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Synthesis and Application of Functionalized Macrocyclic Oligopyrroles

Promotor:
Prof. Dr. Wim Dehaen

Doctoraatsproefschrift
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Dr. Volker Magnus (Rudjer Bošković Institute, Zagreb, Croatia)
Prof. Dr. Luc Van Meervelt

there is this old woman
she lives down the road
you can often find her
kneeling inside of her hole
and i often ask her
"are you looking for the mother lode?"
huh?
no.
no my child, this is not my desire
and then she said

i'm digging for fire

there is this old man
who spent so much of his life sleeping
that he is able to keep awake for the rest of his years
he resides
on a beach
in a town
where i am going to live
and i often ask him
"are you looking for the mother lode?"
huh?
no.
no my child, this is not my desire
and then he said

i'm digging for fire

"Dig for Fire", Black Francis (The Pixies), 1990

Dankwoord

Mijn promotor Prof. Dr. Wim Dehaen moet ik als eerste dankbaar zijn voor zijn voorstel om in Leuven te komen doktoreren op die Weense avond van woensdag 4 augustus 1999. Daarmee is alles begonnen en zonder hem zou mijn leven niet zo grondig veranderd en verrijkt zijn met alle gebeurtenissen van de voorbije jaren.

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Hvala Marti i mom još nerođenom djetetu što su učinili moj život ljepšim, bogatijim i ispunjenijim nego što sam to ikad mogao pretpostavljati.

Summary

Porphyrins and their derivatives are pigments which occur widely in Nature. They play very important roles in various biological processes, including catalysis and transfer of small molecules and electrons. Synthetic porphyrins have found a broad range of applications in science and technology.

The subjects of the work described in this thesis are various cyclic tetrapyrrolic compounds related to porphyrins and precursors and derivatives of these compounds. In the first part oxidative *N*-alkylation of a tetraphenolic porphyrin has been examined. This reaction, poorly documented in the literature, has been carried out using various sets of experimental conditions and with several alkylating agents. A number of novel compounds have been prepared while the syntheses of some known products have been improved. It has been shown that the degree of *N*-alkylation could be controlled. This enabled the preparation of partially alkylated products as well as products of mixed alkylation. A doubly bridged product with the adjacent pyrrole rings two by two connected in an unusual way has also been prepared.

Secondly, syntheses of aromatically substituted *trans*-A_2B-corroles (derivatives of porphyrins lacking one bridging carbon atom) and their application have been described. Several synthetic methods have been used, which allowed some generalization of the reaction conditions required for different types of starting aldehydes. Some of the corroles synthesized have successfully been used in analytical systems for determination of small molecules.

In the last part of the work an optimized synthetic pathway to novel selectively substituted 2,2'-bipyrroles has been developed. The latter could be used as building blocks for porphyrin-related compounds and pyrrole polymers. The first experiments in these directions have been done.

Samenvatting

Porfyrinen en hun derivaten zijn pigmenten die in de natuur veelvuldig voorkomen. Ze spelen een zeer belangrijke rol in diverse biologische processen, onder andere in de katalyse en transfer van elektronen en kleine moleculen. Synthetische porfyrinen hebben een breed bereik van toepassingen in de wetenschap en de technologie.

De onderwerpen van het in deze thesis beschreven werk zijn cyclische tetrapyrrolische verbindingen die aan porfyrinen verwant zijn alsook precursoren en derivaten van deze verbindingen. In het eerste deel van het werk wordt oxidatieve *N*-alkylatie van een tetrafenolisch porfyrine onderzocht. Deze reactie, die weinig beschreven is in de literatuur, werd onder diverse experimentele omstandigheden en met verscheidene alkyleringsreagentia uitgevoerd. Een aantal nieuwe verbindingen werd voorbereid terwijl de synthesen van enkele bekende producten werden verbeterd. Er werd aangetoond dat de graad van de *N*-alkylatie kon worden gecontroleerd. Dit maakte de bereiding van gedeeltelijk gealkyleerde producten en producten van gemengde alkylatie mogelijk. Een dubbel overbrugd product, waarin de aanliggende pyrroolringen twee per twee op een ongewone manier verbonden zijn, werd ook gesynthetiseerd.

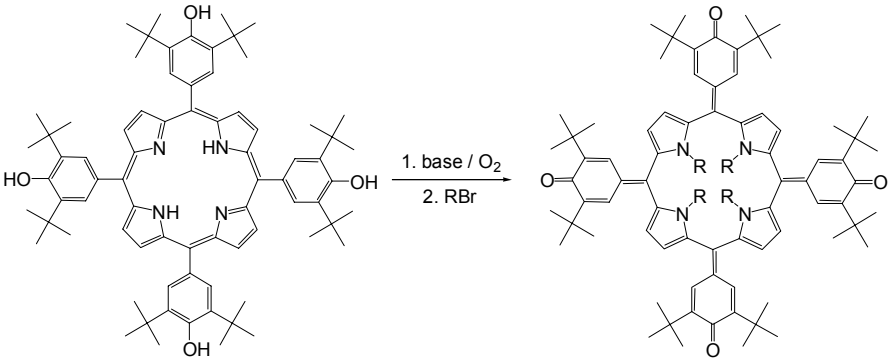
Ten tweede worden in dit proefschrift synthesen van aromatisch gesubstitueerde *trans*-A_2B-corrolen (porfyrinederivaten waar een *meso*-koolstofatoom in ontbreekt) en hun toepassing beschreven. Verscheidene synthetische methoden werden gebruikt, hetgeen enige veralgemening van de reactieomstandigheden voor verschillende typen van beginproducten mogelijk maakte. Enkele gesynthetiseerde corrolen werden succesvol toegepast in systemen voor analytische bepaling van kleine moleculen.

In het laatste deel van het werk werd een nieuwe synthetische methode voor het maken van selectief gesubstitueerde 2,2'-bipyrrolen ontwikkeld. Deze laatste kunnen worden gebruikt als bouwstenen voor de aanmaak van porfyrine-gerelateerde verbindingen alsook pyrroolpolymeren. De eerste experimenten in deze richting werden reeds uitgevoerd.

Table of Contents

Goals and Purposes

The objective of the first part of this work is to investigate the oxidative alkylation of hydroxyphenylporphyrin **1** (Scheme 1), an unexpected reaction observed in our laboratory during the work on porphyrin dendrimers.[1] The formation of tetraalkylated *p*-quinomethane tetrapyrrole derivatives **2** will be studied in terms of selectivity and the extent of substitution with isolation of intermediates.

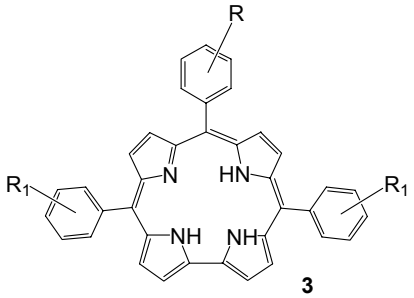


1 **2**

Scheme 1. Oxidative *N*-alkylation of porphyrins

The plan is to carry out the oxidative alkylation of **1** under various reaction conditions and with a number of alkylating agents. The nature and the structure of the products will be analyzed. It will be examined how changing and optimising the reaction conditions affects the extent of the reaction, as well as the possibility to prepare mixed substitution products. Finally, bridging of the tetrapyrrole ring with bifunctional reagents will also be investigated.

In the second part of this project, the synthesis of triarylcorroles, primarily those of A_2B type **3**, from aryldipyrromethanes and aldehydes and their derivatizations and applications will be described.

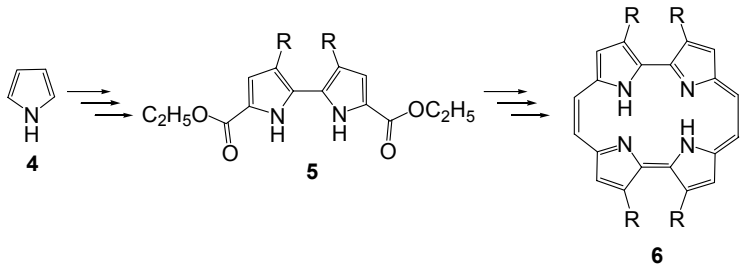


3

It will be examined how varying temperature, solvent, acidic catalyst and reaction time influences the yields of the corroles. For known compounds, an effort will be made to improve the yields reported in the procedures published earlier, whilst a number of new products will also be synthesized.

AB_2 substituted corroles **3** may be used as sensor elements for anions and neutral molecules in membranes or self-assembled monolayers (collaboration with Prof. J. Radecki from Olsztyn, Poland). Samples of these corroles will be given to the group of Prof. Radecki where they are to be incorporated in membranes. The response of the modified membranes towards neutral phenol analytes will be measured. Furthermore, corrole **155** with a long alkylthiol chain (**3** where R = *p*-$O(CH_2)_{11}SH$) provides an alternative sensor system which can form self-assembled monolayers on gold surfaces. Alternatively, **155** may be used to prepare a conjugate with indole, which should serve as a novel probe for indole-binding proteins (collaboration with Dr. V. Magnus from Zagreb, Croatia).

The last part of the research deals with the development of a new optimized synthesis of selectively 3,3'-substituted 2,2'-bipyrroles **5** (Scheme 2) and their further applications. It will be attempted, using pyrrole as the starting material, to work out a novel synthetic pathway towards products of type **5** through a series of regiospecific reactions optimized for yield, each of which could be performed on a gram scale. The final pyrrole-pyrrole coupling is to be achieved by an Ullmann reaction. The 2,2'-bipyrrole **5** may be used as a building block in the synthesis of porphycene **6**. It will also be attempted to use the synthetic pathway to **5** as a monomer source for a pyrrole polymerization reaction whose products could possess electroconductivity.



Scheme 2. Synthesis of selectively substituted bipyrroles and porphycenes

General Introduction

0. 1. Porphyrins

0. 1. 1. A short introduction

Porphyrins and other closely related tetrapyrrolic pigments occur widely in Nature, and they play very important roles in various biological processes. Heme [the iron(II) protoporphyrin-IX complex] is the prosthetic group in hemoglobins and myoglobins, which are responsible for oxygen transport and storage, respectively, in living tissues. Heme can also be found in the enzyme peroxidase, which catalyzes the removal of perilous peroxides from the same tissues. The related enzyme catalase, also containing heme, catalyzes the breakdown of hydrogen peroxide to water and oxygen. Other heme-containing proteins include the cytochromes, which serve as one-electron carriers in the electron transport chain. Closely related chlorophylls, which contain magnesium, play a crucial role in photosynthesis, a biochemical process by which green plants, algae and certain bacteria convert the energy of light into chemical energy at the beginning of every food chain. This natural abundance, combined with a very ample range of applications for a number of purposes, including the search for new sources of energy and new ways of curing cancer, makes porphyrins and their derivatives one of the most studied classes of macrocyclic compounds.

0. 1. 2. The early years

Man cannot give a true reason
for the grass under his feet
why it should be green rather than red
or any other colour

Sir Walter Raleigh[2]

Not more than two centuries later, these words of the famous Renaissance English courtier, explorer, soldier and poet ceased being true. The first breakthrough occurred in France: in 1818, Pelletier and Caventou first used the word *chlorophyll* to describe the pigment complex responsible for the green colour of leaves[3] and in 1844 Verdeil suggested a relationship between chlorophyll and heme, a red coloured iron-containing cofactor from blood, upon chemical conversion of the former to a red pigment.[4] The advance of spectroscopy in the second half of the 19th century prompted further progress. It enabled revealing spectral resemblances between heme and chlorophyll derivatives, involving among others the pioneer of biochemistry and molecular biology and the founder of the well-known *Zeitschrift für Physiologische Chemie*, Felix Hoppe-Seyler.[5,6] Even the birth of chromatography, the most important separation method for organic molecules, is strongly entangled with research on these colourful substances through the original work by the Italian-born Russian botanist M. S. Cvet (Tswett). One of the many Russian chlorophyll

researchers of the time,[7] at the beginning of the 20th century, Cvet worked at the University of Warsaw, Poland. He applied his new technique to separation of plant pigments from petroleum ether/ethanol extracts of green leaves. This resulted in the isolation of two main pigment fractions, which he called *chlorophyllins a* and *b*.[8]

The centre of research then moved to Germany. In the years preceding World War I, Willstätter and his co-workers published a number of papers dealing with structural elucidation of chlorophyll.[5] This work eventually earned Willstätter the Nobel Prize in Chemistry in 1915. However, we can justifiably regard Hans Fischer as the "father of modern porphyrin chemistry". Based at the Technical University of Munich between 1921 and 1945, this German chemist and his immense team of co-workers used the strategy of breaking down natural pigments into fragments using well-defined chemical reactions and then proving the structures of those fragments by re-synthesising them. The work provided a lot of new knowledge, not only about porphyrins and their derivatives but also about pyrrole itself. The results of years of research were published as a monograph in three volumes.[9] The crown on the work was the first total synthesis of hemin (heme chloride)[10] which earned Fischer the Nobel Prize in Chemistry in 1930. He also continued Willstätter's work on chlorophyll, definitely solving its structure. When the latter was confirmed by the total synthesis by another Nobel laureate, Robert B. Woodward in 1960,[11] it meant the end of a long era of pioneering research on porphyrins and related compounds.

0. 1. 3. Structure, nomenclature and general properties

The correct formula for the macrocyclic ring system of porphyrins, in which four pyrrole-like units are linked together by four methine (=CH-) bridges (**7**, Figure 1), was first proposed by Küster.[12] It was initially not ac-

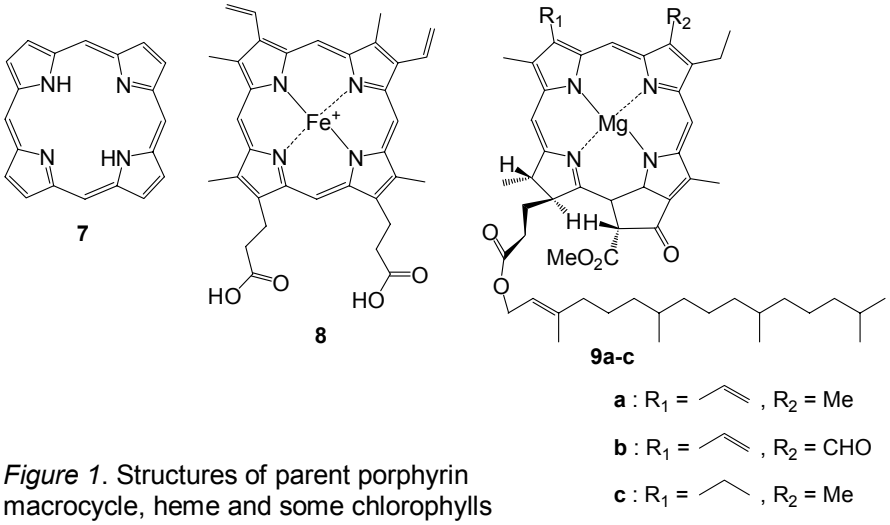


Figure 1. Structures of parent porphyrin macrocycle, heme and some chlorophylls

cepted – Fischer himself thought the ring to be too large to be stable. Nevertheless, it was his own aforementioned total synthesis that eventually proved its correctness. The other structures shown in Figure 1 are heme (or *haem*, **8**) and some types of chlorophyll (**9**).

Two systems of numbering the atoms and pyrrole rings in the porphyrin nucleus are shown in Figure 2. The first one (a) was developed by Fischer. The outer pyrrole carbons (1-8) were generally called β-carbons whilst the bridging methine carbons (α–δ) were termed *meso*-carbons. Fischer also used trivial names that give information on the kind of substituents attached to the porphyrin ring. Thus, the type found in heme, containing 4 methyl, 2 vinyl and 2 propionic acid residues, was called 'protoporphyrin' and *e.g.* a type with only alkyl chains (4 Me, 4 Et) bore the name 'etioporphyrin'. Different possible arrangements of the substituents (15 in case of three different substituents) were marked by Roman numerals. The pattern present in heme protoporphyrin, shared by all the naturally occurring porphyrins, was denoted IX. This system was satisfactory for a long time, but eventually the increasing complexity of synthetic porphyrins rendered it less and less straightforward. The new system (b), devised by IUPAC, uses consistent numbering of all atoms, including those in the substituents (as shown in Figure 2), yet still allows a number of trivial names. The latter helps show the relationship between different structures. The prefixes β and *meso* are still generally accepted.

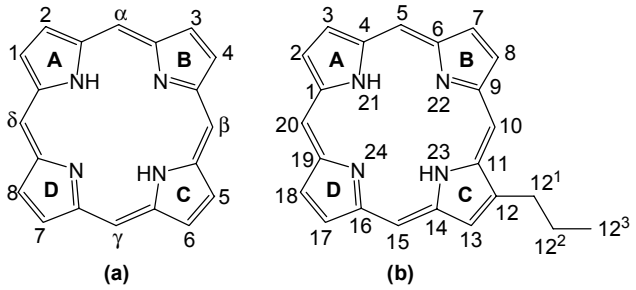


Figure 2. Numbering schemes of the porphyrin nucleus. (a) Fischer's system, (b) modern IUPAC system

The free base porphyrin ring contains 22 π-electrons, but only 18 of them are involved in any delocalization pathway. Therefore, porphyrins are aromatic molecules obeying Hückel's rule (4n + 2 π-electrons; n = 4), a fact which is confirmed experimentally by many properties, one of them being their enhanced stability. It should, however, be borne in mind that all porphyrins display NH-tautomerism. The process is characterized by an almost invariant activation energy of about 50 kJ mol^{-1} in solution and in the solid state, as revealed by variable temperature NMR spectroscopy.[13] Therefore, the porphyrin nucleus actually possesses high D_{4h} symmetry, shared by *meso*-tetrasubstituted and β-octasubstituted derivatives.

The aromatic character of porphyrins can also be seen by NMR spectroscopy. Due to the ring current, the protons H (5), (10), (15) and

(20), frequently called the *meso*-protons, as well as the β-pyrrole protons are deshielded, showing signals with δ = 8 – 11 ppm. On the other hand, the inner NH-protons are strongly shielded, displaying signals at -2 to -4 ppm.

X-ray crystallography reveals that porphyrins are essentially flat molecules, with all the pyrrole rings lying in the same plane. Nevertheless, several reasons can cause distortion and twisting of the macrocycle. Examples of this phenomenon are binding of small metal cations, protonation of porphyrins containing bulky *meso*-substituents and oxidation of the macrocycle (which deprives it of its aromaticity).[14]

The central imine-type nitrogen atoms of porphyrins can be protonated with relative ease. pK_3 Values (for formation of the monocation) usually vary between 3 and 6, and pK_4 values (formation of the dication) between 0.5 and 4. Both values depend on the inductive effects of the substituents groups at the macrocyclic periphery; electron-donating substituents increase the basicity of porphyrins. On the other hand, the NH groups can be deprotonated with strong bases such as alkoxides, pK_2 and pK_1 values being from 13 to 16 and from 15 to about 16, respectively. Expected substituent effects are observed here, too.

Characteristic UV-visible spectra of porphyrins consist of two distinct regions (Figure 3): an intense absorption band between 390 – 425 nm called the Soret band (after its discoverer; sometimes also called the B band) and several (usually four) much weaker bands, called Q bands, situated between 480 – 700 nm. The number and intensity of the latter provides a very strong clue to the substitution pattern and whether the porphyrin is metallated or not (*e.g.* UV-Vis spectra of diprotonated and metallated porphyrins usually display only two Q bands).[15] Large extinction coefficients are a reflection of the most eye-catching property of porphyrins: their intense colour (the word *porphyrin* comes from Greek *πορφυρα (porphura)*, meaning 'purple' and the sea molluscs from which a purple pigment was obtained in the ancient days). Porphyrins also display fluorescence. Protoporphyrin IX related fluorescence in human tissue has

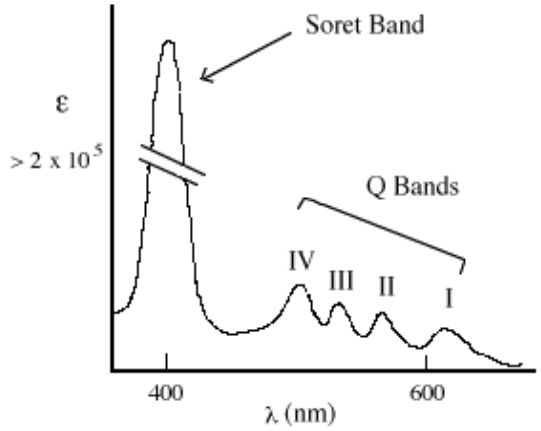


Figure 3. Typical UV-visible absorption spectrum of a porphyrin

a dual peak at about 635 and 705 nm.[16]

Another remarkable feature of porphyrins is their high proclivity to coordinate cations. Nature provides porphyrins containing Fe, Mg, Ni and V (from mineral oils), Cu (from the wing feathers of *Turacus indicus*), Mn (occurs in the blood of the mollusc *Pinna squamosa*) and Zn (yeast mutants).[17] Complexes of 16 other metals were prepared already during the time of Willstätter and Fischer. Until nowadays, virtually every metal from the periodic table and some semimetals have been inserted into the macrocyclic core of these versatile ligands. Since four-coordinate, square-planar geometry is rather rare in coordination chemistry, most central metal ions take up additional axial ligands to complete their coordination sphere.

0. 1. 4. Applications

0. 1. 4. 1. Catalysis by synthetic metalloporphyrins

The catalytic potential of metalloporphyrins *in vivo*, where they are usually involved in various redox processes, was readily recognised for applications of their synthetic counterparts. In 1979, during the studies of chemical fixation of carbon dioxide, potential utility of metalloporphyrins as catalysts for controlled macromolecular synthesis was discovered.[18] It was found that aluminium tetraphenylporphyrin chloride brought about ring-opening polymerization of epoxides to give polyethers with a narrow molecular weight distribution. Generally, metalloporphyrins are used for catalysis of reactions of oxidation, epoxidation, hydroxylation, nitrene and carbene transfer, activation of nitric oxide and oxidative DNA cleavage.[19] Metalloporphyrins of aluminium, zinc, manganese, cobalt and rhodium have been demonstrated to serve as excellent initiators for controlled anionic and free-radical polymerizations.[20]

0. 1. 4. 2. Examples of other applications

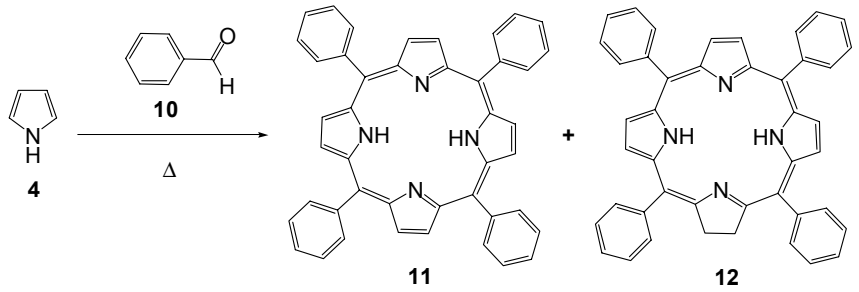
Noncovalent multiporphyrin assemblies have been prepared using a modular approach to mimic and study naturally occurring processes,[21,22] where often similar assemblies of porphyrins or related molecules are arranged in a well-controlled geometry (like in light-harvesting chlorophyll antennae, or the tetraheme cytochrome c_3 from sulphate-reducing bacteria) to attain precisely defined electronic and/or catalytic properties. Porphyrins have also been used as a synthetic base for new materials tailored to display a number of desired properties, like nonlinear optical behaviour[23] and low-dimension conductivity.[24] Porphyrin-based electrochemical sensors have as advantages small size and fast response time.[25] The same can be said for the use of porphyrins as receptor models for recognition of small molecules.[26] Finally, one of the most expanding research fields that include porphyrins today is their application as

photosensitizers in photodynamic therapy for cancer, where they are used for both diagnosis and cure.[27]

0. 1. 5. Synthesis

0. 1. 5. 1. Synthesis from monopyrrolic precursors

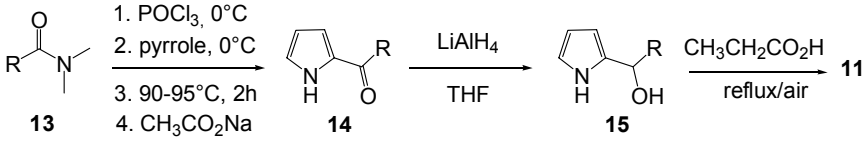
This approach to porphyrin synthesis is relatively simple but usually restricted to fully symmetric (point group D_{4h}) final products. It is particularly successful in the preparation of *meso*-tetraarylporphyrins. The first landmark was the work of Rothemund.[28] He heated pyrrole **4** and benzaldehyde **10** in pyridine to obtain 7.5 - 9% of *meso*-tetraphenylporphyrin **11** (Scheme 3).



Scheme 3. Rothemund synthesis of *meso*-tetraarylporphyrins, exemplified for *meso*-tetraphenylporphyrin **11**

In the 1960s, Adler, Longo and co-workers improved the method by carrying out the reaction in a refluxing acid (propionic acid gave the cleanest results) under air.[29,30] **11** was easily purified and obtained in 20% yield. A drawback in the abovementioned syntheses is the frequent contamination of the product with chlorins (**12**), usually formed at a 2 – 20% level compared with the porphyrin. Nevertheless, the chlorins **12** are readily oxidized to the desired porphyrins **11** using DDQ.[31,32] The recent years saw some further technical improvements, which *e.g.* enabled yields from 10 – 23% within a reaction time of 15 min.[33]

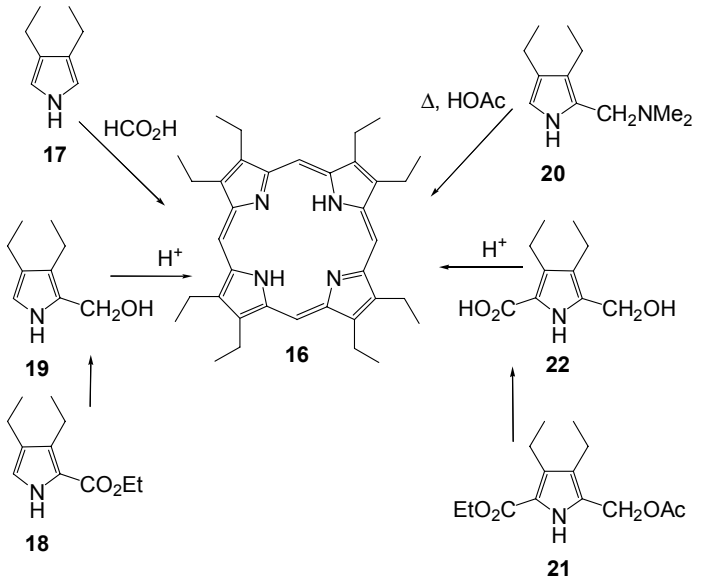
A key intermediate in the pyrrole-aldehyde condensation is believed to be pyrrole-carbinol. Pyrrole-carbinols **15**, prepared as shown in Scheme 4, underwent self-condensations under conditions identical to that



Scheme 4. Porphyrins from pyrrole-carbinols

in the Adler method to afford porphyrins **11**.[34] This is consistent with the above hypothesis. When R = Ph, the yield of the formation of **11** is 41%.

Lindsey performed essentially the same reaction, but using much milder conditions, which consisted of a TFA or $BF_3{\cdot}Et_2O$ catalyzed reaction of pyrrole and an aromatic aldehyde in CH_2Cl_2 at room temperature with subsequent oxidation of the intermediate porphyrinogen by DDQ or *p*-chloranil. The yields achieved were 35 – 40%.[35,36] The method is applicable to a broad scope of products, including many sensitive aldehydes for which Rothemund and Adler-Longo conditions are too harsh. The yields are relatively high, which is especially advantageous for



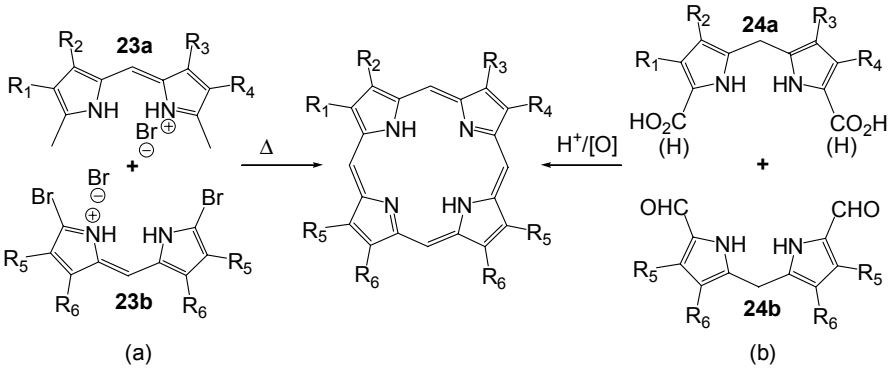
Scheme 5. Different ways to β-octaethylporphyrin

expensive starting aldehydes. The method is also very general, although modifications are sometimes needed. For example, the reaction of mesitaldehyde and pyrrole requires $BF_3{\cdot}Et_2O$ /ethanol cocatalysis,[37] and iron(II)-phthalocyanine-assisted aerobic oxidation can be employed to facilitate chromatographic purification of the product by significantly reducing the amount of the quinone oxidant needed.[38]

Other ways of monopyrrole tetramerization, shown in Scheme 5, are suitable for preparation of β-octaalkylporphyrins like **16**. The largest restriction of the approach is that the substituents at positions 3 and 4 in the monopyrrole precursor mostly must be identical to avoid complex mixtures of products, although some ingenious methods have been devised to prepare regioselectively substituted porphyrins from pyrroles bearing different groups at those two positions.[39]

0. 1. 5. 2. Synthesis from oligopyrrolic precursors

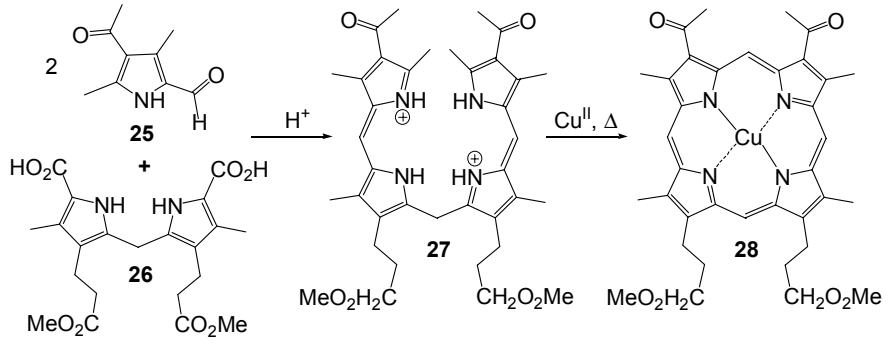
The most commonly used dipyrrolic intermediates for porphyrin synthesis are dipyrromethenes and dipyrromethanes. The former (**23**) were mainly used by Hans Fischer (Scheme 6 (a)), who thought the latter to be too unstable to acid. While this is generally true, the conditions he usually applied (molten succinic or tartaric acid) could hardly be considered gentle. The main breakthrough in the use of dipyrromethanes **24** was the achievement of MacDonald,[40] who discovered that a 1,9-diformyldipyrromethane (**24b**) could be condensed with a 1,9-diunsubstituted dipyrromethane or its 1,9-dicarboxylic acid (**24a**) in the presence of hydriodic acid to afford pure porphyrin in yields often as high as 60% (Scheme 6 (b)). *p*-Toluene sulphonic acid has been shown to be a



Scheme 6. Synthesis of porphyrins from dipyrrolic precursors

much more convenient alternative to hydriodic acid as the catalyst.[41] Both methods have the same symmetry restrictions, *i.e.* at least one of the two dipyrrolic precursors must be symmetrical about its interpyrrolic carbon atom (5), otherwise mixtures of porphyrins inevitably result.

Various open-chain tetrapyrrolic intermediates can be used for



Scheme 7. Johnson's porphyrin synthesis

porphyrin synthesis, but oxidative cyclization of 1,19-dimethyl-a,c-biladiene salts, developed by Alan. W. Johnson and his group, remains one of the best ways to prepare porphyrins with a complex substitution pattern. The original procedure includes cyclization of tetrapyrrolic precursor **27** mediated by Cu(II) salts (Scheme 7, p. 20),[42,43] whereupon the resulting Cu(II)-porphyrin **28** can be demetallated by H_2SO_4 to afford the metal-free product. Different ways to perform the final ring closure have been found, enabling direct synthesis of metal-free porphyrins.[39,44] Other synthetic strategies for porphyrin synthesis from oligopyrroles have also been developed, like the '[2+1+1]' and '[3+1]' approaches.[39]

0. 2. Corroles

0. 2. 1. The term 'corrole'

When Dorothy Crowfoot Hodgkin received the Nobel Prize in Chemistry in 1964 for resolving the structure of, among others, vitamin B_{12}, it was (also) a recognition of the first determination of a chemical formula by means of scattering of X-rays as well as of the first determination of the structure of a metalloenzyme.[45] It was a triumph for Dorothy Hodgkin and her crystallography group of the University of Oxford and the third and so far last Nobel Prize in Chemistry presented to a woman. It was also the first evidence of the existence of a macrocyclic porphyrin-like tetrapyrrole system which differs from a porphyrin in so far as it misses one of the *meso*-carbon bridges (Figure 4).

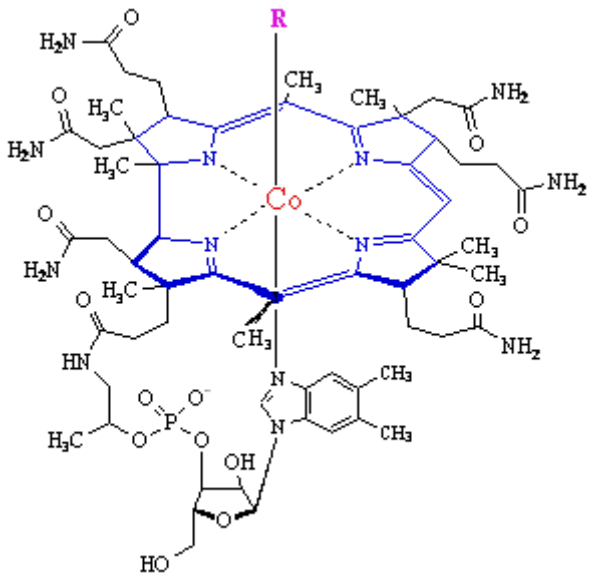
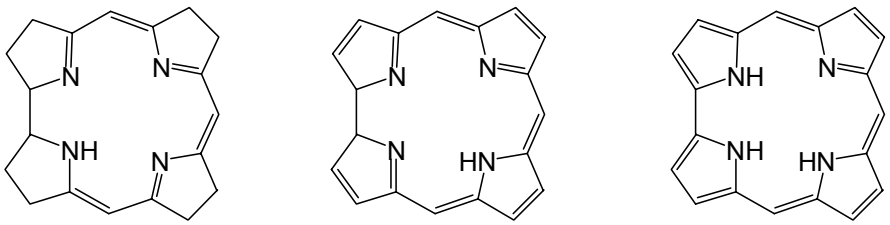


Figure 4. General structure of vitamin B_{12}. The corrin ring is depicted in blue. In isolated vitamin, the group R is mostly –CN, *in vivo*, it is adenosyl

Since the discovery of the corrin system and its molecular structure, much work was done on the synthesis of the corrin ring itself and other products that contain the same macrocyclic framework. The latter products can be described as intermediates between porphyrin and corrin



corrin tetradehydrocorrin corrole

Figure 5. Structures of corrin and related ring systems

whereby all these structures represent a sort of 'contracted porphyrins' (Figure 5). These macrocycles are not only interesting as intermediates (possible 'milestones') on the synthetic pathway to vitamin B_{12} and its derivatives, but also as compounds that possess unique electronic and chemical properties. Studies thereof can contribute to the understanding of the chemistry of all porphyrin analogues.[46]

In the scope of this work, exclusive attention was paid to corroles. Of the macrocycles of the abovementioned kind, they resemble porphyrins most and corrins least concerning structural and chemical properties. The most important structural difference between corroles and porphyrins, the lack of one *meso*-carbon atom in the molecule, is also reflected in their nomenclature. Position 20 is omitted in the numbering of the corrole atoms (Figure 6).

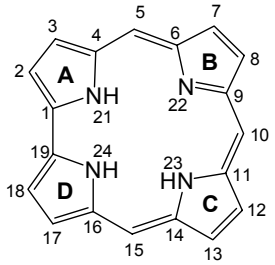


Figure 6. The atom and ring numbering scheme of corrole

0. 2. 2. Structure, general properties and applications

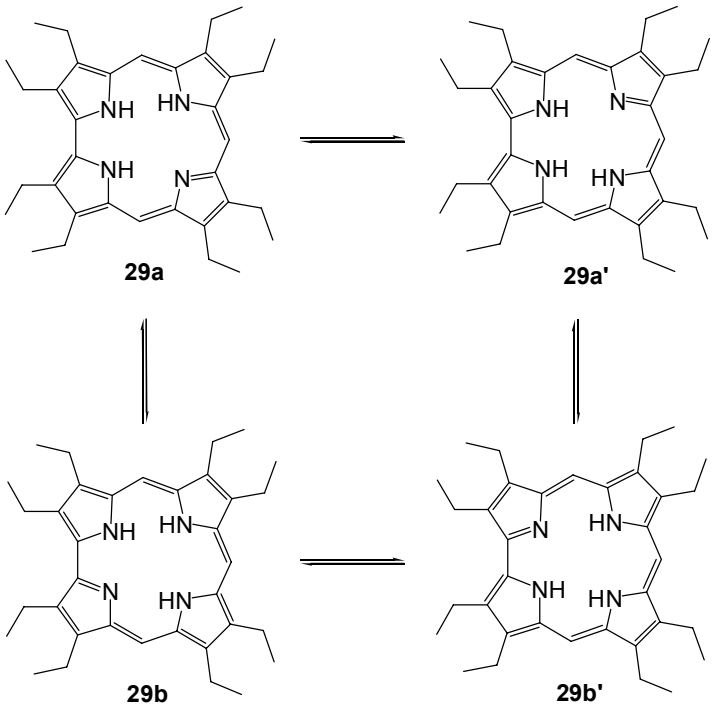
The ring of free base corrole contains, like that of porphyrin, 18 delocalized π-electrons that sustain a diamagnetic aromatic ring current. The aromaticity of corroles is confirmed by their relatively high stability and chemical shifts in NMR spectra: here, too, a strong deshielding of the outer

meso and β-pyrrole protons is observable, as well as a strong shielding of the inner NH protons. Thus, the ^{1}H NMR spectrum of octaethylcorrole **29** (Scheme 8) in $CDCl_3$ at 300 MHz shows resonance peaks of the *meso* protons at δ = 9,38 (H(5), (15)) and 9,21 (H(10)) ppm. On the other hand, the peaks of the imino protons, which are placed within the ring current, appear as a broad singlet at δ = -2,86 ppm (25°C).[47]

The symmetry of this and other NMR spectra of corroles points to the C_{2v} symmetry of the macrocycle. This means that the NH tautomerism in the molecule is rapid (Scheme 8).

The three imino hydrogens can be distributed over the core nitrogen atoms in four different ways. Calculations suggest that the **a**/**a'** couple is energetically more favoured than the **b**/**b'** couple, with a negligible energy difference between **a** and **a'** (0.58 kJ/mol).[48] NMR-measurements confirm these conclusions and clearly demonstrate the exchange between the **a** and **b** forms.[47] For the sake of uniformity, the corrole ring will be depicted as in Figure 6 throughout this work.

The molecular structure of 8,12-diethyl-2,3,7,13,17,18-hexamethylcorrole[49] was resolved by Hodgkin and co-workers in 1971 and

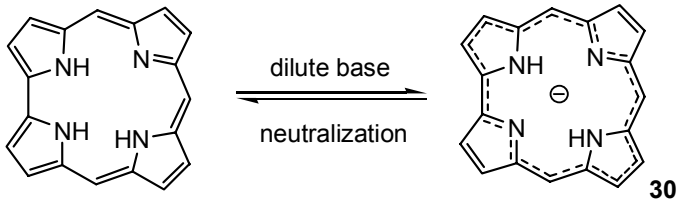


Scheme 8.[47] Schematic representation of the NH tautomerism in octaethylcorrole **29**

remained the only known structure of a free base corrole for several years.[47] The lengths of the peripheral bonds lay between the values for

single and double C-C bonds. The macrocyclic core is mostly planar but with a distortion around the C(1)-C(19) bond. The D ring is turned around by 8 - 10° with respect to the main plane of the molecule. The central cavity, defined by the N-N distances, is significantly smaller than that of porphyrins, with the shortest distance between two nitrogens being 2,53 Å. Based on this structure and molecular calculations,[50] it was determined that the proton hole is located on N(1) while the other three nitrogen atoms are protonated.

Corroles are stronger acids than porphyrins but weaker bases. Contrary to porphyrin, corrole forms a stable anion when treated with aqueous base. This anion that can be best depicted by the structure **30** (Scheme 9), is also an aromatic system. This probably contributes to its particular stability.[46]

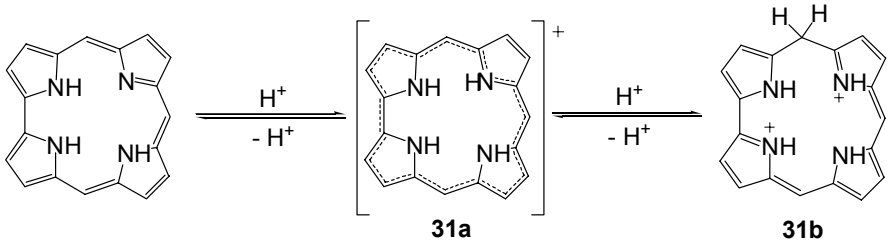


30

Scheme 9. Reaction of corrole with bases

The analogy between porphyrin and corrole anion **30** can best be compared with that between their smaller counterparts with six π-electrons, namely benzene and cyclopentadienyl anion. The neutral form of the macrocycle can always be regenerated by acidification.

Corroles also form stable protonated molecular species. They can be monoprotonated by weak acids. This gives adducts of type **31a** (Scheme 10). These adducts remain, according to their UV-visible absorption spectra, aromatic. This points to the protonation on one of the core nitrogens.[51,52] Structural analysis on a crystal of 8,12-diethyl-2,3,7,13,17,18-hexamethylcorrole hydrobromide helped to confirm this fact.[53] However, if corrole is treated with a strong acid (*e.g.* sulphuric acid), the characteristic absorption maxima (more particular, the Soret band, *vide infra*) disappear. This corresponds to a second protonation on a carbon atom, with interruption of the π-conjugated system and formation of **31b**



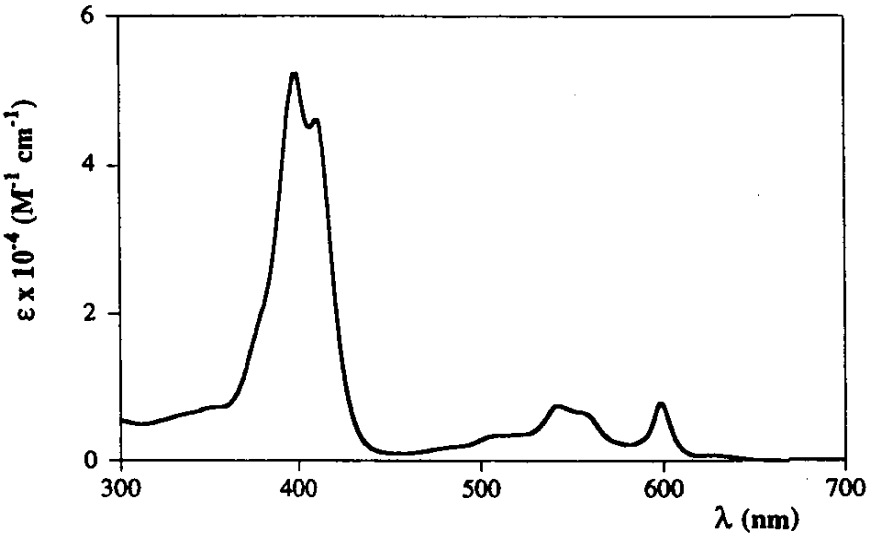
31a **31b**

Scheme 10. Protonation of corrole

(Scheme 10) as a consequence. It was first thought that this protonation occurs on C(10).[54] Nevertheless, as was shown later, the position of the reaction is more probably C(5).[52] More recent research on N-methylated corroles suggests that the corrole ring can actually be protonated *three* times, but the position of this last protonation remains unknown.[55] Furthermore, it is uncertain whether these conclusions may be generalized, since research of the same kind was never extended on other corroles.

NMR measurements have further shown that corroles undergo a fast exchange of the *meso* protons for deuterium in deuteriotrifluoroacetic acid at room temperature.[54] This feature has never been observed for porphyrins.[56] The exchange is complete within 15 minutes.[52] In spite of all that, even multiply protonated forms of corrole remain very stable.

Free base corroles, like their anionic and monoprotonated adducts, display several strong absorption bands in the UV-Vis spectra. As is true for porphyrins, the positions and intensities of these bands reflect the extended aromatic conjugation present in the molecule. Spectra of cor-



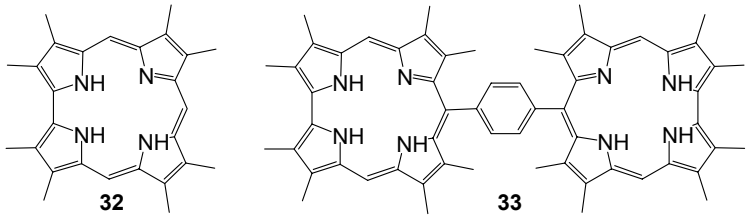


Figure 7. The absorption spectrum of octamethylcorrole **32** in 2-methyltetrahydrofuran[57]

roles contain an intense Soret band in the neighbourhood of 400 nm and weaker Q bands between 500 - 600 nm (Figure 7). It is due to these absorption properties that corroles are, just like porphyrins, strikingly strongly coloured.

Corroles also show an intense luminescence band around 600 nm, with a lifetime on a nanosecond scale (Figure 8).[57]

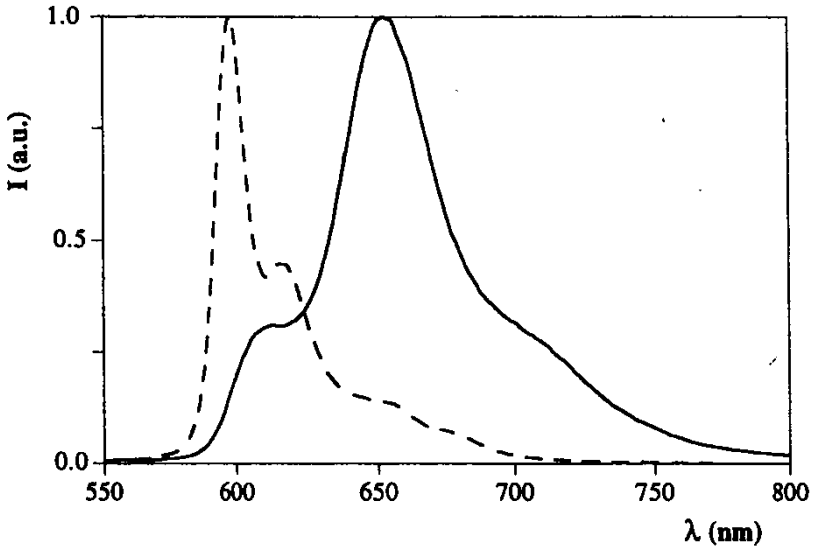


Figure 8. The luminescence spectra (λ_{exc} = 542 nm) of **32** (----------) and **33** (————) in 2-methyltetrahydrofurane at room temperature. The luminescence intensities are normalized on their maxima

The number of different metal ions that have been inserted into the corrole cavity (more than 20 at the present time) is smaller than in the case of porphyrins. Moreover, the broad diversity of binding ways seen by porphyrins has not yet been achieved with corroles, although this can be related to the simple fact that metallocorroles have been much less investigated than metalloporphyrins. Nevertheless, the rather recent unexpected discovery that these trianionic ligands can stabilize unusually high oxidation states of metal ions[58] has given a new impulse to the chemistry of corroles.

