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Synthetic Studies on the Preparation of Shape Selective Mimics of Cytochrome P450

by

Michael M. Pollard 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

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Abstract

Synthetic efforts towards preparing a shape selective mimic of cytochrome P450 using a derivatized porphyrin are described. The target biomimetic catalysts can be described as a metalloporphyrin, modified on one or both faces, with a torus shaped molecular scaffolding restricting access to the porphyrin chelated metal which performs the C-H bond activation. Several general synthetic strategies are presented.

The first strategy focused on capping a tetraphenylporphyrin (TPP) derivative with a cyclic octapeptide on both faces of the porphyrin. To facilitate capping, TPP derivatives with electrophilic functionality in the *meta* positions of TPP were prepared, including tetrakis(3,5-bis(bromomethyl)phenyl)porphyrin (**31**). Synthetic efforts to prepare the peptide cap focused on octapeptides with L-Lys or L-Orn as residues 1, 3, 5, and 7. Linear octapeptides with alternating D-Phe and ω-protected L-Orn residues failed to cyclize under standard coupling conditions, whereas cyclization of linear octapeptides with alternating Gly and ω-protected L-Lys or L-Orn residues proceeded smoothly. Attempts to link the deprotected cyclic octapeptide to the porphyrin did not afford the desired capped porphyrin.

In the second approach, the porphyrin was used as a template to preorganize four segments of the crown cap to address one face of the porphyrin. An intramolecular ring opening metathesis (ROMP) was attempted by tethering 4 strained olefins to the *meso* positions of a porphyrin. This approach may have been unsuccessful because of excessive rigidity in the system. Capping was also attempted using a porphyrin tethered to 4 semi-rigid dienes. When treated with Grubbs' second generation catalyst, this

porphyrin tetra-diene underwent RCM up to three times. None of the desired capped porphyrin, the outcome of four successive RCM reactions, was observed.

The third approach focused on linking porphyrins derivatized with four or eight electrophilic moieties to cyclophanes possessing four amine groups to prepare mono or double capped porphyrins respectively. Similarly, when tetrakis(chloroacetamidophenyl)porphyrin (**92**) was treated with 2,11,20,29-tetraaza[3.3.3.3]paracyclophane (**105**), attachment through only two sites was observed, in addition to a complex insoluble mixture. Attempted coupling of **92**, tetrakis(3,5-bis(2-bromoethoxy)phenyl)porphyrin (**116**), or tetrakis(3-bromopropoxyphenyl)porphyrin (**120**) with **105**, 2,11,20,29-tetraaza[3.3.3.3]metacyclophane (**108**) or 2,11,20,29-tetraaza[3.3.3.3] (*para*)(*meta*)(*para*)(*meta*)cyclophane (**109**) gave similar results.

The fourth class of scaffolding evaluated for its viability as a porphyrin scaffolding is the calix[4]naphthalene derivatives. Synthetic efforts were focused on attachment of the scaffold through straps linked to the methylene bridges between naphthalene spacers. A calixnaphthalene that was strapped through two of its methylene spacers was successfully prepared using an isophthaloyl linker. However, the synthetic studies described suggest that the porphyrin is not a suitable strapping functionality.

Synthetic efforts were invested in strapping the porphyrin with α-cyclodextrin (α-CD) on one and both faces. Preliminary results suggest that a mono strapped porphyrin may be formed by the reaction of $2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-hexadeca-O-benzyl-$6^{I},6^{IV}$-chloroacetyl-α-maltocyclohexaose (**176**) with 5,15-bis(2-mercaptoethyl)-10,20-bis(4-tolyl)porphyrin (**203**). Preliminary mass spectral results suggest a bis capped was

formed by reaction of the amines of $6^{I},6^{IV}$-(amino-O-acetyl)-α-$2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-hexadeca-O-benzyl-maltocyclohexaose (**217**) with the isocyanates of α,β,α,β-5,10,15,20-tetra(2-aminophenyl)porphyrin (**215**).

During the course of this work, a convenient method for the derivatization of both *ortho*-positions of the 5,15-phenyl substituents of C-2 symmetric tetraphenylporphyrins as dithioethers was developed by Lewis acid catalyzed condensation of a 5-(2,6-dithioether-phenyl)dipyrromethane and an aldehyde, followed by oxidation.

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List of Abbreviations

[α]	specific rotation
Anal.	analysis
aq.	aqueous
Ar	aryl
Atm	atmosphere
B.D.E.	bond dissociation energy
Bn	benzyl
br	broad
c	concentration
calcd	calculated
Cbz	benzyloxycarbonyl
Cbz-Cl	benzyl chloroformate
CI	chemical ionization
Conc.	concentrated
COSY	correlated spectroscopy
d	doublet
DABCO	1,4-diazabicyclo[2.2.2.]octane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-*N,N*-dimethylaminopyridine

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DTT	dithiothreitol
ee	enantiomeric excess
EI	electron impact ionization
Equiv	equivalents
ES	electrospray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethoxycarbonyl
Gly	glycine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IBX	*o*-iodoxybenzoic acid
IR	infrared
J	coupling constant
Lys	lysine
MALDI	matrix assisted laser desorption/ionization
Me	methyl
MeOH	methanol
Mes	mesityl
MHz	megahertz
min	minute(s)

mp	melting point
MS	mass spectrometry
MW	molecular weight
Nap	naphthalene
nm	nanometers
NMR	nuclear magnetic resonance
Orn	ornithine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phe	phenylalanine
Por	porphyrin
ppm	parts per million
psi	pounds per square inch
q	quartet
RCM	ring closing metathesis
R_f	retention factor
ROMP	ring opening metathesis polymerization
RP	reverse phase
Rt	room temperature
s	singlet
t	triplet
TAP	tetraaminoporphyrin

TCQ	2,3,5,6-tetrachloroquinone (*p*-chloroanil)
tert-	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TPP	tetraphenylporphyrin
UV	ultraviolet spectroscopy
δ	chemical shift in parts per million downfield from TMS
λ_{abs}	absorbance maxima

1.0 Introduction

The ability to select a CH bond to activate for functionalization is one of the most appealing yet challenging areas of modern organic chemistry. From an industrial perspective, it is attractive because it would give cheap and easy access to important commodity chemicals from simple petroleum isolates.[1] To the synthetic chemist it is attractive because it allows the use of inexpensive starting materials to be elaborated quickly and efficiently, minimizing or eliminating multiple protection/deprotection steps from a retrosynthetic scheme. The late Prof. Derek Barton believed that "selective C-H activation [of unfunctionalized alkanes] is one of the last holy grails of organic chemistry."[2] In honour of Barton's work in this area,[3] Prof. Roberts of Caltech initiated the "Barton Challenge": to oxidize n-hexane to adipic acid, the precursor to nylon, in > 85% yield (Figure 1).

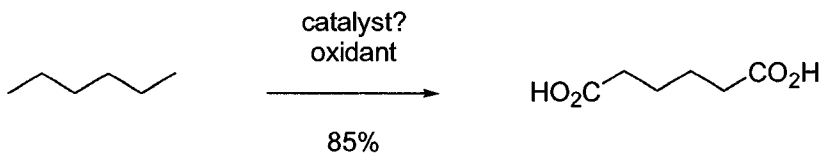


Figure 1: The Barton Challenge

This challenge highlights what is perhaps the most difficult problem in the field of selective CH bond activation:[4] the selective oxidation of primary CH bonds in the presence of secondary CH bonds. This is exceptionally difficult because the C-H bond dissociation energy decreases (B.D.E.) from 104 to 91 kcal/mol[5] proceeding from primary to tertiary bonds (Table 1). The task of generating a catalyst with this selectivity is put in perspective by considering the huge effort invested in developing enantioselective catalysts, which only need to favour one enantiotopic CH bond over another by several $kcal^{-1}$/mol for a catalyst capable of producing 99% ee.[6]

R	Energy (kcal/mol) R-H ⟶ R• + H•
Et	104
i-Pr	95
t-Bu	91

Table 1: Homolytic Bond Dissociation Energies for Hydrocarbons (kcal/mol).

The selective oxidation of primary CH bonds of n-alkanes faces three key challenges:

1) The primary carbon-hydrogen bond is stronger, as demonstrated by its BDE. Primary CH bonds are less reactive on a thermodynamic basis.
2) From a statistical perspective, there are many more secondary CH bonds than primary.
3) The relative inertness of alkanes means that their functionalisation generally requires very reactive reagents and/or drastic conditions.[5]

It is apparent that challenges 1 and 3 are inherently incompatible with generating selectivity based on strictly intrinsic chemical reactivity of the alkanes. The relative stability of primary CH bonds means that conditions used to functionalize them will also functionalize secondary and tertiary CH bonds present.

This long standing challenge has recently been effectively approached from several perspectives. Two of the most notable are the breakthrough contributions of Hartwig[7] using rhenium and iridium catalysed terminal carbon organoborylation, and the terminal carbon selectivity of manganese impregnated molecular sieve oxidation reported by Thomas,[8] both of which take advantage of steric discrimination enforced by the

reagents used. Steric requirements seem to be the most obvious handle to use in obtaining selectivity in CH bond activation. Indeed, this is the handle which has been effectively used for selective CH bond activation for millions of years – by Nature.

1.1 Nature's Hydroxylation Enzymes

Natural systems achieve the oxidation of alkanes with exquisite selectivity using several classes of metalloenzymes, the most common including non-heme monooxygenases and cytochrome P450 oxygenases. Figure 2 shows three examples of selective enzyme catalysed oxidation reactions. The first and third examples show oxidation at the α- and β-position respectively, processes which can be mimicked in the laboratory.[9,10] The middle highlighted example shows an example of the coveted terminal selective oxidation – the ω-oxidation.[11]

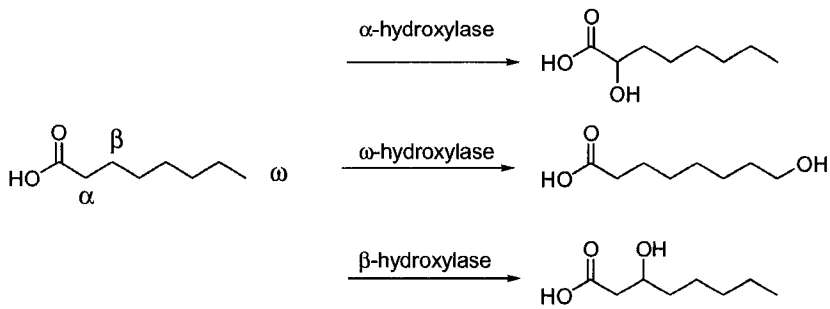


Figure 2: Remarkable differences in enzyme selectivity.

With this type of chemoselectivity available, it is at first surprising that organic chemists have not begun to use these enzymes as routine synthetic reagents, as they have with other enzymes such as the lipases. Unfortunately, there are several reasons for this:

a) these enzymes are extremely substrate sensitive, often to give drastic loss in selectivity and catalytic efficiency with small substrate alterations,[12]

b) at present there are no oxygenase enzymes that are robust enough for routine use by non-specialists, and hence

c) no inexpensive source of the enzymes that hydroxylate selectively primary hydrocarbons has been developed.

Consistent with a long standing interest in our laboratory in understanding and mimicking natural systems, we decided to approach the problem of selective primary CH bond activation from a biomimetic perspective. Key information required for the rational design of an effective biomimetic catalyst include:

1. An understanding of how natural systems operate.
2. Background on what other relevant mimics have been prepared.

These two subjects will be briefly discussed in turn to give the reader the working knowledge of these topics required to appreciate factors considered in the design of further such biomimetic catalysts.

1.2 Hydroxylation Reactions in Nature

The two most ubiquitous enzymes responsible for alkane hydroxylation are the non-heme monooxygenases[13] and the cytochrome P450 oxygenases.[14] The catalytic machinery of the non-heme iron monoxygenase is a diiron complex, chelated by histidine and bridging aspartic and glutamic acid residues subtly arranged to activate molecular oxygen, and subsequently perform the oxidation (e.g. methane to methanol) (Figure 3). This active site is challenging to mimic and has been the subject of significant recent attention.[15,16]

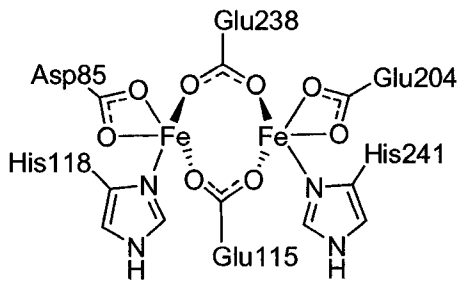


Figure 3: Representation of reduced form of the active site of MMO.[17]

The net transformation effected by the cytochrome P450 enzyme is the oxidation of an alkane to an alcohol consuming the elements of two electrons (originally supplied by NADPH), two protons, and one molecule of molecular oxygen (Figure 4).

$$RH + O_2 + 2e^- + 2H^+ \xrightarrow{\text{P450}} ROH + H_2O$$

Figure 4: Overall transformation catalyzed by P450.

The catalytic machinery of the cytochrome P450 enzyme is an iron metalloporphyrin (Figure 5). This is held by the enzyme by a thiolate from a cysteine residue, which plays a role in both binding the porphyrin in the active site and facilitating the catalytic cycle. We decided to mimic the P450 class of enzymes because of the relative ease of preparation of mimics of its catalytic machinery, the metalloporphyrin, and because some of their derivatives have been shown to be very active and robust catalysts.[18] The P450 oxygenase may be conceptually reduced to two key components (Figure 5):

1. The heme moiety. The heme is the catalytic machinery of the enzyme. It forms a stable chelate with the iron(III) which, upon activation with an oxidant, is responsible for hydroxylating the alkane substrate.
2. The peptide scaffold. This component is responsible for

a) inducing stereo and regioselectivity in the oxidation reaction by creating a shape selective defined space around the metalloporphyrin,

b) facilitating electron transfer reactions in the reduction of oxygen to superoxide, then peroxide,

c) enhancing enzyme stability. This is achieved by aiding the catalytic cycle by providing key hydrogen bonding residues near the peroxide, minimizing the lifetime of potentially damaging intermediates.

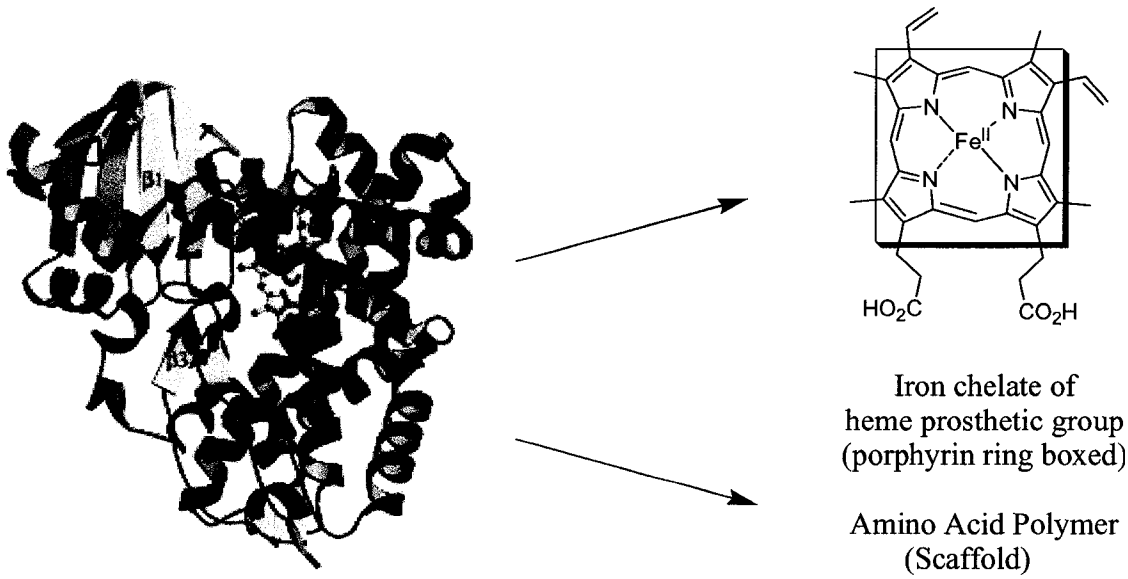


Figure 5: The two key components of P450.[19]

The heme prosthetic group has been demonstrated to perform key roles in four enzyme functions including electron transport, oxygen transport, carbon monoxide sensing, and catalysis of redox reactions (i.e. cytochrome P450, catalase, NO synthase, and NO reductase respectively).[20] The function and activity of the heme group is controlled by the protein scaffolding and the heme's environment. Hence, to effectively

mimic this enzyme, a knowledge of how the key amino acid residues interact with the heme component is of significant interest.

1.3 Mechanism of P450

The mechanism of oxidation by P450 enzymes has been the subject of extensive investigation. Due to the volume of work on this subject, only selected, key work is discussed herein. For an in-depth discussion of the mechanistic studies contributing to our current understanding of this complex process, the reader is directed to an excellent review by Montellano and De Voss.[14]

The most recent and compelling work which has confirmed previously hypothesized key intermediates (**3, 4, 6**) is the "tour de force" cryogenic X-ray low temperature crystallographic studies by Sligar and coworkers.[21] This work was done on the camphor oxidizing enzyme P450cam, though its mechanism is believed to be general among this class of oxygenating enzymes.[22] Their studies built on previous investigations[14] implicating the intermediates in the catalytic cycle shown (Figure 6).

The catalytic cycle begins with substrate alkane binding induced expulsion of a water molecule coordinated to the iron(III) of the heme (**1**→**2**). The substrate bound enzyme complex is then reduced from the ferric to the ferrous state by a flavoprotein mediated one electron reduction (**2**→**3**).[23] This iron(II) chelate (**3**) reversibly binds molecular oxygen to give **4**. This species can undergo autooxidation back to **2** by loss of superoxide, or further reduction to the anionic peroxy species **5**. Peroxy anion **5** has been implicated in biological oxidations which involve O-O heterolytic cleavage similar to the Baeyer-Villager,[24] and in oxidations which result in homolytic cleavage (i.e. oxidation of C14 of lanosterol).[24]

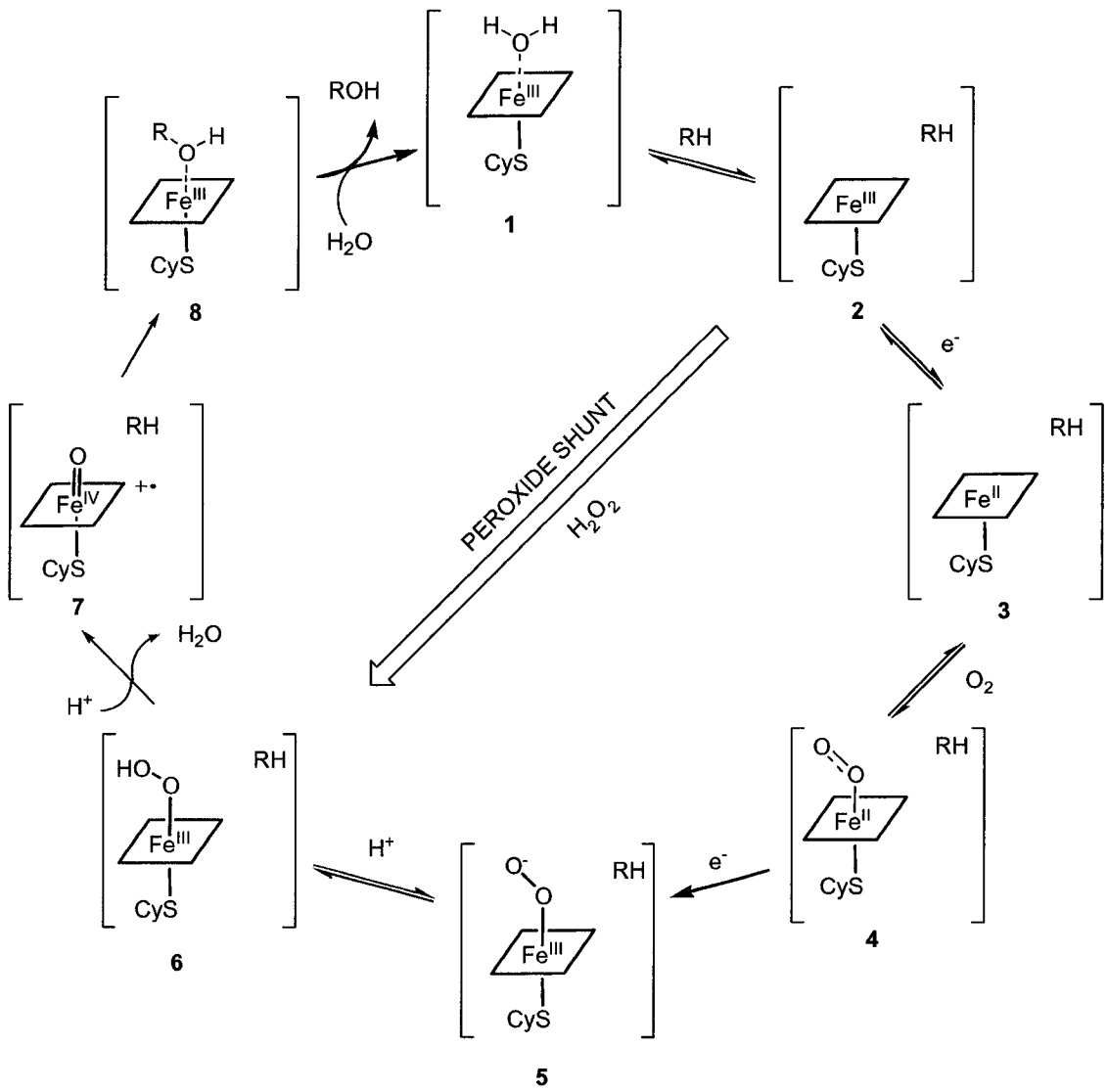


Figure 6: Catalytic cycle of cytochrome P450.

This anion **5** is then protonated by a tyrosine-water-water-aspartic acid proton relay network to give **6** (Figure 7).[25] **6** can also be obtained by treatment of **2** with hydrogen peroxide via the "hydrogen peroxide shunt."[26] Thus, P450 type oxidations can be performed in the laboratory with enzyme and hydrogen peroxide, though these oxidations do not always exactly mimic those obtained with the natural enzymatic cycle.[27] Like intermediate **4**, **6** can undergo nonproductive autooxidation back to **2**, here

via loss of peroxide. Intermediate **6** has also been implicated as the active oxidizing species in enzymatic aromatic oxidation reactions.

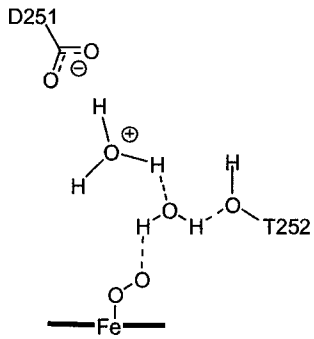


Figure 7: Amino acid/water proton transfer relay for 4 to 5.

Next, **6** is believed to undergo heterolytic bond scission generating the elements of water and the highly reactive ferryl species **7** (best described as an iron(IV)oxoporphyrin cation radical).[28] This transformation (**6**→**7**) has been strongly implicated in the catalytic cycle, though **7** has not been characterized because it immediately reacts with substrate to give **8**. The involvement of **7** instead of **6** as the key oxidant in P450 hydroxylation is supported by the following observations:[29]

a) once protonated to the $FeOOH_2^+$ cation, loss of water to give **7** involves a barrier-less pathway,

b) FeOOH is calculated to be a poorer oxidizing agent not capable of performing the hydroxylation of alkanes or olefin epoxidation,

c) $FeOO^-$ is calculated to be quite basic and nucleophilic.

It is has also been demonstrated that the cysteine residue which coordinates the iron is important for activity.[30, 31] Mutants wherin the cysteine has been replaced with histidine retain only a fraction of the activity of the wild type enzyme.[31] Though the effects of geometric alteration of the enzyme have not been separated from the changes in

electronic factors, several synthetic enzyme models using iron bound thiols also suggest that the thiol aids in the O-O bond heterolysis by the "push-pull" effect.[32] This has been attributed to the added electron density donated to the iron from the thiolate, thus stabilizing the formation of the ferryl product. This peroxy intermediate is also important because, in addition to oxidation catalysis, it can lead to autooxidation and heme degradation via *meso* oxidation (Figure 8).[33]

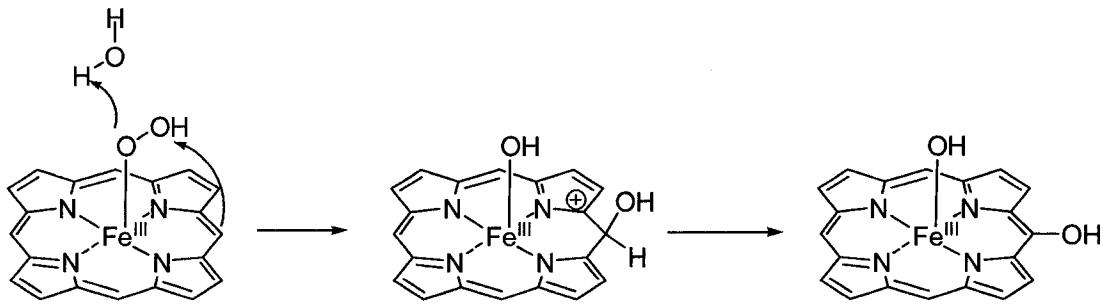


Figure 8: Heme degradation from peroxy intermediate.[14]

The next step in the catalytic cycle is one of the most interesting, yet difficult to study because of its high reactivity. Since it is believed that **7** is the species responsible for all P450 catalyzed oxidations of alkanes to alcohols, the currently accepted mechanism is described below.

This key step (**7**→**8**) in the catalytic cycle was first explored using metalloporphyrins as mimics of P450. Initially, Groves and coworkers[34] observed that when mimicking the alkane hydroxylation of P450 in the laboratory with tetraphenylporphyrin (TPP), the product distribution was consistent with a radical mechanism. This 1979 seminal work lead to the proposal of the "radical rebound mechanism"[34] (Figure 9) which has subsequently gained general acceptance. In this proposed mechanism, intermediate **7** can be imagined to exist in two canonical forms

(though **7a** is the best representation). The oxygen behaves like a radical (analogous to *tert*-BuO˙) and abstracts a hydrogen radical from the alkane. This newly formed alkyl radical quickly recombines with the oxygen, leading to the hydroxylated alkane and the regenerated iron(III) porphyrin. This proposal was consistent with the observed hydroxylation product distribution showing facility of oxidation, easiest to hardest being $3^{\circ} > 2^{\circ} > 1^{\circ}$.

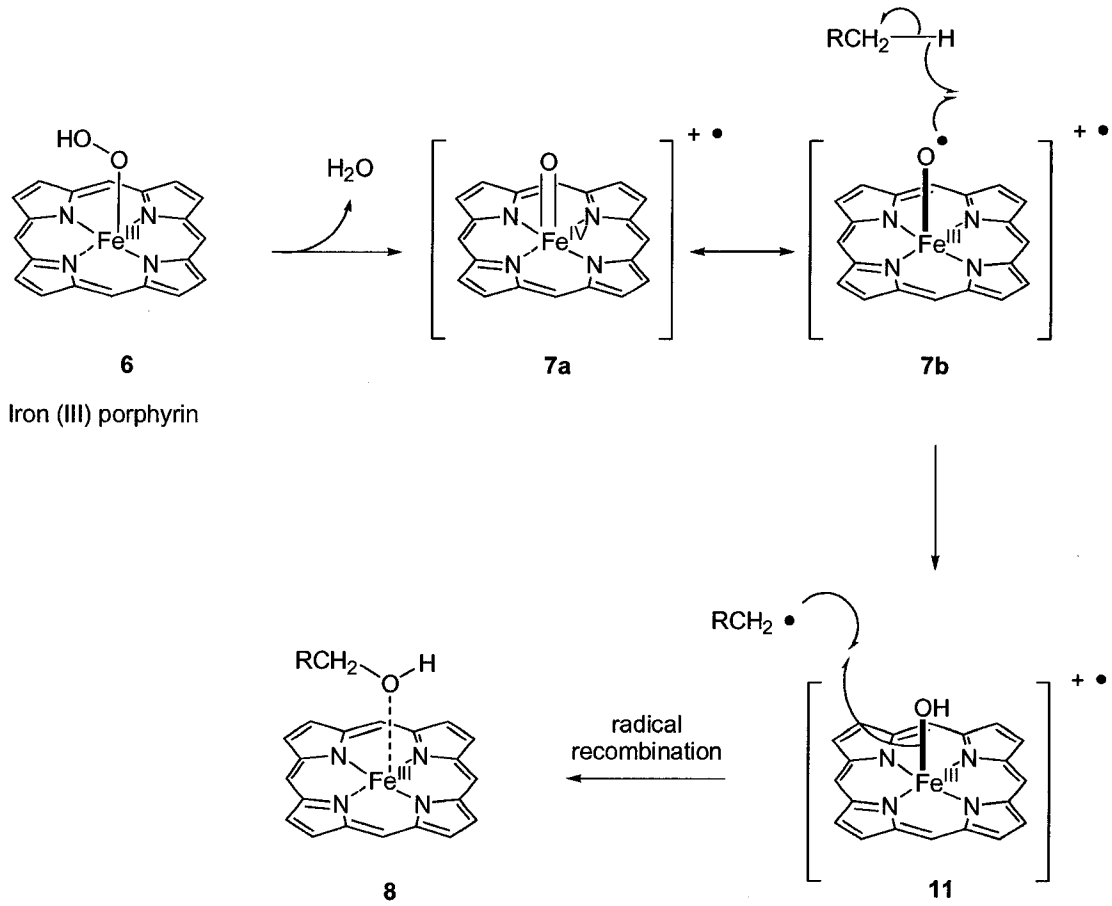


Figure 9: The radical rebound mechanism.[34] Coordinated cysteine and heme periphery are omitted for clarity.

However, in the last two decades a small body of conflicting evidence has emerged in the literature, most of which suggested the existence of a carbocation

intermediate.[14] Recent theoretical calculations by Shaik and coworkers[28] have provided a unified understanding of this body of seemingly contradictory results by applying the two state reactivity paradigm[35] to subtly modify the rebound mechanism.

In the two state reactivity theory (Figure 10), it was proposed that the ferryl species exists as two distinct, interconvertable electromers of high or low spin (doublet or quartet, respectively) which exist at similar energies **7**. Both electromers can perform the hydrogen abstraction step, each leading to an energetically similar, electronically distinct iron(III)porphyrin hydroxyl species that is coordinated to the alkyl radical **11**.

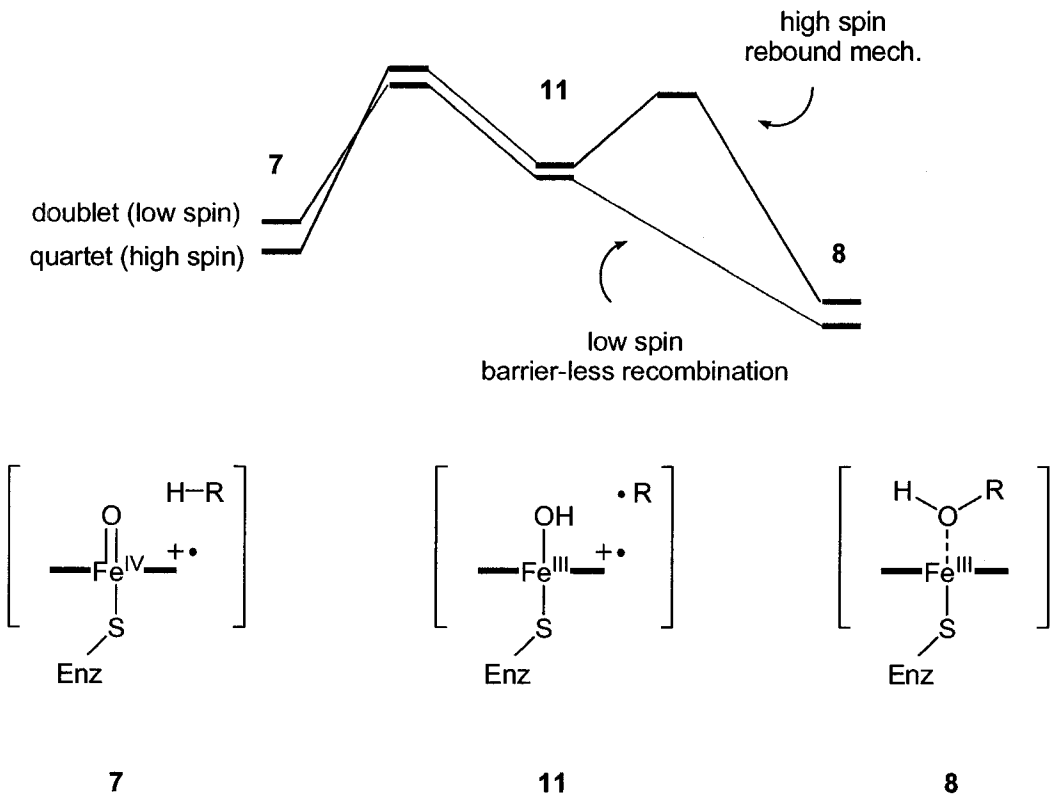


Figure 10: The relative energies of high and low spin intermediates described by the two state reactivity theory.[35]

In the final step the two paths differ significantly. The doublet spin state iron-hydroxyl can recombine with the coordinated radical in a virtually barrierless process (i.e.

essentially concerted) generating **8**. Radical collapse for the electromer in the quartet state, however, is *not* barrierless due to electronic reconfiguration which must occur before recombination with the alkyl radical. It was postulated this high energy intermediate could in some cases lead to competing side reactions including electron transfer. These electron transfer side reactions would explain the products resulting from formation of a carbocation intermediate.

The final step in the catalytic cycle involves loss of the substrate alcohol and coordination of water to the regenerated ferric metalloporphyrin **1**.

1.4 Previous Examples of P450 Mimics

The use of derivatized porphyrins to mimic P450 has been extensively explored, though predominantly in the context of developing stereoselective olefin epoxidation[36] and exploring key intermediates in the oxidation process to illuminate the mechanism in enzymatic systems.[13] Since these are of only peripheral significance to this work, the reader is directed to several references on stereoselective catalysis[37] and mechanistic work.[38] Nevertheless, several examples stand out in the literature of mixed success mimicking regioselective (also termed "shape selective") hydrocarbon oxidation by P450. Selected examples of particularly effective and/or relevant P450 mimics will be discussed to give perspective on the state of the art in the field. For more background on this subject the reader is directed elsewhere.[39,40]

One of the first regioselective hydroxylation P450 mimics that demonstrated truly enzyme-like selectivity was reported by Groves and coworkers.[41] In this clever example, a porphyrin appended with four cholesterol groups was solubilized in a synthetic

phospholipid bilayer in aqueous media. This catalyst showed dramatic regioselectivity for hydroxylation of the C-25 position of cholesterol (oxidized position shown in red in Figure 11). Impressively, they observed no oxidation of any of the other tertiary CH bonds or of the double bond also present in the substrate. When treated with cholesterol unsaturated in the C23-C24 position, epoxidation occurred exclusively in this position (not shown). The origin of this selectivity was believed to arise from the inherent propensity of cholesterol in aqueous bilayer systems to orient with its polar OH group facing out to the bulk water, while the hydrophobic bulk of the molecule is solublized by the alkane chains of the bilayer.

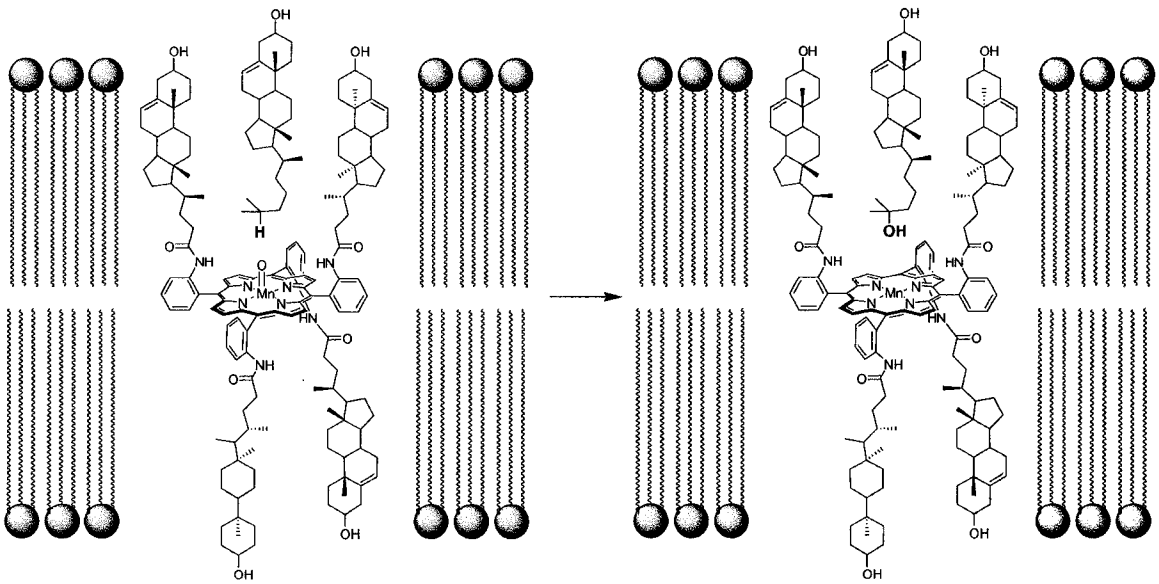


Figure 11: Groves' selective cholesterol oxidant.[41]

The porphyrin, firmly embedded deep within the bilayer, could only access lipophilic tails which can reach into the center of the bilayer. Disadvantages of this catalyst include difficulties in scale up (the product formation was confirmed by GC-MS only due to small reaction scale), low yields, and the fact that it could not be used to

oxidize anything but tertiary alkanes since the competing hydroxylation of the bilayer itself would effectively drown out catalysis on other substrates of similar reactivity toward oxidation.

One of the most inspiring and elegant examples of regioselective P450 mimic has been recently reported by Breslow and coworkers.[42] In this work, a porphyrin appended with four cyclodextrins catalyses the hydroxylation of the C-6 position (OH red in product shown, Figure 12) of a steroid functionalized with two lipophilic *tert*-butylphenyl ester derivatives. The catalysis appears to be completely regio- and stereoselective, with a reported 95% conversion and 100% yield using 1 mol% of the porphyrin CD conjugate. The observed selectivity is remarkable considering that hydroxylation occurs on a single secondary carbon in the presence of eight other methylenes, and perhaps more remarkably, 7 methines, all of which would be predicted to be thermodynamically more susceptible to oxidation by an unmodified porphyrin. This catalyst achieves its selectivity by recognition of the *tert*-butylphenyl groups inside the hydrophobic pockets of two of the β-cyclodextrins, directing the steroid's orientation relative to the porphyrin.

This selectivity suggests that this catalyst is the first example of a P450 mimic which binds its substrate *first*, then becomes activated to the metal-oxene species (like the native P450 enzyme). While this has not been demonstrated by Breslow, it seems likely that the translocation associated with inclusion of the *tert*-butyl appendages into both the cyclodextrins (both of which have been demonstrated as essential for selectivity) would give rise to at least some byproduct formation if it occurred *after* ferryl formation.

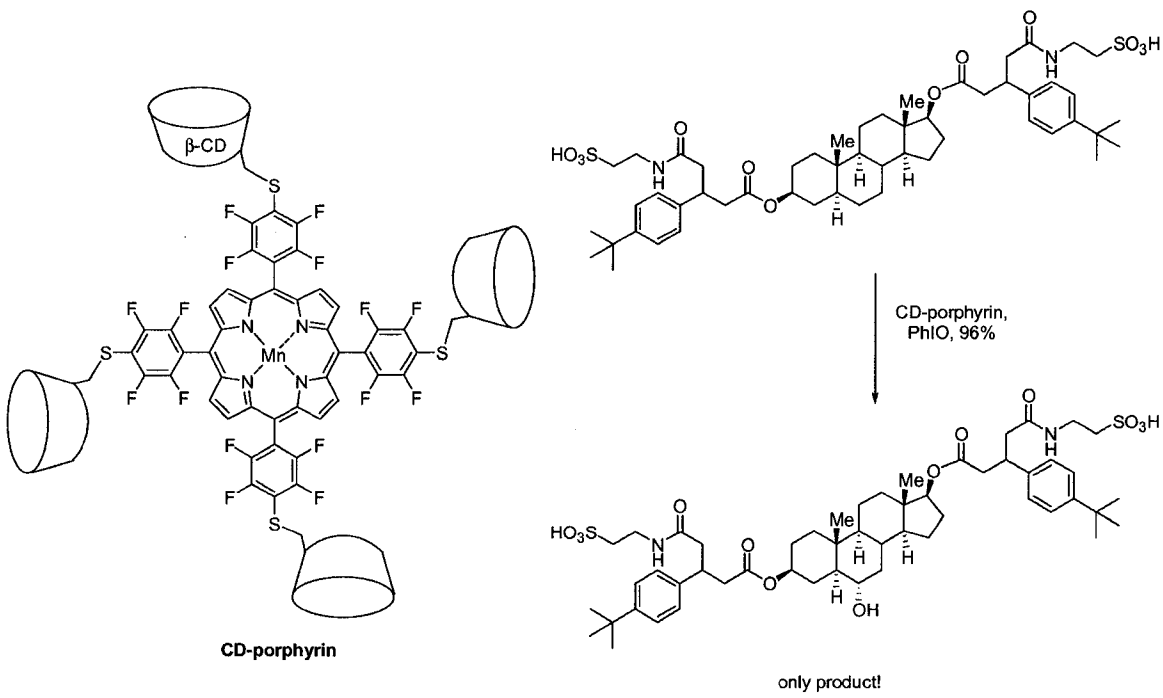


Figure 12: Breslow's CD-porphyrin catalyst.

Advantages of this type of catalyst design include its striking selectivity, facile synthesis, and high catalytic efficiency. It is limited by difficulty in *a priori* prediction of regioselection as well as the requirement for subtle alteration of appended functionalities (the *tert*-butyl phenyl ester derivatives) to achieve the regioselection.

These two catalysts demonstrate effective enzyme mimicry in that they are extremely regioselective. Our project goal was to develop a catalyst capable of terminal alkane oxidation. This has been approached with moderate success using porphyrin catalysts. Previously, steric discrimination in epoxidations of olefins using functionalized porphyrins has been attempted by strapping the porphyrin,[37] and by using the porphyrin as a dendrimer core,[43] though no success was reported using these catalysts for terminal alkane oxidation. The following is a collection of the most promising, relevant, and interesting approaches to primary CH oxidation using functionalized porphyrins.

Shilov explored the use of medium additives to iron tetrakis(p-hexadedecyloxyphenyl)porphyrinate (FeTHDOPP) catalysed oxidation of hexane in aqueous medium.[44] The selectivities of the different systems were compared using a "selectivity index"[45] which attempts to compare the rate of oxidation of primary carbons with secondary and tertiary (if applicable) with allowance made for the number of each bond type.[46]

Of the additives surveyed, β-cyclodextrin (CD) and permethylated β-cyclodextrin (MeCD) exhibited the largest improvement in selectivity over the system free from additives. Whereas the FeTHDOPP alone gave a selectivity factor of only 0.003 corresponding to a relative yield[47] of 0.5%, addition of β-CD gave a drastic improvement in selectivity for primary sites. β-CD and β-MeCD had selectivity factors of 0.211 and 0.234, corresponding to 24% and 26% relative yields respectively. This selectivity can be rationalized by the β-CD first binding the hexane in its hydrophobic core, thus protecting the chain methylenes from oxidation relative to the β-CD free system (Figure 13). Whether β-CD binding of the porphyrin alkoxylphenyls may also play a role is unclear and was not addressed by the original authors.

Although this example is clever and intellectually attractive, its results are a long way from providing a practical solution to primary alkane oxidation, since the actual yields of 1-alkanols are still very low (< 5%).

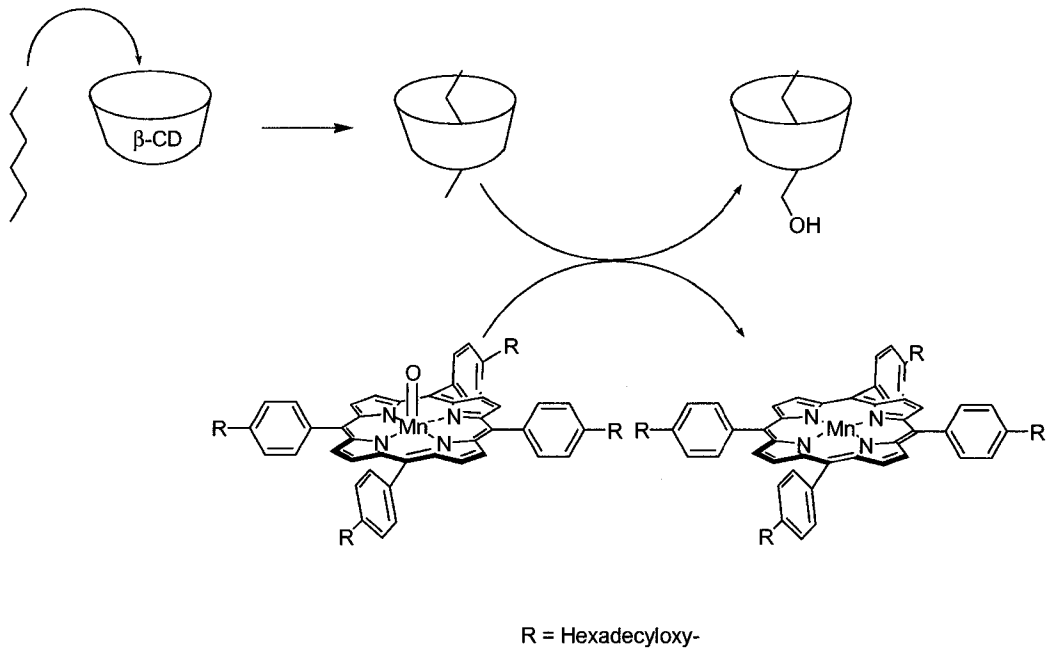


Figure 13: Selectivity enhancement by alkanes binding to β-CD.

Suslick and coworkers examined the shape selectivity of the hindered porphyrin catalyst *meso*-tetrakis(2',4',6'-triphenylphenyl)porphyrinato manganese(III) acetate MnTTPPP(OAc).[48] This catalyst was designed to shield the active oxygenating metalloxo species with four phenyl groups projecting over each face of the porphyrin. The four phenyl rings generate a pocket 4Å wide, and 5Å deep. This design is elegant in its simplicity of construction and because it effectively address both faces of the porphyrin without the need for blocking ligands. This "bis-pocketed" porphyrin catalyst demonstrated a striking improvement in selectivity for oxidation of unhindered CH bonds. These researchers compared the selectivity of MnTTP(OAc), tetrakis(2',6'-dimethoxyphenyl)porphyrinato manganese(III) acetate (MnTTMPP(OAc)), and MnTTPPP(OAc) (Figure 14).

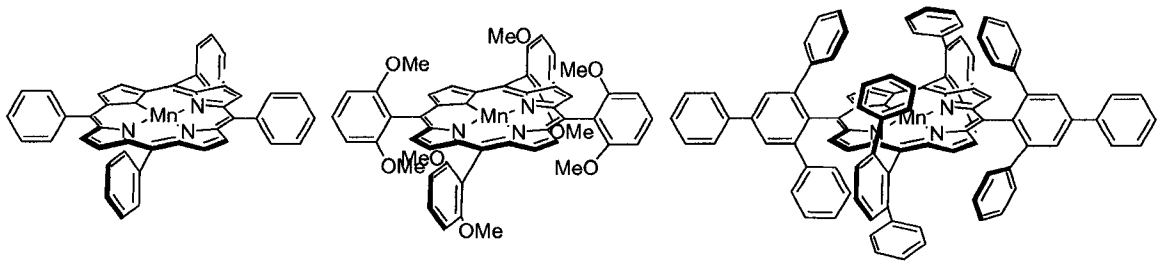
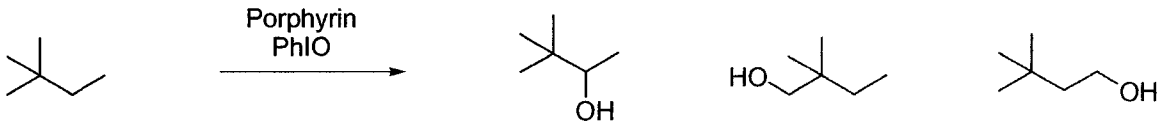


Figure 14: Porphyrin catalysts MnTTP, MnTTMPP, MnTTPPP.

In the oxidation of 2,2-dimethylbutane, catalysis using unmodified MnTTP(OAc) gave a relative yield of 91% of the product of oxidation of the secondary carbon. When the hindered MnTTPPP(OAc) was employed, the relative yield[47] of hydroxylation on the C-4 of the 2,2-dimethylbutane was an impressive 69%!



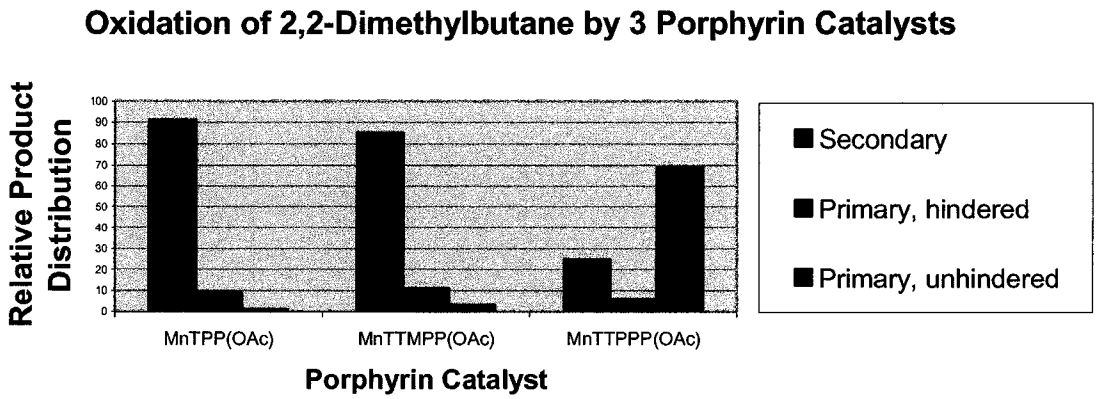


Figure 15: Three isomeric oxidation products of 2,2-dimethylbutane. The colours used match the bar graph.

Unfortunately, when this oxidant was used on n-alkanes, much of the selectivity eroded. For comparison of this catalyst with the porphyrin/CD mixture reported by Sorokin (best selectivity factor 0.23), MnTTPPP(OAc) had a selectivity factor of 0.35 when applied to hexane. In the most efficient example, MnTTPPP(OAc) catalyzed the oxidation of n-heptane to 1-heptanol in 26% relative yield[47] to give a selectivity factor of 0.58 when applied to heptane.[46] Oxidation of alkanes containing tertiary CH bonds demonstrated strong preferences for 3° CH oxidation, likely a result of relative reactivity toward hydrogen abstraction. Nevertheless, the results from this work are still important and impressive because they demonstrate:

a) unprecedented biomimetic selectivity for oxidation of terminal alkanes
b) selectivity between different primary sites on the substrate used. This catalyst's selectivity can be explained by slowing reaction with secondary CH bonds, not by an active rate increase for terminal oxidation.
c) that oxidation of the terminal position of alkanes can be achieved at a significant rate using a catalyst hindered enough to enforce the requisite selectivity. This is encouraging because the primary carbon selection is based exclusively on slowing down the oxidation at all other positions.

It is evident from this selection of P450 mimics that biomimetic hydroxylation catalysis has become genuinely fruitful in less than a handful of cases. Nevertheless, these examples demonstrate that exquisite selectivity is possible in non-enzymatic systems.

Several additional observations must also guide catalyst design (in the interest of brevity, the work which led to the conclusions outlined below will not be discussed):

1) Alteration of the chelated metal can improve yields and alter the selectivity of oxidation. For example, while Fe^{III} more closely mimics the reactivity pattern of P450, Mn^{III} often produces higher yields.[40]
2) Halogenation of the phenyl rings and the β-position of the porphyrin improves catalyst stability and can speed the oxidation reaction.[49]
3) Many oxidants can be used, the most common ones including sodium hypochlorite, hydrogen peroxide, and iodosyl benzene. The latter is generally regarded to generate higher yields,[50] but due to its bulk it may be incompatible with a sterically discriminating catalyst.
4) While it is more attractive to functionalize both faces of the porphyrin to improve reaction rates, improve catalyst stability and avoid unselective oxidation from the unmodified face, nitrogenous ligands such as pyridine or imidazole derivatives can be used as blocking agents by coordinating the metal on the "open" face of the porphyrin.
5) Several porphyrin catalysts that were modified in the *ortho* position of the phenyl ring suffered from oxidation of the molecular scaffolding.[51]

1.5 Project Goal

Our approach to the preparation of a primary carbon selective P450 mimic was to crown a porphyrin creating a sterically limiting space around the catalytic metal-oxo center, preventing access to hindered parts of a molecule. Ideally, this would prevent any secondary or tertiary carbons from accessing the catalytically crucial ferryl species.

Based on previous work in the field, we felt several considerations were essential to guide catalyst design including:

1) The scaffolding should be moderately rigid to aid in maintaining a cavity of defined size to provide access to the catalytic metal-oxo function,
2) The scaffolding should be tethered to the porphyrin in such a way that prevented significant lateral translation of the crown, and hence oxidation of the cap.
3) Catalyst stability to auto oxidation must be prioritized since selectivity of oxidation is being driven by slowing the reaction to secondary sites. Hence the ferryl intermediate may have to 'wait' longer to react than in many previous catalysts.
4) Both faces of the porphyrin must be addressed to ensure selectivity. This could be achieved by i) functionalizing both faces of the porphyrin with a crown-like scaffold, or ii) modifying one face with the crown-like scaffold and blocking catalysis on the other face by added a ligand (such as N-methylimidizole) which coordiantes the metal. This may be acutely problematic if the oxidation was slowed as mentioned in point $^{\#}3$. Addition of symmetry elements might also simplify the retrosynthetic analysis of the desired catalyst.
5) The cap should be constructed in such a way as to allow alterations to design to improve selectivity in a second generation catalyst.

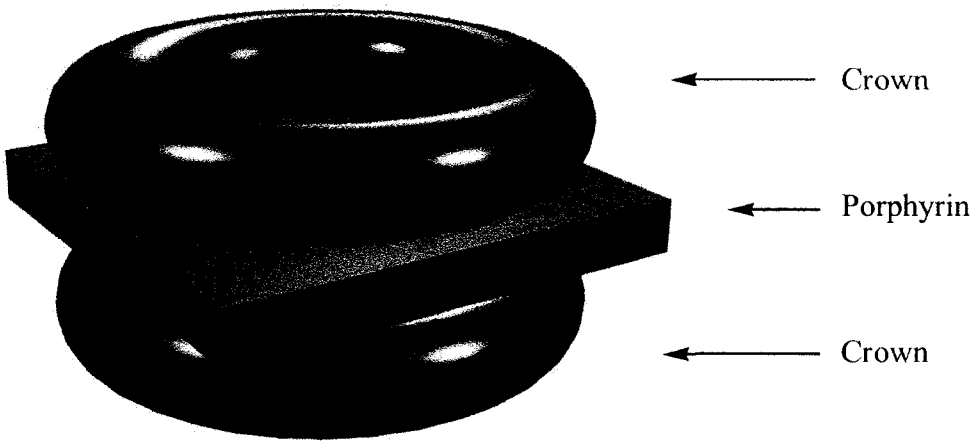


Figure 16: Cartoon representation showing the general topology of the proposed catalyst.

Several methods can be envisioned for attaching this torus-like scaffolding to the porphyrin. It seemed that attachment through the aryl groups of a tetraphenyl porphyrin (TPP) derivative would be the most synthetically accessible. The simplest mode of attachment might be to use the torus scaffolding as a strap (strap = two linkages) between the 5-15 *meso* positions. This has the advantage of less bonds being formed in the scaffolding Attachment step and hence synthetically easier, but may be more prone to intramolecular oxidation if the torus lists to one side as the aryl groups rotate (Figure 16). Attachment of the torus through four positions (capping = four linkages) was also considered, an approach that could take advantage of the porphyrin's inherent C-4 symmetry. This would give the crown less conformational freedom, and might make it

less prone to autooxidation. Linkage through the aryl groups of tetraphenylporphyrin derivatives allows linkage through the phenyl *ortho* or *meta* positions. Intuitively, linkage through the *ortho* positions might also be problematic because the cap might buckle and be oxidized. Linkage through the *meta* positions *a priori* should lead to the scaffolding support least prone to intramolecular oxidation.

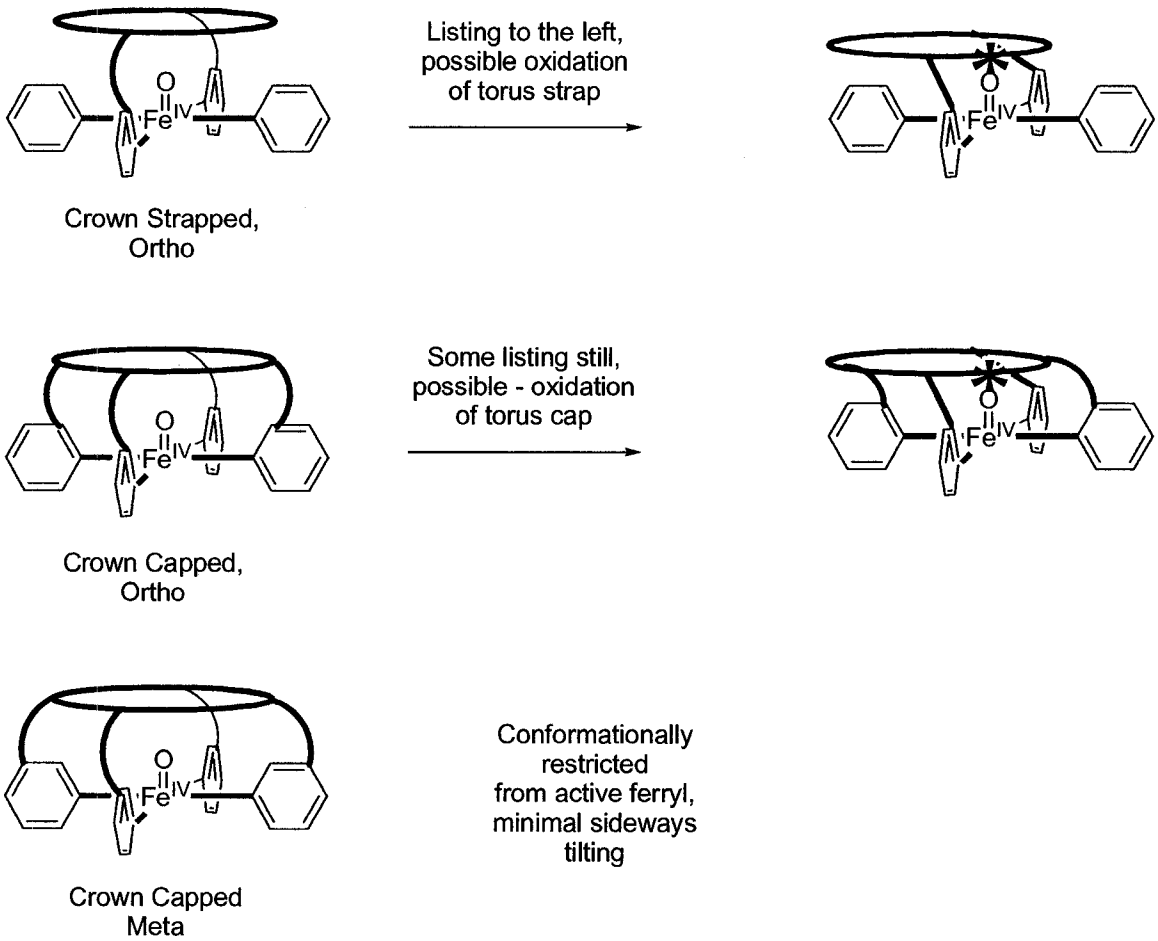


Figure 17: Cartoon representation of possible modes of scaffold attachment to porphyrin.

No porphyrins capped through the meta positions have been prepared to the author's knowledge. Several capped porphyrins linked to the *ortho* positions have been prepared, though usually the cap has been a small molecule such as tetrasubstituted

benzene derivatives. The only reported macrocycle-capped (linked through four points) porphyrins are several calixarenes[52] and (recently) resorcinarene cavitands[53] (excluding cofacial porphyrins). The key capping step of these is shown in Figure 18. Though the yield on this step is poor, it provides access to the structurally complex capped porphyrin shown.

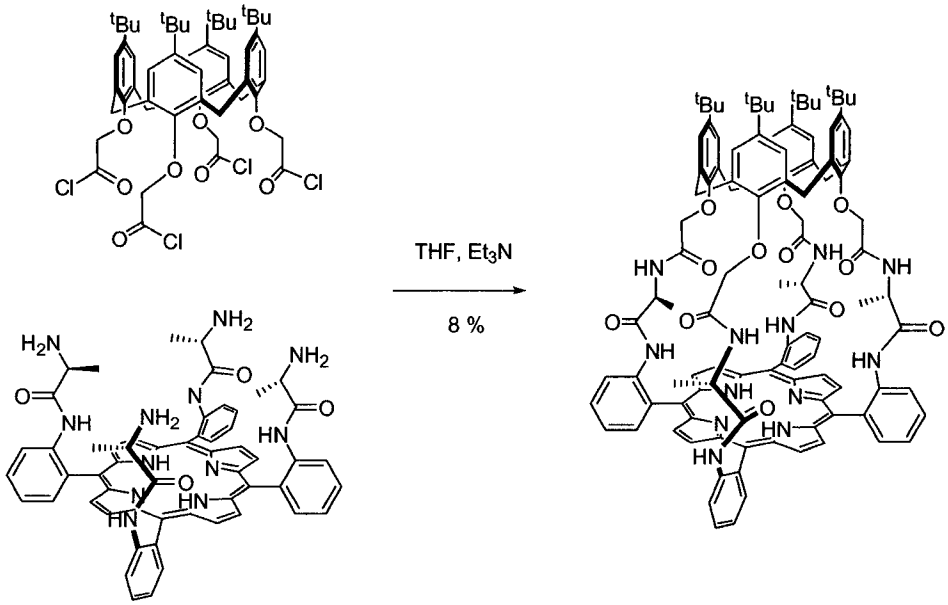


Figure 18: A previous successfully capped porphyrin.

2.0 Results and Discussion

2.1 Porphyrins Modified with Cyclic Peptides

Our initial studies on the preparation of a terminal alkane selective P450 mimic were inspired by Ghadiri's discovery of cyclic peptides with defined tertiary structure.[54] In 1993 Ghadiri and coworkers published the first in a series of papers documenting the stabilized tertiary structure and molecular recognition properties of cyclic octa-, deca- and dodecapeptides composed of amino acids possessing alternating stereochemistry at the α-position.[54] By using alternating D- and L-amino acids in the peptide, each of the residue side chains adopts a pseudo-equatorial conformation minimizing steric interactions (Figure 19), and facilitating the peptide's supramolecular polymerization *via* β-sheet-like interactions. The relative contributions (intermolecular H-bonding *vs.* steric effects) to this conformational preference have not been dissected.

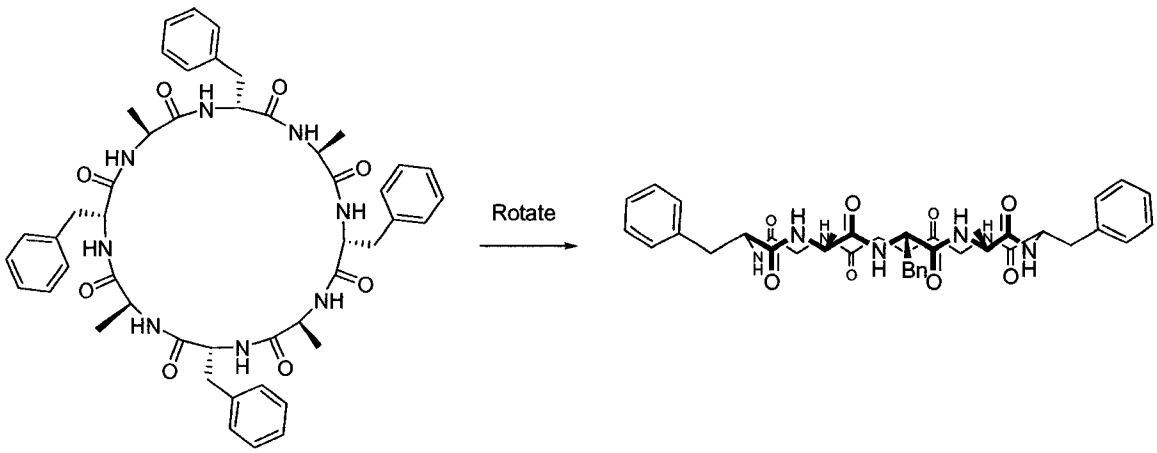


Figure 19: Ghadiri's cyclic peptide with side view showing conformational preference.

From our perspective, the significant feature of this peptide is that by alternating the stereochemistry of the backbone, the commonly observed *intramolecular* H-bonding between residues is prevented. For this reason, we envisioned taking advantage of the peptide's stabilized torus-like conformation to create a defined space around the porphyrin metal center to perform the desired substrate selection. It seemed reasonable to suggest that this peptide would be sufficiently rigid to avoid collapsing on itself, thereby closing the access hole to the metal center, and causing the catalytically active ferryl species to attack the catalyst's framework. It was anticipated that any potential difficulties that arose from the supramolecular polymerization of the peptides could be addressed by using polar solvents (i.e. water) while performing catalysis. Finally, by using a peptide as the cap, alterations can be, in principle, easily incorporated to optimize performance in subsequent catalyst generations.

Modeling studies in our lab[55] which have subsequently been corroborated by Ghadiri's work[56] suggested that only small sterically unencumbered molecules could pass through the cyclic octapeptide's center. This octapeptide was attractive from a design perspective because it could be easily envisioned in a retrosynthetic analysis to possess C-4 symmetry, as does the porphyrin. The plan was to incorporate readily available D-Phe into the octapeptide so that its bulk might further bias the ring conformation, and the L-Lys or L-Orn residues to provide the nucleophilic amine moiety to permit attachment of the cap to the porphyrin *via* an oxidatively robust amide linkage. Catalyst stability toward auto-oxidation should be improved by attaching the peptide to the *meta* position of the phenyl ring of tetraphenylporphyrin (TPP). The rationale for this was to physically prevent the strap, or the ring itself from collapsing and reacting with the catalytically

active M=O species. This problem has subsequently been highlighted in the literature by different peptide strapped porphyrins which suffered autooxidation, and displayed negligible selectivity.[57] With these design features in place, disconnection leads to the precursors shown in Figure 20, the tetraamino peptide **12**, and the octa-acid porphyrin **13**. This porphyrin was chosen because none of the few known porphyrins with substitutions in the 3' and the 5' positions were easily modified to react with common amino acid side chains.[58]

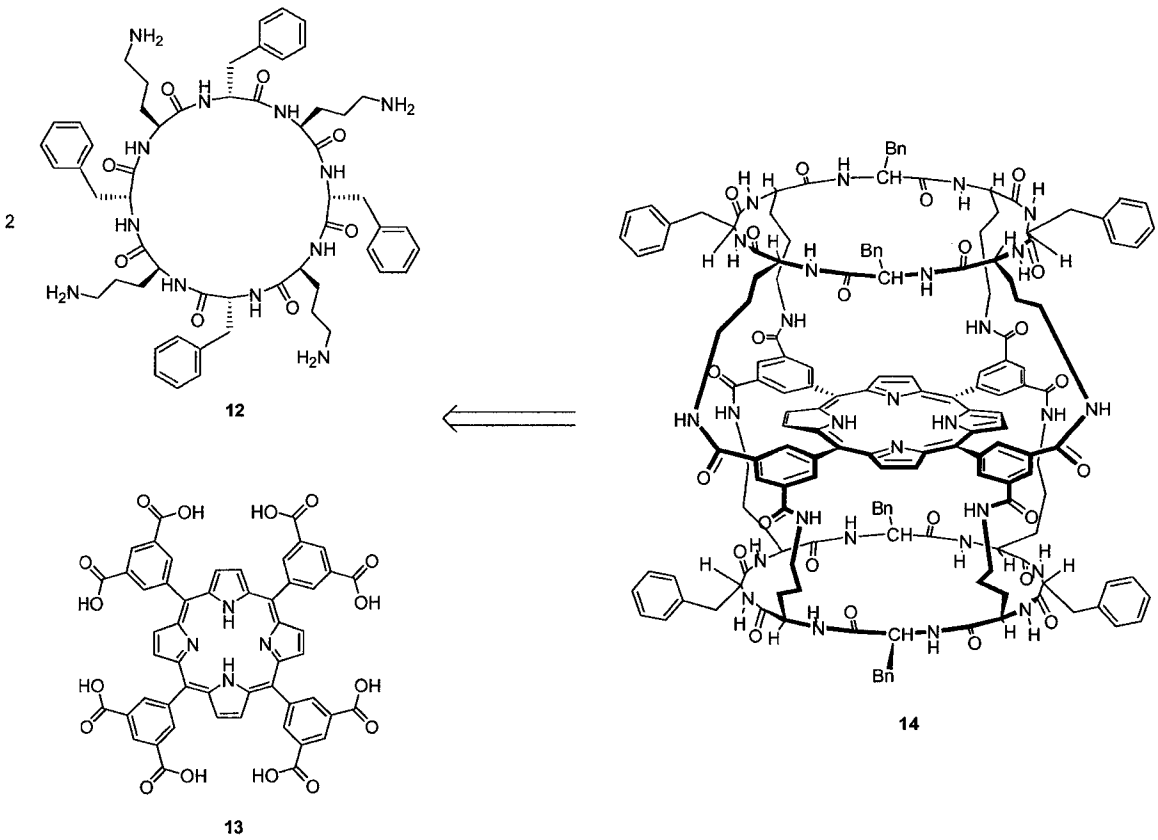
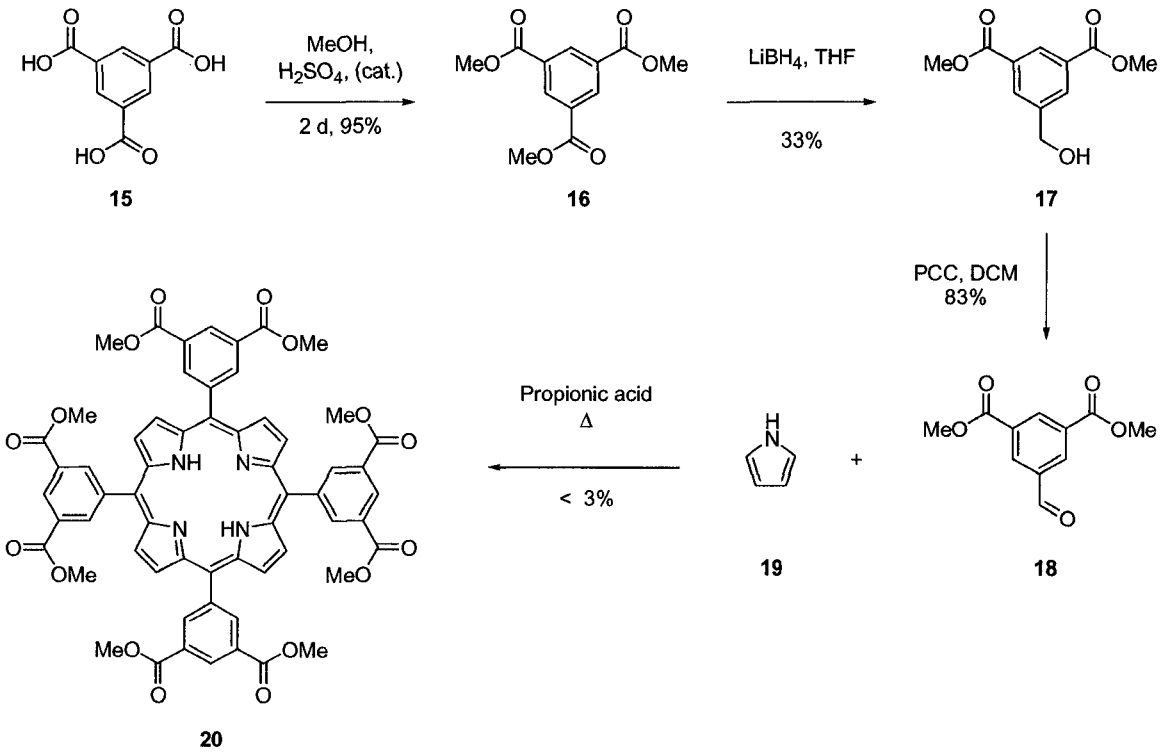


Figure 20: Retrosynthesis of bis peptide cap-crowned porphyrin.

