The Synthesis of the Dimethyl Ester of Quino[4,4a,5,6-*efg*]-Annulated 7-Demethyl-8-deethylmesoporphyrin and Three of Its Isomers with Unprecedented *peri*-Condensed Quinoline Porphyrin Structures. Molecules with Outstanding Properties as Sensitizers for Photodynamic Therapy in the Far-Red Region of the Visible Spectrum

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The mesoporphyrin dimethyl ester nickel complex has been formylated via the Vilsmeier method. The four possible mono meso-formyl derivatives were isolated and characterized. Wadsworth–Emmons coupling with the anion of (diethylphosphono)acetonitrile converted these aldehydes into the four novel meso acrylonitriles. Brief treatment of these acrylonitrile systems in hot trichloroacetic acid resulted in the formation of four achiral porphyrin derivatives with unprecedented nickel complexes of quino-fused porphyrins. Subsequent removal of the nickel gave four quino-porphyrin free bases: quino[4,4a,5,6-*efg*]-annulated 7-demethyl-8-deethylmesoporphyrin dimethyl ester **6a**, 2′-(methoxycarbonyl)quino-[4,4a,5,6-*jkl*]-annulated 12-demethyl-13-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin dimethyl ester **6b**, 2′-(methoxycarbonyl)quino[4,4a,5,6-*qrs*]-annulated 18-demethyl-17-de(2′-methoxycarbonylethyl)mesoporphyrin dimethyl ester **6c** and quino[4,5,6,7-*abt*]-annulated 2-demethyl-3-deethylmesoporphyrin dimethyl ester **6d**. The structures of these systems were unambiguously determined via mass spectroscopy and a plethora of NMR techniques. In the same way, etioporphyrin and octaethylporphyrin were converted into the corresponding *peri*-condensed quinoporphyrins as products, which shows that the formation of novel *peri*-condensed quino-porphyrins is a general reaction in the porphyrin series and will have a wide scope in this field. Also, a plausible reaction mechanism for the formation of the quinoporphyrin systems was derived. As a first test for the use of these systems as sensitizers in far-red phototherapy, the quantum yield of singlet oxygen generation by **6a** in toluene was studied. This quantum yield is 0.77, which is even higher than the singlet oxygen generation by sensitized meso-tetraphenylporphyrin. Secondly, when Chinese Hamster ovary (CHO) cells were incubated in medium which contained up to 15 μg/ml of **6a**, the survival rate of the cells in the dark is complete within experimental error, showing that under these conditions, **6a** is not toxic to CHO cells. When CHO cells incubated in medium containing **6a** in concentrations of 1 μg/ml and higher were treated with white light of intensity 30 mW/cm^2 for 15 minutes, complete cell death was observed. Based on these facts, we expect that all four achiral systems will show very promising properties to form the basis of a photodynamic therapy in far-red light. The fact that these systems are achiral is an additional bonus for medical applications.

Introduction

Porphyrin systems play an essential role in various life processes. The iron-containing porphyrin, haem, is the ligand in haemoglobin and myoglobin. The binding of oxygen to haem in haemoglobin is responsible for oxygen transport in blood, whereas its binding to myoglobin is responsible for oxygen storage in muscle tissues. In cytochromes, catalases and peroxidases, the haem active site is responsible for redox reactions, electron transport in the cell and detoxification of toxic side-products formed during the oxidation processes in the cell. In photosynthetic organisms, chlorophyll and bacteriochlorophyll harvest light-energy, and in the photosynthetic reaction centers, these cofactors are directly involved in the redox processes that lead to the energy-rich organic molecules that are the basis of

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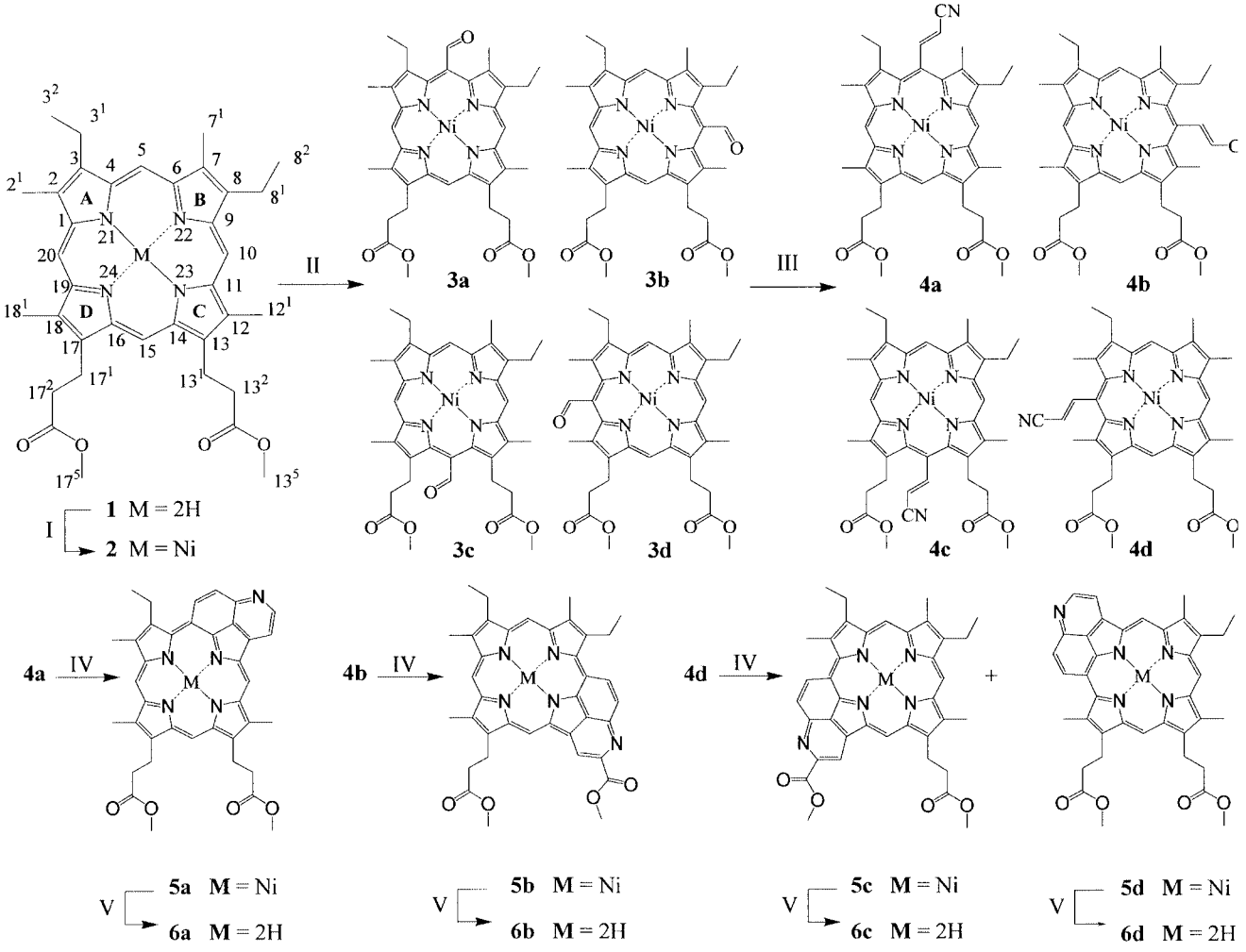
all natural material and the energy requirements of organisms.[1,2]

The physical, chemical and biological properties of porphyrins make them useful in many applications in society; for example, Photofrin, a hematoporphyrin derivative, is used in photodynamic cancer therapy.[3] However, these compounds are not ideal for photodynamic therapy because of their low stability, the presence of chiral atoms, and an inadequate selectivity between uptake by tumor tissue and healthy tissue. Worldwide, many investigators are presently involved in finding new systems based on porphyrins that fulfil the requirements for application in photodynamic therapy much better.[3] Examples of these new photosensitizers include BPD-ME, NPe_6, SnEt, mTHPC[3] and Sylsens B.[4]

Ideally, the photosensitiser that is needed has to be stable in the dark, and non-toxic to cells and tissue in the dark. Preferably, only malignant cells and tissue should preferentially absorb it, and under near infrared irradiation in the presence of oxygen it should produce reactive oxygen species that will destroy the cells in which it is located. The porphyrin itself should be completely stable towards light and singlet oxygen. Some time ago, we described the case of bacteriochlorin as a sensitizer in photodynamic therapy.[5,6] Bacteriochlorin absorbs light in the near infrared at 760 nm, it is not toxic and it shows efficient discrimination between healthy and diseased tissue. However, its instability towards near infrared light in the presence of oxygen and its unavailability in sufficient quantities prevent its successful use as sensitizer in photodynamic therapy.

In our new approach to finding porphyrin derivatives that will fulfil the requirements for an effective photodynamic therapy that we discuss in this paper, we selected mesoporphyrin dimethyl ester **1** (MPdme, Scheme 1, com-



I) $Ni(OAc)_2$ $4H_2O$, dimethylformamide; II) methylformanilide, $POCl_3$, dichloroethane, rt.; III) diethyl phosphono acetontrile, NaH, tetrahydrofuran, reflux. IV) trichloroacetic acid, 175°C, 2 minutes; V) conc. H_2SO_4, rt.

Scheme 1. Structure and semi-systematic IUPAC numbering of mesoporphyrin dimethyl ester (**1**) and its nickel(II) complex **2**. Conversion into the quino[4,4a,5,6-*efg*]-fused 7-demethyl-8-deethylmesoporphyrin dimethyl ester **6a**, the 10^5-(methoxycarbonyl)quino[4,4a,5,6-*jkl*]-fused 12-demethyl-13-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin dimethyl ester **6b**, the 17^4-(methoxycarbonyl)quino[4,4a,5,6-*qrs*]-fused 18-demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin dimethyl ester **6c** and the quino[4,5,6,7-*abt*]-fused 2-demethyl-3-deethylmesoporphyrin dimethyl ester **6d**

pound **1**) as starting material. MPdme (**1**) can be prepared in essentially quantitative yield by catalytic hydrogenation of protoporphyrin dimethyl ester,[7] which is available on a 1000 kg scale at reasonable prices.[8,9] Our approach to the preparation of novel stable porphyrin derivatives using mesoporphyrin dimethyl ester **1** as starting material is based on the special chemical reactivity of sterically constrained porphyrin systems that has been published in the literature.

A key step in the total synthesis of chlorophyll by Woodward is based on the fact that a substituent on a meso position shows unique chemical properties, due to the steric hindrance exerted by the neighboring groups on the pyrrole positions. This allows the simple oxidation of the meso propionic ester group into the corresponding acrylic ester (Figure 1, I → II), which undergoes proton-catalyzed ring closure with the neighboring pyrrole carbon. The purpurin (III) derivative formed in this cyclization reaction was then converted into chlorophyll via a number of steps.[10]

Later, a similar conversion of the meso acrylic ester derivative of octaethylporphyrin was reported. The purpurin system based on octaethylporphyrin has a λ_{max} value shifted to the near infrared (695 nm).[11,12] Related reactions with the corresponding nickel-containing acrylaldehyde (IV) and acrylic alcohol (V) derivatives in sulfuric acid gave benzochlorin (Figure 1, VI) with loss of the Ni^{2+}.[13,14]

Thermolysis of the trimethylammonium salt VII gave the cyclohexadiene system with a 3-*exo*-ethylidene group with a *Z*/*E* ratio of 10:7 (VIII-Z and VIII-E in Figure 1).[15] The nickel-free forms of VIII-Z and VIII-E have also been prepared starting from octaethylporphyrin with a meso 1′-allylic alcohol substituent.[16] Treatment of nickel-free VIII-Z and VIII-E in phosphoric acid at 80 °C gave VI.

It is interesting that different functional groups lead to two different types of products; i.e. the ester, as opposed to the aldehyde and alcohol substituents. In the case of the ester functionality, a bond between the β-atom of a neighboring pyrrole group and the α-carbon atom of the acrylic ester side-chain is formed, giving purpurins without further skeletal rearrangement. In the case of the acrylic aldehyde, the carbonyl carbon attacks the β-pyrrole carbon atom. After the initial attack, skeletal rearrangement, loss of water and reduction take place, leading to the benzochlorin derivative VI. For the allylic alcohol V, after protonation, the elements of water are eliminated, resulting in the formation of an allylic cation. A similar attack of this cation on the β-pyrrole atom gives a dihydro benzochlorin derivative with similar skeletal rearrangement and final oxidation to the same condensed benzene system VI. In the case of the reaction of VII in refluxing 1,2-dichloroethane, the same allylic cation is formed without skeletal rearrangement and with final proton loss to form an *exo*-ethylidene group VIII in both *Z* and *E* forms. Interestingly, during the reactions of V and VII, the same allylic cation must be formed. It is clear that the final product strongly depends on the reaction medium, for example, sulfuric acid in the first case and the neutral 1,2-dichloroethane in the other case.