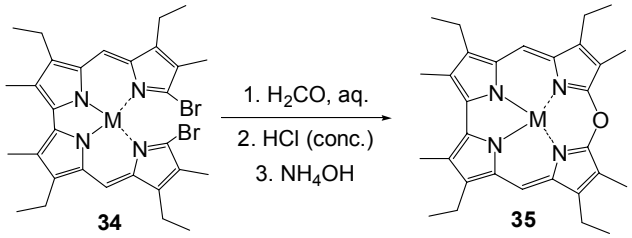
A number of such complexes of both *meso* and β-substituted corroles have been prepared in recent years. The examples described include among others complexes of Fe^{III} [59,60,61] Fe^{IV} [58,60-62] Co^{IV} [63] Mn^{V}, [64] As^{III}, As^{V}, Sb^{III}, Sb^{IV}, Bi^{III}, Bi^{IV}, [65] Ge^{IV}, [60] Sn^{IV}, [60] P^{V}, [60] Cu^{III} [66] en Ag^{III}. [67] These corrole complexes display an important property, which also can be observed with their porphyrin counterparts: catalysis. The Gross group has examined iron, manganese and rhodium complexes of corroles as catalysts for epoxidation, cyclopropanation and hydroxylation reactions.[68] The results are encouraging. A gallium corrole was checked as a

candidate for a molecular magnet.[69] The affinity of certain corroles for cancer cells has also been investigated.[70]

0. 2. 3. Synthesis

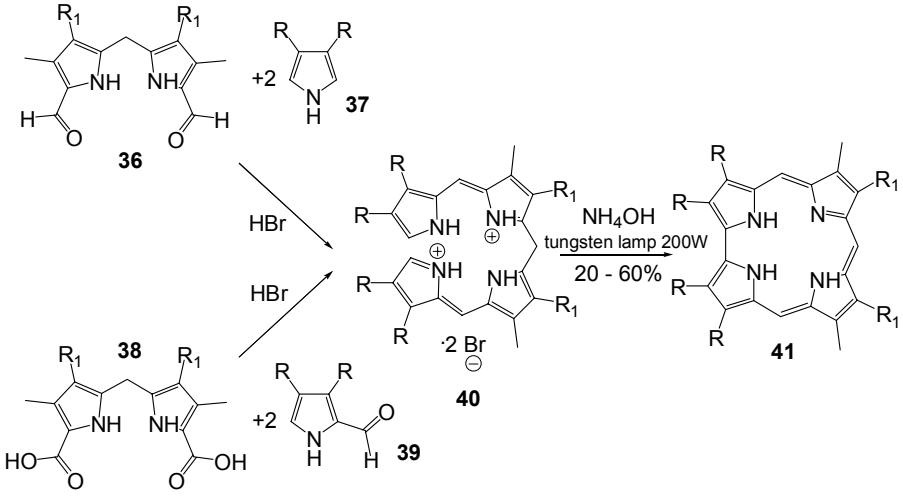
0. 2. 3. 1. Synthesis from tetrapyrrolic precursors

The synthetic chemistry of corroles has begun in the 1960s with the work of Johnson and Kay. In their initial efforts, they had claimed to have obtained metallocorolles by cyclization of metallodihalobiladienes **34** (M = Pd, Co, Cu) with formaldehyde (Scheme 11). However, eventually it was shown that the products of these reactions were metallooxacorroles **35**.[46]



Scheme 11. Johnson's first attempts to synthesize corroles

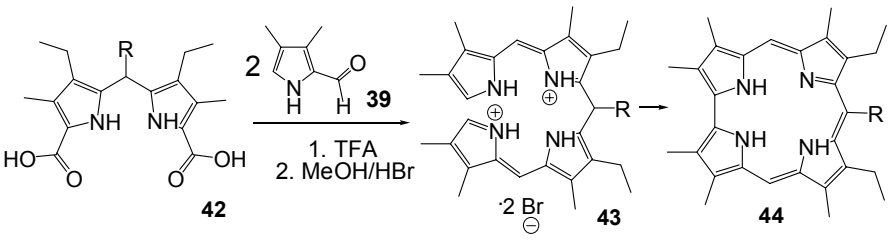
The researchers then treated solutions of a,c-biladiene dihydrobromides **40** (synthesized in two different ways) in CH_3OH/NH_4OH with light. This approach eventually afforded corroles **41** (Scheme 12).[71] The synthesis of various metal-corrole complexes (M = Ni, Co, Cu) is de-



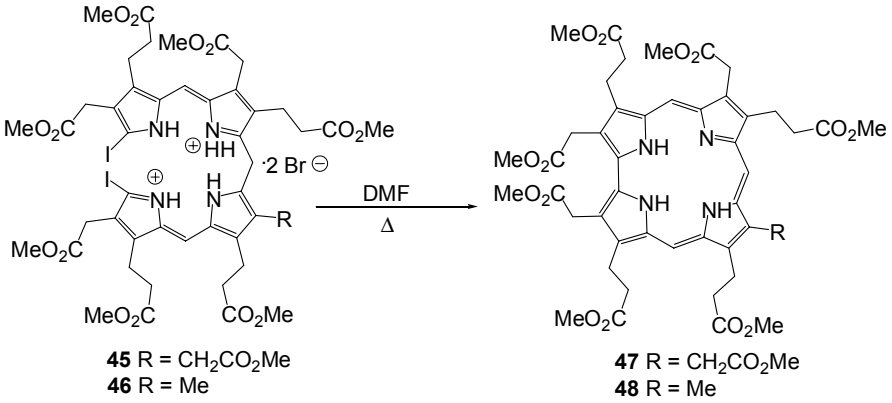
Scheme 12. The original corrole synthesis by Johnson and Kay.
R = Me or Et; (**a**) R_1 = Et, (**b**) $R_1 = CH_2CH_2CO_2Me$

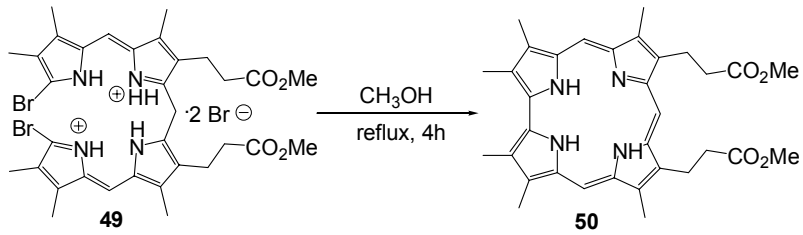
scribed in the same paper. In a later work, Johnson *et al.* reported that, in fact, any of the different catalysts (light, $K_2Fe(CN)_6$, $FeCl_3$, $Ce(HSO_4)_4$, H_2O_2, benzoylperoxide and di-*t*-butylperoxide) was able to bring about the cyclization of **40** free base. The yields were between 68 – 84%.[72] A free radical mechanism was proposed for this reaction. However, this was rejected several years later because free radical scavengers like hydroquinone or *p*-*t*-butylcatechol did not significantly affect the cyclization.[73]

Paolesse and co-workers[74] utilized the approach of base catalyzed cyclization of 1,19-diunsubstituted a,c-biladiene dihydrobromides that had first been described in the Russian literature.[75] They cyclized 10-substitu-



(**a**) R = H
(**b**) R = CO_2Me
(**c**) R = CH_2CO_2Me
(**d**) R = CH_2CH_2Cl *Scheme 13.* The synthesis of corroles **44** by Paolesse



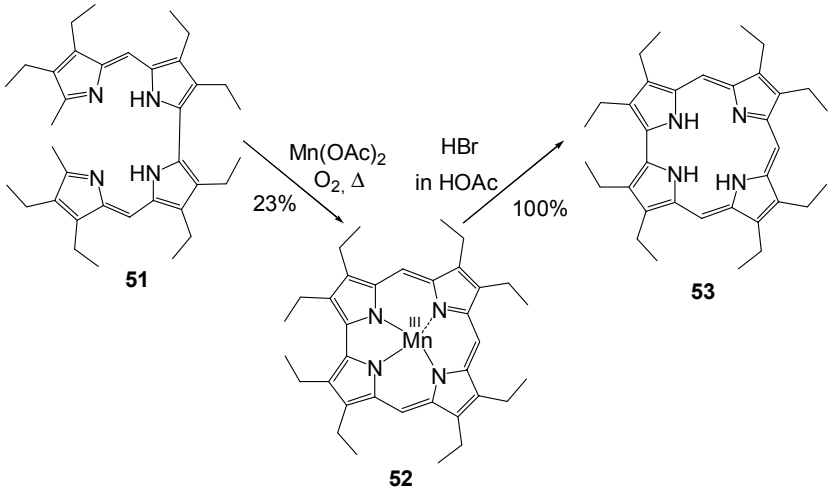


Scheme 14. Syntheses of corroles from dihalobiladienes

ted salts **43** in methanol containing NaOAc (to catalyze the ring closure[72]; Scheme 13, p. 28). The precursors **43** were in turn synthesized from dipyrromethane diacids **42** and formylpyrroles **39**. Co(III) complexes (with PPh_3 as the fifth ligand on the cobalt atom) of all the corroles **44** were also prepared.

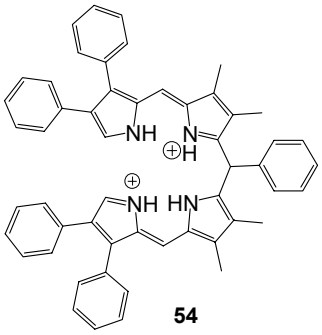
The formation of corroles from dihalobiladienes has also been accomplished 40 years after the first unsuccessful attempts by Johnson *et al*. Thus, the synthesis of corroles **47** and **48**, bearing substitution patterns corresponding to those of uroporphyrin III and its 12-decarboxy derivative respectively, from the diiodo salts **45** and **46** was described in 1975 (Scheme 14, p. 28, above).[76] More recently, Smith and co-workers showed that corrole **50** could be made in >25% yield by heating **49** in methanol at reflux (Scheme 14, below).[77] Some asymmetrically substituted corroles could also be prepared in the same way. However, this approach has found little general use, probably because of the tedious syntheses of the dihalo precursors.

Bröring and Hell effectuated cyclization of a,c-biladienes to corroles using Mn(II) salts. They performed a reaction of several a,c-biladienes of type **51** with Mn(II) acetate tetrahydrate and molecular O_2. This gave Mn(III) corroles **52** which could be readily demetallated to the respective free base corroles **53** (Scheme 15).[78]



Scheme 15. Manganese as template for corrole synthesis

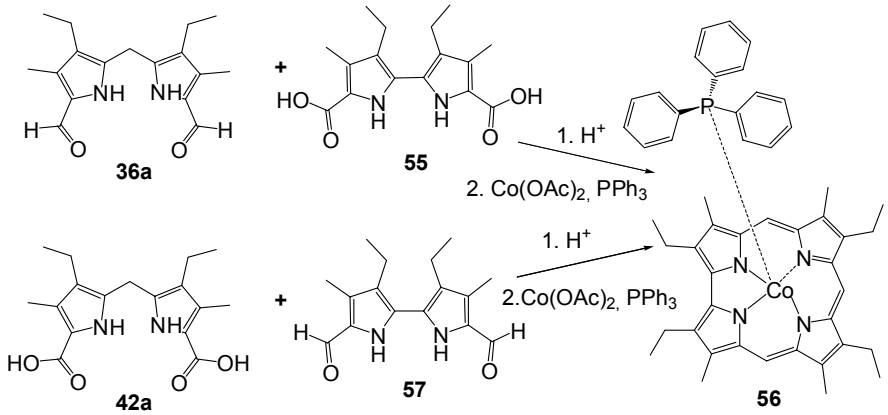
Guilard *et al*. utilized a,c-biladiene cation **54** to obtain a stable corrole with phenyl rings as both *meso*- and β-substituents.[79] They found a simple way for the introduction of those groups in the β-positions of the monopyrrolic precursor. This prevents oxidative ring opening of the final corrole from occurring, a process which had been observed earlier.[80]



54

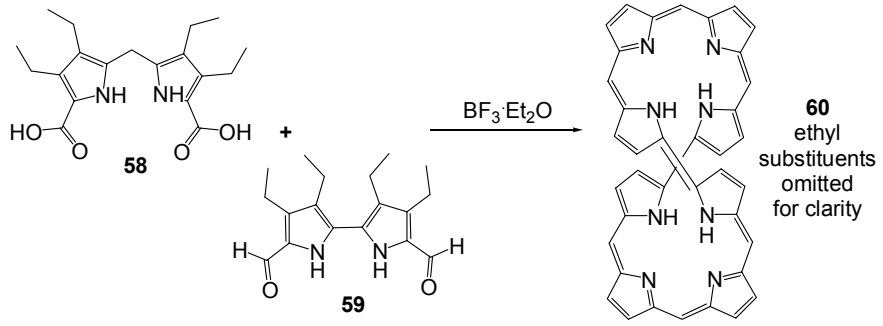
0. 2. 3. 2. Synthesis from bipyrrolic precursors

This method, usually called the '[2+2] approach', accounted for only a few reports in the literature up to the last years. In 1973, Johnson and co-workers condensed dipyrromethane **36a** and bipyrrole **55** under acidic conditions to give a red precipitate that, after reaction with cobalt(II) acetate and triphenylphosphine in methanol, afforded the cobalt(III) corrole complex **56**. The same product was obtained by reaction of dipyrrometha-



36a **55** **42a** **57** **56**

Scheme 16. First synthesis of corroles from bipyrrolic precursors



58 **59**

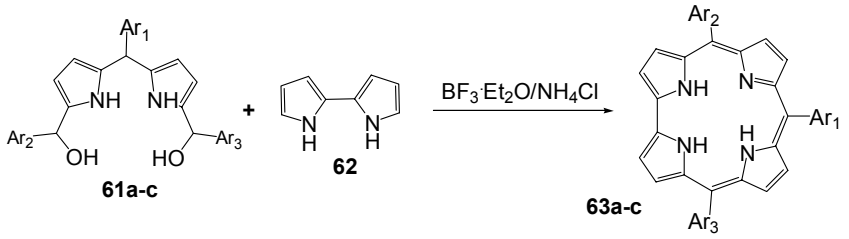
Scheme 17. Vogel's synthesis of cyclooctapyrroles

ne **42a** and bipyrrole **57** (Scheme 16, p. 30).[81] The presence of cobalt was necessary to drive the reaction to completion. It has been proposed that the metal atom stabilizes the supposed tetrapyrrolic intermediate and ensures the right geometry for the cyclization.

The reaction has a different outcome if done without metal ions. In 1995, while attempting to prepare a corrphycene derivative *via* a MacDonald condensation, the Cologne group discovered a new family of pyrrolic macrocycles, the cyclooctapyrroles **60** (also known as octaphyrins; Scheme 17, p. 30).[82]

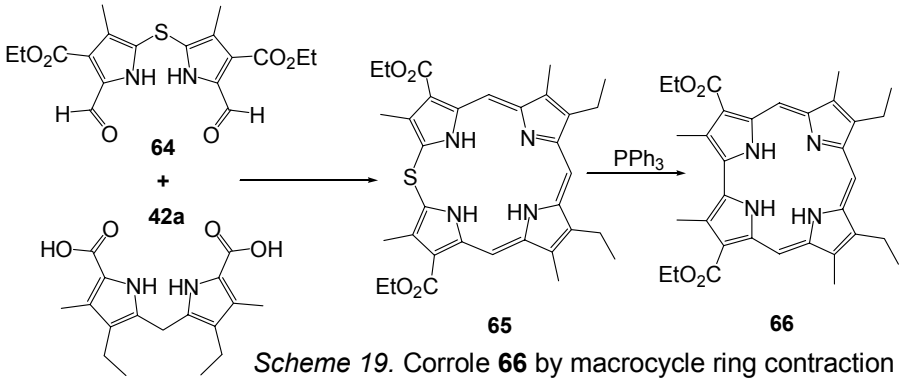
This condensation reaction has been generalized, and a variety of cyclooctapyrroles that differ by the number and/or type of spacers between each pyrrole moiety have been prepared. These octaphyrins adopt a helical 'figure-eight' conformation. A higher order condensation product, namely cyclododecapyrrole, was also obtained using the same synthetic strategy.[83]

However, Decréau and Collman very recently succeeded in preparing several triaryl corroles using the [2+2] approach by changing the nature of the substituents on the bipyrrolic precursors.[84] Having varied the nature of solvent and that of the acid catalyst, the concentration of reagents and that of the acid, and the reaction time, they optimized the syntheses of the corroles **63** in yields up to 12% (Scheme 18).



Scheme 18. Synthesis of corroles **63** by condensation of dipyrromethane dicarbinols **61** and 2,2'-bipyrrole **62**. (**a**) $Ar_1 = Ar_2 = Ar_3$ = mesityl; (**b**) $Ar_1 = Ar_2 = Ar_3$ = 4-methylphenyl; (**c**) Ar_1 = 4-methylphenyl, $Ar_2 = Ar_3$ = phenyl

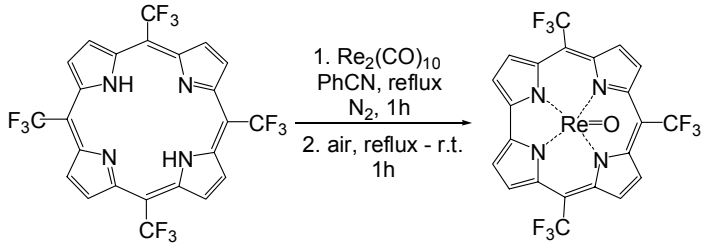
0. 2. 3. 3. Synthesis by macrocycle ring contraction



Scheme 19. Corrole **66** by macrocycle ring contraction

This pathway includes preparation of *meso*-thiaphlorin **65** by a [2+2] reaction from bipyrrolic precursors (Scheme 19, p. 31).[85,86] This compound, which was stable enough to be isolated, gave the corrole **66** in 40% yield when heated in *o*-dichlorobenzene.[82] In the presence of PPh_3, the corrole yield was 60%. No explanation was proposed for this unexpected result.

One example of porphyrin-corrole ring contraction was reported in 1998. The corrole **68** was unexpectedly obtained by reaction of the highly electron deficient porphyrin **67** and $Re_2(CO)_{10}$ in benzonitrile (Scheme 20).[87]



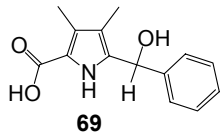
67 **68**

Scheme 20. Corrole **68** by macrocycle ring contraction

0. 2. 3. 4. Early syntheses from monopyrrolic precursors

0. 2. 3. 4. 1. Tetramerization of a 2-substituted pyrrole

The first experiments on corrole synthesis by tetramerization of 2-substituted monopyrrolic starting products were carried out by the Paolesse group in the middle of the 1990s. Various pyrrolic precursors were employed, but the final cyclization step was always effected by the action of $Co(OAc)_2$ and PPh_3 to give **56**-like complexes (Scheme 16).

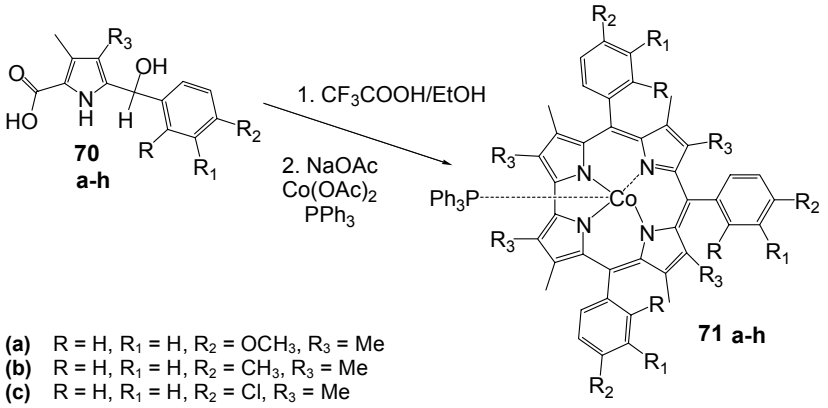


69

Thus, **69** was first reacted in acidic ethanol, whereupon the reaction mixture was buffered with the cobalt salt in the presence of triphenylphosphine to give the corresponding corrolic complex in 25% yield.[88] The presence of cobalt ions was crucial to obtain the corrole ring – in the case of *e.g.* copper, nickel or rhodium salts the octamethyltetraphenylporphyrin complex was obtained. It is worth mentioning that the corrole ring of this cobalt complex is almost completely planar,[84] in contrast to analogous dodecasubstituted porphyrins, which

show severe deviations from planarity due to steric interactions between the *meso* and β-substituents.[89]

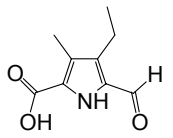
This approach was subsequently extended to prepare a number of Co(III) corroles **71** from monopyrrolic compounds **70** bearing different groups in various positions of the phenyl ring (Scheme 21).[90] Furthermore, this method allowed preparation of corrole **71h** with an 'etio-like' substitution pattern.[91]



(a) R = H, R_1 = H, R_2 = OCH_3, R_3 = Me
(b) R = H, R_1 = H, R_2 = CH_3, R_3 = Me
(c) R = H, R_1 = H, R_2 = Cl, R_3 = Me
(d) R = H, R_1 = Cl, R_2 = H, R_3 = Me
(e) R = Cl, R_1 = H, R_2 = H, R_3 = Me
(f) R = H, R_1 = F, R_2 = H, R_3 = Me
(g) R = F, R_1 = H, R_2 = H, R_3 = Me
(h) R = H, R_1 = H, R_2 = H, R_3 = Et

Scheme 21. Paolesse's 1995 synthesis of Co(III) corroles

The same synthetic procedure, using various metal ions, was applied to 2-formylpyrroles.[92] The reactions yielded mixtures of macrocyclic products, but again corroles were only observed when cobalt salts were used. When 3-ethyl-4-methyl-2-formylpyrrole-5-carboxylic acid **72** was the starting material, Co(II) etioporphyrin-I and three cobalt corrolates were obtained. Chromatographic separation and detailed analysis of the ^{1}H NMR spectra of these compounds identified two different corroles with the substitution pattern analogous to that of etioporphyrin.



72

0. 2. 3. 4. 2. Condensation of pyrrole and aldehydes

Two examples of this route, otherwise very commonly used for porphyrin synthesis, were reported by the end of the 1990s. The corresponding *meso*-5,10,15-triarylcorrole was identified as a by-product in the synthesis of *meso*-5,10,15,20-tetrakis(2,6-dinitro-4-*t*-butylphenyl)

porphyrin, although the only characterization was by NMR.[93] Secondly, a reaction of cymantrene carboxaldehyde and pyrrole in acetic acid provided *meso*-5,10,15-tris-(cymantrenyl)corrole, but here too the choice of reaction conditions proved critical because of the competitive formation of the porphyrin.[94]

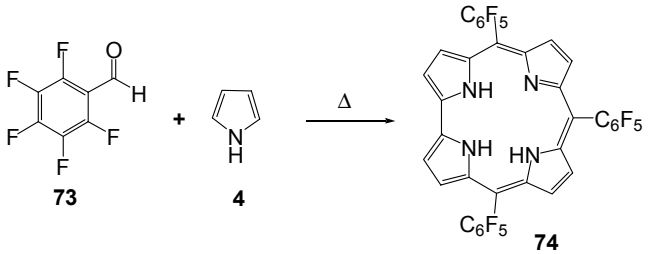
0. 2. 3. 5. The 'modern era' of corrole synthesis

Until several years ago, corroles were considered rather rare chemicals, relatively difficult to prepare, their syntheses being tedious and usually accomplished only by multi-step procedures. A major breakthrough occurred in 1999 through the work of two groups: that of Gross in Haifa, Israel and that of Paolesse in Rome, Italy. These two research teams established new one-pot methods employing commercially available reagents. This meant progress foremostly in syntheses of *meso*-triarylcorroles.

0. 2. 3. 5. 1. *meso*-Substituted A_3-corroles

meso-Trisubstituted free base corroles with three identical substituents, compounds unavailable prior to 1999, are compounds of interest for comparative studies with *meso*-tetrasubstituted porphyrins which are a well-known class of macrocycles whose physicochemical and coordination properties have been extensively studied. To stay in line with the nomenclature of the analogous porphyrins, Gryko proposed to designate such corroles as A_3-corroles.[95]

The pioneering work of the Gross group comprised a reaction of pentafluorobenzaldehyde **73** with pyrrole **4** without any solvent or catalyst. Dissolving the resulting crude mixture in CH_2Cl_2 and oxidising it with DDQ provided *meso*-tris-(pentafluorophenyl)corrole **74** as a major product in 8 – 11% yield (Scheme 22).[96,97] Using basic alumina as solid support and applying a lower temperature for the condensation reaction made scaling up possible and yielded less tarry by-products.

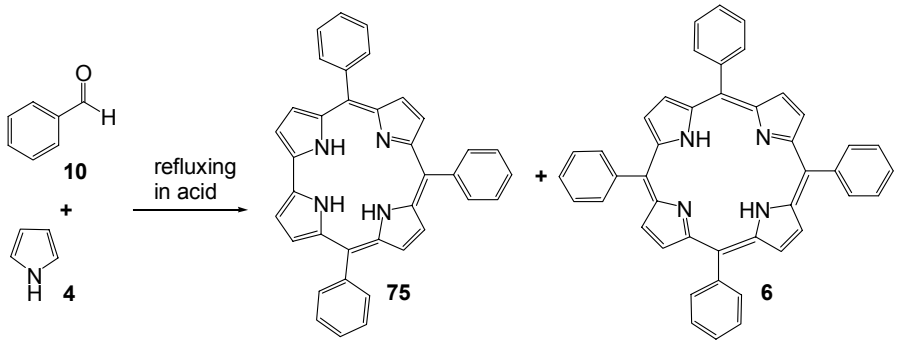


Scheme 22. First direct synthesis of corrole from pyrrole

Some open-chain oligopyrromethenes, *i.e.* oligomers composed of pyrroles bridged by unsaturated carbon centres were also isolated and the

reaction was extended to some other electron-poor aldehydes. No porphyrins are formed under these conditions,[92] although the porphyrin was isolated from the reaction with less reactive benzaldehyde.[91]

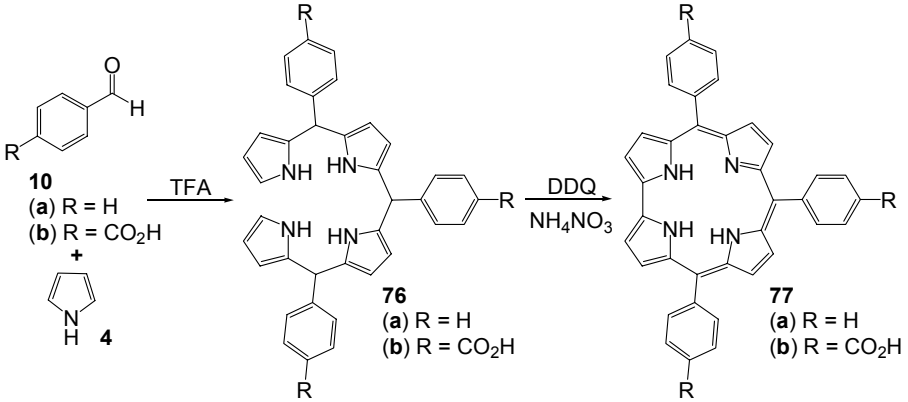
Around the same time, the group of Paolesse showed that *meso*-5,10,15-triphenylcorrole **75** could be obtained by modifying the Adler-Longo conditions of the Rothemund porphyrin synthesis.[98] They changed the pyrrole/benzaldehyde ratio from 1:1 to 3:1 and carried out the reaction in both acetic and propionic acid. The yield of product **75** was 5 – 6% with comparable quantities of the corresponding porphyrin **6** formed (Scheme 23).



Scheme 23. Paolesse's concomitant formation of corrole and porphyrin in the modified Rothemund synthesis

This approach was later expanded to a range of aldehydes with either electron-donating or electron-withdrawing substituents to afford corroles in yields of 4 – 22%. Nevertheless, the reaction failed in the case of sterically hindered 2,6-disubstituted aldehydes.[99]

A different approach to A_3-corroles was developed by Lee and co-workers.[100] The open-chain products bilanes (tetrapyrranes) **76**, which were proposed as the precursors of the final corrole ring in the above Paolesse's and Gross' syntheses, were obtained by an acid catalyzed con-



Scheme 24. Lee's synthesis of corroles from isolated bilanes

densation of aromatic aldehydes **10** with excess pyrrole under solventless conditions. They were isolated by chromatography and their low-concentration (5 mM) solutions in propionitrile were then oxidized by DDQ with addition of a number of inorganic salts to give the corroles **75** in yields of up to 65% (Scheme 24, p. 35). Here bilanes were purified for the first time, subsequently proving that they indeed undergo radical oxidative cyclization.

The Paolesse group now also developed a new methodology which originally consists of a trifluoroacetic acid-catalyzed condensation of an excess of pyrrole with an aromatic aldehyde under neat conditions at room temperature with subsequent dissolving of the crude mixture in CH_2Cl_2 and oxidising of the intermediates with *p*-chloranil. Upon evaporating the solvent and the residual pyrrole the products are isolated by chromatography on silica.[101] The model compound was *meso*-5,10,15-triphenylcorrole **75a** which was obtained in 11% yield, but relatively good results were achieved with several other aldehydes too. The major advantages of this approach compared to the modified Rothemund route are the fact that no porphyrin formation was observed as well as obtaining the desired product from sterically hindered 2,6-dichlorobenzaldehyde which previously yielded no corrole. When performing the synthesis in CH_2Cl_2 solution from the beginning (which can be considered a modification of the Lindsey conditions for the preparation of tetraarylporphyrins), the yield of **75a** rose to 21% and it was even possible to obtain it in gram quantities. The yields of the other corroles were also improved. The first examples of fully substituted corrole free bases (demetallated analogues of the tetramerization product of **69**)[84] were also prepared following this approach, albeit in low yields and in mixtures with porphyrins.

Very recently, Steene and co-workers[102] have expanded the original Gross' solvent-free procedure by showing that not only the aromatic aldehyde component (Gross' group had claimed that the procedure was limited to relatively electron-deficient aldehydes), but also the pyrrole component were variable. Thus, they condensed 3,4-difluoropyrrole with four different *p*-R-substituted benzaldehydes to yield the corresponding β-octafluoro-*meso*-tris-(*p*-R-phenyl)corroles (R = CF_3, H, CH_3, OCH_3).

Collman and Decréau also showed that applying microwave heating instead of classical heating in the same Gross milestone synthesis significantly improved the yields, shortened the reaction times and reduced the quantity of the by-products. They synthesized several new free base *meso*-tris-aryl-corroles and a *meso*-tris-pyrimidyl-corrole. It is demonstrated that short reaction times and high temperatures are required to afford optimum yields.[103]

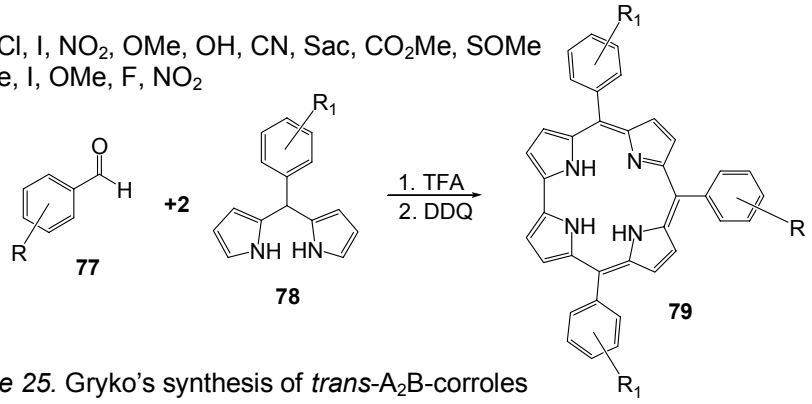
0. 2. 3. 5. 2. *meso*-Substituted A_2B-corroles

In agreement with typical porphyrin nomenclature, this designation can be used for corroles bearing two different kinds of substituents.

Expectedly, most work has been done on symmetrical compounds with two identical substituents at positions 5 and 15, which can be called *trans*-A_2B-corroles. These compounds are usually prepared using modified Lindsey conditions for porphyrin synthesis.

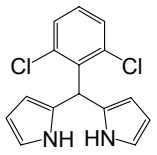
Prompted by his initial work describing an 'uncatalyzed' synthesis of corroles from aromatically substituted dipyrromethanes and aromatic aldehydes possessing at least two fluorine atoms,[104] Gryko developed a new methodology that afforded regioisomerically pure *trans*-A_2B-corroles **79**.[105] Their formation involved an acid-catalyzed condensation of an aldehyde **77** and two equivalents of an aromatically 5-substituted dipyrromethane (DPM; **78**) followed by oxidation with DDQ (Scheme 25). Generalized optimal conditions were: solvent: CH_2Cl_2; c (DPM) = 33 mM; c (aldehyde) = 17 mM; c (TFA) = 1.3 mM for sterically hindered DPMs or 0.26 mM for sterically unhindered DPMs; 5 h; room temperature. The yields of in total 21 corroles were 3 – 25% without detectable scrambling (the undesired acid-catalyzed rearrangement of pyrrole units leading to a mixture of products). In a later publication, a comprehensive method for preparation of corroles with substituents containing basic nitrogen atoms (pyridyl, quinolinyl, quinoxalinyl) was developed.[106]

R = F, Cl, I, NO_2, OMe, OH, CN, Sac, CO_2Me, SOMe
R_1 = Me, I, OMe, F, NO_2



Scheme 25. Gryko's synthesis of *trans*-A_2B-corroles

Briñas and Brückner applied a variation of the same general method to synthesize several further products of the same type using a sixfold molar excess of sterically unhindered DPMs.[107] In our laboratory, $BF_3{\cdot}OEt_2$ was successfully used as a catalyst for the reaction of 5-(2,6-dichlorophenyl)dipyrromethane **80** with reactive electron-deficient aldehydes, in some cases following Lee's approach of isolating the intermediate tetrapyrromethane and oxidising it in low concentration in propionitrile.[108]



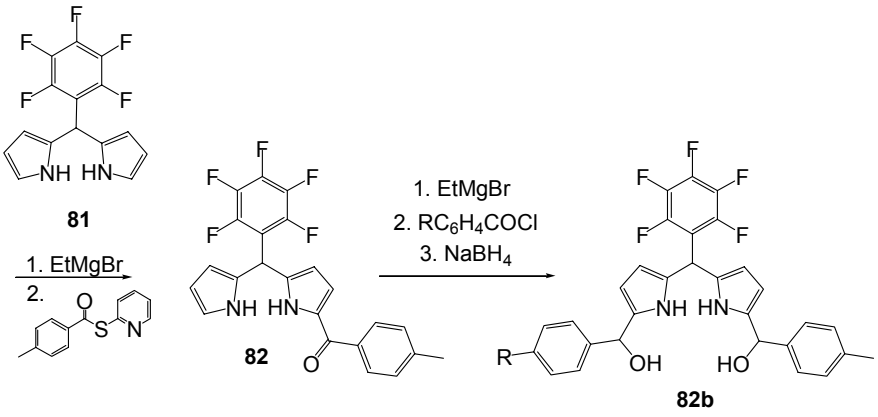
80

Sankar *et al.* developed a synthesis of asymmetric *meso*-A_2 type corroles and oxacorroles, *i.e.* compounds possessing two aromatic (in this case at least) *meso*-substituents and one reactive *meso*-free carbon atom. The products had been obtained in 5 – 11% yield by a TFA catalyzed (3+1) condensation of disubstituted tripyrromethanes and 2-formylpyrrole followed by oxidation with *p*-chloranil. One product was transformed into the A_2B-corrole by a reaction with *n*-butyllithium.[109]

Another thorough investigation of the conditions for a one-pot synthesis of corroles from aromatic aldehydes with different reactivities has been carried out in Gryko's group. Mostly A_3-corroles in improved yields have been prepared, but the synthesis of some *trans*-A_2B-corroles from sterically hindered dipyrromethanes has also been refined. The yields of the latter corroles have been increased by ca. 10%.[110]

0. 2. 3. 5. 3. *meso*-Substituted ABC-corroles

This type of corroles was synthesized for the first time by Guilard *et al*. in 2002.[111] They have worked out a method, based on Lindsey approach, which was here first applied to the synthesis of one A_3-corrole and several *trans*-A_2B-corroles. The critical corrole ring formation step consisted of reacting the appropriate dipyrromethane-dicarbinol with an excess of pyrrole and subsequent oxidation by DDQ ('[2+1+1]' approach), with or without isolation of the intermediate tetrapyrromethane. Finally, the same conditions were applied to the dipyrromethane-dicarbinols **82b** prepared according to the procedure in Scheme 26 to yield the corresponding *meso*-ABC corroles in 36 – 51% yield. It is worth mentioning that all the products were regioisomerically pure without any detectable pyrrole ring scrambling. No porphyrins were formed either.

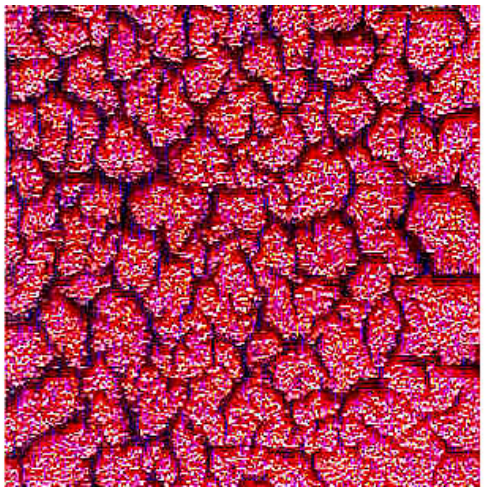


Scheme 26. Guilard's synthesis of dipyrrolic precursors of *meso*-ABC corroles. (**a**) R = OMe; (**b**) R = *t*-Bu

0. 2. 3. 6. Conclusion

The synthetic chemistry of corroles is undergoing a vibrant and rapid change. Now that fairly efficient methodologies for synthesis of these compounds are available, research is likely to focus on their physical and chemical properties. Most of the interest in these compounds stems from the fact that they resemble porphyrins, and thus provide new systems which enable an extended investigation of the coordination chemistry and electronic properties displayed by this large family of cyclic tetrapyrrolic compounds. An especially promising field is catalysis. Other potential applications can also be envisioned. For example, a further improvement in synthetic methodologies could set the path for the development of the synthesis of vitamin B_{12} mimics.

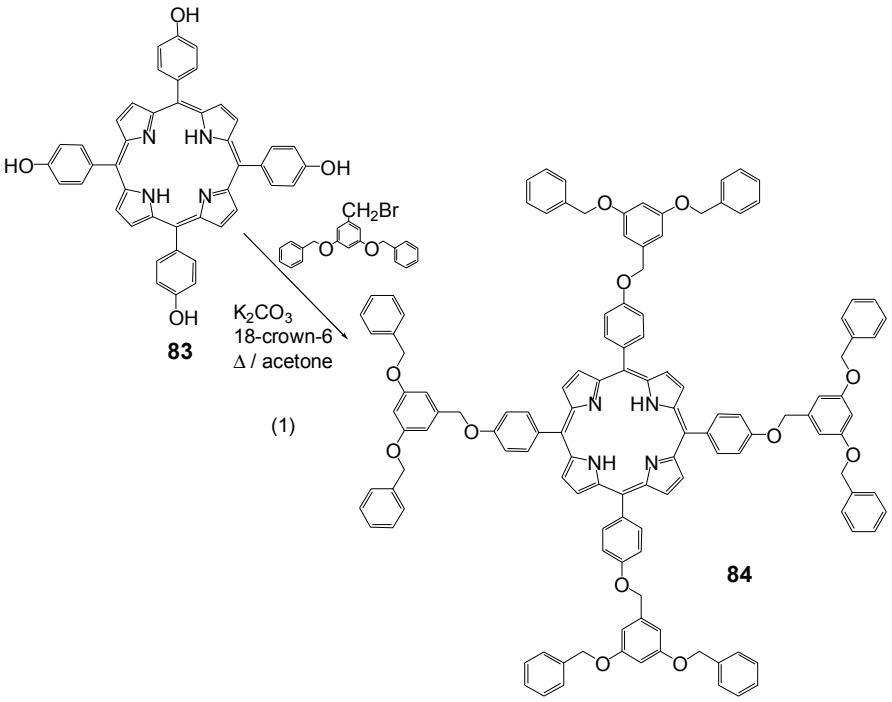
Chapter 1



Porphotetramethenes with 1,3-alternate conformation of pyrrole rings from oxidative N-alkylation of porphyrin tetraphenols

1. 1. Introduction

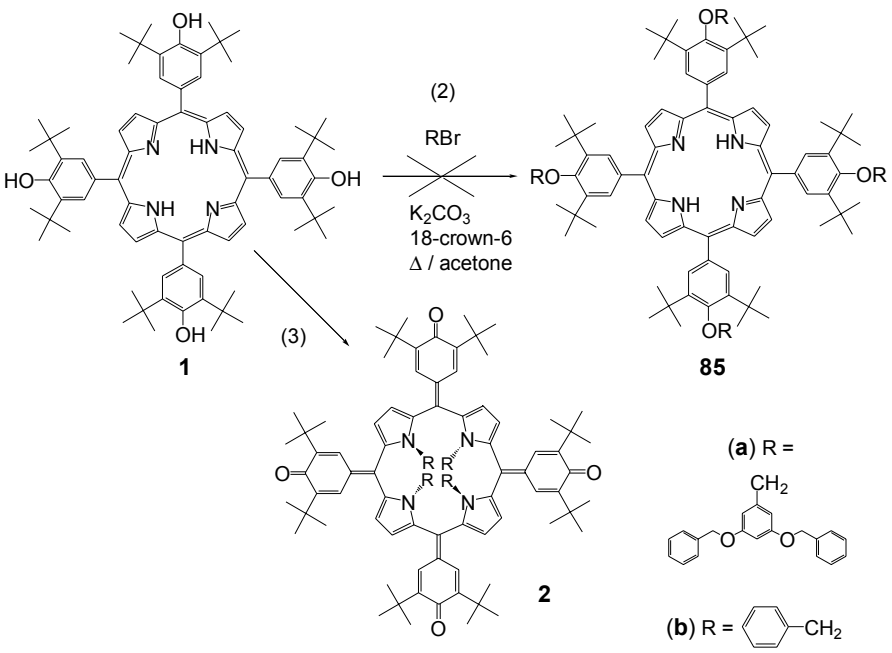
In earlier work carried out in our laboratory, the synthesis and some physical properties of dendrimers having tetraphenol **83** (Scheme 27) as the core were described.[112] Thus, first generation dendrimer **84** was synthesized from **83** under standard conditions (K_2CO_3, 18-crown-6, acetone, reflux; (1)). Compound **83** proved nevertheless too insoluble to prepare dendrimers having porphyrin groups at several tiers of the structure.[1] Therefore, the intention was to study the use of tetrakis(di-*t*-butyl) substituted **1** as a soluble porphyrin core reagent. For that purpose, alkylation (2) of **1** with the first generation Fréchet dendron was attempted under the same conditions. However, the reaction failed to provide the desired porphyrin dendrimer **85a** (Scheme 28, p. 44). Instead, a good yield of a red product (from (3)) was obtained which was shown to possess the oxidized *N*-alkylated structure **2**.



Scheme 27. Synthesis of a first generation Fréchet-type porphyrin dendrimer

The reaction (3) was repeated with benzyl bromide under the same conditions. Again, the same type of product was obtained (**2b**). In principle, four different isomers could form, which we can name, in analogy with calix[4]arene nomenclature, the 'cone', 'partial cone', '1,2-alternate' and '1,3-alternate' form.[113] The ^{1}H NMR spectrum of **2b** (Figure 9, p. 45) showed that all pyrrole hydrogens were equivalent, which does not agree

with the symmetry of partial cone or 1,2-alternate isomers. Obviously, the cone isomer would be much hindered. The related calix[4]pyrroles[114] have a similar 1,3-alternate structure when not complexed with anions.[115] An X-ray crystallographic study showed clearly that the 1,3-alternate tetraalkylated isomer of **2b** belonged to point group S_4 (Figure 10, p. 45).[1] Because of the similarity of the UV and NMR spectra, the 1,3-alternate structure can also be assigned to **2a** by analogy to **2b**.



Scheme 28. Oxidative alkylation of **1**

In a series of articles, Milgrom[116] studied the multistep oxidation (4) of porphyrin **1** and related compounds. *Via* a number of stable radicals, the porphodimethene **86** was obtained in solution as apparent from NMR measurements.[116a] In the solid form however, the structure of the oxidized product is described by X-ray crystallography as a highly puckered porphotetramethene **87** of structure similar to the products **2** (Scheme 29, p. 46).[116b] It can be assumed that **86** is the intermediate before the alkylation of **1** leading to products of type **2**. We decided to study in detail these oxidative alkylation reactions of **1**. The results can be compared to the preliminary experiments of Milgrom, who alkylated isolated porphotetramethenes **87** in refluxing basified DMF.[116c] In his work, only low yields of tetraalkylated products of type **2** were obtained, but mainly partly alkylated compounds.

