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SYNTHESIS OF HIGHLY FUNCTIONALIZED AND STERICALLY
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BAOMIN GUO

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of the requirements for

MASTER OF SCIENCE degree in CHEMISTRY

Chik. Chang
Major professor

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**SYNTHESIS OF HIGHLY FUNCTIONALIZED AND STERICALLY
PROTECTED PORPHYRINS**

By

Baomin Guo

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

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Department of Chemistry

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ABSTRACT

SYNTHESIS OF HIGHLY FUNCTIONALIZED AND STERICALLY PROTECTED PORPHYRINS

By
Baomin Guo

In an effort to study proton effects on heme-bound O₂, we set out to synthesize porphyrins that permit the formation of room-temperature stable metal-O₂ complexes in the presence of intramolecular proton donor. We discovered that xanthene-5-carboxamide can be made into excellent building blocks with which heme models having specific H-bonding at the axial ligation site can be assembled. Thus, 5-[5-carboxamide-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetra ethyl-3,7,12,18-tetramethylporphyrin **a**, 5-[5-carboxhydrazide-4-(9,9-dimethyl) xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin **b** and their metal complexes have been synthesized. X-ray crystallographic structures of the Fe(III) (Cl) carboxamide **a** and the zinc(II) hydrazide **b** revealed that the xanthene oxygen atom is strongly H-bonded to one amide proton leaving the other amide proton, in the case of **a**, H-bonded to the Cl ligand, and the hydrazide N bonded to Zn in **b**.

In order to prevent irreversible auto-oxidation of ferrous heme, terphenyl shielding wings have incorporated to the porphyrin models. Thus, 5-(5-carboxamide-9,9-dimethyl-4-xanthyl)-15-[4-methyl-2,6-bis(4-tert-butylphenyl) phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl porphyrin **c** and 12,18-di[4-methyl-2,6-bis(4-tert-butylphenyl) phenyl]-5-(5-carboxamide-9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethyl porphyrin **d** have been synthesized. The terphenyl units were synthesized in a stepwise fashion using Pd(0)-catalyzed cross coupling of phenyl boronic acid and aryl bromide. Combining both the protective superstructure and the specific hydrogen bonding, we obtained promising models which possess a protein-like binding environment for O₂ binding and activation.

To my family

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May, 1996

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Chapter I

INTRODUCTION

Porphyrins are important naturally occurring macrocycles that involve in many essential biological processes. Many proteins and enzymes in both animals and plants contain porphyrin-metal complexes which are the active sites of biochemical reactions¹⁻³. To name a few, hemoglobin, myoglobin⁴ and cytochromes⁵ all belong to porphyrin-containing bio-molecules.

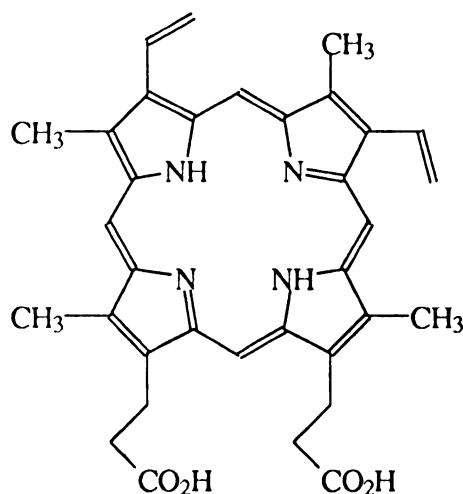


Figure 1-1 Protoheme.

Hemoglobin and myoglobin, which are essential to all mammalian life, transport and store dioxygen. The active site of these heme proteins is iron(II) porphyrin — the heme (Figure 1-1) — embedded in a pocket and bonded to the protein through a single coordinate bond between the imidazole group of the proximal histidine residue and the iron atom⁶. The ferrous heme is in a five-coordinate state in the deoxy form and reversibly binds small ligand at the sixth, vacant coordinate site (figure 1-2)⁷⁻¹⁰. In the vicinity of the heme binding site,

distal amino acid residues also control the binding of ligands such as CO, NO and O₂ by virtue of polarity or steric effects¹¹⁻¹⁵.

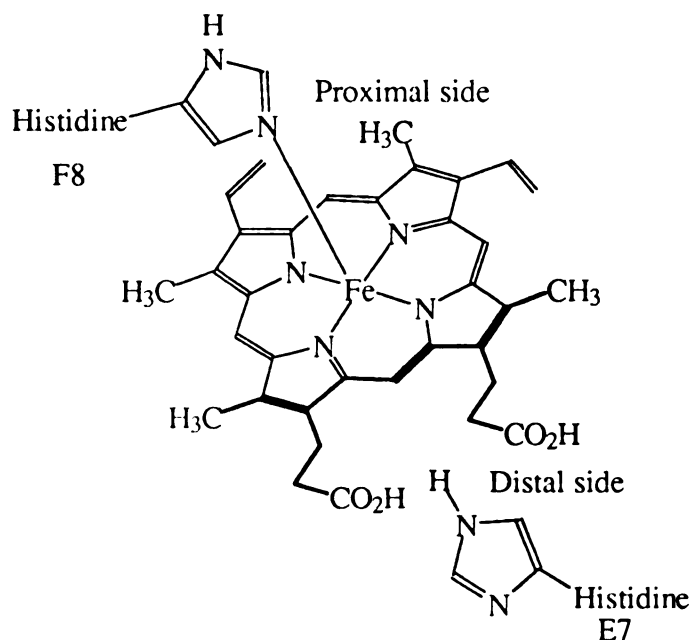


Figure 1-2 Schematic representation of heme protein active site.

Research of heme proteins has been focused on both the protein itself and synthetic models since the beginning. Pioneers found that an isolated heme, an iron(II) porphyrin complex without protein pocket and distal proton, does not reversibly oxygenate and even can not resist oxidation at ordinary condition. Tremendous amounts of effort have been made to understand the chemical basis of the axial ligand and protein pocket influences on the O₂ affinity and the oxidation pathway. We now understand that a successful model of oxyhemoglobin must have a five coordinated structure and the ability to thwart irreversible oxidation pathways typically caused by the formation of μ -peroxo dimer¹⁶⁻¹⁷ and the presence of high proton concentration or nucleophiles at the O₂ binding site.

