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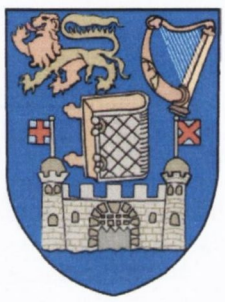
Synthetic Studies for Photo-triggered Release of Bioconjugate Porphyrin Photosensitisers in Photodynamic Therapy



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A thesis submitted to the University of Dublin, Trinity College for the degree of

Doctor of Philosophy

University of Dublin, Trinity College

March 2009

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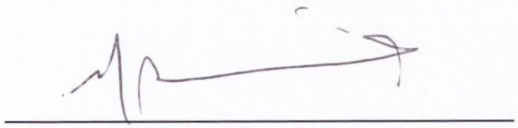

Mohd Bakri Bakar

Summary

The objective of this research was to synthesise porphyrin linked-bioconjugate photosensitisers that can be released upon irradiation with UV light; aiming to improve photodynamic cancer therapy efficiency. This photoreleased-bioconjugate system has potential for use in targeted photosensitiser delivery with a light-triggered control release mechanism. Several approaches were employed towards linking porphyrins to the bioconjugates using thio and *o*-nitrobenzyl labile linkers.

The classic 1,3-dithiane-2-yl synthon residue is an useful anion which has been used both as a functional and protected formyl group. Based on *Umpolung* studies, S_NAr reactions *via* RLi method were carried out to introduce dithianyl residue into porphyrin macrocycle and act as the formyl synthon. The reactivity of related dithio analogues was later investigated to explore their basic chemistry. Subsequent work was focused on constructing labile photocleavable systems using spirobisdithiane and trithiane residues. It has been shown that mono-lithio derivatives of the spirobisdithiane and trithiane can be utilised as nucleophiles for the direct substitution of different porphyrins. However, the possibility to direct cross linking of two to three porphyrins or linking porphyrin to a bioconjugate *via* di- and trilithiated anion species of spirobisdithiane and trithiane was not realised. In most cases, butylation occurred as the competitive reaction. Interestingly, the free base substituted porphyrins exhibit highly photosensitivity towards ambient light and easily converted to formyl porphyrins.

A second labile linker based on *o*-nitrobenzyl group was utilised in subsequent work. Palladium-catalysed coupling of the Suzuki and Heck reactions followed by hydrolysis reactions were performed to obtain carboxylic acid porphyrins. Subsequent esterification reactions were explored *via* carbodiimide method to form the model compounds of porphyrin linked-*o*-nitrobenzyl. The rearrangement products of *N*-acylisourea-porphyrins were obtained under DCC/DMAP reaction conditions, while targeted compounds were achieved using EDAC carbodiimide activating reagent.

The ultimate construction of porphyrin *o*-nitrobenzyl-linked bioconjugate was investigated. *o*-Nitrobenzyl linked-glucose as the example of the carbohydrate ligand was prepared before coupling with carboxylic acid porphyrins was performed. Once the synthesis of the porphyrin linked-glucose compound was achieved, the extent of its photofragmentation was studied and monitored using HPLC. In order to utilise a folic acid moiety as the ligand, different synthetic methods were examined to synthesise hydroxyl-type porphyrin. Its low reactivity currently limits our subsequent studies; however this

precursor provides conveniently naked-eye experimental monitoring due to the colour of porphyrins. A different approach using a palladium catalysed reaction was investigated to prepare *o*-nitrobenzyl porphyrins with carboxylic acid functionalities. These require further reaction optimisation to pave a way for linking the folic acid ligand. Although the present work contains no preclinical or clinical studies, the basic chemistry and the 'proof-of-principle' have been investigated extensively.

Finally, development of new strategies for the synthesis and utilisation of porphyrins containing α,β-unsaturated chains were explored. For comparative studies, different acrylic acid porphyrins were chosen as models which were activated with the subsequent *in-situ* generation of their corresponding acyl chloride. The activated acrylic porphyrins were then reacted with various nucleophiles to prepare various porphyrinic adducts in good yields. This methodology was employed to construct multifunctional dimeric systems of porphyrins. We have also examined the reactivity of the different porphyrinylacrylic adducts. As an example, yne-ene metathesis of the porphyrinylacrylate propargyl ester and allyl porphyrin gave *E/Z* bis-porphyrins. Altogether, these synthetic methods can be utilised for the facile transformation of porphyrin bioconjugate building blocks and serve for medicinal applications.

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Abbreviations

AlClPc	Aluminium phthalocyanine chloride
Ar	Aromatic
ARMD	Age-related macular degeneration
$BF_3.OEt_2$	Boron trifluoride etherate
BODIPY	Boron-dipyrromethene
BPD	Benzoporphyrin derivative
br	Broad
calcd	Calculated
CBT	*N*-Chlorobenzotriazole
d	Doublet
DCC	*N,N'*-Dicyclohexylcarbodiimide
dd	Doublet-doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIC	*N,N'*-Dicycloisopropylcarbodiimide
DIPEA	*N,N*-Diisopropylethylamine
DMAP	Dimethylaminopyridine
DTAD	Di-*tert*-butyl azodicarboxylate
EA	Ethyl acetate
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDAC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
eq	Equivalent
ES	Electrospray
HMBC	Heteronuclear Multiple Bond Correlation
HOBt	*N*-Hydroxybenzotriazole
HpD	Hematoporphyrin derivative
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
ISC	Intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant measured in Hertz
LDA	Lithium di(*iso*-propyl)amide
LDL	Low density lipoprotein
m	Multiplet

m/z	Mass-to-charge ratio
mAb	Monoclonal antibodies
MEM	Methoxyethoxymethyl
MS	Mass spectrometry
MTT	(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium)
n-BuLi	*n*-Butyllithium
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NEt_3	Triethylamine
NHS	*N*-Hydroxysuccinimide
NIR	Near infrared
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
OEP	Octaethylporphyrin
$PdCl_2(PPh_3)_2$	Dichlorobis(triphenylphosphine)palladium(II)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PDT	Photodynamic therapy
Ph	Phenyl
PhSeCl	Phenylselenenyl chloride
PS	Photosensitiser
PTC	Phase-transfer catalysis
R_f	Retention factor
RLi	Organolithium reagent
ROESY	Rotational nuclear Overhauser Effect Spectroscopy
rt	Room temperature
s	Singlet
SCF-MO	Self-Consistent Field Molecular Orbital
S_EAr	Electrophilic aromatic substitution
S_NAr	Nucleophilic aromatic substitution
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAH	Tetrabutylammonium hydroxide
TFA	Trifluoroacetic acid

p-THPP	5,10,15,20-Tetrakis(3-hydroxyphenyl)porphyrin
TLC	Thin layer chromatography
TPA	Two-photon absorption
p-$TPPS_4$	5,10,15,20-Tetrakis(4-sulfonatophenyl)porphyrin
TMEDA	*N,N,N',N'*-Tetramethylethylendiamine
p-TsOH	Toluenesulfonic acid
UV	Ultraviolet
v/v	Volume to volume
vis	Visible
δ	Chemical shift measured in parts per million (ppm)
ε	Molar absorption coefficient
λ	Wavelength measured in nanometre (nm)

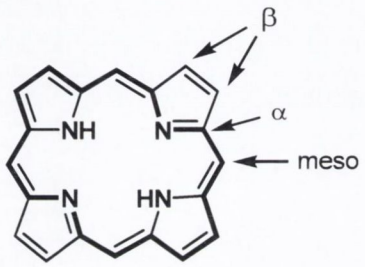
CHAPTER 1:

Introduction

1.1 Tetrapyrrolic macrocyles

1.1.1 Introduction

Porphyrins **1** are a class of aromatic tetrapyrrolic macromolecules consisting of four pyrrole units connected by methine groups. These compounds possess 22 π–electrons, 18 of which participate in a cyclic delocalised conjugation pathway (Figure 1.1).[1] Porphyrins fulfil the requirements for aromaticity according to Hückel's rules (4n+2, n=4) with the presence of two actives sites known as the *meso*-position and the *β*-position.[2]



1

Figure 1.1 The 18 π–electron pathway.

Numbering of the porphyrin nucleus runs along the twenty peripheral carbon atoms according to International Union of Applied Chemistry (IUPAC) system.[3] The inner nitrogens are given locants 21-24. In a non-metallated porphyrin (called free-base), the two inner protons are mobile and tautomerise freely among the four nitrogens.[4] The (21, 23-*H*) tautomer is energetically preferred compared to the (21, 22-*H*) tautomer. Porphyrins have characteristic ^{1}H-NMR spectra where the inner NH protons are highly shielded (δ = -1 to -5 ppm), and the *meso*-protons on the bridging carbons are strongly deshielded (δ = 8 to 11 ppm). Meanwhile, the porphyrin UV–visible spectra are particularly characteristic and have an absorption band in the violet region between 390 - 425 nm known as the Soret band and a number of less intense bands in the visible region, called Q bands, located between 480 - 700 nm.[5]

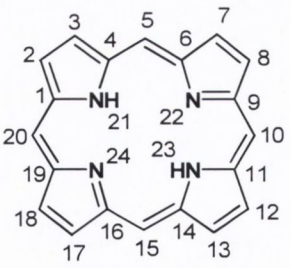


Figure 1.2 Numbering scheme for porphyrins.

The pyrrollic double bonds can undergo addition reaction to form chlorin **2** or bacteriochlorin **3** without substantial loss of the macrocyclic aromaticity. Further investigation of porphyrin macrocycles lead to interesting expanded porphyrin analogs such as porphycene **4**, *N*-confused porphyrin **5** and benzoporphyrin **6**. Saturation of the *meso*-position in porphyrin causes an interruption in the macrocyclic conjugation as shown in porphodimethene **7**, an intermediate between porphyrinogen and porphyrin **1**.

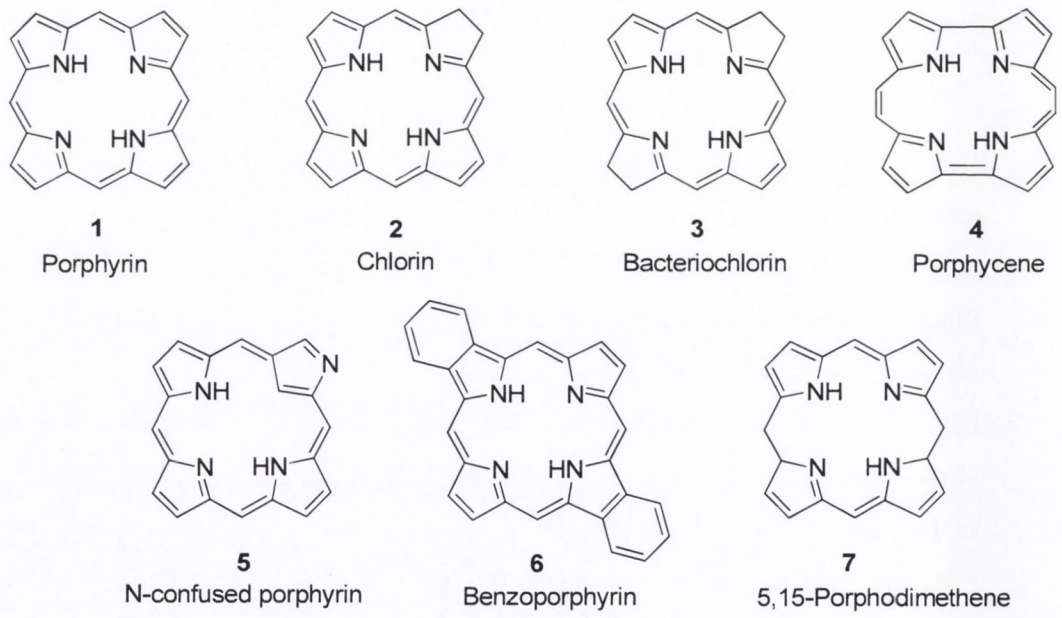


Figure 1.3 Different tetrapyrroles classes.

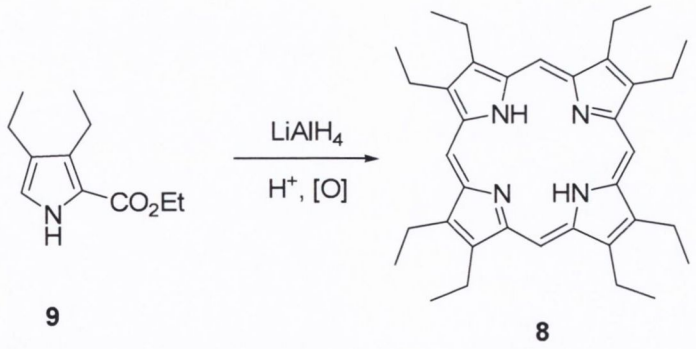
Porphyrins are the reactive centre of various fundamental biological representatives including hemes, chlorophylls, vitamin B_{12}, and others. Heme proteins (which contain iron porphyrins) are mainly involved in O_2 storage and transport (myoglobin and hemoglobin), electron transport (cytochromes b and c), and O_2 activation and utilisation (cytochrome P450 and cytochrome oxidase).[6] Chlorophylls (which have a central magnesium ion) and

pheophytins (which are metal free) are crucial in the photosynthetic process in plants and bacteria as these capture photons of light.[7] Vitamin B_{12} (which contains a cobalt metallated corrin) is present in bacteria and animals as the prosthetic group for a number of enzymes.[8]

1.1.2 Synthesis of functionalised porphyrins - Condensation reactions

The synthetic challenge in the construction of porphyrins is to control the arrangement of diverse substituents in a specific pattern around the macrocyle periphery. Porphyrins can be designed based on two families of porphyrins; the *β*-substituted porphyrins that resemble naturally occurring porphyrins and the *meso*-substituted porphyrins. The *meso*-substituted porphyrins have wide application, even though they have no direct biological counterparts and are only accessible through laboratory synthesis. For example, they have been used in photoactive molecular devices, electro-optic materials[9] and in photodynamic cancer therapy.[10]

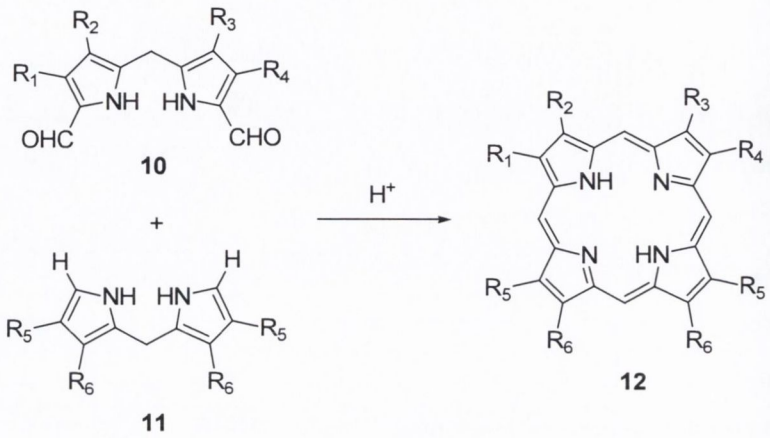
It is well-known in porphyrin chemistry that a condensation reaction between aldehyde and pyrrole or pyrrole derivatives represents a facile and straightforward synthetic method, and thus is widely used in various syntheses of porphyrins. For instance, synthetic approaches to alkylated *β*-porphyrin such as octaethylporphyrin (OEP) **8** or natural porphyrins related to heme or chlorophyll have been developed from the pyrrolic units. OEP is synthesised *via* a number of routes based on the condensation of 3,4-diethylpyrrole and its derivatives.[11] A simple and commonly employed method involved the reduction and cyclisation of 2-ethoxycarbonyl-3,4-diethylpyrrole **9** (Scheme 1.1).[12]



9 **8**

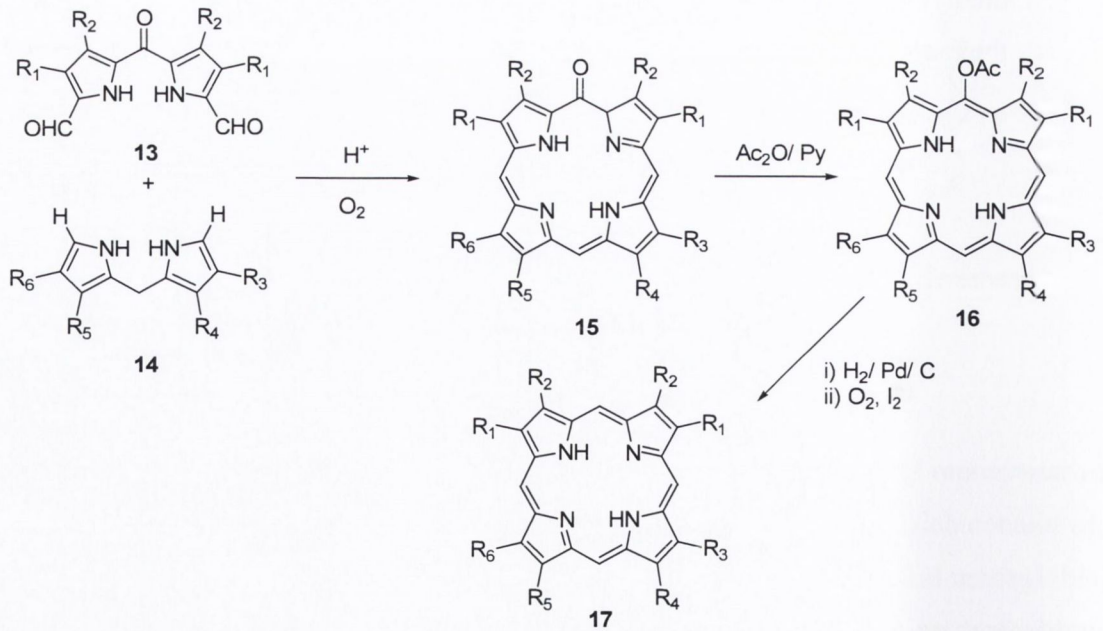
Scheme 1.1 Synthesis of octaethylporphyrin **8**.

Porphyrins may also be synthesised from dipyrrolic precursors such as dipyrromethanes, dipyrromethenes and dipyrroketones. The MacDonald reaction involved an acid-catalysed condensation of 5,5'-diformyldipyrromethane **10** and 5,5-di-unsubstituted dipyrromethanes **11** with toluene sulfonic acid catalyst to give porphyrin **12** (Scheme 1.2).[13] This method was employed by R.B. Woodward for the classical total synthesis of chlorophyll.[14]



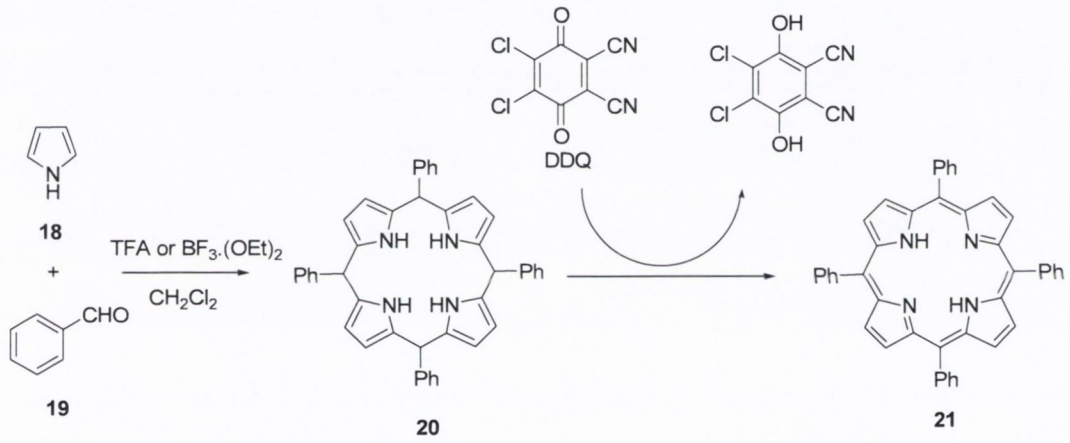
Scheme 1.2 The MacDonald synthesis of porphyrin.

Another variation of the MacDonald route is the condensation of 5,5'-diformyldipyrroketone **13** and 5,5'-unsubstituted dipyrromethane **14 to** give oxophlorin **15**. The oxophlorin was then converted to *meso*-acetoxyporphyrin **16** which upon hydrogenation and re-oxidation gave the *meso*-unsubstituted porphyrin **17** (Scheme 1.3).[15]



Scheme 1.3 Synthesis of porphyrin from 5,5'-diformyldipyrroketone **13**.

Meanwhile, synthetic developments of *meso*-substituted porphyrins have gained more interest as they offer ease of synthesis and amenability towards synthetic elaboration. *meso*-Tetraarylporphyrins were originally synthesised by heating benzaldehyde and pyrrole in a sealed bomb at 150 °C for 24 hours.[16] Due to severe condition, the aldehyde could not be varied much and the yields were very low too. Adler and Longo modified the Rothemund reaction by allowing pyrrole and benzaldehyde to react for 30 minutes in refluxing propionic acid, open to air.[17] The yields were up to 20% and the milder reaction conditions allowed the use of a wider selection of substituted benzaldehydes. The porphyrins synthesis was later improved by Lindsey with even milder conditions, cleaner reactions for facile purification and increased the batch-to-batch reproducibility.[18] In this modified synthesis, acid-catalysed condensation of pyrrole **18** and benzaldehyde **19** form porphyrinogen **20**, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *p*-chloranil produces porphyrin **21** in 30-40% yield (Scheme 1.4).



Scheme 1.4 Synthesis of 5,10,15,20-tetraphenylporphyrin **21**.

The Lindsey-type synthesis can accomodate a variety of both alkyl and aryl aldehydes, ranging from *p*-, *o*-, and *m*-substituted benzaldehydes to heterocyclic and organometallic aldehydes with an average yield of 30% for fully symmetrical porphyrins. Figure 1.4 illustrates some examples of aldehydes used in the Lindsey method for the synthesis of symmetrical porphyrins.

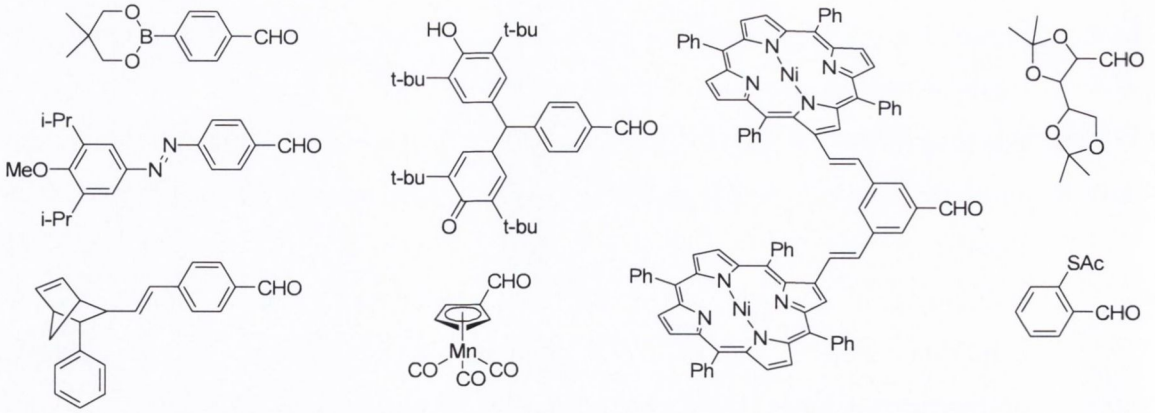


Figure 1.4 Various aldehydes used in the synthesis of symmetrical porphyrins.[19-26]

Unsymmetrical porphyrins that bear different substituents may be synthesised *via* the Lindsey method by varying the stoichiometry of differently substituted benzaldehydes, but the yields are reduced due to the statistical formation of a mixture of products. The mixed-condensation also requires intensive chromatographic separation and purification which depends on differences in polarity between the *meso*-substituents. For example, the reaction of pyrrole with a mixture of two aldehydes (aldehyde A and aldehyde B) will result in the formation a mixture of six different porphyrins; A_4- **22**, A_3B- **23**, 5,10-A_2B_2- **24** and 5,15- A_2B_2- **25**, AB_3- **26** and B_4-porphyrins **27** (Figure 1.5).

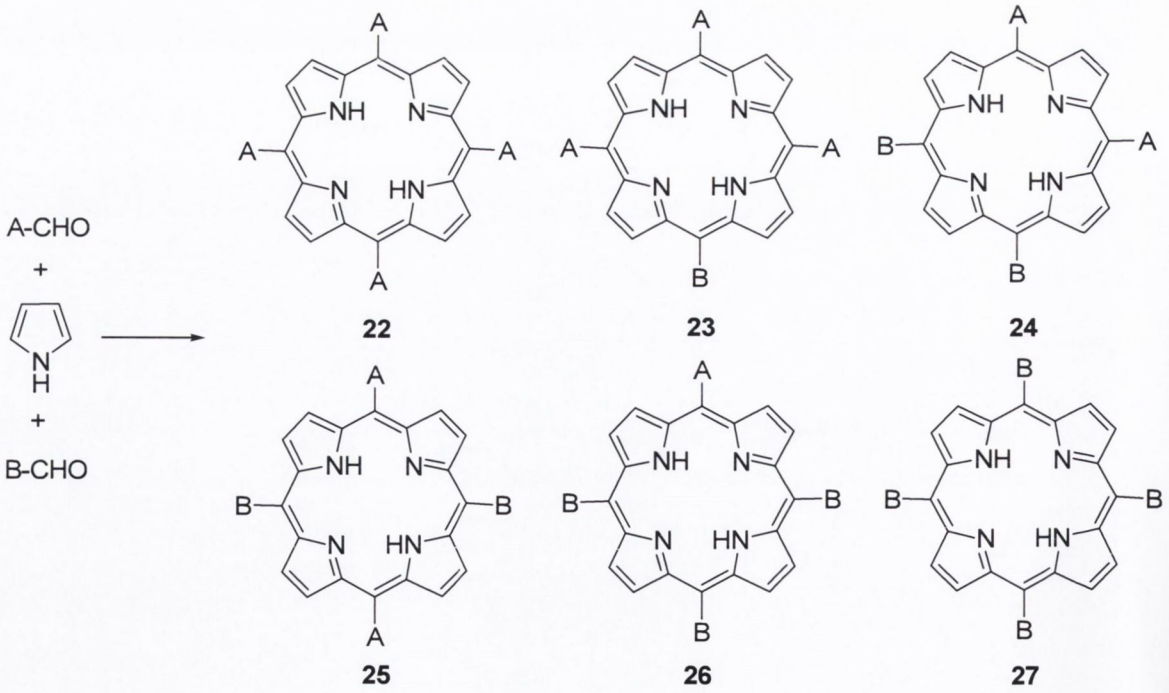
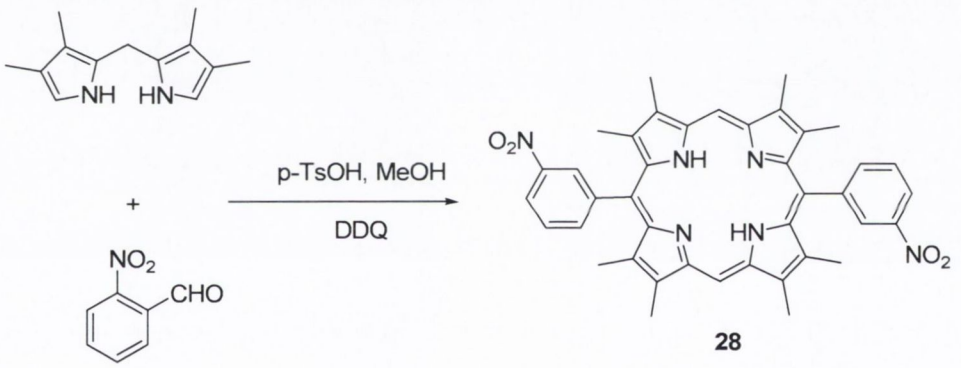


Figure 1.5 Formation of six different porphyrins from a mixed-aldehyde condensation.

One successful approach to minimise the chromatographic separation is to covalently attach one of the aldehydes to a solid phase.[27] However, this method is limited to the use of aldehydes with functional groups that can be conveniently attached to the solid phase resin.

As porphyrins bearing substituents in the 5,15-position are useful in diverse applications, the separation of 5,10- and 5,15-substituted porphyrins from the mixed condensation are often problematic. Rational synthesis of 5,15-substituted porphyrins have been developed based on 2+2 condensations of a dipyrromethane and an aldehyde.[28] The dipyromethanes were prepared according to the method that was established for the synthesis of naturally occurring porphyrins. Gunter and Mander established a high yield route to the formation of 5,15-substituted porphyrin **28** by reacting *meso*-unsubstituted-*β*-substituted dipyrromethane with an aryl aldehyde in methanol containing *p*-toluenesulfonic acid (*p*-TsOH) at 20 °C for 6 hours (Scheme 1.5).[29] The resulting porphyrinogen was then isolated by cooling the mixture to 4 °C for 16 hours and then oxidised with DDQ in THF. A small trace of the 5-substituted porphyrin was also formed in the reaction.



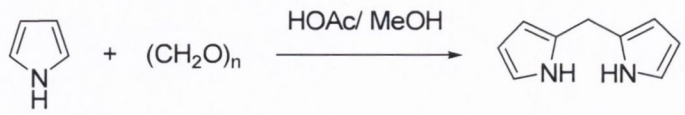
28

Scheme 1.5 Rational synthesis of 5,15-disubstituted porphyrin **28**.

Osuka further developed the method for the synthesis of porphyrin compounds containing an acid-labile substrate such as an acetal. The condensation reaction was carried out at room temperature in acetonitrile using trifluoroacetic acid as a catalyst and *p*-chloranil as oxidant.[30] Lindsey utilised the dipyrromethane-aldehyde condensation in a two-step one-flask room temperature-procedure in dichloromethane with borontrifluoride-diethyl-etherate (BF_3-$O(CH_2CH_3)_2$) as catalyst and oxidation with *p*-chloranil.[31] These routes have been employed to prepare a variety of 5,15-disubstituted porphyrins through varation of the aldehyde and dipyrromethane.[32] The accessible routes to porphyrins *via* the MacDonald 2+2 condensation depend on the availability of various types of dipyrromethanes. Wang and Bruce established a one-step procedure to prepare

dipyrromethane **29**,[33] while Lindsey developed a method to synthesise dipyrromethane derivatives that enable control of the substituents at the *meso*- and *β*-position of porphyrins (Figure 1.6).[34]

a) Wang and Bruce Method

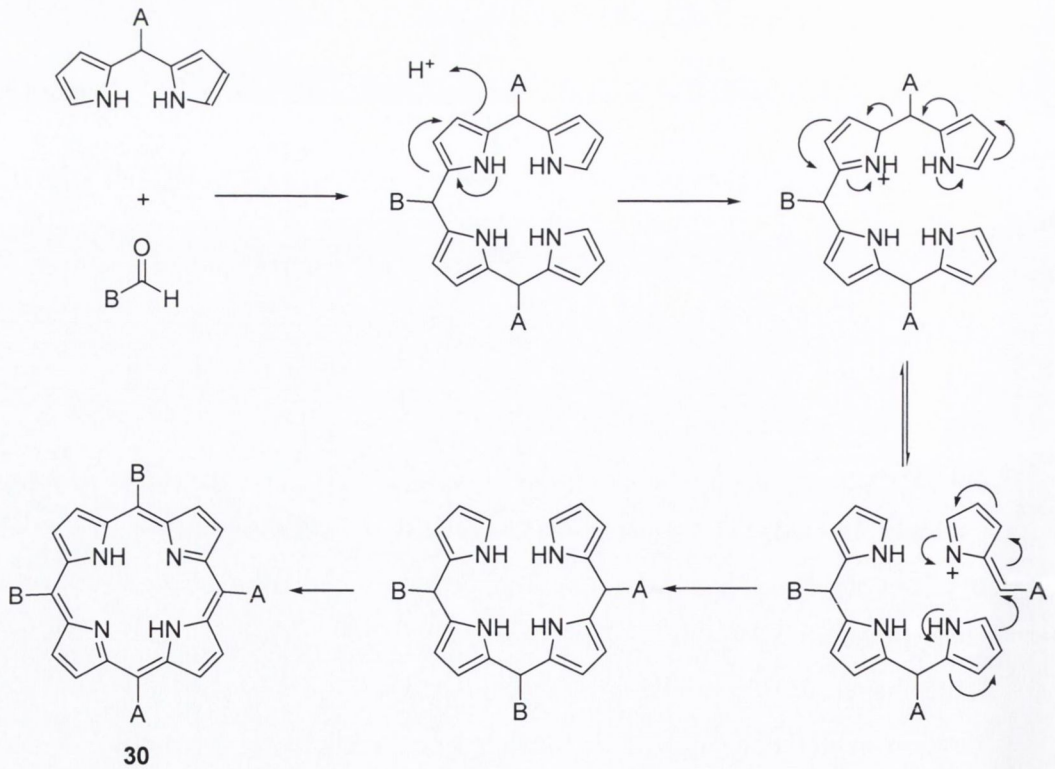


29

b) Lindsey method

Figure 1.6 Synthesis of dipyrromethane.

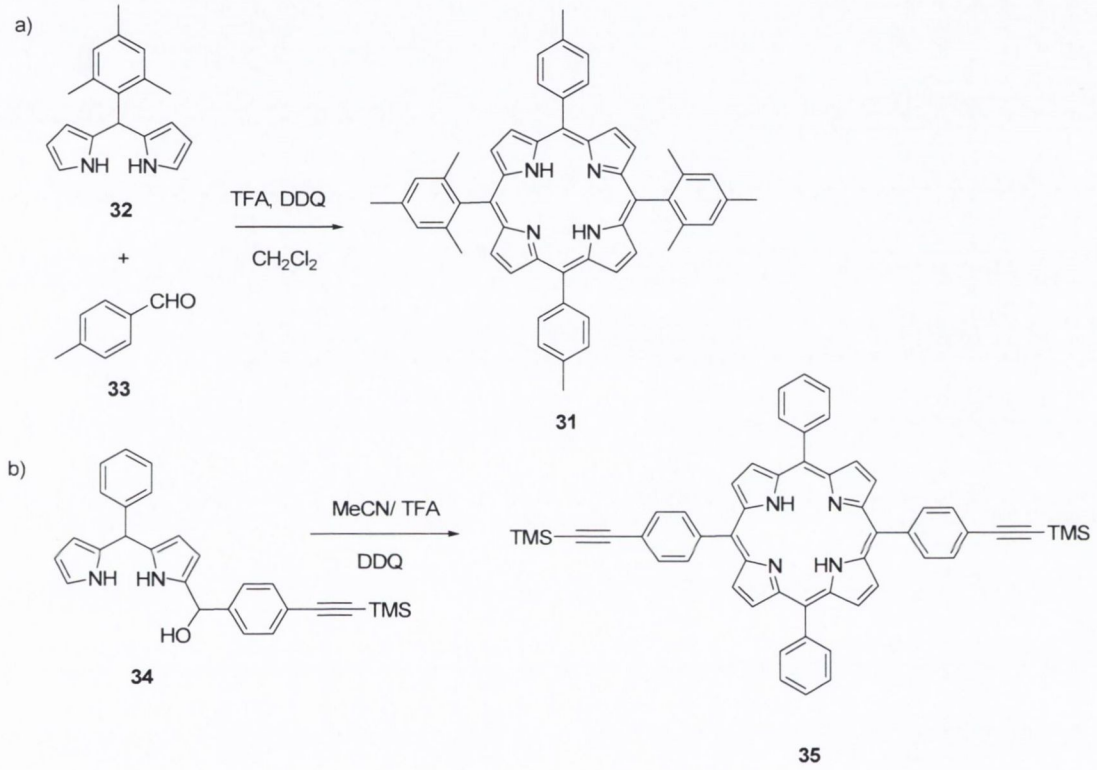
Further works were carried out to minimise the scrambling processes that occurred during the condensation reaction. Figure 1.7 illustrates the formation of 5,10-disubstituted porphyrin **30** *via* scrambling during the condensation reaction of dipyrromethane-A and aldehyde-B.



30

Figure 1.7 Formation of 5,10-disubstituted porphyrin **30** *via* a scrambling mechanism.

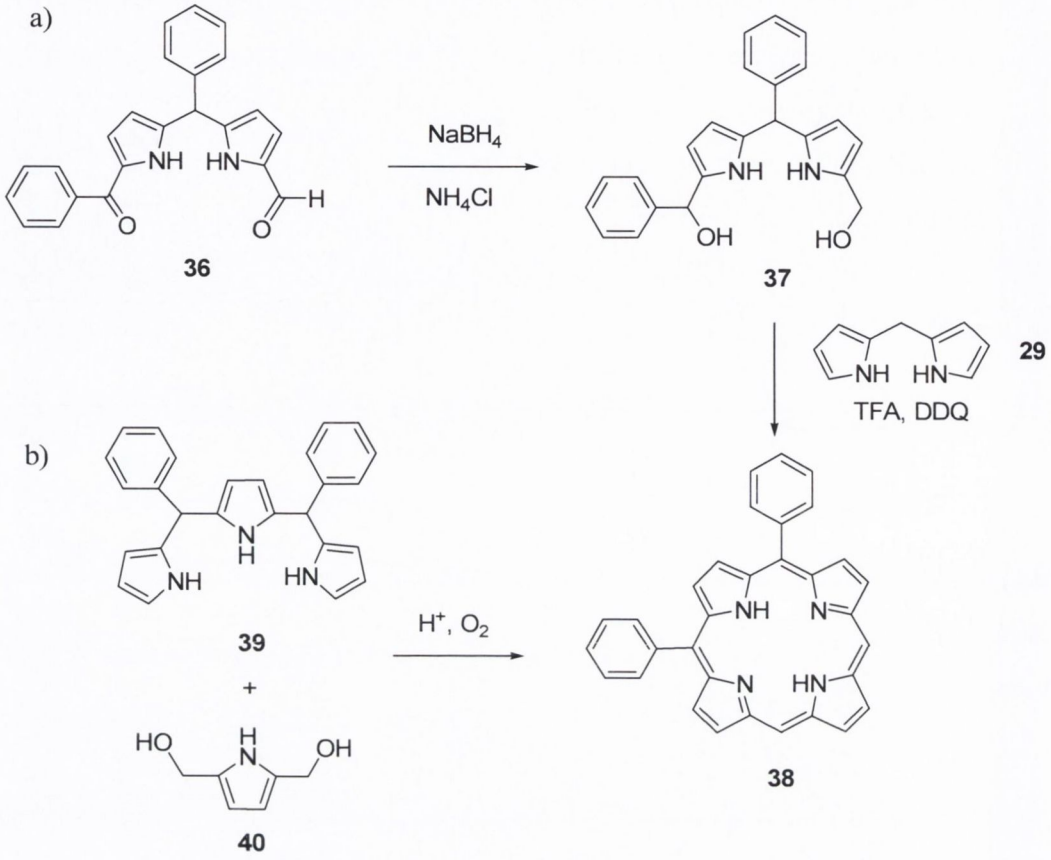
Littler *et al.* have investigated the conditions to synthesise porphyrin **31** that can minimise the scrambling using sterically hindered 5-mesityl dipyrromethane **32** and aldehyde **33** (Scheme 1.6a).[35] However, the condensation of an aldehyde with a sterically unhindered dipyrromethane such as 5-phenyl dipyrromethanes typically results in low yield and a mixture of porphyrin products derived from acidolytic scrambling. Rao *et al.* used an alternative approach to the synthesis of porphyrins with unhindered substituents *via* self-condensation of a dipyrromethanecarbinol **34** to give gram quantities of the desired porphyrin **35** (Scheme 1.6b).[36]



Scheme 1.6 Synthesis of porphyrin from a) sterically hindered dipyrromethane and b) sterically unhindered dipyrromethane.

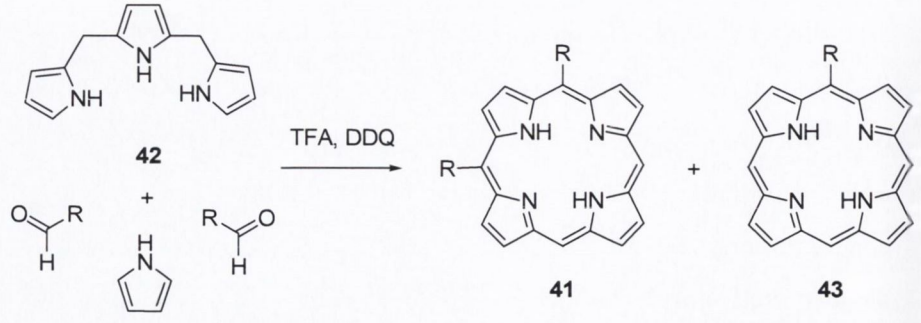
Brinas and Brückner have reported the step wise synthesis of less symmetrical 5,10-diphenylporphyrin based on 2+2 methodology (Scheme 1.7a) and 3+1 approaches (Scheme 1.7b).[37] The key intermediate in 2+2 condensation was identified as the benzoylformyl-dipyrromethane **36**, which was reduced to the dicarbinol **37** and condensed *in situ* with dipyrromethane **29** under low scrambling conditions (CH_3CN, 25 mM reactant concentrations, 30 mM TFA, 25°C, 10 min.). This method afforded analytically pure disubstituted porphyrin **38** in 10-20% yield. Meanwhile, using a 3+1 method for condensation between tripyrrane **39** (a compound containing three pyrrole groups linked

alpha to the ring nitrogen by two saturated carbons) and hydroxylpyrrole **40** leads to formation of a number of unseparable scrambling products due to the susceptibility of tripyrranes to acid catalysed scrambling.



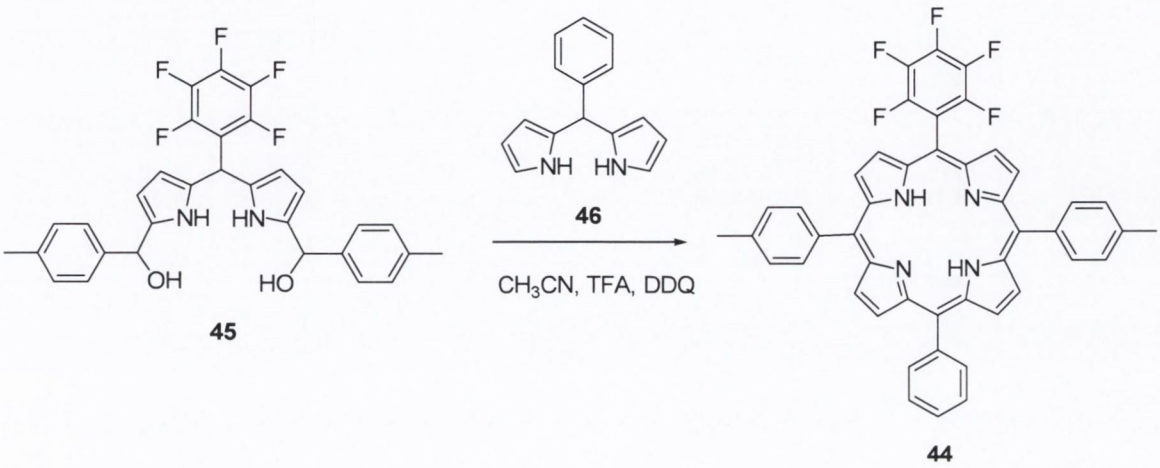
Scheme 1.7 2+2 and 3+1 condensations to synthesise 5,10-disubstituted porphyrin.

Senge and Hatscher extended this by preparing a range of aryl and aliphatic 5,10-disubstituted porphyrins **41** through variation of the 3+1 condensation procedure from tripyrrane **42** and various aldehydes (Scheme 1.8).[38] This method also gave 5-monosubstituted porphyrin **43** as a second product, especially when sterically demanding groups such as *t*-butyl were employed.



Scheme 1.8 3+1 Condensation for synthesis 5,10-disubstituted porphyrin.

More unsymmetrical porphyrins of the 5,15-AB_2C-type **44** were prepared by Rao *et al. via* the condensation of an ABA-dipyrromethane dicarbinol **45** and C-dipyrromethane **46** as shown in Scheme 1.9.[39]



Scheme 1.9 Synthesis of A_2BC-porphyrin.

Meanwhile, the synthesis of a so-called ABCD-porphyrin, which has four different *meso*-substituents has seen significant developments. The first step wise synthesis of this type of unsymmetrical porphyrin was reported by Smith and Wallace in 1990. However, the synthetic route involved two different types of dipyyromethanes and gave a mixture of porphyrin products.[40] Rao *et al.* designed a rational synthesis towards construction of the ABCD-porphyrin and managed to prepare various ABCD-type porphyrins.[39, 41] Figure 1.8[42] shows a general retrosynthetic analysis to synthesise the ABCD-porphyrins; these include the MacDonald 2+2 condensation, condensation of tripyrrane with pyrrole or mixed condensation of four different aldehydes and pyrrole.[43] In addition, ABCD-porphyrin can also be prepared *via* cyclisation of hydroxymethylbilane or bilane with aldehyde.[44]

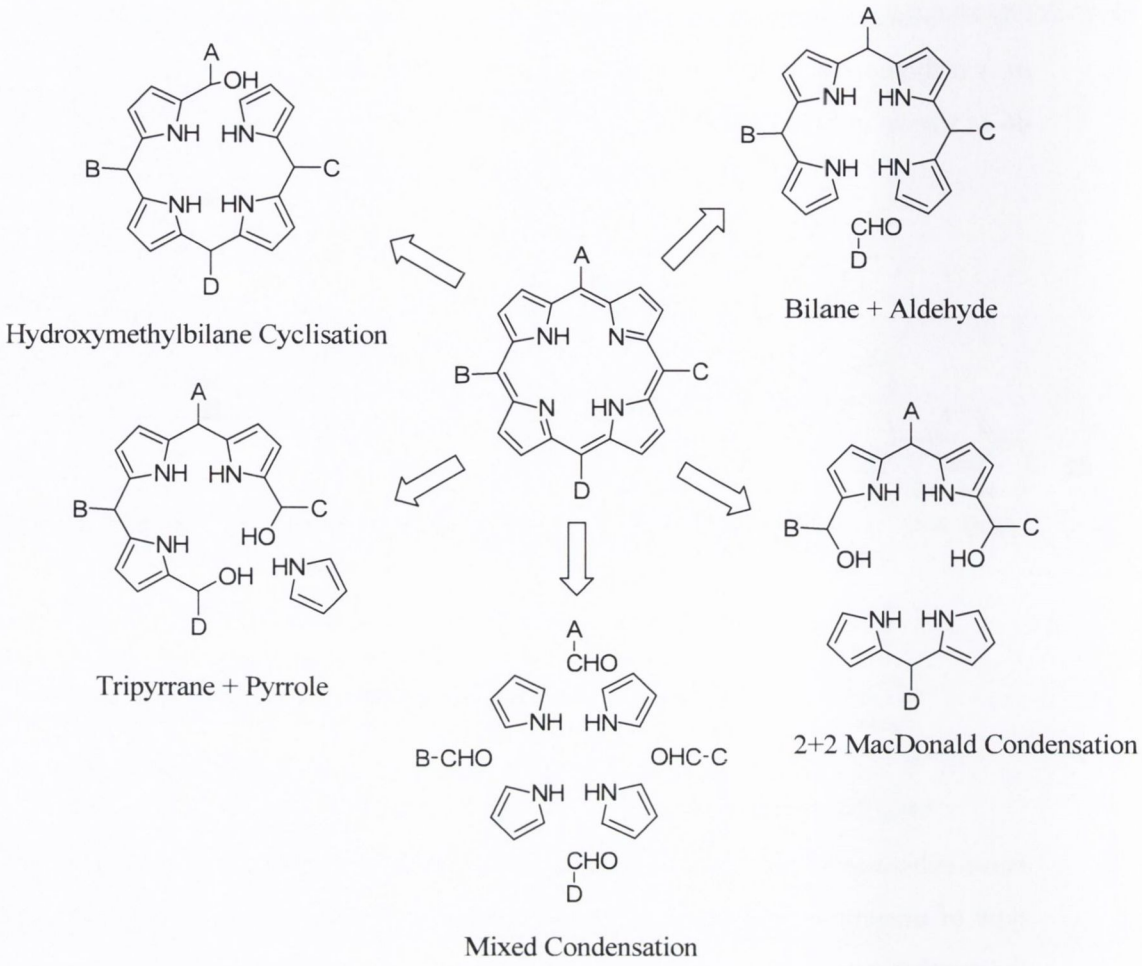
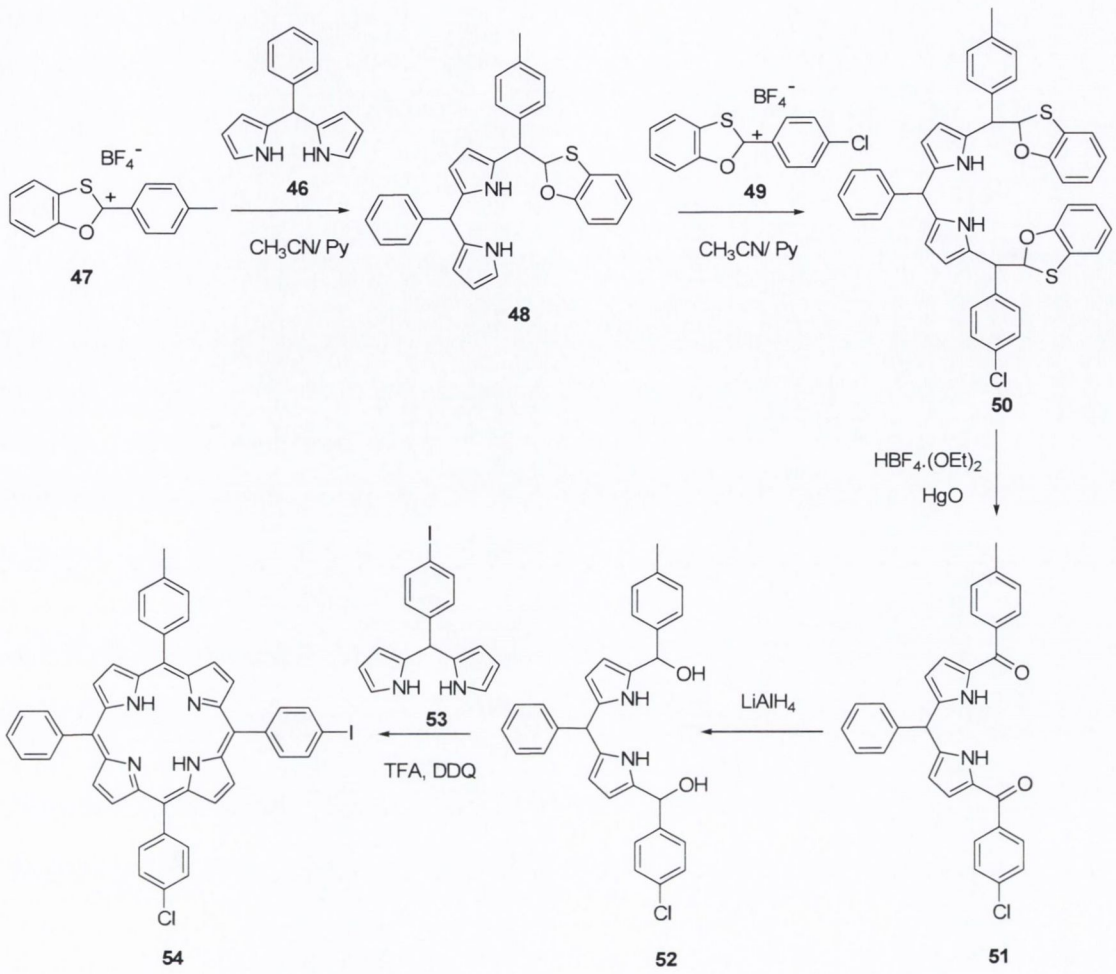


Figure 1.8 Retrosynthetic analysis of ABCD-porphyrins.

Smith *et al.*[45] and Ogoshi *et al.*[46, 47] have described the synthesis of ABCD-porphyrins involving the acid-catalysed condensation of two different dipyrromethanes in refluxing propionic acid. Lindsey *et al.* further investigated and have developed a rational synthesis to prepare porphyrins bearing four different *meso*-substituents (Scheme 1.10).[39] An acyl masked of benzoxathiolium tetrafluroborate **47** is reacted with dipyrromethane **46** to form the first building block of AB-substituents **48**. Another treatment with a benzoxathiolium tetrafluroborate **49** enabled the introduction of the third substituent and afforded the 1,9-dialkylated dipyrromethane **50** in quantitative yield. 1,9-diacyl dipyrromethane **51** was obtained upon hydrolysis and underwent further reduction with $LiAlH_4$ to biscarbinol **52**. The last building block of another substituent was introduced by condensation of **52** with dipyrromethane **53** and gave the ABCD-type porphyrin **54** in 13% yield.



Scheme 1.10 Rational synthesis of ABCD-porphyrin **54**.

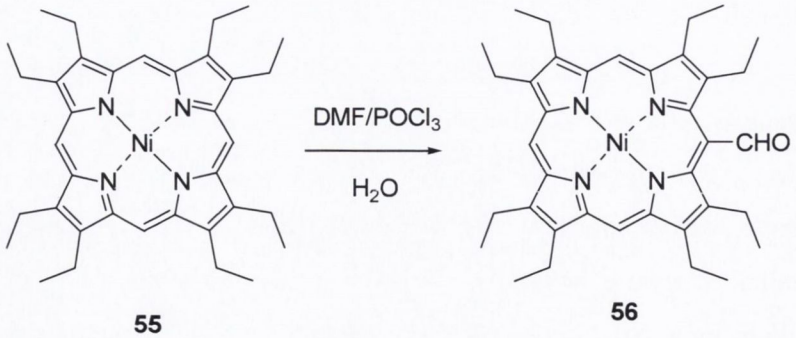
1.1.3 Synthesis of peripherally functionalised porphyrins

As the condensation method offers a path to prepare a range of porphyrins where functionality is introduced during the formation, many other approaches have been developed to introduce various functionalities on preformed porphyrins. There are two different sites where the reactions can occur on the porphyrin macrocycle; the *meso*-position and the *β*-position. The *meso*-carbon has greater electrophilic character relative to *β*-pyrrolic carbon because the two pyrrolenine units in porphyrins tend to achieve an individual aromatic sextet of electrons; thus withdrawing electron density from the neighbouring *meso*-carbons. A more general reactivity pattern was established based on theoretical *ab initio* self-consistent field-molecular orbital (SCF-MO) calculations[48] which predict that most reactions on porphyrins macrocycle take place preferentially at the *meso*-

positions. Steric considerations are also very important since bulky peripheral substituents shield some of the sites on the porphyrin macrocycle. The *meso*-positions are sterically less accessible, especially when one or two of the adjacent β-positions are substituted. The β-pyrrolic positions are sterically favoured and, as a result, will undergo substitution or addition reactions.

1.1.3.1 Electrophilic aromatic substitution, S_EAr

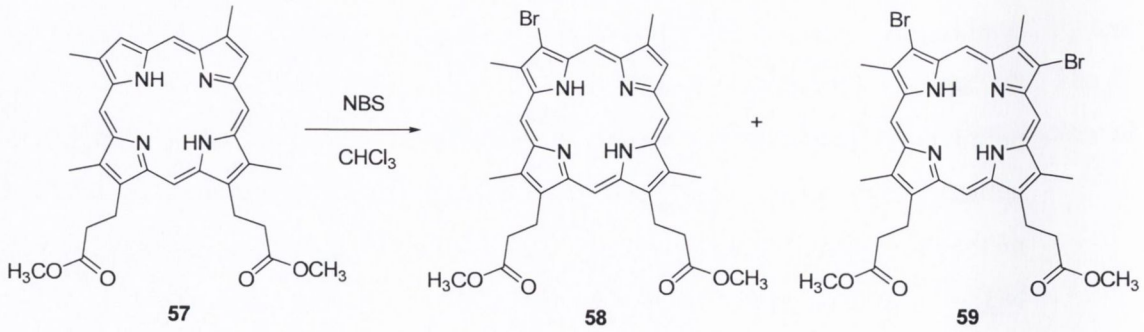
Porphyrins readily undergo many electrophilic aromatic substitution reactions, (S_EAr) such as formylation, halogenation and nitration. Most electrophilic substitutions are employed on metallated porphyrins since these metallocycles are more stable to electrophilic attack whereas the free base porphyrins are easily protonated under acidic conditions.[49] Formylation at the *meso*-position is one of the most common reactions as the aldehyde functionality can offer access to introduce another functional groups *via* various typical aldehyde reactions such as Wittig, Grignard, McMurry or Knoevenagel. The classical Vilsmeier reaction can be utilised to introduce the formyl group on the corresponding copper or nickel complex of the porphyrins. Inhoffen *et al.* has performed *meso*-monoformylation of [2,3,7,8,12,13,17,18-octaalkylporphyrinato]Ni(II) **55** and reported that the reaction gave reproducibly high yields of the formylated product **56** (Scheme 1.11).[50] Labile peripheral substituents such as vinyl groups also react under the Vilsmeier reaction conditions affording the corresponding *trans*-2-formylderivatives as the main products.[51] In general, a mixture of dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$) is used to produce the reactive Vilsmeier complex, however using *N*,*N*-diisobutylformamide in place on DMF produced sterically hindered Vilsmeier complex that favoured substitution at the β-pyrrolic positions.[52]



55 **56**

Scheme 1.11 Vilsmeier reaction of [2,3,7,8,12,13,17,18-octaalkylporphyrinato]Ni(II) **55**.

Porphyrins can also undergo halogenation reactions which can provide an entry to synthetically useful precursors for further porphyrin transformations. *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) have been successfully used for chlorination and bromination reactions on porphyrins. Octachlorination and octabromination of *meso*-tetraarylporphyrin are usually carried out by refluxing a solution of the metalloporphyrin in methanol, carbon tetrachloride or tetracholoroethane in the presence of excess NCS or NBS.[53] Monohalogenation is achieved with one equivalent of NCS or NBS although dihalogenated products are usually also formed in lower yields. Chlorination of Ni(II) or Cu(II) OEP complex with phenylselenyl chloride gives the mono-, di-, tri-, tetra-*meso* halogenated porphyrins as shown by van Lier *et al.*[54] Longo *et al.* performed a bromination reaction on free base porfin with NBS in $CHCl_3$ and this reaction gave predominantly *meso*-brominated product of mixture 5-mono-, 5,15-di- and 5,10,15-tribromo porphyrins.[55] Under similar conditions, 5,15-diphenylporphyrin can be brominated with two equivalents of NBS to afford tetra *meso*-substituted porphyrin. However, deuteroporphyrin IX dimethylester **57**, that contains at least one β-substituent adjacent to *meso*-position reacts with NBS in $CHCl_3$ to produce only β-substituted monobromo- **58** and dibromoporphyrin **59** due to steric reason (Scheme 1.12).[56] The site of halogenation is also determined by the size and reactivity of the halogen, thus *meso*-halogenation is favoured by the smaller and more reactive chlorine. Since bromine is of an intermediate size among halogens, *meso*-bromination is observed when an excess of brominating reagent is used and favoured by porphyrins bearing unsubstituted adjacent β-positions. *meso*-Iodination is more difficult due to less reactive and larger steric bulk of iodinium cation, nevertheless Dolphin *et al* showed that 5,15-diphenyl porphyrin can undergo iodination using bis(trifluoroacetoxy)iodobenzene and iodine with 70% isolated yield.[57] Diiodo species were also formed in which the second iodine occupies at β-position rather than second available *meso*-position. Osuka *et al.* have developed another iodination method using $AgPF_6$ and iodine which afforded the mono- and disubstituted [5,15-diphenylporphyrinato]Zn(II) complex.[58]



Scheme 1.12 Bromination of deuteroporphyrin IX dimethylester **57**.

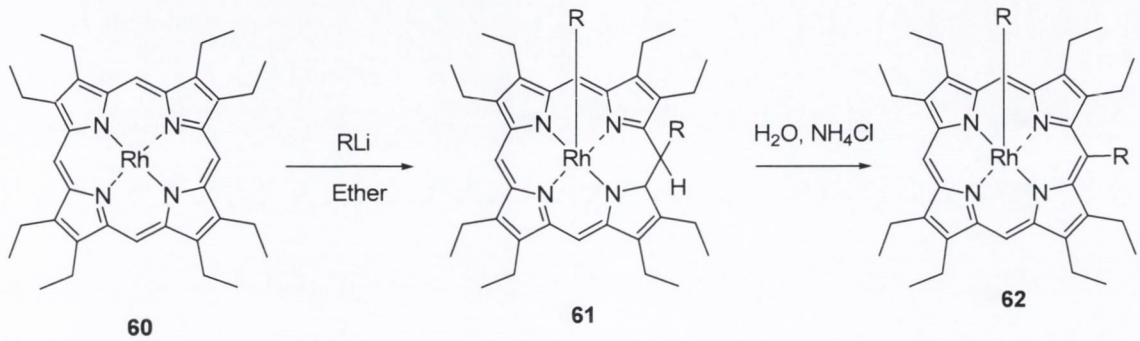
Nitration of OEP using concentrated nitric acid in acetic acid at 0 °C has been employed by Bonnett *et al.* to give the 5-mononitrated compound, whereas using nitric acid in sulphuric acid afforded *meso*- di- and trinitro substituted porphyrin products.[59] The latter procedure was used by Longo *et al.* on porphyrin and afforded *meso*-mono- and di-nitroporphyrin derivatives while the 5,10-dinitro isomer was reported to be the major product.[60] van Lier *et al.* used a mixture of phenylselenyl chloride (PhSeCl), and silver nitrite ($AgNO_2$) for *meso*-nitration of Ni(II)OEP and the reaction gave the nitrated porphyrin in 75% yield.[54] A nitrating reagent from the mixture of trifluoroacetic acid and sodium nitrite was prepared by Arnold *et al.* and reacted with 5,15-diarylporphyrin to afford the nitrated products in good yield.[61] Recently, Banfi *et al.* synthesised a series of nitrosubstituted 5,15-diarylporphyrins where the nitro groups was introduced on the phenyl rings or to the *meso*-position on the porphyrin periphery.[62]

1.1.3.2 Nucleophilic aromatic substitution, S_NAr

Application of nucleophilic aromatic substitution (S_NAr) to the porphyrin macrocycle mostly requires an activated porphyrin core. For example, the activated form of π–cation radical metalloporphyrins reacts with various nucleophiles such as cyanide, nitrite, pyridines, and acetates, affording the corresponding *meso*- or *β*-substituted metalloporphyrins. The π–cation radicals are readily obtained from oxidation of the metalloporphyins with iodine, thalium (III) nitrate, iodine, tris(*p*-bromophenyl) ammonium hexachloroantimonate (TBAH) or *N*-chlorobenzotriazole (CBT).

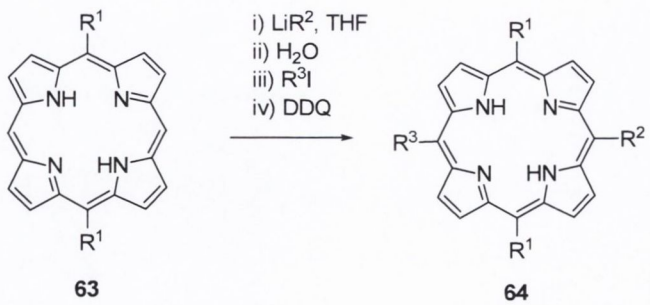
Smith *et al.* treated π–cation radicals of Mg(II), Zn(II) and Cd(II) octa-alkylporphyrins with sodium nitrite affording the corresponding series of *meso*-nitro substituted porphyrins.[63] Reaction of Mg(II), Zn(II) and Co(II) complexes of OEP in the

presence of N_2O_4 in dichloromethane also employed and produced the *meso*-nitro porphyrin derivatives in good yields.[64] Meanwhile, methylation of *meso*-positions of Cu(II) chlorophyll complex have been accomplished by treatment with chloromethyl methyl sulfide and titanium tetrachloride, followed by Raney-Nickel reduction of the resulting *meso*-methylthiomethyl derivatives.[65] Nucleophilic attack of organolithium reagents on Rh(III) OEP **60** is also reported, however the reaction occurred both at the chelated metal and *meso*-position to afford Rh(III) phlorin complex **61**, that readily oxidised to give the corresponding *meso*-substituted porphyrin **62** (Scheme 1.13).[66]



Scheme 1.13 *meso*-Substitution reactions of Rh(III) OEP with organolithium reagents.

Senge *et al.* have successfully developed the S_NAr reaction utilising organolithium on unactivated porphyrin core.[67] This method offers a direct introduction of both aryl and alkyl moieties preferentially at *meso*-positions of porphyrins. Conveniently, the porphyrin anion intermediate which is formed in the S_NAr reaction of 5,15-disubstituted porphyrins **63** can be trapped *in situ* with an organic electrophile to introduce a second, different substituent in the same reaction affording A_2BC-type porphyrins **64** (Scheme 1.14).[68] Thus, this investigation opened a new pathway to prepare unsymmetrical porphyrin systems.



Scheme 1.14 One-pot synthesis of A_2BC-type porphyrins.

1.2 Application in photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a cytotoxic treatment modality based on photoactive substances of photosensitisers such as porphyrins that selectively retain in tumour tissues. Irradiation of the target tissues with appropriate wavelength of light activates the production of highly reactive oxygen and leads to a series of phototoxic reactions that cause selective death of tumor cells. Many investigations have been pursued in the last decades to improve the efficiency of the three PDT basic components namely light, oxygen and photosensitisers (PS), along with understanding the biomedical and biophysical processes. Studies have been conducted on the treatment of a variety of malignant and pre malignant cancer conditions including head and neck cancer,[69] lung cancer,[70] mesothelioma,[71] Barrett's esophagus,[72] prostate[73] and brain tumors.[74] PDT is also employed to treat non-cancerous conditions such as psoriasis[75] and age related macular degeneration (ARMD).[76]

1.2.1 Introduction

Photochemotherapy approaches involve the combined action of light and a systemic photosensitiser agent. The recent PDT impetus began in 1960 as the fluoresecent properties of hematoporphyrin derivatives (HpD) were utilised in tumour imaging studies.[77] Since then, significant works have been carried out in pre-clinical and clinical studies of the first generation photosensitiser such as hematoporphyrin **65**, resulted in the approval of the photosensitising drug Photofrin® **66** in the US, Canada, Japan and throughout Europe (Figure 1.19).[78] However, it has several limitations as it comprises a complex mixture of porphyrins with various monomeric and oligomeric forms and some of the components are not photoactive. The treatment with Photofrin® also renders the patient photosensitive to strong sunlight because the prolonged accumulation can last up to six weeks. Thus, patients are advised to keep away from direct sunlight. The major drawback is mainly due to the relatively weak electronic absorption band of photosensitisers (630 nm), which does not allow for optimal light penetration.[79]

Second generation photosensitisers were actively developed to improve PDT efficiency, notably by increasing the absorption wavelength and strong absorption band in the red wavelength region (650-800 nm). Ideally, the photosensitisers should be non-toxic, water soluble, exhibit selectivity for the enrichment in tumoured tissue and have pharmacokinetic profiles that show it can be cleared in reasonable times from the body.

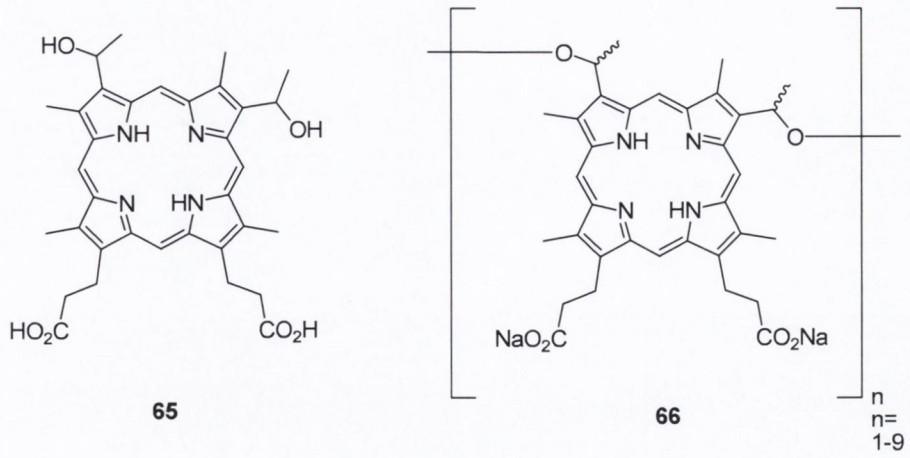


Figure 1.9 First generation photosensitisers.

The absorption of red light by photosensitisers can be shifted to longer wavelengths by introducing suitable substituents. For example, 5,10,15,20-tetrakis(4-sulfonato phenyl)porphyrin (*p*-$TPPS_4$) **67** is substituted porphyrin developed as potential photosensitiser for PDT. *p*-$TPPS_4$ also has hydrophilic character, therefore does not require a carrier to avoid self-aggregration during the PDT process.[80] The reduction of a peripheral double bond of a porphyrin macrocycle increases the longest-wavelength absorption band and shifts the λ_{max} further to the red region as shown for chlorin photosensitisers. Of the purely synthetic chlorins, 5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin (*m*-THPC) **68** or Foscan® has been approved for use in PDT,[81] where only low drug and light doses are needed to achieve photodynamic respons equivalent to Photofrin®.

As reduced porphyrins are prone to being oxidised, large substituents or an exocyclic ring are often introduced close to the reduced pyrrole ring as observed in benzochlorin structures of tin etiopurin ($SnEt_2$) **69** or Purlytin® that have an maximum absorption near to 650 nm.[82] Diamagnetic metals such as Sn(IV) are used to increase the singlet oxygen formation of the photosensitisers. Meanwhile, the benzoporphyrin derivatives (BPD) are reported to have absorption around 690 nm and its approved form; verteporfin **70** or Visudyne® is recommended for treatment of neovasculature on the retina in ARMD.[83]

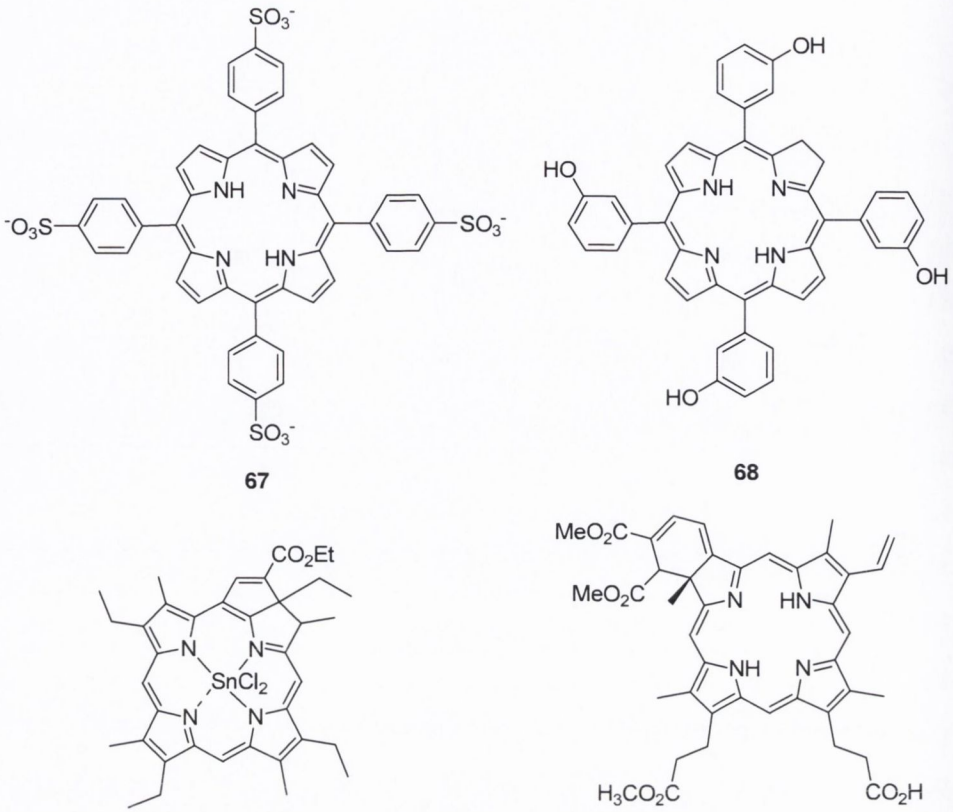


Figure 1.10 Second generation of photosensitisers.

Table 1. Porphyrin and chlorin based photosensitisers[84]

Drug Name	**Active Compound**	**Treatment**	**Activation Wavelength**
Photofrin® **66**	HpD	Cervical, oesophagel, bladder and gastric cancer and brain tumour	630 nm
Foscan® **68**	Temoporfin (*m*-THPC)	Non-melonama skin cancer of head and neck	652 nm
Purlytin® **69**	Tin ethyl etiopurpurin ($SnEt_2$)	Cutaneous metastic breast cancer, basal-cell carcinoma and prostate cancer	664 nm
Visudyne® **70**	Vertiporfin (Benzoporphyrin derivative monoacid A)	Age-related macular degeneration, non-melonama skin cancer	690 nm

PDT has established itself as the fourth modality for cancer treatment next to surgery, chemo- and radio-therapy because of the advantages of no systemic toxicity with high accumulation and selectivity in tumour tissue. It is a selective, non-invasive treatment that does not destroy healthy tissues, repeated treatments can be given without dose limitation which is common in chemotherapy and usually the treatment can be done as an outpatient procedure. PDT treatment can be combined with surgery to remove microscopic tumours after surgery.[85] It may also be used with chemotherapy or radiation treatment to reduce the size of tumour.

1.2.2 Mechanism of photodynamic therapy

The photochemical processes in PDT are represented by the Jablonski diagram (Figure 1.11).[86] Upon absorption of light with a suitable wavelength, the photosensitisers which have ground electronic singlet state (P^0) are excited to the first excited singlet-state ($^1P^*$). The photosensitiser can decay back to the ground state by emitting fluorescence photons enabling identification of tumour tissue. Alternatively, the $^1P^*$ photosensitisers can convert to the first excited triplet state, $^3P^*$ *via* intersystem crossing (ISC). The $^3P^*$ state is sufficiently long-lived that can be involved in chemical reactions. The $^3P^*$ photosensitisers can also return to the ground state by emitting phosphorescence.

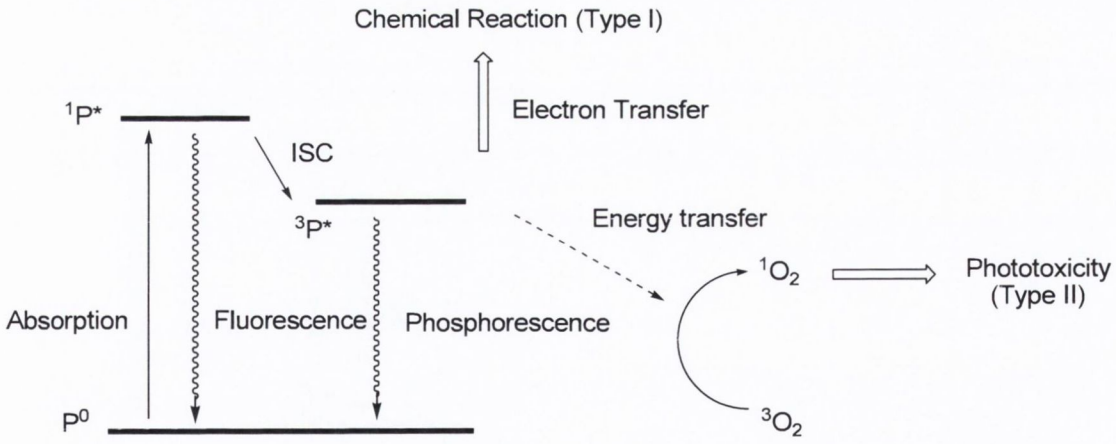


Figure 1.11 A simplified Jablonski diagram for PDT.