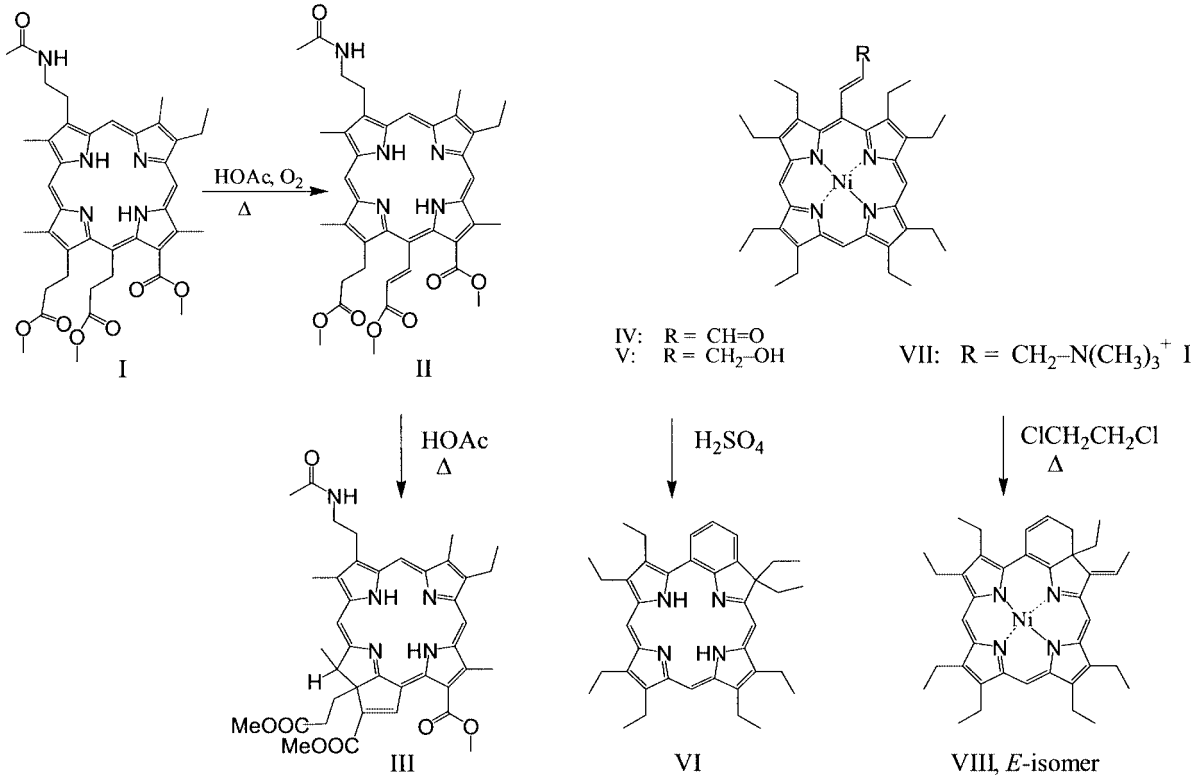


Figure 1. The structures of III, VI, *E*- and *Z*- VIII and their formation from I, IV, V and VII

In the present work, we focussed on the possible reactivity of meso acrylonitrile derivatives. We wondered whether a purpurin or a benzochlorin would be formed, but we hoped that the nitrile functionality would open up a completely new type of reactivity in the porphyrin series.

Syntheses

Mesoporphyrin dimethyl ester (**1**) (Scheme 1, 110 g, 0.18 mol) dissolved in dimethylformamide (1.5 L) containing nickel acetate (50 g, 0.20 mol) was refluxed for 20 minutes. After evaporation of the solvent under reduced pressure at 80 °C and subsequent silica gel chromatography, mesoporphyrin dimethyl ester nickel complex **2** (103 g, 0.16 mol, 86%) was obtained (see Scheme 1). Vilsmeier formylation was accomplished following method B, as described by Kirillova et al. using methylformanilide and $POCl_3$ at room temperature, yielding a mixture of four monoformyl derivatives (93 g, 0.14 mol, 87%).[17] On an analytical scale, the aldehydes **3a** and **3c** could be isolated in pure form by silica gel chromatography together with a mixture of **3b** and **3d**. Using NMR spectroscopy, we established their structures, and deduced that the four formylated isomers were formed in the ratio **3a**:**3b**:**3c**:**3d** = 1:1:0.4:2. This ratio is in agreement with our expectation. The introduction of a formyl group at position 20 (**3d**) leads to the least amount of steric hindrance, because only the very small methyl groups are involved. In **3a** and **3b**, the steric hindrance is due to one methyl group and one (bigger) ethyl group, whereas **3c** suffers from the interaction of two ethyl groups.

The mixture of the four monoformyl derivatives (**3a**, **3b**, **3c** and **3d**) was converted into the corresponding meso acrylonitrile derivatives **4a**, **4b**, **4c** and **4d** (77 g, 0.11 mol, 82%), via a Horner−Emmons reaction with the anion of diethyl phosphono acetonitrile. Silica gel purification of this mixture, followed by crystallization from dichloromethane/hexanes, gave the pure isomer **4a** (6.6 g, 9.4 mmol). The mother liquor contained mainly **4b** and **4d**, and, via a subsequent crystallization, yielded a crystalline material consisting of **4b** and **4d** (63 g, 90 mmol) only, in a 1: 2 ratio. The structures of the compounds in question could be established from their ^1H and ^{13}C NMR spectra.

Treatment of **4a** (500 mg) in trichloroacetic acid for two minutes at 175 °C, followed by quenching of the reaction mixture with sodium acetate solution in water, gave, after purification with silica gel chromatography, a novel green compound **5a** (70 mg, 14%), as well as a mixture of unidentified products. Treatment of **5a** (50 mg) with concentrated sulfuric acid to remove nickel from the porphyrin core gave, after purification, a brown compound **6a** (40 mg). In Figure 2, the electronic absorption spectra of **5a** and **6a** are given, which show features not observed for any known simple porphyrin derivative. Very rewarding is the strong absorption of **6a** in the far-red at 680 nm. For the structural elucidation of **6a** and **5a**, vide infra.

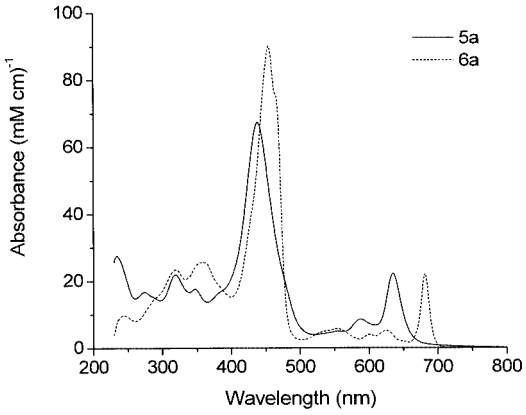


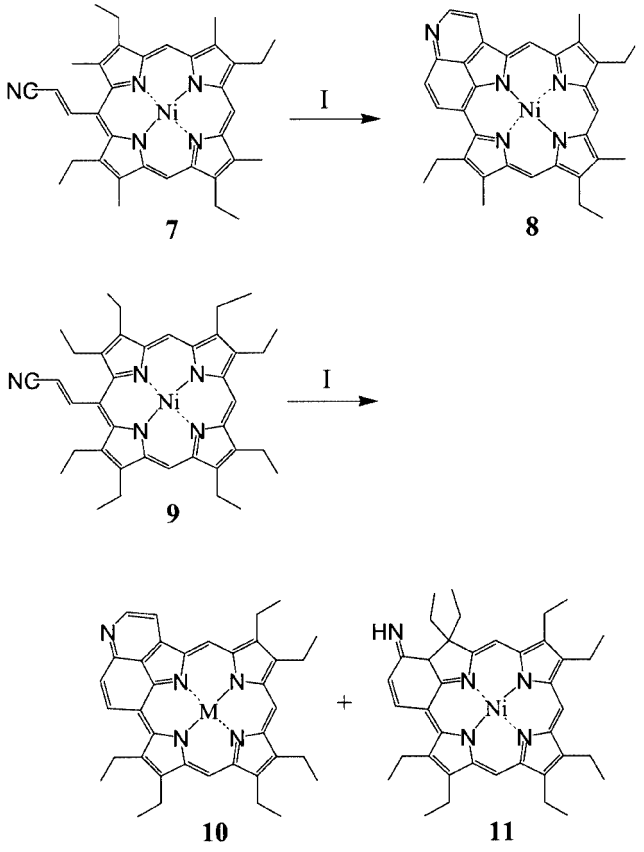
Figure 2. UV/Vis-spectra of the nickel complex **5a** and the free base **6a** of the quino[4,4a,5,6-*efg*]-anulated 7-demethyl-8-deethylmesoporphyrin dimethyl ester in CH_2Cl_2

Similarly, heating the mixture of meso-acrylonitrile-substituted porphyrins **4b** and **4d** (5.0 g, ratio 1:2) with trichloroacetic acid gave a mixture of **5b**, **5c** and **5d**. Two of these three isomers could be isolated by silica gel chromatography. In this way, **5c** (185 mg) and **5d** (225 mg) were obtained along with a mixture of **5b** and **5c** (480 mg) (Scheme 2). Demetallation of the nickel complexes **5b, c** and **d** in concentrated sulfuric acid gave the metal-free porphyrins **6b, 6c** and **6d**. The electronic absorption spectra of the nickel complexes **5b**−**d** and their free bases **6b**−**d** are similar to **5a** and **6a**, respectively.

From the structures, it can be seen that isomer **6b** is the product from **4b** (Scheme 2), in which only the propionic ester group is available for formation of the pyridine part of the quinoline system. Both **6c** and **6d** are derived from **4d**, which has either an ethyl- or a propionic ester side-chain available for the formation of the pyridine ring.

Structural Analysis

The structures of the novel *peri*-condensed quinoporphyrin systems had to be unambiguously established. We started with **6a**; using HR-FAB mass spectrometry, the exact mass of **6a** was found to be *m*/*z* = 628.2921, which corresponds to the elemental composition $^{12}C_{38}{}^{1}H_{38}{}^{14}N_5{}^{16}O_4{}^+$ (calculated: *m*/*z* = 628.2924), corresponding with the singly protonated form of **6a**, which thus has the elemental composition $^{12}C_{38}{}^{1}H_{37}{}^{14}N_5{}^{16}O_4$. The unsaturation number is 23. Comparing this with the elemental composition of the corresponding nickel-free compound **4a** ($^{12}C_{39}{}^{1}H_{43}{}^{14}N_5{}^{16}O_4$) indicates that in the conversion of nickel-free **4a** into **6a**, one carbon and six hydrogen atoms have been lost, and the unsaturation number has increased by two units. These facts are completely supported by the HR FAB mass spectrum of **5a** (found *m*/*z* = 684.2108, elemental composition $^{12}C_{38}{}^{1}H_{35}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$) and **4a** (found *m*/*z* = 702.2593, $^{12}C_{39}{}^{1}H_{42}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$), which also differ by exactly one carbon and six hydrogen atoms.



I: trichloroacetic acid, 175 °C, 2 min

Scheme 2. The conversion of the meso acrylonitrile derivative of etioporphyrinatonickel(II) (**7**) into (8,13,18-triethyl-7,12,17-trimethylquino[4,4a,5,6-*abt*]porphyrinato)nickel(II) (**8**) and conversion of meso acrylonitrile derivative of octaethylporphyrinatonickel(II) (**9**) into 7,8,12,13,17,18-hexaethylquino[4,4a,5,6-*abt*]porphyrinato)-nickel(II) (**10**) and (2^1-imino-3,3,7,8,12,13,17,18-octaethyl-$2,2^1$-dihydrobenzochlorinato)nickel(II) (**11**)

In Figure 3, the 600-MHz ^{1}H NMR spectrum of **6a** is reproduced, and based on the pattern and intensities of the signals, it is clear that all 37 protons are present.

When comparing the ^{1}H NMR spectrum of this new compound **6a** with that of **4a**, it can be seen that in the ^{1}H NMR spectrum of **6a**, the signals of the acrylonitrile functionality and the signals of the 7-methyl group and the 8-ethyl group are absent. Instead, there are two AB-subspectra visible in the aromatic region, one with δ = 9.54 and 8.53 ppm with J_{AB} = 4.6 Hz, and the other one with δ = 9.22 and 8.20 ppm with J_{AB} = 8.9 Hz. Also, two singlets (δ = −4.51 and −4.79 ppm) are present, belonging to the protons at the nitrogen atoms in the center of the porphyrin ring system.

When 2D-NOESY NMR spectroscopy was applied to **6a**, the assignment of all hydrogen atoms except the NH-protons is possible. In Figure 4, the NOE connectivities obtained in this way are indicated, and the assignment of all hydrogen atoms directly bound to carbon atoms are given.

Based on the ^{1}H NMR spectrum, the presence of an unprecedented *peri*-condensed quinoline substructure is proposed. This structure is in full agreement with the elemental composition.

In order to establish this structure rigorously, we used ^{13}C NMR spectroscopy. In Figure 5, the sp^2 part of the attached proton test (APT) ^{13}C- NMR spectrum is reproduced; the signals pointing downward are from the carbons directly attached to hydrogen. The signals pointing upwards are the quaternary carbon signals.

Using 2D ^{13}C-^{1}H heteronuclear single quantum correlation (HSQC) NMR spectroscopy, the tertiary carbon signals could be unambiguously assigned (see Figure 5). When 2D ^{13}C-^{1}H heteronuclear multiple bond quantum correlation (HMBC) spectroscopy was applied, especially the sp^2 ^3J(^{13}C-^{1}H) couplings (8 Hz) are revealed.[18]

In Figure 5, it can be seen that carbon atom 5^3 has ^3J(^{13}C-^{1}H) interactions with H-5^1 and H-5^5. In the 2D ^{13}C-^{1}H HMBC NMR spectrum, the carbon signal at δ = 144.67 ppm is the only carbon resonance that shows these interactions, which unambiguously establishes the assignment of the δ = 144.7 ppm signal to carbon 5^3. In a similar way, all other quaternary carbon signals have unique ^3J(^{13}C-^{1}H) interactions. The ^{13}C chemical shift values of quinoline itself are reproduced in parentheses in Figure 5.[19] Except for the values for carbon atoms 5, 6 and 8, which differ in substitution pattern between quinoline and **6a**, these values are reasonably close, which supports the assignment of a *peri*-condensed quinoline structure in **6a**.