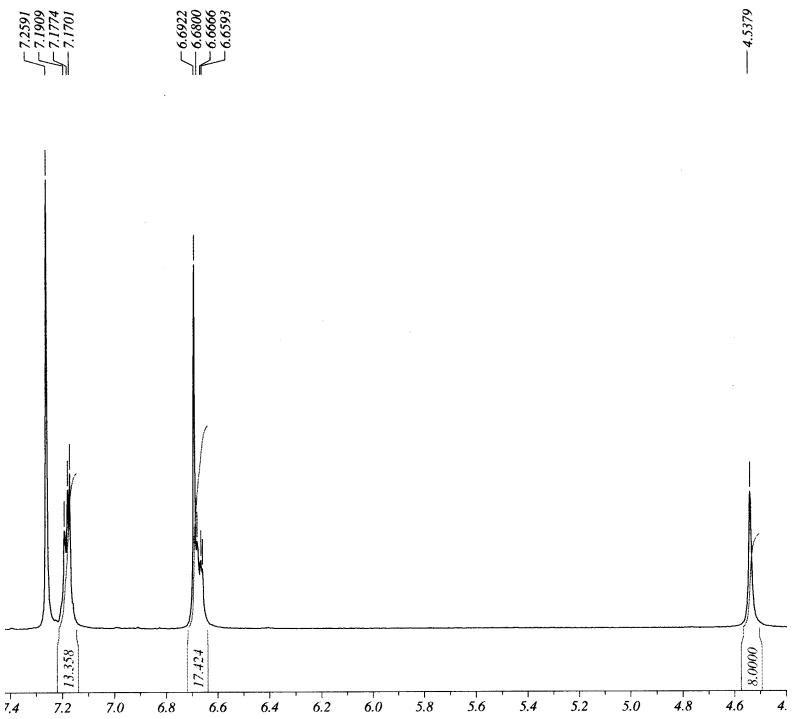


Figure 9. A section of the ^{1}H NMR spectrum of **2b** in $CDCl_3$ at 300 MHz. The signal of the β-pyrrole protons is at δ = 6.69 ppm (partially overlapped with the signals of the *m*-phenyl H)

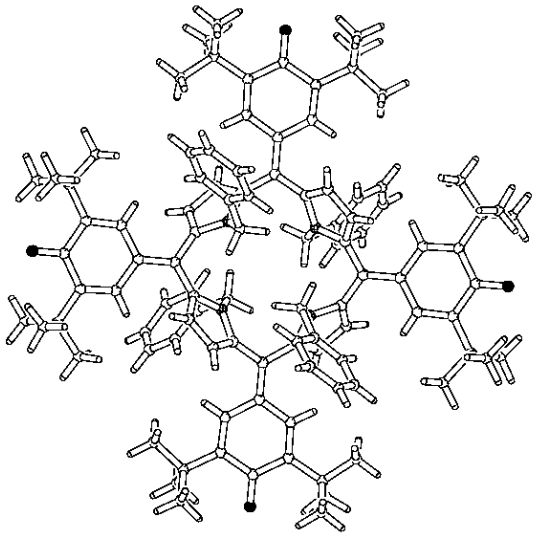
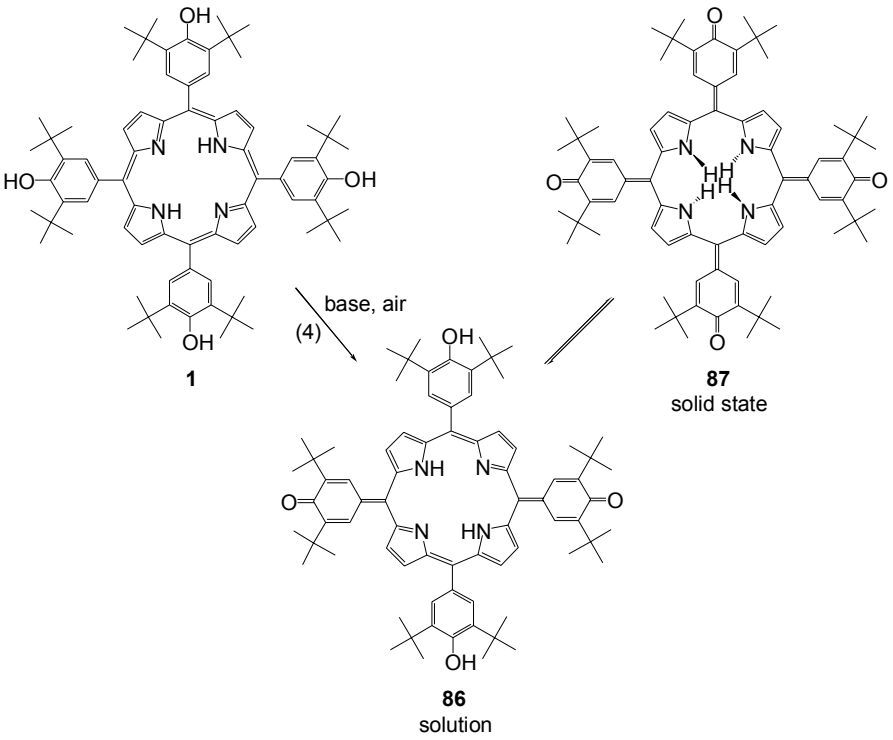


Figure 10. Molecular structure of **2b**



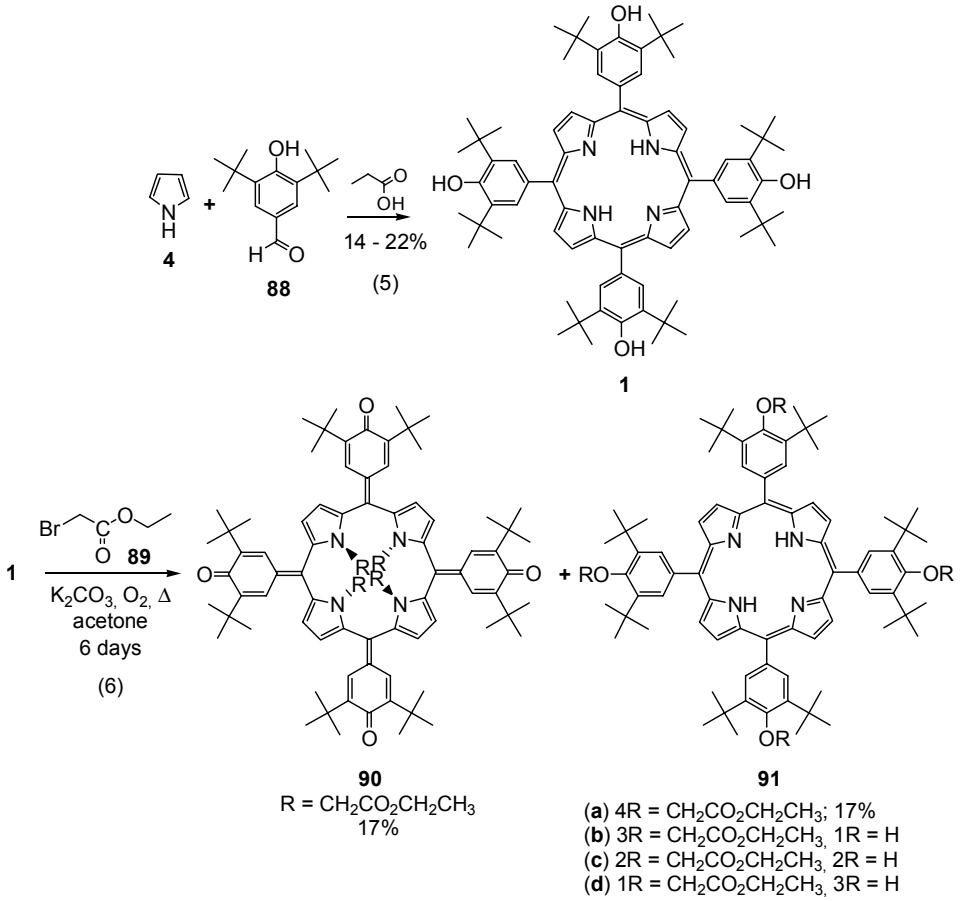
Scheme 29. Milgrom's oxidation of tetraphenol porphyrins

1. 2. Results and discussion

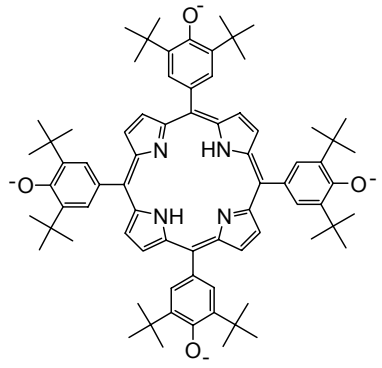
1. 2. 1. Oxidative *N*-alkylations with ethyl bromoacetate and benzyl bromide

To explore the scope of the reaction, we investigated the use of other alkylating agents, such as ethyl iodide. As that did not provide products of type **2**, we decided to try out more reactive ethyl bromoacetate **89**. Porphyrin **1** was first synthesized by a typical Adler-Longo modification of the Rothemund procedure ((5), Scheme 30, p. 47).[116a] The reaction (6) of **1** with an excess of alkylating agent **89** under reflux in acetone in the presence of an excess of K_2CO_3 lasted for several days and gave a complex mixture of products from which the red tetraalkylated porphotetramethene **90** was isolated in 28% yield using column chromatography. An *O*-tetraalkylated porphyrin **91a** could be isolated as a major by-product. On the basis of the mass spectral analyses of other fractions and TLC control of the mixtures, we could assume that several partially *O*-alkylated compounds **91** were present (shown in Scheme 30 with their approximate respective yields). Also, some starting material **1** was recovered.

With the weak base potassium carbonate, no tetraphenolate **92** derived from **1** could be formed[116a] to afford **86** which is the precursor for *N*-alkylation. Therefore, in further experiments, it was necessary to use a stronger base which enables complete oxidation of **1** to **86** prior to alkyla-



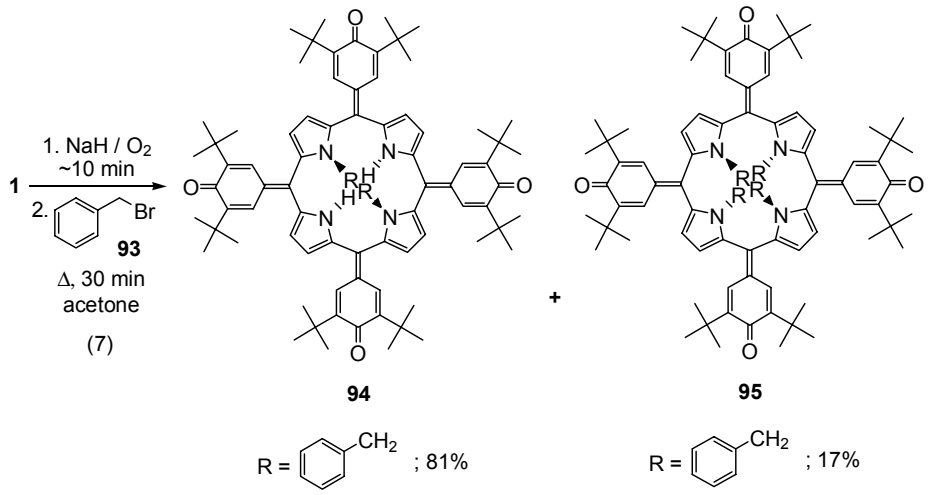
Scheme 30. Synthesis of **1** and its reaction with $BrCH_2CO_2CH_2CH_3$ in the presence of K_2CO_3



92

tion and thus prevents *O*-alkylation from occurring. Indeed, adding excess of sodium hydride to an acetone solution of **1** exposed to air caused immediate disappearance of the starting material as shown by TLC analysis. The product could be isolated by partition of the reaction mixture between dichloromethane and water and purified in 79% yield. Spectral data analysis confirmed its identity as purple species **86** in solution.

Upon addition of excess benzyl bromide **93** to the above reaction mixture at room temperature, TLC control showed very slow formation of a new purple product **94**. On heating at reflux for 30 min **86** was completely consumed and a new red product **95** started to appear. Work-up and chro-



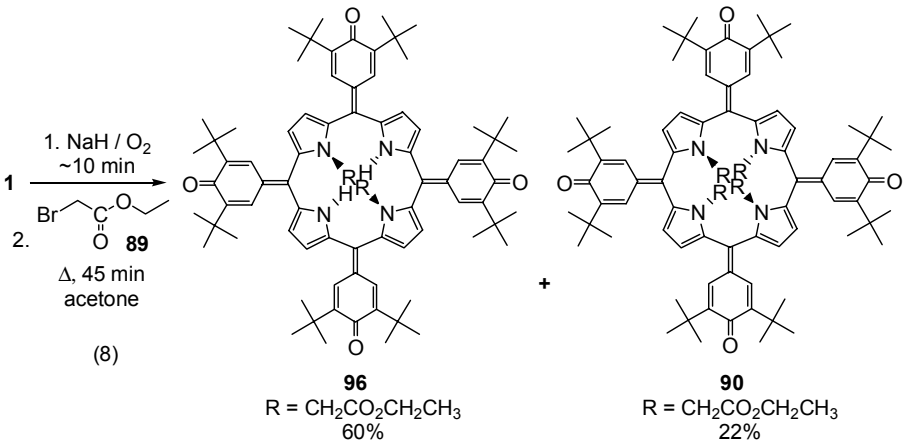
Scheme 31. Oxidative *N*-benzylation (7) of **1**

matography afforded the products **94** and **95**, which were respectively characterized as dibenzylated and tetrabenzylated porphotetramethene, in an almost quantitative combined yield. The intermediate dibenzylated compound was assigned by ^{1}H NMR as having the structure **94** (Scheme 31), with benzyl groups on alternating pyrrole rings. We can assume that the two benzyl substituents are on the same side of the macrocycle since they appear like this in the final product.

Prolonging the reflux time to 6 hours gave only **95** in 86% yield. It is worth stressing that the yields are significantly higher than those reported by Milgrom[116c] (81% instead of 32% for **94**, and 86% instead of 3% for **95**). Mono- and tribenzylated intermediate products were not obtained. A probable reason is a configurational change of the substrate molecule in the process of alkylation of the first nitrogen atom, whereby the pyrrole ring concerned twists out of the molecular plane. The opposite pyrrole ring moves in the same direction, significantly facilitating the next alkylation step. The same analogy can be applied to the alkylation of the other two nitrogen atoms.

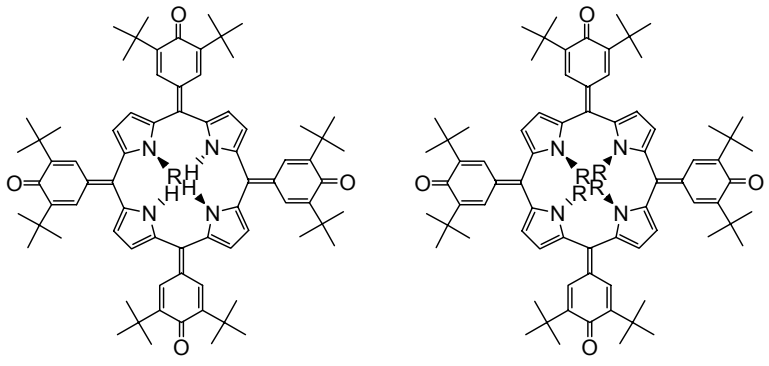
Carrying out the alkylation reaction (8) in acetone with excess ethyl bromoacetate **89** as the alkylating agent for 45 min afforded only 22% of tetraalkylated product **90** and 60% of the intermediate dialkylated product **96** (Scheme 32), indicating a significantly slower reaction. This is, however, the best of the methods investigated if **96** is the target product.

Extending the time of this reaction with repeated addition of aliquots of **89** and base increased the yield of **90**, but even after as much as 3 days of refluxing the dialkylated compound **96** was still present in the reaction mixture. The yield of isolated **90** was 62% and that of **96** amounted to 30% with a small amount of what appeared to be monoalkylated compound **97**.



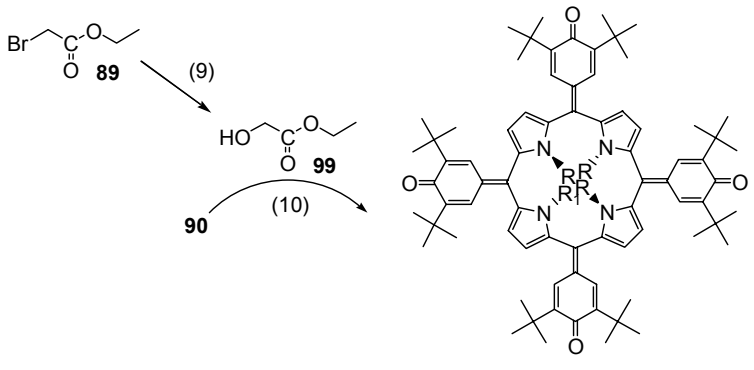
Scheme 32. Products of short-time reaction of **1** with $BrCH_2CO_2CH_2CH_3$

Performing the reaction in dimethyl formamide at 100°C overnight decreased the amount of **96** formed to 19% with again a small amount (~1%) of what was indeed characterized as the monoalkylated product **97**. The yield of the tetraalkylated porphotetramethene **90** was 51% with another red-coloured product formed in a substantial amount. The latter compound was first (because of its asymmetry as indicated by the NMR



spectra) suspected to be an isomer of **90** with the "partial cone" symmetry of the substituent (ethoxycarbonyl)methyl groups, *i.e.* the hypothetical structure **98**.

However, mass spectral analysis and careful examinations of 2D NMR spectra refuted this hypothesis. As can be seen from the HMBC spectrum of the pure by-product (Figure 11, p. 51), the additional (as compared to the spectrum of **90**) singlet at δ = 4.44 ppm, accounting for two protons, doesn't show correlation with the α-pyrrole carbon atoms appearing at δ = 138.7 ppm in the ^{13}C NMR spectrum, indicating that those carbons are more than three bonds away. This is opposed to the situation



100
R = $CH_2CO_2CH_2CH_3$
R_1 = $CH_2CO_2CH_2CO_2CH_2CH_3$

Scheme 33. Formation of **100**

for 'normal' $R_2NCH_2CO_2$-protons of the type as in **90** which are two bonds away from the aforementioned carbons and show a strong correlation. Furthermore, the integration curve shows the presence of two more protons altogether and the downfield shift of the signal at δ = 4.44 ppm suggests its deshielding environment. All these facts are in correspondence with the structure **100** which represents a transesterification product of **90**. This by-product **100** is obtained by the reaction (10) of **90** with ethyl 2-hydroxyacetate **99**, which is in turn formed by hydrolysis (9) of excess ethyl bromoacetate during the reaction (8) performed in DMF (Scheme 33). The yield of **100** was 12%. Mass spectra confirm these findings.

Using extreme excesses of both bromoester **89** (105 equivalents) and base (80 equivalents of sodium hydride) and running a reaction of type (8) for 5 days in refluxing acetone gave an overall yield of 86% with no underalkylated products. However, 26% of the product was the monotransesterified compound **100** and 29% another by-product to which ditransesterified structure **101** was assigned in a similar way as it was done for **100**.

The compounds **100** and **101** can be chromatographically separated from **90** with some difficulty. Treatment (11) of a mixture **90/100/101** with an excess of sodium ethoxide in a refluxing mixture of acetone and ethanol reconverts the mixture almost completely to **90** within

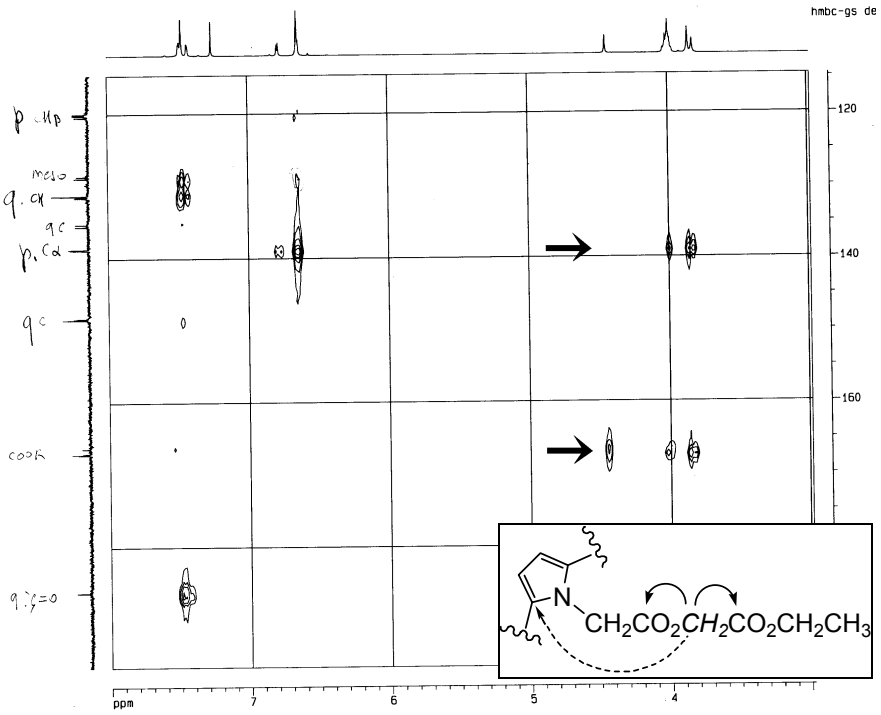
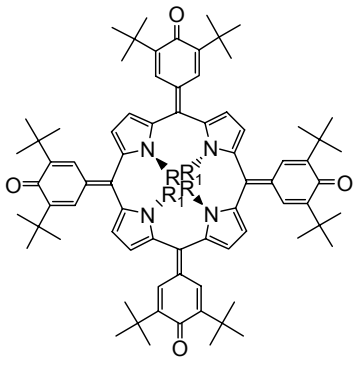
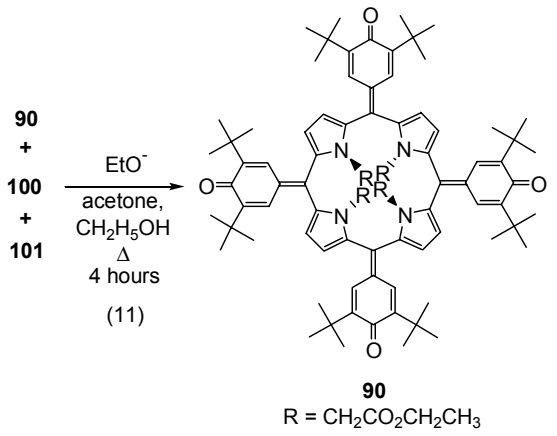


Figure 11. HMBC spectrum of **100** in $CDCl_3$ at 400 MHz. The arrows in the main picture show the peak indicating correlation of the $–CO_2CH_2CO_2-$ protons with the neighbouring carboxyl carbons (below; full arrows in the inset) and absence of correlation of the same protons with the α-pyrrole carbons (above; dashed arrow in the inset)



101
R = $CH_2CO_2CH_2CH_3$
R_1 = $CH_2CO_2CH_2CO_2CH_2CH_3$

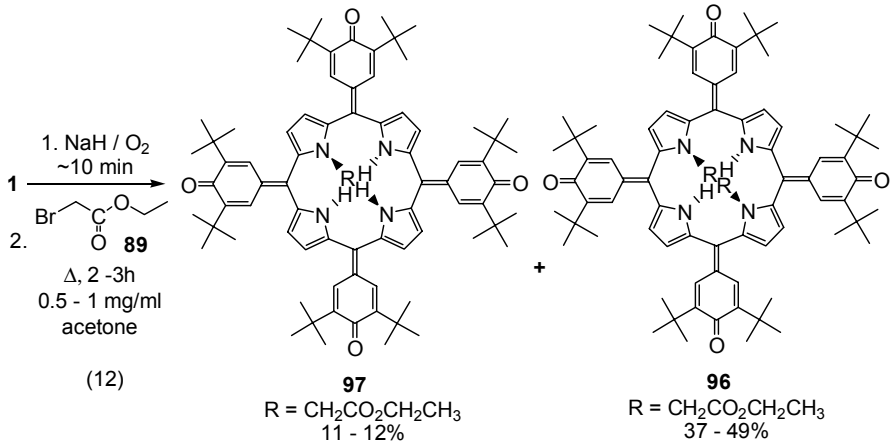
several hours (Scheme 34, p. 52). The main product was isolated and unequivocally confirmed as the compound **90**, thereby confirming the identities of **100** and **101**.



Scheme 34. Reconversion of transesterified products to **90**

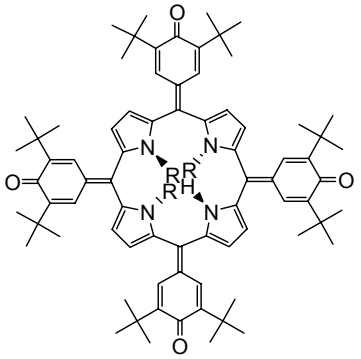
Reducing the time of reaction (8) in DMF to 30 min afforded comparable yields of all products (60% of **90**, 24% of **100** and 12% of **96**), showing that prolonged reaction times were not necessary to complete the reaction in DMF.

Attempts were made to optimize the yield of the monoalkylated porphotetramethene **97**. In that purpose, reaction (8) was carried out under diluted conditions and with a diminished excess of alkylating agent **89**. 8-Fold dilution in acetone (compared to the general conditions; see below) and applying 10 instead of 25 equivalents of **89** gave 11% **97** and 49% **96** within 2 hours, whereas 16-fold dilution of the reaction mixture and using the same reduction of the excess of agent **89** to starting compound **1** provided 12% **97** and 37% **96** after 3h in acetone (Scheme 35). In both cases, a significant amount of **86** remained unalkylated and a small quantity of tetraalkylated compound **90** was formed. Neither of the two was isolated.



Scheme 35. Selective synthesis of porphotetramethenes with low degrees of alkylation

To further explore the scope of this general reaction, the solvent and the reaction temperature have been varied. For the reactions in THF, KO^{t}Bu was used instead of NaH because of the low solubility of the latter. In some cases, and especially when DMSO is the solvent, the tetraalkylated compound **90** contained some trialkylated derivative **102**, which could not be separated by chromatography. Nevertheless, its presence was confirmed by mass spectrometry and its characteristic signals could be observed in the aromatic region of the NMR spectra. In each case, the products or their mixtures were isolated by column chromatography and analysed by ^{1}H NMR. The results are summarized in Table 1 (p. 54). In the case of mixtures, the quantities of the products were determined by the ratios of the integrals of their respective signals in the NMR spectra.



102
R = $CH_2CO_2CH_2CH_3$

The reactions proceed well in a number of organic solvents. In some cases, particularly if the reactions are carried out in acetonitrile or acetone, it seems that applying elevated temperature does not actually have an effect on the outcome of the reaction.

Attempting to carry out reaction (8) in dimethyl sulphoxide at 56°C did not afford any product. The same reaction at 130°C also proved unsuccessful because of vigorous decomposition of the solvent by a reaction with sodium hydride. The solvent forms a sodium salt with a release of gaseous hydrogen.[117]

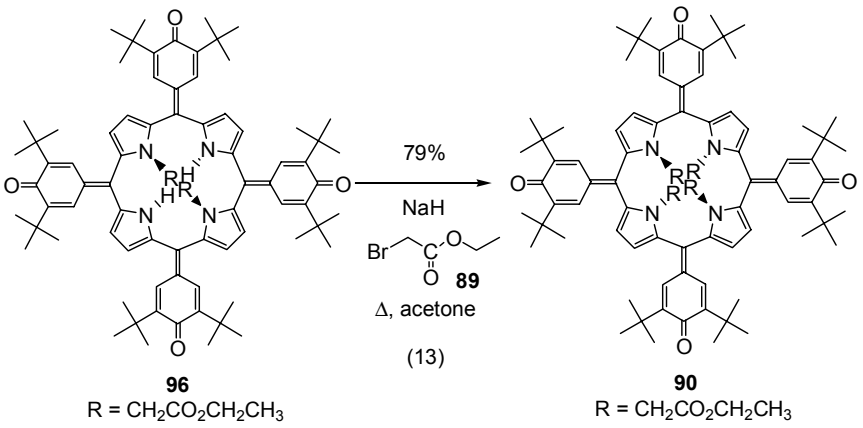
No *N*-dealkylation occurred when tetraalkylated porphotetramethene **90** was heated in boiling acetone with ethyl bromoacetate and sodium hydride even after 6 days. The starting product was almost quantitatively recovered. On the other hand, boiling an acetone solution of the dialkylated product **96** containing the base and the alkylating agent during several days caused complete disappearance of the purple starting material. Again, significant transesterification occurred and formation of the three tetraalkylated products **90**, **100** and **101** in almost equal proportions was observed. A similar result was achieved if a small amount of monoalkylated compound **97** was heated overnight in acetone with large excesses of base and ethyl bromoacetate.

starting compound	solvent	alkylating agent	temp./[°C]	reaction time	total yield/%	mol % of total yield			
						mono	di	tri	tetra
1	DMF	$BrCH_2CO_2Et$	56	15 h	21	43	21	0	36[a]
1		$BrCH_2CO_2Et$	82	15 h	36	37	21	0	42[a]
1		$BrCH_2CO_2{}^tBu$	82	15 h	26	3	10	0	87
1		$BrCH_2CO_2Et$	100	15 h	83	1	23	0	76[a]
1		$BrCH_2CO_2{}^tBu$	100	15 h	41	10	n. i.[b]	0	90
1	CH_3CN	$BrCH_2CO_2Et$	56	15 h	40	5	31	0	64
1		$BrCH_2CO_2{}^tBu$	56	15 h	23	0	0	0	100
1		$BrCH_2CO_2Et$	82	15 h	40	6	28	0	66
1		$BrCH_2CO_2{}^tBu$	82	15 h	43	0	0	0	100
1	THF[c]	$BrCH_2CO_2Et$	56	15 h	100	18	29	0	53
1		$BrCH_2CO_2{}^tBu$	56	15 h	100	10	48	4	38
1	DMSO	$BrCH_2CO_2Et$	82	15 h	23	33	12	35	20
1		$BrCH_2CO_2{}^tBu$	82	15 h	91	5	12	5	78
1		$BrCH_2CO_2Et$	100	15 h	30	28	15	34	23
1		$BrCH_2CO_2{}^tBu$	100	15 h	70	3	8	3	86
1	acetone	$BrCH_2C_6H_5$	56	30 min	98	0	82	0	18
1		$BrCH_2C_6H_5$	56	6 h	86	0	0	0	100
96		$BrCH_2C_6H_5$	56	15 h	63	0	0	0	100
96		$BrCH_2CO_2Et$	56	5 days[d]	86	0	0	0	100[e]
96		$BrCH_2CO_2Et$	56	24 h	79	0	0	0	100[f]
94		$BrCH_2CO_2Et$	56	15 h	75	0	0	0	100
1		$BrCH_2CO_2Et$	56	45 min[g]	82[h]	0	73	0	27
97		$BrCH_2C_6H_5$	56	6 h	55	0	0	0	100
96		$BrCH_2CO_2{}^tBu$	56	4 h	90	0	0	0	100
1		$BrCH_2CO_2{}^tBu$	56	1 h[i]	45	30	70	0	n. i.[b]
1		$BrCH_2CO_2{}^tBu$	r. t.	15 h	100	n. i.[b]	21	n. i.[b]	79
1		$BrCH_2CO_2Et$	56	15 h	72	9	43	0	48
1		$BrCH_2CO_2{}^tBu$	56	15 h	99[j]	n. i.[b]	17	n. i.[b]	83

(a) the tetraalkylated product contained 12 – 20% **100**; (b) not isolated, traces present (TLC); (c) ^{t}BuOK was used as base as we saw no conversion with NaH; (d) 80 eq. of NaH, 105 eq. of the bromoester; (e) the tetraalkylated product contained 26% **100** and 29% **101**; (f) the tetraalkylated product contained ~1% **100**; (g) 13 eq. of the bromoester; (h) the method of choice (60%) for **96**; (i) 8 eq. of the bromoester; 2.5 times diluted; (j) the method of choice (82%) for **111**.

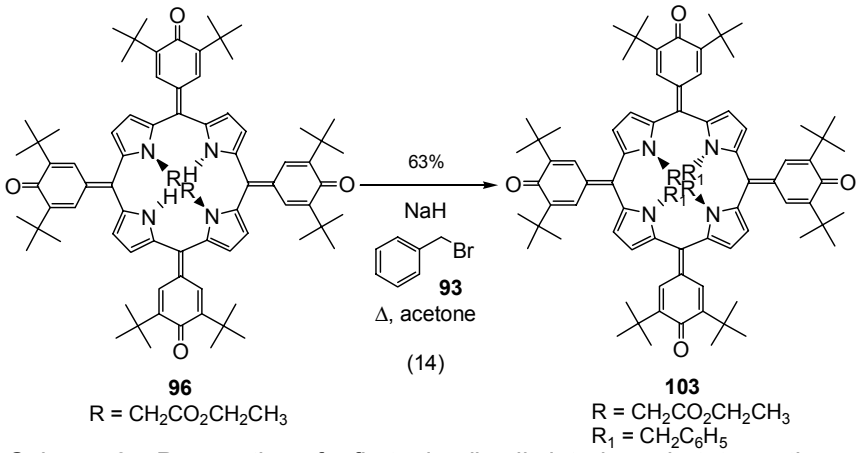
Table 1. Yields and products for the *N*-alkylation reactions

It was possible to find conditions for conversion of dialkylated porphotetramethene **96** to the tetraalkylated derivative **90** without significant transesterification (Scheme 36). Heating **96** in acetone with usual excesses of ethyl bromoacetate and sodium hydride over a limited period of time left only a small portion of the starting material unreacted (3% isolated by column chromatography), with the vast majority of it having been converted to **90** with only about 1% of the end product transesterified to **100**. A surprising result is that **96** can be fully converted to tetraalkylated products if the reaction is started with isolated dialkylated compound, whilst if **1** is the starting material that cannot be achieved even by using large excesses of the alkylating agent and base and a prolonged reaction time.



Scheme 36. Alkylation of isolated **96**

However, successfully performing reaction (13) (Scheme 36) prompted further investigations into the ability to prepare mixedly alkylated

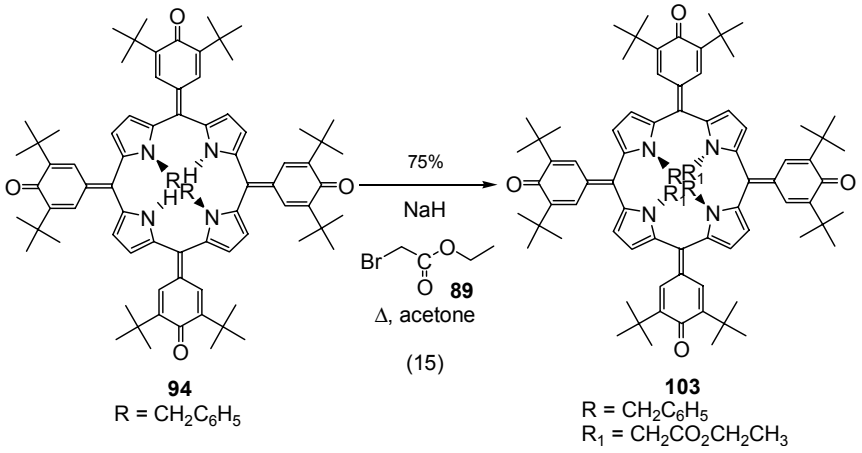


Scheme 37. Preparation of a first mixedly alkylated porphotetramethene

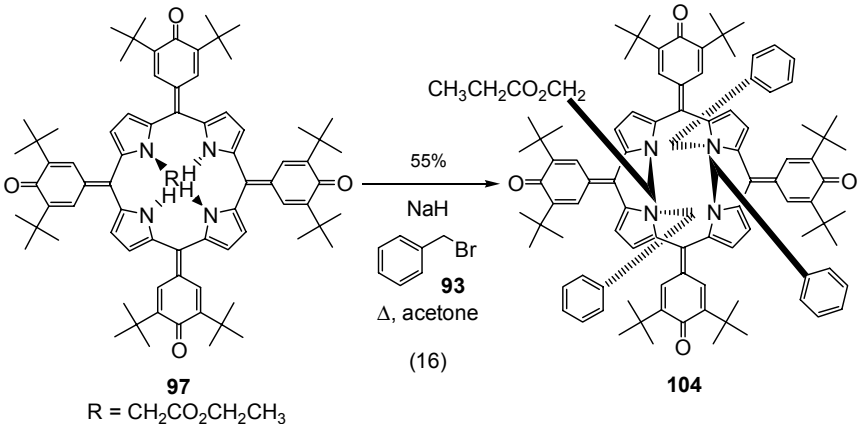
products in a similar way. Acetone was chosen as the solvent for these conversions as it generally provided the most reliable results, highest yields and least complex mixtures of products compared to the other solvents examined.

Thus, **96** was reacted with benzyl bromide overnight under standard conditions in acetone ((14), Scheme 37, p. 55). TLC control showed complete disappearance of the starting material with one major red-coloured product. This was, upon work-up and isolation by column chromatography, characterized as having the structure **103** with two different substituents symmetrically positioned on the nitrogen atoms. One minor red-coloured product with a slightly lower polarity, formed in about 10% amount of **103**, was also observed, but even after spectroscopic investigation its nature remains unclear.

Of course, it seemed convenient to check if the same product **103** could be obtained in the 'reverse' way, *i.e.* by alkylating dibenzyl porphote-



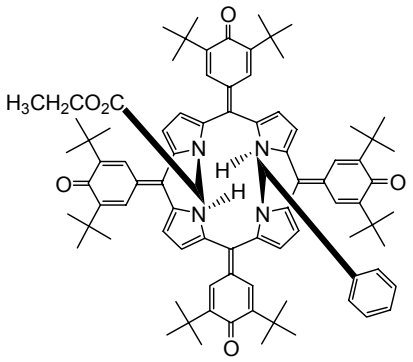
Scheme 38. The 'reverse' way of preparing **103**



Scheme 39. Tribenzylation of **97**

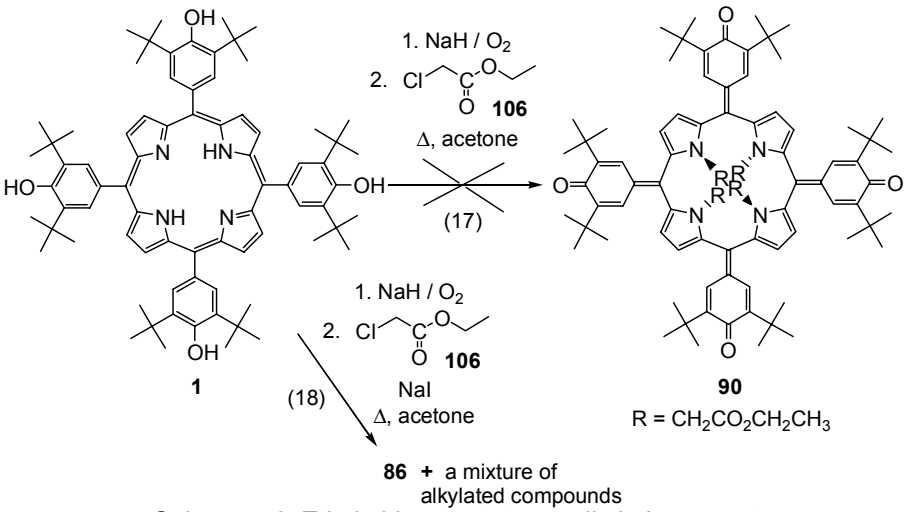
tramethene **94** with ethyl bromoacetate. Reaction (15) was carried out analogously to (14) (Scheme 38, p. 56). The product **103** was indeed obtained in 75% yield. No red-coloured by-products were observed this time. However, the alkylation wasn't driven to completion as 13% of starting **94** could still be detected in the product mixture.

The same idea was followed for isolated monoalkyl porphotetramethene **97** (Scheme 39, p. 56). Its tribenzylation (16) afforded 55% of the product **104** after chromatography and recrystallization. A purple spot was observed on TLC after 30 min of reaction. It could have belonged to a monobenzylated intermediate **105**. Nevertheless, only **104** was isolated after approximately 6 h of reaction.



105

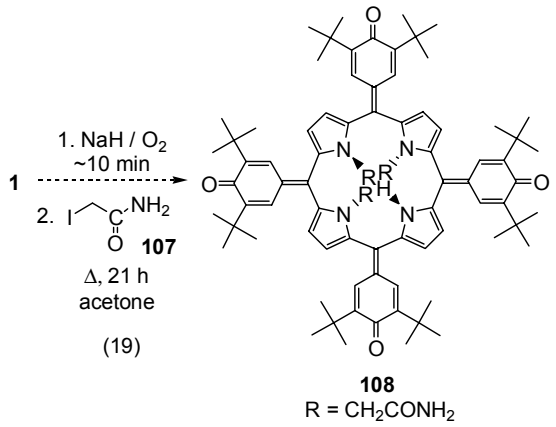
Ethyl chloroacetate **106** was also tried out as an alkylating agent in this type of reactions. It proved virtually unreactive in attempted alkylations (17) of both **1** and **96** under standard conditions for reaction (8) (Scheme 40). Therefore, a catalytic amount of sodium iodide was added to reaction (17) of **1** with **106**. Under these conditions (18), ethyl iodoacetate would form, which is a much better alkylating agent.



Scheme 40. Ethyl chloroacetate as alkylating agent

However, even after 3 days of refluxing the strongest spot on TLC was that of **86** (the oxidized starting compound), with only minor amounts of the mono-, di- and tetraalkylated products formed. The actual quantities of the products formed were not determined. A 15-fold increase of the quantity of sodium iodide didn't significantly improve the TLC picture after 4 days of reaction in a new attempt.

Another iodo compound, iodoacetamide **107** was investigated as an alkylating agent in a reaction of type (8) (Scheme 41). After 21 h of reflux under standard conditions only a small quantity of **86** remained present in the reaction mixture (19) according to TLC. The work-up, isolation and characterization of the product(s) proved difficult, however, due to its (their) very low solubility. An electrospray mass spectrum was obtained wherein a peak plausibly representing trisubstituted compound **108** can be seen.

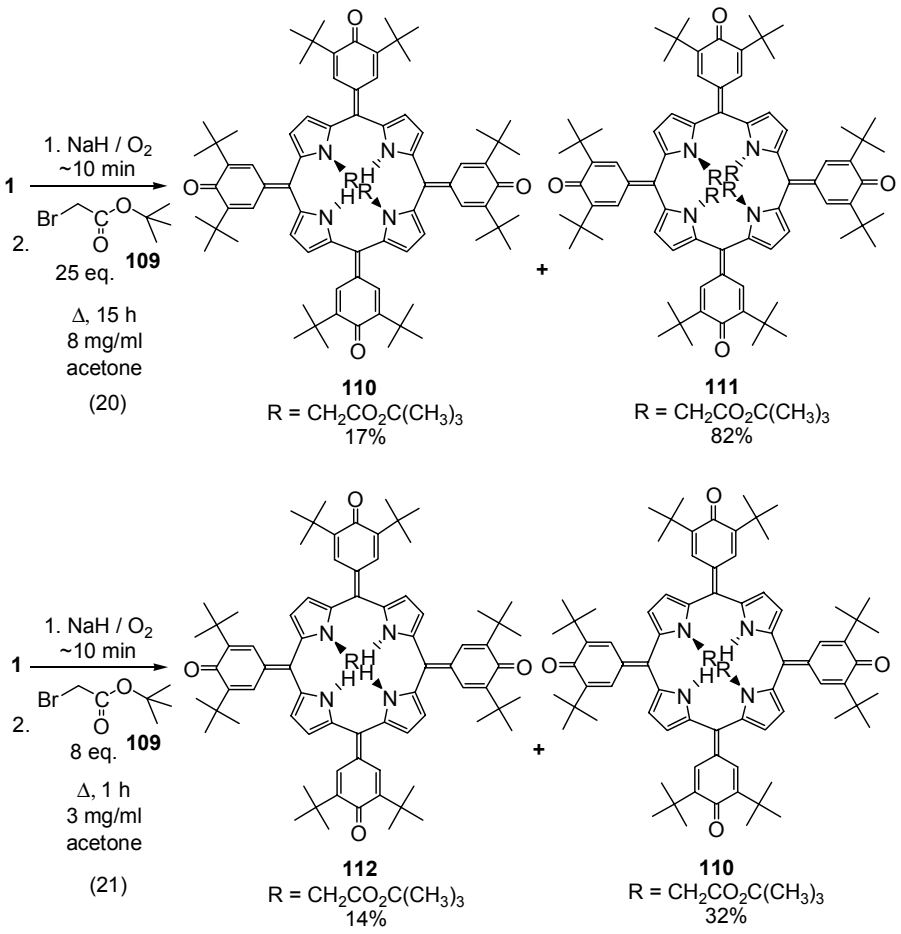


Scheme 41. A plausible reaction of **1** with iodoacetamide

1. 2. 2. Oxidative *N*-alkylations with *t*-butyl bromoacetate

Transesterification (10), which gives the by-products **100** and **101**, often occurs if ethyl bromoacetate **89** is used as the alkylating agent for porphyrin **1**. Therefore, we decided to study the use of sterically hindered *t*-butyl bromoacetate **109**. This feature should prevent transesterification while a new reagent would also provide means for obtaining new alkylated porphotetramethenes.

Reaction of **1** with **109** under the standard conditions for a reaction of type (8) ((20), Scheme 42 above, p. 59) provided 82% of the corresponding tetraalkylated derivative **111** with a smaller amount of the dialkylated product **110**. It can be assumed that the structure of the products is analogous to the structure of the corresponding benzylated and (ethoxycarbonyl)methyl-substituted compounds. This is confirmed by the NMR spectra. Traces of what looked like mono- and trialkylated derivatives were also observed on TLC of the reaction mixture (20).



Scheme 42. Selective synthesis of porphotetramethenes using *t*-butyl bromoacetate **109**

If the reaction of **1** with **109** is performed under conditions similar to those for reaction (12), *i.e.* using a lower concentration of **1**, a smaller excess of the alkylating agent and a shorter reaction time, monoalkylated compound **112** can be isolated in 14% yield along with the dialkylated derivative **110** in 32% yield ((21), Scheme 46 below). Some of the starting material remained in the non-alkylated oxidized form **86** in this case.

It is worth mentioning that carrying out reaction (20) at room temperature instead of in boiling acetone did not significantly affect the outcome of the reaction (Table 1). This suggests that heating to reflux actually is not necessary for this type of reaction in acetone, whilst the temperature effect was observed in some other solvents. This is comparable to the analogous reactions with ethyl bromoacetate.

Reaction (20) was repeated in various solvents and at various temperatures. The results are summarized in Table 1 (p. 52). Again, the ratios of the products have been determined by NMR spectroscopy. In this

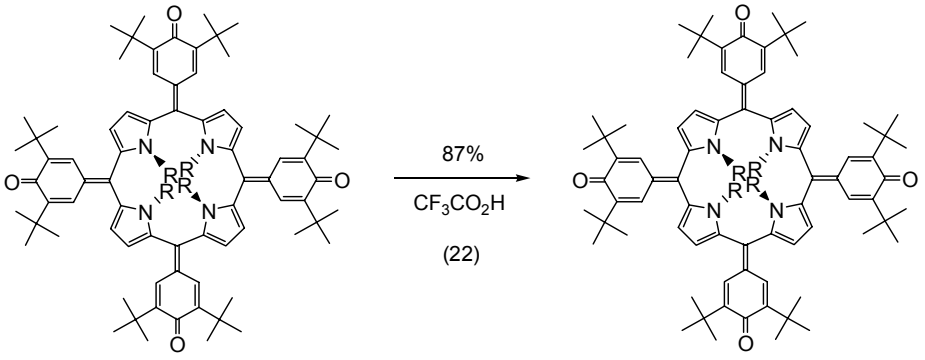
case, too, the trialkylated derivative could not be isolated by chromatography, but it showed separate distinct signals in the NMR and MS spectra. No transesterification was observed in any of the cases.

Dimethyl formamide did not prove to be suitable solvent for reaction (20). At 56°C, only traces of the mono- and dialkylated products **112** and **110** (respectively) were detected by TLC after 15 h. These products were not isolated. An increase of the total yield was obtained with the increase of temperature, but in a lesser extent than observed with the alkylations (8). Just the opposite was true if reaction (20) was performed in dimethyl sulphoxide. No remaining oxidized starting material **86** could be detected by TLC after 15 h at 56°C in this solvent. TLC showed that the major product of the reaction was tetraalkylated compound **111** with some di- and trialkylated derivatives as well as a very small amount of the monoalkylated product. The product mixture could not be fully characterized because of the impossibility to completely remove residual solvent even after extensive drying (heating up to ~170°C during several days actually caused decomposition of the product mixture). In the other cases, an NMR characterization of the product mixture was possible, with the total yield decreasing with the increase of temperature.

In the cases when CH_3CN was the solvent, substantial amounts of unreacted **1** remained in the reaction mixture along with some oxidation product **86**. Surprisingly, in such cases only tetraalkylated **111** was observed of the alkylated species, albeit in relatively low yields (23% at 56°C and 43% at 82°C).

Reaction (20) was repeated with 1 g of starting porphyrin **1** under standard conditions in acetone. The results were roughly the same as with 200 mg of the starting compound.

Deprotection of the ester groups of **111** has been possible. Thus, treating **111** with neat trifluoroacetic acid provides tetraacid **113** in 87% yield within 5 h ((22), Scheme 43). Obtaining this product opens up the possibility to prepare further derivatives of the basic porphotetramethene structure, although such attempts could be impaired by the low solubility of **113**.



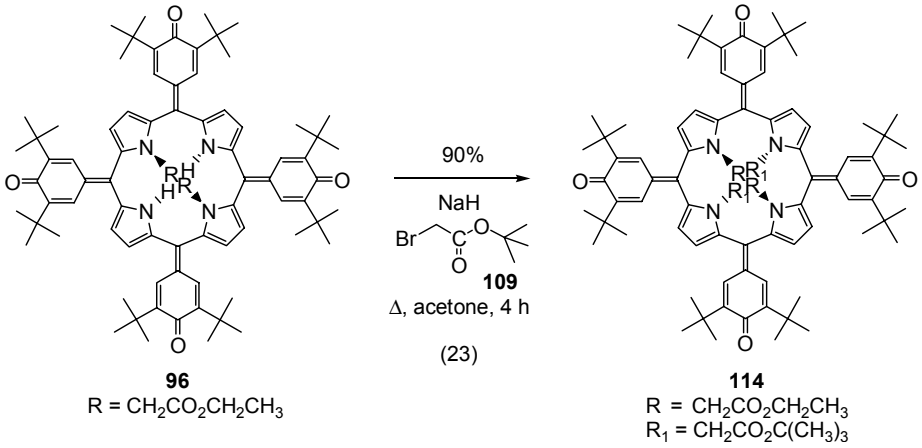
111
R = $CH_2CO_2C(CH_3)_3$

113
R = CH_2CO_2H

Scheme 43. Acidolysis of the ester groups of **111**

Diluting trifluoroacetic acid with CH_2Cl_2 slowed down reaction (22) and peaks corresponding to partially deprotected products (*i.e.* with less than four ester groups acidolyzed) were detected by mass spectrometry. These intermediates have not been isolated. Theoretically, the peaks could also pertain to by-products with acidolyzed ester groups but *t*-butylated elsewhere in the structure, most probably on the β-C-atoms of the pyrrole rings. Adding anisole to the reaction mixture (as scavenger for the *t*-butyl cations formed in the deprotection reaction[118]) apparently has no effect on the overall reaction, thereby excluding the probability of those side alkylations. Absence of these peaks in the case of pure TFA acidolysis is another argument against this hypothesis.

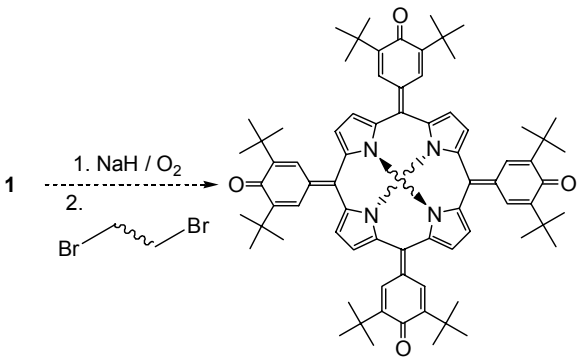
Alkylation of isolated dialkylated porphotetramethene **96** with *t*-butyl bromoacetate provided the 'mixed' product **114**, with the ester groups two by two selectively protected, in 90% yield ((23), Scheme 44).