Synthesis of the octa-*meta*-substituted TPP began with exhaustive Fischer esterification of trimesic acid **15** to give the triester **16**[59] in excellent yield (Scheme 1). Lithium borohydride (or lithium aluminum hydride, not shown) reduces this triester to

the mono alcohol **17**.[60] Attempts to optimize this transformation were complicated by side reactions due to both over-reduction and trans esterification (as determined by EI MS). Oxidation of **17** with PCC gives the aldehyde **18**.[62] Disappointingly, condensation with pyrrole under Lindsey's conditions[61] gives only trace product porphyrin **20**. Attempted optimization of the reaction by monitoring its progress using UV spectroscopy[62] does not afford significant improvement.

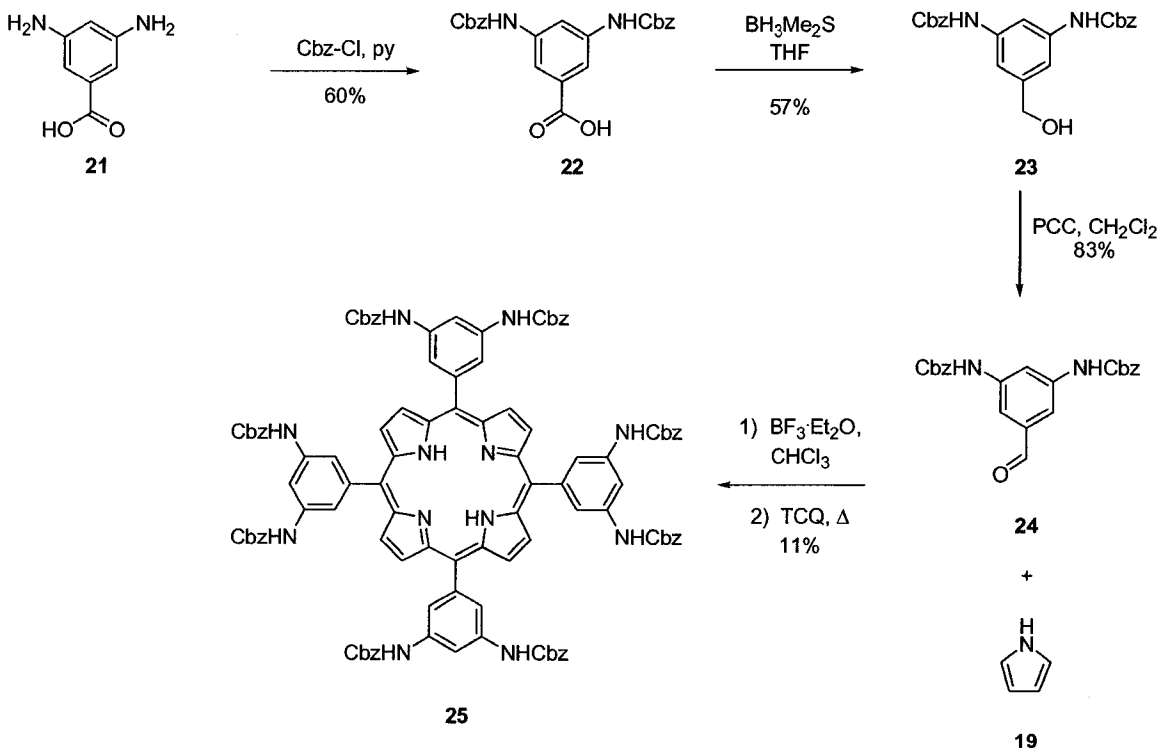


Scheme 1: Preparation of octamethyl ester porphyrin 20.

Condensation using Adler-Longo conditions[63] in refluxing acetic or propionic acid gives the desired porphyrin in very poor yield (<3%). This is in contrast to a recent report by Suslick and coworkers[64] who subsequently successfully prepared the octa*ethyl*ester in moderate yield using the Adler-Longo procedure in acetic acid. While this is surprising, porphyrin yields and solubility can be very sensitive to subtle alterations of substituents. Additionally, Bonar-Law claimed to have prepared this

porphyrin in micelles, though the porphyrin was characterized only by UV-Vis spectroscopy of the crude reaction mixture.[62] Given the poor yield of this porphyrin, we decided to explore other potentially higher yielding and more accessible porphyrin syntheses.

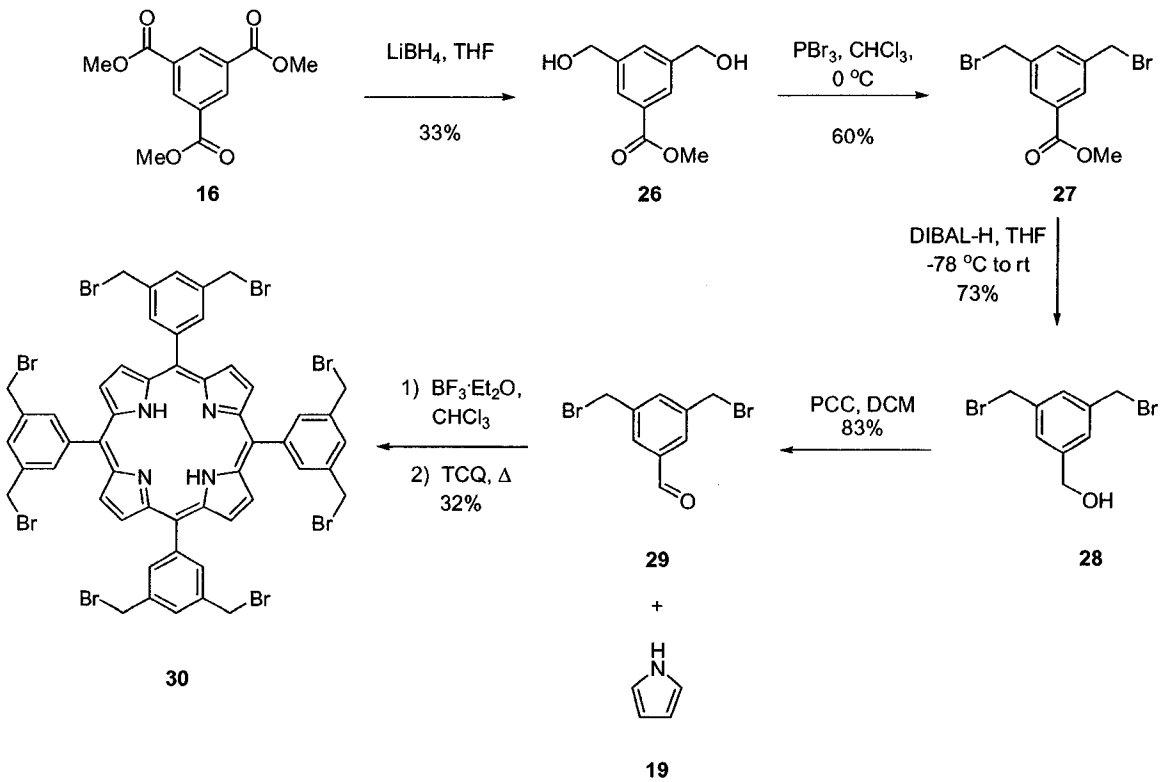
Motivated by a reported synthesis of the aldehyde precursor **24**,[65] we pursued the synthesis of the protected octaaminoporphyrin **25** (Scheme 2). Diprotection of 3,5-diaminobenzoic acid as its benzyl carbamate gives acid **22**, which upon borane reduction to the alcohol **23**, followed by PCC oxidation, gives the desired aldehyde **24** in good yield.[65] Condensation of aldehyde **24** with pyrrole under standard conditions gives the desired porphyrin in moderate yield (11%).[66]



Scheme 2: Synthesis of a protected octaaminoporphyrin 25.

The low solubility of the porphyrin **25** in most organic solvents (excluding DMSO, DMF) hampered isolation, scale up, and removal of the Cbz protecting group.

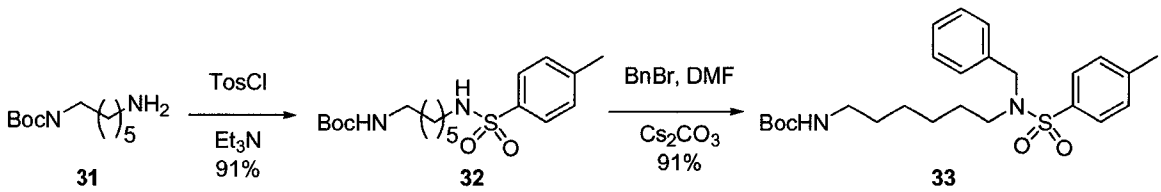
An alternative approach was conceived which drew from previous studies on the trimesic acid derived route (Scheme 3). This included preparing the porphyrin precursor bis-bromomethyl aldehyde **29** from the triester. Thus, lithium borohydride successfully reduces triester **16** to the diol **26** in moderate yield. This diol transforms to the dibromide **27** when treated with PBr_3 in $CHCl_3$. DIBAL reduction of **27** smoothly affords alcohol **28** which is oxidized by PCC to aldehyde **29** in good yield. Reaction of aldehyde **29** with pyrrole, followed by oxidation with tetrachloroquinone (TCQ) gives octabromomethyl porphyrin **30** in good yield.



Scheme 3: Synthesis of the octabromomethylporphyrin 30.

Further consideration of the reaction coupling the tetraamine peptide **12** to the bromomethyl derivative **30** suggested two potential problems. In addition to the obvious problem of producing undesired isomers of attachment (such as capping the side of the

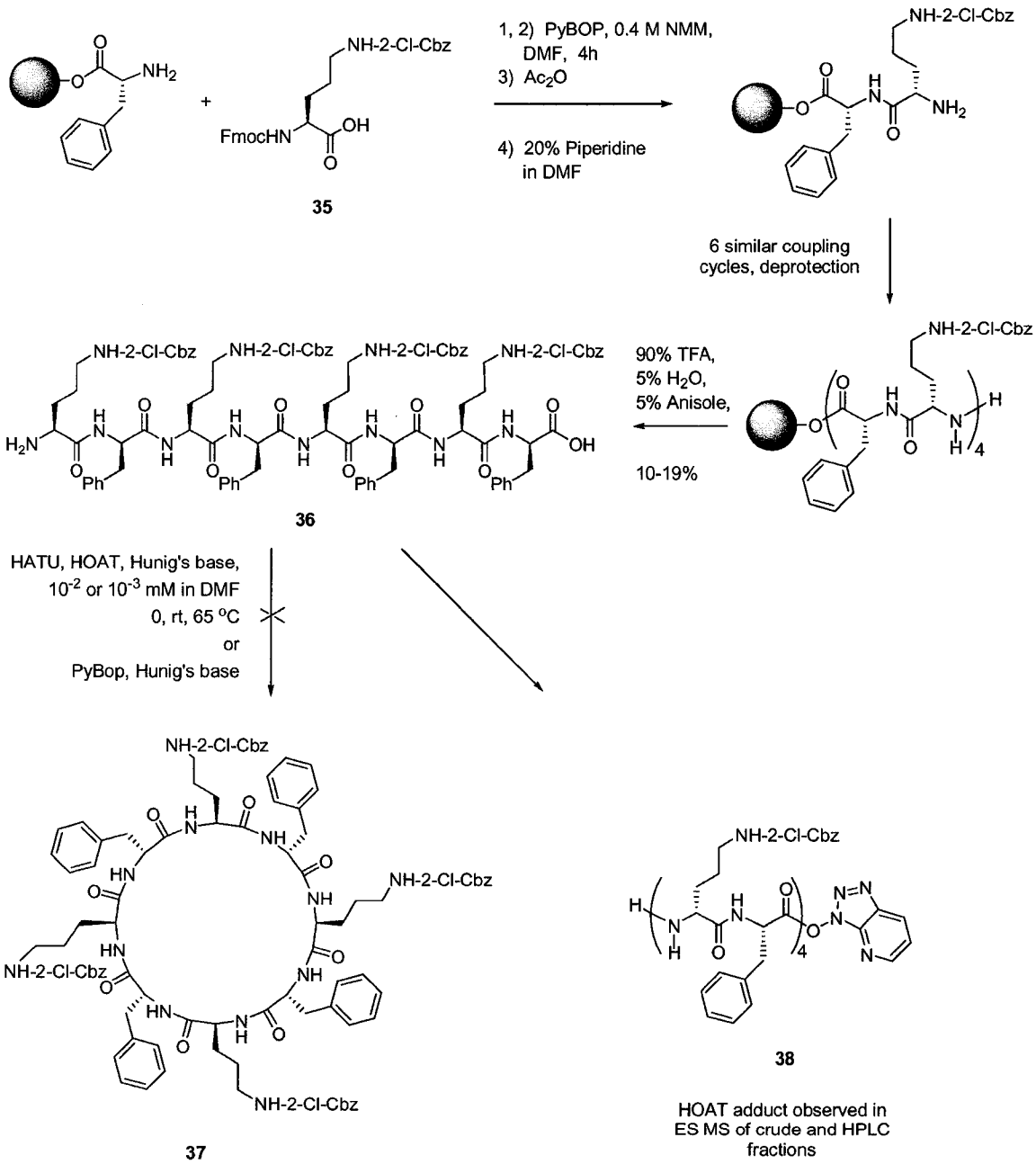
porphyrin), each amino group could participate in two alkylation reactions with two porphyrins, thus to give a tertiary amine. Though high dilution conditions might minimize the latter problem, a model study was performed to explore possible solutions to this. It was rationalized that conversion of the amine to the sulfonamide would prevent the second alkylation reaction. Indeed, once amine **31** was converted to its sulfonamide derivative **32** with tosyl chloride, alkylation with benzyl bromide proceeds efficiently under mild conditions to give **33** (Scheme 4). This suggests that the polyalkylation problem could easily be circumvented by conversion to the sulfonamide.



Scheme 4: Model reaction of derivatized sulfonamide with benzyl bromide.

Concurrently, preparation of the peptide ring to cap the porphyrin was also investigated using standard Fmoc chemistry (Scheme 5).[67] Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP)[68] double coupling of deprotected Wang ester-D-Phe with L-Orn(2-Cl-Z)LysOH, using N-capping[69] gave resin linked dipeptide, which after repetition of the coupling cycle gives the resin linked octapeptide **36**. Acid promoted cleavage from the resin followed by RP HPLC purification gives the octapeptide in low yield. Disappointingly, upon treatment of **36** with a variety of coupling reagents including PyBOP, no trace of the cyclized product **37** could be detected in the electrospray mass spectrum of the crude reaction mixture or of fractions after RP-HPLC purification. Attempted cyclization using PyBOP and 1-hydroxy-7-azabenzotriazole (HOAt)[70] under diverse reaction conditions, including high

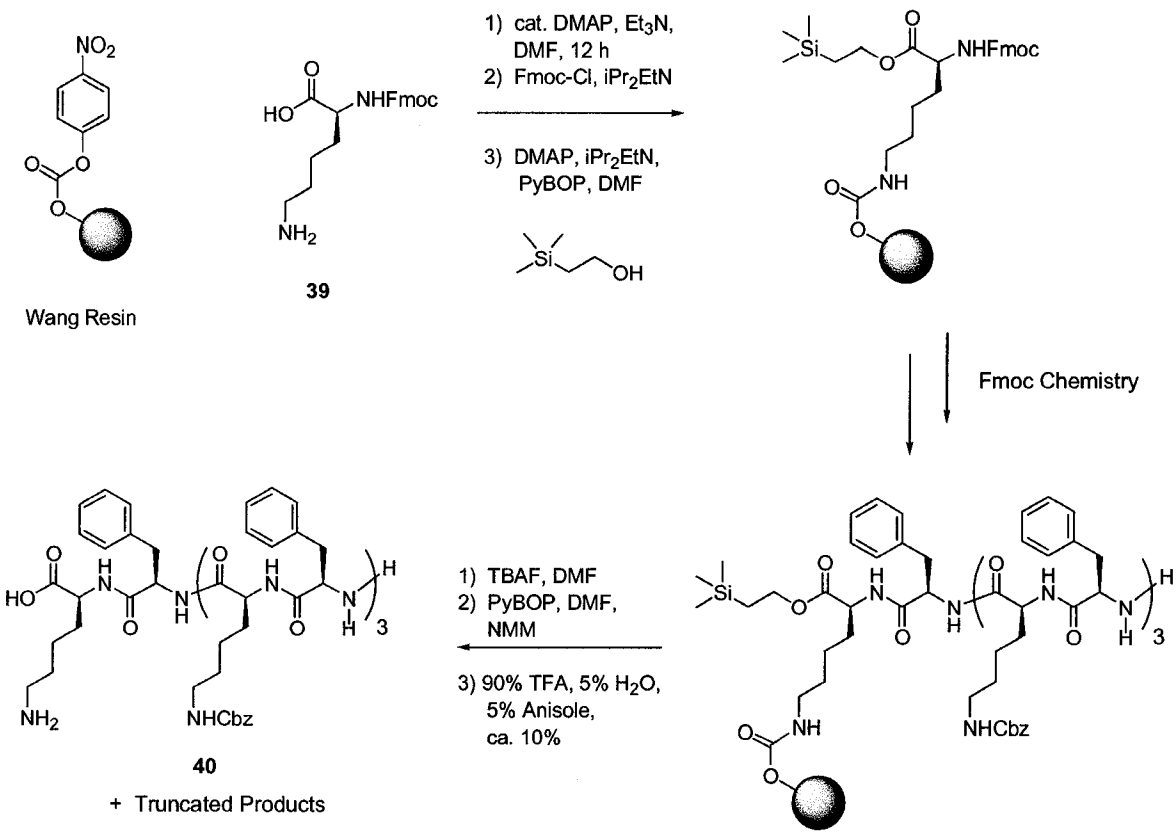
dilution and varied temperature results only in the formation of active ester **38** (detected by the electrospray mass spectrum of crude reaction mixture and HPLC fractions) and polymer (extreme insolubility, very broad peaks in its ^{1}H NMR spectrum).



Scheme 5: Attempted synthesis of protected tetraamino cyclic octapeptide.

Ghadiri's preparation of cyclic peptides accomplished the macrocyclization step while the peptide remained attached to the resin through the ω-position of a side chain of

an aspartic acid residue.[71] This may be the key to the successful synthesis since this would minimize intermolecular reactions and permit the use of increased temperature[72] to promote conformational flexibility. In this strategy the L- amino acid residues were changed from ornithine to lysine since the appropriately protected precursor for attachment to the resin was commercially available (Scheme 6). Hence, N_{α}-FmocLysOH was ω-linked to a Wang resin by reaction with Wang *p*-nitrophenyl carbonate. The linked lysine residue is treated with 9-fluorenylmethyl chloroformate to mask any amines inadvertently deprotected while attaching the amino acid. This is followed by PyBOP promoted esterification of the free acid with 2-trimethylsilylethanol to protect the ester functionality. The success of this reaction was corroborated by the reduction in intensity of relative absorption in the region 3400-2700 cm^{-1} in the IR spectra of the resin after esterification. As in the earlier synthesis, the linear octapeptide was prepared using Fmoc amino acid chemistry. Piperidine deprotection of the Fmoc masking the terminal nitrogen, followed by deprotection of the carboxyl terminal with tetrabutylammonium fluoride (TBAF)[73] gives the resin bound octapeptide. Attempted cyclization with PyBOP followed by acid promoted cleavage from the resin unfortunately gives no desired product. The presence of octapeptide **40** was confirmed by MS of the major peak upon HPLC purification. Unfortunately, exact quantitation of yield was not possible since this peptide could not be chromatographically resolved from truncation products.



Scheme 6: Attempted cyclization of resin bound octapeptide.

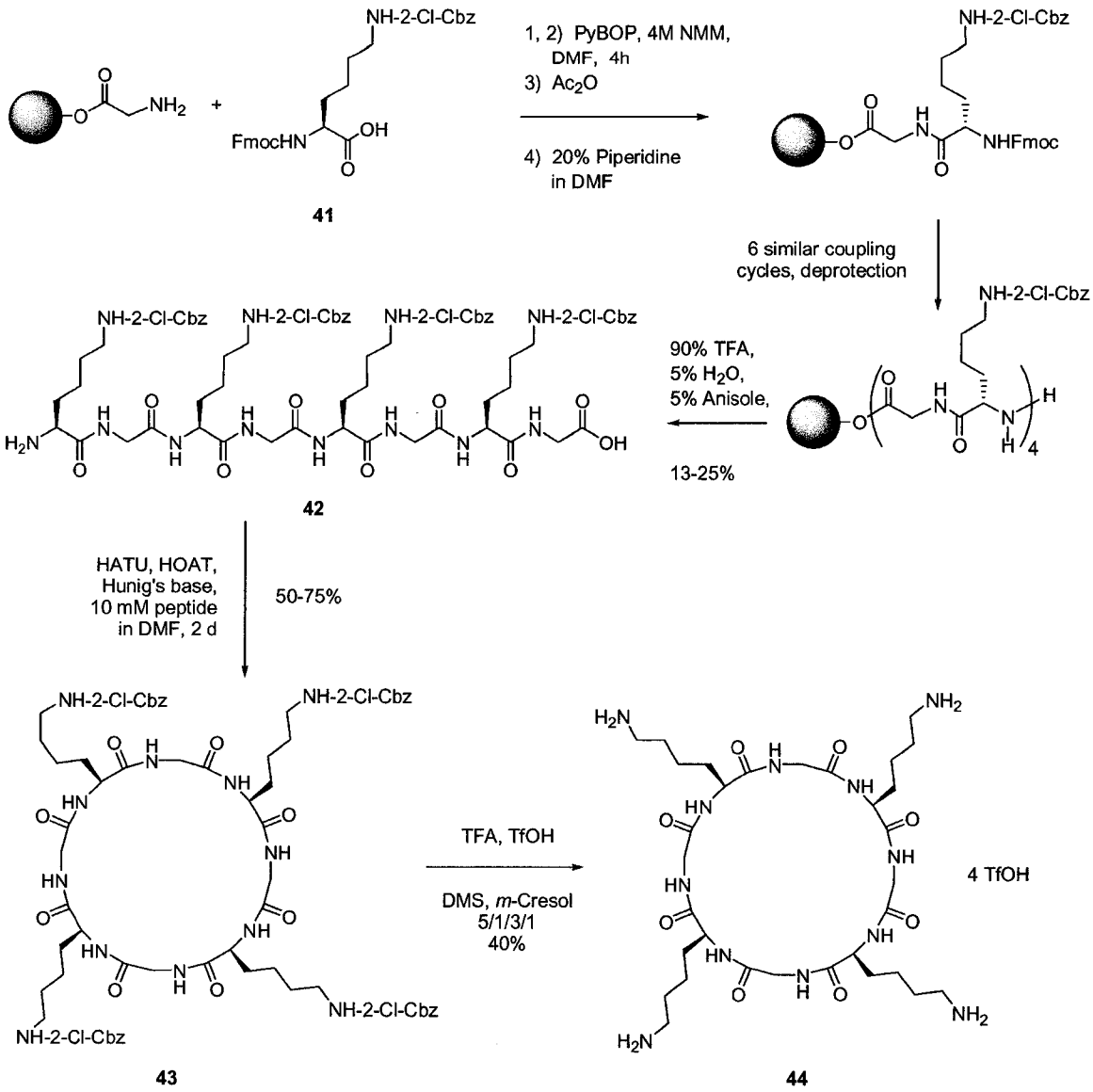
In light of the difficulties encountered in preparing the target peptide with alternating D- and L- stereochemistry, it was decided to simplify the target by using L-lysine residues alternating with the achiral glycine monomer. This should give the peptide backbone more flexibility which would facilitate cyclization, and might confer improved solubility properties. If the preparation of the cyclic peptide were successful, the viability of the key capping step could be explored. This would justify further efforts to prepare a peptide containing residues with alternating stereochemistry.

Treatment of Wang-ester-Fmoc-glycine with piperidine deprotects the α-nitrogen, which then couples to Fmoc(2-Cl-Z)lysine using PyBOP chemistry (Scheme 7). Analogous to the previous synthesis, this dipeptide was elaborated to the octapeptide with

alternating glycine and (2-Cl-Z)-lysine residues. The peptide is cleaved from the resin using TFA/water/anisole (90/5/5), then purified by HPLC to give the linear peptide **42**. The peptide **42** cyclizes smoothly to peptide **43** using PyBOP and HOAT. Gel permeation chromatography proved essential in the purification of this material, since it is too insoluble to purify by RP HPLC.[74] Indeed, the extreme insolubility of cyclic peptides of similar size has been reported and has hampered work in this area prior to Ghadiri's investigations.[75]

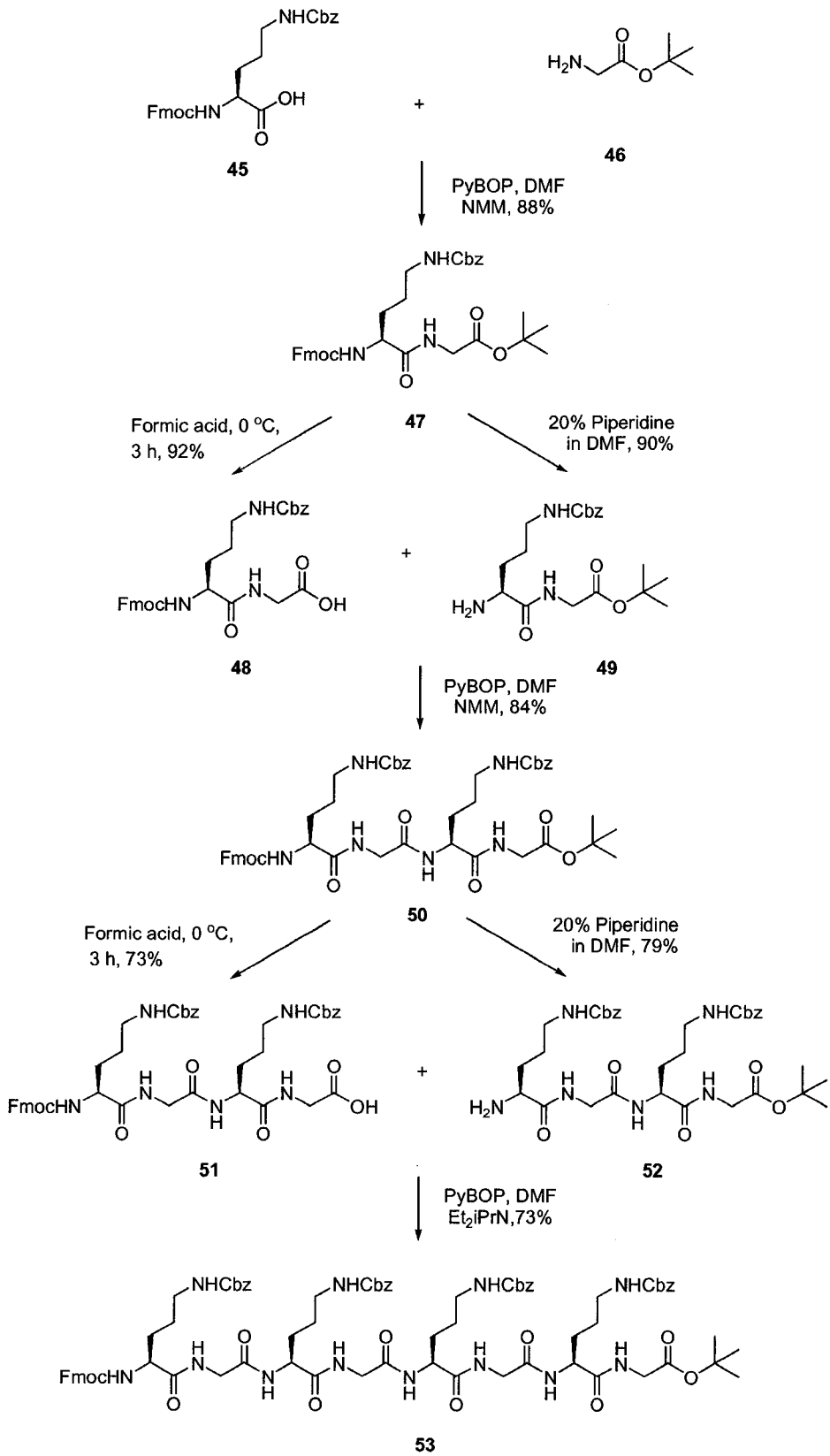
This insolubility precluded deprotection by hydrogenolysis in typical solvents (EtOAc, THF, MeOH, DME). Hydrogenolysis was attempted in DMF and in DMF/MeOH mixtures, with recovery of most starting material (average 80%) and no evidence of partially deprotected products. This may be a result of the Pd either reducing DMF to formaldehyde and dimethylamine, or conducting other chemistry by insertion into the formyl CH, such as catalysis of the disproportionation of DMF to CO and dimethylamine[76] (*vide infra*). This is surprising in light of the fact that many Pd mediated coupling reactions are conducted in DMF. However, a review of the literature failed to uncover any examples of hydrogenolysis conducted in DMF. Interestingly, a method for the hydrogenation of peptides in dimethylacetamide has since been reported.[77]

Standard Lewis acid catalyzed deprotection was also precluded by the necessity to use polar aprotic solvents. Nevertheless, deprotection was achieved using a procedure developed by Tam and coworkers.[78] Under strongly acidic conditions, deprotection of **43** proceeds to give the tetraamino cyclic octapeptide **44** in moderate yield.



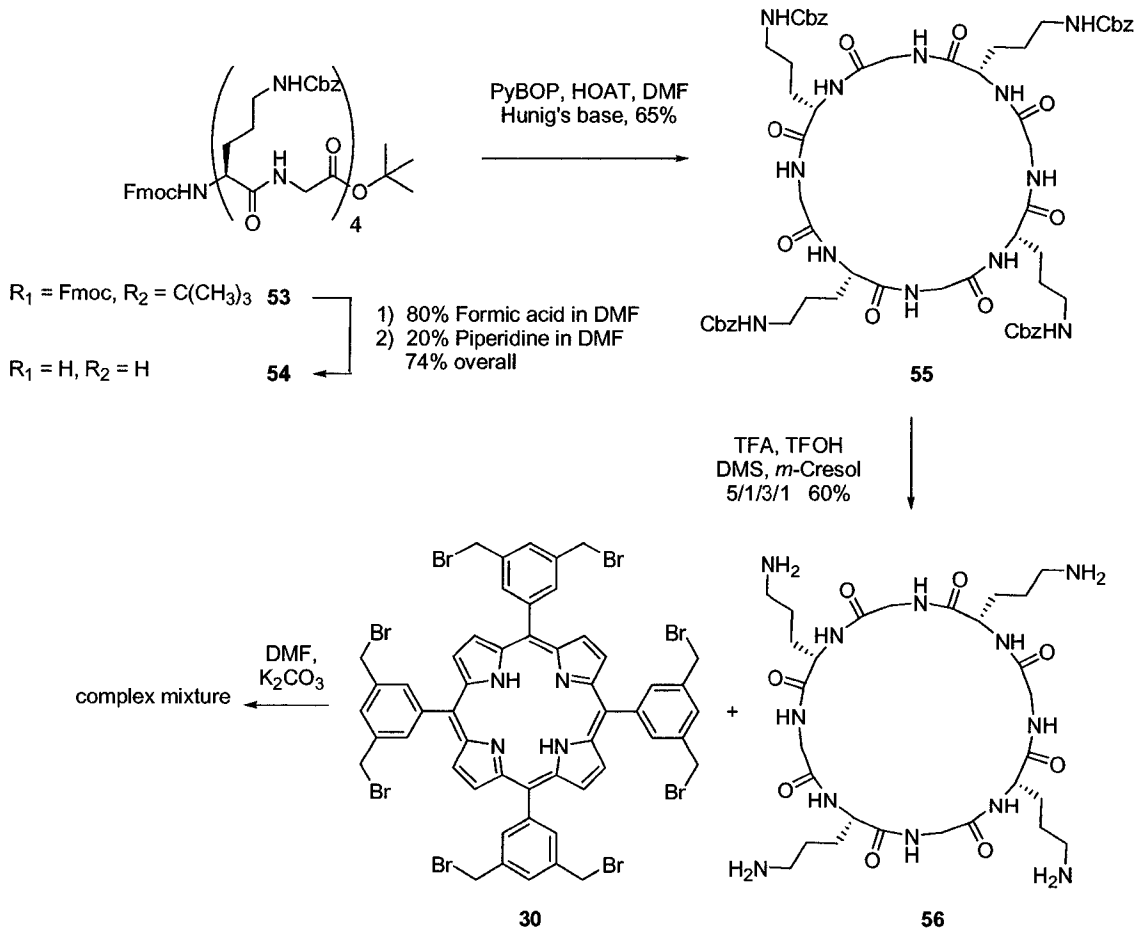
Scheme 7: Successful synthesis of the cyclic octapeptide 44.

In an attempt to produce more material for optimization of the cyclization and deprotection reactions, the linear octapeptide *cyclo*(OrnGly)$_4$ (**53**) was prepared by a more efficient convergent strategy, relying on the inherent symmetry of the target. Protected ornithine **45** was coupled with the *tert*-butyl ester of glycine **46** to give the expected dipeptide **47**. Piperidine deprotects the N-terminus of the dipeptide to afford the free amino dipeptide **49**.



Scheme 8: Solution synthesis of octapeptide 53.

Alternatively, treatment of the dipeptide with formic acid under mild conditions smoothly affords the dipeptide acid **48**. These two dipeptides then couple when treated with PyBOP to give the expected tetrapeptide **50**. Analogously, the tetrapeptide deprotects on the N and C terminus by treatment with formic acid or piperidine, to give **51** or **52**, respectively. These couple with PyBOP to afford the octapeptide **53**. Deprotection on both termini affords the linear octapeptide **54**, which, upon treatment with PyBOP cyclizes to the desired peptide **55** (Scheme 9). Deprotection with strong acid conditions gives the octapeptide tetraamine **56.** However, attempts at coupling the porphyrin to the peptide resulted in complex mixtures even under high dilution.



Scheme 9: Attempted coupling of peptide 56 to porphyrin 30.

We recognized that the next logical step would be to prepare the sulfonamide from the cyclic octapeptide. Despite the success of having prepared the desired cap, its synthesis involved a number of difficult purification steps which hampered attempts at scale up. This, combined with the expected low yield of the final porphyrin capping step due to the many possible isomeric modes of attachment, prompted us to evaluate other methods of preparing a biomimetic catalyst.

2.2 Porphyrin Templated Capping

Instead of building structurally complex molecules requiring laborious preparation *before* the capping step (which may proceed in low yield), it was decided to explore short syntheses to access the key precursor. In Chapter 1, synthesis of the crown-like scaffolding proved to be unpredictably challenging. One possible strategy to simplify the retrosynthetic analysis could take advantage of the C-4 symmetry inherent to the porphyrin, by assembling the crown-like scaffold from four segments already attached to the porphyrin. To explore the synthesis, initial studies focused on capping one side of the porphyrin only. Once the methodology is established, a successful capping protocol could in principle be extended to functionalizing both faces of the porphyrin. Linking the crown to the porphyrin through the *meta* position of the *meso* aryl group would eliminate the problem of atropisomerization of the phenyl substituents encountered with *ortho* substituted tetraphenylporphyrins.[79]

One possible approach is to attach masked dinucleophiles to the phenyl rings (Figure 21). Alkylation with a dielectrophile should link the nucleophiles to form the ring. For this to work well, the intramolecular nucleophilic attack must be faster than intermolecular reaction; a reasonable objective if the reaction is done under high dilution. This approach also necessitates using either a dinucleophile or a dielectrophile which has sufficient rigidity to prevent pseudo-intramolecular reaction of **57b** from leading to four small rings (**57a**) instead of the desired one large crown (**57c**, Figure 21). As before, to ensure the catalysts' stability, the four cap segments were linked to the porphyrin through the *meta* position of the phenyl of TPP.

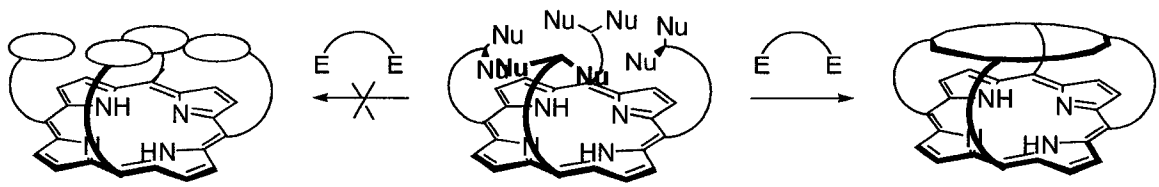
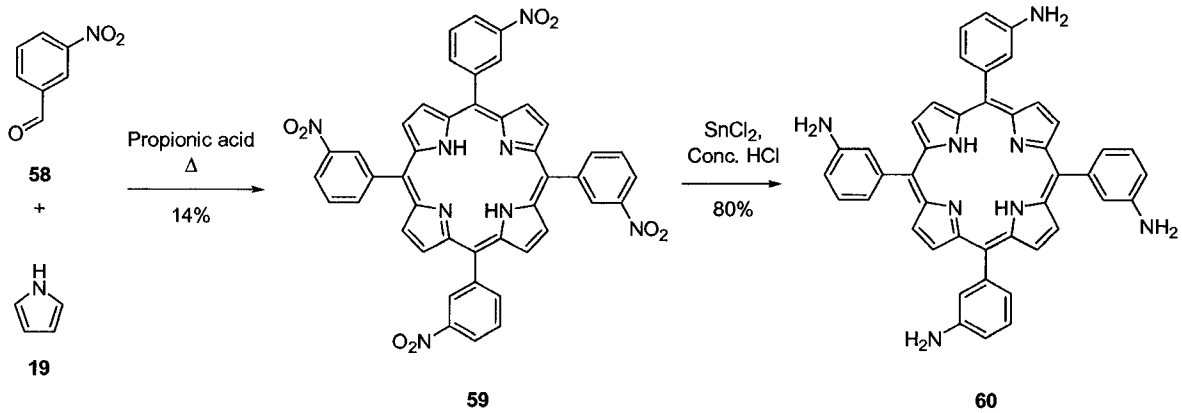


Figure 21: General approach for capping porphyrin with four bis-nucleophiles.

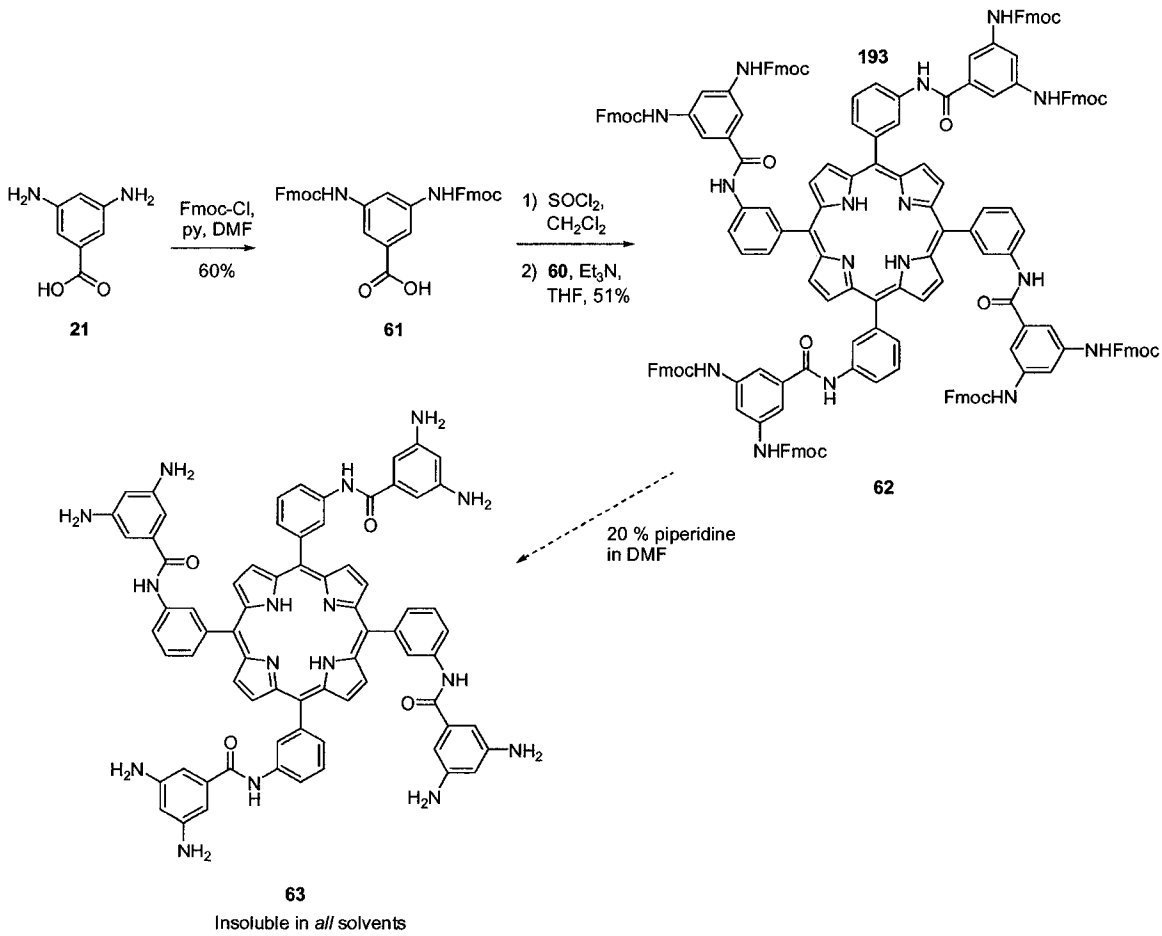
Initial attempts focused on the known *meta* substituted tetraaminophenylporphyrin (TAP) **60** (Scheme 10).[80] 3-Nitroaldehyde **58** condenses with pyrrole **19** under Adler-Longo[81] conditions to give the tetranitroporphyrin **59**. Tin(II) chloride reduces the nitro functionalities in strongly acidic aqueous conditions to afford the TAP **60**.



Scheme 10: Synthesis of *m*-tetraaminoporphyrin 60.

Next the porphyrin was functionalized with a rigid Fmoc protected diamine to prepare for the templated cyclization (Scheme 11). Fmoc-chloride diprotects diaminobenzoic acid **21** in DMF and pyridine to give the acid **61**. This acid converts to the acid chloride upon treatment with $SOCl_2$. This acid chloride reacts with the tetraaminoporphyrin **60** on all amino functionalities to give the porphyrin **62**. Surprisingly, treatment of the octa-Fmoc protected amine **62** with piperidine[70] in DMF

gives a dark solid which remains insoluble in all organic solvents. Treatment of the dark solid with strongly acidic conditions (2 M HCl) results in only trace dissolution, as demonstrated by the faint green colour of the protonated porphyrin.

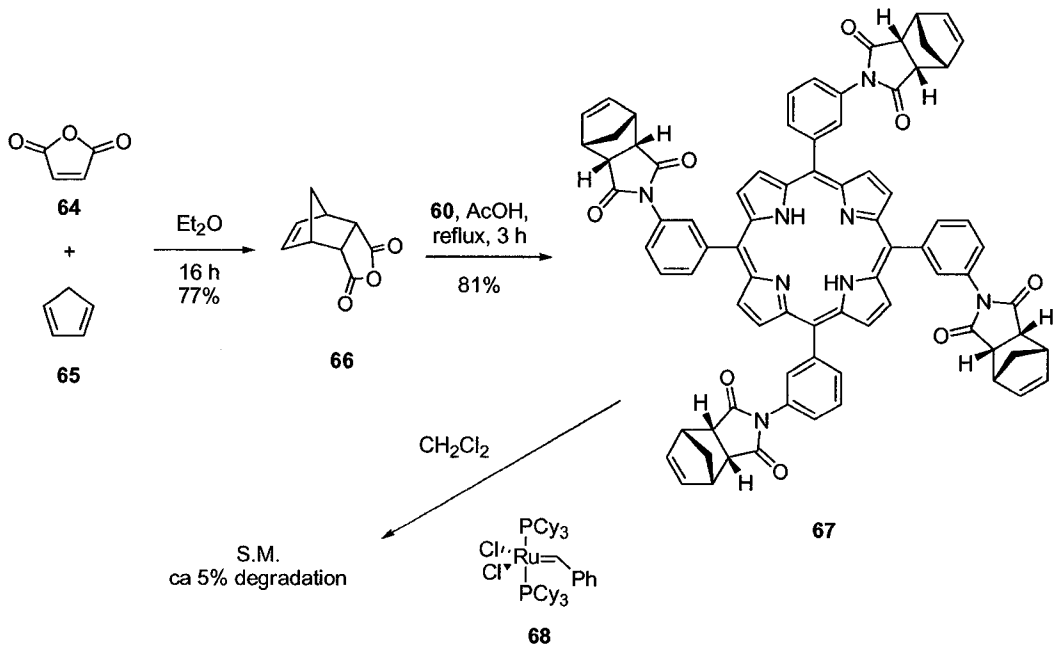


Scheme 11: Striking insolubility upon deprotection.

Since Fmoc deprotection is reported to be extremely fast and efficient,[67] it was concluded that deprotection probably proceeds effectively, and that product insolubility is the key problem (as opposed to polymerization).

A second design depends on an intramolecular ring opening metathesis polymerization (ROMP) strategy (Scheme 12). Modeling suggested that this cavity (20 atoms) would fulfill the steric requirement of the cap. Following classic Diels-Alder

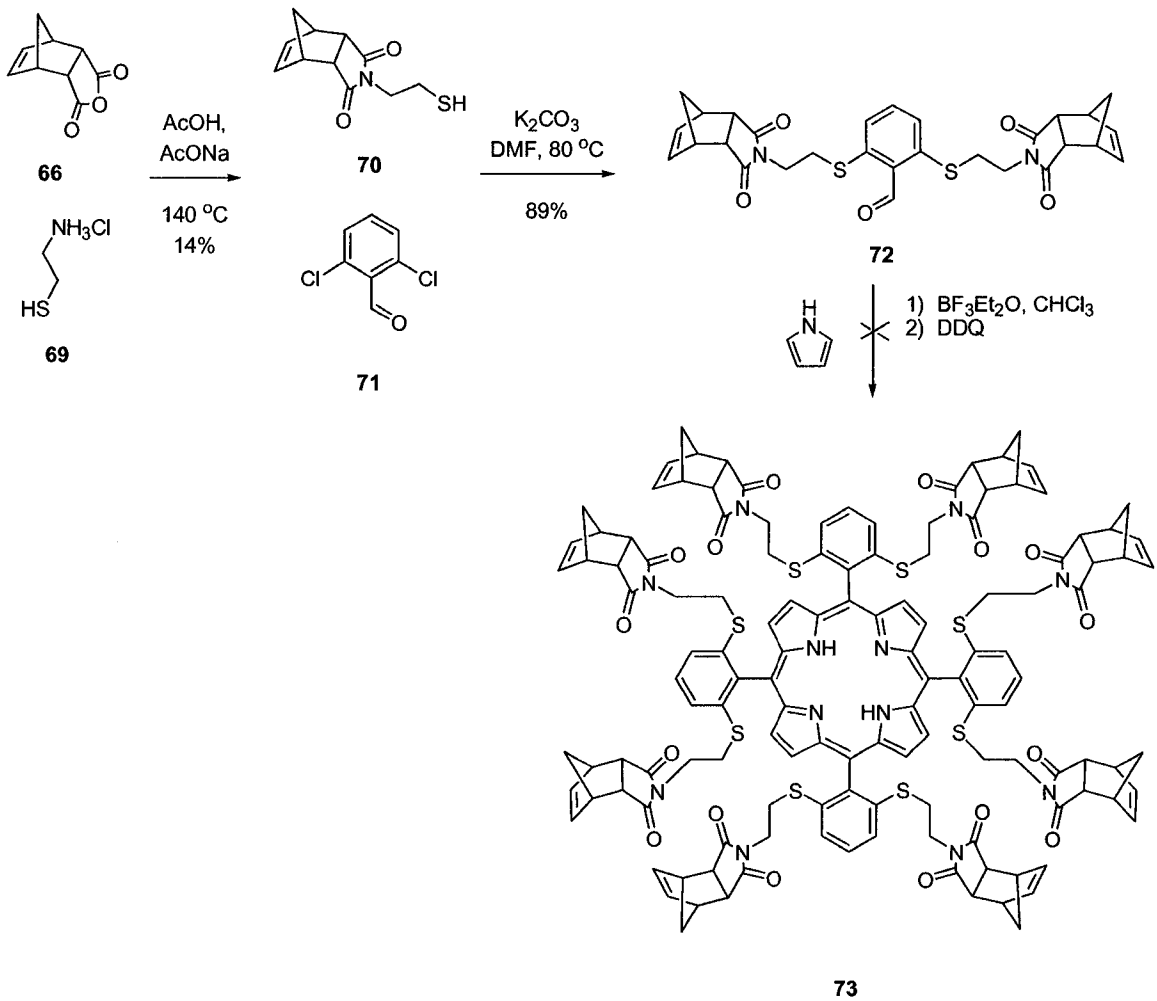
chemistry, cyclopentadiene adds to maleic anhydride to give the anhydride **66**.[82] Four equivalents of this anhydride smoothly condense with the porphyrin tetraamine **60** to generate **67**. Unfortunately, treatment of **67** with Grubbs' catalyst[83] leads to recovery of starting material. Protection of the porphyrin as its zinc chelate under standard conditions[84] followed by treatment with the ruthenium catalyst gives the same result, suggesting that the catalyst does not proceed around the ring, but is 'stalled' in mid reaction (after the first ring-opening reaction). Despite the fact that a crown ether strapped[85] porphyrin has been prepared using aryl substituted amide which is not coplanar, it may be that conformational rigidity prevents reaction in this case.



Scheme 12: Porphyrin 67 precursor for intramolecular ROMP.

To address this problem, a more flexible linker was chosen to tether the porphyrin to the four crown segments (Scheme 13). Upon forcing treatment, anhydride **66** reacts with 2-aminoethanethiol to give thiol **70** in poor yield (unoptimized). Thiol **70**, upon deprotonation to the thiolate, efficiently undergoes nucleophilic substitution with 2,6-

dichlorobenzaldehyde **71** to generate the desired aldehyde **72** in good yield. Quite surprisingly, condensation with pyrrole under Lindsey's conditions[61] leads to the formation of a complex mixture with none of the desired porphyrin **73** being formed.

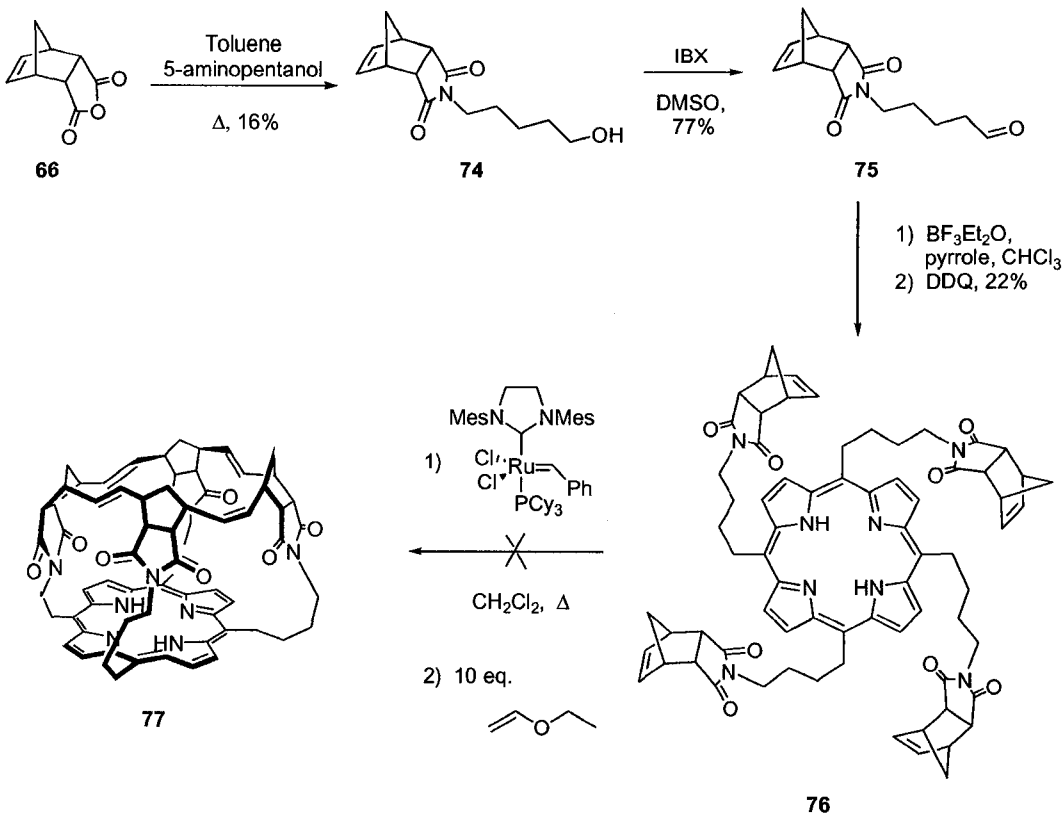


Scheme 13: Attempted synthesis of second generation intramolecular ROMP precursor 73.

The reasons for failure to form porphyrin are not clear, since other di-*ortho*-substituted benzaldehydes have been used in the preparation of tetrasubstituted porphyrins including 2,6-dichlorobenzaldehyde,[86] 4-*tert*-butyl-2,6-dibromobenzaldehyde,[87] mesitylaldehyde,[88] 4-*tert*-butyl-2,6-dinitrobenzaldehyde,[89] and

2,6-dimethoxybenzaldehyde.[90] Moreover, sulfur has a similar atomic radius to chlorine, and has electron donation properties between the methoxy and the chloro substituents. However, in contrast to 2,6-dimethoxybenzaldehyde, aldehydes bearing secondary alkoxy groups in the two and six positions have been shown to give very poor yields under similar conditions, [91] highlighting the potential sensitivity of this system to sterics.

Modeling[55] suggested that the cyclic product formed by three successive intramolecular ROMP reactions followed by one RCM was a reasonable target. Hence, an alternative approach to the preparation of a flexible precursor was considered (Scheme 14). Anhydride **66** condenses with 5-aminopropanol to give the alcohol **74** in poor yield. IBX[92] oxidizes **74** to the desired aldehyde **75**. This aldehyde condenses with pyrrole using Lindsey's conditions[61] to afford the target porphyrin **76** after oxidation. Intramolecular ROMP with Grubbs' second generation catalyst[93] followed by quenching with ethyl vinyl ether gives starting material and insoluble material consistent with polymer formation. TLC showed only one spot corresponding to **76** (subsequently re-isolated and confirmed by ^{1}H NMR spectroscopy) and coloured material on the baseline. Analysis of the electrospray mass spectrum of the crude mixture did not reveal any of the adduct expected from addition of the elements of styrene (from the parent catalyst) which would be expected if the ruthenium catalyst had been "trapped."



Scheme 14: Synthesis of third generation ROMP precursor porphyrin 76.

Once the ruthenium has added to the first olefin, it may add into the second olefin in a productive or non-productive fashion (e.g. the first structure in Figure 22). A strictly statistical analysis of possible yield (assuming 50% chance of addition to each productive and non-productive face) suggests a maximum yield of 12.5%. A second consideration in the intramolecular ROMP is that the reaction is not under thermodynamic control like typical RCM reactions. Since the catalyst is trapped on the molecule until all the strained olefins have opened and the catalyst is extruded by a final RCM, there will not be free catalyst acting to equilibrate the double bonds' stereochemistry between *cis* and *trans*. If a *cis* linkage is required for the successful complete cyclization, and the initial linkage is *trans*, the cyclization will not proceed. Potentially, this problem could be circumvented by adding a second diene which would act to extrude the ruthenium carbene from the

porphyrin, as shown (Figure 22). Unfortunately, addition of 10 eq of 2,2-diallylmalonic acid dimethyl ester[94] did not improve our results.

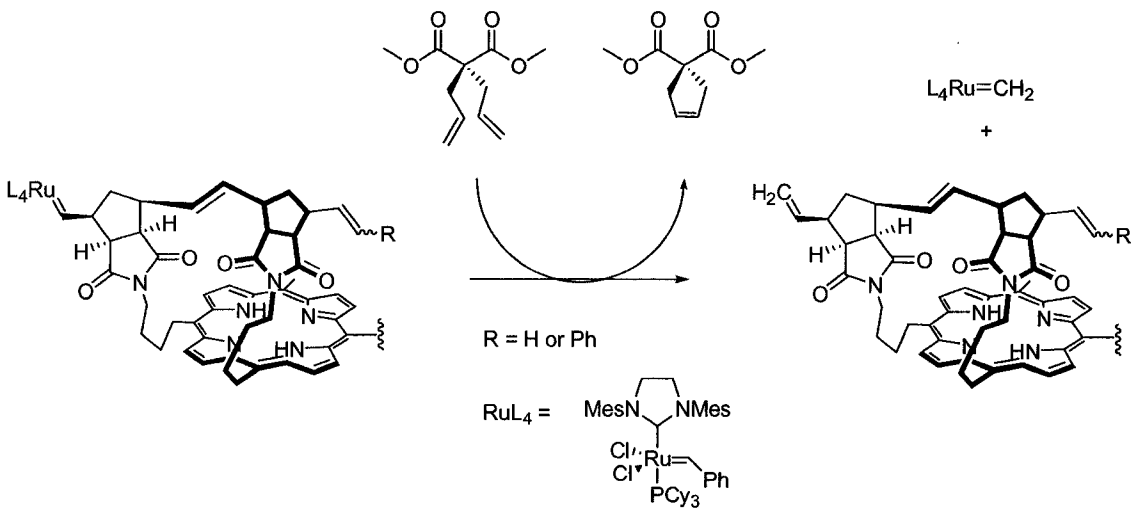


Figure 22: Proposed RCM promoted extrusion of catalyst from non-productive cyclization mode.

A second less ambitious strategy employed used the RCM of semi-rigid dienes. The concept was to attach four semi-rigid dienes onto the four phenyl groups of the porphyrin (Figure 23).

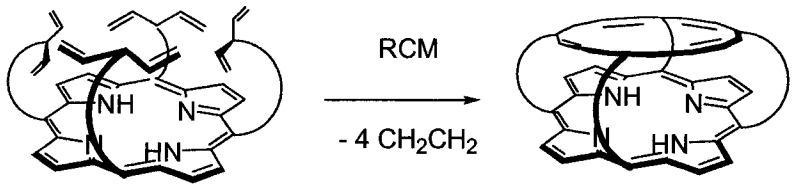
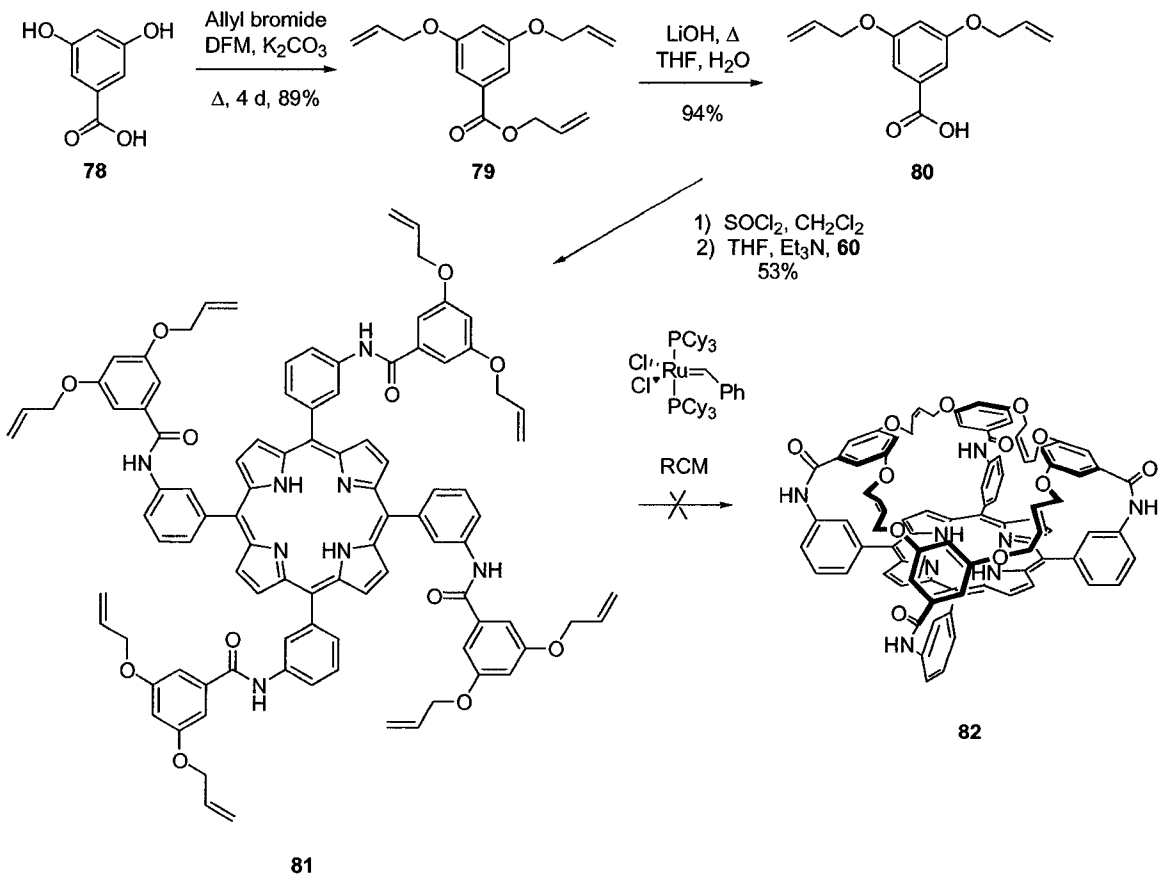


Figure 23: Possible approach to capped porphyrin using RCM.

It is essential to choose dienes which cannot cyclize to form four small rings around the porphyrin, analogous to the problem shown in Figure 21. To facilitate the desired RCM

reactions, dienes with a plane of symmetry were employed to reduce the possibility of the "trapped" catalyst scenario.

The initial idea followed a similar theme as the earlier ROMP chemistry (Scheme 15), using the common porphyrin intermediate, TAP (**60**). Excess allyl bromide alkylates 3,5-dihydroxybenzoic acid under basic conditions to give ester **79**.[95] Hydrolysis of this ester with LiOH affords the acid **80**. Treatment of acid **80** with Grubbs' catalyst generates no RCM product, trace degradation, and reisolation of the diene, thereby confirming that intramolecular cyclization of each of the four cap segments to form four smaller rings should be disfavoured.

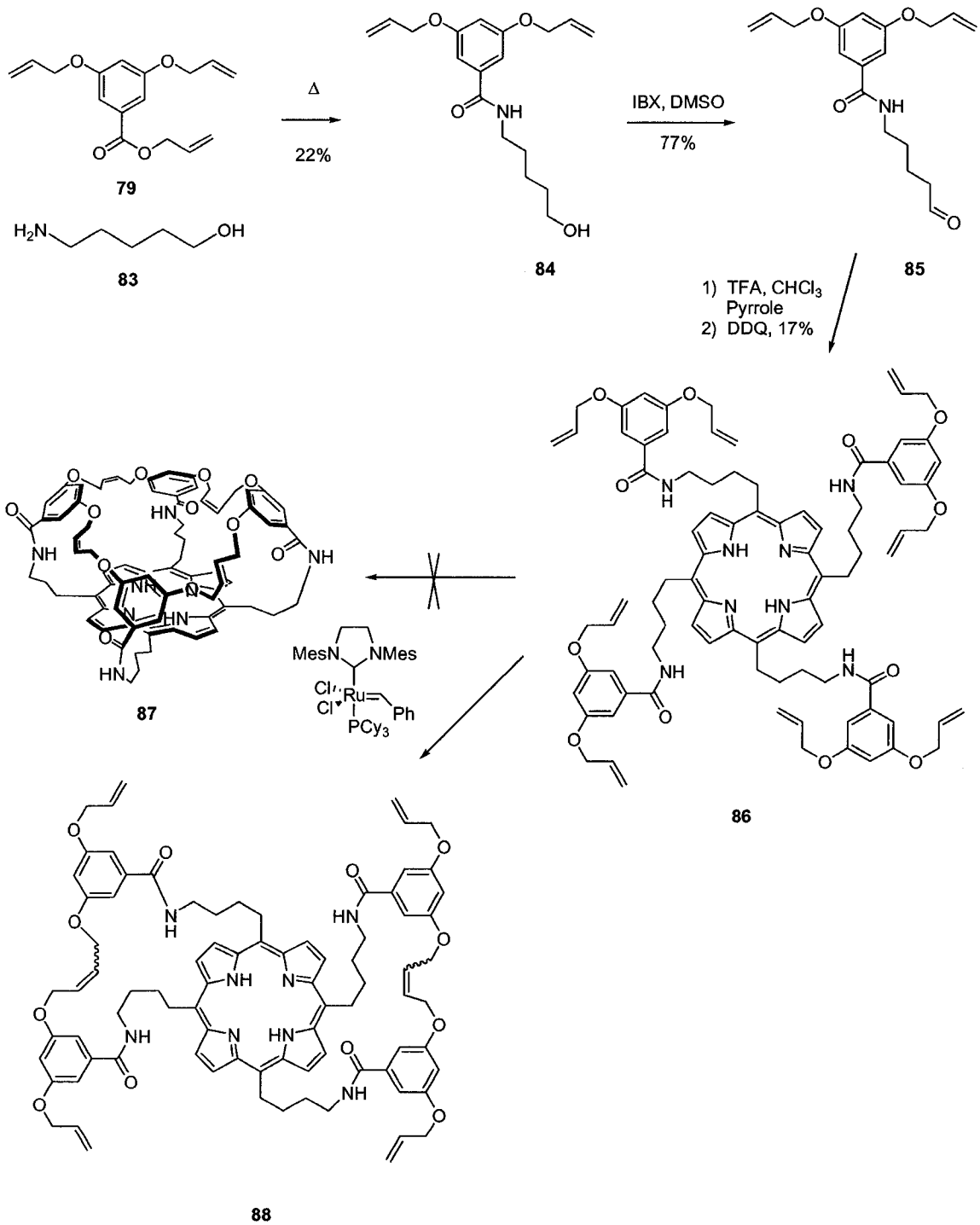


Scheme 15: First generation RCM precursor porphyrin 81.

Acid **80** transforms to its acid chloride upon treatment with $SOCl_2$. Reaction of the acid chloride with TAP **60** gives the tetraacylated product **81**. Disappointingly, RCM with Grubbs' first generation catalyst did not proceed. The problem may originate from the rigidity of the amide linker. To address this problem, a flexible alkyl chain may be used to tether the four bis-olefins to the porphyrin, thus maximizing the chances that the ring could find conformations capable of undergoing the four successive metathesis reactions (Scheme 16).