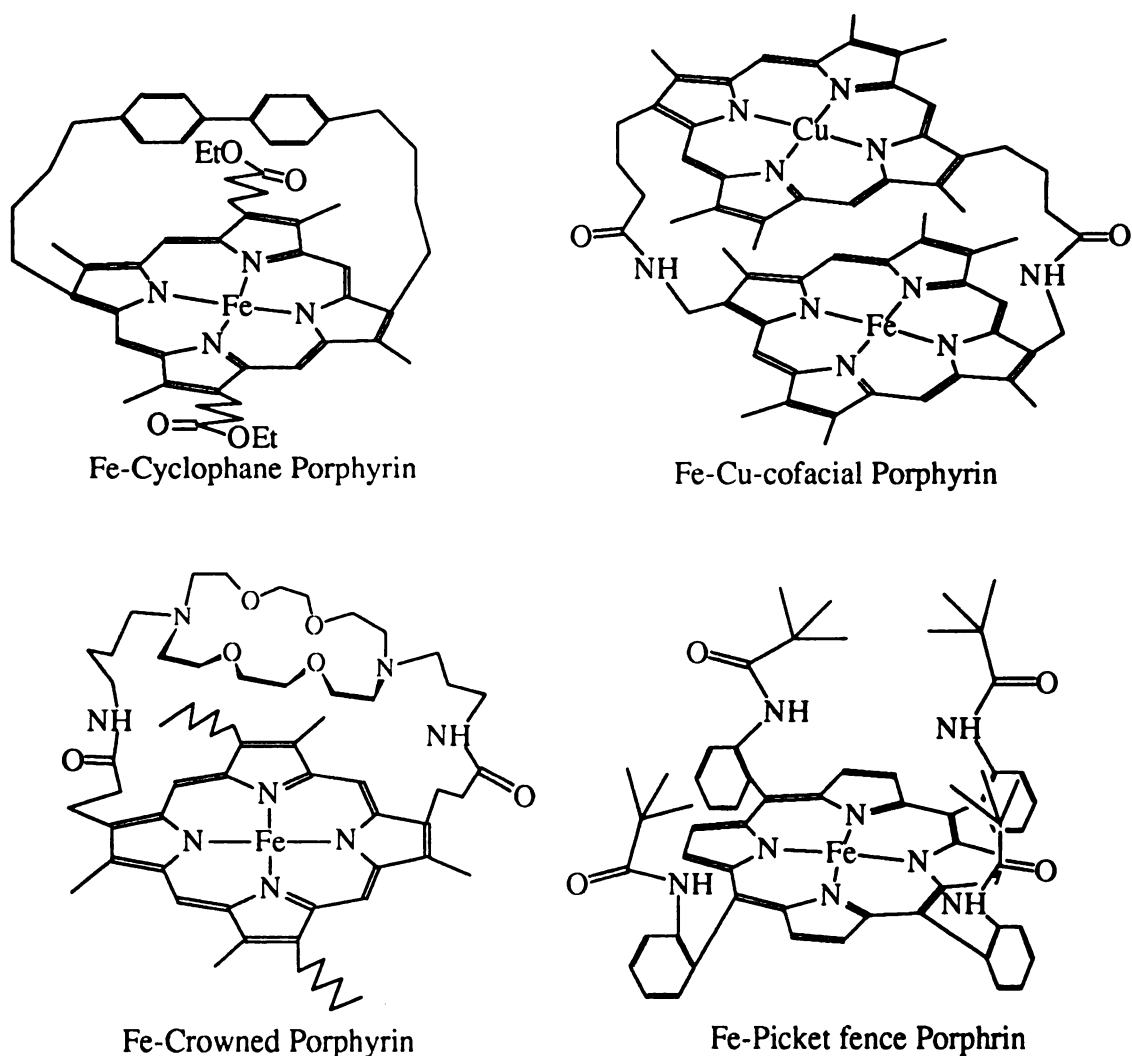


Figure 1-3 Single face sterically hindered porphyrins

Among previous approaches to study reversible dioxygen binding, there are basically two categories of models¹⁸⁻¹⁹: a) superstructured heme models with steric protection on either one side or both sides of the porphyrin resulting in room temperature stable O₂ complex; b) models with distal protons that require low temperature conditions to stabilize the unprotected O₂ complex. In the superstructured heme model family, for example, we find protected porphyrins such as cyclophane porphyrin by Traylor²⁰, crowned porphyrin by Chang²¹, 'picket fence' porphyrin by Collman²²⁻²³, and cofacial porphyrin by Chang²⁴

(Figure 1-3). These models built steric hindrance on one face of the heme and relied on external, often bulky, imidazoles to block the open face.

There are also double face sterically hindered porphyrin models such as the hanging base double bridged porphyrin by Battersby²⁵⁻²⁶ (figure 1-4) which has steric protections as well as a covalently linked base to supply the proximal ligand.

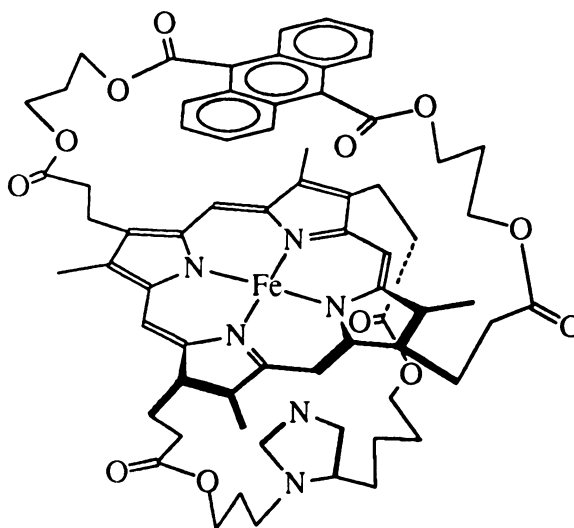
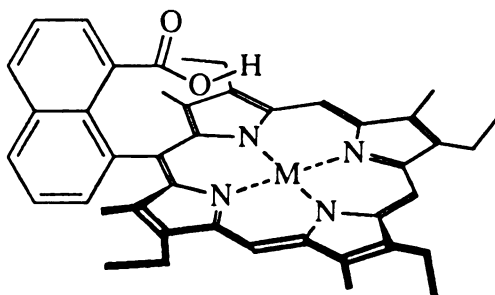