For ^{15}N-^{1}H HMBC NMR spectroscopy, similar rules apply for the ^{15}N signals as discussed for the ^{13}C-case only the natural abundance of ^{15}N is only 0.35% while this is 1.1% for ^{13}C. The ^{15}N-atoms can be observed indirectly via the very sensitive proton signals using the above-mentioned technique. These spectra show the signals of five different nitrogen atoms at −78.7, −127.3, −136.8, −244.9 and −246.1 ppm, with the ^{15}N signal of nitromethane as a reference.[20] The assignments of these nitrogen signals are given in Figure 4. The nitrogen at position 23 has ^3J(^{15}N-^{1}H) connectivities with the two hydrogen atoms at positions 10 and 15. The nitrogen signal at δ = 246.1 ppm shows these connectivities and is therefore assigned to N-23. Also, a ^1J(^{15}N-^{1}H) connectivity is found with the proton signal at δ = −4.50 ppm. The other N−H proton at δ = −4.79 ppm shows a ^1J(^{15}N-^{1}H) connectivity with the signal at δ = −244.9 ppm that is assigned to N-21. This leads us to the conclusion that for **6a**, at room temperature, N−H tautomerism is slow on the NMR time-scale, and that **6a** prefers to exist as the tautomer that has nitrogen 21 and 23 protonated and 22 and 24 as pyridine nitrogens. The ^{15}N signal at δ = −78.7 ppm shows a ^3J(^{15}N-^{1}H) interaction with the hydrogen atom at position 5^6, and is therefore assigned to the quinoline nitrogen at position 5^4. The chemical shift corresponds to the chemical shift found for the nitrogen in quinoline, which resonates at δ = −70.9 ppm. All the ^{15}N signals have now been unambiguously assigned, this is also the case for the ^{13}C and ^{1}H signals.

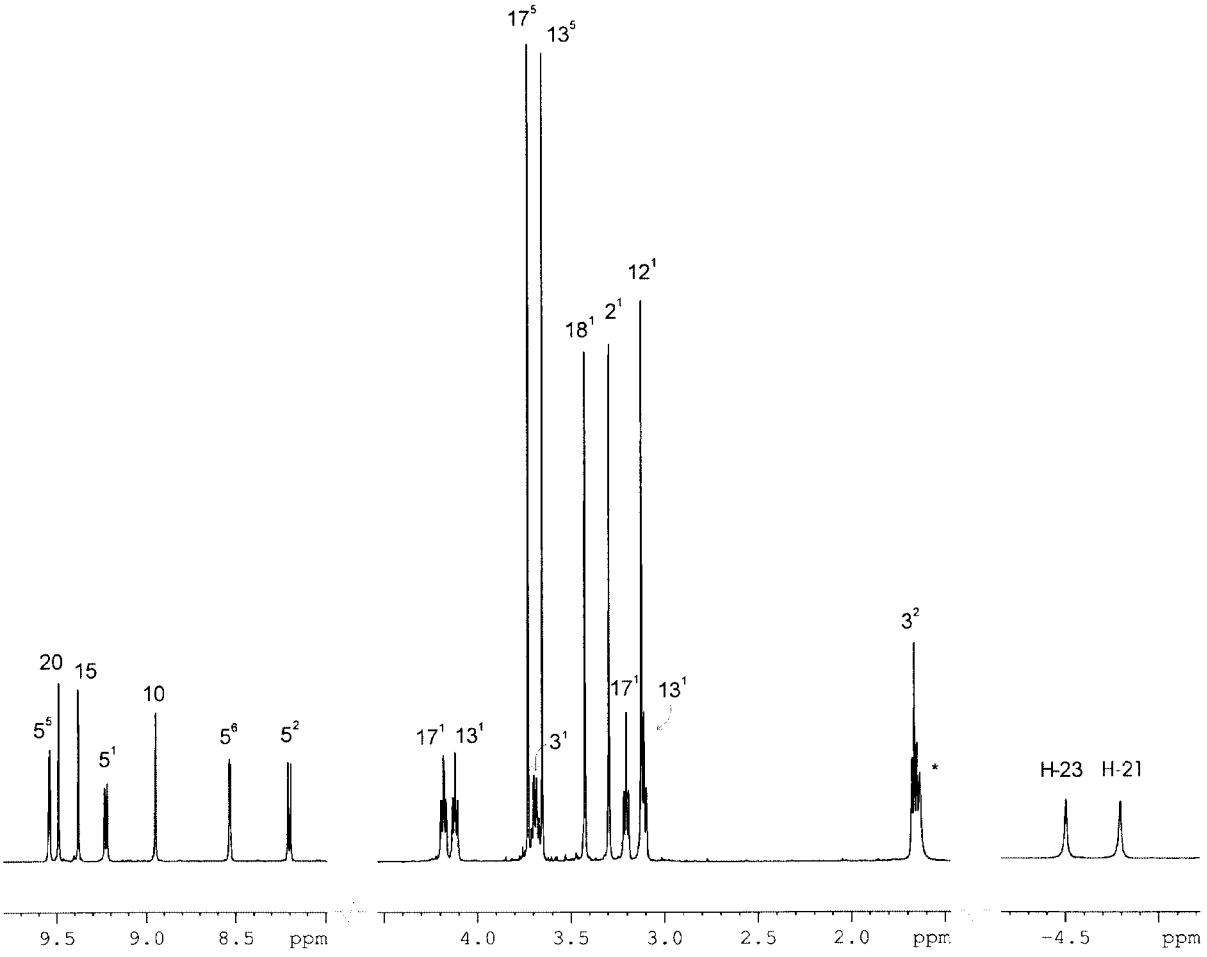


Figure 3. 600-MHz ^{1}H NMR spectrum of **6a**

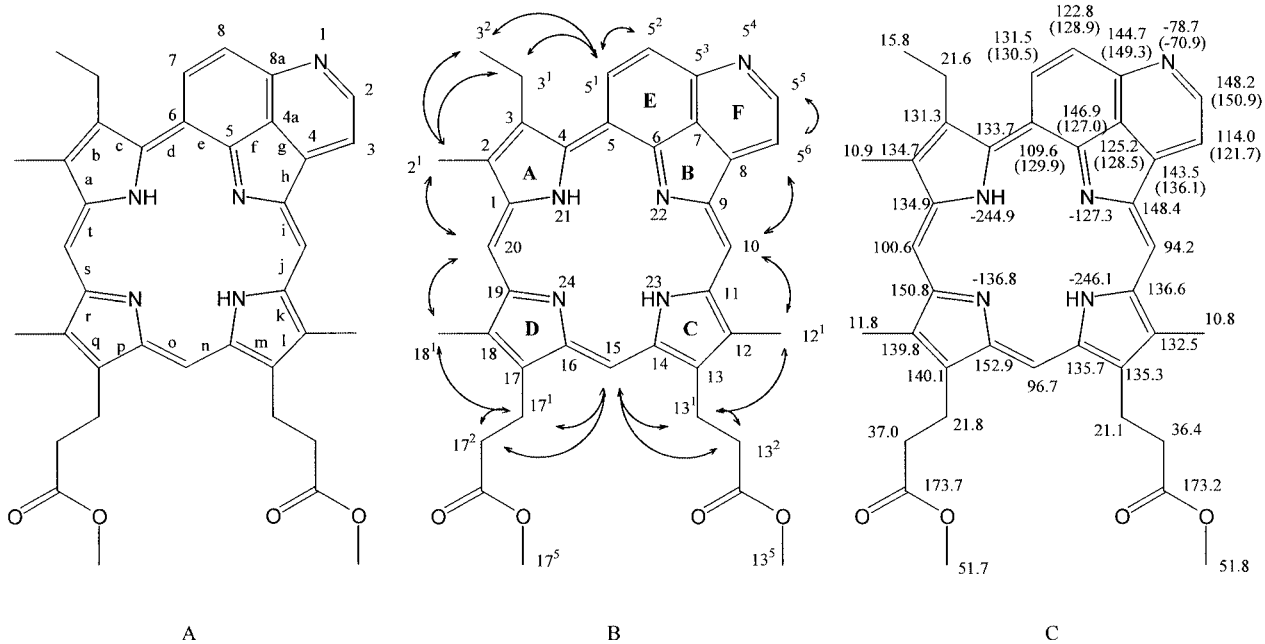


Figure 4. **A**: Structure and numbering of quino[4,4a,5,6-*efg*]-annulated 7-demethyl-8-deethylmesoporphyrin dimethyl ester **6a**. **B**: Numbering of **6a** according to the semi-systematic IUPAC rules for tetrapyrroles. This numbering is used for the NMR studies. Also indicated are the NOE interactions seen in the ^{1}H NMR spectra. **C**: The ^{13}C chemical shift values and the ^{15}N chemical shift values of **6a**. The ^{13}C and ^{15}N chemical shift values of quinoline are reproduced in parentheses.

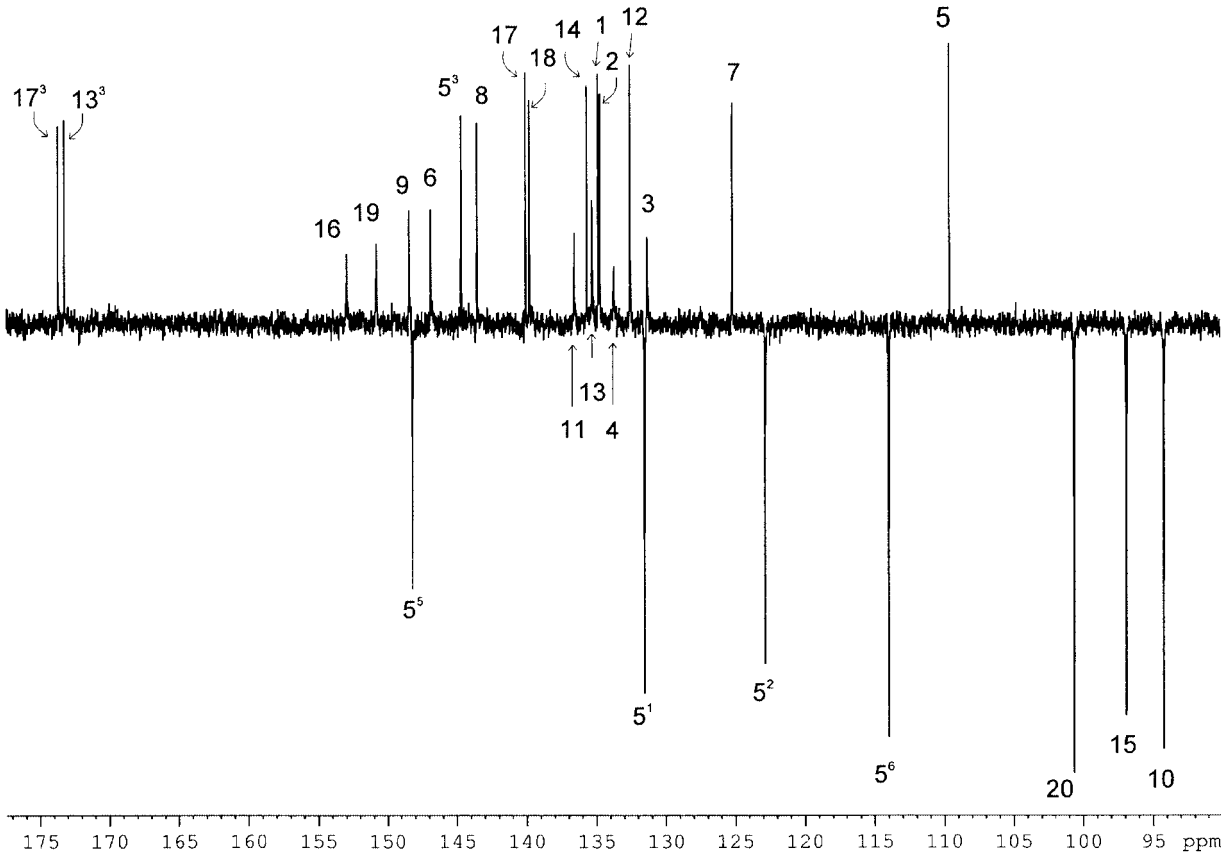


Figure 5. Assignment of all sp^2 carbon signals in the 150-MHz ^{13}C-Attached Proton Test NMR spectrum of **6a**

Now that we had unambiguously established that the structure of **6a** is a quino[4,4a,5,6-*efg*]-fused 7-demethyl-8-deethylmesoporphyrin dimethyl ester, we focussed on the structural elucidation of **6b**, **6c** and **6d**. The high-resolution mass spectra of **6b**, **6c** and **6d** (m/z = 628.2912), (m/z = 628.2869) and (m/z = 628.2933), respectively, correspond to the elemental composition $^{12}C_{38}{}^{1}H_{38}{}^{14}N_5{}^{16}O_4{}^{+}$ (calcd. mass: m/z = 628.2924). This shows that **6b**, **6c** and **6d** are isomers of **6a**.

The 600-MHz ^1H NMR spectrum of **6d** shows the same type of signals as **6a**; they only differ in chemical shift values. The two aromatic AB subspectra may be seen: one with J_{AB} = 9.1 at 8.20 and δ = 9.32 ppm, and the other with J_{AB} = 4.8 Hz at 8.53 and δ = 9.52 ppm. Using NOE studies, we could unambiguously establish that the quinoline system is condensed onto pyrrole A of the porphyrin. The next step was to establish the chemical shift of the sp^2 carbon atoms that are directly bound to a hydrogen atom, using 2D ^{13}C-^1H HSQC NMR spectroscopy. In this way, the sp^2 carbon signals of the quinoline system were observed at 148.1, 131.8, 122.6 and δ = 114.1 ppm, which are similar values to those found for **6a**. These facts establish that **6d** is a quino[4,4a,5,6-*abt*]-annulated 2-demethyl-3-deethylmesoporphyrin dimethyl ester. Its structure is depicted in Scheme 1 with the quinoline group fused to pyrrole ring A.