Heating ester **79** in a sealed tube with 5-aminopropanol affords the alcohol **84** in low yield (Scheme 16). Treatment of **84** with IBX oxidizes the alcohol to the desired aldehyde **85**. Boron trifluoride diethyl etherate promoted condensation with pyrrole followed by oxidation gives porphyrin **86**. Despite quenching of the reaction with ethyl vinyl ether, RCM with Grubbs' second generation catalyst predominantly results in the formation of insoluble material. It seems unlikely that the porphyrin is chelating the ruthenium because ruthenium insertion usually requires forcing conditions with $RuCl_3$,[96] no chelation problems were previously observed with Grubbs' catalyst and porphyrins, and publications have recently reported use of the reagent in the presence of the porphyrin heterocycle.[97] Polymerization seems like a plausible explanation, despite use of high dilution conditions (10 mM of porphyrin). Analysis of the electrospray mass spectrum of the filtered reaction mixture shows molecular ions (and sodium adducts) consistent with the formation of some doubly-linked products **88** (MW = 1403). Smaller peaks consistent with mono- and tri-linked products were also identified.

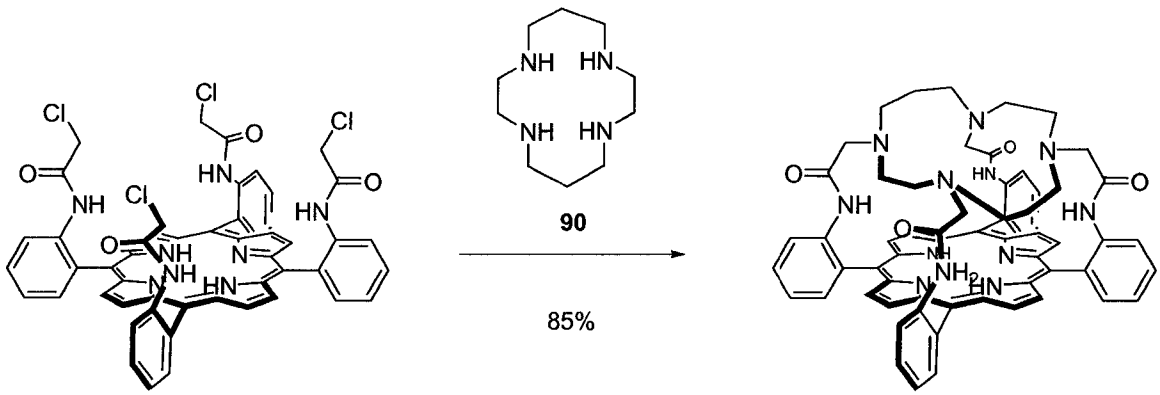
Although RCM templated capping of a correctly chosen porphyrin could be successful, it seemed preferable to investigate alternative capping strategies.



Scheme 16: RCM templated capping attempt on porphyrin 86.

2.3 Tetraamine Derived Crowns

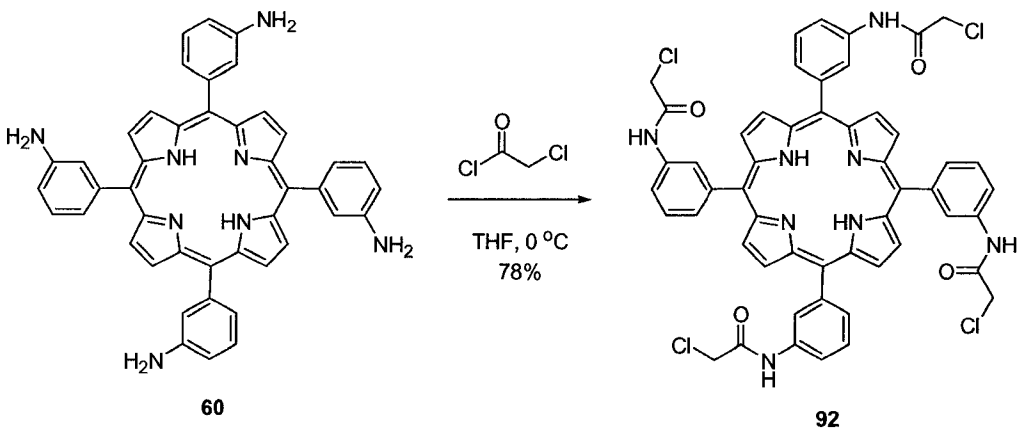
Collman and coworkers reported a crown capped porphyrin, prepared by treatment of α,α',α'',α'''-tetrachloroacetamidoporphyrin **89** with cyclic tetraamine cyclam **90** to give **91** (Scheme 17).[98] This reaction proceeds in very good yield considering that four bonds are being formed in the capping step. The accessibility of the starting materials combined with the high yield makes this approach very attractive. Additionally, functionalizing only one face of the porphyrin could simplify the key step in which the crown scaffold is attached to the porphyrin. Adapting this method to our goals seemed possible using the *meso*-tetrakis(*meta*-aminophenyl)porphyrin (**60**) and a considerably larger tetraamino cap.



89 **91**

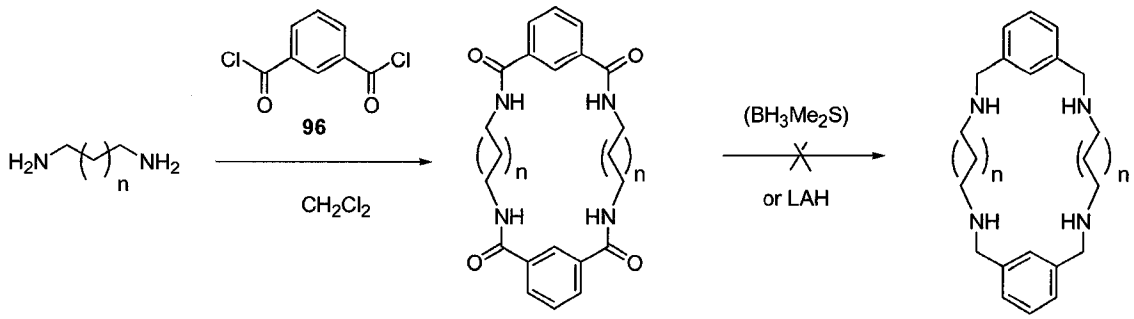
Scheme 17: Collman's cyclam capped porphyrin.[98]

Thus, treatment of tetraaminophenylporphyrin **60** with chloroacetyl chloride[99] gives the tetraacetylated product **92** in good yield (Scheme 18).



Scheme 18: Chloroacetylation of tetraaminophenylporphyrin 60.

The tetraaza caps that were initially selected as the porphyrin's scaffolding had to be considerably larger than Collman's cap, since it had to allow n-alkanes to thread through its centre. The scaffold should be rigid enough to hold the "hole" open, while still permitting some flexibility to facilitate the capping reaction and confer some solubility. It seemed that accessible macrocyclic tetraamides could be reduced to the corresponding tetraamines, providing a facile synthetic route to the cap. Diamines **93**, **94**, and **95** all condense with isophthaloyl chloride to give the tetraamide macrocycles **97**,[100] **98**, and **99**, respectively, in surprisingly good yield. Unfortunately, these macrocycles were soluble in DMF and DMSO only. Because of this, standard reduction reagents (LAH, BH_3) in compatible solvents (THF, DME) were relatively ineffective at converting these materials to the tetraamines **100**, **101**, or **102**. Extensive effort to reduce these compounds employed high temperature (100 °C in diglyme) and adsorption of the tetraamide onto sand and silica gel to increase surface area. In the latter case, 4 days in THF at reflux produced a very low yield of mixed reduction products. Hence, other routes to macrocyclic tetraamines were explored.



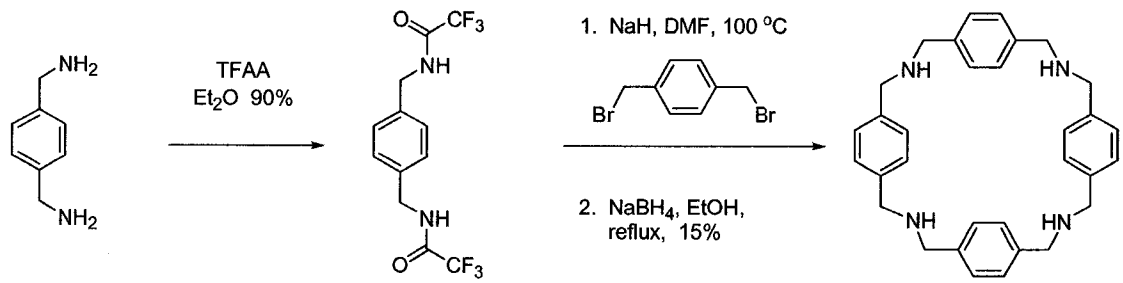
93 n = 1
94 n = 2
95 n = 4

97 n = 1 71%
98 n = 2 65%
99 n = 4 56%

100 n = 1
101 n = 2
102 n = 4

Scheme 19: Preparation of tetraamide macrocycles and attempted reduction.

The synthetic route to the rigid tetraaza macrocycle shown in Scheme 20 relied on the work of Murakami *et al.*[101] Treatment of diamine **103** with trifluoroacetic anhydride affords the expected diamide **104**. Formation of the dianion of **104** in DMF, then alkylation by slow addition of α-α'-dibromo-*p*-xylene at high temperature and high dilution gives a mixture of macrocyclic amides, including the desired tetraamide. Treatment of the crude tetraamide with excess sodium borohydride to remove the trifluoroacetyl groups followed by gel permeation chromatography gives cyclophane **105**.



103

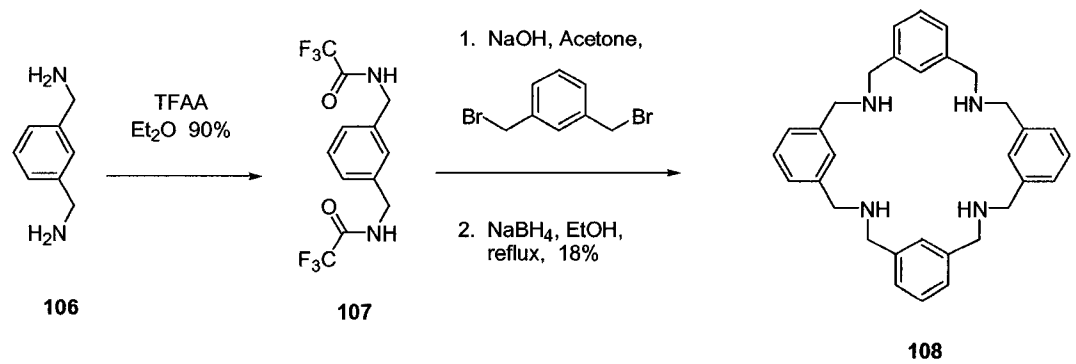
104

105

Scheme 20: Preparation of *para*cyclophane 105

Preparation of the *meta* tetraazacyclophane was done by an analogous procedure (Scheme 21) reported by Shinmyozu *et al.*[102] Trifluoroacetylation of *m*-xylene α,α'-diamine in diethyl ether gives diamide **107**. Deprotonation of **107** with successive

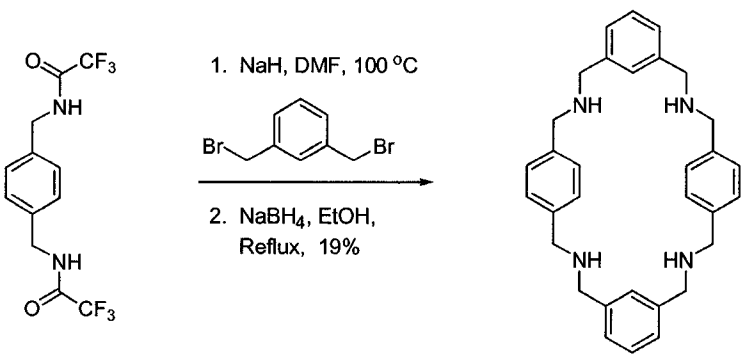
additions of NaOH, followed by alkylation with α,α'-dibromo-*m*-xylene at moderate dilution in acetone gives a mixture of products including the tetraamide, which is reductively transformed into cyclophane **108** with sodium borohydride.



106 **107** **108**

Scheme 21: Preparation of *meta*cyclophane 108.[102]

A third tetraaza macrocycle **109**, which has been synthesized via a route different from the one used in this work,[103] is accessible by extending the methodology used to prepare **105**. Alkylation of the diamide **104** with α,α'-dibromo-*m*-xylene followed by reductive cleavage of the trifluoroacetamides affords **109** (Scheme 22).

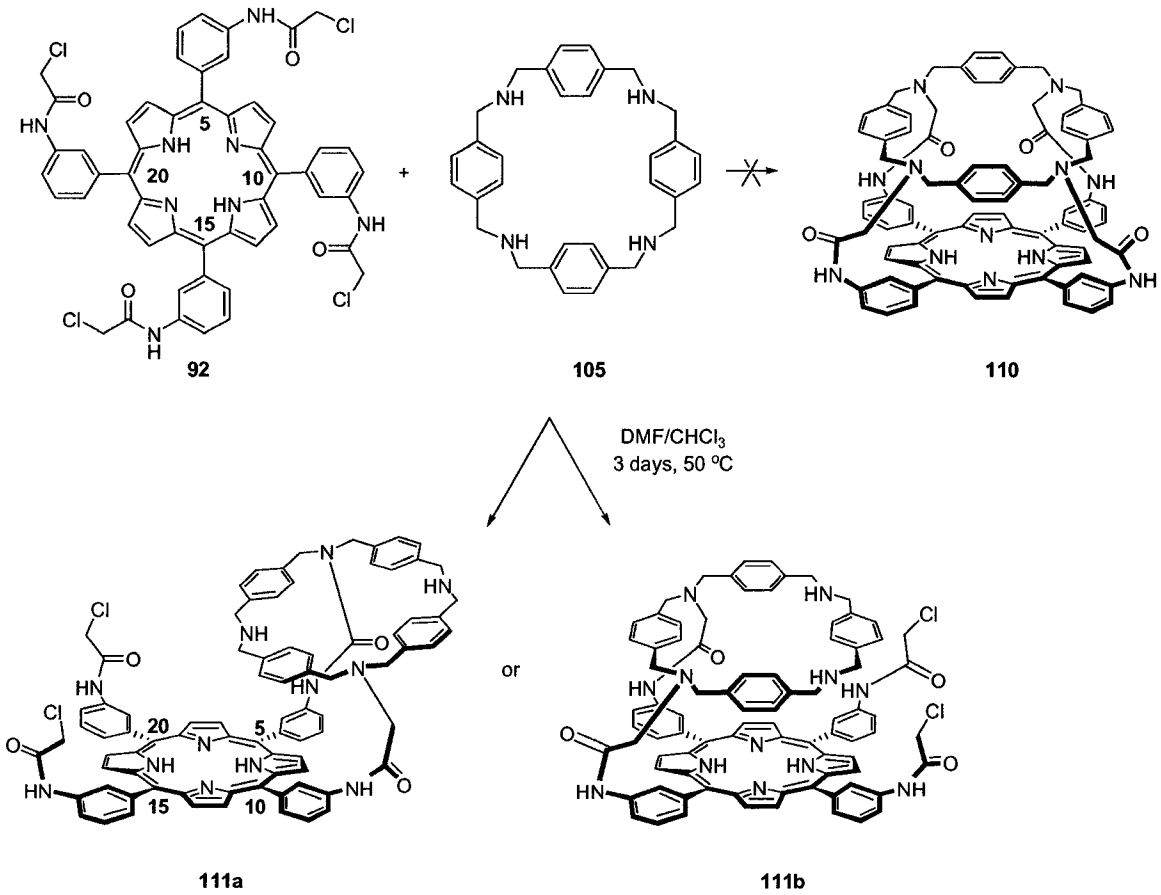


104 **109**

Scheme 22: Preparation of cyclophane 109.

With these tetraaza macrocycles prepared, capping of the porphyrin was attempted using the paracyclophane **105** and the chloroacetamido derivative **92** (Scheme

23). Reaction of these two coupling partners under high dilution gives a complex mixture, with some insoluble material. Filtration, then concentration *in vacuo* generates additional insoluble purple solid, possibly due to further polymerization. Quenching with acetic anhydride does not circumvent the solubility problem. Conducting the reaction under different reaction conditions gives similar results.



Scheme 23: Attempted capping of porphyrin 92 with paracyclophane 105.

Concentration of the mixture to half volume followed by purification by gel permeation chromatography gives a purple band which possesses the mass spectrum consistent with two points of attachment between porphyrin and cap. This product could be either **111a** or **111b** as shown in Scheme 23, or a product of reaction of the tetraamine with the

chloroacetamidophenyl groups at the 5 and 15 positions of the porphyrin (labeled in red on the starting material **92** and on **111a**). Treating this fraction with acetic anhydride before concentration still gives rise to an insoluble material upon concentration *in vacuo*.

Unfortunately, treatment of chloroacetamido porphyrin **92** with cyclophane **109** produces similar results (not shown). These difficulties are attributed to a combination of competing polymerization reactions and low solubility of both starting materials. Amide bonds could be hampering the solubility of the capped and/or partially capped materials because of intermolecular interactions stemming from the increased polarity and increased rigidity of the amide. The desired attachment might also fail because of a size mismatch between the cap and the preferred conformation of the porphyrin. This seems plausible since amides have a conformational preference to minimize gauche interactions (**112b** over **112a**, Scheme 24)[104] which causes additional conformational rigidity. This inflexibility may prevent the chloroacetamido groups from reaching the target amines of the cap.

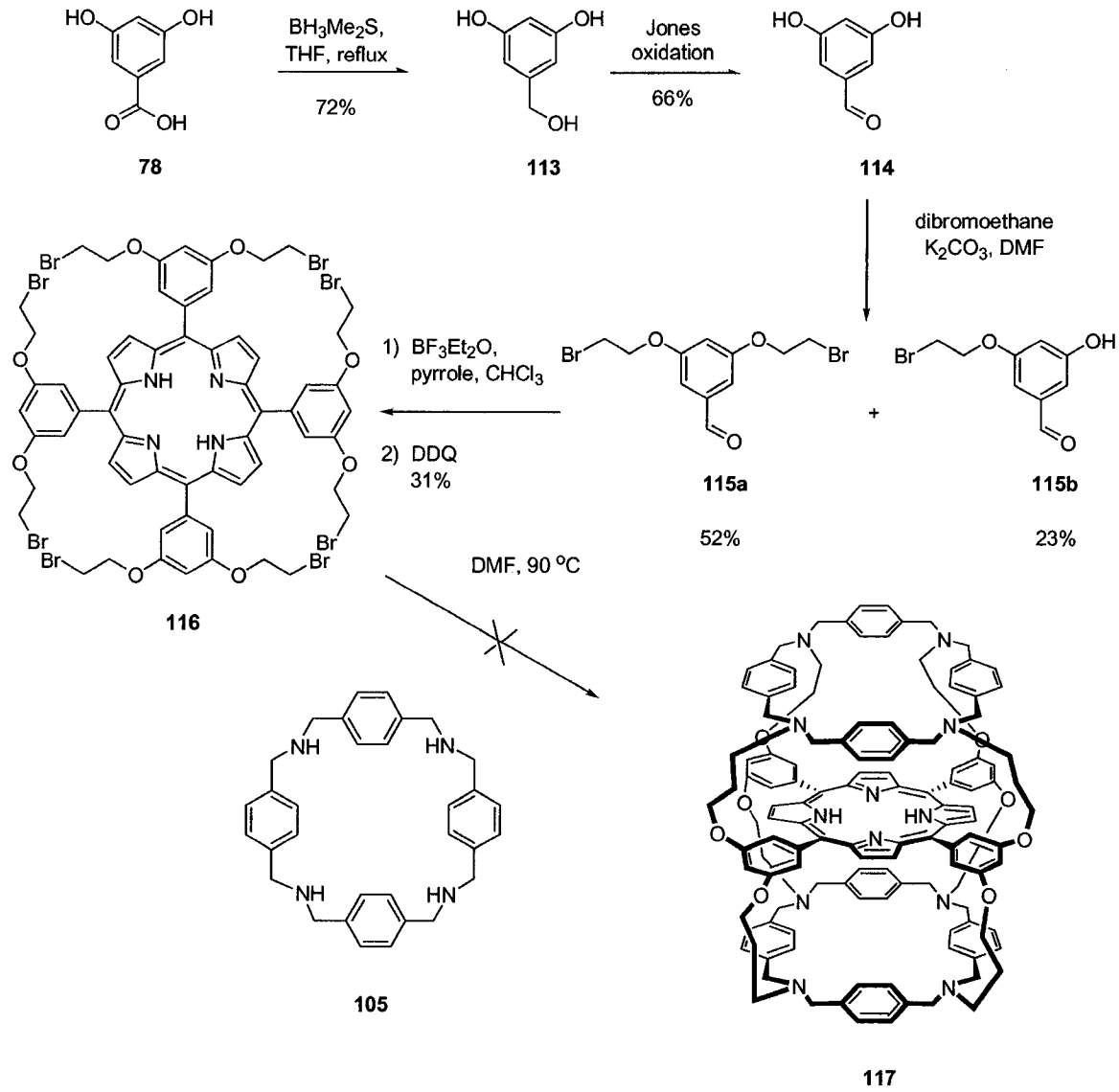
It seemed that the solubility of the product(s) might be improved by changing the amide bonds on the porphyrin to an ether linkage (*vide infra*) such as porphyrin **116** (Scheme 25).

112a **112b**

Scheme 24: Preferred conformations of chloroacetamide.

This new approach could facilitate the preparation of a more soluble porphyrin and allow capping on both faces. Borane dimethylsulfide reduces 3,5-dihydroxybenzoic

acid (**78**) to the benzylic alcohol **113**.[105] In accord with the literature, the alcohol **113** oxidizes to aldehyde **114** when treated with Jones' reagent in aqueous media.[106] This diphenolic aldehyde in basic media is mono- and bis-alkylated to **115a** and **115b**, respectively, in moderate yield using an excess of 1,2-dibromoethane to minimize dimerization. Aldehyde **115a** condenses efficiently with pyrrole under Lewis acid catalysis. Subsequent DDQ oxidation affords the porphyrin **116**. Unfortunately, no alkylation is observed when *meta*- or *para*-cyclophane **105** or **108** is treated with porphyrin **116** at room temperature under high dilution. More forcing conditions (high temperature) give only insoluble purple material and recovered starting materials. Mass spectral analysis of the reaction mixture reveals a complex mixture of multiply alkylated products including mono-, di-, and tri-linked products. These materials are present in only trace quantities, and were not isolated as pure compounds. Moreover, they were not observed in the electrospray mass spectrum of the reaction mixture after extended reaction periods (2 days). The octa-bromide transforms to the octa-iodide using sodium iodide with Finkelstein conditions. Reaction of tetraamine **108** or **109** with this iodo porphyrin gives similar product mixtures in addition to components resulting from elimination.

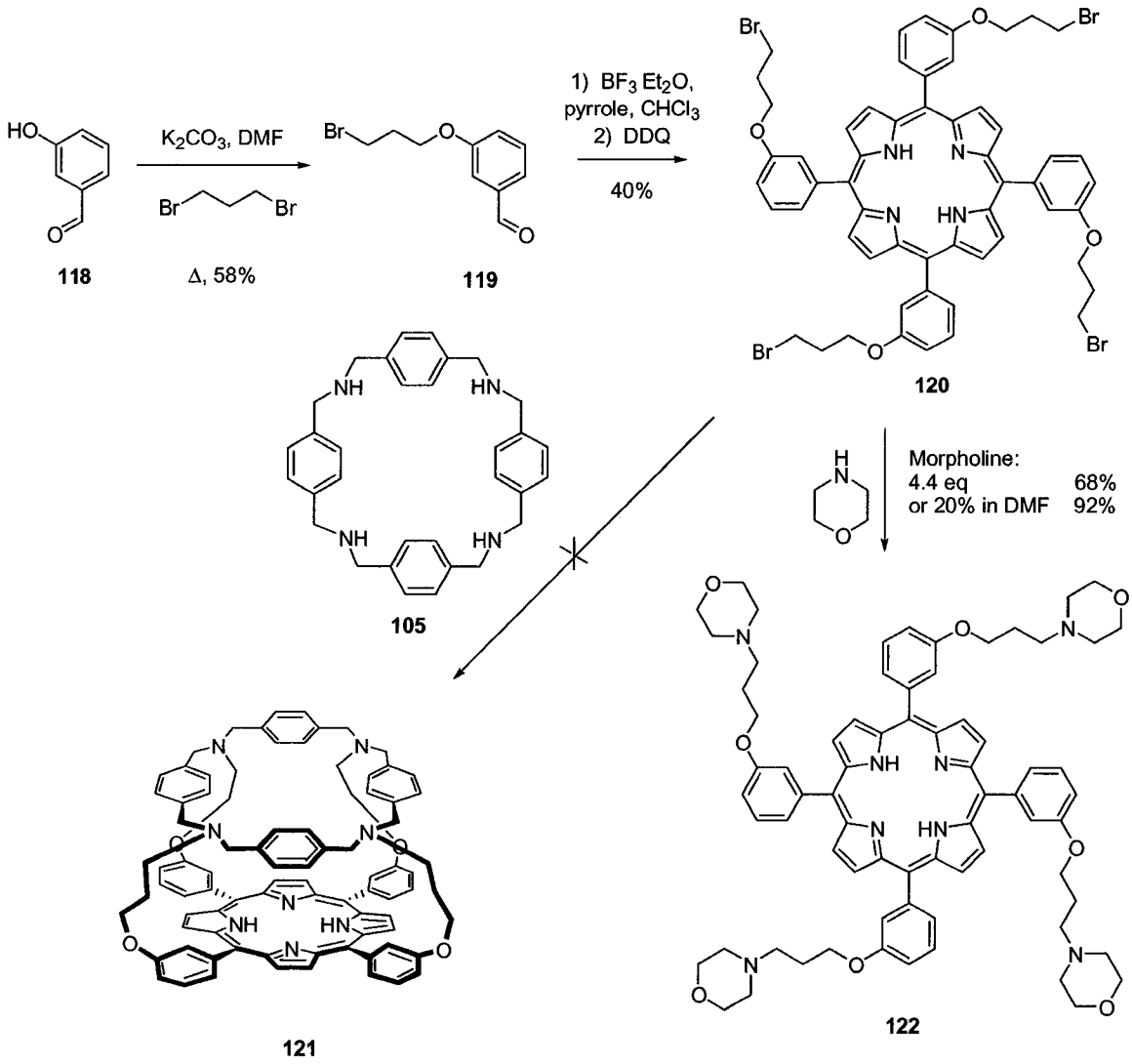


Scheme 25: Attempted capping of octaether porphyrin 116 with cyclophane 105.

To alleviate side reactions and to reduce the number of bonds being formed in the key capping step, it was decided to design a porphyrin that would functionalize on only one face. Homologation of the alkyl tether by one carbon (ethyl to propyl) enhances the conformational mobility of the straps to "reach" the amine (Scheme 26).

As reported previously, excess 1,3-dibromopropane alkylates 3-hydroxybenzaldehyde **118** to give the bromoalkoxyaldehyde **119** in moderate yield.[107]

This smoothly transforms to the porphyrin **120** when condensed with pyrrole using boron trifluoride diethyl etherate catalysis followed by oxidation with DDQ. This porphyrin gives insoluble mixtures when treated with either the *meta* or *para*-tetraazacyclophanes **105** or **108**.



Scheme 26: Attempted capping of porphyrin 120

Several porphyrin amines (distinct from porphyrin anilines) in the literature have been reported to be unstable,[108,109] though others[110] including Collman's[99] have not. Since the generality of this instability has not been addressed, we decided to attempt the

preparation of a simple porphyrin amine to test this idea. In marked contrast to reaction with cyclophanes, treatment of the tetra-bromoporphyrin **120** with 4.4 eq of morpholine under conditions similar to those used with the cyclophanes gives an acceptable yield of the expected tetraamino product **122** arising from four successive nucleophilic displacements by the amine. If 20% morpholine is used, the conversion is almost quantitative. Interestingly, after three weeks exposed to the fluorescent lighting of the laboratory, significant amounts of purple material in deuterochloroform had precipitated on the walls of an NMR tube. Electrospray mass spectral analyses of the material (after dissolution of the material in MeOH/THF) revealed a mixture of compounds, with masses consistent with loss of the pendant side chains (1, 2, and 3 times) corresponding to the free phenol(s)! While this result is preliminary, and has not been repeated, we tentatively rationalize the result by the mechanism outlined in (Figure 24). The amine **122** could react with singlet oxygen formed by the tethered porphyrin sensitizer giving the zwitterionic *N*-peroxide compound **123i**. This peroxide species could then eliminate, forming an iminium salt **123ii**. The peroxide anion could then abstract a proton from the iminium cation, resulting in the formation of enamine **123iii**. The enamine could then eliminate the porphyrin phenoxide **123iv** to give the observed product.

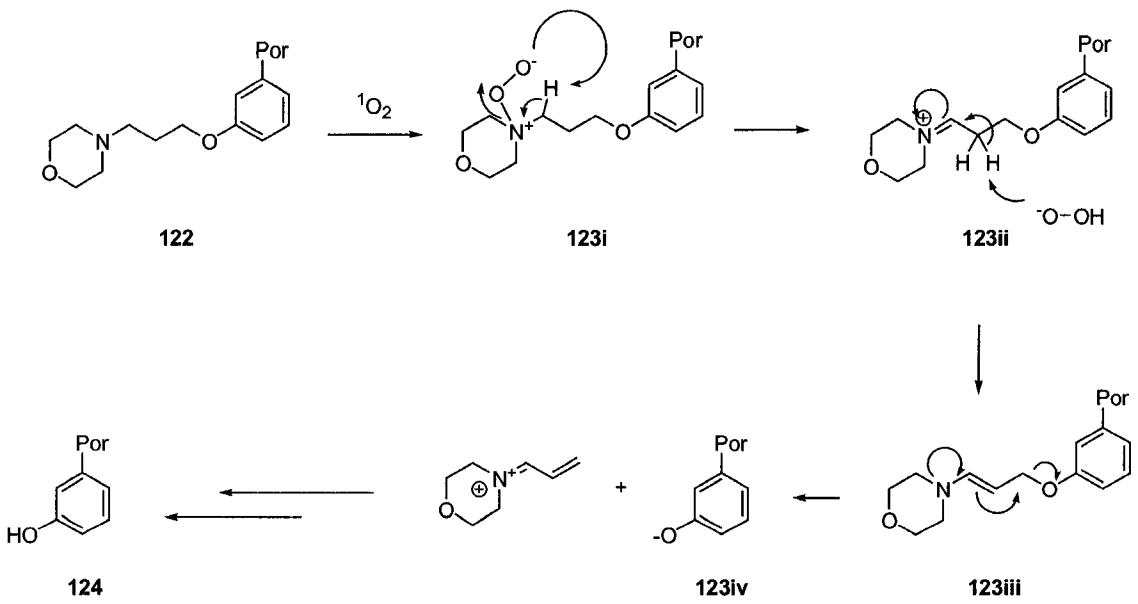


Figure 24: Possible mechanism of dealkylation of porphyrin 122.

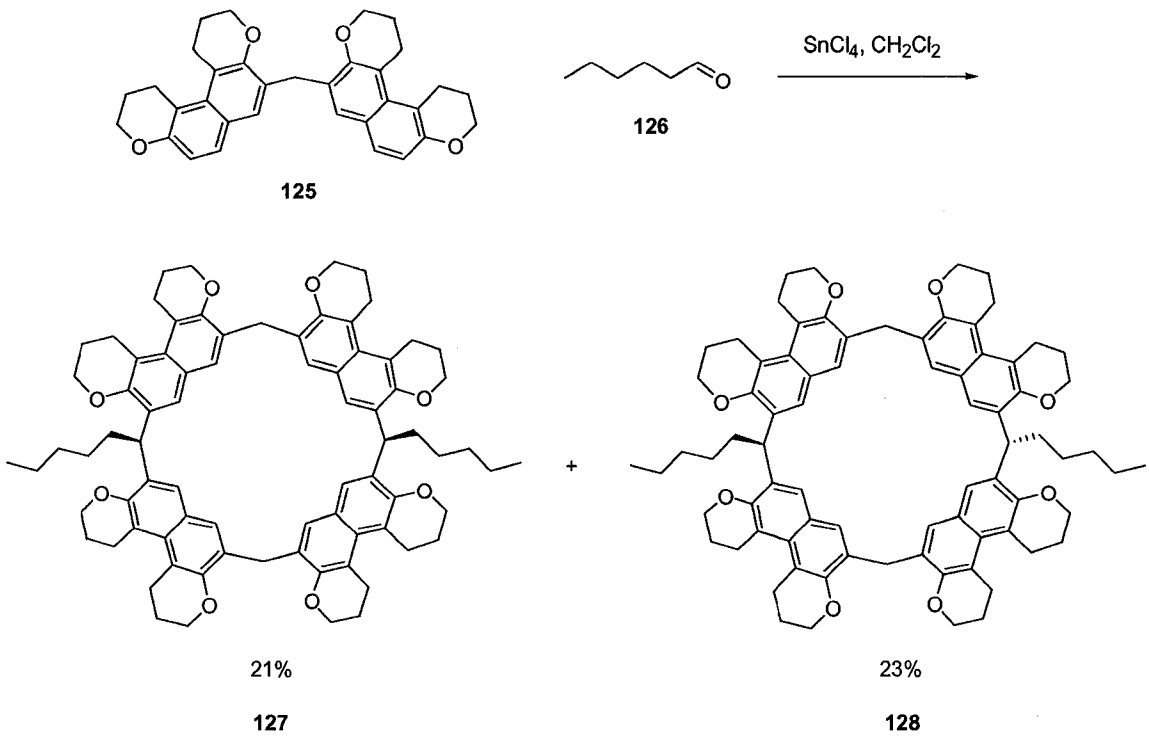
Several approaches to an amine capped porphyrin were explored with no preliminary success. This suggested that this series of tetraamino macrocycles are not well suited to our goal of capping a porphyrin.

2.4 Porphyrin Straps Derived From Calixnaphthalenes

Macrocycles derived from calixarenes and resorcinarenes possess many of the qualities desired in a catalyst scaffolding such as synthetic accessibility and the generation of a defined nanospace for shape selection.[111] Unfortunately, calix[4]arenes and resorcarene cavitands are too small to allow alkyl chains to pass through, making them unsuitable for our purpose. While calix[6]arenes possess a potentially attractive cavity size, they also suffer from conformational lability, and exist in many different conformers.[112] For these reasons, it was initially decided not to pursue calixarene based scaffolds to cap or strap the porphyrin.

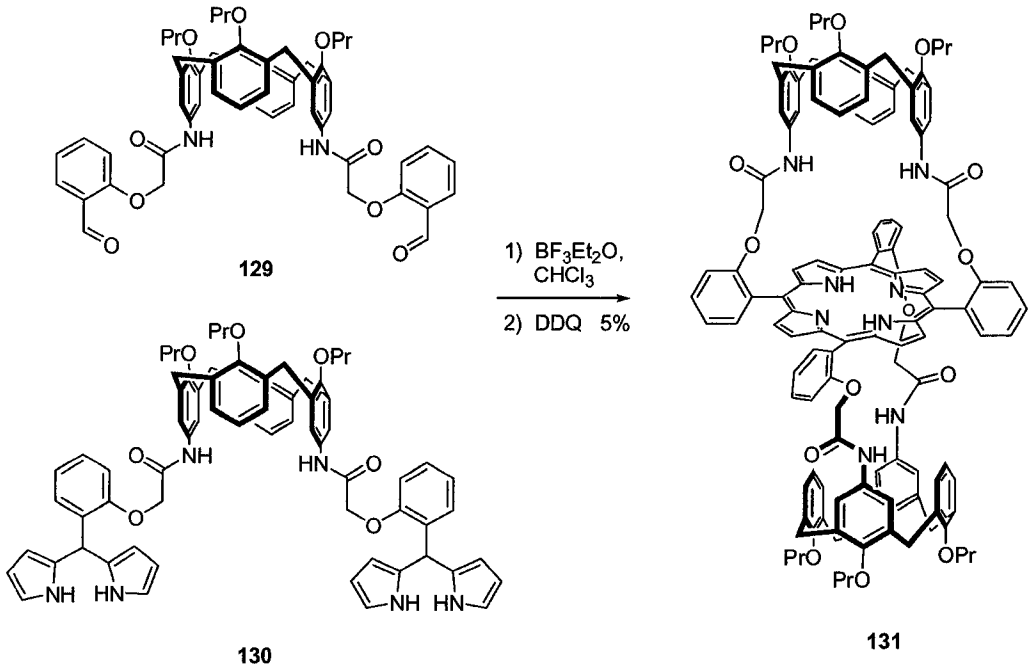
In 2002, Glass and coworkers[113] published the first calixnaphthalene[114] which was synthetically practical, and which might be amenable to further derivatization. This macrocycle was built using alkoxynaphthalene derivative building blocks (Scheme 27).

Inspired by several calixarene bis-strapped porphyrins reported by Reinhoudt (Scheme 28),[115] it seemed that a similar strategy using a calixnaphthalene could be employed to prepare a capped porphyrin with the desired topology and size requirements. In the preparation reported by Reinhoudt, the calixarene was doubly functionalized on the upper rim, providing sites for attachment to the porphyrin.



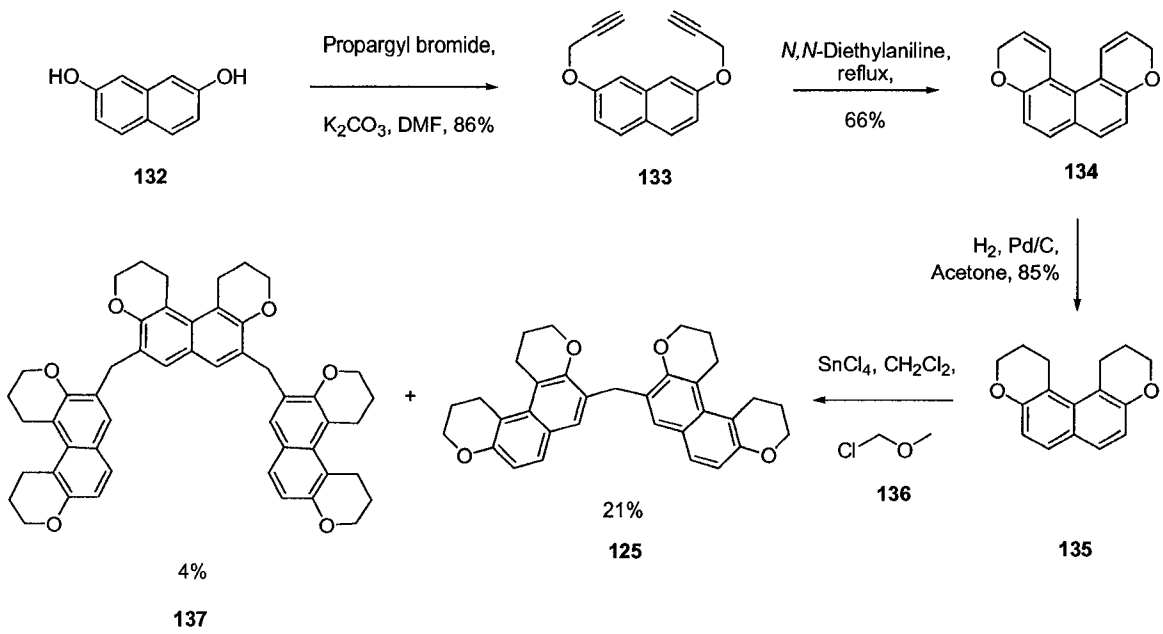
Scheme 27: Glass' synthesis of a calixnaphthalene

Since the successful synthesis of the calix[4]naphthalene involved very subtle alteration of the substituents of the alkoxynaphthalene building blocks,[116] we elected to attempt functionalization of the side chain 'arms'; the pentyl side chains of structure **127/128** (Scheme 27). Use of a modified 'arm' containing a functionalizable element (i.e. an electrophile) could allow the installation of the required aldehyde. Alkyl halides would be unaffected by the strong Lewis acid conditions required for the synthesis of the calixnaphthalene.



Scheme 28: Bis-calixarene capped porphyrin prepared by Reinhoudt.

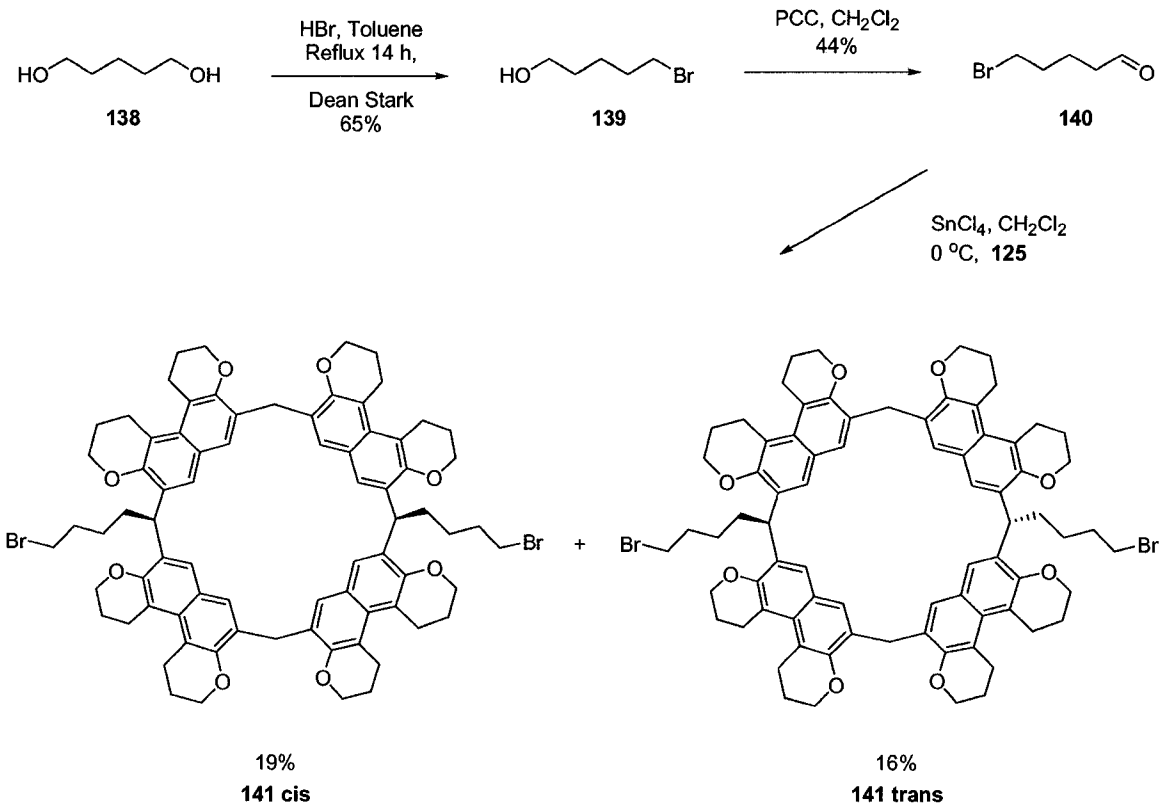
Our preparation of the calixnaphthalene is shown in Scheme 29. Following work of Balasubramanian,[117] 2,7-dihydroxynaphthalene alkylates with propargyl bromide to give the crystalline diether **133**. This bis propargyl ether rearranges to the tetracyclic **134** at high temperature via a [3,3] sigmatropic rearrangement, tautomerization, followed by a second [3,3] sigmatropic rearrangement. Hydrogenation of the air sensitive **134** provides the dihydro compound **135** in good yield. Then, Lewis acid promoted dimerization is accomplished with sub-stoichiometric amounts of chloromethoxymethane and tin(IV) chloride to give the desired dimer **125** and the undesired trimer **137**.



Scheme 29: Preparation of the calixnaphthalene precursor.

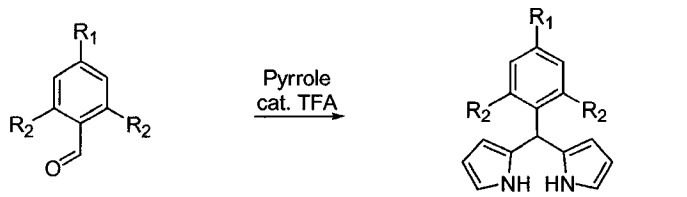
The bromoalkyl pendant arm component of the desired calixnaphthalene originates from the known aldehyde **140**.[118] Its preparation begins by first brominating 1,5-pentanediol **138** with aqueous HBr in toluene under forcing conditions to afford 5-bromopentanol **139** (Scheme 30).[118] This alcohol is smoothly oxidized to the requisite aldehyde **140** by PCC. The aldehyde condenses with an equimolar amount of dimer **125** to give a mixture of *cis* and *trans* calixnaphthalene derivatives **141 cis** and **141 trans**. These interesting compounds exhibited reasonable solubility in chlorinated solvents and THF, yet surprisingly poor solubility in other common organic solvents (Et_2O, EtOAc, acetone). Differentiating the *cis* from *trans* isomers by ^1H NMR spectroscopy was easily accomplished by examining the splitting pattern of the bisnaphthalene substituted methylene protons. Since the *trans* compound possesses a C-2 symmetry element with axis through both methylenes making them chemically equivalent, the attached protons are observed as a singlet. The *cis* compound lacks this symmetry element, resulting in

two chemically inequivalent protons on each methylene, each generating a doublet in the ^{1}H NMR spectrum.



Scheme 30: Synthesis of the calixnaphthalenes 141 *cis* and 141 *trans*.

At ths point it was decided to deviate from the general approach of Reinhoudt by condensing a synthetically accessible dipyrromethane with the calixnaphthalene dialdehyde to give a porphyrin derivative strapped on one face only. Since the calixarene-dipyrromethane derivatives were reported to be unstable,[115] this approach should be advantageous because it does not unnecessarily jeopardize advanced precursors. Condensation of 4-chlorobenzaldehyde or mesityl aldehyde with pyrrole with TFA catalysis gives the expected dipyrromethanes **143**[119] and **145**.[109]



142 R_1 = Cl, R_2 = H
144 R_1 = Me, R_2 = Me

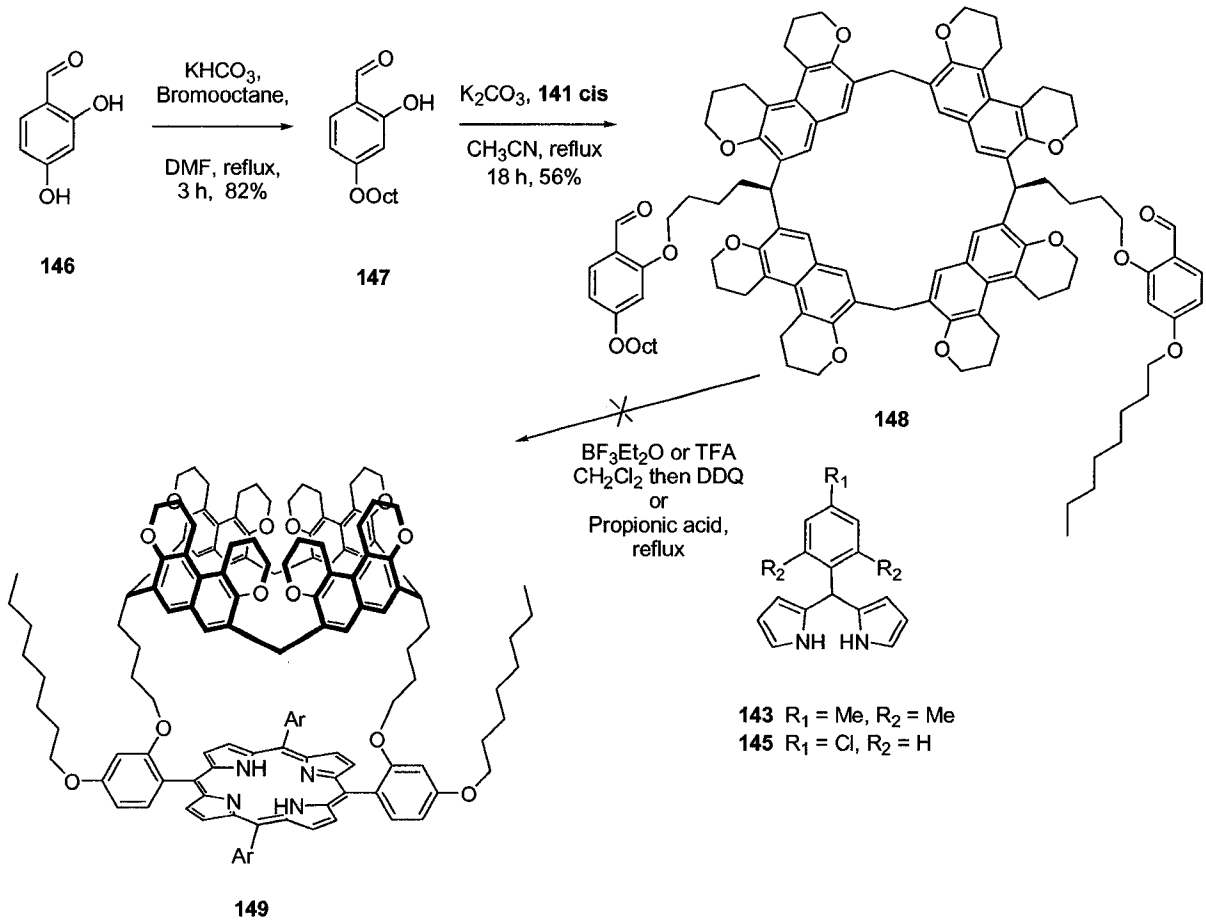
143 41% R_1 = Cl, R_2 = H
145 30% R_1 = Me, R_2 = Me

Scheme 31: Synthesis of dipyrromethanes 143 and 145.

The *cis* dibromide **141 cis** alkylates salicylaldehyde, but this proved to be moderately insoluble. Since the ultimate target in this synthesis is to tether the calixnaphthalene to a porphyrin, it is undesirable to use a capping unit with poor solubility. To improve the solubility of the dialdehyde, a salicylaldehyde derivative substituted with a flexible pendant was prepared (Scheme 32). Selective alkylation of 2,4-dihydroxybenzaldehyde by 1-bromooctane and potassium bicarbonate in refluxing DMF gives monoalkylated product **147**.[120] Two of these aldehydes were then installed on the calixnaphthalene **141 cis** by nucleophilic displacement of the bromide by the phenolate salts in CH_3CN to generate the dialdehyde-tethered calixnaphthalene **148**.

Unfortunately, dialdehyde **148** fails to condense with 5-mesityldipyrromethane **145** to give porphyrin **149** under Lindsey's conditions.[61] Reinhoudt reported that one of his cavitand-capped porphyrins failed to condense under $BF_3 \bullet Et_2O$ catalysis, but successfully forms using the Adler-Longo procedure of refluxing propionic acid, albeit in low yield (3%).[53] Since initial formation of tetraarylporphyrinogen (the aldehyde-pyrrole condensation product) has been shown to be reversible under $BF_3 \bullet Et_2O$ catalysis,[88] it may be that in both cases porphyrinogen formation requires a disfavoured conformation, thus preventing porphyrin formation. This idea is supported by the fact that Reinhoudt successfully used the Adler method[63] under conditions where the porphyrinogen can be

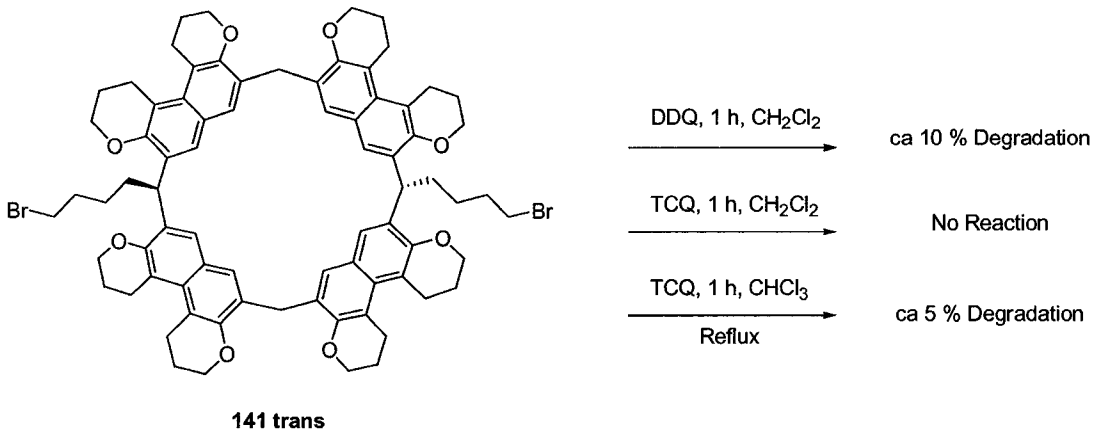
oxidized (trapped) as it forms. Unfortunately, similar attempted condensation of mesityldipyrromethane **145** with dialdehyde **148** does not generate porphyrin **149**.



Scheme 32: Attempted condensation of calixnaphthalenedialdehyde with dipyrromethanes.

Although modeling suggested that the ortho methyl groups of the mesityl should not interfere with condensation due to the tether length used, it was decided to attempt the condensation using the ortho-unsubstituted precursor, 5-(4-chlorophenyl)dipyrromethane (**145**). Unfortunately, this dipyrromethane also fails to condense with dialdehyde **148** to generate the desired porphyrin using standard conditions, generating a complex mixture

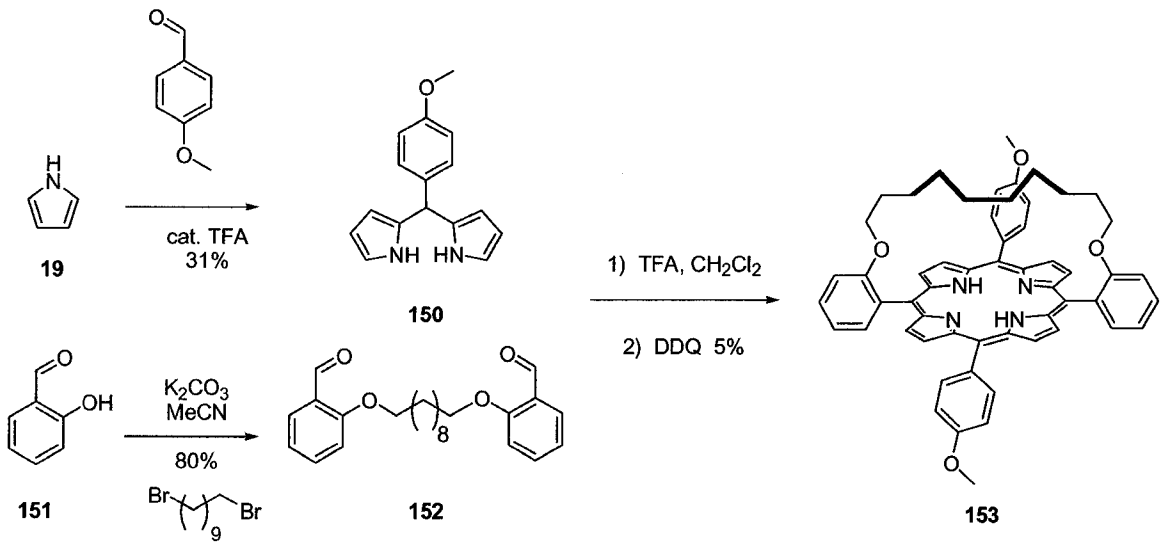
instead. Control studies were done to examine if the problem was due to oxidation of the electron rich benzylic sites of the calixnaphthalene crown. Since the synthetic scheme had no direct need for the **141** ***trans***, it was used to avoid wasting advanced precursors. No degradation was evident upon treatment of **141** ***trans*** with TCQ for 1 h at rt, and minimal loss (<10%) was observed after treatment with DDQ at 20 °C or TCQ at 37 °C for 1 h (Scheme 33). These experiments suggest that oxidative degradation of the calixnaphthalene during the attempted oxidation of porphyrinogen to porphyrin is not the origin of the failure to obtain the target strapped porphyrin **158**.



Scheme 33: Testing stability of 141 *trans* to oxidation conditions used in porphyrin synthesis.

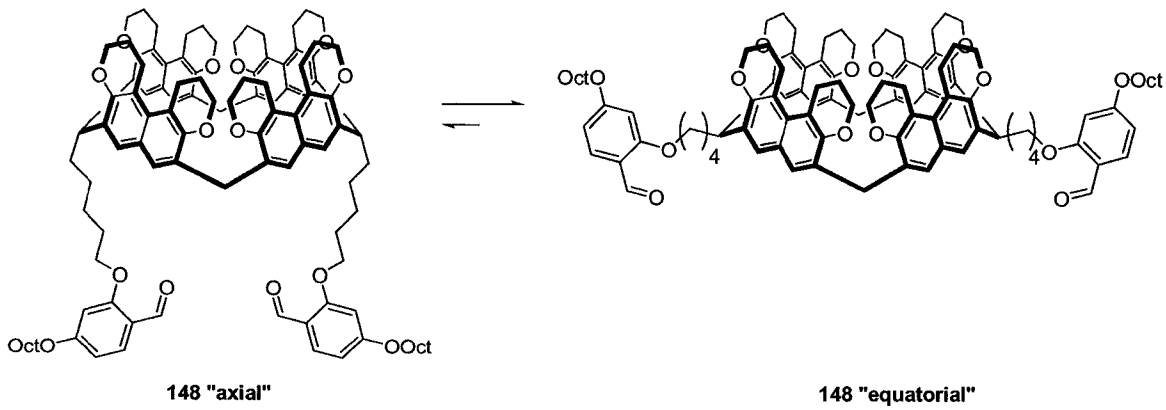
Since porphyrin syntheses are usually performed on larger scale than those being used here, it seemed desirable to confirm that the reagents and techniques were effective on the scales being used (20-40 μmol). To this end, a simplified strap was used to condense with the dipyrromethanes. Two salicylaldehyde units were tethered using 1,10-dibromodecane to afford the dialdehyde **152**[121] (Scheme 34). 5-(4-Methoxyphenyl)dipyrromethane[122,123] (**150**) was prepared from 4-methoxybenzaldehyde

and condensed with **152** under standard conditions to give strapped porphyrin **153** in low yield, which is typical of reported porphyrin syntheses from tethered dipyrromethanes.[124]



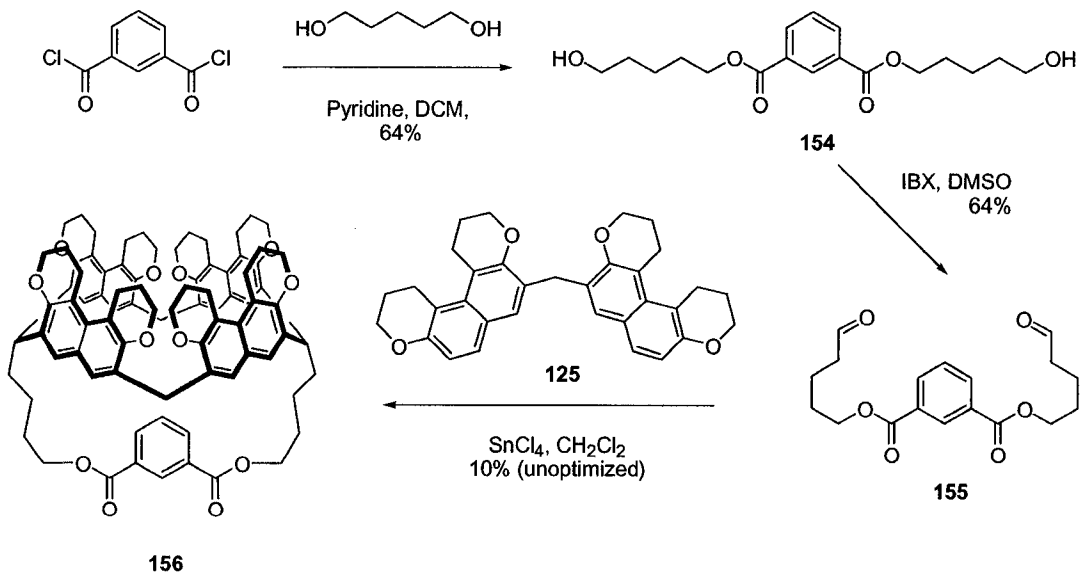
Scheme 34: Trial synthesis of strapped porphyrin 153.

This result suggested that the cap being used might not be suitable. It is possible that the macrocycle adopts an equatorial-like conformation to minimize steric interactions wherein the aldehydes are held too far apart to condense to form the porphyrinogen (Scheme 35).



Scheme 35: Possible disadvantageous conformational bias of side chains.

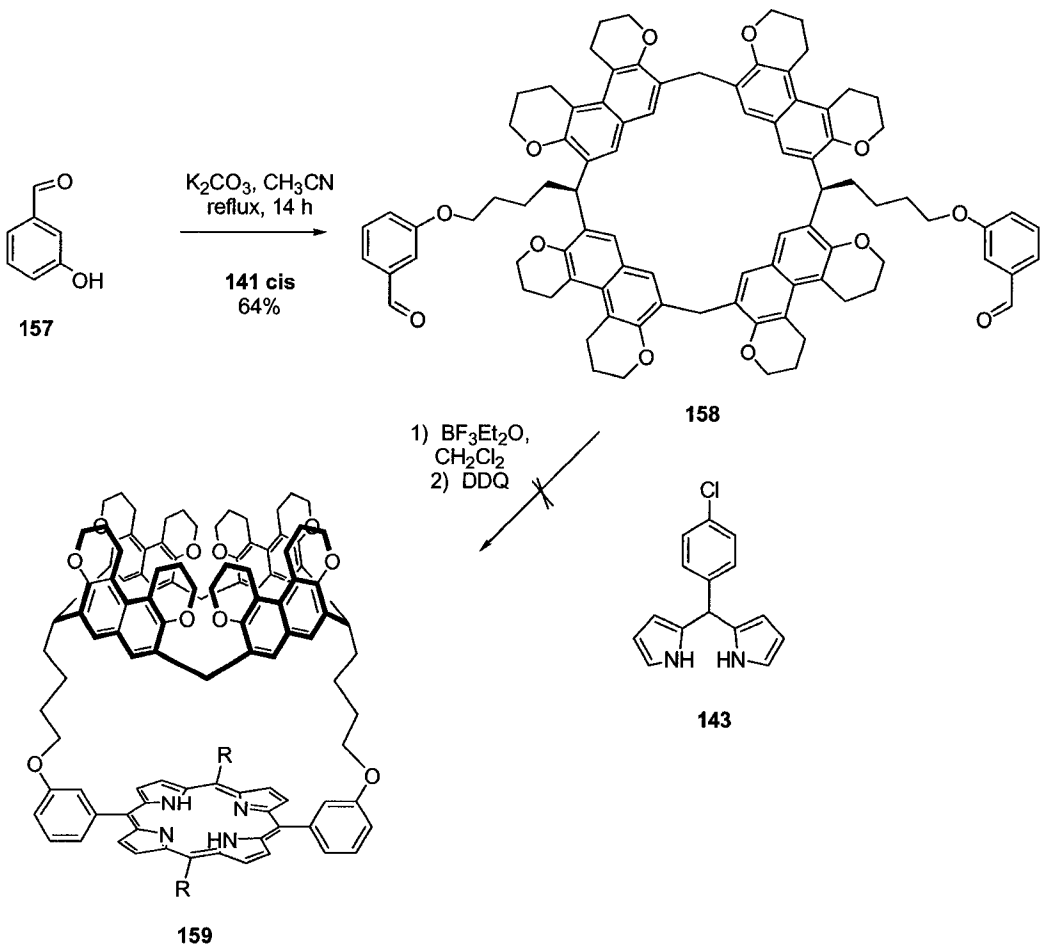
In an effort to determine if a "strapped" geometry could be tolerated and if the yield on the final condensation step could be improved, the calixnaphthalene synthesis was performed using two tethered aldehydes. This dialdehyde could react with the naphthalene dimers in the final step of the synthesis of calixnaphthalenes (Scheme 36). Additionally, this would eliminate the tedious separation of the *cis* and *trans* isomers of the calixnaphthalene, which is a serious practical limitation. An isophthaloyl moiety was employed as the tether for the aldehydes. The synthesis begins by tethering two equivalents of the aldehyde precursor 1,5-pentanediol groups using isophthaloyl chloride with pyridine to give diol **154**. IBX oxidation of this diol generates the dialdehyde **155** in moderate yield. Under Lewis acid catalysis, dimer **125** and aldehyde **155** condense to afford the targeted strapped calixnaphthalene **156** in low yield. This demonstrates that the calixnaphthalene can be strapped through shorter linking arms than those used in the porphyrin synthesis attempt.



Scheme 36: Synthesis of the strapped calixnaphthalene 156.

A last attempt using this capping strategy focused on changing the geometry of the aldehyde tether from the *ortho* position to the *meta* (Scheme 37). Alkylation of 3-hydroxybenzaldehyde **157** with dibromide **141 cis** gives the dialdehyde **158**. Unfortunately, condensation with dipyrromethane **143** generates a complex mixture containing no detectable amount of the desired porphyrin **159**.

A variety of approaches using the calixnaphthalene system as a cap were explored, but showed no promise of being suitable for our purpose of strapping a porphyrin. Thus, it was decided to pursue alternative chemistries discussed in the final chapter.



Scheme 37: *Meta* linkage of benzaldehyde to calixnaphthalene.

2.5 Cyclodextrin Derived Porphyrin Straps

The final set of approaches that were undertaken to crown the porphyrin use a cap with good selectivity for n-alkanes; namely α-cyclodextrin (α-CD). All of the three commercial cyclodextrins are cyclic poly-glucose natural products with a cavity depth of 7 Å.[125] Although β-cylodextrin possesses a cavity large enough to form stable inclusion complexes with unhindered monocyclic aromatics (7.5 Å cavity),[125] α-CD has a smaller hydrophobic cavity (4.5 Å)[125] inside its "flower pot"[126] shaped macrocycle comprised of six α-(1-4) linked glucose residues. It has been demonstrated that these water soluble natural products are excellent for encapsulating alkanes in a lipophilic environment allowing limited conformational flexibility (Figure 25).[127] It seemed that capping with the smaller end of the "flower pot" attached to the porphyrin would achieve maximum shape selectivity.

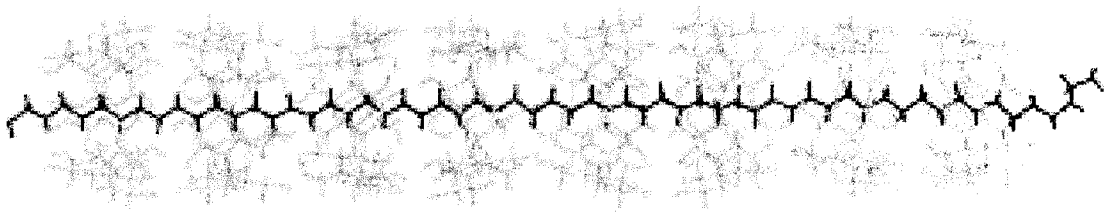
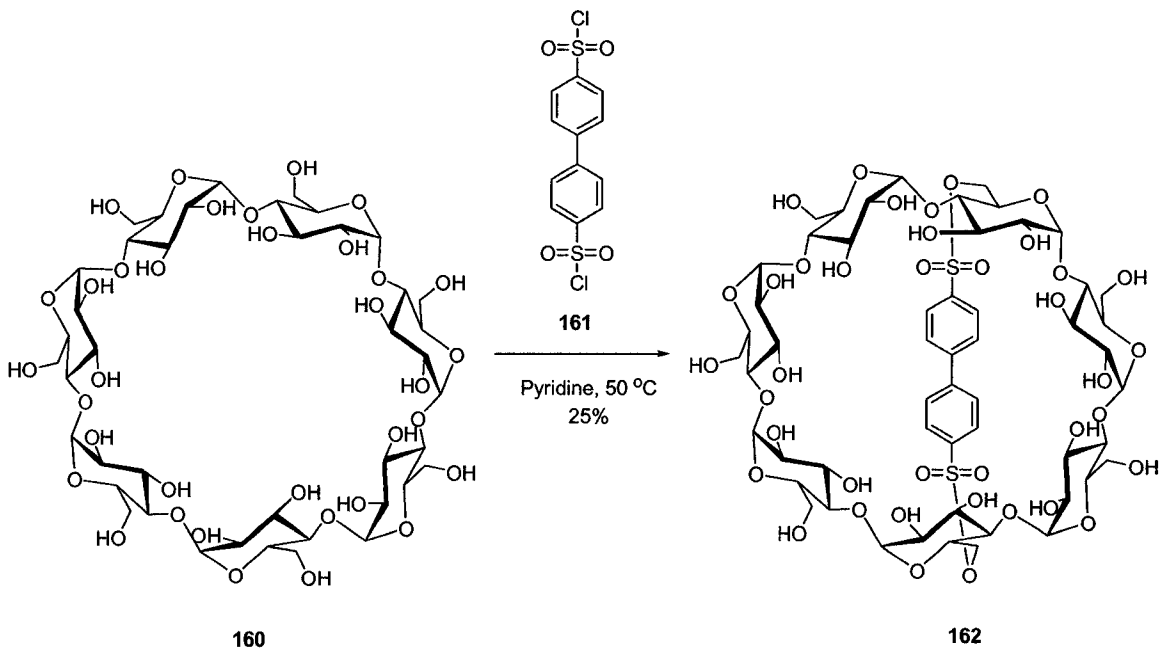


Figure 25: Calculated structure of eight α-CDs threaded with an alkane[127]

Kuroda and coworkers had already successfully capped a porphyrin with β-CD, and evaluated its photophysical properties in binding quinones,[128] and its catalytic properties for photooxygenation of alkanes inside the hydrophobic pocket.[129] One of the most challenging aspects of working with cyclodextrins is selective functionalization.[130] Kuroda and coworkers took advantage of a clever method for modifying β-CD which

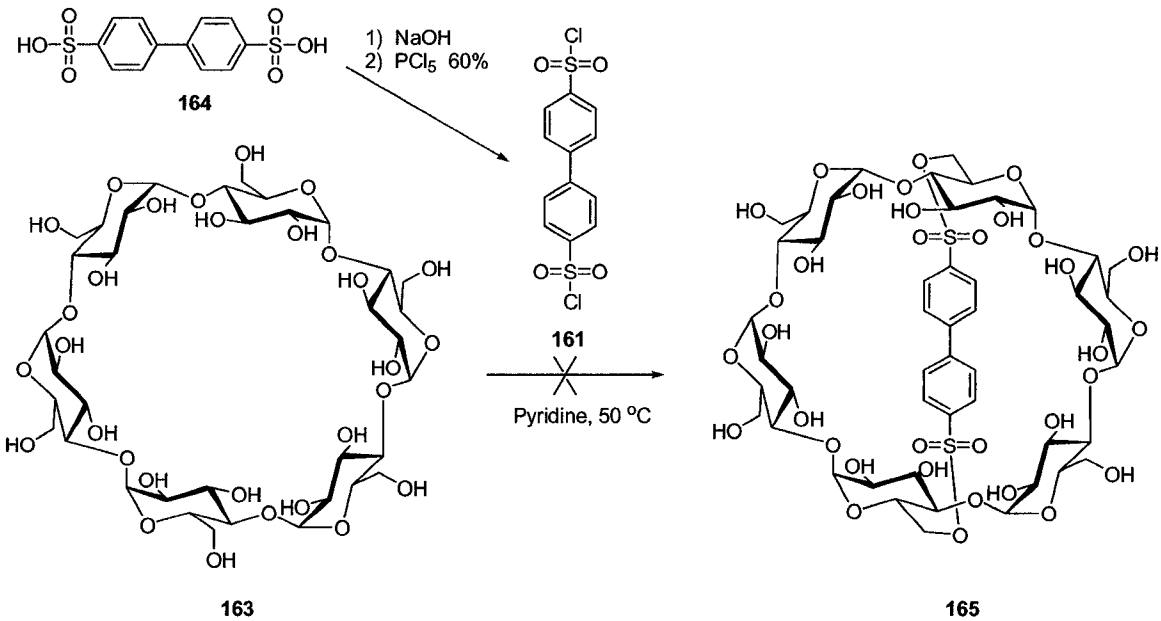
depends on the derivatization with rigid disulfonyl chloride linkers.[131] When used in substoichiometric quantities, 4,4'-biphenylsulfonyl chloride (**161**) effectively sulfonates β-CD **160** exclusively on the more reactive C-6 positions of the sugar residues, thereby strapping through only the A (first) and D (fourth) sugar residues to give **162**.