Figure 1-4 Hanging-base double-bridged porphyrin model

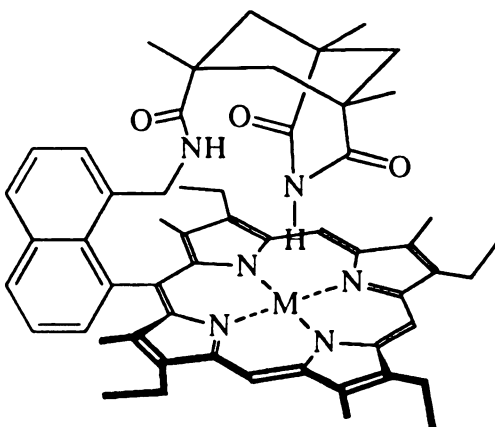
Studies conducted by Chang and Traylor²⁷ showed oxygen adducts of most Fe(II) porphyrins are stable at low temperature because the μ -peroxo dimer formation is dramatically slowed. More importantly, they also demonstrated that the Fe-O₂ binding affinity can be greatly enhanced by polar solvents¹³⁻¹⁴. Later development in this field firmly established the fact that H-bonding at the distal side is the most influential factor that controls the O₂ binding.

Several models designed to probe the distal H-bonding effect are now available. To highlight a few, naphthalene acid porphyrin and naphthalene Kemp's acid porphyrin (Figure 1-5) are capable of providing hydrogen-bonding interaction with the coordinated dioxygen²⁸⁻³¹. Unfortunately, without steric

protections, such hydrogen bonding models bind dioxygen reversibly only at low temperature.



Naphthalene Porphyrin



Naphthalene Kemp Porphyrin

Figure 1-5 Distal H-bonding models

Despite the fact that a large number of heme models were reported to form oxygenated heme adducts, building a realistic porphyrin model with both H-bonding effect and steric protection which forms a room temperature stable O_2 complex in solution remains to be a challenging task. A good model, which can closely mimic the heme environment in hemoglobin as well as in other redox active cytochromes, is badly needed to serve a wide variety of research interests on heme proteins. For our research interest, we started by looking for a proper spacer group from which a distal proton can be anchored to form hydrogen bonding to the heme binding site. We also need a superstructure, which protects

both faces of the heme, to solidly prevent any oxidation through intermolecular dimerization. In this project, a xanthene bridge was chosen to supply a specific H-bonding possibility. For steric protections, we developed a new terphenyl-substituted pyrrole synthesis, based on a Suzuki³²⁻³³ cross coupling reaction, to supply the porphyrin ring with needed steric bulk. Combining these two features, we obtained promising model compounds which have more natural protein-like binding environment and may allow us to study the chemistry of a stable heme-O₂ complex.

Chapter II

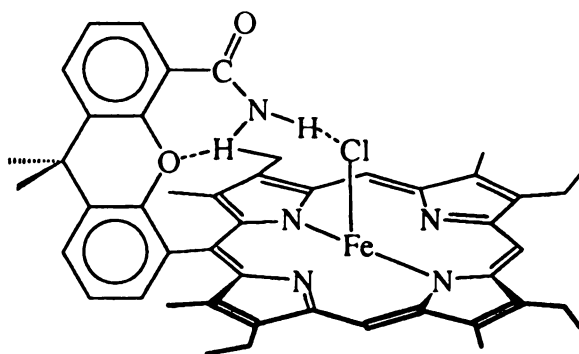
RESULT AND DISCUSSION

I. Functionalizing the Binding Site via Xanthene Bridge:

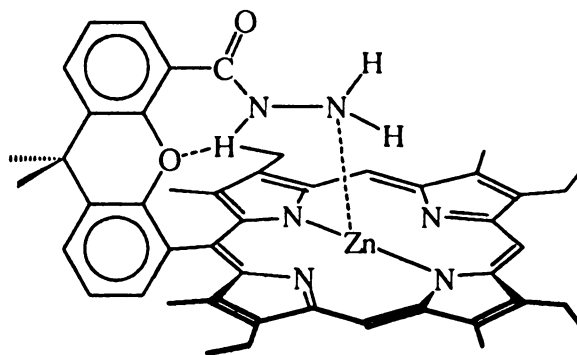
In this project, we set out to introduce specific hydrogen bonding effects at the heme binding site by building novel xanthene bridged porphyrin model compounds such as **a** and **b** (Figure 2-1).

Figure2-1

Xanthene porphyrin derivatives: (a) amide, (b) hydrazide



(a)

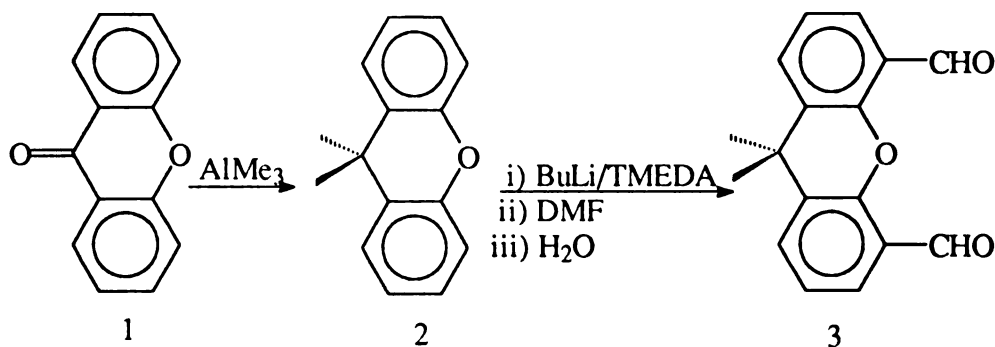


(b)

Xanthene is an interesting spacer group, the oxygen atom on the middle ring of xanthene may function as an anchor which fixes the amide group right on the same plane as that of the xanthene. When incorporated into a porphyrin ring as shown in Figure 2-1, this feature allows precise positioning of a distal functional group near the porphyrin center.

To synthesize such models, we started with the commercially available 9-xanthone **1** and treated it with trimethyl aluminum in toluene to give 9,9-dimethylxanthene³⁴ **2**. The methylated xanthene was reacted with butyl lithium at the presence of tetramethylethylenediamine (TMEDA) and DMF to give 4,5-diformyl-9,9-dimethylxanthene³⁵ **3** after hydrolysis (Scheme 2-1).