There are two types of photodynamic process that promote chemical reactions in a substrate including damage to living tissue; these are referred as type I and type II. Type I photoprocesses involves electron or hydrogen transfer reaction between excited state $^3P^*$ photosensitisers and other molecules. These excited photosensitisers can react directly with

an organic substract (S) by electron exchange producing an oxidised substract (S^+) and a reduced photosensitiser (P^-). The reduced photosensitiser (P^-) can react with oxygen to produce a less reactive superoxide anion (O_2^-), which can then form the highly reactive hydroxyl radical ($^{\cdot}OH$). The excited photosensitiser, $^3P^*$ also can react with superoxide radicals ($O_2^{\cdot}$) to produce superoxide anions (O_2^-) which can then form the highly reactive hydroxyl radical ($^{\cdot}OH$) that is harmfull to cells. The type II photoprocess is an electron spin exchange between $^3P^*$ photosensitisers and ground state oxygen, $^3O_2$. It produces the cytotoxic singlet-state of oxygen, $^1O_2$ that reacts with various biomolecules such as triacyl glycerols, cholesterols, phospholipids, histidine and nucleic acids. The extent of photodamage and cytotoxicity is dependent on the type of photosensitiser, its localisation, the total dose of administered photosensitiser, total light time exposure, the availability of oxygen and the time between the injection of drug and light exposure.

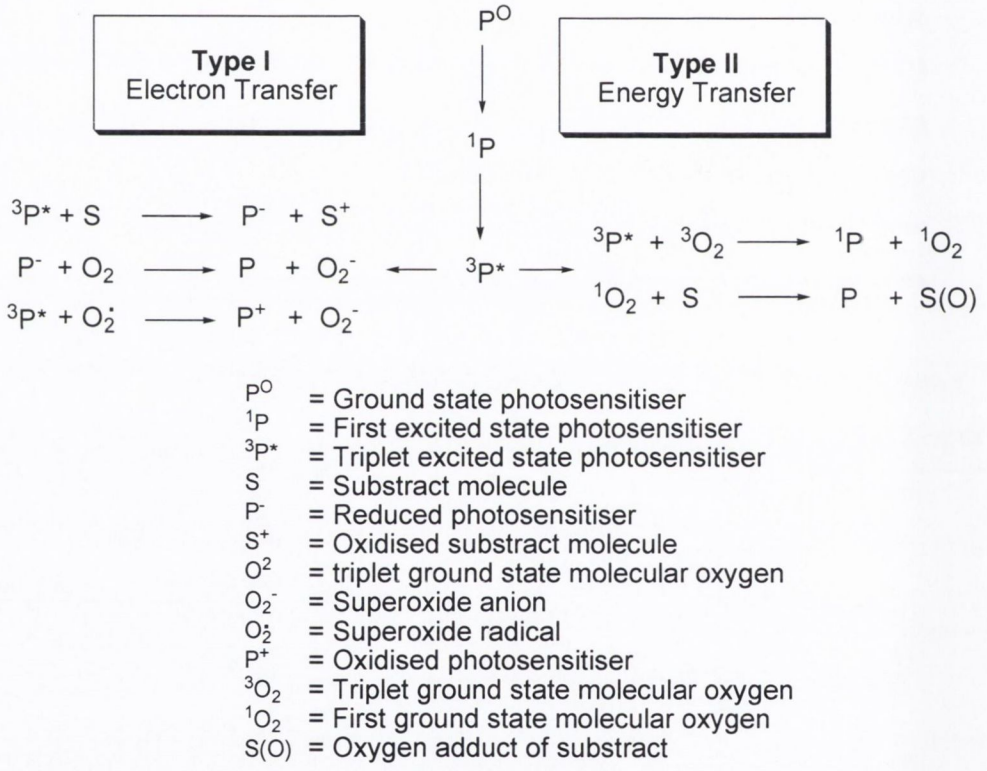


Figure 1.12 Type I and II photochemical reactions in PDT.

1.2.3 Targeted photosensitisers delivery

Most therapeutic drugs distribute throughout the body resulting in general toxicity that causes negative side effects and poor acceptance of the treatment by the patient. Moreover, to reach the site of action, the drug has to cross many biological barriers and intracellular compartments. As a result, a large drug dose is administered to achieve its required therapeutic concentration. In cancer treatments, targeted chemotherapeutic drug delivery offers an enormous potential to improve its efficiency by selectively localised therapeutically effective drug concentrations at the tumour site. For example, such delivery system can be developed by conjugating the drug to the ligand of specific targets in cell. Furthermore, diseased-associated cells express different pathophysiological features and a thorough understanding of the tumour environment and their growth patterns will allow development of an effective targeted delivery where the therapeutic window can be expanded by increasing the target/non-target tissue ratio. In addition, PDT efficiency is depended on reactive singlet oxygen species that has a short life time ~0.01μs with a range of action of about 0.01-0.02 μm,[87] and thus requires exact localisation of photosensitisers.

Approaches to enhance PDT efficacy and selectivity have been investigated in several strategies. At first, an array of photosensitisers based on different structural, charge and hydrophobicity were designed to analyse their biodistribution properties and cell accumulative capabilities.[88] It can be classified into three categories; a) hydrophilic compounds which are mainly bound to plasma proteins of albumin such as the tetra-sulfonated porphyrin derivative **67** b) hydrophobic compounds such as tin-etiopurpurin **69** that require delivery vehicles and c) amphiphilic compounds that localise at the hydrophilic-hydrophobic interfaces in membranes, such as benzoporphyrin monoacid derivative **70**. Photosensitisers need to have a hydrophilic character in order to facilitate its systemic administration *via* injection into the bloodstream. However, the increased hydrophilicity will hamper the ability of the photosensitisers to get into cells through lipid membranes. On other hand, hydrophobic properties of photosensitisers can increase unfavourable self-aggregation of the photosensitisers in plasma. Thus, the amphiphilic structure, containing both hydrophilic and hydrophobic parts, will generate better photodynamically active photosensitisers.

A different strategy utilises targeting ligands such as monoclonal antibodies (mAbs) that can bind specifically to the cell surface proteins. An ideal targeting agent should have high affinity and specificity of binding to the cell surface receptors, be compatible for chemical conjugation and able to be produced in sufficient amounts.[89] The

first study of a photosensitiser-mAb conjugate utilised hematoporphyrin (Hp) and mAb directed to DBA/2J myosarcoma and the investigation showed inhibition of tumour growth compared with Hp alone.[90] It has also been reported that chlorin e6 conjugates with the mAb OC125 accumulate up to threefold higher compared than free chlorin e6 in murine ovarian tumour,[91] while immunoconjugates of chlorin e6 monoethylene diamine monoamide with the mAb IG12 specific for uveal melanoma cells produce four-fold greater damage than the free chlorin e6 at the same concentration.[92] A modified system has been established with mAb-PS conjugates to include additional components that allow for penetration into the cell by an endocytotic mechanism. For example, the attachment of polylysine to a conjugate containing mAb OC125 directed against ovarian cancer cells can enhance photosensitiser uptake up to 17-fold.[93] Meanwhile, *m*-tetrahydroxyphenylchlorin attached to internalisable mAb 425, specific for head and neck squamous cell carcinoma, was shown to be more effective than a conjugate with a non-internalisable antibody.[94]

Another strategy that is commonly used is to employ carriers such as polymers,[95] liposomes,[96] microspheres[97] and emulsions[98] to facilitate the photosensitiser delivery. Liposomes have a high loading capacity and are flexible to accommodate photosensitisers of variable physicochemical properties, hence this mode has been extensively used as the photosensitiser delivery vehicle. For instance, Photofrin®, that consists of hydrophobic dimers and oligomers was shown to be more effective against human glioma brain cancer when the photosensitiser was formulated in liposome form.[99]. Liposomal verteporfin formulation (Visudyne®) has been approved for clinical application to treat age-related macular degeneration as the verteporfin itself has a very low solubility.[100] The use of other vehicles such as microspheres enables the intracellular delivery of photosensitiser to phagolysosomes. The covalent attachment of the chlorin e6 to 1 μm polystyrene microspheres resulted in its entry into MGH-U1 human transitional cell bladder carcinoma cells via phagocytosis.[101] The photodynamic activity of chlorin e6–microsphere conjugates in MGH-U1 cells has proved to be higher than that of free chlorin e6, although the singlet oxygen-generating capacity of free chlorin e6 is higher than in microspheres. Polymer-bound photosensitisers such as HPMA copolymer-mesochlorin mono ethylenediamine (CMA) also demonstrated a substantial increased tumour accumulation.[102]

Photosensitisers can also be conjugated to specific proteins which are preferentially expressed in or on the cancer cells in comparison to normal cells due to their transformed nature. There are a variety of cell surface receptors for peptides, hormones and essential nutrients like iron and folic acid that are over expressed in many cancer cells, thus

providing opportunity for targeting of photosensitisers to tumor cells. This conjugated system can improve photodynamic therapy targeting by improve its intracellular accumulation *via* receptor- mediated endocytosis process.[103] For example, the expression of the low density lipoprotein (LDL) receptor is regulated by the cholesterol demand of the cells and is usually higher in fast-growing cell.[104] Thus, hydrophobic photosensitisers of Hematoporphyrin (Hp) was incorporated into LDL and the result exhibited increased uptake in targeted cell.[105] Chlorin e6 was also conjugated to LDL and the cellular uptake of the conjugate was increased as shown in retinoblastoma and fibroblast cells compared with free chlorin e6.[106] Non-proteic ligands such as vitamin B9 of folic acid have also been evaluated as the targeting moieties that can bind selectively the folate receptor. The folate receptor is a highly specific tumor marker frequently over expressed in more than 90% of ovarian carcinoma patients and in many other cancer types (choriocarcinomas, uterine sarcomas, osteocarcinomas).[107] It has been reported that 5,10,15,20-tetraphenylporphyrin conjugated-folic acid shows increasing cellular uptake seven-fold higher against human nasopharyngeal cell line compared to tetraphenylporphyrin.[108] Subsequent reports using tetra(hydroxyl)phenylchlorin shows increasing uptake up to two-fold while the selectivity between tumour and normal tissue was high (5:1).[109] In the meantime, another folate conjugated fluorescent pyropheophorbide-a photosensitiser was designed to improve the efficiency of targeted delivery PDT agents and use for near-infrared (NIR) imaging purposes.[110]

A number of photosensitiser design approaches have been described with particular consideration to enhance targeting to the site of action, increase the selectivity for killing cancer cells, decreases the peripheral/systemic toxicity and to permit dose escalation. As the ideal systems need to both recognise specific targets on cancer cells and have capabilities of efficiently internalizing into the cells, a combination of different targeting approaches may provide immense promise of enhancing the photosensitiser delivery for cancer therapy.

1.2.4 Controlled release of photosensitiser

The development of an ideal photosensitiser delivery system requires channelling of the active photosensitiser solely to the site of action, that is achievable by impose its delivery to a specific receptor. While the targeted photosensitiser delivery capable of attaining site-specific delivery, the major concern that arises is in controlling its release kinetics in a predictable manner. Thus, there are many circumstances in which are need to

sought-after to deliver the photosensitisers to an individual at a predetermined rate and to extend the action over a suitable time span. All controlled release systems are designed to improve the effectiveness of cancer therapy, to ensure safety and improve patient compliance.[111]

One of the methods of releasing photosensitisers in a controlled mode is to utilise coating materials. In general, the photosensitiser is coated with polymers or inorganic materials that can be gradually released upon biodegradation under certain conditions. It has been suggested that pH-sensitivite triggers would be a beneficial approach in order to release the photosensitisers.[112] Change in acidity is a useful environmental stimulus to be exploited as it is reported that the extracellular pH of tumours is slightly more acidic (pH 7.0) than normal tissues (pH 7.4).[113] In addition, it is proposed that micelles are taken up by cells via an endocytosis process while the endocytic pathway begins near the physiological pH of 7.4 and it drops to a lower pH (5.5–6.3) in endosomes and approaches pH 4.6 in lysosomes.[114] Therefore, polymeric micelles that are responsive to these pH gradients can be designed to release the photosensitisers selectively in tumor tissue or within tumor cells. For example, aluminum phthalocyanine chloride (AlClPc) was loaded into a copolymer of pH sensitive *N*-isopropylacrylamide (NIPA), methacrylic acid (MAA), octadecyl acrylate (ODA) and *N*-vinyl-2-pyrolidone (VP) to form polymeric micelles and tested on EMT-6 mouse mammary tumor cells.[115] The result indicated that upon light treatment, the micelle formulations induced greater PDT photoactivity due to efficient intracellular localisation. It was shown that the presence of 5 mol% MAA in the copolymers caused the polymers to precipitate as the pH decreased below 5.7–5.8, hence caused release of the entrapped photosensitiser and improved the intracellular localisation of the photosensitisers.

Meanwhile, polymeric nanoparticles were also employed as control release vehicles for PDT. Early work described in 1991 involved the use of hematoporphyrin adsorbed in polyalkylcyanoacrylate nanoparticles, however the results show rapid photosensitiser release with poor carrier capacity.[116] A series of *p*-THPP loaded into biodegradable poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles were studied with the chick embryo chorioallantoic membrane (CAM) model that allows for the comparison of the vascular effects of *p*-THPP either as a free solution or encapsulated in polymeric nanoparticles.[117] Photosensitisers necessarily remain in blood vessels during light activation for selective destruction of vasculature. The study suggested that the nanoparticles with *p*-THPP appeared to have a longer residence time inside the vasculature, thus inducing an increased PDT effect; while free *p*-THPP appeared to leak out before generating an efficient vascular

occlusion. Another photosensitiser of verteporin-loaded PLGA nanoparticle type was investigated with different size of nanoparticles (167 and 370 nm) and tested on EMT-6 mammary tumour cells.[118] The result indicated that the PDT effect was improved by using small size particle as it had higher intracellular uptake through the endocytosis mechanism. However, smaller-sized particles show higher release rates due to a corresponding increase in the total particle surface area, resulting in a larger fraction exposed to the leaching medium. Thus, it was suggested that an optimal size for a particle diameter is less than 200 nm for the effective blood tumour transfer of nanoparticles and their long retention in tumour tissue.

As the ultimate goal of a controlled release system is to maintain the photosensitiser levels within a desired range, this system are also helpful to control the delivery of complicated photosensitisers such that to slow release of water soluble-photosensitisers and the fast release of low solubility photosensitisers. Further work is necessary to understand site-controlled release capabilities other than pH-induced to improve the photosensitiser delivery system.

1.3 Light-triggered release systems

1.3.1 Introduction

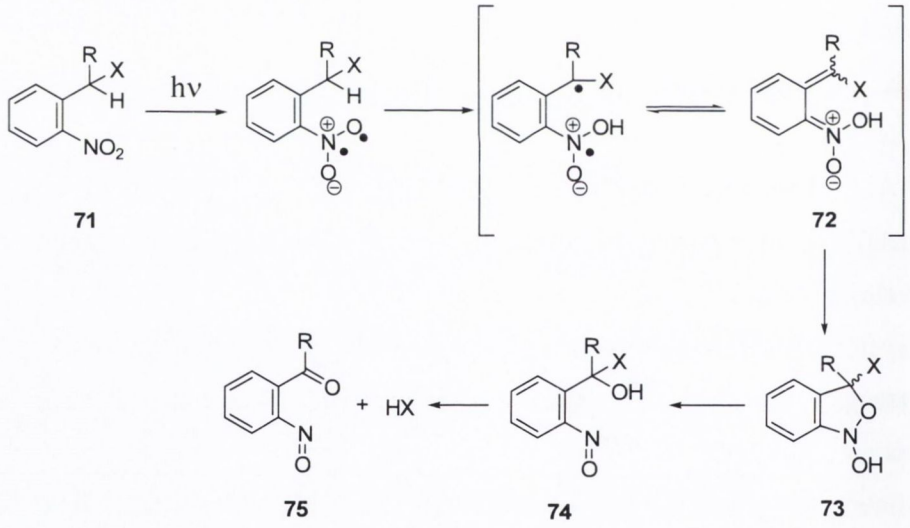
One area of interest is the development of a drug releasing system that can be triggered by external stimulation such as irradiation.[118] This photochemically-triggered release of drug is achieved by photocleavage of specific bonds in a prodrug molecular system. It offers more control and specificity as the light beam can be turned on and off (temporal control) and the light can be focussed at particular sites (spatial control). As the photolabile linker is the weakest site of a molecule under irradiation, development of such linker has gained wide consideration. Furthermore, light is used in photodynamic therapy, thus combination of light-medium process for release and activation of the photosensitiser will provide an attractive approach. In addition, tumour necrosis or induced apoptosis that contributes to cell death is affected by the light activation,[119] therefore utilising photocleavable linkers would be most advantageous.

In general, the photocleavable reaction should be clean, have sufficiently high quantum yield and fast kinetics to ensure that the drug is rapidly released. These linkers should be stable under ambient conditions and be compatible with the necessary synthetic steps. More importantly, they should be cleaved selectively and efficiently with light of an

appropriate energy before the other parts of the compound undergo photoreactions. Upon irradiation, the by-products of the photorelease should be biologically inert and should not absorb light at the associated wavelength of the linkers in order to avoid competitive absorption of the incident light. In this section, several promising photolabile linkages will be discussed in detail albeit most of the linkages are well-established as photoremovable protecting group.

1.3.2 *o*-Nitrobenzyl and derivatives

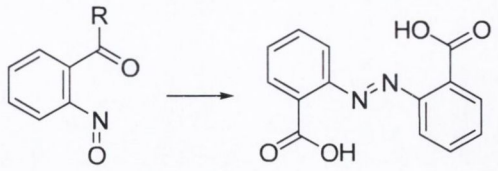
The most common photolabile linkages are based on photochemically-induced photoisomerisation of aromatic nitro compounds containing a benzylic group in an *ortho* position to the nitro group. The photolytic release mechanism of the *o*-nitrobenzyl group can be divided into five major steps (Scheme 1.15) and has been investigated both experimentally[120] and theoretically.[121] It involves an intramolecular hydrogen abstraction by oxygen of the nitro group **71**, photoredox activity give the aci-nitro intermediate **72**, cyclisation to the benzisoxazole **73**, ring opening to the hemiacetal **74** and deprotonation with release of the substrate to form **75**.



Scheme 1.15 Reaction mechanism of the 2-nitrobenzyl group.

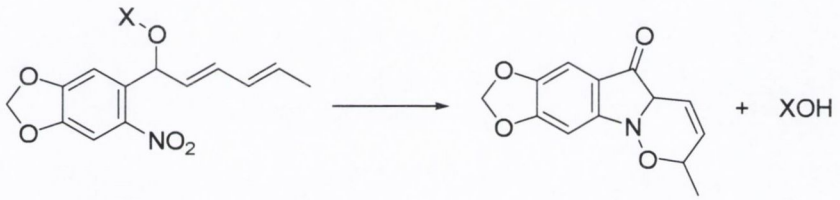
Barltrop *et al.* reported the release of benzoic acid from its parent of *o*-nitrobenzyl ester while irradiated with UV light.[122] Since then, the *o*-nitrobenzyl group and its derivatives have extensively used, but they also have few disadvantages. A major limitation of the unsubstituted 2-nitrobenzyl linker is that the by-product formation of a reactive *o*-nitrosobenzaldehyde can be toxic to the cell and may further react to form secondary by product of azobenzene-2,2'-dicarboxylic acid **76** which acts as internal light

filter, thus slowing the desired photoreaction (Scheme 1.16).[123] This side reaction can be eliminated by using α–substituted *o*-nitrobenzyl compounds that can release less reactive by product such as *o*-nitrosoacetophenone. An alternative method of trapping the nitroso species with pentadienyl group as **77** has been introduced and utilises an intramolecular hetero-Diels-Alder reaction (Scheme 1.17).[124]



76

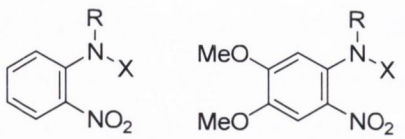
Scheme 1.16 Formation of secondary by product.



77

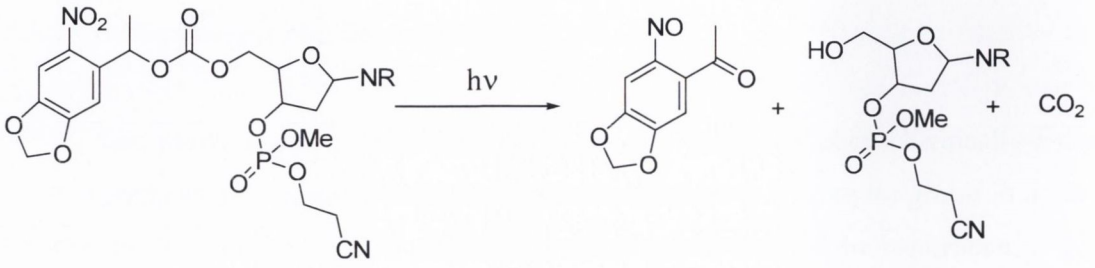
Scheme 1.17 A built-in pentadienyl group to trap nitroso group.

Despite these limitations, the *o*-nitrobenzyl group is still widely used for a variety of functionalities like alcohols,[125] carboxylic acids,[126] carbonyl,[127] amines,[128] phosphates[129] and thiols.[130] Besides its compatibility with the extensive range of functional groups, the *o*-nitrobenzyl is prevalent linkage due to ease of synthesis, protection and deprotection, with appropriate light sensitivities and kinetics. Several modifications of the *o*-nitrobenzyl group have been developed to improve its usability. For example, *o*-nitrophenylamine **78** and 4,5-dimethoxy-*o*-nitrophenylamine **79** (Figure 1.13) were used to protect carboxylic acid functional groups.[126] By attaching an oxycarbonyl building blocks **80**, this linker was designed to photochemically release alcohols or amines as used in light-directed synthesis of oligonucleotide arrays **81** on glass substract (Scheme.1.18).[131]



78 79

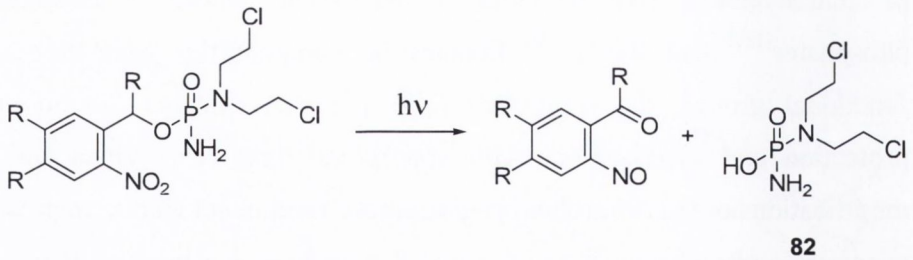
Figure 1.13 Example of 2-nitrobenzyl derivatives.



80 81

Scheme 1.18 Photolabile *o*-nitrobenzyloxycarbonyl group for protecting alcohol.

The *o*-nitrobenzyl linkers have been used in drug studies for photochemical release of the antiproliferative agent of phosphoramide mustard **82** that can treat various types of malignancies such as Hodgkin's disease, leukemia, lymphoma, breast and prostate cancer (Scheme 1.19).[118b] This mechanism offers controllable prodrug activation in comparison to other common pathways such as hydrolytic, bioreductive and biooxidative.



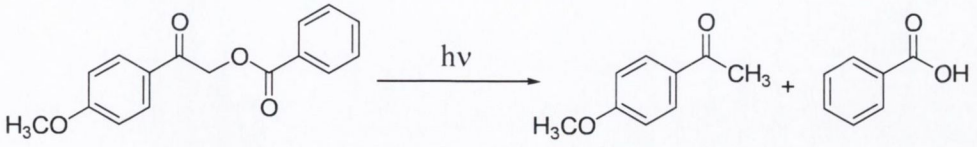
82

Scheme 1.19 UV irradiation to activate phosphoramide mustard agent.

1.3.3 Phenacyl group

The electron delocalisation between a carbonyl group and the phenyl ring makes phenacyl ester photolytically cleavable. The use of the *p*-methoxyphenacyl (*p*-MP) group **83** was introduced by Sheehan *et al.* as a photoremovable protecting group of carboxylic acids that can be photoreleased in a hydrogen donor solvent such as dioxane or ethanol in good yields (Scheme 1.20).[132] Anderson *et al.* monitored the irradiation of *p*-methoxy and

hydroxyl phenacyl ester that form phenylacetate derivatives while irradiated in methanol.[133] The aqueous solubility of the *p*-hydroxyphenacyl group (*p*-HP) was later investigated by Givens *et al.* as a promising cage for light-activated release of bioactive molecule containing nucleotide and phosphate functionalities.[134]

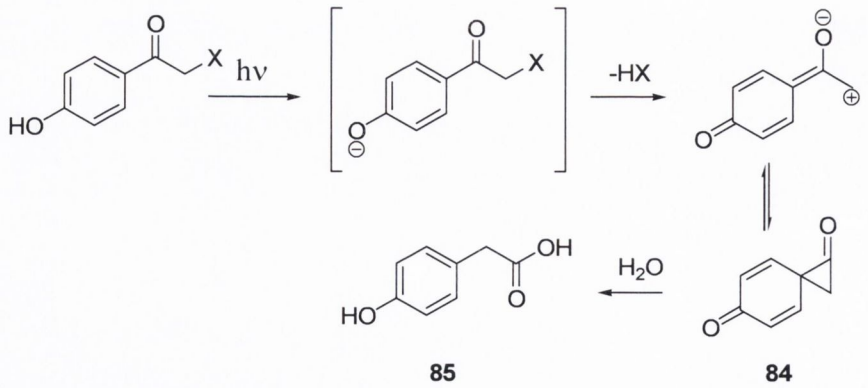


83

Scheme 1.20 Photorelease of phenacyl ester.

p-Hydroxyphenacyl groups (*p*-HP) have several advantages as a light-triggered molecule such as high quantum yield deprotection and fast releasing rates.[135] The group can be easily prepared from commercially available *p*-hydroxyacetophenone and is soluble in water and stable in aqueous solution. The main by-product from the photorelease process is non-toxic and absorbs at different wavelengths in contrast to its parent. Thus, it will allow for a fully quantitative photochemical conversion of *p*-PH. This group has been used to protect different functional groups such as carboxylic acids,[136] amino acids and peptides,[137] alcohols and phosphates.[138] However, it has the disadvantage of having low extinction coefficient at wavelength above 320 nm which require considerable improvements. It was reported that introducing methoxy substituents in phenyl ring will shift the absorption range of *p*-HP above 400 nm, but leads to formation of significantly lower quantum yields.[139] Klan *et al.* have established the use of 2,5-dimethylphenacyl (DMP) for carboxylic acid protection that can undergo self-removable *via* internal hydrogen abstraction without introducing any electron transfer sensitisers[136] or hydrogen atom donors.[140]

The photocleavage mechanism of the *p*-hydroxyphenacyl group which was proposed by Wirz *et al.* showed the formation of spiro[2.5]octa-4,7,diene-1,6-dione **84** upon release of the leaving group.[135] The spiro species is then hydrolysed to yield the *p*-hydroxyphenylacetic acid **85** (Scheme 1.21).



Scheme 1.21 Photorelease of hydroxyphenacyl cage.

An active drug system was devised by using photocleavable phenacyl ester groups and caging a model drug of biotin with oligonucleotide-based stem-loop type probes **86** (Figure 1.14).[141] It was found that 84% yield of biotin is released by photolysis of the photoactive probe upon light irradiation at 312 nm.

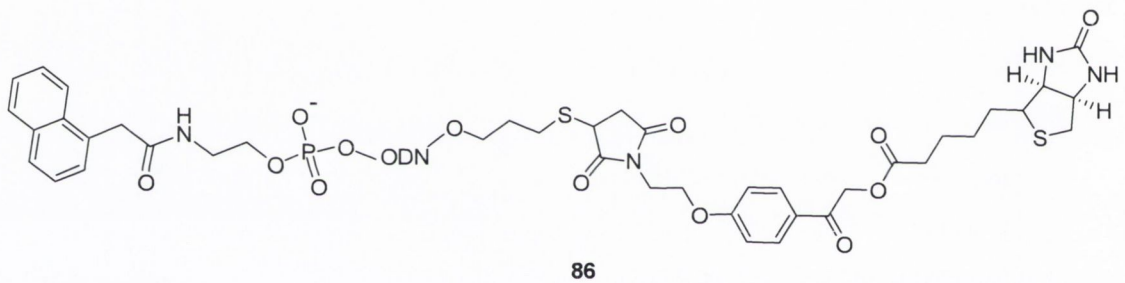
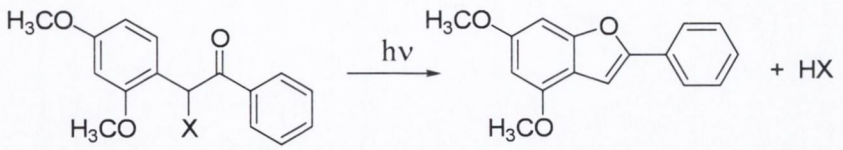


Figure 1.14. Structure of photoactive probe oligonucleotide.

1.3.4 Benzoin group

The benzoin (Bz) group has several interesting features which offer accessibility to use in photolabile molecular systems. It has high chemical and quantum yields with fast photoreleasing times. In addition, the resulting by-product of benzofuran is biologically-inert whilst its maximum absorbance is rendered at 300 nm, thus allowing an efficient irradiation process. Sheehan *et al.* studied the irradiation of benzoin esters **87** that are able to release the free acid and 2-phenylbenzofuran **88** while further optimisation by introducing methoxy groups gave the best yields (Scheme 1.22).[142] The Bz group has been used in caging different functionalities such as carboxylic acids,[142] phosphate

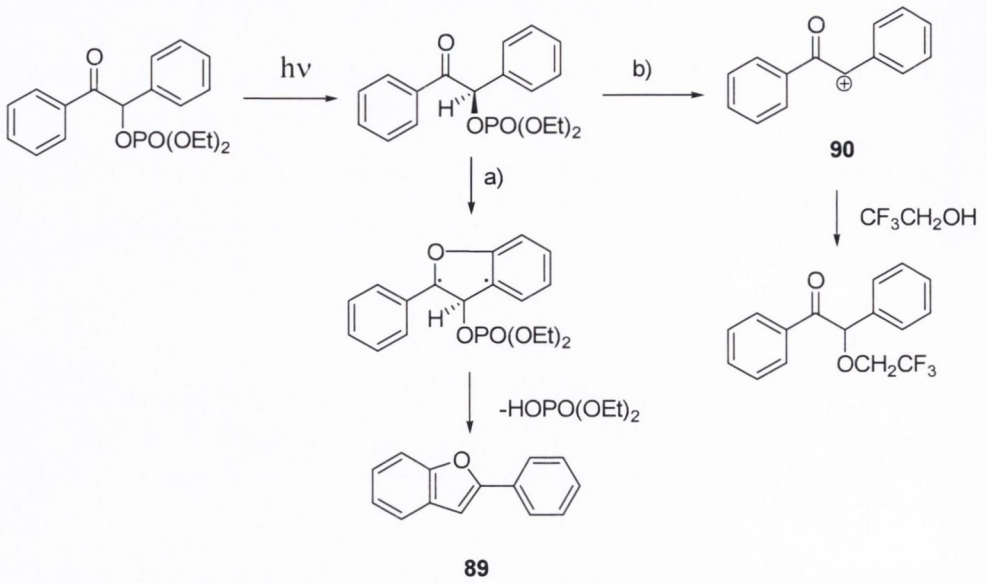
esters,[143] amine,[144] oligopeptides[145] and nucleotides.[146] The Bz group is highly light sensitive and can be released in the presence of ambient light. Moreover, its by-product of benzofuran is inert and does not act as an internal filter. It also has low solubility in aqueous solution which limits its biological application.



87 **88**

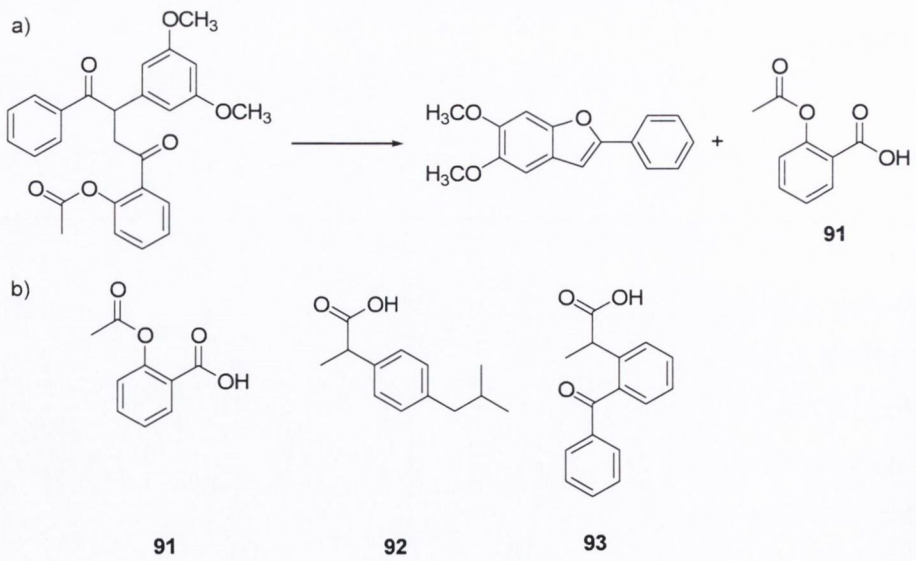
Scheme 1.22 Photoremoval of a benzoin group.

Various photo-triggered mechanisms have been proposed based on substituents at the phenyl ring, solvents and the leaving group influence. It was suggested that the 3,5-dimethoxy benzoin group undergoes a intramolecular Paterno-Büchi reaction to form a strained tricyclic intermediate, followed by ring opening and loss of acetate leaving group to give 2-benzofuran.[142] Studies of releasing benzoin diethyl phosphate in different solvents lead to two different pathways.[147] In most solvents, photoreaction will tend to follow path (a) with formation of 2-phenylbenzofuran **89** and diethylphosphoric acid rapidly. Irradiation in fluorinated alcohol (b) resulted in formation of a different major product of alkoxy-susbtituted benzoin **90** (Scheme 1.23). Pirrung *et al.* proposed the initial heterolytic cleavage and formation of ion pair directly from the singlet state, followed by ring closure and elimination.[148]



Scheme 1.23 Mechanism of photodissociation of benzoin diethyl phosphate.

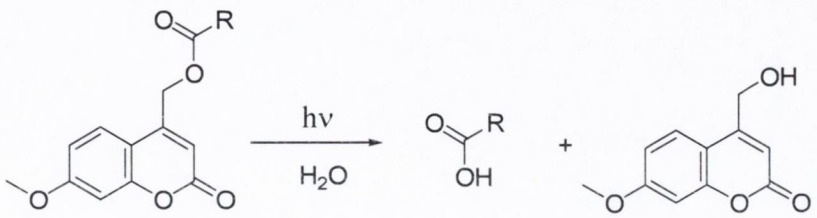
McCoy *et al.* developed the light liberation of a prodrug system based on the 3,5-dimethoxybenzoin (DMB) photoactive group.[149] Three model drugs of acetyl salicyclic acid (aspirin) **91**,[118a] ibuprofen **92** and ketoprofen **93**, that contain carboxylic acids functionalities have been studied (Scheme 1.24) and the reaction mixture was monitored by UV-visible spectra throughout the irradiation progress. The photorelease of by-product and drug and the consumption of the precursors were observed, thus enabling details investigation of the drug dosing level delivery.



Scheme 1.24 a) Photorelease of aspirin **91**, b) chemical structure of model drugs.

1.3.5 Coumarinyl derivatives

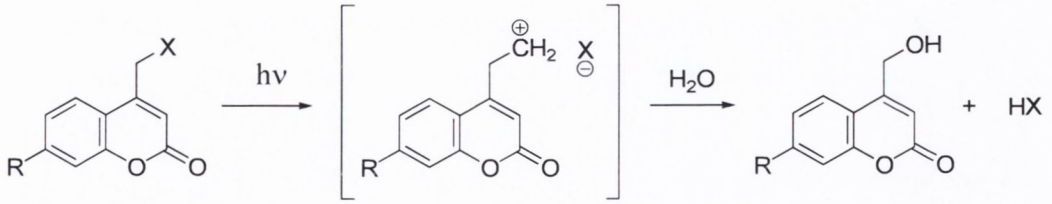
The 7-methoxycoumarin-4-yl-methyl (MCM) group is the first known photolabile protecting group based on coumarin moiety. It was introduced by Givens *et al.* who observed the formation of free carboxylic acid **94** and the hydroxymethylcoumarin **95** after irradiation in aqueous media (Scheme 1.25).[150] The coumarinyl groups were later increasingly employed to cage several functional groups such as carboxylic acids,[151] phosphates,[152] nucleotides[153] and amino acids.[154]



Scheme 1.25 Photorelease of MCM ester.

The coumarin group has the potential to replace conventional labile groups due to its fast rate of photorelease, good stability in biological systems, and it can be utilised in 2-photon excitation.[154] It also shows high extinction coefficient and the spectral absorption extends to the visible region. Introducing different substituents to its macrocycle can red-shift the absorption spectra and increase the amphiphilicity and its quantum yield.[152] There are a few drawbacks of this protecting group as some of the derivatives have low stability in neutral aqueous media and they have moderate quantum yield.

The mechanism of coumarinyl ester photolysis was investigated by Schade *et al.* (Scheme 1.26) who demonstrated that higher quantum yield are achievable by using highly polar solvent because of enhancing the solvation of the ion pair.[151]



Scheme 1.27 Reaction mechanism of coumarin derivative.

A polymerisable coumarin dimer system has been developed[155] to investigate the chlorambucil drug release for tumour treatment. Chlorambucil is selected as the model drug because of its sensitivity towards UV light that allowed the monitoring of single and two-photon absorption effects. It was observed that single-photon absorption induced the linker cleavage and decomposed the drug, while no photodegradation of the drug occurred in two-photon absorption.

1.4 Objectives

The objective of this present study was to design a novel approach based on light activation pro-drug/drug system for selective and controlled treatment of cancer by photodynamic therapy (PDT). This research investigated several synthetic methods towards the construction of such system. While porphyrins will act as photosensitisers, the photocleavable synthon will be used to cross-link biologically relevant groups that are able of binding to specific receptors. The incorporation of a range of functional groups into porphyrin macrocyles has been developed previously in our group based on organolithium reactions. Further investigation employed 1,3-dithianyl group as a precursor for masking formyl group based on *Umpolung* chemistry. In Chapter 2, compounds possessing dithiane and regiochemically substituted dithiane functionalities were explored and their analogue of spirobisdithiane and trithiane as the promising photolabile linkers were prepared.

The main focus of Chapter 3 was the synthesis of photolabile porphyrin based on *o*-nitrobenzyl linker. A wide variety of reactions have been examined for introducing the linker into the porphyrin macrocyle mainly *via* esterification reaction from acid porphyrin. In Chapter 4, an investigation of the labile *o*-nitrobenzyl linkers were further carried out to develop porphyrin linked-bioconjugate system. Several approaches were studied to link potential bioconjugated ligand for targeted receptor such as glucose and folic acid while experimental testing of the photolability of the compound was also investigated. Finally in Chapter 5, a relatively unexplored field of acrylic porphyrins were studied as a building block for synthesis of novel tetrapyrroles. Their reactivity essentially utilised acid porphyrins to generate acyl chloride intermediates which can be converted to a series of multifunctional porphyrins.

These studies will ultimately be the basis for subsequent interdisciplinary studies on the use of photocleavable tetrapyrrole bioconjugates in medicine; notably, the specific use of the drug chromophore as a photosensitising agent in photodynamic cancer therapy

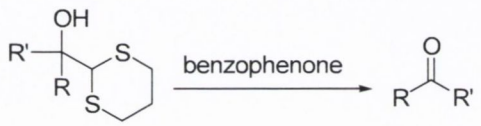
and cancer indication. The research is the first stage in long-term efforts to promote the use of improved photosensitisers in the treatment and indication of various diseases.

CHAPTER 2:

Photolabile Thio Porphyrin Derivatives

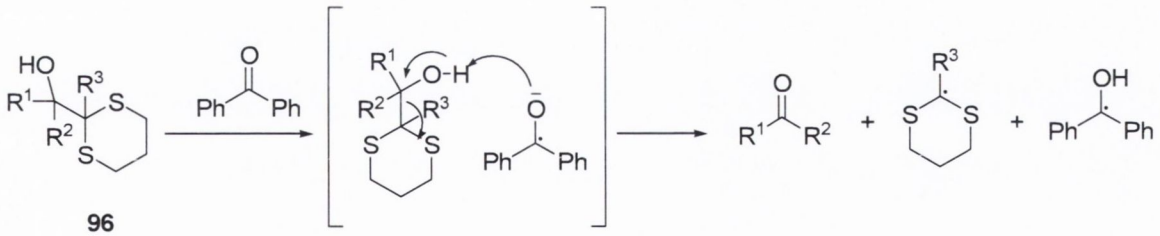
2.1 Introduction

The photochemistry of dithiane derivatives has been of interest for many years. Numerous progress has been made since McHale *et al.* discovered the C-C photocleavage of α-hydroxyalkyl-1,3-dithiane **96**.[156] This type of compound was shown to undergo photosynthetic reaction in the presence of benzophenone upon UV irradiation to generate aldehyde or ketone quantitatively (Scheme 2.1). It has been proposed that the process is initiated by a photoinduced electron-transfer involving a single electron transfer from the dithiane moiety to excited benzophenone, followed by benzophenone radical anion assisted O-deprotonation leading to C-C bond cleavage (Scheme 2.2).[157] This method was originally designed to use dithiane as photoremovable protecting group for aldehydes or ketone. Nevertheless it has a potential application as a photolabile linkage to attach various molecular blocks and build photolabile systems that are capable of releasing a guest molecule upon irradiation.



96

Scheme 2.1 Photofragmentation of α-hydroxyalkyl-1,3-dithiane.

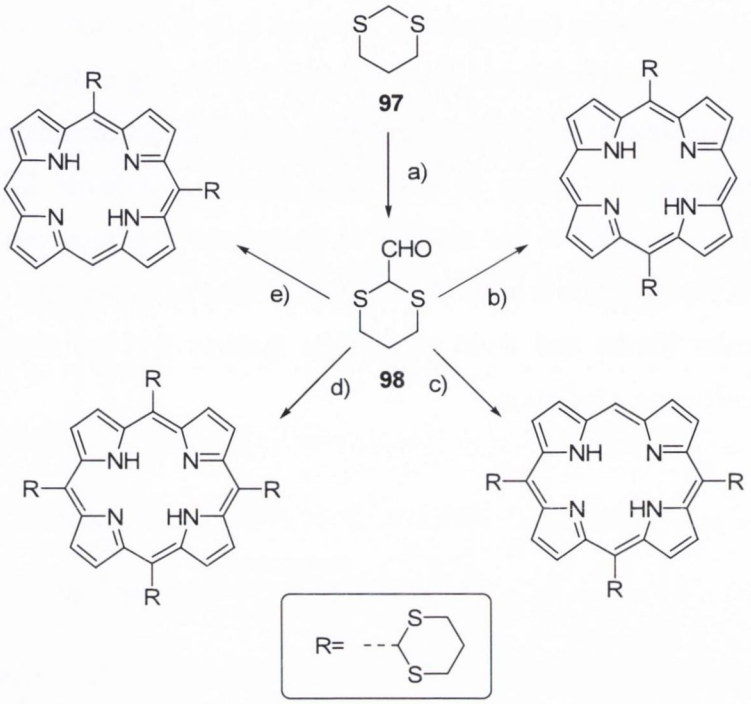


96

Scheme 2.2 Mechanism of α-hydroxyalkyl-1,3-dithiane photo-cleavage assisted by a benzophenone sensitiser.

Our group had already established the basic chemical strategies necessary for the synthesis of functionalised porphyrins containing dithianyl residues.[158] A synthon of 1,3-dithian-2-yl **97**[159] has been utilised as a functional and protected formyl group, where its lithio derivative offers the possibility to introduce the latent formyl groups under nucleophilic substitution reaction based on *Umpolung* chemistry. The dithianyl synthon can also be used in another strategy for the preparation of such porphyrin systems. It can be

converted into the corresponding aldehyde **98**, which we have used to prepare porphyrins with two to four dithianyl residues *via* condensation reactions (Scheme 2.3). Selected dithianylporphyrins could be deprotected to yield the corresponding formylporphyrins, which are important and hitherto often inaccessible for the construction of more complex porphyrin system.



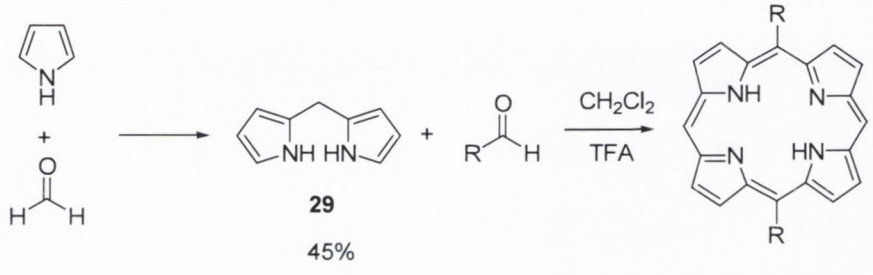
Scheme 2.3 Synthesis of 1,3-dithianylporphyrins *via* condensation reactions. Conditions: (a) *n*-BuLi, THF, -78 °C, 1 h; then -10 °C, DMF, 2 h; then 0 °C, 16 h; then ice, 85%. (b) CH_2Cl_2, dipyrromethane, TFA, 14 h, rt; then DDQ, 10 min, reflux, 16%. (c) CH_2Cl_2, pyrrole, $BF_3.OEt_2$, 1 h, rt; then excess DDQ, 1 h, 46%. (d) CH_2Cl_2, pyrrole, $BF_3.OEt_2$, 1 h, rt; then NEt_3, DDQ, 4 min, 15%. (e) CH_2Cl_2, tripyrrane, pyrrole, 45 min, rt; then TFA, rt, 16 h; then DDQ; then NEt_3, 3%.

Kutaledze *et al.* have shown that combining two dithiane groups in a spiro compound results in the formation of potential cross-linking groups that can be cleaved in a photosensitised reaction.[160] These prompted us to envisage this compound as a key intermediate for the ultimate construction of porphyrin spirobisdithianyl-linked bioconjugates. Such systems would have significant potential for drug delivery in photodynamic cancer therapy owing to the cleavable spirobisdithiane linker. Our approach involved the synthesis of these photosensitiser systems which are photochemically inactive

during transport. However, it could be cleaved in a tumour tissue releasing the active photosensitisers. Thus, this modality involves two prodrug-drug conversion steps. First, cleavage of the photolabile linker to yield the photosensitiser, and then activation of the photosensitiser by light to generate cytotoxic singlet oxygen.

2.2 Synthesis of porphyrin precursor

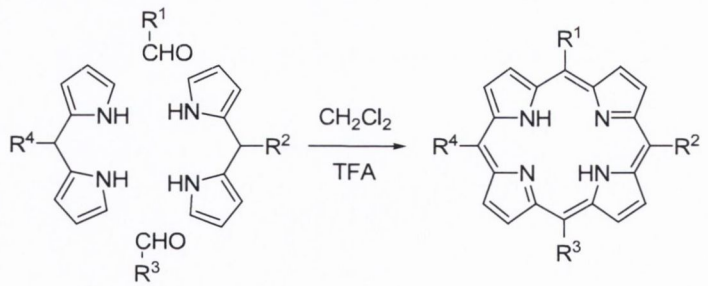
As mentioned in the previous chapter, the synthesis of simple *meso*-modified porphyrins can be achieved *via* condensation of pyrrole or a pyrrolic derivative with various aldehydes. A variety of A_2-type porphyrins (**99-103**) with two unsubstituted *meso*-positions available for subsequent functionalisation were synthesised using the dipyrromethane precursor **29** under conditions optimised by Lindsey *et al* (Scheme 2.4).[31] This starting materials have been previously synthesised and the spectroscopic data are in accordance with those reported in the literature.[33]



R = Phenyl	47%	**99**
R = 3-Methoxyphenyl	48%	**100**
R = Hexyl	28%	**101**
R = 1-Ethylpropyl	7%	**102**
R = 3,5-di-*tert*-butylphenyl	38%	**103**

Scheme 2.4 Synthesis of 5,15-A_2 porphyrins.

Generally, the synthesis of differently *meso*-substituted porphyrin *via* condensation methods depends on the nature of the required substituents. A mixed condensation is usually carried out to produce unsymmetrical porphyrins (Scheme 2.5).



R^1= Phenyl R^2= H R^3= Hexyl R^4= H	R^1= R^3= Phenyl R^2=R^4= H 6%, **99**	R^1= Phenyl R^3= Hexyl R^2=R^4= H 14%, **104**	R^1= R^3= Hexyl R^2=R^4= H 4%, **101**
R^1=R^3= R^4= H R^2= Ethylpropyl **105**	R^1=R^3= Ethylpropyl R^2=R^4= H 14%, **102**	R^1=R^2=R^3= Ethylpropyl R^4= H 20%, **106**	R^1=R^2=R^3=R^4 Ethylpropyl 8%, **107**

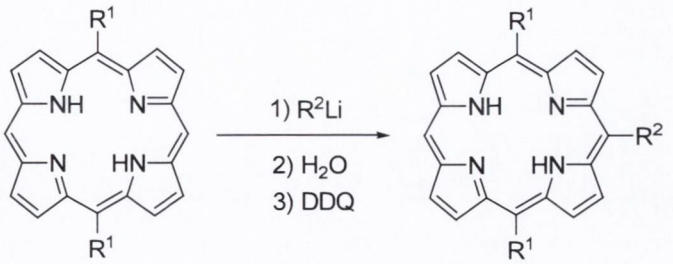
Scheme 2.5 Mixed condensation for m*eso*-substituted porphyrins.

The preparation of AB substituted porphyrins using dipyrromethane and two aldehydes, benzaldehyde and heptaldehyde yielded three products; (A_2-type) 5,15-diphenylporphyrin **99**, (AB-type) 5-hexyl-15-phenylporphyin **104**, and (B_2-type), 5,15-dihexylporphyrin **101**, due to the unselective nature of condensation. A mixed condensation was also performed where two dipyrromethane precursors and 5-(1-ethyl)propyldipyrromethane **105** were reacted with a single aldehyde of ethylbutyraldehyde. The synthesis of dipyrromethane **105** was achieved by heating the mixture of an aldehyde and pyrrole catalysed by Lewis acid, followed by purification using Kugel-Rohr distillation. This variation of a mixed condensation reaction afforded 5,15-di- **102**, 5,10,15-tri- **106** and 5,10,15,20-tetrakis(1-ethylpropyl)porphyrin **107** with relatively low yields due to the multiple products formed.

The number of potential products becomes very large while using this mixed condensation reaction for the preparation of unsymmetrical *meso*-substituted porphyrins bearing three or four different groups. The consequence of this methodology is a complicated purification procedure and ultimately low yields of the desired porphyrins. Although an improvement in the condensation methods has been made involving step-by-step synthesis to produce the unsymmetrical porphyrins, such an approach requires more synthetic steps and currently has only been reported for porphyrins with aryl substituents. Therefore, alternative methods are required to introduce various functionalities on porphyrin periphery and to provide access to the desired unsymmetrical porphyrins.

Senge *et al.* has extensively studied the incorporation of numerous aryl and alkyl substituents into porphyrin macrocycle *via* nucleophilic substitution (S_NAr) reactions with organolithium reagents.[67] The overall process proceeds *via* initial reaction of an organic

nucleophile with a *meso*-carbon yielding an anionic species which is hydrolysed to a hydroporphyrin, followed by oxidation giving *meso*-substituted porphyrin **108-110** in 67%-81% yield (Scheme 2.6). The reactions of porphyrin **99** and **100** with hexyllithium were performed at -78°C while phenyllithium reacted with porphyrin **99** at 0°C.

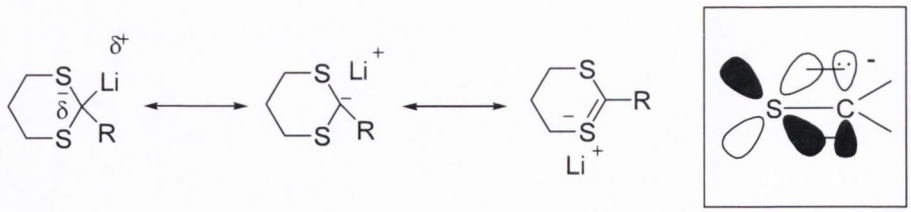


99	R^1= Phenyl R^2= Hexyl	67%	**108**
100	R^1= 3-OMePhenyl R^2= Hexyl	73%	**109**
99	R^1= Phenyl R^2= Phenyl	81%	**110**

Scheme 2.6 S_NAr reaction of porphyrins with an organolithium reagent.

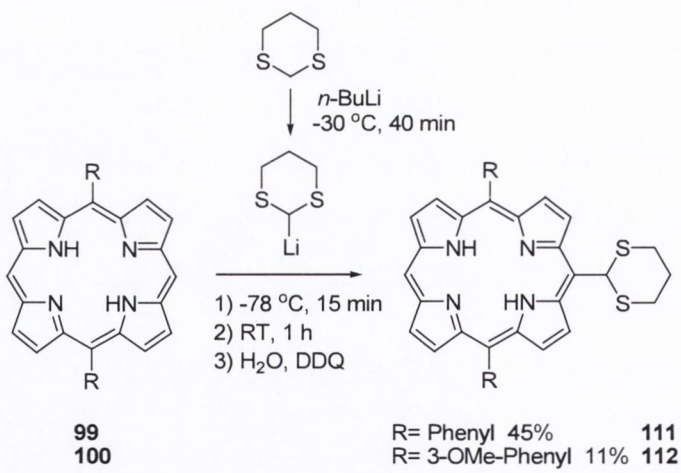
2.3 Synthesis of dithianyl porphyrin derivatives

The success of S_NAr approach for porphyrin modifications using organolithium reagents prompts us to investigate further applications of this method and use it as a versatile nucleophilic tool. The well known formation of lithio-dithiane offers a convenient strategy to introduce the dithianyl residue as a formyl synthon into the porphyrin macrocycle *via* formation of a C-C bond.[158] 1,3-Dithianes have two polarisable sulfur atoms bonded to the –CH group which causes the H atom to be more acidic with a pK_a ~32 compared to a pK_a of ~50 for unactivated C-H bond.[161] Thus, 1,3-dithiane can be deprotonated by strong base such as *n*-butyllithium. The resulted carbanion can be stabilised *via* electron back-donation effect on vacant sulfur d-orbitals (Scheme 2.7).



Scheme 2.7 Carbon-lithium character of 1,3-dithiane.

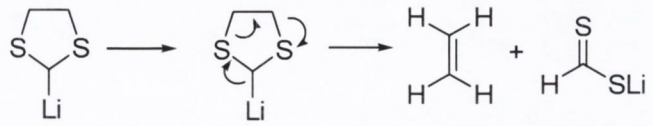
This technique can be applied to the free bases and metalloporphyrins due to the mild reaction conditions to produce dithianyl porphyrins in good to excellent yields. For example, 1,3-dithiane was treated with *n*-butyllithium in THF at -30 °C to generate 2-lithio-1,3-dithiane *in situ*, which then reacted with the porphyrin **99** and **100** leading to the corresponding dithianyl porphyrin **111-112** (Scheme 2.8). The substitution reaction was promoted by tetramethylethylenediamine (TMEDA), quenched with water and oxidised with DDQ. Nevertheless, the reaction of lithio-dithiane with porphyrins is challenging and strongly dependent on porphyrin substituents resulting in inconsistent yields. It was observed that the deprotection of the dithianyl moiety also occurred during chromatography separation processes giving formylporphyrin as the minor product. Occasionally, the *n*-butyllithium from the reaction mixtures tends to react directly with the porphyrin moiety resulting in the formation of *meso*-*n*-butylporphyrin.



Scheme 2.8 Synthesis of dithianyl porphyrins.

The reactivity of organolithium reagents has also been investigated on the β-position of porphyrins to access various chlorins.[162] Therefore, the dithianyl residue presumably can be used in a similar manner. Due to bathochromically shifted absorption

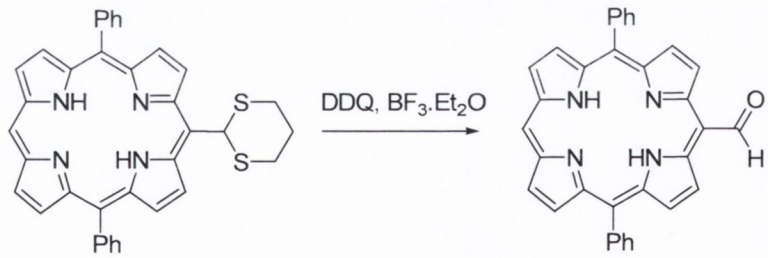
bands (deeper tissue penetration of light), chlorins are of special interest for use in PDT. However, the attempted reactions with *meso*-tetrasubstituted porphyrins have not been successful due to the inherently lower reactivity of the β-position. In order to expand the chemistry of the dithio synthon with porphyrins, the reactivity of 1,3-dithiolane was also investigated. Upon generating the lithio-dithiolane nucleophile, the mixture was reacted with free base porphyrin **99** but only starting material was recovered. It is reported that 2-lithio-1,3-dithiolane is an unstable compound which undergoes elimination to form ethylene **113** and dithiocarbinol **114** as shown in Scheme 2.9.[163]



113 **114**

Scheme 2.9 Ring opening of 1,3-dithiolane upon RLi treatment.

There are several methods for the hydrolysis of the dithianyl group including photolytic cleavage,[160] metal coordination,[164] alkylation[165] and the use of chemical oxidants.[166] It was found that the treatment of the dithianylporphyrins **111** with DDQ and $BF_3.Et_2O$ in CH_2Cl_2 leads to facile deprotection giving the corresponding formylporphyrins **115** (Scheme 2.10).[158, 167]

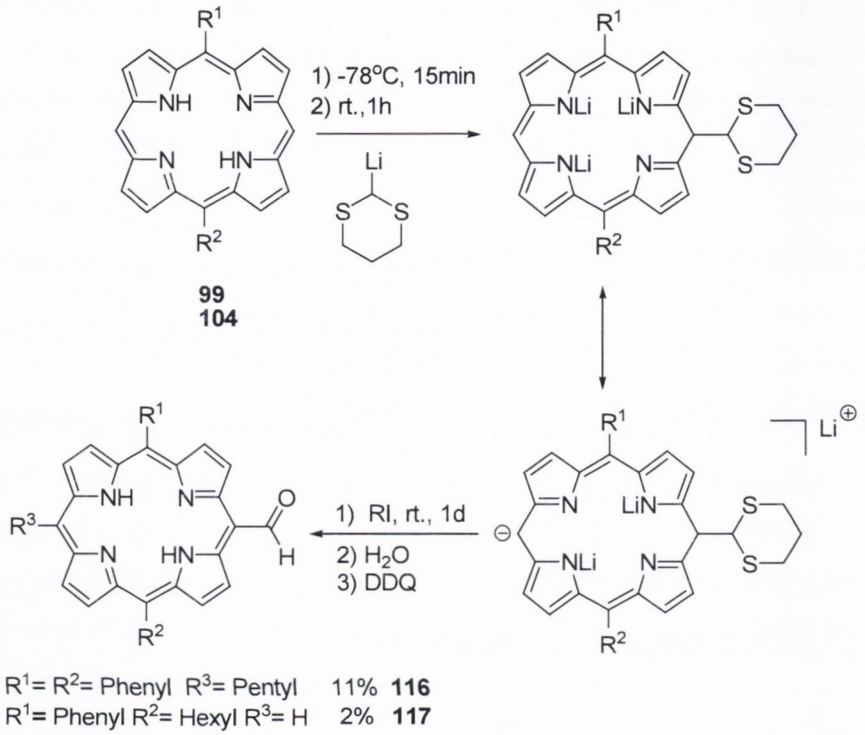


111 39% **115**

Scheme 2.10 Deprotection of dithianyl porphyrin.

It has been shown that one-pot, two-step disubstitution of free base porphyrins is achievable with both nucleophiles and electrophiles under thermodynamically controlled conditions.[68] Thus, we also attempt to trap the *in situ* generated dithianylporphyrin anion with electrophiles, akin to the reaction with standard organolithium reagents. Reaction of porphyrin **99** with 1,3-dithian-2-yl lithium and prolonged heating with pentyliodide followed by standard workup yielded the doubly substituted formylporphyin **116** in low yield (11%). To test the reactivity with more unsymetrical porphyrins, porphyrin **104** was

treated with 1,3-dithiany-2-yl and propyliodide. Workup of this reaction yielded a small amount of the deprotected formyl porphyrin **117**. Various reactions were further investigated using different electrophile such as *n*-butyl- and *n*-hexyl-iodides, and afforded only formylporphyrins along with starting material. All these reactions already indicated that the stability of the dithian-2-yl residue is limited under the reaction conditions necessary for porphyrin substitution.



Scheme 2.11 One pot synthesis of disubstituted porphyrin.

A potentially more useful strategy involved utilising the lithio derivative of 2-substituted-1,3-dithiane which should provide an access to acylporphyrins. However, the reaction of free base porphyrin with sterically more hindered 2-methyl-1,3-dithiane to yield the putative compound of *meso*-substituted porphyrin **118** was problematic. Spectroscopic evidence indicates the formation of *β*-adducts in low yields. ^{1}H-NMR shows the presence of seven *β*-Hs and two free *meso*-Hs (Figure 2.1). This infers that the substitution reaction occurred at the *β*-position of porphyrin [MS (ESI): *m/z*= 595.1990 $(M+H)^+$], which is generally observed for sterically hindered organolithium reagents.[67,162] Several test reactions were carried out to optimise the reaction conditions which two factors affected the results. First, the conversion to the lithio derivatives should go to completion by the addition of an equal amount of *n*-buthyllithium to the substituted 1,3-dithiane and stirring up to 2 hours at 0 °C.[168] It was found that the yield of the product varied from reaction to

reaction which suggests an inconsistent and difficult formation of the lithio intermediate. An excess of *n*-buthyl lithium was used to ensure the formation of the lithio-dithiane went to completion. However, *n*-BuLi reacted with the porphyrin yielding an undesired *n*-butylporphyrin. In addition, the steric hindrance associated with 2-methyl substituent is believed to reduce the reactivity of the 2-lithio-dithiane considerably.

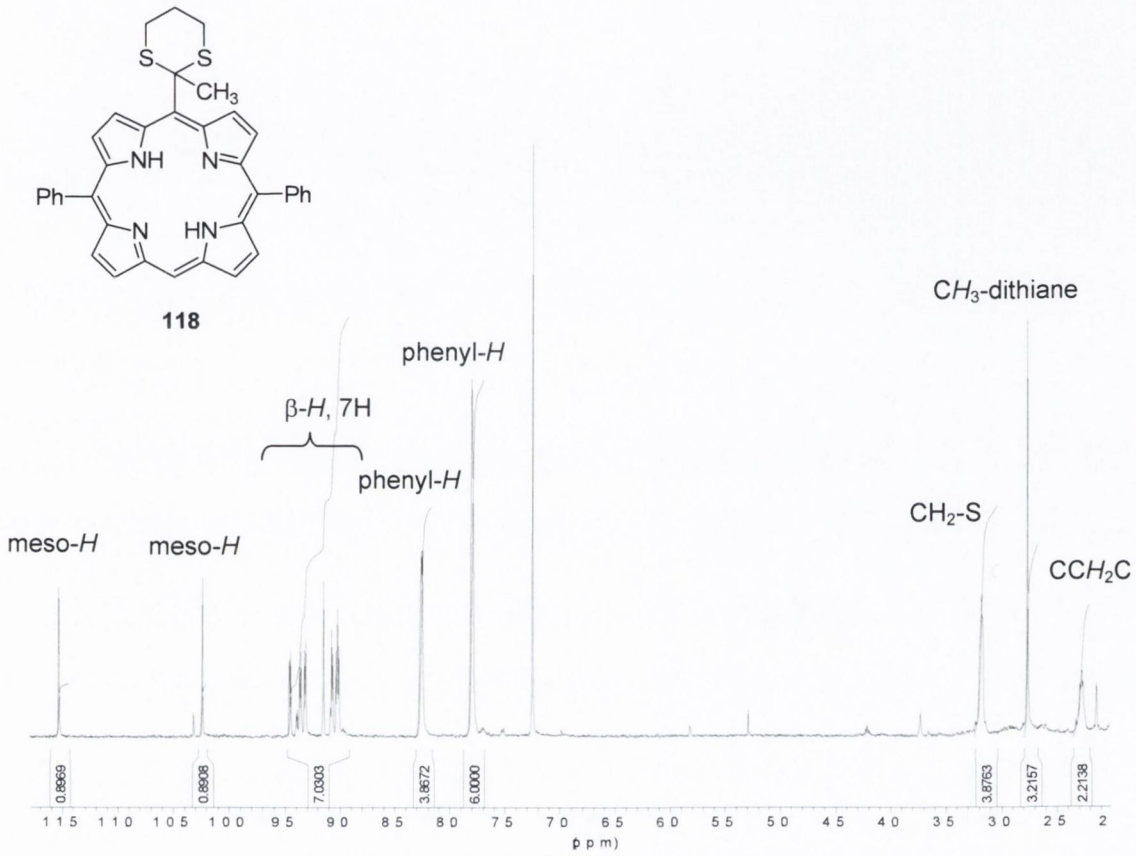


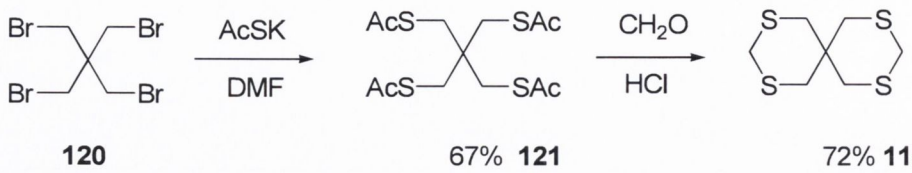
Figure 2.1 ^{1}H-NMR spectrum of *β*-adduct in $CDCl_3$.

2.4 Photolabile spirobisdithianyl- and trithianyl-porphyrin

An assembly of macromolecular hosts equipped with a photolabile latching module based on 2,4,8,10-tetrathiospiro[5.5]undecane, or so-called spirobisdithiane **119,** has been developed by Kutateladze *et al.*[160] This compound has advantages of being the shortest tether possible in the bis-dithane family and also is easy to synthesise. The synthetic feasibility is important because it is impractical to recover the latch itself after the photodiassociation step due to partial degradation of the dithiane moiety in the photoprocess.

The spirobisdithiane was synthesised from commercially available pentaerythrityl tetrabromide **120**. Nucleophilic substitution by potassium thioacetate in DMF yielded the

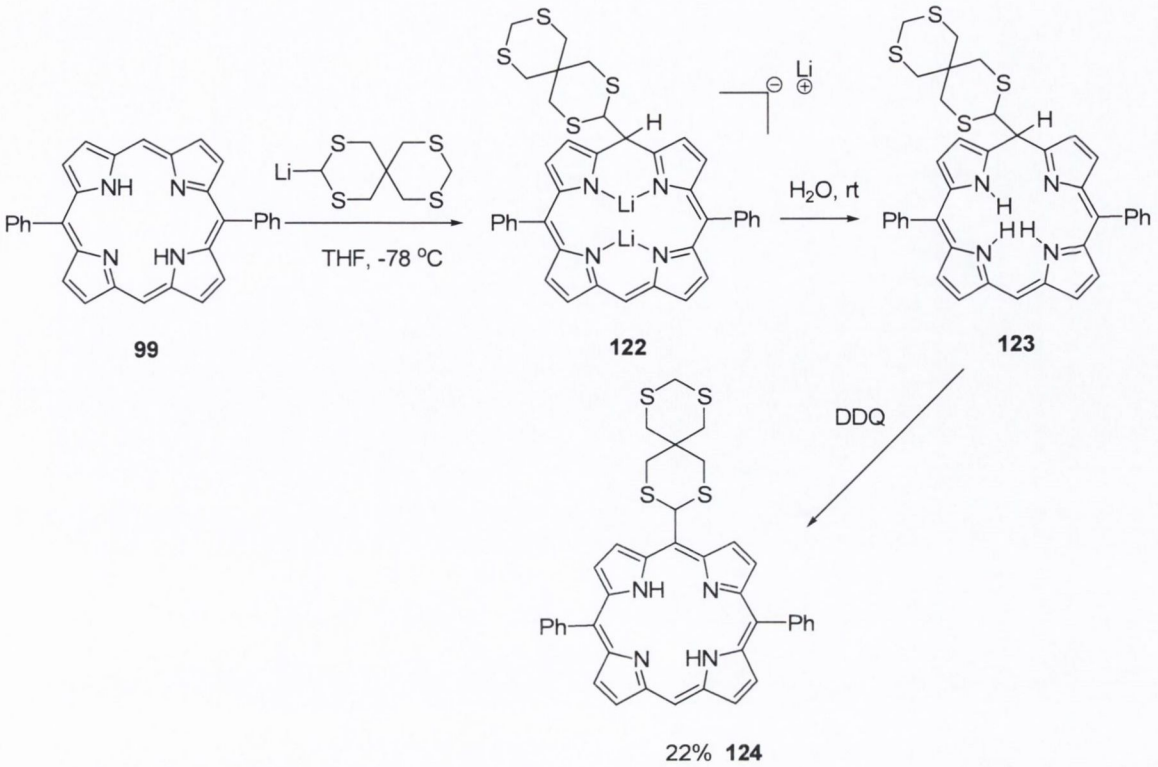
pentaerythrityl thioacetate **121** in 67% yield. The spirobisdithiane was obtained by using hydrochloric acid in the presence of formalin, under acid-catalysed conditions. Both thioacetate hydrolysis and thioacetal formation were performed in one step and afforded the target spiro-bis-dithiane **119** in 72% yield (Scheme 2.12). Excess use of formalin is necessary to enable the complete conversion of the target compound.



120 67% **121** 72% **119**

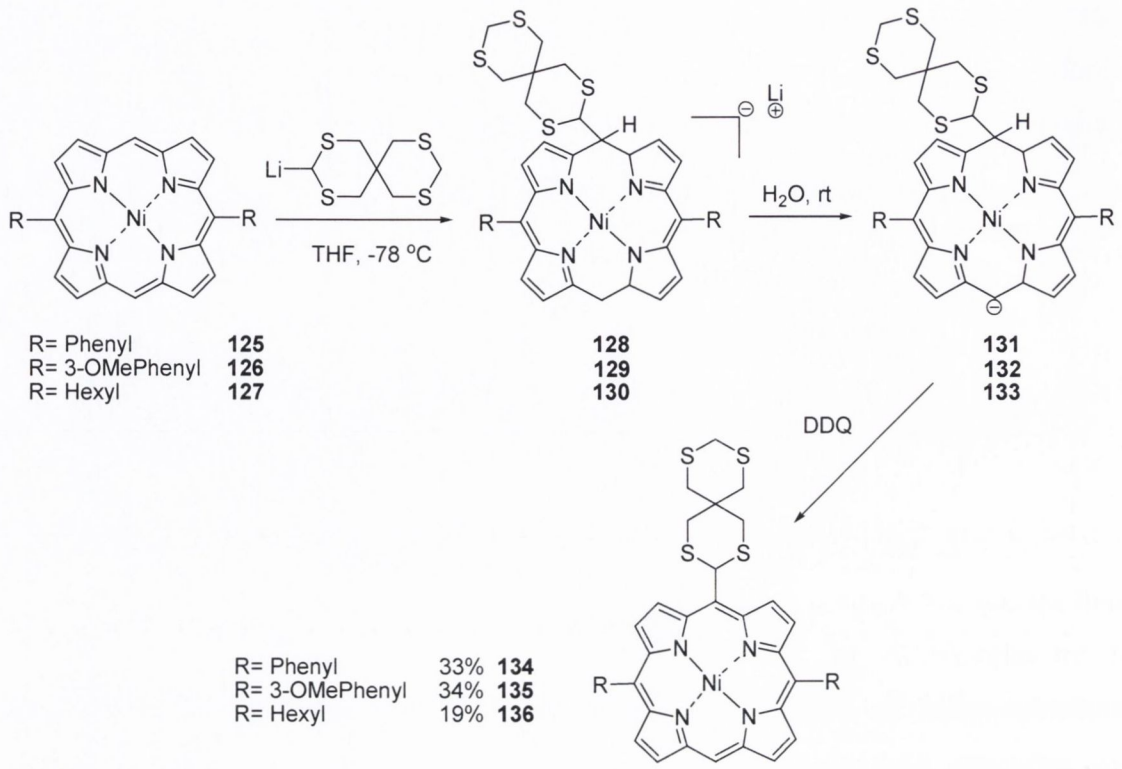
Scheme 2.12 Synthesis of spirobisdithiane.

As described for the 1,3-dithianyl residue, it should also be possible to use the lithio derivatives (both mono- and dilithiated) of the spirobisdithiane as nucleophiles for the direct substitution of porphyrins. In the first stage, a series of mono-substituted spirobisdithiane porphyrins were synthesised. Metallation of porphyrin precursor was achieved by the standard conditions with nickel(II) acetylacetonate in toluene under reflux.[169] Similar to organolithium reactions described earlier, the mechanism involving free base porphyrin **99** comprised the addition of spirobisdithianyl residue into a *meso*-position of the porphyrin macrocycle and the coordination of two lithium atoms to inner nitrogens resulted in the phlorin-type structure **122**. After quenching with water, the hydroporphyrin intermediate **123** is formed and subsequent oxidation with DDQ gave the desired porphyrin **124** in 22% yield (Scheme 2.13).



Scheme 2.13 Reaction of free-base porphyrin **99** with 2-lithio-spirobisdithiane.

The reaction mechanism for a metalloporphyrin is slightly different compared to free base porphyrin. The spirobisdithianyl intermediate is added to Ni(II) porphyrin complex **125-127** to form a Meisenheimer-type complex of **128-130**. Further hydrolysis with water gave the porphodimethene type molecules **131-133** before undergoing oxidation to give the desired porphyrin **134-136** in 19-33% yield (Scheme 2.14). Due to the steric hindrance of the bulky spirobisdithiane residue, the yields of all spirobisdithianyl porphyrins are comparable to those in *iso*-propyl or *sec*-butyllithium reactions.