Scheme 38: Selective disulfonation of β-CD with a rigid bis-electrophile.[128]

Although there is extensive literature precedent on the selective functionalization of cyclodextrins, no methods are reported to directly modify α-CD in analogous manner to the β-CD derivative **162**.[130] This was surprising, since examination of the crystal structure of both α- and β-CD shows a similar distance between the A^6-D^6 oxygens, though this does not consider the conformational lability of these systems in solution. On this basis we prepared the bis sulfonyl chloride **161** and attempted functionalization using a procedure analogous to Kuroda (Scheme 39).[131] Treatment of the disodium salt of **164** with excess PCl_5 affords the rigid bis-sulfonylchloride **161**. However, treatment of α-CD

with **161** gives only mono-sulfonatated products, and none of the bis-functionalized product **165**.



164 161 163 165

Scheme 39: Attempted selective disulfonation of α-CD.

Interestingly, in 2001 Sinaÿ and coworkers[132] found that DIBAL in significant excess (120 eq) was able to selectively debenzylate perbenzyl α-CD. This provided a simple route to functionalize α-CD in a fashion potentially amenable to strapping it onto an appropriately functionalized porphyrin Using an α-CD bis-electrophile with a porphyrin bis-nucleophile (Figure 26) or tetra-nucleophile could afford the mono- or bis-strapped porphyrin, respectively.

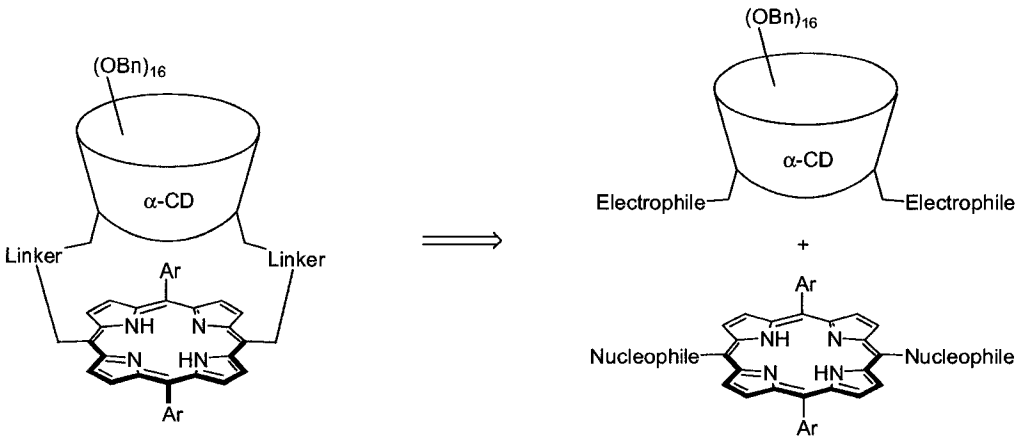
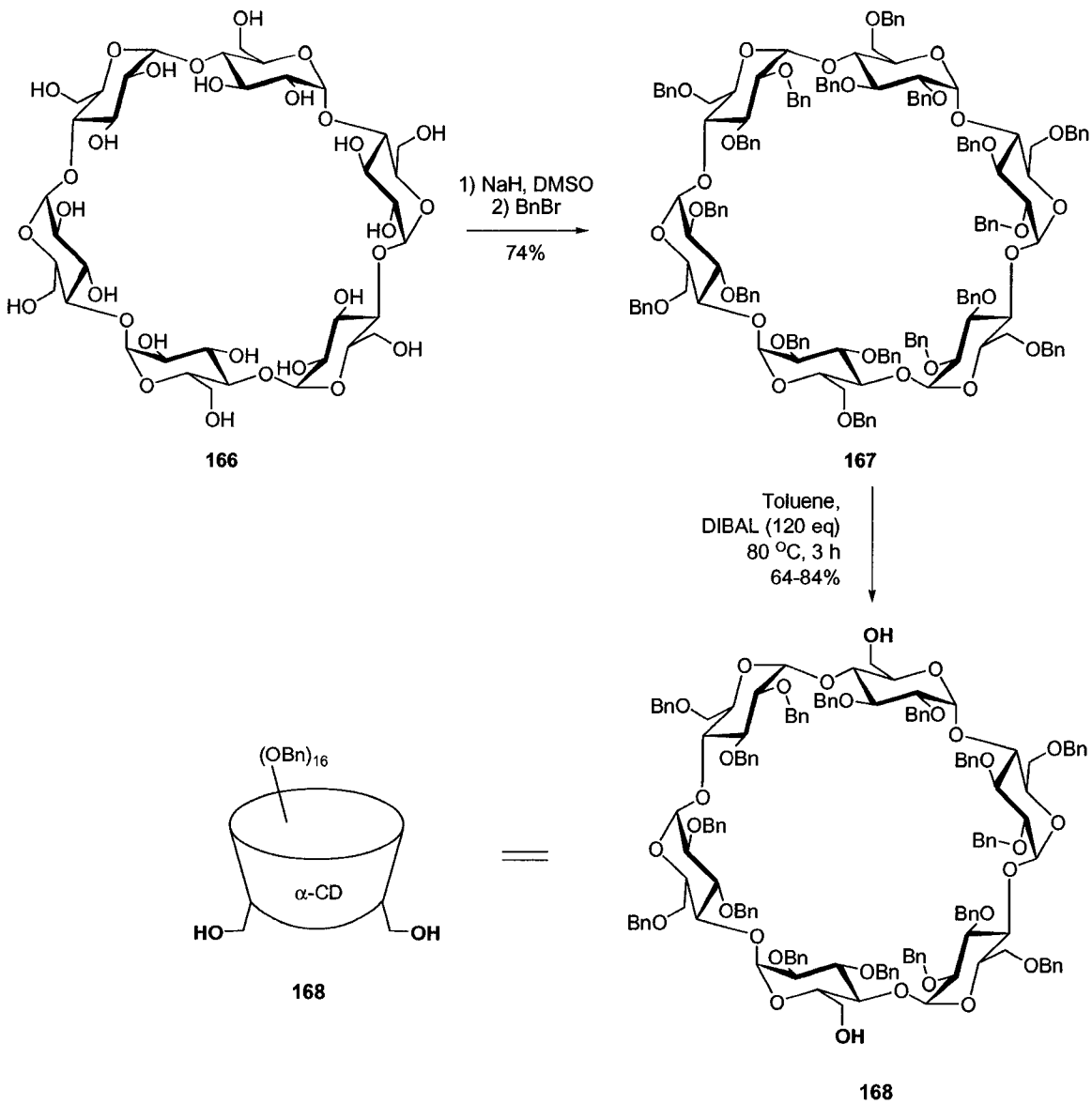


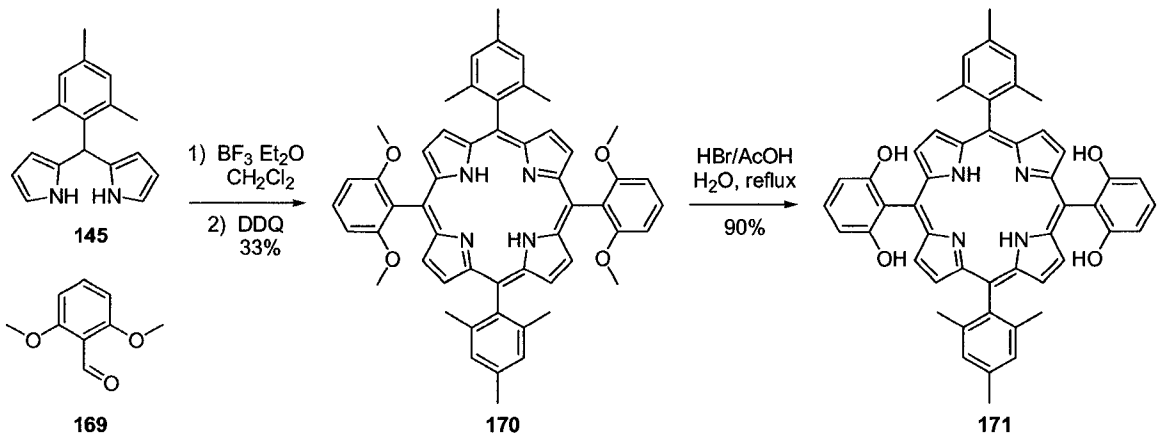
Figure 26: Synthetic approach to α-CD-strapped porphyrin.

α–CD is perbenzylated by deprotonation with sodium hydride, followed by alkylation with benzyl bromide to give **167**.[133] Using the procedure of Sinay,[132] treatment of perbenzyl α-CD with excess DIBAL gives predominantly the A^6,D^6 debenzylated product **168** in good yield.



Scheme 40: Preparation of A^6,D^6 diol derivative of α-CD.

The porphyrin **171** was first chosen for this strategy. It is synthesized by Lewis acid catalyzed condensation of 2,6-dimethoxybenzaldehyde with dipyrromethane **145**, followed by oxidation with DDQ. Demethylation of tetraether **170** with HBr generates the corresponding tetraphenol **171**.

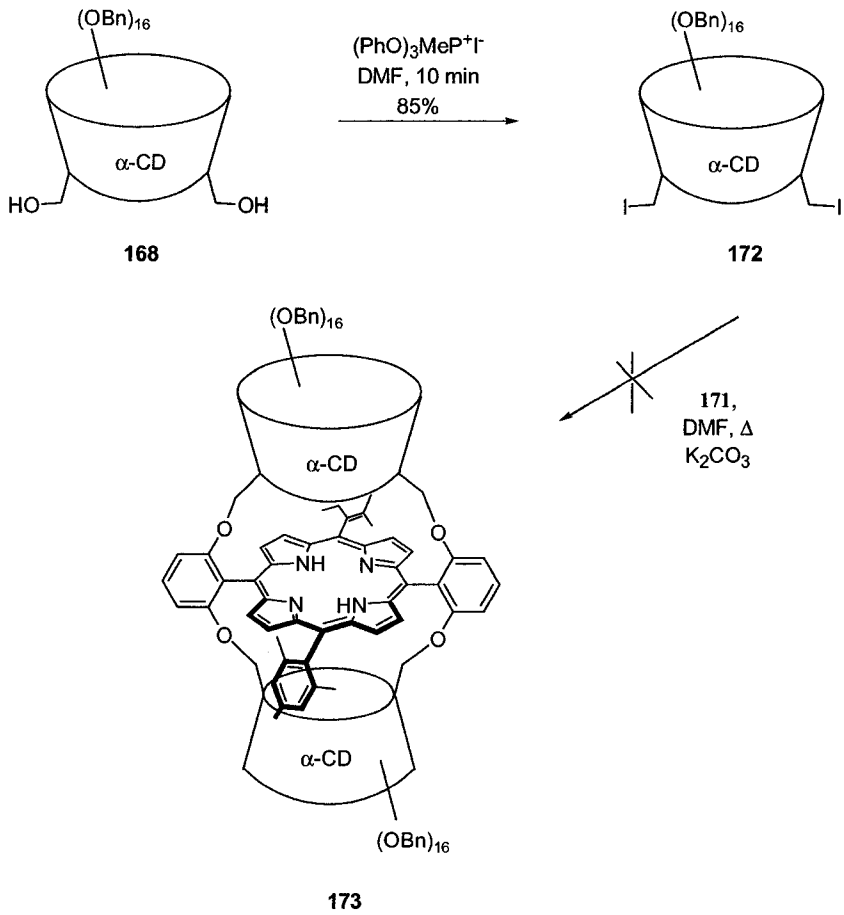


Scheme 41: Synthesis of tetraphenol 171.

To transform the α-CD derivative into the required dielectrophile, **168** was treated with methyltriphenoxyphosphonium iodide to give the diiodide **172**[132] (Scheme 42). Unfortunately, attempted coupling of diiodide **172** with porphyrin **171** at moderate temperatures (50 °C) gave no reaction. More forcing conditions led to the elimination of the elements of HI (based on electrospray mass spectrometry). This could be due to the steric hindrance created by the benzyl groups lining the bottom, smaller rim of the α-CD. To address this, the diiodide **172** was treated with Pd/C under an atmosphere of H_2 which results in very slow and incomplete hydrogenolysis of the benzyl groups. Under more forcing conditions (25 psi of H_2), hydrogenolysis of the C-I bond becomes a competitive side reaction, as might be anticipated.

To remedy this problem it seemed reasonable to exchange the iodides to leaving groups that would be stable to hydrogenolysis. Tosyl groups were chosen since it has been demonstrated that they can be converted to iodides by treatment with NaI in DMF.[128] Treatment of diol **168** with tosyl chloride in pyridine results in a surprisingly sluggish reaction even when an excess of tosyl chloride is used. When the reaction is run

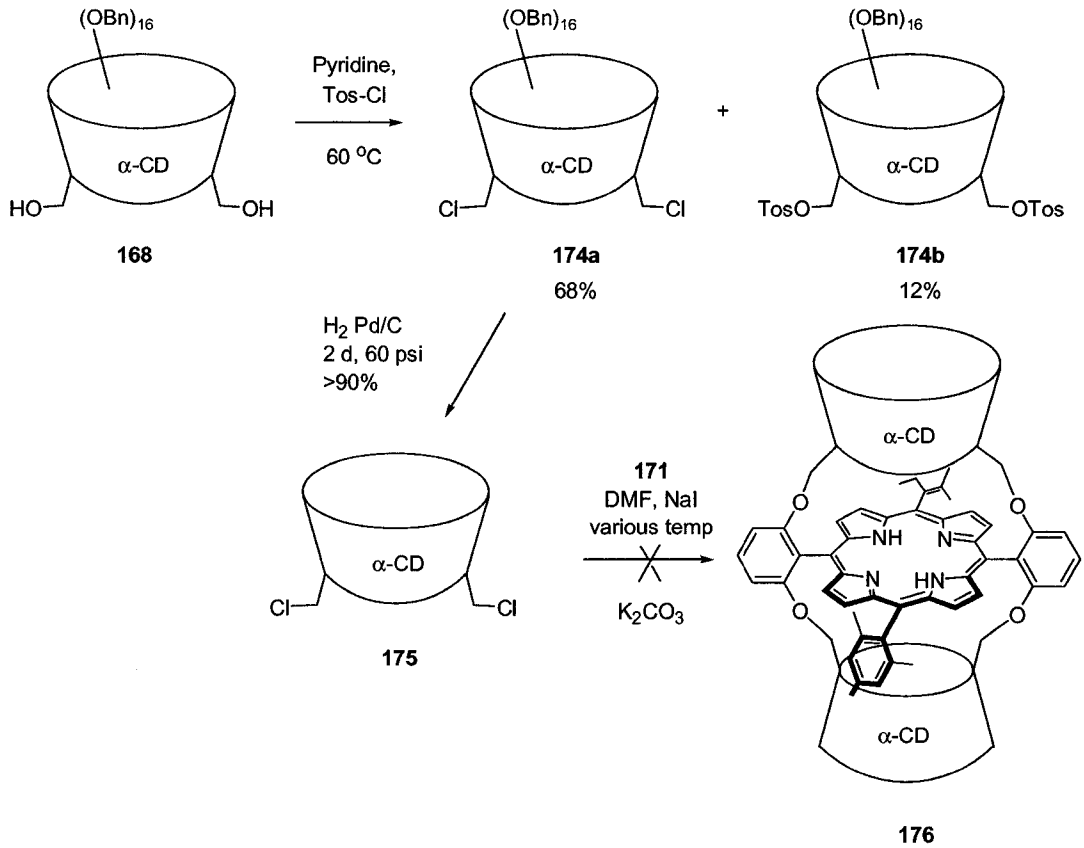
at elevated temperature, the ditosylate **174b** is a minor product and the dichloro **174a** is the major product (Scheme 43).



Scheme 42: Attempted reaction of α-CD diiodide 172 with porphyrin 171.

The sluggishness of tosylation and the facility of chloride displacement of the tosyl group may arise from steric interactions between groups on the smaller rim of the α-CD. This steric cooperation has been taken advantage of previously to selectively modify α-CD.[134] It seemed possible that the dichloro α-CD **174a** could be used for the hydrogenolysis reaction, which could be followed by Finkelstein conversion to the diiodide. Exhaustive hydrogenolysis of the dichloro derivative α-CD **174a** gives the desired product **175**. Unfortunately, presumably due to the low solubility of **175** in acetone and most other non

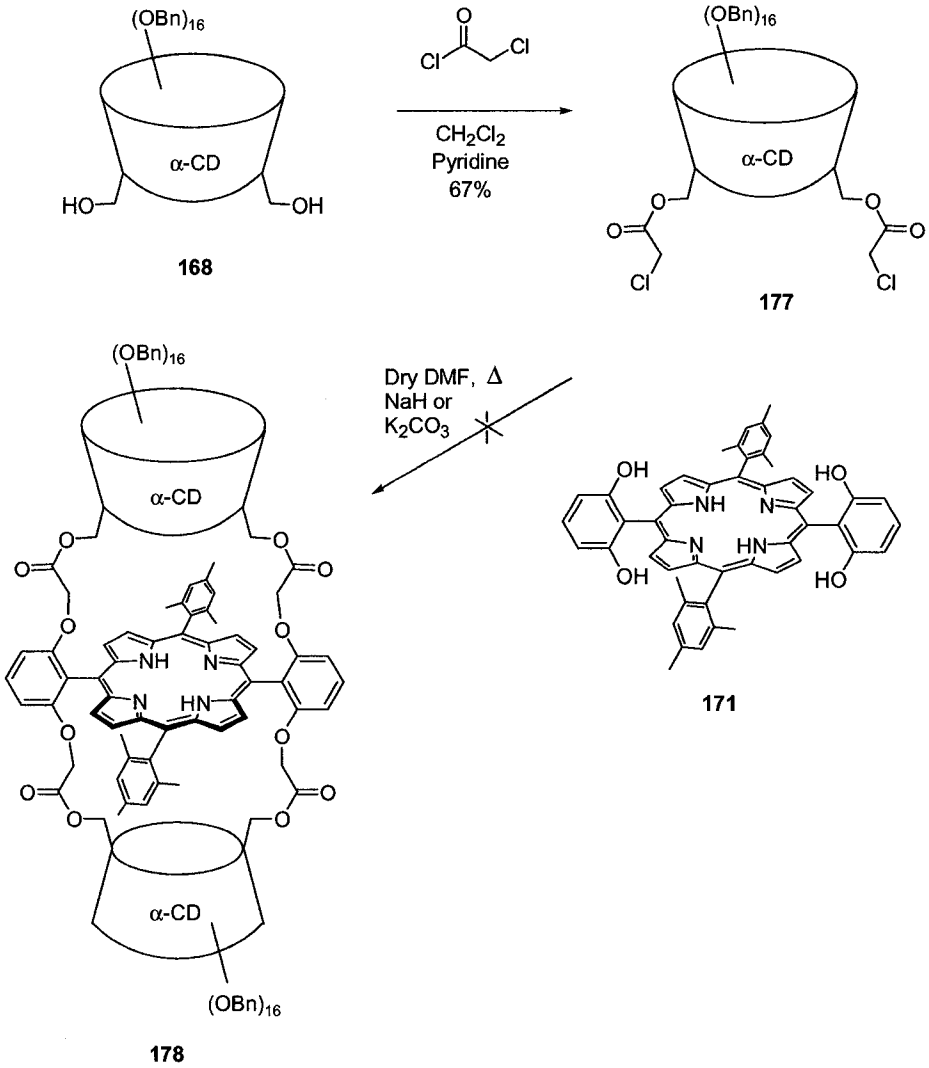
aqueous solvents, attempts at conversion to the diiodide are unsuccessful under standard Finkelstein conditions, such as reflux in methyl ethyl ketone/NaI, or acetone/NaI in a sealed tube at 130 °C. Treatment of the dichloro α-CD **175** with NaI in DMF with the tetraphenol porphyrin **171** to generate the iodide *in situ* does not afford detectable amounts of the desired coupled product **176**.



Scheme 43: Attempted synthesis of double-strapped porphyrin 176.

A different strategy to facilitate the desired coupling reaction between the porphyrin and α-CD dielectrophile is to enhance the reactivity of the electrophile and increase its tether length. Both objectives could be accomplished by derivatizing diol **168** as its bis-α-chloroester. Thus, reaction of α-CD diol **168** with excess chloroacetyl chloride gives the bischloro ester **177** (Scheme 44). However, attempts to couple **177** to the phenolic porphyrin **171** resulted in isolation of diol **168** and a complex mixture of

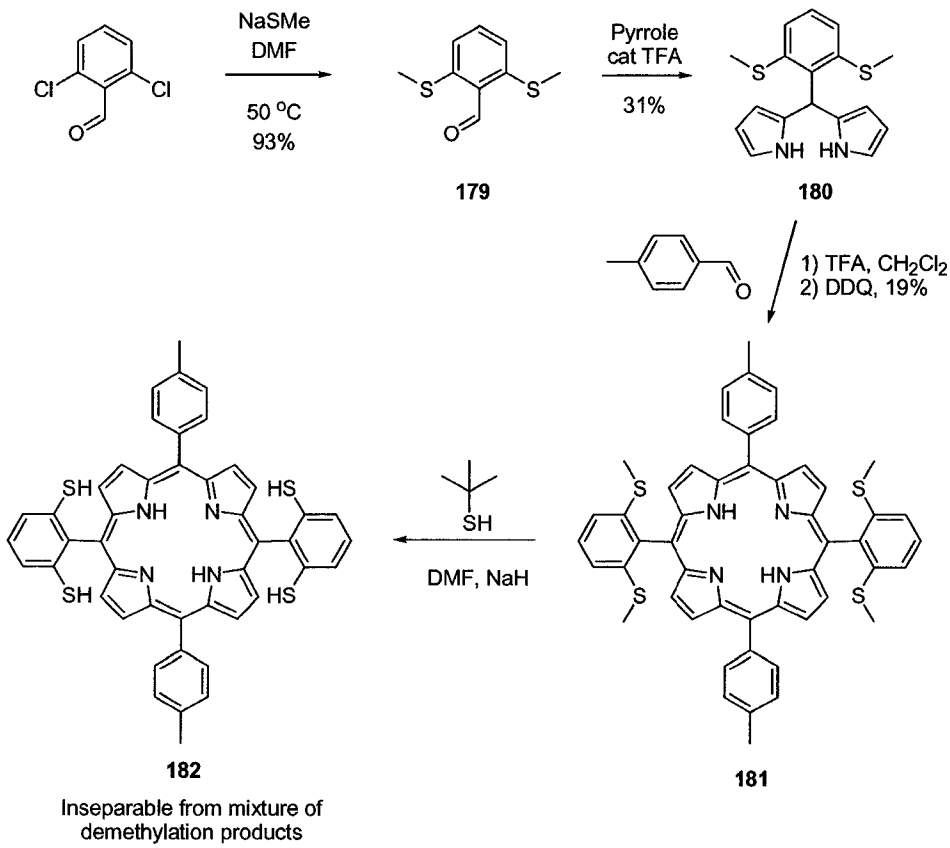
products with masses consistent with the porphyrin tetraphenol alkylated by chloroacetic acid molecules one, two, three, or four times (resulting in the addition of multiple -CH_2COOH groups as judged by mass spectrometry). This problem could not be avoided using strictly anhydrous conditions and sodium hydride as a base.



Scheme 44: Attempted preparation of capped porphyrin 178 with chloroacetyl α-CD derivative 177.

The sulfur analogue of **171** with tolyl groups replacing the bulky mesityl was targeted next to enhance the nucleophilicity of the porphyrinic groups necessary for

attack the electrophilic sites of the α-CD derivative (Scheme 45). Two equivalents of sodium thiomethoxide perform successive nucleophilic aromatic substitutions on 2,6-dichlorobenzaldehyde in DMF to afford the dithiomethoxy compound **179**. This method conveniently avoids the use of toxic HMPA, which is commonly used for S_NAr displacement reactions.[135]



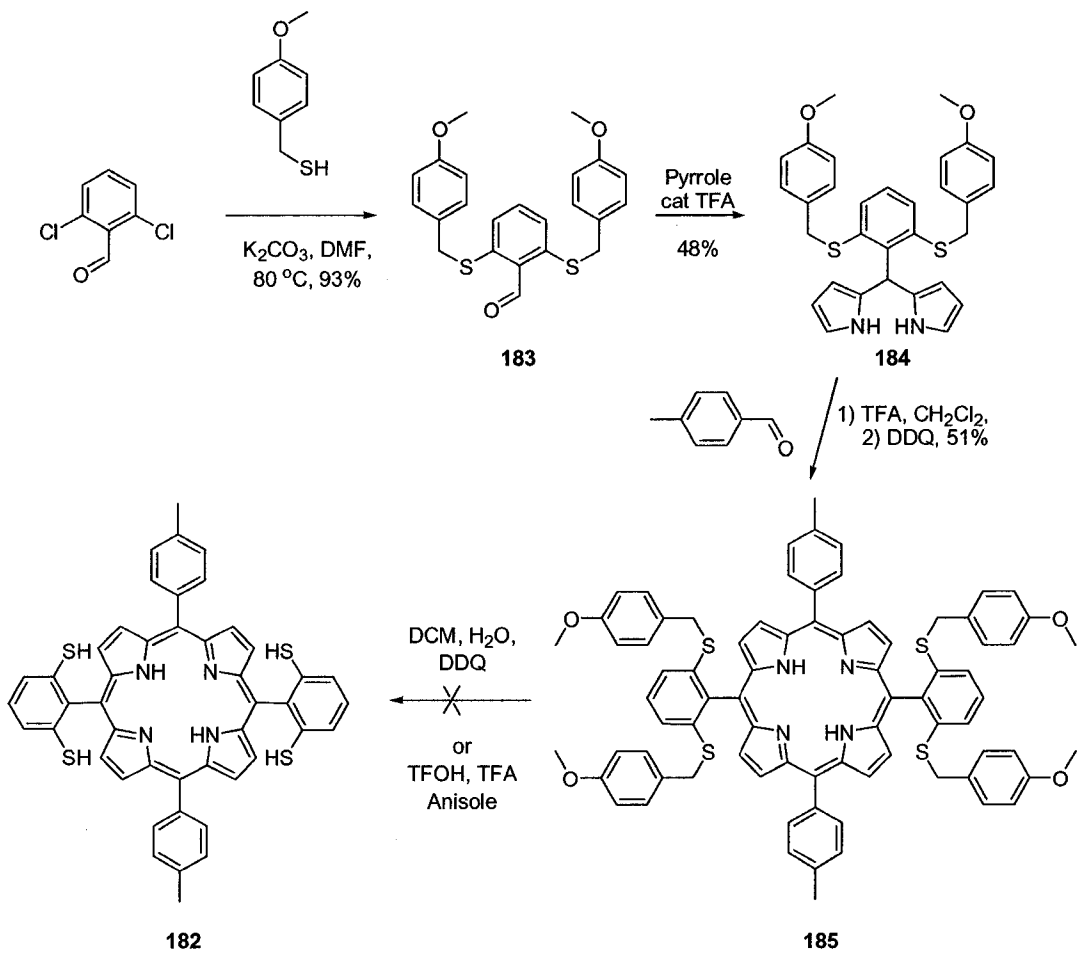
Scheme 45: Attempted synthetic route to tetrathiophenol porphyrin 182.

Treatment of the aldehyde **179** with pyrrole and catalytic TFA gives the corresponding dipyrromethane **180.** Using a recently reported procedure for the preparation of di-*ortho* substitued C-2 symmetric porphyrins,[136] porphyrin **181** could be isolated with no trace of scrambling product, a difficulty that has been observed in some cases with the tetra-

alkoxy analog.[91] It is worthy of note that this provides a very cost effective and synthetically facile route to C2 symmetric porphyrins functionalized at the *ortho* position.

Although demethylation using *tert*-butylthiolate proceeds successfully (confirmed by ES-MS), the reaction also gives significant amounts of disulfide formation despite rigorous exclusion of oxygen.[137] Attempted reduction of this disulfide with dithiothreitol (DTT) affords a complex mixture containing several unstable green pigments. Attempts at chromatographic separation of these pigments were unsuccessful.[138]

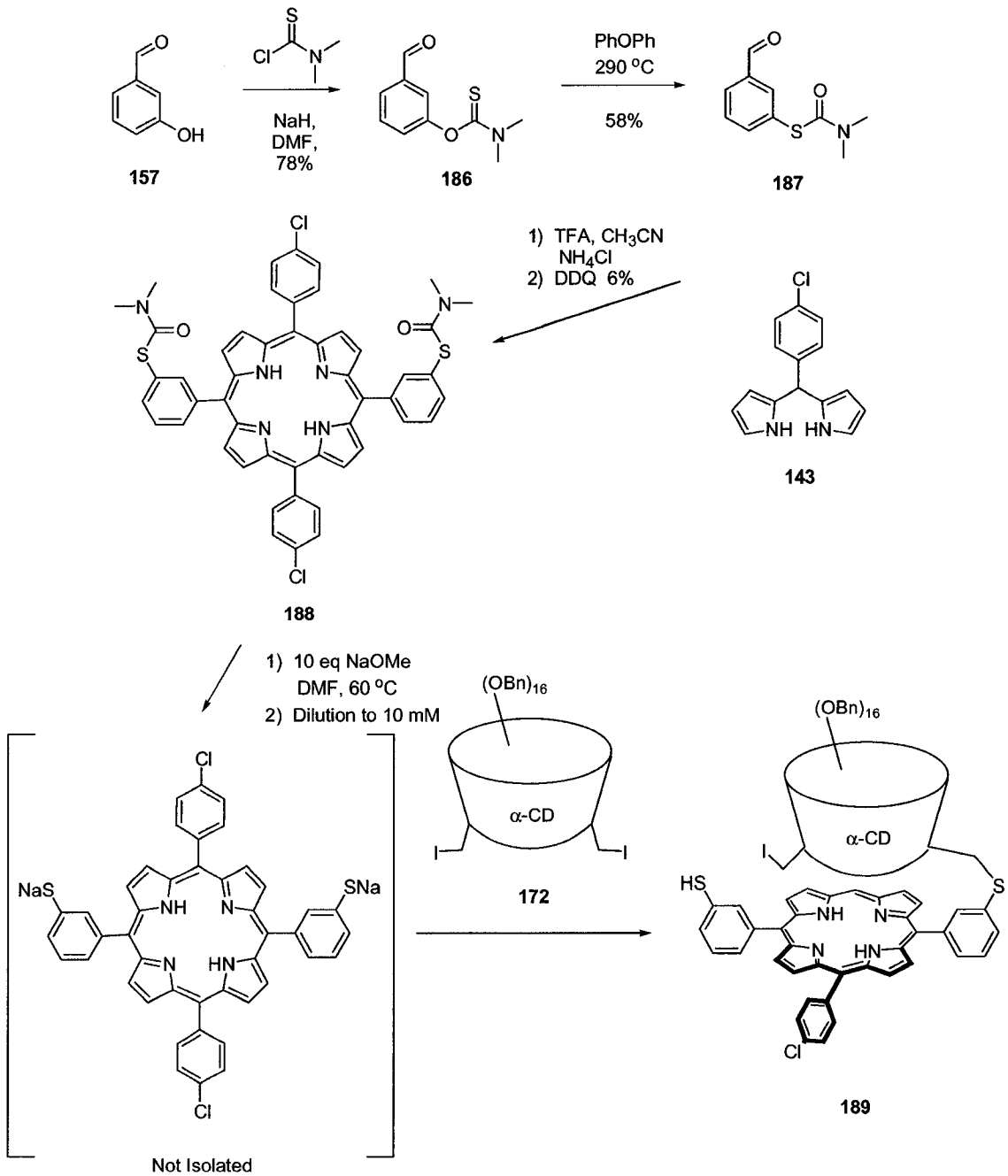
Since 5-(2,6-(bis-thioether)phenyl)dipyrromethanes are effective porphyrin precursors, a different protecting group strategy was employed relying on *p*-methoxybenzyl (PMB) groups that would be removable under strong acid conditions,[139] or under oxidizing conditions with DDQ.[140] In analogy to the previous synthesis, 4-methoxytoluene α-thiolate effects nucleophilic aromatic substitution on 2,6-dichlorobenzaldehyde to give aldehyde **183**, which upon treatment with pyrrole and TFA catalysis transforms to the dipyrromethane **184**. This dipyrromethane successfully condenses with tolualdehyde under acidic conditions, followed by oxidation with DDQ to give the desired porphyrin **185** in excellent yield. The selectivity here is impressive, with the porphyrinogen being oxidized preferentially over the PMB. Removal of the PMB groups, however, was less successful. Acid promoted debenzylation[139] gave a mixture of products resulting from partial deprotection and degradation. Oxidation of **185** with DDQ under standard conditions for deprotection of thiols[140] gives a complex mixture.



Scheme 46: Attempted preparation of tetrathioporphyrin 182 using PMB protection.

To facilitate the preparation of the strapped porphyrin, it was decided to explore functionalization of the molecule on one face only. Since the α-CD is a large macrocycle with a ring size of 30 atoms, and possesses a geometry that is sensitive to functionalization,[126] an attempt was made to try to install the thiol in the *meta* position of the aryl group of TPP. To this end, the synthesis outlined in Scheme 47 was performed. Sodium hydride deprotonates 3-hydroxybenzaldehyde, allowing it to react with *N,N*-dimethylthiocarbamoyl chloride to give the aldehyde **186**. This aldehyde undergoes O→S linkage isomerization under forcing conditions to generate aldehyde **187**. This

aldehyde then condenses with dipyrromethane **143** to give the porphyrin **188** using conditions developed to minimize scrambling of the porphyrinic aryl substituents.[136]

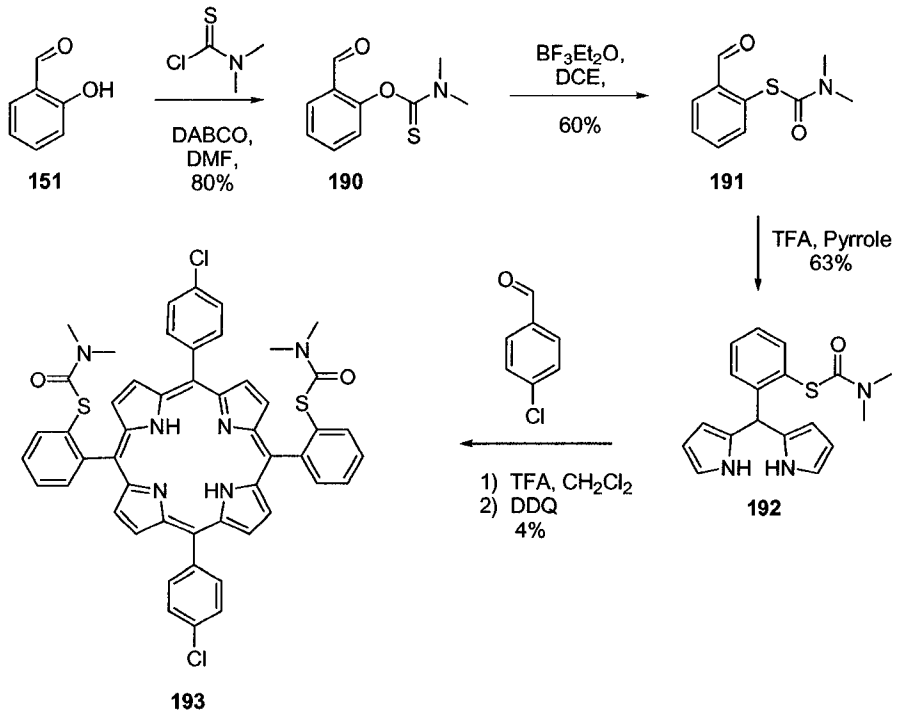


Scheme 47: Synthesis of dithiocarbamate porphyrin 188, attempted strapping with diiodo α-CD derivative 172.

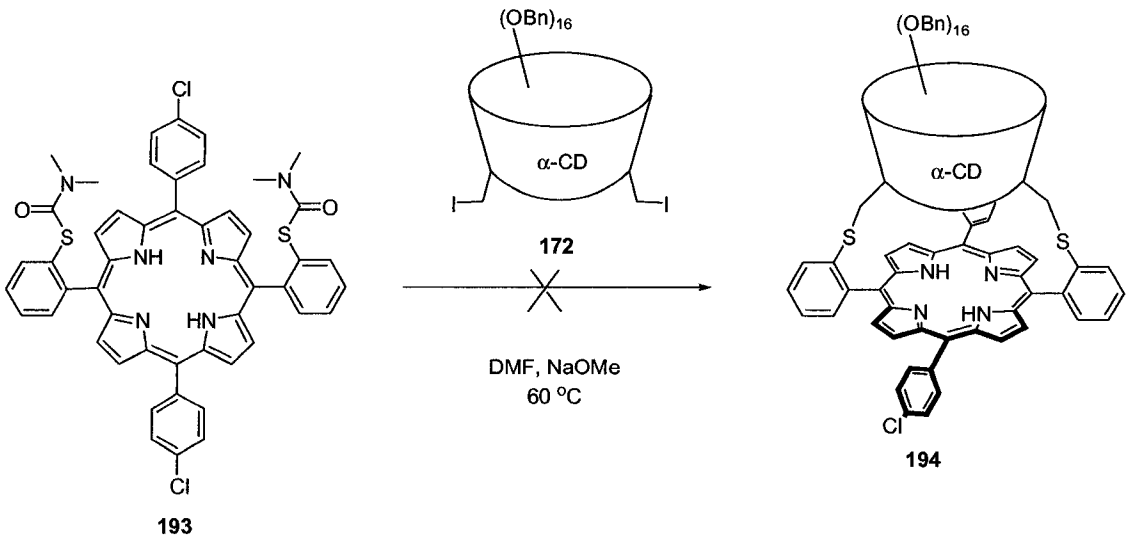
Deprotection of this thiol with NaOMe, and treatment of this thiocarbamate with diiodo α-CD **172** using *in situ* deprotection with NaOMe afforded only α-CD attached to the porphyrin at one position as judged by electrospray mass spectrometry.

The porphyrin analogue which possesses the thiol in the *ortho* position was prepared next in the hope that it would be a geometric match with the α-CD electrophile. It seemed like a reasonable retro-synthetic disconnection of this porphyrin to use a dipyrromethane possessing the thiocarbamate functionality installed in the *ortho* position of the phenyl substituent since these ortho substitutions have been shown minimize scrambling in porphyrin synthesis under standard conditions that give higher yields (CH_2Cl_2 as the solvent).[136]

A precursor to the known aldehyde **191**[141] was prepared by treatment of salicylaldehyde **151** with *N,N*-dimethylthiocarbamoyl chloride and DABCO to give **190** (Scheme 48). This was isomerized under Lewis acid conditions in dichloroethane (DCE) to give the aldehyde **191**. This aldehyde was converted to its dipyrromethane **192** by treatment with pyrrole and TFA. Reaction of the dipyrromethane **192** with *p*-chlorobenzaldehyde gave the expected porphyrin **193**, though in poor yield. *In situ* deprotection of the thiol with methoxide followed by treatment with the diiodo α-CD **172** unfortunately gave no strapped porphyrin **194**. A mixture of porphyrin disulfides was obtained upon purification.



Scheme 48 Synthesis of dithiocarbamate porphyrin 193.

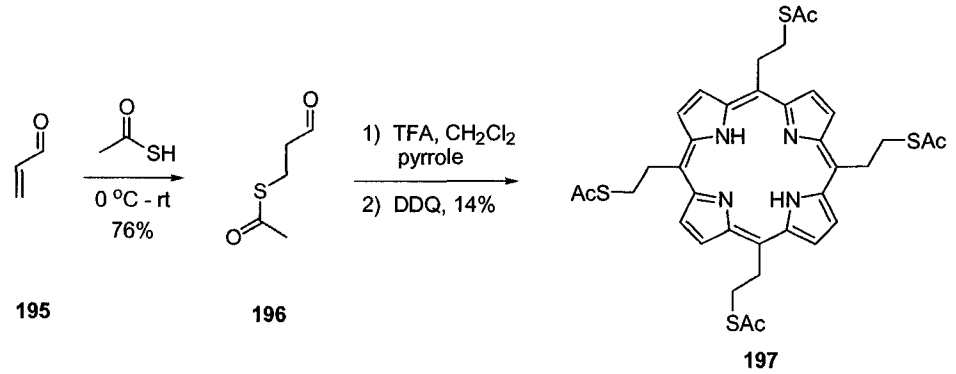


Scheme 49: Attempted strapping of deprotected 193 with α-CD derivative 172.

Since Kuroda reported success strapping the larger β-CD with a tetrathiophenyl porphyrin,[128] it seemed that perhaps a subtle geometric change or increased flexibility in the linker was needed to accommodate the smaller α-CD. A short synthetic route to the

porphyrin is also desirable so that moderate amounts of material could be obtained to scale up the capping step. It appeared that an alkyl linker *directly* off the porphyrin could deliver more accessible conformations to facilitate the nucleophilic attack on the α-CD bis-electrophile derivative (Scheme 50).

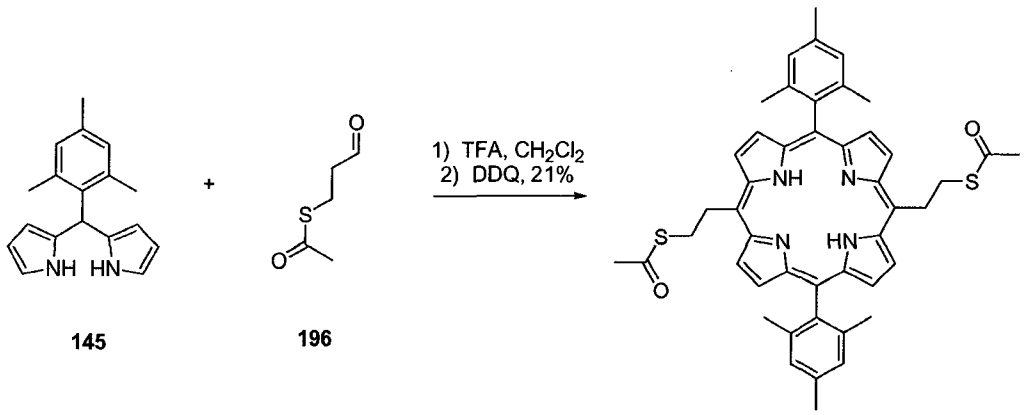
Treatment of acrolein with thioacetic acid gives facile access to aldehyde **196**.[142] Several routes to thioacetyl porphyrins were then explored. First the synthesis of a tetrasubstituted porphyrin was performed to give a 14% isolated yield of porphyrin **197**, which proved to be insoluble in all common organic solvents (actual yield is likely higher, but this material formed a precipitate during column chromatography). Unfortunately, this problem impeded deprotection and subsequent transformations.



Scheme 50: Preparation of porphyrin 197.

To improve solubility and to simplify the strapping step, a C2 symmetric porphyrin dithiol was targetted. Hence thioester aldehyde **196** was condensed with dipyrromethane **145** to give the porphyrin **198** (Scheme 51). *In situ* deprotection by sodium methoxide, and reaction with **172** (not shown) forms only the mono adduct within a complex mixture, as determined by ES-MS and TLC of the reaction mixture. Removal of the *ortho* methyl groups of the mesityl substituents may create less crowding around the nucleophilic thiols, thus faciliating the final macrocylization reaction. This analogue

could be prepared *via* a similar strategy to the one used for **198**, here using 5-(phenyl)dipyrromethane and aldehyde **196**. However, since the dipyrromethane would be unsubstituted in the *ortho* positions of the phenyl group (making it prone to scrambling),[136] the porphyrin condensation reaction would have to be performed using conditions that minmize scrambling[136] and also lower the yield. Alternatively, this porphyrin could be prepared by condensation of the dipyrromethane derived from aldehyde **196**, and benzaldehyde. Selection of the latter route was made based on a reported preparation of 5,15-dialkyl substituted porphyrins which condensed 5-alkyl dipyrromethanes with aldehydes under standard conditions with no scrambling.[143]

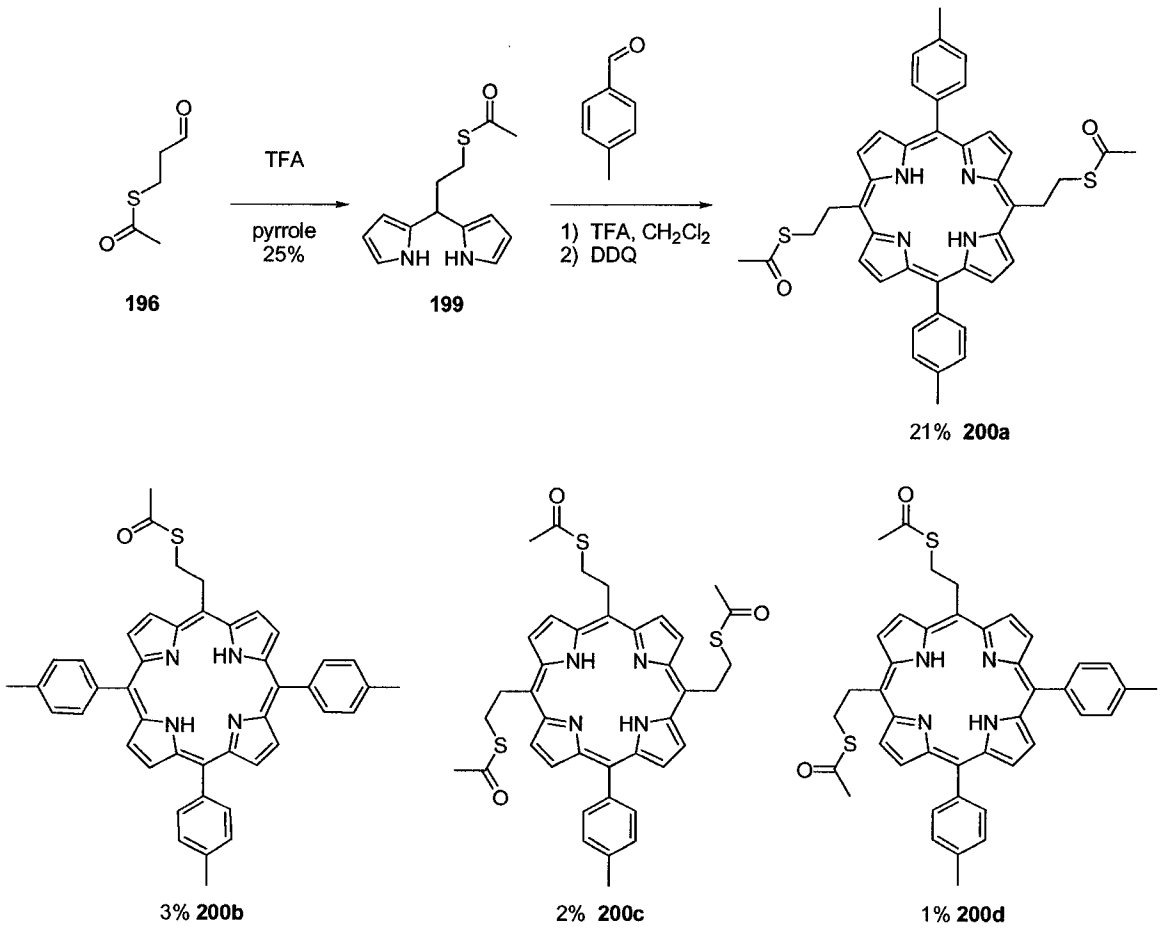


145 196 198

Scheme 51: Synthesis of porphyrin dithioacetate 198.

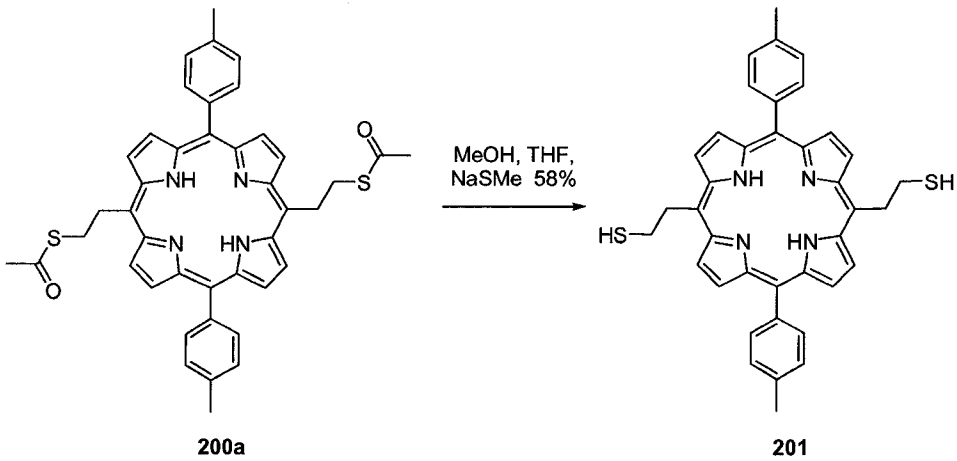
The porphyrin synthesis outlined in Scheme 52 was examined. TFA catalyzed condensation of pyrrole and aldehyde **196** gives dipyrromethane **199**. Disappointingly, condensation of the dipyrromethane **199** with *p*-tolualdehyde gave a mixture of scrambled products. Nevertheless, the desired product was successfully isolated with selective dissolution and careful flash chromatography to give the porphyrin **200a** as the major product in acceptable yield.

It seemed probable that the commonly used strategy of *in situ* deprotection by treatment of the thioester with excess methoxide would result in unwanted transesterification. This was of special concern after our previous difficulties with the phenolate chemistry described in Scheme 42. For this reason, and to minimize all potential variables in the final and key step, it seemed wise to isolate the deprotected thiol prior to coupling with bis-chloroester derivative **177**. Furthermore, in our experience and that of others,[144] chromatography of thiol containing porphyrins is complicated by disulfide formation. This is likely to be exacerbated in this system by the presence of multiple thiols on the molecule.



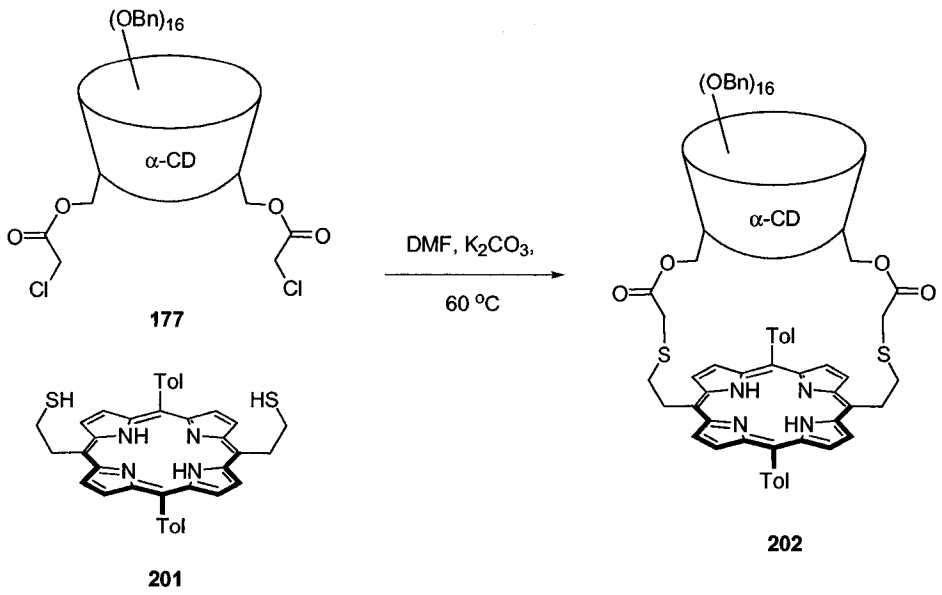
Scheme 52: Preparation of dithioporphyrin 200a and products from scrambling.

Using the modified general procedure of Wallace,[145] sodium thiomethoxide deacetylates the bis-thioester **200a** to give dithioporphyrin **201** in modest yield without the necessity for flash chromatography (Scheme 53). Reaction of **201** with **177** in DMF (Scheme 54) under basic conditions may generate the crown strapped porphyrin **202** (based on the observation of the correct mass at 3106 Da. in the electrospray mass spectrum). Preliminary attempts to optimize this reaction and isolate pure material for full characterization have been unsuccessful. It is noteworthy that Reinhoudt reported several capped porphyrins that were unstable until transformed to their zinc II chelate.[53]



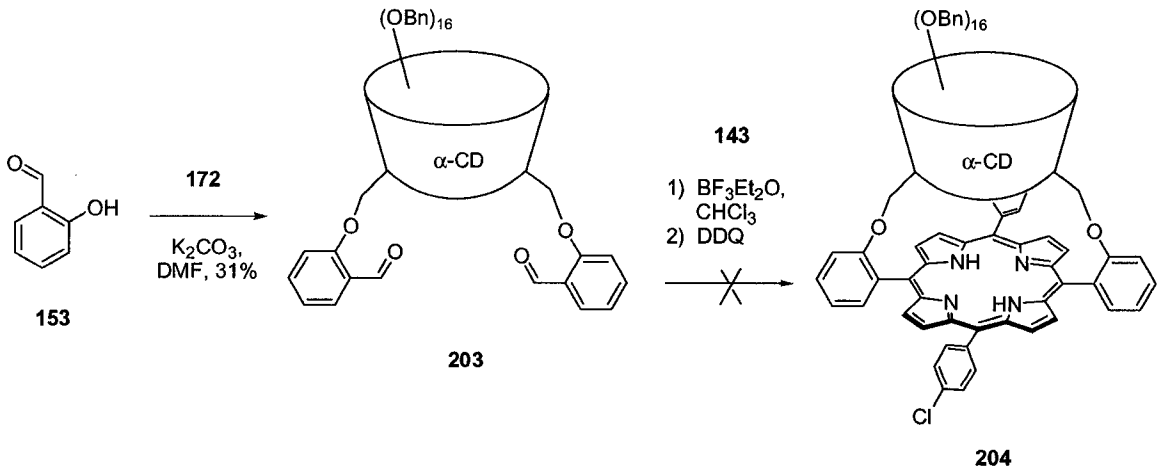
200a **201**

Scheme 53: Deprotection of the dithioacetyl porphyrin 200a.



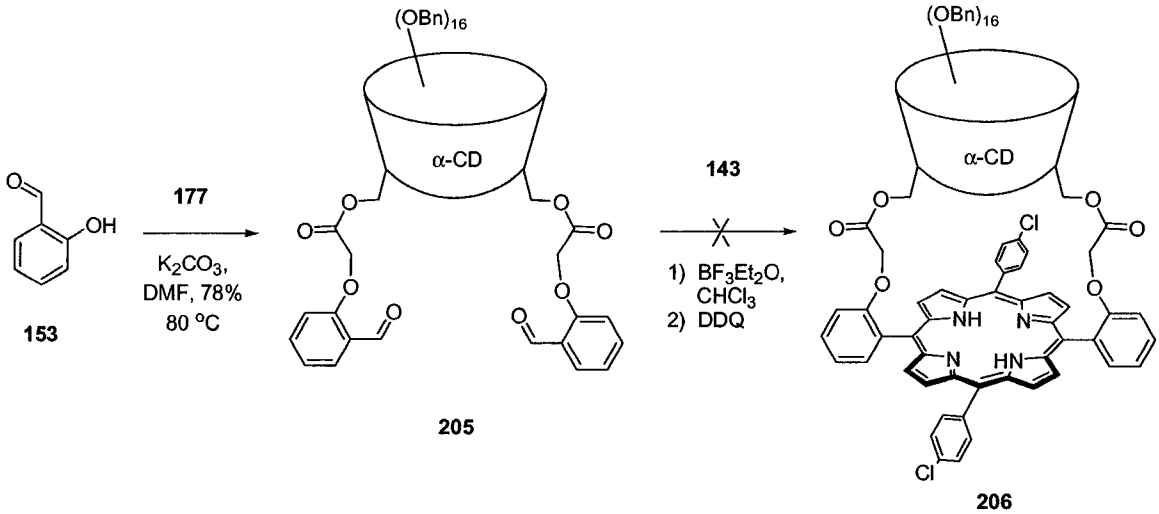
Scheme 54: Attempted strapping of the porphyrin 201 with α-CD 177.

Analogous to our work with the calixnaphthalene, strapping the porphyrin by condensing α-CD dialdehydes with dipyrromethanes was also attempted (Scheme 55). Diiodo α-CD **172** alkylates two equivalents of salicylaldehyde to afford the dialdehyde **203**. Unfortunately, **203** does not condense under standard conditions with dipyrromethane **143** to give **204**, but instead produces a complex mixture of products.



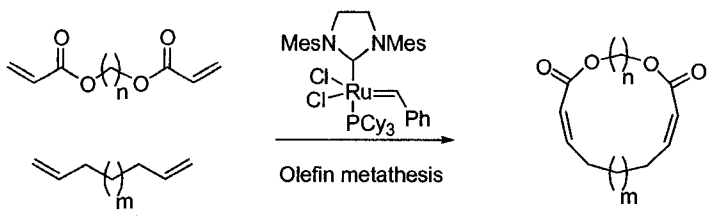
Scheme 55: Attempted preparation of capped porphyrin via α-CD dialdehyde 203.

The benzyl groups on the lower rim of the α-CD may crowd the aldehyde, and prevent formation of the porphyrinogen. To alleviate this, a three atom spacer was installed between the α-CD derivative and the aldehyde (Scheme 56). Dichloroester α-CD **177** alkylates salicylaldehyde under basic conditions to give the dialdehyde **205.** Unfortunately, this dialdehyde also does not condense with the dipyrromethane **143** to give porphyrin **206**.



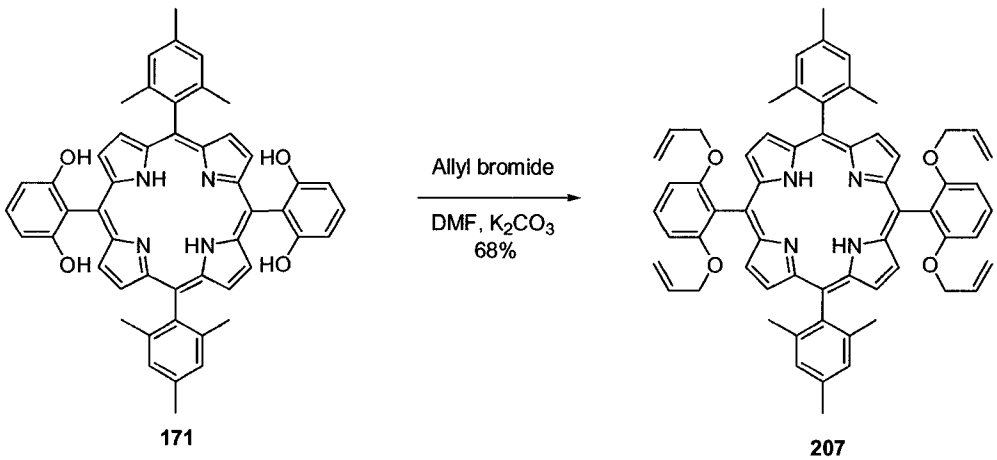
Scheme 56: Attempted synthesis of capped porphyrin via α-CD dialdehyde 205.

One of the most effective cyclization strategies for linking two bis-functionalized monomers is the olefin cross metathesis reaction reported by Grubbs and coworkers.[146] Since this type of chemistry has seen enormous success in macrocyclization reactions, it seemed that it might be a promising approach to completing the final step in connecting a functionalized porphyrin to an α-CD strap.



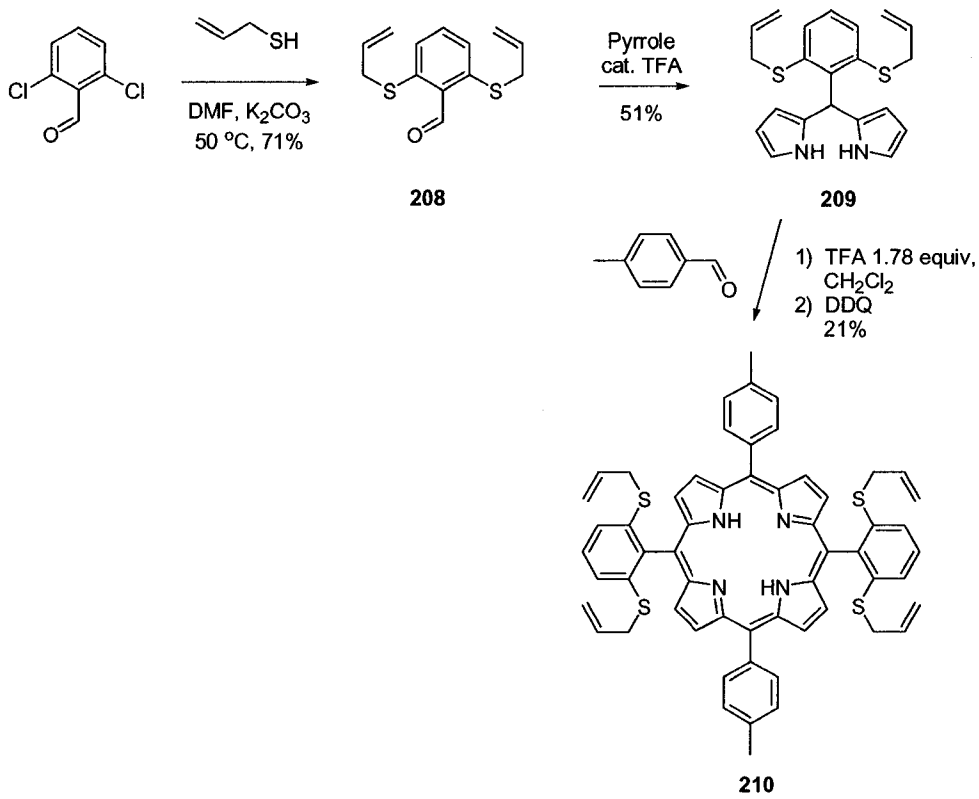
Scheme 57: Cross metathesis using Grubbs' catalyst.

The current approach entailed the functionalization of α-CD derivative **177** with acryloyl chloride so it could participate in cross-metathesis with a bis-olefin bearing porphyrin. Thus, two separate syntheses of the porphyrin coupling partner were conducted – the readily accessible ether **207** (Scheme 58) and its less sterically hindered sulfur analogue **210** (Scheme 59). Global alkylation of the tetraphenol porphyrin **171** with allyl bromide gives the tetraether **207** in good yield.



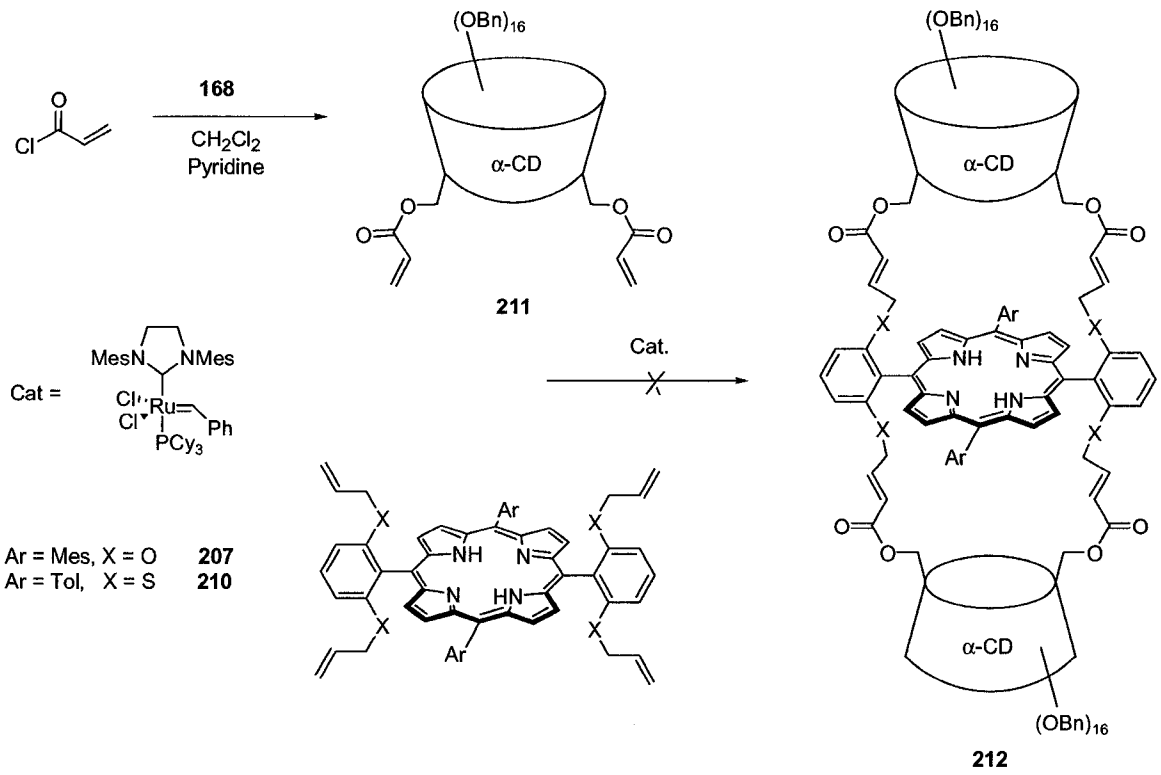
Scheme 58: Alkylation of tetrahydroxy porphyrin 171.

The tetrathioether porphyrin **210** was prepared in 4 steps (Scheme 59). Allyl thiolate effects displacement of the chlorides on 2,6-dichlorobenzaldehyde to give the bis-thioether **208**. Condensing this with pyrrole under standard conditions affords the dipyrromethane **209**. This reacts with *p*-tolualdehyde under Lindsey's scrambling free conditions[136] to afford porphyrin **210** in good yield.



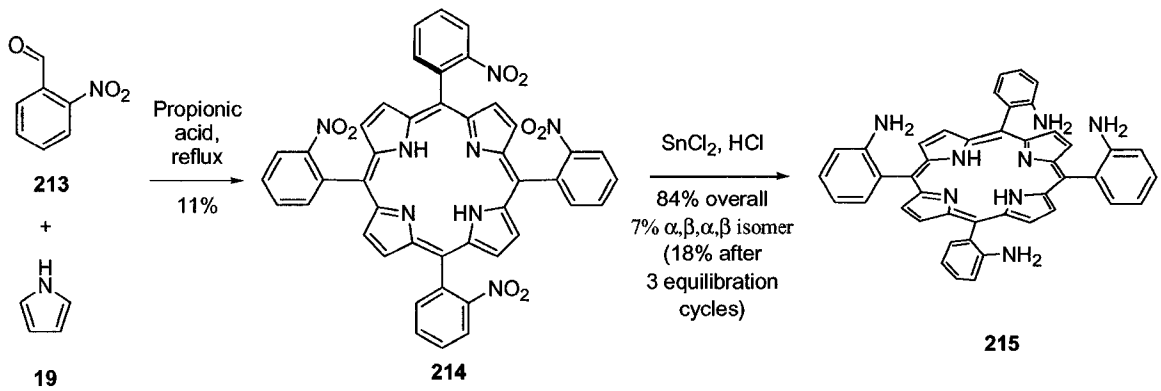
Scheme 59: Convenient synthesis of thioether porphyrin 210.