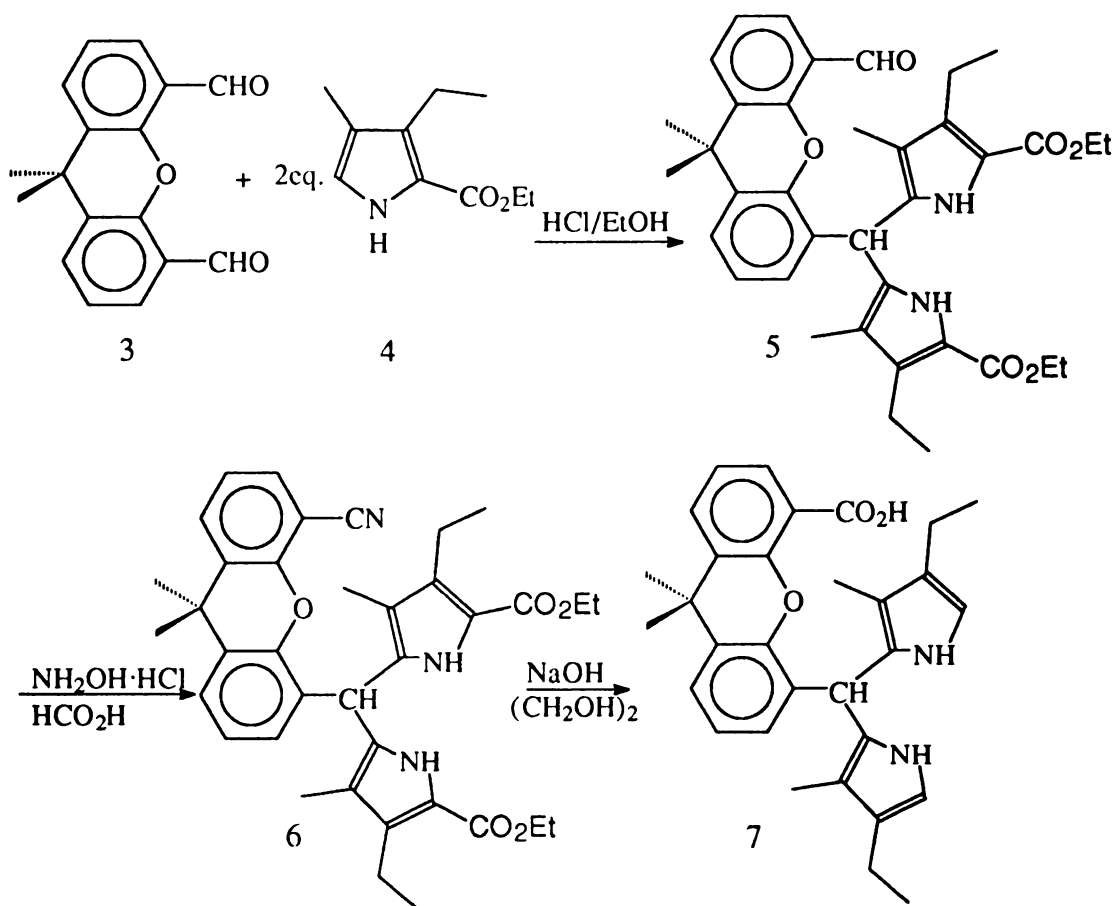
Scheme 2-1



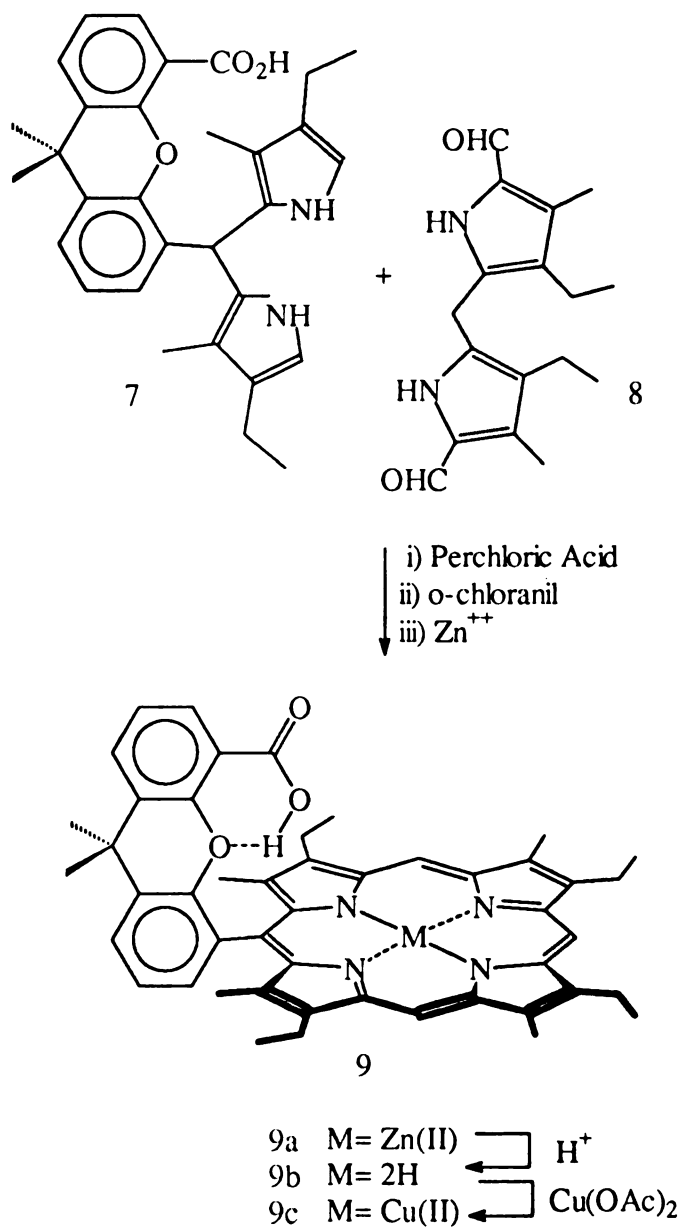
The diformyl xanthene **3** was condensed with two equivalents of ethyl 3-ethyl-4-methyl-2-pyrrolicarboxylate **4** with hydrochloric acid catalyst in refluxing ethanol under argon atmosphere. The resulting formyl-dipyrromethane **5** was treated with hydroxylamine hydrochloride in refluxing 98% formic acid to convert the formyl group to nitrile and followed by an one-step hydrolysis and decarboxylation in refluxing ethylene glycol containing sodium hydroxide to give the α -free dipyrromethane **7** (Scheme 2-2).