Scheme 2.14 Reaction of metalloporphyrin with 2-lithio-spirobisdithiane.

In these reactions, the preparation of the mono-lithiated spirobisdithiane was achieved using 1:1 equivalents of *n*-butyllithium/spirobisdithiane and underwent completion upon stirring for 2 hours. A large excess of the lithiated spirobisdithiane (22 equivalents) is required to react with porphyrin *in situ* in the presence of TMEDA giving the respective spirobisdithianyl porphyrins. Notably, the yields for the metallated porphyrins are higher than for the free base porphyrin analogues. This is believed to be due to a stable nickel(II) complex intermediate which exhibits a high degree of nucleophilic reactivity. Most interestingly, **124** was found to undergo photocleavage completely to form a formylporphyrin during column chromatographic purification, highlighting the photosensitivity of these porphyrins. A separation of the adduct mixture was carried out in the dark to minimise splitting of the photolabile spirobisdithiane upon exposing to ambient light. Meanwhile, the metalloporphyrins showed a much greater stability towards light.

In addition, the formation of dilithio species of spirobisdithiane using two equivalents of *n*-BuLi can be employed for the direct cross-linking of two porphyrins or for the synthesis of porphyrin linked-bioconjugate. Unfortunately, all attempts to use the spirobisdithianyl dianion for the double substitution reactions failed or gave alternative products. For example, the reaction of nickel(II) porphyrin **125** with the dilithio derivative

of spirobisdithiane gave 71% of respective 5-butyl-substituted porphyrin and 6% yield of [10-spirobisdithian-2-yl-5,15-diphenylporphyrinato]nickel(II) **134** respectively. It is reported that the formation of dilithiated spirobsidithiane intermediate is completed by using 3.5 equivalent of *n*-butylithium,[160, 170] however, the excess of *n*-BuLi again increases the risk for its direct addition to the porphyrin.

The ^{1}H-NMR spectrum for **124** shows the presence of two broad peaks assigned to β-H neighbouring the spirobisdithiane group (Figure 2.2). These peaks are due to the intramolecular hydrogen bonding between these β-protons and the sulfur atoms of the spirobisdithiane prevented from free rotation. Similar observations were made under different temperatures of ^{1}H-NMR studies for dithianyl porphyrin. ^{1}H-NMR resonance of the β-proton are fused at above the coalescene temperature of 334 K and below this temperature, they resolve into two broad resonances. In contrast with the nickel(II) complex **134**, the signals for the β-proton are split only once (Figure 2.3).

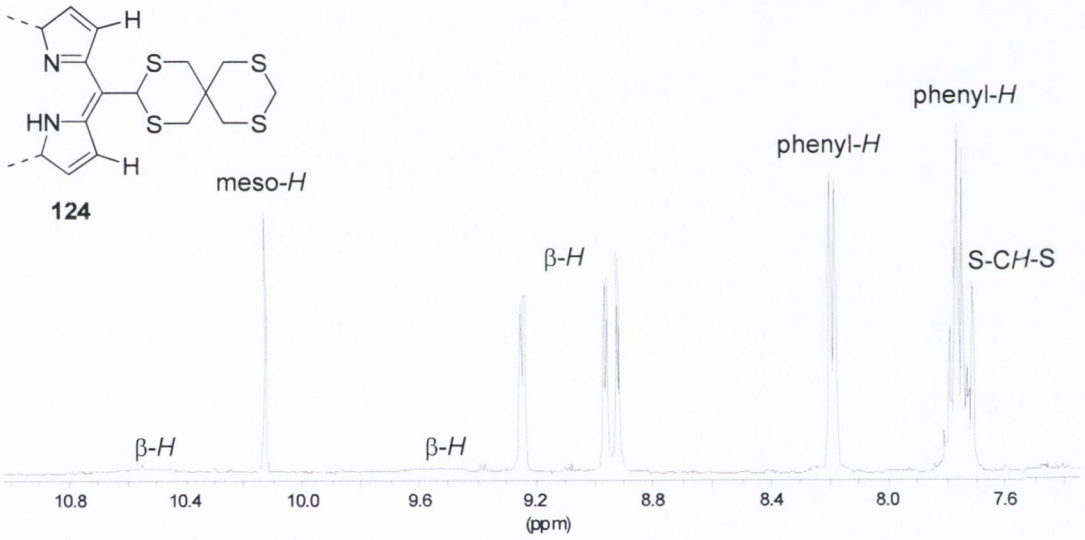
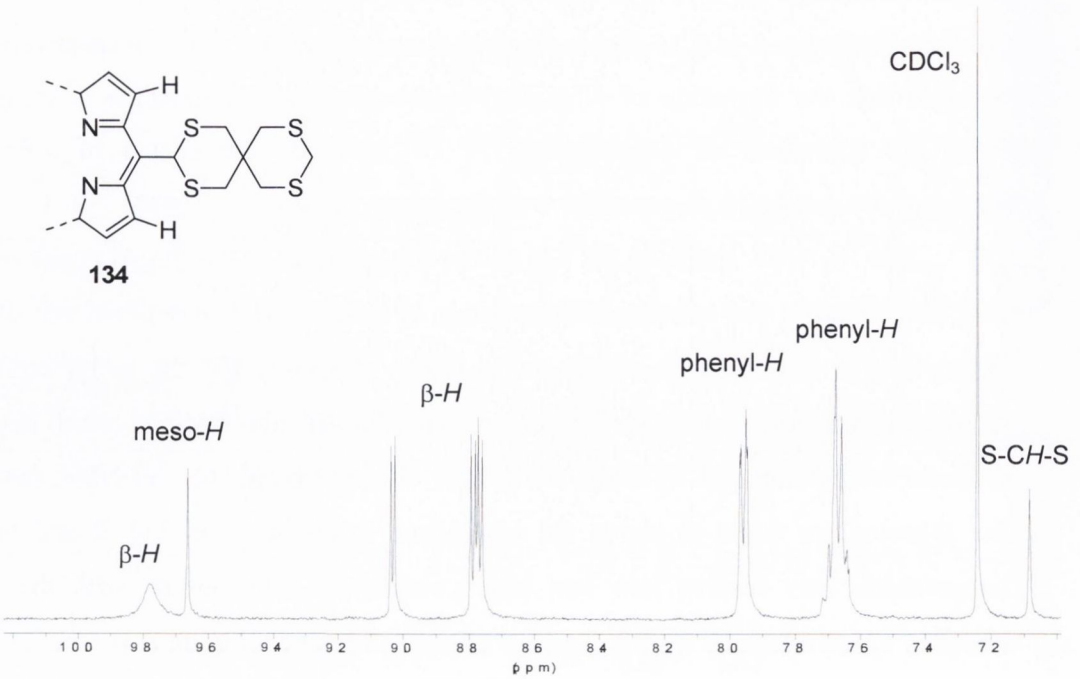


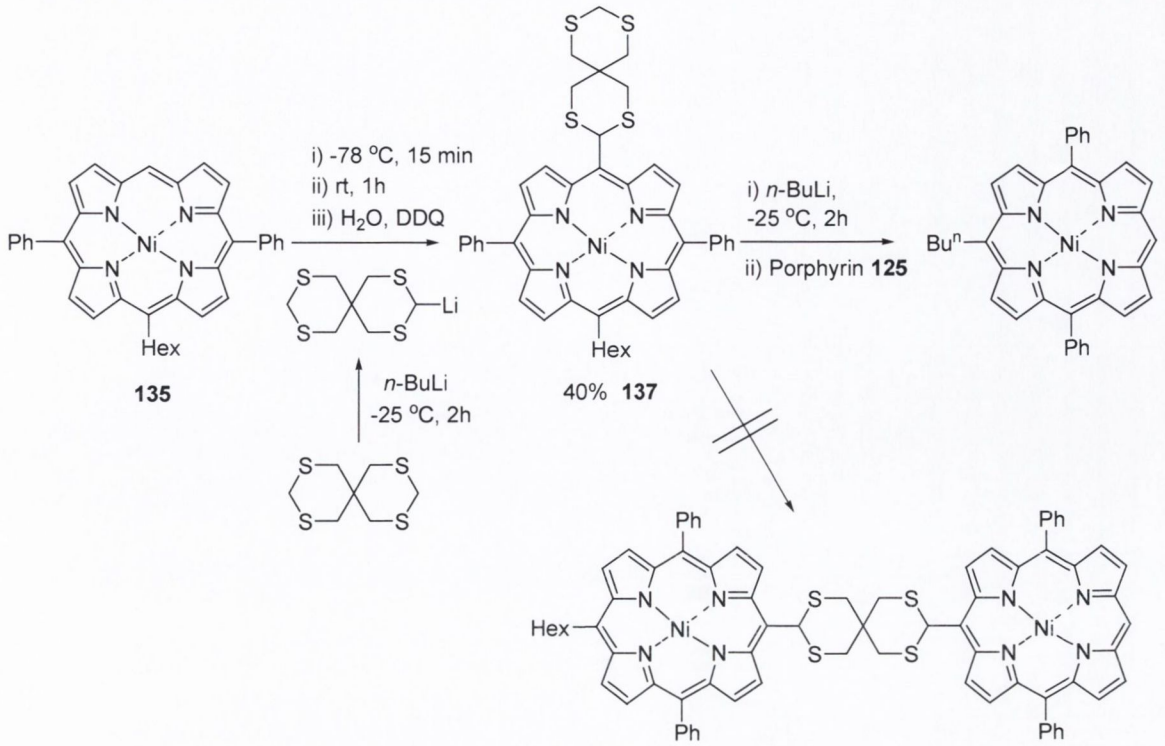
Figure 2.2 ^{1}H-NMR spectrum of porphyrin **124** in $CDCl_3$.



134

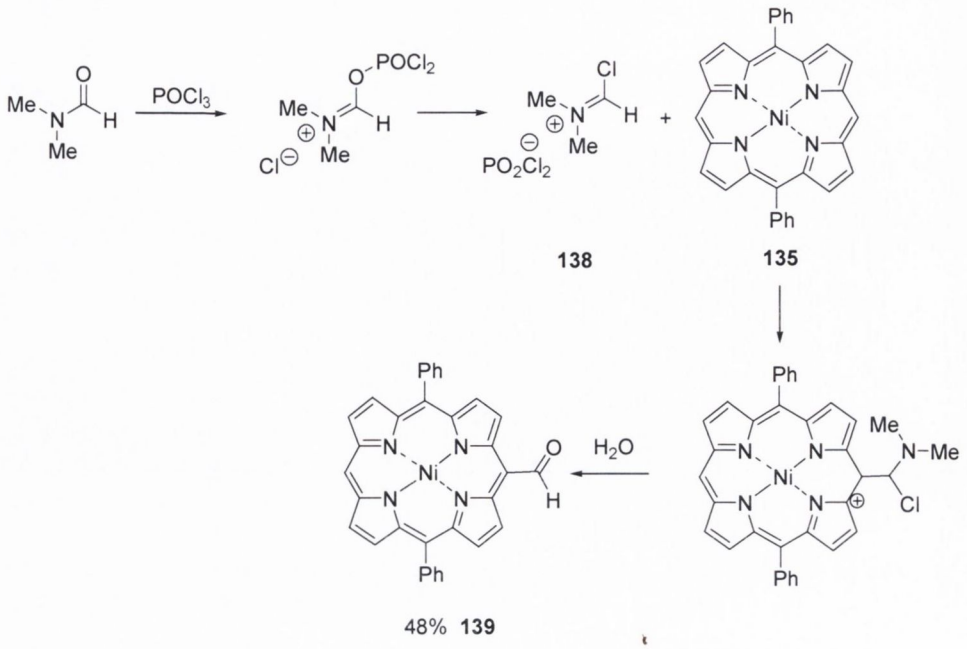
Figure 2.3 ^{1}H-NMR spectrum of porphyrin **134** in $CDCl_3$.

Potentially, these types of monosubstituted spirobisdithianyl compounds may be coupled with a bioconjugate carrier or with a second porphyrin. Such reactions will require a use of porphyrins where all other *meso*-positions are substituted by residues in order to prevent self-reaction of the porphyrinyl-lithiospirobisdithiane resulting in the formation of oligomers or to avoid the *meso*-substitution of porphyrin in the presence of *n*-BuLi. Thus, the metalloporphyrin **135** was reacted *in situ* with spirobisdithinyllithium to afford the corresponding porphyrin complex **137**. Porphyrin **137** was subsequently treated with *n*-BuLi and reacted with a second porphyrin **125**, but yielded the *n*-butyl-*meso* substituted porphyrin (Scheme 2.15). Another reaction was attempted with porphyrin **135**, but gave no formation of the desired porphyrin. As *n*-BuLi has a high tendency to undergo S_NAr on porphyrin macrocycle, lithium diisopropylamide (LDA) was used as non-nucleophilic base that can also deprotonate weak acidic compounds. Porphyrin **136** was reacted with porphyrin **135** under this condition; however, the reaction recovered only both of the starting materials.



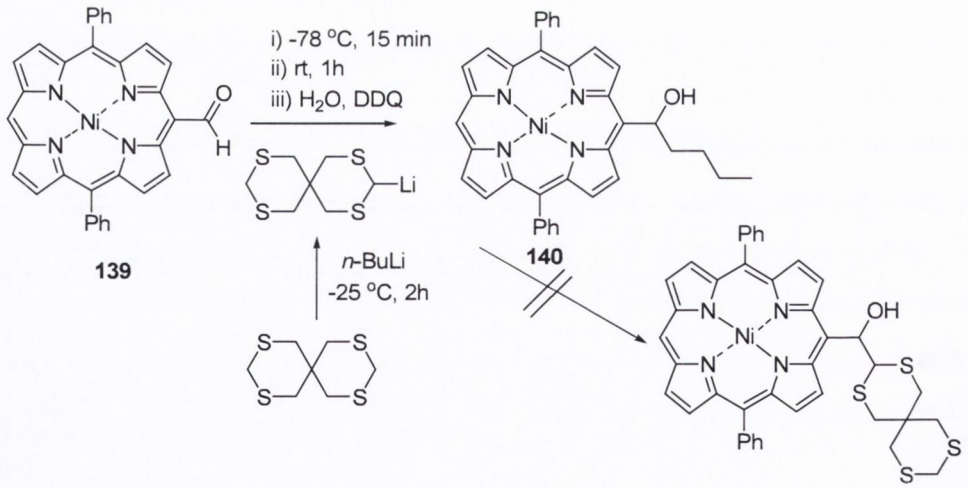
Scheme 2.15 Bridging two porphyrins *via* a spirobisdithianyl linker.

Most of the photocleavable bis-adduct assemblies were synthesised from the formyl derivatives of various macromolecules. The synthetic strategy involved tethering two formylated building blocks with the spirobisdithiane which has one or two photocleavable C-C bonds. Therefore, utilisation of formyl porphyrins as initial precursor provided an alternative method to tether different building blocks. The most common method of porphyrin formylation is the Vilsmeier reaction with an activated metalloporphyrin.[50] A mixture of phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) was used to generate the Vilsmeier complex **138** that subsequently reacted with the nickel(II) porphyrin **135** in 1,2-dichloroethane resulting in the desired porphyrin **139** in 48% yield after aqueous workup (Scheme 2.16).



Scheme 2.16 Vilsmeier formylation of porphyrin.

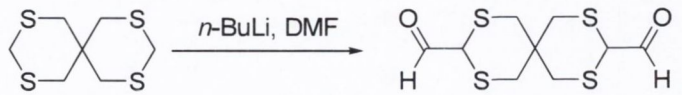
Formyl porphyrin **139** was then reacted with mono-lithiated spirobidithanyl at -78 °C as described by Kutateladze *et al.*,[160] but affording the [5-(hydroxypentyl)-10,20-diphenylporphyrin **140** in 6% yield. Aldehyde functional groups are prone to be attacked by organolithium reagents under nucleophilic addition reaction (Scheme 2.17). A similar reaction was observed in the case of using more simple 1,3-dithianyl residue.



Scheme 2.17 Reaction of formyl porphyrin with lithio-spirobisdithiane.

The spirobisdithiane compound **119** can also be used as a key intermediate in the preparation of bisporphyrin building blocks *via* the condensation reactions as shown for the

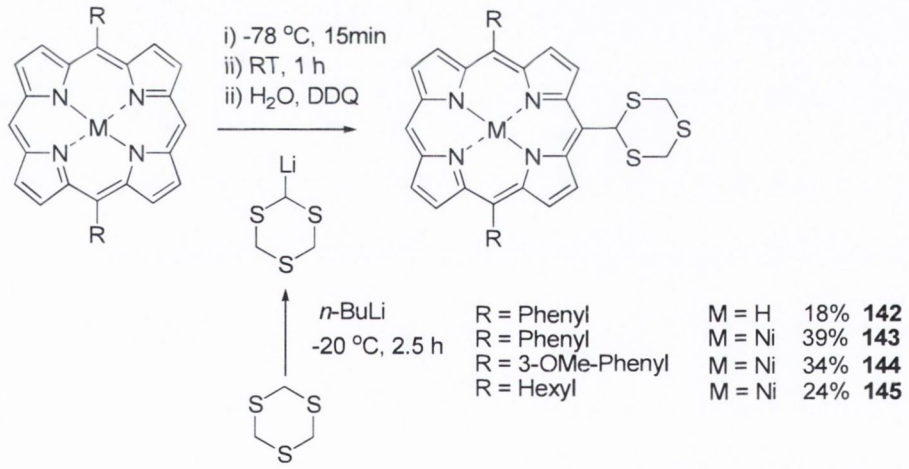
1,3-dithianyl synthon (Scheme 2.3). The diformyl derivative of spirobisdithiane can be transformed into the corresponding dipyrromethane which provides access towards construction of bisporphyrin systems. Preparation of **141** was carried out using 2:1 equivalents of *n*-butyllithium/spirobisdithiane while workup of the reaction was done using dichloromethane instead of diethylether, as described in the 1,3-dithiane reactions afforded the bisaldehyde in 56% yield (Scheme 2.18).[158] However, the conversion of **141** to the respective dipyrromethane did not produce the desired compound, most probably due to its low solubility.



119 56% **141**

Scheme 2.18 Synthesis of a bisaldehyde spirobisdithiane precursor.

In order to access different labile cross-linking geometries, the trithiane moiety was employed in a synthetic sequence similar to the spirobisdithiane linker giving the corresponding porphyrins **142-145** in moderate yields (Scheme 2.19).



Scheme 2.19 Monosubstituted trithianyl porphyrins.

It has been reported that 1,3,5-trithiane can form di- and even trianions when treated with excess *n*-butyllithium.[171] Therefore, successful conversion to these multianion intermediates opens a possibility for the synthesis of photolabile di- and tri-substituted trithianes bearing porphyrins or the targeted bioconjugate systems. However, all attempted reactions usually gave the *n*-butyl porphyrins resulting from S_NAr reactions

of organolithium reagents. As indicated by ^{1}H-NMR spectroscopic data for dithianyl- and spirobisthianyl-porphyrins, the β-H flanking the trithianyl residue exhibits the broad signals in free base and metalloporphyrins, respectively (Figure 2.4 and Figure 2.5).

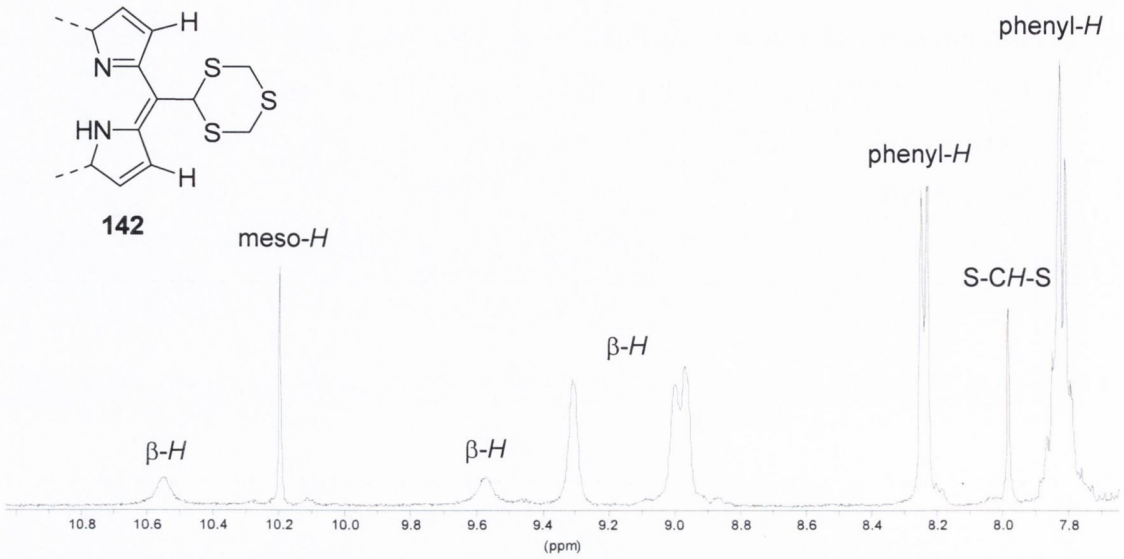


Figure 2.4 ^{1}H-NMR spectrum of porphyrin **142** in $CDCl_3$.

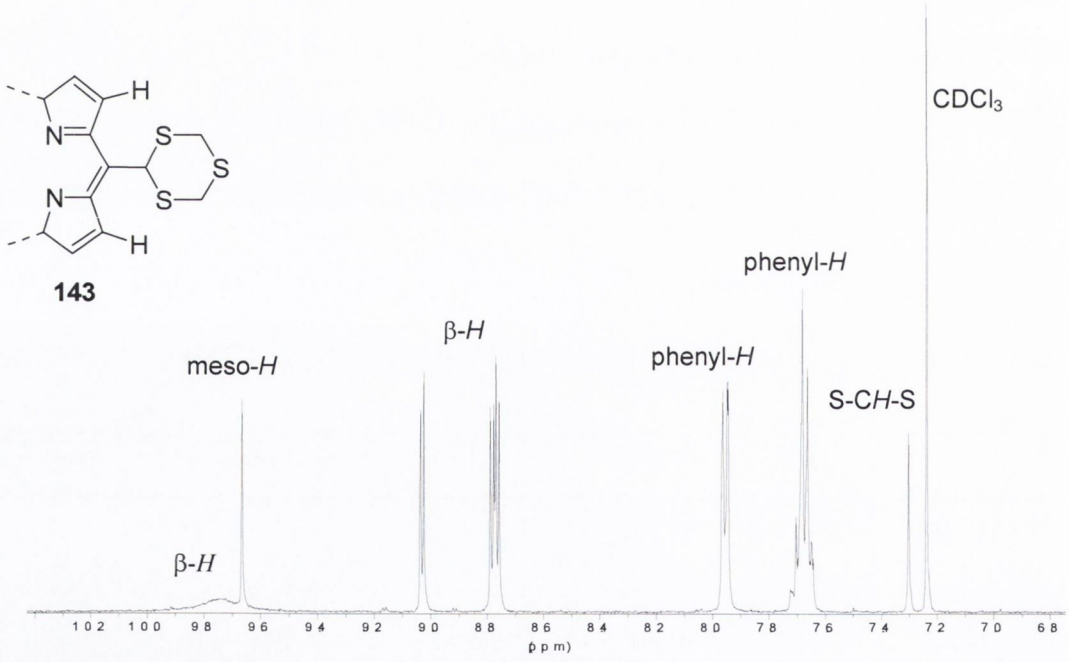


Figure 2.5 ^{1}H-NMR spectrum of porphyrin **143** in $CDCl_3$.

2.5 Conclusions

Starting from the studies on *Umpolung* chemistry of dithianyl synthons, it was shown that this method is useful to introduce formyl group into unactivated or metallated porphyrin macrocycles. An access to acylsubstituted porphyrins *via* substituted dithiane was difficult due to the low reactivity and steric hindrance of its lithio anion. In addition, it has been shown that the dithianyl nucleophile cannot be fully utilised to prepare stable porphyrin anions that can be trapped by an electrophile.

In employing photolabile spirobisdithiane and trithiane linkers, we have successfully synthesised the porphyrins containing one of these functional groups. Direct di or trisubstitution *via* S_NAr reactions on the porphyrin periphery or addition to formyl functionalities gave a high tendency to form alkyl-functionalised porphyrins. Moreover, the highly photosensitive free base compounds hampered our studies for utilising the labile porphyrins system in PDT.

While the work in this area has shown that we can link the porphyrins with the spirobisdithiane and trithiane at the *meso*-position, the major aim was to cross-linking the residues with biologically relevant residues. With all the constraints, further investigations require a key intermediate such as dithiane-bismethol residue which contains available groups for the targeted bioconjugations. This precursor can be used in attaching the specific bioconjugates in the initial step before reacted with porphyrins. Nevertheless, we have described an initial paradigm for using such dual-mode system; photoreleased and photoactivated photosensitisers that enable to control the photosensitiser delivery for PDT applications.

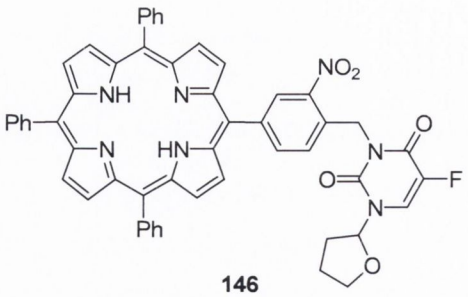
CHAPTER 3:

Lead Structures to Photolabile o-Nitrobenzyl Porphyrins

3.1 Introduction

Light-mediated chemical bond cleavage of nitrobenzyl derivatives has provided a simple and efficient method for masking and releasing numerous functional groups. The nitrobenzyl derivatives are by far the most prevalent photolabile groups and they have gained wide acceptance. Of the linkages properties are high stability under ambient light, they can undergo clean cleavage upon exposure to UV irradiation and fast fragmentation reactions upon photoexcitation. Therefore, we extended our studies to incorporating this cleavable unit into porphyrin macrocycle. Since the absorption of the nitrobenzyl group tails out around 400 nm, photolysis is usually carried out with a light of wavelength longer than 320 nm; typically irradiation at 340-350 nm is employed. This feature fits the mode for releasing the photosensitiser in combination with a second irradiation with red light around 650 nm as porphyrins will produce cyctotoxic singlet oxygen when irradiated at this wavelength.

The *o*-nitrobenzyl group has been used previously in designing photo-prodrug systems.[118, 172] In 2005, Zhang *et al.* proposed a strategy to produce a tumour vascular-targeting photoactivated prodrug of 5-fluorouracil (5-FU) by using a tumour homing peptide CNGRC and photolabile *o*-nitrobenzyl.[173] Such a tumour vascular-targeting photoactivated prodrug is expected to accumulate and then to be activated selectively by controlled photolysis to release anticancer agent 5-FU within tumour tissues with outstanding spatial and temporal precision. Recently, tegafur, which was formed as 5-FU prodrug, was tethered to a porphyrin system through *o*-nitrobenzyl linker to prepare light-triggered anticancer prodrug **146** (Figure 3.1).[174] This system increased the tumour affinity of anticancer drug due to its conjugation to highly accumulative porphyrin moieties. An MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium] assay demonstrated that the conjugate shows photoinduced cytotoxicity for MCF-7 mammary cancer cells because of the efficient release of tegafur upon photoirradiation at 350 nm.



146

Figure 3.1 Light-triggered anticancer prodrug.

Studies of the mode of cell death after photodynamic therapy (PDT) revealed evidence of both necrosis and apoptosis, which are induced under different conditions and differ in morphological and biochemical features.[79] Necrosis is a degenerative cell death resulting from extensive cellular damage whereas apoptosis is a programmed cell death that involves a series of biochemical events leading to a characteristic cell morphology and death. PDT triggers numerous different signalling events that lead to apoptosis such as oxidative stress, alteration of intracellular Ca^{2+} concentration and modulation of gene expression. It has been reported that ultraviolet (UV) light has a role in induced DNA damage that can trigger apoptosis,[119] thus more extensive use of UV light in the photosensitiser activation and cleavable system is advantageous.

In this chapter, we demonstrate the necessary synthetic methodologies for construction of labile systems containing porphyrins photosensitisers based on the cleavable units of *o*-nitrobenzyl group. While various available approaches for porphyrin functionalisation have been established, an esterification procedure was mainly utilised in our effort to develop such a system.

3.2 Synthesis of carboxylic acid porphyrin precursors

A direct route to obtain carboxylic acid porphyrins is by hydrolysis of ester-type porphyrins whereby these compounds can be prepared using several known methods. One of the methods relies upon Heck[175] or Suzuki[176] reactions with halogenated porphyrin precursors. Both of the reactions give a formation of C-C bonds by using a transition metal catalysed coupling process. Complexes involving palladium such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ are the most common and widely used catalysts, because they are stable to air and readily reduced to the active Pd(0) complexes with organometallics or phosphine used in the reaction. A general catalytic cycle for the cross-coupling reaction

involves oxidative addition-transmetallation-reductive elimination sequence (Figure 3.2).[177]

Oxidative addition of alkenyl, alkynyl, allyl, benzyl or aryl halides to a Pd(0) complex gives a *trans*-σ-palladium(II) complex **147** which is prone to react with nucleophiles. The reaction proceeds with complete retention of stereochemistry for alkenyl halides and with inversion for allylic and benzylic halides. The transmetalation step from organopalladium(II) complex is highly dependent on the organometallics or reaction conditions used for the coupling. For instance, an organoboron compound is unlikely to participate in the catalytic cycle of cross-coupling reactions in the absence of base due to its low nucleophilicity. However, the nucleophilicity can be enhanced by quartenisation of the boron with negatively charged bases giving the corresponding active complex. Reductive elimination takes place directly from the *cis*-complex **148** while the *trans*-complex isomerise to the *cis*-complex which can the react (Figure 3.3).

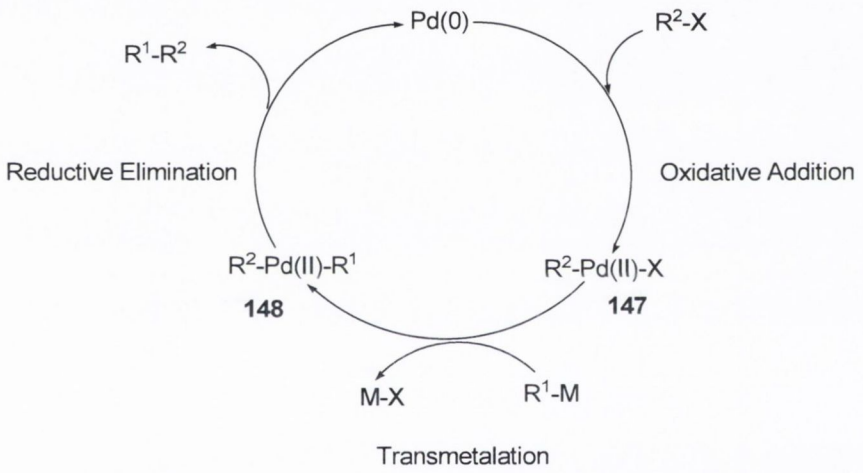


Figure 3.2 A general catalytic cycle for Pd-mediated cross coupling.

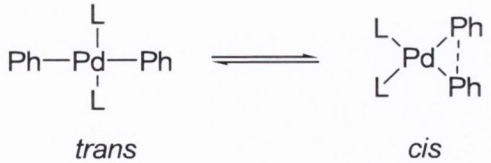
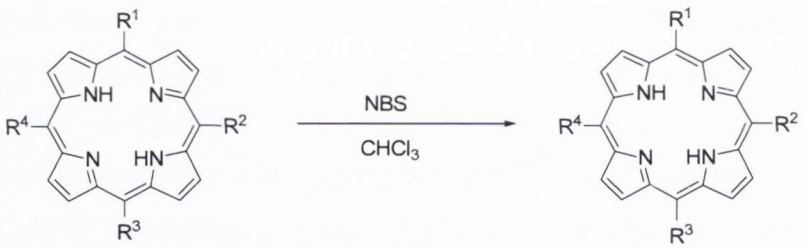


Figure 3.3 Isomerisation of *trans*- to *cis*-complex.

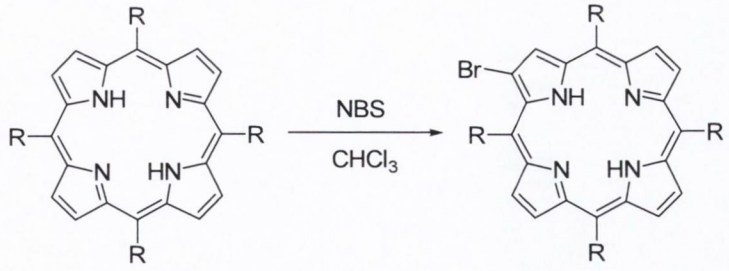
The initial step involved preparation of brominated porphyrins from free base porphyrins that are accessible through standard condensation or RLi-alkylation procedures as described in an earlier chapter. In this work, we employed different porphyrins as

scaffolds for further functionalisations. Porphyrin **99** is a commonly used precursor, whereas porphyrin **110** has the advantage of having only one free *meso*-carbon and this can effectively block any undesired competitive reaction. Porphyrins **103**, **108** and **109** incorporated alkyl functionalities and were used to prepare precursors more soluble in common reaction solvents. Porphyrin **109**, containing methoxy groups, offers the necessarily deprotection opportunity at a later stage to form hydroxyl-type porphyrin that are suitable in the preparation of water soluble photosensitisers. All the porphyrins were brominated according to standard conditions (NBS in chloroform in the presence of pyridine)[178] to give the corresponding brominated porphyrins **149-153** in high yield (Scheme 3.1). Likewise, the tetrasubstituted porphyrin **154** available from a mixed condensation reaction, was brominated with 1.1 equivalents of NBS according to the literature[178] to yield the *β*–monobrominated analogue **155** (Scheme 3.2). The bromination of **99** to afford in high yield of monobromo **149** is tedious because the lack of selectivity and difficulty of chromatographic separation of the mono- **149** and dibrominated products **156**, while porphyrin **103** was brominated with 2.0 equivalent of NBS to yield disubstituted product **150**.



R¹	R²	R³	R⁴		R¹	R²	R³	R⁴	
Phenyl	H	Phenyl	H	**99**	Phenyl	H	Phenyl	Br	85% **149**
3,5-di-*t*-butylPhenyl	H	3,5-di-*t*-butylPhenyl	H	**103**	3,5-di-*t*-butylPhenyl	Br	3,5-di-*t*-butylPhenyl	Br	82% **150**
Phenyl	H	Phenyl	Hexyl	**108**	Phenyl	Br	Phenyl	Hexyl	99% **151**
3-OMePhenyl	H	3-OMePhenyl	Hexyl	**109**	3-OMePhenyl	Br	3-OMePhenyl	Hexyl	95% **152**
Phenyl	H	Phenyl	Phenyl	**110**	Phenyl	Br	Phenyl	Phenyl	99% **153**

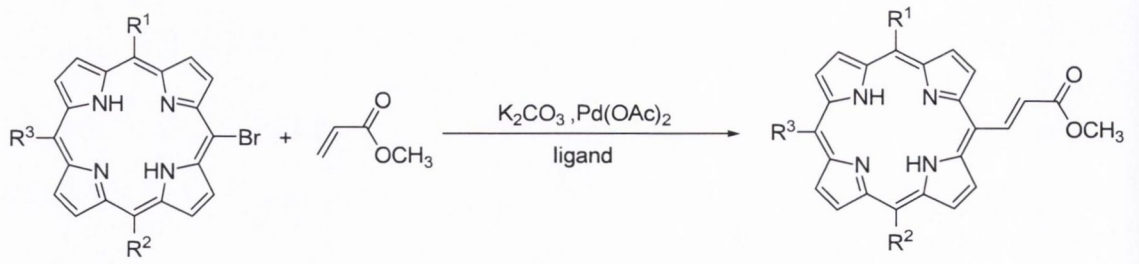
Scheme 3.1 Bromination of *meso*-substituted porphyrins.



R= 3,5-di-*t*-butylPhenyl **154** R= 3,5-di-*t*-butylPhenyl 96% **155**

Scheme 3.2 Synthesis of *β*–brominated porphyrin.

As porphyrins containing unsaturated side chains or extended π–conjugated substituents are of interest due to potential applications for PDT,[179] the Heck reaction has been utilised to introduce ester functionalities into porphyrin macrocycles. It was reported that palladium catalysed Heck coupling has proved to be a useful method for attaching ethenyl substituents to the *β*-positions of porphyrins.[180] In a different manner, protoporphyrin was utilised as the vinyl substituent for coupling with arene halide under Heck conditions.[181] Arnold *et al.* have investigated the reactivity of *meso*-substituted porphyrin by direct coupling of some Heck-type alkenes and *meso*-bromoporphyrins in the presence of palladium acetate catalyst $Pd(OAc)_2$, ligand and potassium carbonate K_2CO_3 under heating condition in a toluene:DMF solvent mixture.[175b] Under similar conditions, bromoporphyrins **151** and **152** were reacted with methyl acrylate. These reactions proceeded with complete consumption of starting material in 12 hours to yield *α,β*-unsaturated porphyrins **157** and **158** in 55% and 60% respectively (Scheme 3.3). These Pd-catalysed couplings required a large excess of methyl acrylate to maximise its concentration in the reaction mixture since it has a low boiling point. The reactions were carried out in a mixture of DMF and toluene (1:1) which conveniently allowed the use of small volumes and high concentration of reactants. This leads to shorter reaction times and avoided solubility problems. It was observed that debromination of the starting material occurred through protolytic cleavage and metallation on porphyrin core with palladium took place to a small extent.



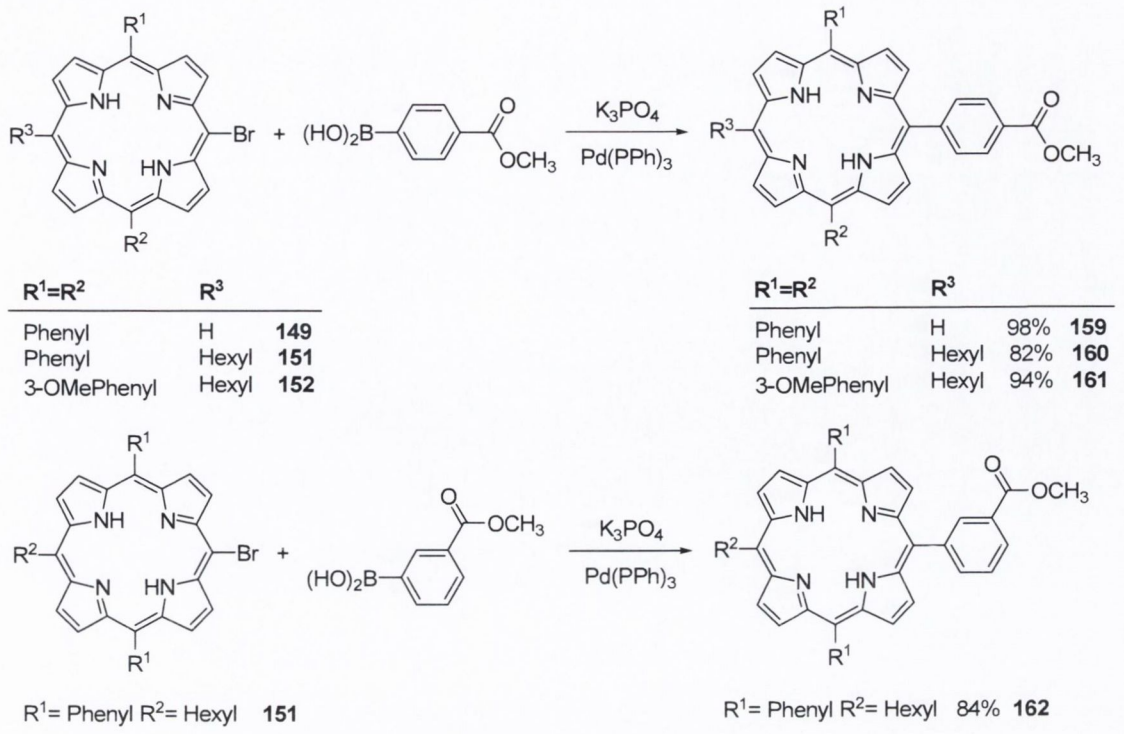
R^1=R^2	R^3		
Phenyl	Hexyl		**151**
3-OMePhenyl	Hexyl		**152**

R^1=R^2	R^3		
Phenyl	Hexyl	55%	**157**
3-OMePhenyl	Hexyl	60%	**158**

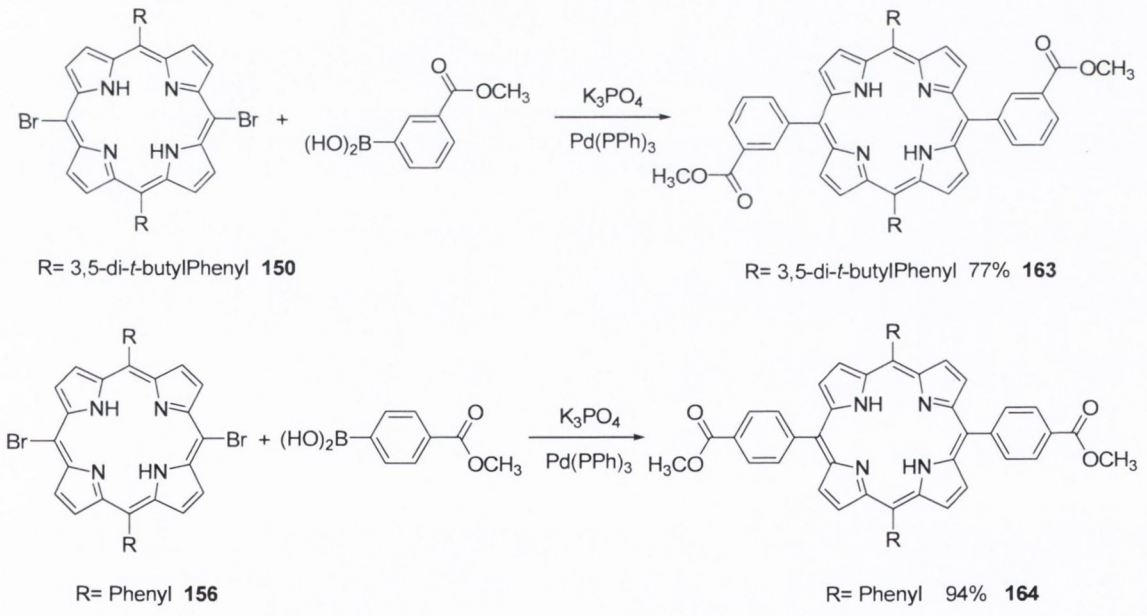
Scheme 3.3 Heck cross-coupling reaction of porphyrins.

In a second approach, the palladium catalysed Suzuki cross coupling was employed to obtain ester type-porphyrin functionalities in high yield. This reaction provides a versatile methodology for formation of C-C bonds by utilising organoboron compounds and organic electrophiles such as halides or triflates in the presence of a base.[177, 182] This method has the advantages of using mild reaction conditions, being highly stable in water, having high regio- and stereoselectivity and tolerance towards numerous functional groups. Furthermore, the boron-containing by-product from the reaction can be easily separated from the desired product. Suzuki cross-coupling has been widely applied previously in porphyrin chemistry, notably in the synthesis of porphyrin array of *meso*,*β*-phenylene-linked dimers,[183] *meso-meso* linked dimers[184] and highly substituted porphyrins.[185]

Thus, the Suzuki cross-couplings reactions with bromo porphyrins were carried out under standard conditions as described in the literature.[176,186] The *meso*-brominated porphyrins **149**, **151** and **152** were reacted with methylesterphenylboronic acid in the presence of potassium phosphate, K_3PO_4 and $Pd(PPh_3)_4$ catalyst under reflux conditions in tetrahydrofuran (THF) and gave porphyrins **159-162** in 82% to 98% yield (Scheme 3.4). Dibrominated porphyrins **150** and **156** were also subjected to Suzuki coupling reaction and afforded ester porphyrin **163** and **164** in 94% and 77% yield, respectively (Scheme 3.5).



Scheme 3.4 Suzuki cross-coupling reaction of *meso*-monosubstituted porphyrins.



Scheme 3.5 Suzuki cross-coupling reaction of *meso*-disubstituted porphyrins.

Figure 3.4 shows the ^{1}H-NMR spectrum for ester porphyrin **163** that contains two ester functional groups at the *meso*-positions. The overlapping singlet peak at 8.75 ppm which represents H_4-proton resonance, is more upfield than other phenyl-H due to

neighbouring carbonyl group. H_6-proton, that is adjacent to H_5- and H_7-protons, appears as triplet while the H_5- and H_7-protons themselves appear as the doublet resonances. The integration ratio between eight β-protons and phenyl-protons shows the incorporation of two phenyl ester groups into *meso*-position of the porphyrin core.

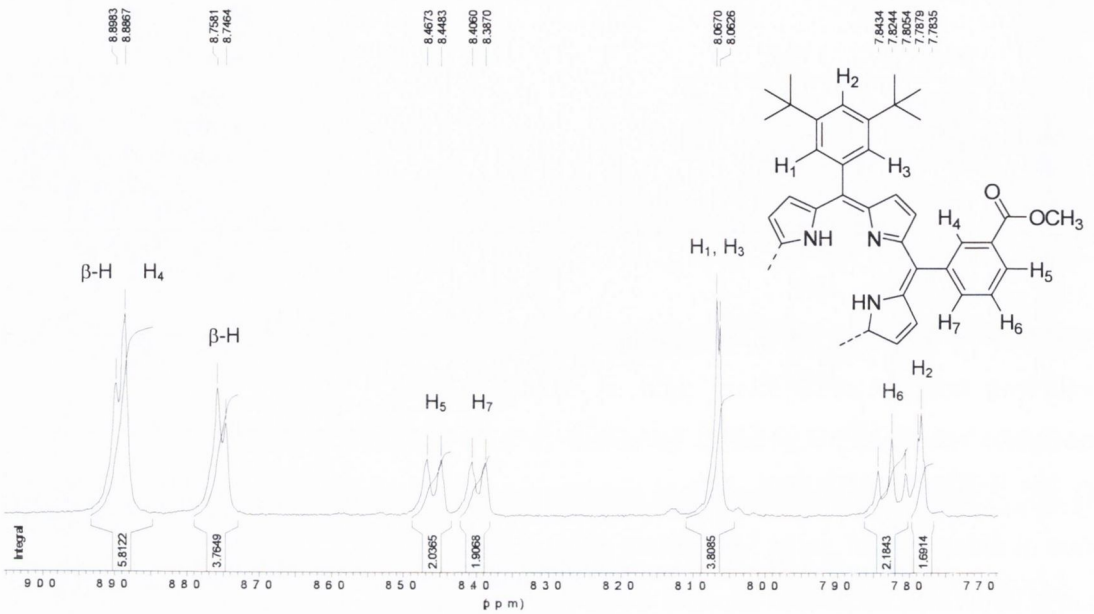
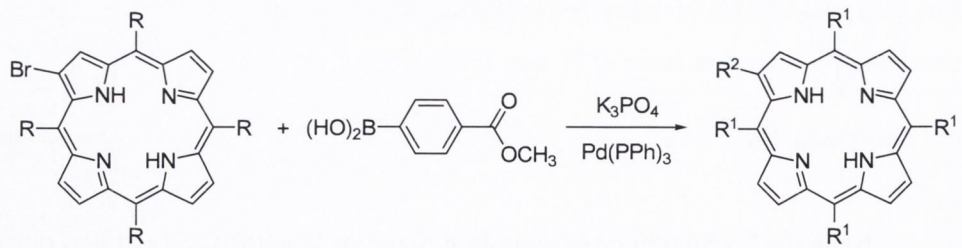


Figure 3.4 ^{1}H-NMR spectrum for porphyrin **163** in $CDCl_3$.

Suzuki coupling of the β-brominated porphyrin **155** was also carried out under similar conditions and afforded the β-substituted porphyrin **165** in 52% yield (Scheme 3.6). The Suzuki coupling reaction requires the use of a base to enhance the transmetallation step. The role of the base is to form a more electron-rich intermediate with the boronic acid resulting in a more reactive species towards attack of the palladium(II) complex compared to the original boronic acid.



R= 3,5-di-*t*-butylPhenyl **155**

R^1= 3,5-di-*t*-butylPhenyl
R^2= 4-CO_2MePhenyl 52% **165**

Scheme 3.6 Suzuki cross-coupling reaction of β–substituted porphyrin.

Figure 3.5 shows the ^{1}H-NMR spectrum for β-substituted porphyrin **165**. The presence of seven protons in the β-region indicates that β-substitution has occurred. One of the significant resonances is the singlet peak at 7.36 ppm which corresponds to the shielded H_3-proton resulting from proximate phenyl ring influence. The doublet peak at ~8.15 ppm corresponds to the *para*-phenyl protons at 5- and 10-*meso*-position of the porphyrin and are assigned as H_2 whereas the *para*-phenyl protons at 15- and 20-*meso*-position resonate at ~7.48 ppm.

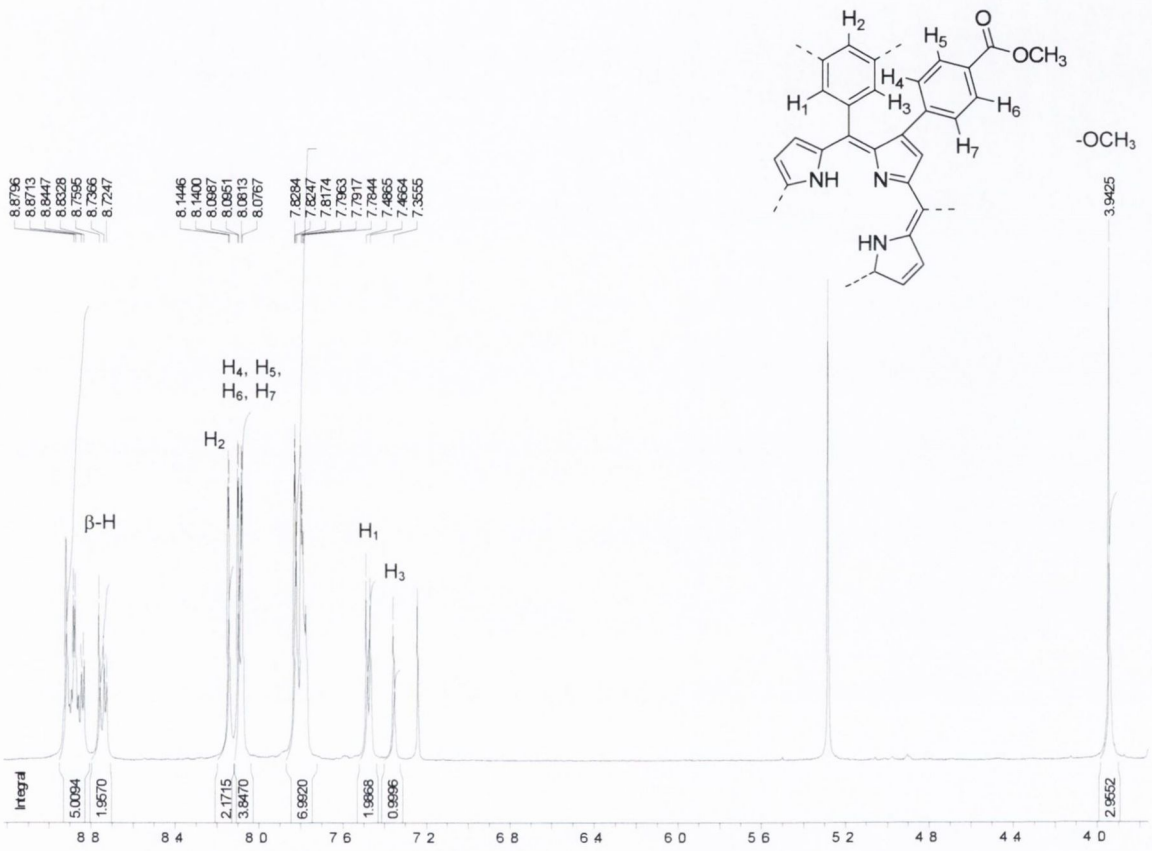
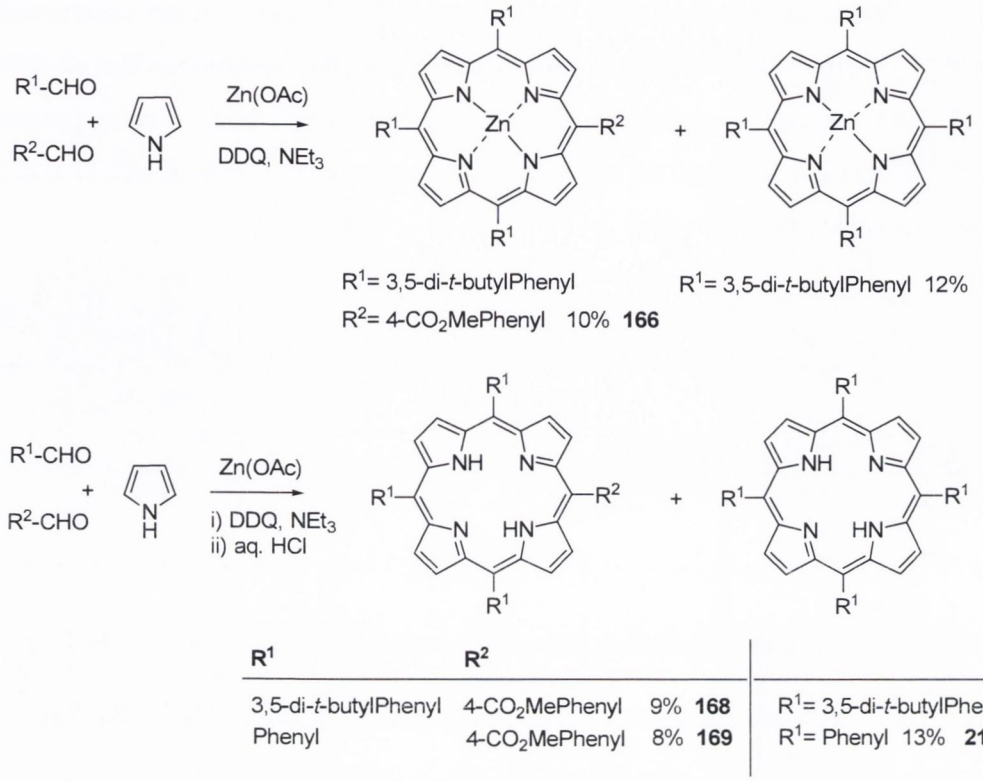


Figure 3.5 ^{1}H-NMR spectrum for porphyrin **165** in $CDCl_3$.

Another method, that enables the introduction of ester functional groups into the porphyrin macrocyle, is to condense a mixture of pyrrole and the appropriately substituted benzaldehyde. This standard condensation reaction was carried out using one equivalent of 4-carboxymethyl benzaldehyde, 3 equivalents of 3,5-di-*tert*-butyl-benzaldehyde and 4 equivalents of pyrrole refluxed in propionic acid in the presence of zinc acetate, to give ester porphyrin **166** in 10% yield and *meso*-tetra substituted compound **167**[9c] as a side product in 12% yield. Addition of zinc acetate as a metal template during the condensation process can facilitate the reaction, thus increasing the yield of the condensed products.[187]

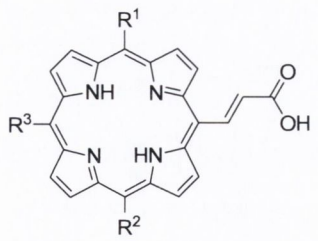
The corresponding free base ester porphyrins **168** or **169** can be obtained in 8%-9% yields under acidic work-up conditions (Scheme 3.7).[188]



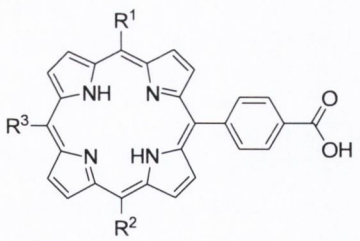
R^1	R^2		
3,5-di-*t*-butylPhenyl	4-CO_2MePhenyl	9% **168**	R^1= 3,5-di-*t*-butylPhenyl 10% **170**
Phenyl	4-CO_2MePhenyl	8% **169**	R^1= Phenyl 13% **21**

Scheme 3.7 Entry to ester porphyrin *via* condensation reaction.

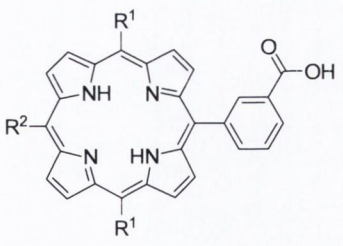
All of the above ester porphyrins were succesfully converted to functionalised carboxylic acids porphyrins using base hydrolysis. The ester porphyrin was dissolved in THF before undergo heating at 110 °C with KOH-EtOH and the reaction was monitored by TLC. Once the reaction was complete, the corresponding carboxylate salt solution was acidified and afforded acid porphyrins **171-182** in 77% to 93% yields (Figure 3.6).[188]



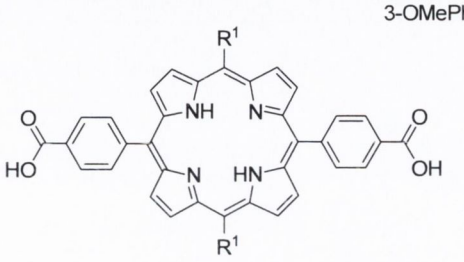
R^1=R^2	R^3		
Phenyl	Hexyl	93%	**171**
3-OMePhenyl	Hexyl	88%	**172**



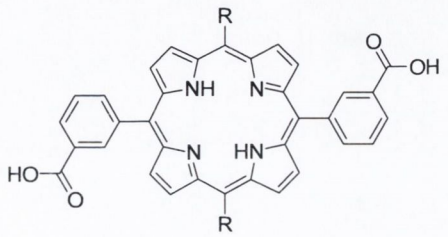
R^1=R^2	R^3		
Phenyl	H	77%	**173**
Phenyl	Hexyl	93%	**174**
3-OMePhenyl	Hexyl	93%	**175**



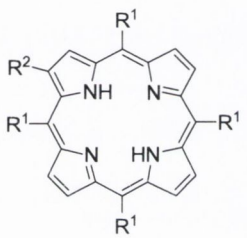
R^1= Phenyl R^2= Hexyl 94% **176**



R= Phenyl 81% **177**

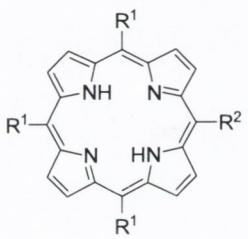


R= 3,5-di-*t*-butylPhenyl 89% **178**



R^1= 3,5-di-*t*-butylPhenyl
R^2= 4-CO_2OHPhenyl 82% **179**

R^1= 3,5-di-*t*-butylPhenyl
R^2= 4-CO_2OHPhenyl 93% **180**



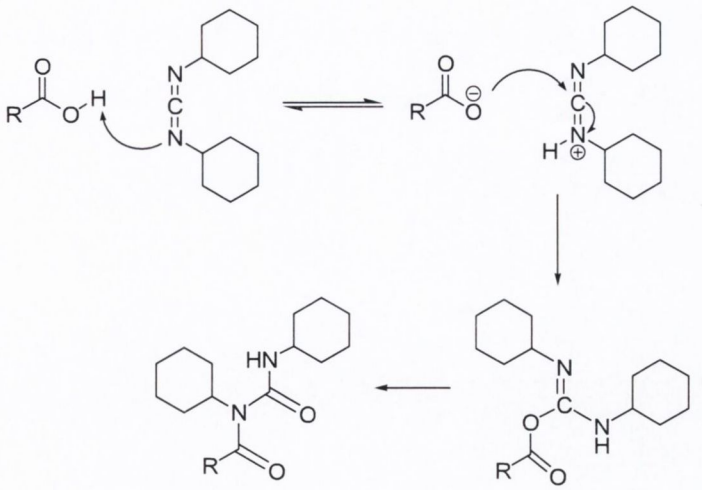
R^1	R^2		
3,5-di-*t*-butylPhenyl	4-CO_2OHPhenyl	93%	**181**
Phenyl	4-CO_2OHPhenyl	88%	**182**

Figure 3.6 Different types of carboxylic acid porphyrins.

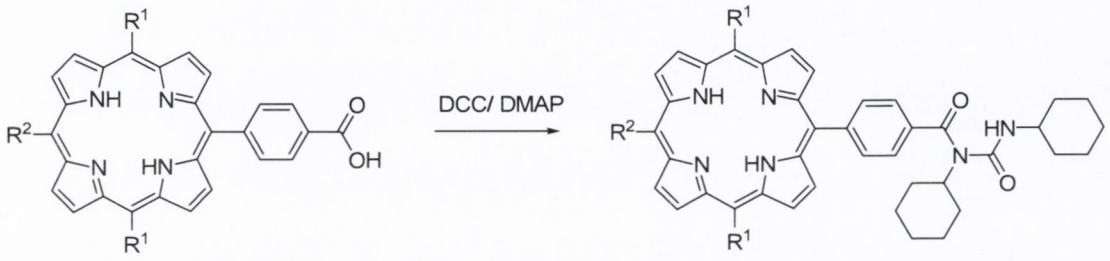
3.3 Nitrobenzyl-linked porphyrins *via* esterification

Further synthetic work was focused on the construction of porphyrins containing labile *o*-nitrobenzyl functionalities *via* esterification between readily prepared carboxylic acid porphyrins and 2-nitrobenzylalcohol as the model linker. Therefore, coupling agents were employed to assist the reaction between carboxylic acid and hydroxyl groups by activating the acid group, making it susceptible to attack by hydroxyl groups. Notably, two common methods for esterification in porphyrin chemistry are acylation[189] and carbodiimide coupling techniques.[190] Carbodiimide coupling offers a more feasible method, as it requires simple and mild conditions. There is a large number of carbodiimide type activating agents, such as *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). We investigated several preliminary esterification reactions using carbodiimide reagent of *N,N'*-dicyclohexylcarbodiimide (DCC) as it has been the coupling reagent of choice for many years.[191, 192]

Carboxylic acid porphyrins **173**, **174**, **181** and **182** were dissolved in THF and 2 equivalents of DCC and 2-nitrobenzyl alcohol were added in the presence of base, dimethylamino pyridine (DMAP). The reaction was completed after 18 hours under reflux conditions. From a mechanistic point of view, DCC reacts with the carboxyl group first and forms a very reactive intermediate, *o*-acylisourea **183**. This is the reactive species that can be attacked by the hydroxyl component to give the corresponding ester. Nevertheless, it was observed that the reactions tend to undergo racemisation to form stable *N*-acylisourea **184** instead of reactive intermediate of *o*-acylisourea and afforded porphyrins **185-188** in 30% to 52% yield (Scheme 3.8).



N-acylisourea **183** *O*-acylisourea **184**



R^1	R^2		
Phenyl	H	**173**	39% **185**
Phenyl	Hexyl	**174**	30% **186**
3,5-di-*t*-butylPhenyl	3,5-di-*t*-butylPhenyl	**181**	27% **187**
Phenyl	Phenyl	**182**	52% **188**

Scheme 3.8 Formation of *N*-acylisourea-substituted porphyrins.

Both of the *O*- and *N*-acylisourea compounds have significantly similar ^{1}H-NMR spectroscopic data except for the differences of the more upfield chemical shift of NH-proton of isourea **183** compared to isourea **184** whereas the ^{13}C NMR data indicate the addition of one C=O resonance in isourea **183** (Figure 3.8). The data from infrared spectroscopy (IR) further support this structure due to the absence of C=N stretch vibration for **183**. The substitution pattern was confirmed by X-ray crystallographic analysis of porphyrin **186** (Figure 3.9). In these studies, the structure of this carbodiimide intermediate was determined and supports a similar observation that was mentioned previously in the preparation glycoporphyrins.[193]

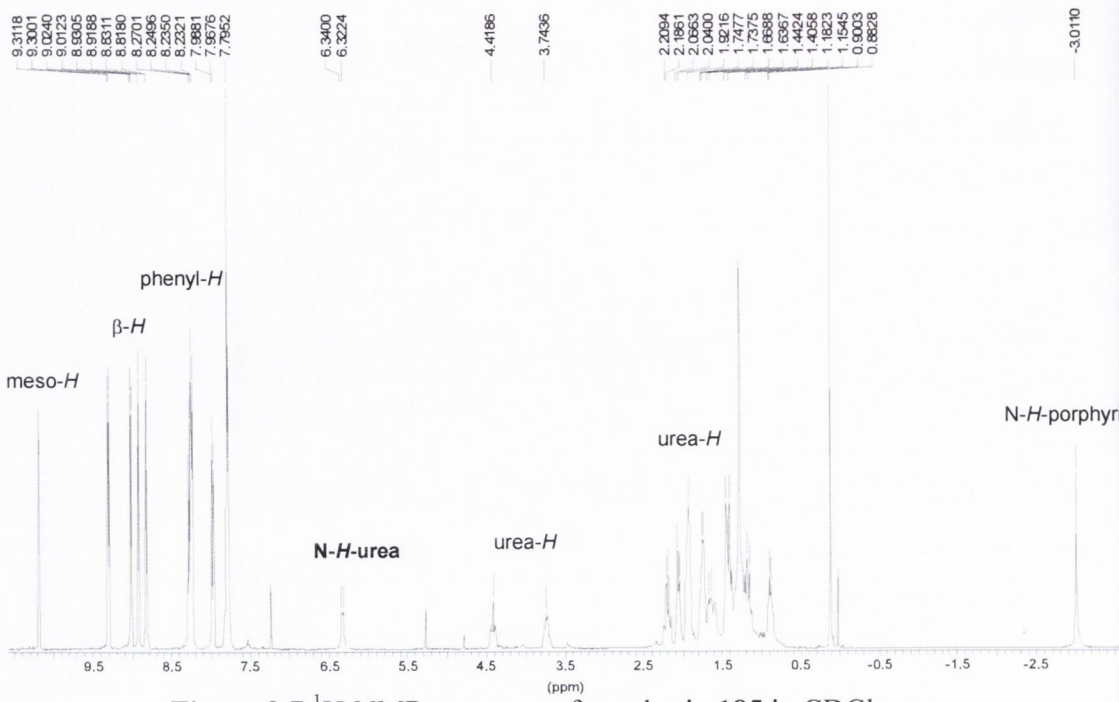


Figure 3.7 ^{1}H-NMR spectrum of porphyrin **185** in $CDCl_3$.

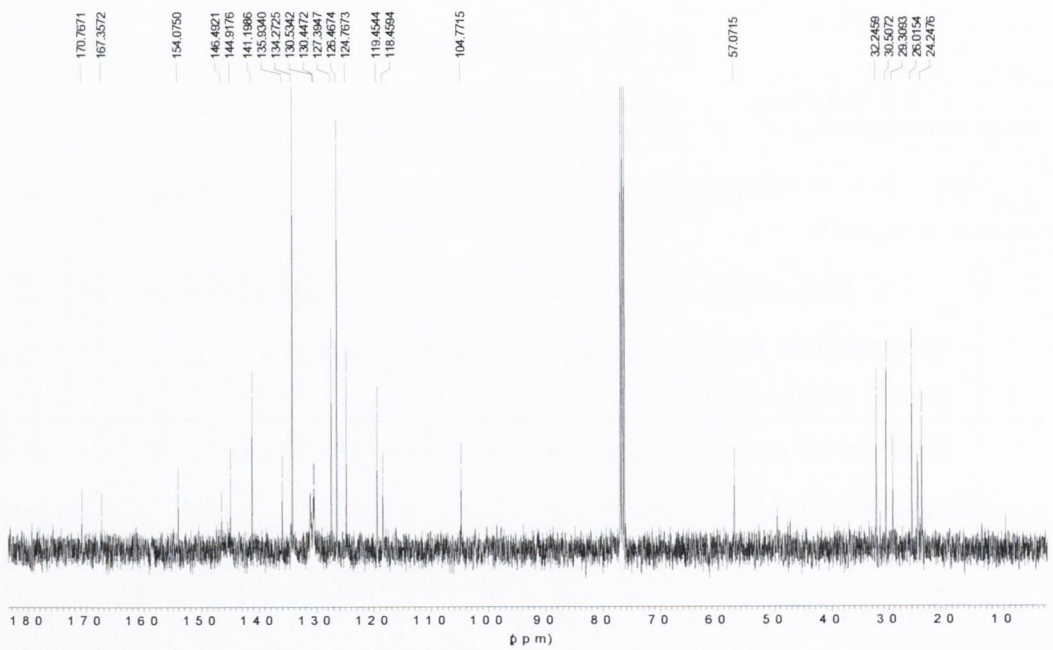


Figure 3.8 ^{13}C-NMR spectrum of porphyrin **185** in $CDCl_3$.

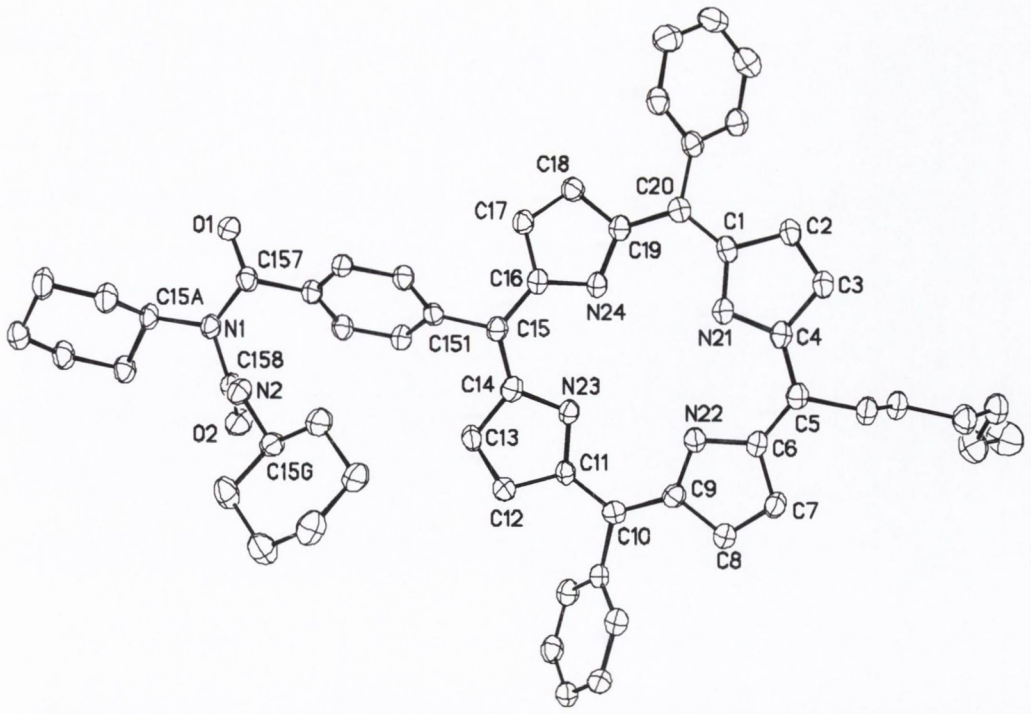


Figure 3.9 View of the molecular structure of **186** in the crystal. Hydrogen atoms have been omitted for clarity; thermal ellipsoids are drawn for 50% occupancy.

Gibson *et al.* have explained in more detail the transformation of this intermediate in the preparation of cholesteryl esters of crown ether.[194] The rearrangement was suggested to occur *via a* four-membered transition state due to the presence of an active aza-enamine moiety in the acylisourea intermediate and the formation of the stable carbon-oxygen double bond (Figure 3.10). It was also reported that the presence of the crown ether moiety makes the acylisourea too sterically hindered to react with cholesterol and contributed to the low yield of ester product.

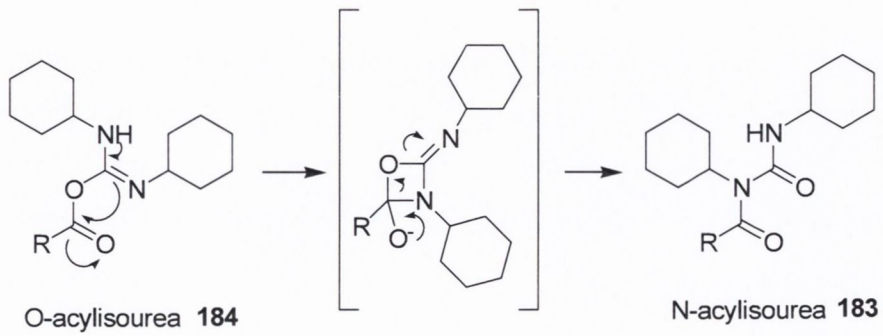
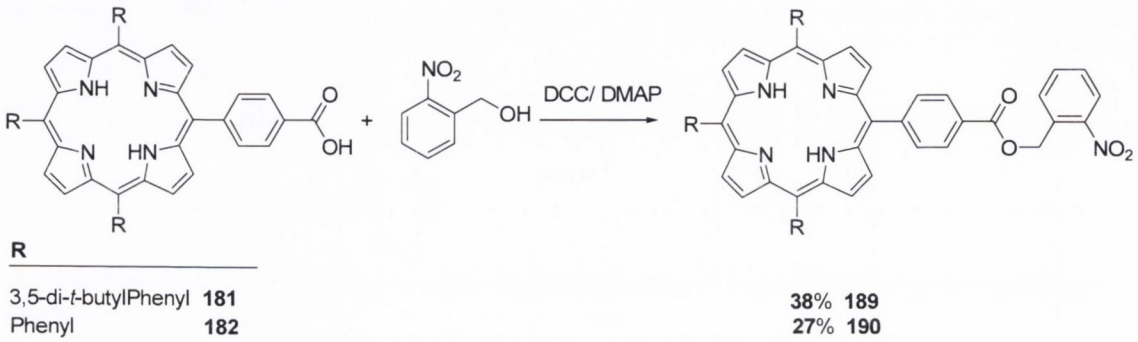


Figure 3.10 Postulated rearrangement of **184** *via* four-membered transition state.

As the rearrangement resulted in low yields and contamination of the desired product, further optimisation reactions between carboxylic acid porphyrins and 2-nitrobenzyl alcohol in the presence of DCC/DMAP were carried out. Using 5 equivalents of DCC, 1 equivalent of DMAP and 5 equivalents of 2-nitrobenzylalcohol, we managed to obtain the desired *o*-nitrobenzyl-porphyrins **189** and **190** in moderate yields along with the rearrangement products of **187** and **188** in 43% and 69% yield, respectively (Scheme 3.9). Table 3.1 shows the optimisation condition reactions utilising 1 equivalent of porphyrin **182** with different stoichiometry in refluxing THF for 18 h.



R

3,5-di-*t*-butylPhenyl **181**
Phenyl **182**

38% **189**
27% **190**

Scheme 3.9 Synthesis of *o*-nitrobenzyl-linked porphyrins.

Table 3.1 Reaction conditions of DCC carbodiimide coupling.