The bis-acrylate ester coupling partner was prepared as shown (Scheme 60). α-CD diol **168** was esterified by treatment with acryloyl chloride in CH_2Cl_2. Attempted coupling between the porphyrin **207** or **210** with the diacryloyl ester **211** gave insoluble degradation product and unreacted starting materials.



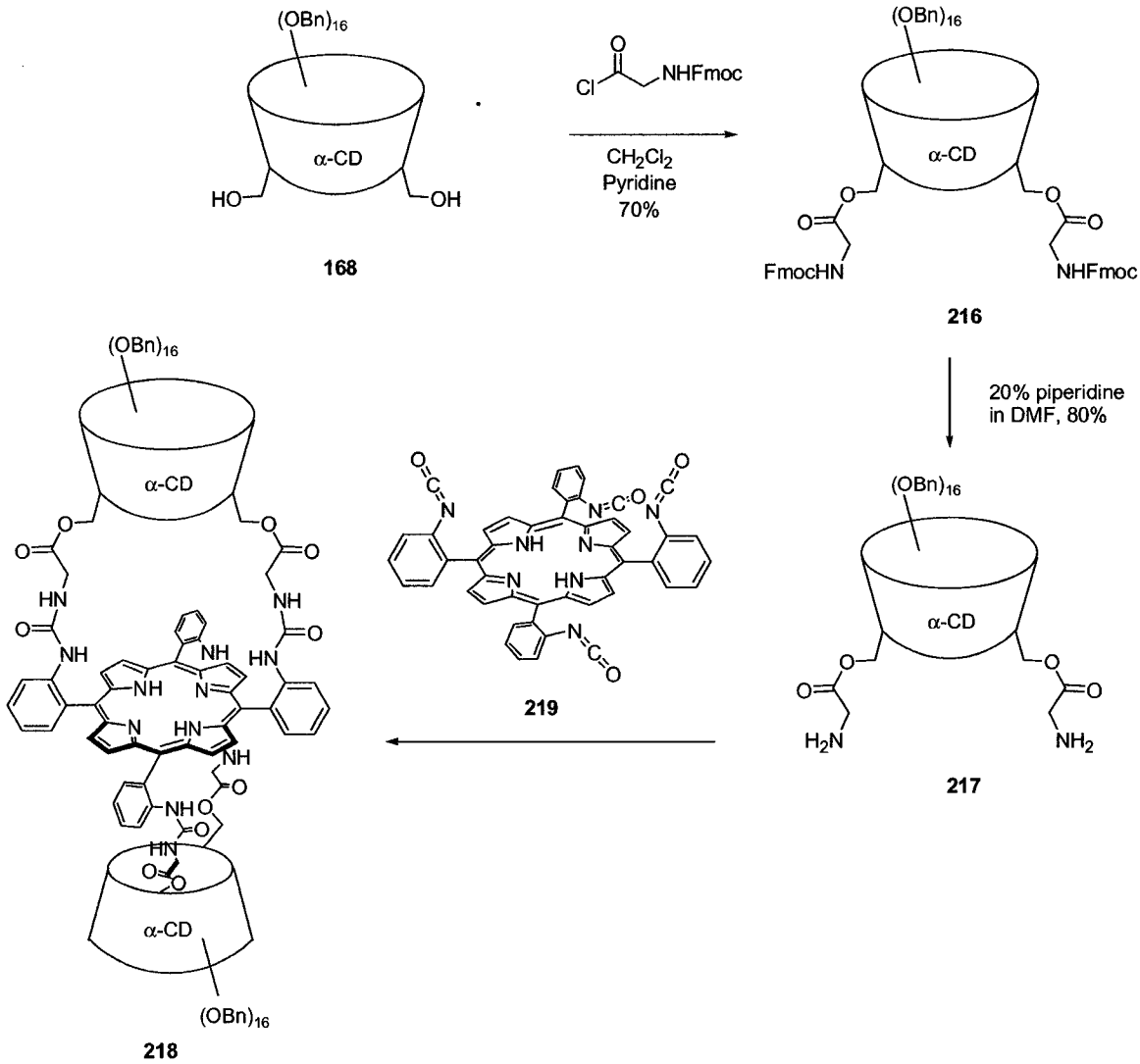
Scheme 60: Attempted strapping of porphyrin by cross metathesis.

An additional approach taken used the tetraamino porphyrin **215** reported by Collman.[79] This porphyrin is prepared under Adler-Longo conditions, condensing 2-nitrobenzaldehyde and pyrrole to afford a mixture of atropisomers of tetranitroporphyrin **214** (Scheme 61). This porphyrin is reduced by $SnCl_2$ to the tetraamino derivative as a mixture of atropisomers. Using flash chromatography, the α,β,α,β isomer **215** could be separated from the other atropisomers.[79] The low yield is due to the fact that this isomer is present as only 12.5% of the total in a statistical mixture. The mixture of undesired atropisomers could be re-equilibrated by heating to give a statistical distribution of isomers, from which additional α,β,α,β isomer **215** could be isolated.



Scheme 61: Preparation of α,β,α,β-tetraaminophenylporphyrin 215.[79]

It was intended to functionalize the α,β,α,β isomer of TAP as its isocyanate using a method recently reported by Collman.[147] The most efficient way of linking to the isocyanate is conversion of the α-CD to a diamine.[147] To this end, α-CD diol **168** is cleanly esterified by the Fmoc-glycine acid chloride (Scheme 62) to give the diester **216**. Treatment of **216** with 20% piperidine in DMF removes both Fmoc groups to afford diamine **217**. Reaction of porphyrin **215** with triphosgene gives the tetra-isocyanate **219**, followed by *in situ* addition of diamine α-CD **217** which gives a mixture of products including mono-strapped porphyrin (MW = 3286) (not shown) and di-strapped porphyrin (MW = 5834) **218** as verified by MALDI MS of different fractions obtained by flash chromatography and gel permeation chromatography. This approach is currently being optimized to obtain enough material for full characterization and for testing for selectivity as a catalyst.

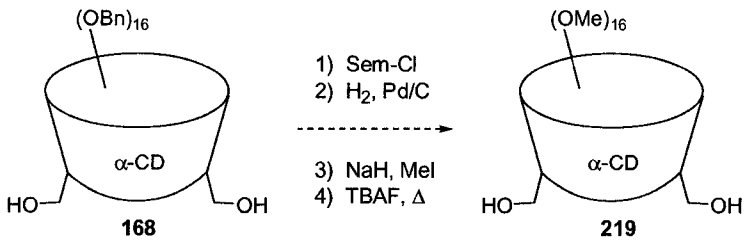


Scheme 62: Possible capping of porphyrin isocyanate with glycine α-CD derivative 217.

3.0 Summary and Future Work.

A foundation for the preparation of further shape-selective porphyrin catalysts has been developed. Based on the simplicity of preparation, its cavity size, and on its rigidity, the α-CD cap seems like the most promising. As suggested in the discussion, the synthesis of these caps requires optimization, and then testing for selectivity as catalysts. Both benzyl protected crowned porphyrins could be tested as organic soluble catalysts as is, or alternatively water soluble catalysts could be accessed by simple hydrogenolysis to give each α-CD with 16 OH groups. In addition to their probable activity as shape selective oxidation catalysts, both of the capped porphyrins **202** and **218** could also find application as shape-selective amine receptors.[148]

One possible elaboration of the described chemistry is the preparation of analogous capped porphyrins with alterations in the cap-porphyrin tether. While the longer tethers used in **202** and **218** seemed to be required for capping when using the bulky benzyl protection, leaving the α-CD's remaining C-6 hydroxyl groups protected with a less hindered group or leaving them unmodified would likely allow reduction in tether length. Both of these derivatives should be accessible using standard protection/deprotection strategy (Scheme 63).



Scheme 63: Plausible strategy for preparation of the methyl protected derivative 219.

Modification of the OH groups on the upper or larger rim (O-2, O-3) with bulky or chiral substituents could confer increased shape selectivity or stereoselectivity respectively. Again, derivatives of this type are likely accessible using known methodology for selective modification of α-CD.[149]

Additionally, the porphyrin templated capping approach merits further investigation. Several features for a successful approach can be gleaned from our work. These include i) incorporating maximum flexibility into the tether between porphyrin and cap segments, ii) incorporating solublizing functionalities into the final product, iii) using segments (including tether to the porphyrin) that are not diastereotopic. This last requirement is necessary to avoid forming non-productive attachment isomers (as was encountered in the intramolecular ROMP work).

During the course of this work, nucleophilic aromatic substitution reactions with 2,6-dichlorobenzaldehyde were explored as a convenient method for preparation of C-2 symmetric porphyrins bearing functionality in both ortho positions of the aryl group on the 5 and 15 positions of TPP.

4.0 Experimental

4.1 General Procedures

All reagents and solvents used were of ACS grade and were used without further purification unless otherwise mentioned. All processes involving air or moisture sensitive reactants and/or requiring anhydrous conditions were performed under a positive pressure of pre-purified argon using oven dried or flame dried glassware. Solvents for anhydrous reactions were dried according to Perrin *et al.*[150] Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled over sodium and benzophenone under an argon atmosphere prior to use. Toluene and benzene were distilled over sodium under argon atmosphere. Dichloromethane, acetonitrile, triethylamine, pyridine, and diisopropylethylamine were distilled over CaH_2 under an atmosphere of argon. Methanol was distilled over magnesium and iodine. Acetonitrile was HPLC grade. The removal of solvent *in vacuo* refers to evaporation under reduced pressure below 40 °C using a Büchi rotary evaporator followed by evacuation to a constant sample mass. Deionized water was obtained from a Milli-Q reagent water system (Millipore Co., Milford, MA). Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$, Na_2CO_3, HCl, and NaOH refer to saturated aqueous solutions.

All reactions and fractions from column chromatography were monitored by thin layer chromatography (TLC) using Merck glass-backed plates precoated with normal silica gel (Merck 60 F254) or reverse-phase gel (Merck RP-8 or RP-18 F254S) One or more of the following methods were used for visualization: UV fluorescence, iodine staining, phosphomolybdic acid/ceric sulfate/sulfuric acid/water (10 g:1.25 g:12 mL: 238 mL) spray for general hydrocarbons and sugars, and ninhydrin/n-BuOH/AcOH (0.32 g:

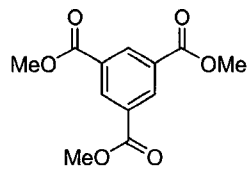
100 mL: 3 mL) spray for amino acids and amines. Flash chromatography was performed according to the Still procedure[151] using 230-400 mesh silica (Merck, silica gel). HPLC separations were performed on either a Rainin Dynamax instrument equipped with a variable wavelength model UV-1 detector, a solvent delivery system model SD-200, and a Rheodyne injector or the Beckman System Gold 125P instrument equipped with a Beckman Gold 166P variable wavelength detector and a Rheodyne injector. HPLC separations were monitored at a wavelength of 218 or 254 nm. The columns used was Waters Bondapak C_{18}. HPLC grade acetonitrile (190 nm cutoff) was obtained from Fischer (Fair Lawn, NJ). All HPLC solvents were filtered with a Millipore vacuum filtration system before use.

Melting points were determined on a Thomas Hoover oil immersion apparatus using open capillary tubes and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter with a microcell (10.00 cm, 0.9 mL) at ambient temperature and are reported in units of 10^{-1} deg cm^2 g^{-1}. All specific rotations were referenced against air and were measured at the sodium D line. Infrared spectra (IR) were recorded on a Nicolet Magna 750 FT-IR spectrometer as either a cast or microscope (μscope). Cast refers to the evaporation of a solution on a NaCl plate. Mass spectra (MS) were recorded on a Kratos AEIMS-50 high resolution mass spectrometer (HRMS), using electron impact ionization (EI), VG 7070E with chemical ionization [(CI), NH_3], Voyager Elite MALDI-TOF instrument, Applied Biosystems (sinapinic acid as the matrix) and Micromass ZabSpec Hybrid Sector-TOF using positive mode electrospray (ES). Microanalyses were obtained on Perkin Elmer 240 or Carlo Erba 1180 elemental analyzers and effected by the spectral services at the University of Alberta. Nuclear

magnetic resonance (NMR) spectra were obtained on a Bruker AM-300, Bruker AM-360, Inova Varian 300, 400, 500, and 600 MHz instruments. ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) using the residual solvent resonance as the reference: $CDCl_3$, δ 7.24; CD_3OD, δ 3.30; *N,N*-$(CD_3)_2CDO$, δ 2.74; $(CD_3)_2SO$, δ 2.49; $(CD_3)_2CO$, δ 2.02. The coupling constants reported are within an error range of 0.2-0.4 Hz. ^{13}C NMR shifts are reported relative to: $CDCl_3$, δ 77.0; CD_3OD, δ 49.0; $(CD_3)_2SO$, δ 39.5; *N,N*-$(CD_3)_2CDO$, δ 30.1; $(CD_3)_2CO$, δ 29.8. Porphyrin α-carbon signals are typically not reported because of signal broadening due to NH tautomerization.[152] Signals are reported within 0.1 ppm except where close peaks necessitate an additional significant figure.

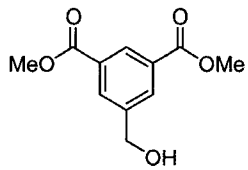
^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet, number of protons, coupling constants(s) in Hertz (Hz), and assignment. Where appropriate the multiplicity is followed by br indicating that the signal was broad. Unless stated otherwise, peptides were prepared using a double coupling procedure with standard Fmoc chemistry[153] on Wang resin,[154] with PyBOP[68] as the coupling reagent (Advanced ChemTech; SA5030) on a Rainin peptide synthesizer (Protein Technologies PS3).

4.2 Experimental Data for Compounds



Trimethyl benzene-1,3,5-tricarboxylate (16)[59]

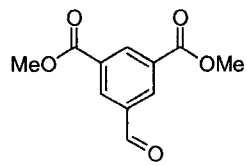
Conc. sulfuric acid (0.5 mL) was added to a solution of trimesic acid (1.10 g, 5.16 mmol) in dry methanol (50 mL). This mixture was heated at reflux for 1 day, after which the solvent was removed *in vacuo*. Fresh dry methanol (50 mL) and conc. sulfuric acid (1 mL) were added. The mixture was heated to reflux for an additional day. The mixture was then cooled to 0 °C. The resulting crystals were filtered, rinsed with sat'd $NaHCO_3$, then water, and then dried *in vacuo* to give the triester as a white powder (1.25 g, 94%): mp 143-144 °C (lit.[59] 144-145 °C), IR ($CHCl_3$, cast) 2955, 1731, 1431, 1261, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 9H, $C\underline{H}_3$), 8.83 (s, 3H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.5, 131.1, 134.5, 165.3; HRMS (EI) calcd for $C_9H_{12}O_6$ 252.0634, found 252.0633 [M^+] (41.9%).



5-Hydroxymethylisophthalic acid dimethyl ester (17)[60]

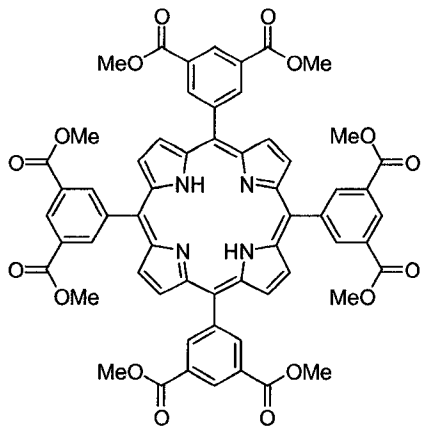
$LiBH_4$ (1.00 g, 20.0 mol) suspended in Et_2O (5 mL) was added dropwise to a stirred solution of benzene 1,3,5-tricarboxylic acid trimethyl ester (5.00 g, 20.0 mmol) in freshly distilled THF (100 mL) stirred under argon (mixture turns orange). The addition was ceased when a major spot (R_f = 0.2, Hex/EtOAc, 4:1) appeared on TLC below the triester. The reaction was quenched by the careful addition of excess solid $Na_2SO_4 \cdot 10$

H_2O. The mixture was stirred an additional 30 min, filtered, concentrated *in vacuo*, and purified by flash chromatography (Hex/EtOAc, 4:1) to give the title compound as a white solid (1.30 g, 30%): mp 100-102 °C (lit.[60] 104 °C), IR (μscope) 3510, 2955, 1702, 1605, 1438, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 6H, C<u>H</u>$_3$), 4.81 (s, 2H, C<u>H</u>$_2$OH), 8.25 (d, 2H, J = 1.5 Hz Ar<u>H</u>), 8.62 (t, 1H, J = 1.5 Hz, Ar<u>H</u>); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.2, 64.2, 129.8, 130.8, 132.0, 141.9, 166.2; HRMS (EI) calcd for $C_{11}H_{12}O_5$ 224.0685, found 224.0684 [M^+] (57.1%).



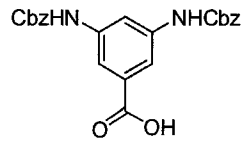
5-Formyl-isophthalic acid dimethyl ester (18)[62]

PDC (1.88 g, 5.00 mmol) was added to a stirred solution of **17** (1.00 g, 4.46 mmol) in CH_2Cl_2. The mixture was stirred overnight, then concentrated *in vacuo*. The residue was triturated with Et_2O, filtered through a pad of silica, and purified by flash chromatography eluting with Hex/EtOAc (6/1) to give a white solid (0.77 g, 78%): mp 96-96.5 °C, (lit.[62] 86-88 °C); IR (μscope) 3072, 2957, 2849, 1730, 1703, 1260, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.98 (s, 6H, C<u>H</u>$_3$), 8.71 (d, 2H, J = 1.6 Hz, Ar<u>H</u>), 8.91 (t, 1H, J = 1.8 Hz, Ar<u>H</u>), 10.12 (s, 1H, C<u>H</u>O); ^{13}C NMR ($CDCl_3$, 75 MHz) 52.7, 131.9, 134.3, 135.7, 190.3; HRMS (EI) calcd for $C_{11}H_{10}O_5$ 222.0528, found 222.0532 [M^+] (62.9%); Anal. calcd $C_{11}H_{10}O_5$ C, 59.46; H, 4.05 found C, 59.24; H, 4.30.



5,10,15,20-Tetrakis(3,5-dicarboxyphenyl)porphyrin octamethyl ester (20)

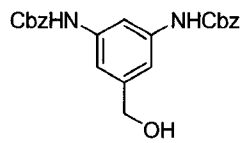
A solution of aldehyde **18** (222 mg, 1.00 mmol) and pyrrole (67 mg, 1.0 mmol) in propionic acid was heated to reflux (open to the atmosphere) for 2 h, cooled, and concentrated *in vacuo*. The resulting tarry residue was triturated with cold MeOH, filtered, and the solid purified by flash chromatography (toluene→acetone/toluene, 1:3) to give a purple crystalline product (7 mg, 3%). This material was contaminated with ca. 9% of a co-running impurity (possibly the corrole, relative amounts are based on ^{1}H NMR). IR (CH_2Cl_2, cast) 3320, 2922, 1739, 1583, 1468, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ -2.82 (s, 2H, NH), 3.93 (s, 24H, CH_3), 8.78 (s, 8H, H_β), 9.03 (s, 8H, ArH), 9.16 (s, 4H, ArH); MS (ES) 1079.3 [MH$^+$]. λ_{abs} 418, 513, 592, 645 nm.



3,5-Bis(*N*-(benzyloxycarbonyl)amino)benzoic acid (22)[65]

Benzyl chloroformate (5.5 mL, 39 mmol) was added dropwise to a solution of diaminobenzoic acid (2.6 g, 17 mmol) in pyridine (22 mL), DMAP (400 mg, 3.30 mmol) and DMF (10 mL) at 0 °C and allowed to warm to rt overnight. Additional benzyl chloroformate was added (2.5 mL) and the mixture stirred 2 h. The reaction was

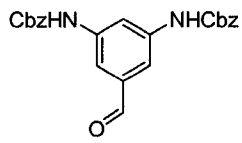
quenched with 1.0 M HCl (200 mL) and extracted with EtOAc (200 mL). The organic layer was washed with 1.0 M HCl (4 x 100 mL) until the washings were acidic (pH ≈ 2), water (2 x 30 mL) and dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2/EtOAc, 1/1, 1% AcOH) gave the product as a solid: (2.90 g, 40%) mp 217-218 °C, IR (CH_2Cl_2, cast) 3292, 1743, 1694, 1534, 1417, 1261 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ 5.15 (s, 4H, C<u>H</u>$_2$), 7.30-7.45 (m, 10H, Ar<u>H</u>), 7.34 (d, 2H, J = 2.0 Hz, Ar<u>H</u>), 7.94 (t, 1H, J = 2.0 Hz, Ar<u>H</u>), 9.93 (s, 2H, N<u>H</u>), 12.83 (s br, 2H, CO_2<u>H</u>); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 67.3, 112.0, 113.5, 115.0, 129.1, 129.5, 133.1, 138.1, 141.1, 154.8, 168.2; HRMS (EI) calcd for $C_{23}H_{20}O_6N_2$ 420.1321, found 420.1339 [M^+] (0.60%); Anal. $C_{23}H_{20}O_6N_2$ calcd C, 65.71; H, 4.79, N, 6.66 found C, 65.79; H, 4.75; N, 6.64.



3,5-Bis(*N*-(benzyloxycarbonyl)amino)benzyl alcohol (23)[65]

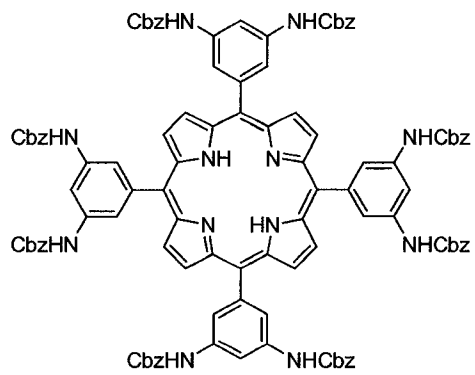
BH_3•Me_2S (1.0 mL, 10.0 M in THF, 10 mmol) was added to a solution of acid **22** (1.63 g, 3.90 mmol) in THF at 0 °C. The solution was stirred for 6 h, then quenched by the addition of 1 M HCl (2 mL). The mixture was diluted with $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 30 mL). The organic layer was washed with water (2 x 30 mL), brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography gave the alcohol as a solid (900 mg, 57%): R_f = 0.7 (CH_2Cl_2/EtOAc, 1/1), mp 138-141 °C, IR (μscope) 3458, 3308, 3124, 1693, 1605, 1479, 1414, 1234, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s br, 1H, O<u>H</u>), 4.58 (s, 2H, C<u>H</u>$_2$OH), 5.16 (s, 4H, PhC<u>H</u>$_2$), 6.79 (s, 2H, N<u>H</u>), 7.08 (s, 2H, Ar<u>H</u>), 7.28-7.40 (m, 10H, Ph<u>H</u>), 7.42 (s, 1H,

ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.5, 71.1, 112.7, 116.5, 133.4, 133.8, 142.3, 144.8, 149.1, 158.8, one overlapping carbon; HRMS (ES) calcd for $C_{23}H_{22}O_5N_2Na$ 429.1426, found 429.1427 [MNa^+].



3,5-Bis(*N*-(benzyloxycarbonyl)amino)benzaldehyde (24)[65]

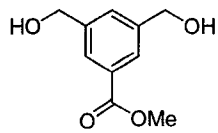
PDC (658 mg, 1.75 mmol) was added to a solution of alcohol **23** (570 mg, 1.25 mmol) in CH_2Cl_2 (20 mL). The solution was stirred 3 h, then filtered over Celite (eluting with Et_2O/CH_2Cl_2, 2/1). The brown filtrate was concentrated, and then purified by flash chromatography (CH_2Cl_2/EtOAc, 5/1) gave a white solid (440 mg, 88%): mp 144-145 °C, IR ($CHCl_3$, cast) 3350-3270, 3091, 1701, 1607, 1550, 1455, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.19 (s, 4H, CH$_2$), 6.86 (s, 2H, NH), 7.35 (m, 10H, ArH), 7.59 (d, 2H, J = 2.1 Hz, ArH), 7.87 (t, 1H, J = 2.1 Hz, ArH), 9.89 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.4, 113.7, 114.2, 128.4, 128.6, 128.7, 135.7, 137.9, 139.6, 153.2, 191.6; HRMS (EI) calcd for $C_{23}H_{20}O_5N_2$ 404.1372, found 404.1382 [M^+] (12.6%).



5,10,15,20-Tetrakis(3,5-bis(*N*-(benzyloxycarbonyl)amino)phenyl)porphyrin (25)

BF_3•Et_2O (42 μL, 0.33 mmol) was added to a stirred solution of aldehyde **24** (404 mg, 1.00 mmol) and pyrrole (67 mg, 1.0 mmol) in argon purged $CHCl_3$. After 1 h, TCQ (187

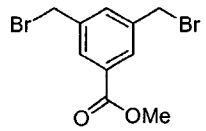
mg, 0.75 mmol) was added, and the solution heated to reflux for 1 h. The solution was cooled, concentrated *in vacuo*, and purified by gradient flash chromatography ($CHCl_3 \rightarrow CHCl_3$/MeOH) to give a purple crystalline solid (50 mg, 11%) which was only moderately soluble in most organic solvents. IR (μscope) 3304, 3031, 1703, 1607, 1548, 1429, 1234, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ –3.04 (s, 2H, NH), 5.17 (s, 16H, C$\underline{H}_2$Ph), 7.10-7.45 (m, 40H, Ph$\underline{H}$), 7.95 (s, 8H, ArH), 8.28 (s, 4H, ArH), 8.89 (s, 8H, H_β), 10.12 (s, 8H, N$\underline{H}$Cbz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.0, 123.4, 126.1, 126.2, 126.3, 126.5, 127.0, 134.7, 135.5, 136.2, 139.6, 151.7; MS (ES) 1808.6 [MH^+];



Methyl 3,5-bis(hydroxymethyl)benzoate (26)[155]

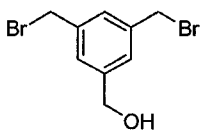
$LiBH_4$ (1.00 g, 20.0 mmol) suspended in THF (5 mL) was added dropwise to a solution of benzene 1,3,5-tricarboxylic acid trimethylester (5.00 g, 20.0 mmol) in freshly distilled THF (100 mL) stirred under argon (mixture turns orange). The addition was ceased when a major spot (R_f = 0.2 in Hex/EtOAc, 1:1) appeared on TLC below the mono-reduction product **17** (complex mixture evident). The reaction was quenched by the careful addition of NH_4Cl. The mixture was stirred an additional 30 min, filtered, concentrated, and purified by flash chromatography (Hex/EtOAc) to give the title compound as a white solid (1.25 g, 31%): mp 103-105 °C, (lit.[155] 105 °C), IR (μscope) 3282, 3025, 2953, 1724, 1606, 1486, 1455, 1433, 1397, 1323, 1305, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.00 (s, 2H, OH), 3.89 (s, 4H, C$\underline{H}_2$OH), 4.71 (s, 3H, CH_3), 7.56 (s, 1H, Ar$\underline{H}$), 7.79 (s, 2H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) 52.2, 64.7, 127.1, 129.7,

130.7, 141.6, 166.8; HRMS (EI) calcd for $C_{10}H_{12}O_4$, 196.0737, found 196.0737 [M^+] (36.8%); Anal. calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; found C, 61.05; H, 6.17.



3,5-Bis(bromomethyl)benzoic acid methyl ester (27)

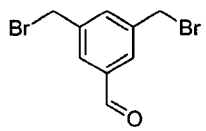
This known compound[156] was prepared by a different route. PBr_3 (3.85 g, 1.40 mmol) was added to a solution of diol **26** (980 mg, 0.500 mmol) in THF (30 mL) stirred at 0 °C. After 4 h the reaction was quenched by pouring the mixture over a crushed ice/brine mixture. The mixture was extracted with EtOAc (2 x 100 mL) which was washed with water (3 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (5:1) afforded the ester as a white solid (960 mg, 60%): mp 92-94 °C, (lit.[156] 95-97 °C); IR (μscope) 3072, 3025, 2980, 2951, 1729, 1450, 1436, 1320, 1221, 1133, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.94 (s, 4H, CH_2Br), 4.50 (s, 3H, CH_3), 7.62 (s, 1H, ArH), 8.00 (d, 2H, J = 1.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.9, 52.4, 130.0, 130.0, 133.9, 140.0, 165.9; HRMS (EI) calcd for $C_{10}H_{10}O_2{}^{79}Br^{81}Br$ 321.9027, found 321.9024 [M^+] (11.2%); Anal. calcd for $C_{10}H_{10}O_2{}^{79}Br^{81}Br$: C, 37.63; H, 3.18 found C, 37.31; H, 3.11.



3,5-Bis(bromomethyl)benzyl alcohol (28)[157]

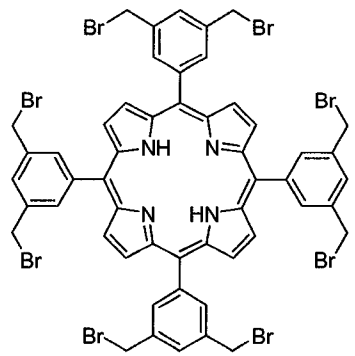
DIBAL (0.59 mL, 3.3 mmol) was added dropwise to a solution of ester **27** (0.44 g, 1.4 mmol) in THF (30 mL) stirred at 0 °C. After 3 h the reaction was quenched by the addition of H_2O. This mixture was allowed to warm to rt, filtered, and concentrated *in*

vacuo. Purification by flash chromatography (Hex/EtOAc, 2/1) gave the alcohol as a solid (0.302 g, 73%): IR (μscope) 3280, 2963, 2909, 2864, 1604, 1435, 1210, 1017, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s br, 1H, OH), 4.45 (s, 4H, CH_2Br), 4.68 (s, 2H, CH_2OH), 7.32 (s, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.7, 64.6, 127.5, 128.8, 138.8, 142.4; HRMS (EI) calcd for $C_9H_{10}O^{81}Br_2$ 293.9078 found 293.9080 [M^+] (33.1%); Anal. calcd $C_9H_{10}OBr_2$ C, 36.77; H, 3.43; found C, 36.99 H, 3.24.



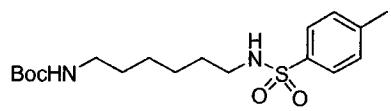
3,5-Bis(bromomethyl)benzaldehyde (29)[157]

3,5-(Bis-bromomethyl)benzyl alcohol (**28**) (0.457 g, 1.57 mmol) was dissolved in CH_2Cl_2 (60 mL) and stirred under an argon atmosphere. PCC (0.500 g, 2.33 mmol) was then added. The solution quickly turned from orange to dark brown. The mixture was stirred for 2.5 h, then vacuum filtered over a silica pad (1.5 cm x 2.5 cm). The filtrate was concentrated *in vacuo* to a brown oil which was purified by flash chromatography (Hex/EtOAc, 4:1) to give the title compound as a white solid (0.402 g, 87%): mp 102-103.5 °C, IR (μscope) 3034, 2857, 2828, 2749, 1688, 1652, 1598, 1440, 1216, 1150, 1125, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.52 (s, 4H, CH_2Br), 7.69 (d, 1H, J = 1.2 Hz, ArH), 7.83 (t, 2H, H = 1.4 Hz, ArH), 10.01 (d, 1H, J = 1.2 Hz, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.4, 129.8, 135.1, 137.4, 139.7, 190.9; HRMS (EI) calcd for $C_9H_8O^{81}Br^{79}Br$ 291.8921, found 291.8924 [M^+] (22.8%); Anal. calcd $C_9H_{10}OBr_2$ C, 37.02; H, 2.76; found C, 37.22 H, 2.63.



5,10,15,20-Tetrakis(3,5-bis(bromomethyl)phenyl)porphyrin (30)

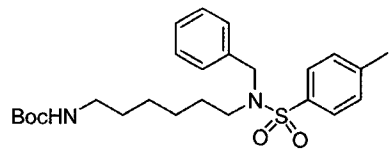
$BF_3 \cdot Et_2O$ (42 μL, 0.33 mmol) was added to a stirred solution of aldehyde **29** (290 mg, 1.00 mmol) and pyrrole (67 mg, 1.0 mmol) in degassed $CHCl_3$ (100 mL). After 1 h, TCQ (184 mg, 0.750 mmol) was added, and the solution was heated to reflux for 1 h. The solution was cooled, concentrated *in vacuo*, and purified by flash chromatography (Hex/CH_2Cl_2, 1:2) to give a purple solid (109 mg, 32%): IR (μscope) 3309, 3100, 2966, 1599, 1476, 1455, 1410, 1256, 1239, 1223, 983, 930, 923, 895, 801 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -2.84 (s, 2H, NH), 4.76 (s, 16H, CH_2Br), 7.86 (s, 4H, ArH), 8.21 (s, 8H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.8, 118.9, 128.9, 131.3 br, 134.9, 137.1, 142.9; ES-MS 1358.7 [MH^+].



***N*^{1}-(tert-butoxycarbonyl)-*N*^{6}-(p-toluenesulfonyl)-1,6-diaminohexane (32)**

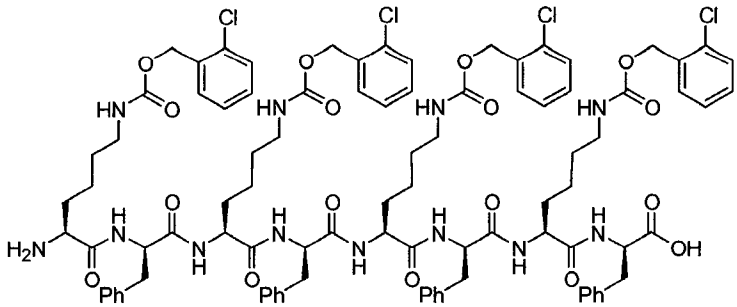
p-Tosyl chloride (190 mg, 1.00 mmol) was added to a stirred solution of *N*-Boc-1,6-diaminohexane (160 mg, 0.63 mmol) and triethylamine (0.35 mL, 2.5 mmol) in DMF. After 3 h, the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with sat'd NH_4Cl, water (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography

(Hex/EtOAc, 5/1) gave an oil (213 mg, 91%): R_f = 0.4 (Hex/EtOAc, 4/1), IR ($CHCl_3$, cast) 3340, 3282, 2933, 1689, 1520, 1327, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16-1.29 (m, 4H, 2 x $C\underline{H}_2$), 1.31-1.48 (m, 4H, 2 x $C\underline{H}_2$), 2.39 (s, 3H, $C\underline{H}_3$), 2.88 (t, 2H, *J* = 7.0 Hz, $NC\underline{H}_2$), 3.02 (t, 2H, *J* = 6.8 Hz, $NC\underline{H}_2$), 4.50 (s br, 1H, N<u>H</u>), 4.70 (s br, 1H, NH), 7.26 (AA'BB', 2H, Ar<u>H</u>), 7.72 (AA'BB', 2H, Ar<u>H</u>); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 26.06, 26.10, 28.4, 29.4, 29.9, 40.4, 43.0, 79.2, 127.1, 129.7, 137.1, 143.3, 156.1; MS (CI) 370.9 (66.7%); Anal $C_{18}H_{30}N_2O_4S$ calcd C, 58.35; H, 8.102, N, 7.567; found: C, 58.30; H, 8.29; N, 7.48.



N^1-(tert-butoxycarbonyl)-N^6-benzyl-N^6-(p-toluenesulfonyl)-1,6-diaminohexane (33)

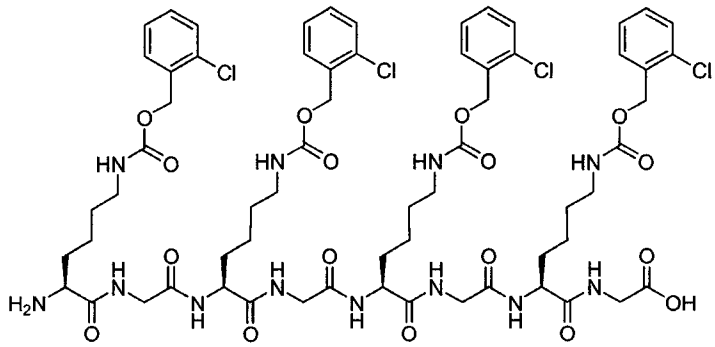
Benzyl bromide (34 mg, 0.20 mmol) was added to a stirred solution of sulfonamide **32** (61 mg, 0.18 mmol) and cesium carbonate (59 mg, 2.5 mmol) in DMF (3 mL). After 1.3 h, the mixture was diluted with water (8 mL) and extracted with Et_2O (2 x 8 mL). The combined organic layers were washed with water (5 x 4 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 6/1) gave an oil (70 mg, 91%) R_f = 0.4 (Hex/EtOAc 6/1), IR ($CHCl_3$, cast) 3397, 2931, 1710, 1514, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16-1.38 (m, 8H, 2 x $C\underline{H}_2$), 2.41 (s, 3H, $C\underline{H}_3$), 2.88-3.05 (m, 4H, 2 x $NC\underline{H}_2$), 4.41 (s br, 1H, N<u>H</u>), 4.24 (s, 2H, $C\underline{H}_2Ph$), 7.26-7.38 (m, 7H, 5 x Ph<u>H</u>, Ar<u>H</u>), 7.72 (AA'BB', 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 26.19, 26.23, 28.0, 28.5, 29.8, 48.1, 52.1, 79.2, 127.2, 127.8, 128.3, 128.6, 129.7, 136.7, 137.1, 143.2, 156.1 ($C(CH_3)_3$ signal not observed possibly due to overlap with $CDCl_3$); MS (CI) 461.0 (7.49%);



NH_2(2-Cl-Cbz)L-Lys-D-Phe(2-Cl-Cbz)L-Lys-D-Phe(2-Cl-Cbz)L-Lys-D-PheOH (36)

This compound was prepared using standard Fmoc chemistry starting with Wang-Fmoc-D-phe ester resin (0.60 g, 0.50 mmol/g 0.30 mmol), with PyBOP used as the coupling reagent, double couplings, N-capping with acetic anhydride after all residues, on a Rainin peptide synthesiser 'Protein Technologies PS3.' On completion of the synthesis the resin was washed with DMF (2 x 15 mL), then alternating CH_2Cl_2 and MeOH (3 x 15 mL ea.). The peptide was cleaved from the resin using 95% TFA/ 5% anisole (2 x 5 mL, 1 h ea.). The combined filtrates of cleaving cocktail were concentrated *in vacuo* and purified by gradient RP HPLC (waters μBondapak C18, 100 x 40 mm eluting with CH_3CN in H_2O, 0.75% TFA 30% → 77%, t_r = 22-25 min at 15 mL/min for 28 min gradient time). The fractions were concentrated to half volume, then lyophilized to give an amorphous white solid (57 mg, 11%): IR (μscope) 3400-2200, 1698, 1650, 1598, 1442, 1277, 1168 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 600 MHz) δ 0.96-1.18 (m, 16H, 4 x $C\underline{H}_2C\underline{H}_2CH_2N$), 1.19-1.31 (m, 4H, 4 x lys α-$CHC\underline{H}_aH_b$), 1.31-1.40 (m, 4H, 4 x lys α-$CHCH_a\underline{H}_b$), 2.58-2.65 (m, 4H, $CHC\underline{H}_aH_bPh$), 2.65-2.92 (m, 8H, $C\underline{H}_2NH$(2-Cl-Cbz]), 2.92-2.98 (m, 4H, $CHCH_a\underline{H}_bPh$), 3.66 (s br, 1H, lys α-$C\underline{H}NH_2$), 4.24 (s br, 1H, lys α-C<u>H</u>), 4.31 (m, 2H, 2 x lys α-C<u>H</u>), 4.46 (s br, 1H, phe α-C<u>H</u>), 4.65 (s br, 2H, 2 x phe α-C<u>H</u>), 4.82 (s br, 1H, phe α-C<u>H</u>), 5.07 (s, 6H, phe $C\underline{H}_2Ph$), 5.09 (s, 2H, phe $C\underline{H}_2Ph$), 7.03-7.13 (m, 4H, $CH_2N\underline{H}$(2-Cl-Cbz)), 7.13-7.50 (m, 20H, Ar<u>H</u>), 7.30 – 7.39 (m, 8H, Ar<u>H</u>), 7.41 – 7.49 (m, 8H, Ar<u>H</u>), 7.93 (s br,

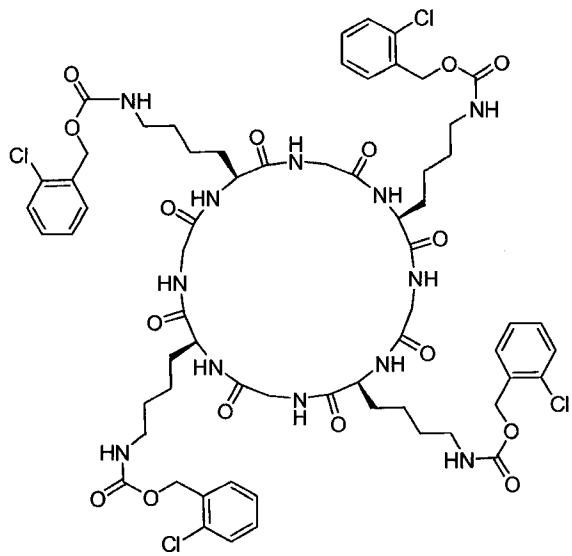
1H, NH), 8.19 (d, 1H, J = 7.6 Hz, NH), 8.20 (d, 1H, J = 7.6 Hz, NH), 8.24 (d, 1H, J = 7.6 Hz, NH), 8.31 (d, 1H, J = 7.9 Hz, NH), 8.67 (d br, 1H, 8.4 Hz, NH); MS (ES) 1737.3 (MH^+).



NH_2(N_ε-(2-Cl-Z)Lys-Gly)$_4$OH (42)

This compound was prepared using standard Fmoc chemistry starting with Wang-Fmoc-Gly ester resin (0.120 g, 0.83 mmol/g 0.10 mmol), with PyBOP as the coupling reagent, double couplings, N-capping with acetic anhydride after all residues, on a Rainin peptide synthesiser 'Protein Technologies PS3.' On completion of the synthesis the resin was washed with DMF (2 x 15 mL), then alternating CH_2Cl_2 and MeOH (3 x 15 mL ea.). The peptide was cleaved from the resin using 95% TFA/ 5% anisole (2 x 5 mL, 1 h ea.). The combined filtrates of cleaving cocktail were concentrated *in vacuo* and purified by gradient RP HPLC (waters μBondapak C18, 100 x 40 mm eluting with CH_3CN in H_2O, 0.75% TFA, 30% → 50%, t_r = 20-22 min at 15 mL/min for 25 min run time). The fraction was concentrated to half volume, then lyophilized to give an amorphous white solid (34 mg, 24%): IR (μscope) 3400-2400, 1657, 1445, 1421, 1320 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 600 MHz) δ 1.30-1.55 (m, 16H, 4 x $C\underline{H}_2C\underline{H}_2CH_2N$), 1.60-1.80 (m, 6H, NH_2, 4 x α-$CHC\underline{H}_aH_b$), 1.80-1.90 (m, 4H, 4 x α-$CHCH_a\underline{H}_b$), 3.01-3.14 (m, 8H, $C\underline{H}_2NHCbz$), 3.80-4.00 (m, 8H, 4 x gly α-$C\underline{H}_2$), 4.15 (m, 1H, lys α-C<u>H</u>), 4.23-4.39 (m, 2H, lys'' α-

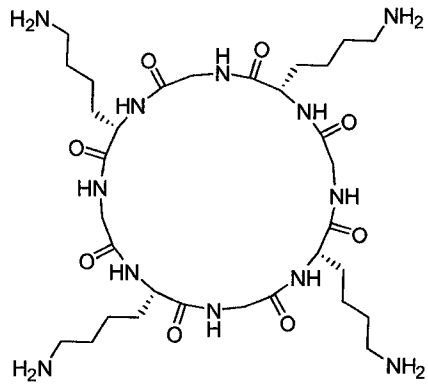
CH, lys''' α-CH), 4.41 (m, 1H, lys'''' α-CH), 5.16 (s, 8H, CH_2Ph), 7.18-7.23 (m, 3H, NHCbz), 7.29 (t, 1H, J = 5.6 Hz, NHCbz), 7.32-7.41 (m, 8H, 8 x Cbz ArH), 7.45-7.55 (m, 8H, Cbz ArH), 7.65 (1H, d, J = 5.6 Hz, lys α-CHNH), 7.84 (1H, d, J = 5.6 Hz, lys'' α-CHNH), 7.95 (1H, d, J = 5.6 Hz, lys'''' α-CHNH), 8.18 (1H, t, J = 6.0 Hz, gly α-CH_2NH), 8.23 (1H, t, J = 5.1 Hz, gly α-CH_2NH), 8.26 (1H, t, J = 4.8 Hz, gly α-CH_2NH), 8.31 (1H, t, J = 4.8 Hz, gly α-CH_2NH); MS (ES) 1433.7 [(MH^+)].



cyclo(Gly-(2-Cl-Cbz)L-Lys) (43)

Hünig's Base (5 μL, 0.4 mmol) was added to a solution of HATU (9 mg, 0.02 mmol), HOAt (3.3 mg, 0.024 mmol), and octapeptide **42** (28 mg, 0.020 mmol) dissolved in DMF (2 mL). The reaction was stirred under an argon atmosphere for 14 h. The reaction was followed by removing 20 μL aliquots, diluting with DMF/THF (200 μL, 1:1) and obtaining a ES MS spectrum. The mixture was concentrated *in vacuo* to approx. 2 mL, and loaded on a size exclusion column (Sephadex LH-20, 2.5 cm x 30 cm, eluting with DMF),[158] collecting 1 mL fractions. Fractions that tested positive for the correct molecular mass by MS were checked by NMR and combined to give a colourless film

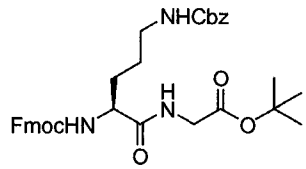
(15 mg, 53%). IR (μscope) 3400-3150, 1650-1680, 1581, 1445, cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 600 MHz) δ 1.32- 1.59 (m, 16H, 4 x $C\underline{H}_2C\underline{H}_2CH_2N$), 1.61-1.79 (m, 4H, 4 x α-$CHC\underline{H}_aH_b$), 1.79-1.89 (m, 4H, 4 x α-$CHCH_a\underline{H}_b$), 3.02-3.16 (m, 8H, $C\underline{H}_2NHCbz$), 3.80-4.00 (m, 8H, 4 x gly α-$C\underline{H}_2$), 4.23-4.39 (m, 4H, 4 x lys α-C<u>H</u>), 5.16 (s, 8H, $C\underline{H}_2Ph$), 7.25 (t, 1H, J = 5.6 Hz, N<u>H</u>Cbz), 7.30-7.40 (m, 8H, 8 x Ph<u>H</u>), 7.45-7.55 (m, 8H, Ph<u>H</u>), 7.65 (s br, 4H, lys α-CHN<u>H</u>), 8.10 (br s, 4H, gly α-$CH_2N\underline{H}$); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 27.5, 28.2, 30.2, 45.9, 48.4, 53.0, 65.5, 127.9, 128.4, 129.7, 136.2, 155.3, 171.4, 172.3; MS (ES) 1415 (MH^+), 1437.3 [(MNa^+)].



cyclo(Gly-Lys)$_4$ • 4TfOH (44)[78]

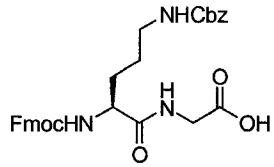
Cyclic peptide **43** (14 mg, 10 μmol) was dissolved in a solution of trifluoromethanesulfonic acid/trifluoroacetic acid/m-cresol/dimethylsulfide (1/5/3/1) (2 mL). This solution was stirred for 2 h, then diluted with diethyl ether (20 mL), then refrigerated for 10 h. The gelatinous material was filtered, triturated thoroughly with diethyl ether, then dried *in vacuo* to give an amorphous off white solid (4.4 mg, 40%): IR (μscope) 3400-3100, 1648, 1439 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.20-1.30 (m, 12H, 4 x $C\underline{H}_aH_bC\underline{H}_2CH_2N$), 1.30-1.40 (s br, 4H, 4 x orn α-$CHCH_a\underline{H}_b$), 2.96-3.06 (m, 8H,

$C\underline{H}_2NH_2$), 3.65-3.88 (m, 8H, 8 x gly CH_2), 4.22-4.25 (m, 4H, orn α-CH); MS (ES) 741.4 [MH^+].



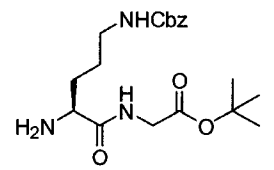
N_α-Fmoc-(N_δ-Cbz)-L-ornithinylglycine-*tert*-butyl ester (47)

Gly(O-*tert*-Butyl) hydrochloride (0.70 g, 0.41 mmol) was added to a solution of Fmoc(Cbz)OrnOH (2.05 g, 4.22 mmol) and PyBOP (2.70 g, 5.19 mmol) in 0.4 M NMM/DMF (25 mL). The solution was stirred for 10 h, then concentrated *in vacuo*, and then purified by flash chromatography (Hex/EtOAc, 3/1) to give a white amorphous solid (2.20 g, 88%). R_f = 0.6 (3:2 Hex/EtOAc); IR (μscope) 3305, 3067, 2842, 1727, 1690, 1652, 1538, 1451, 1369, 1272, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 9H, $C(CH_3)_3$), 1.40-1.65 (m, 2H, $C\underline{H}_2CH_aH_bCH\alpha$), 1.65-1.81 (m, 1H, $C\underline{H}_aH_bCH\alpha$), 1.81-1.93 (m, 2H, $CH_a\underline{H}_bCH\alpha$), 3.10-3.20 (m, 1H, $C\underline{H}_aH_bNHCbz$), 3.35-3.41 (m, 1H, $CH_a\underline{H}_bNHCbz$), 3.94 (dd, 1H, J = 15.0, 6.5 Hz, gly $C\underline{H}_aH_bN$), 3.94 (dd, 1H, J = 14.8, 6.1 Hz, gly $CH_a\underline{H}_bN$), 4.19 (t, 1H, J = 7.0 Hz, Fmoc $C\underline{H}CH_2$), 4.38 (d, 3H, J = 6.5 Hz, orn α-$C\underline{H}$, Fmoc $CHC\underline{H}_2$), 4.93 (s br, 1H, $N\underline{H}Cbz$), 5.06 (s, 2H, $C\underline{H}_2Ph$), 5.55 (s, 1H, lys α-$CHN\underline{H}$), 6.71 (s br, 1H, gly $CH_2N\underline{H}$), 7.22-7.31 (m, 7H, 5 x $Ph\underline{H}$, 2 x Fmoc $Ar\underline{H}$), 7.34 (t, 2H, J = 7.5 Hz, Fmoc $Ar\underline{H}$), 7.55 (d, 2H, J = 7.0 Hz, Fmoc $Ar\underline{H}$), 7.71 (d, 2H, J = 7.5 Hz, Fmoc $Ar\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 28.0, 30.2, 39.7, 42.0, 47.2, 52.8, 66.8, 67.0, 82.3, 119.9, 125.1, 127.0, 127.7, 128.0, 128.5, 136.5, 141.3, 143.7, 143.8, 156.2, 166.4, 168.6; HRMS (ES) calc'd for $C_{34}H_{39}N_3O_7Na$ 624.2686, found 624.2683 [MNa^+].



N_α-Fmoc-(N_δ-Cbz)-L-ornithinylglycine (48)

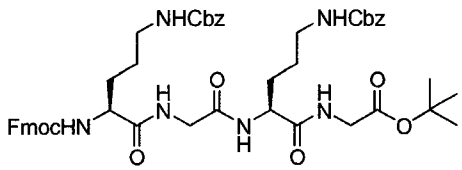
Dipeptide **47** (936 mg, 1.50 mmol) was treated with formic acid at 0 °C for 3 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (Hex/EtOAc, 1/2, 1% AcOH) to give a colourless solid (680 mg, 82%): IR (μscope) 3500-2300, 3300, 3066, 2945, 1687, 1651, 1537, 1257 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 1.50-1.75 (m, 3H, $C\underline{H}_aH_bC\underline{H}_2CH_2N$), 1.80-1.99 (m, 1H, α-$CHCH_aC\underline{H}_b$), 2.68 (s br, 2H, NH_2), 3.10-3.22 (m, 2H, $C\underline{H}_2NHCbz$), 3.58 (s br, 1H, orn α-CH), 3.91 (dd, 1H, J = 6.0, 15.0 Hz, gly α-$C\underline{H}_aH_b$), 4.00 (dd, 1H, J = 6.0, 15.0 Hz, gly α-$CH_a\underline{H}_b$), 5.08 (s, 2H, $PhC\underline{H}_2$), 7.32-7.40 (m, 6H, 5 x $Ph\underline{H}$, $N\underline{H}Cbz$), 7.71 (s br, 1H, gly NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.7, 30.4, 32.2, 44.3, 49.4, 54.7, 57.1, 68.4, 83.3, 122.8, 128.0, 129.8, 130.0, 130.3, 130.4, 131.0, 139.9, 146.5, 158.7, 171.2, 174.5; HRMS (ES) Calc'd for $C_{30}H_{32}N_3O_7$ 546.2240, found 546.2244 [MH^+].



NH_2(N_δ-Cbz)-L-ornithinylglycine *tert*-butyl ester (49)

Dipeptide **47** (936 mg, 1.50 mmol) was treated with 20% piperidine in DMF (10 mL) and stirred under an argon atomsphere for 10 min. The solvent was removed *in vacuo* and the material purified by flash chromatography ($CHCl_3$ → $CHCl_3$/iPrOH/NH_4OH, 30/5/1) to give a colourless solid (510 mg, 90%): IR (μscope) 3500-3250, 3002, 2933, 1675, 1572, 1203, 1180, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 9H, CH_3), 1.58-1.68 (m,

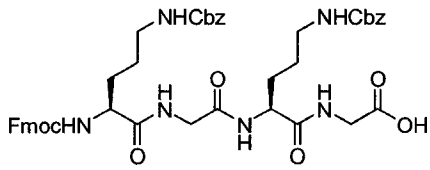
3H, C<u>H</u>$_a$H$_b$C<u>H</u>$_2$CH$_2$N), 1.78-1.90 (m, 1H, α-CHCH$_a$<u>H</u>$_b$), 2.61 (s br, 2H, NH$_2$) 3.10-3.24 (m, 2H, C<u>H</u>$_2$NHCbz), 3.58 (s br, 1H, orn α-CH), 3.88 (dd, 1H, J = 6.0, 15.0 Hz, gly' α-C<u>H</u>$_a$H$_b$), 3.92 (dd, 1H, J = 6.0, 15.0 Hz, gly' α-CH$_a$<u>H</u>$_b$), 5.03 (s, 2H, C<u>H</u>$_2$Ph), 7.23-7.56 (m, 6H, 5 x Ph<u>H</u>, orn α-CHN<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 28.0, 32.1, 40.5, 54.5, 66.5, 66.6, 82.1, 128.0, 128.5, 136.6, 156.5, 166.5, 169.1, 175.0; MS (ES) 379.2 [MNa$^+$].



Fmoc(N_δ-Cbz)Lys-Gly-(N_δ-Cbz)Lys-Gly(O^{t}Bu) (50)

Dipeptide amine **49** (274 mg, 0.720 mmol) was added to a solution of dipeptide acid **48** (393 mg, 0.720 mmol) and PyBOP (412 mg, 0.81 mmol) in 0.4 M NMM in DMF (30 mL). The solution was stirred overnight, concentrated *in vacuo*, then purified by flash chromatography to give an off white amorphous solid (0.53 g, 84%): R_f = 0.3 (Hex/CH_2Cl_2/MeOH, 4/4/1); IR (μscope) 3296, 2944, 1686, 1631, 1537, 1258, 1153 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 1.28-1.55 (m, 6H, C<u>H</u>$_a$H$_b$C<u>H</u>$_2$CH$_2$N), 1.35 (s, 9H, C(CH$_3$)$_3$), 1.56-1.62 (m, 2H, α-CHCH$_a$C<u>H</u>$_b$), 2.80-3.00 (m, 4H, C<u>H</u>$_2$NHCbz), 3.67 (dd, 1H, J = 5.5, 16 Hz, gly α-C<u>H</u>$_2$), 3.70 (dd, 1H, J = 5.5, 16 Hz, gly α-C<u>H</u>$_2$), 3.72 (m, 2H, gly' α-C<u>H</u>$_2$), 3.95-4.00 (m, 1H, orn α-C<u>H</u>), 4.15-4.30 (s, 4H, Fmoc C<u>H</u>C<u>H</u>$_2$, orn' α-C<u>H</u>), 4.97 (s, 2H, PhC<u>H</u>$_2$), 4.98 (s, 2H, PhC<u>H</u>$_2$), 7.13-7.22 (m, 2H, 2 x N<u>H</u>Cbz), 7.22-7.37 (m, 14H, 2 x Fmoc Ar<u>H</u>, 10 x Ph<u>H</u>), 7.38 (t, 2H, J = 7.2 Hz, Fmoc Ar<u>H</u>), 7.51 (d, 1H, J = 7.2 Hz, orn α-CHN<u>H</u>), 7.69 (t, 2H, J = 6.8 Hz, Fmoc Ar<u>H</u>), 7.85 (d, 2H, J = 7.6 Fmoc Ar<u>H</u>), 7.90 (d, 1H, J = 8.0 Hz, orn' α-CHN<u>H</u>), 8.08 (t, 1H, J = 5.5 Hz, gly N<u>H</u>), 8.21 (t, 1H, J =

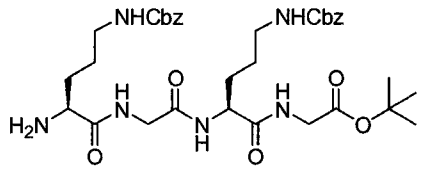
5.8 Hz, gly' NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.5, 28.7, 30.4, 31.8, 32.2, 43.2, 44.0, 44.6, 49.4, 54.7, 57.1, 67.8, 68.4, 83.3, 122.8, 128.0, 129.8, 130.3, 130.4, 131.0, 139.9, 143.4, 146.4, 146.6, 158.7, 158.8, 171.2, 171.4, 174.5, 174.8 (10 coincident carbons); MS (ES) 907.3 [MH^+]



***N*-Fmoc(N_δ-Cbz)Orn-Gly-(N_δ-Cbz)Orn-GlyOH (51)**

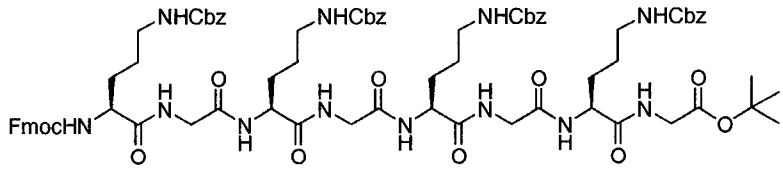
Tetrapeptide **50** (290 mg, 0.320 mmol) was dissolved in THF (5 mL) and formic acid (20 mL) at 0 °C and stirred overnight, then allowed to warm to rt. The mixture was concentrated *in vacuo*, redissolved in THF/EtOH, and concentrated again to afford a white solid. DMF (ca 5 mL) was added to dissolve the solid, then warm Et_2O/Hex (ca 6 mL, 5/1) was added causing the mixture to become cloudy. The mixture was heated to clear and allowed to cool slowly to rt, then at 2 °C overnight to give a fluffy white gelatinous mixture which was filtered, rinsed with Et_2O, and dried *in vacuo* to give 160 mg of pure white amorphous powder. The filtrate could then be purified by column chromatography to afford an additional portion of product (200 mg total, 73%): IR (μscope) 3600-2600, 3300, 3067, 2942, 1688, 1633, 1537, 1450, 1259 cm^{-1}; ^{1}H NMR (CH_3OH, 500 MHz) δ 1.45-1.55 (m, 4H, 2 x NCH_2CH_2), 1.60-1.70 (m, 2H, 2 x $CHCH_aH_b$), 1.72-1.90 (m, 2H, 2 x $CHCH_aH_b$), 3.00-3.10 (m, 2H, CH_2NHCbz), 3.10-3.20 (m, 2H, CH_2NHCbz), 3.70-4.00 (m, 4H, 2 x α-CH_2), 3.95-4.05 (m, 1H, α-CH), 4.2 (t, 1H, J = 6.6 Hz, α-CH), 4.30-4.50 (m, 3H, Fmoc CH_2CH), 5.00 (s, 2H, CH_2Ph), 5.05 (s, 2H, CH_2Ph), 7.25-7.33 (m, 10H, PhH), 7.36 (t, 4H, J = 7.5 Hz, Fmoc ArH), 7.64 (d, 2H, J = 7.5 Hz, Fmoc ArH), 7.36 (d, 2H, J = 7.5 Hz, Fmoc ArH); ^{13}C NMR ($(CD_3)_2SO$, 125

MHz) δ 25.7, 26.0, 27.6, 29.0, 29.4, 41.2, 41.9, 42.0, 46.6, 51.9, 54.2, 54.3, 65.1, 65.6, 112.0, 125.2, 127.0, 127.5, 128.3, 137.16, 137.17, 140.6, 155.9, 156.0, 168.4, 171.4, 172.1 (9 coincident peaks); MS (ES) 850.3.



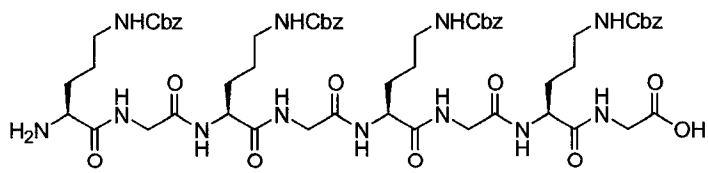
NH_2(N_ω-Cbz)Orn-Gly-(N_ω-Cbz)-Orn-Gly(O^tBu) (52)

Tetrapeptide **50** (81 mg, 0.089 mmol) was treated with 20% piperidine in DMF (10 mL) and stirred under inert atmosphere for 10 min. The solvent was removed *in vacuo* and the material purified by HPLC to give a colourless glass (48 mg, 79%): IR (CH_2Cl_2, cast) 3310, 3064, 2934, 2869, 1690, 1538, 1454, 1367 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.41 (s, 9H, CH_3), 1.46–1.58 (m, 8H, $N\underline{H}_2$, $NCH_2C\underline{H}_2$, α-$CHC\underline{H}_aH_b$), 1.90–1.95 (m, 2H, $CHCH_a\underline{H}_b$), 3.10-3.26 (m, 3H, $C\underline{H}_aH_bNHCbz$, $C\underline{H}_2NHCbz$), 3.32-3.38 (m, 1H, $CH_a\underline{H}_bNHCbz$), 3.53 (d, 1H, gly α-C<u>H</u>), 3.57 (t, 1H, J = 6.0 Hz, lys α-C<u>H</u>), 3.80 (ABX, 1H, J = 18.0, 4.8 Hz, gly α-C<u>H</u>), 3.86 (ABX, 1H, J = 18.0, 4.8 Hz, gly α-$CH_a\underline{H}_b$), 4.10 (d, 1H, J = 15.6 Hz, gly α-$C\underline{H}_aH_b$), 4.58 (s br, 1H, NH), 5.00-5.08 (s br, 1H, N<u>H</u>Cbz), 5.06 (s, 2H, $PhC\underline{H}_2$), 5.07 (s, 2H, $PhC\underline{H}_2$), 5.39 (s br, 1H, N<u>H</u>Cbz), 6.79 (s br, 1H, gly N<u>H</u>), 7.04 (d, 1H, J = 6.5 Hz, lys α-N<u>H</u>), 7.20-7.28 (m, 10H, Ph<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.07, 26.13, 27.6, 31.8, 40.2, 40.3, 40.8, 41.7, 42.6, 52.3, 52.4, 63.6, 65.7, 65.8, 81.0, 127.9, 128.5, 137.8, 137.9, 156.5, 156.8, 168.9, 169.1, 172.1, 173.8; HRMS (ES) Calc'd for $C_{34}H_{48}N_6O_9Na$ 707.3380, found: 707.3381.



Fmoc(Cbz)Orn-Gly-(Cbz)Orn-Gly-(Cbz)Orn-Gly-(Cbz)Orn-Gly(O^{t}Bu) (53)

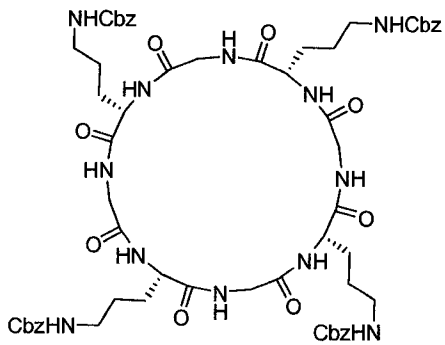
Amine **52** (108 mg, 0.159 mmol) was added to a solution of acid **51** (135 mg, 0.159 mmol), PyBop (91 mg, 0.175 mmol), and triethylamine (22ul, 0.158 mmol) in DMF (5 mL). The solution was stirred 6 h, then concentrated *in vacuo*, then redissolved in a minimum of DMF then purified by size exclusion chromatography (3 x) to give a white amorphous solid (165 mg, 73%): IR (μscope) 3287, 3076, 2934, 1694, 1630, 1537, 1265 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ 1.37-1.60 (m, 12H, 4 x $C\underline{H}_aH_bC\underline{H}_2CH_2N$), 1.38 (s, 9H, $(CH_3)_3$), 1.60-1.70 (s br, 4H, 4 x orn α-$CHCH_a\underline{H}_b$), 2.96-3.06 (m, 8H, $C\underline{H}_2NHCbz$), 3.65-3.78 (m, 8H, 4 x gly CH_2), 3.98 (q, 1H, $J_{NH} \approx J_{CH\alpha\text{-}CH2} = 6.8$ Hz, lys α-CH), 4.18-4.32 (m, 6H, CH_2CH, 3 x lys α-CH), 4.98 (s, 8H, $C\underline{H}_2Ph$), 7.16-7.24 (m, 2H, CH2Cbz), 7.27-7.36 (m, 24H, 20 x Ph$\underline{H}$, 2 x Fmoc Ar$\underline{H}$, N$\underline{H}$Cbz), 7.39 (t, 2H, $J = 7.2$ Hz, Fmoc Ar$\underline{H}$), 7.52 (d, 1H, $J = 6.6$ Hz, lys α-CH), 7.71 (t, 2H, $J = 7.2$ Hz, Fmoc Ar$\underline{H}$), 7.87 (d, 2H, $J = 7.5$ Hz, Fmoc Ar$\underline{H}$), 7.91-8.03 (m, 3H, lys α-CH), 8.09 (s br, 1H, gly NH), 8.14 (s br, 1H, gly NH), 8.15 (s br, 1H, gly NH), 8.24 (t, 1H, $J = 6.0$ Hz, gly-NH); MS (ES) 1629.7 [(MH^+)].



NH_2(Cbz)Orn-Gly-(Cbz)Orn-Gly-(Cbz)Orn-Gly-(Cbz)Orn-GlyOH (54)

Peptide **53** (130 mg, 0.080 mmol) was dissolved in 20% piperidine in DMF (10 mL). The mixture was stirred for 20 min, then concentrated *in vacuo*. The residue was then

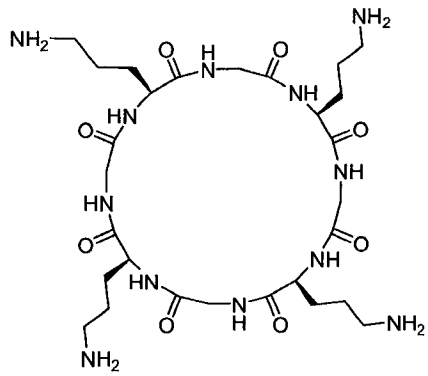
dissolved in a minimum amount of DMF, then purified by size exclusion chromatography (DMF, LH-20) to give an off white amorphous solid (78 mg, 74%): IR (μscope) 3400-2200, 1661, 1576, 1414 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 600 MHz) δ 1.37-1.60 (m, 12H, 4 x $C\underline{H}_aH_bC\underline{H}_2CH_2N$), 1.50-1.70 (s br, 4H, 4 x orn α-$CHCH_a\underline{H}_b$), 2.96-3.06 (m, 8H, $C\underline{H}_2NHCbz$), 3.65-3.78 (m, 8H, 4 x gly CH_2), 4.18-4.32 (m, 4H, 4 x lys α-CH), 4.98 (s, 8H, $C\underline{H}_2Ph$), 7.16-7.24 (m, 4H, $N\underline{H}Cbz$), 7.29-7.49 (m, 20H, 20 x $Ph\underline{H}$), 7.91-8.03 (m, 3H, lys α-$N\underline{H}$), 8.11 (s br, 1H, gly $N\underline{H}$), 8.15 (s br, 3H, gly $N\underline{H}$); MS (ES) 1295.6 [(MH^+)].