The xanthene dipyrromethane **7** was condensed³⁶ with the diformyl dipyrromethane **8** in the presence of perchloric acid in dichloromethane. To facilitate purification, zinc was inserted and the resulting zinc porphyrin complex **9a** could be chromatographed on silica gel. The zinc ion was removed by washing the zinc porphyrin in dichloromethane solution with 10% hydrochloric acid to give the free base porphyrin **9b**. Copper could be inserted by refluxing the porphyrin **9b** and copper acetate in chloroform-methanol solution (Scheme 2-3).

Scheme 2-2

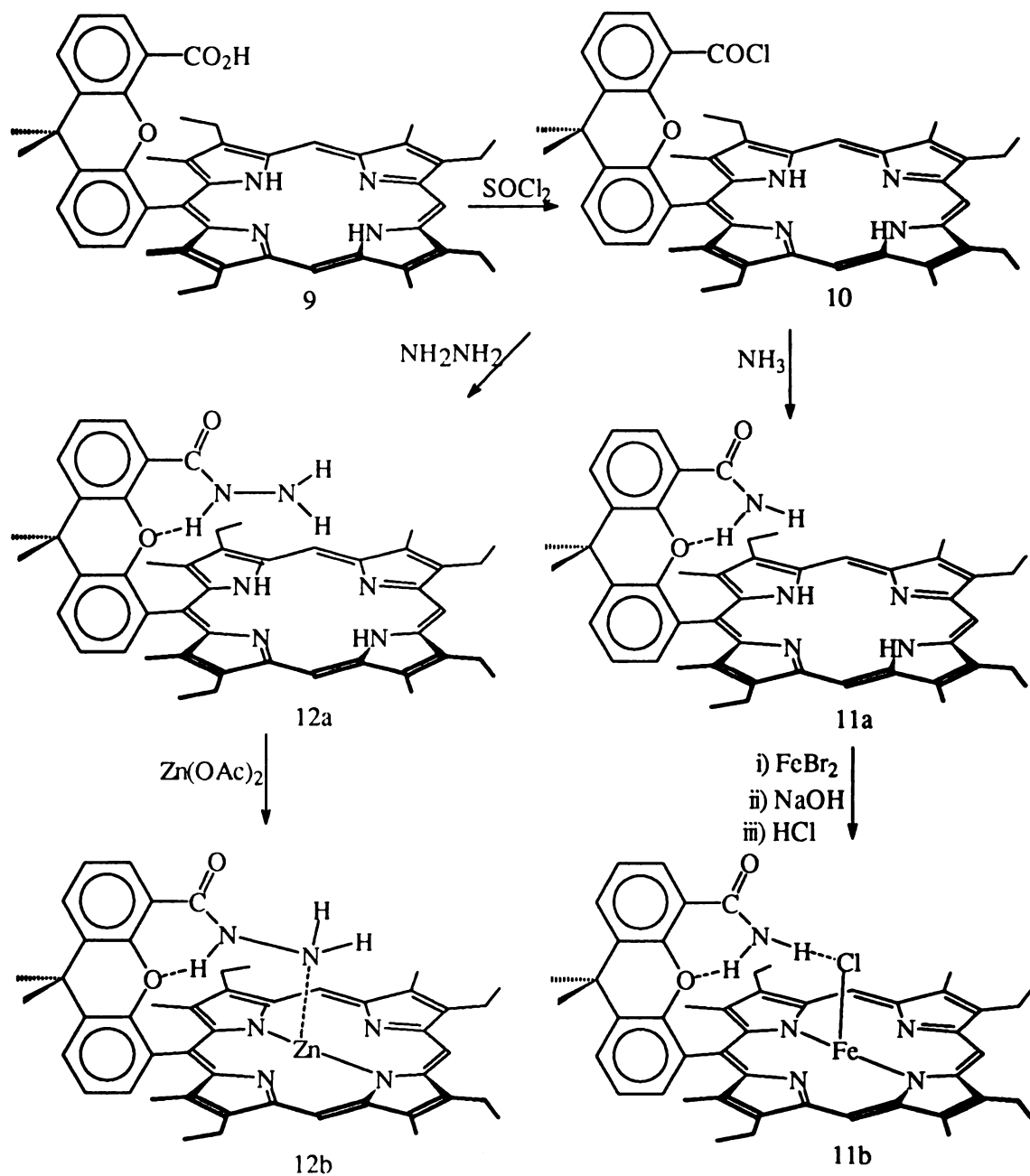


Scheme 2-3



X-ray crystallography of the porphyrin-xanthene-acid zinc(II) complex **9a** (Figure 2-2) showed that the acid proton was attached to the xanthene oxygen and was unavailable to form hydrogen-bonding with ligand at the porphyrin metal center.

Scheme 2-4



In order to explore a hydrogen-bonding possibility to heme-bound substrates, we converted **9b** to the carboxamide porphyrin **11a**, by first converting the acid to an acid chloride **10** using thionyl chloride, then reacting

with ammonia gas in dichloromethane. Similarly, we also obtained the porphyrin carboxhydrazide **12a** by reacting the porphyrin acid chloride **10** with anhydrous hydrazine (Scheme 2-4).

The X-ray structure of the hemin chloride **11b** (Figure 2-3) indeed showed the expected hydrogen bonding with the axial ligand. The X-ray structure of **12b** (Figure 2-4), however, showed that the terminal hydrazide nitrogen formed a nitrogen-zinc bond which both blocked the distal side of porphyrin complex and pulled the xanthene bridge toward the porphyrin ring. Coordination between iron and SP^3 -nitrogen is typically very weak, it occurs in this system undoubtedly because of the steric constraints brought by the unique arrangement.