Scheme 44. Synthesis of a porphotetramethene with two different kinds of ester groups

1. 2. 3. Synthesis of a doubly bridged porphotetramethene

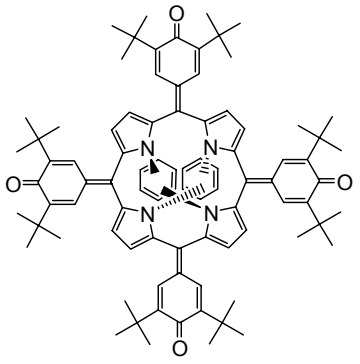
As described above, various *N*-tetraalkylated porphotetramethenes can be readily synthesized under different conditions. The final products possess varying substituents, yet they are always locked in the same 1,3-alternate basic structure. This sparked the idea of preparing a novel class of *N*-alkylated oxidized porphyrins. Theoretically at least, a bifunctional alkylating agent of the right geometry could 'bridge' two opposite pyrrole units. The other two pyrrole rings could be connected in the same way with another molecule of the alkylating agent to afford a strapped structure **115** (Scheme 45, p. 62). Such 'doubly bridged' porphotetramethene derivatives could be used as host compounds for small molecules and ions.



115

Scheme 45. Schematic synthesis of a doubly bridged porphotetramethene

Preliminary molecular modelling studies using Chem3D software suggested that α,α'-dibromoxylenes could possess suitable molecular dimensions for this type of reaction. These compounds have recently been used to prepare cationic doubly bridged derivatives of *p*-2,2'-diazaterphenyls.[119] In our hands, these reagents would give products of the general formula **116**.

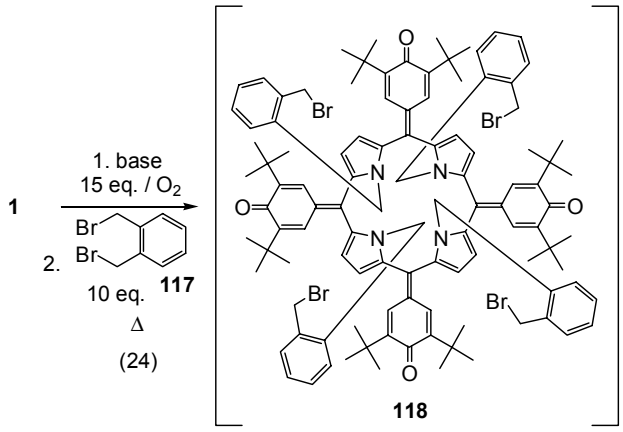


116

A first reaction of porphyrin **1** with a stoichiometric amount of α,α'-dibromo-*o*-xylene **117** in the presence of sodium hydride in acetone at reflux temperature did not show formation of a substantial amount of any alkylated product. On increasing the amount of the alkylating agent to five equivalents, purple and red spots characteristic of alkylated porphotetramethenes appeared on the TLC plate. However, most of the starting material was still in the oxidized form **86** after two days of reaction. None of the abovementioned products was isolated.

Using a 10-fold excess of the alkylating agent **117** with NaH in boiling acetone over 24 h afforded what appeared to be several different alkylated products, with no **86** left in the reaction mixture. The major fraction was isolated by column chromatography and shown by electrospray mass spectrometry to possess the molecular mass

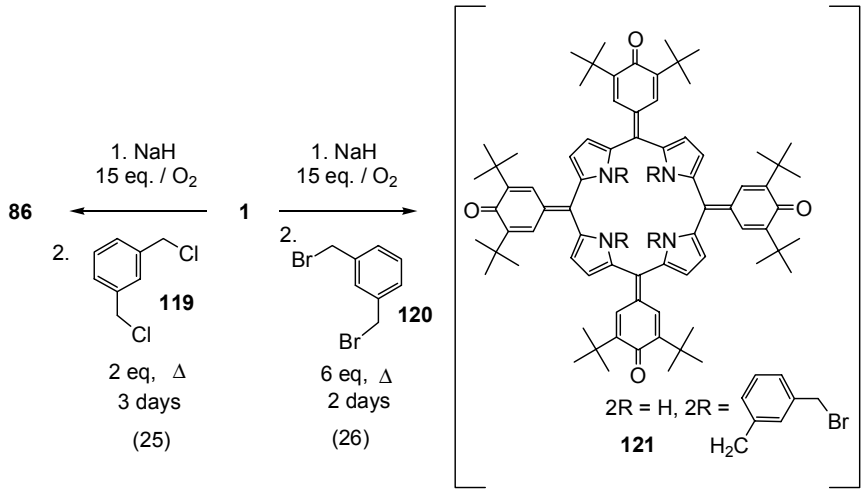
corresponding to the non-bridged tetraalkylated general structure **118**. A similar result was obtained with a 10-fold excess of **117** with KO^{t}Bu in THF, but after a reaction time of one week ((24), Scheme 46). However, the structure of **118** (if it is a single compound) has not yet been determined by any other means than electrospray mass spectrometry.



Scheme 46. Tetraalkylation of porphyrin **1** with α,α'-dibromo-*o*-xylene

Reducing the reaction time of reaction (24) in acetone to 2.5 h enabled isolation of two impure purple products in an approximate 3:1 ratio which were characterized by mass spectral analysis as non-bridged di- and monoalkylated analogues of **118**, respectively.

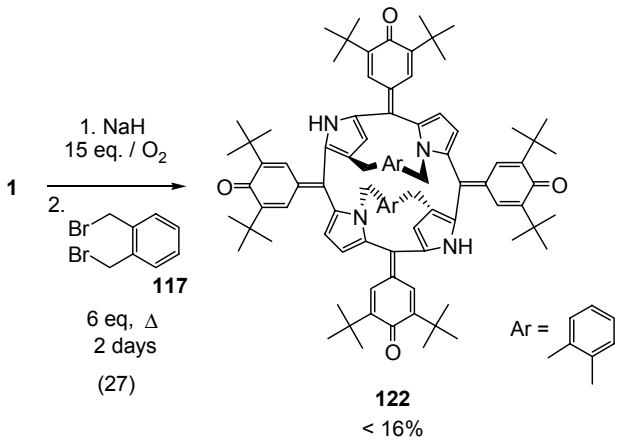
An attempted reaction (25) of porphyrin **1** with α,α'-dichloro-*m*-xylene **119** didn't afford any alkylated products (Scheme 47). On the other hand, reaction (26) of **1** with α,α'-dibromo-*m*-xylene **120** afforded several



Scheme 47. Reactions of **1** with α,α'-dihalo-*m*-xylenes

products in low yield. One of them could be, on the basis of electrospray mass spectrometry, a non-bridged doubly alkylated structure **121**.

Eventually, one of the products of a prolonged reaction of **1** with α,α'-dibromo-*o*-xylene **117** ((27), Scheme 48) showed the molecular ion peak at the m/z ratio expected for a doubly bridged product **116**. However, as apparent from NMR analysis (below), the correct structure of the product is **122**, shown in Scheme 48, with two by two adjacent pyrrole rings bridged by one phenylenedimethylene moiety, one ring being connected *via* its β-carbon rather than its nitrogen atom. It is probably steric strains that cause the reaction to proceed in this unexpected way.



Scheme 48. Synthesis of a 'strapped' *N*-tetraalkylated porphotetramethene

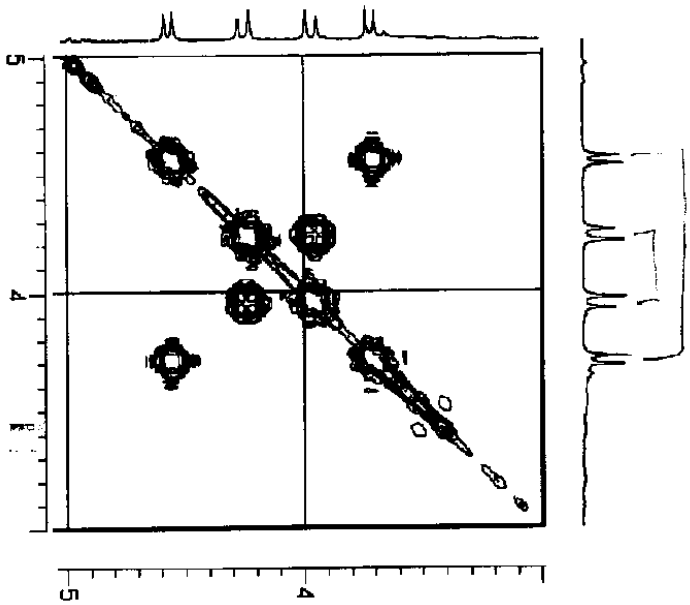


Figure 12. Part of the COSY spectrum of **122** in $CDCl_3$ at 400 MHz

The ^{1}H NMR spectrum of **122** displays four different signals of the phenylenedimethylene CH_2 protons, instead of only one that would be expected in case of a symmetric structure **116**. Large coupling constants in all cases, characteristic of geminal coupling, suggest that the two protons of each methylene group have a different chemical environment. The four different signals of the quinoide protons in the aromatic region are another proof of a rather asymmetric structure (no plane of symmetry through the quinoide rings). The COSY spectrum of **122** (Figure 12, p. 64) shows correlation between the most downfield and the most upfield phenylenedimethylene CH_2 signals, as well as between the two signals in between (Figure 13), confirming which protons are part of the same AB

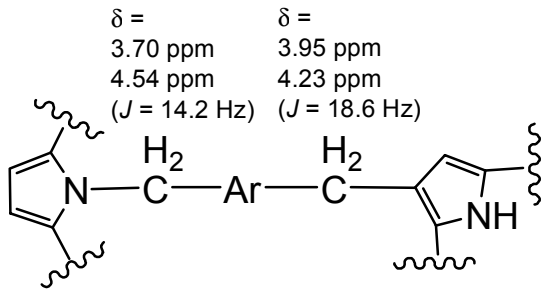


Figure 13. Proton chemical shifts of the phenylenedimethylene CH_2-protons in **122**

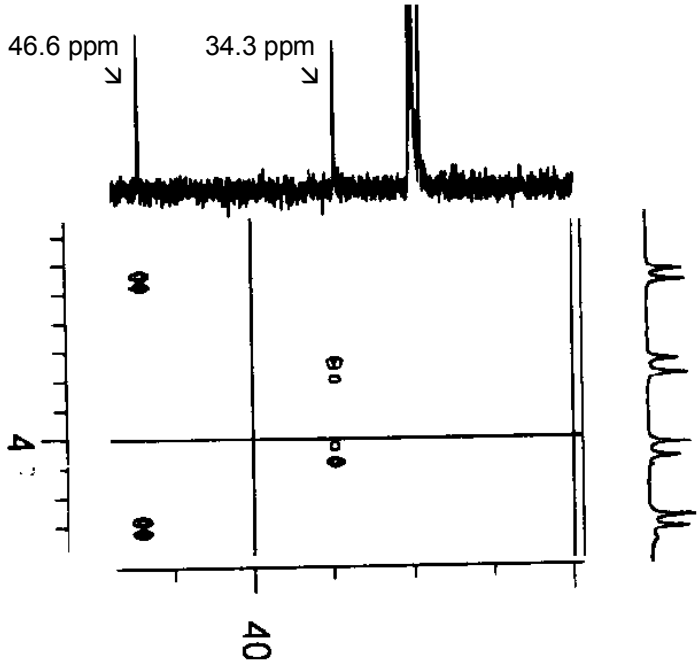
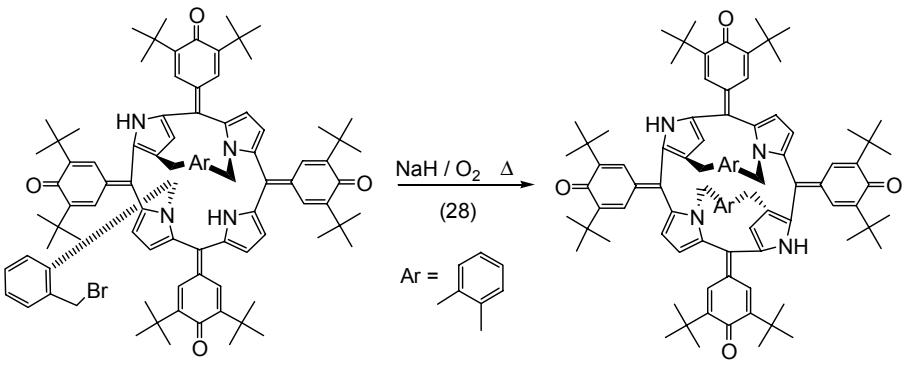


Figure 14. Part of the HMQC spectrum of **122** in $CDCl_3$ at 400 MHz for ^{1}H, 100 MHz for ^{13}C

system. The HMQC spectrum (Figure 14, p. 65) reveals a substantial difference between the carbon atoms of the two kinds of methylene groups (one being bound to a *nitrogen*, the other to a *carbon* atom), while at the same time showing the connectivity of the carbon and hydrogen atoms of the same groups. All this spectroscopic evidence supports the structure **122**. Attempts to prepare crystals suitable for X-ray structure analysis have so far not been successful.

Shortening the reaction (27) time to 14 h again afforded a relatively complex mixture of products, each formed in a rather low yield. Compound **122** was chromatographically isolated from the mixture in 3% yield. Some other products present in the mixture could be partly purified and characterized by electrospray mass spectrometry. The formation of some tetraalkylated porphotetramethene **118** was suggested in this way. Other spectra suggested the presence of monobridged products, with one or both of the remaining nitrogen atoms alkylated in the way as in **118**. The former case is plausibly represented by the structure **123** (Scheme 49). A small amount of this product was isolated by chromatography and treated with sodium hydride in refluxing acetone for several days (reaction (28)). TLC showed that a substantial amount of the starting material had been converted to the product **122**, confirming the structure of compound **123**. This also enabled isolation of a further amount of **122**, increasing its overall yield from the two reactions to 4%.



123 **122**

Scheme 49. Conversion of a partially bridged product

1. 2. 4. Preliminary experiments in microwave-assisted synthesis of *N*-alkylated porphotetramethenes

Two of the oxidative *N*-alkylations of porphyrin **1** described above, namely reaction (8) (Scheme 32, p. 49) with ethyl bromoacetate and reaction (7) (Scheme 31, p. 48) with benzyl bromide which had been performed in the 'classical' way, *i.e.* by heating of the reaction mixture in an oil bath, have also been preliminary carried out using microwave heating in a specially designed reactor. This method is known to generally

speed up chemical reactions significantly, while sometimes also imparting other effects.

In a typical procedure used in this work, a mixture of 10 – 20 mg of porphyrin **1** and an excess of sodium hydride (~20 equivalents) in 1 – 2 ml of solvent were stirred under air for several minutes. An excess of the alkylating agent (25 equivalents) was then added, the tube was sealed and the mixture was exposed to microwave heating (P = 100 W) in a number of 5 min turns (usually one) at a defined temperature. After each turn, a small sample of the reaction mixture was diluted and analysed by thin layer chromatography. However, the reaction mixtures were only checked by TLC and no attempt has been made to isolate and fully characterize the products or to precisely determine their quantities.

In reaction (8) in acetone the main product was always the dialkylated compound **96** with a substantial amount of the unalkylated precursor **86** remaining and a small amount of tetraalkylated product **90**. Better results were achieved with DMF (at 100°C), where the main product was compound **90** after 5 min of reaction.

Reaction (7) gave similar results in acetone. The reaction could nevertheless be driven virtually to completion in DMF at 100°C after two 5-minute turns. DMSO and acetonitrile gave inferior results, while ethyl acetate and *p*-xylene proved unsuitable. An interesting result was obtained with ^{t}BuOK in THF at 100°C, where by far the strongest spot on the TLC plate after 5 min of reaction was that of dialkylated compound **94**.

Generally, the use of microwave heating didn't noticeably improve the yields (even after prolonged exposure) and was limited to small amounts of starting porphyrin **1**. Still, the possibility to accumulate a desired product trough a number of batches under appropriate conditions remains attractive due to a very short running time of the reactions performed in this way. No further work has been done to optimize this method.

1. 3. Conclusion

Oxidative *N*-alkylation of tetraphenolic porphyrin **1** has been thoroughly investigated. It has been shown that this interesting reaction can be carried out with a number of alkylating agents and under various sets of experimental conditions. Usually, mixtures of partially alkylated products were obtained. Acetone proved to be the best solvent for alkylations with *t*-butyl bromoacetate and also gave very satisfying results in the experiments with benzyl bromide, where the reaction could be brought to completion. The main product of the reaction of compound **1** with ethyl bromoacetate in this solvent was the dialkylated derivative **96**. The yield on the fully *N*-alkylated porphotetramethene **90** could be increased by carrying out the reaction in DMF at elevated temperature. However, significant formation of by-products due to transesterification of compound **90** was observed in this case.

The degree of *N*-alkylation of the resulting porphotetramethenes could be controlled and either di- or tetraalkylated derivatives have been

obtained in high yields. These products are generally favoured over the mono- and trialkylated derivatives, respectively. The yields of the known compounds have been improved in relation to the results described in the literature.

A number of mixed alkylation products have been prepared by reacting partially alkylated compounds with another alkylating agent. These reactions typically resulted in fully alkylated products bearing different substituents on the core nitrogen atoms. This substantially expands the scope of this type of reaction. A strapped derivative **122** which is doubly bridged in an unusual way could also be formed in low yield.

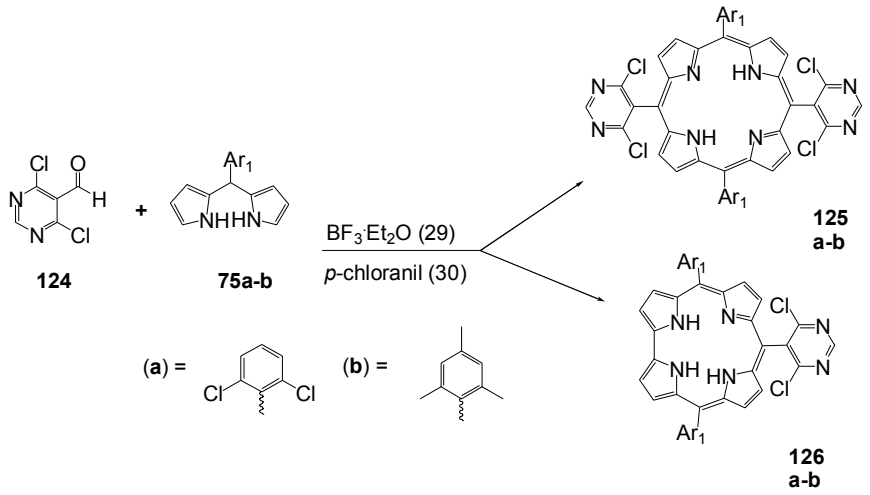
Most of the products were isolated by column chromatography and completely characterized by ^{1}H and ^{13}C NMR spectroscopy, electrospray mass spectrometry and UV-Vis spectroscopy.

Chapter 2

Sterically encumbered triarylcorroles by acid catalysed condensation of dipyrromethanes and aromatic aldehydes: synthesis, derivatization and application

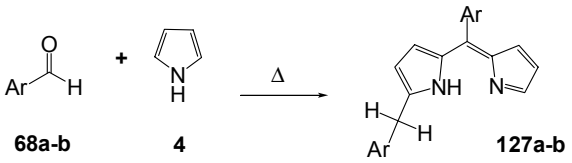
2. 1. Introduction

Interest in the synthesis of corroles in our laboratory was triggered by another unexpected result. As part of a project to prepare porphyrin derivatives **125** of 4,6-dichloropyrimidine-5-aldehyde **124**, a MacDonald condensation (29) of a 1:1 mixture of **124** and (2,6-dichlorophenyl) dipyrromethane **75a** was tried (Scheme 50). Surprisingly, the only identifiable product formed (in 25% yield) after *p*-chloranil oxidation (30) was the corrole **126a**, with no traces of the corresponding porphyrin **125a** detected.[120,121]



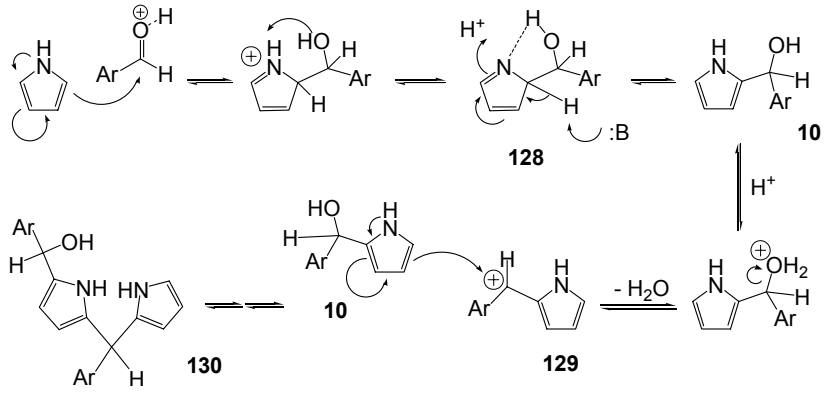
Scheme 50. Corrole *vs*. porphyrin formation in the reaction of **124** and dipyrromethanes

On the other hand, a reaction under the same conditions of **124** with mesityldipyrromethane **75b** gave only the porphyrin **125b**. These results, although intriguing, can be seen as analogous to Gross' data describing preferential formation of corroles from pyrrole and electron-poor *ortho,ortho'*-disubstituted benzaldehydes.[96,97] In Gross' original work,[97] yellow arylmethyldipyrromethenes **127** were identified as by-products (yield < 1%) of such reactions (Scheme 51; interestingly, **127b** crystallizes in a 1:1 ratio of two tautomers, each possessing one pyrrole and one pyrrolenine unit).



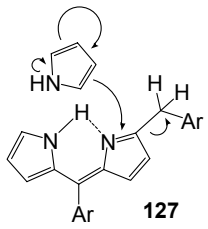
Scheme 51. (**a**) Ar = pentafluorophenyl; (**b**) Ar = 2,6-dichlorophenyl

The reacting species when pyrrole and aldehydes are condensed in acid is the carbonium ion **129**,[122] formed when the aldehyde attacks the α-position of the pyrrole. This is followed by loss of water from the key carbinol intermediate (**10**; Scheme 52). This ion **129** further attacks the free α-position of another pyrrole-carbinol **10** to provide dipyrromethane **130**. Chain propagation continues in the same general way (oligopyrrolic species can also react with each other) to produce open-chain oligopyrrolic products containing various numbers of pyrrole residues. These products can be present at various stages of oxidation. The tetrapyrrolic carbinols eventually cyclize to give reduced cyclic tetrapyrroles that are subsequently oxidized to the final aromatic macrocycle.



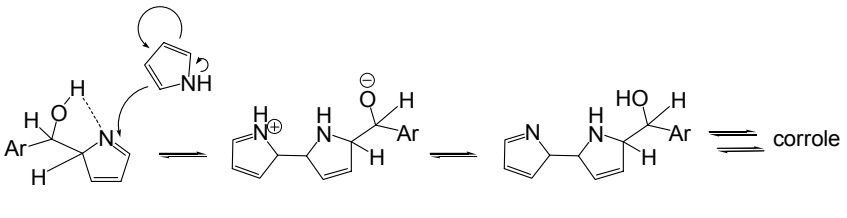
Scheme 52. Reaction mechanism of condensation of pyrrole with aromatic aldehydes

Gross and co-workers argued that dipyrromethenes **127** could be "dead end products" on a mechanistic pathway to porphyrins which is similar to that described above.[97] More importantly, they also suggested that **127** might be precursors of corroles (**69**) by providing an electrophilic site (H-bound imine) for attack by pyrrole with pentafluorophenylmethylene as an anionic leaving group (Scheme 53). This proposal provides an explanation for the fact that, in their case at least, corroles are formed only



Scheme 53. Nucleophilic attack of pyrrole on dipyrromethene **127**

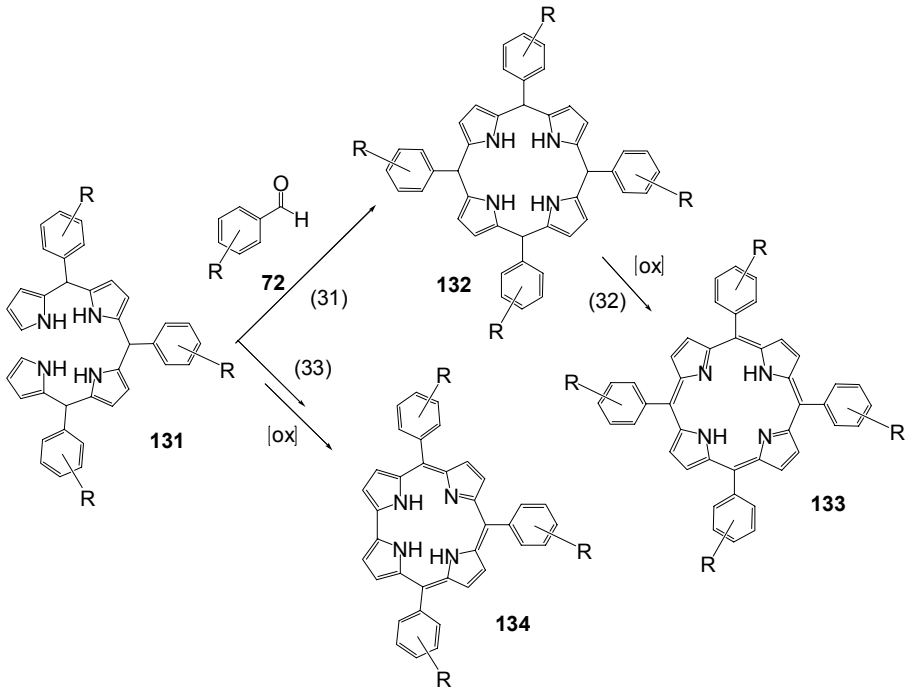
from electron-deficient aldehydes. They proposed other possibilities, too. For example, other imine intermediates such as **128** are certainly formed during the reaction. Stabilized by intramolecular H-bonding between the imine nitrogen and the acidic OH (for Ar = C_6F_5), intermediate **128** can accumulate in quantities sufficient to promote the reaction pathway shown in Scheme 54, triggered by pyrrole attack on **128**, eventually leading to corrole.



128

Scheme 54. Formation of corrole from imine **128**

Whatever the actual mechanism of these oligopyrrole formations might be, some authors agree[99,101,105] that the crucial tetrapyrrolic intermediate on the pathway to the corrole ring is tetrapyrromethane (*tetrapyrrane* or *bilane*) **131**. Compounds of this general structure have recently been isolated by Lee and co-workers[100] for the first time and successfully converted to corresponding corroles, confirming this hypothe-



Scheme 55. Role of tetrapyrromethane **131**

sis. If this intermediate **131** reacts (31; Scheme 55, p. 72) with a further molecule of aldehyde **72**, porphyrinogen **132** is formed. This product affords the parent porphyrin **133** by subsequent oxidation (32). In contrast, in corrole synthesis, **131** is subjected to oxidative ring closure (33) to afford the final product **134**. Which of these two pathways will be preferred is governed by a number of factors. Paolesse[99] explains preferential formation of corroles from electron-poor aldehydes in a modified Rothemund synthesis by high reactivity of the latter and therefore their rapid disappearance from the reaction mixture. In this case, there is little residual aldehyde **72** in the reaction mixture for **131** to react with and less **132** can be formed. This results in the absence of porphyrin as a reaction product and higher yields of corrole. However, syntheses of a number of corroles from aldehydes possessing electron-donating substituents are reported in the same paper, albeit in lower yields.

The pyrrole/benzaldehyde molar ratio is another critical factor. The highest corrole yields were obtained using a 3:1 ratio with significant formation of porphyrins and open-chain polypyrroles at lower and higher ratios, respectively. The reaction failed in the case of 2,6-disubstituted benzaldehydes, which could be ascribed to steric factors that prevent formation of the intermediate **131**.[99]

Only months later, Gryko and Jadach published an extensive study on the synthesis of *trans*-A_2B-corroles from dipyrromethanes and aromatic aldehydes in a modified Lindsey procedure.[105] Various starting compounds furnished corroles in moderate to good yields, regardless of the electronic nature of their substituents. Even sterically hindered aldehydes reacted equally well. Nevertheless, corresponding *trans*-A_2B_2-porphyrins were always present as minor side-products. Recently, Paolesse and co-workers applied a similar procedure to the synthesis of various triarylcorroles directly from pyrroles and aldehydes with similar results, but with no porphyrin formation observed.[101]

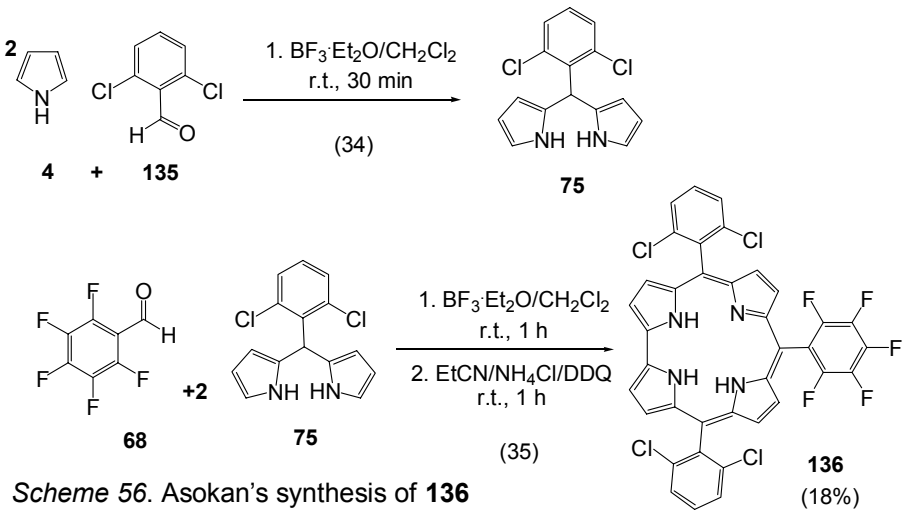
The course of conversion (33) (Scheme 55, p. 73) raises more questions. Whether **131** is first transformed, through coupling of the adjacent pyrrole rings, to a reduced corrole precursor (analogous to **132**) which is then oxidized to **134**, or oxidation occurs simultaneously with the ring closure, remains not fully clear. Yet it has been suggested that the former should be the case;[106] one of the terminal pyrrole rings should attack the other pyrrole terminus which has been protonated by the acid catalyst, with subsequent oxidation of the newly formed macrocycle. All these considerations taken together suggest that a lot of work is still needed to fully elucidate the mechanisms of corrole formation.

2. 2. Results and discussion

2. 2. 1. Synthesis and derivatization of *trans*-A_2B-corroles

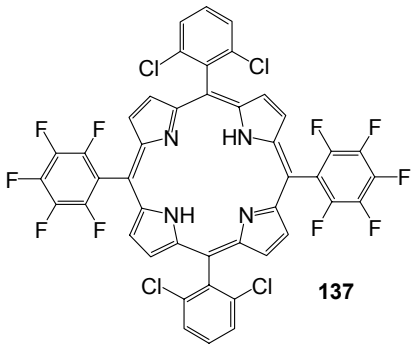
As a starting point for this work, 5,15-bis(2,6-dichlorophenyl)-10-pentafluorophenylcorrole **136** was chosen due to the fact that its synthesis had been carried out, but not optimized in our laboratory.[108] The synthetic

method that had been used was a modified Lindsey approach for the initial acid-catalyzed [2+2] condensation of 5-(2,6-dichlorophenyl)-dipyrromethane **75** (prepared by an acid-catalyzed condensation of 2,6-dichlorobenzaldehyde **135** and an excess of pyrrole) and pentafluorobenzaldehyde **68**. The crude product was not purified but subjected as such to oxidation with the Lee method[100] to afford corrole **136** in an overall yield of 18% (Scheme 56). We decided to further explore reaction (35).



Scheme 56. Asokan's synthesis of **136**

Only *trans*-A_2B_2-porphyrin **137** was formed in 23% yield, with no corrole observed, if the DPM **75**/aldehyde **68** molar ratio was ~1.5:1. No



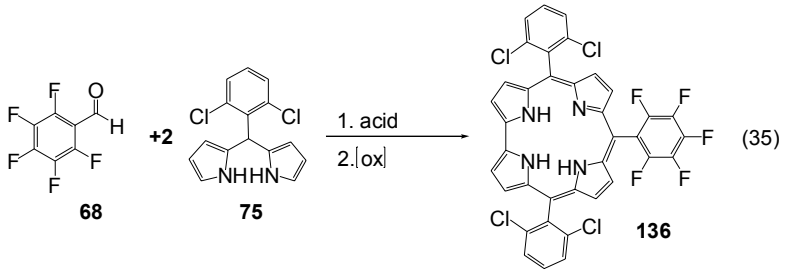
corrole was observed either even after extending the reaction time to 6 h if the ratio of **75** to **68** was kept roughly the same, but the concentration of both components was increased three times and a lower concentration of TFA was used as catalyst. While it is well known that the porphyrin-forming reaction as well as many other macrocyclization reactions require a rather low concentration of reactants to achieve a reasonable yield of product and a rather high concentration of acid is also needed for porphyrin formation, it appears from Gryko's work[104] that exactly the opposite, *i.e.* a

high concentration of reactants and a low concentration of acid catalyst is beneficiary if corroles are to be obtained. However, most probably due to the low DPM/aldehyde ratio, the reaction didn't afford any corrole while no porphyrin was not detected either.

Increasing the DPM/aldehyde ratio to 3:1 while also lowering the concentrations of the substrates and the acid catalyst at the same time provided the title corrole **136** in 9% yield with no observable formation of porphyrin **137**. With a further increase of the DPM/aldehyde ratio to 4:1 but using three times less the concentrations of the reactants than in the previous experiment, the yield of corrole **136** dropped only slightly (8%) but 11% of porphyrin **137** was also isolated from the reaction mixture. Also in this case Lee's method of oxidation, which generally seemed to have a beneficiary effect on the overall yield, was used.

Eventually, keeping relatively low concentrations of the substrates but increasing the DPM/aldehyde ratio to 5:1 (approaching the preferred DPM/aldehyde ratio of Briñas and Brückner corrole synthesis[107]) with a relatively low concentration of $BF_3{\cdot}Et_2O$ as the acid catalyst and using Lee-type oxidation, corrole **136** was obtained in 22% yield without detectable porphyrin formation.

One more experiment has been carried out with reaction (35), with similar concentrations of all components but with a significantly shorter re-



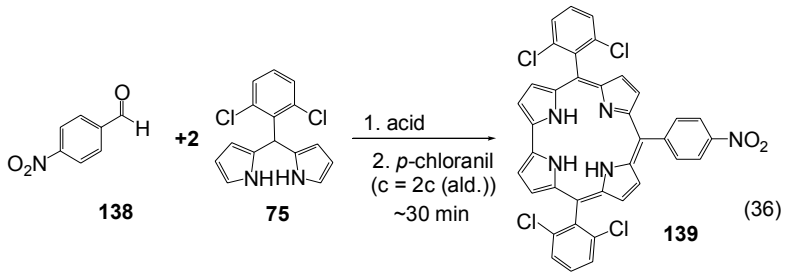
68 **75** **136** (35)

Entry	c(Ald.) /mM	Ratio DPM/ald.	Acid	Time of condensation	Oxidation	Yield, %	By-products, %
1	11.7	1.5	$BF_3{\cdot}Et_2O$ 10 mM	1 h	DDQ CH_3CH_2CN	0	**137** 23
2	34.2	1.5	TFA 16.4 mM	6 h	*p*-chloranil	0	-
3	17.9	3	TFA 5.9 mM	5 h	*p*-chloranil	9	-
4	5.9	3.9	$BF_3{\cdot}Et_2O$ 1.4 mM	1 h	*p*-chloranil NH_4Cl CH_3CH_2CN	8	**137** 11
5	**4.3**	**5.2**	**$BF_3{\cdot}Et_2O$ 1.6 mM**	**1 h**	***p*-chloranil CH_3CH_2CN**	**22**	**-**
6	3.5	6.4	$BF_3{\cdot}Et_2O$ 1.3 mM	30 min	*p*-chloranil CH_3CH_2CN	11	-

Scheme 57. Optimization of conditions for synthesis (35)

action time (30 min instead 1 h). In this case, the yield of corrole was also halved (11%) with some other pyrrolic side-products but no porphyrin detected. The results of using various conditions for reaction (35) are summarized in Scheme 57. The experiments were carried out under argon and at room temperature and oxidation was effected using 2 – 3 equivalents of indicated quinone for ~1 h. When an attempt has been made to characterize one or more by-products, this is also indicated in the Scheme.

Contrary to the synthesis of corrole **136**, preparation of 5,15-bis(2,6-dichlorophenyl)-10-(4-nitrophenyl)corrole **139** had not been accomplished using the conditions previously examined in the work in our laboratory.[108] Therefore, we decided to try out synthetic conditions similar to those described by Gryko and Jadach.[105] Reacting DPM **75** and *p*-nitrobenzaldehyde **138** in a 3.5:1 ratio in dichloromethane with trifluoroacetic acid as the catalyst with subsequent oxidation by direct addition of a two molar excess (with respect to aldehyde) of *p*-chloranil afforded corrole **139** in 6% yield (Entry 1, Scheme 58). However, several side-products formed. The most prominent of them was identified by NMR spectroscopy and mass spectrometry as 5,10,15-tris(2,6-dichlorophenyl)-

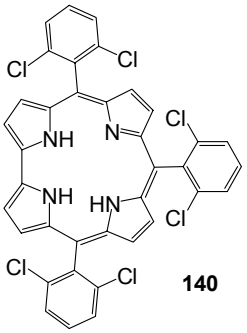


138 **75** **139** (36)

Entry	c(aldehyde) /mM	Ratio DPM/ald.	Acid	Time of condensation	Conditions	Yield, %	By-products, %
1	17.9	3.5	TFA 5.8 mM	5 h	r.t.	6	**140** 2*
2	11.9	3	TFA 0.9 mM	7 h	0°C	9	**140** 4*
3	11.9	3	TFA 0.9 mM	2 h	0°C	10	**140**
4	12.4	4	$BF_3 \cdot Et_2O$ 1.4 mM	3 days	0°C	4	
5	**11.1**	**3.2**	**CCl_3CO_2H 0.16 mM**	**1 day**	**0°C light protection**	**17**	**140 2*** **open chain product(s) ~10%** **A_2B_2-porphyrin, traces**
6	11.8	3.1	CCl_3CO_2H 0.15 mM	6 h	0°C light protection	12	**140**

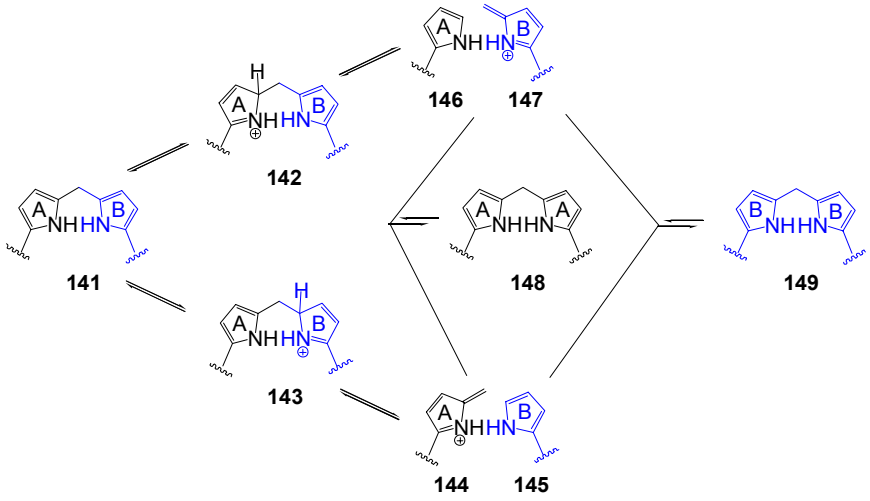
*with respect to **75**

Scheme 58. Optimization of conditions for synthesis (36)



140

corrole **140**. Its formation can be explained by acid-induced 'scrambling' or 'redistribution' of the pyrrole rings of the oligopyrrolic intermediates (Scheme 59). This is caused by acidic reagents which are used to effect macrocyclization. It is known that the more saturated species (such as bilanes and bilenes) are particularly susceptible to this phenomenon, due to notorious instability of the dipyrromethane link to acids, particularly when it lacks stabilizing electronegative substituents on adjacent pyrrole rings.[39] Protonation at either the 4- or 6-positions of a dipyrromethane **141** bearing two different rings, A and B, can give either **142** or **143**. Of course, deprotonation of each causes reversion to **141**, but fragmentation can (and does) also occur, giving rise to the species **144** – **147**. Nothing prevents these species from recombining in the 'wrong' way to give new dipyrromethanes **148** and **149**. Since all of the reactions in Scheme 63 are reversible, it is clear that treatment of the A-B dipyrromethane **141** with acid eventually gives an equilibrium mixture of the A-B, A-A and B-B forms. Additional factors, such as substituents on the pyrrole rings, can affect this equilibrium, but in principle complex mixtures can form if diffe-

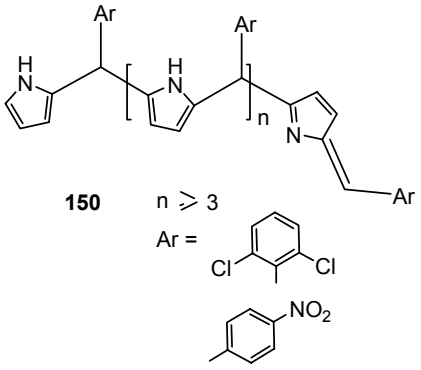


Scheme 59. Acid-catalyzed scrambling of pyrrole rings in dipyrromethanes. For better clarity, the A and B rings are depicted in different colours

rent substituents are present in the system. This has been extensively documented in the literature.[39]

To avoid the phenomenon of scrambling, which is a kinetic process, we decided to carry out further experiments at 0°C. However, this did not suppress this unwanted side reaction and corrole **140** could always be observed and isolated in 1 – 2% yield with respect to the starting dipyrromethane **75**. Using a strong acid TFA rather than boron trifluorate etherate as the acid catalyst is probably responsible for bringing about the formation of **140**.

Applying a lower concentration of trifluoroacetic acid (Entry 2, Scheme 58, p. 77) caused an increase in the yield of the title corrole **139**, in agreement with Gryko's findings.[105] Monitoring the reaction by TLC suggested it was probably completed earlier than in the indicated 7 hours. Indeed, shortening the reaction time to 2 h gave a similar yield of corrole **139**. In fact, carefully monitoring of reaction by UV-Vis spectroscopy (taking a sample of the reaction mixture, diluting it with CH_2Cl_2, oxidizing with a small amount of *p*-chloranil, preparing the UV-Vis sample by further dilution with CH_2Cl_2 and taking the spectrum; the absorption maximum of **139** is at 411 nm) suggested completion of the condensation reaction within 15 minutes. Nevertheless, when the reaction was repeated following the same procedure as for Entry 3 except a reaction time of 20 min, the product could not be separated from a red impurity. This non-fluorescing red band probably consisted, based on the results of electrospray mass analysis, of one or more open-chain **150**-type oligopyrroles suggested in the previous paper of our group.[108] In their seminal paper,[97] Gross and co-workers also isolated and described an orange-red pentapyrrotetramethene (oligomer composed of five pyrroles bridged by sp^2-hybridized carbon atoms) formed in large yield as a by-product of corrole synthesis. This result indicates that the 'normal' pathway towards pyrrolic oligomers (Scheme 52, p. 72) still operates under the conditions of corrole synthesis.



$BF_3{\cdot}Et_2O$ has also been tested as the acid catalyst for reaction (36). 5,10,15-Tris(2,6-dichlorophenyl)corrole **140** was not detected among the reaction products, but the formation of the title product **139** was also severely impeded. Only 4% of **139** was isolated even after 3 days of reaction.

Using trichloroacetic acid (TCA) as the catalyst for reaction (36) so far provided the best yields of corrole **139**. However, reaction with the TCA in a concentration as low as ~1/80 compared to the concentration of the starting aldehyde **138** is sluggish and optimal yields of **139** are achieved only overnight. In this case, traces of the corresponding A_2B_2 porphyrin were also observed as well as a substantial amount of red oligopyrrolic material (its yield in mass units being about one third that of compound **139**).

Over the past several years, our laboratory has worked on development of sensor systems for small analytes in the framework of a collaboration with the group of Prof. Radecki from Olsztyn, Poland.[123] We have been particularly interested in macrocyclic hosts containing nitrogen atoms, like calixpyrroles. To expand the scope of this collaboration, we have decided to investigate the use of corroles, which have been being prepared in our laboratory since recently, as completely novel compounds for this purpose. Furthermore, they possess very interesting acid-base properties (they, unlike calixpyrroles, can exist as both anions and cations). Part of the project was the preparation of compounds which could be used to form self assembled monolayers (SAMs) on metal (gold) surfaces (Figure 15). This useful multipurpose approach[124] could be applied for designing a new class of corrole-based sensors (group X = corrole, Fig. 15). The synthesis of a novel corrole for this purpose did start

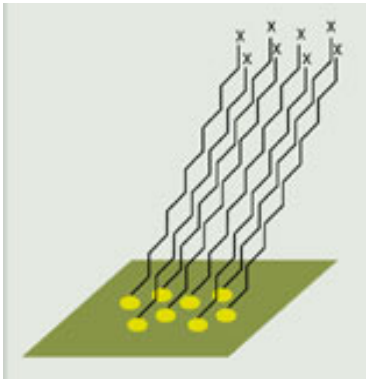
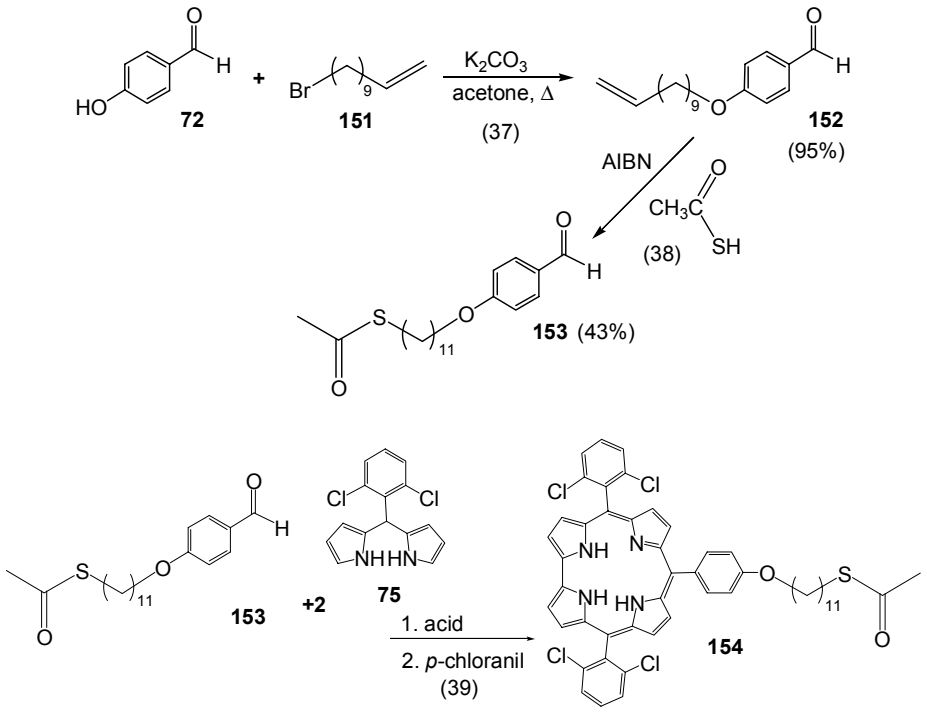


Figure 15. Functionalized simple carbon chains with sulphide groups on one end and functional groups of various types (X) on the other self-assemble to form ordered monolayers on gold surfaces

with the building of a suitable aldehyde[124d] for the condensation reaction (Scheme 60, p. 81). Commercial *p*-hydroxybenzaldehyde **72** was reacted (37) with 11-bromo-1-undecene **151** with potassium carbonate in refluxing acetone to afford aldehyde **152** in 95% yield. This product was converted to aldehyde thioacetate **153** *via* a radical promoted addition (38) of thioacetic acid. The yield was 43%.

With this product **153** in hand, the synthesis (39) of corrole **154** was also tried out in several different ways (Scheme 61, p. 81). The condensation reaction (39-1) tended to be rather slow in each case. The o-



Scheme 60. Synthesis of aldehyde thioacetate **153**

xidation was always performed by adding *p*-chloranil (2 molar equivalents with respect to aldehyde **75**) directly into the reaction mixture and stirring at room temperature for ~1 h.