The 600-MHz ^1H NMR spectra of **6b** and **6c** were recorded, and these spectra had similar signals to one another, but differed from those of **6a** and **6d**. In the case of **6b** and **6c**, each has a new AB- and a new A subspectrum. **6b** has its AB subspectrum at δ = 8.38 ppm and δ = 9.38 ppm with J_{AB} = 9.2 Hz, and the singlet of the A subspectrum appears at δ = 9.32 ppm; **6c** has its AB subspectrum at δ = 8.15 ppm and δ = 9.09 ppm with J_{AB} = 9.2 Hz, and the singlet appears at δ = 9.22 ppm.

It could be established from NOE studies that the quinoline moiety is condensed onto ring C in **6b** and ring D in **6c**. This means that in both cases, the propionyl side-chain has participated in the formation of the quinoline system. Similarly, the chemical shift values for the protonated carbons were established via 2D ^{13}C-^1H HSQC NMR spectroscopy.

Because of the different substitution patterns in the quinoline rings of **6b** and **6c** compared to those of **6a** and **6d**, we selected **6c** to also establish all the chemical shift values of the quaternary carbons and nitrogens, as discussed for **6a**. The assignment of all carbon and nitrogen signals for **6c** are given in Figure 6. The values of 2-(methoxycarbonyl)quinoline are given in parentheses.[21] In **6c**, the nitrogen atoms 21 and 23 are protonated; the other three are pyridine-type, which is similar to **6a**. Based on the comparison of the ^{1} H, ^{13}C and ^{15}N values of **6c** and those

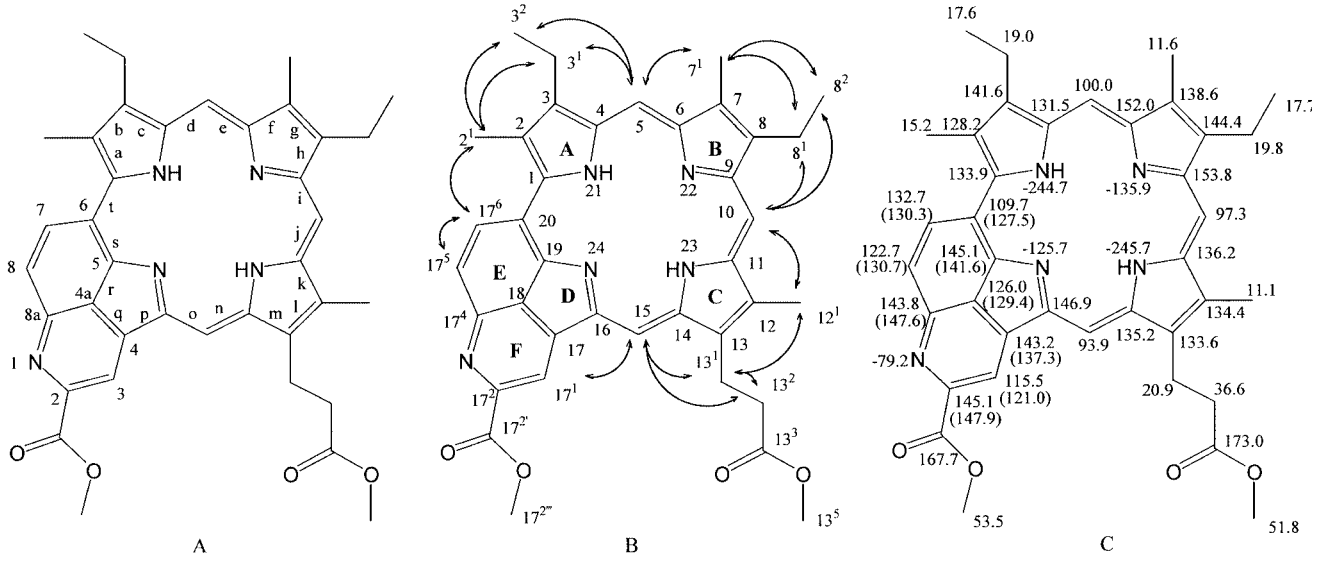
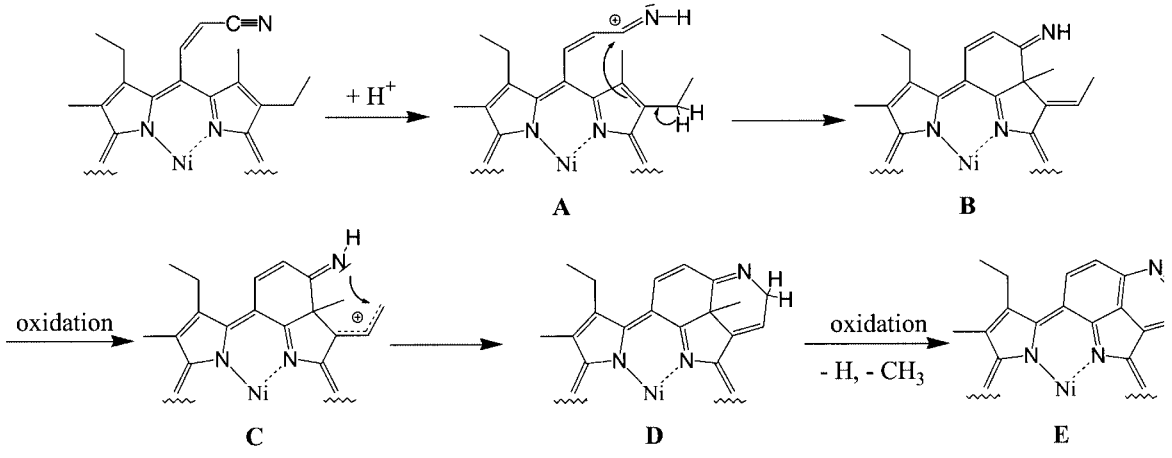


Figure 6. **A**: Structure and numbering of 17^4-(methoxycarbonyl)quino[4,4a,5,6-*qrs*]-annulated 18-demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin dimethyl ester **6c**. **B**: Numbering of **6c** according to the semi-systematic IUPAC rules for tetrapyrroles. This numbering is used for the NMR studies. Also indicated are the NOE interactions seen in the ^{1}H NMR spectra. **C**: The ^{13}C- chemical shift values and the ^{15}N-chemical shift values of **6c**. The ^{13}C-chemical shift values of 2-(methoxycarbonyl)quinoline are reproduced in parentheses, except for those of the methoxycarbonyl group.

of 2-(methoxycarbonyl)quinoline, it is clear that the structure of the 17^4-(methoxycarbonyl)quino[4,4a,5,6-*qrs*]-annulated 18-demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin dimethyl ester **6c** is rigorously established, as it is for **6a** above. It is curious that the protonated carbon 5^6 of the quinoline system in **6a** and the corresponding carbon 17^1 in **6c** show very similar chemical shifts. Also, the chemical shift values of the nitrogen atoms are very similar. For **6b**, the chemical shift values of the ^{1}H and the ^{13}C NMR signals, which are given in the Experimental Section, establish that **6b** is a 10^5-(methoxycarbonyl)quino[4,4a,5,6-*jkl*]-annulated 12-demethyl-13-de[2′-(methoxycarbonyl)ethyl]-mesoporphyrin dimethyl ester, with the structure given in Scheme 1. In compounds **6b** and **6d**, the nitrogen atoms at positions 22 and 24 are protonated and the pyridine nitrogens are at positions 21 and 23.

Plausible Steps in the Formation of the Peri-Condensed Quinoline Porphyrin System

In order to establish that the formation of *peri*-condensed quinoline porphyrins is more general than the meso acrylonitrile derivatives of the nickel(II) complex of mesoporphyrin dimethyl ester, we prepared the meso acrylonitriles of etioporphyrin nickel(II) complex and the related derivative of octaethylporphyrin[22] (Scheme 2). Due to the symmetry of the porphyrins, only one acrylonitrile derivative is possible, and thus difficult separating problems are avoided. By treating **7** in trichloroacetic acid at 175 °C and subsequent work up, the nickel complex of the quino-annulated porphyrin **8** was obtained. It is clear that this must be the result of an attack of the acrylonitrile on the methylated β-pyrrole carbon atom. The quino-fused porphyrin **10** was



Scheme 3. Plausible mechanism for the formation of *peri*-condensed quino-fused porphyrins

formed from **9** in a similar way. It is clear that attack on a pyrrole carbon bound to an ethyl group also leads to these results. In this case, the difference in elemental composition between **10** and **9** is two carbon atoms and eight hydrogen atoms. In all the other cases we have described in this paper, it has been one carbon and six hydrogens. In the case of **9**, we also obtained the *gem*-diethyl derivative **11** from the same reaction mixture. When isolated, **11** was treated with trichloroacetic acid at 175 °C, but no traces of **10** were detected. Therefore, we think that **11** is not an intermediate in the formation of **10** from **9**.

In Scheme 3, we have depicted plausible steps that lead from a meso acrylonitrile porphyrin derivative into the *peri*-condensed quinoline system. The cis acrylonitrile is protonated on the nitrile nitrogen, allowing the positively charged nitrile carbon to attack the pyrrole β-carbon. After deprotonation of the resulting cation, this leads to product B, which is fully analogous to the formation of derivative VIII as shown in Figure 1. We have observed by ^{1}H NMR spectroscopy that all porphyrin acrylonitrile derivatives undergo an efficient acid-catalyzed *trans*/*cis* isomerization.

The next steps are the oxidation of the *exo*-ethylidene group into an allylic cation (C) that subsequently attacks the neighboring imino nitrogen to form the 1,4-dihydropyridine derivative D. Upon further oxidation, both a methyl group and a hydrogen are removed, resulting in the formation of the aromatic *peri*-condensed quinoline system E. In the case of the conversion of **9** into **10**, a similar final loss of a quaternary ethyl group once again gives a quinoporphyrin.

The fact that the final quinolines are not formed via the skeletal rearrangement as indicated for compound **11** (Scheme 2) is supported by the fact that **11** does not give any trace of **10** upon further treatment with trichloroacetic acid, and that **4c** does not give any quinoline product. In the case of **4c**, initial attack must always take place at a pyrrole β carbon attached to a propionic acid substituent. According to our mechanism, no 1,4-dihydropyridine ring closure can occur because only an *exo*-methylene group will be present.

Photochemical Singlet Oxygen Generation

6a dissolved in toluene was irradiated with 532 nm light (frequency-doubled Nd:YAG 1064 nm light). With 1200 nm and 1270 nm filters the sensitizer (**6a**) fluorescence and laser scattering are removed and the phosphorescence of singlet oxygen can be measured by an InGaAs diode. When the sample was flushed with argon, no signal in the 1200−1270 nm range was observed. When the sample is flushed with oxygen, an intense signal due to singlet oxygen is observed with an overall quantum yield of 0.77, which is even higher than the quantum yield obtained with tetraphenyl porphyrin ($\Phi = 0.70$). Compound **6a** is completely stable under these conditions. The wavelength 532 nm was chosen to obtain optimal results for tetraphenylporphyrin. As can be seen in Figure 2, **6a** shows a low-intensity absorption around 630−660 nm.

The Ni complex **5a** is not supposed to be a good photochemical singlet oxygen generator. In order to prove that the presence of the Ni^{2+} leads to low sensitizer efficacy, the nickel(II) mesoporphyrin dimethyl ester (**2**) was investigated in the same way. No singlet oxygen could be observed (Φ ν 0.01).

Biological Effects of 6a

First, a toxicity test of **6a** in cultures of Chinese Hamster ovary cells (CHO cells) were carried out in the dark. The cells were incubated in a medium containing **6a** at various concentrations. The cultures were left overnight in the dark at 37 °C. Using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay based on the methods of Tada[23] and Carmichael,[24] the cell survival was obtained as a percentage of untreated cells as control. Even at concentrations up to 15 μg/ml of **6a** in the medium, cell survival was complete within experimental error, showing that **6a** is essentially non-toxic towards the Chinese Hamster ovary cells in the dark. After incubating the ovary cells for four hours with **6a** in the dark followed by illumination for 15 minutes with white light of 30 mW/cm^2 (270 kJ/m^2), the cells were completely killed for concentrations of **6a** of 1 μg/ml and higher. This shows that in the presence of air and light, **6a** acts as an efficient photodynamic agent.

Conclusions

Four novel *peri*-condensed quinoline porphyrins have been synthesized in a simple fashion in reasonable yield starting from mesoporphyrin dimethyl ester (**1**). All four systems are achiral, which is a great advantage for systems that are intended to be used in medical therapy. Mesoporphyrin dimethyl ester **1** is available for a reasonable price on a 1000 kg scale, which means that there should be no problem in the supply of sufficient amounts. Amounts of the quinoporphyrins described in this paper in the gram range are now available. Also, a reasonable mechanism for the formation of these systems has been worked out, allowing us to rationally design a whole series of achiral derivatives based on the four new structures we described in this paper. The investigation of one of our new molecules as a photochemical singlet oxygen source indicates that it has a higher efficiency than meso tetraphenylporphyrin. Also, this system is completely stable during extended irradiation in the presence of oxygen. Furthermore, the same system does not show any toxicity towards Chinese Hamster ovary cells in the dark, whereas in the presence of light, a total cell killing was observed at concentrations of the photosensitizer below 1 μg/ml. We expect that the other three novel compounds we describe in this paper will also show these promising properties. It is clear that we have found a completely unprecedented reactivity in the porphy-

rin field that leads to novel achiral systems in a few steps in reasonable yield. The products also fulfil the requirements we have discussed for systems that may be developed for use in photodynamic cancer therapy.