Figure 2-2

X-ray structure of zinc carboxylic acid porphyrin complex **9a**

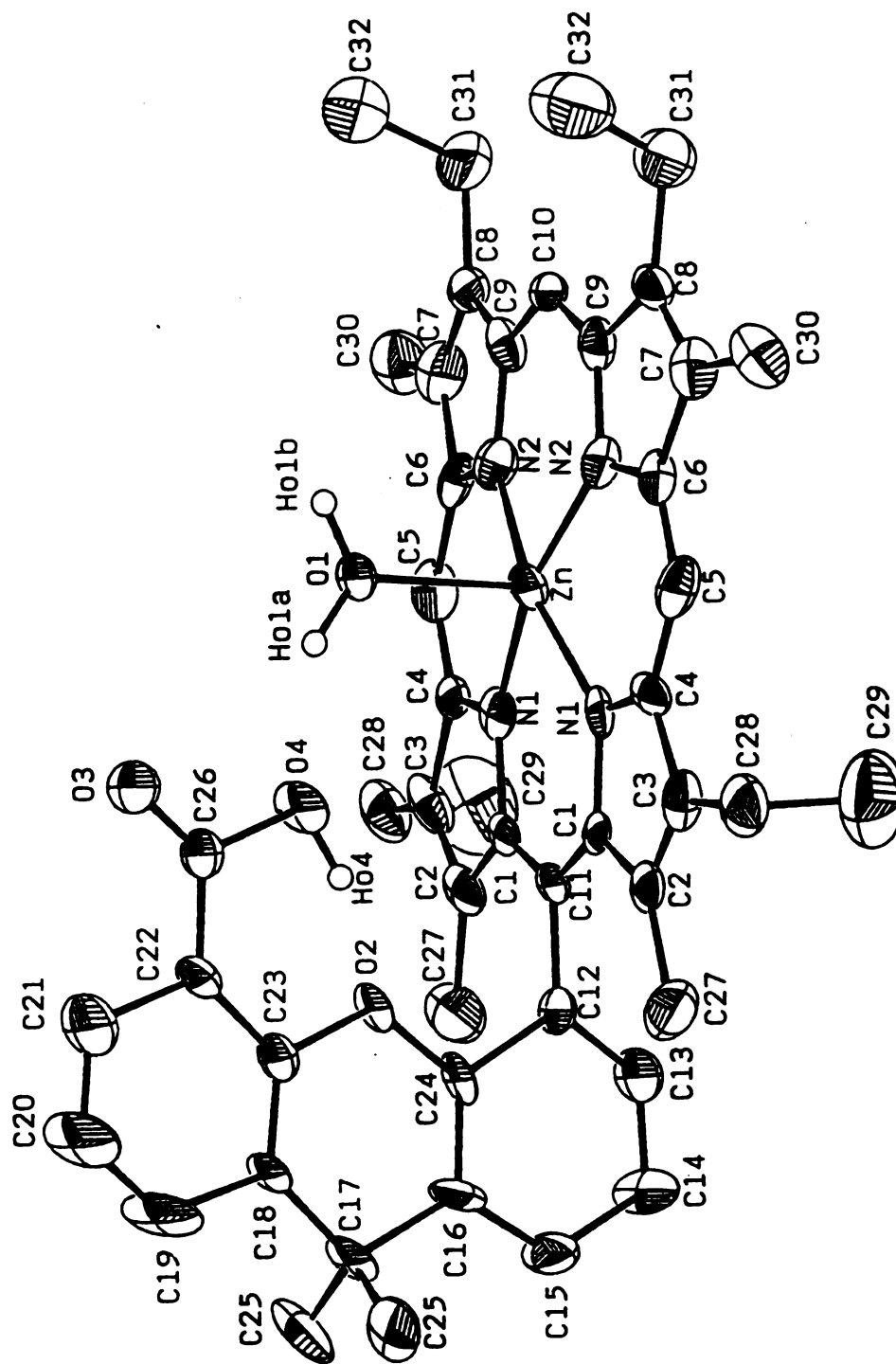


Figure 2-3

X-ray structure of iron carboxamide porphyrin complex **11b**

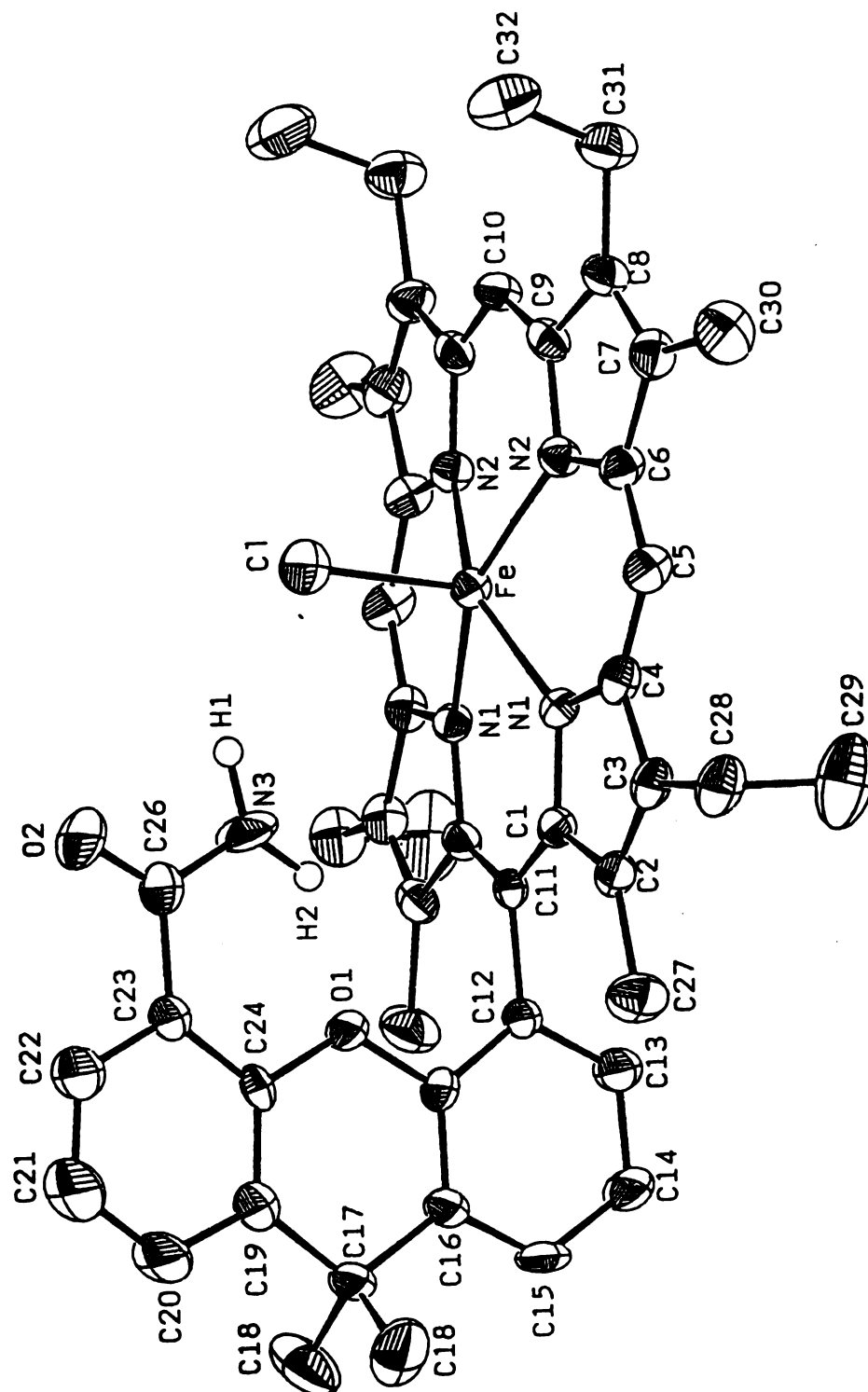


Table 1. Selected Bond Distances and Angles for **9a**

Distance (Å) (ESD)		Angle (degree) (ESD)	
Zn-O1	2.250 (14)	O1-Zn-N1	99.5 (4)
Zn-N1	2.055 (13)	O1-Zn-N1	99.5 (4)
Zn-N1	2.055 (13)	O1-Zn-N2	94.7 (5)
Zn-N2	2.053 (14)	O1-Zn-N2	94.7 (5)
Zn-N2	2.053 (14)	Zn-O1-Ho1a	122.3 (13)
O1-Ho1a	0.955 (15)	Zn-O1-Ho1b	120.0 (11)
O1-Ho1b	0.960 (17)	C23-O2-Ho4	97.7 (15)
O2-Ho4	1.584 (18)	C26-O4-Ho1a	117.7 (16)
O4-Ho1a	1.888 (19)	C26-O4-Ho4	99.2 (17)
O4-Ho4	0.969 (20)		

Table 2. Selected Bond Distances and Angles for **11b**

Distance (Å) (ESD)		Angle (degree) (ESD)	
Fe-Cl	2.199 (3)	Cl-Fe-N1	106.72 (12)
Fe-N1	2.069 (4)	Cl-Fe-N1	106.72 (12)
Fe-N1	2.069 (4)	Cl-Fe-N2	99.27 (13)
Fe-N2	2.062 (4)	Cl-Fe-N2	99.27 (13)
Fe-N2	2.062 (4)	Fe-Cl-H1	110.12 (10)
Cl-H1	2.3795 (24)	C24-O1-H2	103.9 (5)
O1-H2	1.839 (5)	C26-N3-H1	106.5 (7)
O2-C26	1.180 (10)	C26-N3-H2	116.7 (8)
N3-C26	1.306 (11)	H1-N3-H2	136.8 (9)
N3-H1	0.957 (7)		
N3-H2	0.960 (7)		