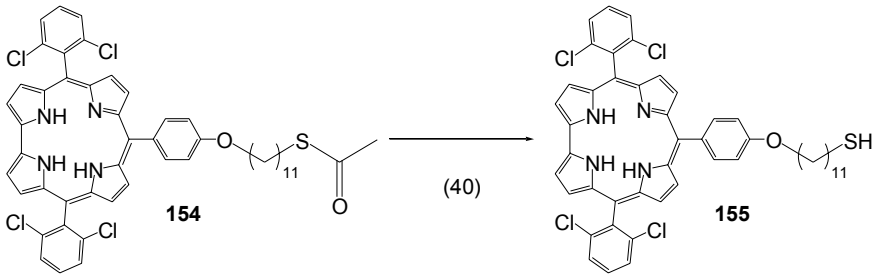
Entry	c(Ald.) /mM	Ratio DPM/ald.	Acid	Time of condens.	Conditions	Yield, %	By-products, %
1	11.8	3	TFA 0.9 mM	2 d	r.t. no Ar	13	**140** 4*
2	11.4	3.2	CCl_3CO_2H 0.18 mM	22 h	0°C light protection no Ar	10	**140** 2*
3	11.4	3.2	CCl_3CO_2H 0.18 mM	5 d	r.t. light protection Ar	8	**153**
4	**11.8**	**3**	**TFA 0.9 mM**	**2 d**	**0°C light protection Ar**	**29**	*with respect to **75**

Scheme 61. Optimization of conditions for synthesis (39)

The first experiment provided a moderate yield of corrole **154**. However, a lot of dipyrromethane **75** remained unreacted and a substantial amount of 5,10,15-tris(2,6-dichlorophenyl)corrole **140** was isolated from

the reaction mixture. Further experiments, performed with trichloroacetic acid, did not bring about any improvement, regardless of the experimental conditions. On the contrary, in the experiment 3, TLC showed the persisting presence of starting aldehyde **153** even after 5 days of reaction. In these experiments, the reaction flask was wrapped in aluminium foil throughout the condensation step to protect light-sensitive oligopyrromethane intermediates. Eventually, a combination of the protecting conditions (light exclusion, carrying out the reaction at 0°C and under an argon atmosphere) gave a very good yield of the title corrole **154** when applied to the original TFA-catalyzed reaction.

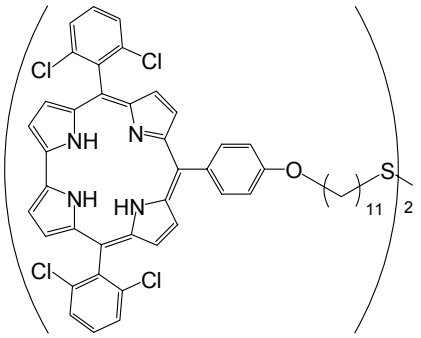
S-deacetylation (40) of corrole **154** (Scheme 62) was required to prepare compound **155** with a free thiol group, suitable for binding to gold surfaces. A first deacetylation attempt with sodium methoxide, followed by



Entry	Reagent(s)	Conditions	Time of (1)	Yield, %	By-products, %
1	1. CH_3ONa 2. HCl	0°C Ar (HCl at r.t.)	45 min	18	**156** 37
2	**1. CH_3ONa 2. HCl**	**0°C (HCl at r.t.)**	**30 min**	**21**	**156**
3	HCl	r.t. Ar	3 h	0	**154**
4	HCl conc.	r.t. Ar	1 d	0	**154**

Scheme 62. Optimization of conditions for reaction (40)

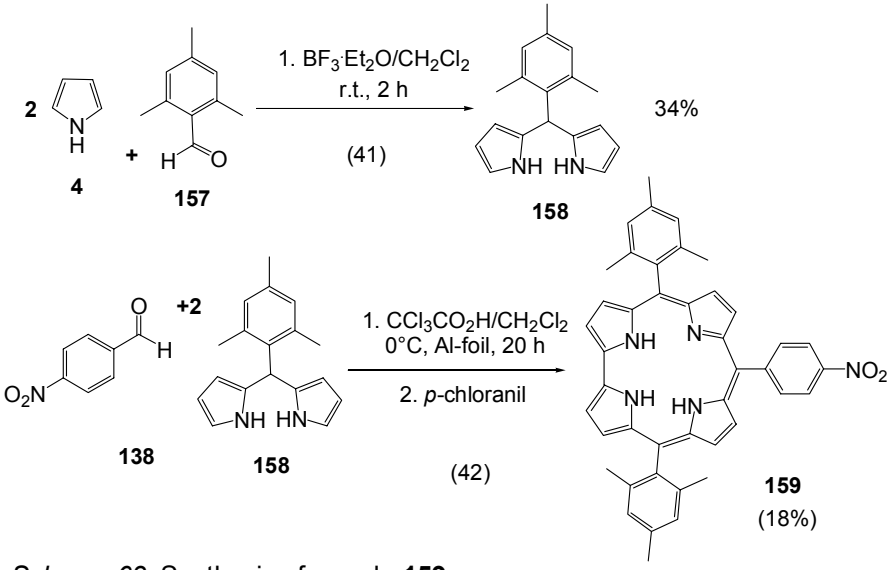
neutralization of the reaction mixture with HCl and isolation of the product (Entry 1), proceeded smoothly and no starting compound **154** remained after 45 min of reaction. However, careful TLC analysis showed that *two* compounds (giving spots very close to each other) were present in the product mixture. NMR and mass spectral analysis identified the major isolated product as dimeric disulphide **156**. This compound was not reconverted to thiol **155** for the reason mentioned in Section 2. 2. 2., p. 96.



156

Further experiments failed to give an increase in yield, whether or not carried out under argon. Shortening the reaction time by one third (Entry 2) improved the yield of **155** only slightly. As basic conditions should favour the oxidative dimerization, we have attempted to use hydrochloric acid as the deacylation reagent. Unfortunately, even after having treated corrole **154** with concentrated HCl for 24 h, the only macrocyclic compound identified in the reaction mixture was the starting material.

Syntheses of other corroles have been carried out. 5,15-Dimesityl-10-(4-nitrophenyl)corrole **159** has been prepared according to Scheme 63.

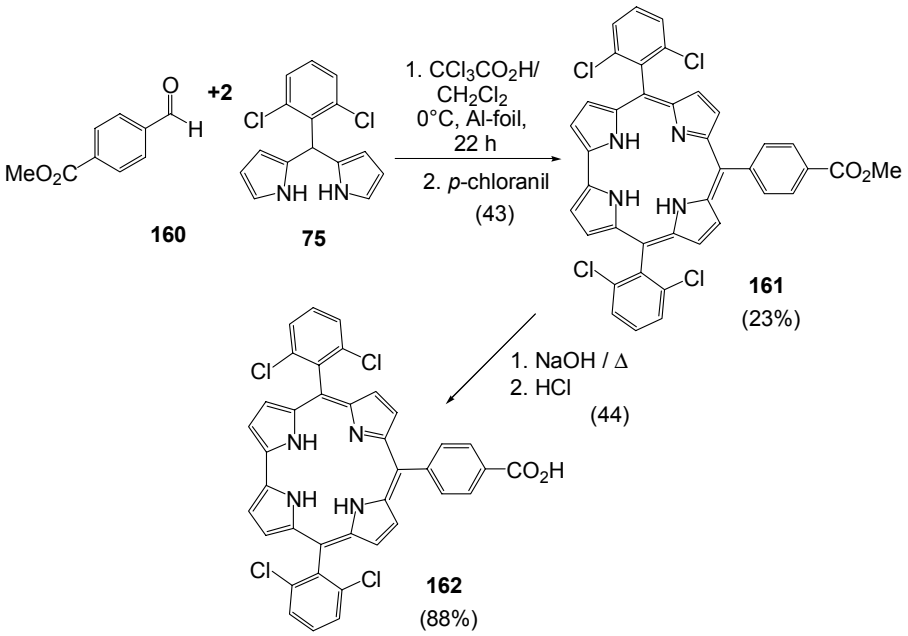


Scheme 63. Synthesis of corrole **159**

5-Mesityldipyrromethane **158** has been prepared analogously to **75**. This product was then subjected to trichloroacetic acid-catalyzed condensation with *p*-nitrobenzaldehyde **138** (in a concentration of 11.6 mM with 3.2 equivalents of **158** and 0.014 (1/71) equivalents of acid) for 20 h. Upon oxidation with *p*-chloranil in the usual way and purification by column chromatography and recrystallization, corrole **159** was isolated in 18% yield. Several minor products were observed on TLC, but only a few

milligrams of each could be isolated, making characterization difficult. Nevertheless, it can be said with certainty that none of these compounds is A_2B_2 porphyrin.

A novel corrole **161** has been synthesized from the corresponding aldehyde and pyrrole components using the same conditions as for reaction (42) (Scheme 64). The usual small amount (~1%) of 5,10,15-tris-



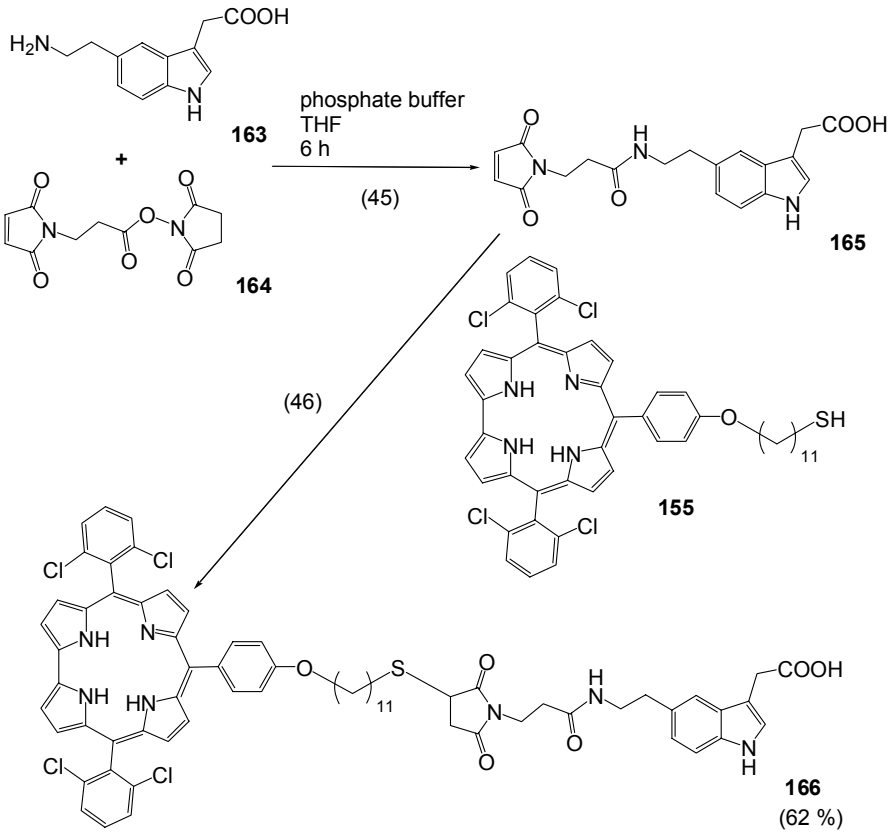
Scheme 64. Syntheses of corroles **161** and **162**

(2,6-dichlorophenyl)corrole **140** was isolated from the reaction mixture but the largest impurity was unreacted dipyrromethane **75** which could be chromatographically separated with some difficulty. The yield of the main product was rather high (for corrole synthesis) and several hundred milligrams (in one batch) of compound **161** could be collected and smoothly saponified to afford corrole acid **162** in a high yield.

Another collaboration project has been envisioned for application of selectively substituted corrole derivatives. In the framework of my MSc thesis in the laboratory of Dr. Magnus, Zagreb, Croatia, we developed a synthesis of indole-biotin conjugates (molecules possessing a biotin and an indole moiety separated by oligopeptide spacers of defined lengths) as molecular probes which should enable detection and isolation of indole-binding proteins, particularly enzymes included in the biosynthesis of plant growth hormone indole-acetic acid (auxin), from natural material.[125] The goal of this new collaboration is to prepare indole-corrole conjugates, which could be used in the same way. Detection would be achieved in this

case by measuring fluorescence of the corrole part of the probe. Corroles display strong fluorescence[57,101] in a wavelength range well beyond that of natural protein fluorescence based on tryptophan residues.[126]

Corrole **155** was chosen for this purpose, since it contains a long alkyl chain which can function as a necessary spacer. 5-Aminoethylindole-3-acetic acid **163**, synthesized in the laboratory of Dr. Magnus, was sub-

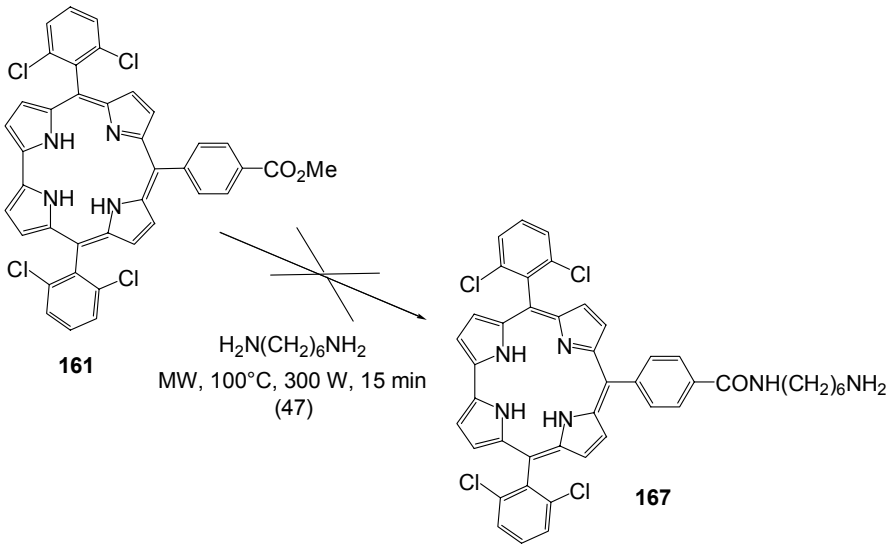


Scheme 65. Synthesis of indole-corrole conjugate **166**

jected to a reaction (45) with the commercial bifunctional reagent **164** in phosphate buffer. This afforded **165** in quantitative yield. This product was not isolated. By mixing (46) of solutions of **155** in THF and **164** in phosphate buffer the desired conjugate **166** was obtained in a good yield, as confirmed by NMR and ESI MS spectroscopy (Scheme 65).

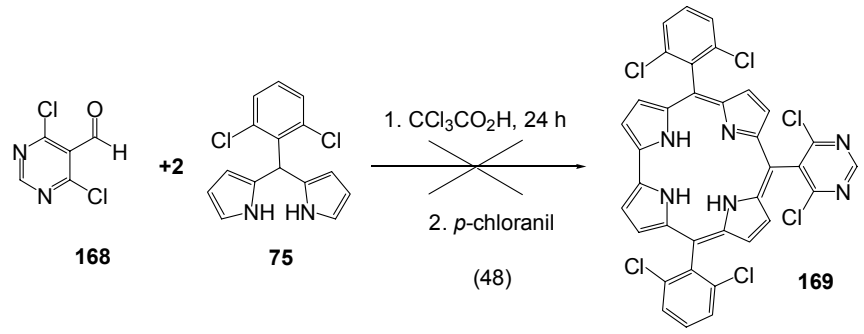
An attempt to apply a different approach to indole-corrole conjugates has also been tried out. The idea was to use the reactivity of the side ester group in corrole **161** to attach a precursor of the future spacer *via* an amide bond. An appropriate indolic component would then been attached to the other side of the side chain in a similar fashion.

However, attempted melting of **161** with 1,6-diaminohexane in a microwave reactor (Scheme 66) did not afford the desired product **167**. It seems that mainly starting material in ionized form has been obtained *i. e.* the diamine is protonated by the corrole.



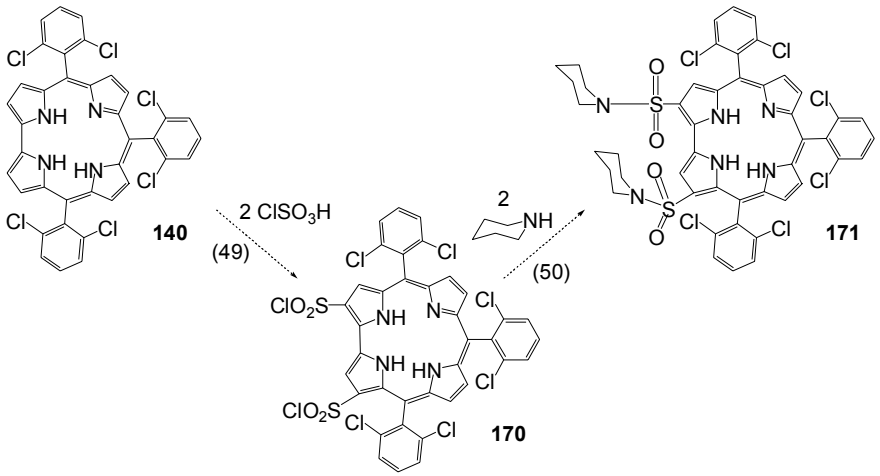
Scheme 66. Attempted synthesis of corrole **167**

Interestingly, only 5,10,15-tris(2,6-dichlorophenyl)corrole **140** (in 3% yield with respect to the dipyrromethane) was isolated as a product of attempted synthesis (48) of corrole **169**, that under different conditions[108] was formed in a high yield (Scheme 67).



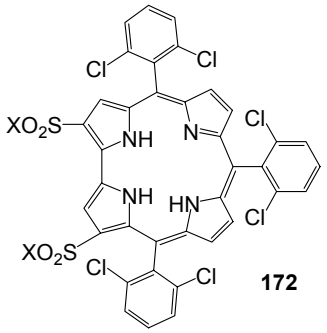
Scheme 67. Attempted synthesis of corrole **169**

Another troublesome experiment was an attempt to prepare corrole sulphonamides, *i.e.* corrole derivatives bearing strongly electron-withdrawing substituent groups which should increase the acidity of the inner-core NH-groups. This would expand the scope of using corroles as potentiometric sensors for small nitrophenolic analytes. Such corrole sulphonamides have recently been prepared by Gross' group from *meso*-tris-(pentafluorophenyl)corrole **69** and its gallium(III)-complex *via* a simple two-step sequence utilizing commercial reagents.[127,128] In my hands, when trying to repeat the same reaction sequence with 5,10,15-tris(2,6-dichlorophenyl)corrole **140** (49, 50; Scheme 68), unexpected problems were encountered. Separation of the organic and aqueous phases after reaction (49) proved rather difficult, with most of the corrole in the aqueous layer, as could be seen by its green colour. According to another recent paper of the Gross group,[129] disulphonato derivatives of corrole **74** remain neutral only in quite a limited pH range (2.5 – 5.2), with protonation and deprotonation progressing readily below and above these values, respectively. Strong quenching of red corrole fluorescence at low pH values (due to extensive protonation) is reported in the same paper. This effect was also observed here while working on the compounds presented in Scheme 68. It is quite probable that protonated **170** remains in the aqueous layer because of its high polarity. By basifying the suspension (49), some green colour could be extracted into the dichloromethane layer. However, addition (50) of piperidine to that solution apparently did not afford compound **171**, as seen in mass spectrometry. In the mass spectrum of one of the fractions, a peak corresponding to the structure **172** was observed, suggesting that most probably partial or total hydrolysis of intermediate **170** occurred.



Scheme 68. Planned synthesis of sulphonamide **171**

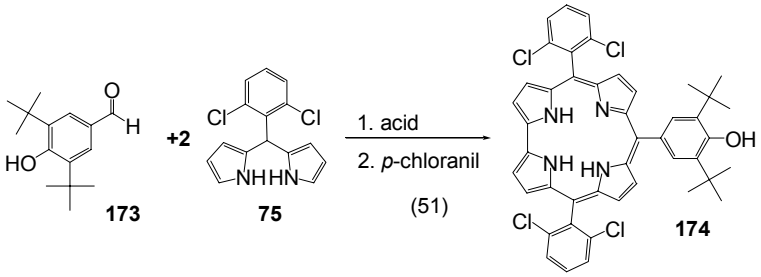
Finally, prompted by the interesting results of oxidative *N*-alkylation of porphyrins described in Chapter 1 of this thesis, we reasoned that the



172

1X = OH
1X = Cl

same type of reaction could be carried out with corroles, which would give a new class of macrocyclic compounds. For that purpose, ostensibly a synthesis of *meso*-hydroxyphenyl substituted corroles was necessary. Such procedures are hardly documented in the literature. Gryko and Jadach[105] reported a synthesis of a broad array of corroles under optimized conditions. Starting from (among other dipyrromethanes) 5-mesityldipyrromethane **158**, a number of corroles were prepared in moderate to good yields (10 – 22%), except from 3-hydroxybenzaldehyde, where the product was obtained in only 3% yield. It is possible that an oxidation of the final product *via* a radical mechanism takes place in this case.

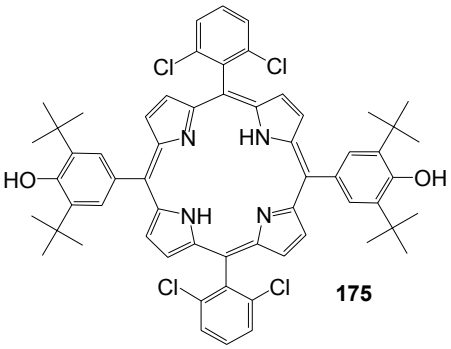


173 **75** **174**

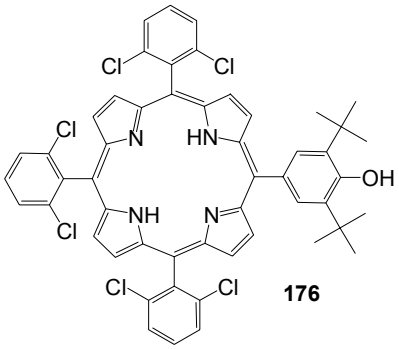
Entry	c(Ald.) /mM	Ratio DPM/a.	Acid	Time of condens.	Conditions	Ox.	Yield, %	By-products, %
1	11.6	3.2	CCl_3CO_2H 0.19 mM	1 d	0°C light protection no Ar	*p*-chl. 2 eq.	0.2	**140** 2*
2	4.4	5	$BF_3{\cdot}Et_2O$ 1.27 mM	1 h	r.t. light protection Ar	*p*-chl. in CH_3CH_2CN	-	**175** 12.0 **176** 2.8
3	21.9	1	$BF_3{\cdot}Et_2O$ 6.35 mM	1 h	r.t. light protection Ar	*p*-chl. in CH_3CH_2CN	-	**175** 0.3 **176** 0.7
4	**15.3**	**3**	**TFA 2.8 mM**	**2 d**	**r.t. light protection Ar**	***p*-chl. 2 eq.**	**30**	**175** **0.7** *with respect to **75**

Scheme 69. Optimization of conditions for synthesis (51)

Attempted synthesis (51) of compound **174** from commercial aldehyde **173** and dipyrromethane **75** (Scheme 69) afforded only traces of the title product when trichloroacetic acid was applied as the acid catalyst (Entry 1). As indicated by TLC, most of the dipyrromethane remained unreacted under these conditions. Using boron trifluoride etherate in higher concentrations and Lee's oxidation method (Entries 2 and 3) lead to significant formation of A_2B_2- and A_3B-porphyrins **175** and **176**. No corrole was detected in these experiments. In one case (Entry 2), with lowered concentrations of starting compounds, the porphyrins were obtained in rather high yields, even though the DPM/aldehyde ratio should have strongly favoured corrole formation. This turned out to be actually a good method for preparation of porphyrin **175**.

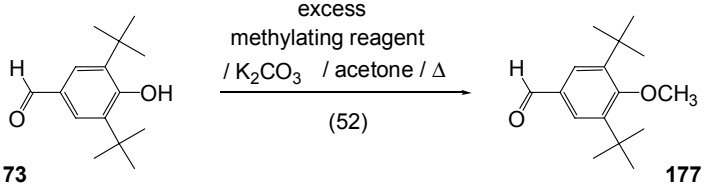


175



176

The failure to obtain large amounts of the desired corrole **174** was first attributed to an oxidation of the bis-*t*-butyl-*p*-hydroxyphenyl substituent. Therefore we tried to methylate aldehyde **173** in different ways to obtain compound **177** with a methoxy substituent which should be stab-



173 **177**

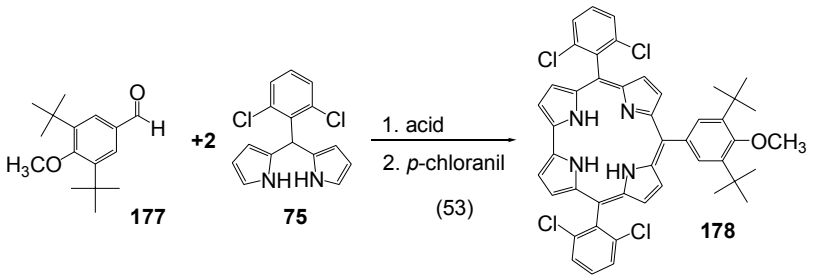
Entry	Methylating reagent	Extra	Time	Yield, %
1	$(CH_3)_2SO_4$		6 h	16
2	$(CH_3)_2SO_4$	18-c.-6	5 d	0
3	$(CH_3)_2SO_4$	argon	1 d	18
4	$(CH_3)_2SO_4$	DMF, 90°C argon	2 d	0
5	**$(CH_3)_2SO_4$**		**42 h**	**40**
6	**CH_3I**		**41 h**	**32**

Scheme 70. Optimization of conditions for reaction (52)

le to oxidation in subsequent corrole synthesis.

This methylation (52) of sterically hindered aldehyde **173** did not proceed smoothly (Scheme 70, p. 89). Dimethyl sulphate as the methylating agent[130] was examined several times and gave 40% yield of *p*-methoxy aldehyde **177** in one case (Entry 5). However, the same conditions were used more than once and the results were highly irreproducible. Much better reliability was achieved with the use of methyl iodide.[131] The yields were rather low (usually 20 - 32 %), but reproducible.

With aldehyde **177** in hand, synthesis (53) of the corresponding corrole **178** has been attempted under the usual conditions (Scheme 71). In each case, the oxidation was carried out by adding 2 equivalents (with respect to aldehyde **177**) of *p*-chloranil directly into the reaction mixture and stirring at room temperature for an additional half hour.



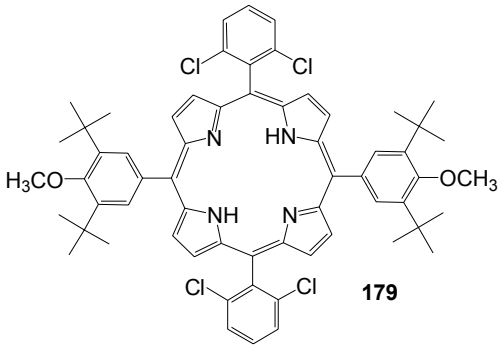
177 **75** **178**

Entry	c(Ald.) /mM	Ratio DPM/ald.	Acid	Time of cond.	Conditions	Yield, %	By-products, %
1	15.4	4	CCl_3CO_2H 0.22 mM	5 h	0°C light protection Ar	1	**140**
2	14.8	5.7	CCl_3CO_2H 0.19 mM	3.5 d	r.t. light protection Ar	-	**140**
3	15.5	3	TFA 0.93 mM	2 d	r.t. light protection Ar	23	**179** **140** traces
4	**15.3**	**3.2**	**TFA 2.75 mM**	**18 h**	**r.t. light protection Ar**	**27**	**179** **1.8** **some non-fluorescent green material**

Scheme 71. Optimization of conditions for synthesis (53)

If the condensation reaction in (53) is catalyzed by 1/80 – 1/70 eq. (with respect to aldehyde **177**) trichloroacetic acid, only small amounts of compound **178** could be observed. Most of the starting materials remained unreacted under these conditions.

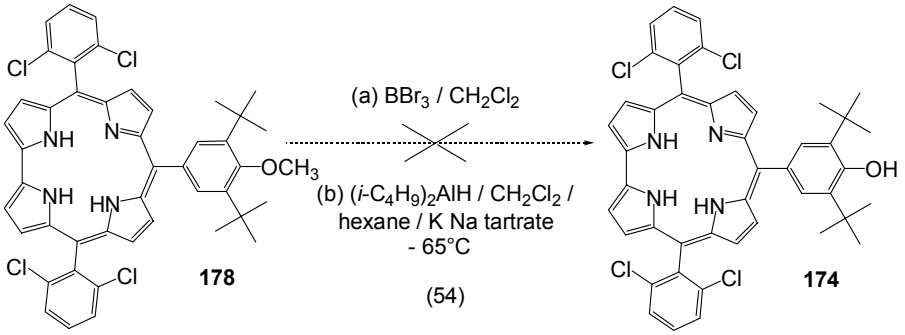
Applying TFA in higher concentrations changed the picture. Good yields of corrole **178** could be isolated upon column chromatography. In the synthesis which provided the highest yield of **178** a small amount of A_2B_2-porphyrin **179** was also isolated.



179

Demethylation (54) of **178** to afford the desired corrole **174** proved a difficult task (Scheme 72). Small amounts of boron tribromide[132] did not work, while adding more reagent promoted a side reaction, possibly bromination. No unambiguous characterization of the product has been achieved, although the mass spectra suggest it could be a mixture of brominated products.

Diisobutylaluminium hydride has been used as a general reducing agent in organic synthesis, including its application for cleavage of aromatic methyl ethers, *i.e.* demethylation of methoxy-aromatic compounds.[133] Nevertheless, it did not afford any product when tried out for reaction (54) as shown in Scheme 72. It seems that the steric hindrance of the methoxy group of **178** is the major factor inhibiting the reaction.



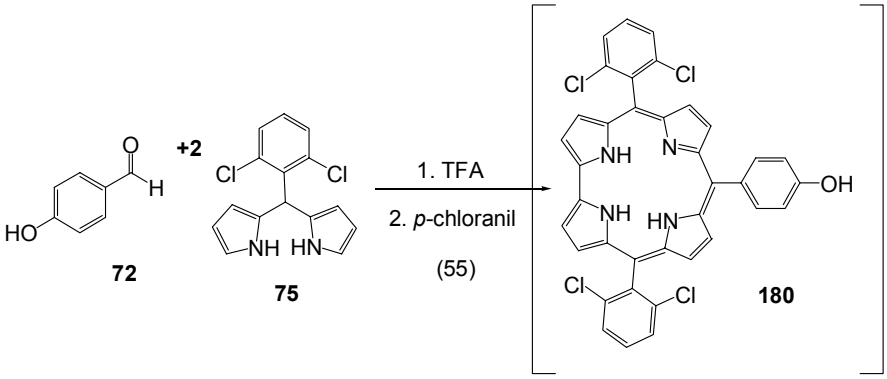
178 **174**

Scheme 72. Attempted demethylation of **178**

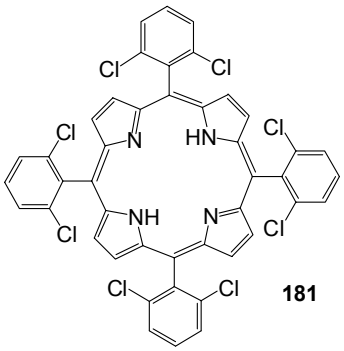
Eventually, we tried out trifluoroacetic acid for catalysis of the first step of the synthesis (51) (Entry 4, Scheme 69, p. 88). Upon oxidation with *p*-chloranil and purification, hydroxyphenylcorrole **174** was directly obtained in 30% yield.

Synthesis of the related corrole **180** (Scheme 73, p. 92) has also been attempted under exactly the same conditions as the conditions of choice for the preparation of **174** (Entry 4, Scheme 69). After a tedious chromatographic procedure, compound **180**, as apparent from NMR, could be isolated in yield as high as 34%. However, the product seems to be

rather unstable and could not be kept in pure form. The apparent yield after the next column chromatography (done 2 days after the previous yield estimation) was only 10%. A very small amount of *meso*-5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin **181** was also present among the reaction products, as confirmed by mass spectrometry.

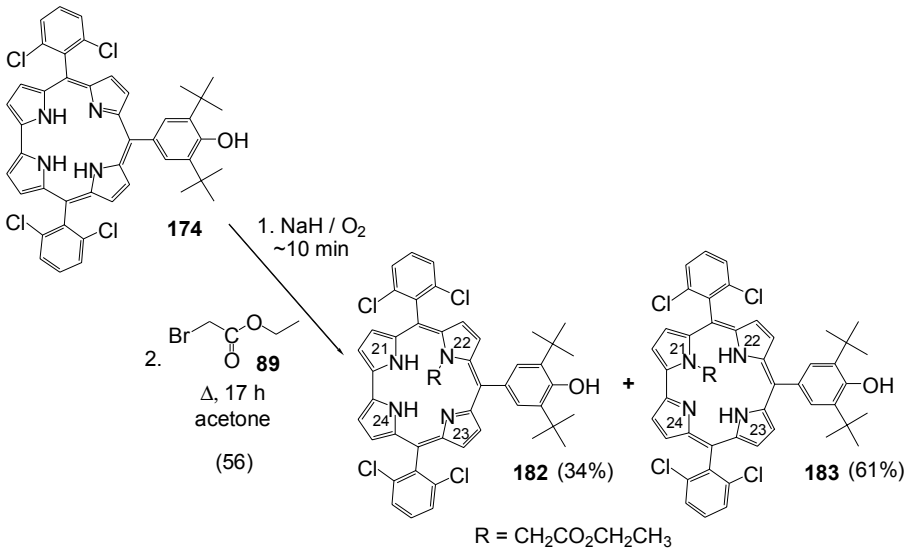


Scheme 73. Attempted synthesis of **180**



Once a good and reliable method for the synthesis of corrole **174** was established, it was possible to obtain enough of this product to serve as a substrate for the oxidative *N*-alkylation of the type described in Chapter 1. Reaction (56) has been attempted as reported in the general conditions in the Experimental part of that Chapter.

Within 15 min of the addition of the alkylating agent, the strongest spot on TLC was that of the starting compound **174** with no spot similar to that of the oxidized intermediate **86** in the analogous reactions of porphyrins. Running the reaction overnight changed the TLC picture into two (main) spots, one weaker, less polar green-brownish with a weak red fluorescence under 366 nm excitation and another stronger, somewhat more polar blue-greenish spot with strong red fluorescence. Upon isolation



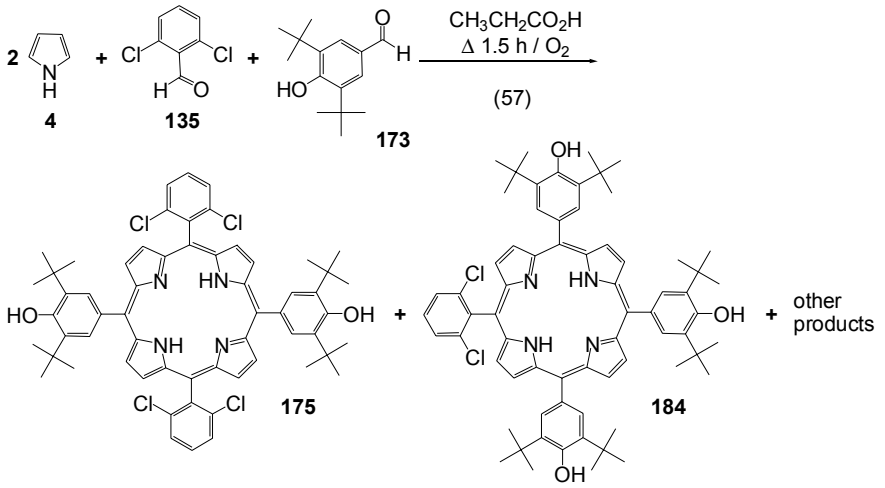
Scheme 74. *N*-alkylation of corrole. Numbering of the core nitrogen atoms is also shown

of the two products by column chromatography, it became rapidly clear that two isomeric *N*-alkylated non-oxidized corroles **182** and **183** in about 1:2 ratio had been obtained (Scheme 74).

Lack of porphyrin **1**-type conjugation inhibits formation of necessary intermediates on the oxidation pathway. Furthermore, this absence of oxidation provides one more argument against our original assumption that corrole **174** could not be obtained by synthesis (51) because of the sensitivity of the final product towards oxidation. The ability to introduce only one substituent moiety per macrocycle molecule reflects the much smaller size of the corrole central cavity (although *N,N'*-disubstituted corrole salts of limited stability have reportedly been prepared under more forcing conditions[46]). The distribution of the substituent groups over the core nitrogen atoms *i.e.* the ratio of the isomers is in accordance with the published research[46,134] It has been shown that substitution on N(22) of triarylcorroles results in a much more 'crowded' environment (as compared to the N(21)-substituted isomer), reflected in higher deformation of the corrole ring from planarity and of the *meso*-aryls from perpendicular orientation, rendering this isomer (**182** in this case) the less stable of the two.[135]

Finally, an effort has been made to prepare porphyrin **175** (and at the same time other related porphyrins, *e.g.* **176**) by a mixed condensation (57) of aldehydes **135** and **173** with pyrrole using Adler-Longo modification of the Rothemund procedure (Scheme 75, p. 94). To that purpose, a mixture of the two aldehydes was refluxed with pyrrole (**4**) in propionic acid for 1.5 h. Upon cooling of the reaction mixture and removing the acid by evaporation under reduced pressure and extraction, chromatographic separation of the products was attempted. A complete resolution of the

mixture has not been achieved due to its complexity and similar polarities of many of the component compounds. Nevertheless, it was observed that porphyrins **175** and **184** (as apparent from the mass and NMR spectra) had been formed in approximate yields of 3 and 5%, respectively.



Scheme 75. A mixed condensation of aldehydes **135** and **173** with pyrrole

2. 2. 2. Application of A_2B-corroles as host molecules for recognition of neutral nitrophenol isomers

Corroles **136**, **139** and **140** have been examined as host molecules for potentiometric measurements of neutral nitrophenol isomers in the laboratory of Prof. J. Radecki from Olsztyn, Poland. These compounds have been incorporated into liquid PVC membranes in a concentration of 1%. All membranes were able to generate potentiometric responses after stimulation with the neutral form of nitrophenols. The substituents around the corrole central cavity have no crucial effect on the response. The sensitivities of the membranes increase with decreasing the pH value of a sample solution. Changes of pH have no influence on the selectivity of responses towards the nitrophenol guests. Another characteristic property of the corrole membranes was very fast signal generation. The results are presented graphically in Fig. 16 (p. 95-96).[136]

Some corrole derivatives presented in this work have also been applied for gold modification in collaboration with the group of Prof. Radecki. Thus, compounds **154**, **155** and **156** had been used to prepare

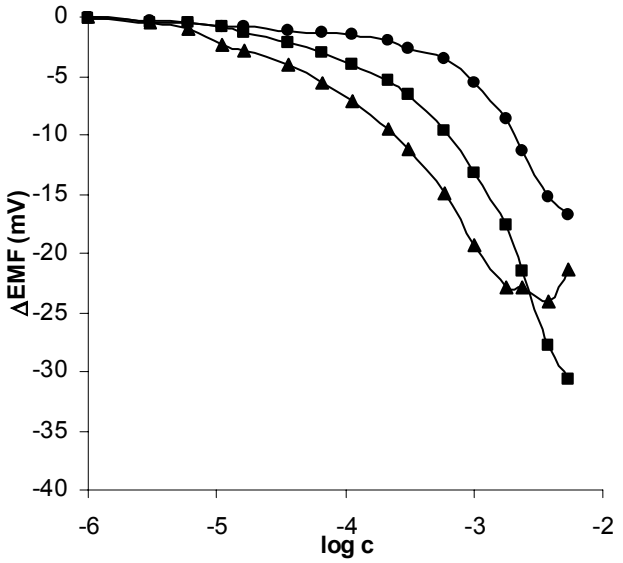


Figure 16a. Potentiometric responses of the membrane modified with **136** towards nitrophenol isomers at pH 4.0; ● = *o*-nitrophenol, ■ = *m*-nitrophenol, ▲ = *p*-nitrophenol

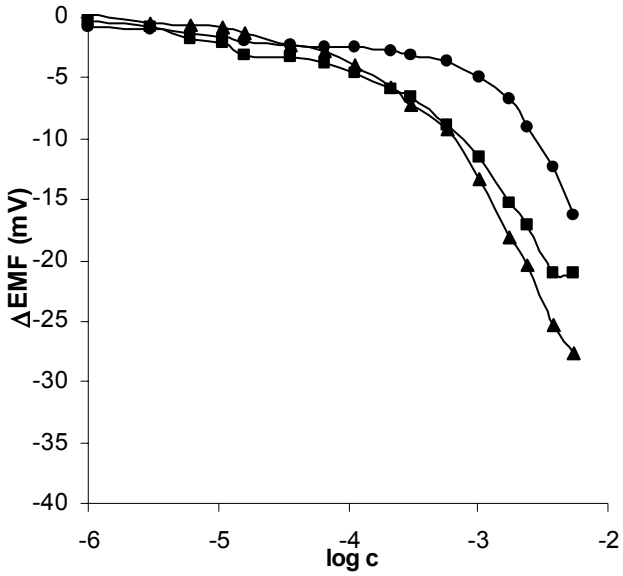


Figure 16b. Potentiometric responses of the membrane modified with **139** towards nitrophenol isomers at pH 4.0; ● = *o*-nitrophenol, ■ = *m*-nitrophenol, ▲ = *p*-nitrophenol

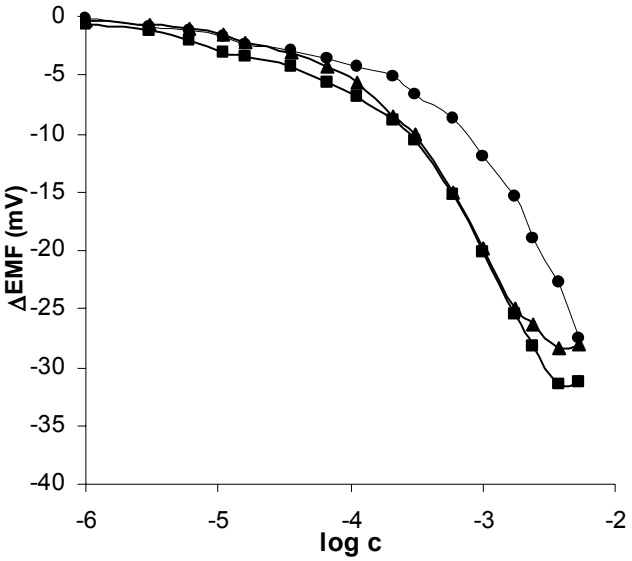


Figure 16c. Potentiometric responses of the membrane modified with **140** towards nitrophenol isomers at pH 4.0; • = *o*-nitrophenol, ■ = *m*-nitrophenol, ▲ = *p*-nitrophenol

SAMs, which have then been analyzed by several techniques. As expected, both corrole thiol (**155**) and disulfide (**156**) derivatives form well organized layers on gold, in contrast to corrole thioacetate (**154**). For this reason, no attempt has been made to convert disulfide **156** to thiol **155**. All corrole SAMs show response towards protons. The work on forming better ordered corrole-terminated SAMs and investigating their sensing capabilities is in progress.

2. 3. Conclusion

A number of aromatic *trans*-A_2B-corroles has been synthesized *via* several methods. Several new compounds have been prepared and the yields of some others, previously known from the literature, have been improved. Trichloroacetic acid (and in one case boron trifluoride etherate) was the acid catalyst of choice, giving best yields, for preparations of corroles from more reactive aldehydes possessing electron-withdrawing substituents (-C_6F_5, -$C_6H_4NO_2$, -$C_6H_4CO_2Me$), whilst the use of stronger trifluoroacetic acid was preferred with less reactive substrates with electron-donating substituents (-C_6H_5OR, $C_6H_2R_2(OCH_3)$, $C_6H_2R_2(OH)$, C_6H_4OH). Direct oxidation of the tetrapyrromethane formed, without its previous isolation, with adding an excess of *p*-chloranil into the crude reaction mixture, was the preferred method for the final oxidative ring closure.

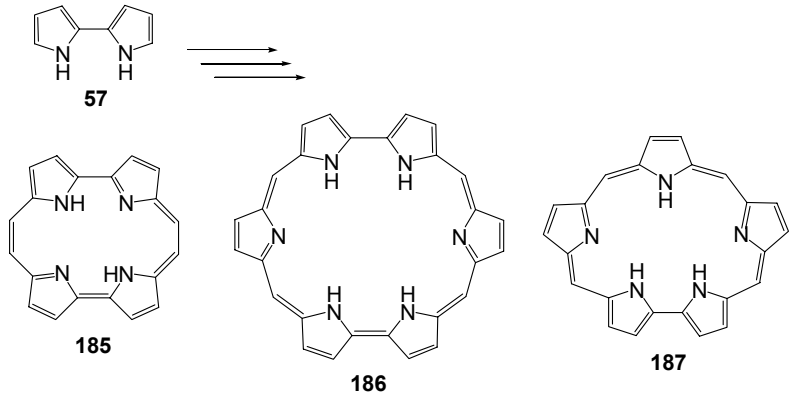
Corrole derivatives (**155**, **166**) for application in various analytical techniques have also been synthesized. Corrole-indole conjugate **166** should find its purpose in detection of indole-binding proteins in natural plant tissue (making use of strong and specific corrole fluorescence), whilst the use of corrole thiol **155**, bearing a long alkyl chain, for formation of self-assembled monolayers (SAMs) on gold surfaces is also being investigated. These SAMs should enable measurement of small analytes. A number of other corroles described herein have been successfully incorporated into liquid PVC membranes and applied for potentiometric measurement of neutral nitrophenol isomers. We are trying to prepare more acidic corrole ligands (compounds bearing electron-withdrawing substituents in one or more β-pyrrole positions) to enlarge the scope of this last application.

Chapter 3

Selective synthesis of 3,3′,5,5′-tetrasubstituted 2,2′-bipyrroles: towards the synthesis of porphycenes and polypyrroles

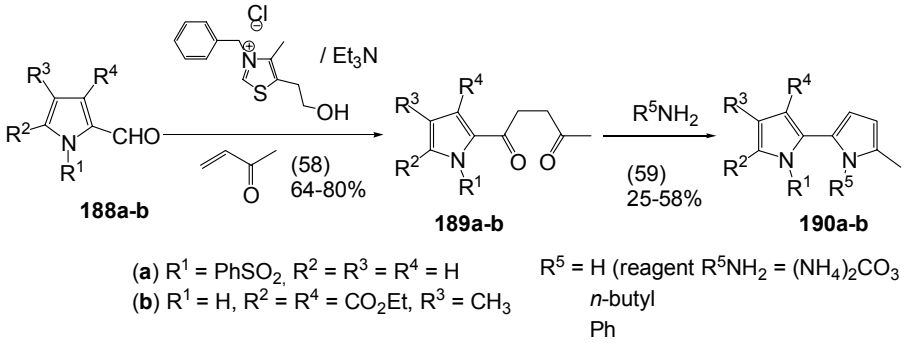
3. 1. Introduction

2,2'-Bipyrroles, *i.e.* dipyrrolic compounds containing the structural fragment **57**, are critical precursors in the syntheses of various porphyrin analoga, such as corrole, porphycene **185**,[137] rubyrin **186**,[138] sapphyrin **187**,[139] (Scheme 76) cyclo[8]pyrrole **55** [82,140] and other related compounds. The interest in these synthetic products lies mainly in the fact that they resemble porphyrins, sharing some of their features while at the same time differing in some other distinctive aspects. Therefore, research on their synthesis and electronic, ligand binding and other properties can and has contributed significantly to improve our knowledge and understanding of porphyrins, compounds of immense importance in Nature. But far from being just molecular 'guinea pigs' to mimic porphyrins, these 'contracted, expanded and isomeric' porphyrins have also found several applications in their own right. Uses in magnetic resonance imaging, photodynamic therapy (PDT) and X-ray radiation therapy enhancement, nucleic acid cleavage and anion binding have been described.[141]



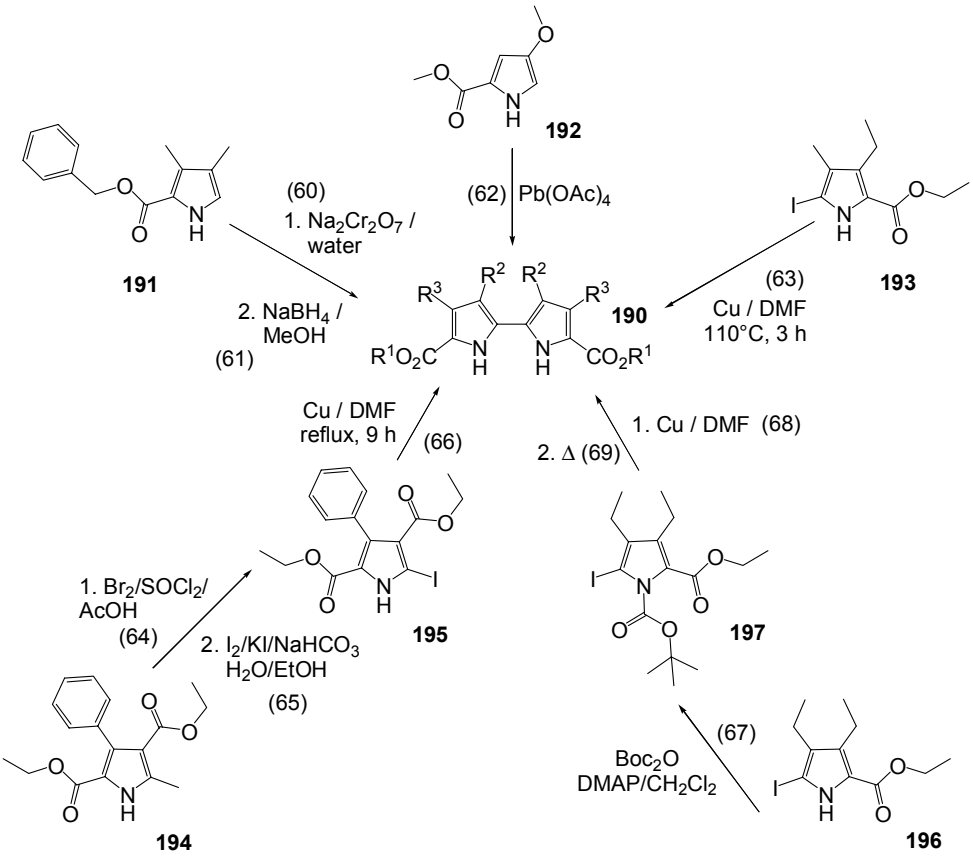
Scheme 76. Bipyrrole as precursor of isomeric and expanded porphyrins

A number of syntheses of the 2,2'-bipyrrole system have been developed over the past years. Hinz and co-workers employed an interesting approach, which consisted of preparing pyrrolyl diones **189** by a 1,3-thiazolium salt-catalyzed nucleophilic addition (58) of 2-formylpyrroles **188** to but-1-en-3-one (Scheme 77, p. 102).[142] The dione moiety of intermediate **189** was then converted to a pyrrole ring by a classical Paal-Knorr pyrrole cyclization (59) to afford bipyrroles **190** in moderate to good yields. In the same paper an alternative route is described; pyrrole is first converted into a propenal derivative, which subsequently reacts with ethyl 2-azidoethanoate to give a thermally unstable azido ester that cyclizes to bipyrrole on heating to 70°C.