DCC(eq.)	DMAP (eq.)	2-Nitrobenzylalcohol (eq.)	Porphyrin **190**	Porphyrin **188**
1	1	1	-	-
1	2	2	-	52%
1	1	5	-	27%
1	2	5	13%	31%
1	5	5	27%	69%
1	5	10	13%	52%

To overcome this rearrangement problem, it is necessary to stabilise the intermediate *o*-acylisourea using an additive such as *N*-hydroxysuccinimide (NHS).[195] In the presence of NHS, the intermediate is immediately attacked by the *N*-hydroxyl alcohol to give the NHS-type ester, which is reactive towards alcohol, but not prone to racemisation. Besides NHS, 1-hydroxybenzotriazole (HOBt) was proposed as an additive that can suppress the racemisation through formation of active ester intermediate **191** (Figure 3.11).[196]

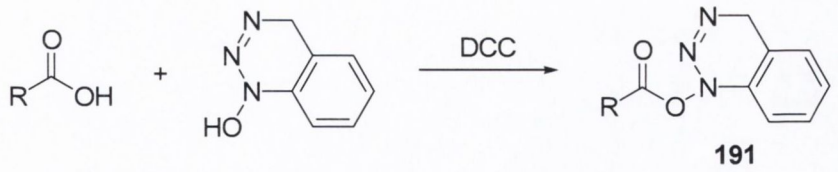
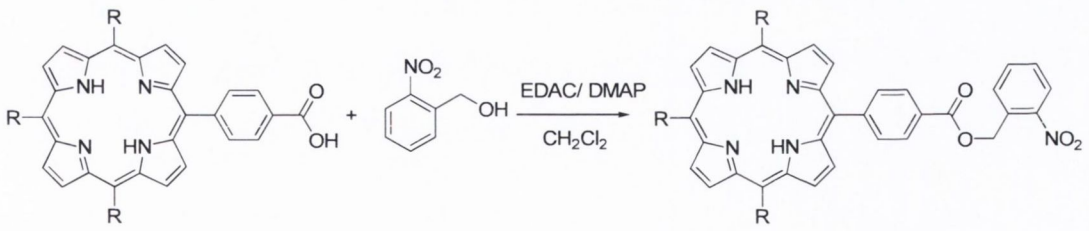


Figure 3.11 HOBt as an additive in carbodimide coupling.

Further esterification reactions were investigated using another carbodiimide reagent: 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride (EDAC). It is easier to use due to its high solubility in solvents while the urea produced is water soluble, and thus easily separated from the product. The EDAC-assisted esterification reaction was first carried out using porphyrin **181** with 1 equivalent each of EDAC, DMAP and 2-nitrobenzyl in CH_2Cl_2 at room temperature for 18 hours, and afforded ester porphyrin **192** in 50% yield. Meanwhile, increasing the reagent amounts to 2 equivalents gave porphyrin **192** in 86% (Scheme 3.10) Therefore, all of the further esterification reactions involving carboxylic acid porphyrins were employed with these general reaction conditions and they afforded a large number of nitrobenzyl ester porphyrins **193-199** (Figure 3.12). Disubstituted *o*-nitrobenzyl porphyrin **198** is an example of attaching two linkers to porphyrins macrocycle that will allow to potentially doubly increasing the conjugation to targeting receptor.

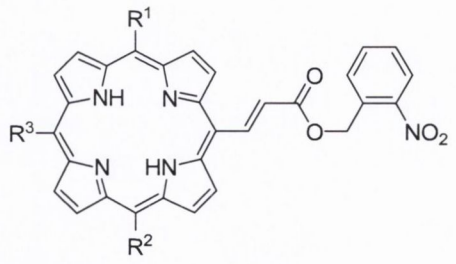


R= 3,5-di-*t*-butylPhenyl **181**

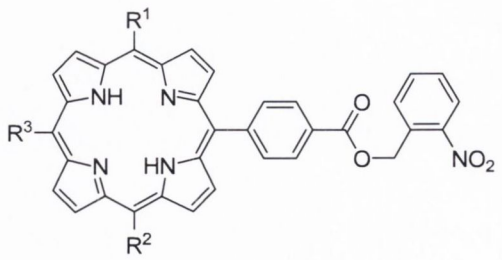
R= 3,5-di-*t*-butylPhenyl **192**

EDAC(eq.)	DMAP (eq.)	2-Nitrobenzylalcohol (eq.)	
1	1	1	50%
2	2	2	86%

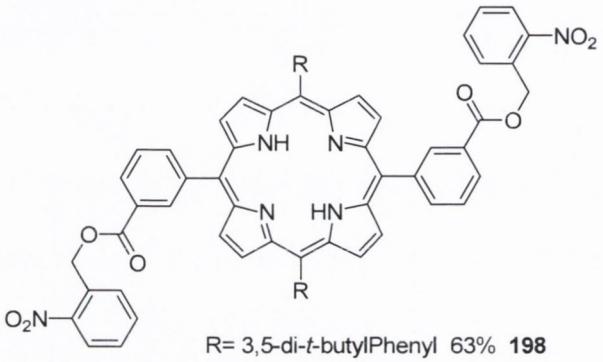
Scheme 3.10 EDAC coupling of porphyrin and 2-nitrobenzylalcohol.



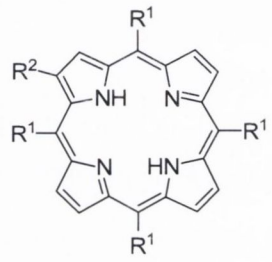
R^1=R^2	R^3		
Phenyl	Hexyl	81%	**193**
3-OMePhenyl	Hexyl	83%	**194**



R^1=R^2	R^3		
Phenyl	Hexyl	81%	**195**
3-OMePhenyl	Hexyl	83%	**196**
3,5-di-*t*-butylPhenyl	3,5-di-*t*-butylPhenyl	86%	**192**
Phenyl	Phenyl	81%	**197**

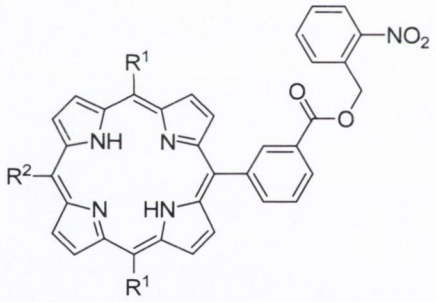


R= 3,5-di-*t*-butylPhenyl 63% **198**

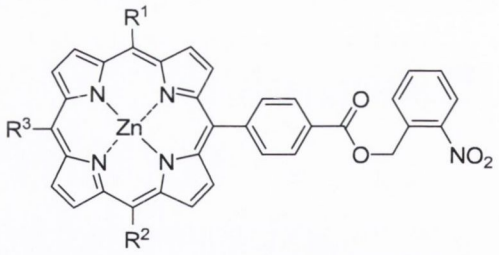


R^1= 3,5-di-*t*-butylPhenyl

R^2= 4-CO_2(*o*-nitrobenzyl)Phenyl 68% **199**



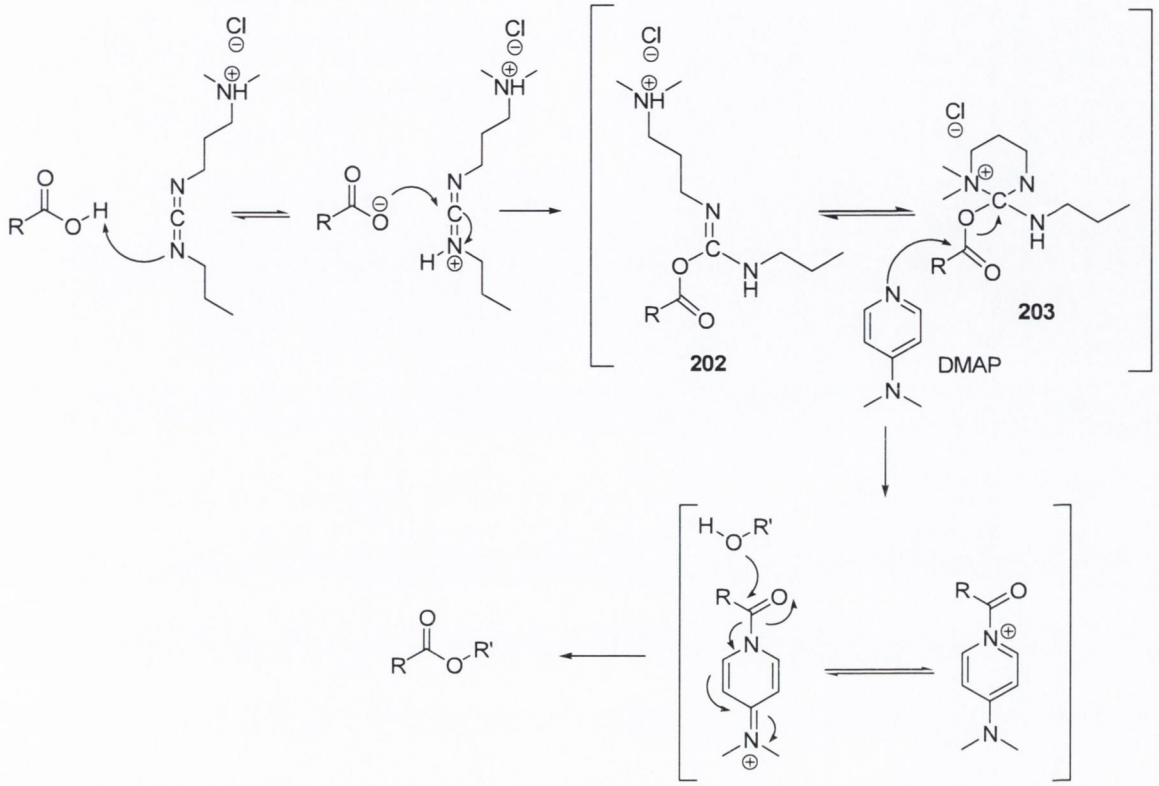
R^1= Phenyl R^2= Hexyl 81% **200**



3,5-di-*t*-butylPhenyl 3,5-di-*t*-butylPhenyl 81% **201**

Figure 3.12 *o*-Nitrobenzyl-linked porphyrins.

The reaction mechanism in using EDAC activating reagent proceeds in similar fashion to other carbodiimide couplings. The O-acylisourea **202** is a highly reactive species that can form the cyclic intermediate **203**, and thus prevent unnecessary racemisation. DMAP[197] is used to liberate the amine salt form of isourea before coupling with a carboxyl group (Scheme 3.11).



Scheme 3.11 Mechanism of EDAC carbodiimide coupling.

Figure 3.13 shows the ^{1}H-NMR spectrum of porphyrin **192** as representative of *o*-nitrobenzyl type porphyrins. Two peaks appeared as triplets at 7.55 and 7.75 ppm represent the H_7- and H_8-protons that are located between two neighbouring protons. The doublet resonance at 8.20 ppm refers to H_9-proton which is closer to the ester group while the doublet resonance at 7.87 ppm corresponds to H_6-proton. Figure 3.14 shows the ^{1}H-NMR spectrum of porphyrin **193** as an example of acrylic-type porphyrins. The resonance which appeared as doublets at 6.87 ppm and 10.28 ppm, respectively represent the H_1 and H_2-protons. The magnitude of the coupling constant, J (15.8 Hz) indicates the *E*-conformation. Figure 3.15 represents *meta*-substituted phenyl moiety as shown in porphyrin **200** with the resonance appeared that as triplet at 7.85 ppm belonging to H_2-proton, whereas two peaks at 8.41 ppm and 8.49 ppm represent its neighbouring protons H_1 and H_3. Resonance for H_4-proton appeared more downfield as a singlet due to its adjacent carbonyl group.

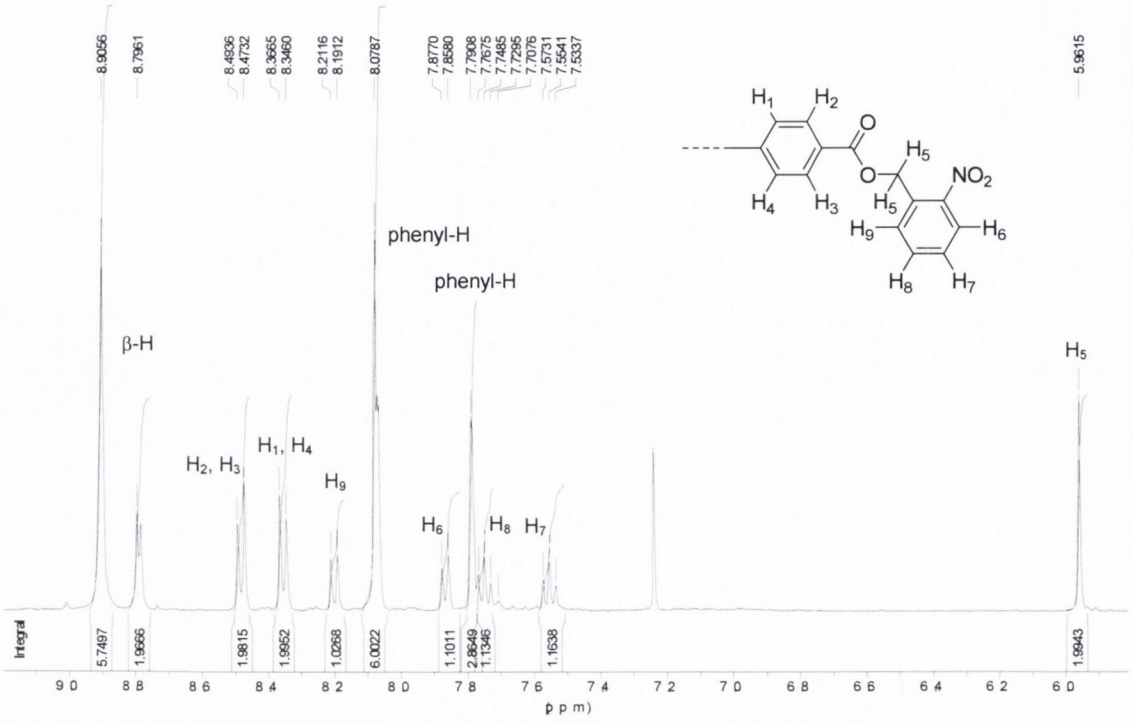


Figure 3.13 ^{1}H-NMR spectrum of porphyrin **192** in $CDCl_3$.

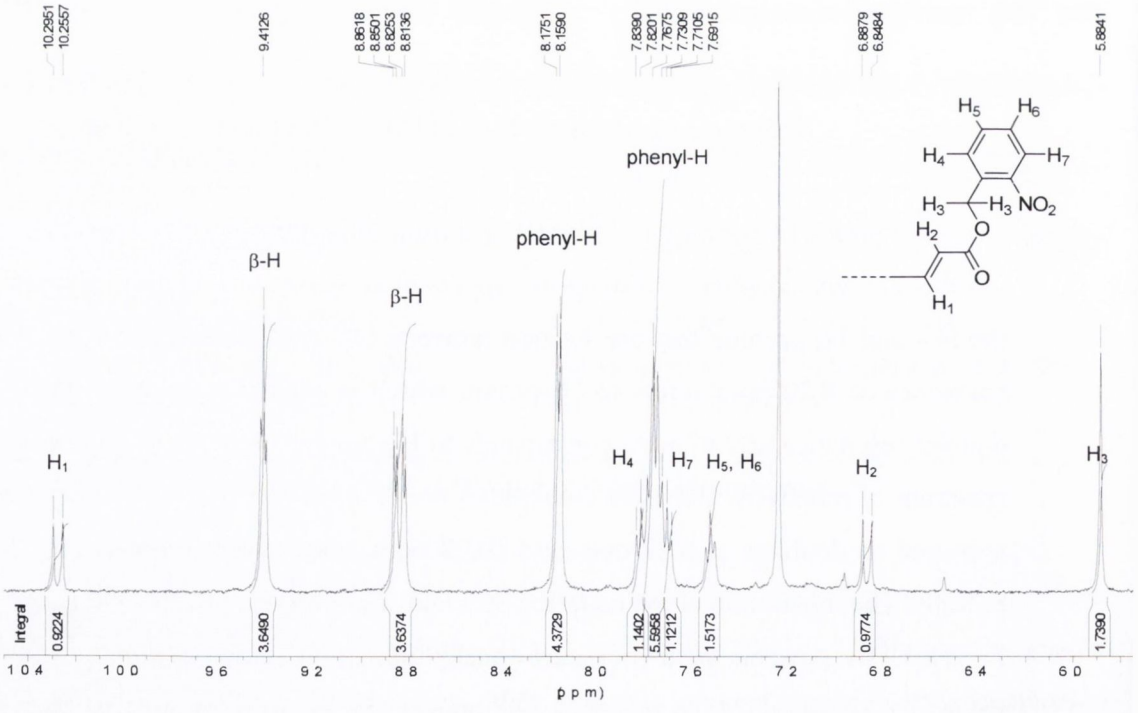


Figure 3.14 ^{1}H-NMR spectrum of porphyrin **193** in $CDCl_3$.

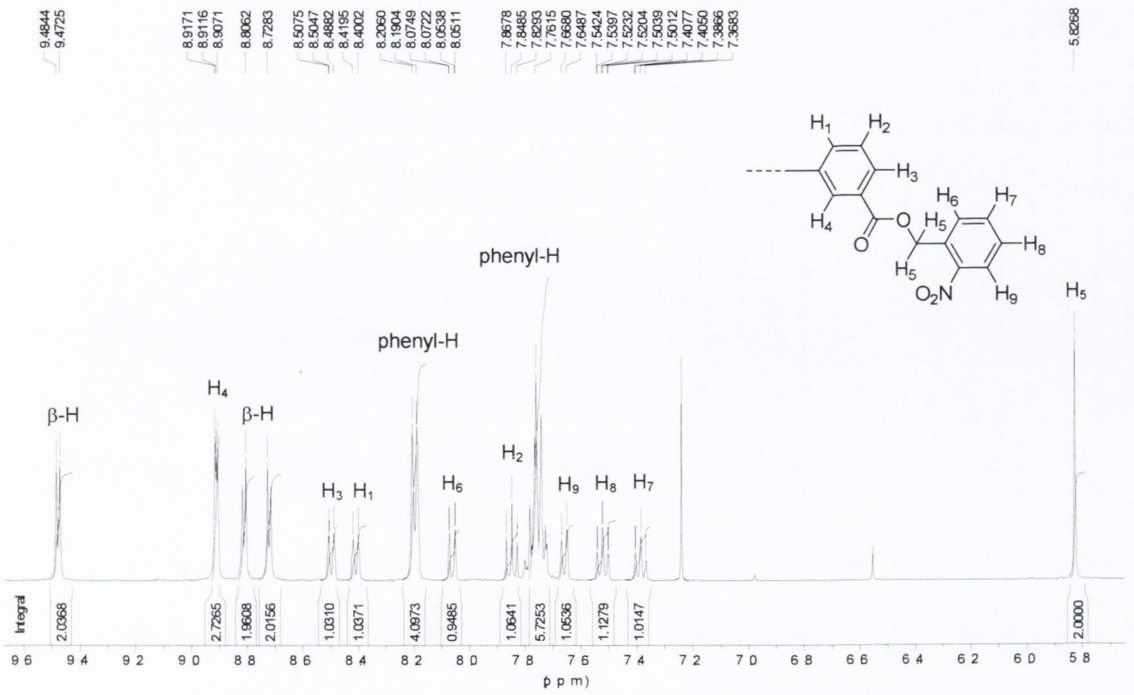


Figure 3.15 ^{1}H-NMR spectrum of porphyrin **200** in $CDCl_3$.

3.4 Conclusions

A number of synthetic methods were investigated with the aim of preparing porphyrins bearing nitrobenzyl functionalities as a model of a labile linker, and the esterification reaction was choosen as the key pathway. We started by utilising transition metal catalysed reactions to introduce simple ester functional groups into porphyrin moeities. Thus, the first step required the synthesis of brominated porphyrins as precursors, followed by palladium catalysed Heck and Suzuki reactions which afforded the ester porphyrins in moderate to good yields. Typical condensation reactions of porphyrins were also employed to introduce the ester functional group. Subsequent base hydrolysis of the porphyrins lead to the formation of carboxylic acid porphyrins.

Esterification reactions towards the preparation of nitrobenzyl-linked porphyrins were carried out *via* the carbodiimide coupling method which are widely used in peptide synthesise. Numerous types of carboxylic acid porphyrins were esterified with 2-nitrobenzyl alcohol as the model linker. Unfortunately, while employing DCC as the coupling reagent, the major products formed were the result of the rearrangement of the isourea intermediate. Therefore, coupling reagent EDAC was used to obtain the desired

porphyrins in high yields. After we established the use of esterification pathway to incorporate the labile linker, subsequent research was towards the ultimate construction of porphyrin-linker-bioconjugate as discussed in the following chapter.

CHAPTER 4:

Photolabile o-Nitrobenzyl Bioconjugate Porphyrins

4.1 Introduction

The cytotoxic effects of photodynamic therapy (PDT) rely on the photosensitiser localisation and accumulation within the diseased sites, thus requiring the accurate delivery of the photosensitiser agent to specific-PDT susceptible sites of the target cells or tissues. This targeted delivery system will increase the selectivity for destroying cancer cells, minimise the uptake of photosensitisers by normal cells, decrease the systemic toxicity and could permit a dose control. As the limited life-time of the generated reactive oxygen species will also constrain the oxidative damage to a minimal volume of surrounding tissues, construction of such system will be essential. Numerous studies have been investigated to develop delivery strategies that recognise the specific target of receptors on cancer cells and that are capable of efficiently increasing the concentrations of photosensitisers internalised into the cells.

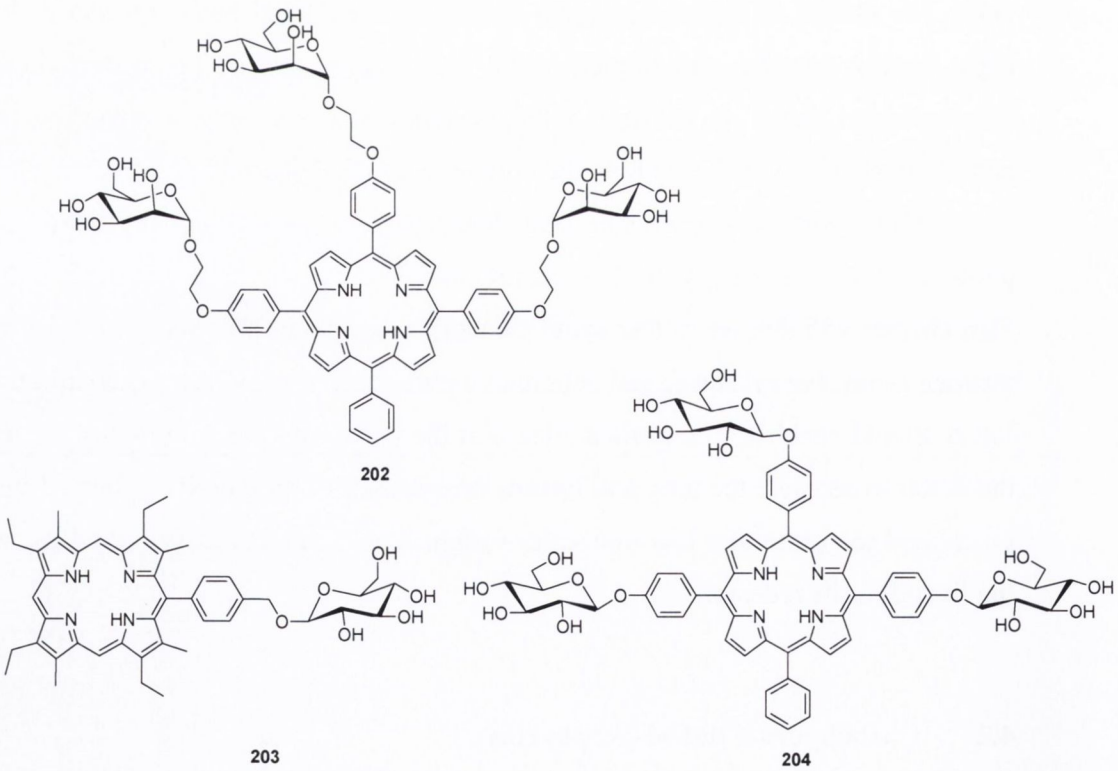
There are a number of cell surface receptors located within the cellular membranes of malignant cells that are overexpressed as compared to normal cells due to their transformed nature.[103] Therefore, antibodies or ligands that are specific to these membrane receptors can be used to selectively target the photosensitisers to the tumour cells. The choice of targeted receptor should be considered based on two main criteria; high density on the pathological cells but largely absent on normal cells and a heterogeneity factor as its high level of expression on only a small percentage of pathological cells would not allow the drug to enter the diseased tissue evenly.[103,198]

Our work has examined the feasibility of modifying the labile porphyrin photosensitisers to target specific receptors based on carbohydrates and folic acid ligands. This chapter will discuss further synthetic work to attach porphyrins to the selected ligands through *o*-nitrobenzyl linker and subsequent photolysis studies. As noted earlier, the labile linker should enable the controlled release of the photosensitisers. Furthermore, addition of the linker to separate the drug and ligands is necessary in drug delivery since drug moieties positioned too close to a low molecular weight ligand can sterically reduce the affinity of the ligand for its receptor.

4.2 Carbohydrate linked-porphyrins

Porphyrins with carbohydrate moieties have been reported as efficient photosensitiser candidates for PDT.[199] They not only alter the amphiphilicity of the

photosensitisers to facilitate their cellular uptake, but also have specific membrane interactions with glycoprotein receptors, and thus exhibit specific targeting of tumour cells.[200] Many glycoporphyrin conjugates have been synthesised to specifically target the lectin family of receptors which are overexpressed in certain malignant cells. For example, Pandey *et al.* demonstrated that galactose and lactose-benzochlorin conjugates, which have high affinity for β-galactoside-recognised proteins, produced an enhanced photosensitising ability compared that non-conjugate analogues.[201] Similar studies were also carried out with glycoconjugates of manno-conjugated porphyrins **202** (Figure 4.1) to utilise the expression of sugar receptors on retinoblastoma cells.[202] The amphiphilic glycosylated porphyrins **203** also associate strongly with plasma lipoproteins and can be incorporated into tumour cells through receptor mediated endocytosis of low-density lipoprotein (LDL) due to high level of the LDL receptor in cancer cells.[203] Recently, glycoporphyrin **204** was conjugated to the B-subunit of Shiga toxin (STxB) which has binding affinity for cellular receptor of glycosphingolipid globotriaocsylceramide, Gb3 that is expressed on a number of cell malignancies. It was shown that the photosensitising activity of the conjugated glycoporphyrins is 5-fold higher than of the parent porphyrins.[204]



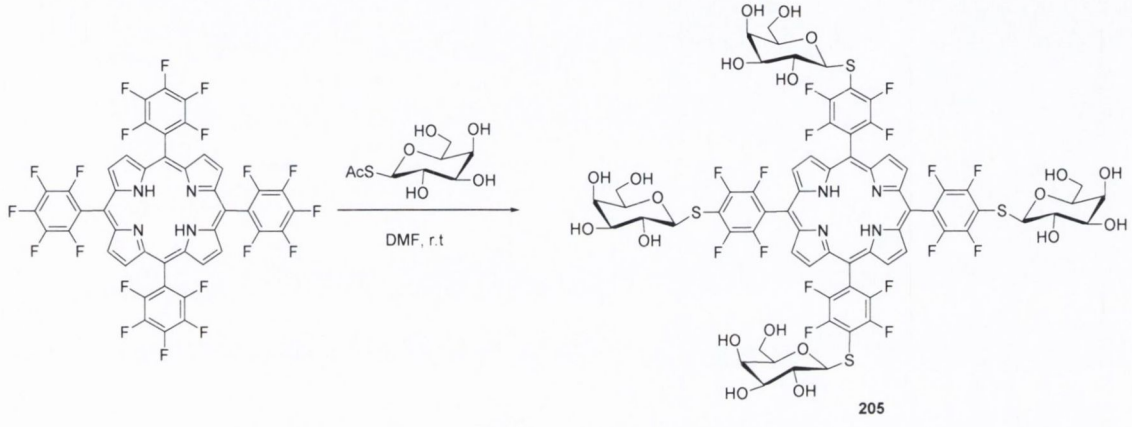
202

203

204

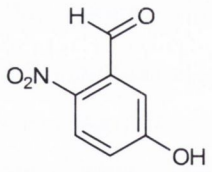
Figure 4.1 Different types of glycoporphyrins.

Synthetic pathways to functionalise porphyrins with glycoconjugates are mainly based on condensation reactions which employ benzaldehydes bearing sugar derivatives.[203,205] The carbohydrate moieties also can be introduced after formation of porphyrin macrocyle to give porphyrin **205** (Scheme 4.1).[200] Most of the carbohydrates have been conjugated to the phenyl rings of tetraarylporphyrins through an oxygen linkage. A different method has been developed utilising click chemistry from readily available carbohydrate azides and the alkyne porphyrins to prepare porphyrin-carbohydrate conjugates.[206]



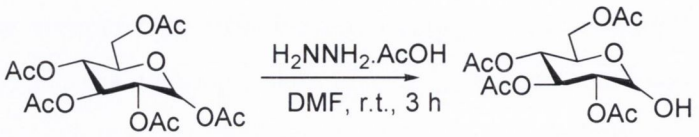
Scheme 4.1 Synthesis of thio-glycosylated porphyrin.

Our approach involved employing carboxylic acid porphyrins as starting materials to react with *o*-nitrobenzyl-carbohydrate conjugate derivatives. Therefore, the first step required the synthesis of hydroxyl-functionalised conjugates which can be esterified with the acid porphyrins at a later stage. We decided to utilise 5-hydroxyl-2-nitrobenzaldehyde **206** as the precursor which contains hydroxyl group as the active site. It has been reported that the Mitsunobu reaction can be used to convert an alcohol into a variety of functional groups using triphenyl phosphine base and azo ester as shown in formation of aryl ether from a phenolic group.[207] Thus, we intended to explore this reaction in incorporating hemicetal glucose **207** to the precursor. Selective deacetylation at the anomeric centre of 1,2,3,4,6-pentaacetyl-*D*-glucose **208** by treatment with hydrazinium acetate in dimethylformamide at room temperature afforded the hemiacetal **207** in 83% yield with 5:1 ratio of α/β product (Scheme 4.2).[208]



206

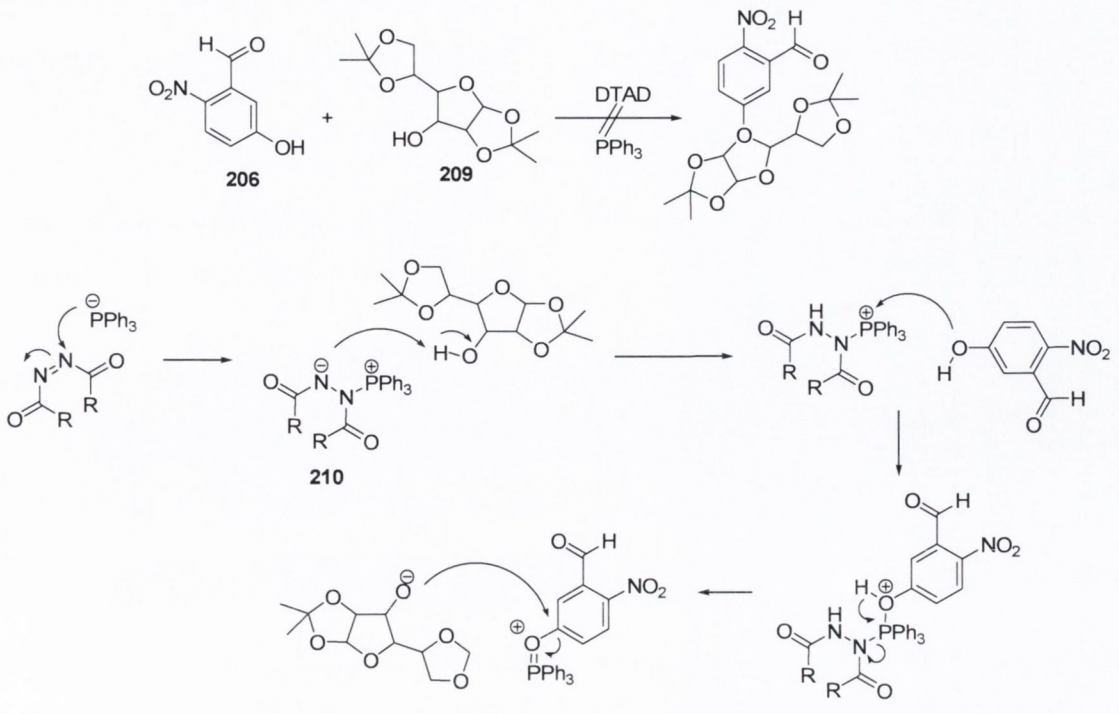
Figure 4.2 Precursor of 5-hydroxyl-2-nitrobenzaldehyde **206**.



208 83% **207**

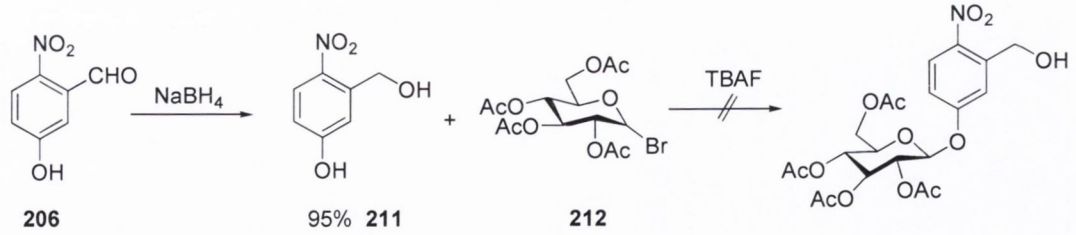
Scheme 4.2 Selective deacetylation of glucose **208**.

Subsequent reaction of hemiacetal **207** with benzaldehyde **206** was carried out under typical Mitsonobu conditions. The reagents **206**, **207** and triphenyl phosphine were dissolved in tetrahydrofuran (THF) and di-*tert*-butylazodicarboxylate (DTAD) was added at 0 °C and the reaction was stirred at room temperature for several hours with TLC monitoring. However, this reaction did not proceed as expected. In the second attempt utilising commercially available glucose **209**, a different approach was investigated by initial preparation of the preformed betaine **210** by adding the azoester DTAD to triphenylphosphine in tetrahydrofuran (THF) at 0 °C, followed by addition of glucose **209** and hydroxyl benzaldehyde **206**. Nevertheless, this method of choice proved to be unsuccessful for preparation of the conjugate (Scheme 4.3). There were several conditions that need to be considered to improve the Mitsunobu reaction. It is necessary to allow the complete formation of oxyphosphonium intermediate by stirring of the betaine **210** longer. Moreover, the basicity of diazo anion can be enhanced using strong electron donating group as piperidine[207] instead of *tert*-butyl to react with weakly acid phenolic functionality.



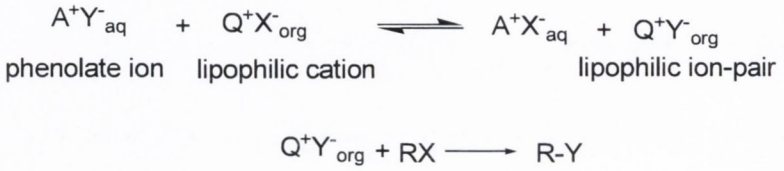
Scheme 4.3 Preparation of nitrobenzyl conjugated glucose *via* Mitsunobu reaction.

Another useful method for glycosylation is the Koenigs-Knorr reaction, which involves the substitution reaction of a glycosyl halide with an alcohol to give glycoside.[209] The attempted preparation of the nitrobenzyl-bioconjugate is shown in Scheme 4.4. The benzaldehyde precursor **206** was reduced with sodium borohydride to give compound **211** in 95%, which was subsequently reacted with acetobromoglucose **212** in the presence of tetra-*n*-butyl ammonium fluoride (TBAF) catalyst as described in the literature.[210] This reaction yielded only starting materials and thus a different approach was employed according to a strategy developed by Thiem and Kruger using phase transfer catalysis (PTC).[211]



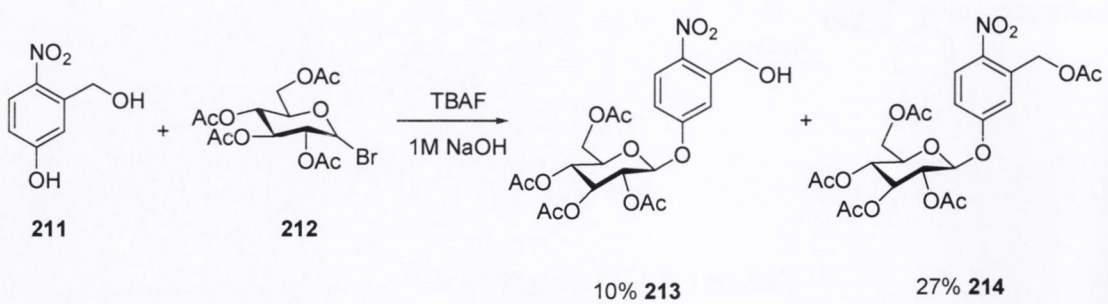
Scheme 4.4 Attempted synthesis of nitrobenzyl-linked glucose.

The PTC technique can accelerate the reaction by facilitating the migration of a reactant in a heterogeneous system between aqueous and organic phases in the presence of a cheap and non-toxic phase-transfer catalyst. The aqueous phase contains bases such as sodium hydroxide (NaOH), whereas the organic phase contains the anion precursor and the electrophile reactant. Typical phase-transfer catalysts are quaternary ammonium salts such as TBAF that are soluble in both the organic and aqueous phase. This catalyst forms a lipophilic ion-pair together with the deprotonated phenolate anion and migrates into the organic phase. In an aprotic nonpolar solvent such as dichloromethane, the ion-pair is not solvated, while the phenolate shows enhanced nucleophilicity (Scheme 4.5).



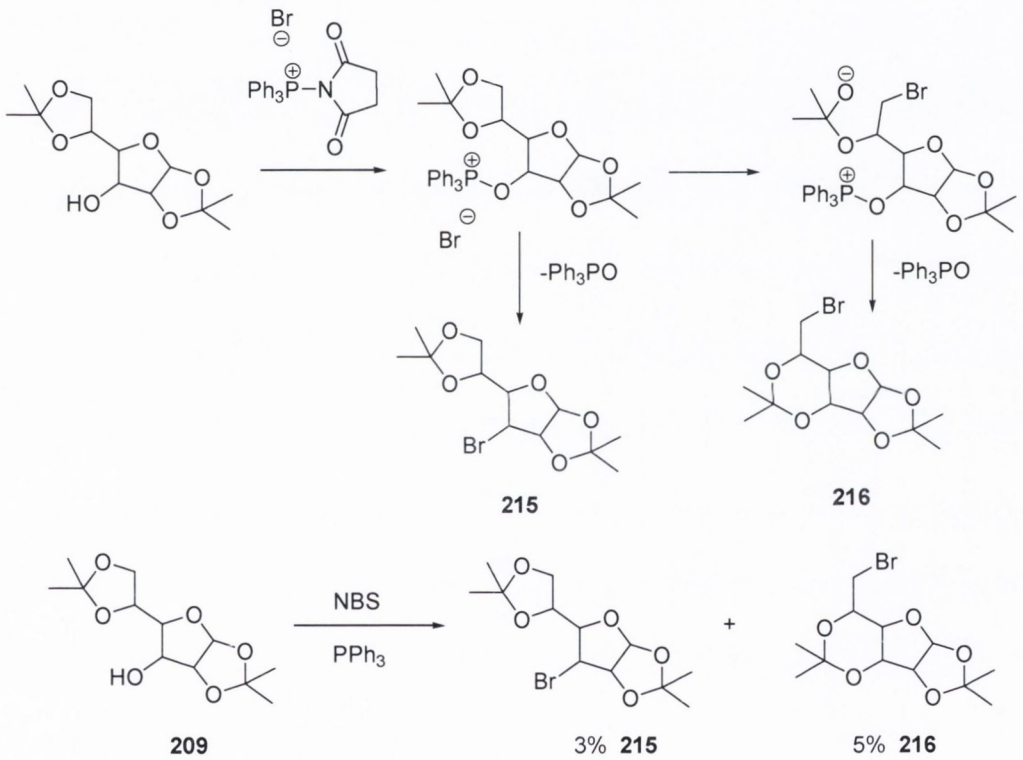
Scheme 4.5 Phase-transfer catalyst reaction.

As only phenols react under phase transfer catalysis, 5-hydroxy-2-nitrobenzyl alcohol **211** can undergo glycosylation selectively at the phenolic position with acetobromoglucose **212** and afforded a mixture of two aryl β-glycosides, (3-hydroxymethyl-4-nitrophenyl)-2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranoside **213** and **214** in 10% and 27%, respectively (Scheme 4.6).[212] The acetylated glycoside **214** was obtained due to partial intermolecular acetyl migration, however both of these compounds were easily separated by column chromatography, eluting with ethyl acetate (EtOAc): hexane = 1:10. The glycoslyated products formed in lower yield due to good solubility of phenol **211** in water, thus reducing the concentration of the reactive phenolate in organic phase.



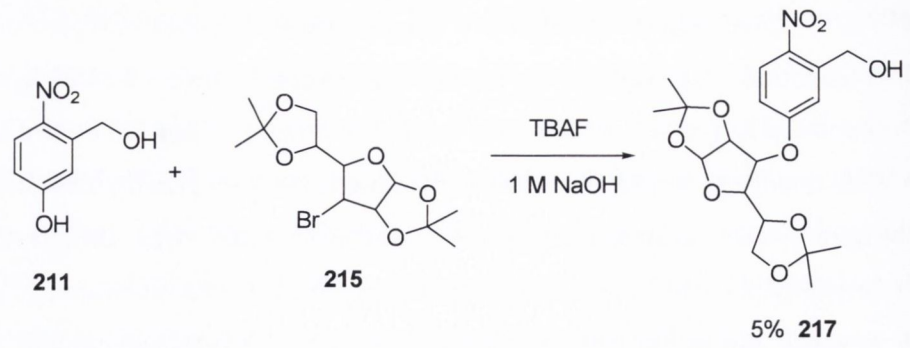
Scheme 4.6 Glycosylation of 5-hydroxy-2-nitrobenzyl alcohol.

The success of the above reaction paved a way to prepare different glycosylated compounds, but required the presence of glycosyl halide. Another synthetic sequence was explored to synthesise the halide due to the limited commercially available glycosyl halide. We choose to employ the glucose **209** due to its susceptibility to undergo deprotection and form water soluble moieties.[203] Therefore, **209** was brominated with NBS and triphenylphosphine in chlorobenzene according to the literature,[213] to give brominated glucose **215** in 3% yield and the side product of rearrangement **216** in 5% (Scheme 4.7). This rearrangement occurred when employing cyclic acetals containing secondary hydroxyl group where the attack of halogens is significantly hindered.[214] A more facile halogenation has been reported by displacement of triflate intermediate of carbohydrates with tetrabutylammonium halides.[215]



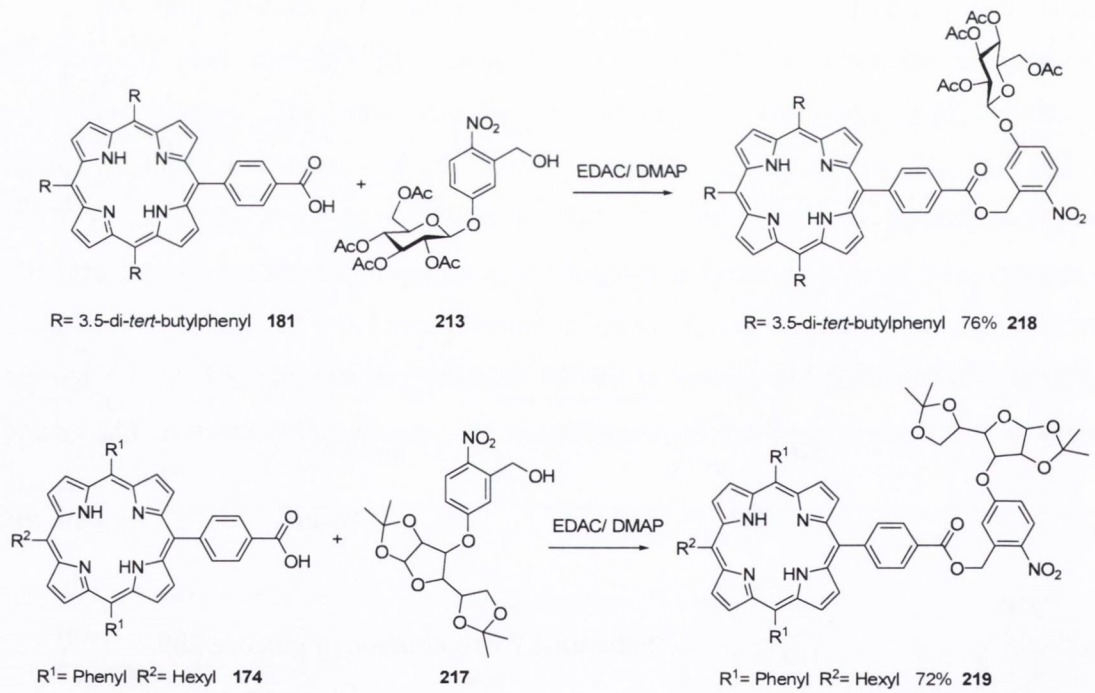
Scheme 4.7 Bromination of glucose **209**.

The lesser yield of **215** limited the reaction scale, however, we managed to perform glycosylation *via* the PTC method with nitrobenzyl phenol **211** and this afforded the β-glycoside of **217** in 5% yield (Scheme 4.8). Due to tedious chromatography, we were only able to separate (3-hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranoside **217** from the reaction mixture in low yield.



Scheme 4.8 Preparation of *o*-nitrobenzyl-linked glucose **217**.

A model compound of porphyrin-linker-bioconjugate was prepared by reacting carboxylic acid porphyrin **181** with glycoside **213** and this yielded the target compound **218** in 76% yield. However, due to a lower quantity of available nitrobenzyl-linked glucose **217**, the similar esterification reaction between porphyrin **174** and glycoside **217** was carried out on small scale and afforded the porphyrin **219** in 72% yield [MS (ESI): *m/z*= 1060.4479 $(M+H)^+$] (Scheme 4.9). Nevertheless, this type of precursor was attractive due to facile deprotection of the glucose moieties.

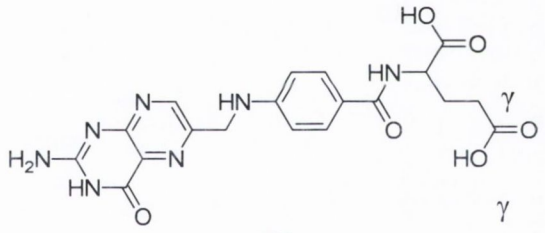


Scheme 4.9 Preparation of porphyrin-linked glucose **218** and **219**.

4.3 Folic acid-linked porphyrins

Folic acid **220** is a ligand that can selectively bind the folate receptor (FR), a glycosylphosphatidylinositol-anchored cell surface receptor that is over-expressed in many cancer cells including >90% of ovarian carcinomas.[107] Upon receptor interaction, the folic acid-(FR) complex is taken into cells through folate receptor-mediated endocytosis. The folic acid is taken up by cancer cells preferentially to normal cells, and thus presents an attractive target for cancer selective drug delivery. Folate as a targeting ligand offers many potential advantages over macromolecules such as monoclonal antibodies (mAb) because of its small size, lack of immunogenicity, convenient availability and high tumour specificity.

It was reported that folic acid retains its receptor binding properties when functionalised *via* its γ–carboxyl group (Figure 4.3). Furthermore, it shows high stability and compatibility with both organic and aqueous solvent and defined conjugation chemistry. Therefore, numerous synthetic procedures has been developed to link folic acid to molecules such as cyclodextrins,[216] radiopharmaceutical imaging agents,[217] polymer nanoparticles,[218] micelles,[219] dendrimers,[220] microgels,[221] along with PDT agents.[108]

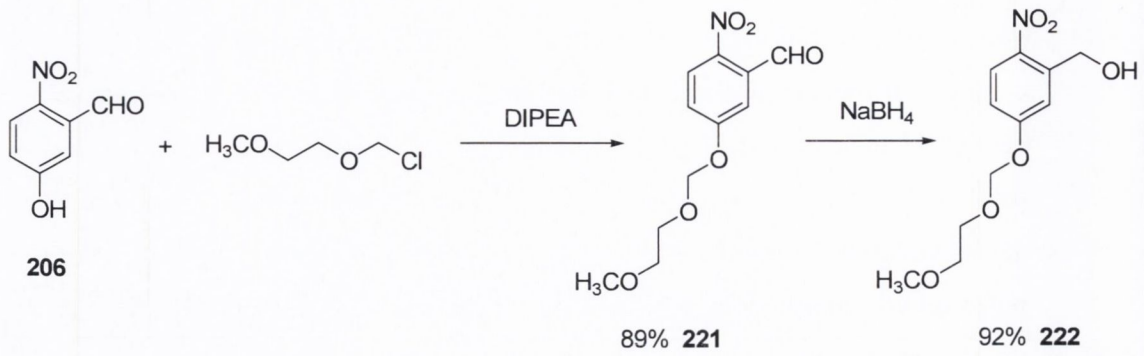


220

Figure 4.3 γ–Carboxyl group of folic acid **220**.

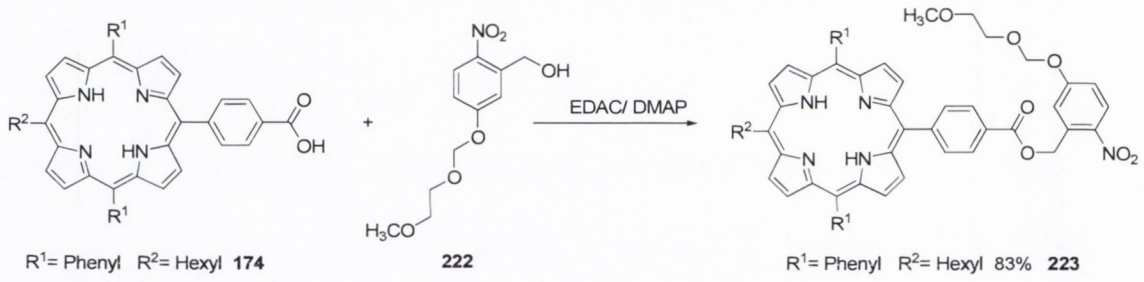
Our approach was to couple the hydroxyl functional of nitrobenzyl-porphyrin with the carboxyl site of the folic acid by employing a protecting group synthon. Synthesis of the nitrobenzyl-porphyrin analog containing an active phenolic group started with the protection of the phenolic group of 5-hydroxy-2-nitrobenzaldehyde **206** using the acid-sensitive protecting group of 2-methoxyethoxymethyl (MEM) ether in the presence of Hünig base, *N,N'*-diisopropylethylamine (DIPEA) and afforded the protected nitrobenzyl benzaldehyde **221** in 89% yield.[222] Reduction of **221** with sodium borohydride[210] at room temperature gave the respective nitrobenzyl alcohol **222** in quantitative yield (Scheme 4.10). It is noted that different protecting groups for phenol functionality such as silyl

derivatives[222, 223] can also be used, particularly to avoid acidic conditions in the final deprotection step.



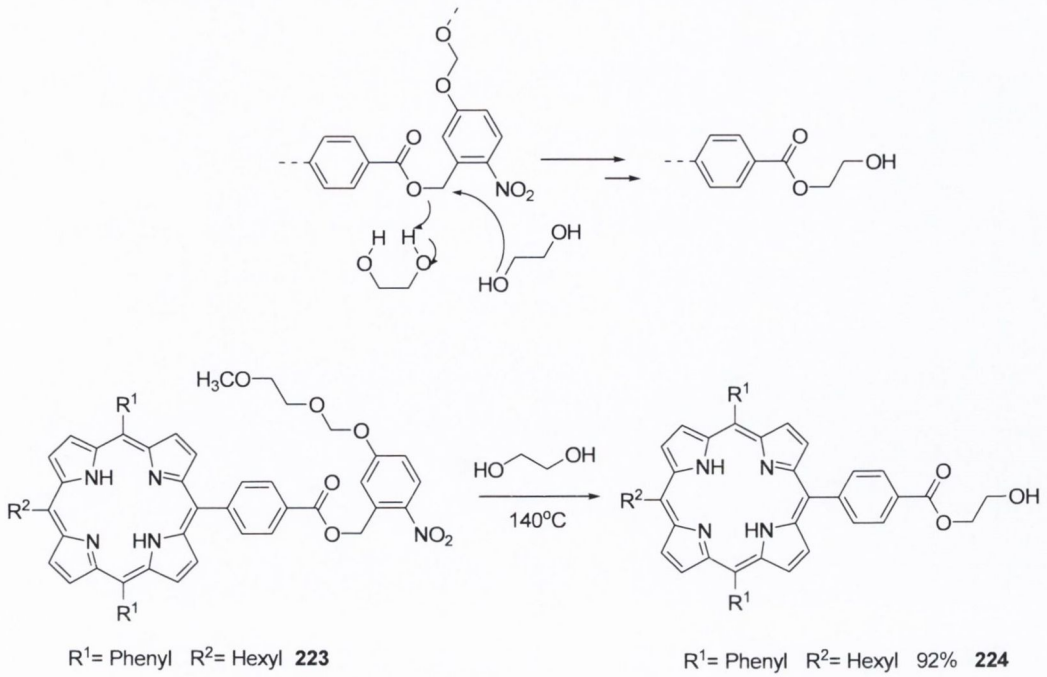
Scheme 4.10 Synthesis of protected nitrobenzyl alcohol.

The next step involved an esterification process of carboxylic acid porphyrin **174** with nitrobenzyl derivative **222** *via* EDAC carbodiimide coupling and gave hydroxyl-protected nitrobenzylporphyrin **223** in 83% yield (Scheme 4.11).



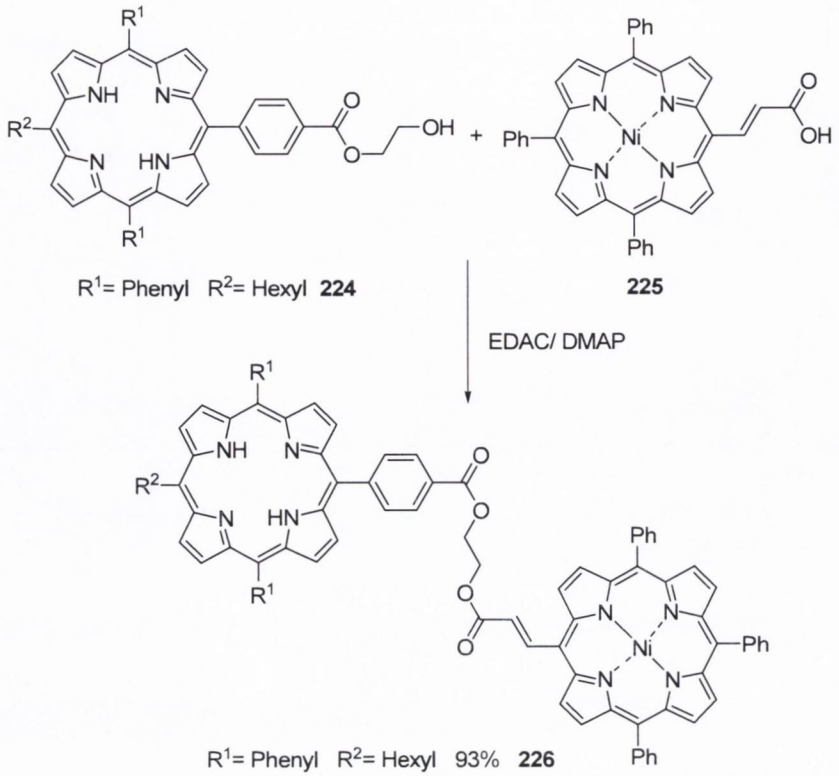
Scheme 4.11 Esterification of porphyrin **223**.

Subsequent deprotection of the acetal type of methoxyethoxymethyl (MEM) group was carried out under neutral conditions to avoid adverse reactions from acidic conditions. Heating of porphyrin **223** with ethylene glycol for 5 hours (TLC monitoring) gave hydroxyl porphyrin **224** in 92% yield. Miyake *et al.* reported that the solvolysis of the ester group is observed to some extent even though in general, the deprotection of the MEM-protected phenyl ester proceeded without destruction of the ester groups.[224] In our case, the deprotection occurred due to nucleophilic attack from hydroxyl group of ethylene glycol to the prone benzylic carbon.



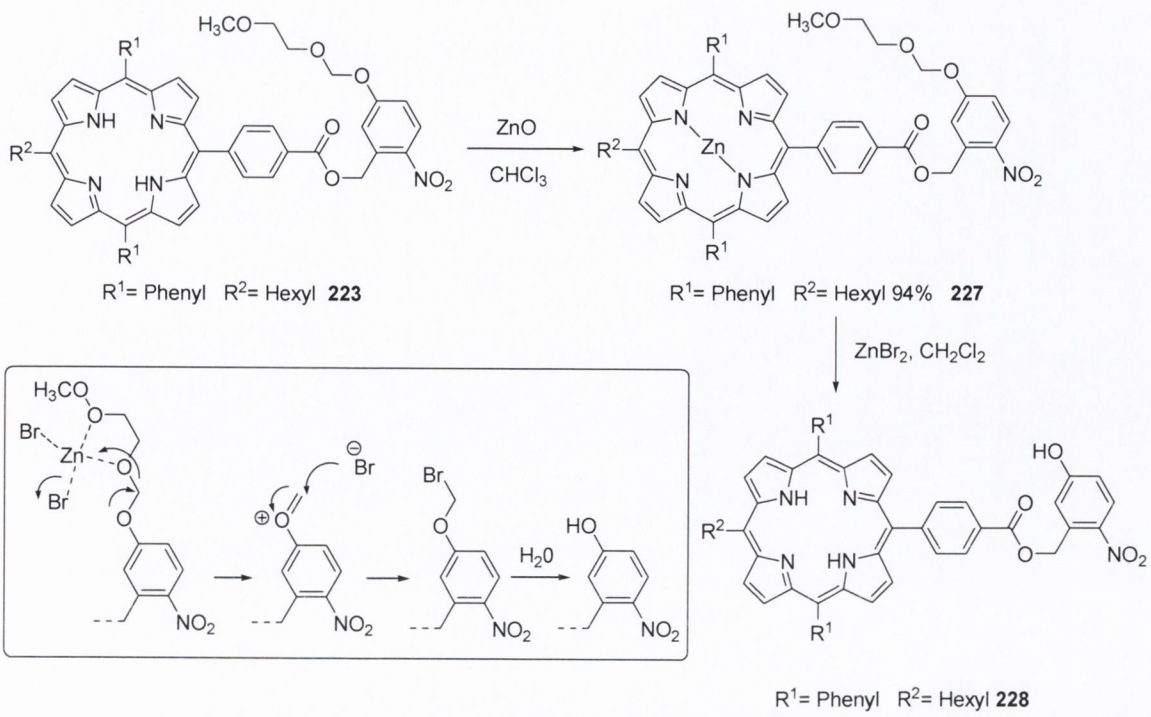
Scheme 4.12 Ethylene glycol deprotection of porphyrin **223**.

Nevertheless, porphyrin **224**, bearing a hydroxyl group, can be utilised as a precursor to introduce numerous functionalities to produce bioconjugate porphyrins such as porphyrin linked-carbohydrate **202**. Moreover, the linkages can be used to construct covalently linked porphyrin dimers that have interesting interaction energy and photoinduced electron transfer process. Notably, different types of porphyrin dimers have been employed in mimicking natural photosynthetic process or for use in electronic devices.[225] Therefore, the reactivity of porphyrin **224** was examined by esterification reaction with carboxylic acid porphyrin **225** to give dimer porphyrin **226** in 93% yield (Scheme 4.13).



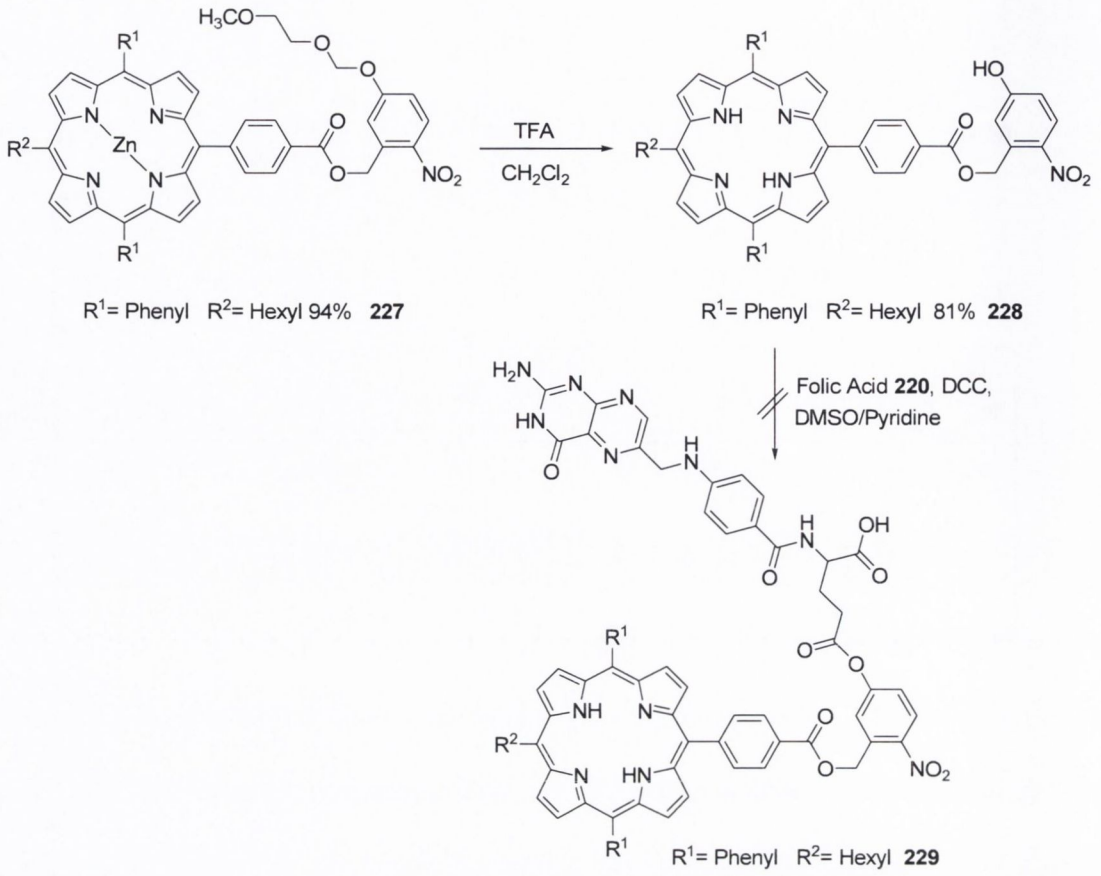
Scheme 4.13 Preparation of porphyrin dimer **226**.

A different neutral MEM-cleavage method was utilised based on bidentate coordination of zinc bromide, $ZnBr_2$ with the methoxyethoxymethyl group.[226] To avoid unnecessary zinc metallation of free base porphyrin due to the presence of $ZnBr_2$, the MEM functionalised porphyrin **223** was metallated with zinc oxide and afforded zinc porphyrin **227** in 94% yield. Consequently, selective deprotection of porphyrin **227** was continued by treatment with $ZnBr_2$ in dichloromethane at room temperature. The initial reaction was set up using 7.0 equivalents of $ZnBr_2$ and stirred in 18 hours, however, only starting material was recovered. While increasing the amount of $ZnBr_2$ to 20 equivalents with similar reaction conditions, mixtures of free base product and starting material were observed but were inseparable due to the close polarity of both compounds (Scheme 4.14). ^{1}H-NMR analysis indicated that the product was free base porphyrin **228** as proton signals from methoxyethoxymethyl-group have disappeared. Mass spectrometry also confirmed the composition of the product [MS (ESI): *m/z*= 818.3323 $(M+H)^+$].



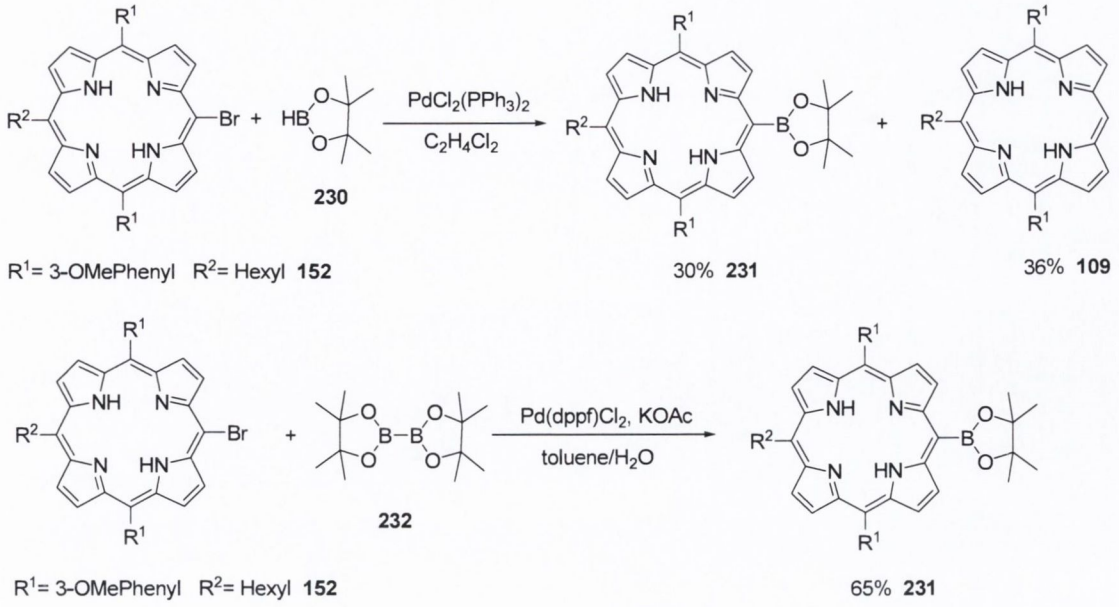
Scheme 4.14 Zinc bromide deprotection of porphyrin **227**.

Afterwards, we decided to use trifluoroacetic acid (TFA)[227] as the MEM removal reagent for metalloporphyrin **227** which could prevent unnecessary porphyrin core protonation under acidic conditions. After treatment of zinc porphyrin **227** with an excess amount of TFA in CH_2Cl_2 (1:1 eq.), the reaction progressed smoothly to eliminate the MEM-group and undergo demetallation process and afforded porphyrin **228** in 81% yield (Scheme 4.15). Subsequently, we attempted to incorporate folic acid **220** as the targeted bioconjugate *via* carbodiimide esterification. Folic acid **220** was dissolved in dimethylsulfoxide in the presence of pyridine followed by addition of DCC.[109] The reaction was stirred for 30 min and porphyrin **228** was added to the reaction mixture (Scheme 4.15). Unfortunately, the expected folic conjugate porphyrin **229** was observed only in very low yield and was detected as the polar spot in TLC analysis. Although this approaches is limited due to its low reactivity, porphyrin **228** still has potential to be used to construct various secondary functionalities such as attaching second photosensitiser of boron-dipyrromethene (BODIPY),[228] or linked with fluorescent marker such as rhodamine B for imaging studies.[229]



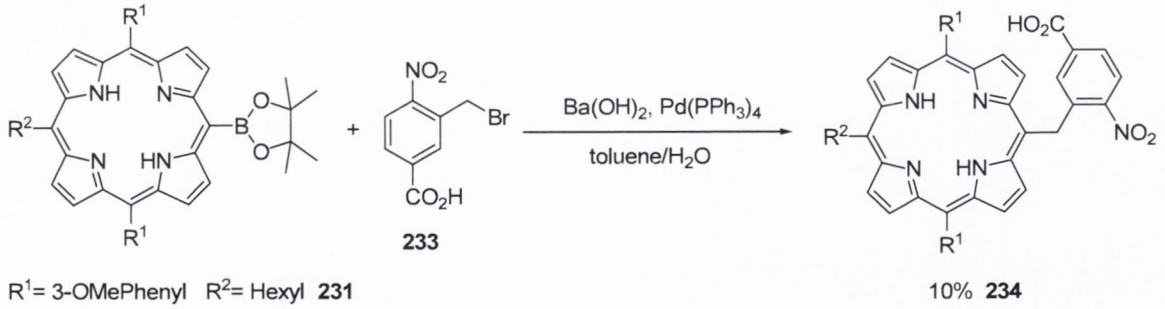
Scheme 4.15 Proposed route to the preparation of folic acid porphyrin conjugate **229**.

Therefore, another pathway was examined to prepare porphyrin precursors that were accessible for linking the folic acid. This method was developed based on reactivity between boronylated porphyrin and its counterpart of halide nitrobenzyl compound *via* a palladium catalysed cross-coupling reaction. The initial step involved preparation of borolanyl porphyrin from bromo porphyrin according to method described by Therien *et al.*[230] Mono bromo porphyrin **152** was coupled with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **230** as the transmetallating reagent with $PdCl_2(PPh_3)_2$ catalyst in 1,2-dichloroethane. The reaction was heated at 90 °C for 20 minutes when the starting material was completely consumed and afforded borolanyl porphyrin **231** in 30% yield and the deprotected porphyrin **109** in 36%. Due to major formation of porphyrin **109**, a different reaction system[231] was employed using bis(pinacolato)diboron **232** in the presence of potassium acetate, KOAc and palladium catalyst $Pd(dppf)Cl_2$ in toluene/H_20 to give porphyrin **231** in 65% yield (Scheme 4.16).



Scheme 4.16 Preparation of borolanyl porphyrin **231**.

4-Bromomethyl-3-nitrobenzoic acid **233** was chosen as transmetallation reagent due to the existence of carboxylic acid functionality that has been shown to be useful group for attaching folic acid conjugates.[109] Porphyrin **231** was then subjected to palladium cross-coupling reaction with bromo nitrobenzoic acid **232** according to the literature[231] using $Pd(PPh_3)_4$ as catalyst and $Ba(OH)_2$ in toluene/H_2O (Scheme 4.17). Under unoptimised conditions, the reaction produced only a small amount of desired porphyrin **234** [MS (ESI): *m/z*= 786.3275 $(M+H)^+$] along with unreacted starting material. This problem presents a challenge in achieving our main target, hence requires extensive synthetic investigation.



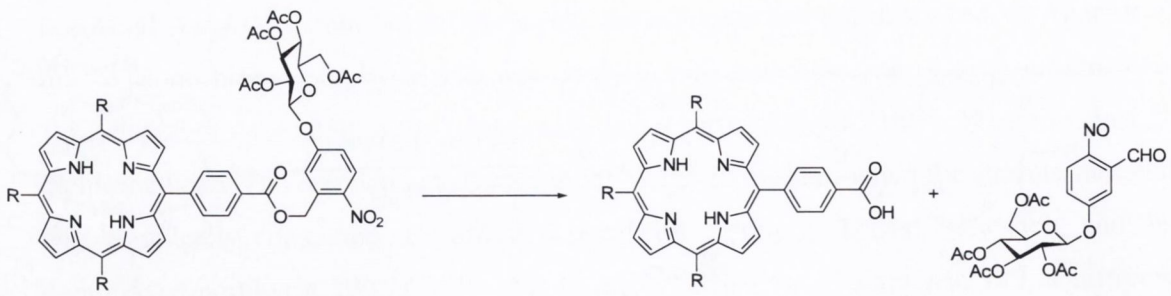
Scheme 4.17 Palladium catalysed cross-coupling reaction of porphyrin **231**.

4.3 Photolysis studies

The photolysis rates of the model porphyrin-linked bioconjugate **218** were measured by photolysing aliquots of the compound solution for various times followed by determination of the rate of disappearance of the starting material and formation of the cleavage compound. Photolysis measurements were performed using a photochemical reactor (Rayonet Model RMR-600) equipped with 350 nm UV lamp. The light fluency rate was calculated as 16 mW/cm^2. Times were chosen such that 70% to 80% of the starting material was cleaved in order to derive kinetic parameters, although the cleavage usually showed good linearity over the course of complete cleavage.

The UV spectrum of porphyrin **218** exhibited the anticipated absorption of porphyrin with two electronic transitions of Soret and Q bands. The Soret band has a very large extinction coefficient and is characteristic for the macrocyclic conjugation. At longer wavelengths, four Q bands, with significantly lower intensity than the Soret band, can be detected. The UV spectra of the fragmented *o*-nitrobenzyl group resulting from the photolysis shows adequate absorption around 350 nm. Consequently, the photolysis progress of the porphyrin **218** could not be detected by UV measurement and required a different analytical measurement such as high performance liquid chromatography (HPLC).

For the photolysis studies, a 50 μM solution of **218** in a Acetone: H_2O (98%:2%) was irradiated with long wavelength UV light (350 ±25 nm) and the photolysis reaction was monitored by HPLC. The compound was photolysed *via* aci-nitroso mechanism to give *o*-nitrosobenzaldehyde along with the carboxylic acid porphyrin substrate **178** (Scheme 4.18). The conversion of **218** to **181** was then followed as a function of time.



Scheme 4.18 Photofragmentation of porphyrin **227** upon irradiation.

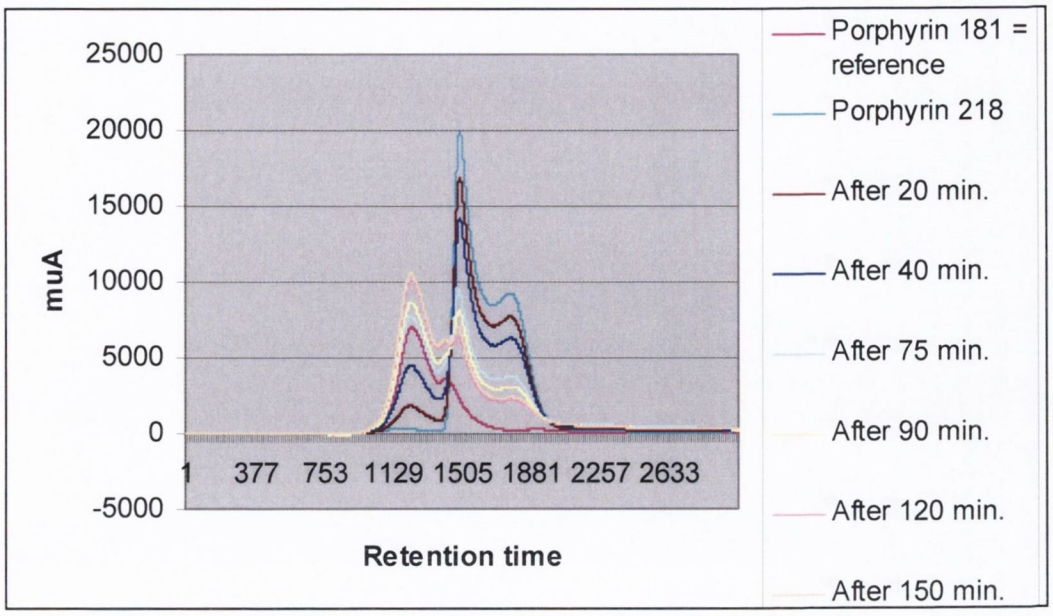


Figure 4.4. HPLC measurement for different photolysis times of porphyrin **218**.