***cyclo*-((*N*-Cbz)Orn)(Gly))$_4$ (55)**

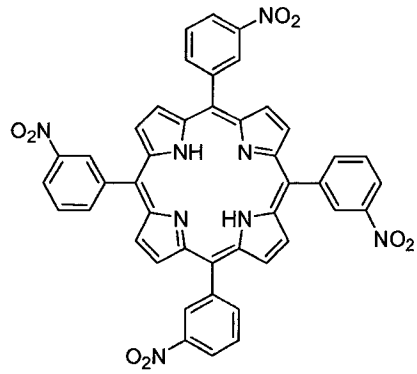
Hünig's Base (5 μL, 0.44 mmol) was added to a solution of PyBOP (12 mg, 0.022 mmol), HOAt (3.1 mg, 0.022 mmol), and octapeptide **54** (26 mg, 0.020 mmol) in DMF (mL). The mixture was stirred under an argon atmosphere for 14 h. The reaction was followed by removing 20 μL aliquots, diluting with DMF/THF (200 μL, 1:1) and obtaining a ES MS. The mixture was concentrated *in vacuo* to approx. 2 mL, and loaded on a size exclusion column (Sephadex LH-20, 2.5 cm x 30 cm),[158] collecting 1 mL fractions. Fractions that tested positive for the correct molecular mass by MS were checked by NMR and combined to give a colourless film (18 mg, 70%): IR (μscope) 3400-2200, 1688, 1576, 1414 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 600 MHz) δ 1.37-1.60 (m, 12H,

4 x C$\underline{H}_a$H$_b$C$\underline{H}_2$CH$_2$N), 1.50-1.70 (s br, 4H, 4 x orn α-CHCH$_a\underline{H}_b$), 2.96-3.06 (m, 8H, C$\underline{H}_2$NHCbz), 3.65-3.78 (m, 8H, 4 x gly C$\underline{H}_2$), 4.18-4.32 (m, 4H, 4 x lys α-C$\underline{H}$), 4.98 (s, 8H, C$\underline{H}_2$Ph), 7.16-7.24 (m, 4H, N$\underline{H}$Cbz), 7.29-7.49 (m, 20H, 20 x Ph$\underline{H}$), 7.91-8.03 (m, 4H, lys α-C$\underline{H}$), 8.15 (s br, 4H, gly NH); MS (ES) 1220 [MH$^+$], 1243 [MNa$^+$].



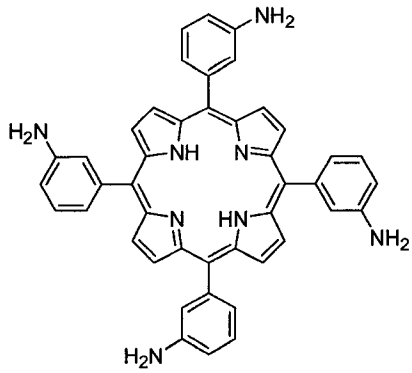
cyclo(Gly-L-Orn)$_4$ • 4TfOH (55)

Cyclic peptide **54** (24 mg, 20 μmol) was dissolved in a solution of trifluoromethanesulfonic acid/trifluoroacetic acid/m-cresol/dimethylsulfide (1/5/3/1) (2 mL). This solution was stirred for 2 h, then diluted with diethyl ether (20 mL), then refrigerated for 10 h. The gelatinous material was filtered, triturated thoroughly with diethyl ether, then dried *in vacuo* to give an amorphous white solid (17 mg, 70%): IR (μscope) 3300-2900, 1648, 1439 cm^{-1}; ^{1}H NMR (CD$_3$OD, 500 MHz) δ 1.20-1.30 (m, 12H, 4 x C$\underline{H}_a$H$_b$C$\underline{H}_2$CH$_2$N), 1.30-1.40 (s br, 4H, 4 x orn α-CHCH$_a\underline{H}_b$), 2.96-3.06 (m, 8H, C$\underline{H}_2$NH$_2$), 3.65-3.88 (m, 8H, 8 x gly CH$_2$), 4.22-4.25 (m, 4H, orn α-CH); MS (ES) 684 [MH$^+$].



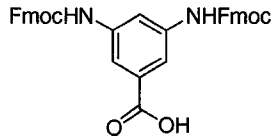
5,10,15,20-Tetrakis(3-nitrophenyl)porphyrin (59)[80]

Pyrrole (3.46 mL, 50.0 mmol) was added to a solution of 3-nitrobenzaldehyde (6.06 g, 50.0 mmol) in propionic acid (250 mL) at reflux. The mixture was held at reflux for 1.5 h, then allowed to cool to rt. After standing at 2 °C for 16 h, the slurry was filtered, and rinsed with MeOH. The resulting precipitate required flash chromatography (Hexane/CH_2Cl_2, 7:2) to afford a purple solid (0.741 g 7.5%). Additional pure material was obtained by refrigeration of the filtrate for 3 days at 2 °C, filtration, and thorough washing with H_2O (50 mL) and MeOH (100 mL) to give 0.080 g of a purple solid (8.3% total yield): IR (μscope) 3322, 3083, 1695, 1529, 1348, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -2.82 (s br, 2H, NH), 7.98 (t, 4H, J = 8.7 Hz, ArH), 8.69 (d, 4H, J = 8.7 Hz, ArH), 8.70 (d, 4H, J = 8.4 Hz), 8.80 (s, 8H, H_β), 9.07 (s, 4H, ArH); MS (ES) 795.2 [MH^+].



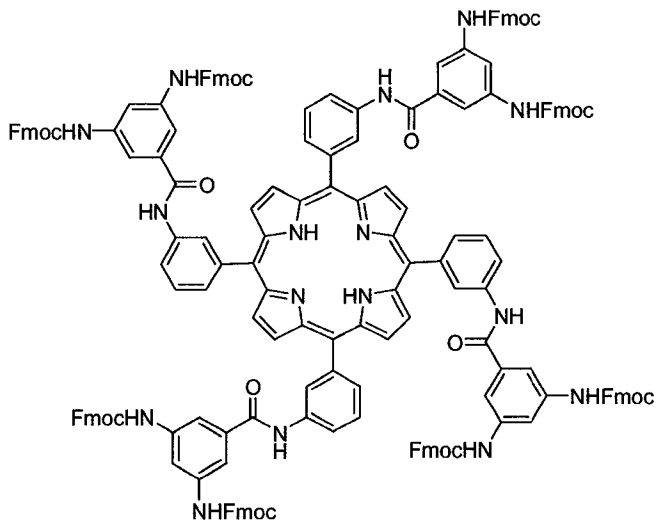
5,10,15,20-Tetrakis(3-aminophenyl)porphyrin (60)[79]

A solution of nitroporphyrin **59** (606 mg, 0.763 mmol) in conc. HCl (100 mL) was degassed with argon for 1 h. Concurrently, a solution of $SnCl_2$ (2.60 g, 13.8 mmol) in conc. HCl (30 mL) was also purged. The solutions were then combined, heated at 78 °C and stirred under an argon atmosphere for 30 min., then cooled to 0 °C, then carefully neutralized with conc. ammonium hydroxide, keeping the solution at or below 20 °C. The resulting brown sludge was extracted/triturated with THF (10 x 20 mL) until the extracts were free of product. The extracts were combined, dried (Na_2SO_4), and filtered through a silica pad. The filtrate was concentrated *in vacuo* to ca. 20 mL, diluted with $CHCl_3$ (30 mL). This mixture was concentrated to ca. 15 mL then rediluted with $CHCl_3$, concentrated to 15 mL, then filtered to give a purple crystalline solid (386 mg, 75%): IR (μscope) 3402, 3319, 3031, 1620, 1444, 1330 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ -2.96 (s, 2H, NH), 5.44 (s, 8H, NH_2), 7.01 (dd, 4H, J = 2.8, 7.6 Hz ArH), 7.34 (s, 4H, ArH), 7.35-7.45 (m, 8H, 2 x ArH), 8.90 (s, 8H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 113.5, 120.5, 121.0, 123.2, 127.3, 131.0 br, 141.9, 147.0; HRMS (ES) calcd for $C_{44}H_{35}N_8$ 675.2979, found 675.2920 [MH^+].



3,5-Bis(9-fluorenylmethoxycarbonylamino)benzoic acid (61)

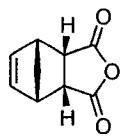
9-Fluorenylmethyl chloroformate (2.58 g, 10.0 mmol) was added to a solution of 3,5-diaminobenzoic acid (506 mg, 3.33 mmol) and pyridine (5 mL) in DMF (10 mL). The mixture was stirred overnight, diluted with EtOAc (200 mL) and 2.0 M HCl (200 mL) separated, washed with water (3 x 100 mL), brine (50 mL), dried (Na_2SO_4), then concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 4/1→1/1 1% AcOH) to give a white solid (1.11 g, 53%): mp 240-245 °C dec, IR ($CHCl_3$, cast) 3500-2900, 3330, 3066, 2958, 1709, 1610, 1553, 1450, 1217 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 300 MHz) δ 4.31 (t, 1H, J = 5.7 Hz, OC$\underline{H}_2$), 4.49 (d, 2H, J = 5.8 Hz, $CH_2C\underline{H}$), 7.33 (dt, 2H, J = 6.6, 0.9 Hz, Fmoc Ar$\underline{H}$), 7.39 (t, 2H, J = 6.2 Hz, Fmoc Ar$\underline{H}$), 7.75 (d, 2H, J = 6.3 Hz, Fmoc Ar$\underline{H}$), 7.86 (d, 2H, J = 6.3 Hz, Fmoc Ar$\underline{H}$), 7.97 (d, 2H, J = 1.6 Hz, Ar$\underline{H}$), 8.08 (s, 1H, Ar$\underline{H}$), 9.08 (s, 2H, N$\underline{H}$); ^{13}C NMR (Acetone D_6, 75 MHz) δ 47.9, 67.2, 113.2, 114.8, 120.8, 126.1, 128.0, 128.6, 132.6, 140.1, 142.1, 144.9, 154.3, 167.3; HRMS (EI) calcd for $C_{37}H_{28}O_6N_2Na$ 619.1845, found 619.1846 [MNa+].



5,10,15,20-Tetrakis(3-(3,5-bis(9-fluorenylmethoxycarbonylamino)benzamido)phenyl)porphyrin (62)

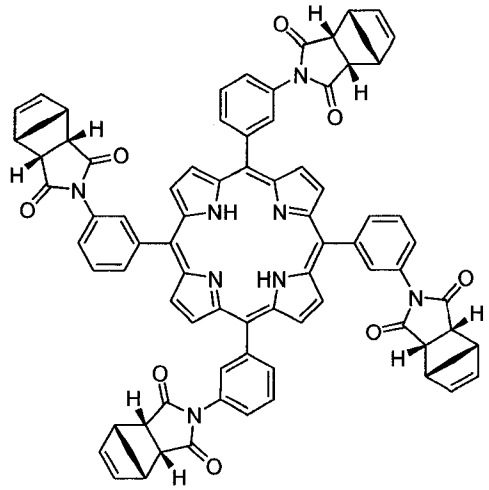
Thionyl chloride (0.5 mL) was added to a stirred suspension of acid **61** (619 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) with DMF (1 drop). The solution was heated at reflux for 2 h, and then cooled to rt. The mixture was concentrated *in vacuo*, resdissolved in CH_2Cl_2, concentrated again, redissolved in distilled THF, then added dropwise to a stirred solution of TAP **60** (68 mg, 0.13 mmol) and triethylamine (140 μL, 1.00 mmol) in THF at 0 °C. The solution was stirred 3 h, then concentrated *in vacuo*. Purification by flash chromatography ($CHCl_3$ → $CHCl_3$/MeOH, 15/1) then gel permeation chromatography (LH-20 in DMF) gave a purple solid (227 mg, 61%): IR (μscope) 3315, 3300-3000, 3022, 1710, 1607, 1255 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ –2.86 (s, 2H, NH), 4.35-4.40 (m, 8H, C<u>H</u>CH_2), 4.40-4.50 (m, 16H, CHC<u>H</u>$_2$), 7.20-2.40 (m, 32H, Fmoc Ar<u>H</u>), 7.60-7.77 (m, 24H, 16 x Fmoc Ar<u>H</u>, 8 x ArH), 7.79-7.88 (m, 20H, 16 x Fmoc Ar<u>H</u>, 4 x Ar<u>H</u>), 7.98 (s, 8H, Ar<u>H</u>), 8.28 (s, 4H, Ar<u>H</u>), 8.64-8.67 (m, 4H, Ar<u>H</u>), 8.96 (s, 8H, H_β), 9.92 & 9.94 (2 x s, 8H, N<u>H</u>Fmoc), 10.66 (s, 4H, N<u>H</u>Ar); ^{13}C NMR (CD_3SOCD, 125 MHz) δ 46.5, 65.7, 111.3, 112.2, 119.6, 119.8, 120.1, 125.1, 126.0, 127.0, 127.3, 127.6,

128.9, 130.0, 131.5 br, 136.6, 137.9, 139.6, 140.7, 141.5, 143.7, 153.3, 162.3; MS (ES) 2990.



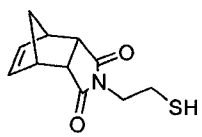
Norborn-5-ene-2,3-*endo*-dicarboxylic anhydride (66)[159]

Cyclopentadiene (1.40 mL, 16.7 mmol) was added to a solution of maleic anhydride (1.60 g, 21.6 mmol) in Et_2O (40 mL). The mixture was stirred overnight, then filtered to give the product anhydride (2.09 g, 77%). The filtrate could then be concentrated and recrystallized from Et_2O/Hex to yield an additional 186 mg of white needles to give a total yield of 84%: R_f = 0.2 (Hex/Et_2O, 3:2); mp 166-168 °C (lit.[159] 165-167 °C); IR (CH_2Cl_2, cast) 2980, 1840, 1773, 1333, 1229, 1089, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (d, 1H, J = 8.5 Hz, C$\underline{H}_{bridge}$), 1.76 (dt, 1H, J = 8.0, 3.0 Hz, C$\underline{H}_{bridge}$), 3.48 (dd, 2H, J = 1.5, 3.0 Hz, C$\underline{H}CH_2$), 3.55 (m, 2H, C$\underline{H}$CO), 6.29 (t, 2H, J = 1.5 Hz, C$\underline{H}$=C$\underline{H}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.1, 47.1, 52.7, 135.5, 171.2; HRMS (EI) calcd for $C_9H_8O_3$ 164.0474, found 164.0469 [M^+] (4.3%).



Tetrakis(3-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)phenyl)porphyrin (67)

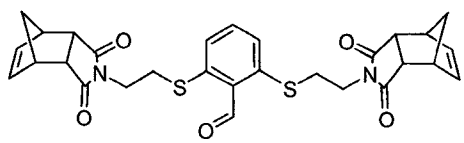
A solution of TAP **60** (134 mg, 0.200 mmol) and anhydride **66** (136 mg, 1.00 mmol) in AcOH (4 mL) was heated at reflux for 5 h. The solution was cooled, concentrated *in vacuo* and purified by flash chromatography (Hex/EtOAc, 2/1) to give a purple solid (179 mg, 71%): IR (μscope) 3318, 1773, 1708, 1602, 1436, 1374, 1180, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ -2.85 (s, 2H, NH), 1.60 (d, 4H, J = 8.0 Hz, CH_aH_b), 1.76 (d, 4H, J = 7.5 Hz, CH_aH_b), 3.48 (s, 8H, CH), 3.51 (s, 8H, CH), 6.25 (s, 8H, CH=CH), 7.57 (d, 4H, J = 7.5 Hz, ArH), 7.79 (t, 4H, J = 7.5 Hz), 8.03 (s, 4H, ArH), 8.17 (t, 4H, J = 7.3 Hz, ArH), 8.97 (s, 8H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 45.6, 46.0, 52.3, 118.8, 125.7, 130.5, 131.6 br, 132.5, 132.6, 132.7, 134.7, 142.7, 176.7; MS (ES) 1259.3 [MH$^+$].



5-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)ethanethiol (70)

The anhydride (1.64 g, 10.0 mmol), triethylamine (2.02 g, 20.0 mmol) and thioethanolamine hydrochloride (1.13 g, 10.0 mmol) were dissolved in DMF (10 mL) and placed in a sealed tube. The solution was purged with argon (20 min), sealed, and heated

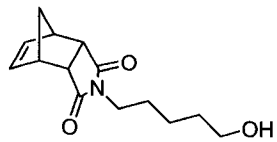
at 140 °C for 14 h. The tube was then cooled, diluted with EtOAc/H_2O (100 mL/50 mL), separated, and the organic layer washed with water (3 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (4:1) afforded a white solid (290 mg, 11%): mp 111-114 °C, IR ($CHCl_3$, cast) 3062, 2989, 2944, 2871, 2559, 1766, 1701, 1395, 1336, 1159, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.33 (t, 1H, S<u>H</u>), 1.50 (dt, 1H, J = 9.0, 1.5 Hz, bridge $CH_a\underline{H}_bCH$), 1.69 (dt, 2H, J = 8.5, 1.5 Hz, $C\underline{H}_aH_bCH$), 2.53 (m, 2H, $C\underline{H}_2S$), 3.22 (dd, 2H, J = 1.5, 3.0 C<u>H</u>CH=CH), 3.35 (m, 2H, COC<u>H</u>), 3.47 (m, 2H, $NC\underline{H}_2$), 6.07 (t, 2H, J = 2.0 Hz, C<u>H</u>=C<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.0, 41.3, 45.0, 45.8, 52.3, 134.4, 177.2; HRMS (EI) calcd for $C_{13}H_{15}O_2NS$ 265.0772, found 265.0774 [M^+] (21.3%).



2,6-Bis(2-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)ethanethio)benzaldehyde (72)

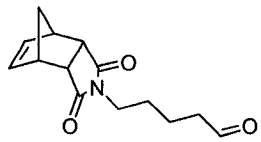
A solution of thiol **70** (223 mg, 0.842 mmol) and 2,6-dichlorobenzaldehyde (85 mg, 0.49 mmol) in dry DMF (2 mL) was degassed with a stream of argon for 30 min. K_2CO_3 (138 mg, 1.00 mmol) was added under an argon blanket and the mixture maintained at this temperature for a further 5 min under argon. The mixture was heated to 60 °C and stirred for 4 h. The mixture was cooled, diluted with EtOAc/H_2O (20 mL/10 mL), separated, and the organic layer washed with water (3 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (2:1 → 1:2) afforded the aldehyde **72** as yellow solid (239 mg, 89%): R_f = 0.2 (Hex/EtOAc 4:3) mp 117-119 °C, IR ($CHCl_3$, cast) 2989, 2860, 1764, 1698, 1670, 1562, 1396, 1335, 1203,

1126, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, 2H, J = 8.5 Hz, $CH_a\underline{H}_bCH$), 1.69 (dt, 2H, J = 8.5, 1.5 Hz, $C\underline{H}_aH_bCH$), 2.93 (m, 4H, $C\underline{H}_2S$), 3.21 (dd, 4H, J = 1.5, 3.0 $C\underline{H}CH{=}CH$), 3.34 (m, 4H, $COC\underline{H}$) 3.54 (m, 4H, $NC\underline{H}_2$), 6.07 (t, 2H, J = 1.8 Hz $C\underline{H}{=}C\underline{H}$), 7.36 ($A\underline{B}_2$, 2H, Ar$\underline{H}$), 7.45 ($\underline{A}B_2$, 1H, Ar$\underline{H}$), 10.61 (s, 1H, $C\underline{H}O$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9, 40.0, 44.9, 45.8, 52.2, 124.9, 131.7, 133.2, 134.5, 142.2, 177.2, 190.6; HRMS (EI) calcd for $C_{29}H_{28}O_5S_2N_2$ 548.14398, found 548.14340 [M^+] (1.20%).



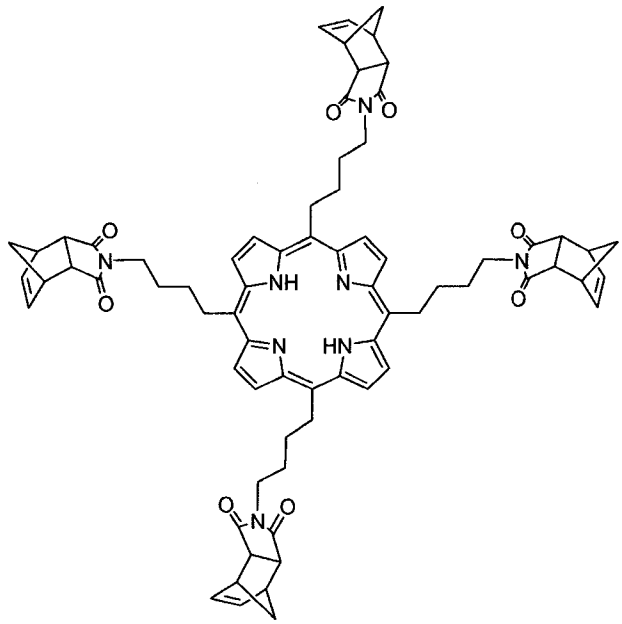
5-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)pentanol (74)

Anhydride **66** (1.64 g, 10.0 mmol) and 5-aminopentanol (1.03 g, 10.0 mmol) dissolved in toluene (80 mL) were heated at reflux for 15 h. The mixture was cooled, extracted with Na_2CO_3 (50 ml), water (50 mL), then dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography gave an oil (400 mg, 16%): IR (CH_2Cl_2, cast) 3444, 2931, 2857, 1765, 1693, 1399, 1337, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (quint, 2H, J = 7.0 Hz, $CH_2C\underline{H}_2CH_2$), 1.42 (quint, 2H, J = 7.0 Hz, $CH_2C\underline{H}_2CH_2$), 1.50 (m, 3H, $C\underline{H}_{bridge}$, $CH_2C\underline{H}_2CH_2$), 1.63 (s, 1H, O$\underline{H}$), 1.69 (dt, 1H, J = 8.7, 3.3 Hz, $C\underline{H}_{bridge}$), 3.19 (dd, 2H, J = 1.5, 3.0 Hz, $C\underline{H}CH_2$), 3.29 (t, 2H, J = 8.0 Hz, $C\underline{H}_2N$), 3.34 (m, 2H, $C\underline{H}CO$), 3.57 (t, 2H, J = 6.60 Hz, $C\underline{H}_2OH$), 6.05 (t, 2H, J = 1.9 Hz, $C\underline{H}{=}C\underline{H}$);$^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 23.0, 27.5, 32.1, 38.2, 44.9, 45.7, 52.2, 62.5, 134.4, 177.8; HRMS (EI) calcd for $C_{14}H_{19}O_3N$ 249.1365, found 249.1267 [M^+] (35.1%).



5-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)pentanal (75)

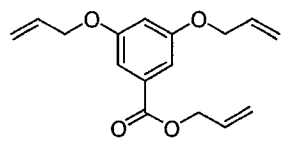
IBX (1.46 g, 5.2 mmol) was added to a solution of **74** (996 mg, 4.00 mmol) in DMSO (10 mL) and the mixture was stirred for 2 h at rt. The mixture was diluted with EtOAc (50 mL), filtered, washed with water (5 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and then concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (3:1) afforded the aldehyde **75** as an oil (770 mg, 77%): (R_f = 0.4, Hex/EtOAc, 2:1); IR (CH_2Cl_2, cast) 2945, 1764, 1695, 1399, 1337, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.56 (m, 5H, C<u>H</u>$_{bridge}$, 2 x $CH_2C\underline{H}_2CH_2$), 1.68 (dt, 1H, J = 8.7, 3.3 Hz, C<u>H</u>$_{bridge}$), 2.39 (dt, 2H, J = 1.4, 7.1 Hz, $C\underline{H}_2CHO$), 3.19 (dd, 2H, J = 1.5, 3.0 Hz, $C\underline{H}CH_2$) 3.30 (t, 2H, J = 8.2 Hz, $C\underline{H}_2N$), 3.35 (m, 2H, C<u>H</u>CO), 6.05 (t, 2H, J = 1.9 Hz, C<u>H</u>=C<u>H</u>), 9.69 (t, 1H, J = 1.5 Hz, C<u>H</u>O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 27.1, 37.8, 43.1, 44.9, 45.7, 52.3, 134.5, 177.7, 201.7; MS (ES) 247.7.



5,10,15,20-Tetrakis(5-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)-pentyl)porphyrin (76)

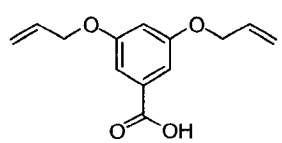
TFA (144 μL, 1.78 mmol) was added to a degassed solution of aldehyde **75** (250 mg, 1.00 mmol) and pyrrole (67 mg, 1.0 mmol) in $CHCl_3$ (100 mL). After the solution was stirred for 60 min, DDQ (181 mg, 0.750 mmol) was added. After an additional 1 h, the reaction mixture was filtered through a Florisil column (2 cm x 10 cm) and eluted with $CHCl_3$. The purple fractions were combined and concentrated *in vacuo* to give a purple solid. This was further purified by flash chromatography (CH_2Cl_2/EtOAc, 2:1→1:2) to give the title compound as a purple solid (79 mg, 22%): R_f = 0.2 (CH_2Cl_2/EtOAc, 3:1) IR (CH_2Cl_2, cast) 2941, 1764, 1694, 1435, 1398, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ -2.74 (s, 2H, NH), 1.50 (d, 4H, J = 8.0 Hz, CH_{bridge}), 1.71 (dt, 4H, J = 8.0, 3.0 Hz, CH_{bridge}), 1.98 (quint, 8H, J = 7.0 Hz, chain CH_2), 2.46 (m, 8H, chain CH_2), 3.24 (dd, 8H, J = 1.5, 3.0 Hz, =CHCH), 3.37 (m, 8H, CHCO), 3.58 (t, 8H, J = 6.6 Hz, CH_2N), 4.97 (t, 8H, J = 6.8 Hz, *meso*CH_2), 5.98 (t, 2H, J = 1.9 Hz, CH=CH), 9.48 (s, 8H, H_β); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 28.7, 35.0, 35.4, 38.2, 45.0, 45.8, 52.3, 117.7, 134.5, 177.8; MS (ES) 1179.6 [MH^+].



Allyl 3,5-bis(allyloxy)benzoate (79)[95]

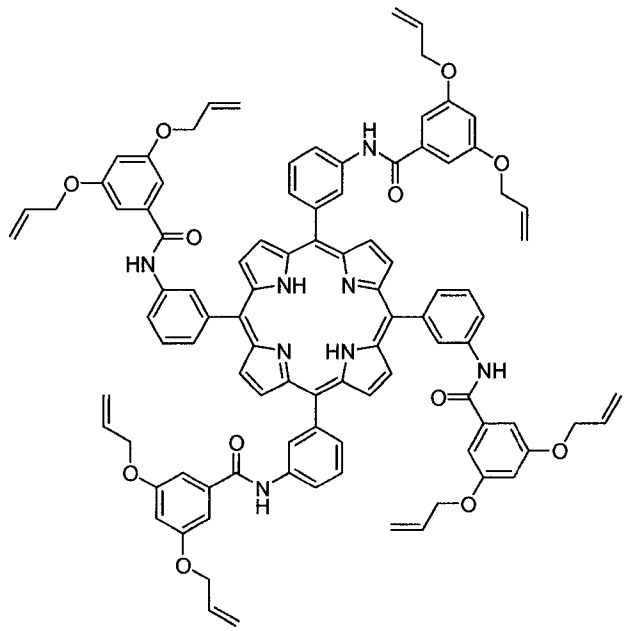
Allyl bromide (10.9 g, 90.0 mmol) was added to a mixture of 3,5-dihydroxybenzoic acid (3.8 g, 25 mmol) and K_2CO_3 (12.4 g, 90.0 mmol). This mixture was heated at 80 °C with stirring for 48 h, after which it was diluted with EtOAc (300 mL), washed with 2.0 M NaOH (3 x 100 mL) water (5 × 150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a liquid (22.1 g, 91%): IR (μscope) 3085, 2985, 2931, 2868, 1722, 1648, 1596, 1446, 1320, 1300, 1225, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.55 (dt, 4H, J = 5.4, 1.5 Hz, $OC\underline{H}_2$), 4.80 (dt, 2H, J = 5.4, 1.5 Hz, $COOC\underline{H}_2$), 5.28 (ddt, 1H, J = 1.5, 10.5 Hz ester $CH{=}C\underline{H}_{cis}H_{trans}$), 5.29 (ddt, 2H, J = 1.5, 10.5 Hz ether $CH{=}C\underline{H}_{cis}H_{trans}$), 5.40 (dd, 1H, J = 17.1, 1.5 Hz $CH{=}CH_{cis}\underline{H}_{trans}$), 5.42 (dd, 1H, J = 17.4, 1.5 Hz $CH{=}CH_{cis}\underline{H}_{trans}$), 6.04 (m, 3H, 3 x $C\underline{H}{=}CH_2$), 6.71 (t, 1H, J = 2.1 Hz, Ar$\underline{H}$), 7.20 (d, 2H, J = 2.4 Hz Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 65.9, 69.3, 107.3, 108.5, 118.2, 118.5, 132.3, 132.5, 133.1, 159.9, 166.1; HRMS (EI) calcd for $C_{13}H_{14}O_4$ 274.1205, found 274.1201 [M^+] (35.2%)



3,5-Bis(allyloxy)benzoic acid (80)[160]

A solution of ester **79** (1.01 g, 4.00 mmol) in THF (10 mL) was added to aqueous 1.0 M LiOH (20 mL). The solution was heated at reflux overnight, then cooled and washed

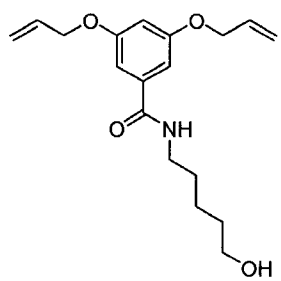
with EtOAc (2 x 10 mL). The mixture was acidified with 1.0 M HCl to pH 1, then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (20 mL), and dried (Na_2SO_4) to give a white solid (880 mg, 94%): mp 39-41 °C (lit.[160] 39-40 mp °C), IR (μscope) 3200-2100, 1693, 1596, 1303, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.56 (d, 4H, J = 5.4 Hz, OC$\underline{H}_2$), 5.29 (dd, 2H, J = 1.2, 10.5 Hz CH=C$\underline{H}_{cis}H_{trans}$), 5.41 (dd, 2H, J = 1.5, 17.1 Hz CH=CH$_{cis}\underline{H}_{trans}$), 6.04 (m, 2H, C$\underline{H}$=CH$_2$), 6.72 (t, 1H, J = 2.1 Hz, Ar$\underline{H}$), 7.24 (d, 2H, J = 2.4 Hz Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 69.1, 108.1, 108.7, 118.0, 130.95, 132.7, 159.7, 171.1; HRMS (EI) calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0892 [M^+] (100%); Anal. calcd for $C_{13}H_{14}O_4$: C, 66.63; H, 5.98; found: C, 66.65; H, 5.99.



5,10,15,20-Tetrakis(3,5-bis(allyloxy)benzamidophenyl)porphyrin (81)

Thionyl chloride (1.0 mL) was added to a solution of acid **80** (234 mg, 1.00 mmol) in CH_2Cl_2 (5 mL). The solution was heated at reflux for 1 h, then concentrated *in vacuo*. The residue was dissolved in THF (5 mL) then added to a solution of porphyrin **60** (84

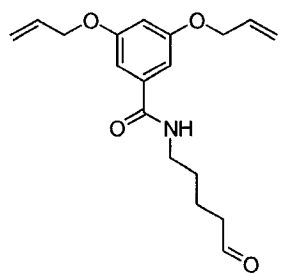
mg, 0.13 mmol) and triethylamine (140 μL, 1.00 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 12 h, concentrated *in vacuo*, then purifed by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH, 20/1), then gel permeation chromatography (DMF, LH-20) to give a purple solid (106 mg, 53%): IR (μscope) 3314, 3082, 2924, 1651, 1591, 1539, 1307, 1165 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ -2.88 (s, 2H, NH), 4.67 (d, 16H, J = 3.5 Hz, CH_2O), 5.24 (m, 16H, CH=$CH_{cis}H_{trans}$), 5.35 (d, 8H, J = 11.0 Hz, CH=$CH_{cis}H_{trans}$), 6.02 (m, 8H, CH=CH_2), 6.75 (s, 4H, ArH), 7.19 (s, 8H, ArH), 7.82 (t, 4H, J = 7.5 Hz, ArH) 8.00 (t, 4H, J = 6.0 Hz, ArH), 8.30 (d, 4H, J = 9.0 Hz, ArH), 8.71 (d, 4H, J = 13.0, ArH), 8.97 (s, 8H, H_β), 10.52 (s, 4H, NHCO); MS (ES) 1539.4 [MH^+].



3,5-Bis(allyloxy)-*N*-(5-hydroxypentyl)benzamide (84)

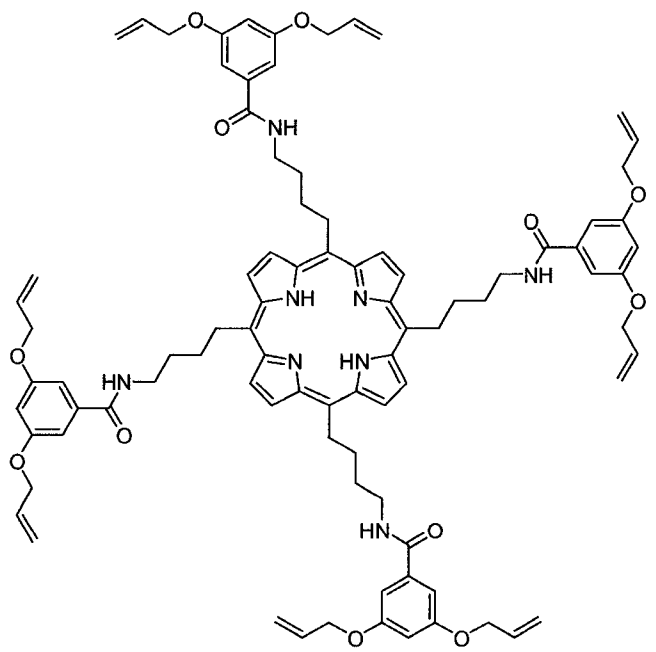
Ester **79** (1.10 g, 4.00 mmol) and 5-aminopentanol (435 mg, 4.00 mmol) were heated in a sealed tube at 140 °C for 12 h. The mixture was cooled, then purifed by flash chromatography to give an oil (593 mg, 55%): mp 61-62 °C, IR (CH_2Cl_2, cast) 3317, 3082, 2935, 2863, 1639, 1592, 1545, 1168, 1054, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40 (m, 2H, $CH_2CH_2CH_2$), 1.57 (m, 4H, $CH_2CH_2CH_2$), 2.03 (s, 1H, OH), 3.38 (q, 2H, J = 6.7 Hz, CH_2NH), 3.60 (t, 2H, J = 6.3 Hz, CH_2OH), 4.48 (d, 4H, J = 5.5 Hz, OCH_2CH), 5.25 (dd, 2H, J = 1.0, 10.5 Hz, CH=$CH_{cis}H_{trans}$), 5.36 (dd, 2H, J = 1.5, 17.5 Hz, CH=$CH_{cis}H_{trans}$), 5.99 (m, 2H, CH_2=CH), 6.38 (s br, 1H, NH), 6.56 (s, 1H, ArH),

6.87 (d, 2H, J = 2.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.2, 29.3, 32.2, 40.0, 62.5, 69.0, 104.7, 105.8, 117.8, 132.7, 136.8, 159.6, 167.2; HRMS (EI) calcd for $C_{18}H_{25}O_4N$ 319.1783, found 319.1783 [M^+] (37.3%).



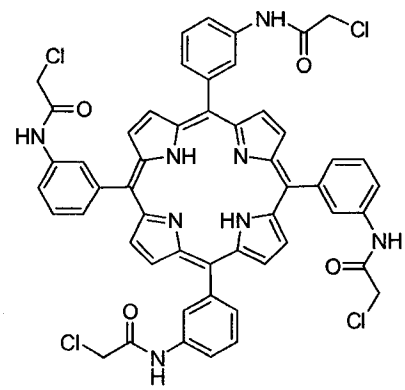
3,5-Bis(allyloxy)-*N*-(5-oxopentyl)benzamide (85)

IBX (1.35 g, 4.80 mmol) was added to a solution of alcohol **84** (510 mg, 1.6 mmol) in EtOAc (15 mL). The resulting suspension was heated at reflux for 2 h, cooled, then filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography (Hex/EtOAc) to give the aldehyde as an oil (370 mg, 72%): R_f = 0.5 (Hex/EtOAc, 1:1), IR (CH_2Cl_2, cast) 3317, 3082, 2935, 2865, 1738, 1592, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (m, 2H, $CH_2CH_2CH_2$), 1.67 (m, 2H, $CH_2CH_2CH_2$), 2.47 (dt, 2H, J = 1.0, 7.0 Hz, CH_2CHO), 3.39 (q, 2H, J = 6.3 Hz, CH_2NH), 4.49 (dt, 4H, J = 5.5, 1.5 Hz, OCH_2CH), 5.25 (dd, 2H, J = 1.2, 10.5 Hz, $CH{=}CH_{cis}H_{trans}$) 5.36 (dd, 2H, J = 1.5, 17.5 Hz, $CH{=}CH_{cis}H_{trans}$), 5.99 (ddt, 2H, J = 17.5, 10.5, 5.3 Hz, $CH_2{=}CH$), 6.42 (s br, 1H, NH), 6.56 (t, 1H, J = 2.0 Hz, ArH), 6.89 (d, 2H, J = 2.0 Hz, ArH), 9.74 (t, 1H, J = 1.5 Hz, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 29.0, 39.5, 43.4, 69.0, 104.9, 105.8, 117.9, 132.8, 136.8, 159.8, 167.3; HRMS (EI) calcd for $C_{16}H_{25}O_4N$ 317.1783, found 317.1783 [M^+] (11.3%)



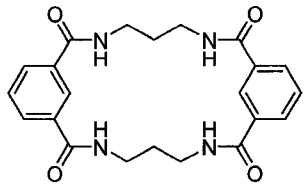
5,10,15,20-Tetrakis(4-*N*-(3,5-bis(allyloxy)benzamido)butylporphyrin (86)

BF_3•Et_2O (45 μL, 0.36 mmol) was added to a stirred solution of aldehyde **85** (340 mg, 1.07 mmol) and pyrrole (72 mg, 1.1 mmol) in $CHCl_3$ (0.75% EtOH). After 1 h, DDQ (182 mg, 0.801 mmol) was added, and the solution stirred 1 h further, then filtered through Florisil. The column was eluted with $CHCl_3$ until the eluant was light pink. Purple fractions were concentrated *in vacuo* (17 mg, 4%): IR (CH_2Cl_2, cast) 3318, 2931, 1645, 1591, 1538, 1166, 1053, 926 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -2.83 (s, 2H, NH), 1.80 (m, 8H, $CH_2CH_2CH_2$), 2.39 (m, 8H, $CH_2CH_2CH_2$), 3.40 (m, 8H, CH_2N), 4.40 (dt, 16H, J = 1.6, 5.6 Hz, $CHCH_2O$), 4.69 (t, 8H, J = 6.8 Hz, CH_2Por), 5.25 (dd, 2H, J = 1.2, 10.6 Hz, $CH{=}CH_{cis}H_{trans}$), 5.36 (dd, 2H, J = 1.6, 16.0 Hz, $CH{=}CH_{cis}H_{trans}$), 5.99 (dq, 2H, $½J_{cis} \approx J_{CHCH2}$ = 5.2 Hz, J_{trans} = 16.0 Hz, $CH_2{=}CH$), 6.42 (t, 4H, J = 5.2 Hz, NH), 6.51 (t, 4H, J = 2.2 Hz, ArH), 6.81 (d, 8H, J = 2.4 Hz, ArH), 9.22 (s, 8H, H_β); MS (ES) 1459 [MH^+]; λ_{abs} 419, 520, 556, 600, 667 nm.



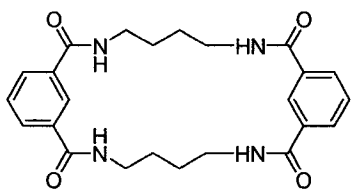
5,10,15,20-Tetrakis(3-chloroacetamidophenyl)porphyrin (92)

This compound was prepared by an adaptation of a procedure reported by Collman.[98] A solution of chloroacetyl chloride (201 μL, 2.50 mmol) in THF (30 mL) was added dropwise over 30 min to a stirred solution of **60** (337 mg, 0.500 mmol) and triethylamine (522 μL, 3.00 mmol) in THF (30 mL) at 0 °C. The solvent was removed *in vacuo* and the purple residue purified by flash chromatography (CH_2Cl_2 → CH_2Cl_2, 5% MeOH) to give a purple solid (372 mg, 76%): IR (μscope) 3270, 2953, 1681, 1649, 1605, 1587, 1550, 1484, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.79 (s, 2H, NH), 4.29 (s, 8H, CH_2Cl), 7.81 (t, 4H, J = 8.0 Hz ArH), 7.99 (d, 4H, J = 6.0 Hz, ArH), 8.09 (m, 4H, ArH), 8.53 (d, 4H, J = 13.5 Hz, ArH), 8.91 (s, 8H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.6, 118.9, 119.6, 125.4, 127.5, 130.1, 131.4, 137.1, 141.6, 165.1, 168.5; HRMS (ES) calcd for $C_{52}H_{39}O_4N_8{}^{35}Cl_4$ 979.1848, found 979.1846, λ_{abs} 419, 449, 514, 660 nm.



3,7,15,19-Tetraaza-tricyclo[19.3.1.1^{9,13}]hexacosa-1(25),9,11,13(26),21,23-hexaene-2,8,14,20-tetraone (97)

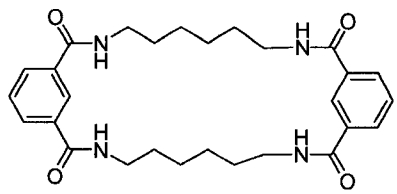
Thionyl chloride (3.93 g, 18.2 mmol) was added to a suspension of isophthalic acid (1.00 g, 6.02 mmol) in CH_2Cl_2 (50 mL) and DMF (1 drop). This solution was heated at reflux for 8 h, after which it was concentrated *in vacuo*, dissolved in CH_2Cl_2 (20 mL) then concentrated again *in vacuo*. This residue was dissolved again in CH_2Cl_2 (120 mL) and cooled to 0 °C. 1,3-Propanediamine (0.445 g, 6.02 mmol) was added dropwise (exothermic!) to the solution of isophthaloyl dichloride. Precipitate was immediately formed. The solution was stirred for 1 h, then filtered. The filtrate was triturated with CH_2Cl_2, MeOH (5% DMF), and THF, then dried *in vacuo* (0.72 g, 71%): IR (μscope) 3305, 3073, 2953, 1645, 1546, 1295 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 1.80 (quint, 8H, J = 6.0 Hz, C<u>H</u>$_2$CH$_2$N), 3.34 (q, 8H, J = 6.2 Hz, CH$_2$N), 7.52 (t, 2H, J = 7.5 Hz, Ar<u>H</u>), 7.94 (d, 4H, J = 7.5 Hz, Ar<u>H</u>), 8.31 (s, 2H, Ar<u>H</u>), 8.61 (s br, 4H, N<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.1, 37.1, 125.9. 128.1, 129.4, 134.6, 165.6; MS (ES) 408 [MH$^+$].



3,8,17,22-Tetraaza-tricyclo[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-2,10,16,22-tetraone (98)

Thionyl chloride (3.93 g, 18.2 mmol) was added to a suspension of isophthalic acid (1.00 g, 6.02 mmol) in CH_2Cl_2 (50 mL) and DMF (1 drop). This solution was heated at reflux

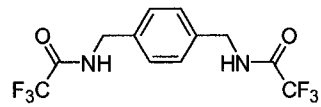
for 8 h, after which it was concentrated *in vacuo*, dissolved in CH_2Cl_2 (20 mL) then concentrated again *in vacuo*. This residue was dissolved again in CH_2Cl_2 (120 mL) and cooled to 0 °C. 1,4-Butanediamine (0.530 g, 6.02 mmol) was added dropwise (exothermic!) to the solution of isphthaloyl dichloride. Precipitate was immediately formed. The solution was stirred for 1 h, then filtered. The filtrate was triturated with CH_2Cl_2, MeOH (10% DMF), and THF, then dried *in vacuo* (0.70 g, 65%): IR (μscope) 3300, 3069, 2937 1639, 1537, 1300 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ ; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ 1.70-1.80 (m, 8H, 8 x $C\underline{H}_2CH_2N$), 3.2-3.30 (m, 8H, 4 x $CH_2\underline{N}$), 7.50 (t, 2H, J = 7.5 Hz, Ar$\underline{H}$), 7.91 (d, 4H, J = 7.5 Hz, Ar$\underline{H}$), 8.31 (s, 2H, Ar$\underline{H}$), 8.61 (s br, 4H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 37.2, 125.9. 128.1, 129.4, 134.6, 165.6; HRMS EI calcd $C_{24}H_{28}O_4N_4$ 436.2111 found: 436.2096 [M^+] 16.5%.



3,12,18,25-Tetraaza-tricyclo[25.3.1.1^{12,16}]dotriaconta-1(31),12,14,16(32),27,29-hexaene-2,13,15,23-tetraone (99)

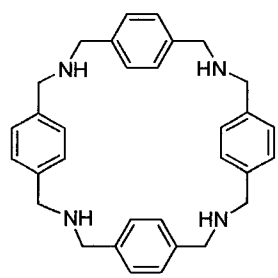
Thionyl chloride (3.93 g, 18.2 mmol) was added to a suspension of isophthalic acid (1.00 g, 6.02 mmol) in CH_2Cl_2 (50 mL) and DMF (1 drop). This solution was heated at reflux for 8 h, after which it was concentrated *in vacuo*, redissolved in CH_2Cl_2 (20 mL) then concentrated again *in vacuo*. This residue was dissolved again in CH_2Cl_2 (120 mL) and cooled to 0 °C. 1,6-Hexanediamine (698 mg, 6.02 mmol) was added dropwise (exothermic!) to the solution of isophthaloyl dichloride. Precipitate formed immediately. The solution was stirred for 1 h, then filtered. The filtrate was triturated with CH_2Cl_2,

MeOH (5% DMF), and THF, then dried *in vacuo* (860 mg, 56%): IR (μscope) 3350-3220, 2961, 1628, 1169 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 1.33 (s br, 8H, 4 x $N(CH_2)_2C\underline{H}_2$), 1.52 (s br, 8H, 4 x $NCH_2C\underline{H}_2$), 3.20-3.26 (m, 8H, 4 x $NC\underline{H}_2$), 7.50 (t, 2H, J = 7.8 Hz, Ar$\underline{H}$), 7.92 (d, 4H, J = 7.8 Hz, Ar$\underline{H}$); 8.27 (s br, 2H, Ar$\underline{H}$), 8.53 (s br, 4H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2, 29.0, 40 (obtained from HMQC), 126.1, 128.2, 129.5, 134.9, 165.7; HRMS EI calcd $C_{28}H_{36}O_4N_4$ 492.2737 found: 492.2731 [M^+] 16.5%.



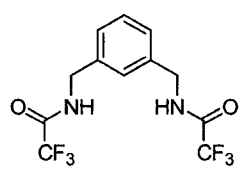
1,4-Bis(trifluoroacetamidomethyl)benzene (104)[101]

TFAA (5.0 mL, 35 mmol) was added dropwise (exothermic!) to a solution of 1,4-bis(aminomethyl)benzene (2.2 g, 16 mmol) in dry Et_2O (35 mL) at 0 °C with vigorous stirring. A white precipitate was immediately produced. The mixture was stirred for 12 h and allowed to warm to rt. The mixture was filtered, rinsed with cold Et_2O, and recrystallized from acetone/CH_2Cl_2 to give white needles (4.08 g, 76%): mp 197-198 °C (lit.[101] 199-201.5 °C); IR (μscope) 3263, 3097, 2887, 1782, 1676, 1606, 1571, 1518, 1461, 1334, 1168, 701 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ 4.36 (d, 4H, J = 5.2 Hz, $C\underline{H}_2$), 7.25 (s, 4H, Ar$\underline{H}$), 9.96 (t, 2H, J = 5.1 Hz, N$\underline{H}$); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 42.3, 115.8 (q, $^1J_{HF}$ = 283.3 Hz, $\underline{C}F_3$), 127.4, 136.4, 156.0 (q, $^2J_{HF}$ = 36.1 Hz, $\underline{C}OCF_3$); HRMS (EI) calcd for $C_{12}H_{10}O_2N_2F_6$ 328.0646 found: 328.0643 [M^+].



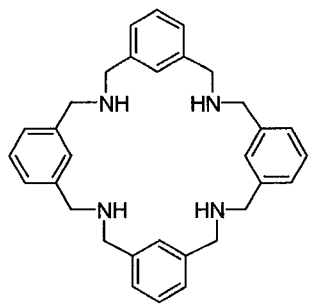
2,11,20,29-Tetraaza[3.3.3.3]paracyclophane (105)[101]

Diamide **104** (2.19 g, 6.66 mmol) in DMF (10 mL) was added to a dispersion of sodium hydride (536 mg, 13.3 mmol) in DMF (50 mL) over 10 min, then heated to 100 °C for 30 min. 1,3-α,α-Dibromoxylene (1.77 g, 6.66 mmol) in DMF (30 mL) was added dropwise by cannula over 1 h. The mixture was heated overnight at 100 °C, cooled, concentrated *in vacuo*, and extracted with CH_2Cl_2 (200 mL). These extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was taken up in EtOH (100 mL) and treated with $NaBH_4$ (3.5 g, 84 mmol), and heated at reflux for 5 h. The solvent was removed *in vacuo*. The residue was acidified with 1.0 M HCl to pH 1, washed with CH_2Cl_2 (50 mL), made basic (pH 11) with 1.0 M NaOH, then extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were washed with water (100 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The resultant oil was triturated with CH_3CN (50 mL) and sonicated (20 min) to give a white precipitate (mixture of tetramer and hexamer as determined by MS). This precipitate was purified by gel permeation chromatography (Sephadex LH-20 in $CHCl_3$/MeOH 3:1) to give the cyclophane as a white powder (301 mg, 19%): mp 197-198 °C (lit.[101] 199-201.5 mp °C) IR (μscope) 3273, 2912, 2883, 1451, 1112, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 4H, N<u>H</u>), 3.68 (s, 16H, C<u>H</u>$_2$), 7.05 (s, 16H, Ar<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.7, 128.3, 139.2; HRMS (ES) calcd for $C_{24}H_{37}N_4$ 477.3018, found 477.3017 [MH^+].



1,3-Bis(trifluoroacetamidomethyl)benzene (107)[102]

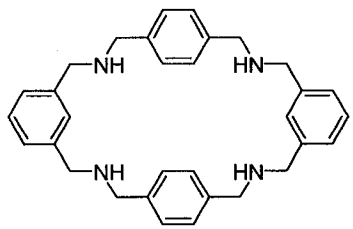
TFAA (5.0 mL, mmol) was added dropwise to a solution of 1,4-bis(aminomethyl)benzene in dry Et_2O (35 mL) at 0 °C with vigorous stirring. A white precipitate was immediately produced. The mixture was stirred overnight and allowed to warm to rt. The mixture was filtered, rinsed with cold Et_2O, and recrystallized from acetone/CH_2Cl_2 to give white needles (3.94 g, 75%): mp 163-164 °C (lit.[102] 165-167.5 °C); IR (μscope) 3291, 3101, 2951, 1705, 1556, 1448, 1361, 1177, 702 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ 3.97 (d, 4H, J = 6.0 Hz, C<u>H</u>$_2$), 6.77 (d, 2H, J = 7.4 Hz, Ar<u>H</u>), 6.79 (s, 1H, Ar<u>H</u>), 6.93 (t, 1H, J = 8.0 Hz, Ar<u>H</u>), 9.59 (s br, 2H, J = 6.0 Hz, N<u>H</u>); ^{13}C NMR ($(CD_3)_2SO$, 500 MHz) δ 42.4, 115.9 (q, $^1J_{HF}$ = 286.3 Hz, <u>C</u>F$_3$), 125.8, 126.2, 128.5, 137.6, 155.8 (q, $^2J_{HF}$ = 36.1 Hz, <u>C</u>OCF$_3$) δ HRMS (ES) calcd for $C_{12}H_{10}O_2N_2F_6Na$ 351.0539, found: 351.0537 [MNa^+].



2,11,20,29-Tetraaza[3.3.3.3]metacyclophane (108)[102]

Four portions of freshly ground KOH (1.0 g ea.) were added at 15 minute intervals to a refluxing solution of 1,3-α,α'-dibromoxylene (5.28 g, 20.0 mmol) and diamide **107** in acetone (450 mL). The mixture was heated at reflux for a further 2 h, concentrated *in vacuo*, triturated with CH_2Cl_2 (700 mL), dried (Na_2SO_4), then again concentrated *in vacuo*. This mixture was taken up in EtOH (350 mL), and heated to reflux with $NaBH_4$ (10 g, excess) for 5 h, cooled, and concentrated *in vacuo*. The residue was diluted with

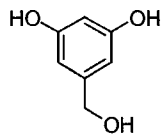
water, acidified to pH 1 with conc. HCl, then washed with CH_2Cl_2 (100 mL x 2). The aqueous extract was basified to pH 11, then extracted with CH_2Cl_2 (150 mL x 3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by gel permeation chromatography (Sephadex LH-20 in $CHCl_3$/MeOH 3:1) gave a white powder (0.86 g, 18%): mp 197-198 °C (lit.[102] 199-201.5 °C), IR (CH_2Cl_2, cast) 3303, 3023, 2912, 2814, 1607, 1589, 1546, 1055, 1087, 781, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 4H, NH), 3.78 (s, 16H, CH_2N), 7.16-7.21 (m, 12H, ArH), 7.22-7.28 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.7, 73.2, 76.6, 77.1, 77.5, 127.1, 127.8, 128.4, 140.5; HRMS (ES) calcd for $C_{32}H_{37}N_4$ 477.3018, found 477.3018 [M+H].



2,11,20,29-Tetraaza[3.3.3.3] (para)(meta)(para)(meta)cyclophane (109)

Diamide **104** (2.19 g, 6.66 mmol) in DMF (10 mL) was added to a dispersion of sodium hydride (536 mg, 13.3 mmol) in DMF (50 mL) over 10 min, then heated to 100 °C for 30 min. 1,3-α,α'-Dibromoxylene in DMF (30 mL) was added dropwise by cannula over 1 h. The mixture was stirred overnight at 100 °C, cooled, concentrated *in vacuo*, and extracted with CH_2Cl_2 (200 mL). These extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was taken up in EtOH and treated with $NaBH_4$ (3.5 g, 84 mmol), and heated at reflux for 5 h. The mixture was concentrated *in vacuo,* acidified to pH 1 with 1.0 M HCl, washed with CH_2Cl_2 (50 ml), made basic to pH 11 with 1.0 M NaOH, then extracted with CH_2Cl_2 (3 x 80 mL). The combined orgainc layers were washed with water (100 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The resultant oil was

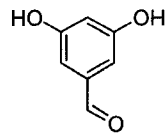
triturated with CH_3CN (50 mL) and sonicated (20 min) to give a white precipitate (mixture of tetramer and hexamer as determined by MS). This precipitate was purified by gel permeation chromatography (Sephadex LH-20 in $CHCl_3$/MeOH, 3:1) to give the cyclophane as a white powder (330 mg, 21%): mp 106-107 °C; IR (μscope) 3297, 3265, 3015, 2805, 1609, 1510, 1455, 1334, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 4H, NH), 3.50 (s, 8H, CH_2) 3.88 (s, 8H, CH_2), 5.54 (s, 2H, ArH), 6.76 (s, 8H, ArH), 6.86 (d, 4H, J = 7.8 Hz, ArH), 7.09 (t, 2H, J = 7.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.8, 54.4, 125.1, 127.6, 128.3, 129.0, 140.0, 142.8; HRMS (EI) calcd for $C_{32}H_{36}N_4$ 476.2940, found 476.2938.



3,5-Dihydroxybenzyl alcohol (92)[105]

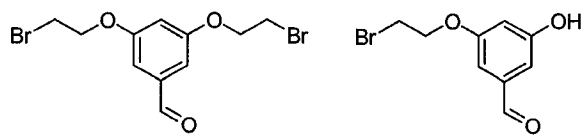
$BH_3 \cdot Me_2S$ in THF (26 mL of 10.0 M solution, 260 mmol) was added to a solution of 3,5-dihyroxybenzoic acid (12.5 g, 80 mmol) in distilled THF (200 mL) at 0 °C. The mixture was allowed to warm to rt over 1 h, then heated at reflux for 3 h. The reaction mixture was cooled, quenched with H_2O (80 mL), then acidified with 1.0 M HCl to pH 8, and stirred for 30 min. Brine was added (80 mL), the layers were separated, and the aqueous layer was saturated with solid sodium chloride. The aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (2 x 80 mL), dried (Na_2SO_4) and concentrated *in vacuo*. This material was recrystallized from acetone/hexanes to give a white solid (8.06 g, 72%): mp 178-181°C, (lit.[161] 181-184 °C); IR (μscope) 3600-2300, 3307, 2979, 2948, 1644, 1545, 1294 cm^{-1}; ^1H NMR (DMSO, 300

MHz) δ 4.30 (s, 2H, CH_2), 6.05 (t, 1H, J = 2.1 Hz, ArH), 6.17 (d, 2H, J = 2.1 Hz, ArH); HRMS (EI) calcd for $C_7H_8O_3$ 140.0474, found 140.0474 [M^+] (100%).



3,5-Dihydroxybenzaldehyde (114)[106]

Jones' reagent (50 mL) was added to a stirred solution of 3,5-dihyroxybenzyl alcohol (1.40 g, 10.0 mmol) in acetone. After 5 min, the solution was extracted with EtOAc (2 x 100 mL). The combined extracts were washed with water (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 3/1) gave a tan solid which was pure judged by ^{1}H NMR (0.470 g, 66%). This solid could be recrystallized from Hex/EtOAc to give a white solid (0.36 g, 51%): mp 158-160 °C (lit.[106] 162-163 °C); IR (μscope) 3600-2500 (br), 1679, 1605, 1493, 1343, 1177, 1146 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 6.52 (t, 1H, J = 2.4 Hz, ArH), 7.77 (d, 2H, J = 2.4 Hz, ArH), 9.75 (s, 1H, CHO); ^{13}C NMR (CD_3OD, 75 MHz) δ 108.7, 109.8, 140.1, 160.5, 194.1; HRMS (EI) calcd for $C_7H_6O_3$ 138.0317, found 138.0316 [M^+] (100%).

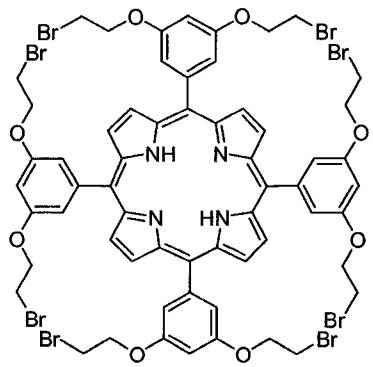


3,5-Bis(2-bromoethoxy)benzaldehyde (115a)

3-(2-Bromoethoxy)-5-hydroxybenzaldehyde (115b)

1,2-Dibromoethane (7.00 g, 37.6 mmol) was added to a degassed suspension of 3,5-dihydroxybenzaldehyde (440 mg, 3.19 mmol) and K_2CO_3 (1.80 g, 13.0 mmol) in CH_3CN (30 mL). This was heated to reflux with stirring for 14 h under an argon atmosphere. The mixture was allowed to cool, diluted with H_2O (10 mL), extracted with ethyl acetate

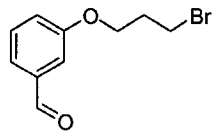
(2 x 20 mL). The organic layer was washed with sat'd Na_2CO_3 (3 x 10 mL), H_2O (2 x 5 mL), brine (5 mL) and then dried (Na_2SO_4). This residue was purified by flash chromatography in Hex/EtOAc (10/1 → 5/1) to give **115a** (468 mg, 42%) and **115b** (235 mg, 30%) as a white powders: Data for **115a**: mp 94-95 °C, IR (μscope) 3065, 3033, 2803, 2721, 1707, 1589, 1326, 1316, 1176, 1079, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.64 (t, 4H, J = 6.0 Hz, C$\underline{H}_2$Br), 4.32 (t, 4H, C$\underline{H}_2$O), 6.74 (t, 1H, J = 2.4 Hz, Ar$\underline{H}$), 7.02 (d, 2H, J = 2.4, Ar$\underline{H}$), 9.89 (s, 1H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.8, 68.3, 108.4, 108.5, 138.6, 159.8, 191.3; HRMS (EI) calcd for $C_{11}H_{12}O_3{}^{79}Br_2$ 349.9153, found 349.9153 [M^+] (50.7%). Data for **115b**: ^1H NMR ($CDCl_3$, 600 MHz) δ 3.63 (t, 2H, J = 6.0 Hz, C$\underline{H}_2$Br), 4.31 (t, 2H, C$\underline{H}_2$O), 5.45 (s, 1H, O$\underline{H}$), 6.67 (t, 1H, J = 2.4 Hz, Ar$\underline{H}$), 6.97 (m, 2H, Ar$\underline{H}$), 9.86 (s, 1H, C$\underline{H}$O); HRMS (EI) calcd for $C_9H_9O_3{}^{81}Br$ 245.9714, found: 245.9715 [M^+] (70.1%).



5,10,15,20-Tetrakis(3,5-bis(2-bromoethoxy)phenyl)porphyrin (116)

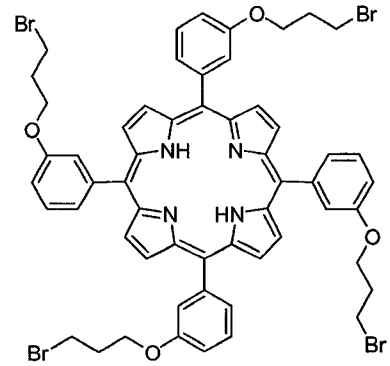
$BF_3{\cdot}Et_2O$ (19 μL, 0.15 mmol) was added to a stirred solution of aldehyde **115a** (175 mg, 0.500 mmol) and pyrrole (33.5 g, 0.500 mmol) in argon purged $CHCl_3$. After 1 h, DDQ (85 mg, 0.38 mmol) was added and the mixture was stirred for 1 h. The solution was dried *in vacuo* to dampness, and purified by flash chromatography (Hex/CH_2Cl_2, 1:1) to give a purple solid (76 mg, 38%): IR (μscope) 3296, 3137, 2919, 1718, 1594, 1452,

1432, 1162, 1051, 925 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.79 (s, 2H, NH), 3.71 (t, 8H, J = 6.3, CH_2Br), 4.52 (t, 8H, J = 6.3 Hz, OCH_2), 6.93 (t, 4H, J = 1.1 Hz, ArH), 7.41 (d, 8H, J = 2.3 Hz, ArH), 8.90 (s, 8H, H_β), 7.84 (d, 4H, J = 7.5 Hz ArH), 8.91 (s, 8H, CH_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.5, 65.6, 132.2, 138.7, 143.5, 157.1; 3 carbon signals not observed due to dilute solution; ES-MS 1599 [M+H].



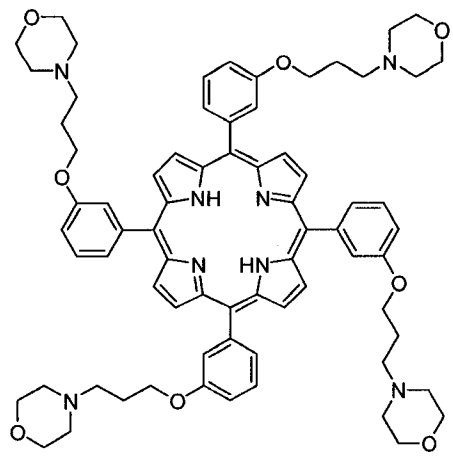
3-(3-Bromopropoxy)benzaldehyde (119)[107]

3-Hydroxybenzaldehyde (2.40 g, 20.0 mmol), 1,3-dibromopropane (8.08 g, 40.0 mmol), and K_2CO_3 (3.31 g, 24.0 mmol) were heated to reflux in CH_3CN (60 mL) for 6 h under an argon atmosphere. The mixture was concentrated *in vacuo* to ¼ volume and dissolved in EtOAc/H_2O (200/100 mL), separated, and washed with 2N NaOH (4 x 50 mL), water (2 x 50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (10/1) afforded the aldehyde as an oil (2.10 g, 58%): IR (μscope) 3374, 3067, 2934, 2820, 2729, 1697, 1597, 1584, 1287, 1264, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33 (quint, 4H, J = 6.4 Hz, CH_2CH_2), 3.60 (t, 2H, CH_2Br), 4.16 (t, J = 5.8 Hz, 2H, OCH_2), 7.17 (dt, 1H, J = 7.0, 2.4 Hz, ArH), 7.39 (m, 3H, ArH), 9.95 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.8, 32.3, 65.6, 112.8, 121.8, 123.6, 130.0, 137.8, 159.1, 191.8; HRMS (EI) calcd for $C_{10}H_{11}{}^{81}BrO_2$ 243.9922, found 243.9917 [(M+)] (46.3%); Anal. calcd for $C_{10}H_{11}BrO_2$ C, 49.41; H, 4.56; found C, 49.06; H, 4.64.



5,10,15,20-Tetrakis[3-(3-bromopropoxy)phenyl]porphyrin (120)

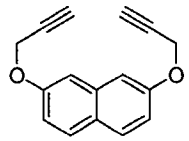
$BF_3{\cdot}Et_2O$ (190 μL, 1.50 mmol) was added to a stirred solution of aldehyde **119** (1.21 g, 5.00 mmol) and pyrrole (335 μL, 5.00 mmol) in $CHCl_3$ (500 mL, 0.75% EtOH). After 1 h, DDQ (851 mg, 2.25 mmol) was added, and the solution stirred for a further 1 h, then filtered through Florisil, and concentrated *in vacuo* to give the title compound (697 mg, 40%): IR (μscope) 3318, 3061, 2927, 2876, 1596, 1575, 1468, 1432, 1349, 1285, 1257, 1181, 1165, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ –2.52 (s, 2H, NH), 2.40 (quint, 8H, J = 6.1 Hz, $CH_2C\underline{H}_2$), 3.67 (t, 8H, J = 6.5, $C\underline{H}_2Br$), 4.29 (t, 8H, J = 5.8 Hz, $OC\underline{H}_2$), 7.32 (t, 4H, J = 8.0 Hz, Ar$\underline{H}$), 7.64 (t, 4H, J = 8.0 Hz, Ar$\underline{H}$), 7.80 (s, 4H, Ar$\underline{H}$), 7.84 (d, 4H, J = 7.5 Hz, Ar$\underline{H}$), 8.91 (s, 8H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 32.5, 65.6, 114.1, 119.8, 121.2, 127.6, 127.9, 130.9 143.5, 157.1; ES-MS 1162.9, Anal. calcd for $C_{56}H_{50}Br_4N_4O_4$: C, 57.85; H, 4.33; N, 4.82; found: C, 57.61; H, 4.12; N, 4.60.



5,10,15,20-Tetrakis[3-(*N*-morpholinylpropoxy])phenyl]porphyrin (122)

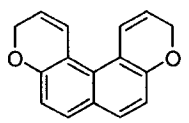
Method A: Morpholine (37 mg, 0.44 mmol) was added to a solution of tetrabromoporphyrin **120** (116 mg, 0.100 mmol) in CH_2Cl_2/DMF (2 mL, 4 mL) at 60 °C. The solution was stirred for 16 h, concentrated *in vacuo*, redissolved in EtOAc (10 mL), washed with $NaHCO_3$ (5 mL), water (3 x 5 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography to give a purple solid (81 mg, 68%).

Method B: Tetrabromoporphyrin **120** (12 mg, 0.01 mmol) was dissolved in a solution of 20% morpholine in DMF (5 mL). The solution was stirred for 2 h, concentrated, and worked up as above without the need for chromatography (11 mg, 92%): IR (μscope) 3316, 2953, 2853, 2811, 1595, 1287, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (quint, 8H, J = 7.0 Hz, $CH_2C\underline{H}_2CH_2$), 2.46 (s br, 16H, ring $C\underline{H}_2N$), 2.57 (t, 8H, J = 4.5 Hz, chain $NC\underline{H}_2$), 3.67-3.70 (m, 16H, ring $C\underline{H}_2O$), 4.20 (t, 8H, J = 6.5 Hz, $C\underline{H}_2OAr$), 7.32 (dd, J = 7.5 Hz, Ar$\underline{H}$), 7.64 (t, 4H, J = 8.0 Hz Ar$\underline{H}$), 7.80 (s, 4H, Ar$\underline{H}$), 7.84 (d, 4H, J = 7.5 Hz Ar$\underline{H}$), 8.87 (s, 8H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 32.5, 65.6, 114.1, 119.8, 121.2, 127.6, 127.9, 130.9 143.5, 157.1; ES-MS 1187.6 [M+H].



2,7-Bis(prop-2-ynyloxy)naphthalene (133)[117]

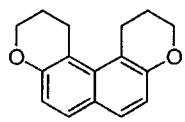
A solution of 80% propargyl bromide in toluene (220 mmol, 24.5 mL) was added to a suspension of 2,7-dihydroxynaphthalene (16 g, 0.10 mol) in acetone (300 mL). The mixture was heated at reflux for 16 h, and then cooled to rt, diluted with EtOAc, washed with H_2O (2 x 100 mL) and Na_2CO_3 (2 x 100 mL) and brine (2 x 75 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a dark brown solid. This was purified by flash chromatography (Hex/EtOAc, 10:1) to give the diyne (20.2 g, 86%): mp 93-94 °C (lit.[117] 93-94 °C), IR (μscope) 3296, 3287, 3271, 2109, 1628, 1513, 1214, 1202, 1032, 819, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.54 (t, 2H, J = 5.0 Hz, $CH_2CC\underline{H}$), 4.78 (d, 4H, J = 2.5 Hz, $C\underline{H_2}$), 7.05 (dd, J = 9.0, 2.5 Hz, 2H, Ar H_3, H_6), 7.15 (d, 2H, J = 2.5 Hz, Ar H_1, H_8), 7.67 (d, 2H, J = 9.0 Hz, H_4, H_5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.9, 75.6, 78.5, 107.0, 116.5, 125.0, 129.2, 135.3, 156.1, HRMS (EI) calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0821 [M+] (80%).