Scheme 77. Hinz and Jones synthesis of 2,2'-bipyrroles

Most synthetic procedures towards symmetrically substituted 2,2'-bipyrroles described in the recent literature start with synthesis of conveniently substituted monopyrroles. The preformed monopyrrolic precursors are then subjected to a critical coupling step in a number of ways. Several approaches are outlined in Scheme 78. It is noteworthy that



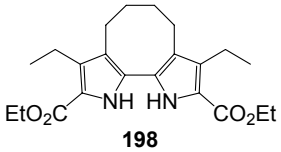
Scheme 78. Selected examples of 2,2'-bipyrrole synthesis

the monopyrrolic precursors in all these examples bear an electron withdrawing carboxyl group. It has been shown that higher yields of substituted 2,2'-bipyrroles are obtained if one or more electron-withdrawing groups are present in the pyrrolic system.[143]

The method of Falk and Flödl[144] utilizes an oxidative coupling (60) of **191** to achieve 25% yield of **190** over the two reactions. Ribo and co-workers[145] used a similar oxidative method (62), but with an electron-rich substrate **192**. The yield amounted to only 9 – 10% and the method is not generally applicable. The method of Guilard and co-workers[137b] is an Ullmann coupling (63) of a persubstituted 2-iodopyrrole **193**. The yield is 47% but a multistep procedure is necessary to obtain **193**.

Nonell and co-workers[146] also used Ullmann coupling (66) to obtain 44% yield of bipyrrole from phenyl-substituted pyrrole diester **195**. The latter was obtained in two steps from the methyl derivative **194**. The Sessler group added a new element to this Ullmann coupling.[147] They first protected (67, yield ~ 100%) the pyrrole nitrogen atom of **196** by the labile electron-withdrawing *t*-Boc group to obtain derivative **197**. This improved the coupling (68) yield to 65 – 83%. The remaining *t*-Boc group could readily and quantitatively be removed by simply heating (69) the neat crude product under an inert atmosphere to 180°C. Pure 2,2'-bipyrrole **190** could be isolated by recrystallization.

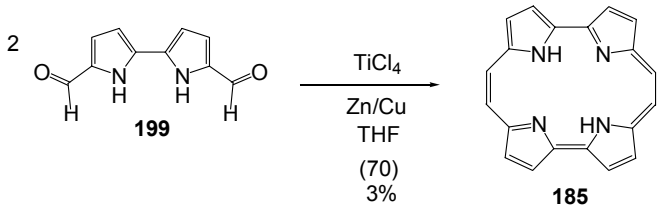
Other 2,2'-bipyrrole syntheses have been carried out recently. In their paper on novel corrole synthesis,[84] Decréau and Collman prepared unsubstituted bipyrrole **57** using benzoyl-pyrrole coupling catalyzed by Pd(II) acetate in hot acetic acid, followed by amide hydrolysis. However, the yield was only 12% and the method uses large quantities of acetic acid, which is not practical. On the other hand, Bröring and Link recently published an elegant synthesis of a conformationally restricted 2,2'-bipyrrole **198** as the precursor of a conformationally locked open-chain tetrapyrrolic 2,2'-bidipyrrin ligand. The final Ullmann coupling, performed following the Sessler method,[147a] afforded compound **198** in 87% yield.[148]



198

These examples show that the synthesis of 2,2'-bipyrroles, and particularly those selectively substituted on the β-pyrrole atoms, is not a simple task and requires some tedious work. The yields are frequently not satisfying and expensive reagents are often used. We wanted to develop a cheap and reliable procedure, on a gram scale if possible, for the synthesis of selectively 3,3'-substituted 2,2'-bipyrroles. These important building blocks could then be used for further preparation of corroles and other porphyrin-related macrocycles, as well as pyrrole polymers. The use of symmetrically substituted bipyrroles for the latter purpose should allow a better control of the polymer structure.

The macrocycle whose synthesis we have carried out is porphycene **185**, a porphyrin isomer, first mentioned by Vogel and co-workers in 1986. It was then prepared in *ca*. 3% purified yield from two 5,5'-diformyl-2,2'-bipyrrole subunits **199**, *via* a reductive McMurry-type coupling (70) as shown in Scheme 79.[137a] The initial (non-oxidized) condensation product was not isolated.



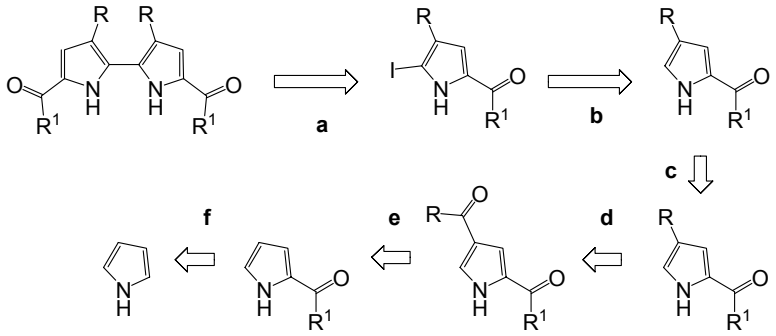
Scheme 79. Vogel's synthesis of porphycene in 1986

Porphycene is an 18-π-electron aromatic product. This is confirmed by the chemical shifts of its signals in the NMR spectra, the existence of the same types of bands at similar wavelengths as for porphyrins in the UV/Vis spectra and the planarity of its structure as shown by X-ray crystallography.[149]

3. 2. Results and discussion

3. 2. 1. Synthesis of 2,2'-bipyrroles

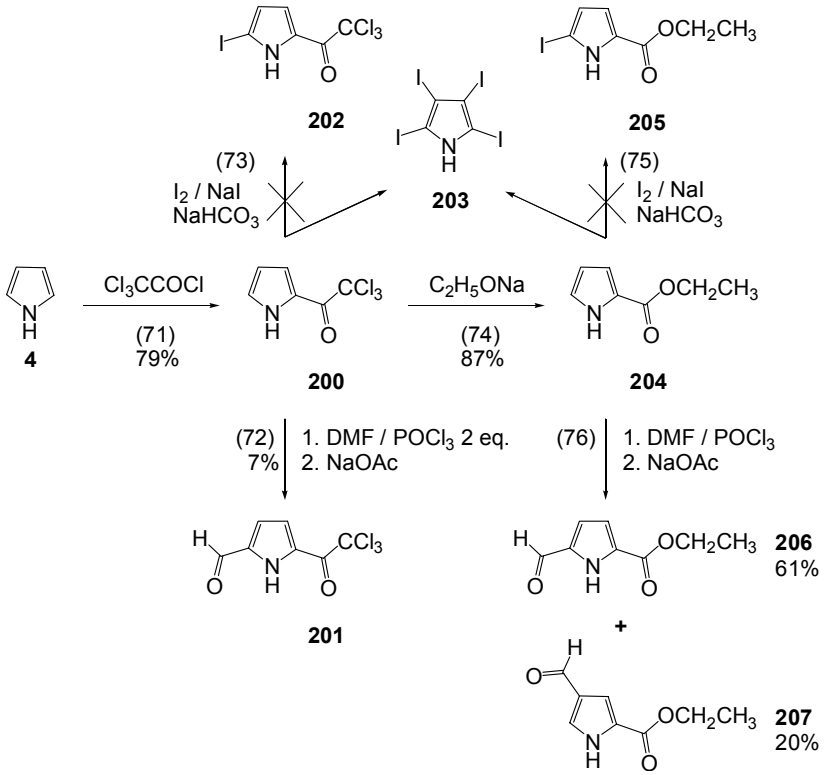
Our synthetic strategy towards 2,2'-bipyrrole has included the Ullmann coupling (**a**) as the final pyrrole-pyrrole bond forming step (Scheme 80). The Ullmann precursor was to be obtained by iodination (**b**) from a functionalized pyrrole derivative bearing an electron withdrawing group. Two functional groups had to be introduced onto the pyrrole ring by electrophilic substitution, one of which had to be subsequently reduced to form an alkyl chain in the final product. An exact sequence (**c**) – (**f**) was to



Scheme 80. Retrosynthetic analysis of bipyrrole synthesis

be determined by experiment.

Starting from pyrrole **4** itself, we first wanted to introduce electrophiles onto the pyrrole core. To exclude the possibility of polysubstitution, it was necessary to lower the reactivity of the aromatic system. This was possible through the introduction of a strongly electron-withdrawing trichloromethylcarbonyl group. Reaction (71; Scheme 81), carried out as previously published[150] and in a very good yield, stops at the

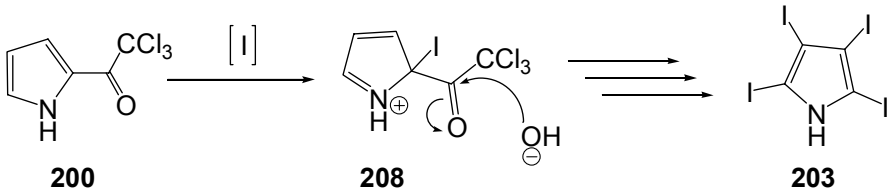


Scheme 81. Flowchart of the first reaction steps in the synthesis of 2,2'-bipyrroles

stage of the monoacylated product **200**. The -C(O)CCl_3 group has also got a solubilizing effect.

Attempts to further functionalize the pyrrole ring bearing this group afforded poor results. Vilsmeier-Haack formylation (72) of **200**, even with 2 equivalents of formylating agent, gave only 7% of **201**. Attempted iodination (73), first tried out with I_2/NaI in a basic aqueous solution at 75°C, did not afford any **202**. The same outcome was obtained under all reaction conditions investigated (room temperature, less iodine, triethylamine instead of $NaHCO_3$ as base). The only isolated product was tetraiodopyrrole **203**. A probable explanation is that an ipso-iodination of **200** to **208** takes place (Scheme 82, p. 106). This intermediate is then

attacked by base, whereupon the side chain is cleaved and periodination follows to form **203** as the final product.



200 **208** **203**

Scheme 82. Formation of tetraiodopyrrole **203**

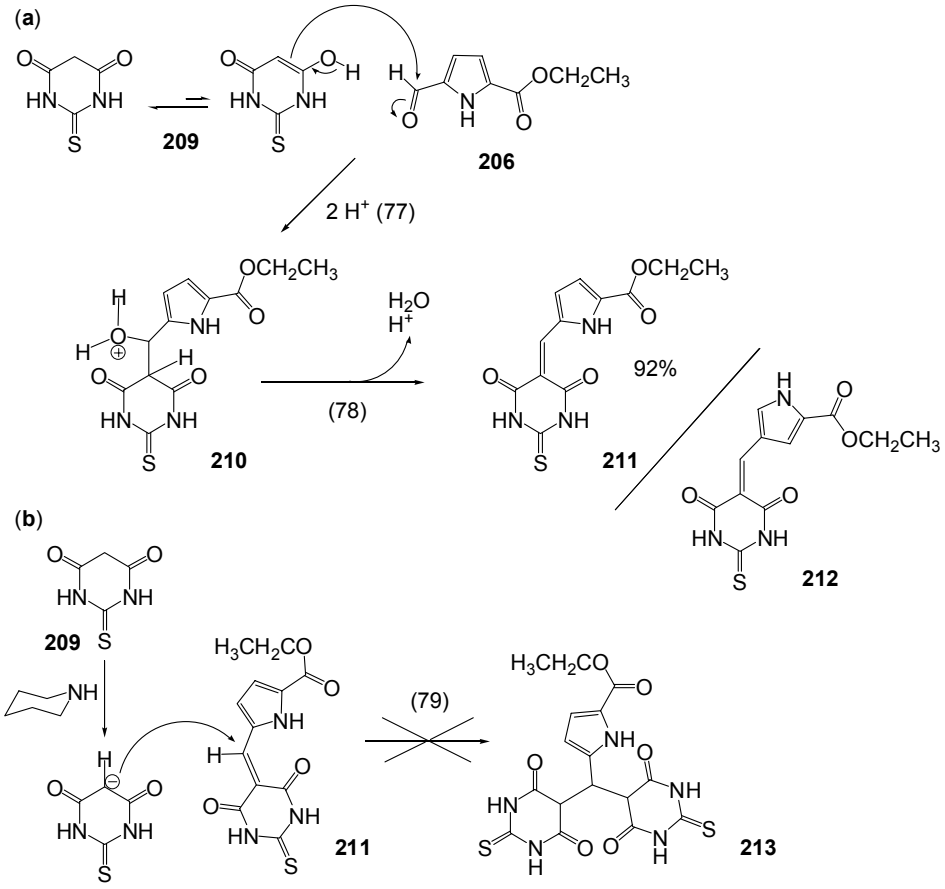
To solve the problem of the lability of the $–C(O)CCl_3$ group, we decided to transform it into a more sable –C(O)OEt group. Reaction (74)[150] proceeded smoothly to give ester **204** in high yield. This ester group fulfils a triple role. Firstly, it stabilizes the pyrrole system against oxidation. Secondly, this substituent should have a desired directing effect on the following electrophilic attack (onto the 4-position). Finally, the ester group is (in the last stages of the synthesis) readily removable by saponification and decarboxylation.

However, an attempt to iodinate (75) ester **204** again gave only tetraiodopyrrole **203**. Compound **204** probably reacts *via* the same mechanism as shown in Scheme 82 to afford compound **203** *via* a **208**-like intermediate.

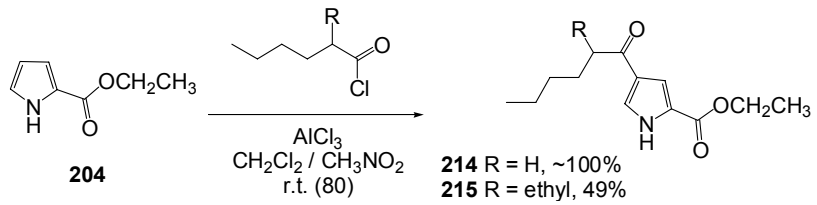
Formylation (76) of **204** under Vilsmeier-Haack conditions gave two stable products in a 3:1 ratio in high combined yield. Based on spectroscopic evidence and comparison of our data to those reported in the literature,[151] it soon became clear that the main product of our reaction was the 5-formylated product **206** rather than the desired 4-formylated isomer **207**. This unexpected reverse regioselectivity is also in contradiction with the abovementioned literature reference, wherein formylation of **204** with dichloromethoxymethane (with $AlCl_3$ as catalyst) to give **207** in 80% yield was reported.

Reactivity of aldehydes **206** and **207** allows their further specific functionalization. As an example, we subjected them to reactions (77) with 2-thiobarbituric acid **209** (Scheme 83a, p. 107), which could potentially give products with biological activity. In the case of pyrrole aldehyde **206**, a secondary alcohol in its protonated form **210** is first obtained. An elimination (78) of water affords eventually pure product **211** in 92% yield. Regioisomer **212** is formed if pyrrole aldehyde **207** is the starting material. A further reaction (79) of **211** with a second equivalent of 2-thiobarbituric acid did not give any product **213** after refluxing overnight (Scheme 83b).

Eventually, desired derivatization of pyrrole ester **204** by selective electrophilic substitution in 4-position worked well with Friedel-Crafts acylation (80) with hexanoyl chlorides (Scheme 84, p. 107). A modified literature procedure[151] was first applied, reacting **204** with hexanoyl chloride at -25°C under standard Friedel-Crafts conditions. Product **214** was isolated in 86% yield. Surprisingly, performing the same reaction at



Scheme 83. Reaction of pyrrole aldehydes **206** and **207** with 2-thiobarbituric acid

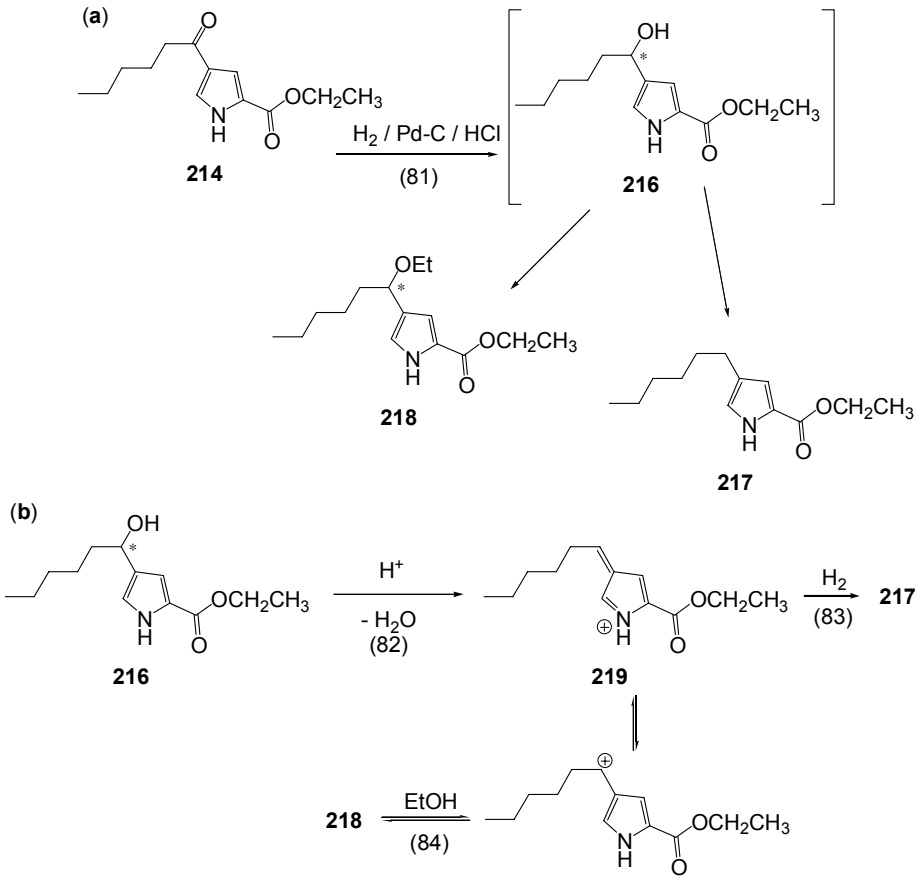


Scheme 84. Friedel-Crafts acylation of pyrrole ester **204**

room temperature rather than -25°C did not bring about any unwanted side reactions and **214** was obtained in quantitative yield. (2-Ethyl)hexanoyl derivative **215** was also synthesized following the same procedure, but in this case the reaction was much more sluggish due to the unstability of the acylating agent (*i.e.* enhanced stability of the cation formed from it). Only 49% of **215** was obtained even after 4 days of reaction at room

temperature. The latter product is needed for a planned polymerization reaction, whereby the ethyl side chains should increase the solubility of the final product.

The next required step is a chemoselective reduction of the ketone groups in the 4-positions of **214** and **215** without altering the ester groups in the 2-positions. We first opted for catalytic hydrogenation (81, Scheme 85a), which has been carried out a number of times with compound **214**. A minor by-product was usually obtained in this reaction. This compound was first erroneously thought to be an unsaturated derivative of the desired product **217** with a double bond between the 1- and 2-positions of the he-



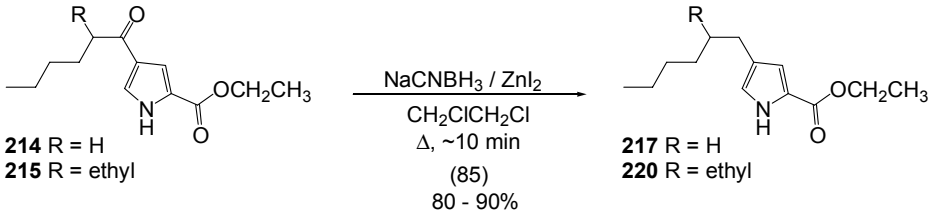
Scheme 85. Catalytic hydrogenation of **214**

xyl chain. However, careful NMR and MS analysis showed that the correct structure of that by-product is in fact **218**; *i.e.* it is formed by a reaction of intermediate secondary alcohol **216** (not isolated) with ethanol. This is a chiral product and the characteristic pattern of the diastereotopic protons of the ethoxy group connected to the hexyl chain can be observed in the ^{1}H NMR spectrum. In the reaction pathway, alcohol **216** is protonated and

subsequently dehydrated (82) to give cation **219**, stabilized by mesomeric electron donation from the pyrrole nitrogen. Species **219** can then directly (83) give product **217**, but alternatively it can be attacked (84) by a solvent (ethanol) molecule, which explains the formation of **218** (Scheme 85b). Nevertheless, reaction (84) is reversible and **218** is (given enough time) eventually further reduced to **217**. That can be accelerated by increasing acid concentration.

The yield of product **217** was in one case as high as 97%. However, this result proved to be highly irreproducible and most of the times much lower yields were obtained, whereby substantial amounts of by-product **218** as well as of starting material **214** could be isolated from the reaction mixture even after reaction times of several days or performing the reaction under hydrogen pressure of 90 bar overnight. We are not certain about what causes these large variations in the outcome of the reaction. It appears that the quality of the catalyst could be of significant importance and that scaling up tends to lower the yield.

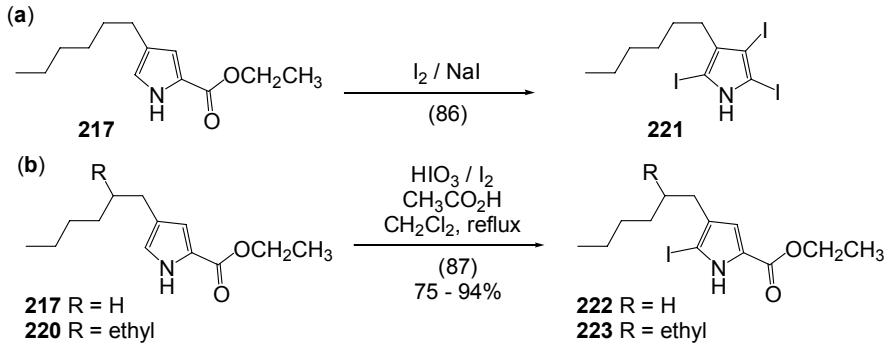
Due to the inconsistency of catalytic hydrogenation (81), we decided to try out a new reduction method. Both **214** and **215** could be smoothly converted into the corresponding 4-alkylpyrrole-2-esters **217** and **220**, respectively, by reaction (85) with excesses of sodium cyanoborohydride (≥3 equivalents) and zinc iodide (1.5 equivalents; Scheme 86).[152] Within several minutes of heating at reflux in 1,2-dichloroethane near-quantitative yields of both products were achieved with a very easy work-up and isolation. Nevertheless, the major drawbacks



214 R = H
215 R = ethyl

217 R = H
220 R = ethyl

Scheme 86. $NaCNBH_3$ reduction of **214** and **215**



217

221

217 R = H
220 R = ethyl

222 R = H
223 R = ethyl

Scheme 87. Iodination of alkylpyrrole esters **217** and **220**

of the method are the toxicity and the high price of sodium cyanoborohydride. Lowering the amount of $NaCNBH_3$ to 1.5 equivalents dropped the yield of the conversion of **214** to **217** to only 39%, even with significantly extended reaction time.

Selective monoiodination of alkylpyrrole esters **217** and **220** was the next step to be achieved in order to prepare precursors suitable for the final Ullmann condensation. This stage of the procedure development also posed significant problems to find the optimal reaction conditions. We first tried out a mixture of iodine and sodium iodide as the iodinating agent for **217**, *i.e.* a method (86) analogous to those (73 and 75) presented in Scheme 81. Two experiments with variation of the reaction parameters failed. Most probably, analogously to the mechanism presented in Scheme 82, ipso-iodination of the pyrrole ring occurred under the reaction conditions with cleavage of the ester group and periodination of the pyrrole carbon atoms (with the exception of 4-C bearing the hexyl substituent; Scheme 87a). However, there is no spectral evidence thereof.

We then subjected compound **217** to a reaction with a solution of iodine, pyridine and bis(trifluoracetoxy)iodobenzene $(CF_3COO)_2IC_6H_5$, a iodination method for aromatic compounds known from the literature.[153] This method afforded 47% of compound **222**. The next experiment consisted of reacting **217** with a mixture of I_2 and mercury(II) acetate in CH_2Cl_2. After several hours of reaction, TLC showed a complete disappearance of the starting material. Nevertheless, several products formed and chromatographic separation of the mixture was very difficult. The use of a toxic mercury compound is another disadvantage of this method.

Finally, we used a method (87) described by Vogel and co-workers,[137a] which uses a mixture of iodine and iodic acid in glacial acetic acid and water as the iodinating agent (Scheme 87b). The first experiment with compound **217** was carried out by heating the mixture at reflux in carbon tetrachloride under vigorous stirring to avoid separation of the phases. A yield of 63% of product **222** was achieved within a reaction time of 1 hour. Using 1.5 equivalents of the iodinating agent did not result in an increase of the yield. The yield did increase to 76% when dichloromethane (a chemical also less harmful than CCl_4) was used as the solvent. The reason could be a lower boiling point of CH_2Cl_2 and consequently a lower reaction temperature, resulting in less by-products. However, in this case the time needed to complete the reaction was extended to 7 h. Similar yields have been obtained for the iodination of **220** to **223** with HIO_3/HI.

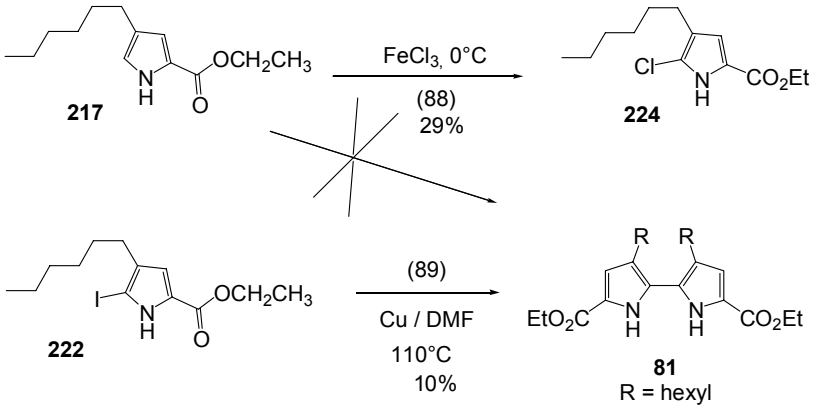
The question can be raised if the iodination indeed occurred in the desired 5-position rather than the 3-position. This question was in the case of compound **222** answered by application of NOESY. By radiation at the absorption frequency of the NH-proton, no effect was observed for the signal at 6.69 ppm, confirming that this hydrogen atom is not in the close proximity of the NH-group. The ^1H coupled ^{13}C NMR spectrum confirmed this finding. The HMQC and HMBC spectra (results not shown here) suggest the same regioselectivity for compound **223**.

A first attempt to synthesize a 2,2'-bipyrrole **81** was carried out *via* an oxidative coupling (88) of alkylpyrrole ester **217** mediated by ferric

chloride. A $CHCl_3$ solution of 4 equivalents of anhydrous $FeCl_3$ was thus added to a $CHCl_3$ solution of **217** and the mixture was stirred at room temperature (Scheme 88). TLC indicated formation of a main product and several by-products. The latter were, according to mass spectral analysis, most probably various polypyrrolic adducts. The main product was isolated by chromatography in 5% yield.

Lowering the reaction temperature to 0°C increased the yield of this main product to 29%. Unfortunately, characterization revealed that it was not 2,2'-bipyrrole **81** but chlorinated compound **224**.

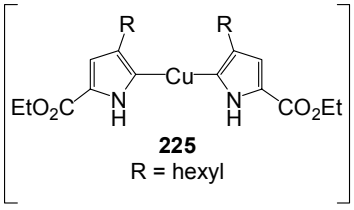
The formation of polypyrrolic by-products in reaction (88) is in accordance with the results of Ribo and co-workers, who obtained oxidized open-chain tri- and tetrapyrroles in attempts to effect 2,2'-bipyrrole synthesis from 4-methoxy-2-methoxycarbonylpyrrole by ferric chloride.[145]



Scheme 88. First experiments towards the synthesis of bipyrrole **81**

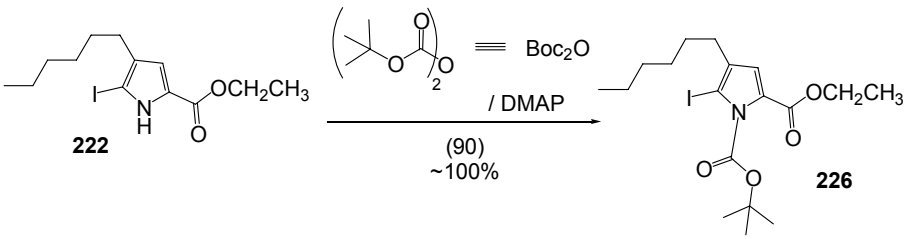
Nevertheless, the mass spectra of our reaction (88) also showed a minor peak at m/z = 445, which corresponds to protonated **81**. Conclusively, a trace of compound **81** did form in the reaction but could not be isolated and characterized in detail.

The next experiment was an Ullmann coupling (89; Scheme 88) of iodopyrrole **222**, a copper-catalyzed formation of biaryls from aryl halogenides. Compound **222** was reacted with copper bronze in hot DMF



under an argon atmosphere. In this reaction organocopper intermediate **225** should form. This species undergoes reductive elimination to give **81**.

Under these conditions, only about 10% of the theoretical quantity of product **81** was isolated as an off-white crystalline powder. According to the mass spectra, extensive deiodination occurred and compound **217** was formed in a substantial quantity. This was also confirmed by TLC. We next decided to apply the recent Sessler approach, *i.e. t*-Boc protection of the starting pyrrolic material prior to the Ullmann reaction.[147a,b]



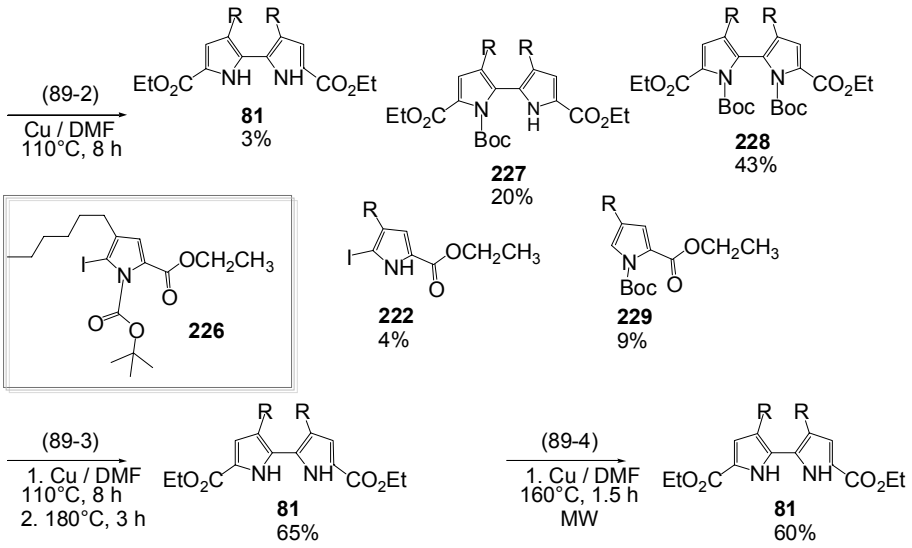
The *N*-protection reaction (90) of iodopyrrole **222** was completed in quantitative yield within minutes. Almost 6 g of *N*-*t*-Boc protected product **226** was prepared in one batch.

Once gram quantities of Ullmann precursor **226** were readily accessible, it was possible to try out reaction (89) in different ways. All experiments were carried out under an argon atmosphere.

After having performed reaction (89-2; Scheme 89, p. 113) under the standard conditions for 8 hours, several fractions were isolated by column chromatography in mixtures of light petroleum ether and ethyl acetate and analyzed by mass spectrometry. The total yield of bipyrrolic products **81**, **227** and **228** was 66%, but by far most of the product was in di-*t*-BOC form **228**. Deiodination occurred again in a significant measure to give compound **229**, and some *N*-deprotected **222** was also isolated.

Repeating the same procedure with subsequent heating of the crude reaction mixture to 180°C (to induce *N*-deprotection of the products) for 3 h (89-3), enabled chromatographic isolation of **81** in 65% yield, which represents the best yield of this compound we have so far obtained.

Another approach was heating the reaction mixture (89-4) by microwave radiation instead of 'classic' heating in an oil bath. The reasoning is that in this case higher temperatures during a much shorter time could be applied, avoiding long-term exposures of the starting material and the products to elevated temperatures, plausibly causing their decomposition. This should result in shorter reaction times and cleaner reaction mixtures, although with certain limitation of the amount of material that can be subjected to the reaction at once. Still, as much as 1.5 g of **226** could be processed in one turn. Efforts to examine the same sets of reactions with the branched side chain pyrrolic derivatives (series of compounds starting with 2-ethoxycarbonyl-4-(2-ethylhexanoyl)pyrrole **215**) have not yet been carried out.



Scheme 89. Bipyrrole **81** synthesis from **226**. R = hexyl

3. 2. 2. Anion binding properties of 2,2'-bipyrrole **81**

Binding of small anions is a well-known property of oligopyrrolic compounds.[154,155] However, to the best of our knowledge this phenomenon has not been reported yet for bipyrroles. We investigated the interaction of **81** with F^-, Cl^-, Br^-, CN^-, $H_2PO_4^-$ and HSO_4^- in the form of their tetrabutylammonium salts using extra dry acetonitrile or HPLC dichloromethane as the solvent. While most of the anions didn't show any binding to **81**, fluoride bound with the constant $K = 4.7 \cdot 10^3 \pm 1 \cdot 10^2$ dm^3mol^{-1} (Figure 17, p. 114). The constant was calculated graphically from a plot of absorption changes in the UV-Vis spectra of compound **81** vs. concentration of added fluoride using Origin® 6.0 software.

The lack of binding of the other anions could probably be ascribed to steric reasons (the proximity of the lateral $-CO_2Et$ groups and/or a too small distance between the pyrrole rings). In any case, these preliminary results have to be confirmed and improved by further sets of measurements.

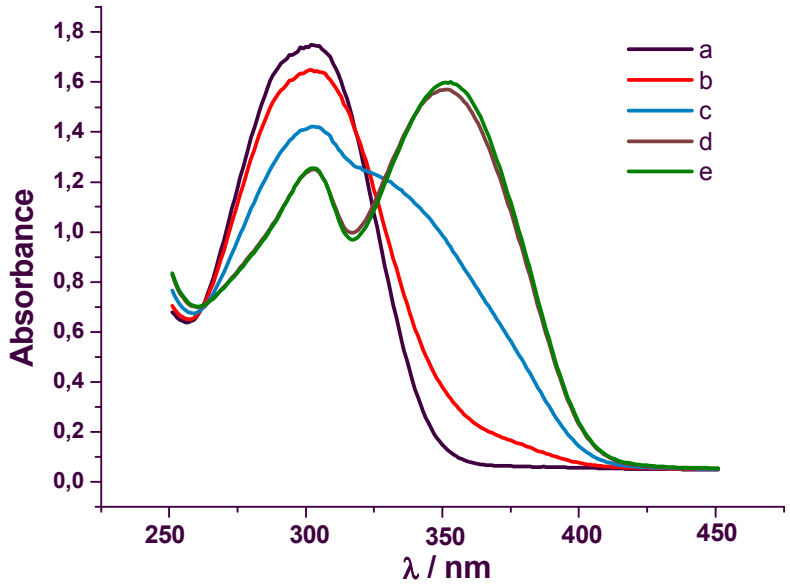
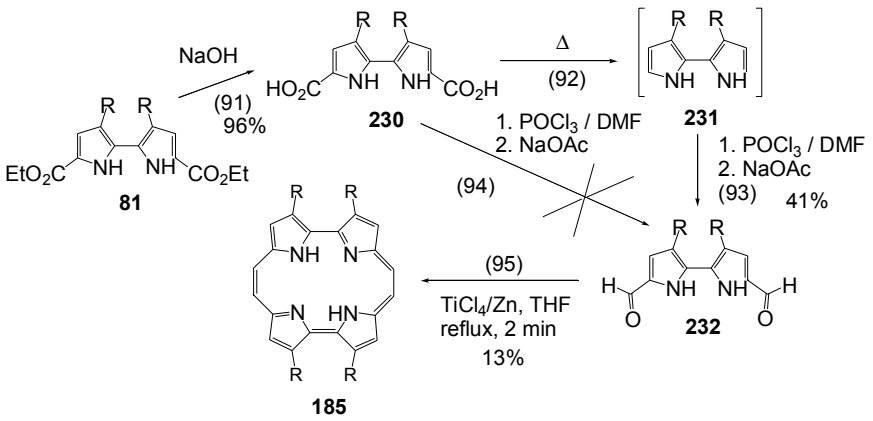


Figure 17. UV spectra of 3 ml $7.4 \cdot 10^{-5}$ M acetonitrile solution of **81** upon addition of aliquots of $(C_4H_9)_4NF$. *Legend:* a, 0; b, 5; c, 10; d, 15 and e, 20 ml $8.0 \cdot 10^{-2}$ M solution of $(C_4H_9)_4NF$ in CH_3CN. The binding constant was calculated using Origin® 6.0 software (Microcal Software, Northampton, MA, USA)

3. 2. 3. Synthesis of a porphycene

A porphycene synthesis based on the new 2,2'-bipyrrole building blocks developed in our laboratory has been carried out following literature methods (Scheme 90, p. 115).[137b,147b] Bipyrrole **81** was saponified (91) to afford diacid **230** in almost quantitative yield. The synthesis of dialdehyde **232**, appears to be the critical step of the procedure. α,α'-Unsubstituted bipyrrole **231** can readily be made by thermic decomposition (92) of compound **230** (by heating to ~180°C under an inert atmosphere). However, product **231** is unstable in air and at best not isolated to minimize losses. Therefore we tried to decarboxylate compound **230** and convert **231** formed *in situ* directly to dialdehyde **232** by a Vilsmeier-Haack reaction (93). To avoid long exposure of the intermediates to elevated temperatures, microwave heating was used for reaction (92). The overall yield from **230** to **232** was still rather low and this is the first point for practical improvement of this sequence. It is worth mentioning that performing Vilsmeier-Haack conditions (94) directly on diacid **230** did not afford desired dialdehyde **232**.

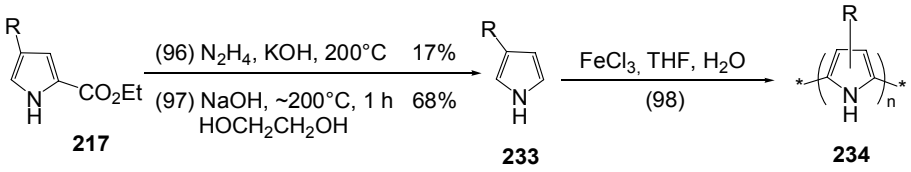
Once enough product **232** had amassed, we tried out a McMurry-type porphycene synthesis as described in the literature.[137b] Although a full characterization of the blue product (~6 mg) was not possible due to the low amount obtained, according to the data we have collected (including a mass spectrum), it is 3,6,13,16-tetrahexylporphycene **185**. The yield obtained (~13%) is higher than reported for the Vogel synthesis of unsubstituted porphycene.[137a]



Scheme 90. Synthesis of porphycene **185**. R = hexyl

3. 2. 4. Synthesis of a polypyrrole

We have also prepared a first polypyrrolic derivative of compound **217**. Two methods to obtain 3-hexylpyrrole monomer **233** have been used. Wolff-Kishner reaction (96; Scheme 91) afforded monomer **233** in only 17% yield. It is not obvious where the loss comes from, but it could be due to uncareful handling of the crude reaction mixture (product should not be exposed to the air while hot *i.e.* it needs to be kept under argon constantly).



Scheme 91. Synthesis of polypyrrole **234**. R = hexyl

Saponification and thermic decarboxylation (97) of **217** with sodium hydroxide in ethylene glycol gave a good yield of **233**. This product is also relatively unstable.

In the final step, we subjected a small quantity of compound **233** to an overnight reaction with iron(III) chloride in a mixture of water and THF. A black reaction mixture was obtained. A small amount of very thin, flaky dark grey material with metallic lustre was isolated by filtration. NMR of some fractions showed peaks of the starting material, suggesting that the reaction did not proceed to completion. However, any chemical characterization of the grey material (which should be polypyrrole **234**) failed because of its insolubility. Hopefully polymers prepared from bipyrroles and/or branched 4-(2-ethylhexyl)pyrrole (derivatives) will possess better properties in that sense.

3. 3. Conclusion

A new synthesis of selectively 3,3'-substituted 2,2'-bipyrroles has been developed. This substitution pattern is rarely encountered in 2,2'-bipyrrole chemistry and provides a pathway towards novel building blocks for the syntheses of porphyrin-related macrocycles.

All reaction steps described herein towards these 2,2'-bipyrroles have been optimized to give very good yields and could be carried out on a multigram scale. Microwave heating has been successfully employed to bring about the final Ullmann condensation step in the 2,2'-bipyrrole synthesis. This shortens the reaction times significantly.

A porphycene synthesis has probably been achieved using a building block developed in this procedure. Although there is still no unambiguous evidence this compound has been formed, strong indications exist (colour, MS, UV-Vis, parts of the NMR spectrum). A polypyrrole synthesis has also been carried out from one of the monopyrrolic precursors, but the product could not be characterized due to extremely low solubility. Nevertheless, both of these procedures are still being optimized to fully make use of the novel 2,2'-bipyrroles.

General Conclusion

Several novel syntheses of various cyclic tetrapyrroles and their precursors and derivatives have been described in this Thesis. The subject of the work relates to porphyrin-related compounds rather than porphyrins themselves. Some parts of the work have been done in an international collaboration with two laboratories.

In the first Chapter, oxidative *N*-alkylation of a tetraphenolic porphyrin has been thoroughly examined. The reaction has been carried out under various sets of experimental conditions and with a number of various alkylating agents. It has been shown that the degree of *N*-alkylation could be controlled, thus enabling to obtain fully as well as partially alkylated compounds in high yields. The latter could be smoothly further alkylated to afford products with different groups on the core nitrogen atoms. Both the variety of the products and the yields achieved represent improvements as compared to preliminary results described in the literature. A doubly bridged porphotetramethene with an unusual bridging pattern has been obtained for the first time.

The second Chapter deals with the synthesis of aromatic *trans*-A_2B-corroles. Several methods have been applied, enabling the preparation of a number of new compounds and yield enhancements in the syntheses of the known ones. It has been found that weaker acids were generally better catalysts in the syntheses of corroles from reactive aldehydes possessing electron-withdrawing substituents. On the contrary, a stronger acid is preferred if the substrate is an aldehyde bearing electron-donating substituents and generally being less reactive.

Some of the corroles have been tested in or even specially prepared for various analytical techniques. A corrole-indole conjugate prepared here should serve for detection of indole-binding proteins in plant tissue extracts. On the other hand, other corrole derivatives could or have already been used in systems for analytical measurement of small analytes.

A new synthetic pathway for selectively prepared 3,3'-substituted 2,2'-bipyrroles as building blocks for isomeric, contracted and expanded porphyrins as well as pyrrole polymers has also been developed. All steps have been optimized for yields and could be carried out on a gram scale. A novel building block prepared in this way has been successfully used in a synthesis of porphycene, a porphyrin isomer. A polypyrrole has been prepared from one of the monopyrrolic precursors.

The results described in this Thesis are not only important from the point of view of synthesis of new compounds. Many of the products have potential for various further applications, mainly in analytical chemistry.

Experimental part of Chapter 1

General for all Chapters: ^{1}H NMR and ^{13}C NMR data in $CDCl_3$ solution at 25°C were recorded on a Bruker AMX 400 MHz spectrometer unless otherwise indicated. The spectra at 300 MHz were taken on Bruker Avance 300 MHz spectrometer. The chemical shifts are reported in ppm relative to TMS as internal standard. *J* values are given in Hz. The absorption spectra were taken on Perkin-Elmer Lambda 20 UV-Vis spectrophotometer. The UV/Vis data are given as λ_{max}/nm (ε/mol^{-1}dm^{3}cm^{-1}) in CH_2Cl_2. The electrospray MS data were obtained on a Micromass Quatro II mass spectrometer in ESI (infusion of 50 µl MeOH/CH_2Cl_2-NH_4Oac (0.1 M in MeOH) with a Harvard pump, model 11). Chemical and electron impact ionization experiments were taken on Hewlett Packard 5989 A Quadrupole mass spectrometer; CI: with CH_4, source temperature 200°C. EI: 70 eV, source temperature 250°C. Column chromatographies were performed on silica gel (63 – 200 mesh). TLC inspections were performed on silica gel F_{254} plates. THF (unless otherwise stated) and diethyl ether were freshly distilled prior to use. All other reagents and solvents were commercially available and used as purchased.

General conditions for the reactions reported in Table 1: *Meso*-tetrakis(3,5-di-*t*-butyl-4-hydroxyphenyl)porphyrin **1** was prepared by a literature procedure.[116a] 0.18 mmol (200 mg) of the starting porphyrin **1** and 60-65 mg of NaH (80% wt. in mineral oil, ~ 10 eq.) were stirred in 20 ml of solvent at room temperature for 10 - 15 min. Then, 4.43 mmol (25 eq.) of the alkylating agent (787 mg of $BrCH_2CO_2Et$, 873 mg of $BrCH_2CO_2{}^tBu$, 769 mg of $BrCH_2C_6H_5$) in 5 ml of solvent was added and the reaction mixture was heated (oil bath) to the indicated temperature. After the reaction time indicated in the table, the reaction mixture was cooled, taken into CH_2Cl_2, the solution was washed three times with water, dried over $MgSO_4$, and evaporated to dryness. The mixture of products was then isolated by column chromatography on silica with CH_2Cl_2 as the eluent. The ratio of the products was estimated by the integrals of their signals in the ^{1}H NMR spectra (300 MHz, $CDCl_3$) of the product mixtures. The products could be further separated from the mixtures by careful column or plate chromatography. For the reactions in THF, KO^tBu (465 mg) was used instead of NaH and the synthetic procedure was carried out in the same way.

***Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dieny-lene)-N_{21},N_{22},N_{23},N_{24}-tetra(3,5-di(benzyloxy)benzyl)porphyrinogen 84**

A mixture of 500 mg (0.44 mmol) of **1**, 561 mg of 3,5-di(benzyloxy)benzyl bromide (1.46 mmol) 202 mg of K_2CO_3 (1.46 mmol) and 12 mg of 18-crown-6 (0.04 mmol) in 15 ml of acetone was refluxed for 4 hours. Upon cooling, the mixture was taken into 30 ml of CH_2Cl_2 and washed three times with 30 ml of water, dried over $MgSO_4$, and evaporated to dryness. Column chromatography on silica gel with CH_2Cl_2/hexane (3:1) as the eluent afforded the title compund in 60% yield (623 mg). δ_H 7.24 – 7.30 (m, 48H), 6.52 (s, 8H, pyrrole H), 6.39 (t, *J* 2.0, 4H), 5.85 (d, *J* 2.0, 8H), 4.79 (s, 16H), 4.28 (s, 8H), 1.19 (s, 72H, tert-butyl); δ_C 186.0 (quinoid C=O),

160.1 (3- and 5-C of the trisubstituted benzyl), 148.2 (3-quinoid), 139.5 (1-C of the trisubstituted benzyl), 138.1 (pyrrole α-C), 136.2 (1-C of the phenyl), 133.8 (1-quinoid), 131.5 (2-quinoid), 130.7 (*meso* C), 128.6 (3- and 5-C of the phenyl), 128.1 (4-C of the phenyl), 127.5 (2- and 6-C of the phenyl), 120.8 (pyrrole β-C), 105.9 (2 and 6-C of the trisubstituted benzyl), 100.4 (4-C of the trisubstituted benzyl), 70.1 (CH_2 of the monosubstituted benzyl), 48.6 (N*C*H_2Ar), 35.4 (tert-butyl quaternary C), 29.3 (tert-butyl CH_3); ESI-MS 2336 (MH^+).

Meso-tetrakis-5,10,15,20-(3,5-di-_t_-butyl-4-oxacyclohexa-2,5-dienylene)-porphyrinogen 87 [116a]

0.05 mmol (51 mg) of the porphyrin **1** and 11 mg (8 eq.) of NaH were stirred in 5 ml of acetone for 15 min. The reaction mixture was taken into CH_2Cl_2 and the solution washed with water, dried over $MgSO_4$, and evaporated to dryness. Recrystallisation from CH_2Cl_2/light petroleum ether afforded the title compound in 79% yield (40 mg). Spectral data for tautomer **86** in solution: δ_H (300 MHz) 9.36 (br. s, 2H, NH), 7.45 (s, 8H, quinoid H), 6.79 (s, 4H, pyrrole H), 1.33 (s, 72H, tert-butyl); ESI-MS 1125 (MH^+).

Meso-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-(ethoxycarbonyl)methoxy)porphyrin 91a

A mixture of 475 mg (0.42 mmol) of the porphyrin **1**, 450 mg (2.61 mmol) of $BrCH_2CO_2Et$ and 500 mg (3.61 mmol) of K_2CO_3 in 20 ml of acetone was refluxed for 6 days. Further aliquots of $BrCH_2CO_2Et$ were added at irregular time intervals up to a total of 2.22 g (12.89 mmol). The reaction mixture was cooled, taken into 70 ml CH_2Cl_2, washed three times with water and dried over Na_2SO_4. Repeated column chromatography in CH_2Cl_2/hexane mixtures on silica afforded 103 mg (17 %) of **91a** and 108 mg (17 %) of **90**. δ_H 8.90 (br. s, 8H, pyrrole H), 8.14 (s, 8H, phenyl H), 4.71 (s, 8H, OCH_2CO_2), 4.42 (q, *J* 7.2, 8H, ethyl CH_2), 1.61 (s, 72H, tert-butyl), 1.42 (t, *J* 7.2, 12H, ethyl CH_3), -2.69 (s, 2H, inner NH) ; δ_C 168.7 (CO_2), 156.0 (4-phenyl), 141.6 (3-phenyl), 137.3 (1-phenyl), 131.1 (pyrrole β-C), 133.8 (2-phenyl), 120.5 (*meso* C), 73.3 (O*C*H_2CO_2), 61.2 (ethyl CH_2), 36.1 (tert-butyl quaternary C), 32.4 (tert-butyl CH_3), 14.3 (ethyl CH_3); UV/Vis 422.3, 455.4, 519.0, 555.5, 593.5, 649.4; ESI-MS 1472 (MH^+).

Meso-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23}-dibenzylporphyrinogen 94 [116c]

A mixture of 100 mg (0.09 mmol) of **1**, 25 mg of NaH (0.83 mmol) and 390 mg (2.28 mmol) of benzyl bromide in 15 ml of acetone was reacted for 30 min in the usual way. The reaction mixture was taken into CH_2Cl_2 and the solution washed with water, dried over $MgSO_4$, and evaporated to dryness. After column chromatography in CH_2Cl_2 on silica the title compound was isolated in 81% overall yield (95 mg), along with some **95** (Table 1).

Meso-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23},N_{24}-tetrabenzylporphyrinogen 95 [116c]

Method A: A mixture of 500 mg (0.44 mmol) of **1**, 344 mg of benzyl bromide (1.95 mmol) 270 mg of K_2CO_3 (1.95 mmol) and 12 mg of 18-crown-6 (0.04 mmol) in 15 ml of acetone was refluxed under argon for 12 hours. Upon cooling, the mixture was taken into 30 ml of CH_2Cl_2 and washed three times with 30 ml of water, dried over $MgSO_4$, and evaporated to dryness. Column chromatography on silica with CH_2Cl_2/hexane (3:1) as the eluent afforded the title compund in 60% yield (400 mg). *Method B*: A mixture of 100 mg (0.09 mmol) of **1**, 25 mg of NaH (0.83 mmol) and 390 mg of (2.28 mmol) benzyl bromide in 15 ml of acetone was reacted in the usual way for 6 h. The crude product was purified by recrystallisation from CH_2Cl_2/methanol to afford the title compound in 86% yield (115 mg).

Analytical data for the compounds reported in Table 1 and prepared according to the general conditions above

- _Meso_-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23},N_{24}-tetra((ethoxycarbonyl)methyl)porphyrinogen 90

δ_H 7.47 (s, 8H, quinoid H), 6.64 (s, 8H, pyrrole H), 4.00 (q, *J* 7.1, 8H, ethyl CH_2), 3.83 (s, 8H, NCH_2CO_2), 1.31 (s, 72H, tert-butyl), 1.08 (t, *J* 7.1, 12H, ethyl CH_3); δ_C 186.2 (quinoid C=O), 167.1 (CO_2), 148.4 (3-quinoid), 138.7 (pyrrole α-C), 135.2 (1-quinoid), 131.3 (2-quinoid), 128.8 (*meso* C), 120.1 (pyrrole β-C), 61.9 (ethyl CH_2), 46.3 (NCH_2CO_2), 35.5 (tert-butyl quaternary C), 29.4 (tert-butyl CH_3), 14.2 (ethyl CH_3); UV/Vis 495.0 ($2.46 \cdot 10^5$); ESI-MS 1470 (MH^+).

- _Meso_-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23}-di((ethoxycarbonyl)methyl)porphyrinogen 96

δ_H 9.26 (br. s, 2H, NH), 7.58 (d, *J* 2.5, 4H, quinoid H), 7.35 (d, *J* 2.5, 4H, quinoid H), 6.83 (d, *J* 2.3, 4H, pyrrole bearing NH), 6.56 (s, 4H, pyrrole bearing NR), 3.99 (q, *J* 7.1, 4H, ethyl CH_2), 3.91 (s, 4H, NCH_2CO_2), 1.34 (s, 36H, tert-butyl), 1.29 (s, 36H, tert-butyl), 1.05 (t, *J* 7.1, 6H, ethyl CH_3); δ_C 186.2 (quinoid C=O), 167.1 (CO_2), 148.5, 147.6 (3-quinoid), 137.6 (pyrrole (bearing NR) α-C), 134.9 (pyrrole (bearing NH) α-C), 133.2 (1-quinoid), 132.0, 130.6 (2-quinoid), 129.8 (*meso* C), 119.5, 118.8 (pyrrole β-C), 62.1 (ethyl CH_2), 46.5 (NCH_2CO_2), 35.6, 35.4 (tert-butyl quaternary C), 29.6, 29.5 (tert-butyl CH_3), 14.0 (ethyl CH_3); UV/Vis 502.2 ($1.34 \cdot 10^5$); ESI-MS 1298 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-*N*-((ethoxycarbonyl)methyl)porphyrinogen 97

δ_H 10.24 (br. s, 1H, NH), 9.05 (s, 2H, NH), 7.65 (d, *J* 2.1, 2H, quinoid H), 7.45 (d, *J* 2.2, 2H, quinoid H), 7.42 (d, *J* 2.0, 2H, quinoid H), 7.17 (d, *J* 1.9, 2H, quinoid H), 6.74 (dd, 4H, pyrroles bearing NH), 6.69 (dd, 2H, a pyrrole bearing NH), 6.57 (s, 2H, pyrrole bearing NR), 4.26 (s, 2H, NCH_2CO_2), 3.73 (q, *J* 7.1, 2H, ethyl CH_2), 1.34 (s, 18H, tert-butyl), 1.33 (s, 18H, tert-butyl), 1.32 (s, 18H, tert-butyl), 1.27 (s, 18H, tert-butyl), 1.01 (t, *J* 7.1, 3H, ethyl CH_3); δ_C 186.1, 185.9 (3 :1, quinoid C=O), 166.2 (CO_2), 149.0, 148.2, 147.3 (1 :1 :2, 3-quinoid), 137.2 (pyrrole (bearing NR) α-C), 135.0, 134.4, 134.1, 132.8, 132.0, 131.84 (quinoid), 131.79 (quinoid), 131.3, 130.6, 130.4, 130.3, (120.6, 120.0, 117.7, 116.3 (pyrrole β-C)), 61.9 (ethyl CH_2), 46.7 (N*C*H_2CO_2), 35.6, 35.5, 35.3 (1 :2 :1, tert-butyl quaternary C), 29.50, 29.46 (tert-butyl CH_3), 13.8 (ethyl CH_3); UV/Vis 515.8 ($1.05 \cdot 10^5$); ESI-MS 1212 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23}-tri((ethoxycarbonyl)methyl)-N_{24}-(((ethoxy-carbonyl)methoxycarbonyl)methyl)porphyrinogen 100

δ_H 7.49 (d, *J* 2.3, 2H, quinoid H), 7.47 (s, 4H, quinoid H), 7.43 (d, *J* 2.2, 2H, quinoid H), 6.78 (d, *J* 3.7, 2H, pyrrole H), 6.65 (s, 4H, pyrrole H), 6.64 (hidden d, 2H, pyrrole H), 4.44 (s, 2H, $CO_2CH_2CO_2$), 3.98-4.01 (m, 10H, 4 ethyl CH_2, NCH_2CO_2), 3.85 (s, 4H, NCH_2CO_2), 3.82 (s, 2H, NCH_2CO_2), 1.31 (s, 54H, tert- butyl), 1.28 (s, 18H, tert-butyl), 1.07-1.13 (m, 12H, ethyl CH_3); δ_C 186.3, 186.2, (quinoid C=O), 167.12, 167.11, 167.0, 166.3 (2 :1 :1 :1, CO_2), 148.4, 148.33, 148.26 (2 :1 :1, 3-quinoid), 138.8, 138.74, 138.69, 138.67 (pyrrole α-C), 135.5, 135.2 (1-quinoid), 131.5, 131.3 (1 :3, 2-quinoid), 128.9, 128.6 (*meso* C), 120.4, 120.2, 120.1, 120.0 (pyrrole β-C), 61.9, 61.7, 61.3 (3 :1 :1, ethyl CH_2), 46.3, 46.2, 45.7 (2 :1 :1, N*C*H_2CO_2), 35.5 (tert-butyl quaternary C), 29.4 (tert-butyl CH_3), 14.2 14.0 (3 :1, ethyl CH_3); UV/Vis 494.6 ($1.82 \cdot 10^5$); ESI-MS 1528 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23}-di((ethoxycarbonyl)methyl)-N_{22},N_{24}-di(((ethoxy-carbonyl)methoxycarbonyl)methyl)porphyrinogen 101

δ_H 7.50 (d, *J* 2.2, 4H, quinoid H), 7.43 (d, *J* 2.2, 4H, quinoid H), 6.78 (s, 4H, pyrrole H), 6.65 (s, 4H, pyrrole H), 4.44 (s, 4H, $CO_2CH_2CO_2$), 3.98-4.02 (m, 12H, 4 ethyl CH_2, 2 NCH_2CO_2), 3.88 (s, 4H, NCH_2CO_2), 1.31 (s, 36H, tert-butyl), 1.29 (s, 36H, tert-butyl), 1.12 (t, *J* 7.1, 6H, ethyl CH_3), 1.09 (t, *J* 7.1, 6H, ethyl CH_3); δ_C 186.3 (quinoid C=O), 167.1, 167.0, 166.3 (CO_2), 148.3, 148.2 (3-quinoid), 138.8, 138.7 (pyrrole α-C), 135.5 (1-quinoid), 131.5, 131.3 (2-quinoid), 128.6 (*meso* C), 120.5, 119.9 (pyrrole β-C), 61.9, 61.7, 61.3 (ethyl CH_2), 46.3, 45.7 (N*C*H_2CO_2), 35.5 (tert-butyl quaternary C), 29.4 (tert-butyl CH_3), 14.2, 14.0 (ethyl CH_3); UV/Vis 494.3 ($1.62 \cdot 10^5$); ESI-MS 1586 (MH^+) ; MALDI-TOF MS 1584.6.

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23}-tri((ethoxycarbonyl)methyl)porphyrinogen 102

Obtained in a mixture with **90**. δ_H 7.61 (unresolved d, 2H, quinoid H), 7.50 (d, *J* 2.2, 2H, quinoid H), 7.38 (br. s, 2H, quinoid H), 7.34 (unresoluted d, 2H, quinoid H), 6.82 (d, *J* 2.2, 2H, pyrrole bearing NH), 6.61 (s, 2H, a pyrrole bearing NR), 6.50 (br. s, 2H, a pyrrole bearing NR), 6.44 (br. s, 2H, a pyrrole bearing NR), 4.04 – 3.97 (m, 6H, ethyl CH_2), 3.91 (br. s, 6H, NCH_2CO_2), 1.35 – 1.26 (m, 72H, tert-butyl), 1.10 – 1.03 (m, 9H, ethyl CH_3); ESI-MS 1384 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23},-di((ethoxycarbonyl)methyl)-N_{22},N_{24}-dibenzyl-porphyrinogen 103

δ_H 7.46 (s, 4H, quinoid H), 7.25 (s, 4H, quinoid H), ~7.15 (m, 6H, *m*- and *p*-Ar), 6.65 - 6.67 (m, 12H, pyrrole H + *o*-Ar), 4.42 (s, 4H, N*C*H_2Ar), 4.00 (q, *J* 7.0, 4H, ethyl CH_2), 3.92 (s, 4H, NCH_2CO_2), 1.30 (s, 36H, tert-butyl), 1.25 (s, 36H, tert-butyl), 1.08 (t, *J* 7.0, 6H, ethyl CH_3); δ_C 186.1 (quinoid C=O), 167.2 (CO_2), 148.20, 148.17 (3-quinoid), 139.2, 138.0, 137.4, (134.5 (1-quinoid)), 131.6, 131.1 (2-quinoid), 129.7 (*meso* C), 128.7 (*m*-Ar), 128.0 (*p*-Ar), 125.9 (*o*-Ar), 120.6, 120.4 (pyrrole β-C)), 61.9 (ethyl CH_2), 48.3 (N*C*H_2Ar), 46.6 (N*C*H_2CO_2), 35.5, 35.4 (tert-butyl quaternary C), 29.4, 29.3 (tert-butyl CH_3), 14.2 (ethyl CH_3); UV/Vis 499.8 ($1.65 \cdot 10^5$); ESI-MS 1478 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23}-tribenzyl-N_{24}-((ethoxycarbonyl)methyl)-porphyrinogen 104

δ_H 7.50 (d, *J* 2.0, 2H, quinoid H next to the pyrrole bearing $CH_2CO_2CH_2CH_3$), 7.31 (d, *J* 1.9, 2H, neighboring quinoid H), 7.23 (s, 4H, quinoid H), 7.17 (m, 9H, *m*- and *p*-Ar), 6.67 - 6.71 (m, 14H, pyrrole H + *o*-Ar), 4.48 (s, 4H, N*C*H_2Ar), 4.40 (s, 2H, N*C*H_2Ar), 4.06 (s, 2H, NCH_2CO_2), 4.03 (q, *J* 7.1, 2H, ethyl CH_2), 1.32 (s, 18H, tert-butyl next to the pyrrole bearing $CH_2CO_2CH_2CH_3$), 1.27 (s, 18H, tert-butyl), 1.243 (s, 18H, tert-butyl), 1.236 (s, 18H, tert-butyl), 1.09 (t, *J* 7.1, 3H, ethyl CH_3); δ_C 186.1, 186.0 (quinoid C=O), 167.2 (CO_2), 148.1, 148.0 (3-quinoid), 139.2, 138.5, 138.4, 138.0, 137.5 (pyrrole α-C), 134.5, 133.9 (1-quinoid), 131.7 (quinoid C correlated with the H at 7.50 ppm), 131.3 (quinoid C correlated with the H at 7.23 ppm), 131.2 (quinoid C correlated with the H at 7.31 ppm), 130.5, 129.7 (*meso* C), 128.7 (*m*-Ar), 128.0 (*p*-Ar), 126.1, 126.0 (*o*-Ar), 120.8, 120.7, 120.6 (2 :1 :1, pyrrole β-C), 61.9 (ethyl CH_2), 48.6, 48.5 (1 :2, N*C*H_2Ar), 46.8 (N*C*H_2CO_2), 35.52, 35.46, 35.4 (tert-butyl quaternary C), 29.4, 29.31, 29.27 (1 :1 :2, tert-butyl CH_3), 14.2 (ethyl CH_3); UV/Vis 501.4 ($2.66 \cdot 10^5$); ESI-MS 1482 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23}-tri((2-amino-2-oxoethyl)porphyrinogen 108

ESI-MS 1297 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23}-di(tert-butoxycarbonyl)methyl)porphyrinogen 110

δ_H 9.27 (br. s, 2H, NH), 7.60 (d, *J* 2.3, 4H, quinoid H), 7.37 (d, *J* 2.3, 4H, quinoid H), 6.83 (d, *J* 2.2, 4H, pyrrole bearing NH), 6.54 (s, 4H, pyrrole bearing NR), 3.78 (s, 4H, NCH_2CO_2), 1.35 (s, 36H, ring tert-butyl), 1.29 (s, 36H, ring tert-butyl), 1.22 (s, 18H, $CH_2CO_2C(CH_3)_3$); δ_C 186.2 (quinoid C=O), 166.3 (CO_2), 148.5, 147.5 (3-quinoid), 137.7 (pyrrole (bearing NR) α-C), 135.0 (pyrrole (bearing NH) α-C), 133.2 (1-quinoid), 132.4, 130.6 (2-quinoid), 130.1 (*meso* C), 119.4, 118.4 (pyrrole β-C), 83.1 ($CH_2CO_2C(CH_3)_3$), 47.5 (NCH_2Ar), 35.6, 35.4 (tert-butyl quaternary C), 29.6, 29.5 (ring tert-butyl CH_3), 27.9 ($CH_2CO_2C(CH_3)_3$); UV/Vis 505.6 ($1.21 \cdot 10^5$); ESI-MS 1354 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23},N_{24}-tetra(tert-butoxycarbonyl)methyl)porphyrinogen 111

δ_H 7.52 (s, 8H, quinoid H), 6.64 (s, 8H, pyrrole H), 3.70 (s, 8H, NCH_2CO_2), 1.32 (s, 72H, ring tert-butyl), 1.26 (s, 36H, $CH_2CO_2C(CH_3)_3$); δ_C 186.3 (quinoid C=O), 166.3 (CO_2), 148.2 (3-quinoid), 138.7 (pyrrole α-C), 135.0 (1-quinoid), 131.6 (2-quinoid), 129.3 (*meso* C), 119.9 (pyrrole β-C), 82.7 ($CH_2CO_2C(CH_3)_3$), 47.2 (NCH_2Ar), 35.5 (ring tert-butyl quaternary C), 29.4 (ring tert-butyl CH_3), 28.0 ($CH_2CO_2C(CH_3)_3$); UV/Vis 498.3 ($1.86 \cdot 10^5$); ESI-MS 1582 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23}-tri(tert-butoxycarbonyl)methyl)porphyrinogen 111a

Obtained in a mixture with **111**. δ_H 7.61 (hidden d, 2H, quinoid H), 7.51 (hidden d, 2H, quinoid H), 7.36 (hidden, 4H, quinoid H), 6.83 (hidden d, 2H, pyrrole bearing NH), 6.63 (hidden s, 2H, a pyrrole bearing NR), 6.48 (br. s, 4H, pyrroles bearing NR), 3.79 (hidden s, 6H, NCH_2CO_2), 1.57 – 1.22 (m, 99H, tert-butyl); ESI-MS 1468 (MH^+).

- *Meso*-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-*N*-(tert-butoxycarbonyl)methyl)porphyrinogen 112

δ_H 10.44 (br. s, 1H, NH), 8.91 (s, 2H, NH), 7.67 (d, *J* 2.3, 2H, quinoid H), 7.45 (hidden d, 2H, quinoid H), 7.44 (hidden d, 2H, quinoid H), 7.35 (br. s, 2H, quinoid H), 6.74 (dd, *J* 7.6, 2.2, 4H, pyrroles bearing NH), 6.65 (m, 2H, a pyrrole bearing NH), 6.54 (s, 2H, pyrrole bearing NR), 4.08 (s, 2H,

NCH_2CO_2), 1.35 (s, 18H, ring tert-butyl), 1.34 (s, 18H, ring tert-butyl), 1.33 (s, 18H, ring tert-butyl), 1.27 (s, 18H, ring tert-butyl), 1.22 (s, 9H, $CH_2CO_2C(CH_3)_3$); δ_C 186.2, 186.0 (quinoid C=O), 169.0 (CO_2), 147.3 (3-quinoid), 134.5, 133.9, 132.7, 131.8, 131.2, 130.5, 130.3, (120.8 (pyrrole β-C)), 81.8 ($CH_2CO_2C(CH_3)_3$), 35.6, 35.5, 35.3 (1 :2 :1, tert-butyl quaternary C), 29.54, 29.48, 29.3 (tert-butyl CH_3), 28.1 ($CH_2CO_2C(CH_3)_3$); UV/Vis 519.1 ($0.36 \cdot 10^5$); ESI-MS 1240 (MH^+).

Meso-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{22},N_{23},N_{24}-tetra(carboxymethyl)porphyrinogen 113

28 mg (17.7 μmol) of porphotetramethene **111** was stirred in ~1 ml of trifluoroacetic acid for 12 h. The reaction mixture was diluted with diethyl ether and evaporated to dryness. Purification by preparative TLC in acetone afforded 21 mg (87%) of the title compound. NMR in CD_3OD at 300 MHz: δ_H 8.45 (br. s, 4H, COOH), 7.69 (s, 8H, quinoid H), 6.55 (s, 8H, pyrrole H), 3.73 (s, 8H, NCH_2CO_2), 1.21 (s, 72H, tert-butyl); ESI-MS 1357 (MH^+).

- _Meso_-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-N_{21},N_{23},-di((ethoxycarbonyl)methyl)-N_{22},N_{24}-di(tert-butoxycarbonyl)methyl)porphyrinogen 114

δ_H 7.49 - 7.50 (2 overlapped d, 8H, quinoid H), 6.64 (s, 4H, pyrrole bearing $CH_2CO_2CH_2CH_3$), 6.63 (s, 4H, pyrrole bearing $CH_2CO_2C(CH_3)_3$), 4.00 (q, *J* 7.1, 4H, ethyl CH_2), 3.83 (s, 4H, NCH_2CO_2Et), 3.69 (s, 4H, $NCH_2CO_2{}^tBu$), 1.32 (s, 36H, ring tert-butyl), 1.31 (s, 36H, ring tert-butyl), 1.25 (s, 18H, $CH_2CO_2C(CH_3)_3$), 1.07 (t, *J* 7.1, 6H, ethyl CH_3); δ_C 186.2 (quinoid C=O), 167.1, 166.3 (CO_2), 148.3, 148.2 (3-quinoid), 138.7 (pyrrole α-C), 135.1 (1-quinoid), 131.6, 131.3 (2-quinoid), 129.1, 128.7 (*meso* C), 120.05, 119.96 (pyrrole β-C), 82.8 ($CH_2CO_2C(CH_3)_3$), 61.8 (ethyl CH_2), 47.2, 46.3 (NCH_2), 35.5 (ring tert-butyl quaternary C), 29.43, 29.38 (ring tert-butyl CH_3), 27.9 ($CH_2CO_2C(CH_3)_3$), 14.2 (ethyl CH_3); UV/Vis 496.4 ($1.76 \cdot 10^5$); ESI-MS 1526 (MH^+).

Meso-tetrakis-5,10,15,20-(3,5-di-tert-butyl-4-oxacyclohexa-2,5-dienylene)-C_2,N_{22},C_{12},N_{24}-bis(1,2-phenylenedimethylene)-porphyrinogen 122

89 μmol (100 mg) of the starting porphyrin **1** and 36 mg of NaH (80% wt. in mineral oil, ~ 14 eq.) were stirred in 13 ml of acetone at room temperature for 10 - 15 min. Then, 541 μmol (6 eq.) of α,α'-dibromo-*o*-xylene **117** was added and the reaction mixture refluxed (oil bath) for two days. The reaction mixture was cooled, taken into CH_2Cl_2, the solution was washed three times with water, dried over $MgSO_4$, and evaporated to dryness. The mixture of products was then chromatographed on silica with CH_2Cl_2 as the eluent. 19 mg (16%) of compound **122** was isolated. δ_H 7.76 (s, 2H, pyrrole NH), 7.65 (d, *J* 2.2, 2H, quinoid H), 7.57 (d, *J* 2.2, 2H, quinoid H),

7.11 (d, *J* 2.3, 2H, quinoid H), 6.93 (quintet, *J* 6.6, 4H, *m*-phenylene H), 6.75 (d, *J* 7.1, 2H, *o*-phenylene H next to CH_2C), 6.65 (d, *J* 7.0, 2H, *o*-phenylene H next to CH_2N), 6.55 (d, *J* 2.0, 2H, A- and C-pyrrole β-H), 6.48 (d, *J* 2.3, 2H, quinoid H), 6.47 (d, *J* 3.6, 2H, B- and D-pyrrole β-H), 6.41 (d, *J* 3.6, 2H, B- and D-pyrrole β-H), 4.54 (d, *J* 14.2, 2H, N*CH*$_2$-phenylene), 4.23 (d, *J* 18.6, 2H, C*CH*$_2$-phenylene), 3.95 (d, *J* 18.6, 2H, C*CH*$_2$-phenylene), 3.70 (d, *J* 14.2, 2H, N*CH*$_2$-phenylene), 1.37 – 1.31 (m, 54H, tert-butyl), 1.07 (s, 18H, tert-butyl); δ_C 186.2 (quinoid C=O), 185.8 (quinoid C=O), 149.2, 149.1, 148.6, 148.1 (3-quinoid), 137.3, 136.3, 135.8, 133.42, 133.40, 132.8, 132.7, 132.5 (pyrrole α-C), 131.7, 131.2 (pyrrole β-C), 130.9 (phenylene C correlated with the H at 6.65 ppm), 130.8 (quinoid C correlated with the H at 7.57 ppm), 130.5 (phenylene C correlated with the H at 6.75 ppm), 130.2 (quinoid C correlated with the H at 7.65 ppm), 129.65 (quinoid C correlated with the H at 7.11 and 6.48 ppm), 128.6 (phenylene C correlated with the H at 6.93 ppm), 128.1 (β-C of a pyrrole bearing NH), 126.6 (phenylene C correlated with the H at 6.93 ppm), 115.8, 115.21, 115.16 (pyrrole β-C correlated with the H at 6.55, 6.47 and 6.41 ppm), 46.6 (N*CH*$_2$Ar), 35.6 (2 tert-butyl quaternary C), 35.4 (tert-butyl quaternary C), 35.1 (tert-butyl quaternary C), 34.3 (C*CH*$_2$Ar), 29.6 (tert-butyl CH_3), 29.4 (2 tert-butyl CH_3) 29.0 (tert-butyl CH_3); UV/Vis 485.5; ESI-MS 1329 (MH^+).

Experimental part of Chapter 2

Dipyrromethanes **75** and **158** and 4-methoxy-3,5-di-*t*-butylbenzaldehyde **177** were prepared according to published procedures.[131,156] 5-aminoethylindole-3-acetic acid **163** was obtained courtesy of Dr. Magnus, Ruđer Bošković Institute, Zagreb, Croatia. All other reagents and solvents were commercially available and used as purchased, including most of the aromatic aldehydes.

***Meso*-5,15-bis(2,6-dichlorophenyl)-10-pentafluorophenylcorrole 136** [95]

197 mg (0.67 mmol) of dipyrromethane **75** and 25 mg (0.13 mmol) of pentafluorobenzaldehyde **68** were stirred in 30 ml of dichloromethane under an argon atmosphere at room temperature for 15 minutes. 50 μl of 10% solution of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (0.05) was added and the flask was wrapped in aluminium foil. After 1 h, the reaction was quenched with diluted aqueous NaOH. The reaction mixture was washed with water and dried over $MgSO_4$. Upon filtration and evaporation to dryness, 70 mg (1.3 mmol) of ammonium chloride was added to the crude residue and the mixture was dissolved in 100 ml of propionitrile. 100 mg (0.4 mmol) of *p*-chloranil was added and the mixture was stirred overnight. The solvent was evaporated and 22 mg (22%) of product **136** was isolated from the mixture by chromatography in mixtures of dichloromethane and light petroleum ether (1:1 to 1:4) with addition of 1% triethylamine.

***Meso*-5,15-bis(2,6-dichlorophenyl)-10,20-bis(pentafluorophenyl)porphyrin 137**

380 mg (1.31 mmol) of dipyrromethane **75** and 138 mg (0.70 mmol) of pentafluorobenzaldehyde **68** were stirred in 60 ml of dichloromethane under an argon atmosphere at room temperature for 20 minutes. 75 μl of 10% solution of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (0.07 mmol) was added. After 1 h, the reaction was quenched with diluted aqueous NaOH. The reaction mixture was washed twice with water and dried over $MgSO_4$. Upon filtration and evaporation to dryness, the yellow half-solid was dissolved in 350 ml propionitrile. 377 mg (7.1 mmol) of ammonium chloride and 475 mg (2.1 mmol) of DDQ were added and the mixture was stirred for 1 h. Upon evaporation of the solvent, 75 mg (23%) of product **137** was isolated by chromatography in mixtures of dichloromethane and light petroleum ether (1:1) with addition of 1% triethylamine. δ_H (300 MHz) 8.78 (m, 8H, β-pyrrole H), 7.83 (m, 4H, dichlorophenyl *m*-H), 7.75 (m, 2H, dichlorophenyl *p*-H), -2.71 (br. s, 2H, NH); UV/Vis 415.5 ($2.57{\cdot}10^5$), 509.3 ($0.26{\cdot}10^5$); ESI-MS 931 (MH^+).

***Meso*-5,15-bis(2,6-dichlorophenyl)-10-(4-nitrophenyl)corrole 139**

2.077 g (7.13 mmol) of dipyrromethane **75** and 335 mg (2.22 mmol) of 4-nitrobenzaldehyde **138** were dissolved in 200 ml of dichloromethane. 5 mg of CCl_3CO_2H (0.03 mmol) in 1 – 2ml of CH_2Cl_2 was added and the mixture was stirred at 0°C for ~24 h. The bath was warmed to ~40°C, 1.110 g (4.43 mmol) of *p*-chloranil was added and the mixture was further stirred

for 3 h. The mixture was evaporated with silica and chromatographed in mixtures of dichloromethane and *n*-heptane (1st column: 1:1, 2nd column: 2:1) to afford 267 mg (17%) of product **139**. δ_H 9.01 (d, *J* 4.2, 2H, 2-H and 18-H of corrole), 8.59 (d, *J* 8.6, 2H, *p*-nitrophenyl *m*-H), 8.57 (d, *J* 4.8, 2H, 8-H and 12-H of corrole), 8.51 (d, *J* 4.8, 2H, 7-H and 13-H of corrole), 8.43 (d, *J* 4.2, 2H, 3-H and 17-H of corrole), 8.36 (d, *J* 8.6, 2H, *p*-nitrophenyl *o*-H), 7.77 (d, *J* 8.0, 4H, dichlorophenyl *m*-H), 7.65 (dd, J_1 8.0, J_2 8.6, 2H, dichlorophenyl *p*-H) -2.20 (br. s, 3H, NH); δ_C 149.1, 147.5, 138.5, 137.1, 135.3 (*p*-nitrophenyl *o*-C), 134.3, 130.5 (dichlorophenyl *p*-C), 130.1, 128.1 (dichlorophenyl *m*-C), 126.9 (7-C and 13-C of corrole), 126.5 (8-C and 12-C of corrole), 122.3 (*p*-nitrophenyl *m*-C), 121.0 (C-3 and C-17 of corrole), 116.3 (C-2 and C-18 of corrole), 109.3; UV-Vis 410.4 ($1.02 \cdot 10^5$), 568.3 ($0.24 \cdot 10^5$); ESI-MS 708 (MH^+).

Meso-5,10,15-tris(2,6-dichlorophenyl)corrole 140

Obtained as a by-product in most corrole syntheses from dipyrromethane **75**. δ_H 8.92 (d, *J* 4.1, 2H, 2-H and 18-H of corrole), 8.50 (d, *J* 4.7, 2H, 7-H and 13-H of corrole), 8.35 (overlapped d, 2H, 3-H and 17-H of corrole), 8.34 (overlapped d, 2H, 8-H and 12-H of corrole), 7.72 (d, *J* 8.1, 6H, dichlorophenyl *m*-H) 7.59 (dd, J_1 8.1, J_2 8.1, 3H, dichlorophenyl *p*-H) -2.03 (br. s, 3H, NH); δ_C 141.8 (9-C and 11-C of corrole), 140.1 (6-C and 14-C of corrole), 139.2 (1-C of 10-dichlorophenyl), 139.1 (1-C of 5,15-dichlorophenyl), 138.5 (2-C and 6-C of 5,15-dichlorophenyl), 137.1 (2-C and 6-C of 10-dichlorophenyl), 134.3 (A and D ring α-pyrrole C), 130.4 (4-C of 5,15-dichlorophenyl), 130.1 (4-C of 10-dichlorophenyl), 128.0 (3-C and 5-C of 5,15-dichlorophenyl), 127.9 (3-C and 5-C of 10-dichlorophenyl), 127.0 (7-C and 13-C of corrole), 125.5 (8-C and 12-C of corrole), 120.6 (A and D ring β-pyrrole C), 115.8 (A and D ring β-pyrrole C), 109.9 (5-C and 15-C of corrole), 105.3 (10-C of corrole); UV-Vis 409.4 ($1.12 \cdot 10^5$), 422.9 ($1.02 \cdot 10^5$), 566.5 ($0.20 \cdot 10^5$); ESI-MS 731 (MH^+).

4-(10-Undecenoxy)benzaldehyde 152

A mixture of 7.030 g (28.64 mmol) of 11-bromo-1-undecene **151**, 4.892 g (39.66 mmol) of *p*-hydroxybenzaldehyde **72** and 8.328 g (60.26 mmol) of potassium carbonate was heated at reflux in 105 ml of acetone (p.a.) for 15 h. Upon cooling, the reaction mixture was filtered, evaporated to dryness and the residue was taken into dichloromethane. The solution was washed three times with aqueous NaOH, then three times with water and dried over $MgSO_4$. Upon filtration and removal of CH_2Cl_2 by distillation under reduced pressure, product **152** was purified by column chromatography on silica. Eluting with 1:1 dichloromethane / light petroleum ether afforded 7.450 g (95%) of the title product. δ_H (300 MHz) 9.88 (s, 1H, aldehyde H), 7.82 (d, *J* 8.1, 2H, aryl H), 6.99 (d, *J* 8.1, 2H, aryl H), 5.81 (m, 1H, undecenyl 10-H), 4.97 (m, 2H, undecenyl 11-H) 4.04 (t, *J* 6.6, 2H, undecenyl 1-H), 2.04 (q, *J* 7.0, 2H, undecenyl H), 1.81 (quintet, *J* 7.0, 2H, undecenyl 2-H), 1.46 – 1.31 (m, 12H, undecenyl H).

4-(11-Thioacetoxyundecyl)benzaldehyde 153

7.450 g (27.15 mmol) of aldehyde **152**, 4 ml (56.23 mmol) of thioacetic acid and 229 mg (1.37 mmol) of azo-*bis*-isobutyronitrile were dissolved in 90 ml of toluene (p.a.). The mixture was degassed with a stream of argon and then refluxed for 6.5 h. The reaction was quenched with 5% aqueous $NaHCO_3$ (400 ml) and extracted three times with ethyl acetate. The combined organic layers were washed with 5% aqueous $NaHCO_3$, then brine and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, the yellow solid residue was chromatographed on silica eluting with a gradient of 5:1 to 1:1 light petroleum ether / ethyl acetate. The crude product obtained was recrystallized from methanol to afford 4.086 g (43%) of **153** as a white powder. δ_H (300 MHz) 9.88 (s, 1H, aldehyde H), 7.83 (d, *J* 8.6, 2H, aryl H), 6.99 (d, *J* 8.6, 2H, aryl H), 4.04 (t, *J* 6.6, 2H, undecenyl 1-H), 2.86 (t, *J* 7.3, 2H, undecenyl 11-H), 2.32 (s, 3H, CH_3), 1.81 (quintet, *J* 7.3, 2H, undecenyl 2-H), 1.46 – 1.28 (m, 16H, $8CH_2$).

***Meso*-5,15-bis(2,6-dichlorophenyl)-10-(4-(11-thioacetoxy-1-dodecyloxy) phenyl)corrole 154**

1.522 g (5.23 mmol) of dipyrromethane **75** and 606 mg (1.73 mmol) of aldehyde **153** were dissolved in 146 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and placed in an ice bath. Argon was bubbled through the solution for 15 min. 10 μl of TFA (0.13 mmol) was added and the mixture was stirred under an argon atmosphere for ~48 h. The ice bath was removed and 935 mg (3.77 mmol) of *p*-chloranil was added. After additional 1 h at room temperature, the mixture was evaporated with silica and chromatographed twice in a 1.5:1 mixture of dichloromethane and *n*-heptane to afford 452 mg (29%) of product **154**. δ_H 9.00 (d, *J* 4.1, 2H, 2-H and 18-H of corrole), 8.62 (d, *J* 4.7, 2H, 8-H and 12-H of corrole), 8.53 (d, *J* 4.7, 2H, 7-H and 13-H of corrole), 8.42 (d, *J* 4.1, 2H, 3-H and 17-H of corrole), 8.08 (d, *J* 8.5, 2H, aryl *o*-H), 7.78 (d, *J* 7.7, 4H, dichlorophenyl *m*-H), 7.66 (dd, J_1 7.7, J_2 8.7, 2H, dichlorophenyl *p*-H), 7.27 (d partially overlapped with $CHCl_3$, *J* 8.5, 2H, aryl *m*-H), 4.24 (t, *J* 6.5, 2H, OCH_2), 2.89 (t, *J* 7.3, 2H, SCH_2), 2.32 (s, 3H, CH_3), 1.98 (quintet, *J* 7.4, 2H, β-CH_2), 1.62 – 1.36 (m, 16H, $8CH_2$), -2.30 (br. s, 3H, NH); δ_C 196.0, 158.9, 138.6 (quaternary C), 137.4 (quaternary C), 135.5 (CH), 134.0 (quaternary C), 130.3 (dichlorophenyl *p*-C), 128.0 (dichlorophenyl *m*-C), 127.2 (pyrrole CH), 125.7 (pyrrole CH), 120.8 (C-3 and C-17 of corrole), 116.2 (C-2 and C-18 of corrole), 113.2 (CH), 111.7 (quaternary C), 108.8 (quaternary C), 68.3, 30.6, 29.6, 29.5, 29.1, 28.8, 26.2; UV-Vis 410.1 ($1.35 \cdot 10^5$), 566.1 ($0.22 \cdot 10^5$); ESI-MS 907 (MH^+).

***Meso*-5,15-bis(2,6-dichlorophenyl)-10-(4-(11-mercapto-1-dodecyloxy) phenyl)corrole 155**

130 mg (0.14 mmol) of compound **154** was dissolved in 7.5 ml of THF and 3 ml of methanol. The flask was placed in an ice bath and 1 ml of a 1.65 M solution of CH_3ONa in methanol (1.65 mmol of CH_3ONa) was added. The

reaction mixture was stirred at 0°C for 30 min and then poured into diluted aqueous HCl (~0.02 M). This solution was extracted with ethyl acetate (some brine had to be added for a better separation) and then washed with brine, distilled water and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, 26 mg (21%) of product **155** was isolated by chromatography in mixtures of CH_2Cl_2 and hexane (1.5:1, column and 1:1, preparative plate). δ_H 8.97 (d, *J* 3.9, 2H, 2-H and 18-H of corrole), 8.61 (d, *J* 4.5, 2H, 8-H and 12-H of corrole), 8.51 (d, *J* 4.5, 2H, 7-H and 13-H of corrole), 8.39 (d, *J* 3.9, 2H, 3-H and 17-H of corrole), 8.07 (d, *J* 8.2, 2H, aryl *o*-H), 7.72 (m, 4H, dichlorophenyl *m*-H), 7.59 (dd, J_1 8.3, J_2 8.3, 2H, dichlorophenyl *p*-H), 7.24 (d partially overlapped with $CHCl_3$, *J* 8.2, 2H, aryl *m*-H), 4.20 (t, *J* 6.4, 2H, OCH_2), 2.50 (t, *J* 6.8, 2H, SCH_2), 1.93 (quintet, 2H, β-CH_2), 1.60 (m, 4 H, 2 CH_2), 1.39 – 1.26 (m, 13H, 6CH_2 and SH), ~ -1.9 (br. s, 3H, NH); δ_C 158.8 (CO), 142.1 (9-C and 11-C of corrole), 139.8 (6-C and 14-C of corrole), 138.5, 137.4, 135.5, 134.6, 134.0, 130.7, 130.3, 128.0 (3-C and 5-C of 5,15-dichlorophenyl), 127.1, 125.7 (8-C and 12-C of corrole), 120.8 (A and D ring β-pyrrole C), 116.2 (A and D ring β-pyrrole C), 113.2 (A and D ring β-pyrrole C), 111.7 (5-C and 15-C of corrole), 108.9 (10-C of corrole); ESI-MS 865 (MH^+).

O-(4-(*Meso*-5,15-bis(2,6-dichlorophenyl)corrolyl)phenyl)-12-oxadodecyl disulfide 156

Isolated as a by-product in the synthesis of corrole thiol **155**. δ_H (300 MHz) 8.98 (d, *J* 4.4, 4H, 2-H and 18-H of corrole), 8.61 (d, *J* 4.8, 4H, 8-H and 12-H of corrole), 8.51 (d, *J* 4.8, 4H, 7-H and 13-H of corrole), 8.40 (d, *J* 4.4, 4H, 3-H and 17-H of corrole), 8.06 (d, *J* 8.8, 4H, aryl *o*-H), 7.75 (d, *J* 7.4, 8H, dichlorophenyl *m*-H), 7.62 (dd, J_1 7.4, J_2 9.0, 4H, dichlorophenyl *p*-H), 7.24 (d overlapped with $CHCl_3$, 4H, aryl *m*-H), 4.20 (t, *J* 6.4, 4H, OCH_2), 2.70 (t, *J* 7.3, 4H, SCH_2), 1.95 (quintet, 4H, β-CH_2), 1.68 – 1.35 (m, 32H, 16CH_2), -2.23 (br. s, 6H, NH); ESI-MS 864 ($M/2 + H^+$).

Meso-5,15-dimesityl-10-(4-nitrophenyl)corrole 159 [104]

1.597 g (6.04 mmol) of dipyrromethane **158** and 289 mg (1.91 mmol) of *p*-nitrobenzaldehyde were dissolved in 165 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and placed in an ice bath. 4.3 mg of trichloroacetic acid (0.026 mmol) was added and the mixture was stirred for 20 h. The bath was replaced with a warm water bath (40°C) and 990 mg (3.99 mmol) of *p*-chloranil was added. After 1 h, the mixture was evaporated with silica. Repeated chromatography on silica in mixtures of dichloromethane and *n*-heptane (ratios ranging from 2:1 to 1:1) and recrystallization from dichloromethane/*n*-heptane afforded 230 mg (18%) of product **159**.

Meso-5,15-(2,6-dichlorophenyl)-10-(4-methoxycarbonylphenyl)corrole 161

2.138 g (7.34 mmol) of dipyrromethane **75** and 395 mg (2.29 mmol) of *p*-methoxycarbonylbenzaldehyde were dissolved in 200 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and placed in an ice bath. 6.0 mg of trichloroacetic acid (0.036 mmol) was added and the mixture was stirred for 22 h. The bath was replaced with a warm water bath (40°C) and 1.180 g (4.76 mmol) of *p*-chloranil was added. After 1 h, the mixture was evaporated with silica. The residue was chromatographed twice on silica in a mixture of dichloromethane and *n*-heptane (2:1) and the crude product was recrystallized from dichloromethane/*n*-heptane to afford 374 mg (23%) of compound **161**. δ_H (300 MHz) 9.00 (d, *J* 4.4, 2H, 2-H and 18-H of corrole), 8.55 – 8.54 (m, 4H), 8.42 – 8.38 (m, 4H), 8.27 (d, *J* 8.0, 2H, methoxycarbonylaryl H), 7.76 (m, 4H, dichlorophenyl *m*-H), 7.64 (dd, J_1 7.1, J_2 9.0, 2H, dichlorophenyl *p*-H), 4.08 (s, 3H, CH_3), -2.06 (br. s, 3H, NH); UV-Vis 421.8 ($1.16 \cdot 10^5$), 567.8 ($0.20 \cdot 10^5$), 608.4 ($0.17 \cdot 10^5$); ESI-MS 721 (MH^+).

Meso-5,15-(2,6-dichlorophenyl)-10-(4-carboxyphenyl)corrole 162

257 mg (0.356 mmol) of corrole **161** was dissolved in 20 ml ofethanol. 350 μl of a 5 M aqueous solution of NaOH (1.75 mmol) was added. The reaction mixture was stirred at room temperature at some time before reflux was started. As a spot of the starting material could still be observed on TLC after 1 h 20 min after the beginning of reflux, another aliquot (350 μl, 1.75 mmol) of NaOH solution was added. After 2 h 20 min of reflux in total, the reaction mixture was cooled to room temperature. 25 ml of water was added and the whole mixture was poured into 15 ml of water containing 0.3 ml of conc. HCl (3.54 mmol). The precipitate formed was filtered through a Büchner funnel and rinsed with an abundant volume of water. Upon drying, 223 mg (88%) of product **162** was obtained. δ_H (300 MHz, DMSO-d_6) 13.17 (br. s, 1 H, COOH), 9.07 (d, *J* 4.0, 2H, 2-H and 18-H of corrole), 8.46 (s, 4H), 8.34 (d, *J* 8.0, 2H, carboxyaryl H), 8.25 – 8.22 (m, 4H), 7.96 (d, *J* 7.7, 4H, dichlorophenyl *m*-H), 7.85 (m, 2H, dichlorophenyl *p*-H), -2.70 (br. s, 3H, NH); ESI-MS 707 (MH^+).

Corrole-indole conjugate 166

25 mg (93 μmol) of 3-maleimidopropionic acid *N*-hydroxysuccinimide ester **164** and 18 mg (83 μmol) of 5-aminoethylindole-3-acetic acid **163** were stirred in a mixture of 2.5 ml of freshly distilled THF and 1.7 ml of 0.5 M phosphate buffer pH 7 for 6 h (until complete disappearance of the **164** spot on TLC).[157] To this solution, a solution of 26 mg (30 μmol) of corrole **155** in 2.6 ml of THF was added. The resulting mixture was stirred at room temperature for 3.5 h (until complete disappearance of the **155** spot on TLC) and then partitioned between ethyl acetate and water. The organic layer was washed with brine, water and dried over $MgSO_4$. Upon filtration

and removal of the solvent under reduced pressure, 23 mg (62%) of olive green product **166** was isolated by preparative thin layer chromatography in dichloromethane / methanol 94:6. However, the product could not be fully characterized due to decomposition under the conditions of keeping. This process could have occurred through radical formation by light-induced electron transfer between the corrole and indole moieties, a phenomenon that has been observed for other indolic conjugates with macrocyclic aromatic dyes.[158] δ_H (300 MHz, CD_3OD) 9.33 (d, *J* 4.4, 2H, 2-H and 18-H of corrole), 8.72 - 8.69 (two overlapped d, 4H, B and C ring corrole H), 8.56 (d, *J* 4.4, 2H, 3-H and 17-H of corrole), 8.28 (d, *J* 8.4, 2H, phenoxy H), 7.96 (m, 4H, dichlorophenyl *m*-H), 7.88 (dd, J_1 6.9, J_2 9.2, 2H, dichlorophenyl *p*-H), 7.44 (d, *J* 8.4, 2H, phenoxy H), 7.36 (br. s, 1 H, 4-H of indole), 7.28 (d, *J* 8.8, 1 H, 7-H of indole), 7.14 (s, 1 H, 2-H of indole), 6.96 (d, *J* 8.8, 1 H, 6-H of indole), 4.28 (t, 2H, OCH_2). The remaining part of the spectrum shows signals plausibly belonging to the product; however, interpretation of this part is difficult due to impurities signals present; ESI-MS 1234 (MH^+).

