}NiC_{49}H_{35}DN_4O_4$, 803.2153; found: 803.2160.

Reduction of 5f with $NaBH_4$. To a solution of **5f** (40 mg, 4.9×10^{-5} mol) in CH_2Cl_2 (20 mL) was added a solution of $NaBH_4$ (80 mg, 2.1×10^{-3} mol) in CH_3OH (4 mL) at 0 °C, under N_2. The solution became reddish-green and was stirred for 30 min. Acetic acid (2.5 mL) was added to quench the excess of $NaBH_4$. The organic phase was quickly washed with water and dried over Na_2SO_4. The products were separated as fast as possible on a Chromatotron (eluent CH_2Cl_2 + 1% CH_3OH); chromatography yielded monocyclized nickel porphyrins **6c**, **6d**, and **5f** and then the alcohol **10** (which was immediately analyzed) and the chlorin **11**, which was recrystallized from CH_2Cl_2/pentane (1 mg, 2% yield).

10: ^{1}H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 9.38 (1H, d, J = 5.0 Hz), 8.83 (1H, d, J = 1.5 Hz), 8.79 (1H, d, J = 5.0 Hz), 8.64, 8.63, 8.61 and 8.58 (4H, 4d, J = 5.0 Hz), 7.94 (1H, d, J = 8.7 Hz), 7.87 (6H, m), 7.67 (1H, dd, J = 2.7 Hz, J = 0.8 Hz), 7.22 (6H, m), 7.17 (1H, dd, J = 8.7 Hz, J = 2.7 Hz), 6.58 (1H, br d, J = 8.8 Hz), 4.04, 4.03, 4.01, and 3.99 (12H, 4s), 2.80 (1H, d). UV-vis: λ_{max} (rel int): 444 (1), 558 (0.06), 600 (0.07).

11: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ (ppm): 8.64 (1H, d, H_7, J = 4.9 Hz), 8.54 (1H, d, H_8, J = 4.9 Hz), 8.33, 8.10, 8.21 and 8.17 (4H, 4d, coupled pairs of H pyrrole, J = 4.9 Hz), 7.77 (6H, br m, H ortho phenyl), 7.56 (1H, d, H_{3^6}, J = 8.5 Hz), 7.57 (1H, dd, H_{3^3}, J = 2.6 Hz, J = 0.9 Hz), 7.15 (6H, m, H meta phenyl), 7.10 (1H, dd, H_{3^5}, J = 8.5 Hz, J = 2.6 Hz), 5.64 (1H, d, *CH*OH, J = 10.7 Hz), 4.33 and 3.87 (2H, 2d, CH_2, J = 16.2 Hz), 2.94 (1H, d, CHO*H*), 2.05 (1H, s, O*H*), 4.00, 3.98, 3.96, and 3.95 (12H, 4s, OCH_3). Peak assignments were confirmed by addition of D_2O and a ^{1}H–^{1}H COSY spectrum. UV-vis: λ_{max} (rel int) 408 sh (0.29), 432 (1), 590 sh (0.10), 616 (0.16). FAB MS m/z 837 (M^+ + 1).

Reduction of 5f by $NaBD_4$. Acid Treatment of Deuterated 10. ^{1}H NMR Study. To a solution of **5f** (3 mg, 3.7×10^{-6} mol) in CH_2Cl_2 (1 mL) was added, with magnetic stirring, a large excess of $NaBD_4$ (20 mg, 4.8×10^{-4} mol) partly dissolved in CH_3OH (0.1 mL) at 0 °C and under N_2. The solution was stirred for 30 min and evaporated to dryness (vacuum pump, room temperature). $CDCl_3$ (1 mL) was added to the residue and the solution filtered and transferred into an NMR tube. The ^{1}H NMR spectrum (300 MHz) exhibited the characteristic features of **10** except that the C*H*OH peak at 6.58 ppm had disappeared and the H_2 signal had collapsed to a singlet, the H_{3^3} signal to a doublet and the OH signal to a singlet. The spectrum showed the other characteristic peaks of **5f**. Yield was 95% (estimated by NMR).

CF_3COOD (0.1 mL) was then added to the tube and the solution shaken for 5 min. The color turned from red to brown, and the ^{1}H NMR spectrum exhibited the peaks characteristic of **7** and **5f** (proportions 74:26), except that the signal at 7.37 ppm (for H_{3^1}, compound **7**) was missing.

Reduction and Subsequent Acid Treatment of 5a. The reaction was run on an analytical scale. **5a** (1 mg, 1.2×10^{-6} mol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled in an ice bath, and a solution of $NaBH_4$ (2 mg, 5.3×10^{-5} mol) in CH_3OH (0.1 mL) was added with stirring. The reaction mixture was stirred for 1 h and the disappearance of the ketone checked by UV-vis. 15% H_2SO_4 in TFA (v:v; 0.4 mL) was added to the mixture. The color turned brown from red-green and then slowly became dark green. The solution was stirred for 4 h and then worked up (see experimental on double cyclization of **1a**). TLC (eluant CH_2Cl_2 + 1% CH_3OH) and EI-MS indicated the presence of **2a** and **4** and to a smaller extent **3a** and **5a** in the crude product.

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Supplementary Material Available: ^{1}H-NMR spectra for compounds **1c,d**, **5b**, **2b**, **3b**, **6c**, **6d**, **5f**, **7**, **10**, and **11** and a COSY spectrum for **11** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.