Column: Nucleosile 5μ Si 100A, Size: 250 X 4.00 mm, Eluent: *n*-hexane: ethylacetate (50:50), Flow rate: 1.5 ml/min, Detection UV: 350 nm

Figure 4.4 shows HPLC analysis of samples upon UV irradiation for 20, 40, 75, 90, 120, and 150 minutes as compared with the starting material of porphyrin **218** and carboxylic acid porphyrin **181** based on the difference of porphyrins retention time. During the irradiation process, the peak represent porphyrin **218** is decreased while the formation of the new peak occurred which is comparable to the retention time of carboxylic acid porphyrin **181**. It was observed that upon irradiation for 80 min, approximately 50% of the porphyrin **218** was photolysed (Figure 4.5). The photolysis product was identified as porphyrin **181** [MS (ESI): *m/z*= 995.6233 $(M+H)^+$]. The mechanism of *o*-nitrobenzyl alcohol ester cleavage involves photoinduced intramolecular hydrogen abstraction and redox rearrangement to form *o*-quinonoid intermediate, followed by the released of the carboxylic acid and formation of nitrosobenzaldehyde. *o*-Nitroso benzaldehyde may further react to form a secondary by-product of azobenzene-2,2'-dicarboxylic acid that can act as internal filter, hence presumably slowing the desired photoreaction. While this technique was unable to quantify the amount of product produced, it did provide an expedient method for determination of relative cleavage kinetics for compounds.

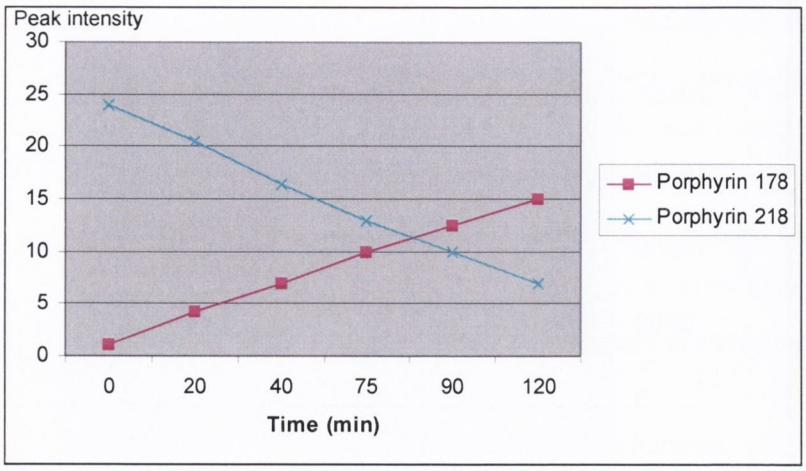


Figure 4.5. Photolysis conversion of starting material and formation of carboxylic acid porphyrin.

With regards to photolabile linker studies, future work should focus on the investigation of more advanced nitrobenzyl derivatives to improve its modest rates of cleavage. For example, incorporation of two alkoxy groups in the benzene ring and introduction of an additional benzylic methyl group increased the rate of cleavage 5-folds. Moreover, a less damaging release group should be considered because the ubiquitous presence of UV light inducing by one-photon excitation is damaging to cells and absorbed by biological chromophores such as DNA. As most of current caging groups such as *o*-nitrobenzyl absorb UV light, different approach has been developed to utilise two-photon infrared (IR) excitation as employed in photolabile species of coumarin moieties.[154] Two photon excitation method confines the substrate activation to the focal point. This technique will minimise the phototoxicity to cells and has better tissue penetration than UV. Recently, strategies to enhance two-photon absorption (TPA) of porphyrin photosensitisers have been of great interest to improve the PDT efficiency.[232] The possibility of carrying out PDT by TPA activation in combination with two-photon labile releasing system should make this type of therapy more applicable to deeper tumors in spatial controlled.

4.4 Conclusions

The results showed our synthetic work for selective targeting and control releasing of the photosensitiser *via* the porphyrin linked-bioconjugate system. The conjugates can act as a ligand which can covalently link to photosensitisers, aiming to enrich the loading of photosensitiser in the target tissue. Carbohydrate residues have been shown as a candidate to enhance photosensitiser binding to LDL due to glycosyl substituents where the LDL can be incorporated into liposome and uptake in cells by receptor mediated endocytosis mechanism. Therefore, initial studies utilised the carbohydrate ligand as shown in the preparation of porphyrin **218** and **219**. While current progress demonstrates that we were able to synthesise a compound containing the required structural motifs, such synthetic sequence need additional improvement as the lower yield of targeted compound gave limitation for our subsequent works in the *in vivo* and *in vitro* studies. Nevertheless, we have showed the photolability of this material upon UV-light irradiation, thus providing a novel strategy for future improvement.

In addition, cell membrane folate receptors have been investigated as a molecular target for tumour-selective drug delivery. Thus, folic acid vitamin that target specifically to the folate receptor can be utilised as the ligand. The second target aims to exploit this folic acid residue by employing porphyrin precursor **228**. Its low reactivity currently limits subsequent studies; however, this precursor provides conveniently naked-eye experimental monitoring due to colour of porphyrins. A different approach using palladium catalysed reactions were attempted to prepare porphyrin precursor **234**, which should pave a way for linking the folic acid. It is noted that the biomolecule consisting double bond character that used as the ligand, potentially quenched the formation of active singlet oxygens from the PDT process, thus incorporating the linker into the system will disconnecting photosensitiser from its bioconjugates.

These studies are the basis for subsequent interdisciplinary studies on the use of photocleavable tetrapyrrole bioconjugates in medicine; notably, the specific use of the drug chromophore as a photosensitising agent in photodynamic cancer therapy and cancer indication. The ultimate target that remains is to find the ideal photosensitiser with a suitable receptor mediated delivery system for each specific pathological condition. Although the present work contains no preclinical or clinical studies, the basic chemistry and the 'proof-of-principle' have been established. This research is the first stage in a long-term effort to promote the use of improved photosensitisers in the treatment and indication of various diseases.

CHAPTER 5:

Reactivity of Porphyrin-Acrylic Acids and Their Homologues

5.1 Introduction

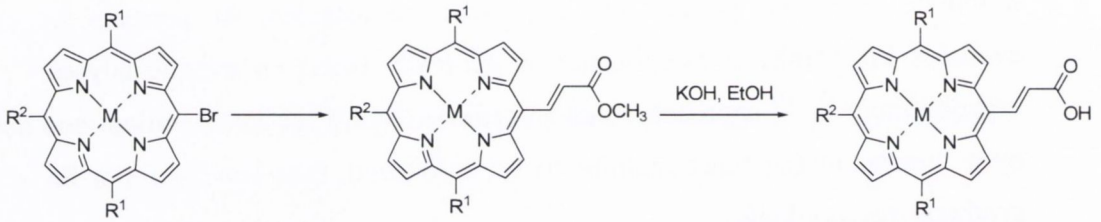
The chemistry of acyl compounds has a long history that can be traced back to the early part of the last centuries.[233] Acyl building blocks are usually derived from carboxylic acids and are some of the best know and valuable synthons that are widely used in fine chemical synthesis. A variety of the synthetic methodologies has been developed to access these highly reactive molecules. The acyl α,β-unsaturated compounds are a subclass of these derivatives and are subunits of numerous natural and synthetic products displaying a wide range of biological activities. These multimodal materials possess two reactive sites consisting of a carbonyl unit as an electrophile and a double bond as a nucleophile. Depending on the conditions and reagents used, these reactive sites can either be activated or deactivated at the same time in a favourable manner. Therefore, their chemistry offers further synthetic prospects based on the different types of the reactions such as Claisen condensation and related acylations, substitutions or additions reactions that can be carried on affording novel materials.

Development of new and more efficient methods have been widely investigated to introduce functional groups into porphyrin macrocycles. At present, the chemistry available for porphyrin modification is generally based on metal-catalysed[177, 234] and organolithium[67, 235] approaches that sometimes require special conditions and are limited by a number of the functionalities to be introduced, thus leaving room for alternative synthetic methodologies.

Thus far, acyl chemistry has not been used much for porphyrin modifications. Several reports described the utilisation of porphyrin-benzoic acids as the building blocks for construction of porphyrin thin films[236] and surface porphyrin monolayers for use as sensor materials,[237] where functionalisation of these compounds mostly involved carbodiimide chemistry that was discussed in an earlier chapter. Only a few reports have been published using porphyrin benzoyl acyl chlorides[189, 238] to leave the chemistry almost untouched. Similarly, while the synthesis of acrylic porphyrins is well-known,[239] their chemistry remains relatively unexplored. In the context of our aim to develop of novel porphyrin bioconjugates suitable for cell targeting, we have systematically studied the reactivity of porphyryl acyl acrylates and their homologues. In this chapter, we present the results on the synthesis, transformations and comparative studies of a series of the porphyryl acrylic derivatives.

5.2 Reactivity of acyl chloride porphyrins

For initial studies to evaluate the reactivity of acyl chloride porphyrins, compounds **239** and **240**, with either one or two acroleinyl groups, were chosen as model compounds. The porphyrins **239** and **240** were synthesised *via* Heck cross-coupling reactions[175] from bromoporphyrins **236** and **237** and methyl acrylate in 80% and 95% yield, respectively. Both of the porphyrins were hydrolysed in KOH-EtOH to the acrylic acid porphyrins **225** and **241** in 80% and 95 % yields, respectively (Scheme 5.1). The corresponding acyl chlorides **242** and **243** were generated upon treatment of porphyrin **225** and **241** with $SOCl_2$-THF *in situ*. Heating at 35 °C is essential to accelerate the formation of these green-purple intermediates. Moreover, acyl chlorides are moisture sensitive and can hydrolyse back to the corresponding acids **225** and **241**. Hence, they were used immediately for further transformations. The reactivity of these intermediates **242** and **243** was examined by use of nucleophiles such as alcohol and amine derivatives. These studies have shown that the acyl chloride porphyrins **242** and **243** *in situ* generated can be converted into the novel porphyrin adducts **239**, **244-247** in good yields (Scheme 5.2).

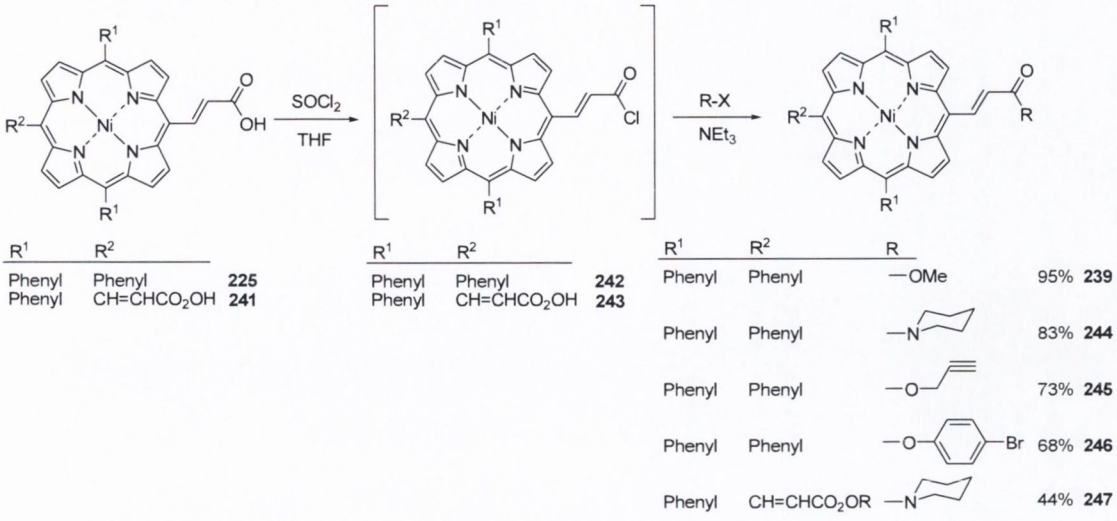


R^1	R^2		
Phenyl	Phenyl	M= H	**153**
Phenyl	Phenyl	M= Ni	**236**
Phenyl	Br	M= Ni	**237**

R^1	R^2			
Phenyl	Phenyl	M= H	95%	**238**
Phenyl	Phenyl	M= Ni	80%	**239**
Phenyl	$CH=CHCO_2Me$	M= Ni	80%	**240**

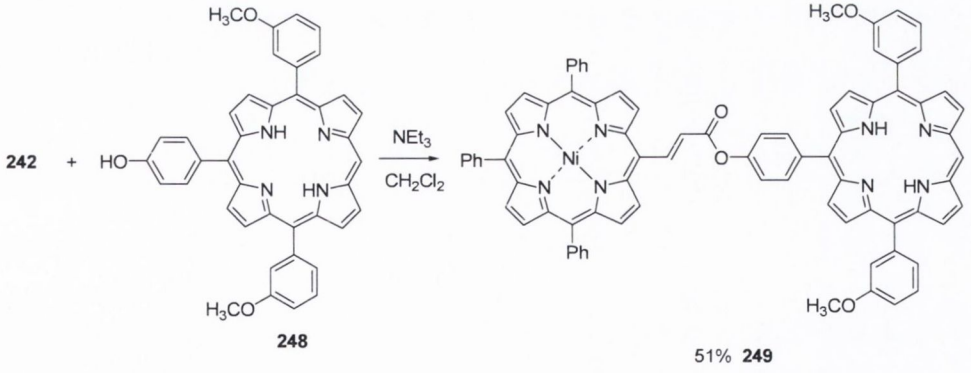
R^1	R^2			
Phenyl	Phenyl	M= Ni	95%	**225**
Phenyl	$CH=CHCO_2OH$	M= Ni	80%	**241**

Scheme 5.1 Route to the synthesis of carboxylic acid porphyrins **225** and **241**.



Scheme 5.2 Generation of the acyl chlorides **242, 243** and synthesis of the porphyrins **239, 244-247**.

This methodology can also be applied for the preparation of dimeric porphyrins. For example, the reaction of **242** with 5-(4-hydroxyphenyl)-10,20-bis(3-methoxyphenyl) porphyrin **248** resulted in the formation of dimer porphyrin **249**. Noteworthy, the first attempt to carry out this reaction in THF, which was shown to be successful for the synthesis of **239** and **244-247**, resulted in a very low yield of **249**. However, replacement of THF by dichloromethane provided dimer **249** in 51% yield (Scheme 5.3).



Scheme 5.3. Synthesis of porphyrin dimer **249**.

Figure 5.1 shows the ^{1}H-NMR spectrum for porphyrin dimer **249**. The signals for alkene proton, H_1 and H_2 appeared as doublets at around 6.73 ppm and 10.28 ppm respectively where H_1 which closer to porphyrin core shifted downfield and overlapping with *meso*-H.

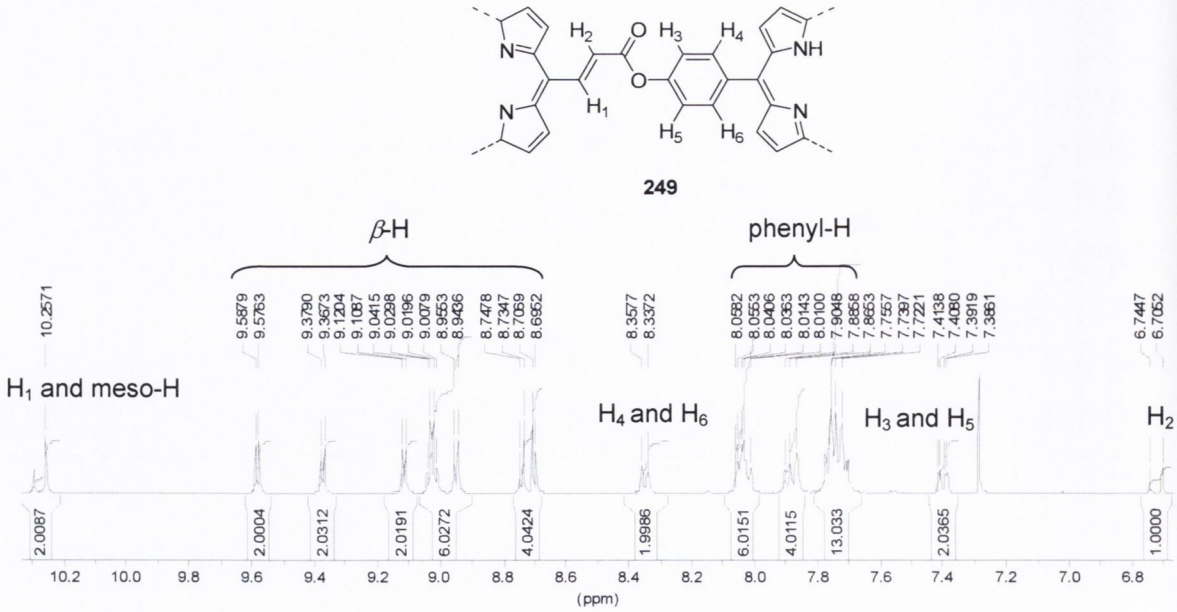
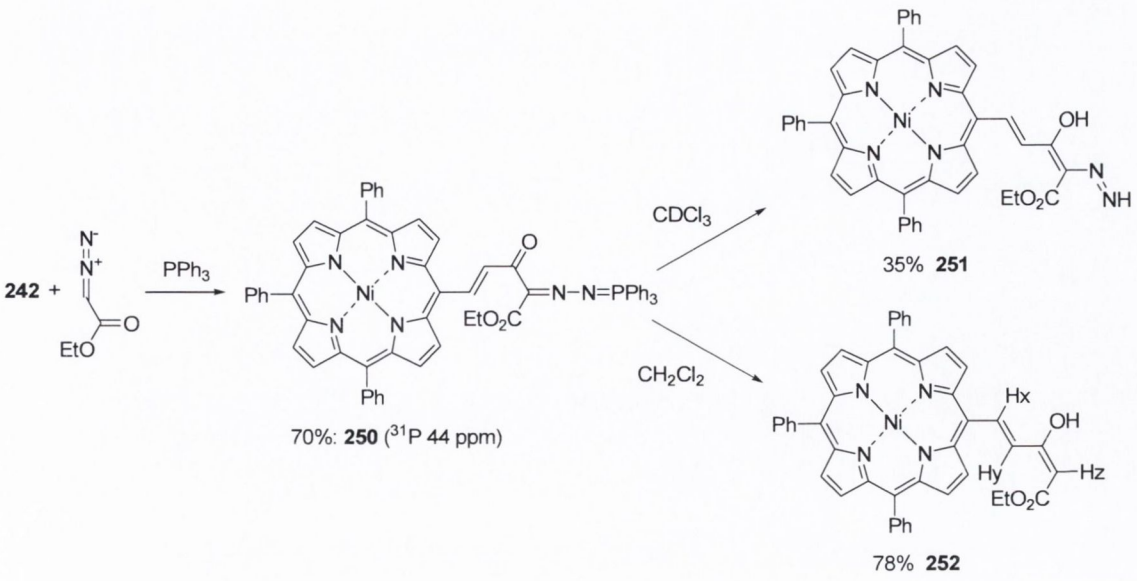


Figure 5.1 ^{1}H-NMR spectrum of porphyrin **249** in $CDCl_3$.

Subsequent work was focused on the reactivity of β-keto ester derivatives. It has been reported that porphyrins bearing keto ester substituents at the β-position of the porphyrin macrocycle can be converted into biologically active phaeoporphyrins *via* photoinduced cyclisation.[240] While diazo compounds are widely used as precursors in synthetic chemistry,[241] only one strategy was applied for the synthesis of diazo β-keto esters using the acrylic acid halides in the reaction of the latter with mercuryl diazoacetate as reported by Padwa *et al.*[242] In our studies, the reaction of acyl chloride **242** with ethyl diazoacetate in the presence of PPh_3 offers an entry into the important and unexplored class of porphyryl β-keto esters. Acyl chloride **242** generated *in situ* was treated with the mixture of ethyl diazoacetate and PPh_3 in dichloromethane at 35 °C for several hours to give phosphazine **250** in 70%, which was confirmed by ^{31}P-NMR spectroscopy (Scheme 5.4). Some structural diversity was observed in solutions of deuterated chloroform ($CDCl_3$) where slow conversion of **250** and formation of **251** were detected over the course of 7 days. Compound **251** trapped in $CDCl_3$ appears to be a product of a partial hydrolysis of the phosphazine **250**. However, compound **250** proved to be quite unstable in dichloromethane and autotransformed (24 h) into the stable β-keto ester **252** in 78% (Scheme 5.4).

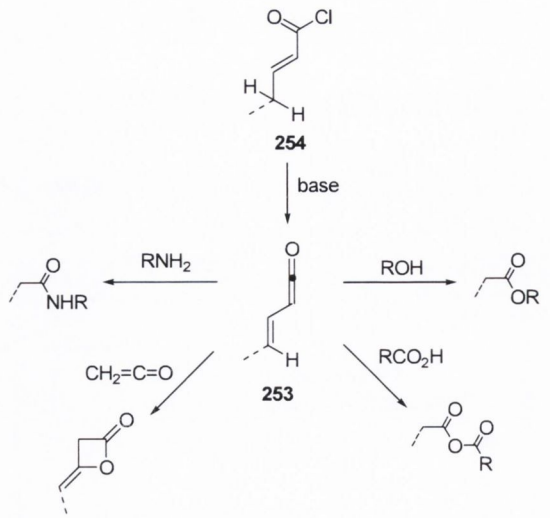


Scheme 5.4 Reaction of **242** with ethyl diazoacetate *via* formation of phosphazine **250** and conversion to **251** and **252**.

According to ^{1}H-NMR data, porphyrin **252** exists only in the enol-form in a solution of $CDCl_3$ or CD_2Cl_2. More detailed NMR analysis showed that compound **252** consists of only one stereoisomer. Importantly, no response between either H_x and H_z or in the pair of H_y with H_z were observed in 1D NOE experiments (see experimental part). Strong NOE were detected for the CH_2-group of CO_2Et and H_z, and also between H_x, H_y with β-Hs. These results confirm that **252** has a *2E,4E*-configuration as shown in scheme 5.4. Noteworthy, the synthesis of β-keto esters generally requires the hydrolysis of the phosphazines formed in the reaction of the nonacrylic acid chlorides with diazoacetate and further elimination of the NNH_2 group.[243] In our case, this reaction offers a versatile approach to access porphyryl hydroxydienoates in just one-step.

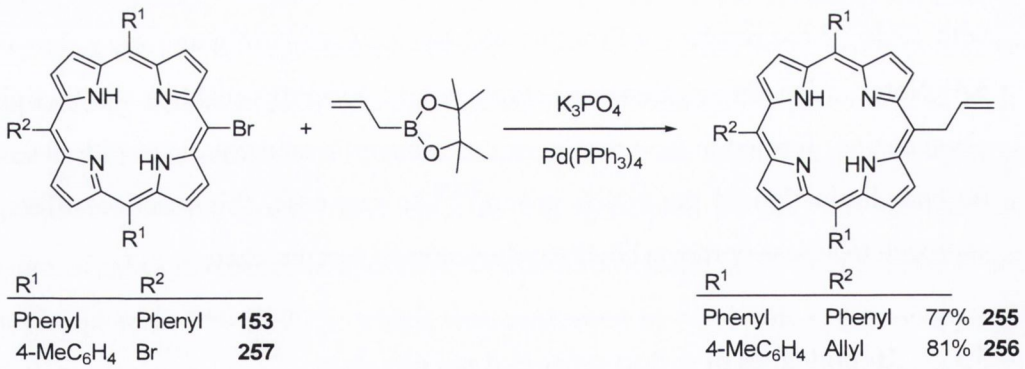
5.3 Homologues of α,β-unsaturated porphyrins

The reaction of acyl chlorides bearing α-Hs with tertiary amines is an old and common method for the synthesis of ketenes **253** and is used often in cycloadditions and other reactions typical for ketenes.[244] Our investigations were further encouraged by the fact that substituted vinyl ketenes can be formed *in situ* by dehydrohalogenation of α,β-unsaturated acyl chlorides **254** and as unstable species; they can be activated and trapped (Scheme 5.5).[245]



Scheme 5.5 Reactivity of ketene intermediate **253**.

Strategically, the series of the next homologues of the acrylates **238-240** bearing CH_2 groups are essential to provide an access for a double bond migration. Therefore, precursor of ally porphyrin **255** and **256** were prepared from brominated porphyrins **153** and **257** with allyboronic acid pinacol ester using Suzuki cross-coupling reaction as described previously (Scheme 5.6).[246]



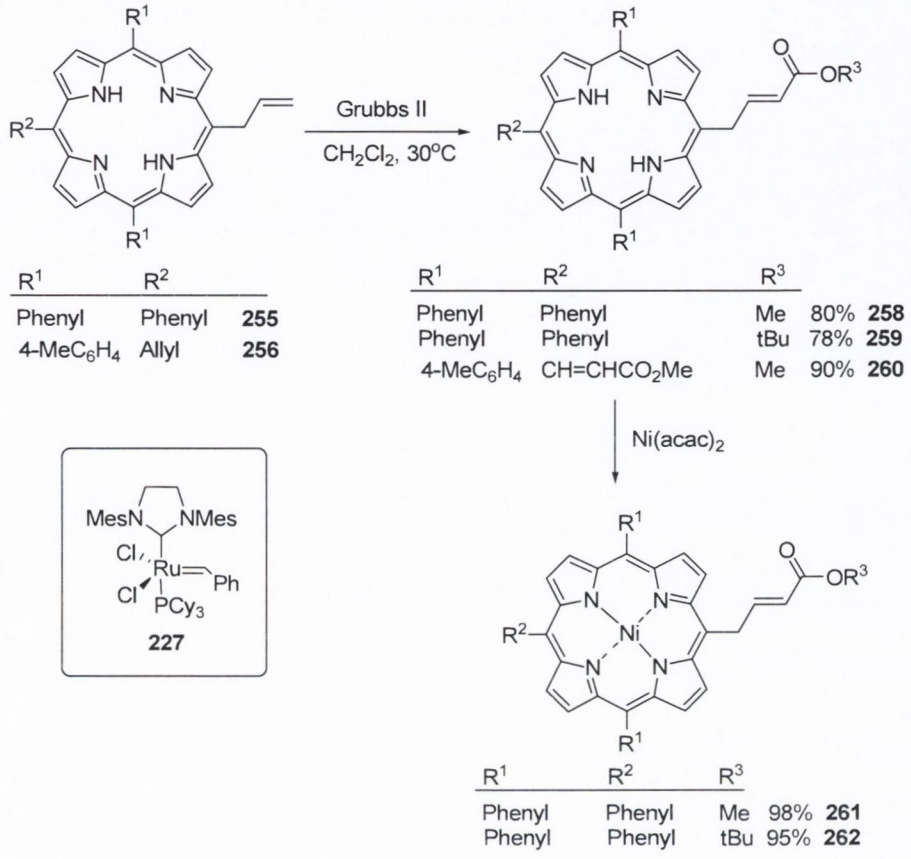
R^1	R^2	
Phenyl	Phenyl	**153**
4-MeC_6H_4	Br	**257**

R^1	R^2		
Phenyl	Phenyl	77%	**255**
4-MeC_6H_4	Allyl	81%	**256**

Scheme 5.6 Synthesis of allyl porphyrins *via* Suzuki cross-coupling reaction.

Subsequent preparation of acrylate ester porphyrins was carried out using an cross-metathesis (CM) approach,[246] followed by ester hydrolysis. It is noted that metathesis conditions have also been utilised for different porphyrin modifications due to their mild reaction conditions and high tolerance towards numerous functional groups.[247] Allyl porphyrins **255**, **256** were then reacted with the corresponding acrylate esters in the

presence of second generation Grubbs catalyst; **257**. These reactions were performed in dichloromethane and afforded the corresponding esters **258-260** in 78% to 90% yields. Porphyrins **258** and **259** were subjected to Ni-metallation reactions to give porphyrin **261** and **262** before undergoing further transformations (Scheme 5.7).



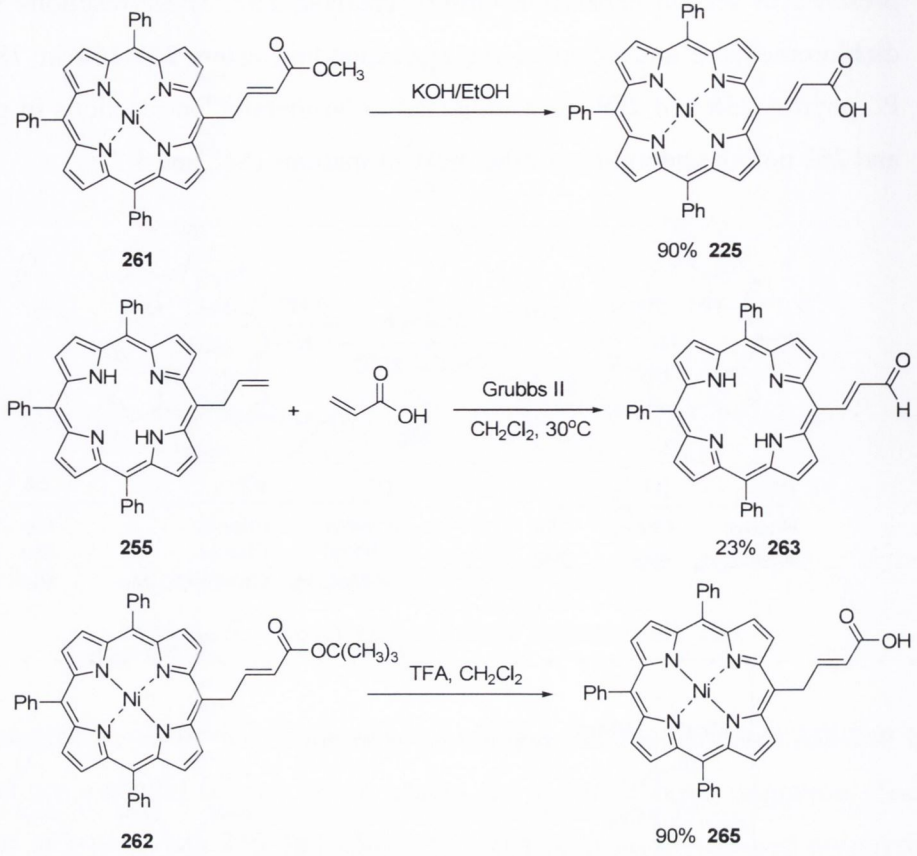
R^1	R^2	
Phenyl	Phenyl	**255**
4-MeC_6H_4	Allyl	**256**

R^1	R^2	R^3		
Phenyl	Phenyl	Me	80%	**258**
Phenyl	Phenyl	tBu	78%	**259**
4-MeC_6H_4	$CH=CHCO_2Me$	Me	90%	**260**

R^1	R^2	R^3		
Phenyl	Phenyl	Me	98%	**261**
Phenyl	Phenyl	tBu	95%	**262**

Scheme 5.7 Synthesis of acrylic ester porphyrins **258-262**.

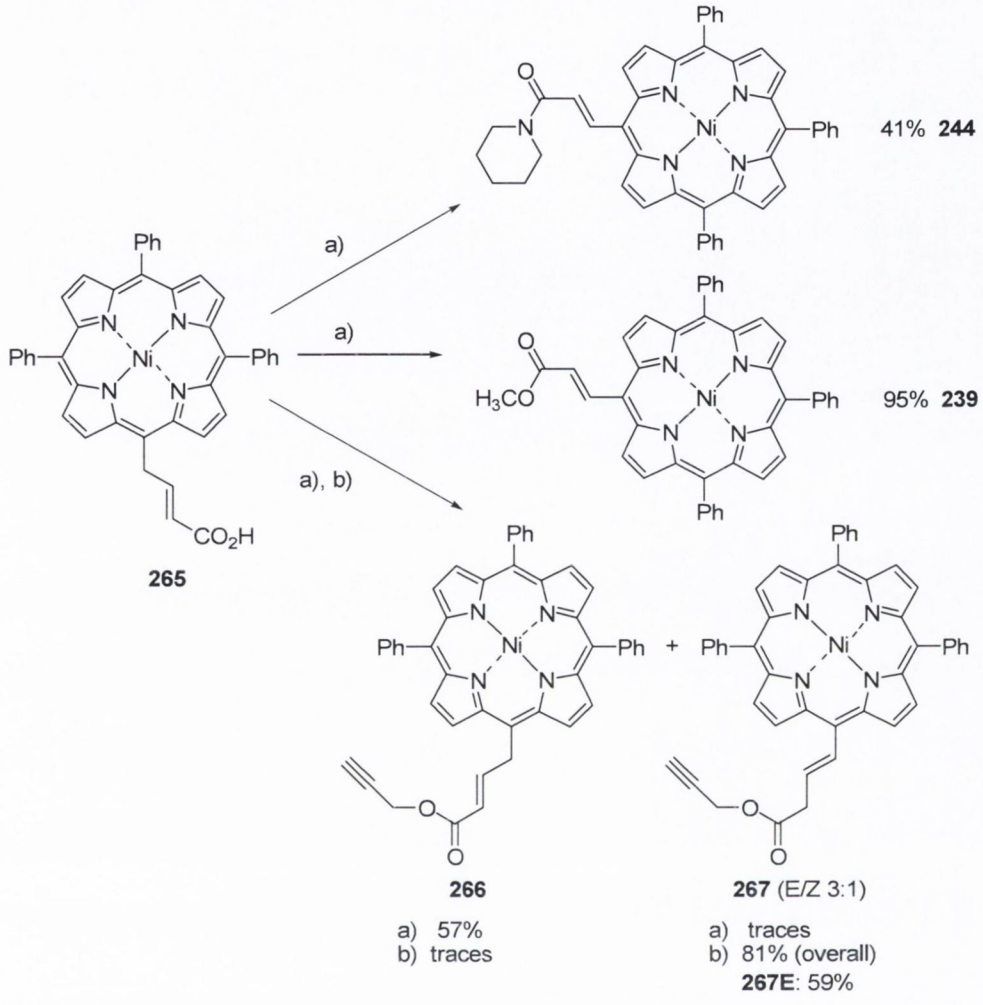
Unexpectedly, the first attempt to hydrolyse the methyl ester **261** in KOH-EtOH resulted in the formation of a very polar compound, which was treated with HCl (1N) yielding **225** in 90% yield. The analytical data obtained were in accordance with the structure of a product prepared through Heck cross-coupling reaction. In order to avoid the basic conditions, an alternative approach for the synthesis of a porphyrin acrylic acid involving allyl porphyrin **255** and the acrylic acid in the presence of Grubbs II catalyst was considered. However, a test reaction gave the acrolein porphyrin **263** in 23% yield. Similar transformations of (allyl porphyrinato)nickel(II) complexes into porphyryl acroleins, albeit catalysed by $Ni(OAc)_2$ were previously reported.[248] Finally, the hydrolysis was successfully employed on porphyrin *tert*-butyl ester **262** in the presence of trifluoroacetic acid in dichloromethane, leading to the free acid porphyrin **265** in 95% (Scheme 5.8).



Scheme 5.8 Synthesis of porphyrins **225**, **263** and **265**.

The corresponding acyl chloride generated from porphyrin **265** by treatment with $SOCl_2$ in THF, reacted with piperidine in the absence of NEt_3 to give porphyrin **244** in 41% yield (Scheme 5.9). Reaction of acyl chloride of **265** with MeOH and Hünig base, DIPEA (4 equivalent) led to the formation of porphyrin **239** in almost quantitative yield (95%). Analytical data for the porphyrins **244** and **239** prepared *via* these routes were in accordance with those derived for the compounds prepared using the alternative approach as shown in Scheme 5.2. The reaction pathway of porphyrin **265** to **239** and **244** seems to be similar to the one for the hydrolytic conversion of **261** into **225**, where "elimination" of a CH_2 fragment was also observed. Assuming, that a vinylketene might be an intermediate of these transformations; different synthetic approach was made by use of a bulky soft base (DMAP) and the reactive propargyl alcohol. Indeed, the reaction of **265** with propargyl alcohol provided only the esterification product **266** in 57% yield. However, traces of rearrangement product **267** could be detected as well. In order to improve the yield of **267** and to confirm its structure, porphyrin **265** was alternatively treated with the mixture of EDAC/DMAP[190] in dichloromethane followed by addition of propargyl alcohol. Surprisingly, two regioisomeric products **266** and **267** were detected, with regioisomer **267**

being the major product. Moreover, porphyrin **267** presented a mixture of stereoisomers in a ratio of 3:1, with an overall yield for the two stereomers of 81% (Scheme 5.9).



Scheme 5.9. Reactivity of porphyrin **265**. Condition: a) i: $SOCl_2$, THF, +35°C ii: RX, CH_2Cl_2; b) EDAC/DMAP, $HC{\equiv}CCH_2OH$, rt., CH_2Cl_2

^{1}H-NMR analysis confirmed the differences between **266** and **267** (Figure 5.2 and Figure 5.3). The signal for a double bond hydrogen atom $H_{3'}$ in **267E** was shifted to 8.76 ppm (doublet) compared to 5.83 ppm (doublet) for H_3 in **266**. Likewise, the signals for the methylene hydrogen atoms, H_1 (5.48 ppm, doublet) and a double-bond hydrogen atom H_2 (7.92 ppm, doublet of triplets) in **266** were shifted towards higher field compared to **267*E*** (methylene hydrogen atoms, $H_{1'}$ appeared as doublet at 3.79 ppm and H_2, appeared at 6.17 ppm as doublet of triplet respectively. This confirms compound **267*E*** to be a rearrangement product. An analysis of the ^{1}H NMR ^3J coupling constants of the CH=CH fragment in the stereomeric mixture **267** (J for E 15.2 Hz and for Z 11.3. Hz) revealed the

stereochemistry of the major product to be *E* (Figure 5.3). This major stereoisomer **267E** was isolated in 59% yield.

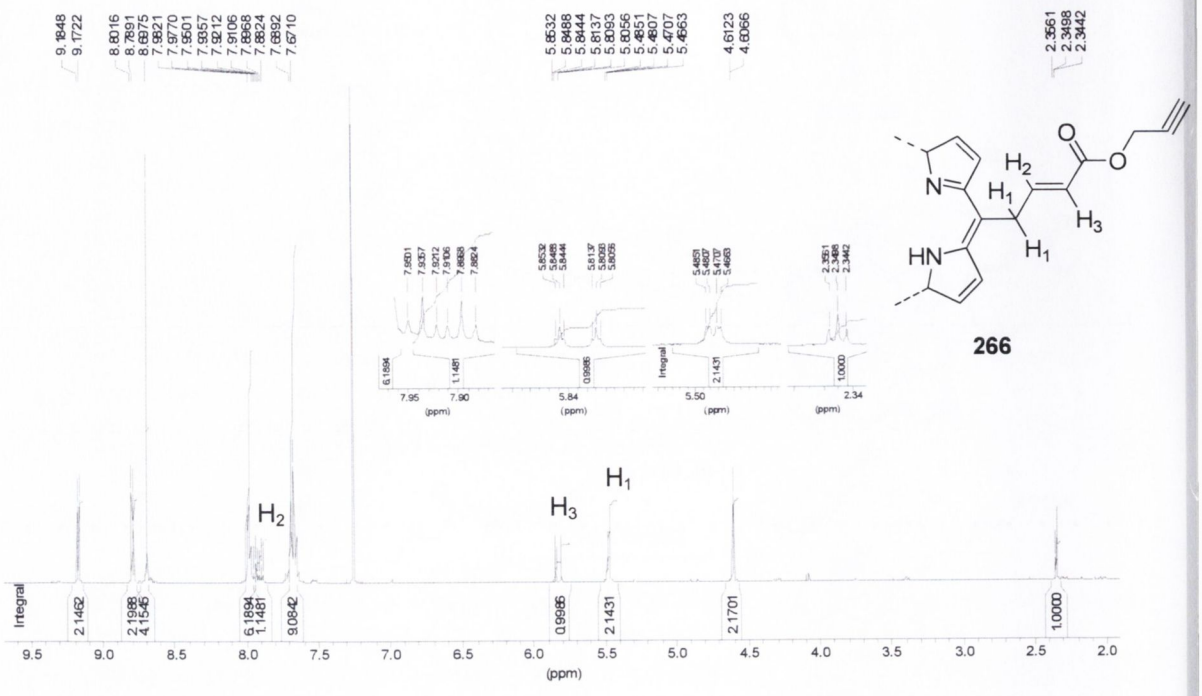


Figure 5.2 ^{1}H-NMR spectrum of porphyrin **266** in $CDCl_3$.

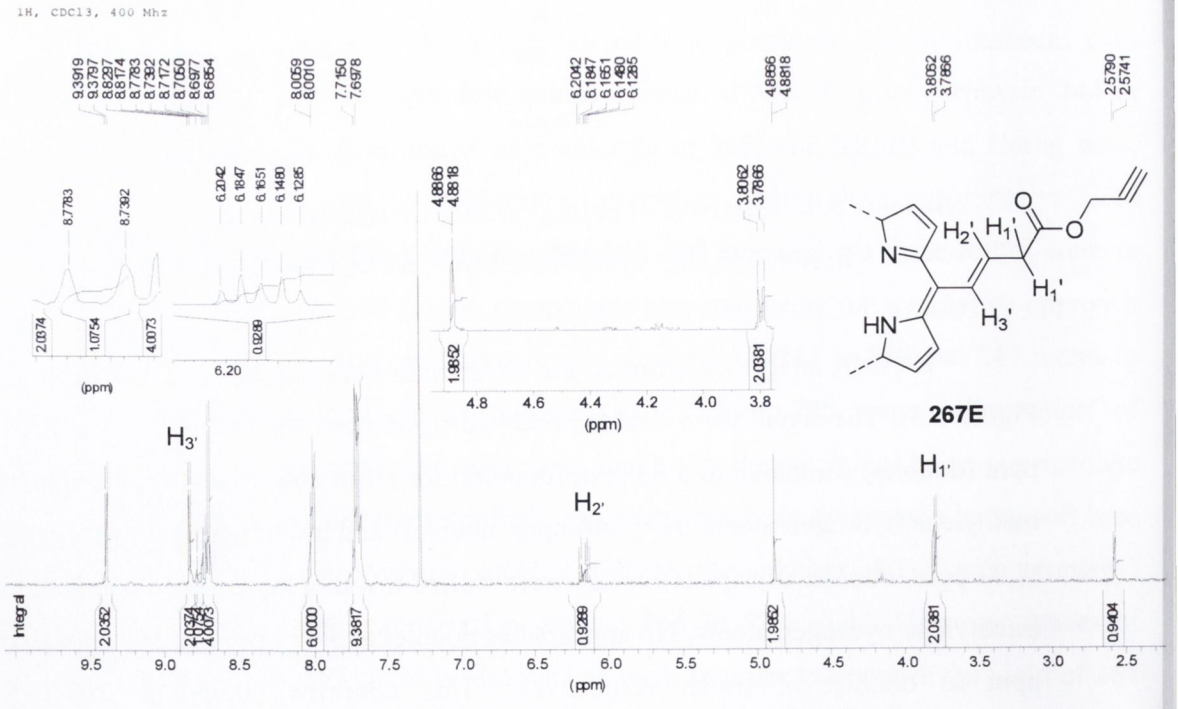
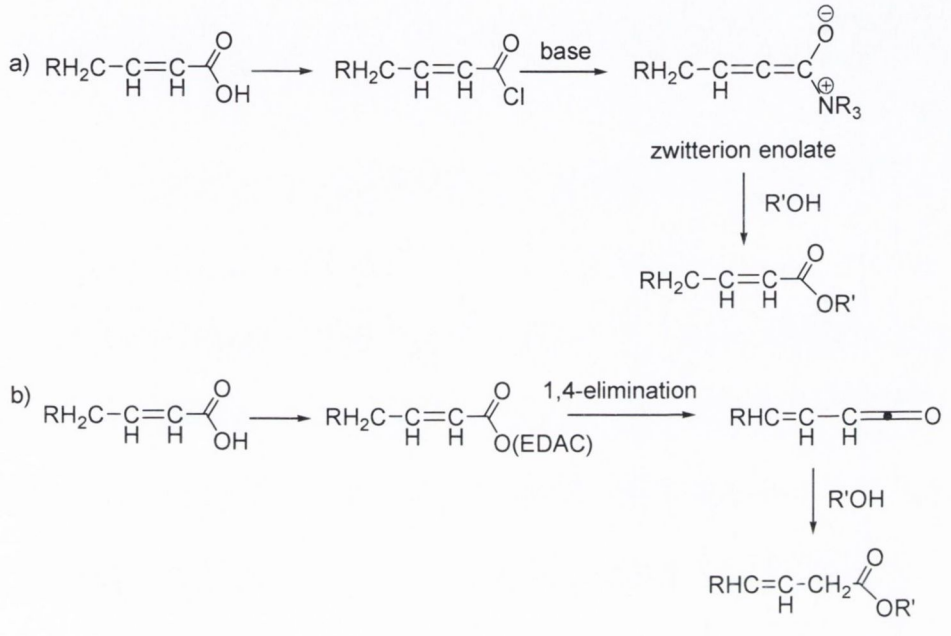


Figure 5.3 ^{1}H-NMR spectrum of porphyrin **277E** in $CDCl_3$.

The formation of both regioisomers **266** and **267** under different reaction conditions suggests a competition[245] of the two reaction pathways involving substitution and elimination processes. The vinyl ketene is the result of an elimination reaction causing a migration of the double bond and formation of **267**. The observation of the *E/Z* mixture **267** suggests a pathway *via* a vinyl ketene intermediate where the original stereochemistry is lost. In contrast, the intermediate of the substitution reaction leading to the esterification product **266** is most likely a zwitterionic dienolate (Scheme 5.10).

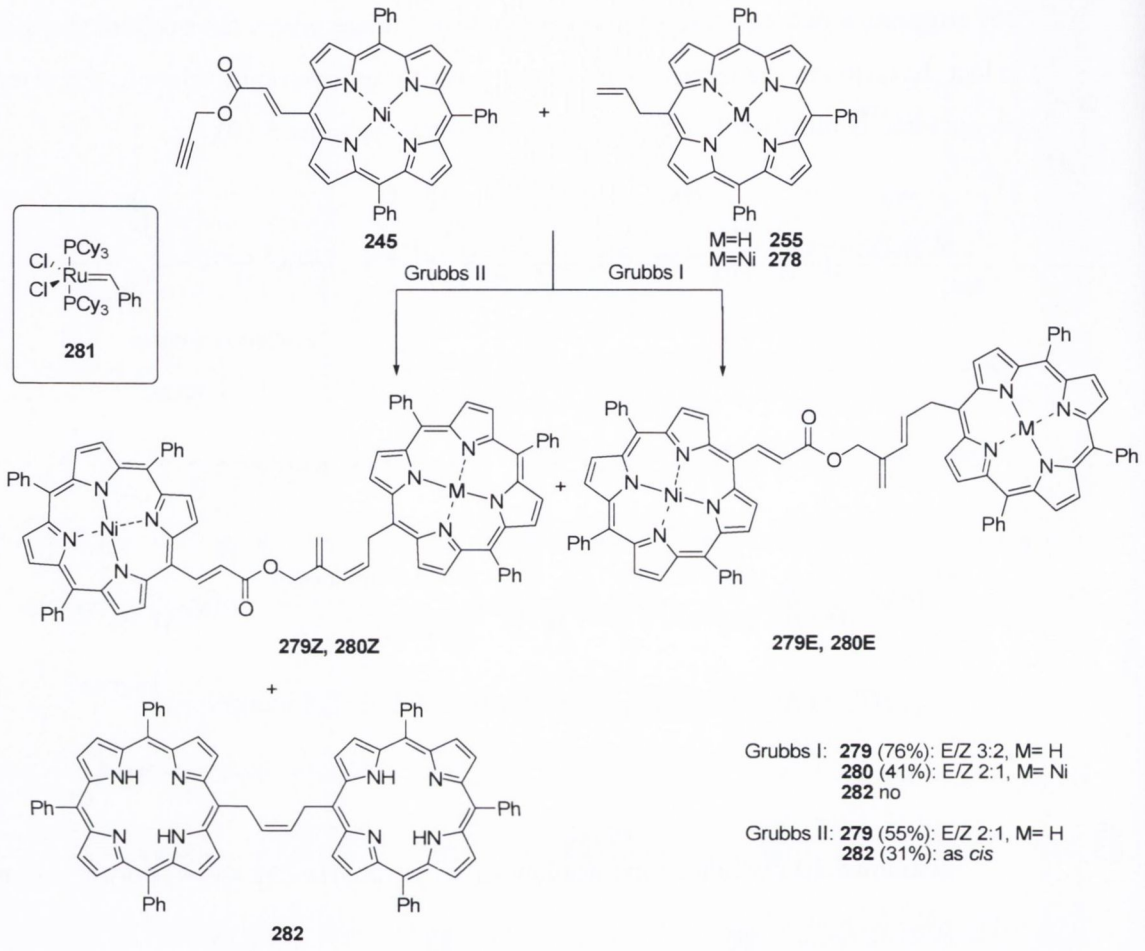


Scheme 5.10 Postulated mechanism for a) porphyrin **266** and b) porphyrin **267**.

5.4 C-C Coupling reactions

Enyne metathesis is a unique and interesting transformation involving the reaction between an alkene and an alkyne partner.[249] Therefore, we used the enyne metathesis starting from propargyl ester porphyrin **245** and allyl porphyrins **255** and **278** to prepare synthetically useful 1,3-disubstituted butadiene porphyrin derivatives **279** and **280** (Scheme 5.11). Such compounds offer themselves towards structural elaboration *via* Diels–Alder and other cycloaddition reactions. We next compared the reactivity and chemoselectivity of both generations of Grubbs catalysts I **281** and II **227**. Enyne metathesis of the porphyrin **245** and the allyl porphyrin **255** resulted only in the formation of **279**, with *E/Z* = 3:2 in a good yield of 76%. Although the selectivity of the reaction of allyl porphyrinatonickel **278** and **245** using the same catalyst was slightly improved to give *E/Z* = 2:1, compound **280** was isolated in 41% yield. In the case of Grubbs II catalyst, a

competing CM homodimerization of the allyl porphyrin **255** took place, resulting in a mixture of alkene **282** (31%, *cis* isomer) and the 1,3-disubstituted butadiene derivatives **279** (55%).



Scheme 5.11 Enyne metathesis of porphyrin **245** and allyl porphyrins **255**, **278**. Synthesis of 1,3-disubstituted butadienes **279** and **280**.

The assignment of the stereochemistry of the 1,3-disubstituted butadienes **279** and **280** was based on NMR analyses involving 1D NOE, 2D-ROESY, HSQC, and HMBC experiments (see experimental part). For the major stereomer in the **280*E/Z*** mixture, ROESY experiments showed a reliable correlation between H_x and H_b and between H_y and H_z. A strong response was found for each of the H_x–H_b and H_y–H_z pairs in 1D NOE as well. ROESY analysis of the minor isomer of **280** showed the appropriate correlations between H_a and H_z and between H_y and H_b. The stereochemistry of the minor product in **280** could be assigned as *Z* and the major one as the *E*-isomer as illustrated in Figure 5.4.

Similar results were obtained for the porphyrin **279**. Thus, based on these analytical data, the major stereomer has *E* stereochemistry in both mixtures of **279** and **280**.

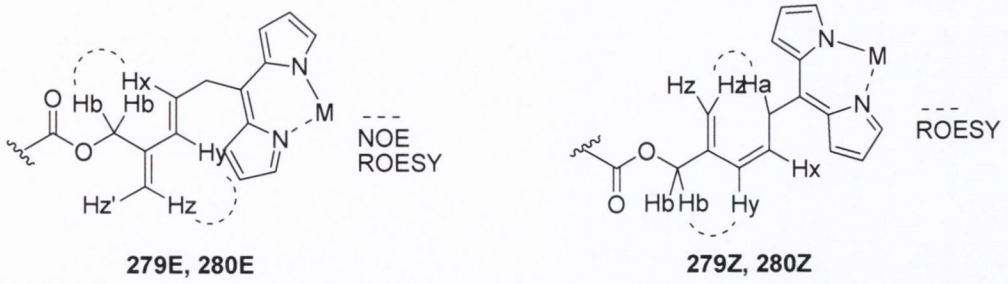


Figure 5.4. Assignments of the stereochemistry for 1,3-disubstituted butadienes **279** and **280**.

5.5 Conclusions

Based on acrylic porphyrins and their homologues, a new synthetic approach has been developed for multifunctional porphyrins. Our studies show that the acyl chlorides **242** and **243** generated *in situ* can be easily converted into the corresponding acyl derivatives using simple nucleophiles. The reaction of **242** with ethyl diazoacetate *via* the unstable phosphazine **250** represents a convenient entry into the important class of *β*-keto esters **252**. It was shown that the phosphazine **242** was self-converted into the *β*-keto ester, possibly via intermediate **251**. Interestingly, compound **252** exists only as the enol form in halogenated solvents, and its stereochemistry was assigned as the 2*E*,4*E*-configuration. The next homologues **265** of the acrylic porphyrins can undergo rearrangement *via* vinyl ketenes under basic conditions to yield both regioisomers **266** and **267**. Variation of the reaction conditions regioselectively provides access to either a rearrangement (**267**, 81%) or an esterification product (**266**, 57%). Finally, enyne metathesis of the novel propargyl esters with allyl porphyrins provided an easy access to 1,3-disubstituted butadienes **279** and **280** in up to 76% yield. Porphyrin arrays can be constructed using cycloaddition reactions based on the dimeric porphyrins **279**–**280**, **282** presented. The syntheses described provide access to novel porphyrins and expand the repertoire of porphyrin based reagents to be utilised for the further functionalisation of the porphyrin periphery. They can serve as versatile building blocks for the facile transformation into porphyrin bioconjugates such as amino and hydroxy acid derivatives, especially, for medicinal applications.

EXPERIMENTAL

6.1 Instrumentations and general methods

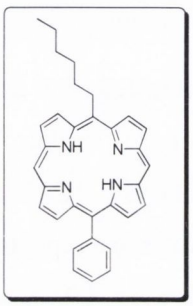
All chemicals used were of analytical grade and were purchased from Aldrich Co. unless stated otherwise. Dichloromethane was dried over phosphorus pentoxide followed by distillation; THF was dried over sodium followed by distillation. All condensation reactions were performed under an argon atmosphere with the reaction flask shielded from ambient light. Melting points were acquired on Stuart SMP10 melting point apparatus and are uncorrected. Silica gel 60 (Merck or Machery & Nagel) was used for column chromatography. Flash chromatography was carried out using Fluka Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 plates (precoated sheets, 0.2 mm thick, with and without fluorescence indicator F_{254}).

NMR spectra were recorded on a Bruker DPX 400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C-NMR) and/or Bruker AV 600 (600.13 MHz for ^{1}H-NMR and 150.90 MHz for ^{13}C-NMR). NOE, ROESY, HMBC and HSQC NMR spectra were recorded using Bruker AV 600. Chemical shifts are reported in ppm referenced to tetramethylsilane set at 0.00 ppm unless stated otherwise. UV–vis measurements were performed on Shimadzu MultiSpec-1501 spectrometer using dichloromethane as solvent. Mass spectra were recorded using a Varian MAT 711 or MAT 112 S mass spectrometer using the EI technique with direct insertion probe and excitation energy of 80 eV. HRMS spectra were measured on Micromass/ Waters Corp. USA LCT time-of-flight spectrometer equipped with ES source and MALDI Q-TOF spectrometer with α–cyano-4-hydroxycinnamic acid (CHCA) as the matrix.

6.2 Synthesis of porphyrin precursors

Dipyrromethane **29** and **105** were prepared as reported in the literature.[34] Spectroscopic data for *meso*-disubstituted porphyrins **99**, **100**, **101**, **102** and **103** were in accordance to the literature[67e,67f,250,251,252] and were prepared using mixed condensation reactions. Porphyrin **107** formed as the second product from mixed condensation reaction was reported previously.[253] RLi reaction conditions were used to prepare porphyrins **108**, **109** and **110** as reported in literature.[67a,67e] Dithianyl porphyrin **112** was prepared according to method developed by Senge *et al.*[158]

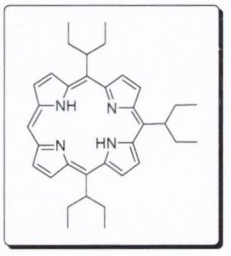
5-Hexyl-15-phenylporphyrin (104)



Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **209** (1.2 g, 8.2 mmol), benzaldehyde (0.46 mL, 4.6 mmol), and heptanal (0.64 mL, 4.6 mmol) were added. The flask was shielded from ambient light and then 140 mL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 hours at room temperature. After this time, 2.77 g (12.2 mmol) of DDQ, suspended in 100 mL of dry dichloromethane were added, and the mixture was stirred for 1 hour. Then, 6 mL of triethylamine were added and the reaction mixture was concentrated *in vacuo* to about 200 mL. The reaction mixture was filtered through 500 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrins were separated by column chromatography on silica using dichloromethane/hexane (1:1, v/v) as eluent. The first fraction was 5,15-dihexylporphyrin **101** (45 mg, 0.09 mmol, 4%), the second fraction, 5-hexyl-15-phenylporphyrin **104** (189 mg, 0.40 mmol, 14%) and the third fraction, 5,15-diphenylporphyrin **99** (65 mg, 0.14 mmol, 6%). Porphyrin **104** were redissolved/suspended in dichloromethane and then layered with a 2–3-fold excess of methanol. After 24 h, the solution was filtered through D3 frit leaving behind purple crystals. Title compound: mp >310 °C ; R_f=0.86 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^1H NMR (400 MHz, $CDCl_3$): δ= –3.08 (s, 2H, N-*H*), 1.05 (t,

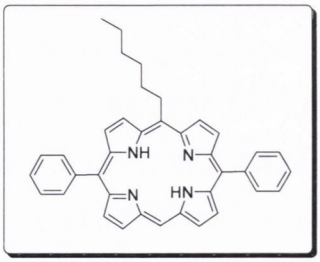
J=7.6 Hz, 3H, -C*H*$_3$), 1.48 (m, 2H, -C*H*$_2$), 1.51 (m, 2H, -C*H*$_2$), 1.86 (m, 2H, -C*H*$_2$), 2.58 (m, 2H, -C*H*$_2$), 4.96 (t, *J*=8.0 Hz, 2H, -C*H*$_2$), 7.89 (m, 3H, phenyl-*H*), 8.33 (m, 2H, phenyl-*H*), 9.12 (d, *J*=4.5 Hz, 2H, β-*H*), 9.38 (d, *J*=4.5 Hz, 4H, β-*H*), 9.56 (d, *J*=7.6 Hz, 2H, β-*H*), 10.19 ppm (s, 2H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.8, 22.4, 29.9, 31.5, 34.3, 38.4, 104.3, 117.9, 126.6, 127.5, 130.3, 131.3, 134.5, 141.0, 144.3, 147.0 ppm; UV/ vis (CH_2Cl_2): λ_{max} (log ε)= 408 (4.55), 427 (4.74), 503 (2.90), 539 (3.13), 573 (3.39), 620 nm (3.33); HRMS (ES+) [$C_{32}H_{30}N_4$]: calcd for $[M+H]^+$ 471.2549, found 471.2553.

5,10,15-Tris(1-ethylpropyl)porphyrin (106)



The reaction was performed using the same conditions as for the preparation of **104** using dipyrromethane **29** (1.2 g, 8.2 mmol), 5-(1-ethylpropyl)dipyrromethane **105** (1.2 g, 4.1 mmol) and 2-ethylbutyraldehyde (2.02 mL, 16.4 mmol). The first fraction was 5,15-bis(1-ethylpropyl)porphyrin **102** (152 mg, 0.34 mmol, 14%), the second fraction, 5,10,15-tris(1-ethylpropyl)porphyrin **106** (213 mg, 0.41 mmol, 20%) and the third fraction, 5,10,15,20-tetrakis(1-ethylpropyl)porphyrin **107** (97 mg, 0.16 mmol, 8%). Title compound: mp >310 °C; R_f=0.49 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ= –2.67 (s, 2H, N-*H*), 0.99 (m, 18H, -CH(CH_2CH_3)$_2$), 2.84 (m, 12H, -CH(CH_2CH_3)$_2$), 5.02 (m, 2H, -C*H*(CH_2CH_3)$_2$), 5.19 (m, 1H, -C*H*$_2$(CH_2CH_3)$_2$), 9.31 (d, *J*=4.7 Hz, 2H, β-*H*), 9.61 (s, 4H, β-*H*), 9.70 (s, 2H, β-*H*), 9.98 ppm (s, 1H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.0, 34.6, 49.7, 102.5, 127.9, 128.5, 129.2, 130.8 ppm; UV/ vis (CH_2Cl_2): λ_{max} (log ε)= 412 (4.77), 433 (4.38), 512 (3.44), 546 (3.18), 588 (3.28), 642 nm (3.29); HRMS (ES+) [$C_{35}H_{38}N_4$]: calcd for $[M+H]^+$ 521.3644, found 521.3645.

5-Hexyl-10,20-diphenylporphyrin (108)



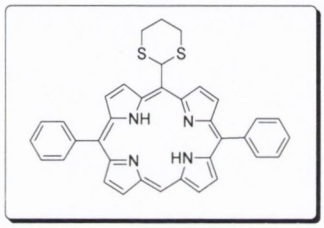
5,15-Diphenylporphyrin **99** (220 mg, 0.47 mmol) was dissolved in 40 mL of dry THF and cooled to -78 °C. *n*-Hexyllithium (1.7 mL of a 2.5 M solution in hexane, 3.4 mmol) was subsequently added dropwise under an argon atmosphere. The colour of the mixture changed from deep purple to brown within 30 minutes. The reaction mixture was stirred for 5 hours and monitored by TLC. Water (2 mL) was added for hydrolysis. After stirring of the mixture for 20 minutes, a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 1.6 mmol) was added and the reaction mixture was stirred for another 1 hour at room temperature. The mixture was filtered through silica gel and the organic solvent was removed under vacuum. Final purification was achieved by column chromatography using silica gel and ethyl acetate/*n*-hexane (1:7, v/v) as eluent; yielding the title compound **108** (175 mg, 0.32 mmol, 67%) as a purple solid, mp >310 °C; R_f=0.61 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.02 (s, 2H, N*H*), 0.90 (t, *J*=7.6 Hz, 3H, -CH_3), 1.38 (m, 2H, -CH_2), 1.54 (m, 2H, -CH_2), 1.80 (m, 2H, -CH_2), 2.53 (m, 2H, -CH_2), 5.06 (t, *J*=8.2 Hz, 2H, -CH_2), 7.78 (m, 6H, phenyl-*H*), 8.23 (d, *J*=8.2 Hz, 4H, phenyl-*H*), 8.95 (m, 4H, β-*H*), 9.25 (d, *J*=5.0 Hz, 2H, β-*H*), 9.54 (d, *J*=5.0 Hz, 2H, β-*H*), 10.08 pm (s, 1H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 16.4, 22.4, 28.0, 29.9, 31.5, 39.8, 119.7, 122.1, 127.2, 128.2, 134.2, 151.3 ppm; UV/ vis (CH_2Cl_2): λ_{max} (log ε)= 425 (4.17), 503 (3.74), 526 (3.68), 573 (3.69), 620 nm (3.69); HRMS (ES+) [$C_{36}H_{46}N_4$]: calcd for $[M+H]^+$ 546.2783, found 546.2771.

6.3 Synthesis of dithianyl porphyrins and their derivatives.

General Procedure: A dried out, septum-equipped Schlenk-flask under argon was charged with 1,3-dithiane (1.16, 9.64 mmol). The flask was evacuated for 30 min with an oil pump and 25 mL of freshly distilled THF was added. The solution was cooled to –40 °C and butyllithium (3.84 mL of a 2.5 M solution, 9.6 mmol) was added drop-wise via a syringe through the septum. The reaction mixture was stirred for 2 h at –30 to –40 °C. The solution of the organometallic compound was cooled to –78 °C and mixed with a

suspension (–78 °C) of 0.45 mmol porphyrin in 20 mL of absolute THF. After transfer of the porphyrin suspension, *N,N,N,N*-tetramethylethylenediamine (0.25 mL, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 1 min the cold bath was removed and the reaction mixture was stirred for 15 min. Water (6 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 min at room temperature, followed by addition of 10 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF) resulting in a colour change to purple. Stirring was continued for 15 min followed by filtration of the reaction mixture through 200 mL silica, washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and washed with *n*-hexane (2 × 10 mL). The residue was purified by column chromatography on silica gel in dichloromethane/*n*-hexane (3:1, v/v).

5-(1,3-Dithian-2-yl)-10,20-diphenylporphyrin (111)



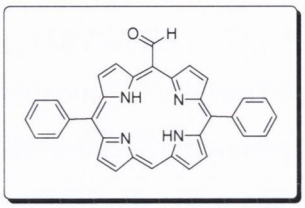
Prepared from porphyrin **99**: Yield: 0.11 g (0.207 mmol, 45%) of purple crystals, mp 295 °C; R_f=0.23 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.03 (s, 2H, N*H*), 2.53 (m, 2H, -CH_2), 3.31 (m, 2H, S-CH_2), 3.63 (m, 2H, S-CH_2), 7.78 (m, 6H, phenyl-*H*), 7.87 (s, 1H, -C*H*), 8.21 (m, 4H, phenyl-*H*), 8.92 (m, 4H, β-*H*), 9.25 (d, J = 4.6 Hz, 2H, β-*H*), 9.71 (s, br., 1H, β-*H*), 10.12 (s, 1H, meso-*H*), 10.71 ppm (s, br., 1H, β-*H*); ^{13}C NMR (600 MHz, $CDCl_3$): δ= 26.21, 35.87, 54.51, 105.74, 114.53, 126.74, 127.77, 132.0, 134.60, 141.90 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)= 416 (5.49), 512 (4.02), 544 (3.23), 586 (3.45), 640 nm (2.72); MS (EI, 80 eV), *m/z* (%): 580 (100) [M^+], 519 (33) [M^+–C_2H_5S], 506 (62) [M^+–C_3H_6S], 476 (86) [M^+–$C_3H_4S_2$], 462 (17) [M^+–$C_4H_6S_2$], 290 (8) [M^{2+}]; HRMS (ES+) [$C_{36}H_{28}N_4S_2$]: calcd for [M] 580.1755, found 580.1772.

Deprotection of the Dithian-2-ylporphyrins

To a solution of dithian-2-ylporphyrin (0.06 mmol) in dichloromethane (60 mL) DDQ (500 mg, 2.20 mmol) and BF_3•Et_2O (0.5 mL, 9.95 mmol) were added and the colour of the red solution changed over yellow to green. After stirring for 45 min the reaction was quenched by the addition of aqueous sodium hydrogen carbonate. The organic phase was washed

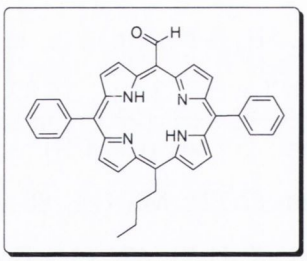
several times with a saturated solution of sodium hydrogen carbonate, followed by drying over anhydrous sodium sulfate and evaporation of the solvent in vacuum. After filtration through silica gel and recrystallisation from dichloromethane/methanol the pure product could be obtained.

5-Formyl-10,20-diphenylporphyrin (115)



Prepared from porphyrin **111**: Yield: 12 mg (0.03 mmol, 39%) of purple crystals: mp > 310 °C; R_f=0.53 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= –2.47 (s, 2H, N*H*), 7.79 (m, 6H, phenyl-*H*), 8.18 (dd, 4H, *J* = 6.0 Hz, *J* = 1.5 Hz, phenyl-*H*), 8.87 (d, 2H, *J* = 4.5 Hz, β-*H*), 9.04 (d, 2H, *J* = 4.9 Hz, β-*H*), 9.27 (d, 2H, *J* = 4.5 Hz, β-*H*), 10.07 (br. s , 2H, β-*H*), 10.25 (s, 1H, meso-*H*), 12.58 ppm (s, 1H, C*H*O); ^{13}C NMR (600 MHz, $CDCl_3$): δ= 108.1, 109.9, 122.1, 124.9, 126.9, 127.8, 128.1, 128.6, 130.2, 131.2, 133.9, 134.4, 141.2, 195.2 ppm; UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 41 (5.49), 508 (3.95), 561 (3.47), 581 (3.56), 647 nm (3.30); MS (80 eV): *m/z* (%) = 490 (23) $[M]^{\bullet+}$, 462 (6) $[M^+-CO]$, 245 (16) $[M]^{2+}$; HRMS (ES+) $[C_{33}H_{22}N_4O]$: calcd for $[M+H]^+$ 491.1872, found 491.1885.

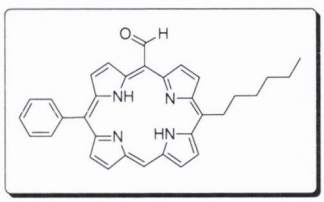
5-Formyl-15-pentyl-10,20-diphenylporphyrin (116)



1,3-Dithiane (0.58 g, 4.82 mmol) was placed in a dried, septum-equipped Schlenk flask under argon. The flask was evacuated for 30 minutes, followed by introducing argon and charged with 25 ml of freshly distilled THF. The solution was cooled to -40 °C and *n*-butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added dropwise via a syringe through the septum. The reaction mixture was stirred for 30-40 minutes at -30 to -40 °C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin **99** (100 mg, 0.22 mmol) in 20 mL of THF.

After transfer of the porphyrin suspension, *N,N,N',N'*-tetramethylethylendiamine (0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. The solution was treated with 0.7 mL (0.42 mmol) of *n*-pentyl iodide and stirred for 2 days. Water (3 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was allowed to continue for 15 minutes followed by filtration of the mixture through 200 mL silica with washing with dichloromethane. The eluted porphyrins were evaporated to dryness and further purified by column chromatography on silica gel using dichloromethane/*n*-hexane (2:1, v/v) as eluent yielding the compound (13.55 mg, 0.02 mmol, 11%) as purple solid: mp >310 °C; R_f=0.87 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −1.81 (s, 2H, N*H*), 0.98 (t, 3H, J = 7.6 Hz, -CH_3), 1.55 (m, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 2.50 (m, 2H, -CH_2), 4.88 (t, J = 8.2 Hz, 2H, -CH_2), 7.79 (m, 6H, phenyl-*H*), 8.16 (d, 4H, J = 7.0 Hz, phenyl-*H*), 8.75 (d, 2H, J = 4.7 Hz, β-*H*), 8.90 (d, 2H, J = 4.7 Hz, β-*H*), 9.37 (d, 2H, J = 4.7 Hz, β-*H*), 9.94 (d, 2H, J = 5.2 Hz, β-*H*), 12.41 ppm (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.3, 29.3, 31.5, 38.0, 126.3, 127.4, 129.8, 133.7, 141.3, 194.0 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 422 (4.91), 441 (4.99), 523 (4.12), 563 (4.13), 592 (4.13), 652 nm (4.15); HRMS (ES+) [$C_{38}H_{33}N_4O$]: calcd for $[M+H]^+$ 561.2665, found 561.2654.

5-Formyl-10-hexyl-20-phenylporphyrin (117)

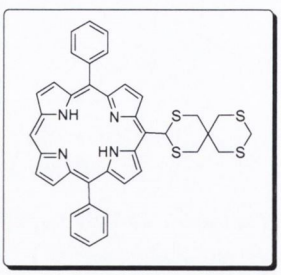


1,3-Dithiane (0.58 g, 4.82 mmol) was placed in a dried, septum-equipped Schlenk flask under argon. The flask was evacuated for 30 minutes, followed by introducing argon and charged with 25 ml of freshly distilled THF. The solution was cooled to -40 °C and *n*-butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added dropwise via a syringe through the septum. The reaction mixture was stirred for 30-40 minutes at -30 to -40° C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin **99** (100 mg, 0.22 mmol) in 20 mL of THF.

After transfer of the porphyrin suspension, *N,N,N',N'*-tetramethylethylendiamine (0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. The solution was treated with 0.7 mL (0.42 mmol) of *n*-pentyl iodide and stirred for 2 days. Water (3 mL) was added via a syringe resulting in an immediate colour change to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was allowed to continue for 15 minutes followed by filtration of the mixture through 200 mL silica with washing with dichloromethane. The eluted porphyrins were evaporated to dryness and further purified by column chromatography on silica gel using dichloromethane/*n*-hexane (2:1, v/v) as eluent yielding the compound (13.55 mg, 0.02 mmol, 11 %) as purple solid: mp >310 °C; R_f=0.87 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ= –1.81 (s, 2H, N*H*), 0.98 (t, 3H, J = 7.6 Hz, -CH_3), 1.55 (m, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 2.50 (m, 2H, -CH_2), 4.88 (t, J = 8.2 Hz, 2H, -CH_2), 7.79 (m, 6H, phenyl-*H*), 8.16 (d, 4H, J = 7.0 Hz, phenyl-*H*), 8.75 (d, 2H, J = 4.7 Hz, β-*H*), 8.90 (d, 2H, J = 4.7 Hz, β-*H*), 9.37 (d, 2H, J = 4.7 Hz, β-*H*), 9.94 (d, 2H, J = 5.2 Hz, β-*H*), 12.41 ppm (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.3, 29.3, 31.5, 38.0, 126.3, 127.4, 129.8, 133.7, 141.3, 194.0 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 422 (4.91), 441 (4.99), 523 (4.12), 563 (4.13), 592 (4.13), 652 nm (4.15); HRMS (ES+) [$C_{38}H_{33}N_4O$]: calcd for $[M+H]^+$ 561.2665, found 561.2654.

6.4 Synthesis of spirobisdithianyl-porphyrins

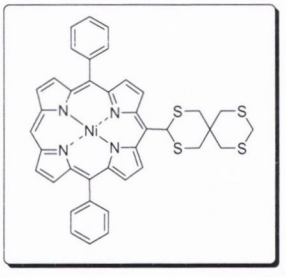
5,15-Diphenyl-10-(spirobis-1,3-dithian-2-yl)porphyrin (124)



Spirobisdithiane (1.08 g, 4.84 mmol) was dried *in vacuo* in a septum equipped Schlenk flask for 30 minutes. Dry THF (20 ml) was then added under argon and the suspension cooled to –40 °C. *n*-Butyllithium (1.92 mL of a 2.5 M solution, 4.84 mmol) was added drop-wise via a syringe through the septum and the reaction mixture was stirred for 2 hours

at –25 °C. The solution of the organometallic compound was cooled to –78 °C and mixed with a suspension (–30 °C) of 5,15-diphenylporphyrin **99** (100 mg, 0.22 mmol) in 20 mL of dry THF. After transfer of the porphyrin suspension, *N,N,N',N'*-tetramethylethylendiamine (0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes, the cold bath was removed and the reaction mixture was stirred for one hour at room temperature. Upon addition of 3 mL water, the reaction mixture changed its colour to dark-green. The mixture was stirred for 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change from green to purple. Stirring was continued for a further 15 minutes and the organic solvent was removed under reduced pressure. Final purification was achieved by column chromatography in the dark and eluting with ethyl acetate/*n*-hexane (1:20, v/v) to yield the title compound (33 mg, 0.05 mmol, 22 %) as a purple solid: mp >310 °C; R_f=0.76 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.04 (s, 2H, N*H*), 3.38 (d, 2H, J = 14.7 Hz, S-CH_2-S), 3.65 (m, 8H, S-CH_2), 7.71 (s, 1H, S-C*H*-S), 7.76 (m, 6H, phenyl-*H*), 8.18 (d, 4H, J = 6.4 Hz, phenyl-*H*), 8.92 (dd, 4H, J = 4.7 Hz, β-*H*), 9.25 (d, 2H, J = 4.7 Hz, β-*H*), 9.53 (s, 1H, β-*H*), 10.13 (s, 1H, meso-*H*), 10.55 ppm (s, 1H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.0, 31.8, 35.1, 41.5, 55.0, 105.5, 112.7, 126.3, 127.4, 134.2, 141.4 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 415(4.42), 511 (3.54), 549 (3.39), 586 (3.42), 638 nm (3.34); HRMS (ES+) [$C_{39}H_{32}N_4S_4$]: calcd for $[M+H]^+$ 685.1588, found 685.1578.