3*H*,10*H*-4,9-Dioxabenzo[c]phenanthrene (134)[117]

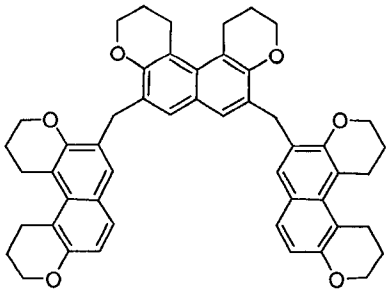
A suspension of diyne **133** (14.0 g, 59.3 mmol) in *N*,*N*-diethylaniline (140 mL) was degassed with Ar (g) for 10 min. The solution was then brought to reflux for 9 min and then cooled to rt. The mixture was poured into 1:1 conc. HCl:H_2O (250 mL) and ice (100 g), then extracted with Et_2O (4 x 200 mL). The combined organic layers were washed with 1.0 M HCl (4 x 100 mL), H_2O (2 x 100 mL), sat'd $NaHCO_3$ (100 mL) and brine (2 x

75 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a dark green/brown viscous oil. Flash chromatography (Hex:CH_2Cl_2, 4:1) gave 9.20 g (66%) of **134** as a yellow:orange solid which slowly decomposed on exposure to light and air: mp dec. 94-97 °C (lit.[117] mp 97-98 °C); IR (μscope) 3058, 2982, 1625, 1377, 1233, 1003, 837, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.73, (dd, 2H, J = 1.5, 4.5 C$\underline{H}_2$), 5.73 (dt, 2H, J = 4.2, 9.6 Hz, $CH_2C\underline{H}$), 6.94 (dd, J = 9.0, 0.5 Hz, 2H, Ar H_3, H_6), 7.00 (dd, 2H, J = 9.5, 0.5 Hz, Ar H_1, H_8), 7.53 (d, 2H, J = 9.0 Hz, H_4, H_5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.5, 114.9, 115.2, 115.8, 125.77, 126.02, 129.3, 130.593, 154.9, HRMS (EI) calcd $C_{16}H_{12}O_2$ 236.0837, found 236.0832 [M^+] (100%).

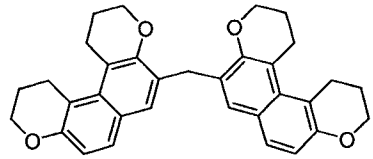


2,3,11,12-Tetrahydro-1*H*,10*H*,-4,9-dioxabenzo[c]phenanthrene (135)[117]

Diene **134** (9.20 g, 38.7 mmol) and Pd/C (5%, 80 mg) were stirred in acetone (100 mL) under an atmosphere of H_2 for 16 h. The mixture was diluted with EtOAc to dissolve a white precipitate formed, then filtered, and concentrated in vacuo to afford **135** as a light gray powder. Recrystallization from minimal MeOH/acetone gave the title compound as a white powder (7.80 g, 85%): mp 196-198 °C (lit.[117] 193 °C), IR (CH_2Cl_2, cast) 2956, 2920, 2873, 1610, 1441, 1246, 1234, 1117, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.98 (tt, 4H, J = 5.0, 6.2 Hz, $CH_2C\underline{H}_2CH_2$), 3.30 (t, 4H, J = 6.2 Hz, C$\underline{H}_2$Ar), 4.23 (t, 4H, J = 5.0 Hz, OC$\underline{H}_2$), 6.84 (d, 2H, J = 8.8 Hz, Ar$\underline{H}$), 7.44 (d, 2H, J = 8.8 Hz, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 27.1, 65.5, 114.7, 116.3, 125.2, 128.7, 135.9, 153.9 HRMS (EI) calcd $C_{16}H_{16}O_2$ 240.1150, found 240.1144 [M^+] (100%).



137



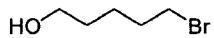
125

4,4'-Bis(2,3,11,12-tetrahydro-1*H*,10*H*,-4,9-dioxabenzo[c]phenanthrene)methane (125)[113]

4,7-Bis(4-(2,3,11,12-Tetrahydro-1*H*,10*H*,-4,9-dioxabenzo[c]phenanthrenyl)-2,3,11,12-tetrahydro-1*H*,10*H*,-4,9-dioxabenzo[c]phenanthrene (137)

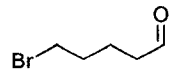
A solution of compound **136** (1.00 g, 4.20 mmol) and $MeOCH_2Cl$ (79 μL, 1.0 mmol) in CH_2Cl_2 was cooled to 0 °C under argon. $SnCl_4$ (1.7 mL of a 1.0 M solution in CH_2Cl_2, 1.7 mmol) was added dropwise, and the mixture allowed to warm to rt over 50 min. After being quenched with sat'd $NaHCO_3$ (2 mL), the mixture was diluted with CH_2Cl_2 (30 mL), separated, and the organic layer was washed with water (2 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/CH_2Cl_2 (1:1) afforded the title compound **125** as white solid (0.241 g, 23%), and by-product **137** (58 mg, 6%) and starting material **136** (45%). Higher oligomers were also isolated as a mixture (*vide infra,* MS). Data for **125**: mp (dec) 262-270 °C, (lit.[116] dec. 267-269 °C); IR (CH_2Cl_2, cast) 2956, 2868, 1610, 1498, 1431, 1383, 1239, 1222, 1160, 1119 cm^{-1}: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.96 (quint, 4H, J = 6.5 Hz, $C\underline{H}_2CH_2O$), 1.97 (quint, 4H, J = 6.5 Hz, $C\underline{H}_2CH_2O$), 3.30 (t, 4H, J = 6.5 Hz, $C\underline{H}_2Ar$), 3.33 (t, 4H, J = 6.5 Hz, $C\underline{H}_2Ar$), 4.22 (t, 4H, J = 5.0 Hz $ArC\underline{H}_2$), 4.23 (t, 4H, J = 5.0 Hz, $ArC\underline{H}_2$), 6.77 (d, 2H, J = 8.8 Hz, Ar$\underline{H}$), 7.13 (s, 2H, Ar$\underline{H}$), 7.30 (d, 2H, J = 8.5, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$,

125 MHz) δ 23.1, 23.2, 27.2, 27.5, 30.7, 65.5, 65.6, 114.3, 114.4, 116.0, 124.8, 127.2, 128.3, 128.4, 134.5, 152.7, 153.1; HRMS (EI) calcd for 492.2301, found: 492.2300 [M^+] (100%). Data for trimer **137**: dec 244-250 °C; IR (μscope) 2962, 2948, 1608, 1429, 1364, 1238 cm^{-1} : ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (m, 12H, $CH_2C\underline{H_2}CH_2$), 3.29 (q, 8H, 4 $ArC\underline{H_2}$), 3.34 (t, 4H, J = 6 Hz $ArC\underline{H_2}$), 3.96 (s, 4H, $ArC\underline{H_2}Ar$), 4.20 (br s, 12H, 6 $C\underline{H_2}O$), 6.74 (d, 2H, J = 8.4 Hz, $Ar\underline{H}$), 7.03 (s, 2H, $Ar\underline{H}$), 7.08 (s, 2H, $Ar\underline{H}$) 7.27 (d, 2H, J = 9.2 Hz, $Ar\underline{H}$); ^{13}C NMR ($CDCl_3$, 125MHz) δ 23.0, 23.1, 27.1, 27.3, 27.4, 30.6, 65.50, 65.52, 65.55, 114.1, 114.28, 114.31, 115.9, 124.4, 124.8, 126.9, 127.4, 128.1, 128.2, 128.3, 133.4, 134.4, 152.1, 152.8, 153.1; HRMS (EI) calcd for $C_{50}H_{48}O_6$ 744.3451, found 744.3436 [M^+] (100%).



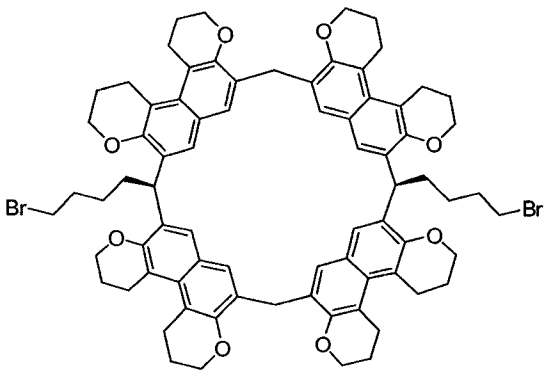
5-Bromopentanol (139)[118]

48% HBr (10 mL) and 1,5-pentanediol (10 g, 0.10 mol) in toluene (100 mL) were heated at reflux for 12 h with azeotropic removal of water using a Dean Stark trap. The mixture was cooled, washed with $NaHCO_3$ (2 x 30 mL), brine (30 mL), and dried (Na_2SO_4), and concentrated *in vacuo*, and distilled to give the bromo alcohol as a colourless liquid (10.3 g, 65%): IR (μscope) 3319, 2938, 2864, 1456, 1431, 1248, 1254, 1058, 643 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48-1.52 (m, 2H, chain $C\underline{H_2}$), 1.56-1.60 (m, 2H, chain $C\underline{H_2}$), 1.93 (quint, 2H, J = 7.1 Hz, $C\underline{H_2}$), 3.40 (t, 2H, J = 6.8 Hz, $C\underline{H_2}Br$), 3.65 (t, 2H, J = 6.3 Hz, $C\underline{H_2}OH$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2, 31.7, 32.5, 33.7, 62.5; HRMS (EI) calcd for $C_5H_{10}{}^{81}Br$, 166.9895; found 166.9897 [M^+] (0.13%).

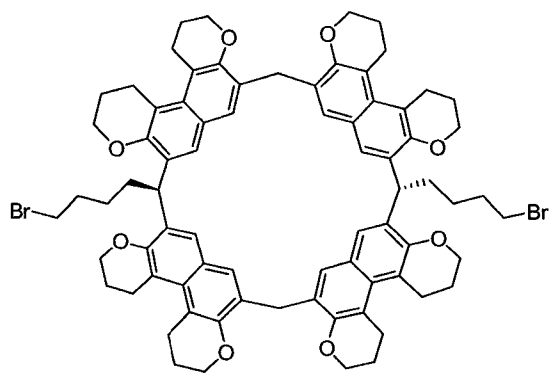


5-Bromopentanal (140)[118]

PCC (4.97 g, 23.0 mmol) was added to a solution of bromo alcohol **139** (1.67 g, 19.2 mmol) in CH_2Cl_2 (20 mL) resulting in a rapid colour change. After 1.5 h, the alcohol was consumed (TLC) and the mixture was concentrated, triturated with Et_2O (3 x 20 mL) and filtered through silica. The resulting clear orange solution was concentrated *in vacuo* and purified by flash chromatography (Et_2O/Pentane, 1:1) to afford the unstable and volatile bromoaldehyde (737 mg, 44%). Storage at –80 °C is recommended: R_f = 0.6 (Hex/EtOAc, 2:1); IR (μscope) 2940, 2869, 1727, 1453, 1135, 1119, 1077, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.78 (m, 2H, $C\underline{H}_2$), 1.89 (m, 2H, $C\underline{H}_2$), 2.44 (dt, J = 1.3, 7.3 Hz, 2H, $CHOC\underline{H}_2$), 3.40 (t, 2H, J = 6.5 Hz, $C\underline{H}_2Br$), 9.76 (t, 1H, J = 1.25 Hz, $CH_2C\underline{H}O$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 31.7, 32.9, 42.7, 201.5, HRMS (EI) calcd for $C_5H_{11}O$ 85.0653, found 85.0647 [$(M\text{-}Br)^+$] (100%).



141 cis



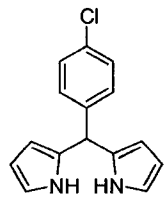
141 trans

***cis*-A,C-Bis-(4-bromobutyl)calix[4]naphthalene (141 *cis*)**

***trans*-A,C-Bis-(4-bromobutyl)calix[4]naphthalene (141 *trans*)**

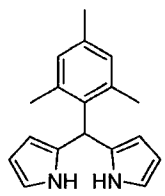
$SnCl_4$ (90 uL, 0.35 mmol) was added to a solution of dimer (**125**) (246 mg, 0.500 mmol) and freshly prepared aldehyde **140** (82 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (10 mL) and stirred at 0 °C under an argon atmosphere. The mixture was stirred while allowed to warm to rt over 1 h. The reaction was quenched with $NaHCO_3$ (2 mL), diluted with CH_2Cl_2 (15 mL), separated, washed with water (3 x 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography, eluting with Hex:CH_2Cl_2 (1:1) gave a mixture of *cis* and *trans* isomers, and recovered **125** (80 mg, 32%). Further flash chromatography eluting with Hex/EtOAc (2/1) afforded pure **141 *cis*** (58 mg, 19%) and **141 *trans*** (51 mg, 16%). Data for **141 *cis*** IR (CH_2Cl_2, cast) 2942, 2862, 1723, 1610, 1515, 1434, 1396, 1364, 1243, 1234, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (quint, 4H, J = 7.5 Hz, C$\underline{H_2}$CH_2CH_2Br), 1.88–2.00 (m, 24H, 4 x C$\underline{H_2}$CH_2O, 2 x BrCH_2C$\underline{H_2}$, 2 x CHC$\underline{H_2}$), 3.29-3.40 (m, 16H, 4 NapC$\underline{H_2}$), 3.34 (t, 4H, J = 7.0 Hz C$\underline{H_2}$Br), 3.59 (d, 4H, J = 16.4 Hz, NapC$\underline{H_2}$Nap), 4.14-4.22 (m, 16H, C$\underline{H_2}$O), 4.45 (d, 4H, J = 16.0 Hz, NapC$\underline{H_2}$Nap), 4.69 (t, 2H, J = 8.0 Hz, C$\underline{H}$CH_2), 7.07 (s, 4H, NapH), 7.15 (s, 4H, NapH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.22, 23.24, 26.57, 27.62, 27.63, 29.68, 32.8, 33.3, 34.1, 36.2, 65.5, 65.6, 114.0, 114.3, 124.2, 125.8, 126.9, 128.3, 131.2, 132.9, 151..9, 152.1; MS (ES) 1278 $[M]^{+\bullet}$. Data for **141 *trans*** IR (μscope) 2941, 1621, 1433, 1396, 1364, 1159, 794 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.45 (quint, 4H, J = 7.5 Hz, C$\underline{H_2}$CH_2CH_2Br), 1.80-1.98 (m, 24H, C$\underline{H_2}$CH_2O, 2 x BrCH_2C$\underline{H_2}$, 2 x CHC$\underline{H_2}$), 3.30 (q, 16H, J = 7.0, C$\underline{H_2}$Nap), 3.42 (t, 4H, J = 7.0 Hz C$\underline{H_2}$Br), 3.96 (s, 4H, NapC$\underline{H_2}$Nap), 4.04-

4.20 (m, 16H, C<u>H</u>$_2$ONap), 4.71 (t, 2H, J = 7.0 Hz, Nap$_2$C<u>H</u>CH$_2$), 7.07 (s, 4H, Nap<u>H</u>), 7.14 (s, 4H, Nap<u>H</u>); MS (ES) 1279 [MH$^+$].



5-(4-Chlorophenyl)dipyrromethane (143)[119]

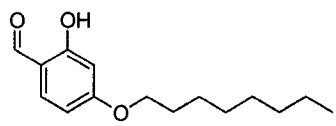
TFA (170 mg, 0.15 mmol) was added to a solution of 4-chlorobenzaldehyde (2.30 g, 1.50 mmol) in pyrrole (20 g). The solution was stirred 30 min., then quenched by the addition of 0.1 M NaOH (10 mL). The mixture was diluted with EtOAc (40 mL), separated, then washed with water (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 8/1) gave a solid (1.53 g, 40%): mp 104-105 °C (lit.122 112 °C), IR (CH_2Cl_2, cast) 3378, 3099, 1490, 1089, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.44 (s, 1H, C<u>H</u>ArPyrr$_2$), 5.87 (m, 2H, pyrr<u>H</u>), 6.15 (q, 2H, J = 2.9 Hz, Pyrr<u>H</u>), 6.70 (m, 2H, Pyrr<u>H</u>), 7.13 (AA'BB', 2H, Ar<u>H</u>), 7.32 (AA'BB', 2H, Ar<u>H</u>), 7.91 (s br, 2H, N<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 39.9, 107.7, 108.3, 116.6, 124.8, 127.6, 130.6, 138.4, 139.1; ES MS 256.1 [MH$^+$].



5-Mesityldipyrromethane (145)[109]

This known compound was prepared using the procedure of Lindsey and coworkers.[109] TFA (57 μL, 0.50 mmol) was added to a degassed solution of mesitylaldehyde (740 mg, 5.00 mmol) in pyrrole (10.1 g, 30.0 mmol), and stirred for 15 min. The reaction was

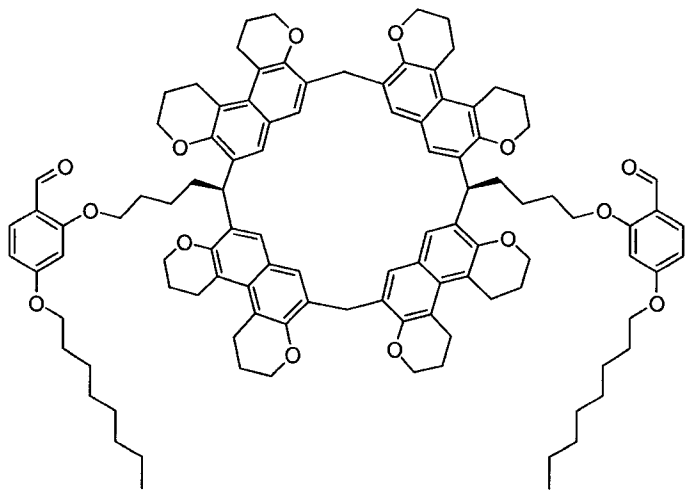
quenched by the addition of 0.10 M NaOH (5 mL), then diluted with EtOAc (50 mL), separated, washed with water (3 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (6:1) afforded a tan solid which was triturated with cold cyclohexane and filtered to afford a white powder (396 mg, 30%). (R_f = 0.3, Hex/EtOAc, 1:1); mp 163-165 °C (lit.[109] 166-167 °C), IR (CH_2Cl_2, cast) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 6H, $ArC\underline{H}_3$), 2.27 (s, 3H, $ArC\underline{H}_3$), 5.92 (s, 1H, $(Pyrr)_2C\underline{H}Ar$), 6.00 (m, 2H, Pyrr$\underline{H}$), 6.17 (q, 2H, J = 6.0 Hz, Pyrr$\underline{H}$), 6.4 (m, 2H, NCH), 6.85 (s, 2H, ArH) 7.92 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 10.8, 38.4, 106.5, 108.6, 116.1, 130.1, 131.2, 134.5, 136.5, 137.6; HRMS (EI) calcd for $C_{18}H_{20}N_2$ 264.16266, found 264.16231 [M^+] (100%).



2-Hydroxy-4-octyloxybenzaldehyde (147)[120]

2,4-Dihydroxybenzaldehyde (610 mg, 5.00 mmol), 1-bromooctane (960 mg, 5.00 mmol) and $KHCO_3$ (495 mg, 5.00 mmol) in DMF (10 mL) was heated at reflux under an argon atmosphere for 3 h. The mixture was cooled, concentrated *in vacuo*, taken up in EtOAc:H_2O (200 mL:100 mL), and separated. The organic layer washed with water (3 x 50 mL), then extracted with 2N NaOH (5 × 50 mL) (some precipitate obtained which eventually dissolved in the aqueous base). The aqueous extracts were acidified with conc HCl to pH 4, back extracted with EtOAc (3 x 200 mL), washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (18/1) afforded the aldehyde **147** as a liquid (1.10 g, 88%): R_f = 0.7 Hex/EtOAc (10/1), IR (μscope) 3400-2500 br, 2927, 2855, 1629, 1575, 1507, 1299,

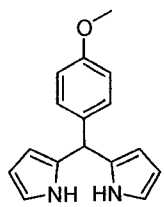
1223, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$), 1.27 (m, 10H, $(C\underline{H}_2)_5CH_3$), 1.77 (quint, 2H, J = 7.2 Hz, $C\underline{H}_2CH_2OAr$), 3.98 (t, 2H, J = 6.6, $OC\underline{H}_2$), 6.39 (d, 1H, J = 2.4 Hz, Ar$\underline{H}$), 6.51 (dd, 1H, J = 2.4, 8.4 Hz, Ar$\underline{H}$), 7.38 (d, 1H, J = 9.0 Hz, Ar$\underline{H}$), 9.68 (s, 1H, C$\underline{H}$O), 11.45 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.6, 25.9, 28.9, 29.15, 29.24, 29.3, 31.8, 68.6, 101.0, 108.7, 115.0, 135.1, 164.5, 166.4, 194.2; HRMS (EI) calcd for $C_{15}H_{22}O_3$ 250.1569, found: 250.1565 [M^+] (42.8%).



***cis*-A,C-Bis-(4-(2-formyl-(5-octyloxyphenoxy)butyl)calix[4]naphthalene (148)**

Dibromide **141** ***cis*** (67 mg, 41 μmol), phenol **147** (33 mg, 0.13 mmol), and K_2CO_3 (18 mg, 0.13 mmol) were heated to reflux in CH_3CN (15 mL) for 2 days under an argon atmosphere. The mixture was concentrated in vacuo and taken up in EtOAc/H_2O (50/30 mL), separated, and extracted with 2N NaOH (4 x 20 mL), washed with water (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (4:1→1:1) afforded the dialdehyde **148** as a white solid (39 mg, 56%): R_f = 0.5 (Hex/EtOAc 2:1); IR (CH_2Cl_2, cast) 2926, 2854, 1678, 1601, 1482, 1434, 1396, 1365, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 6H, J = 7.0 Hz, CH_3), 1.22-1.35 (m, 28H, 14 x $C\underline{H}_2$ chain), 1.39-1.42 (m, 4H, $C\underline{H}_2CH$),

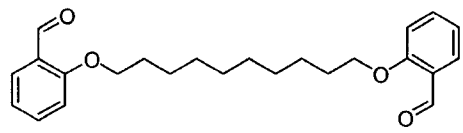
1.74 (quint, 4H, J = 7.1 Hz, C$\underline{H}_2$CH$_2$OAr), 1.78-1.99 (m, 20H, C$\underline{H}_2$CH$_2$Nap, 2 x C$\underline{H}_2$CH$_2$OAr), 3.22-3.35 (m, 16H, C$\underline{H}_2$Nap), 3.45 (d, 2H, J = 16.4 Hz, NapC$\underline{H}_a$H$_b$Nap), 3.98 (t, 4H, J = 6.0 Hz, C$\underline{H}_2$OAr), 3.98 (t, 4H, J = 7.0 Hz, C$\underline{H}_2$OAr), 4.05-4.14 (m, 12H, C$\underline{H}_2$ONap), 4.16-4.22 (m, 4H, C$\underline{H}_2$ONap), 4.44 (d, 2H, J_{ab} = 16.4 Hz, NapCH$_a$$\underline{H}_b$Nap), 4.74 (t, 2H, J = 7.8 Hz, Nap$_2$C$\underline{H}$CH$_2$), 6.36 (d, 2H, J = 2.4 Hz, ArH), 6.45 (dd, 2H, J = 8.8, 2.4 Hz, Ar$\underline{H}$), 7.07 (s, 4H, Nap$\underline{H}$), 7.12 (s, 4H, Nap$\underline{H}$), 7.74 (d, 4H, J = 8.8 Hz, Ar$\underline{H}$), 7.36 (m, 8H, Ar$\underline{H}$), 10.26 (s, 2H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 23.22, 23.24, 27.48, 27.52, 28.2, 28.9, 29.3, 31.8, 33.8, 36.1, 65.4, 65.5, 68.1, 114.0, 114.2, 118.9, 124.2, 125.8, 126.9, 128.3, 128.8, 129.9, 131.3, 132.9, 138.9, 163.4, 152.1, 152.0, 165.7, 188.4; MS (ES) 1618 [MH$^+$].



5-(4-Methoxyphenyl)dipyrromethane (150)[123]

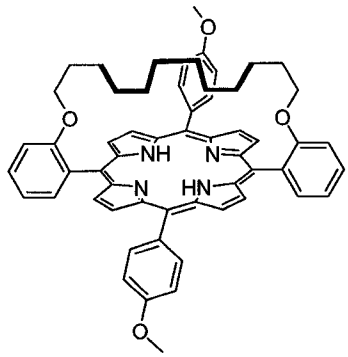
TFA (77 μL, 0.10 mmol) was added to a solution of 4-methoxybenzaldehyde (1.34 g, 1.00 mmol) in pyrrole (10 ml). The solution was stirred for 30 min., then quenched by the addition of 0.1 M NaOH (10 mL). The mixture was diluted with EtOAc (40 mL), separated, then washed with water (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 7/1) gave a tan solid that was recrystallized (EtOAc/Hex) giving an off white powder (780 mg, 31%): mp 95-97 °C (lit. 99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H, CH_3), 5.42 (s, 1H, *meso*$\underline{H}$), 5.91 (m, 2H,), 6.15 (q, 2H, J = 2.6 Hz, pyrr$\underline{H}$), 6.68 (m, 2H, pyrr$\underline{H}$), 6.85 (AA'BB', 2H, Ar$\underline{H}$), 7.12 (AA'BB', 2H, Ar$\underline{H}$), 7.91 (br s, 2H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.1, 55.3,

107.0, 108.2, 113.8, 117.1, 129.2, 132.8, 134.2, 158.3; HRMS (EI) Calcd for $C_{16}H_{16}N_2O$, 252.1209 found: 242.1214 [M^+], (54.7%).



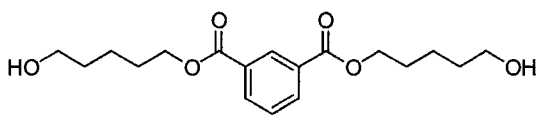
2,2'-Decanediyldioxy-dibenzaldehyde (152)[121]

A solution of K_2CO_3 (1.38 g, 10.0 mmol), salicylaldehyde (1.21 g, 10.0 mmol) and 1,10-dibromodecane (0.90 g, 3.30 mmol) was heated in DMF at 90 °C overnight, then cooled. The mixture was diluted with EtOAc (40 mL) and water (40 mL), separated, and washed with 1.0 M NaOH (20 mL), water (3 x 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 8/1) gave an oil (1.01 g, 80%): IR (μscope) 3075, 2924, 2853, 2757, 1687, 1598, 1486, 1472, 1458, 1287, 1242, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34 (m, 12H, $CH_2(C\underline{H}_2)_6CH_2$), 1.47 (quint, 4H, J = 7.4 Hz, $C\underline{H}_2CH_2CH_2O$), 1.82 (quint, 4H, J = 7.0 Hz, 4H, $C\underline{H}_2CH_2O$), 4.05 (t, 4H, J = 6.5 Hz, $C\underline{H}_2O$), 6.96 (t, 1H, J = 8.0 Hz, Ar$\underline{H}$), 6.98 (d, 2H, J = 8.0 Hz, Ar$\underline{H}$), 7.50 (dt, 1H, J = 2.0, 7.5 Hz, Ar$\underline{H}$), 7.78 (dd, 1H, J = 1.75, 7.8 Hz, Ar$\underline{H}$), 10.48 (s, 1H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 26.0, 28.2, 68.4, 112.4, 124.7, 128.1, 135.8, 161.4, 189.7; HRMS (EI) calcd for $C_{24}H_{30}O_4$ 382.2144, found 382.2148 [M^+] (50.8%), Anal calcd for $C_{24}H_{30}O_4$ C, 75.36; H, 7.91; found C, 75.02; H, 8.14.



5→15 Decane strapped porphyrin (153)

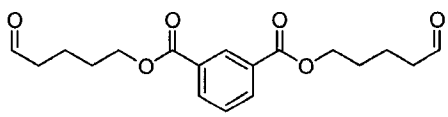
BF_3•Et_2O in $CHCl_3$ (8.3 μL, 2.5 M) was added to a degassed solution of 5-(4-methoxyphenyl)dipyrromethane (5.0 mg, 0.10 mmol) and dialdehyde **152** (3.8 mg, 0.10 mmol) in $CHCl_3$ (1 mL). After the mixture was stirred for 1.5 h, DDQ (7 mg, 3 mmol) was added. After an additional 1 h, the mixture was concentrated *in vacuo*, then purified by flash chromatography eluting with CH_2Cl_2. Concentration of purple fractions gave the porphyrin **153** as a purple solid (ca 0.4 mg, 5%). Though this compound appeared as one spot on TLC, ca. 5% scrambling was evident by a small peak beside the pyrrole NH peak in the ^1H NMR spectrum. ^1H NMR ($CDCl_3$, 500 MHz) δ –2.70 (s, 2H, NH), -1.30 (m, 4H, $O(CH_2)_4C\underline{H}_2$), -0.83 (m, 4H, $O(CH_2)_3C\underline{H}_2$), -0.61 (m, 4H, $O(CH_2)_2C\underline{H}_2$), 1.12 (m, 4H, $OCH_2C\underline{H}_2$), 3.63 (m, 4H, $OC\underline{H}_2$), 4.02 (m, 6H, $OC\underline{H}_3$), 7.41 (m, 4H, Ar$\underline{H}$), 7.65-71 (m, 4H, Ar$\underline{H}$), 8.01 (m, 2H, Ar$\underline{H}$), 8.21 (m, 2H, Ar$\underline{H}$), 8.25 (m, 2H, Ar$\underline{H}$), 8.75-8.81 (m, 8H, H_β); ES MS 845.4.



Isophthalic acid bis-(5-hydroxypentyl) ester (154)

1,5-Pentanediol (1.04 g, 10.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of isophthaloyl dichloride (402 mg, 2.00 mmol) and pyridine (300 mg, 3.00 mmol) at

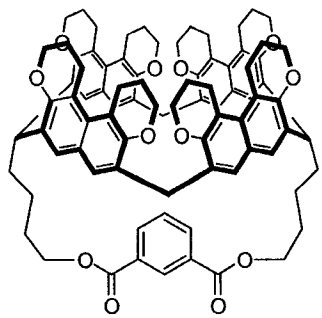
0 °C. The mixture was stirred 3 h, and quenched by the addition of Na_2CO_3 (5 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and separated. The mixture was then washed with 1.0 M HCl (2 x 10 mL), and sat'd aqueous $CuSO_4$ until no pyridine-copper complex was evident in the washing, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Et_2O afforded a clear oil (402 mg, 61%): (R_f = 0.6, Et_2O); IR (μscope) 3349, 2938, 2865, 1723, 1305, 1241, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (m, 4H, $CH_2C\underline{H}_2CH_2$), 1.64 (m, 4H, $CH_2C\underline{H}_2CH_2$), 1.81 (quint, 4H, J = 7.5 Hz $CH_2C\underline{H}_2CH_2$), 3.67 (t, 4H, J = 6.5 Hz, $C\underline{H}_2OH$), 4.35 (t, 4H, J = 6.75 Hz, $C\underline{H}_2OC(O)Ar$) 7.05 (t, 1H, J = 7.8 Hz, Ar$\underline{H}$), 8.20 (dd, 2H, J = 8.0, 2.2 Hz, Ar$\underline{H}$), 8.42 (t, 1H, J = 1.5 Hz, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.5, 28.6, 32.4, 62.7, 65.3, 128.5, 130.5, 130.8, 133.6, 165.7; HRMS (EI) calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1720 [(M+)] (0.37%)



Isophthalic acid bis-(5-oxopentyl) ester (155)

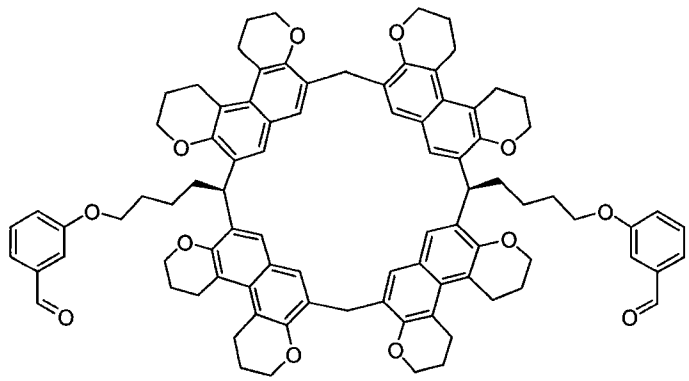
Diol **154** (160 mg, 0.47 mmol) in DMSO (2 mL) was added to a solution of IBX (757 mg, 1.18 mmol) in DMSO (10 mL) and the mixture was then stirred for 2 h at rt. The mixture was diluted with EtOAc (50 mL), filtered, washed with water (5 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (1:1) afforded the ester **155** as an oil (100 mg, 64%): (R_f = 0.3, Hex/EtOAc 1:1); IR (μscope) 3076, 2955, 2827, 1720, 1609, 1586, 1457, 1436, 1411, 1390, 1304, 1243, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 8H, 2 x $CH_2C\underline{H}_2C\underline{H}_2$), 2.50 (dt, 4H, J = 1.6, 6.1 Hz $C\underline{H}_2CHO$), 4.33 (t, 4H, J = 6.1 Hz,

$C\underline{H}_2OC(O)Ar$)), 7.49 (t, 1H, J = 8.0 Hz, Ar$\underline{H}$), 8.18 (dd, 2H, J = 1.6, 7.6 Hz, Ar$\underline{H}$), 8.18 (dd, 2H, J = 1.6, 7.6 Hz, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.6, 28.1, 43.3, 64.8, 128.6, 130.6, 130.7, 133.7, 165.7, 201.7; HRMS (EI) Calcd. for $C_{18}H_{23}O_6$ 335.1494, found 335.1492 [(M-H)+] (0.64%)



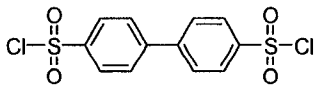
***cis*-A→C-strapped bis-(butyl(isophthalic ester))calix[4]naphthalene (156)**

$SnCl_4$ (90 uL, 0.35 mmol) was added to a solution of dimer **125** (123 mg, 0.250 mmol) and dialdehyde **155** (84 mg, 0.25 mmol) in dry CH_2Cl_2 (10 mL) stirred at 0 °C under inert atmosphere. The mixture was stirred and allowed to warm to rt over 1 h. The reaction was quenched with $NaHCO_3$ (2 mL), diluted with CH_2Cl_2 (15 mL), separated, washed with water (3 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography eluting with Hex/EtOAc (3/2) afforded pure **156** (16 mg, 10%): IR ($CHCl_3$, cast) 2955, 1720, 1608, 1304, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.76-1.84 (m, 8H, $C\underline{H}_2C\underline{H}_2CH_2CH$), 1.86-1.94 (m, 16H, $C\underline{H}_2CH_2ONap$), 2.08-2.14 (dt, 4H, 9.0, 7.5 Hz, $C\underline{H}_2CH$), 3.22-3.35 (m, 16H, $C\underline{H}_2Nap$), 3.54 (d, 2H, J = 16.8 Hz, $NapC\underline{H}_aH_bNap$), 4.01-4.05 (m, 4H, $C\underline{H}_2ONap$), 4.10-4.16 (m, 8H, $C\underline{H}_2ONap$), 4.18-4.22 (m, 4H, $C\underline{H}_2ONap$), 4.29 (t, 4H, J = 5.7 Hz, $C\underline{H}_2OCO$), 4.38 (d, 2H, J_{ab} = 16.8 Hz, $NapCH_a\underline{H}_bNap$), 4.87 (t, 2H, J = 6.9 Hz, $Nap_2C\underline{H}CH_2$), 7.03 (s, 4H, Nap$\underline{H}$), 7.24 (s, 4H, Nap$\underline{H}$), 7.21 (t, 1H, J = 7.8 Hz, ArH), 8.07 (dd, 2H, J = 7.8, 1.8 Hz, ArH), 8.66 (d, 1H, J = 1.8 Hz, Ar$\underline{H}$); MS (ES) 1284 [MH^+].



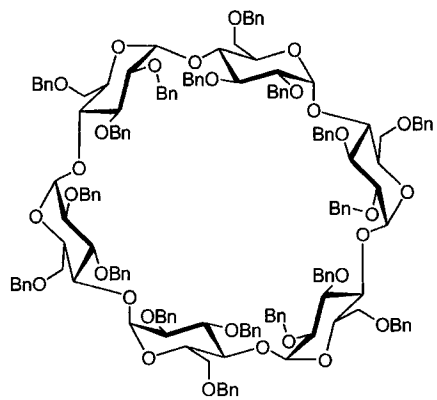
***cis*-A,C-Bis-(4-(2-formylphenoxy)butyl)calix[4]naphthalene (158)**

3-Hydroxybenzaldehyde (120 mg, 1.00 mmol), dibromide **141** ***cis*** (29 mg, 0.23 mmol), and K_2CO_3 (126 mg, 0.900 mmol) were heated to reflux in CH_3CN (15 mL) for 2 days under inert atmosphere. The mixture was concentrated in vacuo and taken up in EtOAc/H_2O (100/50 mL), separated, and extracted with 2M NaOH (4 x 20 mL), washed with water (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (4:1→2:1) afforded the dialdehyde **158** as a white solid (24 mg, 64%): R_f = 0.3 (Hex:$CHCl_3$ 1:3); IR (μscope) 2956, 2929, 2859, 2726, 1726, 1699, 1483, 1434, 1396, 1287, 1264, 1239, 1150, 794 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.83 (quint, 8H, J = 7.5 Hz, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.86-1.99 (m, 16H, $C\underline{H}_2CH_2ONap$), 3.31 (m, 16H, CH_2O), 3.45 (d, 2H, J_{ab} = 16.5, $ArCH_aH_bAr$), 3.97 (t, 4H, J = 6.8 Hz, $C\underline{H}_2OAr$), 4.12 (m, 12H, $C\underline{H}_2ONap$), 4.20 (m, 4H, $C\underline{H}_2ONap$), 4.44 (d, 2H, J_{ab} = 16.5, $ArCH_a\underline{H}_bAr$), 4.72 (t, 2H, J = 7.5 Hz, $ArC\underline{H}Ar$), 7.07 (s, 4H, $Nap\underline{H}$), 7.09 (m, 4H, $Ar\underline{H}$), 7.12 (s, 4H, $Nap\underline{H}$), 7.32 (d, 4H, J = 1.5 Hz, $Ar\underline{H}$), 7.36 (m, 8H, $Ar\underline{H}$), 9.90 (s, 2H, $C\underline{H}O$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.2, 24.2, 27.58, 27.64, 29.0, 29.6, 33.9, 36.3, 65.5, 65.6, 68.3, 113.3, 114.1, 114.3, 121.9, 122.9, 124.4, 125.9, 127.0, 128.4, 130.0, 131.5, 133.0, 137.8, 152.1, 152.2, 159.9, 192.3; MS (ES) 1383 [M+H].



4,4'-Biphenyldisulfonyl chloride (161)

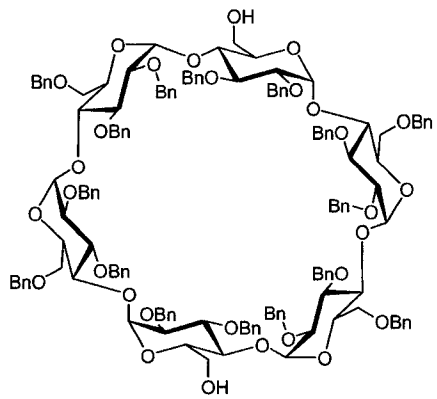
This known compound was prepared by a literature procedure.[162] Potassium 4,4'-biphenyldisulfonate (14.0 g, 0.395 mmol) was treated with PCl_5 (35.0 g, 0.168 mmol) for 5 h at 100 °C. Unreacted PCl_5 was removed *in vacuo*, and the residue was poured over ice water. The solid was filtered and recrystallized from $CHCl_3$ to give white crystals (7.5 g, 60%): mp 206-208 °C, (lit.[162] 209-212 °C IR (CH_2Cl_2, cast) 3105, 1590, 1595, 1392, 1371, 1354, 1170, 817, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (AA'BB', 4H, ArH), 8.26 (AA'BB', 4H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 128.5, 130.2, 144.9, 146.3, HRMS (EI) $C_{16}H_8O_4S_2{}^{35}Cl^{37}Cl$ calcd 351.9211, found 351.9215 [M^+] (24.8%).



2,3,6-Tri-O-benzyl-α-cyclomaltohexaose (167)[133]

This known compound was prepared by a modified procedure of Sato *et al.*[133] Sodium hydride (3.00 g, 126 mmol) suspended in DMSO (50 mL) was added to a solution of α-cyclodextrin (4.29 g, 5.00 mmol) in DMSO (250 mL). After the H_2 evolution had stopped (*vide infra,* 15 min), benzyl chloride (14 mL, 122 mmol) was added dropwise over the course of 30 min. The mixture was stirred overnight, then quenched with ammonium chloride (30 mL). The mixture was diluted with water (200 mL) and

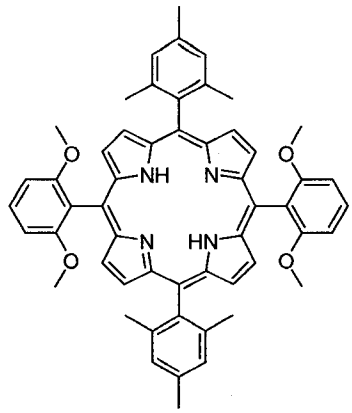
extracted with EtOAc (2 x 200 mL). The organic layer was washed with water (4 x 100 mL), with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (10:1→6:1) afforded the product as a white foam (8.49 g, 74.2%): R_f = 0.5 (Hex/EtOAc, 6:1): $[\alpha]_D^{23}$ = +26.9 (*c* 1.2, $CHCl_3$), IR (cast, CH_2Cl_2) 3063, 3029, 2926, 2867, 1496, 1453, 1354, 1207, 1093, 1038, 734, 697 cm^{-1}; 1H NMR ($CDCl_3$, 500 MHz) δ 3.48 (dd, 6H, *J* = 2.7, 9.9 Hz, H-2), 3.50 (d, 6H, *J* = 10.8 Hz, H-6_a), 3.92 (d, 6H, *J* = 8.0 Hz, H-5), 4.02 (6H, dd, *J* = 2.5 Hz, 9.5 Hz, H-6_b), 4.06 (t, 6H, *J* = 7.5 Hz, H-4), 4.16 (t, 6H, *J* = 9.0 Hz, H-3), 4.33 (d, 6H, *J* = 12.0 Hz, PhC$\underline{H}_2$), 4.42 (d, 6H, *J* = 12.0 Hz, PhC$\underline{H}_2$), 4.46 (d, 6H, *J* = 12.0 Hz, PhC$\underline{H}_2$), 4.50 (d, 6H, *J* = 12.0 Hz, PhC$\underline{H}_2$), 4.89 (d, 6H, PhC$\underline{H}_e$H$_f$, *J* = 9.5 Hz), 5.11 (d, 6H, *J* = 2.5 Hz, H-1), 5.20 (6H, d, *J* = 9.0 Hz, ArCH$_e\underline{H}_f$), 7.10-7.27 (m, 90H, Ph$\underline{H}$); ($CDCl_3$, 125 MHz) δ69.1, 71.6, 72.7, 73.4, 75.6, 79.1, 79.2, 81.0, 98.6, 126.9, 127.3, 127.4, 127.55, 127.59, 127.7, 128.0, 128.1, 128.3, 138.2, 138.4, 139.4 (6 C not observed due to overlap), MS (ES) found: 2617 (MNa^+).



$2^I,3^I,6^I,2^{II},3^{II},6^{II},2^{III},3^{III},2^{IV},3^{IV},6^{IV},2^V,3^V,6^V,2^{VI},3^{VI}$-Hexadeca-O-benzyl-α-cyclomaltohexaose (168)[132]

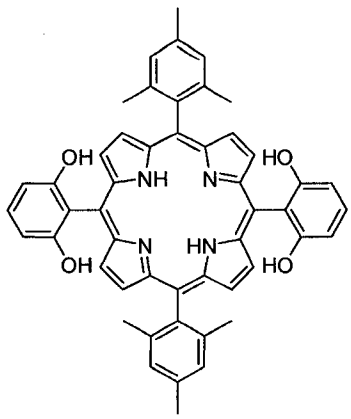
This diol was prepared by the procedure of Sinay and coworkers.[132] DIBAL (1.31 g, 9.24 mmol) was added to a solution of **163** (200 mg, 0.077 mmol). The mixture was heated

under an argon atmosphere for 5 h at 55 °C, cooled on an ice bath (15 min) and quenched by the addition of water (30 mL). This mixture was stirred until a white precipitate had formed (1 h). The mixture was filtered through celite, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 6:1→3:1) gave the diol (163 mg, 84%, scale up yields on 2.0 g scale gave 68-78%): R_f = 0.3 Hex/EtOAc (3:1): $[\alpha]_D^{23}$ = +31.3 (*c* 0.8, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = +34 (*c* 1.0, $CHCl_3$), IR (cast, CH_2Cl_2) 3365 br, 3027, 2925, 2855, 1454, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.39 (m, 4H, H-2, H-2'), 3.55 (dd, 2H, *J* = 4.0, 9.5, H-2''), 3.63 (d, 2H, *J* = 11.0 Hz, 2 x H-6), 3.68-3.80 (m, 8H, 8 x H-6), 3.80-3.95 (m, 14H, 2 x H-6, 6 x H-5, 6 x H-4), 4.00 (t, 2H, *J* = 9.0 Hz, H-3), 4.08 (t, 2H, *J* = 9.3 Hz, H-3'), 4.19 (dd, 2H, *J* = 9.5, 7.0 Hz, H-3''), 4.30 (d, 2H, *J* = 12.5 Hz, PhC$\underline{H}_2$), 4.35 (d, 2H, *J* = 12.5 Hz, PhC$\underline{H}_2$), 4.69 (d, 2H, *J* = 3.0 Hz, H-1), 4.71 (d, 2H, *J* = 3.5 Hz, H-1'), 4.75-4.80 (m, 6H, 6 x PhC$\underline{H}_2$), 5.86 (d, 2H, *J* = 10.5 Hz, PhC$\underline{H}_2$), 5.87 (d, 2H, *J* = 12.0 Hz, PhC$\underline{H}_2$), 5.16 (d, 2H, *J* = 10.5 Hz, PhC$\underline{H}_2$), 5.41 (d, 2H, *J* = 10.5 Hz, PhC$\underline{H}_2$), 5.70 (d, 2H, *J* = 4.0 Hz, H-1''), 7.1-7.35 (m, 80H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 65.2, 68.7, 69.0, 69.1, 71.7, 71.9, 72.3, 72.7, 73.1, 73.3, 73.4, 75.0, 75.9, 78.3, 78.9, 79.2, 79.3, 80.5, 80.58, 80.63, 80.65, 98.6, 99.3, 99.8, 126.84, 126.89. 126.94, 127.25, 127.27, 127.4, 127.46, 127.5, 127.68, 127.72, 127.77, 127.82, 127.84, 127.90, 127.92, 127.94, 127.97, 128.03, 128.1, 128.17, 128.25, 128.3, 138.0, 138.08, 138.14,138.3, 138.4, 139.25, 139.31, 139.32 (4 carbon signals not observed due to overlap); MS (ES) 2437 [MNa+].



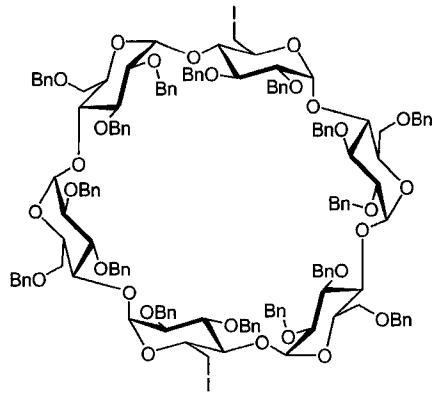
5,15-Bis(2,6-dimethoxyphenyl)-10,20-dimesitylporphyrin (170)

$BF_3 \bullet Et_2O$ (66 μL, 0.66 mmol) was added to a stirred, degassed solution of dipyrromethane **145** (528 mg, 2.00 mmol) and 2,6-dimethoxybenzaldehyde (332 mg, 2.00 mmol) in $CHCl_3$ (0.75% EtOH). The mixture was stirred for 30 min after which DDQ (681 mg, 3.00 mmol) was added. This mixture was then loaded directly onto a column (Brockman activity I neutral alumina). The column was eluted with CH_2Cl_2. The fractions were concentrated *in vacuo*, then further purified by flash chromatography (SiO_2, Hex/EtOAc, 5/1) to separate some minor scrambled porphyrinic products (275 mg, 33.5%): IR ($CHCl_3$, cast) 3312, 2920, 2851, 2832, 1586, 1469, 1430, 1248, 1108, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.42 (s, 2H, NH), 1.88 (s, 12H, $ArC\underline{H}_3$), 2.63 (s, 6H, $ArC\underline{H}_3$), 3.53 (s, 12H, $OC\underline{H}_3$), 7.02 (d, 4H, J = 8.5 Hz, Ar$\underline{H}$), 7.27 (s, 4H, Ar$\underline{H}$), 7.23 (t, 2H, J = 8.5 Hz, Ar$\underline{H}$), 8.61 (d, 4H, J = 4.5, H_β), 8.71 (d, 4H, J = 4.5 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 21.8, 56.1, 104.4, 111.2, 116.9, 120.0, 127.5, 130.0. 137.2, 138.7, 139.5, 160.5; HRMS (ES) calcd for $C_{54}H_{51}N_4O_4$ 819.3910, found 819.3918 [MH^+].



5,15-Bis(2,6-dihydroxyphenyl)-10,20-dimesitylporphyrin (171)

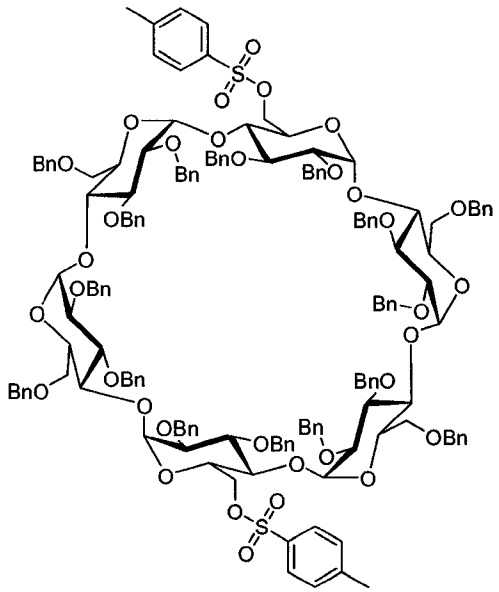
Porphyrin **170** dissolved in AcOH (10 mL) and 48% HBr (10 mL) was degassed with a stream of argon, then heated to reflux overnight. The mixture was cooled to rt, neutralized with solid NaOH (3 g), then sat'd $NaHCO_3$. The purple mixture was extracted with EtOAc (20 mL), washed with water (5 mL) and dried (Na_2SO_4), and concentrated *in vacuo*. Purification with flash chromatography (Hex/EtOAc) afforded a purple solid (144 mg, 90%): IR ($CHCl_3$, cast) 3544, 3321, 2968, 2916, 1620, 1583, 1463, 1344, 1172, 1148, 967, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -2.71 (s, 2H, NH), 1.88 (s, 12H, $ArCH_3$), 2.63 (s, 6H, $ArCH_3$), 7.02 (d, 4H, J = 8.5 Hz, ArH), 7.27 (s, 4H, ArH), 7.23 (t, 2H, J = 8.5 Hz, ArH), 8.61 (d, 4H, J = 4.4 H_β), 8.71 (d, 4H, J = 4.8 Hz, H_β), 9.29 (s, 4H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) 21.2, 30.7, 106.4, 113.1, 115.8, 116.1, 127.8, 129.8, 137.3, 137.9, 138.4, 158.1, CN and C_β signals not observed; HRMS (ES) calcd for $C_{50}H_{43}N_4O_4$ 763.3284, found 763.3290 [MH^+].



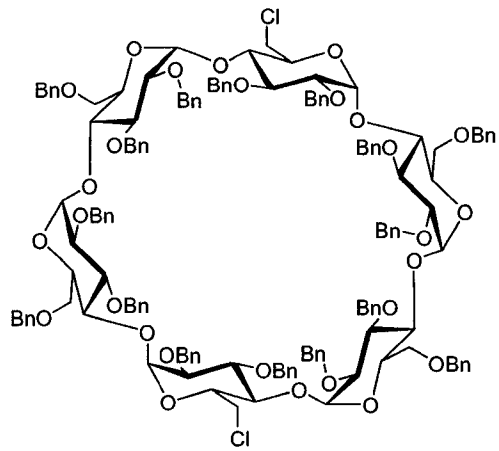
$2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^{I},6^{IV}$-dideoxy-$6^{I},6^{IV}$-diiodo-α-maltocyclohexaose (172)

Freshly recrystallized methyltriphenylphosphonium iodoide[163,164] (139 mg, 0.31 mmol) was added to a solution of diol **168** (186 mg, 77 μmol) in dry DMF (3 mL) and stirred for 10 min under Ar(g). Methanol (1.0 mL) was added and the mixture stirred for an additional 5 min. The mixture was diluted with EtOAc (15 mL), washed with water (5 x 10 mL), washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an amber oil. Purification by flash chromatography eluting with Hex/EtOAc (10:1) gave the title compound as a foam (160 mg, 78%): R_f = 0.3 (Hex/EtOAc, 7:1); $[\alpha]_D^{23}$ = +26.8 (*c* 0.7, CH_2Cl_2), IR (CH_2Cl_2, cast) 3062, 3029, 2867, 1496, 1453, 1354, 1038, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.40 (dd, 2H, *J* = 3.3, 9.9 Hz, H-2''), 3.47 (dd, 2H, *J* = 3.3, 9.9 Hz, H-2'), 3.50 (dd, 2H, *J* = 3.3, 9.9 Hz, H-2), 3.50-3.80 (m, 12H, 12 x H-6), 3.90-4.05 (m, 18H, H-3, H-3', H-3'', H-4, H-4', H-4'', H-5, H-5', H-5''), 4.05-4.20 (m, 12H, H-4, H-4', H-4'', H-5, H-5', H-5''), 4.38-4.55 (m, 18H, PhC$\underline{H}_2$), 4.82 (d, 2H, J_{cd} = 11.1 Hz, PhC$\underline{H}_c$H$_d$), 4.86 (d, 2H, J_{ef} = 11.1 Hz, PhC$\underline{H}_e$H$_f$), 4.89 (d, 2H, J_{gh} = 11.1 Hz, PhC$\underline{H}_g$H$_h$), 4.96 (d, 2H, $J_{1,2}$ = 3.3 Hz, H-1'), 5.04 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1''), 5.06 (d, 2H, J_{cd} = 11.1 Hz, PhCH$_c\underline{H}_d$), 5.17 (d, 2H, $J_{1,2}$ = 2.7 Hz, H-1), 5.18 (d, 2H, J_{ef} = 9.3 Hz, PhCH$_e\underline{H}_f$), 5.23 (d, 2H, J_{gh} = 10.8 Hz, PhCH$_g\underline{H}_h$), 7.05-7.18 (m, 80H, Ph$\underline{H}$); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 9.81, 69.2, 69.5, 70.3, 71.9, 72.6, 72.8, 72.9, 73.5, 73.6, 75.3, 75.5, 75.7, 76.7, 77.0, 77.2, 77.3, 78.6, 78.8, 79.3, 80.11, 80.15, 80.5, 80.8, 84.4, 98.4, 99.3, 99.4, 126.88, 126.92, 126.95, 127.2m 127.4, 127.6, 127.67, 127.74, 127.77, 127.82, 127.9, 128.09, 128.12, 128.13, 128.30, 128.35, 138.0, 138.07, 138.10, 138.2, 138.4, 139.1, 139.30, 139.32 (6 coincident aromatic carbon signals); MS (ES) 2656.9 [MNa+].



174a



174b

$2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^{I},6^{IV}$-ditoluenesulfonyl-α-maltocyclohexaose (174a)

$2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^{I},6^{IV}$-dichloro-$6^{I},6^{IV}$-dideoxy-$6^{I},6^{IV}$-α-maltocyclohexaose (174b)

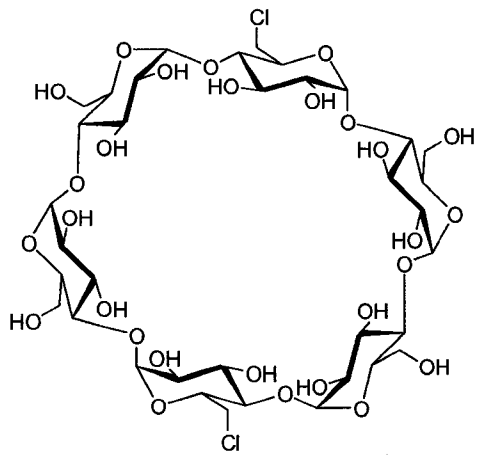
Tosyl chloride (500 mg, 2.63 mmol) was added to diol **168** (763 mg, 0.32 mmol) dissolved in dry pyridine (15 mL). The mixture was stirred for 10 min under argon, then heated to 60 °C for 8 h. When the diol was absent by TLC analysis, the mixture was concentrated *in vacuo* and dissolved in EtOAc (40 mL), washed with $CuSO_4$ (3 x 10 mL), water (1 x 10 mL), brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification

by flash chromatography eluting with Hex/EtOAc (4:1→2:1) gave the dichloro species as a glass (382 mg, 49%) and the ditosylate as a glass (80 mg, 9%).

Data for ditosylate **174a**: IR (CH_2Cl_2, cast) 3088, 3063, 3030, 2926, 1496, 1453, 1362, 1176, 1040, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.23 (s, 6H, C$\underline{H}_3$), 3.34 (dd, 2H, J = 9.9, 3.3 Hz, 2 x H-2'), 3.42 (dd, 2H, J = 9.9, 3.3 Hz, 2 x H-2''), 3.50 (dd, 2H, J = 9.6, 3.6 Hz, 2 x H-2), 3.56 (d, 2H, J = 8.0 Hz, 2 x H-6), 3.66-3.70 (m, 4H, 4 x H-6), 3.92-4.20 (m, 28H, 6 x H-5, 6 x H-4, 6 x H-6, 6 x H-3, 4 x C$\underline{H}_2$Ph), 4.49 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 4.51 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 4.79 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 4.82 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 4.88 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 4.92 (d, 2H, $J_{1,2}$ = 3.0 Hz, H-1), 4.99 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1'), 5.00 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1''), 5.06 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 5.14 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 5.24 (d, 2H, J = 10.8 Hz, ArC$\underline{H}_g\underline{H}_h$), 7.02 (AA'BB', 4H, Tos$\underline{H}$), 7.13-7.29 (m, 80H, Ar$\underline{H}$); 7.62 (AA'BB', 4H, Tos$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 69.0, 69.1, 69.9, 70.1, 71.5, 72.1, 72.5, 72.7, 72.9, 73.4, 73.5, 75.3, 75.7, 75.8, 76.8, 77.1, 77.3, 78.6, 78.99, 79.04, 79.3, 80.3, 80.4, 80.5, 80.7, 80.9, 98.3, 99.6, 99.8, 126.88, 126.91, 126.8, 127.2, 127.4, 127.46, 127.50, 127.52, 127.53, 127.6, 127.7, 127.8, 127.86, 127.91, 127.93, 127.98, 128.00, 128.15, 128.18, 128.21, 128.3, 128.4, 129.7, 133.5, 138.1, 138.26, 138.34, 138.48, 138.53, 139.38, 139.41, 139.43, 144.5; MS (ES) 2745.1 [MH^+].

Data for **174b**: R_f = 0.3 Hex/EtOAc (7:1); $[\alpha]_D^{23}$ = +22.3 (*c* 0.5, CH_2Cl_2), IR (CH_2Cl_2, cast) 3063, 2924, 2869, 1496, 1453, 1354, 1096, 1041, cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.37 (dd, 2H, J = 9.9, 3.3 Hz, H-2' or H-2''), 3.43 (dd, 2H, J = 9.9, 3.3 Hz, H-2' or H-2''), 3.50 (dd, 2H, J = 9.6, 3.6 Hz, H-2), 3.54 (d, 2H, J = 11.4 Hz, H-6), 3.67 (d, 2H, J = 10.2 Hz, H-6), 3.70-7.74 (m, 4H, H-5, H-6), 3.82 (dd, 2H, J = 4.8, 12.0 Hz, H-5''), 3.86

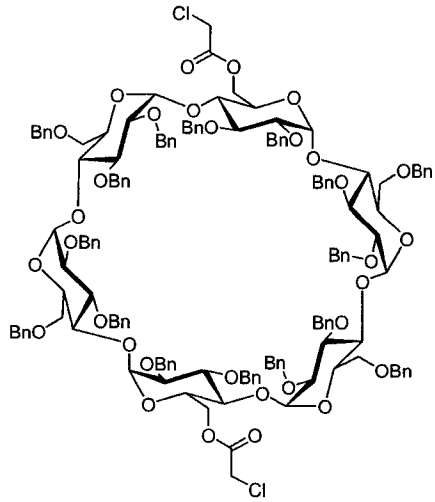
(dd, H-5, J = 9.3, 2.7 Hz, H-5), 3.90-4.10 (m, 16H, H-3, H-3', 6 x H-6, H-4, H-4', H-4''), 4.12 (dd, 2H, J = 9.3, 8.1 Hz, H-3''), 4.33 (d, 2H, J_{ab} = 12.0 Hz, PhC$\underline{H}_a$ H_b), 4.35 (m, 16H, C$\underline{H}_2$Ph), 4.57 (d, 2H, J_{ab} = 12.6 Hz, PhCH_a $\underline{H}_b$), 4.806 (d, 2H, J_{cd} = 11.4 Hz, PhC$\underline{H}_c H_d$), 4.813 (d, 2H, J_{ef} = 11.4 Hz, PhC$\underline{H}_e H_f$), 4.85 (d, 2H, J_{gh} = 10.8 Hz, PhC$H_g\underline{H}_h$), 4.94 (d, 4H, $J_{1,2}$ = 3.0 Hz, H-1', H-1''), 5.00 (d, 2H, J_{cd} = 11.4 Hz, PhC$H_c\underline{H}_d$), 5.12 (d, 2H, J_{ef} = 10.8 Hz, PhC$\underline{H}_e H_f$), 5.17 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1), 5.23 (d, 2H, J_{gh} = 10.8 Hz, PhC$\underline{H}_g H_h$), 7.08-7.29 (m, 80H, Ph$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 45.7, 69.0, 69.3, 71.0, 71.5, 71.8, 72.6, 72.8, 73.1, 73.5, 75.1, 75.6, 75.8, 78.4, 79.0, 79.1, 80.1, 80.2, 80.6, 80.8, 80.9, 98.4, 98.7, 99.0, 126.9, 127.0, 127.3, 127.4, 127.5, 127.6, 127.7, 127.78, 127.82, 128.0, 128.1, 128.2, 128.3, 138.0, 138.05, 138.14, 138.4, 139.2, 139.3 (16 carbon signals not obs due to overlap); MS (ES) 2474 [MNa^+].



Dichloro-6^{I},6^{IV} -dideoxy-6^{I},6^{IV}-α-maltocyclohexaose (175)

Dichloroperbenzylcyclodextrin **174b** (212 mg) was dissolved in EtOAc/EtOH 3:1 (20 mL). Pd/C was added, and the mixture was shaken at 60 psi H_2(g) for 3 d. The reaction was followed by ES MS. Additional Pd/C was added after 30 h. EtOH and water were added periodically to dissolve a white precipitate that formed as the solubility of the product(s) changed. When the reaction was complete by ES MS, the mixture was filtered

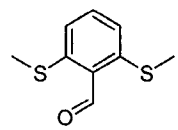
and the solvent removed *in vacuo* to give a white solid (90 mg, isolated as a hydrate, ca 90%): IR (μscope) 3400-2800, 1444, 1258, 1221 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 3.40-4.20 (m, 18H, 3 x H-2, 3 x H-3, 3 x H-4, 3 x H-5, 6 x H-6), 5.03 (d, 2H, J = 3.2 Hz, H-1), 5.05 (d, 2H, J = 3.6 Hz, H-1), 5.09 (d, 2H, J = 3.6 Hz, H-1); MS (ES) 1031.2, [MH^+].



$2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^I,6^{IV}$-$2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^I,6^{IV}$-chloroacetyl-α-maltocyclohexaose (177)

Chloroacetyl chloride (8 μL, 0.9 mmol) was added to a solution of diol **168** (80 mg, 33 μmol) in CH_2Cl_2 (2 mL) and THF (2 mL) at 0 °C. Pyridine (8.0 mg, 100 μmol) was added, and the mixture stirred for 4 h, and then warmed to rt. The reaction was quenched by the addition of water (10 mL). The mixture was diluted with EtOAc (20 mL), separated, then washed with water (2 x 5 mL), and then dried (Na_2SO_4). Purification by flash chromatography (Hex/EtOAc, 5/1) gave a colourless foam (54.5 mg, 67%): IR (CH_2Cl_2, cast) 3030, 1720, 1522, 1453, 1354, 1233, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.40-3.49 (m, 6H, H-2, H-2', H-2''), 3.49-3.55 (m, 4H,), 3.90-4.05 (m, 14H, H-3, H-3', H-3'', H-6a', H-6b', H-6a'', H-6b''), 4.05-4.55 (m, 33H, H-4, H-4', H-4'', H-5, H-5', H-5'', H-6a, H-6b, 9 x $C\underline{H}_2Ar$, $ArC\underline{H}_aH_b$), 4.58 (d, 2H, J_{ab} = 12.4 Hz, $ArCH_a\underline{H}_b$),

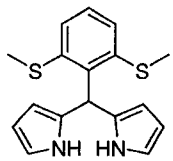
4.86 (m, 8H, H-1', H-1'', ArC$\underline{H}_c$H$_d$, ArC$\underline{H}_e$H$_f$) 4.92 (d, 2H, J_{gh} = 11.6 Hz, ArCH$_g\underline{H}_h$), 5.08 (d, 2H, J_{cd} = 11.2 Hz, ArCH$_c\underline{H}_d$), 5.22 (d, 2H, J_{ef} = 10.8 Hz, ArC$\underline{H}_e$H$_f$), 5.27 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1), 5.34 (d, 2H, J_{gh} = 11.2 Hz, ArC$\underline{H}_g$H$_h$), 6.67 (d, 2H, J = 8.8 Hz, Ar$\underline{H}$), 7.00 (t, 2H, J = 7.4 Hz, Ar$\underline{H}$), 7.10-7.35 (m, 80H, Ar$\underline{H}$), 7.37 (ddd, 2H, J = 1.8, 7.2, 8.6 Hz, Ar$\underline{H}$), 7.77 (dd, 2H, J = 8.2, 1.8 Hz, Ar$\underline{H}$), 10.44 (d, 2H, J = 0.8 Hz, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.7, 65.2, 68.7, 69.0, 69.1, 71.7, 71.9, 72.3, 72.7, 73.1, 73.3, 73.4, 75.0, 75.9, 78.3, 78.9, 79.2, 79.3, 80.5, 80.58, 80.63, 80.65, 98.6, 99.3, 99.8, 126.84, 126.89. 126.94, 127.25, 127.27, 127.4, 127.46, 127.5, 127.68, 127.72, 127.77, 127.82, 127.84, 127.90, 127.92, 127.94, 127.97, 128.03, 128.1, 128.17, 128.25, 128.3, 138.0, 138.08, 138.14, 138.3, 138.4, 139.25, 139.31, 139.32, 166.8; MS (ES) 2590 [MNa+].



2,6-Dithiomethoxybenzaldehyde (179)

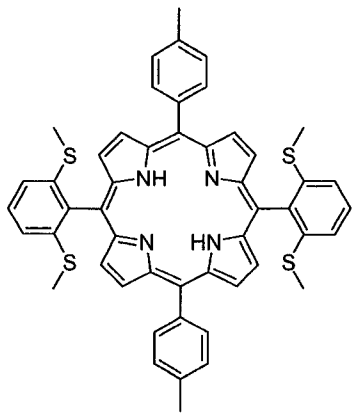
Under inert atmosphere (glove box), NaSMe (1.46 g, 21.0 mmol) was added portionwise to a solution of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) in DMF (10 mL) (Exothermic!). The mixture was stirred for 20 min, then heated to 60 °C and stirred 1 h. The mixture was cooled, diluted with EtOAc (25 mL), and washed with water (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by recrystallization gave a white solid (1.85 g, 93%): mp 95-97 °C; IR ($CHCl_3$, cast) 2981, 2921, 2861, 2767, 1670, 1550, 1437, 1416, 1200, 949, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 6H, C$\underline{H}_3$), 7.05 (d, 2H, J = 8.0 Hz, Ar$\underline{H}$), 7.36 (t, 1H, J = 8.0 Hz, Ar$\underline{H}$), 10.64 (s, 1H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 121.9, 129.4, 132.9, 145.7, 189.9; HRMS (EI) calcd for

$C_9H_{10}OS_2$ 198.01730, found 198.01749 [M^+] (100.0%). Anal. calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; found: C, 54.25; H, 5.06.



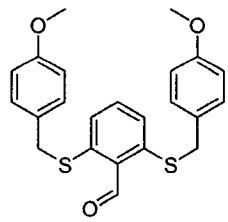
5-(2,6-Dithiomethoxyphenyl)dipyrromethane (180)

TFA (129 μL, 1.66 mmol) was added to a degassed stirred solution of aldehyde **179** (990 mg, 5.0 mmol) in pyrrole (20 mL). After the solution was stirred for 25 min, the reaction was quenched by the addition of 0.1 M NaOH (20 mL). The mixture was diluted with EtOAc (30 mL) and separated. The organic layer was washed with water (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* and purified by flash chromatography (Hex/EtOAc, 5/1) to give a white foam (509 mg, 31%): mp 102-104 °C, IR ($CHCl_3$, cast) 3373, 2917, 1557, 1433, 1027, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 6H, CH_3), 6.08 (m, 2H, pyrr H), 6.19 (m, 2H, pyrr H), 6.52 (s, 1H, Ar(pyrr)$_2$CH), 6.72 (m, 2H, pyrr H), 7.13 (d, 2H, J = 8.0 Hz, ArH), 7.21 (t, 1H, J = 7.6 Hz, ArH), 8.67 (s, 2H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 39.9, 107.7, 108.3, 116.6, 124.8, 127.6, 130.6, 138.4, 139.1; HRMS (EI) calcd for $C_{17}H_{18}S_2N_2$ 314.0912, found 314.0907 [M^+] (100.0%). Anal. calcd for $C_{17}H_{18}S_2N_2$ C, 64.97; H, 5.73; N, 8.92; found: C, 65.12; H, 5.44, N, 8.89.