Experimental Section

General: Protoporphyrin dimethyl ester (PPdme) was kindly provided by Harimex. Mesoporphyrin dimethyl ester (MPdme, 1) was prepared from PPdme following a literature procedure.[7] (Octaethylporphyrinato)nickel(II) was obtained from Porphyrin Products. Etioporphyrin I was obtained from Porphyrin systems. *N*-Methylformanilide, phosphorus oxychloride, (diethylphosphono)acetonitrile, nickel(II) acetate tetrahydrate and diethyl ether were obtained from Aldrich. Trichloroacetic acid and sodium hydride were obtained from Merck. Palladium on activated carbon and hexane were purchased from Acros. Sulfuric acid was obtained from Boom. Silica gel 60 (230−400 mesh) was obtained from Fluka, and dichloromethane, dichloroethane, chloroform, tetrahydrofuran (THF), methanol and dimethylformamide were obtained from Biosolve. Tetrahydrofuran (THF) and diethyl ether were distilled prior to use to remove the stabilizer. $CDCl_3$ used for NMR spectroscopy was treated with potassium carbonate to remove traces of acid. Thin Layer Chromatography (TLC) was accomplished with TLC aluminum sheets covered with silica gel 60, F254 from Merck. NMR spectra were measured on Bruker DPX300 or Bruker DMX600 spectrometers. ^{1}H-2D-COSY, ^{1}H-2D-NOESY, Attached Proton Test (APT), ^{13}C, 2D ^{13}C-^{1}H-HSQC, 2D ^{13}C-^{1}H-HMBC and ^{15}N-^{1}H-HMBC NMR spectroscopy were applied to establish the structure of new compounds. 60.8 MHz ^{15}N inverse-detected NMR spectra were derived from 2D ^{15}N-^{1}H-HMBC NMR spectra. UV/Vis spectra were measured with a Perkin−Elmer Lambda-900 UV/Vis/NIR spectrophotometer. Melting points were measured with a Büchi apparatus and are uncorrected. Fast Atom Bombardment (FAB) mass spectrometry was carried out using a JEOL JMS SX/SX 102A four-sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system Program. Samples were loaded in a matrix solution (3-nitrobenzyl alcohol) onto a stainless steel probe and bombarded with Xenon atoms with an energy of 3 keV. During the high-resolution measurements, a resolving power of 10,000 (10% valley definition) was used.

(Mesoporphyrin Dimethyl Ester) Nickel(II) Complex 2: A suspension of MPdme (**1**) (110 g) and nickel acetate tetrahydrate (50 g, 200 mmol) in dimethylformamide (1.5 L) was refluxed for 20 minutes, after which time the color had changed from red-brown to pink. After this mixture had been allowed to cool down, the dimethylformamide was distilled off under reduced pressure and the product was purified over silica gel using dichloromethane, yielding mesoporphyrin dimethyl ester nickel complex **2** (103 g, 0.16 mol, 86%). M.p. 186−188 °C. HR-FABMS [M + H] found: m/z = 651.2469, calcd. for $^{12}C_{36}{}^{1}H_{41}{}^{14}N_4{}^{16}O_4{}^{58}Ni^+$: 651.2481. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (2t, 12 H, $^3J(3^1\text{-H-}3^2\text{-H})$ = 8 Hz, 3^2-CH_3 and 8^2-CH_3), 3.16 (2t, 4 H, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8 Hz, 13^2-CH_2 and 17^2-CH_2), 3.48, 3.47, 3.46 and 3.44 (4s, 12 H, 2^1-CH_3, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3), 3.69 and 3.68 (2s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 3.89 (2q, 4 H, $^3J(3^1\text{-H-}3^2\text{-H})$ = 8 Hz, 3^1-CH_2 and 8^1-CH_2), 4.24 (2t, 4 H, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8 Hz, 13^1-CH_2 and 17^1-CH_2), 9.74 (s, 4 H, CH-5, 10-CH, 15-CH and 20-CH) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 288 (4.1), 392 (5.3), 517 (4.0), 553 (4.4).

Formylmesoporphyrin Dimethyl Ester Nickel(II) Complexes 3a, 3b, 3c and 3d: $POCl_3$ (75 mL, 123 g, 0.80 mol) was added dropwise to *N*-methylformanilide (100 mL, 110 g, 0.81 mol) over a period of one hour, during which time the temperature rose to 35 °C. The solid orange mixture was then added to a suspension of **2** (103 g) in dichloroethane (2 L). After two hours of stirring at room temperature, the initially red suspension had turned into a green solution. After concentrating under reduced pressure, hot methanol (500 mL) was added, after which this mixture was hydrolyzed by pouring into a stirred solution of sodium acetate (500 g) in water (2 L). After one hour, the hydrolysis was complete, and the product mixture was filtered off and washed with hot water. The filtrate was dried in an oven at 100 °C, yielding the crude product (110 g). Eluting this over silica gel with dichloromethane yielded a mixture of four monoformylated isomers **3a**, **3b**, **3c** and **3d** (93 g).

On a gram scale, the separation of **3a** and **3c** and a mixture of **3b** and **3d** was accomplished by silica gel chromatography using a mixture of tetrahydrofuran, dichloromethane and hexanes (ratio 1:70:29). The four isomers were identified by ^{1}H, ^{1}H-COSY- and ^{1}H-NOESY NMR spectroscopy. In the ^{1}H NMR spectrum of the mixture of **3b** and **3d**, the signals of **3d** were two times more intense than those of **3b**. The exact mass of the mixture of four isomers has been measured: HR-FABMS [M + H] found: m/z = 679.2414, calcd. for $^{12}C_{37}{}^{1}H_{41}{}^{14}N_4{}^{16}O_5{}^{58}Ni^+$: 679.2430.

5-Formylmesoporphyrin Dimethyl Ester Nickel (II) Complex 3a: M.p. 228 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.63 (t, $^3J(7^1\text{-H-}7^2\text{-H})$ = 7.7 Hz, 3 H, 7^2-CH_3), 1.71 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 3 H, 3^2-CH_3), 3.06 (2t, 4 H, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.7 Hz, 13^2-CH_2 and 17^2-CH_2), 3.26 (s, 3 H, 2^1-CH_3), 3.30 (s, 9 H, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3), 3.67 and 3.67 (2s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 3.69 (q, 2 H, $^3J(7^1\text{-H-}7^2\text{-H})$ = 7.7 Hz, 8^1-CH_2), 3.76 (q, $^3J(3^1\text{-H-}3^2\text{-H})$ = 7.7 Hz, 2 H, 3^1-CH_2), 4.06 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.7 Hz, 4 H, 13^1-CH_2 and 17^1-CH_2), 9.30 (s, 1 H, 10-CH), 9.31 (s, 1 H, 20-CH), 9.38 (s, 1 H, 15-CH), 11.91 (s, 1 H, 5-CHO) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 404 (5.0), 529 (3.8), 564 (4.0), 645 (3.9).

15-Formylmesoporphyrin Dimethyl Ester Nickel(II) Complex 3c: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.66 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 6 H, 3^2-CH_3 and 8^2-CH_3), 3.15 (2t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8.0 Hz, 4 H, 13^2-CH_2 and 17^2-CH_2), 3.30, 3.29, 3.28 and 3.26 (4s, 12 H, 2^1-CH_3, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3), 3.71 (2q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 4 H, 3^1-CH_2 and 8^1-CH_2), 3.77 (s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 4.06 (2t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8 Hz, 4 H, 13^1-CH_2 and 17^1-CH_2), 9.33, 9.31 and 9.30 (3s, 3 H, 5-CH, 10-CH, 20-CH), 11.81 (s, 1 H, 15-CHO) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 405 (5.0), 529 (3.8), 564 (4.0), 645 (4.0).

10-Formylmesoporphyrin Dimethyl Ester Nickel(II) Complex 3b and 20-Formylmesoporphyrin Dimethyl Ester Nickel(II) Complex 3d: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.66 (m, 3^2-CH_3 (**3b**) and 3^2-CH_3 (**3d**) and 8^2-CH_3 (**3d**)), 1.73 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 8^2-CH_3 (**3b**)), 3.08 (m, 13^2-CH_2 and 17^2-CH_2 (**3b** and **3d**)), 3.34−3.26 (overlapping 2^1-CH_3, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3 (**3b** and **3d**)), 3.70 and 3.68 (2s, 6 H, 13^5-OCH_3 and 17^5-OCH_3, (**3b** and **3d**)), 3.73 (3^1-CH_2 (**3b**), 3^1-CH_2 and 8^1-CH_2 (**3d**)), 3.77 (q, 2 H, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 8^1-CH_2 (**3b**)), 4.06 (13^1-CH_2- and 17^1-CH_2, (**3b** and **3d**)), 9.38, 9.35, 9.30 (s, 3 H, 5-CH, 15-CH and 20-CH (**3b**)), 9.40, 9.36, 9.31 (s, 3 H, 5-CH, 10-CH and 15-CH (**3d**)), 11.93 (s, 1 H, CHO (**3b**)), 12.00 (s, 1 H, CHO (**3d**)) ppm.

(2′-Cyanovinyl)mesoporphyrin Dimethyl Ester Nickel(II) Complexes 4a, 4b, 4c and 4d: Sodium hydride (80% in mineral oil) (12.5 g, 0.41 mol) was washed three times with hexanes, after which tetrahydrofuran (500 mL) and diethyl phosphono acetonitrile (75 mL, 0.46 mol) were added. The mixture was stirred at room temperature for 15 minutes until the sodium hydride was dissolved completely, after

which the solution was added to a suspension of the mixture of formyl nickel MPdme (**3a**−**d**) (93 g) in THF (1.5 L). After 12 hours of stirring at room temperature, the color had changed from green to brown, and the reaction was complete as observed by TLC. After evaporation of the THF, the crude mixture of the four acrylonitrile nickel(II) MPdme (**4a**−**d**) isomers was separated into two fractions by silica gel chromatography using dichloromethane as the eluent. The first fraction (20 g) contained mainly **4a**, but also **4b** and **4d** in a 3:1:2 ratio, while the second fraction (57 g) contained all isomers **4a**, **b**, **c**, **d**. Crystallization with dichloromethane/hexanes of the first fraction gave **4a** (6.6 g, 9.4 mmol) as a bright red solid. The mother liquor of the first fraction was added to the second fraction, and crystallization of this mixture gave a mixture of **4b** and **4d** (63 g, 90 mmol) as a black powder. The mother liquor contained a mixture of **4a**, **b**, **c**, and **d**.

The separation of the isomers also has been accomplished on a gram scale by silica gel chromatography using DCM/hexanes/THF (70:29:1) as the eluent. In this way, nickel complexes of mesoporphyrin dimethyl ester, 5-acrylonitrilo- and the 15-acrylonitrilo-mesoporphyrin dimethyl ester could be isolated as pure compounds (**4a** and **4c**, respectively). In addition, a mixture of only the 10- and 20-acrylonitrilo mesoporphyrin nickel complexes **4b** and **4d** was isolated.

5-(2′-Cyanovinyl)mesoporphyrin Dimethyl Ester Nickel(II) Complex 4a: M.p. 216−218 °C. HR-FABMS [M + H] found: *m*/*z* = 6702.2593, calcd. for $^{12}C_{39}{}^{1}H_{42}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: 702.2590. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.66 (2t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 6 H, 3^2-CH_3 and 8^2-CH_3), 3.09 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.7 Hz, 4 H, 13^2-CH_2 and 17^2-CH_2), 3.28, 3.30, 3.35 and 3.36 (4s, 12 H, 2^1-CH_3, 7^1-CH_3, 12^1-CH_3 and 18^1-CH_3), 3.67 and 3.68 (2s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 3.76 (2q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7 Hz, 4 H, 3^1-CH_2 and 8^1-CH_2), 4.13 (t, $^3J(13^1\text{-H-}13^2\text{-H})$, $J(17^1\text{-H-}17^2\text{-H})$ = 7.7 Hz, 4 H, 13^1-CH_2 and 17^1-CH_2), 4.60 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.1 Hz, 1 H, 5^2-CH_2), 9.42, 9.43 and 9.45 (3s, 3 H, 10-CH, 15-CH and 20-CH), 9.70 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.1 Hz, 1 H, 5^1-CH) ppm. (600 MHz, [D$_6$]DMSO): δ = 1.52 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 3 H, 3^2-CH_3), 1.60 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 3 H, 8^2-CH_3), 3.09 (2t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.7 Hz, 4 H, 13^2-CH_2 and 17^2-CH_2), 3.26 (s, 3 H, 7^1-CH_3), 3.35 (s, 3 H, 2^1-CH_3), 3.37 (s, 6 H, 12^1-CH_3 and 18^1-CH_3), 3.54 and 3.53 (s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 3.75 (q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 2 H, 3^1-CH_2), 3.83 (q, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 2 H, 8^1-CH_2), 4.12 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.7 Hz, 4 H, 13^1-CH_2 and 17^1-CH_2), 5.20 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.1 Hz, 1 H, 5^2-CH), 9.64 (s, 1 H, 10-CH), 9.65 (s, 1 H, 20-CH), 9.66 (s, 1 H, 15-CH), 10.12 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.1 Hz, 1 H, 5^1-CH) ppm. ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 11.4, 11.4 and 11.5 (CH_3-2^1, CH_3-12^1, CH_3-18^1), 16.0 (CH_3-3^2), 17.2 (CH_3-7^1), 17.3 (CH_3-8^2), 19.7 (CH_2-8^1), 21.5 (CH_2-13^2 and CH_2-17^2), 22.4 (CH_2-3^1), 36.5 (CH_2-13^1 and CH_2-17^1), 51.8 (OCH_3-13^5 and OCH_3-17^5), 97.5 (CH-15), 98.0 (CH-10), 98.0 (CH-20), 105.4 (C-5), 108.5 (CH-5^2), 117.7 (CN), 136.9 (C-7), 137.9 (2 peaks, C-12 and C18), 138.6 (C-4), 138.7 (C-9) 139.7 (C-1), 139.9 (C-6), 140.2 (C-14 and C-16), 140.2 (C-2), 140.4 and 140.5 (C-13 and C-17), 141.1 (C-11 and C-19), 144.27 (C-3), 147.1 (C-8), 150.4 (CH-5^1), 173.4 (C-13^4 and C-17^4) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 286 (4.2), 405 (5.0), 530 (3.8), 565 (4.0).