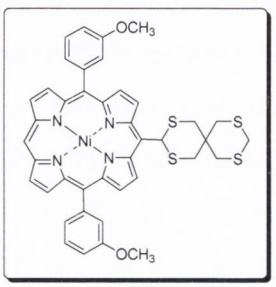
[5,15-Diphenyl-10-(spirobis-1,3-dithian-2-yl)porphyrinato]nickel(II) (134)



The reaction was performed using the same conditions as given for free base **124** using spirobisdithiane (0.89 g, 4.01 mmol), *n*-butyllithium (1.59 mL of a 2.5 M solution, 4.0 mmol) and [5,15-diphenylporphyrinato]nickel(II) **125** (100 mg, 0.18 mmol). The mixture was purified by column chromatography with dichloromethane/*n*-hexane (1:1, v/v) as eluent and yielded the title compound (45 mg, 0.06 mmol, 33 %) as a red solid: mp >310 °C; R_f=0.82 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 3.31

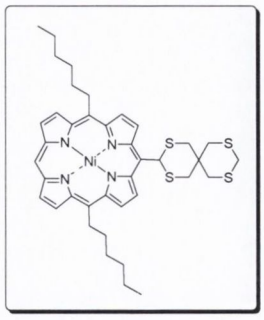
(d, 2H, J = 14.0 Hz, S-CH_2-S), 3.67 (m, 8H, S-CH_2), 7.08 (s, 1H, S-CH-S), 7.68 (m, 6H, phenyl-H), 7.95 (d, 4H, J = 6.4 Hz, phenyl-H), 8.77 (m, 4H, J = 4.7 Hz, β-H), 9.02 (d, 2H, J = 4.7 Hz, β-H), 9.66 (s, 1H, meso-H), 9.77 ppm (s, 2H, β-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.3, 27.4, 29.3, 36.7, 52.8, 104.8, 126.7, 127.4, 132.1, 132.4, 133.2, 140.0, 141.5, 141.8, 142.2 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 413 (5.52), 530 (4.34), 569 nm (3.84).

[5,15-Bis(3-methoxyphenyl)-10-(spirobis-1,3-dithian-2-yl)porphyrinato]nickel(II) (135)



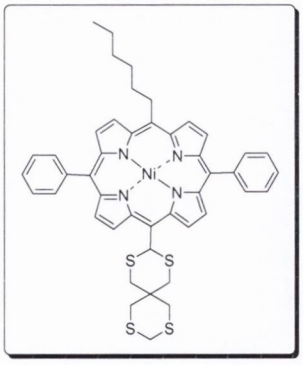
The reaction was performed using the same conditions as given for the free base **124** using spirobisdithiane (0.85 g, 3.81 mmol), n-butyllithium (1.51 mL of a 2.5 M solution, 3.81 mmol) and [5,15-bis(3-methoxyphenyl)porphyrinato]nickel(II) **126** (100 mg, 0.17 mmol). The mixture was purified by column chromatography with dichloromethane/ n-hexane (1:1, v/v) as eluent and yielded the title compound (47 mg, 0.06 mmol, 34 %) as a red solid: mp >310 °C; R_f=0.45 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 3.33 (d, 2H, J = 14.0 Hz, S-CH_2-S), 3.74 (m, 8H, S-CH_2), 3.92 (s, 6H, -OCH_3), 7.09 (s, 1H, S-CH-S), 7.57 (m, 8H, phenyl-H), 8.82 (m, 4H, β-H), 9.03 (d, 2H, J = 4.1 Hz, β-H), 9.67 (s, 1H, meso-H), 9.77 ppm (s, 2H, β-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.3, 29.3, 31.6, 38.1, 55.0, 104.8, 113.2, 119.1, 126.2, 127.4, 130.5, 132.1, 140.5, 141.3, 141.3, 141.9, 157.7 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 414 (4.96), 530 (3.78), 567 nm (3.48).

[5,15-Dihexyl-10-(spirobis-1,3-dithian-2-yl)porphyrinato]nickel(II) (136)



The reaction was performed using the same conditions as given for free base **124** using spirobisdithiane (0.92 g, 4.11 mmol), *n*-butyllithium (1.63 mL of a 2.5 M solution, 4.11 mmol) and [5,15-dihexylporphyrinato]nickel(II) **127** (100 mg, 0.19 mmol). The mixture was purified by column chromatography with dichloromethane/ *n*-hexane (1:1, v/v) as eluent and yielded the title compound (28 mg, 0.02 mmol, 19 %) as a red solid: mp >310 °C; R_f=0.67 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 0.91 (t, 3H, J = 7.0 Hz, -C*H*$_3$), 1.32 (m, 2H, -C*H*$_2$), 1.34 (m, 2H, -C*H*$_2$), 1.58 (m, 2H, -C*H*$_2$), 2.27 (m, 2H, -C*H*$_2$), 3.26 (d, 2H, J = 14.0 Hz, S-C*H*$_2$-S), 4.49 (t, 2H, J = 7.6 Hz, -C*H*$_2$), 4.80 (m, 8H, S-C*H*$_2$), 6.95 (s, 1H, S-C*H*-S), 9.03 (d, 2H, J = 4.7 Hz, β-*H*), 9.26 (dd, 4H, J = 5.28 Hz, β-*H*), 9.45 (s, 1H, meso-*H*), 9.75 ppm (s, 2H, β-*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 13.8, 22.3, 23.8, 24.3, 29.7, 31.3, 33.6, 35.1, 37.1, 38.8, 41.5, 43.4, 53.1, 103.8, 117.5, 120.9, 129.4, 129.7, 132.2, 139.3, 140.6, 141.0, 142.0 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 416 (4.98), 535 (3.70), 568 nm (3.48).

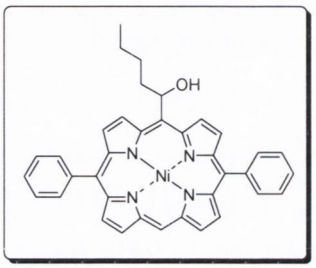
[5-Hexyl-10,20-diphenyl-15-(spirobis-1,3-dithian-2-yl)-porphyrinato]nickel(II) (137)



The reaction was performed using the same conditions as given for free base **124** using spirobisdithiane (0.82 g, 3.65 mmol), *n*-butyllithium (1.45 mL of a 2.5 M solution, 3.65 mmol) and [5-hexyl-10,20-diphenylporphyrinato]nickel(II) **135** (100 mg, 0.17 mmol). The mixture was purified by column chromatography with dichloromethane/*n*-hexane (2:1, v/v) as eluent and yielded the title compound (54 mg, 0.06 mmol, 40 %) as a red solid: mp

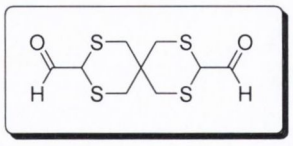
>310 °C; R_f=0.78 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 0.85 (t, 3H, J = 7.6 Hz, -CH_3), 1.36 (m, 2H, -CH_2), 1.55 (m, 2H, -CH_2), 2.39 (m, 2H, -CH_2), 2.61 (m, 2H, -CH_2), 3.14 (d, 2H, J = 14.6 Hz, S-CH_2-S), 3.59 (m, 8H, S-CH_2), 4.46 (t, 2H, J = 7.6 Hz, -CH_2), 6.88 (s, 1H, S-CH-S), 7.65 (m, 6H, phenyl-H), 7.91 (d, 4H, J = 6.4 Hz, phenyl-H), 8.67 (dd, 4H, J = 4.7 Hz, β-H), 9.18 (d, 2H, J = 4.7 Hz, β-H), 9.62 ppm (s, 2H, β-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.2, 23.8, 24.3, 29.3, 31.6, 33.6, 37.0, 38.0, 52.9, 109.6, 118.0, 119.6, 126.5, 127.3, 129.6, 132.0, 132.5, 133.1, 139.9, 140.7, 140.8, 141.4, 141.5 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 421 (4.95), 539 (4.01), 577 nm (3.79).

[5-(Hydroxypentyl)-10,20-diphenylporphyrinato]Ni(II) (140)



The reaction was performed using the same conditions as given for free base **124** using spirobisdithiane (0.82 g, 3.65 mmol), *n*-butyllithium (1.45 mL of a 2.5 M solution, 3.65 mmol) and [5-formyl-10,20-diphenylporphyrinato]Ni(II) **139** (100 mg, 0.18 mmol). The mixture was purified by column chromatography with dichloromethane/*n*-hexane (2:1, v/v) as eluent and yielded the title compound (7 mg, 6%) as a red solid: mp >310 °C; R_f=0.85 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.04 (t, 3H, J= 3.5 Hz, -CH_3), 1.41 (s, 1H, -CH-OH), 1.59 (m, 2H, -CH_2), 2.31 (m, 2H, -CH_2), 3.47 (d, J= 5.2 Hz, 1H, -OH), 4.66 (m, 2H, -CH_2), 7.67 (m, 6H, phenyl-H), 8.01 (m, 4H, phenyl-H), 8.44 (d, 1H, J= 4.7 Hz, β-H), 8.81 (d, 3H, J= 4.7 Hz, β-H), 9.05 (d, 2H, J= 5.2 Hz, β-H), 9.35 (m, 2H, β-H), 9.69 ppm (s, 1H, meso-H); ^{13}C NMR (600 MHz, $CDCl_3$): δ= 13.62, 23.01, 29.27, 33.77, 39.28, 103.41, 117.52, 118.80, 126.42, 127.24, 128.95, 131.55, 131.92, 132.11, 133.28, 140.51, 141.59, 142.33 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 421 (4.95), 535 (4.00), 567 nm (3.48).

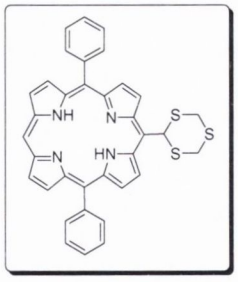
2,8-Diformylspirobisdithiane(141)



Spirobisdithiane **119** (1.00 g, 4.40 mmol) was dried in vacuo in a septum equipped Schlenk flask for 30 minutes. Dry THF (25 ml) was then added under argon and the suspension cooled to -78 °C. *n*-Butyllithium (9.9 mL of a 2.5 M solution, 15.99 mmol) was added drop-wise via a syringe through the septum and the reaction mixture was stirred for 2 hours at -25 °C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-10 °C) of dimethylformamide (10 mL). The solution was stirred for 2 hours at -10 °C and the colour turned to light yellow. The solution was then stored in freezer for overnight. For work-up, the solution was poured into ice and the aqueous phase was extract with hexane. The aqueous phase was then neutralised with 1M HCL solution before extraction with dichloromethane for the second time. The organic phase was dried over $MgSO_4$ and the organic solvent was removed under vacuum. The remaining yellow oil was recrystallised from *n*-hexane:dichloromethane and gave the title compound (0.70 g, 2.49 mmol, 56 %) as a yellow solid; mp 165 °C: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) : δ= 2.86 (s, 4H, -S-CH_2-), 2.94 (s, 4H, -S-CH_2-), 4.03 (s, 2H, -S-C*H*-S-), 9.39 ppm (s, 2H, -C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7, 31.0, 36.1, 46.6, 186.9 ppm.

6.5 Synthesis of trithianyl-porphyrins

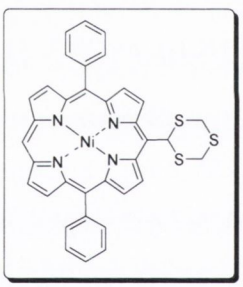
5,15-Diphenyl-10-(1,3,5-trithian-2-yl)porphyrin (142)



n-Butyllithium (1.92 mL of a 2.5 M solution, 4.8 mmol) was added under argon atmosphere to a 100 mL Schlenk flask charged with a solution of 1,3,5-trithiane (0.67, 4.84 mmol) in 20 ml dry THF at -40 °C. Then, the reaction mixture was stirred for 2.5 hours at 20°C. The solution of the organometallic compound was cooled to -78 °C and mixed with a suspension (-30 °C) of 5,15-diphenylporphyrin **99** (100 mg, 0.22 mmol) in 20 mL of THF. After transferring the porphyrin suspension, *N,N,N',N'*-tetramethylethylendiamine

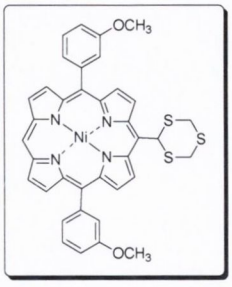
(0.2 ml, 1.6 mmol) was added and the reaction mixture turned dark-brown. After stirring for 15 minutes the cold bath was removed and the reaction mixture was stirred for a further hour at room temperature. Subsequently, water (3 mL) was added for hydrolysis. The mixture was stirred for another 15 minutes at room temperature, followed by addition of 10 mL of a solution of DDQ (0.3 g DDQ in 10 mL THF, ca. 0.75 mmol) resulting in a colour change to purple. Stirring was continued for another 15 minutes and the organic solvent was removed under vacuum. Final purification was achieved by column chromatography under dark conditions and eluting with ethyl acetate/*n*-hexane (1:20, v/v) yielded the title compound (24 mg, 0.04 mmol, 18 %) as a purple solid: mp >310 °C; R_f=0.83 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS): δ= –3.06 (s, 2H, N*H*), 4.36 (d, 2H, J = 14.6 Hz, S-CH_2-S), 5.06 (d, 2H, J = 14.6 Hz, S-CH_2), 7.78 (m, 6H, phenyl-*H*), 7.94 (s, 1H, S-C*H*-S), 8.18 (d, 4H, J = 7.0 Hz, phenyl-*H*), 8.91 (d, 4H, J = 15.2 Hz, β-*H*), 9.25 (s, 2H, β-*H*), 9.52 (s, 1H, β-*H*), 10.13 (s, 1H, meso-*H*), 10.50 ppm (s, 1H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 30.5, 40.9, 57.7, 105.6, 113.3, 126.4, 127.4, 134.2, 141.3 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 415 (4.25), 512 (3.52), 548 (3.42), 587 (3.43), 640 nm(3.39); HRMS (ES+) [$C_{39}H_{32}N_4S_4$]: calcd for $[M+H]^+$ 599.1398, found 599.1411.

[5,15-Diphenyl-10-(1,3,5-trithian-2-yl)porphyrinato]nickel(II) (143)



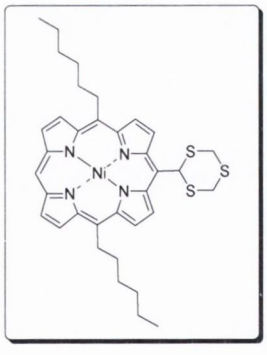
The reaction was performed using the same conditions as for free base **142** using 1,3,5-trithiane (0.55 g, 4.01 mmol), *n*-butyllithium (1.60 mL of a 2.5 M solution, 4.0 mmol) and [5,15-diphenylporphyrinato]nickel(II) **125** (100 mg, 0.18 mmol). Elution with dichloromethane/*n*-hexane (1:1, v/v) yielded the title compound (46 mg, 0.07 mmol, 38 %) as a purple solid: mp > 310 °C; R_f=0.89 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 4.27 (d, J = 15.2 Hz, 2H, S-CH_2-S), 4.92 (d, 2H, J = 14.6 Hz, S-CH_2-S), 7.30 (s, 1H, S-C*H*-S), 7.68 (m, 6H, phenyl-*H*), 7.95 (d, 4H, J = 6.4 Hz, phenyl-*H*), 8.77 (m, 4H, J = 4.7 Hz, β-*H*), 9.02 (d, 2H, J = 4.7 Hz, β-*H*), 9.67 (s, 1H, meso-*H*), 9.72 ppm (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 35.0, 40.3, 56.0, 102.6, 104.9, 126.5, 127.4, 132.1, 132.2, 133.2, 139.9, 141.6, 141.8, 142.3 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 413 (5.73), 530 (4.54), 565 nm (4.11).

5,15-Bis[3-methoxyphenyl-10-(1,3,5-trithian-2-yl)]porphyrinato]nickel(II) (144)



The reaction was performed using the same conditions as for free base **142** using 1,3,5-trithiane (0.53 g, 3.80 mmol), *n*-butyllithium (1.51 mL of a 2.5 M solution, 3.80 mmol) and [5,15-di(3-methoxyphenyl)porphyrinato]nickel(II) **126** (100 mg, 0.17 mmol). Elution with dichloromethane/*n*-hexane (1:1, v/v) yielded the title compound as a red solid (42 mg, 0.06 mmol, 34 %): mp > 310 °C; R_f=0.74 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.92 (s, 6H, -OC*H*$_3$), 4.29 (d, 2H, J = 15.2 Hz, S-C*H*$_2$-S), 4.90 (d, 2H, J = 14.6 Hz, S-C*H*$_2$-S), 7.29 (s, 1H, S-C*H*-S), 7.50 (s, 2H, phenyl-*H*), 7.57 (d, 6H, J = 5.3 Hz, phenyl-*H*), 8.81 (m, 4H, β-*H*), 9.00 (d, 2H, J=4.6 Hz, β-*H*), 9.63 (s, 1H, meso-*H*), 9.74 (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 26.7, 29.3, 30.6, 40.3, 55.0, 55.9, 61.6, 104.9, 111.4, 113.2, 117.9, 119.2, 123.4, 126.2, 127.4, 132.2, 141.2, 141.9, 157.7 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 413 nm (5.05), 531 (4.23), 574 (4.17).

[5,15-Dihexyl-10-(1,3,5-trithian-2-yl)porphyrinato]nickel(II) (145)



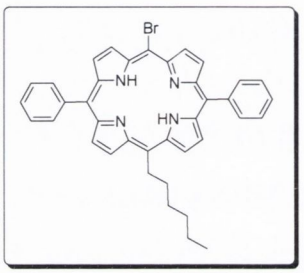
The reaction was performed using the same conditions as for free base **142** using 1,3,5-trithiane (0.57 g, 4.11 mmol), *n*-butyllithium (1.63 mL of a 2.5 M solution, 4.11 mmol) and [5,15-dihexylporphyrinato]nickel(II) **127** (100 mg, 0.19 mmol). Elution with dichloromethane/*n*-hexane (1:1, v/v) gave the title compound as a red solid (31 mg, 0.05 mmol, 24 %): mp > 310 °C; R_f=0.88 (SiO_2, CH_2Cl_2/ C_6H_{14}, 3:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 0.88 (t, J=7.0 Hz, 3H, -C*H*$_3$), 1.30 (m, 2H, -C*H*$_2$), 1.51 (m, 2H, -C*H*$_2$), 2.12 (m, 2H, -C*H*$_2$), 2.20 (m, 2H, -C*H*$_2$), 4.38 (t, 2H, J = 14.6 Hz, S-C*H*$_2$-S), 4.26 (t, 2H, J = 7.6 Hz, -C*H*$_2$), 4.80 (t, 2H, J = 14.6 Hz, S-C*H*$_2$-S), 7.10 (s, 1H, S-C*H*-S), 9.08 (d, 2H, J = 4.7 Hz, β-*H*), 9.15 (m, 4H, β-*H*), 9.36 ppm (s, 1H, meso-*H*), 9.52 (s, 2H, β-*H*); ^{13}C NMR

(100 MHz, $CDCl_3$): δ= 13.7, 19.0, 22.2, 29.6, 31.3, 33.5, 37.0, 40.2, 55.7, 103.8, 108.9, 110.0, 112.9, 117.5, 129.0, 129.3, 132.2, 140.4, 141.1, 142.0 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 418 (5.53), 539 (4.65), 576 nm (4.52).

6.6 Synthesis of bromoporphyrins

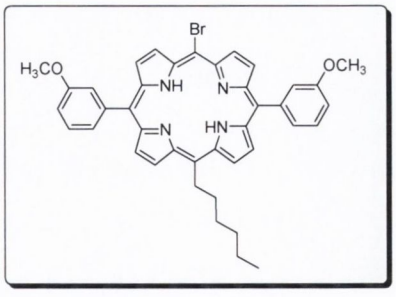
Bromoporphyrins **149**, **150** and **153** were prepared according to the literature.[254, 255] Porphyrin precursor **154** was synthesised from mixed condensation reaction as reported previously.[256]

5-Bromo-15-hexyl-10,20-diphenylporphyrin (151)



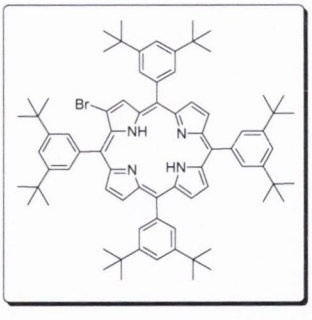
A solution of 5-hexyl-10,20-diphenylporphyrin **108** (0.40 g, 0.73 mmol), 0.3 ml pyridine and *N*-bromosuccinimide (0.14 g, 0.81 mmol) was dissolved in chloroform (150 ml) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (2:1, v/v) to yield **151** 0.46 g (0.29 mmol, 99%) as a purple solid: mp >310 °C; R_f=0.75 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.72 (s, 2H, N*H*), 0.92 (t, *J*=7.0 Hz, 3H, -CH_3), 1.36 (m, 2H, -CH_2), 1.49 (m, 2H, -CH_2), 1.75 (m, 2H, -CH_2), 2.47 (m, 2H, -CH_2), 4.84 (t, *J*=8.1 Hz, 2H, -CH_2), 7.77 (m, 6H, phenyl-*H*), 8.16 (d, *J*=6.4 Hz, 4H, phenyl-*H*), 8.84 (s, 4H, β-*H*), 9.37 (d, *J*=4.7 Hz, 2H, β-*H*), 9.58 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.3, 29.8, 31.4, 35.1, 38.4, 101.5, 119.8, 121.3, 126.4, 127.4, 130.5, 131.5, 141.6 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (5.21), 520 (3.90), 554 (2.64), 598 (3.48), 654 nm (3.62); HRMS (ES+) [$C_{38}H_{33}N_4Br$]: calcd for $[M+H]^+$ 625.1953, found 625.1967.

5-Bromo-15-hexyl-10,20-bis(3-methoxyphenyl) porphyrin (152)



A solution of 5-hexyl-10,20-bis(3-methoxyphenyl) porphyrin **109** (0.50 g, 0.82 mmol), 0.3 ml pyridine and *N*-bromosuccinimide (0.16 g, 0.91 mmol) was dissolved in chloroform (150 ml) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield 0.54 g of **152** (0.37 mmol, 95%) as a purple solid: mp =225 °C; R_f=0.36 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.71 (s, 2H, N*H*), 0.91 (t, *J*=7.4 Hz, 3H, -C*H*$_3$), 1.37 (m, 2*H*, -C*H*$_2$), 1.48 (m, 2*H*, -C*H*$_2$), 1.76 (m, 2*H*, -C*H*$_2$), 2.48 (m, 2H, -C*H*$_2$), 3.99 (s, 6H, -OC*H*$_3$), 4.87 (t, *J*=7.7 Hz, 2H, -C*H*$_2$), 7.34 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 2H, phenyl-*H*), 7.64 (t, *J*=8.1 Hz, 2H, phenyl-*H*), 7.76 (m, 4H, phenyl-*H*), 8.89 (d, *J*=4.4 Hz, 4H, β-*H*), 9.37 (d, *J*=4.8 Hz, 2H, β-*H*), 9.58 ppm (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.7, 29.8, 30.3, 31.9, 35.5, 38.8, 55.5, 101.9, 113.6, 119.9, 120.5, 121.7, 127.5, 129.6, 143.4, 158.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 421 (5.50), 520 (4.25), 554 (4.00), 598 (3.78), 654 nm (3.70); HRMS (ES+) [$C_{40}H_{37}N_4O_2Br$]: calcd for $[M+H]^+$ 685.2178, found 685.2166.

2-Bromo-5,10,15,20-tetrakis(3,5-di-*tert*-butyl-phenyl)porphyrin (155)



A solution of 5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin **154** (0.20 g, 0.19 mmol), 0.5 ml pyridine and *N*-bromosuccinimide (0.04 g, 0.21 mmol) was dissolved in chloroform (100 ml) and stirred for 1 hour. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield **155** (0.21 g, 0.24 mmol, 96%) as a purple solid: mp >310 °C; R_f=0.75 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1,

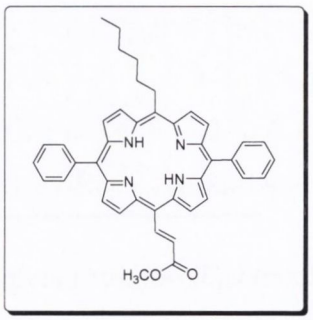
v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.79 (s, 2H, N*H*), 1.50 (s, 18H, -C(C*H*$_3$)$_3$), 1.52 (s, 54H, C(C*H*$_3$)$_3$), 7.78 (t, *J*=1.8 Hz, 3H, phenyl-*H*), 7.80 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 7.92 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 7.93 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.03 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 8.04 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.06 (t, *J*=1.8 Hz, 3H, phenyl-*H*), 8.09 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.82 (d, *J*=1.8 Hz, 1H, β-*H*), 8.90 (m, 5H, β-*H*), 8.94 ppm (d, *J*=4.8 Hz, 1H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7, 32.0, 35.1, 120.9, 121.4, 129.1, 129.7, 141.0, 141.4, 148.7, 148.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 423 (5.10), 520 (3.64), 554 (2.64), 598 (3.48), 654 nm (3.62); HRMS (ES+) [$C_{76}H_{94}N_4Br_1$]: calcd for $[M+H]^+$ 1141.6662, found. 1141.6544.

6.7 Synthesis of ester porphyrins

Method A: Heck coupling approach

Bromoporphyrin (1 eq.), palladium acetate (0.2 eq.) di-*tert*-butylbiphenylphosphine (0.5 eq.) and K_2CO_3 (1.2 eq.) were added to a Schlenk tube and dried under vacuum. The vessel was filled with argon, followed by addition of dry DMF, dry toluene, and the vinyl reagent (50-fold excess). The mixture was then degassed via three freeze-pump-thaw cycles before the vessel was purged with argon again to ensure the reaction mixture was free of oxygen. The Schlenk flask was sealed and heated to 105 °C and the mixture was stirred for 15 hours. The progress of reaction was monitored by TLC and, upon completion, the mixture was diluted with toluene and washed with water. The organic layer was separated, dried over $MgSO_4$ and the residue was purified by column chromatography.

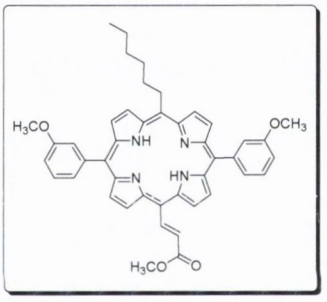
5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-diphenylporphyrin (157)



Methyl acrylate (0.72 mL, 7.97 mmol) was added to the solution of 5-bromo-15-hexyl-10,20-diphenylporphyrin **151** (0.10 g, 0.16 mmol), palladium acetate (7.22 mg, 0.03 mmol), di-*tert*-butylbiphenylphosphine (24.59 mg, 0.08 mmol) and K_2CO_3 (27.33 mg, 0.20

mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 hours. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded 0.06 g (0.04 mmol, 60 %) of **157** as a purple solid: mp >310 °C; R_f=0.61 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) : δ= −2.44 (s, 2H, N*H*), 0.90 (t, *J*=7.4 Hz, 3H, -C*H*$_3$), 1.36 (m, 2H, -C*H*$_2$), 1.49 (m, 2H, -C*H*$_2$), 1.77 (m, 2H, -C*H*$_2$), 2.49 (m, 2H, -C*H*$_2$), 4.04 (s, 3H, -OC*H*$_3$), 4.91 (t, *J*=7.7 Hz, 2H, -C*H*$_2$), 6.79 (d, *J*=15.8 Hz, 1H, -C*H*=), 7.78 (m, 6H, phenyl-*H*), 8.16 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.83 (dd, J_1=4.8 Hz, J_2=4.8 Hz, 4H, β-*H*), 9.40 (t, *J*=4.4 Hz, 4H, β-*H*), 10.20 ppm (d, *J*=15.8 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.2, 22.7, 30.3, 31.9, 35.5, 38.8, 52.1, 111.2, 120.6, 122.7, 130.3, 142.2, 146.0, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.11), 526 (3.97), 565 (3.96), 600 (3.79), 654 nm (3.79); HRMS (ES+) [$C_{42}H_{38}N_4O_2$]: calcd for $[M+H]^+$ 631.3073, found 631.3062.

5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-bis(3-methoxyphenyl)porphyrin (158)



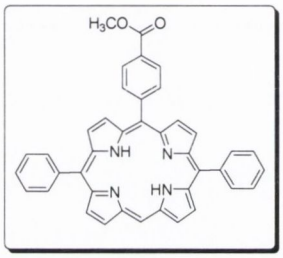
Methyl acrylate (0.66 mL, 7.26 mmol) was added to a solution of 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin **152** (0.10 g, 0.15 mmol), palladium acetate (6.59 mg, 0.03 mmol), di-*tert*-butylbiphenylphosphine (22.42 mg, 0.08 mmol) and K_2CO_3 (24.85 mg, 0.18 mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 hours (see 4.38). The mixture was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:4, v/v) and yielded 0.06 g (0.04 mmol, 55%) of **158** as a purple solid: mp =275 °C; R_f=0.65 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.43 (s, 2H, N*H*), 0.96 (t, *J*=7.6 Hz, 3H, -C*H*$_3$), 1.36 (m, 2H, -C*H*$_2$), 1.49 (m, 2H, -C*H*$_2$), 1.77 (m, 2H, -C*H*$_2$), 2.48 (m, 2H, -C*H*$_2$), 3.99 (s, 6H, -OC*H*$_3$), 4.04 (s, 3H, -OC*H*$_3$), 4.90 (t, *J*=7.6 Hz, 2H, -C*H*$_2$), 6.80 (d, *J*=15.8 Hz, 1H, -C*H*=), 7.34 (dd, J_1=2.3 Hz, J_2=2.3 Hz, 2H, phenyl-*H*), 7.65 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.77 (t, *J*=7.6 Hz, 4H, phenyl-*H*), 8.89 (dd, J_1=4.7 Hz, J_2=4.7 Hz, 4H, β-*H*), 9.39 (q, *J*=4.7 Hz, 4H, β-*H*), 10.21 ppm (d, *J*=15.8 Hz, 1H, =C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 29.8, 31.5, 35.0, 38.4, 51.6, 55.1, 110.8, 113.2, 119.8, 120.0, 122.3, 129.9, 131.9, 143.0, 145.5, 157.5, 166.4 ppm;

UV-vis (CH_2Cl_2): λ_{max} (log ε)= 427 (5.23), 526 (4.01), 566 (4.00), 5.99 (3.79), 657 nm (3.81); HRMS (ES+) [$C_{44}H_{42}N_4O_4$]: calcd for $[M+H]^+$ 691.3284, found 691.3293.

Method B: Suzuki cross coupling approach

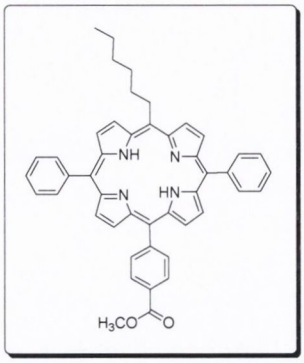
To a stirred slurry of K_3PO_4 (40 eq.) in anhydrous THF were added bromoporphyrin (1 eq.), boronic acid (20 eq.), and $Pd(PPh_3)_4$ (0.2 eq.). The reaction was heated to reflux at 85 °C for 18 hours and shielded from light. The solvent was evaporated after completion and the residue was dissolved in CH_2Cl_2. This mixture was washed with saturated $NaHCO_3$, H_2O, and brine followed by drying over Na_2SO_4. The organic solvent was evaporated and the crude product was purifed by column chromatography.

5-(4-Methoxycarbonylphenyl)-10,20-diphenylporphyrin (159)



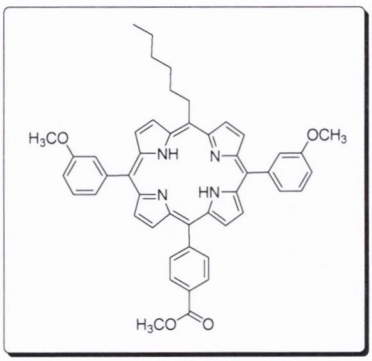
K_3PO_4 (1.57g, 7.38 mmol), 5-bromo-10,20-diphenylporphyrin **149** (0.20 g, 0.37 mmol), 4-methoxy carbonylphenyl boronic acid (0.66 g, 3.69 mmol) and $Pd(PPh_3)_4$ (0.04 g, 0.04 mmol) were reacted in anhydrous THF (70 ml) according to method A. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded 0.22 g of **159** (0.13 mmol, 98%) as a purple solid: mp >310 °C; R_f=0.42 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.02 (s, 2H, N*H*), 4.11 (s, 3H, -OCH_3), 7.79 (m, 6H, phenyl-*H*), 8.24 (dd, J_1=2.3 Hz, J_2=1.8 Hz, 4H, phenyl-*H*), 8.31 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=4.7 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=4.7 Hz, 2H, β-*H*), 8.92 (d, *J*=4.7 Hz, 2H, β-*H*), 9.03 (d, *J*=4.7 Hz, 2H, β-*H*), 9.32 (d, *J*=4.7 Hz, 2H, β-*H*), 10.20 ppm (s, 1H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.9, 52.0, 65.5, 104.8, 118.5, 119.4, 126.4, 127.4, 129.1, 130.6, 134.3, 141.2, 147.0, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 413 (5.57), 509 (4.04), 542 (3.60), 584 (3.64) 638 nm (3.30); HRMS (ES+) [$C_{40}H_{29}N_4O_2$]: calcd for $[M+H]^+$ 597.2291, found 597.2285.

5-Hexyl-15-(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin (160)



K_3PO_4 (1.36 g, 6.39 mmol), 5-bromo-15-hexyl-10,20-diphenylporphyrin **151** (0.2 g, 0.32 mmol), 4-methoxy carbonylphenylboronic acid (0.58 g, 3.20 mmol) and $Pd(PPh_3)_4$ (0.04g, 0.03 mmol) were reacted in anhydrous THF (70 ml) following method A. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) and yielded **160** (0.29 g, 0.20 mmol, 82 %) as a purple solid: mp >310 °C; R_f=0.60 (SiO_2, EtOAc/*n*-hexane, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.67 (s, 2H, N*H*), 0.96 (t, *J*=7.0 Hz, 3H, -C*H*$_3$), 1.39 (m, 2*H*, -C*H*$_2$), 1.50 (m, 2H, -C*H*$_2$), 1.78 (m, 2H, -C*H*$_2$), 2.53 (m, 2H, -C*H*$_2$), 4.13 (s, 3H, -OC*H*$_3$), 4.91 (t, *J*=8.2 Hz, 2H, -C*H*$_2$), 7.79 (m, 6H, phenyl-*H*), 8.23 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.32 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.85 (d, *J*=4.7 Hz, 2H, β-*H*), 8.93 (d, *J*=4.7 Hz, 2H, β-*H*), 9.44 pm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.8, 22.3, 29.8, 31.5, 35.1, 38.5, 52.0, 117.3, 119.4, 120.8, 127.3, 127.6, 129.1, 134.2, 141.9, 146.6, 167.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.52), 517 (3.20), 551 (3.91), 593 (3.76), 649 nm (3.83); HRMS (ES+) [$C_{46}H_{41}N_4O_2$]: calcd for $[M+H]^+$ 681.3230, found 681.3256.

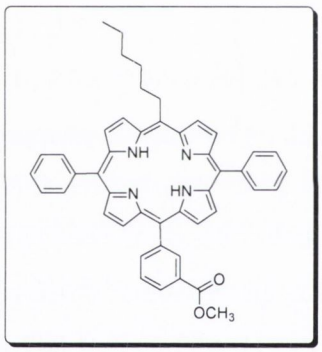
5-Hexyl-15-(4-methoxycarbonylphenyl)-10,20-bis(3-methoxyphenyl)porphyrin (161)



K_3PO_4 (3.10, 14.59 mmol), 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin **152** (0.50 g, 0.73 mmol), 4-methoxycarbonylphenylboronic acid (1.31 g, 7.29 mmol) and

$Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) were reacted in anhydrous THF (80 ml) following method A. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded **161** (0.41 g, 0.30 mmol, 63%) as a purple solid: mp =210 °C; R_f=0.36 (SiO_2, EtOAc/*n*-hexane, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.73 (s, 2H, N*H*), 0.92 (t, *J*=7.4 Hz, 3H, -C*H*$_3$), 1.38 (m, 2*H*, -C*H*$_2$), 1.52 (m, 2*H*, -C*H*$_2$), 1.80 (m, 2H, -C*H*$_2$), 2.54 (m, 2H, -C*H*$_2$), 3.99 (s, 6H, -OC*H*$_3$), 4.10 (s, 3H, -OC*H*$_3$), 4.98 (t, *J*=7.8 Hz, 2H, -C*H*$_2$), 7.37 (dd, J_1=2.4 Hz, J_2=2.0 Hz, 2H, phenyl-*H*), 7.64 (t, *J*=8.3 Hz, 2H, phenyl-*H*), 7.79 (t, *J*=7.8 Hz, 4H, phenyl-*H*), 8.27 (d, *J*= 7.8 Hz, 2H, phenyl-H), 8.42 (d, *J*= 8.3 Hz, 2H, phenyl-H), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.86 (d, *J*=4.9 Hz, 2H, β-*H*), 8.96 (d, *J*=4.4 Hz, 2H, β-*H*), 9.46 ppm (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.2, 22.8, 30.3, 31.9, 35.6, 38.9, 52.5, 55.5, 113.6, 117.8, 119.5, 120.5, 121.3, 127.5, 127.6, 128.0, 129.5, 134.6, 143.6, 147.0, 157.9, 167.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.34), 516 (4.26), 551 (4.06), 593 (3.98), 650 nm (3.94); HRMS (ES+) [$C_{48}H_{44}N_4O_4$]: calcd for $[M+H]^+$ 741.3441, found 741.3441.

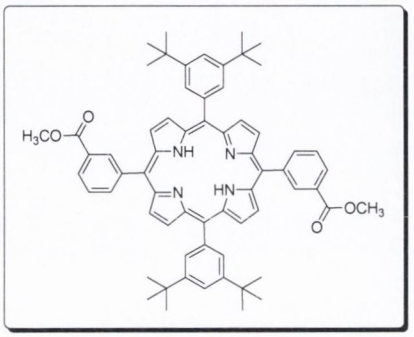
5-Hexyl-15-(3-methoxycarbonylphenyl)-10,20-diphenylporphyrin (162)



K_3PO_4 (1.36 g, 6.39 mmol), 5-hexyl-15-bromo-10,20-diphenylporphyrin **151** (0.20 g, 0.32 mmol), 3-methoxycarbonylphenylboronic acid (0.58 g, 3.20 mmol), and $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol) were reacted in anhydrous THF (70 ml) according to method A. The title compound was isolated by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to give 0.18 g of **162** (0.12 mmol, 84%) as a purple solid: mp >310 °C; R_f=0.77 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.71 (s, 2H, N*H*), 0.93 (t, *J*= 7.3 Hz, 3H, -C*H*$_3$), 1.38 (m, 2H, -C*H*$_2$), 1.52 (m, 2H, -C*H*$_2$), 1.80 (m, 2H, -C*H*$_2$), 2.54 (m, 2H, -C*H*$_2$), 3.98 (s, 3H, -OC*H*$_3$), 4.98 (t, *J*=8.0 Hz, 2H, -C*H*$_2$), 7.77 (m, 6H, phenyl-*H*), 7.82 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.21 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.37 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.46 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.82 (d, *J*=4.4 Hz, 2H, β-*H*), 8.89 (s, 1H, phenyl-*H*), 8.92 (d, *J*=4.8 Hz, 2H, β-*H*), 9.47 ppm (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$):

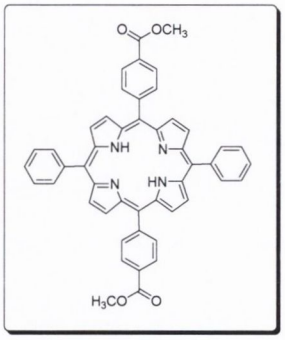
δ=14.2, 22.8, 30.3, 31.9, 35.6, 38.9, 52.4, 117.8, 119.8, 121.1, 126.7, 126.9, 127.7, 128.9, 129.0, 134.5, 134.9, 138.5, 142.4, 142.5, 167.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.14), 516 (4.08), 551 (3.93), 593 (3.88), 651 nm (3.89); HRMS (ES+) [$C_{46}H_{40}N_4O_2$]: calcd for $[M+H]^+$ 681.3230, found 681.3238.

5,15-Bis(3,5-di-*tert*-butylphenyl)-10,20-bis(3-methoxycarbonylphenyl)porphyrin (163)



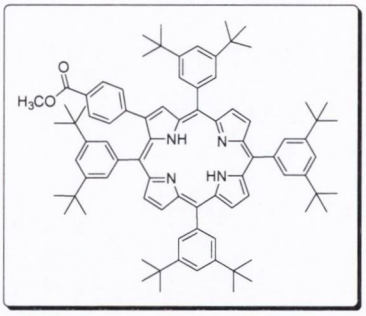
K_3PO_4 (1.01 g, 4.74 mmol), 5,15-dibromo-10,20-bis(3,5-di-*tert*-butylphenyl)-porphyrin **150** (0.10 g, 0.12 mmol), 3-methoxycarbonylphenylboronic acid (0.43 g, 2.47 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.02 mmol) were heated to reflux in anhydrous THF (50 ml) following method A. The title compound was isolated by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) to yield 0.09 g of **163** (0.09 mmol, 77 %) as a purple solid: mp =260 °C; R_f=0.56 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.76 (s, 2H, N*H*), 1.51 (s, 36H, -(CH_3)$_3$), 3.96 (s, 6H, -OCH_3), 7.79 (d, *J*=8.8 Hz, 2H, phenyl-*H*), 7.83 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.06 (d, *J*=1.8 Hz, 4H, phenyl-*H*), 8.39 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.75 (d, *J*=4.7 Hz, 4H, β-*H*), 8.89 ppm (d, *J*=4.6 Hz, 6H, phenyl-*H* and β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 22.3, 29.3, 31.4, 34.6, 51.9, 118.1, 120.7, 121.4, 126.4, 128.3, 128.6, 129.5, 134.3, 137.9, 140.5, 142.3, 148.4, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 421 (5.20), 517 (3.86), 553 (3.68), 595 (3.64), 654 nm (3.90); HRMS (ES+) [$C_{64}H_{66}N_4O_4$]: calcd for $[M+H]^+$ 955.5162, found 955.5205.

5,15-Bis(4-methoxycarbonylphenyl)-10,20-diphenylporphyrin (164)



K_3PO_4 (2.74 g, 12.90 mmol), 5,15-dibromo-10,20-diphenylporphyrin **156** (0.20 g, 0.32 mmol), 4-methoxycarbonylphenylboronic acid (1.16 g, 6.44 mmol) and $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) were reacted in anhydrous THF (70 ml) following procedure A. The crude mixture was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) and yielded **164** (0.24 g, 94%) as a purple solid: mp >310 °C; R_f=0.38 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.80 (s, 2H, N*H*), 4.10 (s, 6H, -OCH_3), 7.64 (d, *J*=8.2 Hz, 6H, phenyl-*H*), 7.76 (m, 4H, phenyl-*H*), 8.09 (d, *J*=8.8 Hz, 2H, phenyl-*H*), 8.18 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.31 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.80 (d, *J*=4.7 Hz, 4H, β-*H*), 8.86 ppm (d, *J*=4.7 Hz, 4H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 51.8, 118.5, 120.2, 126.3, 126.8, 127.5, 129.8, 134.1, 141.5, 143.9, 146.5, 166.4, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.43), 515 (4.04), 550 (3.62), 592 (3.45), 648 nm (3.45); HRMS (ES+) [$C_{48}H_{34}N_4O_4$]: calcd for $[M+H]^+$ 731.2658, found 731.2620.

2-(4-Methoxycarbonylphenyl)-5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin (165)



K_3PO_4 (0.37 g, 1.75 mmol), 2-bromo-5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin **155** (0.10 g, 0.09 mmol), 4-methoxycarbonylphenylboronic acid (0.16 g, 0.88 mmol) and $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) were reacted in anhydrous THF (50 ml) according to method A. The product was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield 0.04 g of **165** (0.05 mmol, 52 %) as a purple

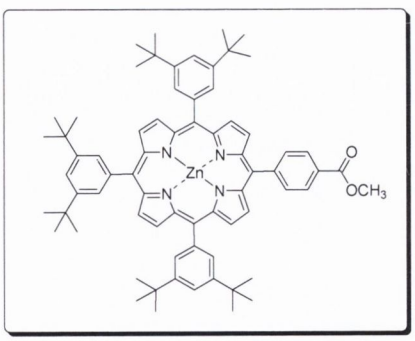
solid: mp >310 °C; R_f=0.57 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.54 (s, 2H, N*H*), 1.35 (s, 18H, -C(C*H*$_3$)$_3$), 1.53 (s, 54H, -C(C*H*$_3$)$_3$), 3.94 (s, 3H, -OC*H*$_3$), 7.24 (s, 1H, phenyl-*H*), 7.47 (d, *J*= 8.0 Hz, 2H, phenyl-*H*), 7.81 (m, 7H, phenyl-*H*), 8.08 (dd, J_1= 1.8 Hz , J_1= 1.4 Hz, 4H, phenyl-*H*), 8.15 (d, *J*= 1.4 Hz, 2H, phenyl-*H*), 8.74 (m, 2H, β-*H*), 8.87 ppm (m, 5H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7, 31.9, 35.1, 52.0, 53.4, 121.0, 121.3, 122.2, 127.0, 128.6, 129.8, 130.7, 140.2, 141.4, 141.6, 148.6, 148.7, 167.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.43), 5.22 (4.00), 559 (3.56), 598 (3.08), 655 nm (3.51); HRMS (ES+) [$C_{84}H_{100}N_4O_2$]: calcd for $[M+H]^+$ 1197.7930, found. 1197.7880.

Method C: Condensation approach

Ester porphyrin **168** and **169** were synthesised using condensation reaction as reported previously.[188, 256]

General procedure: To a mixture of aldehyde (4 eq.) and $Zn(OAc)_2$ (1 eq.) in propionic acid, pyrrole (4 eq.) was added at 100 °C over the course of 1 hours under vigorous stirring. The resulting dark solution was refluxed for further 4h and then cooled to room temperature. The solvent was evaporated and the solid residue was filtered through silica gel and all product containing fractions were collected. The volume was reduced to 100 ml and pyridine and excess DDQ were added. The resulting mixture was refluxed for 1 hour. The solution was cooled to room temperature and evaporated to give a black-purple crude product followed by column chromatography on silica gel.

[5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20-(4-methoxycarbonylphenyl)porphyrinato] zinc(II)) (166)



4-Carboxylmethylbenzaldehyde (0.25 g, 1.53 mmol), 3,5-di-*tert*-butylbenzaldehyde (1.00 g, 4.58 mmol), $Zn(OAc)_2$ (0.34 g, 1.53 mmol) and pyrrole (0.42 mL, 6.12 mmol) were reacted in propionic acid (30 mL) following method C. The solution volume was reduced

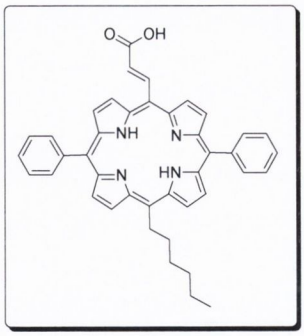
to 100 ml and pyridine (0.5 mL) and DDQ (0.5 g) were added. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1 v/v) gave a red solid of **166** as the second fraction (0.16 g, 0.17 mmol, 10%): mp >310 °C; R_f=0.44 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.53 (s, 54*H*, -C-(CH_3)$_3$), 4.03 (s, 3H, -OCH_3), 7.80 (d, *J*= 1.76 Hz, 3H, phenyl-*H*), 8.10 (s, 6H, phenyl-*H*), 8.31 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.36 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 9.02 ppm (d, *J*=5.3 Hz, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.34, 34.62, 51.91, 118.69, 120.42, 122.22, 127.29, 128.71, 129.25, 130.83, 131.83, 131.98, 141.30, 147.59, 148.14, 149.03, 149.96, 150.16, 166.99 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 423 (5.34), 549 (4.87), 589 nm (4.77); HRMS (ES+) [$C_{70}H_{78}O_2N_4Zn$]: calcd for [M] 1070.5416, found 1070.5425. The first fraction contained [5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrinato]zinc(II)[9c] **167** (0.198 g, 0.22 mmol, 12%) as a red solid. mp >310 °C; R_f=0.73 (SiO_2, EtOAc/C_6H_{14}, 1:3 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) : δ= 1.63 (s, 72H, -C-(CH_3)$_3$), 7.89 (s, 4H, phenyl-*H*), 8.22 (s, 8H, phenyl-*H*), 9.13 ppm (s, 8H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 31.5, 34.7, 120.4, 122.0, 129.3, 131.8, 141.6, 148.1, 150.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 422 (5.12), 549 (4.87), 654 nm (4.84); HRMS [$C_{70}H_{77}N_4O_2Zn$]: calcd for [M+H$^+$] 1070.5416, found 1070.5428.

6.8 Synthesis of carboxylic acid porphyrins

Carboxylic acid porphyrins **177**, **178**, **181** and **182** were prepared as reported previously using base hydrolysis.[188, 256]

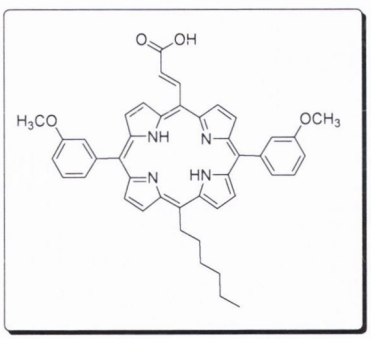
General method: A solution of porphyrin in THF, was mixed with ethanol and 2N NaOH and the suspension was heated to reflux (TLC monitoring) before cooled to room temperature. The mixture was acidified with aqueous HCl (1N) and extracted with chloroform. The organic extract was washed with saturated sodium bicarbonate aqueous solution and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure and undergo purification.

5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin (171)



5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-diphenylporphyrin **157** (0.03 g, 0.02 mmol) was heated in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 3 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of **171** (0.03 g, 0.02 mmol, 93%): mp >310 °C; R_f=0.19 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.40 (s, 2H, N*H*), 0.93 (t, *J*=7.4 Hz, 3H, -CH_3), 1.39 (m, 2H, -CH_2), 1.43 (m, 2H, -CH_2), 1.74 (m, 2H, -CH_2), 2.25 (m, 2H, -CH_2), 5.09 (t, *J*=7.7 Hz, 2H, -CH_2), 6.83 (d, *J*=15.8 Hz, 1H, -CH=), 7.92 (m, 6H, phenyl-*H*), 8.26 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.80 (d, *J*=4.7 Hz, 4H, β-*H*), 8.96 (d, *J*=5.3 Hz, 2H, β-*H*), 9.71 (t, *J*=4.4 Hz, 2H, β-*H*), 10.16 ppm (d, *J*=15.8 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.2, 24.2, 29.2, 29.7, 31.3, 38.3, 55.0, 94.3, 106.6, 126.3, 127.6, 128.0, 128.6, 133.7, 141.3 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.26), 527 (3.78), 569 (3.86), 601 (3.30), 654 nm (3.48); HRMS (ES+) [$C_{41}H_{36}N_4O_2$]: calcd for $[M+H]^+$ 617.2917, found. 617.2901

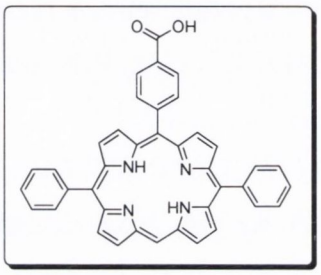
5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (172)



5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-bis(3-methoxyphenyl)porphyrin **158** (0.06 g, 0.08 mmol) was heated in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 3 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of **172** (0.05 g, 0.03 mmol, 88%): mp =197 °C; R_f=0.19 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=

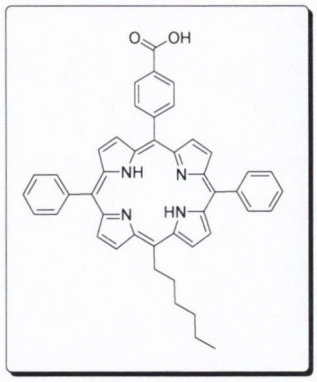
−2.43 (s, 2H, N*H*), 0.98 (t, *J*=7.6 Hz, 3H, -CH_3), 1.30 (m, 2H, -CH_2), 1.58 (m, 2H, -CH_2), 1.86 (m, 2H, -CH_2), 2.58 (m, 2H, -CH_2), 4.06 (s, 6H, -OCH_3), 5.12 (t, *J*=7.6 Hz, 2H, -CH_2), 6.85 (d, *J*=15.8 Hz, 1H, -C*H*=), 7.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 7.75 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.84 (t, *J*=7.6 Hz, 4H, phenyl-*H*), 8.94 (d, *J*=13.4 Hz, 4H, β-*H*), 9.72 (d, *J*=4.7 Hz, 2H, β-*H*), 9.91 (d, *J*=4.7 Hz, 2H, β-*H*), 10.20 ppm (d, *J*=15.8 Hz, 1H, =C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 21.3, 22.7, 25.6, 29.5, 31.8, 34.3, 38.7, 54.4, 55.6, 68.0, 112.3, 118.9, 119.8, 120.5, 126.8, 128.3, 135.8, 142.6, 143.3, 151.6, 156.8 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 427 (5.33), 525 (4.32), 571 (4.32), 599 (4.18), 654 nm (4.15); HRMS (ES+) [$C_{43}H_{40}N_4O_4$]: calcd for $[M+H]^+$ 677.3128, found. 677.3121.

5-(4-Carboxyphenyl)-10,20-diphenylporphyrin (173)



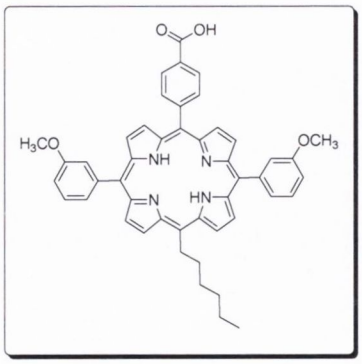
5-(4-Methoxycarbonylphenyl)-10,20-diphenylporphyrin **159** (0.15 g, 0.09 mmol) was heated to reflux in THF, ethanol (40mL) and 2N NaOH (95 ml) for 11 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1) and evaporation of the solvent followed by recrystallization from MeOH/H_2O gave a purple solid of **173** (0.11 g, 0.06 mmol, 77%): mp >310 °C; R_f=0.29 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.30 (s, 2H, N*H*), 7.60 (m, 6H, phenyl-*H*), 8.03 (m, 6H, phenyl-*H*), 8.17 (d, *J*=7.5 Hz, 2H, phenyl-*H*), 8.68 (d, *J*=14.0 Hz, 4H, β-*H*), 8.82 (s, 2H, β-*H*), 9.17 (s, 2H, β-*H*), 10.05 ppm (s, 1H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 30.7, 31.4, 32.0, 97.0, 107.4, 109.5, 113.2, 118.7, 120.9, 122.2, 122.4, 129.9, 130.2, 133.9, 136.6, 144.0, 147.5, 176.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 413 (5.27), 509 (4.23), 542 (4.04), 582 (4.04), 636 nm (3.95); HRMS (ES+) [$C_{39}H_{27}N_4O_2$]: calcd for $[M+H]^+$ 583.2134, found. 583.2134.

5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenyl porphyrin (174)



5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenyl-porphyrin **160** (0.10 g, 0.15 mmol) was heated in THF (20 mL), ethanol (25 mL) and 2N NaOH (50 mL) for 2 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1) followed by evaporation of the solvent gave a purple solid of **174** (0.09 g, 0.06 mmol, 93%): mp >310 ^oC; R_f=0.24 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.67 (s, 2H, N*H*), 0.96 (t, *J*=7.0 Hz, 3H, -C*H*$_3$), 1.21 (m, 2H, -C*H*$_2$), 1.58 (m, 2H, -C*H*$_2$), 1.76 (m, 2H, -C*H*$_2$), 2.53 (m, 2H, -C*H*$_2$), 5.17 (t, *J*=8.2 Hz, 2H, -C*H*$_2$), 7.90 (m, 6H, phenyl-*H*), 8.08 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.40 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.52 (d, *J*=4.7 Hz, 2H, β-*H*), 8.87 (d, *J*=4.7 Hz, 2H, β-*H*), 8.96 (d, *J*=4.7 Hz, 2H, β-*H*), 9.21 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 27.8, 29.0, 29.8, 31.5, 34.0, 34.9, 38.3, 99.9, 118.4, 119.7, 122.8, 125.1, 126.1, 127.3, 128.4, 130.9, 134.1, 135.1, 141.0, 143.9, 149.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.26), 518 (4.60), 552 (4.54), 594 (4.49), 647 nm (4.47); HRMS (ES+) [$C_{45}H_{39}N_4O_2$]: calcd for $[M+H]^+$ 667.3073, found. 667.3068.

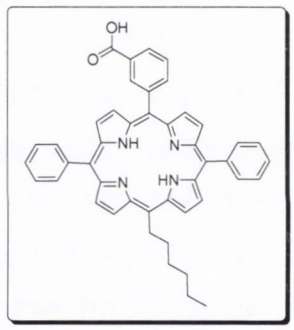
5-(4-Carboxyphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (175)



5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-bis(3-methoxy-phenyl)porphyrin **161** (0.18 g, 0.24 mmol) was heated in THF (15 mL), ethanol (30 mL) and 2N NaOH (30 mL) for 5

hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1 v/v) and evaporation of the solvent gave a purple solid of **175** (0.16 g, 0.11 mmol, 93%): mp >310 °C; R_f=0.13 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −3.07 (s, 2H, N*H*), 0.95 (t, *J*=7.4 Hz, 3H, -C*H*$_3$), 1.36 (m, 2*H*, -C*H*$_2$), 1.45 (m, 2*H*, -C*H*$_2$), 1.71 (m, 2H, -C*H*$_2$), 2.40 (m, 2H, -C*H*$_2$), 3.98 (s, 6H, -OC*H*$_3$), 5.00 (t, *J*=7.8 Hz, 2H, -C*H*$_2$), 7.37 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 7.72 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.85 (t, *J*=7.8 Hz, 4H, phenyl-*H*), 8.14 (d, *J*= 7.8 Hz, 2H, phenyl-H), 8.47 (d, *J*= 8.3 Hz, 2H, phenyl-H), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.86 (d, *J*=4.9 Hz, 2H, β-*H*), 8.90 (d, *J*=4.4 Hz, 2H, β-*H*), 9.12 ppm (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 21.3, 22.8, 25.7, 29.5, 30.4, 31.9, 34.3, 38.8, 54.5, 68.1, 112.5, 118.6, 119.6, 125.6, 126.3, 126.6, 128.1, 134.7, 135.9, 142.8, 144.6, 151.6, 156.9, 176.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (5.27), 516 (4.35), 551 (4.13), 593 (4.08), 648 nm (4.08); HRMS (ES+) [$C_{47}H_{43}N_4O_4$]: calcd for $[M+H]^+$ 727.3284, found. 727.3256.

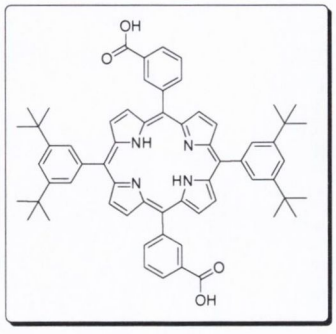
5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin (176)



5-(3-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenylporphyrin **162** (0.14 g, 0.21 mmol) was heated in THF (20 mL), ethanol (30 mL) and 2N NaOH (30 mL) for 2 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1 v/v) followed by evaporation of the solvent gave a purple solid of **176** (0.13 g, 0.09 mmol, 94%): mp >310 °C; R_f=0.24 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.78 (s, 2H, N*H*), 0.88 (t, *J*=7.3 Hz, 3H, -C*H*$_3$), 1.32 (m, 2H, -C*H*$_2$), 1.44 (m, 2H, -C*H*$_2$), 1.77 (m, 2H, -C*H*$_2$), 2.49 (m, 2H, -C*H*$_2$), 4.96 (t, *J*=7.8 Hz, 2H, -C*H*$_2$), 7.70 (m, 6H, phenyl-*H*), 7.76 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.13 (d, *J*=6.8 Hz, 4H, phenyl-*H*), 8.27 (d, *J*=6.8 Hz, 1H, phenyl-*H*), 8.49 (d, *J*= 7.8 Hz, 1H, phenyl-*H*), 8.72 (d, *J*=4.9 Hz, 4H, β-*H*), 8.85 (d, *J*=4.9 Hz, 2H, β-*H*), 8.93 (s, 1H, phenyl-*H*), 9.43 ppm (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 20.7, 22.2, 27.7, 31.4, 33.8, 35.1, 38.4, 65.9, 67.5, 117.9, 119.2, 120.4, 124.4, 125.0, 126.1, 127.2, 128.7, 134.0, 135.0, 137.6, 143.9, 144.3, 151.1, 168.9

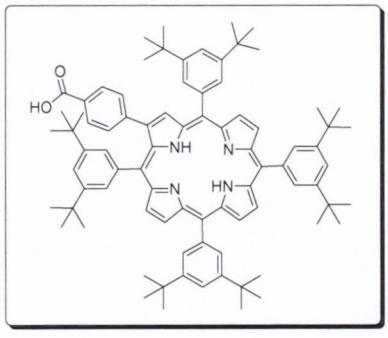
ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.31), 517 (4.30), 550 (4.18), 595 (4.00), 651 nm (4.00); HRMS (ES+) [$C_{45}H_{38}N_4O_2$]: calcd for $[M+H]^+$ 667.3073, found. 667.3072.

5,15-Bis(3-carboxyphenyl)-10,20-bis(3,5-di-*tert*-butylphenyl)porphyrin (178)



5,15-Bis(3-methoxycarbonylphenyl)-10,20-bis(3,5-di-*tert*-butylphenyl)porphyrin **163** (0.02 g, 0.02 mmol) was heated in THF (10 mL), ethanol (20 mL) and 2N NaOH (20 mL) for 5 hours. Filtration through a plug of silica gel eluting with (CH_2Cl_2: EtOAc = 5:1 v/v) followed by evaporation of the solvent gave a purple solid of **178** (16.5 mg, 0.02 mmol, 89%): mp > 310 °C; R_f=0.23 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.83 (s, 2H, N*H*), 1.50 (s, 36H, -(C*H*$_3$)$_3$), 7.29 (s, 2H, phenyl-*H*), 7.92 (m, 6H, phenyl-*H*), 8.04 (t, *J*=4.0 Hz, 2H, phenyl-*H*), 8.44 (dd, J_1=1.5 Hz, J_2=3.4 Hz, 4H, phenyl-*H*), 9.07 (d, *J*=4.7 Hz, 4H, β-*H*), 9.37 ppm (d, *J*=4.6 Hz, 4H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 31.3, 32.1, 44.7, 119.2, 123.7, 124.4, 126.7, 127.6, 128.4, 129.6, 132.2, 140.7, 142.2, 149.5, 165.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 408 (5.11), 503 (4.61), 573 (4.58), 598 (4.54), 652 nm (4.54); HRMS (ES+) [$C_{62}H_{63}N_4O_4$]: calcd for $[M+H]^+$ 927.4849, found 927.4872.

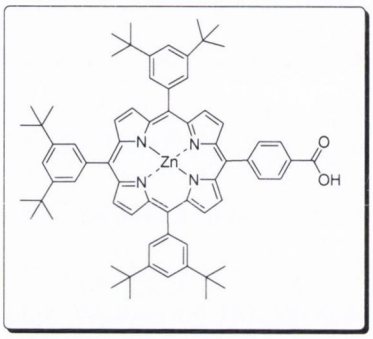
2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (179)



2-(4-Methoxycarbonylphenyl)-5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)-porphyrin (0.03 g, 0.03 mmol) **165** was heated to reflux in THF (5 mL), ethanol (10 mL) and 2N NaOH (10 mL) for 5 hours. Filtration through a plug of silica gel eluting with CH_2Cl_2 followed by

evaporation of the solvent gave a purple solid of **179** (0.03 g, 0.03 mmol, 82%): mp >310 °C; R_f=0.28 (SiO_2, EtOAc/C_6H_{14}, 1:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.77 (s, 2H, N*H*), 1.22 (s, 48H, -C(C*H*$_3$)$_3$), 1.22 (s, 24H, -C(C*H*$_3$)$_3$), 7.52 (s, 2H, phenyl-*H*), 7.79 (s, 1H, phenyl-*H*), 7.89 (s, 5H, phenyl-*H*), 8.06 (s, 2H, phenyl-*H*), 8.42 (br. s, 2H, phenyl-*H*), 8.73 (d, *J*= 1.8 Hz, 2H, phenyl-*H*), 8.81 (d, *J*= 1.8 Hz, 2H, phenyl-*H*), 8.85 (d, *J*=4.8 Hz, 5H, β-*H*), 8.95 ppm (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.7, 31.9, 35.1, 52.0, 53.5, 121.0, 121.5, 122.2, 127.0, 128.6, 129.8, 130.7, 141.6, 148.7, 167.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.25), 523 (4.20), 560 (4.04), 598 (3.90), 653 nm (3.95); HRMS (ES+) [$C_{83}H_{98}N_4O_2$]: calcd for [M+H]$^+$ 1183.7768, found. 1183.7727.

[5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrinato]zinc(II) (180)



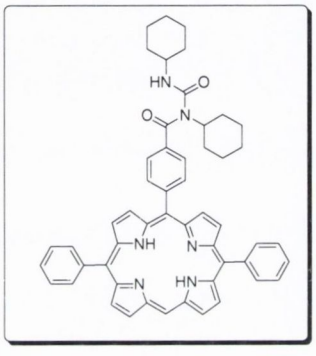
[5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20(4-methoxycarbonylphenyl)porphyrinato]zinc(II) **166** (0.12 g, 0.13 mmol) was heated to reflux in THF (5 mL), ethanol (20 mL) and 2N NaOH (20 mL) for 5 hours. Filtration through a plug of silica gel eluting with CH_2Cl_2 followed by evaporation of the solvent yielded a purple solid of **180** (0.10 g, 0.10 mmol, 82%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.40 (s, 36H, -C(C*H*$_3$)$_3$), 1.52 (s, 18H, -C(C*H*$_3$)$_3$), 7.68 (s, 1H, phenyl-*H*), 7.78 (s, 2H, phenyl-*H*), 8.01 (s, 4H, phenyl-*H*), 8.08 (s, 2H, phenyl-*H*), 8.44 (s, 2H, phenyl-*H*), 8.97 (s, 2H, phenyl-*H*), 8.97 ppm (s, 8H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.2, 34.5, 120.2, 122.1, 128.1, 129.2, 131.1, 131.7, 134.1, 141.3, 148.0, 149.2, 149.9, 149.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 423 (5.11), 551 (4.86), 589 nm (4.78); HRMS (ES+) [$C_{69}H_{76}N_4O_2Zn$]: calcd for [M+H]$^+$ 1056.526, found. 1056.530.

6.9 Synthesis of *o*-nitrobenzyl porphyrins

Method A: DCC carbodiimide reagent approach

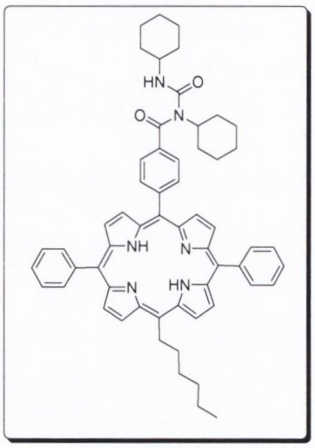
To a solution of porphyrin, *N,N*-dicyclohexylcarbodiimide (DCC), and dimethylamino-pyridine (DMAP) in dry THF, a solution of 2-nitrobenzylalcohol in THF was added at room temperature. The mixture was heated to reflux for 18 hours and diluted with THF before being extracted with a solution of aq. NH_4Cl. The organic solvent was washed with brine and dried over Na_2SO_4 followed by evaporation of the solvent under reduced pressure and purification by column chromatography.

5-(4-Di-cyclohexylurea-carbonylphenyl)-10,20-diphenylporphyrin (185)



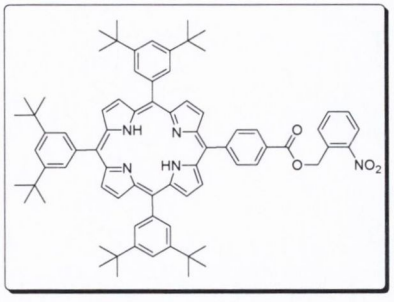
5-(4-Carboxyphenyl)-10,20-diphenylporphyrin **173** (0.05 g, 0.09 mmol), DCC (17.7 mg, 0.09 mmol), DMAP (9.25 mg, 0.09 mmol) and 2-nitrobenzylalcohol (65.6 mg, 0.43 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **185** as a purple solid (26.4 mg, 0.02 mmol, 39%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –3.01 (s, 2H, N*H*), 0.89 (m, 2H,-CH_2), 1.18 (m, 2H, -CH_2), 1.42 (m, 4H, -CH_2), 1.63 (m, 2H, -CH_2), 1.74 (m, 2H, -CH_2), 1.92 (m, 4H, -CH_2), 2.05 (m, 2H, -CH_2), 2.19 (m, 2H, -CH_2), 3.73 (m,1H, -N-C*H*), 4.42 (m, 1H, -CON-C*H*), 6.33 (d, *J*= 7.0 Hz, 1H, -N*H*), 7.79 (t, *J*= 7.6 Hz, 6H, phenyl-*H*), 7.97 (d, *J*= 7.6 Hz, 2H, phenyl-*H*), 8.24 (d, 4H, *J*=6.4 Hz, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.82 (d, *J*=4.7 Hz, 2H, β-*H*), 8.92 (d, *J*=4.7Hz, 2H, β-*H*), 9.02 (d, *J*=4.7 Hz, 2H, β-*H*), 9.31 (d, *J*=4.7 Hz, 2H, β-*H*), 10.19 ppm (s, 1H, meso-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.5, 26.0, 29.3, 30.5, 32.3, 57.1, 104.8, 118.5, 119.5, 124.8, 126.5, 127.4, 134.3, 135.9,141.2, 144.9, 154.1, 167.4, 170.8 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 413 (5.29), 509 (3.87), 542 (3.04), 586 (3.11), 654 nm (2.90); HRMS (ES+) [$C_{52}H_{49}N_6O_2$]: calcd for $[M+H]^+$ 789.3917 found 789.3934.

5-(4-Di-cyclohexylurea-carbonylphenyl)-15-hexyl-10,20-diphenylporphyrin (186)



5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **174** (0.03 g, 0.04 mmol), DCC (9.3 mg, 0.04 mmol), DMAP (4.84 mg, 0.04 mmol) and 2-nitrobenzylalcohol (34.4 mg, 0.03 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **186** as a purple solid (11.7 mg, 0.01 mmol, 30%): mp >310 °C; R_f=0.37 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.71 (s, 2H, N*H*), 0.89 (m, 2H,-CH_2), 0.96 (t, *J*= 14.6 Hz, 3H,-CH_3), 1.17 (m, 2H, -CH_2), 1.42 (m, 4H, -CH_2), 1.53 (m, 2H, -CH_2), 1.61 (m, 2H, -CH_2), 1.67 (m, 4H, -CH_2), 1.75 (t, *J*=15.2 Hz, 2H, -CH_2), 1.91 (m, 4H, -CH_2), 2.01 (m, 2H, -CH_2), 2.19 (m, 2H, -CH_2), 2.58 (m, 2H, -CH_2), 3.74 (m, 1H, -N-C*H*), 4.41 (m, 1H, -CON-C*H*), 5.04 (t, *J*= 8.2 Hz, 2H, -CH_2), 6.31 (d, *J*=7.0 Hz, 1H, -N*H*), 7.81 (t, *J*= 7.6 Hz, 6H, phenyl-*H*), 7.98 (d, *J*= 7.6 Hz, 2H, phenyl-*H*), 8.24 (d, 4H, *J*=6.4 Hz, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.76 (d, *J*=4.7 Hz, 2H, β-*H*), 8.84 (d, *J*=4.7 Hz, 2H, β-*H*), 8.95 (d, *J*=4.7 Hz, 2H, β-*H*), 9.52 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 24.2, 26.0, 30.5, 31.5, 35.2, 38.5, 49.5, 57.1, 62.1, 119.4, 120.8, 124.9, 126.2, 127.3, 134.0, 141.9, 144.4, 154.1 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.31), 517 (3.94), 551 (3.64), 594 (4.51), 653 nm (3.75); HRMS (ES+) [$C_{58}H_{61}N_6O_2$]: calcd for $[M+H]^+$ 873.4856 found 873.4874.