Meso-5,15-(2,6-dichlorophenyl)-10-(4-hydroxy-3,5-di-tert-butylphenyl)corrole 174

1.630 g (5.60 mmol) of dipyrromethane **75** and 454 mg (1.88 mmol) of aldehyde **173** were dissolved in 123 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and argon was bubbled through the solution for 30 min. 27 μl of TFA (0.35 mmol) was added and the mixture was stirred under an argon atmosphere for ~48 h. 945 mg (3.81 mmol) of *p*-chloranil was added and the reaction mixture was stirred for additional 45 min at room temperature. The mixture was evaporated with silica and chromatographed twice in mixtures of dichloromethane and *n*-hexane (solvent ratios 4:3 and 1:1 respectively) to afford 444 mg (30%) of product **174**. δ_H 8.98 (d, *J* 4.1, 2H, 2-H and 18-H of corrole), 8.65 (d, *J* 4.7, 2H, 8-H and 12-H of corrole), 8.52 (d, *J* 4.7, 2H, 7-H and 13-H of corrole), 8.40 (d, *J* 4.1, 2H, 3-H and 17-H of corrole), 7.98 (s, 2H, 2-H and 6-H of hydroxydialkylphenyl), 7.75 (d, *J* 8.1, 4H, dichlorophenyl *m*-H), 7.62 (dd, J_1 8.1, J_2 8.1, 2H, dichlorophenyl *p*-H), 5.47 (s, 1H, OH), 1.61 (s, 18H, *t*-butyl), ~ -2 (br. s, 3H, NH); δ_C 153.4 (COH), 138.5 (2-C and 6-C of dichlorophenyl), 137.5 (1-C of dichlorophenyl), 134.5 (3-C and 5-C of hydroxydialkylphenyl), 132.7, 131.6 (2-C and 6-C of hydroxydialkylphenyl), 130.2 (4-C of dichlorophenyl), 128.0 (3-C and 5-C of dichlorophenyl), 127.5 (B and C ring β-pyrrole C), 125.6 (B and C ring β-pyrrole C), 121.0 (A and D ring β-pyrrole C), 116.1 (A and D ring β-pyrrole C), 113.3 (10-C of corrole), 34.6 (*t*-butyl quaternary C), 30.7 (*t*-butyl CH_3); UV-Vis 411.5 ($1.05 \cdot 10^5$), 421.9 ($1.00 \cdot 10^5$), 561.6 ($0.17 \cdot 10^5$); ESI-MS 791 (MH^+).

Meso-5,15-bis(2,6-dichlorophenyl)-10,20-bis(4-hydroxy-3,5-di-tert-butylphenyl)porphyrin 175

δ_H 8.92 (d, *J* 4.7, 4H, β-pyrrole H), 8.65 (d, *J* 4.7, 4H, β-pyrrole H), 8.04 (s, 4H, 2-H and 6-H of hydroxydialkylphenyl), 7.78 (d, *J* 7.9, 4H, 3-H and 5-H of dichlorophenyl), 7.67 (m, 2H, 4-H of dichlorophenyl), 5.52 (s, 2H, OH), 1.62 (s, 36H, *t*-butyl), ~ -2.5 (s, 2H, NH); δ_C 153.7 (COH), 140.3 (1-C of dichlorophenyl), 138.8 (2-C and 6-C of dichlorophenyl), 134.2 (3-C and 5-C of hydroxydialkylphenyl), 132.8 (1-C of hydroxydialkylphenyl), 132.0 (β-pyrrole C correlated with the H at 8.91 ppm), 130.3 (4-C of dichlorophenyl), 129.2 (β-pyrrole C correlated with the H at 8.65 ppm), 127.7 (3-C and 5-C of dichlorophenyl), 121.6 (porphyrin *meso*-C bearing hydroxydialkylphenyl), 113.7 (porphyrin *meso*-C bearing dichlorophenyl), 34.6 (*t*-butyl quaternary C), 30.7 (*t*-butyl CH_3); UV-Vis 423.8 ($2.00 \cdot 10^5$), 465.6 ($0.79 \cdot 10^5$), 517.6 ($0.15 \cdot 10^5$), 666.5 ($0.16 \cdot 10^5$); ESI-MS 1007 (MH^+).

Meso-5,15-(2,6-dichlorophenyl)-10-(4-methoxy-3,5-di-tert-butylphenyl)corrole 178

2.283 g (7.84 mmol) of dipyrromethane **75** and 609 mg (2.45 mmol) of aldehyde **177** were dissolved in 160 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and argon was bubbled through the solution for 10 min. 35 μl of TFA (0.45 mmol) was added and the mixture was stirred under an argon atmosphere for 18 h. 1200 mg (4.83 mmol) of *p*-chloranil was added and the reaction mixture was stirred for additional 30 min at room temperature. The mixture was evaporated with silica gel and chromatographed twice using a mixture of dichloromethane and *n*-hexane (changing the ratio from 1:1 to 2:1) to afford 536 mg (27%) of product **178**. δ_H 9.02 (d, *J* 4.2, 2H, 2-H and 18-H of corrole), 8.69 (d, *J* 4.7, 2H, 8-H and 12-H of corrole), 8.57 (d, *J* 4.7, 2H, 7-H and 13-H of corrole), 8.43 (d, *J* 4.2, 2H, 3-H and 17-H of corrole), 8.11 (s, 2H, 2-H and 6-H of hydroxydialkylphenyl), 7.78 (d, *J* 8.0, 4H, 3-C and 5-C of dichlorophenyl), 7.65 (dd, 2H, 4-C dichlorophenyl), 3.99 (s, 3H, CH_3), 1.63 (s, 18H, *t*-butyl), -2.37 (br. s, 3H, NH); δ_C 158.9 ($COCH_3$), 142.3, 142.0, 139.8, 138.5 (2-C and 6-C of dichlorophenyl), 137.4 (1-C of dichlorophenyl), 135.8, 134.4 133.4 (2-C and 6-C of hydroxydialkylphenyl), 130.3 (4-C of dichlorophenyl), 128.0 (3-C and 5-C of dichlorophenyl), 127.5 (B and C ring β-pyrrole C), 125.8 (B and C ring β-pyrrole C), 120.6 (A and D ring β-pyrrole C), 116.1 (A and D ring β-pyrrole C), 112.9 (5-C and 15-C of corrole), 108.8 (10-C of corrole), 64.5 (CH_3), 36.0 (*t*-butyl quaternary C), 32.4 (*t*-butyl CH_3); UV-Vis 420.2 ($1.83 \cdot 10^5$), 616.8 ($0.25 \cdot 10^5$); ESI-MS 805 (MH^+).

***Meso*-5,15-bis(2,6-dichlorophenyl)-10,20-bis(4-methoxy-3,5-di-tert-butylphenyl)porphyrin 179**

Isolated as a by-product (up to 1.8%) in syntheses of corrole **178**. UV-Vis 421.2 ($3.79 \cdot 10^5$), 456.8 ($0.64 \cdot 10^5$), 516.5 ($0.25 \cdot 10^5$), 652.9 ($0.15 \cdot 10^5$); ESI-MS 1035 (MH^+).

***Meso*-5,15-(2,6-dichlorophenyl)-10-(4-hydroxyphenyl)corrole 180**

1.823 g (6.26 mmol) of dipyrromethane **75** and 259 mg (2.10 mmol) of *p*-hydroxybenzaldehyde **72** were dissolved in 137 ml of dichloromethane. The reaction flask was wrapped in aluminium foil and argon was bubbled through the solution for 10 min. 30 μl of TFA (0.39 mmol) was added and the mixture was stirred under an argon atmosphere for 17 h. 1.077 g (4.34 mmol) of *p*-chloranil was added and the reaction mixture was stirred for additional 40 min at room temperature. The mixture was evaporated with silica gel. After repeated chromatography in dichloromethane, 139 mg (10%) of product **180**, which decomposed throughout the purification process, was obtained. δ_H 8.98 (d, *J* 4.0, 2H, 2-H and 18-H of corrole), 8.58 (d, *J* 4.6, 2H, B and C ring β-pyrrole H), 8.51 (d, *J* 4.6, 2H, B and C ring β-pyrrole H), 8.39 (d, *J* 4.0, 2H, 3-H and 17-H of corrole), 7.96 (d, *J* 8.0, 2H, 2-H and 6-H of hydroxyphenyl), 7.73 (d, *J* 8.1, 4H, 3-H and 5-H of dichlorophenyl), 7.60 (dd, 2H, 4-H of dichlorophenyl), 7.00 (d, *J* 8.0, 2H, 3-H and 5-H of hydroxyphenyl), δ_C 155.1 (COH), 142.2 (B and C ring α-pyrrole C), 139.7 (B and C ring α-pyrrole C), 138.5 (2-C and 6-C of dichlorophenyl), 137.3 (1-C of dichlorophenyl), 132.7, 135.5 (2-C and 6-C of hydroxyphenyl), 134.6 (A and D ring α-pyrrole C), 134.1 (1-C of hydroxyphenyl), 130.6 (A and D ring α-pyrrole C), 130.3 (4-C of dichlorophenyl), 128.0 (3-C and 5-C of dichlorophenyl), 127.1 (B and C ring β-pyrrole C), 125.7 (B and C ring β-pyrrole C), 120.8 (A and D ring β-pyrrole C), 116.2 (A and D ring β-pyrrole C), 114.0 (3-C and 5-C of hydroxyphenyl), 111.4 (10-C of corrole), 109.0 (5-C and 15-C of corrole); ESI-MS 679 (MH^+).

***Meso*-5,15-(2,6-dichlorophenyl)-10-(4-hydroxy-3,5-di-tert-butylphenyl)-N_{22}-(ethoxycarbonyl)methylcorrole 182** and ***meso*-5,15-(2,6-dichlorophenyl)-10-(4-hydroxy-3,5-di-tert-butylphenyl)-N_{21}-(ethoxycarbonyl)methylcorrole 183**

109 mg (0.14 mmol) of corrole **174** and 35 mg of NaH (80% wt. in mineral oil; 1.17 mmol) were stirred in 19 ml of acetone (p.a.) for 7 min. A solution of 400 μl of ethyl bromoacetate **89** (94%; 3.39 mmol) in 6 ml of acetone (p.a.) was added and the mixture was refluxed for ~24 h. Upon the cooling, the reaction mixture was taken into diethyl ether and washed thrice with water and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, the mixture was fractionated by column chromatography on silica gel. Eluting with dichloromethane / *n*-hexane (changing the ratio from 7:8 to 1.6:1) gave 41 mg (34%) of green-brownish

compound **182** and 73 mg (61%) of its blue-greenish isomer **183**. Analysis, compound **182**: δ_H 9.01 (d, *J* 4.1, 1H, 2-H or 18-H of corrole), 8.96 (d, *J* 4.2, 1H, 2-H or 18-H of corrole), 8.60 (d, *J* 4.6, 1H, 12-H of corrole), 8.56 (d, *J* 4.1, 1H, 3-H or 17-H of corrole, correlated with the H at 9.01 ppm), 8.47 (d, *J* 4.6, 1H, 13-H of corrole), 8.36 (overlapped d, 1H, 3-H or 17-H of corrole, correlated with the H at 8.96 ppm), 8.33 (br. s, 1H, hydroxydialkylphenyl H close to the B pyrrole ring), 8.24 (d, *J* 4.7, 1H, 7-H of corrole), 8.10 (d, *J* 4.7, 1H, 8-H of corrole), 7.88 (br. s, 1H, hydroxydialkylphenyl H close to the C pyrrole ring), 7.74 (m, 4H, 3-H and 5-H of dichlorophenyl), 7.61 (m, 2H, 4-H of dichlorophenyl), 5.52 (s, 1H, OH), 3.11 (m, 1H, ethyl CH_2), 3.05 (m, 1H, ethyl CH_2), 1.65 (m, 9H, *t*-butyl closer to the B pyrrole ring), 1.59 (m, 9H, *t*-butyl closer to the C pyrrole ring), 0.45 (t, *J* 7.1, 3H, ethyl CH_3), -2.78 (br. s, 1H, NH), -3.73 (d, ^2J 18.0, 1H, NCH_2), -3.76 (d, ^2J 18.0, 1H, NCH_2); δ_C 165.0 (COO), 153.9 (COH), 151.8 (9-C of corrole), 147.3 (6-C of corrole), 145.1 (α-pyrrole C), 141.8 (α-pyrrole C), 138.7 (quaternary C of dichlorophenyl), 138.5 (quaternary C of dichlorophenyl), 137.9 (quaternary C of dichlorophenyl), 137.3 (quaternary C of dichlorophenyl), 135.8 (α-pyrrole C), 135.6 (α-pyrrole C), 134.9 (hydroxydialkylphenyl C bearing *t*-butyl), 134.2 (hydroxydialkylphenyl C bearing *t*-butyl), 133.4 (hydroxydialkylphenyl CH), 132.1 (hydroxydialkylphenyl CH), 130.4 (4-C of dichlorophenyl), 130.0 (4-C of dichlorophenyl), 129.8 (β-pyrrole C, correlated with the H at 8.56 ppm), 129.0 (α-pyrrole C), 128.3 (*m*-dichlorophenyl C), 128.1 (*m*-dichlorophenyl C), 127.9 (*m*-dichlorophenyl C), 127.8 (*m*-dichlorophenyl C), 127.6 (α-pyrrole C), 124.7 (12-C of corrole), 123.2 (13-C of corrole), 122.9 (B ring β-C), 122.7 (B ring β-C), 121.4 (β-pyrrole C, correlated with the H at 9.01 ppm), 119.0 (β-pyrrole C, correlated with the H at 8.36 ppm), 115.8 (β-pyrrole C, correlated with the H at 8.96 ppm), 113.9 (*meso*-C), 113.7 (*meso*-C), 106.1 (10-C of corrole), 59.8 (ethyl CH_2), 43.2 (NCH_2), 34.6 (*t*-butyl quaternary C), 30.7 (*t*-butyl CH_3), 13.3 (ethyl CH_3); UV-Vis 424.2 ($1.49 \cdot 10^5$), 661.7 ($0.21 \cdot 10^5$); ESI-MS 877 (MH^+); compound **183**: δ_H 8.87 (d, *J* 4.2, 1H, 18-H of corrole), 8.59 (d, *J* 4.7, 1H, 12-H of corrole), 8.46 (d, *J* 4.5, 1H, 8-H of corrole), 8.43 (d, *J* 4.2, 1H, 17-H of corrole), 8.36 (overlapped d, 3H, 2-H, 7-H and 13-H of corrole), 8.03 (d, *J* 1.8, 1H, hydroxydialkylphenyl H), 7.78 (m, 3H, 2 dichlorophenyl H and 1 hydroxydialkylphenyl H), 7.62 (m, 5H, 4 dichlorophenyl H and 3-H of corrole), 5.43 (s, 1H, OH), 3.32 (m, 1H, ethyl CH_2), 3.24 (m, 1H, ethyl CH_2), 1.62 (s, 9H, *t*-butyl), 1.56 (s, 9H, *t*-butyl), 0.61 (t, *J* 7.1, 3H, ethyl CH_3), -2.89 (br. s, 1H, NH), -2.13 (d, ^2J 18.0, 1H, NCH_2), -2.19 (d, ^2J 18.0, 1H, NCH_2); δ_C 165.7 (COO), 154.2 (B ring α-C), 153.2 (COH), 149.9 (B ring α-C), 148.8 (A ring α-C), 141.7 (A ring α-C), 139.3, 138.3, 138.2 (quaternary C of dichlorophenyl), 137.9 (quaternary C of dichlorophenyl), 137.4 (quaternary C of dichlorophenyl), 134.7 (α-pyrrole C), 134.4 (hydroxydialkylphenyl C bearing *t*-butyl), 134.3 (hydroxydialkylphenyl C bearing *t*-butyl), 133.7 (α-pyrrole C), 132.7 (1-C of hydroxydialkylphenyl), 131.4 (2 hydroxydialkylphenyl CH), 131.2 (8-C of corrole), 131.1 (α-pyrrole C), 131.0 (β-pyrrole C, correlated with an H at 8.36 ppm), 130.0 (4-C of dichlorophenyl), 129.9 (4-C of dichlorophenyl), 128.3 (*m*-dichlorophenyl C),

128.1 (*m*-dichlorophenyl C), 127.9 (*m*-dichlorophenyl C), 127.8 (*m*-dichlorophenyl C), 127.3 (12-C of corrole), 124.0 (13-C of corrole), 122.6 (17-C of corrole), 115.2 (β-pyrrole C, correlated with an H at 8.36 ppm), 115.0 (18-C of corrole), 114.2 (10-C of corrole), 113.7 (*meso*-C), 112.1 (3-C of corrole), 106.9 (*meso*-C), 60.1 (ethyl CH_2), 44.8 (NCH_2), 34.6 (*t*-butyl quaternary C), 30.7 (*t*-butyl CH_3), 13.4 (ethyl CH_3); UV-Vis 414.3 ($1.15 \cdot 10^5$), 432.8 ($0.86 \cdot 10^5$), 577.2 ($0.28 \cdot 10^5$), 621.4 ($0.16 \cdot 10^5$); ESI-MS 877 (MH^+).

Experimental part of Chapter 3

2-Trichloroacetylpyrrole **200** and 2-ethoxycarbonylpyrrole **204** were prepared according to published procedures.[150]

2-Trichloroacetyl-5-formylpyrrole 201

3.970 g (26 mmol) of $POCl_3$ was added dropwise into 1.892 g (26 mmol) of DMF in an ice bath while the temperature was maintained at 15-20°C. The ice bath was removed and the mixture was stirred for 15 min. The ice bath was replaced and 6 ml of 1,2-dichloroethane was added to the mixture. At 3°C, a solution of 2.034 g (10 mmol) of 2-trichloroacetylpyrrole **200** in 11 ml of 1,2-dichloroethane was added within 10 min. The reaction mixture was then refluxed for 4 h. Upon cooling to room temperature, a solution of 10.6 g (129 mmol) of NaOAc in 24 ml of water was added. The mixture was again brought to reflux and vigorously stirred for 15 min. The layers were then allowed to separate and the aqueous layer was extracted thrice with diethyl ether. The combined organic layers were washed thrice with a saturated Na_2CO_3 solution and dried over Na_2CO_3. Upon filtration and removal of the solvent under reduced pressure, the product was isolated by chromatography with ethyl acetate / *n*-heptane (1:1) as 153 mg (7%) of a grey solid. δ_H (300 MHz) 9.86 (s, 1H, CHO), 7.78 (s, 1H, NH), 7.75 (d, *J* 3.3, 1H, 3-H of pyrrole), 7.52 (d, *J* 3.3, 1H, 4-H of pyrrole); MS (chemical ionization (CI)) 240 (MH^+).

2-Ethoxycarbonyl-5-formylpyrrole 206 and **2-ethoxycarbonyl-4-formylpyrrole 207**

7.789 g (50.8 mmol) of $POCl_3$ was added dropwise into 3.713 g (50.8 mmol) of DMF in an ice bath while the temperature was maintained at 15-20°C. The ice bath was removed and the mixture was stirred for 15 min. The ice bath was replaced and 11.6 ml of 1,2-dichloroethane was added to the yellow solution. At 5°C, a solution of 5.680 g (46.2 mmol) of 2-ethoxycarbonylpyrrole **204** in 30 ml of 1,2-dichloroethane was added within 15 min. The reaction mixture was then refluxed for 4 h. Upon cooling to room temperature, a solution of 20.84 g (254.1 mmol) of NaOAc in 75 ml of water was added. The mixture was again brought to reflux and vigorously stirred for 15 min. The layers were then allowed to separate and the aqueous layer was extracted thrice with diethyl ether with addition of brine for a better separation of the layers. The combined organic layers were washed thrice with a saturated Na_2CO_3 solution and dried over Na_2CO_3. Upon filtration and removal of the solvent under reduced pressure, the products were isolated by chromatography with ethyl acetate / light petroleum ether (1:1). The yield of **206** (light brown solid) was 4232 mg (61%). The yield of **207** was 1455 mg (21%). Analysis, compound **206**: m.p. 71.8 – 72.5°C; δ_H (300 MHz) 9.85 (s, 1H, CHO), 9.72 (s, 1H, NH), 6.95 (m, 2H, 3-H and 4-H of pyrrole), 4.39 (q, *J* 7.0, 2H, CH_2), 1.40 (t, *J* 7.0, 3H, CH_3); δ_C (75 MHz) 180.4 (CHO), 160.3 (COO), 134.3 (β-pyrrole C), 128.3 (β-pyrrole C), 119.8 (α-pyrrole C), 115.6 (α-pyrrole C), 61.4 (CH_2), 14.3 (CH_3); MS (electron impact (EI)) 167 ($M^{+\cdot}$), 138 ($M^{+\cdot}$ - CHO);

compound **207**: m.p. 101.2 – 102.5°C; δ_H (300 MHz) 9.86 (s, 1H, CHO), 9.59 (br. s, 1H, NH), 7.57 (m, 1H, 5-H of pyrrole), 7.34 (m, 1H, 3-H of pyrrole), 4.37 (q, *J* 7.0, 2H, CH_2), 1.39 (t, *J* 7.0, 3H, CH_3); δ_C (75 MHz) 185.7 (CHO), 161.0 (COO), 128.5 (pyrrole C), 127.5 (pyrrole C), 125.1 (pyrrole C), 114.1 (pyrrole C), 61.1 (CH_2), 14.3 (CH_3).

5-(4,6-Dioxo-2-thioxo-tetrahydropyrimidin-5-ylidenemethyl)-2-ethoxycarbonylpyrrole 211 and **5-(4,6-dioxo-2-thioxo-tetrahydropyrimidin-5-ylidenemethyl)-3-ethoxycarbonylpyrrole 212**

A solution of 240 mg (1.67 mmol) of 2-thiobarbituric acid in glacial acetic acid was added dropwise into a solution of 278 mg (1.67 mmol) of compound **206** (for regioisomer **211**) or compound **207** (for regioisomer **212**) within 20 min under stirring and reflux. The product was filtered off on a Büchner funnel and washed with water to afford 450 mg (92%) of lemon yellow compound **211** (465 mg (95%) regioisomer **212**). Analysis, compound **211**: δ_H (DMSO-d_6, 300 MHz) 13.51 (s, 1H, NH of pyrrole), 12.66 and 12.51 (2s, 2H, NHCSNH), 8.23 (s, 1H, ylidenemethyl H), 7.49 (m, 1H, 3-H of pyrrole), 7.04 (m, 1H, 4-H of pyrrole), 4.35 (q, *J* 7.0, 2H, CH_2), 1.32 (t, *J* 7.0, 3H, CH_3); δ_C (DMSO-d_6, 75 MHz): 178.9 (CS), 163.2 (COO), 162.6 (*cis*-CO), 160.3 (*trans*-CO), 142.1 (ylidenemethyl C), 131.9 (2-C of pyrrole) 131.1 (5-C of pyrrole), 117.8 (3-C of pyrrole), 115.9 (2-C of pyrrole), 62.1 (CH_2), 15.0 (CH_3); MS (CI) 294 ($M^{+\cdot}$), 248 ($M^{+\cdot}$ – CH_2CH_3OH); compound **212**: δ_H (DMSO-d_6, 300 MHz): 13.00 (s, 1H, NH of pyrrole), 12.31 and 12.22 (2s, 2H, NHCSNH), 8.41 (m, 1H, 5-H of pyrrole), 8.33 (s, 1H, ylidenemethyl H), 7.97 (s, 1H, 3-H of pyrrole), 4.30 (q, *J* 7.0, 2H, CH_2), 1.32 (t, *J* 7.0, 3H, CH_3); δ_C (DMSO-d_6, 75 MHz): 179.0 (CS), 163.3 (COO), 161.3 (*trans*-CO), 160.9 (*cis*-CO), 150.3 (ylidenemethyl C), 138.5 (2-C of pyrrole) 126.0 (4-C of pyrrole), 121.8 (5-C of pyrrole), 121.5 (3-C of pyrrole), 61.3 (CH_2), 15.1 (CH_3).

2-Ethoxycarbonyl-4-hexanoylpyrrole 214

A solution of 9.086 g (67.49 mmol) of hexanoyl chloride in 39.5 ml of dry CH_2Cl_2 was added dropwise into a mixture of 7.610 g (54.69) of compound **204**, 8.932 g (66.99) of $AlCl_3$, 60 ml of dry CH_2Cl_2 and 60 ml of dry nitromethane under an argon atmosphere. The mixture was stirred for 1 h and then poured on ice water. Upon separation of the phases, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Upon filtration and removal of all solvent under reduced pressure, the dark yellow solid residue was 12.970 g (100%) of pure product. m.p. 66.1°C; δ_H (300 MHz) 9.66 (s, 1H, NH), 7.54 (m, 1H, 5-H of pyrrole), 7.29 (s, 1H, 3-H of pyrrole), 4.35 (q, *J* 7.0, 2H, CH_2), 2.76 (t, *J* 7.0, 2H, 2-CH_2 of hexanoyl), 1.71 (m, 2H, 3-CH_2 of hexanoyl), 1.36 (m, 7H, 4-CH_2 and 5-CH_2 of hexanoyl, ethyl CH_3) 0.90 (t, *J* 7.0, 3H, CH_3 of hexanoyl); δ_C (75 MHz) 196.8 (CO), 161.5 (COO), 127.5 (pyrrole C), 126.5 (pyrrole C), 124.5 (pyrrole C), 115.2 (pyrrole C), 61.4 (CH_2), 40.2, 37.4, 32.0, 24.7, 22.9, 14.8 (CH_3), 14.4 (CH_3).

2-Ethoxycarbonyl-4-(2-ethylhexanoyl)pyrrole 215

A solution of 2.420 g (14.73 mmol) of 2-ethylhexanoyl chloride in 100 ml of dry CH_2Cl_2 was added dropwise at -25°C into a mixture of 1.850 g (13.28) of compound **204**, 2.030 g (15.2) of $AlCl_3$, 140 ml of dry CH_2Cl_2 and 132 ml of dry nitromethane under an argon atmosphere. The mixture was stirred for 4 days at room temperature and then poured on ice water. Upon separation of the phases, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, the product was isolated by repeated column chromatography with mixtures of light petroleum ether and ethyl acetate (solvent ratios from 5:1 to 1:1). The yield was 1.727 g (49%). δ_H 9.70 (br. s, 1H, NH), 7.55 (s, 1H, 5-H of pyrrole), 7.30 (s, 1H, 3-H of pyrrole), 4.35 (q, *J* 7.1, 2H, O*CH*$_2$CH$_3$), 2.94 (m, 1H, CH of hexanoyl), 1.74 (m, 2H, 3-CH_2 of hexanoyl), 1.53 (m, 2H, CH_2 of ethyl on the hexyl chain), 1.37 (t, *J* 7.1, 2H, OCH$_2$*CH*$_3$), 1.23 (m, 4H, 4-CH_2 and 5-CH_2 of hexanoyl) 0.85 (m, 6H, 2 CH_3 of the side chain); δ_C 200.1 (CO), 161.0 (COO), 128.2 (2-C of pyrrole), 126.1 (5-C of pyrrole), 124.2 (4-C of pyrrole), 114.7 (3-C of pyrrole), 60.9 (CH_2), 50.0 (tertiary C), 31.2, 29.9, 25.6, 22.9, 14.4 (OCH$_2$*CH*$_3$), 13.9 (6-C of hexyl), 12.0 (CH_3 of ethyl on the hexyl chain).

2-Ethoxycarbonyl-4-hexylpyrrole 217

Modus A. A mixture of 11.0 g (46.4 mmol) of compound **214**, 1 g (0.47 mmol) of 5% Pd/C and 5 ml (58 mmol) of conc. HCl was stirred in 750 ml of ethanol under a hydrogen atmosphere at room temperature and atmospheric pressure for 24 h. The catalyst was filtered off and washed with ethanol. The solution was extracted with diethyl ether and that solution was washed with aqueous $NaHCO_3$ and brine. The organic phase was evaporated to dryness. The product was purified by column chromatography with light petroleum ether / ethyl acetate (3:1) to afford 10.06 g (97%) of compound **217** as a viscous yellow liquid. *Modus B*. A mixture of 6.2 g (26.3 mmol) of compound **214**, 12.7 g (201.3 mmol, 7.65 eq.) of $NaCNBH_3$ and 12.7 g (39.8 mmol) of ZnI_2 in 250 ml of 1,2-dichloroethane was refluxed for 10 min. The yellow reaction mixture was filtered and the filtrate was washed thrice with water and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, 5150 mg (88%) of compound **217** was obtained. Repeating the same procedure with 3.0 equivalents of $NaCNBH_3$ gave 79% yield of the title product. δ_H (300 MHz) 10.03 (br. s, 1H, NH), 6.75 (m, 1H, 3-H of pyrrole), 6.71 (m, 1H, 5-H of pyrrole), 4.30 (q, *J* 7.0, 2H, CH_2 of ethyl), 2.44 (t, *J* 7.0, 2H, 1-CH_2 of hexyl), 1.55 (m, 2H, 2-CH_2 of hexyl), 1.33 (m, 9H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, CH_3 of ethyl) 0.88 (t, *J* 7.0, 3H, CH_3 of hexyl); δ_C (75 MHz) 161.2 (CO), 126.8 (4-C of pyrrole), 122.6 (2-C of pyrrole), 120.3 (5-C of pyrrole), 114.8 (3-C of pyrrole), 60.1 (CH_2 of ethyl), 31.7 (CH_2 of hexyl), 30.9 (CH_2 of hexyl), 29.0 (CH_2 of hexyl), 26.7 (CH_2 of hexyl), 22.6 (CH_2 of hexyl), 14.9 (CH_3 of ethyl), 14.5 (CH_3 of hexyl); MS (CI) 224 (MH^+), 178 (MH^+ - CH_3CH_2OH).

2-Ethoxycarbonyl-4-(1-ethoxy)hexylpyrrole 218

Isolated by incomplete reaction (81). δ_H (300 MHz) 9.41 (br. s, 1H, NH), 6.88 (s, 1H, pyrrole H), 6.86 (s, 1H, pyrrole H), 4.32 (q, *J* 7.0, 2H, CH_2 of 2-ethoxycarbonyl), 4.15 (t, *J* 7.0, 1H, CH of hexyl), 3.45 (m, 1H, CH_2 of 1-ethoxyhexyl), 3.36 (m, 1H, CH_2 of 1-ethoxyhexyl), 1.82 (m, 1H, 2-CH_2 of hexyl), 1.65 (m, 1H, 2-CH_2 of hexyl), 1.27 (br. m, 12H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, 2CH_3 of ethyl) 0.83 (t, *J* 7.0, 3H, CH_3 of hexyl); δ_C (75 MHz) 161.3 (CO), 127.8 (4-C of pyrrole), 122.9 (2-C of pyrrole), 120.8 (5-C of pyrrole), 113.6 (3-C of pyrrole), 75.7 (CH of hexyl), 63.4 (CH_2 of 1-ethoxyhexyl), 60.3 (CH_2 of 2-ethoxycarbonyl), 37.3 (CH_2 of hexyl), 31.7 (CH_2 of hexyl), 25.5 (CH_2 of hexyl), 22.6 (CH_2 of hexyl), 15.3 (CH_3 of ethyl), 14.4 (CH_3 of ethyl), 14.0 (CH_3 of hexyl); MS (CI) 268 (MH^+), 222 (MH^+ - CH_3CH_2OH).

2-Ethoxycarbonyl-4-(2-ethylhexyl)pyrrole 220

A mixture of 8.735 g (32.92 mmol) of compound **215**, 6.884 g (109.55 mmol, 3.33 eq.) of $NaCNBH_3$ and 16.584 g (51.76 mmol) of ZnI_2 in 350 ml of 1,2-dichloroethane was refluxed for 15 min. The reaction mixture was filtered and the filtrate was concentrated by evaporation under reduced pressure and then washed twice with water and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, the product was purified by column chromatography with light petroleum ether / ethyl acetate (4:1) to afford 6.172 mg (75%) of compound **220**. MS (CI) 252 (MH^+).

2-Ethoxycarbonyl-4-hexyl-5-iodopyrrole 222

A solution of 970 mg (4.35 mmol) of 2-ethoxycarbonyl-4-hexylpyrrole **217** in 9 ml of CH_2Cl_2 was added to a solution of 189 mg (1.07 mmol) of HIO_3 and 546 mg (2.15 mmol) of I_2 in a mixture of 6.9 ml of glacial acetic acid and 0.4 ml of H_2O. The mixture was stirred under reflux for 7 h. Upon cooling, the mixture was diluted with 20 ml of CH_2Cl_2 and treated with saturated aqueous $Na_2S_2O_3$ until decolouration occurred. 4% NaOH was carefully added until neutral pH was achieved. The organic layer was washed twice with water and dried over $MgSO_4$. The salt was filtered off and the filtrate was evaporated under reduced pressure. The product was purified by column chromatography with light petroleum ether / ethyl acetate 4:1 to afford 1150 mg (76%) of compound **222** as a white yellow solid. m.p. 59.8 – 60.4°C; δ_H (300 MHz) 9.05 (br. s, 1H, NH), 6.69 (d, *J* 2.2, 1H, 3-H of pyrrole), 4.31 (q, *J* 7.0, 2H, CH_2 of ethyl), 2.35 (t, *J* 7.0, 2H, 1-CH_2 of hexyl), 1.53 (m, 2H, 2-CH_2 of hexyl), 1.33 (m, 9H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, CH_3 of ethyl) 0.89 (t, *J* 7.0, 3H, CH_3 of hexyl); δ_C (75 MHz) 160.1 (CO), 131.8 (4-C of pyrrole), 126.9 (2-C of pyrrole), 115.1 (3-C of pyrrole), 72.9 (5-C of pyrrole), 60.5 (CH_2 of ethyl), 31.6 (CH_2 of hexyl), 30.2 (CH_2 of hexyl), 28.9 (CH_2 of hexyl), 28.1 (CH_2 of hexyl), 22.6 (CH_2 of hexyl), 14.4 (CH_3 of ethyl), 14.1 (CH_3 of hexyl); MS (CI) 350 (MH^+).

2-Ethoxycarbonyl-4-(2-ethyl)hexyl-5-iodopyrrole 223

A solution of 4.966 g (13.13 mmol) of 2-ethoxycarbonyl-4-(2-ethyl)hexylpyrrole **220** in 32 ml of CH_2Cl_2 was added to a solution of 764 mg (4.04 mmol) of HIO_3 and 2 g (7.88 mmol) of I_2 in a mixture of 20.8 ml of glacial acetic acid and 1.2 ml of H_2O. The mixture was stirred under reflux for 7 h. Upon cooling, the mixture was diluted with 75 ml of CH_2Cl_2 and treated with saturated aqueous $Na_2S_2O_3$ until decolouration occurred. 4% NaOH was carefully added until neutral pH was achieved. The organic layer was washed twice with water and dried over $MgSO_4$. The salt was filtered off and the filtrate was evaporated under reduced pressure. The product was purified by column chromatography with light petroleum ether / ethyl acetate 4:1 to afford 4.654 g (94%) of compound **223**. δ_H (300 MHz) 8.91 (br. s, 1H, NH), 6.69 (d, *J* 2.9, 1H, 3-H of pyrrole), 4.31 (q, *J* 7.0, 2H, CH_2 of O*CH*$_2$CH$_3$), 2.29 (d, *J* 7.3, 2H, 1-CH_2 of hexyl), ~1.5 (m, 1H, CH of hexyl), 1.35 (t, *J* 7.0, 3H, OCH$_2$*CH*$_3$), 1.32 – 1.27 (m, 9H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl and CH_3 of ethyl on the hexyl chain), 0.88 (m, 6H, 2CH_3); MS (CI) 378 (MH^+).

5-Chloro-2-ethoxycarbonyl-4-hexylpyrrole 224

At 0°C and under an argon atmosphere, a solution of 305 mg (1.37 mmol) of 2-ethoxycarbonyl-4-hexylpyrrole **217** in 12 ml of $CHCl_3$ was added to 907 mg (5.59 mmol) of $FeCl_3$. After 70 min of stirring, 75 ml of CH_2Cl_2 was added and the solution was extracted thrice with water. The organic layer was dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, 87 mg (29%) of the title product **224** was isolated by column chromatography with light petroleum ether / ethyl acetate (5:1). δ_H (300 MHz) 9.04 (br. s, 1H, NH), 6.74 (unresolved d, 1H, 3-H of pyrrole), 4.31 (q, *J* 7.0, 2H, CH_2 of ethyl), 2.40 (t, *J* 7.0, 2H, 1-CH_2 of hexyl), 1.55 (m, 2H, 2-CH_2 of hexyl), 1.34 (m, 9H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, CH_3 of ethyl) 0.87 (t, *J* 7.0, 3H, CH_3 of hexyl); δ_C (75 MHz) 160.8 (CO), 122.9 (pyrrole C), 121.0 (pyrrole C), 118.1 (pyrrole C), 116.1 (3-C of pyrrole), 60.9 (CH_2 of ethyl), 32.2 (CH_2 of hexyl), 30.2 (CH_2 of hexyl), 29.2 (CH_2 of hexyl), 25.5 (CH_2 of hexyl), 23.0 (CH_2 of hexyl), 14.8 (CH_3 of ethyl), 14.5 (CH_3 of hexyl); MS (EI) 257 ($M^{+\cdot}$), 222 ($M^{+\cdot}$ - Cl), 212 ($M^{+\cdot}$ - OEt), 186, 140.

5,5'-Diethoxycarbonyl-3,3'-dihexyl-2,2'-bipyrrole 81

Modus A; classic heating: 2.040 g (4.54 mmol) of *N*-protected pyrrole **226** (*vide infra*) and 1.630 g (25.7 mmol) of copper bronze were placed into a small three-necked flask. The mixture was degassed and brought under an argon atmosphere. 5 ml of DMF dried over molecular sieves was added with a syringe through the septum. The flask was heated to ~110°C for 8 h and allowed to cool to room temperature. The copper bronze was filtered off on a pad of Celite 535, which was subsequently extensively washed with CH_2Cl_2. All solvent was removed by evaporation under reduced pressure and the dark solid residue was placed in a round bottom flask

and heated in an oil bath to 180°C for 3 h under an argon atmosphere. Gas evolution occurred. The dark residue was fractionated by repeated column chromatography with light petroleum ether / ethyl acetate (changing the solvent ratio from 5:1 to 3:1) to afford 657 mg (65%) of the title product. The product could be recrystallized from methanol to give stable pure white crystals. *Modus B; microwave heating*: A mixture of 750 mg (1.67 mmol) of compound **226**, 600 mg (9.44 mmol) of copper bronze and 2 ml of dry DMF was brought under an argon atmosphere in a microwave tube. Microwave heating (t = 160°C, P = 100 W) was applied for 1.5 h. No significant pressure increase was observed. Upon cooling, the dark green solution was filtered through a pad of Celite 535 and the filter was washed extensively with CH_2Cl_2, extracted with water to remove DMF and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, column chromatography of the residue with mixtures of light petroleum ether and ethyl acetate afforded 224 mg (60%) of compound **81**. M.p. 82 - 83°C. δ_H (300 MHz) 8.85 (br. s, 2H, NH), 6.83 (unresolved d, 2H, 4-H and 4'-H of bipyrrole), 4.31 (q, *J* 7.0, 4H, CH_2 of ethyl), 2.44 (t, *J* 7.0, 4H, 2x 1-CH_2 of hexyl), 1.53 (m, 4H, 2x 2-CH_2 of hexyl), 1.30 (m, 18H, 2x (3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, CH_3 of ethyl)), 0.86 (t, *J* 7.0, 6H, 2CH_3 of hexyl); δ_C (75 MHz) 161.2 (CO), 126.0 (quaternary C of pyrrole), 124.9 (quaternary C of pyrrole), 122.4 (quaternary C of pyrrole), 115.5 (pyrrole CH), 60.4 (CH_2 of ethyl), 31.6 (CH_2 of hexyl), 30.7 (CH_2 of hexyl), 29.0 (CH_2 of hexyl), 26.1 (CH_2 of hexyl), 22.6 (CH_2 of hexyl), 14.4 (CH_3 of ethyl), 14.0 (CH_3 of hexyl); MS (CI) 445 (MH^+), 399 (MH^+ - CH_3CH_2OH).

_N-t_-Butoxycarbonyl-2-ethoxycarbonyl-4-hexyl-5-iodopyrrole 226

A solution of 4.336 g (12.42 mmol) of compound **222**, 3.282 g (14.90 mmol) of di-*t*-butyl dicarbonate and 156 mg (1.24 mmol) of *N*,*N*-dimethylaminopyridine in 60 ml of CH_2Cl_2 (p.a.) was stirred for 20 min, then concentrated by evaporation under reduced pressure and filtered through a pad of silica. The filter was washed extensively with CH_2Cl_2 and the filtrate was evaporated under reduced pressure to afford 5.580 g (100%) compound **226**. δ_H 6.76 (s, 1H, 3-H of pyrrole), 4.28 (q, *J* 7.1, 2H, CH_2 of ethyl), 2.37 (t, *J* 7.6, 2H, 1-CH_2 of hexyl), 1.63 (s, 9H, *t*-butyl), 1.35 – 1.31 (m, 9H, 3-CH_2, 4-CH_2 and 5-CH_2 of hexyl, CH_3 of ethyl) 0.89 (t, *J* 6.6, 3H, CH_3 of hexyl); δ_C 159.5 (CO of ethoxycarbonyl), 149.1 (CO of *t*-BOC), 132.2 (4-C of pyrrole), 128.2 (2-C of pyrrole), 118.3 (3-C of pyrrole), 85.9 (quaternary C of *t*-BOC), 76.6 (5-C of pyrrole), 60.6 (CH_2 of ethyl), 31.6 (CH_2 of hexyl), 29.8 (CH_2 of hexyl), 28.8 (CH_2 of hexyl), 28.6 (CH_2 of hexyl), 27.6 (CH_3 of *t*-BOC), 22.5 (CH_2 of hexyl), 14.3 (CH_3 of ethyl), 14.0 (CH_3 of hexyl).

3,3'-Dihexyl-2,2'-bipyrrole-5,5'-dicarboxylic acid 230

A solution of 193 mg (4.83 mmol) of NaOH in 13 ml of H_2O was added to a solution of 352 mg (0.78 mmol) of diester **81** in 2.6 ml of ethanol. The mixture was refluxed for 1 h. Upon cooling, the pH was brought to ~1 with

1M HCl. A white precipitate that formed was filtered off and extensively washed with water. Drying *in vacuo* gave 293 mg (96%) of light greyish white product. δ_H (DMSO) 11.29 (br. s, 2H, NH), 6.59 (s, 2H, 4-H and 4'-H of bipyrrole), 2.31 (t, *J* 7.6, 4H, 2x 1-CH_2 of hexyl), 1.41 (m, 4H, 2x 2-CH_2 of hexyl), 1.24 – 1.18 (m, 12H, 2x (3-CH_2, 4-CH_2 and 5-CH_2 of hexyl)), 0.81 (t, *J* 6.8, 6H, 2CH_3 of hexyl); δ_C (DMSO) 162.3 (CO), 124.7 (2-C of pyrrole), 124.0 (3-C of pyrrole), 123.5 (5-C of pyrrole), 114.2 (4-C of pyrrole), 31.0 (CH_2 of hexyl), 29.9 (CH_2 of hexyl), 28.4 (CH_2 of hexyl), 25.7 (CH_2 of hexyl), 22.0 (CH_2 of hexyl), 13.8 (CH_3 of hexyl).

5,5'-Diformyl-3,3'-Dihexyl-2,2'-bipyrrole 232

94 mg (0.24 mmol) of diacid **230** was dissolved in 3 ml of DMF and subjected to microwave heating at 200°C for 10 min (P = 100 W). A small sample of the reaction mixture was partitioned between diethyl ether and water; a mass spectrum of the organic layer showed a strong peak of 3,3'-unsubstituted bipyrrole **231** (301, MH^+). The reaction mixture was transferred into a round bottom flask and cooled to 0°C (ice bath) under an argon atmosphere. 91 µl (1.00 mmol) of $POCl_3$ was added through the septum and the mixture was stirred at 60°C for 2 h. A solution of 271 mg (6.78 mmol) of NaOH in 10 ml of water was added and the resulting mixture was stirred at 80°C for 1 h. Upon cooling, the reaction mixture was filtered and 35 mg (41%) of product **232** was isolated by column chromatography with light petroleum ether / ethyl acetate. δ_H (300 MHz) 9.50 (s, 2H, CHO), ~9.2 (br. s, 2H, NH), 6.90 (s, 2H, 4-H and 4'-H of bipyrrole), 2.53 (t, *J* 7.7, 4H, 2x 1-CH_2 of hexyl), 1.55 (hidden m, 4H, 2x 2-CH_2 of hexyl), 1.28 (m, 12H, 2x (3-CH_2, 4-CH_2 and 5-CH_2 of hexyl)), 0.87 (t, *J* 6.6, 6H, 2CH_3 of hexyl); MS (CI) 357 (MH^+).

3,6,13,16-Tetrahexylporphycene 185

367 mg (5.61 mmol) of Zn, 90 mg (0.63 mmol) of CuBr and 16 ml of THF dried over molecular sieves were placed into a dry round bottom flask under an argon atmosphere. Under constant stirring, 0.30 ml (2.72 mmol) of $TiCl_4$ was added dropwise through the septum using a syringe. The resulting mixture was refluxed for 2 h under an argon atmosphere. A solution of 50 mg (0.14 mmol) of **232** in 5 ml of warm dry THF was added dropwise, whereupon the mixture was refluxed for 2 min. Upon cooling in an ice bath, the pH was adjusted to neutral with aqueous Na_2CO_3. The dark green solution was filtered through Celite 535 and the filter was extensively washed with CH_2Cl_2. The filtrate was washed several times with water and dried over $MgSO_4$. Upon filtration and removal of the solvent under reduced pressure, 6 mg (13%) of deep blue product was isolated by preparative thin layer chromatography with CH_2Cl_2 / *n*-hexane (1:2). ^1H NMR at 300 MHz in $CDCl_3$ of an impure sample shows two singlets of equal integration at 9.52 and 8.87 ppm, respectively (*meso*-H and β-pyrrole H); UV-Vis 378.8 ($6.95 \cdot 10^3$), 570.4 ($1.76 \cdot 10^3$), 610.3 ($1.55 \cdot 10^3$), 652.0 ($1.56 \cdot 10^3$); MS (CI) 648 (MH^+).

3-Hexylpyrrole 233 [159]

A mixture of 547 mg (2.45 mmol) of compound **217** and 100 mg (2.50 mmol) of NaOH in 10 ml of ethanediol was refluxed for 1 h under an argon atmosphere. Upon cooling, the reaction mixture was partitioned between diethyl ether and water and the organic layer was dried over $MgSO_4$. 251 mg (68%) of product **233** was obtained.

Poly(3-hexylpyrrole) chloride 234

The synthetic procedure was based on that described by Guernion and co-workers.[160] A solution of 2.17 g (13.38 mmol) of $FeCl_3$ in water was added to a solution of 251 mg (1.66 mmol) of compound **233** in 6 ml of THF. The mixture was stirred overnight under an argon atmosphere. Upon filtration, the precipitate was washed with THF, methanol and acetone. A portion of the precipitate was collected. Drying overnight at ~120°C afforded 17 mg of insoluble solid material.

List of Abbreviations

AIBN	azo-*bis*-isobutyronitrile
COSY	correlation spectroscopy
DDQ	dichlorodicyanoquinone
DMAP	*N*,*N*-dimethylaminopyridine
DMF	dimethyl formamide
DMSO	dimethyl sulphoxide
DPM	dipyrromethane
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple-quantum coherence
MS	mass spectrometry
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
SAM	self-assembled monolayer
TCA	trichloroacetic acid
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV-Vis	ultraviolet-visible

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