15-(2′-Cyanovinyl)mesoporphyrin Dimethyl Ester Nickel(II) Complex 4c: M.p. 212−214 °C. HR-FABMS [M + H] found: *m*/*z* = 702.2618, calcd. for $^{12}C_{39}{}^{1}H_{42}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: 702.2590. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.70 (2t, 6 H, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8 Hz, 3^2-CH_3 and 8^2-CH_3), 2.99 (2t, 4 H, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8 Hz, 13^2-CH_2 and 17^2-CH_2), 3.35, 3.34 and 3.33 (3s, 12 H, 2^1-CH_3, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3), 3.78 (2q, 4 H, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8 Hz, 3^1-CH_2 and 8^1-CH_2), 3.80 (s, 6 H, 13^5-OCH_3 and 13^5-OCH_3), 4.11 (2t, 4 H, $^3J(13^1\text{-H-}13^2\text{-H})$ = 8 Hz, 13^1-CH_2 and 17^1-CH_2), 4.62 (d, 1 H, $^3J(15^1\text{-H-}15^2\text{-H})$ = 16 Hz, 15^2-CH), 9.44 and 9.43 (2s, 3 H, 5-CH, 10-CH and 20-CH), 9.83 (d, 1 H, $^3J(15^1\text{-H-}15^2\text{-H})$ = 16 Hz, 15^1-CH) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 286 (4.2), 405 (5.1), 532 (3.8), 568 (4.1).

10-(2′-Cyanovinyl)mesoporphyrin Dimethyl Ester Nickel(II) Complex 4b and 20-(2′-Cyanovinyl)mesoporphyrin Dimethyl Ester Nickel(II) Complex 4d: HR-FABMS [M + H] found for this mixture: *m*/*z* = 702.2585, calcd. for $^{12}C_{39}{}^{1}H_{42}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: 702.2590. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.66 (t, ^3J = 7.7 Hz, 6 H, 3^2-CH_3 and 8^2-CH_3 (**4b**)), 1.69 (t, ^3J = 7.7 Hz, 6 H, 3^2-CH_2 and 8^2-CH_2 (**4d**)), 3.12 and 3.04 (2t, 4 H, 13^2-CH_2 and 17^2-CH_2 (**4b** and **4d**)), 3.37, 3.34, 3.32 and 3.31 (4s, 12 H, 2^1-CH_3, 7^1-CH_3, 12^1-CH_3, 18^1-CH_3 (**4b** and **4d**)), 3.69 (s, 6 H, 13^5-OCH_3 and 17^5-OCH_3 (**4b** and **4d**)), 3.78 (2q, 4 H, J = 8 Hz, 3^1-CH_2 and 8^1-CH_2 (**4b** and **4d**)), 4.12 (m, 13^1-CH_2 and 17^1-CH_2 (**4b** and **4d**)), 4.63 (d, J = 16.1 Hz, 1 H, 10^2-CH (**4b**)), 4.65 (d, J = 16 Hz, 1 H, 20^2-CH (**4d**)), 9.53−9.45 (s, 3 H, 5-CH, 15-CH (**4b** and **4d**), 20-CH (**4b**) and 10-CH (**4d**)), 9.69 (d, J = 16 Hz, 1 H, 10^1-CH (**4b**)) 9.70 (d, J = 16.1 Hz, 1 H, 20^1-CH (**4d**)) ppm.

Quino[4,4a,5,6-*efg*]-Annulated 7-Demethyl-8-deethylmesoporphyrin Dimethyl Ester Nickel(II) Complex 5a: Compound **4a** (500 mg, 0.71 mmol) was poured into trichloroacetic acid (5.0 g) at 175 °C and stirred for two minutes at this temperature. During the reaction, gas formation was observed. After two minutes, the mixture was poured into a solution of sodium acetate in water. The crude product mixture was extracted with chloroform, dried over magnesium sulfate and purified on silica gel: first dichloromethane was used to remove unidentified impurities, then, with a mixture of THF/diethyl ether (4:1, v/v), the green fraction was collected and the solvent was evaporated under reduced pressure. The green compound was dissolved in dichloromethane, filtered, and recrystallized from a mixture of dichloromethane and hexane to give pure **5a** (70 mg, 0.10 mmol, 14%). M.p. 204−205 °C. HR-FABMS [M + H] found: *m*/*z* = 684.2108, calcd. for $^{12}C_{38}{}^{1}H_{36}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: 684.2121. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.60 (t, ^3J ($3^1\text{-H-}2^2\text{-H}$) = 7.5 Hz, 2 H, 3^2-CH_3), 2.93 (s, 3 H, 12^1-CH_3), 2.96 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.8 Hz, 2 H, 13^2-CH_2), 3.05 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 7.8 Hz, 2 H, 17^2-CH_2), 3.09(s, 3 H, 2^1-CH_3), 3.26 (s, 3 H, 18^1-CH_3), 3.57 (q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.5 Hz, 2 H, 3^1-CH_2), 3.68 (s, 3 H, 13^5-OCH_3), 3.70 (s, 3 H, 17^5-OCH_3), 3.86 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.8 Hz, 2 H, 13^1-CH_2), 4.00 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 7.8 Hz, 2 H, 17^1-CH_2), 8.14 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 9.7 Hz, 5^2-CH), 8.46 (d, $^3J(5^5\text{-H-}5^6\text{-H})$ = 5.0 Hz, 5^6-CH), 8.96 (s, 1 H, 10-CH), 9.11 (s, 2 H, 15-CH and 20-CH), 9.17 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 9.7 Hz, 5^1-CH), 9.46 (d, $^3J(5^5\text{-H-}5^6\text{-H})$ = 5.0 Hz, 5^5-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 11.0 (CH_3-12^1), 11.1 (CH_3-2^1), 11.4 (CH_3-18^1), 15.9 (CH_3-3^2), 21.3 (CH_2-13^2), 21.5 (CH_2-17^2), 22.3 (CH_2-3^1), 36.5 (CH_2-13^1), 36.6 (CH_2-17^1), 51.8 (OCH_3-17^5 and OCH_3-13^5), 96.9 (CH-10), 100.6 and 98.2 (CH-15 and CH-20), 107.8 (C-5), 112.1 (CH-5^6), 122.1 (CH-5^2), 123.2 (C-7), 131.3 (CH-5^1), 135.6 (C-6), 135.8 (C-12), 136.7 (C-18), 137.0 (C-9), 138.5 (C-17 and C-1, overlapping), 139.2 (C-13), 139.4 (C-14), 139.7−139.5 (C-2, C-3, C-11 and C-19 overlapping), 139.8 (C-8), 140.0 (C-4), 142.2 (C-11), 144.7 (C-5^3), 147.4 (CH-5^5), 173.4 and 173.3 (C-17^4 and C-13^4) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 274 (4.3), 319 (4.5), 348 (4.4), 439 (4.8), 588 (3.9), 635 (4.4).

2′-(Methoxycarbonyl)quino[4,4a,5,6-*jkl*]-Annulated 12-Demethyl-13-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin Dimethyl Ester Nickel(II) Complex 5b, 2′-(Methoxycarbonyl)quino[4,4a,5,6-*qrs*]-Annulated 18-Demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphy-

rin Dimethyl Ester Nickel(II) Complex 5c and Quino[4,4a,5,6-*abt*]-Annulated 2-Demethyl-3-deethylmesoporphyrin Dimethyl Ester Nickel(II) Complex 5d: A mixture of **4b** and **4d** (ratio 1:2) (5.00 g) was treated with trichloroacetic acid (50 g) in the same way as for **5a**. The green fraction obtained after the first silica gel purification was separated again on silica with THF/diethyl ether (60:40) into three fractions. The first fraction contained a mixture of **5b** and **5c** (480 mg), the second fraction yielded **5c** (185 mg, 0.29 mmol), and the third and last fraction contained **5d** (225 mg, 0.36 mmol).

2′-(Methoxycarbonyl)quino[4,4a,5,6-*qrs*]-Annulated 18-Demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin Dimethyl Ester Nickel(II) Complex 5c: M.p. 272 °C. HR-FABMS [M + H] found: *m*/*z* = 684.2112, calcd. for $^{12}C_{38}{}^{1}H_{36}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: *m*/*z* = 684.2121. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.53 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8.1 Hz, 3 H, 3^2-CH_3), 1.68 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 8.1 Hz, 3 H, 8^2-CH_3), 2.72 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.8 Hz, 2 H, 13^2-CH_2), 3.05 (s, 3 H, 12^1-CH_3), 3.06 (s, 3 H, 2^1-CH_3), 3.22 (s, 3 H, 7^1-CH_3), 3.40 (q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8.1 Hz, 2 H, 3^1-CH_2), 3.49 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.8 Hz, 2 H, 13^1-CH_3), 3.66 (q, $^3J(8^1\text{-H-}8^2\text{-H})$ = 8.1 Hz, 2 H, 8^1-CH_2), 3.69 (s, 3 H, 13^5-OCH_3), 4.47 (s, 3 H, $17^{2'''}$-OCH_3), 8.12 (d, $^3J(17^5\text{-H-}17^6\text{-H})$ = 9.0 Hz, 1 H, 17^5-CH), 8.51 (s, 1 H, 15-CH), 8.90 (s, 1 H, 10-CH), 8.97 (s, 1 H, 5-CH), 9.05 (d, $^3J(17^5\text{-H-}17^6\text{-H})$ = 9.0 Hz, 1 H, 17^6-CH), 9.17 (s, 1 H, 17^1-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 11.2 (CH_3-12^1 and CH_3-7^1, overlap), 16.2 (CH_3-2^1), 17.5 (CH_3-8^2), 17.6 (CH_3-3^2), 19.2 (CH_2-3^1), 19.6 (CH_2-8^1), 20.9 (CH_2-13^1), 36.3 (CH_2-13^2), 51.7 (OCH_3-13^5), 53.5 (OCH_3-$17^{2'''}$), 96.4 (CH-10), 98.4 (CH-15), 100.0 (CH-5), 108.4, 113.6 (CH-17^1), 122.0 (CH-17^5), 123.4, 132.4 (CH-17^6), 132.5, 133.9, 135.8, 135.9, 137.1, 137.6, 138.1, 138.8, 140.0, 140.3, 140.4, 140.5, 140.6, 142.8, 144.3, 146.2, 167.7, 173.1 ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 282 (4.2), 322 (4.4), 389 (4.2), 446 (4.5), 596 (4.0), 643 (4.3).

Quino[4,4a,5,6-*abt*]-Annulated 2-Demethyl-3-deethylmesoporphyrin Dimethyl Ester Nickel(II) Complex 5d: M.p. 208 °C. HR-FABMS [M + H] found: *m*/*z* = 684.2149, calcd. for $^{12}C_{38}{}^{1}H_{36}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: *m*/*z* = 684.2121. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.59 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.8 Hz, 3 H, 8^2-CH_3), 2.69 (s, 3 H, 7^1-CH_3), 2.84 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 8.0 Hz, 3 H, 17^2-CH_2), 2.95 (s, 3 H, 18^1-CH_3), 3.05 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^2-CH_2), 3.26 (s, 3 H, 12^1-CH_3), 3.46 (q, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.8 Hz, 2 H, 8^1-CH_2), 3.68 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 8.0 Hz, 2 H, 17^1-CH_3), 3.70 and 3.72 (2s, 6 H, 13^5-OCH_3 and 17^5-OCH_3), 3.99 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^1-CH_2), 7.86 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 9.0 Hz, 1 H, 3^2-CH), 8.03 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 4.5 Hz, 1 H, 3^6-CH), 8.44 (s, 1 H, 5-CH), 8.84 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 9.0 Hz, 1 H, 3^1-CH), 8.94 (s, 1 H, 10-CH), δ 9.01 (s, 1 H, 15-CH), 9.24 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 4.5 Hz, 1 H, 3^5-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 10.5 (CH_3-7^1), 11.4 (CH_3-12^1), 16.2 (CH_3-18^1), 17.3 (CH_3-8^2), 19.4 (CH_2-8^1), 21.1 (CH_2-17^1), 21.5 (CH_2-13^1), 36.7 and 36.8 (CH_2-13^2 and CH_2-17^2), 51.7 (OCH_3-13^5 and OCH_3-17^5), 96.3 (CH-5), 98.3 (CH-10), 100.0 (CH-15), 108.0, 111.6 (CH-3^6), 121.5 (CH-3^2), 122.4, 130.9 (CH-3^1), 132.8, 134.4, 135.1, 136.1, 136.9, 137.0, 138.5, 138.8, 139.0, 139.5, 139.7, 140.7, 141.8, 142.5, 143.1, 147.0 (CH-3^5), 173.0, 173.3 ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 273 (4.3), 318 (4.5), 346 (4.4), 437 (4.8), 586 (2.9), 633 (4.4).