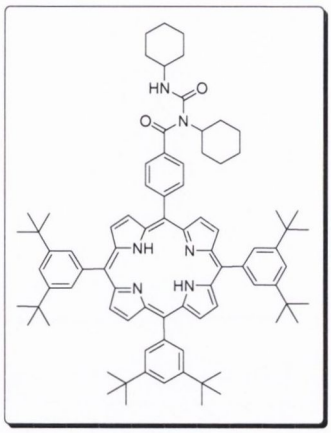
5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20-(4-(*o*-nitrobenzyl-carboxy)phenyl)porphyrin (189)



5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin **181** (0.02 g, 0.02 mmol), DCC (23.25 mg, 0.10 mmol), DMAP (12.10 mg, 0.10 mmol) and 2-nitrobenzylalcohol (0.11 g, 0.10 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. The crude product was purified on silica gel (*n*-hexane/dichloromethane = 2:1, v/v) and the first fraction corresponded to the title compound **189** as purple solid (8.6 mg, 0.01 mmol 38%): mp >310 °C; R_f=0.48 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.71 (s, 2H, N*H*), 1.52 (s, 54H, -C(C*H*$_3$)$_3$), 5.96 (s, 2H, -OC*H*$_2$), 7.55 (t, *J*= 7.6 Hz, 1H, phenyl-*H*), 7.73 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 7.76 (s, 3H, phenyl-*H*), 7.86 (d, *J*=7.9 Hz, 1H, phenyl-*H*), 8.08 (t, *J*=7.9 Hz, 6H, phenyl-*H*), 8.20 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.35 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.91 ppm (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 29.3, 31.3, 34.6, 63.2, 120.6, 121.2, 127.6, 128.7, 129.4, 134.3, 140.7, 148.3, 165.8 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 422 (5.16), 518 (4.66), 571 (4.65), 599 (4.61), 651 nm (4.65); HRMS (ES+) [$C_{76}H_{83}N_5O_4$]: calcd for $[M+H]^+$ 1130.6523, found 1130.6526.

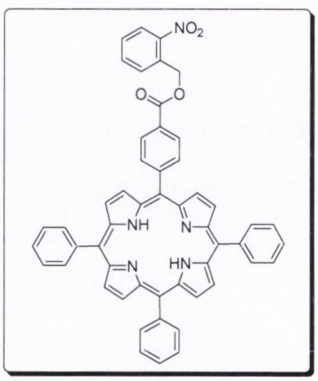
Alternatively compound **189** was prepared *via* method B. 5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin **181** (0.02 g, 0.02 mmol), EDAC (7.66 mg, 0.04 mmol), DMAP (4.88 mg, 0.04 mmol) and 2-nitrobenzylalcohol (12.4 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL). Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **189** as a purple solid (19.5 mg, 0.02 mmol, 86%).

5-(4-Di-cyclohexylurea-carbonylphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl) porphyrin (187)



The second fraction from the synthesis of porphyrin **189** *via* method A corresponded to 5-(4-di-cyclohexylurea-carbonyl phenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin **187** as a purple solid (10.3 mg, 0.01 mmol, 43%): mp >310 °C; R_f=0.46 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.69 (s, 2H, N*H*), 0.89 (m, 2H, -CH_2), 1.18 (m, 2H, -CH_2), 1.43 (m, 4H, -CH_2), 1.52 (s, 54H, -C(CH_3)$_3$), 1.80 (m, 2H, -CH_2), 1.96 (m, 4H, -CH_2), 2.06 (m, 2H, -CH_2), 2.20 (m, 2H, -CH_2), 2.56 (m, 2H, -CH_2), 3.74 (d, *J*=7.6 Hz, 1H, -N-C*H*), 4.45 (t, *J*=11.7 Hz, 1H, CON-C*H*), 6.23 (d, *J*=6.4 Hz, 1H, -N*H*), 7.85 (d, *J*=1.8 Hz, 3H, phenyl-*H*), 8.00 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.12 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 6H, phenyl-*H*), 8.34 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.82 (d, 2H, β-*H*), 8.95 ppm (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.3, 26.0, 29.3, 31.3, 32.3, 34.6, 62.1, 117.4, 120.6, 121.2, 124.6, 128.0, 129.5, 133.7, 136.3, 140.7, 148.3, 154.1, 165.7 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 421 (5.33), 518 (3.64), 554 (3.20), 596 (2.60), 655 nm (3.64); HRMS (ES+) [$C_{82}H_{101}N_6O_2$]: calcd for $[M+H]^+$ 1201.799 found 1201.804.

5-(4-(*o*-Nitrobenzylcarboxy)phenyl)-10,15,20-triphenylporphyrin (190)

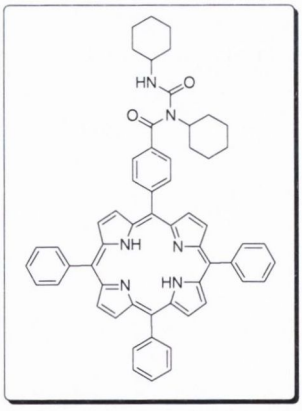


5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **182** (0.02 g, 0.03 mmol), DCC (34.88 mg, 0.15 mmol), DMAP (18.15 mg, 0.15 mmol) and 2-nitrobenzylalcohol (0.17 g, 0.15

mmol) were heated to reflux for 18 h in THF (10 mL) according to method A. The crude product was purified on silica gel (*n*-hexane/dichloromethane = 2:1, v/v) and the first fraction corresponded to the title compound of 5-(4-(*o*-nitrobenzyl carboxy)phenyl)-10,15,20-triphenylporphyrin **190** as a purple solid (6.6 mg, 0.01 mmol, 27%). >310 °C; R_f=0.69 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.80 (s, 2H, N*H*), 5.95 (s, 2H, -OCH_2), 7.55 (t, *J*= 8.2 Hz, 1H, phenyl-*H*), 7.72 (d, *J*=2.8 Hz, 1H, phenyl-*H*), 7.76 (t, *J*=7.3 Hz, 9H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 1H, phenyl-*H*), 8.18 (s, 1H, phenyl-*H*), 8.20 (m, 6H, phenyl-*H*), 8.32 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.47 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.84 ppm (t, *J*=5.2 Hz, 6H, β-*H*); ^{13}C NMR (100 MHz, CDCl3): δ=13.70, 22.27, 29.27, 31.49, 63.25, 117.84, 119.97, 124.79, 126.29, 127.67, 131.93, 133.49, 134.11, 141.57, 147.17, 147.28, 165.73 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.15), 516 (4.59), 551 (4.51), 597 (4.48), 649 nm (4.54); HRMS (ES+) [$C_{52}H_{36}N_5O_4$]: calcd for $[M+H]^+$ 794.2767, found 794.2781.

Alternatively compound **190** was prepared *via* method B. 5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **182** (0.02 g, 0.03 mmol), EDAC (5.83 mg, 0.03 mmol), DMAP (3.71 mg, 0.03 mmol) and 2-nitrobenzylalcohol (4.66 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) at rt. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **190** as a purple solid (17.6 mg, 0.01 mmol, 73%).

5-(4-Di-cyclohexylurea-carbonylphenyl)-10,15,20-triphenylporphyrin (188)



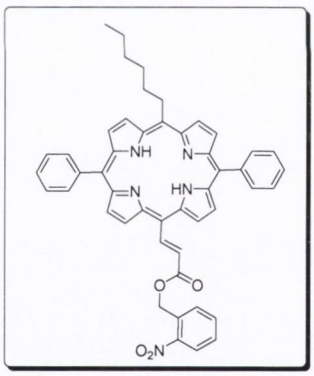
The second fraction from the synthesis of porphyrin **190** *via* method A corresponded to 5-(4-dicyclohexylurea-carbonylphenyl)-10,15,20-triphenyl porphyrin **188** as a purple solid (13.7 mg, 0.12 mmol, 52%): mp >310 °C; R_f=0.52 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.83 (s, 2H, N*H*), 0.86 (m, 2H, -CH_2), 1.16 (m, 2H, -CH_2), 1.38 (m, 4H, -CH_2), 1.61 (m, 2H, -CH_2), 1.71 (m, 2H, -CH_2), 1.89 (m, 4H, -CH_2), 2.02 (m, 2H, -CH_2), 2.14 (m, 2H, -CH_2), 3.73 (m, 1H, -N-C*H*), 4.37 (m, 1H, CON-C*H*),

6.30 (d, 1H, -N*H*), 7.75 (d, *J*= 6.4 Hz, 9H, phenyl-*H*), 7.95 (d, *J*= 7.0 Hz, 2H, phenyl-*H*), 8.20 (d, 6H, *J*=7.0 Hz, phenyl-*H*), 8.26 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.77 (s, 2H, β-*H*), 8.83 ppm (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.3, 32.2, 62.1, 124.6, 126.3, 127.4, 128.0, 129.5, 133.7, 134.1, 141.6, 167.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.16), 515 (3.95), 550 (3.75), 597 (3.64), 649 nm (3.72); HRMS (ES+) [$C_{58}H_{53}N_6O_2$]: calcd for $[M+H]^+$ 865.423, found 865.4211.

Method B: EDAC carbodiimide reagent approach

To a solution of porphyrin (1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (2 eq.) and dimethylaminopyridine, (DMAP) (2 eq.) in dry DCM, a solution of 2-nitrobenzylalcohol (4 eq.) in DCM was added at rt. The mixture was stirred at rt for 18 hours. Upon completion, the solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product and purification by column chromatography.

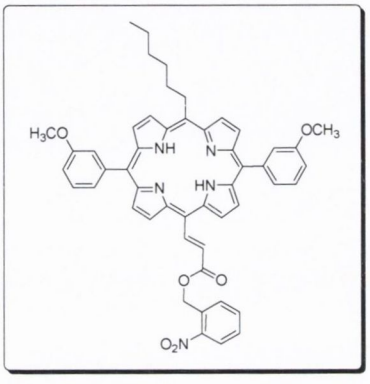
5-Hexyl-15-(2-*o*-nitrobenzyl-carboxyethenyl)-10,20-diphenylporphyrin (193)



5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin **171** (0.01 g, 0.02 mmol), EDAC (6.21 mg, 0.03 mmol), DMAP (3.95 mg, 0.03 mmol) and 2-nitrobenzylalcohol (10.05 mg, 0.06 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **193** as a purple solid (9.88 mg, 0.01 mmol, 81%): mp >310 °C; R_f=0.53 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.39 (s, 2H, N*H*), 0.88 (t, *J*=7.3 Hz, 3H, -CH_3), 1.36 (m, 2H, -CH_2), 1.47 (m, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 2.49 (m, 2H, -CH_2), 4.93 (t, *J*=7.6 Hz, 2H, -CH_2), 5.88 (s, 2H, -OCH_2), 6.86 (d, *J*=15.8 Hz, 1H, -C*H*=), 7.53 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.70 (d, *J*=7.6 Hz, 1H, phenyl-*H*), 7.77 (m, 6H, phenyl-*H*), 7.83 (d, *J*=7.6 Hz, 1H,

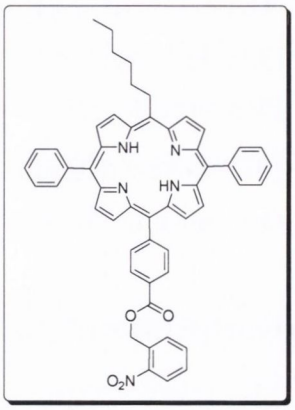
phenyl-*H*), 8.16 (dd, J_1=7.6 Hz, J_2=7.0 Hz, 4H, phenyl-*H*), 8.84 (dd, J_1=4.7 Hz, J_2=4.7 Hz, 4H, β-*H*), 9.41 (t, *J*=4.7 Hz, 4H, β-*H*), 10.27 ppm (d, *J*= 15.8 Hz, 1H, =C*H*-); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 29.3, 29.8, 31.4, 35.1, 38.4, 62.1, 62.9, 120.3, 122.6, 124.6, 126.3, 127.5, 128.0, 128.7, 129.5, 134.0, 136.3, 141.7, 146.7 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 427 (5.46), 526 (4.62), 572 (4.66), 599 (4.56), 653 nm (4.56); HRMS (ES+) [$C_{48}H_{41}N_5O_4$]: calcd for $[M+H]^+$ 752.3231, found 752.3237.

5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(2-*o*-nitro-benzylcarboxyethenyl)porphyrin (194)



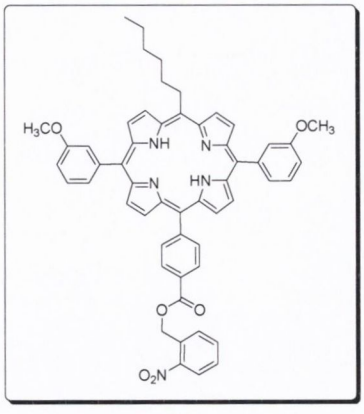
5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin **172** (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.05 mmol), DMAP (6.71 mg, 0.05 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.10 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **194** as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; R_f=0.36 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.41 (s, 2H, N*H*), 0.90 (t, *J*=7.3 Hz, 3H, -CH_3), 1.37 (m, 2H, -CH_2), 1.48 (m, 2H, -CH_2), 1.78 (m, 2H, -CH_2), 2.49 (m, 2H, -CH_2), 4.13 (t, *J*=7.6 Hz, 2H, -CH_2), 4.94 (s, 6H, -OCH_3), 5.89 (s, 2H, -OCH_2), 6.86 (d, *J*=15.8 Hz, 1H, -C*H*=), 7.33 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 7.45 (t, *J*=8.0 Hz, 2H, phenyl-*H*), 7.53 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.64 (t, *J*=7.7 Hz, 4H, phenyl-*H*), 7.83 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.07 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.17 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 8.88 (dd, J_1=4.4 Hz, J_2=4.4 Hz, 4H, β-*H*), 9.41 (s, 4H, β-*H*), 10.26 ppm (d, *J*=15.8 Hz, 1H, =C*H*-); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 22.7, 28.2, 31.9, 35.5, 38.9, 55.5, 62.6, 110.6, 117.9, 120.4, 126.3, 128.9, 134.2, 143.4, 144.6, 148.0, 165.6, 169.7 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.26), 527 (3.72), 575 (4.79), 600 (4.75), 652 nm (4.75); HRMS (ES+) [$C_{50}H_{45}N_5O_4$]: calcd for $[M+H]^+$ 812.3455, found 812.3448.

5-Hexyl-15-(4-(*o*-nitrobenzylcarboxy)phenyl)-10,20-diphenylporphyrin (195)



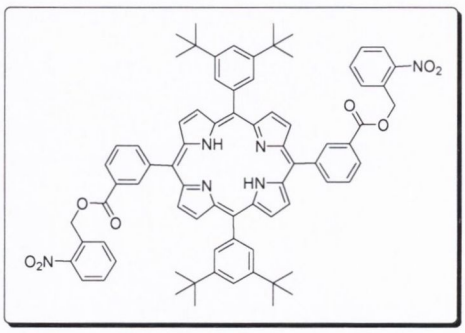
5-Hexyl-15-(4-carboxyphenyl)-10,20-diphenylporphyrin **174** (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **195** as a purple solid (13.0 mg, 0.01 mmol, 81%): mp >310 °C; R_f=0.75 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.75 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, -CH_3), 1.40 (m, 2H, -CH_2), 1.46 (m, 2H, -CH_2), 1.76 (m, 2H, -CH_2), 2.54 (m, 2H, -CH_2), 5.01 (t, *J*=8.0 Hz, 2H, -CH_2), 5.95 (s, 2H, -OCH_2), 7.50 (t, *J*=8.2 Hz, 1H, phenyl-*H*), 7.56 (d, *J*=2.8 Hz, 1H, phenyl-*H*), 7.74 (m, *J*=7.3 Hz, 6H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 1H, phenyl-*H*), 8.18 (dd, J_1=1.8 Hz, J_2=1.1 Hz, 4H, phenyl-*H*), 8.24 (s, 1H, phenyl-*H*), 8.29 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.72 (d, *J*=4.8 Hz, 2H, β-*H*), 8.79 (d, *J*=4.8 Hz, 2H, β-*H*), 8.89 (d, *J*=4.8 Hz, 2H, β-*H*), 9.48 ppm (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1, 22.7, 29.4, 30.1, 30.3, 31.5, 32.0, 35.0, 63.7, 124.2, 124.4, 125.3, 126.7, 127.8, 128.0, 128.9, 128.9, 129.2, 130.9, 133.9, 134.7, 142.3, 151.2, 151.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.48), 516 (4.48), 551 (4.37), 592 (4.33), 651 nm (4.29); HRMS (ES+) [$C_{52}H_{44}N_5O_4$]: calcd for $[M+H]^+$ 802.3393, found 802.3401.

5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(4-(*o*-nitrobenzylcarboxy)phenyl)-porphyrin (196)



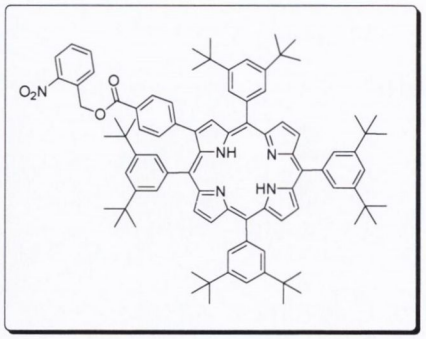
5-(3-carboxyphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin **175** (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.06 mmol), DMAP (6.71 mg, 0.06 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.11 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:1, v/v) yielded **196** as a purple solid (19.6 mg, 0.02 mmol, 83%): mp =227 °C; R_f=0.38 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.84 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, -CH_3), 1.38 (m, 2H, -CH_2), 1.51 (m, 2H, -CH_2), 1.60 (m, 2H, -CH_2), 1.82 (m, 2H, -CH_2), 3.98 (s, 6H,-OCH_3), 4.99 (t, *J*=7.7 Hz, 2H, -CH_2), 5.93 (s, 2H, -OCH_2), 7.33 (d, *J*=8.1 Hz, 2H, phenyl-*H*), 7.53 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.58 (t, *J*=8.0 Hz, 2H, phenyl-*H*), 7.72 (t, *J*=7.36 Hz, 1H, phenyl-*H*), 7.78 (t, *J*=7.7 Hz, 4H, phenyl-*H*), 7.83 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.17 (d, *J*= 8.1 Hz, 1H, phenyl-*H*), 8.29 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.46 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.85 (d, *J*=4.8 Hz, 2H, β-*H*), 8.95 (d, *J*=4.8 Hz, 2H, β-*H*), 9.46 ppm (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 22.7, 29.7, 30.3, 31.9, 35.6, 39.0, 55.6, 62.4, 63.7, 113.6, 117.5, 119.6, 120.5, 121.4, 125.0, 127.5, 128.4, 128.9, 129.8, 132.4, 133.9, 134.8, 136.8, 143.5, 147.5, 157.9, 166.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.31), 514 (4.26), 550 (4.15), 578 (4.30), 654 nm (4.45); HRMS (ES+) [$C_{54}H_{47}N_5O_6$]: calcd for $[M+H]^+$ 862.3605, found 862.3610.

5,15-Bis(3,5-di-*tert*-butylphenyl)-10,20-bis(3-(*o*-nitrobenzylcarboxy)phenyl)porphyrin (198)



5,15-Bis(3,5-di-*tert*-butylphenyl)-10,20-bis(3-carboxyphenyl)-porphyrin **178** (0.01 g, 0.01 mmol), EDAC (10.91 mg, 0.11 mmol), DMAP (6.94 mg, 0.11 mmol) and 2-nitrobenzylalcohol (17.63 mg, 0.23 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:1, v/v) yielded the title compound **198** as a purple solid (8.30 mg, 0.01 mmol, 58%): mp >310 °C; R_f=0.48 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.76 (s, 2H, N*H*), 1.51 (s, 36H, -C(C*H*$_3$)$_3$), 5.85 (s, 4H, -OC*H*$_2$), 7.42 (t, *J*=7.3 Hz, 2H, phenyl-*H*), 7.57 (t, *J*=7.7 Hz, 2H, phenyl-*H*), 7.69 (d, *J*=7.7 Hz, 2H, phenyl-*H*), 7.79 (s, 2H, phenyl-*H*), 7.87 (t, *J*=7.7 Hz, 2H, phenyl-*H*), 8.08 (d, *J*=9.6 Hz, 6H, phenyl-*H*), 8.44 (d, *J*=8.1 Hz, 2H, phenyl-*H*), 8.51 (d, *J*=8.51 Hz, 2H, phenyl-*H*), 8.77 (s, 2H, phenyl-*H*), 8.78 (s, 2H, β-*H*), 8.90 (d, *J*=4.76 Hz, 4H, β-*H*), 8.94 ppm (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.9, 29.7, 31.7, 35.1, 36.2, 52.3, 59.4, 63.6, 118.4, 121.2, 122.0, 125.1, 126.6, 128.4, 129.6, 132.3, 133.9, 137.6, 138.8, 140.9, 142.9, 147.5, 148.9, 151.6, 166.2, 171.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (5.30), 514 (4.53), 545 (4.48), 577 (4.53), 652 nm (4.51); HRMS (ES+) [$C_{76}H_{72}N_6O_8$]: calcd for $[M+H]^+$ 1197.5490, found 1197.5450.

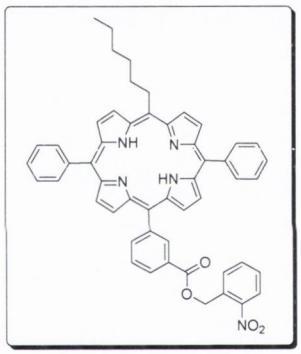
5,10,15,20-Tetrakis(3,5-di-*tert*-butylphenyl)-2-(4-(*o*-nitrobenzylcarboxy)phenyl) porphyrin (199)



2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-*tert*-butyl-phenyl)porphyrin **179** (0.01 g, 0.01 mmol), EDAC (3.24 mg, 0.02 mmol), DMAP (2.06 mg, 0.02 mmol) and 2-

nitrobenzylalcohol (5.24 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:1, v/v) yielded **199** as a purple solid (7.57 mg, 0.01 mmol, 68%): mp >310 °C; R_f=0.82 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.56 (s, 2H, -N*H*), 1.50 (s, 72H, -C(C*H*$_3$)$_3$), 5.81 (s, 2H, -OC*H*$_2$), 7.34 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 7.50 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 7.69 (m, 4H, phenyl-*H*), 7.77 (m, 4H, phenyl-*H*), 7.82 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 7.85 (d, *J*=8.4 Hz, 1H, phenyl-*H*), 8.06 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 4H, phenyl-*H*), 8.12 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 8.18 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.71 (d, *J*=4.8 Hz, 1H, β-*H*), 8.74 (s, 1H, β-*H*), 8.82 (m, 1H, β-*H*), 8.85 (d, *J*=3.6 Hz, 2H, β-*H*), 8.90 ppm (m, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 23.9, 29.4, 30.1, 32.8, 34.9, 37.1, 121.0, 128.7, 129.6, 130.0, 130.7, 133.8, 140.0, 148.0, 148.6, 148.8, 165.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 426 (5.23), 525 (4.23), 576 (4.30), 601 (4.28), 653 nm (4.33); HRMS (ES+) [$C_{90}H_{103}N_5O_4$]: calcd for $[M+H]^+$ 1318.8090, found 1318.8030.

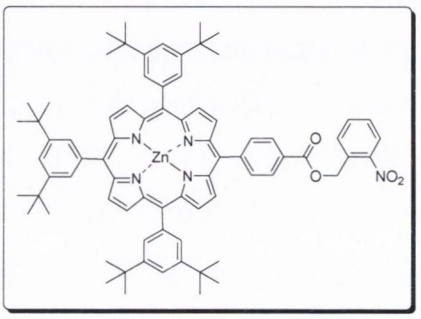
5-Hexyl-15-(3'-(*o*-nitrobenzylcarboxy)phenyl)-10,20-diphenylporphyrin (200)



5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **176** (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) according to method B. Purification on silica gel (*n*-hexane/dichloromethane = 1:1, v/v) yielded **200** as a purple solid (16.8 mg, 0.01 mmol, 70%): mp >310 °C; R_f=0.60 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.74 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, -C*H*$_3$), 1.36 (m, 2H, -C*H*$_2$), 1.50 (m, 2H, -C*H*$_2$), 1.80 (m, 2H, -C*H*$_2$), 2.54 (m, 2H, -C*H*$_2$), 5.00 (t, *J*=8.0 Hz, 2H, -C*H*$_2$), 5.83 (s, 2H, -OC*H*$_2$), 7.38 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.52 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.65 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 7.76 (m, 6H, phenyl-*H*), 7.85 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.06 (d, *J*=8.4 Hz, 1H, phenyl-*H*), 8.19 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.41 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.49 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.72 (d, *J*=4.8 Hz, 2H, β-*H*), 8.80 (d, *J*=4.8 Hz, 2H, β-*H*), 8.91 (t, *J*=2.2 Hz, 3H, β-*H* and phenyl-*H*), 9.48 ppm (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 22.7, 29.5, 29.7, 30.3, 31.9,

35.6, 39.0, 63.6, 117.5, 119.8, 121.2, 125.1, 126.7, 127.1, 127.8, 128.3, 129.2, 133.8, 134.9, 138.9, 142.3, 147.4, 166.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.48), 516 (4.47), 551 (4.36), 594 (4.32), 650 nm (4.33); HRMS (ES+) [$C_{52}H_{44}N_5O_4$]: calcd for $[M+H]^+$ 802.3393, found 802.3380.

[5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20-(4-(*o*-nitrobenzylcarboxy)phenyl) porphyrinato]zinc(II) (201)



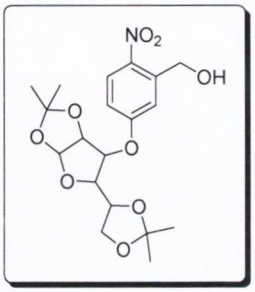
[5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butyl-phenyl)porphyrinato]zinc(II) **180** (0.02 g, 0.02 mmol), EDAC (7.21 mg, 0.04 mmol), DMAP (4.59 mg, 0.04 mmol) and 2-nitrobenzylalcohol (11.5 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **201** as a purple solid (19.4 mg, 0.02 mmol, 81%): mp >310 °C; R_f=0.65 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.52 (s, 54H, -C(CH_3)$_3$), 5.91 (s, 2H, -OCH_2), 7.52 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.73 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.79 (m, 3H, phenyl-*H*), 7.83 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 8.08 (m, 6H, phenyl-*H*), 8.18 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 1H, phenyl-*H*), 8.35 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 8.91 ppm (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.7, 29.7, 31.8, 35.1, 63.6, 118.9, 120.9, 122.7, 125.2, 127.9, 128.9, 129.6, 132.4, 133.9, 134.6, 141.7, 148.6, 149.4, 150.4, 166.3 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 423 (5.29), 549 (4.65), 650 nm (4.54); HRMS (ES+) [$C_{76}H_{81}N_5O_4Zn$]: calcd for [M] 1191.5580, found 1191.5614.

6.10 Synthesis of porphyrin linked-bioconjugates

1-Hydroxyl-2,3,4,6-pentaacetyl-D-glucose **207**,[208] 5-hydroxy-2-nitrobenzylalcohol **211**,[210] (3-hydroxymethyl-4-nitrophenyl)-2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranoside **213**,[212] 3-bromo-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranoside **215**[213] and 5-

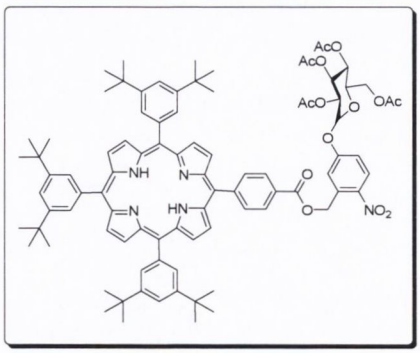
(methoxyethoxymethyl)-2-nitrobenzaldehyde **221**[222] were prepared according to literature procedure and their spectroscopic data were in accordance with the references.

(3-Hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (217)



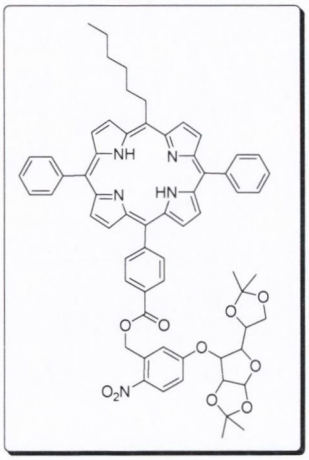
3-Bromo-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranoside **215** (1.80 g, 5.80 mmol) was dissolved in CH_2Cl_2 (15 mL) together with 1 equivalent of tetrabutylammonium fluoride (1.50 g, 5.80 mmol) and 3 equivalents of 5-hydroxy-2-nitrobenzyl alcohol **211** (2.95 g, 17.40 mmol). 1M NaOH solution (15 mL) was added and the reaction mixture was stirred vigorously at 35 °C in h. After dilution with EtOAc, the organic phase was washed three times with a 1M NaOH solution, twice with water and finally with brine. The organic phase was dried with magnesium sulphate and then the solvent removed under diminished pressure. Purification was carried out by chromatography (SiO_2, EtOAc/C_6H_{14}= 20:1, v/v) and yielded **217** as a white solid (0.12 g, 0.15 mmol, 5%): mp = 145 °C; MALDI-TOF MS (ES+): calcd for [M+Na^+-$C_4H_7NO_2$] 333.0950, found 333.0945.

5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20-(4'-(*o*-nitro-*p*-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyrano-side)benzyl)carboxy)phenyl)porphyrin (218)



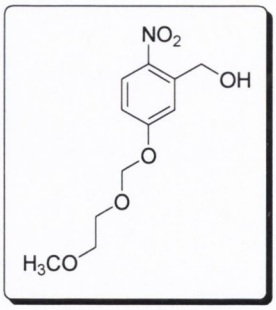
5-(Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin **181** (0.08 g, 0.08 mmol), EDAC (30.8 mg, 0.16 mmol), DMAP (19.6 mg, 0.16 mmol) and 5-((aceto-glucose)-2-nitrophenyl)methanol (0.16 g, 0.32 mmol) were stirred for 18 h in DCM (15 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane= 1:1, v/v) yielded **218** as a purple solid (90.3 mg, 0.02 mmol, 76%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.71 (s, 2H, N*H*), 1.52 (s, 54H, -C(C*H*$_3$)$_3$), 1.83 (s, 3H, -COC*H*$_3$), 1.99 (s, 3H, -COC*H*$_3$), 2.06 (s, 6H, -COC*H*$_3$), 3.91 (m, 1H, -C*H*), 4.16 (d, *J*=10.5 Hz, 1H, -C*H*), 4.28 (dd, J_1=5.0 Hz, J_2=5.0 Hz, 1H, -C*H*), 5.18 (m, 1H, -C*H*), 5.31 (m, 3H, -C*H* and -C*H*$_2$CO), 5.97 (s, 2H, -OC*H*$_2$), 7.10 (dd, J_1=2.2 Hz, J_2=2.2 Hz, 1H, phenyl-*H*), 7.42 (d, *J*=2.28 Hz, 1H, phenyl-*H*), 7.79 (s, 3H, phenyl-*H*), 8.07 (s, 6H, phenyl-*H*), 8.27 (d, *J*=9.0 Hz, 1H, phenyl-*H*), 8.38 (d, *J*= 8.0 Hz, 2H, phenyl-*H*), 8.49 (d, *J*=8.0 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.5 Hz, 2H, β-*H*), 8.91 ppm (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.8, 35.1, 61.7, 63.7, 67.8, 70.9, 72.4, 98.1, 115.7, 116.8, 117.6, 121.1, 121.7, 122.1, 128.1, 128.6, 129.8, 134.8, 135.7, 141.1, 142.4, 148.3, 160.5, 169.2, 170.1, 170.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 421 (5.18), 518 (3.81), 553 (3.60), 593 (3.41), 667 nm (3.75); HRMS (ES+) [$C_{90}H_{101}N_5O_{14}$]: calcd for $[M+H]^+$ 1476.7420, found 1476.7410.

5-Hexyl-15-(4'-(*o*-nitro-*m*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside)benzyl)-carboxy)phenyl)-10,20-diphenylporphyrin (219)



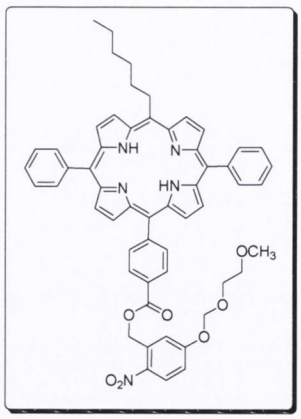
5-Hexyl-15-(4-carboxyphenyl)-10,20-diphenylporphyrin **174** (10 mg, 0.06 mmol), EDAC (18.2 mg, 0.12 mmol), DMAP (14.6 mg, 0.12 mmol) and (3-hydroxymethyl-4-nitrophenyl)-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranoside **217** (98 mg, 0.24 mmol) were stirred for 18 h in DCM (10 mL). Purification (SiO_2, *n*-hexane/dichloromethane= 1:1 v/v) yielded **219** as a purple solid (46 mg, 0.02 mmol, 72%): mp >310°C; R_f=0.30 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.76 (s, 2H, N*H*), 0.97 (t, *J*=7.0 Hz, 3H, -C*H*$_3$), 1.21 (m, 2H, -C*H*$_2$), 1.51 (s, 12H, -C(C*H*$_3$)$_2$), 1.68 (m, 2H, -C*H*$_2$), 1.93 (m, 2H, -C*H*$_2$), 2.67 (m, 2H, -C*H*$_2$), 4.00 (m, 1H, C-C*H*$_2$-O), 4.04 (m, 1H, C-C*H*$_2$-O), 4.27 (m, 1H, -CC*H*-CH$_2$), 4.31 (d, *J*= 3.0 Hz, 1H, O-C*H*-), 4.38 (m, 1H, O-C*H*-CHCH$_2$-), 4.44 (m, 1H, OC*H*-C), 4.49 (d, *J*= 3.8 Hz, 1H, OC*H*-O), 4.86 (t, *J*=8.2 Hz, 2H, -C*H*$_2$), 5.04 (s, 2H, -OC*H*$_2$), 7.49 (dd, *J*= 2.8 Hz, 2.8Hz, 1H, phenyl-*H*), 7.84 (d, *J*= 2.5 Hz, 1H, phenyl-*H*), 7.98 (m, 6H, phenyl-*H*), 8.19 (d, *J*= 6.3 Hz, 1H, phenyl-*H*), 8.53 (m, 6H, phenyl-*H*), 8.59 (d, *J*= 3.8 Hz, 2H, phenyl-*H*), 8.77 (m, 4H, β-*H*), 8.91 (d, *J*= 4.8 Hz, 1H, β-*H*), 9.10 (d, *J*= 4.0 Hz, 4H, β-*H*), 9.49 ppm (d, *J*= 4.8 Hz, 1H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.6, 25.3, 25.6, 26.3, 26.5, 26.6, 26.8, 27.5, 38.4, 65.6, 66.0, 68.0, 73.0, 74.6, 75.6, 79.8, 80.5, 84.1, 105.0, 106.4, 108.5, 110.1, 110.9, 111.8, 114.2, 121.4, 122.4, 122.7, 125.0, 126.7, 127.1, 127.5, 128.5, 130.2, 130.4, 134.5, 138.8, 139.0, 145.1, 145.2, 145.9, 146.2, 155.2, 164.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.25), 514 (3.90), 551(3.56), 593 (3.45), 667 nm (3.51); HRMS (ES+) [$C_{64}H_{61}N_5O_{10}$]: calcd for $[M+H]^+$ 1060.4497, found 1060.4479.

5-(Methoxyethoxymethyl)-2-nitrophenylmethanol (222)



5-(Methoxyethoxymethyl)-2-nitrobenzaldehyde **221** (0.62 g, 2.44 mmol) was dissolved in THF and the solution was cooled to 0 °C. Sodium borohydride (92 mg, 2.44 mmol) was added and the mixture was stirred for 2 hours. The mixture was filtered through silica gel and the solvent was evaporated *in vacuo* to yield the title compound **222** as a yellow solid (0.62 g, 0.16 mmol, 98%): mp 98-101 °C; R_f=0.29 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 3.22 (s, 3H, -OC*H*$_3$), 3.45 (m, 2H, -C*H*$_2$O), 3.72 (m, 2H, -OC*H*$_2$), 4.11 (br.s, 1H, -O*H*), 4.84 (s, 2H, -C*H*$_2$OH), 5.24 (s, 2H, -OC*H*$_2$O), 6.88 (dd, J_1=2.4 Hz, J_2=2.3 Hz, 1H, phenyl-*H*), 7.30 (s, 1H, phenyl-*H*), 7.95 (d, *J*=9.36 Hz, 1H, phenyl-*H*), ^{13}C NMR (100 MHz, $CDCl_3$): δ=58.3, 61.3, 67.6, 70.9, 92.6, 113.8, 114.6, 127.0, 139.8, 140.7, 161.2 ppm; HRMS (ES+) [$C_{11}H_{14}NO_6$]: calcd for $[M+Na]^+$ 280.0797, found 280.0800.

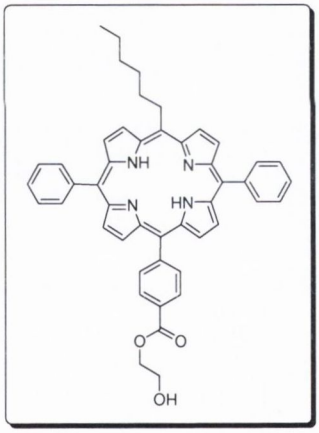
5-Hexyl-15-(4-(*o*-nitro-*p*-methoxyethoxymethylbenzylcarboxy)phenyl)-10,20-diphenyl porphyrin (223)



5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **174** (0.05 g, 0.08 mmol), EDAC (28.8 mg, 0.15 mmol), DMAP (18.3 mg, 0.15 mmol) and 5-(methoxyethoxymethyl)-2-nitrophenylmethanol **222** (77.2 mg, 0.30 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the

solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded **223** as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; R_f=0.36 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.72 (s, 2H, N*H*), 0.93 (t, *J*=6.8 Hz, 3H, -C*H*$_3$), 1.38 (m, 2H, -C*H*$_2$), 1.50 (m, 2H, -C*H*$_2$), 1.80 (m, 2H, -C*H*$_2$), 2.52 (m, 2H, -C*H*$_2$), 3.31 (s, 3H, -OC*H*$_3$), 3.53 (t, *J*=3.9 Hz, 2H, -OC*H*$_2$), 3.82 (t, *J*=3.9 Hz, 2H, -C*H*$_2$OCH$_3$), 4.96 (t, *J*=8.8 Hz, 2H, -CH$_2$), 5.34 (s, 2H, -OC*H*$_2$), 5.92 (s, 2H, -OC*H*$_2$O), 7.09 (dd, J_1=2.0 Hz, J_2=2.0 Hz, 1H, phenyl-*H*), 7.43 (d, *J*=1.96 Hz, 1H, phenyl-*H*), 7.76 (m, 6H, phenyl-*H*), 8.20 (s, 1H, phenyl-*H*), 8.22 (d, *J*=5.8 Hz, 4H, phenyl-*H*), 8.33 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 8.49 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 8.77 (d, *J*=4.9 Hz, 2H, β-*H*), 8.84 (d, *J*=4.9 Hz, 2H, β-*H*), 8.92 (d, *J*=4.9 Hz, 2H, β-*H*), 9.46 ppm (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 29.3, 29.8, 31.5, 35.2, 38.5, 58.6, 62.1, 62.7, 63.4, 67.9, 71.0, 93.0, 114.4, 115.7, 117.1, 119.4, 120.9, 126.2, 127.3, 127.7, 128.45, 134.0, 140.7, 141.8, 147.1, 159.7, 161.2, 165.7, 169.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.16), 516 (3.90), 551 (3.65), 594 (3.58), 653 nm (3.78); HRMS (ES+) [$C_{56}H_{51}N_5O_7$]: calcd for $[M+H]^+$ 906.3867, found 906.3899.

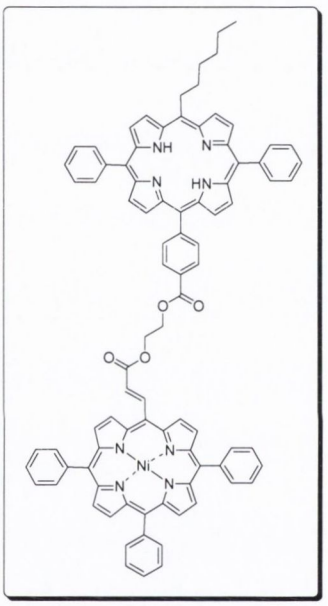
5-Hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin (224)



5-Hexyl-15-(4-(*o*-nitro-p-(methoxyethoxymethyl)benzylcarboxy)phenyl)-10,20-di-phenyl porphyrin **223** (0.05 g, 0.06 mmol) was dissolved in a small amount of THF. Ethylene glycol (10 mL) was added to the solution and was heated at 140 °C for 5 hours (TLC monitoring). The reaction was cooled to room temperature and was washed with saturated aqueous sodium bicarbonate and brine. The solution was dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to yield **224** as a purple solid (64.7 mg, 0.05 mmol, 92%): mp >310 °C; R_f=0.44 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.75 (s, 2H, N*H*), 0.91 (t, *J*=7.0 Hz, 3H, -C*H*$_3$), 1.37 (m, 2H, -C*H*$_2$), 1.50 (m, 2H, -C*H*$_2$), 1.80 (m, 2H, -C*H*$_2$), 2.52 (m, 2H, -C*H*$_2$), 4.09 (s, 2H,

-OCH_2), 4.64 (t, *J*=4.0 Hz, 2H, -CH_2OH), 5.00 (t, *J*=8.2 Hz, 2H, -CH_2), 7.74 (m, 6H, phenyl-*H*), 8.18 (d, *J*=6.4 Hz, 4H, phenyl-*H*), 8.27 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.43 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.71 (d, *J*=5.3 Hz, 2H, β-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.90 (d, *J*=5.2 Hz, 2H, β-*H*), 9.47 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 22.7, 30.3, 31.9, 35.6, 39.0, 61.6, 67.0, 93.5, 114.9, 116.5, 117.6, 119.8, 121.3, 127.9, 128.9, 134.8, 142.3, 147.3, 167.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (5.17), 517 (2.30), 551 (3.45), 594 (3.28), 650 nm (3.38); HRMS (ES+) [$C_{47}H_{42}N_4O_3$]: calcd for $[M+H]^+$ 711.3335, found 711.3354.

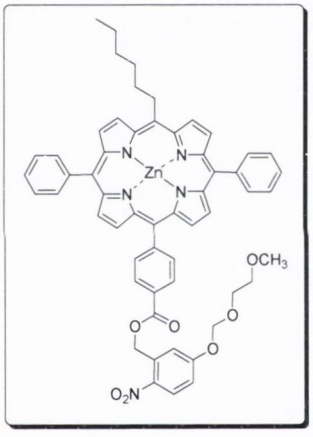
[5-(4-(Ethoxycarbonylphenyl-)-15-hexyl-10,20-diphenylporphyrin)-carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (226)



5-(2-Carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) **225** (0.01 g, 0.02 mmol), EDAC (2.88 mg, 0.03 mmol), DMAP (1.83 mg, 0.03 mmol) and 5-hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin **224** (11 mg, 0.02 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane = 1:2, v/v) yielded the title compound as a purple solid (19.0 mg, 0.03 mmol, 93%): mp >310 °C; R_f=0.15 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.78 (s, 2H, N*H*), 0.97 (t, *J*=7.3 Hz, 3H, -CH_3), 1.64 (m, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 1.96 (m, 2H, -CH_2), 2.53 (m, 2H, -CH_2), 4.54 (m, 4H, -CH_2), 5.00 (t, *J*=7.6 Hz, 2H, -CH_2), 6.41 (d, *J*=15.2 Hz, 1H,-C*H*=C), 7.51 (m, 6H, phenyl-*H*),

7.69 (m, 9H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 4H, phenyl-*H*), 7.91 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.13 (d, *J*=6.44 Hz, 4H, phenyl-*H*), 8.25 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.57 (d, *J*=4.7 Hz, 2H, β-*H*), 8.63 (d, *J*=4.7 Hz, 2H, β-*H*), 8.66 (d, *J*=4.7 Hz, 2H, β-*H*), 8.69 (d, *J*=4.7 Hz, 2H, β-*H*), 8.77 (d, *J*=5.2 Hz, 2H, β-*H*), 8.87 (d, *J*=4.7 Hz, 2H, β-*H*), 9.39 (d, *J*=4.7 Hz, 2H, β-*H*), 9.46 (d, *J*=4.7 Hz, 2H, β-*H*), 9.98 ppm (d, *J*=15.8 Hz, 1H, =C*H*CO); ^{13}C NMR (100 MHz, CDCl3): δ=14.2, 20.8, 22.7, 23.4, 23.8, 25.0, 25.6, 29.1, 29.5, 29.7, 30.3, 31.9, 35.6, 38.9, 62.8, 63.2, 68.0, 73.6, 91.2, 109.3, 117.6, 119.5, 119.8, 120.5, 121.3, 126.6, 127.0, 127.0, 129.2, 130.7, 131.4, 132.3, 132.8, 133.5, 133.5, 134.5, 134.7, 140.2, 141.5, 142.2, 142.8, 144.8, 147.3, 166.2, 166.8 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (5.11), 523 (4.41), 546 (4.41), 597 (4.40), 653 nm (4.45); HRMS (ES+) [$C_{88}H_{66}NiN_8O_4$]: calcd for $[M+H]^+$ 1357.4639, found 1357.4669.

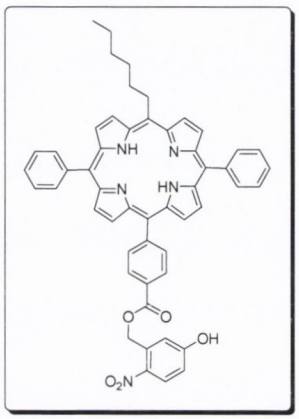
[5-Hexyl-15-(3-*o*-nitro-*p*-(methoxyethoxymethyl)-benzylcarboxyphenyl)10,20-diphenylporphyrinato]zinc(II) (227)



5-Hexyl-15-(4-(*o*-nitro-*p*-(methoxyethoxy-methyl)benzylcarboxyphenyl)-10,20-di-phenyl-porphyrin **223** (0.10 g, 0.11 mmol) was dissolved in $CHCl_3$. Two drops of TFA were added, followed by zinc(II)oxide (26.9 mg, 0.33 mmol). The solution was stirred for 18 hours and filtered. The solvent was evaporated and subjected to column chromatography (SiO_2, *n*-hexane/dichloromethane = 1:2, v/v) and gave the **227** as a purple solid (100.24 mg, 0.10 mmol, 94%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=0.93 (t, *J*=7.0 Hz, 3H, -CH_3), 1.40 (m, 2H, -CH_2), 1.50 (m, 2H, -CH_2), 1.84 (m, 2H, -CH_2), 2.55 (m, 2H, -CH_2), 3.15 (s, 3H, -OCH_3), 3.35 (t, *J*=4.1 Hz, 2H, -OCH_2), 3.39 (t, *J*=4.1 Hz, 2H, -CH_2OCH$_3$), 4.97 (t, *J*=8.2 Hz, 2H, -CH$_2$), 5.24 (s, 2H, -OCH_2), 5.85 (s, 2H, -OCH_2O), 7.03 (d, *J*=2.9 Hz, 1H, phenyl-*H*), 7.36 (d, *J*=2.4 Hz, 1H, phenyl-*H*), 7.74 (m, 6H, phenyl-*H*), 8.16 (s, 1H, phenyl-*H*), 8.18 (d, *J*=5.8 Hz, 4H, phenyl-

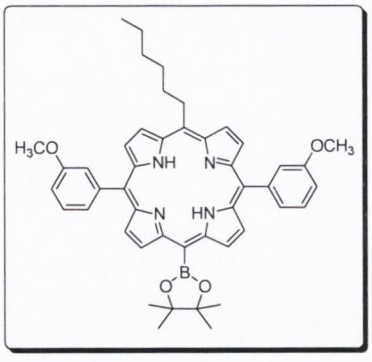
H), 8.29 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.82 (d, *J*=4.7 Hz, 2H, β-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 8.97 (d, *J*=4.6 Hz, 2H, β-*H*), 9.53 ppm (d, *J*=4.6 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 22.3, 29.3, 30.0, 31.5, 35.4, 38.8, 58.5, 62.1, 62.7, 63.3, 67.7, 70.9, 92.9, 114.2, 114.6, 115.3, 118.1, 120.3, 121.8, 127.1, 127.5, 128.2, 128.6, 130.8, 134.2, 135.1, 140.6, 142.4, 147.9, 149.3, 149.7, 159.7, 161.1, 165.7, 169.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (5.23), 549 (3.86), 588 nm (3.00); HRMS (ES+) [$C_{56}H_{49}N_5O_7Zn$]: calcd for $[M+H]^+$ 968.3002, found 968.2964

5-Hexyl-15-(4'-(*o*-nitro-*p*-hydroxybenzyl-carboxy)-phenyl)-10,20-diphenylporphyrin (228)



A solution of [5-hexyl-15-(3-*o*-nitro-*p*-(methoxyethoxymethyl)benzyl carboxyphenyl)-10,20-diphenylporphyrinato]zinc(II) **227** (0.06 g, 0.06 mmol) in CH_2Cl_2 (3.30 ml) was treated with trifluoroacetic acid (3.30 ml), stirred at rt for 7 hours and concentrated. The solution was neutralized with aqueous-KOH and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield the title compound **228** as a purple solid (34.8 mg, 0.03 mmol, 71%): mp >310 °C; R_f=0.28 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= –2.62 (s, 2H, N*H*), 0.93 (t, *J*=7.0 Hz, 3H, -CH_3), 1.38 (m, 2H, -CH_2), 1.49 (m, 2H, -CH_2), 1.79 (m, 2H, -CH_2), 2.53 (m, 2H, -CH_2), 4.98 (t, *J*=7.6 Hz, 2H, -CH_2), 5.86 (s, 2H, -OCH_2), 6.63 (dd, J_1=2.8 Hz, J_2=2.5 Hz, 1H, phenyl-*H*), 7.03 (s , 1H, phenyl-*H*), 7.73 (m, 6H, phenyl-*H*), 8.10 (dd, J_1=2.0 Hz, J_2=1.8 Hz, 1H, phenyl-*H*), 8.18 (m, 4H, phenyl-*H*), 8.26 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.71(d, *J*=4.6 Hz, 2H, β-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.90 (d, *J*=4.7 Hz, 2H, β-*H*), 9.46 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2, 20.8, 22.7, 29.4, 32.0, 35.7, 39.0, 62.6, 114.9, 121.1, 126.7, 127.8, 128.2, 128.4, 129.7, 134.8, 142.3, 148.7, 161.3, 169.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (5.45), 517 (4.06), 551 (3.69), 594 (3.56), 650 nm (3.68); HRMS (ES+) [$C_{52}H_{43}N_5O_5$]: calcd for $[M+H]^+$ 818.3342, found 818.3313.

5-Hexyl-15-(4',4',5',5'-tetramethyl(1',3',2')dioxaborolan-2'-yl)-10,20-bis(3-methoxy phenylporphyrin (231)

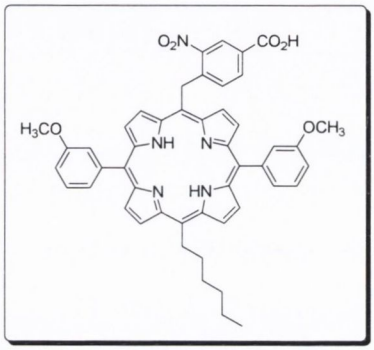


A Schlenk flask was charged with 5-bromo-15-hexyl-10,20-di(3'-methoxyphenyl)porphyrin **152** (0.5 g, 0.73 mmol), pinacolborane (0.18 mL, 1.22 mmol), triethylamine (0.26 mL, 1.90 mmol), *trans*-dichlorobis(triphenylphosphine)palladium(II) (4.38 mg, 0.004 mmol) and 1,2-dichloroethane (15 mL) under argon. The mixture was stirred at 90 °C for 30 min, at which point TLC showed that the 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl) porphyrin **152** was completely consumed. The reaction was quenched with aq. KCl (10 mL), washed with water and dried over MgSO4. The solvent was evaporated and the residue was taken up in CH_2Cl_2 and subjected to column chromatography (SiO_2, *n*-hexane/dichloromethane= 1:2 v/v). The first isolate band corresponded to 5-hexyl-10,20-bis(3-methoxyphenyl) porphyrin **109** (0.16 g, 0.10 mmol, 36%), while the second band contained the title compound **231** as purple solid (0.16 g, 0.12 mmol, 30%).

Alternatively, a suspension of 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl) porphyrin **152** (0.2 g, 0.29 mmol), KOAc (0.29 g, 3.0 mmol) and bis(pinacolato)diboron (0.29 g, 1.16 mmol) in toluene (10 mL) and de-ionised water (20 ml) was degassed with nitrogen for 10 min, Pd(dppf)Cl_2 (47.6 mg, 0.06 mmol) was added and the reaction mixture heated to 110 °C for 3.5 h with vigorous stirring. After addition of water and CH_2Cl_2 to the reaction mixture, the separated aqueous phase was extracted with CH_2Cl_2 and the combined organic layers then dried over MgSO4. Removal of the solvent in *vacuo* and purification by column chromatography (SiO_2, *n*-hexane/dichloromethane= 1:2 v/v) yielded **231** as a purple solid (0.14 g, 0.10 mmol, 65 %). mp >310 °C; R_f=0.42 (SiO_2, EtOAc/C_6H_{14}, 1:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= -2.54 (s, 2H, N*H*), 1.01 (t, *J*=7.0 Hz, 3H, -CH_3), 1.45 (m, 2H, -CH_2), 1.57 (m, 2H, -CH_2), 1.84 (m, 2H, -CH_2), 1.89 (s, 12H, -CH_3), 2.59 (m, 2H, -CH_2), 4.01 (s, 6H, -OCH_3), 5.02 (t, *J*=7.6 Hz, 2H, -CH_2), 7.42 (dd, *J*= 2.3 Hz, *J*= 2.4 Hz, 2H, phenyl-*H*), 7.23 (t, *J*= 8.2 Hz, 2H, phenyl-*H*), 7.90 (t, *J*= 7.04 Hz, phenyl-*H*), 9.01 (d, *J*=4.7 Hz, 2H, β-*H*), 9.07 (d, *J*=4.7 Hz, 2H, β-*H*), 9.13 (d, *J*=4.7 Hz,

2H, β-*H*), 9.21 (d, *J*=4.6 Hz, 2H, β-*H*), 9.99 ppm (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.3, 24.9, 29.9, 31.5, 35.1, 38.5, 55.1, 84.7, 105.9, 113.2, 118.9, 119.9, 122.3, 127.0, 127.2, 130.7, 131.4, 143.6, 157.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 414 (5.08), 511 (3.83), 545 (3.41), 585 (3.48), 641 nm (3.30); HRMS (ES+) [$C_{46}H_{49}BN_4O_4$]: calcd for $[M+H]^+$ 733.3925, found 733.3911.

5-(3-Benzyl-4'-nitrobenzoic acid)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (233)



A Schlenk flask filled with 4-bromomethyl-3-nitrobenzoic acid (0.02 g, 0.07 mmol), boronic ester porphyrin **231** (0.05 g, 0.07 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (0.22 g, 0.68 mol) was evacuated and flushed with argon. Toluene (10 mL) and de-ionised water (2 mL) were added and the solution was degassed with argon for 10 min. Then, $Pd(PPh_3)_4$ (15.8 mg, 13.6 μmol) was added and the reaction mixture heated to 110 °C for 14 h with vigorous stirring. After addition of water and CH_2Cl_2, the organic phase was separated, the aqueous layer extracted three times with CH_2Cl_2, and the combined organic layers dried over $MgSO_4$. Concentration of the filtrate and purification of the resulting residue by column chromatography (SiO_2, EtOAc/C_6H_{14}= 1:10 v/v) afforded **233** as purple solid (5.34 mg, 4.19 μmol, 10 %). mp >310 °C; R_f=0.28 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= -2.21 (s, 2H, N*H*), 0.94 (t, *J*=7.0 Hz, 3H, -CH_3), 1.45 (m, 2H, -CH_2), 1.53 (m, 2H, -CH_2), 1.74 (m, 2H, -CH_2), 1.84 (s, 12H, -CH_3), 2.58 (m, 2H, -CH_2), 3.90 (s, 6H, -OCH_3), 4.01 (d, *J*= 5.8 Hz, 2H, -CH_2), 5.10 (t, *J*=7.6 Hz, 2H, -CH_2), 7.21 (s, 1H, phenyl-*H*), 7.34 (t, *J*= 8.8 Hz, 1H, phenyl-*H*), 7.54 (t, *J*= 7.6 Hz, phenyl-*H*), 7.77 (m, 6H, phenyl-*H*), 8.00 (d, *J*=4.7 Hz, 2H, β-*H*), 8.55 (d, *J*=3.5 Hz, 2H, β-*H*), 8.99 (d, *J*=4.7 Hz, 2H, β-*H*), 9.55 (d, *J*=4.7 Hz, 2H, β-*H*); UV-vis (CH_2Cl_2): λ_{max} (log ε)= 416 (5.09), 523 (4.29), 558 (3.72), 595 (3.76), 652 nm (3.41); HRMS (ES+) [$C_{48}H_{44}N_5O_6$]: calcd for $[M+H]^+$ 786.3292, found 786.3275.

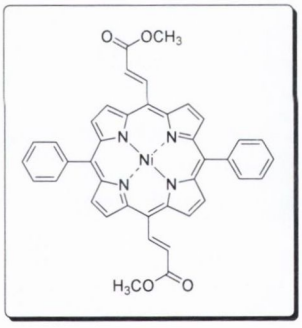
6.11 Photolysis experiment

A solution of 50 μM 5,10,15-tris(3,5-di-*tert*-butylphenyl)-20-(4'-(*o*-nitro-*p*-(2',3',4',6'-tetra-*O*-acetyl-β-*D*-galacto pyrano-side)benzyl)carboxy)phenyl)porphyrin **218** in 2% water/ 98% acetone was placed in a quartz cuvette. Photolysis was performed using a photochemical reactor (Rayonet Model RMR-600) with 350 ±25 nm UV lamps. Aliquots of 20 μL were removed at different time intervals of photolysis and analyzed by analytical HPLC (detection UV: 350 nm) using a nucleosile 5u Si 100A (250 X 4.00 mm) column and eluting with a mixture of *n*-hexane: ethyl acetate (50:50) at a flow rate of 1.5 ml/min.

6.12 Reactivity of acyl chloride porphyrins

Bromoporphyrin precursor **236**, **237**, **238** and **239**; and hydroxyl porphyrin **248** were prepared according to procedure as previously reported.[246, 67e]

[5,15-Bis(2-methoxycarbonylethenyl)-10,20-diphenylporphyrinato]nickel(II) (240)



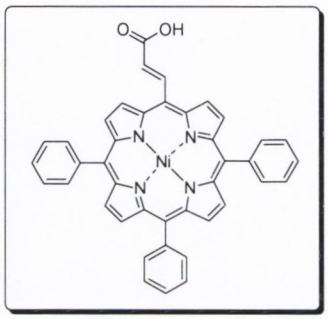
A heterogeneous solution of (5,15-dibromo-10,20-diphenylporphyrinato)nickel(II) **237** (200 mg, 0.32 mmol), methyl acrylate (0.58 mL, 6.4 mmol), PPh_3 (420 mg, 1.6 mmol), $Pd(OAc)_2$ (14.4 mg, 0.064 mmol), and K_2CO_3 (885 mg, 6.4 mmol) in toluene (120 mL) was heated under argon at 110 °C for 72 h (TLC control). The reaction mixture was filtered through a plug of silica and washed with ethyl acetate. After removal of the solvents under reduced pressure, the residue was recrystallised from CH_2Cl_2/MeOH to give **240** (200 mg, 91%) as a green-violet solid: mp >310 °C; R_f=0.7 (SiO_2, EtOAc/C_6H_{14}, 1:2 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.97 (s, 6H, -OC*H*$_3$), 6.28 (d, *J* = 15.6 Hz, 2H, =C*H*-), 7.71 (m, 6H, phenyl-*H*), 7.95 (m, 4H, phenyl-*H*), 8.75 (d, *J* = 4.9 Hz, 4H, β-*H*), 9.31 (d, *J* = 4.9 Hz, 4H, β-*H*), 9.81 ppm (d, *J* = 15.6 Hz, 2H, -C*H*=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 51.6, 110.5, 119.5, 126.7, 127.6, 131.3, 131.5, 133.0, 133.2, 139.3, 140.6,

141.3, 143.0, 166.2 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 438 (5.3), 568 (4.2), 610 nm (4.3); TOF MS LD+ ($C_{40}H_{28}N_4NiO_4$): calcd for [M + Na] 709.1362, found 709.1369.

General procedure for the synthesis of 225 and 241 *via* hydrolysis with EtOH–KOH

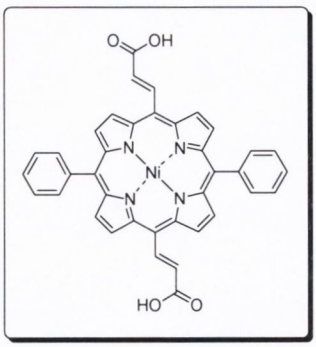
To porphyrins **239** and **240** (0.3 mmol) in EtOH (30 mL) was added an aqueous solution (2 mL) of KOH (400 mg). The reaction was heated at 70 °C for 24–72 h (TLC control) resulting in complete dissolution of the porphyrin. Ethanol was removed under reduced pressure, and the violet solid left was treated with HCl (1 N). The crystals formed were filtered off and washed with HCl (1 N) (10 mL) and distilled H_2O (20 mL). The free acid was dried in vacuo to yield the products **225** and **241** (91–95%).

[5-(2-Carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (225)



Purple solid (189 mg, 95%); mp >310 °C; R_f=0.2 (SiO_2, EtOAc/C_6H_{14}, 1:2 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 6.39 (d, *J* = 15.4 Hz, 1H, =C*H*-), 7.72 (m, 9H, phenyl-*H*), 8.00 (m, 6H, phenyl-*H*), 8.69 (m, 4H, β-*H*), 8.87 (d, *J* = 4.8 Hz, 2H, β-*H*), 9.42 (d, *J*= 4.8 Hz, 2H, β-*H*), 10.03 ppm (d, *J*= 15.4 Hz, 1H, -C*H*=); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ= 108.4, 119.6, 120.7, 126.8, 126.9, 127.8, 129.0, 131.0, 132.2, 132.7, 133.3, 133.4, 133.8, 140.0, 141.4, 142.1, 142.9, 146.7, 159.4, 169.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 429 (5.3), 546 (4.3), 585 (4.2) nm; TOF MS LD+ ($C_{41}H_{26}N_4NiO_2$): calcd for [M] 664.14, found 664.11.

[5,15-Bis-(2-carboxyethenyl)-10,20-diphenylporphyrinato]nickel(II) (241)

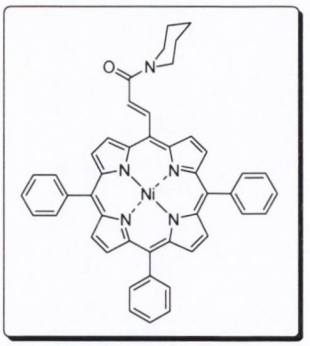


Violet solid (180 mg, 91%); mp >310 °C; R_f=0.1 (SiO_2, EtOAc/C_6H_{14}, 1:2 v/v); ^{1}H NMR (400 MHz, THF-d_8): δ= 6.24 (d, *J* =15.8 Hz, 2H, =C*H*-), 7.71 (m, 6H, phenyl-*H*), 7.97 (m, 4H, phenyl-*H*), 8.72 (d, *J*= 4.7 Hz, 4H, β-*H*), 9.40 (d, *J*= 4.7 Hz, 4H, β-*H*), 9.80 (d, *J*= 15.8 Hz, 2H, -C*H*=), 11.28 ppm (br, 2H, -CO_2*H*); ^{13}C NMR (100.6 MHz, THF-d_8): δ 112.6, 120.6, 128.2, 129.1, 133.0, 134.2, 134.4, 134.5, 141.2, 142.3, 142.9, 143.5, 167.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 435 (4.2), 561 (3.2), 607 nm (3.2); TOF MS LD+ ($C_{38}H_{24}N_4NiO_4$): calcd for [M] 658.1151, found 658.1132.

General procedure for synthesis of 244–247: generation of acyl chloride 242 and 243 and its reactions with nucleophiles

To a solution of acid **225** (30 mg, 0.045 mmol) in anhydrous THF (4 mL) was added $SOCl_2$ (0.025 mL, 0.225 mmol) in 1 mL of THF and DMF (2–3 drops) under argon. The mixture was warmed to 35 °C and stirred for 60 min (color change from red to green). The volatiles were removed under reduced pressure, and the remaining acyl chloride **242** (purple-greenish solid) was dissolved in anhydrous CH_2Cl_2 (ca. 5 mL). The respective nucleophile (0.09–0.225 mmol) dissolved in CH_2Cl_2 (ca. 2–5 mL) followed by NEt_3 (0.013 mL, 0.09 mmol) in CH_2Cl_2 (0.5 mL) were added, and the reaction was stirred for several hours (TLC control) at 35 °C under argon. The reaction mixture was filtered through a plug of silica and washed with CH_2Cl_2, and the solvents were removed *in vacuo*. The crude products were purified by flash chromatography on silica with CH_2Cl_2/hexane or ethyl acetate/hexane to give the corresponding porphyrins **244–246** (68–95%).

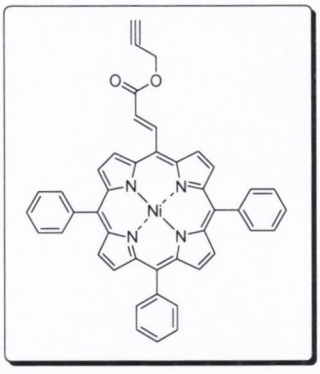
[5-(2-(Piperidiny-1-yl)carbonylethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (244)



To a solution of the acyl chloride **242** generated from **225** (30 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (5 mL) were added piperidine (0.015 mL, 0.15 mmol) in CH_2Cl_2 (1 mL) and NEt_3 (0.008 mL, 0.06 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred for 1 h (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by column chromatography on silica (hexane/CH_2Cl_2, 2:1 v/v) to give **244** (18.2 mg, 83%) as a violet solid.

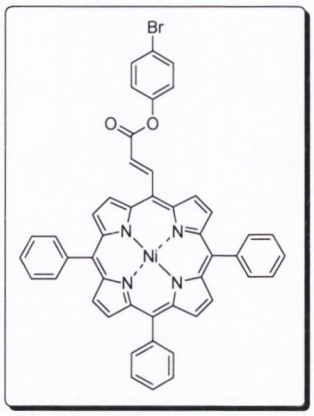
244 *via* **265**: To a solution of acid **265** (30 mg, 0.044 mmol) in anhydrous THF (5 mL) were added $SOCl_2$ (0.016 mL, 0.22 mmol) in 1 mL of THF and DMF (2−3 drops) under argon. The mixture was stirred at 35 °C for 1 h. The volatiles were removed under reduced pressure, and the remained acyl chloride was dissolved in anhydrous CH_2Cl_2 (5 mL). Piperidine (0.031 mL, 0.309 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture, which was stirred for 18 h (TLC control) at 35 °C under argon. The reaction mixture was filtered through a plug of silica and washed with CH_2Cl_2, and the solvents were removed in vacuo. The crude products were purified by flash chromatography on silica (hexane/CH_2Cl_2, 1:1 v/v) to give **244** (13.8 mg, 42%) as a violet solid: mp >310 °C; R_f=0.5 (SiO_2, EtOAc/C_6H_{14}, 1:3 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.68 (m, 6H, -C*H*$_2$), 3.50 (m, 2H, -C*H*$_2$N), 3.77 (m, 2H, -C*H*$_2$N), 6.79 (d, *J*= 15.8 Hz, 1H, -C*H*=), 7.66 (m, 9H, phenyl-*H*), 7.93 (m, 6H, phenyl-*H*), 8.60 (m, 4H, β-*H*), 8.79 (d, 2H, *J* = 4.4 Hz, β-*H*), 9.33 (d, 2H, *J* = 4.4 Hz, β-*H*), 9.82 ppm (d, *J* = 15.8 Hz, 1H, -C*H*=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.5, 25.7, 26.5, 29.7, 42.6, 47.3, 108.3, 109.7, 114.3, 120.1, 121.4, 127.1, 128.1, 131.2, 132.4, 133.0, 133.5, 134.2, 136.5, 140.0, 141.5, 141.8, 142.2, 143.2, 147.0, 165.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 423 (4.3), 538 nm (3.1); TOF MS LD+ ($C_{46}H_{35}N_5ONi$): calcd for [M] 731.2195, found 731.2225.

[5-(2-(Propargyl)carbonylethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (245)



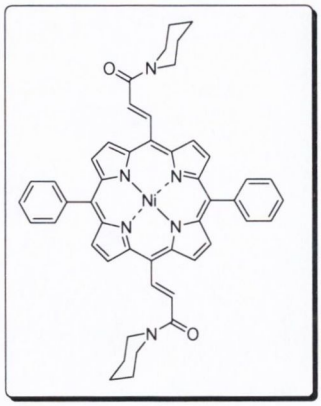
To a solution of acyl chloride **242** generated from **225** (30 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (5 mL) were added propargyl alcohol (0.013 mL, 0.225 mmol) in CH_2Cl_2 (1 mL) and NEt_3 (0.013 mL, 0.09 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred for several hours (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by flash chromatography on silica (CH_2Cl_2/hexane = 1/1) to give **245** (31.7 mg, 73%) as a purple solid: mp 143−158 °C dec; R_f=0.6 (SiO_2, CH_2Cl_2/C_6H_{14} = 1/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 2.62 (br, 1H, ≡C*H*), 5.01 (br, 2H, -CH_2), 6.37 (d, *J* = 15.8 Hz, 1H, =C*H*-), 7.71 (m, 9H, phenyl-*H*), 7.99 (m, 6H, phenyl-*H*), 8.68 (dd, *J* = 4.7, 4.7 Hz, 4H, β-*H*), 8.85 (d, *J* = 4.7 Hz, 2H, β-*H*), 9.39 (d, *J* = 4.7, 2H, β-*H*), 9.97 ppm (d, *J* = 15.8 Hz, 1H, -C*H*=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 51.9, 74.7, 108.6, 119.1, 120.1, 126.5, 126.6, 127.47, 127.5, 129.5, 130.9, 131.9, 132.4, 133.06, 133.1, 133.2, 133.3, 139.7, 141.0, 141.1, 141.7, 142.4, 144.7, 165.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 429 (5.4), 547 (4.3), 587 nm (4.2); TOF MS LD+ ($C_{44}H_{28}N_4NiO_2$): calcd for [M] 702.1566, found 702.1531.

[5-(2-(4-Bromophenyl)carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (246)



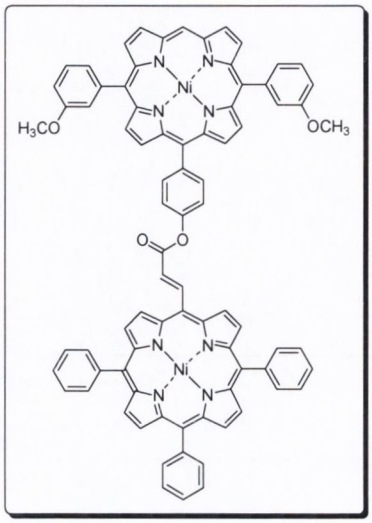
To a solution of acyl chloride **242** generated from **225** (30 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (5 mL) were added 4-bromophenol (15.6 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) and NEt_3 (0.013 mL, 0.09 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred for several hours (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. The crude product was purified by flash chromatography on silica (CH_2Cl_2/hexane, 1:1 v/v) to give **246** (25.1 mg, 68%) as a violet solid: mp 173 °C; R_f=0.25 (SiO_2, CH_2Cl_2/C_6H_{14} = 1/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 6.50 (d, *J* = 15.2 Hz, 1H, =C*H*-), 7.24 (d, *J* = 8.8 Hz, 2H, phenyl-*H*), 7.61 (d, *J* = 8.8 Hz, 2H, phenyl-*H*), 7.71 (m, 9H, phenyl-*H*), 7.99 (m, 6H, phenyl-*H*), 8.66 (d, *J* = 5.2 Hz, 2H, β-*H*), 8.70 (d, *J* = 5.2 Hz, 2H, β-*H*), 8.87 (d, *J* = 5.2 Hz, 2H, β-*H*), 9.44 (d, *J* = 5.2 Hz, 2H, β-*H*), 10.08 ppm (d, *J* = 15.2 Hz, 1H, -CH=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 108.3, 118.5, 119.3, 120.4, 123.1, 123.6, 125.1, 126.5, 126.6, 127.5, 127.6, 129.2, 130.8, 132.0, 132.1, 132.5, 132.6, 133.05, 133.1, 133.5, 139.7, 141.1, 141.8, 142.5, 145.7, 149.5, 163.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 430 (5.3), 547 (4.3), 592 nm (4.3); TOF MS LD+ ($C_{47}H_{29}BrN_4NiO_2$): calcd for [M] 818.0827, found 818.0826.

[5,15-Bis(2-(piperidiny-1-yl)carbonylethenyl)-10,20-diphenylporphyrinato]nickel(II) (247)



To a solution of acid **241** (30 mg, 0.045 mmol) in anhydrous THF (5 mL) were added $SOCl_2$ (0.013 mL, 0.18 mmol) in 1 mL of THF and DMF (2–3 drops) under argon, and the mixture was stirred for 2 h. The volatiles were removed under reduced pressure, and the remaining purple-greenish acyl chloride **243** was dissolved in anhydrous THF (5 mL). NEt_3 (0.013 mL, 0.09 mmol) in THF (1 mL) was added, and stirring was continued for 15 min. Piperidine (0.09–0.225 mmol) dissolved in THF (1 mL) was added, and the reaction was stirred for 30 min (TLC control) at rt under argon. The mixture was filtered through a plug of silica and washed with ethyl acetate, followed by removal of the solvents *in vacuo*. The residue was purified by flash chromatography on silica with ethyl acetate/hexane = 1:2 v/v to give **247** (16 mg, 44%) as a green-purple solid: mp 282 °C; R_f=0.15 (SiO_2, EtOAc/C_6H_{14} = 1/2, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.67 (m, 12H, -C*H*$_2$), 3.54 (m, 4H, -C*H*$_2$N), 3.82 (m, 4H, -C*H*$_2$N), 6.67 (d, *J*= 15.2 Hz, 2H, =C*H*-), 7.70 (m, 6H, phenyl-*H*), 7.96 (m, 4H, phenyl-*H*), 8.74 (d, *J*= 4.7 Hz, 4H, β-*H*), 9.32 (d, *J* = 4.7 Hz, 4H, β-*H*), 9.80 ppm (d, *J* = 15.2 Hz, 2H, -C*H*=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.2, 25.2, 26.3, 43.1, 46.6, 112.1, 119.0, 126.7, 127.6, 131.5, 132.7, 132.9, 133.0, 139.5, 140.6, 141.1, 164.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 436 (5.5), 557 (4.6), 604 nm (4.6); TOF MS LD+ ($C_{48}H_{42}N_6NiO_2$): calcd for [M] 792.2723, found 792.2720.