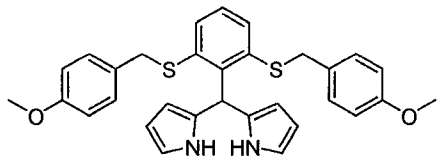
5,15-Bis(2,6-thiomethoxyphenyl)-10,20-bis(4-tolyl)porphyrin (181)

TFA (69 μL, 0.89 mmol) was added to a solution of dipyrromethane **182** (157 mg, 0.500 mmol) and *p*-tolualdehyde (60 mg, 0.50 mmol) in freshly distilled CH_2Cl_2 (50 mL). After the solution was stirred for 30 min, DDQ (170 mg, 0.75 mmol) was added and the mixture stirred a further 45 min. The crude mixture was filtered through a Florisil column (2.5 x 15 cm) and eluting with CH_2Cl_2. Concentration *in vacuo* gave a purple solid (40 mg, 19%): IR (CH_2Cl_2, cast) 3319, 2916, 1555, 1428, 965, 786 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.43 (s, 2H, NH), 2.20 (s, 12H, SCH_3), 2.66 (s, 6H, $ArCH_3$), 7.40 (AA'BB', 4H, TolH), 7.47 (d, 4H, J = 8.0 Hz, ArH), 7.75 (t, 2H, J = 8.3 Hz, ArH), 8.06 (AA'BB', 4H, TolH), 8.56 (d, 4H, J = 4.5 Hz, H_β), 8.82 (d, 4H, J = 4.5 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 21.6, 114.7, 119.7, 120.5, 127.3, 129.5, 129.8 (br), 131.8 (br), 134.5, 137.2, 137.4, 139.0, 143.4; HRMS (ES) calcd for $C_{50}H_{43}N_4S_4$ 827.2371, found: 827.2371 (MH+).



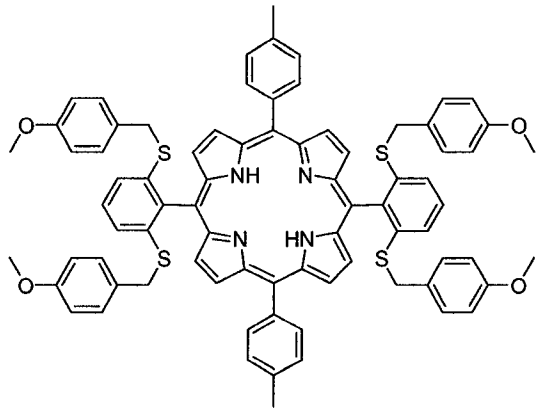
2,6-Bis(4-methoxybenzylsulfanyl)benzaldehyde (183)

4-Methoxybenzylmercaptan (900 μL, 6.00 mmol) was added to an argon flushed (20 min) mixture of 2,6-dichlorobenzaldehyde (525 mg, 3.00 mmol), K_2CO_3 (996 mg, 7.00 mmol), and DMF (3 mL). The mixture was stirred 5 min, then heated to 100 °C for 2 h until an off white solid had precipitated. The mixture was diluted with water (15 mL) and EtOAc (25 mL). This mixture was filtered, the solid washed with cold EtOAc (3 x 5 mL) to give analytically pure product after drying *in vacuo* (290 mg). The filtrate was washed with water (5 x 15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by recrystalization from Hex/EtOAc (4/1) gave a further 810 mg (total 1.10 g, 89%): mp 142-143 °C, IR (CH_2Cl_2, cast) 2953, 2930, 2833, 2755, 1664, 1609, 1557, 1304, 1257, 1177, 1031, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 6H, C$\underline{H}_3$), 4.11 (s, 4H, C$\underline{H}_2$), 6.86 (AA'BB', 4H, Ar$\underline{H}$), 7.26 (m, 6H, 4 x Ar$\underline{H}$ of AA'BB', 2 x Ar$\underline{H}$), 7.26 (t, 1H, J = 8.0 Hz, Ar$\underline{H}$), 10.67 (s, 1H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.3, 55.3, 114.1, 126.0, 127.8, 130.1, 131.9, 132.7, 143.6, 159.6, 191.3; HRMS (EI) calcd for $C_{23}H_{22}O_3S_2$ 410.1010, found 410.1010 [M^+] (14.6%) Anal. $C_{23}H_{22}O_3S_2$ calcd: C, 67.29; H 5.40, S 15.62; found C, 66.96; H, 5.58, S, 15.40.



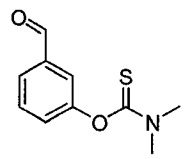
5-(2,6-Bis(4-methoxybenzylsulfanyl)phenyl)dipyrromethane (184)

TFA (710 mg μL, 6.23 mmol) was added to a degassed stirred solution of aldehyde **183** (1.44 g, 3.5 mmol) in pyrrole (35 mL) and CH_2Cl_2 (ca. 5 mL added to dissolve the aldehyde). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (20 mL). The mixture was diluted with EtOAc (50 mL) and separated. The organic was washed with water (2 x 40 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (Hex/EtOAc, 4/1) to give a light yellow foam (880 mg, 48%): dec 65-70 °C, R_f = 0.2 (Hex/EtOAc, 4/1) IR (CH_2Cl_2, cast) 3387, 2932, 2834, 1609, 1554, 1511, 1249 cm^{-1}; ^1H NMR. ($CDCl_3$, 500 MHz) δ 3.70 (s, 6H, C<u>H</u>$_3$), 4.02 (s, 4H, C<u>H</u>$_2$), 6.02 (m, 2H, pyrr<u>H</u>), 6.13 (q, *J* = 3.0 Hz, 2H, pyrr<u>H</u>), 6.58 (dt, 2H, *J* = 1.5, 2.7 Hz, pyrr<u>H</u>), 6.72 (s, 1H, *meso*-C<u>H</u>), 6.82 (AA'BB', 4H, Ar<u>H</u>), 7.08-7.18 (m, 6H, 6 x Ar<u>H</u>), 7.89 (br s, 2H, N<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.1 br, 40.7, 55.6, 107.8, 108.6, 114.3, 116.9, 127.6, 129.6, 130.3, 131.0, 131.4, 137.6, 143.7, 159.2; HRMS (EI) calcd for $C_{31}H_{30}O_2N_2S_2$ 526.1749, found 526.1753 [M^+] (61.3%).



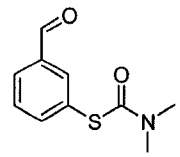
5,15-Bis(2,6-bis(4-methoxybenzylsulfanyl)phenyl)-10,20-bis(4-tolyl)porphyrin (185)

TFA (137 μL, 1.78 mmol) was added to a solution of dipyrromethane **184** (526 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in freshly distilled CH_2Cl_2 (100 mL). After the solution was stirred 30 min, DDQ (340 mg, 1.5 mmol) was added and the mixture stirred a further 45 min. The crude mixture was filtered through an alumina column (2.5 x 15 cm) and eluted with CH_2Cl_2. Concentration of the purple eluant gave a purple solid (322 mg, 51%): IR (CH_2Cl_2, cast) 3350, 3317, 2924, 2933, 1609, 1582, 1511, 1249, 798 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -2.36 (s, 2H, NH), 2.75 (s, 6H, $ArCH_3$), 3.64 (s, 12H, OCH_3), 3.82 (s, 8H, CH_2S), 6.57 (AA'BB', 8H, ArH), 6.86 (AA'BB', 8H, ArH), 7.61 (m, 6H, ArH), 7.52 (AA'BB', 4H, TolH), 8.05 (AA'BB', 4H, TolH), 8.56 (d, 4H, J = 4.5 Hz, H_β), 8.82 (d, 4H, J = 4.5 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 37.9, 55.2, 113.6, 115.5, 124.6, 128.6, 129.0, 129.6, 131.3 (br), 134.6, 137.1, 139.2, 140.6, 141.5, 158.4; MS (ES) 1251.4 (MH+); λ_{abs} 430, 523, 555, 602, 660 nm.



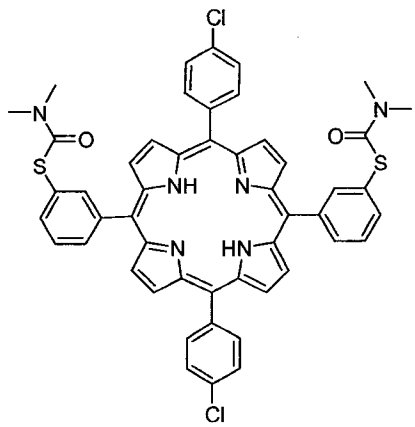
***N,N*-Dimethylthiocarbamic acid *O*-(3-formyl-phenyl) ester (186)**

NaH (240 mg, 10.0 mmol) was added portionwise to a stirred solution of 3-hydroxybenzaldehyde (1.22 g, 10.0 mmol) in DMF (20 mL). Dimethyl thiocarbamoyl chloride (1.77 g, 1.43 mmol) was added, and the solution stirred 20 h. The reaction was quenched with water (100 mL), then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (4 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was recrystallised from $CHCl_3$/EtOAc/Hex to give a yellow crystalline solid (1.20 g, 58%). The filtrate from the recrystallization was concentrated and purified by flash chromatography (Hex/EtOAc, 6/1) to give an additional portion of material (400 mg, 1.60 g total, 78%): mp 74-75 °C, IR (CH_2Cl_2, cast) 2941, 2839, 2733, 1705, 1694, 1588, 1538, 1395, 1289, 1230, 1145, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.35 (s, 3H, C<u>H</u>$_3$), 3.44 (s, 3H, C<u>H</u>$_3$), 7.33 (ddd, 1H, J = 8.2, 2.4, 1.0 Hz, ArH), 7.54 (t, 1H, J = 7.6 Hz, Ar<u>H</u>), 7.57 (m, 1H, Ar<u>H</u>), 7.75 (dt, 1H, J = 7.6, 1.2 Hz, Ar<u>H</u>), 10.03 (s, 1H, C<u>H</u>O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.8, 43.4, 123.5, 127.3, 129.1, 129.7, 137.6, 154.5, 187.2, 191.1; HRMS (EI) calcd for $C_{10}H_{11}O_2SN$ 209.0511, found 209.0501 [M^+] (20.9%); Anal calcd for $C_{10}H_{11}O_2SN$: C, 57.39; H, 5.30; N, 6.69; found C, 57.14; H, 5.21; N, 6.64.



***N,N*-Dimethyl-thiocarbamic acid *S*-(3-formyl-phenyl) ester (187)**

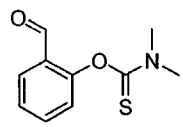
A solution of aldehyde **186** (1.50 g, 7.30 mmol) in diphenyl ether (10 mL), was degassed with argon (20 min.), and then brought to reflux for 2 h. The mixture was cooled to ca 50 °C, and the solvent was distilled *in vacuo*. The mixture was purified by flash chromatography (Hex/EtOAc, 6:1 → 4:1) to give a light yellow solid (1.38 g, 92%): mp 78-80 °C, IR (CH_2Cl_2 cast) 2931, 2728, 1698, 1670, 1588, 1364, 1199, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.02 (s, 3H, C<u>H</u>$_3$), 3.09 (s, 3H, C<u>H</u>$_3$), 7.52 (t, 1H, J = 7.6 Hz, ArH), 7.73 (dt, 1H, J = 7.5, 1.5 Hz, Ar<u>H</u>), 7.87 (dt, 1H, J = 8.0, 1.3 Hz Ar<u>H</u>), 7.97 (t, 1H, J = 1.8 Hz, Ar<u>H</u>), 9.98 (s, 1H, C<u>H</u>O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.0, 129.4, 129.7, 130.5, 136.9, 136.9, 141.3, 165.8, 191.2; HRMS (EI) calcd for $C_{10}H_{10}O_2SN$ 208.0432, found 208.0428 [M-H+] (19.2%); Anal calcd for $C_{10}H_{11}O_2SN$: C, 57.39; H, 5.30; N, 6.69; found C, 57.14; H, 5.21; N, 6.64.



5,15-Bis(4-chlorophenyl)-10,20-bis(3-dimethylthiocarbamoylphenyl)porphyrin (188)

TFA (137 μL, 1.78 mmol) was added to a suspension of dipyrromethane **143** (234 mg, 1.00 mmol) and **187** (208 mg, 1.00 mmol) and ammonium chloride (530 mg, 10 mmol) in

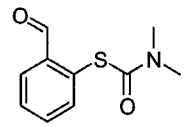
freshly distilled CH_3CN (100 mL). After the solution was stirred for 5 h, DDQ (340 mg, 1.5 mmol) was added and the mixture was stirred a further 45 min. The crude mixture was filtered through an alumina column (2.5 x 15 cm) and eluted with CH_2Cl_2. Concentration of the purple eluant gave a purple solid (18 mg, 4%): IR (CH_2Cl_2, cast) 3317, 2916, 1672, 1466, 1362, 1093, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -2.64 (s, 2H, NH), 1.85 (s, 12H, ArC$\underline{H}_3$), 2.63 (s, 6H, ArC$\underline{H}_3$), 3.11 (s, 12H, NC$\underline{H}_3$), 7.28 (s, 4H, Mes$\underline{H}$), 7.75 (t, 2H, J = 7.8 Hz, Ar$\underline{H}$), 7.91 (d, 2H, J = 8.2 Hz, Ar$\underline{H}$), 8.23 (d, 2H, J = 7.5 Hz, Ar$\underline{H}$), 8.40 (s, 2H, Ar$\underline{H}$), 8.72 (d, 4H, J = 4.5 Hz, H_β), 8.90 (d, 4H, J = 5.0 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 21.6, 21.7, 37.0, 118.2, 118.4, 127.1, 127.5, 127.7, 130.3 br, 131.6 br, 134.9, 135.3, 137.3, 138.4, 139.4, 141.2, 142.6, 146 br, 166.8; HRMS (ES) calcd for $C_{56}H_{53}S_2N_2O_2$, 905.3671, found 905.3668 [MH^+].



_N,N_-Dimethylthiocarbamic acid _O_-(2-formyl-phenyl) ester (190) [141]

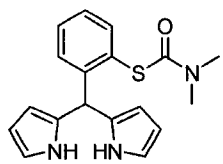
_N,N_-Dimethyl thiocarbamoyl chloride (3.75 g, 30.0 mmol) was added to a stirred solution (35 °C) of salicylaldehyde (2.40 g, 20.0 mmol) and DABCO (4.50 g, 40.0 mmol) in dry DMF (60 mL). The mixture was stirred overnight, resulting in a yellow precipitate. Water (250 mL) was added, and the solution extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with Na_2CO_3 (30 mL), water (4 x 30 mL), dried (Na_2SO_4) and concentrated _in vacuo_. The yellow residue was recrystallized from Hex/EtOAc to afford (2.98 g, 80%): mp 84-86 °C, IR (CH_2Cl_2, cast) 3063, 2941, 2832, 2734, 1694, 1588, 1538, 1395, 1288, 1230, 793 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 3H, C$\underline{H}_3$), 3.50 (s, 3H, C$\underline{H}_3$), 7.17 (d, 1H, J = 8.0 Hz, Ar$\underline{H}$), 7.42 (t, 1H, J = 8.0 Hz,

ArH), 7.65 (dt, 1H, J = 1.9, 7.8 Hz, ArH), 7.93 (dd, 1H, J = 1.8, 7.7 Hz, ArH), 10.10 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.0, 43.5, 124.4, 126.4, 129.2, 129.7, 134.8, 155.2, 187.1, 188.2; HRMS (EI) calcd for $C_{10}H_{11}O_2NS$ 209.0511, found 209.0509 [M^+] (23.2%).



***N,N*-Dimethylthiocarbamic acid *S*-(2-formyl-phenyl) ester (191)**[141]

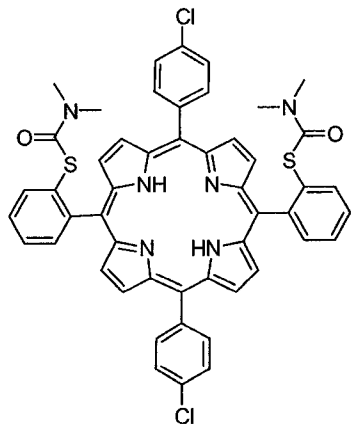
BF_3•Et_2O (1.50 mL, 2.2 mmol) was added dropwise into a stirred solution of aldehyde **190** (2.32 g, 1.13 mmol) in dichloroethane (50 mL) at 60 °C. The mixture was heated to 85 °C, and the solution stirred for 24 h. The yellow solution was cooled, washed with $NaHCO_3$ (20 mL), water (20 mL), dried (Na_2SO_4) and purified by flash chromatography (EtOAc/Hex; 3/1) to give a yellow oil (1.37 mg, 60%): R_f = 0.2 (Hex/EtOAc 5/1); IR (CH_2Cl_2, cast) 3062, 2932, 1697, 1668, 1587, 1367, 1262, 1098, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.03 (s, 3H, CH$_3$), 3.17 (s, 3H, CH$_3$), 7.56 (m, 3H, ArH), 7.54 (d, 1H, J = 6.5 Hz, ArH), 10.37 (d, 1H, J = 1.0 Hz, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.1, 128.6, 130.0, 132.3, 133.7, 137.4, 137.8, 165.1, 191.2; HRMS (EI) calcd for $C_{10}H_{11}O_2NS$ 209.0511, found 209.0506 [M^+] (8.4%).



5-(2-(Dimethylthiocarbamoyl)phenyl)dipyrromethane (192)

TFA (31 mg, 0.27 mmol) was added to a degassed stirred solution of aldehyde **191** (570 mg, 2.73 mmol) in pyrrole (10 mL). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (10 mL). The mixture was diluted

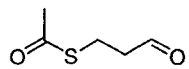
with EtOAc (10 mL) and separated. The organic was washed with water (2 x 2 mL), brine (2 mL), dried (Na_2SO_4), concentrated *in vacuo,* and purified by flash chromatography (Hex/EtOAc, 3/1) to give an amber solid (574 mg, 63%): R_f = 0.4 (Hex/EtOAc, 2:1); IR (CH_2Cl_2, cast) 3372, 3100, 3057, 2929, 1710, 1649, 1467, 1405, 1370, 1260, 1096, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.06 (s, 3H, NC<u>H</u>$_3$), 3.15 (s, 3H, NC<u>H</u>$_3$). 5.91 (m, 2H, pyrrC<u>H</u>), 6.01 (s, 1H, C<u>H</u>Ar), 6.13 (q, 2H, J = 2.7 Hz, pyrr<u>H</u>), 7.24 (dt, 1H, J = 2.4, 7.5 Hz, Ar<u>H</u>), 7.34 (dd, 1H, J = 2.4, 7.5 Hz, Ar<u>H</u>), 7.38 (dt, 1H, J = 2.4, 7.5 Hz, Ar<u>H</u>), 7.53 (dd, 1H, J = 7.5, 2.4 Hz, Ar<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 41.3, 106.8, 107.6, 117.5, 126.9, 127.4, 130.5, 130.98, 132.9, 137.0, 147.6, 168.3; HRMS (EI) calcd for $C_{18}H_{19}ON_3S$ 325.12450, found 325.1250 [M^+] (49.6%).



5,15-Bis(4-chlorophenyl)-10,20-bis(2-dimethylcarbamoylthiophenyl)porphyrin (193)

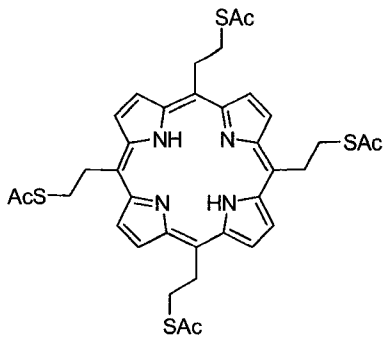
TFA (137 μL, 1.78 mmol) was added to a solution of dipyrromethane **192** (325 mg, 1.00 mmol) and p-chlorobenzaldehyde (140 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.5 mmol) was added and the mixture was stirred a further 45 min. The crude mixture was filtered through an alumina column (2.5 x 15 cm) and eluted with CH_2Cl_2. Concentration of the purple eluant gave a purple solid (20 mg, 4.5%): (mixture of αα and αβ isomers) IR (CH_2Cl_2, cast) 3317, 2916,

1672, 1466 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (integrations given for sum of isomers) δ - 2.77 (s, 4H, NH), 2.05 (s br, 6H, $NC\underline{H}_3$), 2.12 (s br, 6H, $NC\underline{H}_3$), 2.62 (s br, 12H, $NC\underline{H}_3$),7.72-7.76 (m, 12H, ArH), 7.88 (dt, 4H, J = 1.0, 8.0 Hz, ArH), 8.03-8.06 (m, 2H, ArH), 8.08 (d br, 2H, J = 8 Hz), 8.11 (dd, 2H, J = 8.0, 1.0 Hz, ArH), 8.17 (m, 6H, ArH), 8.22 (d br, 2H, J = 8 Hz, ArH), 8.68 (d, 4H, J = 4.5 Hz, H_β), 8.90 (d, 4H, J = 5.0 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.6, 118.6, 118.8, 127.0, 128.3, 129.2, 132.7, 134.3, 134.8, 134.9, 135.5, 135.6, 135.7, 136.9, 137.0, 140.4, 146.0, 166.1; HRMS (ES) $C_{50}H_{39}S_2N_2O_2Cl_2$ calcd for 889.1953, found 889.1957 [MH^+].



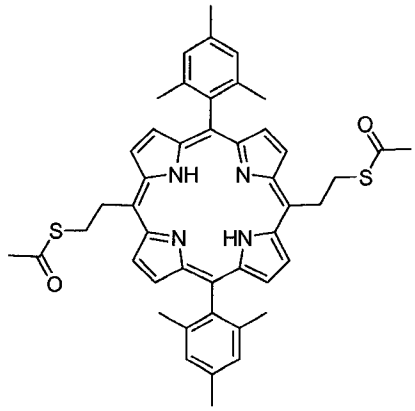
3-(*S*-Acetylthio)propanal (196)[142]

Thioacetic acid (6 mL) was added dropwise to stirred acrolein (4.32 g, 60.0 mmol) at 0 °C. The solution was allowed to warm to rt overnight. The mixture was concentrated *in vacuo*, to give an amber oil (6.00 g, 76%). This material was >95% pure by NMR analysis, and was successfully used in subsequent reactions with no apparent change in yield. This material could be purified by flash chromatography (Hex/EtOAc, 8:1) to give a colourless oil (2.00 g, 25%): IR (neat, cast) 2934, 2845, 1723, 1693, 1429, 1356, 1128, 957, 627 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H, $C\underline{H}_3$), 2.76 (dt, 2H, J = 1.0, 6.6 Hz $C\underline{H}_2CHO$), 3.08 (t, 2H, J = 6.8 Hz, $C\underline{H}_2S$), 9.71 (t, 1H, J = 0.9 Hz, $C\underline{H}O$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 30.5, 43.7, 195.4, 199.8; HRMS (EI) calcd for $C_5H_8O_2S$ 132.0245, found 132.0243 [M^+] (83.4%).



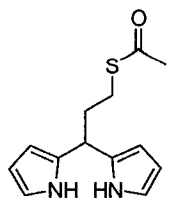
Tetrakis-(3-(*S*-acetylthio)ethyl))porphyrin (197)

BF_3•Et_2O (100 μL, 0.830 mmol) was added to a degassed solution of aldehyde **196** (300 mg, 2.46 mmol) and pyrrole (165 mg, 2.46 mmol) in $CHCl_3$ (250 mL). After being neutralized with triethylamine (246 mg, 2.46 mmol), the solution was diluted with CH_2Cl_2 (150 mL), then poured over a silica column. Elution with a large volume of $CHCl_3/CH_2Cl_2$ gave the desired porphyrin (60 mg, 14%) and mixed fractions which were not further purified. This material is very insoluble. IR ($CHCl_3$, cast) 3320, 2921, 2852, 1688, 1679, 1462, 1350, 1132, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.84 (s, 2H, N<u>H</u>), 2.92 (s, 12H, COC<u>H</u>$_3$), 3.92 (m, 8H, C<u>H</u>$_2$S), 5.20 (m, 8H, C<u>H</u>$_2$), 9.73 (s, 8H, H_β); No adequate carbon spectrum could be obtained due to insolubility of this material; HRMS (ES) calcd for $C_{36}H_{39}S_4N_4O_4$ 719.1854, found 719.1853 [MH^+], λ_{abs} 420, 520, 554, 598, 656 nm.



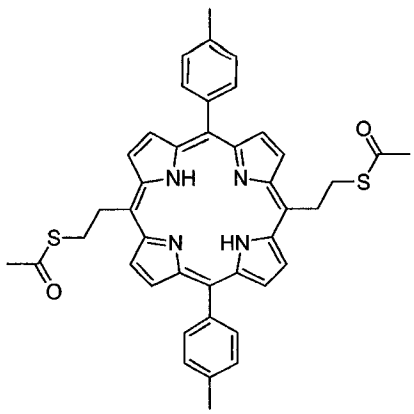
5,15-Bis(2-(*S*-acetylthio)ethyl)-10,20-bis(mesityl)porphyrin (198)

TFA (69 μL, 0.89 mmol) was added to a solution of dipyrromethane **145** (115 mg, 0.50 mmol) and aldehyde **196** (61 mg, 0.50 mmol) in freshly distilled CH_2Cl_2 (50 mL). After the solution was stirred for 30 min, DDQ (180 mg, 0.75 mmol) was added and the mixture was stirred for a further 45 min. The crude mixture was treated with Et_3N (101 mg, 1.00 mmol), then filtered through a silica column (2.5 x 15 cm) and eluted with CH_2Cl_2 until no further porphyrin eluted (52 mg, 28%): IR (μscope) 3318, 3021, 2923, 1688, 1559, 1510, 1475, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -2.60 (s, 2, NH), 1.82 (s, 12H, CH_3), 2.51 (s, 6H, C<u>H</u>$_3$), 2.64 (s, 6H, C<u>H</u>$_3$), 3.91 (m, 4H, C<u>H</u>$_2$SAc), 5.18 (m, 4H, PorC<u>H</u>$_2$), 7.29 (s, 4H, Mes<u>H</u>), 8.75 (d, 4H, J = 5.1 Hz, H_β), 9.57 (d, 4H, J = 4.8 Hz, H_β); ^{13}C NMR ($CDCl_3$, 75.44 MHz) δ 21.8, 21.9, 31.2, 35.4, 35.7, 100.2, 115.9, 118.0, 128.0, 128.6 br, 131.3 br, 138.0, 138.9, 139.7, 196.8; HRMS (ES) calcd for $C_{46}H_{47}S_2O_2N_4$ 751.3140 found 751.3141 [MH^+].

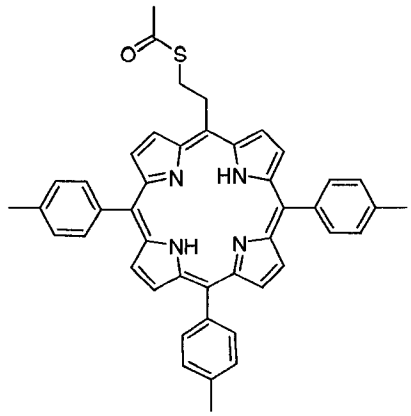


5-(2-(*S*-Acetylthioethyl)dipyrromethane (199)

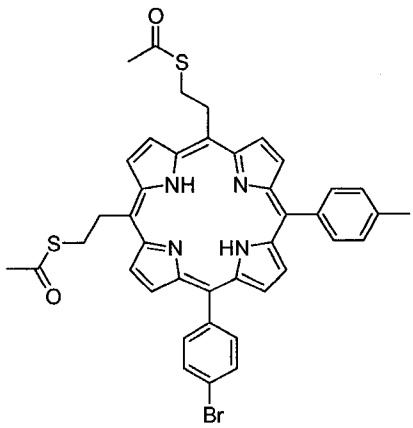
TFA (88 μL, 1.1 mmol) was added to a degassed stirred solution of aldehyde **196** (1.33 g, 10.9 mmol) in pyrrole (15 mL). After the solution was stirred for 20 min, the reaction was quenched by the addition of 0.1 M NaOH (10 mL). The mixture was diluted with EtOAc (20 mL) and separated. The organic layer was washed with water (10 x mL), dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography (Hex/EtOAc, 5/1) to give an amber oil (664 mg, 25%): IR (μscope) 3379, 3098, 2932, 1682, 1094, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_2S$), 2.32 (s, 3H, $C\underline{H}_3$), 2.82 (t, 2H, J = 7.5 Hz, $C\underline{H}_2S$), 2.76 (t, 1H, J = 7.5 Hz $C\underline{H}CH_2$), 6.13 (q, 2H, J = 3.0 Hz, Ar$\underline{H}$), 6.43 (m, 2H, Ar$\underline{H}$), 6.64 (m, 2H, Ar$\underline{H}$), 7.96 (br s, 2H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2, 30.6, 34.5, 36.7, 105.8, 108.3, 117.3, 132.2, 196.3; HRMS (EI) calcd for $C_{13}H_{16}OSN_2$ 248.0983, found 248.0981 [M^+] (71.5%) Anal. calcd for $C_{13}H_{16}OSN_2$: C, 62.90; H, 6.45; N, 11.29; found: C, 62.38; H, 5.94; N, 11.01.



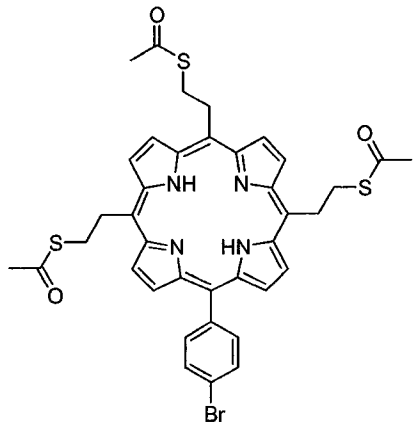
200a



200b



200c



200d

5,15-bis(2-(*S*-acetylthio)ethyl)-10,20-bis(4-tolyl)porphyrin (200a)

5-(2-(*S*-acetylthio)ethyl)-10,15,20-tris(4-tolyl)porphyrin (200b)

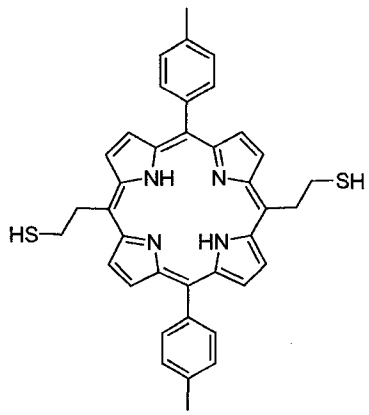
5,10-bis(2-(*S*-acetylthio)ethyl)-15,20-bis(4-tolyl)porphyrin (200c)

5,10,15-tris(2-(*S*-acetylthio)ethyl)-20-(4-tolyl)porphyrin (200d)

TFA (144 μL, 1.78 mmol) was added to degassed solution of dipyrromethane **199** (366 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.50 mmol) was added. After an additional 1 h, the reaction mixture was neutralized with triethylamine (280 μL), filtered through a silica column (2 x 10 cm), and eluted with CH_2Cl_2. The purple fractions were combined, and concentrated *in vacuo* to give a purple solid. This solid was further

purified by flash chromatography (Hex/EtOAc, 6:1) to give the title compounds **(200a)** (8 mg, 2%), **(200b)** (74 mg, 21%) **(200c)** (10 mg, 3%), **(200d)** (5 mg, 1%). Data for **200a**: R_f = 0.6 (Hex/CH_2Cl_2, 1:2); IR ($CHCl_3$, cast) 3315, 2921, 2851, 1683, 1473, 1350, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ-2.78 (s, 2H, NH), 2.50 (s, 6H, $COCH_3$), 2.72 (s, 6H, $ArCH_3$), 3.61 (m, 4H, CH_2S), 5.17 (m, 4H, $ArCH_2$), 7.55 (AA'BB', 4H, TolH), 8.06 (AA'BB', 4H, TolH), 8.93 (d, 4H, J = 5.0 Hz, H_β), 9.58 (d, 4H, J = 5.0 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 30.9, 35.3, 35.7, 116.1, 119.6, 127.3, 127.7 (br), 132.0 (br), 134.4, 137.3, 139.3, 146 (br), 203.3; HRMS (ES) calcd for $C_{42}H_{39}S_2N_4O_2$ 695.2515, found 695.2517 [MH^+], λ_{abs} 420, 518, 553, 595, 651 nm. Data for **200b** R_f = 0.8 (Hex/CH_2Cl_2, 1:2); IR (CH_2Cl_2, cast) 3318, 3022, 2920, 1688, 1562, 1510, 1475, 1341, 983, 964, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -2.81 (s, 2H, NH), 2.51 (s, 3H, $COCH_3$), 2.68 (s, 3H, $ArCH_3$), 2.70 (s, 6H, $ArCH_3$), 3.85 (m, 2H, CH_2SAc), 5.22 (m, 2H, $ArCH_2$), 7.52 (AA'BB', 2H, TolH), 7.52 (CC'DD', 4H, TolH), 8.05 (AA'BB', 2H, TolH), 8.07 (CC'DD', 4H, TolH), 8.80 (s, 4H, H_β), 8.96 (d, 2H, J = 4.8 Hz, H_β), 9.63 (d, 2H, J = 4.8 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.56, 21.59, 30.9, 35.4, 35.9, 116.2, 119.9, 120.1, 127.4, 127.5, 127.6, 131 (br), 132 (br), 134.6, 137.5, 139.2, 139.4, 196.0; MS (ES) 683.2 [M+H]. Data for **200c**: R_f = 0.35 (Hex/CH_2Cl_2, 1:2); IR ($CHCl_3$, cast) 3319, 2921, 1686, 1510, 1478, 1352, 1134, 1108, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ-2.83 (s, 2H, NH), 2.53 (s, 6H, $COCH_3$), 2.72 (s, 6H, $ArCH_3$), 3.93 (m, 4H, CH_2S), 5.13 (m, 4H, $porCH_2$), 7.53 (AA'BB', 4H, TolH), 8.04 (AA'BB', 4H, TolH), 8.79 (s, 2H, H_β), 8.93 (d, 2H, J = 4.8 Hz, H_β), 9.59 (d, 2H, J = 4.8 Hz, H_β), 9.77 (s, 2H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 30.9, 35.4, 35.9, 115.9, 119.6, 127.4, 127.4 (br), 132.0 (br), 134.4, 137.3, 139.3, 207.6; MS (ES) calcd for $C_{42}H_{39}S_2N_4O_2$ 695.2, found 695.3 [MH^+],

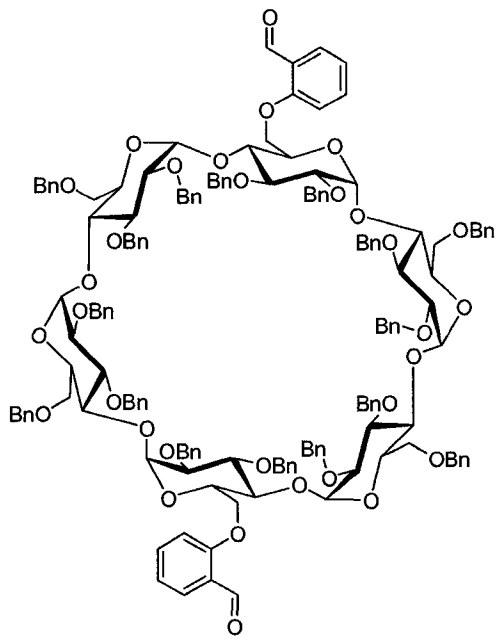
λ_{abs} 420, 443, 518, 553, 595, 652 nm. Data for **200d:** This material was contaminated with ca. 5% **200c**. R_f = 0.55 (Hex/CH_2Cl_2, 1:2); IR ($CHCl_3$, cast) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ-2.90 (s, 2H, NH), 2.53 (s, 6H, $COCH_3$), 2.55 (s, 3H, $COCH_3$), 2.72 (s, 6H, $ArCH_3$), 3.89 (m, 6H, CH_2S), 5.13 (m, 6H, $porCH_2$), 7.55 (AA'BB', 2H, TolH), 8.04 (AA'BB', 2H, TolH), 8.89 (d, 2H, J = 4.8 Hz, H_β), 9.53 (d, 2H, J = 4.8 Hz, H_β), 9.68 (s, 4H, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 30.8, 35.25, 35.33, 35.7, 35.9, 115.6, 119.58, 119.61, 127.29, 127.34, 127.8 br, 128.8 br, 131.9 br, 134.38, 134.41, 137.31, 137.35, 139.15, 139.19, 207.6, 207.7; HRMS (ES) calcd for $C_{39}H_{39}S_3N_4O_3$ 707.2184, found 707.2182 [MH^+], λ_{abs} 420, 520, 554, 598, 656 nm.



5,15-Bis(2-mercaptoethyl)-10,20-bis(4-tolyl)porphyrin (201)

This deprotection procedure used here was adapted from one described by Wallace *et al.*[145] Bis-thioester **200a** (47 mg, 0.068 mmol) was dissolved in MeOH/THF 1:1 (4 mL), then flushed with argon for 1 h. Sodium thiomethoxide (43 mg) was dissolved in MeOH (2.0 mL), then added to the mixture. The mixture was stirred 1 h, then quenched by the addition of 1.0 M HCl until a slight green colour persisted (vigorous stirring). This mixture was diluted with water (3 mL), extracted with EtOAc (2 x 10 mL), dried under argon (Na_2SO_4), then concentrated *in vacuo* to give 23 mg of pure porphyrin (23 mg, 54%, similar scale yields varied 30-62%): IR (CH_2Cl_2, cast) 3316, 3020, 2922, 1735,

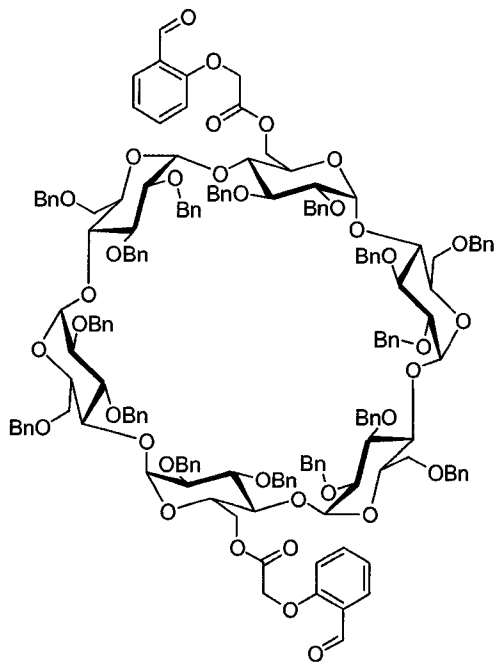
1561, 1476, 1354, 1311, 984, 793, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -2.78 (s, 2H, NH), 1.66, (t, 2H, J = 7.8 Hz, SH), 2.72 (s, 6H, CH_3), 3.61 (q, 4H, J = 8.0 Hz, $C\underline{H}_2SH$), 5.22 (t, 4H, J = 8.0 Hz, $ArC\underline{H}_2$), 7.56 (m, 4H, Ar$\underline{H}$), 8.05 (m, 4H, Ar$\underline{H}$), 8.96 (d, 4H, J = 4.8 Hz, H_β), 9.40 (d, 4H, J = 4.8 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 31.0, 39.7, 116.2, 119.8, 127.4, 132.3, 134.4, 137.5, 139.4, 146 (br); HRMS (ES) calcd for $C_{38}H_{35}S_2N_4$ 611.2303, found 611.2306 [MH^+].



$2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^I,6^{IV}$-(2-formylphenoxy)-α-maltocyclohexaose (203)

Diiodo α-CD derivative **172** (110 mg, 0.0420 mmol), salicylaldehyde (104 mg, 0.840 mmol), and K_2CO_3 (104 mg, 0.756 mmol) were stirred in DMF (7 mL) at 65 °C for 7 h, diluted with EtOAc/H_2O (15/10 mL) and separated. The organic layer was washed with 2 M NaOH (3 x 10 mL), washed with water (2 x 10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (5/1) afforded the dialdehyde as an oil (35 mg, 31%): R_f = 0.3 (Hex/EtOAc

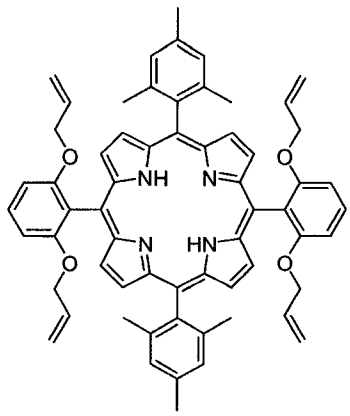
5:1); IR (CH_2Cl_2, cast) 3062, 3029, 2867, 1763, 1742, 1690, 1203, 1163, 1094, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40-3.52 (m, 10H, 6 x H-2, 4 x H-6), 3.90-4.05 (m, 14H, 6 x H-4, 6 x H-5, 2 x H-6), 4.05-4.46 (m, 28H, 18 x C$\underline{H}_2$Ph, 6 x H-3, 4 x H-6), 4.49 (dd, 2H, J = 2.8, 8.8 Hz, H-6), 4.57 (d, 2H, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.84-4.96 (m, 10H, 4 x H-1, 6 x C$\underline{H}_2$Ph), 5.08 (d, 2H, J = 11.2 Hz, C$\underline{H}_2$Ph), 5.21 (d, 2H, J = 11.2 Hz, C$\underline{H}_2$Ph), 5.27 (d, 2H, J = 3.6 Hz, H-1), 5.33 (d, 2H, J = 11.2 Hz, C$\underline{H}_2$Ph), 6.65 (d, 2H, J = 8.5 Hz, Ar$\underline{H}$), 6.99 (t, 2H, J = 7.0 Hz, Ar$\underline{H}$), 7.10-7.31 (m, 80H, Ph$\underline{H}$), 7.35 (t, 2H, J = 7.0 Hz, Ar$\underline{H}$), 7.76 (d, 2H, J = 7.0 Hz, Ar$\underline{H}$), 10.44 (d, 2H, J = 0.8 Hz, C$\underline{H}$O); MS (ES) 2645 [MNa^+].



$2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-$6^I,6^{IV}$-(2-formylphenoxy-O-acetyl)-α-maltocyclohexaose (205)

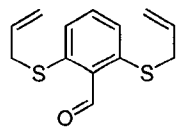
Dichloroester **177** (66 mg, 0.024 mmol), salicylaldehyde (100 mg, 0.83 mmol), and K_2CO_3 (60 mg, 0.43 mmol) were stirred in DMF (3 mL) at 60 °C for 6 h. The mixture was diluted with EtOAc/H_2O (100/50 mL), separated, and extracted with 2N NaOH (3 x

10 mL), washed with water (2 x 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography eluting with Hex/EtOAc (4/1) afforded the aldehyde **205** as an oil (55 mg, 78%): R_f = 0.35 (Hex/EtOAc, 3:1); ($[\alpha]_D^{23}$ = +31.6 (*c* 1.5, CH_2Cl_2), IR (CH_2Cl_2, cast) 3062, 3029, 2867, 1763, 1742, 1690, 1203, 1163, 1094, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.34 (dd, 2H, *J* = 9.5, 3.3 Hz, H-2'), 3.45 (dd, 2H, *J* = 9.5, 3.3 Hz, H-2''), 3.51 (dd, 2H, *J* = 10.0, 3.5 Hz, H-2), 3.55 (d, 2H, *J* = 11.0 Hz, H-6a), 3.60 (d, 2H, *J* = 10.5 Hz, H-6a), 3.67 (t, 2H, $J_{5\text{-}6a\cong 6a\text{-}6b}$ = 9.0 Hz, H-6a), 3.85-3.92 (m, 4H, 4 x H-5), 3.92-4.02 (m, 10H, 4 x H-6, 6 x H-4), 4.05-4.19 (m, 8H, H-3, H-3', H-3", 2 x H-6), 4.35-4.61 (m, 28H, 24 x C<u>H</u>$_2$Ph, 4 x COC<u>H</u>$_2$O), 4.85-4.92 (m, 6H, C<u>H</u>$_2$Ph), 4.95 (d, 2H, *J* = 3.5 Hz, H-1), 4.99 (d, 2H, *J* = 3.0 Hz, H-1'), 5.06 (d, 2H, *J* = 2.5 Hz, H-1''), 5.07 (d, 2H, *J* = 11.0 Hz, C<u>H</u>$_2$Ph), 5.17 (d, 2H, *J* = 11.0 Hz, C<u>H</u>$_2$Ph), 5.29 (d, 2H, *J* = 11.0 Hz, C<u>H</u>$_2$Ph), 6.71 (d, 2H, *J* = 8.5 Hz, Ar<u>H</u>), 6.97 (t, 2H, *J* = 7.5 Hz, Ar<u>H</u>) 7.10-7.31 (m, 81H, Ph<u>H</u>) 7.83 (dd, 2H, *J* = 1.2, 5.8 Hz, Ar<u>H</u>), 10.56 (s, 2H, C<u>H</u>O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.1, 65.3, 69.0, 69.1, 69.2, 71.8, 72.1, 72.4, 72.7, 73.2, 73.3, 73.4, 75.2, 75.2, 75.79, 75.83, 78.6, 79.0, 79.4, 80.3, 80.5, 80.57, 80.63, 80.7, 98.8, 99.3, 99.7, 112.6, 121.8, 125.3, 126.87, 126.90, 126.93, 127.2, 127.29, 127.31, 127.4, 127.45, 127.47, 127.49, 127.52, 127.6, 127.8, 127.86, 127.91, 127.93, 128.0, 128.13, 128.15, 128.22, 128.24, 128.5, 135.6, 137.9, 138.0, 138.1, 138.28, 138.30, 139.19, 139.20, 139.22, 159.8, 167.5, 189.1 (3 carbon signals not observed due to overlap); MS (ES) 2762.1 [MH^+].



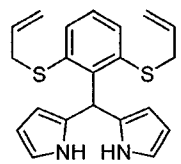
5,15-Bis(2,6-diallyloxy-benzene)-10,20-bismesitylporphyrin (207)

Allyl bromide (60 mg, 0.50 mmol) was added to a mixture of porphyrin **171** (20 mg, 27 μmol) and K_2CO_3 (75 mg, 0.43 mmol) in DMF (5 mL). The solution was stirred at rt for 6 h, then 4 h at 60 °C, diluted with EtOAc (20 mL), then washed with water (3 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography gave a purple solid (17 mg, 68%): IR (CH_2Cl_2, cast) 3318, 3090, 2917, 1679, 1466, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.43 (s, 2H, NH), 1.85 (s, 12H, CH_3), 2.61 (s, 12H, CH_3), 4.36 (dt, 8H, J = 5.0, 1.4, Hz, CH_2O), 4.52 (dq, 4H, J = 18.5, 1.7 Hz, $CH{=}CH_{cis}H_{trans}$), 4.56 (dq, 4H, J = 12.5, 1.5 Hz, $CH{=}CH_{cis}H_{trans}$), 5.51 (ddt, 4H, J = 17.3, 10.8, 5.0 Hz, $CH{=}CH_2$), 6.98 (d, 4H, J = 8.5 Hz, ArH), 7.26 (s, 4H, MesH), 7.65 (t, 2H, J = 8.5 Hz, ArH), 8.58 (d, 4H, J = 5.0 Hz, H_β), 8.73 (d, 4H, J = 4.5 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 21.8, 69.2, 106.0, 111.3, 116.3, 116.8, 118.9, 121.0, 127.5, 129 br, 129.8, 132.9, 137.2, 138.8, 139.5, 159.4; HRMS (ES) calcd for $C_{62}H_{59}O_4N_4$ 923.4536, found 923.4535 [MH^+].



2,6-Diallylsulfanylbenzaldehyde (208)

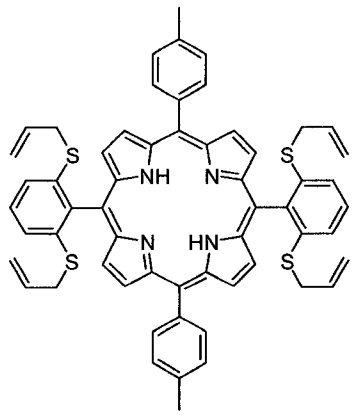
Allyl mercaptan (5.0 mL, 70% purity; Stench!) was added to an argon flushed, stirred suspension of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) and K_2CO_3 (4.14 g, 30.0 mmol) in DMF (10 mL). The mixture was heated to 65 °C for 10 h, cooled, diluted with EtOAc (20 mL) and water (10 mL), then separated. The organic layer was washed with Na_2CO_3 (2 x 20 mL), water (4 x 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc, 7/1) gave an oil (1.77 g, 71%): IR (neat film) 3081, 2978, 2858, 1670, 1636, 1561, 1552, 1435, 1406, 1202, 988, 922, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.56 (dt, 4H, J = 1.2, 6.8 C$\underline{H}_2$S), 5.13 (dq, 2H, J = 1.1, 10.0Hz, CH=C$\underline{H}_{cis}H_{trans}$), 5.21 (dq, 2H, J = 1.4, 17.2 Hz, CH=C$H_{cis}\underline{H}_{trans}$), 5.86 (ddt, 2H, J = 17.0, 10.2, 6.8 Hz C$\underline{H}$=CH$_2$), 7.23 ($A\underline{B}_2$, 2H, Ar$\underline{H}$), 7.36 ($\underline{A}B_2$, 1H, Ar$\underline{H}$), 10.73 (s, 1H, C$\underline{H}$O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.9, 118.8, 125.9, 132.0, 132.4, 132.5, 143.1, 191.4; HRMS (EI) calcd for $C_{13}H_{14}OS_2$ 250.0486, found 250.0479 [M^+] (14.5%).



5-(2,6-Diallylsulfanylphenyl)dipyrromethane (209)

TFA (30 μL, 0.40 mmol) was added to a degassed stirred solution of aldehyde **208** (1.00 g, 4.00 mmol) in pyrrole (10.7 g). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (4 mL). The mixture was diluted with EtOAc (20 mL) and separated. The organic was washed with water (3 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc

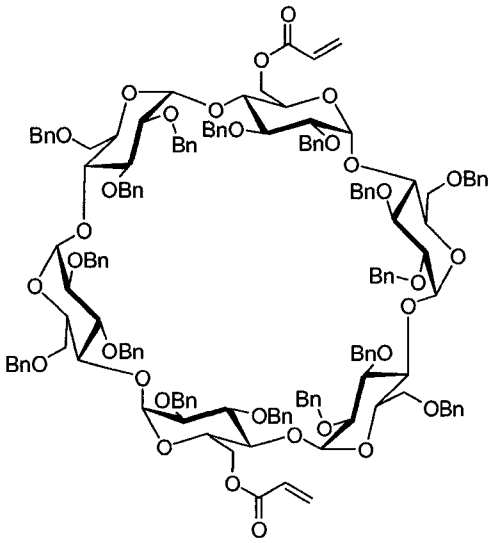
8/1) gave an amber solid (760 mg, 51%): IR (CH_2Cl_2, cast) 3380, 3080, 2976, 1665, 1634, 1555, 1427, 1027, 922, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.49, (d, 4H, J = 7.2 Hz, C$\underline{H}_2$S), 5.10 (m, 4H, =C$\underline{H}_2$), 5.82 (m, 2H, C$\underline{H}$=CH$_2$), 6.07 (m, 2H, pyrrC$\underline{H}$), 6.20 (m, 2H, pyrrC$\underline{H}$), 6.72 (m, 2H, pyrrC$\underline{H}$), 6.78 (s, 1H, C$\underline{H}$Ar), 7.18 (t, 1H, J = 8.0 Hz, Ar$\underline{H}$), 7.33 (d, 2H, J = 8.0 Hz, Ar$\underline{H}$), 8.65 (s (br), 2H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.4, 40.4, 107.5, 108.5, 116.5, 118.1, 127.2, 130.1, 131.1, 133.3, 137.0, 143.1; HRMS (EI) calcd for $C_{21}H_{22}S_2N_4$ 366.1224, found 366.1221 [M^+], (100%).



5,15-Bis(2,6-diallylsulfanylphenyl)-10,20-bis(4-tolyl)porphyrin (210)

TFA (144 μL, 1.78 mmol) was added to a degassed solution of **209** (366 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min., DDQ (340 mg, 1.50 mmol) was added. After an additional 1 h, the reaction mixture was filtered through a Florisil column (2 cm x 10 cm), and eluted with CH_2Cl_2. The purple fractions were combined, and concentrated *in vacuo* to give a purple solid. This solid was purified further by flash chromatography (Hex/EtOAc, 6:1) to give the title compound (96 mg, 21%): R_f = 0.5 (Hex/EtOAc, 3:1) IR (CH_2Cl_2, cast) 3318, 3021, 2918, 1636, 1553, 1347, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -2.40 (s, 2H, NH), 2.67 (s, 6H, CH_3), 3.49 (dt, 8H, J = 5.5, 1.3, Hz, C$\underline{H}_2$S), 4.92 (dq, 4H, J = 10.0, 1.3

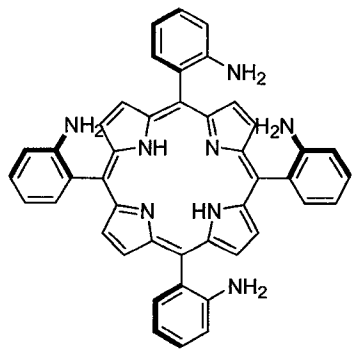
Hz, CH=C$\underline{H}_{cis}H_{trans}$), 5.02 (dq, 4H, J = 17.0, 1.5 Hz, CH=C$H_{cis}\underline{H}_{trans}$), 5.51 (ddt, 4H, J = 17.5, 10.0, 6.8 Hz, C$\underline{H}$=CH_2), 7.51 (AA'BB', 8H, Tol$\underline{H}$), 7.67 (t, 2H, J = 7.5 Hz, Ar$\underline{H}$), 8.10 (AA'BB', 4H, Tol$\underline{H}$), 8.59 (d, 4H, J = 5.0 Hz, H_β), 8.78 (d, 4H, J = 4.8 Hz, H_β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 36.5, 115.4, 117.8, 124.2, 127.4, 128.9, 129.8 (br), 131.5 (br), 133.2, 134.6, 137.2, 139.2, 140.6, 141.3; HRMS (ES) calcd for $C_{58}H_{51}S_4N_4$ 931.2997, found 931.3004 [MH^+].



6^I,6^{IV}-Acryloyl-2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}-hexadeca-O-ben6^I,6^{IV}-Acryloyl-2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}-hexadeca-O-

Acryloyl Chloride (80 μL, 0.22 mmol), was added to a solution of diol **168** (189 mg, 78.3 μmol) in CH_2Cl_2 (4 mL) at 0 °C. Triethylamine (33 μL, 0.33 mmol) was added, and the mixture was stirred 4 h, then warmed to rt. The reaction was quenched by the addition of water (10 mL). The mixture was diluted with EtOAc (20 mL), separated, then washed with water (2 x 5 mL) then dried (Na_2SO_4). Purification by flash chromatography (Hex/EtOAc, 5/1) gave a colourless foam (76 mg, 37%): IR (CH_2Cl_2, cast) 3030, 1725, 1605, 1453, 1354, 1038, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.35 (dd, 2H, J = 9.9, 2.7 Hz, H-2), 3.41 (dd, 2H, J = 9.6, 3.0 Hz, H-2'), 3.50 (dd, 2H, J = 1.5, 10.8 Hz, H-6),

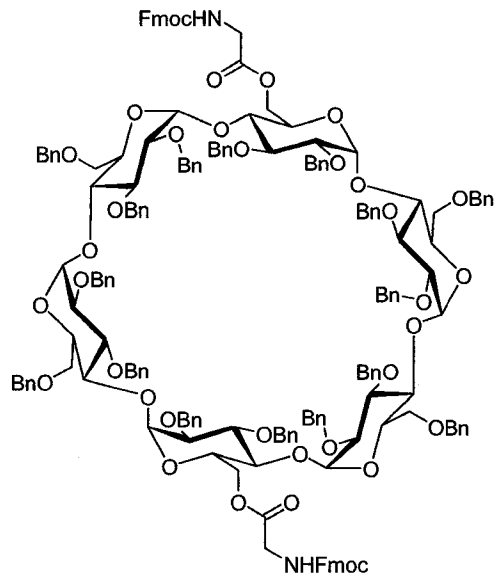
3.536 (dd, 2H, J = 9.6, 3.6 Hz, H-2''), 3.542 (dd, 2H, J = 11.4, 1.0 Hz, H-6), 3.78 (d, 2H, J = 9.0 Hz, H-5), 3.80 (dd, 2H, J = 9.6, 8.4 Hz, H-6), 3.86 (m, 2H, J = 9.0 Hz, H-5), 3.95-4.12 (m, 16H, 6 x H-3, 6 x H-4, 2 x H-5, 2 x H-6), 4.21 (t, 2H, $J_{2\text{-}3} \approx J_{3\text{-}4}$ = 9.0 Hz, H-3''), 4.22 (dd, 2H, J = 3.0, 12.0 Hz, H-6), 4.29 (d, 2H, J = 11.4 Hz, PhC$\underline{H}_a$H$_b$), 4.33-4.42 (m, 18H, 2 x H-6: C$\underline{H}_2$OCO, 7 x PhC$\underline{H}_2$), 4.47 (d, 2H, J = 12.0 Hz, PhC$\underline{H}_a$H$_b$), 4.66 (d, 2H, J = 12.0 Hz, PhC$\underline{H}_a$H$_b$), 4.78 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_a$H$_b$), 4.80 (d, 2H, J = 3.0 Hz, H-1), 4.87 (d, 2H, J = 3.0 Hz, H-1'), 4.88 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_a$H$_b$), 4.90 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_a$H$_b$), 5.17 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_a$H$_b$), 5.39 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_a$H$_b$), 5.40 (d, 2H, J = 3.6 Hz, H-1''), 5.68 (dd, 2H, J = 10.8, 1.2 Hz, CH=C$\underline{H}_{cis}$H$_{trans}$), 6.04 (dd, 2H, J = 17.4, 10.2 Hz, C$\underline{H}$=CH$_{cis}$H$_{trans}$), 6.28 (d, 2H, J = 17.4 Hz, CH=CH$_{cis}\underline{H}_{trans}$), 7.04-7.16 (m, 80H, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.6, 68.7, 68.9, 71.75, 71.82, 73.2, 73.27, 73.32, 74.6, 75.8, 76.2, 76.7-77.3 (at least 2 carbons confirmed by HMQC), 77.4, 78.3, 79.0, 79.7, 80.5, 80.6, 80.7, 81.0, 81.1, 98.0, 98.9, 99.1, 126.7, 126.8, 126.9, 127.0, 127.2, 127.31, 127.34, 127.4, 127.46, 127.52, 127.57, 127.63, 127.64, 127.8, 127.86, 127.93, 127.97, 128.02, 128.20, 128.24, 131.3, 138.0, 138.2, 138.26, 138.30, 138.6, 139.2, 139.3, 139.4, 165.5 (21 C not obs due to overlap); MS (ES) 2545.1 [MNa$^+$].



α,β,α,β-5,10,15,20-Tetrakis(2-aminophenyl)porphyrin (215)[79]

Pyrrole (4.65 mL, 0.67 mol) was added dropwise to a refluxing solution of *o*-nitrobenzaldehyde (10.1 g, 0.67 mol) in refluxing glacial acetic acid. After 20 min, the solution was allowed to cool. When the solution had cooled to ca. 65 °C, $CHCl_3$ (25 mL) was added. This mixture was cooled to ca. 35 °C, then filtered. The filtrate was washed with $CHCl_3$ (ca. 200 mL), and dried *in vacuo* (1.48 g, 11%). A solution of the nitroporphyrin (1212 mg, 1.56 mmol) in conc. HCl (200 mL) was degasseed with argon for 1 h. Concurrently, a solution of $SnCl_2$ (5.20 g, 27.6 mmol) in conc. HCl (60 mL) was also purged. The solutions were then combined, heated at 78 °C and stirred under an argon atmosphere for 30 min., then cooled to 0 °C, then carefully neutralized with conc. ammonium hydroxide, keeping the solution at or below 20 °C. The resulting brown sludge was extracted/triturated with THF (20 x 20 mL) until the extracts were free of product. The extracts were combined, dried (Na_2SO_4), and filtered through a silica pad. The filtrate was concentrated *in vacuo* to ca. 20 mL and diluted with $CHCl_3$ (60 mL) This mixture was concentrated to ca. 15 mL then diluted with $CHCl_3$, concentrated to 3 mL, then filtered to give a purple crystalline solid. This mixture of atropisomers was separated by flash chromatography (toluene→toluene/Et_2O, 20/1) to give the αβαβ isomer as the first eluting fraction (R_f = 0.7, Toluene Et_2O, 1/1) (8%, 84 mg): IR

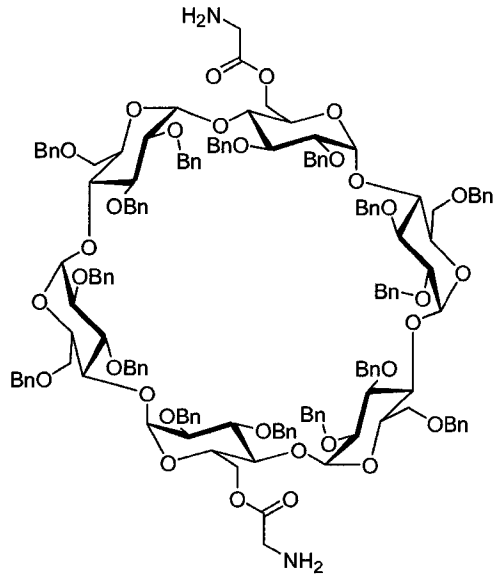
(μscope) 3402, 3319, 3031, 1620, 1444, 1330 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 500 MHz) δ -2.91 (s, 2H, NH), 3.60 (s br, 8H, NH_2), 7.01 (dd, 4H, J = 2.8, 7.6 Hz ArH), 7.34 (t, 4H, J = 7.6 Hz, ArH), 7.41-7.49 (m, 8H, 2 x ArH), 8.90 (s, 8H, H_β); HRMS (ES) calcd for $C_{44}H_{35}N_8$ 675.2979, found 675.2920 [MH^+].



$6^I,6^{IV}$-Bis-(*N*-(9-fluorenylmethoxycarbonylamino)-O-acetyl)-α-$2^I,3^I,2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^V,3^V,6^V,2^{VI},3^{VI},6^{VI}$-Hexadeca-O-benzyl-maltocyclohexaose (216)

Thionyl chloride (200 μL) was added to a suspension of *N*-Fmoc glycine (296 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) with pyridine (10 μL, cat). The mixture was heated at reflux for 2 h, then cooled. This mixture was concentrated *in vacuo*, resdissolved in CH_2Cl_2 (5 mL), then again concentrated *in vacuo*. This residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. To this solution was added a solution of diol **168** (241 mg, 0.100 mmol). Hunig's base (177 μL, 1.00 mmol) was added, and the solution stirred over 8 h, and allowed to warm to rt. The solution was the diluted with EtOAc (25 mL), the washed with $NaHCO_3$ (10 mL), water (10 mL), then brine (5 mL), dried (Na_2SO_4), and

concentrated *in vacuo*. Purification by flash chromatography (toluene→toluene/acetone, 19/1) gave the product as a clear film (150 mg, 50%): IR (CH_2Cl_2, cast) 3380, 3300, 3029, 2927, 1744, 1453, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.36 (dd, 2H, J = 9.9, 3.3 Hz, H-2), 3.42 (dd, 2H, J = 9.9, 3.3 Hz, H-2), 3.48 (dd, 2H, J = 9.0, 3.0 Hz, H-2), 3.52 (d, 2H, J = 10.8 Hz, H-6), 3.57 (d, 2H, J = 10.2 Hz, H-6), 3.75 (t, 2H, J = 9.0 Hz, H-4), 3.80-4.00 (m, 20H, 4 x gly C$\underline{H}_2$N, 4 x H-4, 4 x H-5, 6 x H-6), 4.03 (dt, 2H, J = 10.2, 2.4 Hz, H-5), 4.05-4.15 (m, 6H, 6 x H-3), 4.17 (t, 2H, J = 6.9 Hz, Fmoc C$\underline{H}$CH$_2$), 4.30-4.48 (m, 22H, 2 x H-6, 18 x C$\underline{H}_2$Ph, 2 x Fmoc CHC$\underline{H}_2$), 4.55 (d, 2H, J = 12.6 Hz, C$\underline{H}_2$Ph), 4.80-4.86 (m, 6H, CH$_2$Ph), 4.96 (d, 2H, $J_{1,2}$ = 3.0 Hz, H-1), 4.96 (d, 2H, $J_{1,2}$ = 3.0 Hz, H-1), 5.05 (d, 2H, J = 10.8 Hz, PhC$\underline{H}_2$), 5.14 (d, 2H, J = 10.8 Hz, C$\underline{H}_2$Ph), 5.19 (t, 2H, J = 5.4 Hz, N$\underline{H}$), 5.22 (d, 2H, J = 11.0 Hz, PhC$\underline{H}_2$), 7.03-7.35 (m, 84H, 4 x Fmoc Ar$\underline{H}$, 80 x Ar$\underline{H}$), 7.32 (t, 4H, J = 7.4 Hz, Fmoc Ar$\underline{H}$), 7.54 (t, 4H, J = 6.0 Hz, Fmoc Ar$\underline{H}$), 7.73 (d, 4H, J = 7.2 Hz, Fmoc Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.9, 47.4, 64.5, 67.4, 69.1, 69.3, 69.6, 71.9, 72.2, 72.8, 73.0, 73.4, 73.6, 75.6, 75.8, 76.0, 76.0, 77.0, 77.3, 77.6, 79.0, 79.2, 79.3, 79.6, 80.4, 80.5, 80.9, 81.0 98.9, 99.3, 99.7, 120.2, 125.3, 127.2, 127.30, 127.34, 127.5, 127.6, 127.7, 127.79, 127.84, 127.79, 128.01, 128.1, 128.3, 128.38, 128.42, 128.46, 128.56, 128.60, 138.4, 138.6, 139.6, 144.0, 156.4, 169.6; MS (ES) 2990 [MH^+].



$6^{I},6^{IV}$-Bis-(amino-O-acetyl)-α-$2^{I},3^{I},2^{II},3^{II},6^{II},2^{III},3^{III},6^{III},2^{IV},3^{IV},2^{V},3^{V},6^{V},2^{VI},3^{VI},6^{VI}$-hexadeca-O-benzyl-maltocyclohexaose (217)

Diester **216** was dissolved in a solution of 20% piperidine in DMF (10 mL), and stirred 20 min. The mixture was concentrated *in vacuo*, then purifed by flash chromatography (R_f = 0.3; $CHCl_3$/MeOH, 30/1, 1% NH_4OH) to give the product as a clear film (91 mg, 75%): IR (CH_2Cl_2, cast) 3352, 3063, 1728, 1452, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.25 (d, 2H, *J* = 18.0 Hz, gly CH), 3.36 (d, 2H, *J* = 18.0 Hz, gly CH), 3.38 (dd, 2H, *J* = 10.0, 2.3 Hz, H-2), 3.44 (dd, 2H, *J* = 10.0, 3.7 Hz, H-2), 3.52 (dd, 2H, *J* = 10.0, 4.0 Hz, H-2), 3.56 (d, 4H, *J* = 12.0 Hz, 4 x H-6), 3.76 (t, 2H, *J* = 9.3 Hz, H-4), 3.84 (d br, 2H, *J* = 8.0 Hz, H-5), 3.92 (d br, 2H, *J* = 8.0 Hz, H-5), 3.96–4.06 (m, 12H, 2 x H-5, 4 x H-4, 4 x H-6, 2 x H-3), 4.08 (t, 2H, *J* = 9.0 Hz, H-3), 4.09 (t, 2H, *J* = 8.5 Hz, H-3), 4.20 (t, 2H, *J* = 9.0 Hz, H-3), 4.29 (dd, 2H, *J* = 12.0, 3.3 Hz, H-6), 4.32-4.50 (m, 18H, 2 x H-6, 16 x PhH), 4.62 (d, 2H, *J* = 12.0 Hz, PhH), 4.82-4.92 (m, 6H, 6 x PhH), 4.85 (d, 2H, *J* = 3.0 Hz, H-1), 4.88 (d, 2H, *J* = 2.0 Hz, H-1), 5.00 (d, 2H, *J* = 11.0 Hz, PhH), 5.22 (d, 2H, *J* = 11.0 Hz, PhH), 5.23 (d, 2H, $J_{1,2}$ = 3.0 Hz, H-1), 5.32 (d, 2H, *J* = 11.0 Hz, PhH); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 43.8, 66.9, 68.9, 71.7, 71.9, 72.7, 73.3, 75.8, 76.0, 76.2, 79.6, 80.8, 81.1, 82.5, 98.4, 99.0, 99.4, 126.8, 126.9, 127.0, 127.3, 127.50, 127.53, 127.56, 127.61, 127.64, 127.89, 127.90, 127.94, 128.01, 128.03, 128.2, 128.25, 128.31, 138.0, 138.1, 138.2, 138.3, 138.5, 139.2, 139.3, 173.8 20 C not observed due to overlap; MS (ES) 2514 [MH^+].

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