2′-(Methoxycarbonyl)quino[4,4a,5,6-*jkl*]-Annulated 12-Demethyl-13-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin Dimethyl Ester Nickel(II) Complex 5b: This compound was not separated as a single pure compound but rather as a mixture of **5b** and **5c**, therefore 600-MHz ^{1}H NMR spectral characterization has not been done for this compound.

Quino[4,4a,5,6-*efg*]-Annulated 7-Demethyl-8-deethylmesoporphyrin Dimethyl Ester 6a: Concentrated sulfuric acid (4 mL) was added to quinoporphyrin **5a** (50 mg, 0.073 mmol) and the mixture was swirled at room temperature until it was completely dissolved. Then the mixture was neutralized by pouring into an aqueous solution of sodium acetate, and the yellowish brown product was extracted with dichloromethane, dried over magnesium sulfate and purified by silica gel chromatography with THF/diethyl ether, 4:1 (v/v). The product was recrystallized from dichloromethane/hexanes to give the nickel-free quinoporphyrin **6a** (40 mg, 0.063 mmol, 86%). M.p. 244−246 °C. HR-FABMS [M + H] found: *m*/*z* = 628.2921, calcd. for $^{12}C_{38}{}^{1}H_{37}{}^{14}N_5{}^{16}O_4{}^+$: 628.2924. ^{1}H NMR (600 MHz, $CDCl_3$): δ = −4.79 (s, 1 H, 21-NH), −4.50 (s, 1 H, 23-NH), 1.66 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 2 H, 3^2-CH_3), 3.11 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^2-CH_2), 3.12 (s, 3 H, 12^1-CH_3), 3.20 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 7.9 Hz, 2 H, 17^2-CH_2), 3.29 (s, 3 H, 2^1-CH_3), 3.42 (s, 3 H, 18^1-CH_3), 3.65 (s, 3 H, 13^5-OCH_3), 3.69 (q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 2 H, 3^1-CH_2), 3.72 (s, 3 H, 17^5-OCH_3), 4.12 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^1-CH_2), 4.18 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 7.9 Hz, 2 H, 17^1-CH_2), 8.20 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 8.9 Hz, 1 H, 5^2-CH), 8.53 (d, $^3J(5^5\text{-H-}5^6\text{-H})$ = 4.6 Hz, 1 H, 5^6-CH), 8.95 (s, 1 H, 10-CH), 9.22 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 8.9 Hz, 1 H, 5^1-CH), 9.49 (s, 1 H, 15-CH), 9.38 (s, 1 H, 20-CH), 9.54 (d, $^3J(5^5\text{-H-}5^6\text{-H})$ = 4.6 Hz,1 H, 5^5-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 10.8 (CH_3-12^1), 10.9 (CH_3-2^1), 11.8 (CH_3-18^1), 15.8 (CH_3-3^2), 21.2 (CH_3-13^1), 21.6 (CH_2-3^1), 21.8 (CH_2-17^1), 36.4 (CH_2-13^2), 37.0 (CH_2-17^2), 51.8 and 51.7 (OCH_3-17^5 and OCH_3-13^5), 94.2 (CH-10), 96.7 (CH-15), 100.6 (CH-20), 109.6 (C-5), 114.0 (CH-5^6), 122.8 (CH-5^2), 125.2 (C-7), 131.3 (C-3), 131.5 (CH −5^1), 132.5 (C-12), 133.7 (C-4), 134.7 (C-2), 134.9 (C-1), 135.3 (C-13), 135.7 (C-14), 136.6 (C-11), 139.8 (C-18), 140.1 (C-17), 143.5 (C-8), 144.7 (CH −5^3), 146.9 (C-6), 148.2 (CH-5^5), 148.4 (C-9), 150.8 (C-19), 153.9 (C-16), 173.2 (C-13^4), 173.7 (C-17^4) ppm. ^{15}N NMR ($CDCl_3$): δ = −246.1 (NH-23), −244.9 (NH-21), −136.8 (N-24), −127.3 (N-22), −78.7 (N-5^4) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 319 (4.4), 361 (4.5), 454 (5.0), 553 (3.8), 601 (3.7) 626 (3.8), 681 (4.4).

2′-(Methoxycarbonyl)quino[4,4a,5,6-*jkl*]-Annulated 12-Demethyl-13-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin Dimethyl Ester 6b: This compound was not separated as a single pure compound but rather as a mixture of **6b** and **6c**. HR-FABMS [M + H] found: *m*/*z* = 628.2912, calcd. for $^{12}C_{38}{}^{1}H_{37}{}^{14}N_5{}^{16}O_4{}^+$: 628.2924. ^{1}H NMR (600 MHz, $CDCl_3$): δ = −4.97 and −5.24 (s, 1 H, 22-NH and 23-NH), 1.73 (t, ^3J $(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 2 H, 3^2-CH_3), 1.82 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 2 H, 8^2-CH_3), 2.84 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 8.0 Hz, 2 H, 17^2-CH_2), 3.32 (s, 3 H, 18^1-CH_3), 3.39 (s, 3 H, 7^1-CH_3) 3.40 (s, 3 H, 2^1-CH_3), 3.63 (s, 3 H, 17^5-OCH_3), 3.69 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 8.0 Hz, 2 H, 17^1-CH_2), 3.82 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.7 Hz, 2 H, 3^1-CH_3), 3.88 (t, ^3J $(8^1\text{-H-}8^2\text{-H})$ = 7.7 Hz, 2 H, 8^1-CH_2), 4.51 (s, 3 H, $10^{5''}$-OCH_3), 8.36 (d, $^3J(10^1\text{-H-}10^2\text{-H})$ = 9.0 Hz, 1 H, 10^2-CH), 8.66 (s, 1 H, 15-CH), 9.27 (s, 1 H, 20-CH), 9.33 (d, $^3J(10^1\text{-H-}10^2\text{-H})$ = 9.0 Hz, 1 H, 5^1-CH), 9.34 (s, 1 H, 10^1-CH), 9.68 (s, 1 H, 5-CH) ppm.

2′-(Methoxycarbonyl)quino[4,4a,5,6-*qrs*]-Annulated 18-Demethyl-17-de[2′-(methoxycarbonyl)ethyl]mesoporphyrin Dimethyl Ester 6c: The same procedure as applied for **6a** was used starting from **5c** (180 mg, 0.26 mmol) to give **6c** (130 mg, 0.21 mmol, 79%). M.p. 252−254 °C. HR-FABMS [M + H] found: *m*/*z* = 628.2933, calcd. for $^{12}C_{38}{}^{1}H_{37}{}^{14}N_5{}^{16}O_4{}^+$: 628.2924. ^{1}H NMR (600 MHz, $CDCl_3$): δ = −5.41 (s, 1 H, 21-NH), −5.10 (s, 1 H, 23-NH), 1.63 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8.0 Hz, 3 H, 3^2-CH_3), 1.81 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 8.0 Hz, 3 H, 8^2-CH_3), 2.88 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^2-CH_2), 3.20 (s, 3 H, 2^1-CH_3), 3.35 (s, 3 H, 12^1-CH_3), 3.42 (s, 3 H, 7^1-CH_3),

3.66 (s, 3 H, 13^5-OCH_3), 3.67 (q, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8.0 Hz, 2 H, 3^1-CH_2), 3.77 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.8 Hz, 2 H, 13^1-CH_3), 3.87 (q, $^3J(8^1\text{-H-}8^2\text{-H})$ = 8.0 Hz, 2 H, 8^1-CH_2), 4.51 (s, 3 H, $17^{2'''}$-OCH_3), 8.15 (d, $^3J(17^5\text{-H-}17^6\text{-H})$ = 9.0 Hz, 1 H, 17^5-CH), 8.54 (s, 1 H, 15-CH), 9.09 (d, $^3J(17^5\text{-H-}17^6\text{-H})$ = 9.0 Hz, 1 H, 17^6-CH), 9.22 (s, 1 H, 17^1-CH), 9.30 (s, 1 H, 10-CH), 9.43 (s, 1 H, 5-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 11.1 (CH_3-12^1), 11.6 (CH_3-7^1), 15.2 (CH_3-2^1), 17.6 (CH_3-3^2), 17.7 (CH_3-8^2), 19.0 (CH_2-3^1), 19.8 (CH_2-8^1), 20.9 (CH_2-13^1), 36.3 (CH_2-13^2), 51.8 (OCH_3-13^5), 53.5 (OCH_3-17^5), 93.9 (CH-15), 97.3 (CH-10), 100.0 (CH-5), 109.7 (C-20), 115.5 (CH-17^1), 122.7 (CH-17^5), 126.0 (C-18), 128.2 (C-2), 131.0 (C-4), 132.7 (CH-17^6), 133.6 (C-13), 133.9 (C-1), 134.4 (C-12), 135.2 (C-14), 136.2 (C-11), 138.6 (C-7), 141.4 (C-3), 143.2 (C-17), 143.8 (C-17^4), 144.4 (C-8), 145.1 (C-19), 146.9 (C-16), 152.0 (C-6), 153.8 (C-9), 167.7 (C-17^4), 173.0 (C-13^4) ppm. ^{15}N NMR ($CDCl_3$): δ = −245.7 (NH-23), −244.7 (NH-21), −135.9 (N-22), −125.7 (N-24), −79.2 (N-17^3) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 320 (4.5), 358 (4.4), 464 (4.8), 561(3.9), 627 (3.8), 688 (4.4).

Quino[4,5,6,7-*abt*]-Annulated 2-Demethyl-3-deethylmesoporphyrin Dimethyl Ester 6d: The same procedure as applied for **6a** was used starting from **5d** (100 mg, 0.15 mmol) to give **6d** (74 mg, 0.12 mmol, 81%). HR-FABMS [M + H] found: *m*/*z* = 628.2869, calcd. for $^{12}C_{38}{}^1H_{36}{}^{14}N_5{}^{16}O_4{}^{58}Ni^+$: *m*/*z* = 628.2924. ^1H NMR (600 MHz, $CDCl_3$): δ = −4.44 (s, 1 H, NH), −4.20 (s, 1 H, NH), 1.79 (t, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.9 Hz, 3 H, 8^2-CH_3), 3.05 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 7.8 Hz, 3 H, 17^2-CH_2), 3.19 (s, 3 H, 7^1-CH_3), 3.21 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^2-CH_2), 3.35 (s, 3 H, 18^1-CH_3), 3.64 (s, 3 H, 12^1-CH_3), 3.64 (s, 3 H, 17^5-OCH_3), 3.71 (s, 3 H, 13^5-OCH_3), 3.90 (q, $^3J(8^1\text{-H-}8^2\text{-H})$ = 7.8 Hz, 2 H, 8^1-CH_2), 4.14 (t, $^3J(17^1\text{-H-}17^2\text{-H})$ = 8.0 Hz, 2 H, 17^1-CH_3), 4.25 (t, $^3J(13^1\text{-H-}13^2\text{-H})$ = 7.9 Hz, 2 H, 13^1-CH_2), 8.20 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 8.9 Hz, 1 H, 3^2-CH), 8.53 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 4.5 Hz, 1 H, 3^6-CH), 9.04 (s, 1 H, 5-CH), 9.52 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 9.0 Hz, 1 H, 3^1-CH), 9.60 (overlapping s and d, 2 H, 10-CH and 3^5-CH), 9.65 (s, 1 H, 15-CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 10.6 (CH_3-7^1), 11.6 (CH_3-12^1), 15.2 (CH_3-18^1), 17.2 (CH_3-8^2), 19.2 (CH_2-8^1), 20.9 (CH_2-17^1), 21.7 (CH_2-13^1), 36.6 (CH_2-13^1), 36.7 (CH_2-17^2), 51.7 (OCH_3), 94.0 (CH-5), 96.8 (CH-10), 100.3 (CH-15), 113.6 (CH-3^1), 122.4 (CH-3^2), 131.6 (CH-3^6), 147.8 (CH-3^2) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 320 (4.2), 355 (4.2), 458 (4.7), 555 (3.6), 625 (3.5), 683 (4.1).

(Etioporphyrin-I-ato)nickel(II) (12): Nickel(II) acetate tetrahydrate (1.00 g, 4.01 mmol) was added to a solution of etioporphyrin I (1.00 g, 2.09 mmol) in dimethylformamide (150 mL), after which the mixture was refluxed for 15 minutes. The dimethylformamide was removed by distillation and then water was added, after which the porphyrin was filtered off and washed with water. The product was purified by silica gel chromatography using dichloromethane as the eluent to give **12** (0.960 g, 1.79 mmol, 86%). HR-FABMS [M + H] found: *m*/*z* = 535.2346, calcd. for $^{12}C_{32}{}^1H_{37}{}^{14}N_4{}^{58}Ni^+$: *m*/*z* = 535.2372. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.78 (t, $^3J(CH_2\text{-}CH_3)$ = 7.6 Hz, 12 H, ethyl CH_3), 3.48 (s, 12 H, methyl CH_3), 3.93 (q, $^3J(CH_2\text{-}CH_3)$ = 7.6 Hz, 8 H, ethyl CH_2), 9.77 (s, 4 H, meso-CH) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 295 (3.9), 334 (3.9), 395 (4.4), 520 (3.9), 556 (4.2).