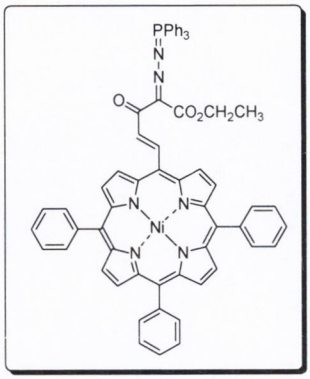
[5-(5-Phenyl-10,20-bis(3-methoxyphenylporphyrin)-carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II) (249)



To a solution of acyl chloride **242** generated from **225** (30 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (5 mL) were added 5-(4-hydroxyphenyl)-10,20-bis(3-methoxyphenyl)porphyrin **248** (26.3 mg, 0.43 mmol) in CH_2Cl_2 (1 mL) and NEt_3 (0.013 mL, 0.09 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred for 24 h (TLC control) at 35 °C under argon, and the resulting mixture was worked up as described above. Purification by flash chromatography on silica (ethyl acetate/hexane, 1:2 v/v) afforded **249** (27.6 mg, 51%) as a purple solid: mp 247 °C; R_f=0.8 (SiO_2, EtOAc/C_6H_{14}, 1:2 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.97 (s, 2H, -N*H*), 4.05 (s, 6H, -OCH_3), 6.73 (d, *J*= 15.8 Hz, 1H, =C*H*-), 7.40 (m, 2H, phenyl-*H*), 7.74 (m, 13H, phenyl-*H*), 7.89 (m, 4H, phenyl-*H*), 8.04 (m, 6H, phenyl-*H*), 8.35 (m, 2H, phenyl-*H*), 8.72 (dd, *J* = 4.7, 4.7 Hz, 4H, β-*H*), 8.94 (d, *J* = 4.7 Hz, 2H, β-*H*), 9.02 (dd, *J* = 4.7, 4.7 Hz, 4H, β-*H*), 9.12 (d, *J* = 4.7 Hz, 2H, β-*H*), 9.37 (d, *J* = 4.7 Hz, 2H, β-*H*), 9.58 (d, *J* = 4.7 Hz, 2H, β-*H*), 10.28 ppm (m, 2H, -C*H*=); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 55.1, 104.5, 108.3, 113.1, 119.0, 119.3, 119.5, 120.2, 120.3, 126.6, 126.7, 127.3, 127.4, 127.5, 127.6, 129.8, 130.5, 131.0, 131.1 (br), 132.0, 132.5, 133.1, 133.2, 133.5, 134.9, 139.7, 139.8, 141.2, 141.8, 142.5, 142.6, 145.6, 146.2 (br), 150.4, 157.6, 164.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 413 (5.5), 432 (5.2), 508 (4.4), 543 (4.3), 585 (4.3), 635 nm (4.0); TOF MS LD+ ($C_{81}H_{54}N_8NiO_4$): calcd for [M + H] 1261.3700, found 1261.366.

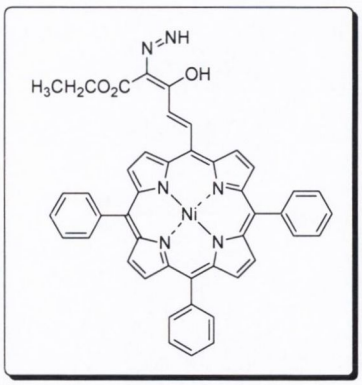
Reaction of 242 with ethyl diazoacetate. synthesis of 250–252

[5-(Ethyl-2((triphenylphosphinylidene)hydrazono)acetate)-carbonylethenyl-10,15,20-triphenylporphyrinato]nickel(II) (250)



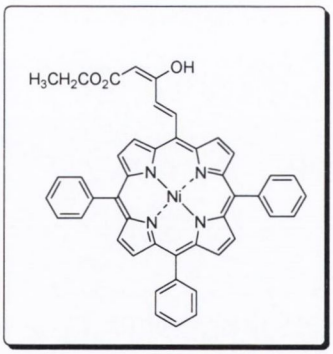
Ethyl diazoacetate (20.6 mg, 0.18 mmol) in CH_2Cl_2 (1 mL), PPh_3 (47.3 mg, 0.18 mmol), and NEt_3 (0.013 mL, 0.09 mmol) in CH_2Cl_2 (0.5 mL) were added to a solution of acyl chloride **242** generated from **225** (30 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (5 mL). The reaction was stirred for 2 h (TLC control) at 35 °C under argon, and the resulting mixture was diluted with hexane and quickly filtered through a short column of silica. The volatiles were removed *in vacuo*, and the solid residue was washed with hexane (3 × 5 mL) and dried under vacuum to give **250** (32.2 mg, 70%) as a pale purple solid: R_f=0.4 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1 v/v); ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 1.45 (t, *J*= 7.0 Hz, 3H, -C*H*$_3$), 4.44 (q, *J* = 7.0 Hz, 2H, -C*H*$_2$), 6.84 (d, *J*= 15.4 Hz, 1H, =C*H*-), 7.54 (m, 9H, phenyl-*H*), 7.74 (m, 15H, phenyl-*H*), 8.00 (m, 6H, phenyl-*H*), 8.68 (dd, *J*= 5.0 Hz, 5.0 Hz, 4H, β-*H*), 8.83 (d, *J* = 5.0 Hz, 2H, β-*H*), 9.38 (d, *J* = 5.0, 2H, β-*H*), 9.80 ppm (d, *J* = 15.4 Hz, 1H, -C*H*=); ^{31}P NMR (162 MHz, CD_2Cl_2): 44.26 ppm; ^{13}C NMR (150.9 MHz, CD_2Cl_2): δ= 14.2, 62.5, 110.2, 120.0, 120.8, 127.2, 127.3, 128.2, 128.7, 128.8, 131.2, 131.8, 131.9, 132.4, 132.5 (m), 132.9, 133.1, 133.6, 133.7, 133.8, 133.9, 136.0, 140.4, 140.5, 141.6, 141.7, 141.9, 142.6, 143.2, 145.8, 148.6, 162.6 ppm; TOF MS LD+ ($C_{63}H_{45}N_6NiO_3P$): calcd for [M + 2H − O] 1008.2852, found 1008.2845; calcd for [M − H_2O − PPh_3] 745.1862, found 745.1868.

[5-(Ethyl-2-diazenyl-3-hydroxy-3-acrylate)-carbonylethenyl-10,15,20-triphenyl porphyrinato]nickel(II) (251)



Yield 12 mg (35%); R_f=0.6 (SiO_2, EtOAc/C_6H_{14}, 2:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.38 (t, *J*= 7.0 Hz, 3H, -C*H*$_3$), 4.32 (q, *J* = 7.0 Hz, 2H, -C*H*$_2$), 6.75 (br, 1H, -N*H*), 7.35 (d, *J* = 15.8 Hz, 1H, =C*H*-), 7.71 (m, 9H, phenyl-*H*), 7.99 (m, 6H, phenyl-*H*), 8.67 (dd, *J* = 5.3 Hz, 5.0 Hz, 4H, β-*H*), 8.85 (d, *J* = 5.3 Hz, 2H, β-*H*), 9.44 (d, *J* = 5.3, 2H, β-*H*), 10.06 (d, *J* = 15.8 Hz, 1H, -C*H*=), 12.46 ppm (br, 1H, -O*H*); UV-vis (CH_2Cl_2): λ_{max} (log ε)= 433 (1.0), 547 (0.1), 592 nm (0.09); TOF MS LD+ ($C_{45}H_{32}N_6NiO_3$): calcd for [M + Na] 785.1787, found 785.1779.

[5-(Ethyl-3-hydroxy-3-phenylacrylate)-carbonylethenyl-10,15,20-triphenyl porphyrinato]nickel(II) (252)



Phosphazine **250** (32 mg, 0.31 mmol) was dissolved in dichloromethane and allowed to stand for 24 h. The solvent was removed under reduced pressure, and the residue was recrystallised from CH_2Cl_2/MeOH to give **252** (18 mg, 78%) as a violet solid: mp >310 °C; ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= 1.46 (t, *J* = 7.0 Hz, 3H, -C*H*$_3$), 4.47 (q, *J* = 7.0 Hz, 2H, -C*H*$_2$), 6.84 (d, *J* = 15.2 Hz, 1H, =C*H*-), 7.59 (s, 1H, =C*H*), 7.71 (m, 9H, phenyl-*H*), 7.99 (m, 6H, phenyl-*H*), 8.67 (dd, *J* = 4.7, 4.7 Hz, 4H, β-*H*), 8.85 (d, *J* = 5.2 Hz, 2H, β-*H*), 9.37 (d, *J* = 5.2, 2H, β-*H*), 9.79 ppm (d, *J* = 15.2 Hz, 1H, -C*H*=); ^{13}C NMR (150.9 MHz,

$CDCl_3$): δ= 14.2, 62.2, 109.7, 119.7, 120.6, 126.9, 127.0, 127.9, 128.0, 131.1, 132.4, 132.8, 133.5, 133.6, 133.7, 135.7, 140.2, 141.4, 141.6, 142.3, 142.9, 145.6, 147.8, 162.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 435 (5.8), 547 (4.8), 597 nm (4.8); TOF MS LD+ ($C_{45}H_{32}N_4NiO_3$): calcd for [M + 2H + 2Na] 782.1780, found 782.1621.

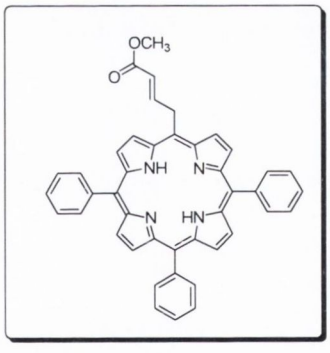
6.13 Synthesis of α,β-unsaturated porphyrins

Ally porphyrin precursors **255** and **256** were prepared according to procedure as previously reported.[246]

General Procedure: synthesis of 258–260 via cross-metathesis

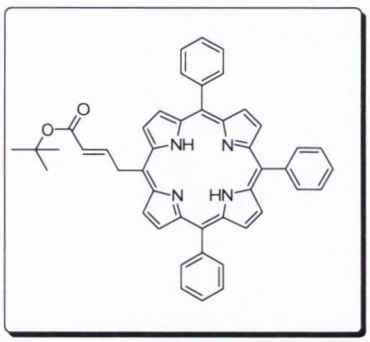
A mixture of allyl porphyrin (0.3 mmol), acrylate (1.5–3.0 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) in dry CH_2Cl_2 (25 mL) was stirred at 35 °C under argon for 12 h (TLC control). The solution was filtered through a plug of silica and washed with CH_2Cl_2. The solvent was removed under reduced pressure followed by recrystallization of the solid residue from CH_2Cl_2/MeOH to give **258–260** (78–90%).

5-(Methylbut-2-enoate)-10,15,20-triphenylporphyrin (258)



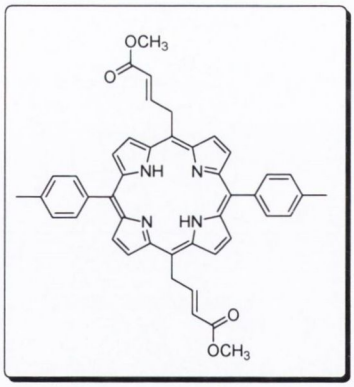
Porphyrin **255** (174 mg, 0.3 mmol), methyl acrylate (129 mg, 1.5 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave **258** (153 mg, 80%) as a violet solid: mp >310 °C; R_f=0.45 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.74 (s, 2H, -N*H*), 3.55 (s, 3H, -OCH_3), 5.72 (d, *J* = 15.8 Hz, 1H, =C*H*-), 5.87 (d, *J* = 5.9 Hz, 2H, -CH_2), 7.76 (m, 9H, phenyl-*H*), 7.94 (m, 1H, -C*H*=), 7.99 (m, 6H, phenyl-*H*), 8.81 (br, 4H, β-*H*), 8.91 (d, *J* = 4.8 Hz, 2H, β-*H*), 9.34 ppm (d, *J* = 4.8 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 37.4, 51.4, 113.2, 120.0, 120.3, 123.0, 126.6, 127.8, 134.5, 142.0, 142.6, 150.7, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 419 (4.3), 517 (3.1), 553 (2.8), 657 nm (2.8); HRMS (ES+) [$C_{43}H_{32}N_4O_2$]: calcd for [M + H] 637.2604, found 637.2596.

5-(*tert*-Butyl but-2-enoate)-10,15,20-triphenylporphyrin (259)



Porphyrin **255** (174 mg, 0.3 mmol), *tert*-butyl acrylate (192 mg, 1.5 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave **259** (159 mg, 78%) as a violet solid: mp >310 °C; R_f=0.4 (SiO_2, EtOAc/C_6H_{14}=1/5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.70 (s, 2H, -N*H*), 1.34 (s, 9H, -CH_3), 5.66 (d, *J* = 15.8 Hz, 1H, =C*H*-), 5.91 (d, *J* = 5.8 Hz, 2H, -CH_2), 7.80 (m, 9H, phenyl-*H*), 7.90 (dt, *J* = 15.8, 5.8 Hz, 1H, -C*H*=), 8.25 (m, 6H, phenyl-*H*), 8.86 (br, 4H, β-*H*), 8.97 (d, *J* = 4.7 Hz, 2H, β-*H*), 9.42 ppm (d, *J* = 4.7 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 27.5, 36.8, 79.8, 113.2, 119.5, 119.8, 124.8, 126.2, 126.3, 127.3, 127.6 (br), 130.6 (br), 134.1, 141.5, 141.7, 148.8, 165.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (4.0), 444 (3.6), 516 (2.6), 550 (2.3), 594 (2.3), 654 nm (2.7); HRMS (ES+) [$C_{46}H_{38}N_4O_2$]: calcd for [M + H] 679.3073, found 679.3085.

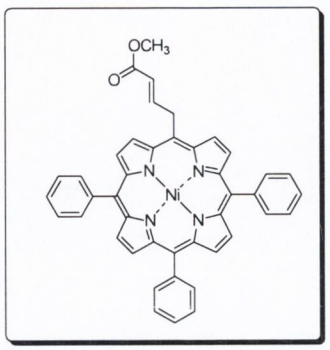
5,15-Bis(methylbut-2-enoate)-10, 20-ditolylporphyrin (260)



Porphyrin **256** (171 mg, 0.3 mmol), methyl acrylate (258 mg, 3.0 mmol), and Grubbs II catalyst (25.5 mg, 0.03 mmol) gave **260** (186 mg, 90%) as a violet solid: mp >310 °C; R_f=0.4 (SiO_2, EtOAc/C_6H_{14}, 1:2 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.68 (s, 2H, -N*H*), 2.75 (s, 6H, -CH_3), 3.56 (s, 6H, -OCH_3), 5.74 (d, *J* = 15.8 Hz, 2H, =C*H*-), 5.91 (d, *J* = 5.3 Hz, 4H, -CH_2), 7.59 (m, 4H, phenyl-*H*), 7.96 (dt, *J* = 15.8, 5.3 Hz, 1H, -C*H*=), 8.09 (m, 4H, phenyl-*H*), 8.93 (d, *J* = 4.7 Hz, 4H, β-*H*), 9.35 ppm (d, *J* = 4.7 Hz, 4H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.3, 36.8, 51.0, 112.7, 119.5, 122.5, 127.0, 134.0, 137.0,

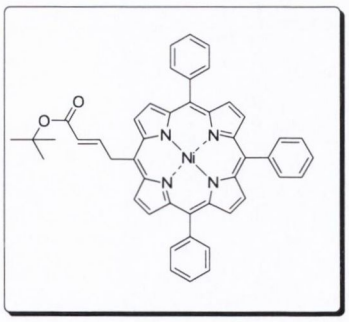
138.7, 150.3, 166.5 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 516 (4.1), 552 (4.0), 592 nm (3.0); HRMS (ES+) [$C_{44}H_{38}N_4O_4$] calcd for [M + H]: 687.2971, found 687.2972.

[5-(Methylbut-2-enoate)-10,15,20-triphenylporphyrinato]nickel(II) (261)



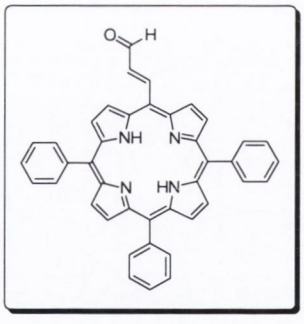
A mixture of porphyrin **258** (191 mg, 0.3 mmol) and Ni(II)(acac)$_2$ (308 mg, 1.2 mmol) in toluene (100 mL) was stirred at 110 °C for 2 h (TLC control). The reaction mixture was filtered through a plug of silica and washed with CH_2Cl_2. The solvents were removed under reduced pressure, and the residue was recrystallized from CH_2Cl_2/MeOH to give **261** (204 mg, 98%) as a purple solid: mp >310 °C; R_f=0.33 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 3.60 (s, 3H, -OC*H*$_3$), 5.36 (d, *J* = 4.4 Hz, 2H, -C*H*$_2$), 5.81 (d, *J* = 15.6 Hz, 1H, =C*H*-), 7.67 (m, 9H, phenyl-*H*), 7.82 (m, 1H, -C*H*=), 7.98 (m, 6H, phenyl-*H*), 8.71 (br, 4H, β-*H*), 8.77 (d, *J* = 4.8 Hz, 2H, β-*H*), 9.13 ppm (d, *J* = 4.4 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 36.5, 51.5, 111.9, 118.8, 122.8, 126.9, 127.8, 129.2, 132.4, 133.1, 133.7, 140.7, 142.2, 142.3, 142.5, 142.7, 150.3, 166.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 416 (4.3), 530 (3.0) nm; TOF MS LD+ [$C_{43}H_{30}N_4O_2Ni$] calcd for [M + Na]: 715.1620, found 715.1596.

[5-(*tert*-Butyl-but-2-enoate)-10,15,20-triphenylporphyrinato]nickel(II) (262)



Compound **262** was prepared from **259** (203 mg, 0.3 mmol) using the same procedure as for the synthesis of **261**. Recrystallisation from CH_2Cl_2/MeOH gave **264** (210 mg, 95%) as a purple solid: mp >310 °C; R_f=0.75 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.40 (s, 9H, -C*H*$_3$), 5.26 (d, *J* = 4.9 Hz, 2H, -C*H*$_2$), 5.73 (d, *J* = 15.6 Hz, 1H, =C*H*-), 7.70 (m, 10H, -C*H*=, phenyl-*H*), 8.03 (m, 6H, phenyl-H), 8.78 (br, 4H, β-*H*), 8.81 (d, *J* = 4.9 Hz, 2H, β-*H*), 9.13 ppm (d, *J* = 4.9 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 28.1, 36.3, 80.4, 112.3, 118.8, 119.0, 124.9, 127.0, 127.9, 129.4, 132.4, 133.1, 133.8, 140.8, 142.2, 142.4, 142.5, 142.8, 148.8, 166.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 416 (4.4), 530 nm (3.2); TOF MS LD+ [$C_{46}H_{36}N_4O_2Ni$]: calcd for [M] 734.2219, found 734.2192.

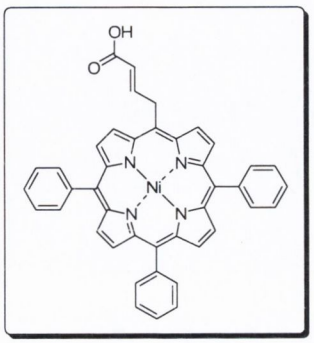
5-Acroleinyl-10,15,20-triphenylporphyrin (263)



Grubbs II catalyst (8.5 mg, 0.01 mmol) and acrylic acid (0.03 mL, 0.43 mmol) were added to a solution of porphyrin **255** (51 mg, 0.09 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred for 18 h and then filtered through a plug of silica eluting with CH_2Cl_2. Purification by column chromatography (hexane/CH_2Cl_2, 2:1 v/v) gave **263** (12 mg, 0.02 mmol, 23%) as a purple solid: mp >310 °C; R_f=0.48 (SiO_2, EtOAc/C_6H_{14}, 1:3 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.40 (s, 2H, -N*H*), 7.16 (d, *J*= 7.8 Hz, 15.6 Hz, 1H, =C*H*-), 7.76 (m, 9H, phenyl-*H*), 8.17 (m, 6H, phenyl-*H*), 8.77 (dd, *J*= 4.8, 4.8 Hz, 4H, β-*H*), 8.91 (d, *J* = 4.8 Hz, 2H, β-*H*), 9.39 (d, *J*= 4.8 Hz, 2H, β-*H*), 10.02 (d, *J*= 15.6 Hz, 1H,

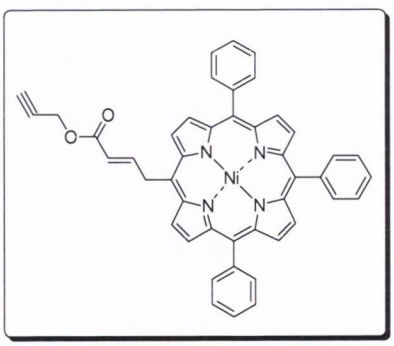
-C*H*=), 10.23 ppm (d, *J* = 7.8 Hz, 1H, -C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7, 32.0, 110.8, 121.7, 122.7, 126.8, 128.0, 134.4, 141.2, 141.8, 154.0, 192.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 429 (4.3), 523 (2.9), 570 (3.0), 660 (2.7), 666 nm (2.6); HRMS (ES+) [$C_{41}H_{28}N_4O$]: calcd for [M + H] 593.2341, found 593.2357.

[5-(But-2-enoic acid)-10,15,20-triphenylporphyrinato]nickel(II) (265)



A solution of porphyrin **262** (100 mg, 0.136 mmol) and TFA (0.85 mL) in CH_2Cl_2 (20 mL) was stirred at 35 °C for 12 h (TLC control). The solvent was removed under reduced pressure, and the solid residue was dried *in vacuo* to give **265** (88 mg, 95%) as red solid: mp >310 °C; R_f=0.1 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 5.40 (d, *J*= 4.8 Hz, 2H, -C*H*$_2$), 5.80 (d, *J*= 15.6 Hz, 1H, =C*H*-), 7.66 (m, 9H, phenyl-*H*), 7.95 (m, 7H, phenyl-*H*, -C*H*=), 8.69 (br, 4H, β-*H*), 8.77 (d, *J* = 5.0 Hz, 2H, β-*H*), 9.10 ppm (d, *J* = 5.0 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.1, 31.0, 36.6, 111.9, 118.9, 119.2, 126.9, 127.8, 129.0, 132.4, 132.4, 133.2, 133.8, 140.7, 142.2, 142.5, 142.8, 154.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 415 (5.3), 529 nm (4.2); TOF MS LD+ ($C_{42}H_{28}N_4NiO_2$): calcd for [M] 678.1566, found 678.1564.

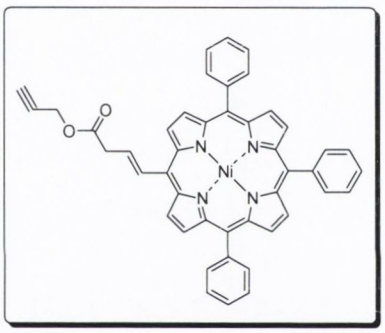
[5-(Propargyl-but-2-enoate)-10,15,20-triphenylporphyrinato]nickel(II) (266)



DMAP (15 mg, 0.124 mmol) in CH_2Cl_2 (1 mL) was added to a solution of the acyl chloride generated from **265** (42 mg, 0.062 mmol) in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was stirred for 10 min, and propargyl alcohol (0.036 mL, 0.62 mmol) in

CH_2Cl_2 (0.5 mL) was added. Stirring was continued for 1 h (TLC control) at 35 °C under argon. The resulting mixture was filtered through a plug of silica and washed with CH_2Cl_2. Purification using silica TLC plates (CH_2Cl_2/hexane, 1:2 v/v) afforded **266** (25 mg, 57%) as a purple solid: mp >310 °C; R_f=0.4 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= 2.35 (t, *J* = 2.3 Hz, 1H, ≡C*H*), 4.61 (d, *J* = 2.3 Hz, 2H, -CH_2), 5.48 (d, *J* = 5.8 Hz, 2H, -CH_2), 5.83 (d, *J* = 15.6 Hz, 1H, =C*H*-), 7.68 (m, 9H, phenyl-*H*), 7.92 (dt, *J* = 5.8 Hz, 15.6 Hz, 1H, -C*H*=), 7.98 (m, 6H, phenyl-*H*), 8.70 (s, 4H, β-*H*), 8.79 (d, *J* = 5.0 Hz, 2H, β-*H*), 9.18 ppm (d, *J* = 5.0 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 36.6, 51.9, 74.8, 111.5, 118.8, 119.1, 122.3, 126.9, 127.78, 127.8, 129.2, 132.4, 133.2, 133.7, 140.7, 142.2, 142.3, 142.5, 142.7, 151.6, 165.6 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 415 (4.7), 530 nm (3.7); TOF MS ($C_{45}H_{30}N_4NiO_2$) calcd for [M − H] 717.1598, found 717.1612.

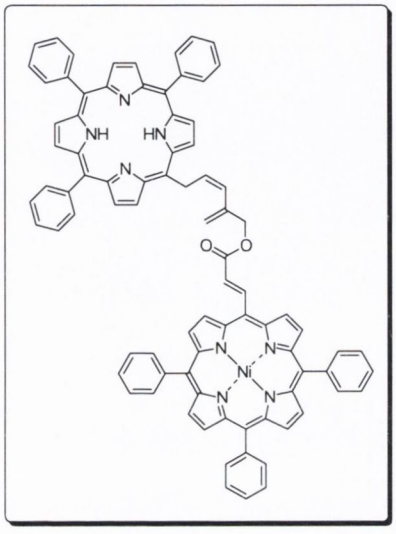
[5-(Propargyl but-3-enoate)-10,15,20-triphenylporphyrinato]nickel(II) (267E)



N-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.7 mg, 0.124 mmol) and propargyl alcohol (0.036 mL, 0.62 mmol) were added to a solution of **265** (42 mg, 0.062 mmol) in anhydrous CH_2Cl_2 (5 mL) and DMAP (15 mg, 0.124 mmol). The reaction mixture was stirred for 12 h (TLC control) at rt. The resulting mixture was filtered through a plug of silica and washed with CH_2Cl_2. Purification by column chromatography (CH_2Cl_2/hexane, 1:2 v/v) afforded **267-*E/Z*** (ratio *E*/*Z* = 3:1, 36 mg, 81%) as a purple solid. Additional purification on silica TLC plates (ethyl acetate/hexane = 1:10 v/v) gave **267E** (26.2 mg, 59%): mp >300 °C; R_f=0.45 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.57 (t, *J*= 2.0 Hz, 1H, ≡C*H*), 3.79 (d, *J*= 7.8 Hz, 2H, -CH_2), 4.88 (d, *J* = 2.0 Hz, 2H, -CH_2), 6.17 (dt, *J* = 7.8 Hz, 15.2 Hz, 1H, =C*H*-), 7.71 (m, 9H, phenyl-*H*), 8.00 (m, 6H, phenyl-*H*), 8.71 (dd, *J* = 4.9 Hz, 4.9 Hz, 4H, β-*H*), 8.76 (d, *J* = 15.2 Hz, 1H, -C*H*=), 8.82 (d, *J* = 4.9 Hz, 2H, β-*H*), 9.38 ppm (d, *J* = 4.9 Hz, 2H, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 38.7, 52.1, 74.8, 113.4, 118.3, 118.5, 126.5, 127.3, 131.1, 131.76, 131.8, 132.2, 133.17, 133.2, 135.0, 140.2, 141.0, 141.4, 141.86, 141.9, 170.3 ppm; UV-vis (CH_2Cl_2):

λ_{max} (log ε)= 419 (5.2), 534 nm (4.1); TOF MS LD+ ($C_{45}H_{30}N_4NiO_2$): calcd for [M] 716.1722, found 716.1746.

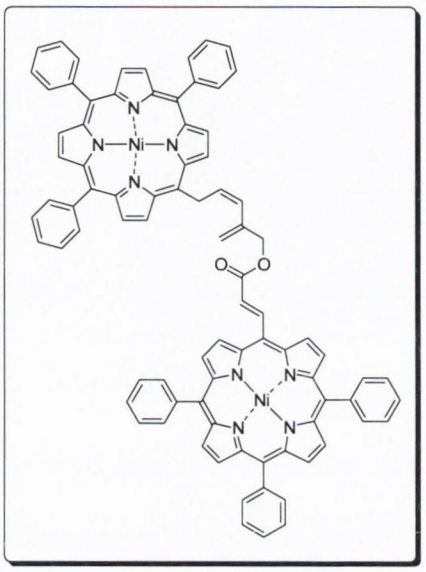
2-Methylene-5-[(5,10,15-triphenylporphyrin-20-yl)pent-3-enyl-3-[(5,10,15-Triphenyl porphyrinato-20-yl)nickel(II)]acrylate (279)



The allyl porphyrin **255** (8.2 mg, 0.014 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise under argon to a solution of porphyrin propargyl ester **245** (10 mg, 0.014 mmol) and Grubbs I catalyst (2.34 mg, 0.003 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 18 h at 35 °C and then filtered through a plug of silica and washed with CH_2Cl_2. The volatiles were removed in vacuo, and the remaining solid was purified by flash chromatography on silica (hexane/CH_2Cl_2, 1:1 v/v) to yield **279** (13.9 mg, 76%, *E*/*Z* 3:2) as a purple solid: mp >310 °C; R_f=0.3 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (4.0), 519 (3.0), 550 (3.0), 596 (3.0), 656 nm (3.2); TOF MS LD+ ($C_{85}H_{58}N_8O_2Ni$): calcd for [M] 1280.4036, found 1280.4056; NMR key data (**279*E***) ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= 5.01 (m, 3H, -CH_2OCO, -CCH*H*), 5.24 (s, 1H, -CCH*H*), 5.93 (d, *J* = 5.6 Hz, 2H, -CH_2CH), 6.29 (d, *J* = 15.8 Hz, 1H, -C*H*CHCH$_2$) 6.30 (d, *J* = 15.4 Hz, 1H, -CHC*H*CO), 6.95 (dt, *J* = 5.6 Hz, 15.8 Hz, 1H, -CHC*H*CH$_2$), 9.83 ppm (d, *J* = 15.4 Hz, 1H, -C*H*CHCO); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 38.0 (*C*H$_2$CH), 64.2 (*C*H$_2$OCO), 116.8 (*C*CH$_2$), 130.9 (CH*C*HCO), 134.2 (CH*C*HCH$_2$), 133.9 (*C*HCHCH$_2$), 144.2 (*C*HCHCO), 165.3 ppm (*C*O$_2$); (**279*Z***) ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= 5.30 (s, 2H, -CH_2OCO), 5.97 (s, 1H, -CCH*H*), 6.04 (s, 1H, -CCH*H*), 6.16 (m, 3H, -CH_2CH, -C*H*CHCH$_2$), 6.48 (d, *J* = 15.4 Hz, 1H, -CHC*H*CO), 6.83 (dt, *J* = 6.8 Hz, 11.3 Hz, 1H, -CHC*H*CH$_2$), 10.03 ppm (d, *J* = 15.4 Hz, 1H, -C*H*CHCO); ^{13}C NMR (150

MHz, $CDCl_3$): δ= 35.1 (*C*H_2CH), 68.0 (*C*H_2OCO), 118.2 (*CC*H_2), 124.2 (*C*HCHCH$_2$), 130.9 (CH*C*HCO), 137.5 (CH*C*HCH$_2$), 144.5 (*C*HCHCO), 165.6 ppm (*C*O_2).

2-Methylene-5-[(5,10,15-triphenylporphyrinato-20-yl)nickel(II)]pent-3-enyl-[(5,10,15-Triphenylporphyrinato-20-yl)nickel(II)]acrylate (280)

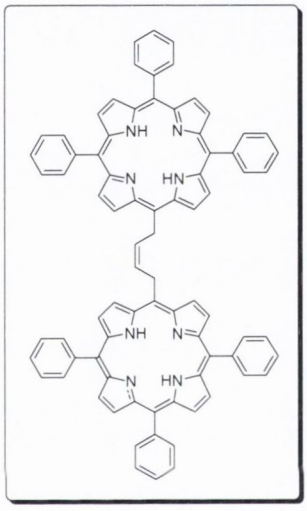


The synthesis of **280** was carried out as described above for **279** using the porphyrin propargyl ester **245** (10 mg, 0.014 mmol), Grubbs I catalyst (2.34 mg, 0.003 mmol), and allyl porphyrin **278** (9.0 mg, 0.014 mmol). The mixture of **280** (7.8 mg, 41%, *E*/*Z* 2:1) was obtained as as a purple solid: mp >310 °C; R_f 0.49 (SiO_2, ethyl acetate/hexane, 1:5 v/v); UV-vis (CH_2Cl_2): λ_{max} (log ε)= 418 (4.0), 533 (2.9) 590 nm (2.0); TOF MS LD+ ($C_{85}H_{56}N_8O_2Ni_2$) calcd for [M + H] 1337.3311, found 1337.3322; NMR selected data (**280*E***) ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= 5.02 (s, 2H, -C*H*$_2$OCO), 5.16 (s, 1H, -*C*CH*H*), 5.31 (s, 1H, -*C*CH*H*), 5.46 (d, *J* = 5.6 Hz, 2H, -C*H*$_2$CH), 6.29 (d, *J* = 15.8 Hz, 1H, -CHC*H*CO), 6.43 (d, *J*= 16.2 Hz, 1H, -C*H*CHCH$_2$), 6.84 (dt, *J*= 5.6 Hz, 16.2 Hz, 1H, -CHC*H*CH$_2$), 9.82 ppm (d, *J*= 15.8 Hz, 1H, C*H*CHCO); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 36.8 (*C*H_2CH), 64.0 (*C*H_2OCO), 117.0 (*CC*H_2), 130.4 (*C*HCHCH$_2$), 130.9 (CH*C*HCO), 133.7 (CH*C*HCH$_2$), 144.0 (*C*HCHCO), 165.3 ppm (*C*O_2); (**280*Z***) ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ= 5.24 (s, 2H, -C*H*$_2$OCO), 5.68 (d, *J* = 6.4 Hz, 2H, -C*H*$_2$CH), 5.83 (s, 1H, -*C*CH*H*), 5.94 (s, 1H, -*C*CH*H*), 6.18 (d, *J* = 11.7 Hz, 1H, -C*H*CHCH$_2$), 6.44 (d, *J* = 15.4 Hz, 1H, -CHC*H*CO), 6.77 (dt, *J* = 6.4 Hz, 11.7 Hz, 1H, -CHC*H*CH$_2$), 10.01 (d, *J* = 15.4 Hz, 1H, -C*H*CHCO); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ= 33.7 (*C*H_2CH), 67.4 (*C*H_2OCO), 118.0 (*CC*H_2), 124.7 (*C*HCHCH$_2$), 130.8 (CH*C*HCO), 136.9 (CH*C*HCH$_2$), 144.4 (*C*HCHCO), 165.4 ppm (*C*O_2).

Synthesis of 279 and 280 using Grubbs II catalyst

The allyl porphyrin **255** (8.2 mg, 0.014 mmol in 10 mL dry CH_2Cl_2) was added dropwise under argon to a solution of the porphyrin propargyl ester **245** (10 mg, 0.014 mmol) and Grubbs II catalyst (2.41 mg, 0.003 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 18 h at 35 °C and then filtered through a plug of silica. Flash column chromatography on silica (hexane/CH_2Cl_2, 1:1 v/v) gave **279** (10 mg, 55%, *E*/*Z* 3:2) as the first fraction and **282** (18.2 mg, 31%) as the second fraction.

1,4-Bis[5,10,15-triphenylporphyrin-20-yl]but-2-ene (282)



Yield 18.2 mg (31%); mp 310 °C; R_f=0.54 (SiO_2, EtOAc/C_6H_{14}, 1:3 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ= −2.73 (s, 4H, -N*H*), 5.70 (br, 4H, -CH_2), 6.67 (br, 2H, -C*H*=), 7.75 (m, 20H. phenyl-*H*), 8.19 (m, 12H, phenyl-*H*), 8.81 (br, 12H, β-*H*), 9.40 ppm (d, 4H, *J* = 5.2 Hz, β-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.3, 116.3, 119.2, 126.1, 126.3, 127.2, 128.4, 134.0, 134.1, 135.1, 141.8 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε)= 420 (4.2), 517 (3.0), 551 (2.6), 593 (2.5), 650 nm (2.5); HRMS (ES+) [$C_{41}H_{28}N_4O$]: calcd for [M + H] 1129.4710, found 1129.4679.

279 (key data)

279*E*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.01 (m, 3H, C*H*$_2$OCO, C=CH*H*), 5.24 (s, 1H, C=CH*H*), 5.93 (d, *J* = 5.6 Hz, 2H, C*H*$_2$CH=), 6.29 (d, *J* = 15.8 Hz, 1H, C*H*=CHCH$_2$) 6.30 (d, *J* = 15.4 Hz, 1H, CH=C*H*CO), 6.95 (dt, *J* = 5.6 Hz, 15.8 Hz, 1H, CH=C*H*CH$_2$), 9.83 (d, *J* = 15.4 Hz, 1H, C*H*=CHCO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.0 (*C*H$_2$CH=), 64.2 (*C*H$_2$OCO), 116.8 (C=*C*H$_2$), 130.9 (CH=*C*HCO), 134.2 (CH=*C*HCH$_2$), 133.9 (*C*H=CHCH$_2$), 144.2 (*C*H=CHCO), 165.3 (*C*O$_2$);

279*Z*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.30 (s, 2H, C*H*$_2$OCO), 5.97 (s, 1H, C=CH*H*), 6.04 (s, 1H, C=CH*H*), 6.16 (m, 3H, C*H*$_2$CH=, C*H*=CHCH$_2$), 6.48 (d, *J* = 15.4 Hz, 1H, CH=C*H*CO), 6.83 (dt, *J* = 6.8 Hz, 11.3 Hz, 1H, CH=C*H*CH$_2$), 10.03 (d, *J* = 15.4 Hz, 1H, C*H*=CHCO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 35.1 (*C*H$_2$CH=), 68.0 (*C*H$_2$OCO), 118.2 (C=*C*H$_2$), 124.2 (*C*H=CHCH$_2$), 130.9 (CH=*C*HCO), 137.5 (CH=*C*HCH$_2$), 144.5 (*C*H=CHCO), 165.6 (*C*O$_2$);

279*E* ROESY		**279*Z* ROESY**	
6.95	5.01	6.83	-
6.29	5.01	6.16	5.30
	5.93		5.97
5.93	6.95	6.04	5.30
	6.29		5.97
5.24	6.01	5.97	6.04
			6.16
5.01	5.24	5.30	6.04
	6.29		6.16
	6.95		

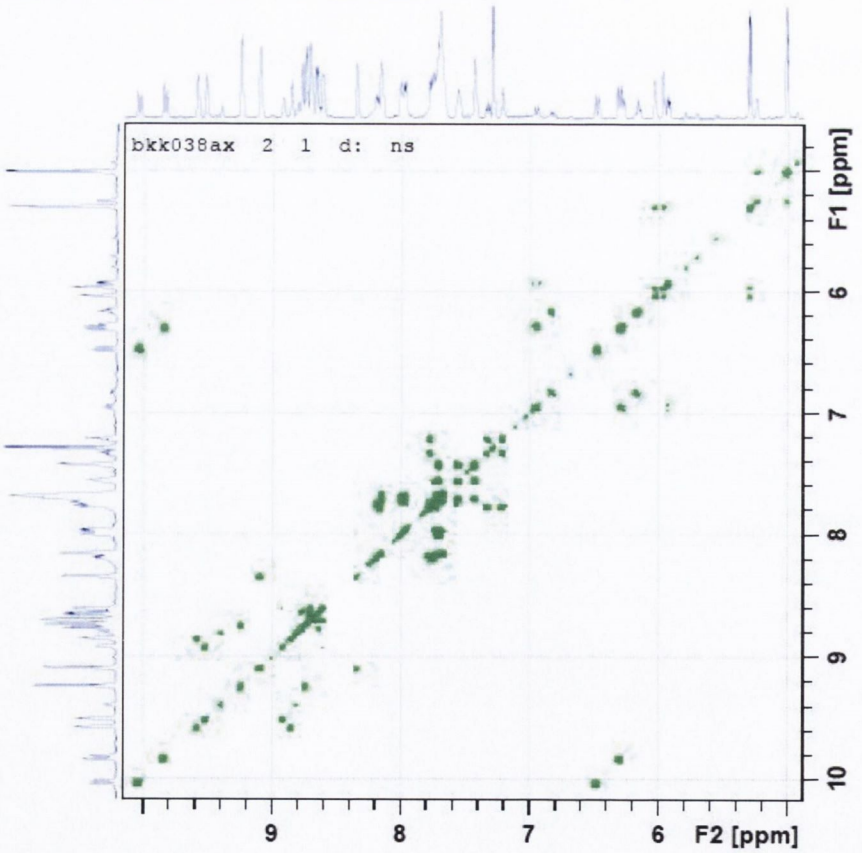


Figure 6.1 HH COSY spectrum of porphyrin **279**.

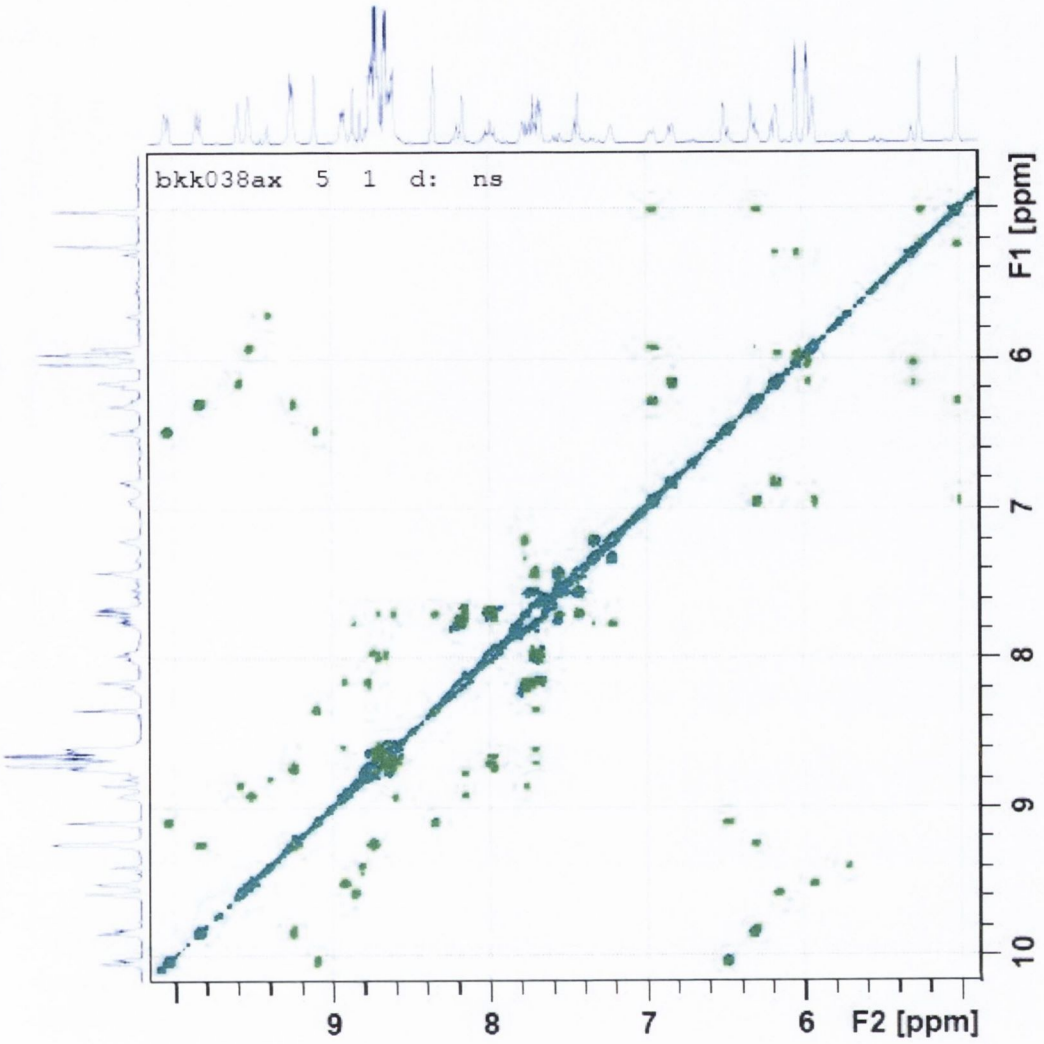


Figure 6.2 ROESY spectrum of porphyrin **279**.

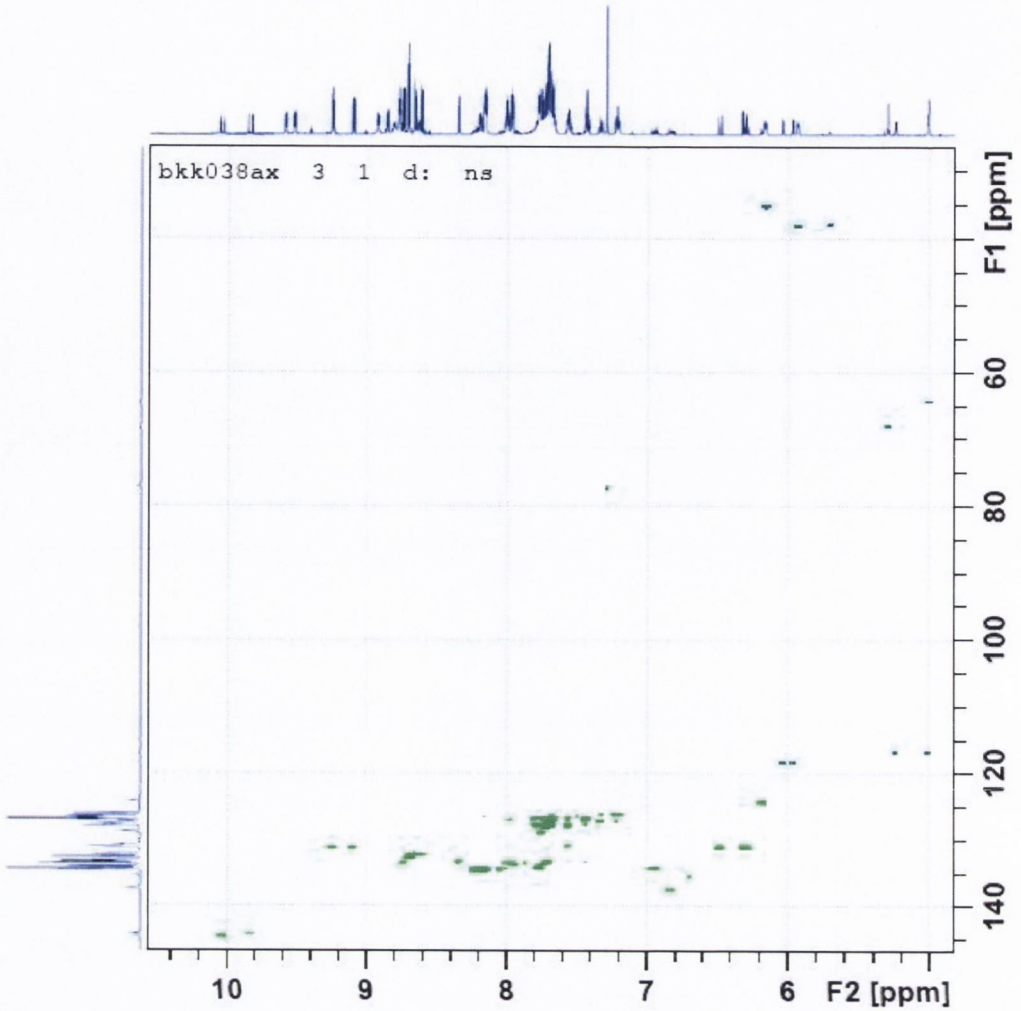


Figure 6.3 HSQC spectrum of porphyrin **279**.

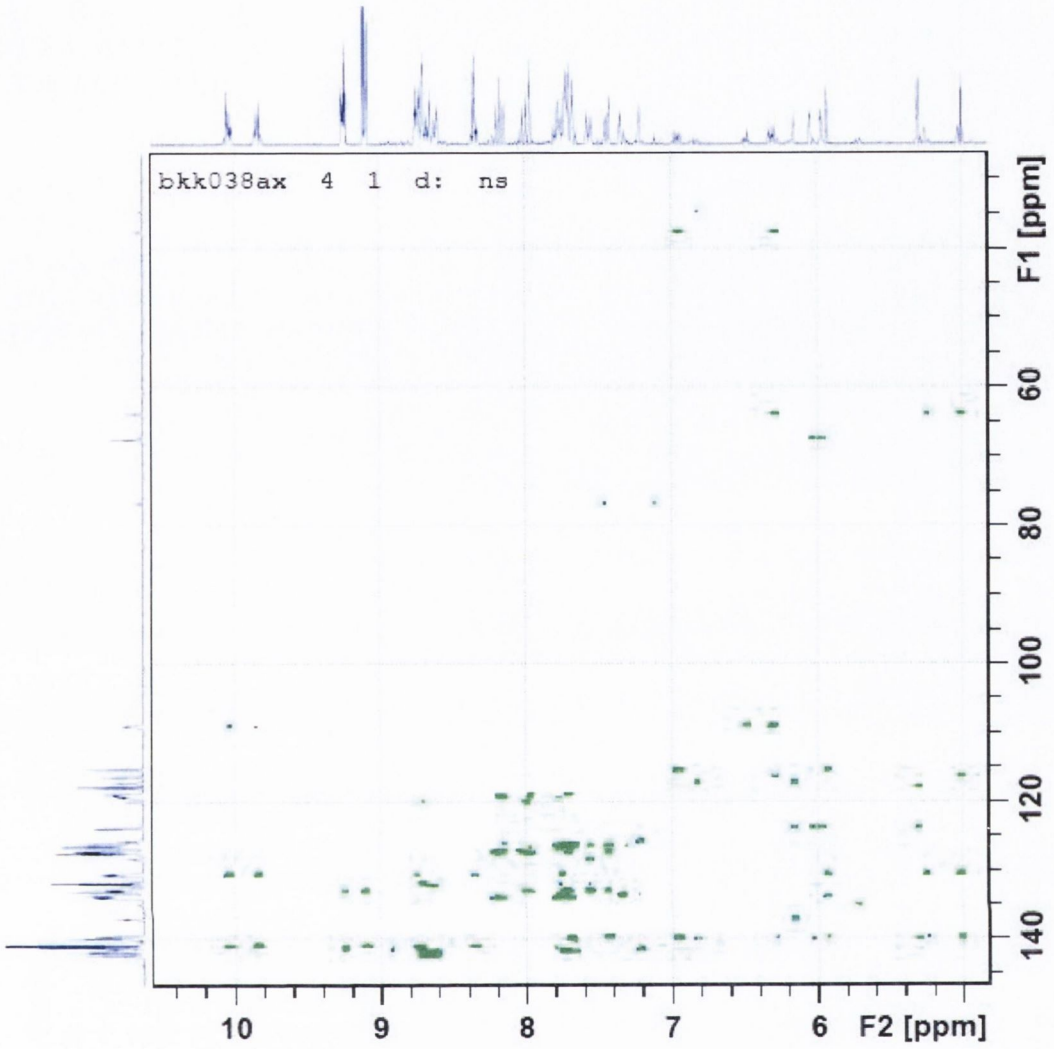


Figure 6.4 HMBC spectrum of porphyrin **279**.

280 (key data)
280*E*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 (s, 2H, CH_2OCO), 5.16 (s, 1H, C=CH*H*), 5.31 (s, 1H, C=CH*H*), 5.46 (d, *J* = 5.6 Hz, 2H, CH_2CH=), 6.29 (d, *J* = 15.8 Hz, 1H, CH=C*H*CO), 6.43 (d, *J* = 16.2 Hz, 1H, C*H*=CHCH$_2$), 6.84 (dt, *J* = 5.6 Hz, 16.2 Hz, 1H, CH=C*H*CH$_2$), 9.82 (d, *J* = 15.8 Hz, 1H, C*H*=CHCO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 36.8 (*C*H$_2$CH=), 64.0 (*C*H$_2$OCO), 117 (C=*C*H$_2$), 130.9 (CH=*C*HCO), 130.4 (*C*H=CHCH$_2$), 133.7 (CH=*C*HCH$_2$), 144.0 (*C*H=CHCO), 165.3 (*C*O$_2$);

280*Z*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (s, 2H, CH_2OCO), 5.68 (d, *J* = 6.4 Hz, 2H, CH_2CH=), 5.83 (s, 1H, C=CH*H*), 5.94 (s, 1H, C=CH*H*), 6.18 (d, *J* = 11.7 Hz, 1H, C*H*=CHCH$_2$), 6.44 (d, *J* = 15.4 Hz, 1H, CH=C*H*CO), 6.77 (dt, *J* = 6.4 Hz, 11.7 Hz, 1H, CH=C*H*CH$_2$), 10.01 (d, *J* = 15.4 Hz, 1H, C*H*=CHCO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 67.4 (*C*H$_2$OCO), 33.7 (*C*H$_2$CH=), 118 (C=*C*H$_2$), 124.7 (*C*H=CHCH$_2$), 130.8 (CH=*C*HCO), 136.9 (CH=*C*HCH$_2$), 144.4 (*C*H=CHCO), 165.4 (*C*O$_2$);

280*E* ROESY		**280*E* NOE**		**280*Z* ROESY**		**280*Z* NOE**	
6.84	5.01	6.84	5.01	6.77	5.68	6.77	5.68
6.43	5.46 5.16			6.18	5.24		
5.46	6.84 6.43	5.46	6.84 6.43	5.94	5.24		
5.16	6.43	5.16	6.43	5.83	5.68		
5.02	6.84	5.03	6.84	5.68	6.77 5.83	5.68	6.77
				5.24	5.94 6.18	5.24	5.94 6.18

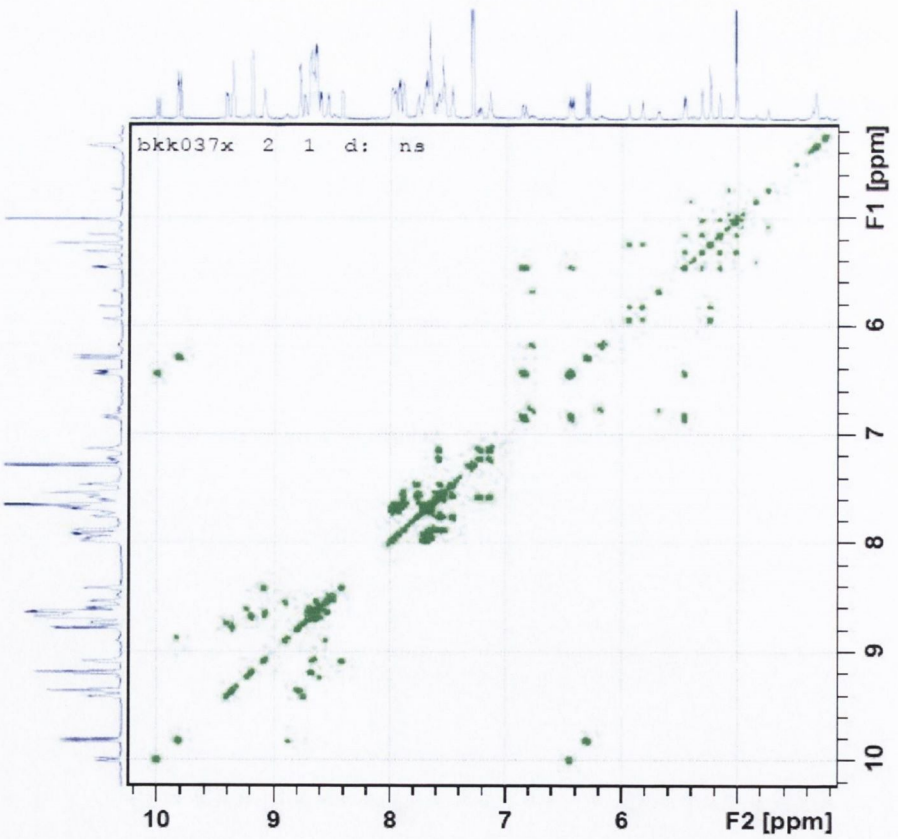


Figure 6.5 HH COSY spectrum of porphyrin **280**.

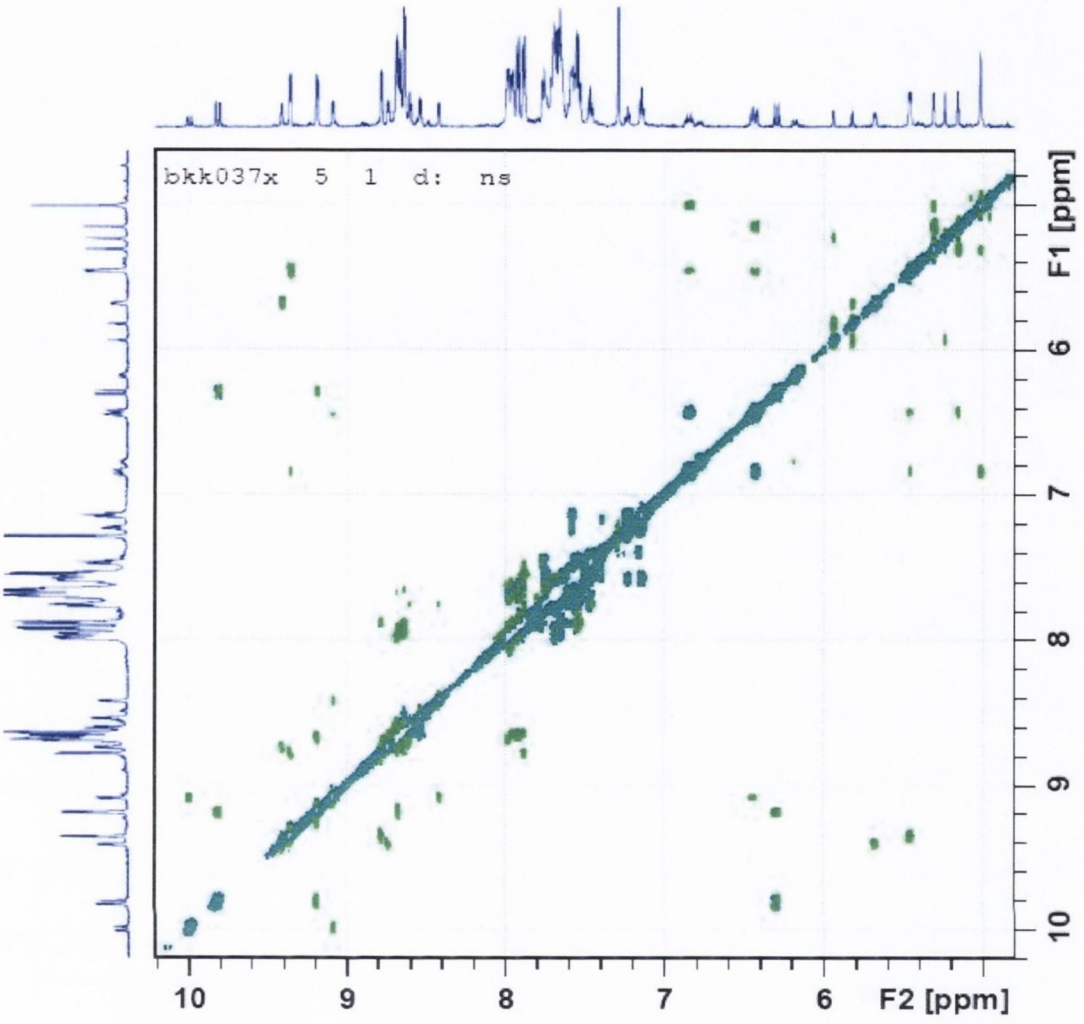


Figure 6.6 ROESY spectrum of porphyrin **280**.

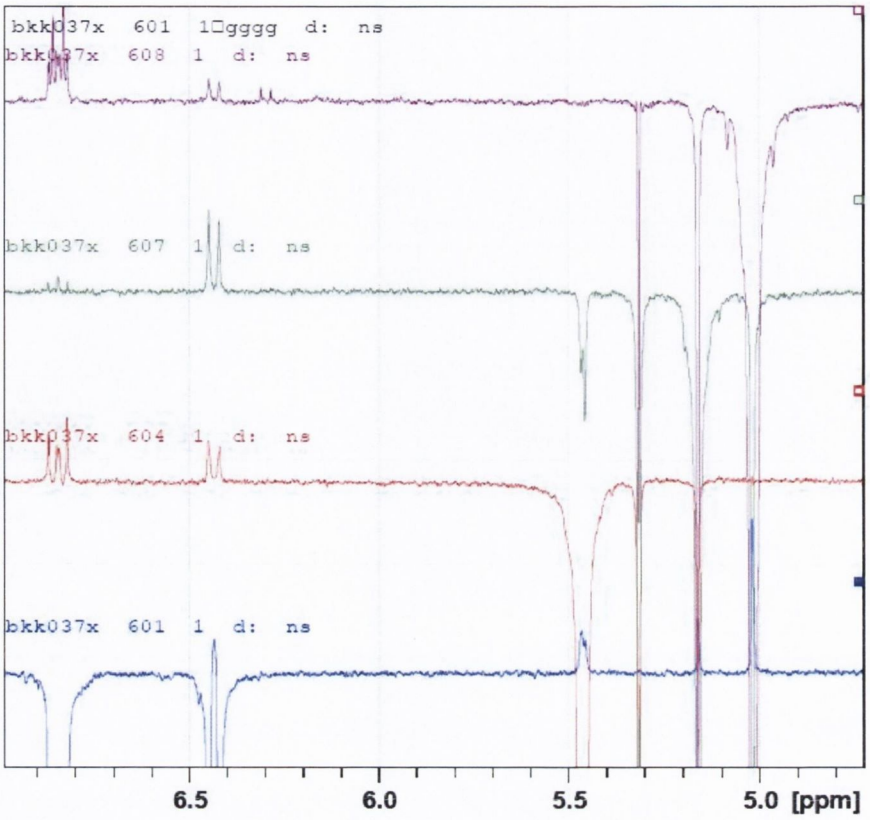


Figure 6.7 NOE spectrum of porphyrin **280*E***.

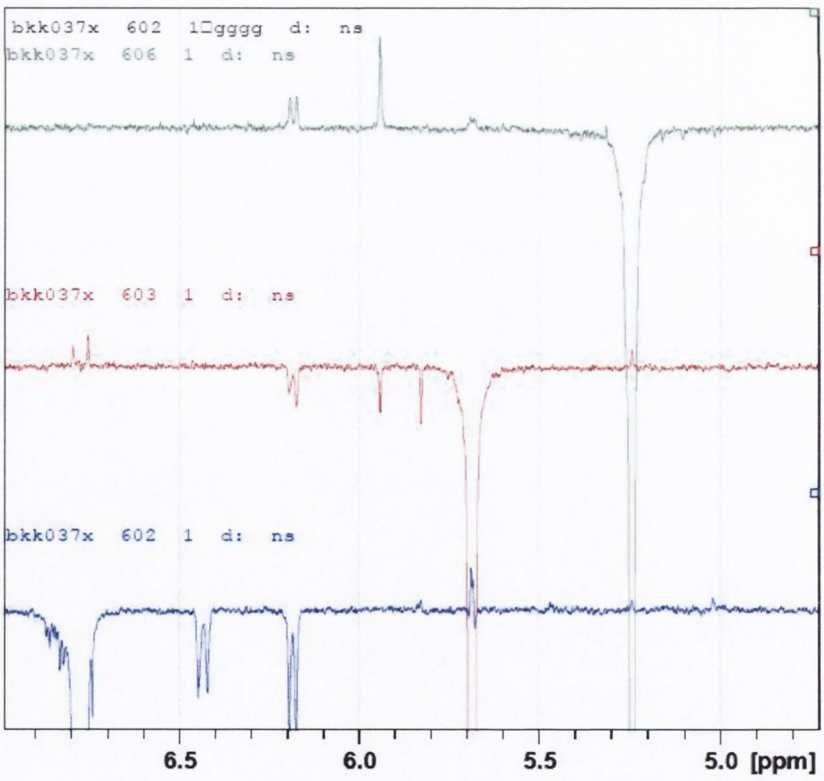


Figure 6.8 NOE spectrum of porphyrin **280*Z***.

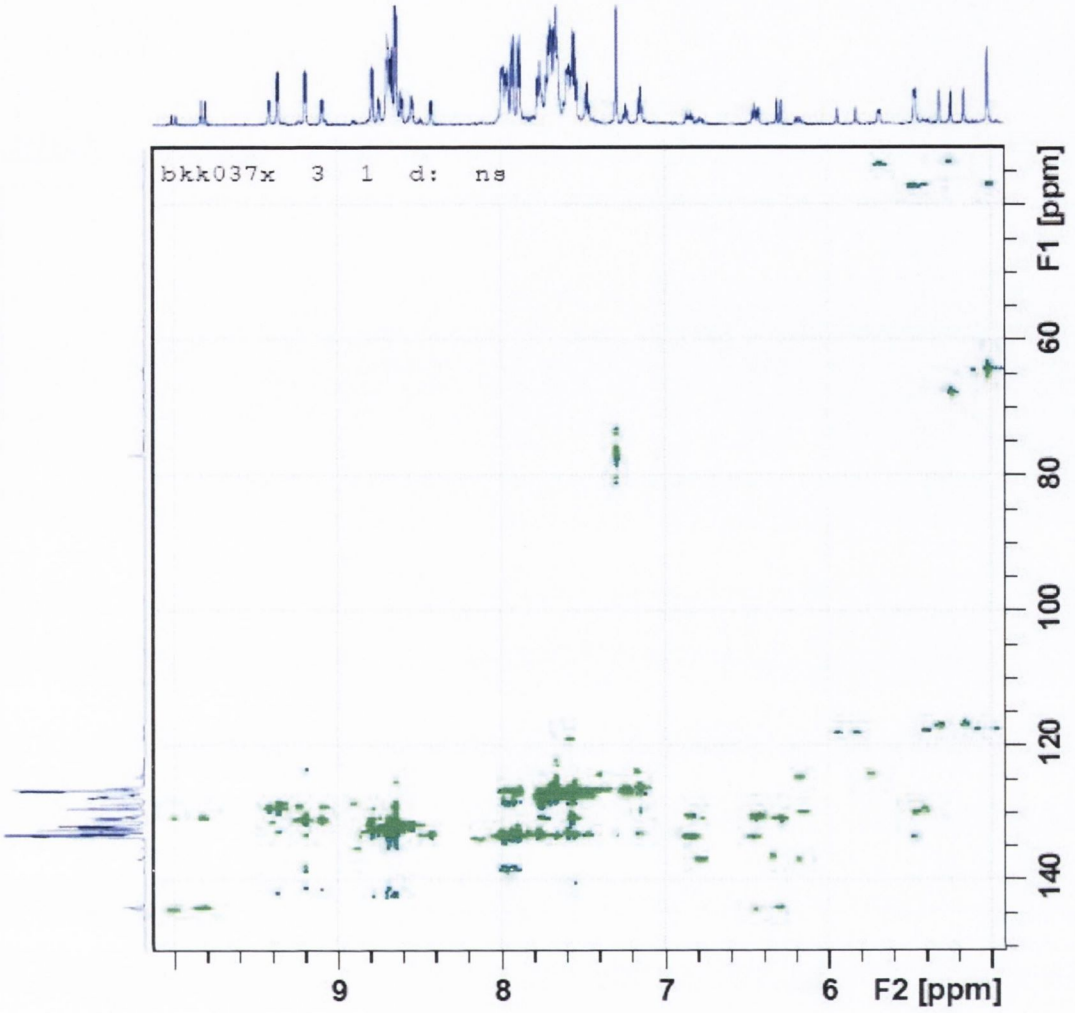


Figure 6.9 HSQC spectrum of porphyrin **280**.

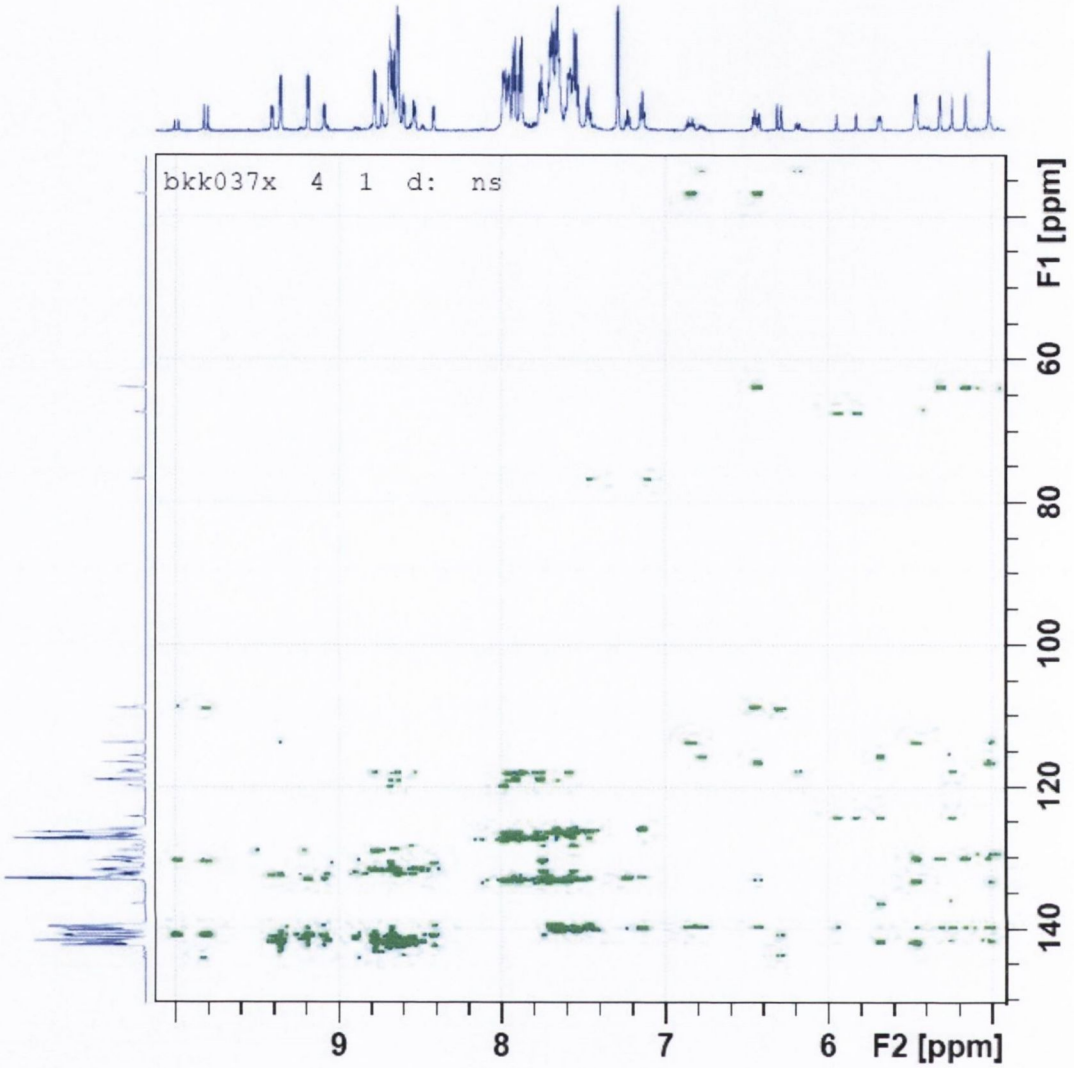


Figure 6.10 HMBC spectrum of porphyrin **280**.

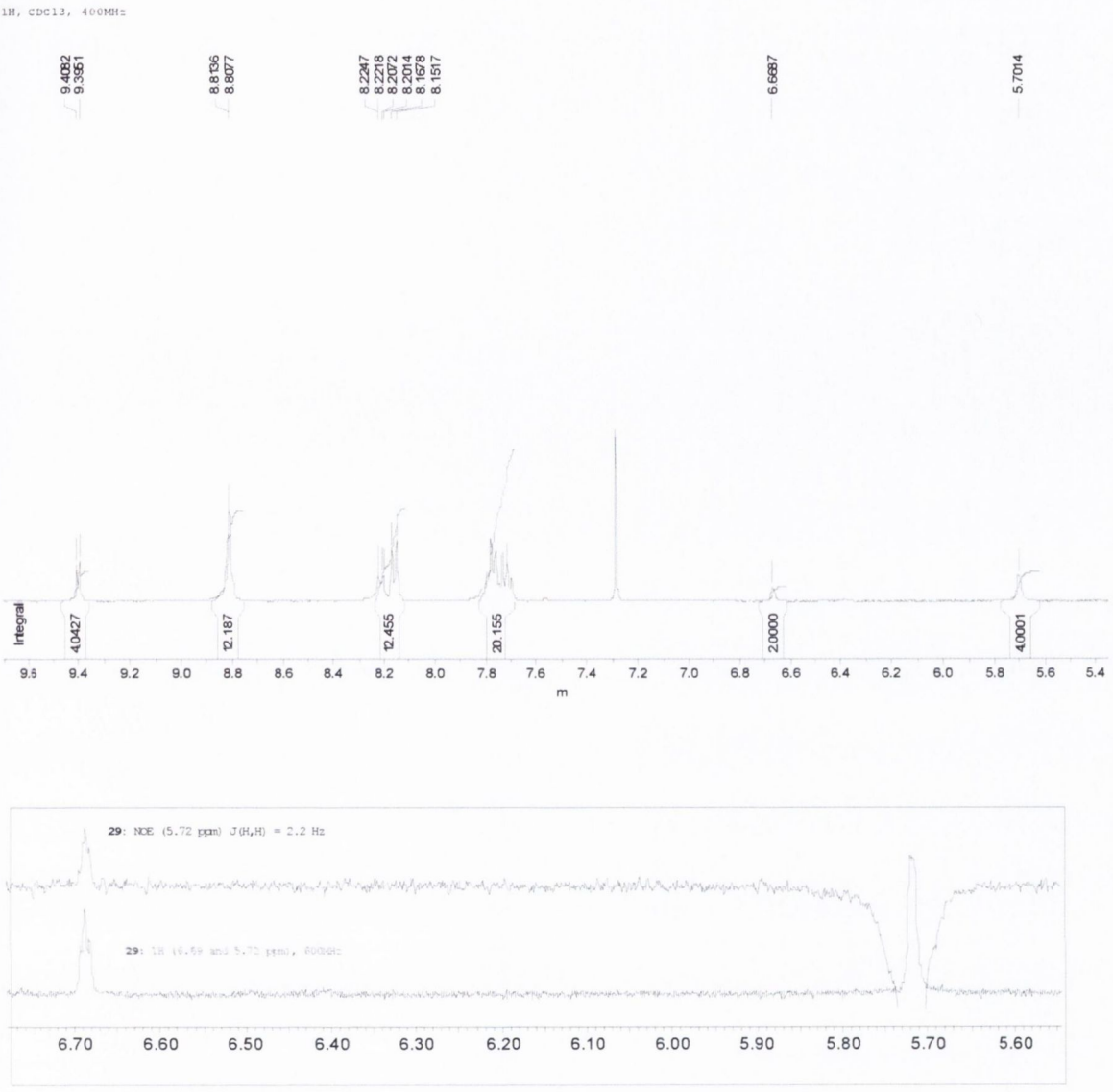


Figure 6.11 ^{1}H-NMR and NOE spectrum of porphyrin **282**.

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