(5-Formyletioporphyrinato)nickel(II) (13): Phosphorus oxychloride (0.73 mL) was added to a stirred solution of *N*-methylformamide (1.23 mL) in dichloroethane (5 mL) at room temperature. After 15 minutes, nickel etioporphyrin (415 mg, 0.775 mmol) in dichloroethane (100 mL) was added, and the mixture was stirred for four days. After this time, an aqueous saturated sodium carbonate solution (100 mL) was added to hydrolyse the Vilsmeier adduct, and after 1 hour of stirring, the green organic layer was separated. The solvent was distilled off, after which 80% methanol in water (100 mL) was added to the oily suspension to precipitate the porphyrin mixture. The precipitate was filtered off and purified by silica gel chromatography with dichloromethane/hexanes (1:1) as the eluent. After recrystallization from dichloromethane/hexanes, **13** (300 mg, 0.533, 69%) was obtained as purple needles. HR-FABMS [M + H] found: *m*/*z* = 563.2304, calcd. for $^{12}C_{33}{}^1H_{37}{}^{14}N_4{}^{16}O^{58}Ni^+$: *m*/*z* = 563.2321. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.73−1.60 (m, 12 H, ethyl CH_3), 3.24−3.29 (overlapping singlets 12 H, methyl CH_3), 3.79−3.64 (m, 8 H, ethyl CH_2), 9.27 (s, 2 H, 10-CH and 20-CH), 9.30 (s, 1 H, 15-CH) 11.91 (s, 1 H, 5-CHO) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 297 (4.1), 329 (4.1), 413 (4.4), 527 (3.7), 649 (3.8).

[5-(2′-Cyanovinyl)etioporphyrinato]nickel(II) (7): Sodium hydride (80% in mineral oil) (37 mg, 1.2 mmol) was washed with hexanes before THF (50 mL) was added. Diethyl (cyanomethyl)phosphonate (0.29 mL, 0.32 g, 1.8 mmol) was added and the mixture was stirred for 15 minutes until the reaction had ceased. **13** (300 mg, 0.53 mmol) was added to the mixture, which was then heated to reflux to dissolve the porphyrin. The mixture was left at room temperature for 20 hours over which time the color changed from green to brown. Then, water was added and the THF was removed by distillation. The solid porphyrin mixture was filtered off, dissolved in dichloromethane and purified by silica gel chromatography using a mixture of dichloromethane and hexanes (1:1). **7** (260 mg, 0.44, 83%) was obtained as a purple microcrystalline powder, also **13** (30 mg 0.05 mmol, 10%) was recovered. HR-FABMS [M + H] found: *m*/*z* = 586.2454, calcd. for $^{12}C_{35}{}^1H_{38}{}^{14}N_5{}^{58}Ni^+$: *m*/*z* = 586.2481. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75−1.60 (m, 12 H, ethyl CH_3), 3.37−3.30 (overlapping singlets 12 H, methyl CH_3), 3.87−3.75 (m, 8 H, ethyl CH_2), 4.62 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.5 Hz, 1 H, 5^2-CH), 9.44 (s, 3 H, 10-CH, 15-CH and 20-CH), 9.70 [d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.5 Hz, 1 H, 5^1-CH] ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 310 (4.1), 338 (4.1), 414 (4.5), 533 (3.8), 567 (4.0).

(8,13,18-Triethyl-7,12,17-trimethylquino[4,4a,5,6-*abt*]porphyrinato)-nickel(II) (8): **7** (100 mg, 0.17 mmol) was added to trichloroacetic acid (5.0 g). A flame was used to heat the mixture rapidly to 180 °C and the mixture was stirred for two minutes before pouring into a saturated $NaHCO_3$ solution in water (150 mL). The aqueous phase was extracted four times with dichloromethane, and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated and a crude separation of the product mixture was accomplished by silica gel chromatography, first using dichloromethane as eluent in order to remove side-products. The product was eluted with THF, after which it underwent a second purification over silica gel using a mixture of THF and diethyl ether (3:2). The bright green band that was eluted last was collected and contained quinoporphyrin **8** (14 mg, 0.025 mmol, 14%). HR-FABMS [M + H] found: *m*/*z* = 568.1982, calcd. for $^{12}C_{34}{}^1H_{32}{}^{14}N_5{}^{58}Ni^+$: *m*/*z* = 568.2011. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.65 (t, $^3J(CH_2\text{-}CH_3)$ = 7.8 Hz, 3 H, 8^2-CH_3), 1.72 (t, $^3J(CH_2\text{-}CH_3)$ = 7.8 Hz, 3 H, 13^2-CH_3), 1.77 (t, $^3J(CH_2\text{-}CH_3)$ = 7.8 Hz, 3 H, 7^2-CH_3), 3.12 (s, 3 H, 7^1-CH_3), 3.30 (s, 3 H, 17^1-CH_3), 3.32 (s, 3 H, 12^1-CH_3), 8.39 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 9.1 Hz, 1 H, 3^5-CH), 8.79 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 4.2 Hz, 1 H, 3^1-CH), 9.24 (s, 1 H, 10-CH), 9.41 (s, 1 H, 15-CH), 9.42 (s, 1 H, 5-CH), 9.56 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 9.1 Hz, 1 H, 3^6-CH), 9.62 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 4.2 Hz, 1 H, 3^2-CH) ppm. ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 11.1 (CH_3-17^1), 11.3 (CH_3-12^1), 11.5 (CH_3-7^1), 16.1 (CH_3-18^2), 17.5 (CH_2-8^2), 17.6 (CH_3-13^2), 19.5 (CH_2-8^1), 19.6 (CH_2-13^1), 22.5 (CH_2-18^1), 95.9 (CH-5), 97.5 (CH-10), 100.9 (CH-15), 108.2, 112.4 (CH-3^1), 122.3 (CH-3^5), 131.8 (CH-3^6), 135.1, 135.6, 135.9, 136.8, 137.5, 138.8, 139.3, 139.8, 139.9 (overlap), 140.1, 140.3, 140.5, 141.2, 143.0, 143.8, 145.1, 147.6 (CH-

3^2) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 272 (4.2), 320 (4.3), 350 (4.2), 445 (4.4), 638 (4.2).

(5-Formyl-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) (14): The same procedure as for **13** was applied to the synthesis of **14**. *N*-methylformanilide(1.04 mL, 8.42 mmol), phosphorus oxychloride (0.71 mL, 7.62 mmol) and (octaethylporphyrinato)nickel (1.00 g, 1.69 mmol) were used. Yield: **14** (0.72 g, 1.2 mmol, 69%) also starting material (0.11 g, 0.2 mmol, 11%) was recovered. m.p. 269 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79−1.61 (m, 24 H, ethyl CH_3), 3.81−3.67 (m, 16, ethyl CH_2), 9.30 (s, 2 H, 5-CH and 20-CH), 9.33 (s, 1 H, 15-CH), 11.89 (s, 1 H, 5-CHO) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 405 (4.9), 529(3.7), 564 (4.0), 650 (4.0).

[5-(2′-Cyanovinyl)-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel-(II) (9): This compound **9** was prepared in the same way as **7** starting from sodium hydride (80% in mineral oil) (70 mg, 2.3 mmol), diethyl (cyanomethyl)phosphonate (0.52 g, 2.9 mmol) and **14** (0.72 g, 1.2 mmol). Yield: **9** (0.65 g, 1.0 mmol, 87%) as brown needles, also starting material (0.10 g, 0.2 mmol, 13%) was recovered; m.p. 225 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78−1.65 (m, 24 H, ethyl CH_3), 3.91- 3.68 (m, 16 H, ethyl CH_2), 4.57 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.0 Hz, 1 H, 5^2-CH,), 9.42 (s, 3 H, 10-CH, 15-CH and 20-CH) and 9.72 (d, $^3J(5^1\text{-H-}5^2\text{-H})$ = 16.0 Hz, 1 H, 5^1-CH) ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 409 (4.9), 534 (3.9), 571 (4.1).

(7,8,12,13,17,18-Hexaethylquino[4,4a,5,6-*abt*]porphyrinato)nickel-(II) (10) and (2^1-Imino-3,3,7,8,12,13,17,18-octaethyl-2,2^1-dihydrobenzo[*at*]chlorinato)nickel(II) (11): 9 (100 mg, 0.16 mmol) was added to trichloroacetic acid (0.50 g) at a temperature of 180 °C, after which the mixture was refluxed for two minutes the mixture became solid. Then an aqueous $NaHCO_3$ solution (20 mL) and dichloromethane (20 mL) were added, the organic layer was collected and the aqueous phase was extracted four times, after which the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated and the crude product was separated into two fractions using silica gel chromatography. The first fraction (52 mg) was eluted with dichloromethane, the second fraction (32 mg), which contained impure quinoporphyrin **10** was eluted with THF. Further purification of this second fraction using THF/diethyl ether (3:2, v/v) yielded the pure quinoporphyrin **10** (16 mg, 0.03 mmol, 19%). Further silica gel purification with dichloromethane/hexanes (70:30, v/v) of the first fraction gave, among unidentified products, pure **11** (7 mg, 0.01 mmol, 7%).

(7,8,12,13,17,18-Hexaethylquino[4,4a,5,6-*abt*]porphyrinato)nickel-(II) (10): HR-FABMS [M + H] found: *m*/*z* = 610.2504, calcd. for $^{12}C_{37}{}^1H_{38}{}^{14}N_5{}^{58}Ni^+$: *m*/*z* = 610.2481. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.73−1.81 (m, 15 H, 7^2-CH_3, 8^2-CH_3,12^2-CH_3,13^2-CH_3 and 17^2-CH_3), 1.85 (t, ^3J = 7.7 Hz, 3 H, 18^2-CH_3), 3.73−3.87 (m, 10 H, 7^1-CH_2, 8^1-CH_2,12^1-CH_2,13^1-CH_2 and 17^1-CH_2), 4.04 (q, ^3J = 7.7 Hz, 2 H, 7^1-CH_3), 8.49 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 9.2 Hz, 1 H, 3^5-CH), 9.07 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 4.5 Hz, 1 H, 3^1-CH), 9.53 (s, 1 H, 10-CH), 9.65 (s, 1 H, 15-CH), 9.69 (d, $^3J(3^1\text{-H-}2^2\text{-H})$ = 4.5 Hz, 1 H, 3^2-CH), 9.76 (d, $^3J(3^5\text{-H-}3^6\text{-H})$ = 9.2 Hz, 1 H, 3^6-CH), 9.93 (s, 1 H, 5-CH) ppm. ^{13}C NMR (75.1 MHz, $CDCl_3$, detected via HMQC): δ = 16.8, 18.0, 18.3 and 18.5 (overlapping ethyl CH_3 signal), 19.4, 19.6 and 22.3 (overlapping ethyl CH_2 signal), 97.8 (CH-20), 99.2 (CH-15), 101.1 (CH-10), 112.8 (CH-2^1), 122.7 (CH-2^5), 132.0 (CH-2^6), 147.9 (CH-2^2) ppm.

(2^1-Imino-3,3,7,8,12,13,17,18-octaethyl-2,2^1-dihydrobenzo[*at*]-chlorinato)nickel(II) (11): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.27 (t, $^3J(3^1\text{-H-}2^2\text{-H})$ = 7.3 Hz, 6 H, 2× 3^2-CH_3), 1.53−1.62 (m, 15 H, 7^2-, 8^2-, 12^2-, 13^2- and 17^2-CH_3), 1.65 (t, $^3J(18^1\text{-H-}18^2\text{-H})$ = 7.5 Hz, 3 H, 18^2-CH_3), 2.64 (m, 2 H, 2× 3^1-CH^a), 2.80 (m, 2 H, 2× 3^1-CH^b), 3.35 (q, $^3J(7^1\text{-H-}7^2\text{-H})$ = 7.6 Hz, 2 H, 7^1-CH_2), 3.40−3.46 (m, 6 H, 8^1-, 12^1- and 13^1-CH_2), 3.51 (q, $^3J(19^1\text{-H-}19^2\text{-H})$ = 7.5 Hz, 2 H, 19^1-CH_2), 3.62 (q, $^3J(18^1\text{-H-}18^2\text{-H})$ = 7.5 Hz, 2 H, 18^1-CH_2), 6.25 (s, 1 H, 2-CH), 7.74 (s, 1 H, 5-CH), 8.38 (d, $^3J(2^2\text{-H-}2^3\text{-H})$ = 8.9 Hz, 1 H, 2^2-CH), 8.50 (s, 1 H, 10-CH), 8.83 (s, 1 H, 15-CH), 8.90 (s, 1 H, $2^{1\prime}$-NH, disappears when MeOD is added), 9.01 (d, $^3J(2^2\text{-H-}2^3\text{-H})$ = 8.9 Hz, 1 H, 2^3-CH) ppm. ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 8.8 (CH_3-3^2), 16.0 (CH_3-18^2), 17.1, 17.6, 17.6, 18.1 and 18.2 (CH_3-7^2, CH_3-8^2, CH_3-12^2, CH_3-13^2, CH_3-17^2), 19.0, 19.0, 19.2, 19.2 and 21.4 (CH_2-7^1, CH_2-8^1, CH_2-12^1, CH_2-13^1 and CH_2-17^1), 33.6 (CH_2-3^1), 67.3 (CH-2), 87.6 (CH-5), 98.8 (CH-10), 107.3 (CH-15), 114.6 (CH-2^2), 125.1 (CH-2^3), 126.9, 128.9, 133.5, 135.3, 136.1, 138.2, 140.0, 140.3, 141.7, 142.0, 142.7, 143.5, 144.8, 144.9, 148.5, 161.9, 163.8, 207.2 ppm. UV/Vis (CH_2Cl_2): λ_{max} (log ε) = 291 (4.1), 365 (4.0), 425 (4.4), 632 (3.5), 683 (4.0).

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