Figure 2-4
X-ray structure of zinc carboxyhydrazide porphyrin complex **12b**

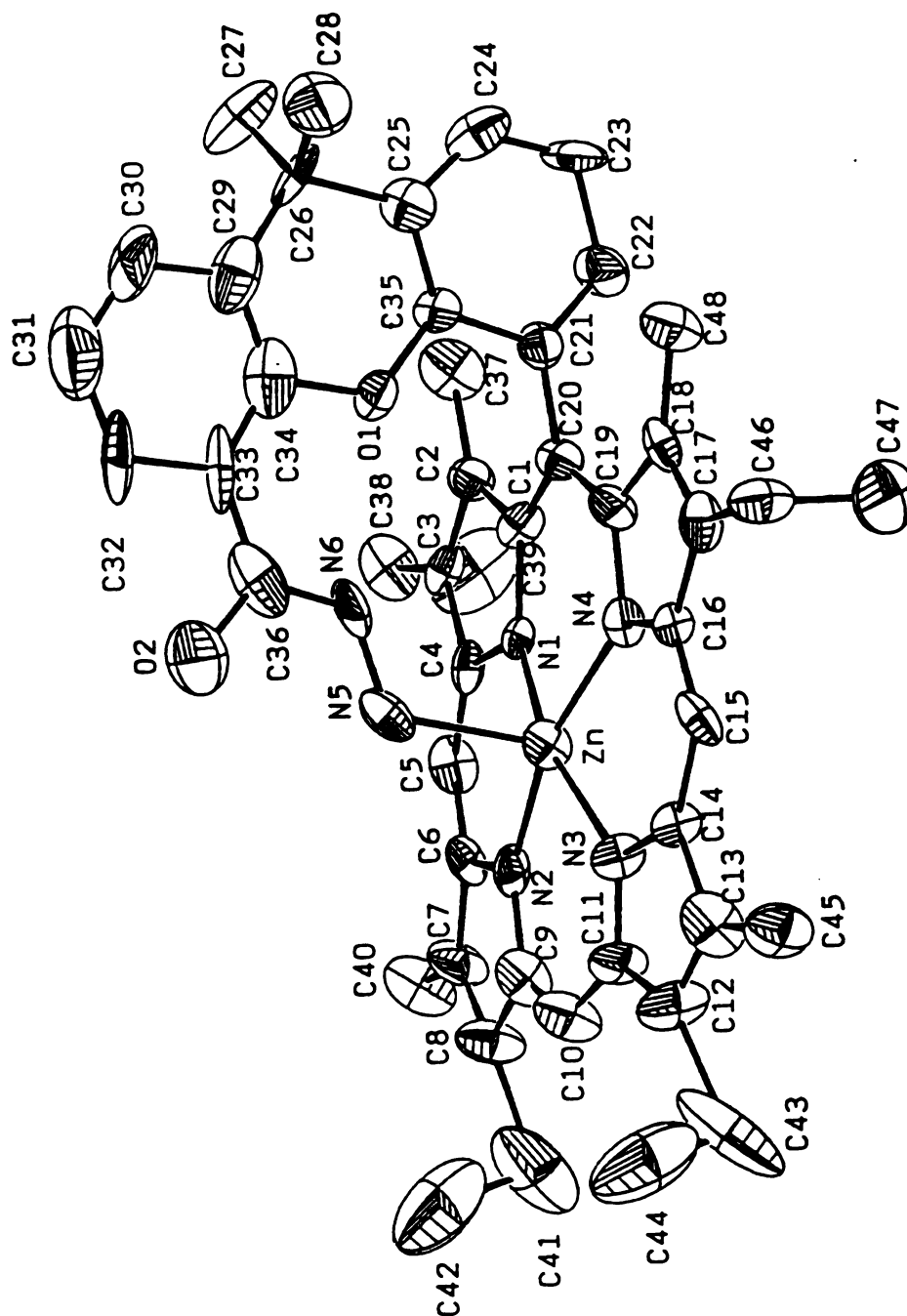


Table 3. Selected Bond Distances and Angles for **12b**

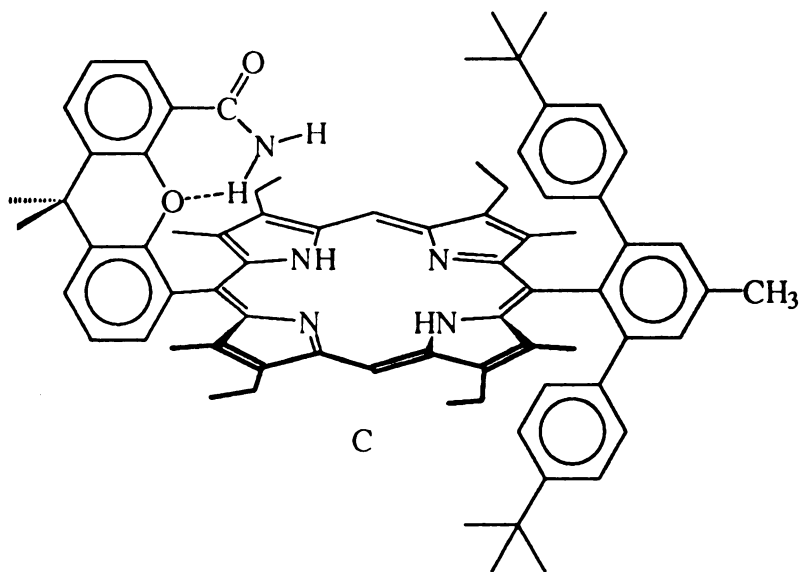
Distance (Å) (ESD)		Angle (degree) (ESD)	
Zn-N1	2.029 (7)	N5-Zn-N1	91.6 (3)
Zn-N2	2.031 (8)	N5-Zn-N2	100.4 (3)
Zn-N3	2.075 (7)	N5-Zn-N3	104.6 (3)
Zn-N4	2.024 (8)	N5-Zn-N4	96.5 (3)
Zn-N5	2.247 (9)	Zn-N5-N6	117.4 (6)
O2-C36	1.298 (15)	N5-N6-C36	124.6 (9)
N5-N6	1.408 (14)	O2-C36-N6	115.4 (13)
N6-C36	1.278 (17)	C1-C20-C21	120.2 (9)
		C19-C20-C21	119.5 (9)
		C20-C21-C35	117.1 (9)

II. Synthesis of Sterically Encumbered Porphyrin with single meso-Terphenyl Shield:

A preliminary dioxygen binding study, conducted by our group member, indicated that the carboxamide heme **11b** auto-oxidized rapidly in solution. To help stabilize the O₂ adduct, we designed a terphenyl “picket fence” substituted at a single meso position of the carboxamide xanthene porphyrin. In theory, this sterically hindered model (c) should retard the heme-O₂ oxidation process (Figure2-5).

Figure 2-5

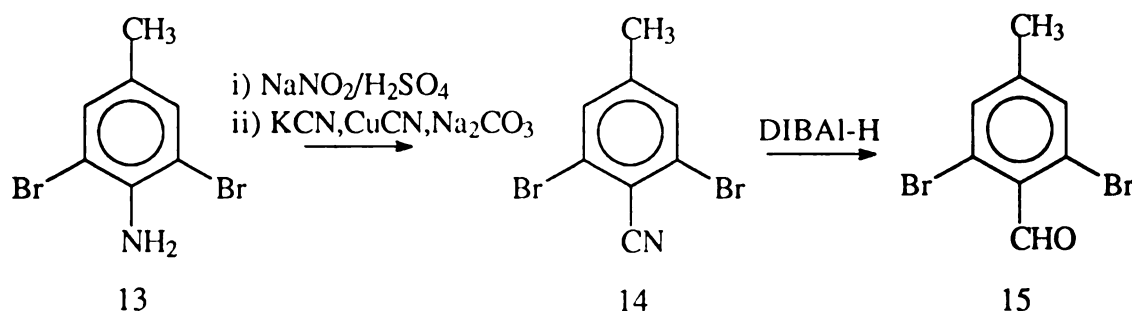
Porphyrin with single meso-terphenyl shield



In traditional porphyrin synthesis, meso-substituted porphyrins are made by direct condensation of benzaldehyde and pyrrole. Such reactions do not work very well with highly crowded benzaldehyde. Therefore, a new strategy has been developed to build the terphenyl wing by using Pd⁰ catalyzed cross-coupling between aryl boronic acids and bromobenzene (the Suzuki³²⁻³³ Coupling).

The synthesis of the meso substituted porphyrin (c) began from the commercially available 2,6-dibromo-4-methylaniline **13**. The aniline **13** was first carefully treated with a nitrosyl sulfuric acid solution at room temperature, then followed by substitution of cyanide with KCN/CuCN at 0 °C. The crude 2,6-dibromo-4-methylbenzonitrile **14** product was purified by flash chromatography on silica gel column. The benzonitrile **14** was then reduced by diisobutyl aluminum hydride (DIBAL) to give 2,6-dibromo-4-methylbenzaldehyde **15**. All reactions were smooth and in good yield under careful handling (Scheme 2-5).

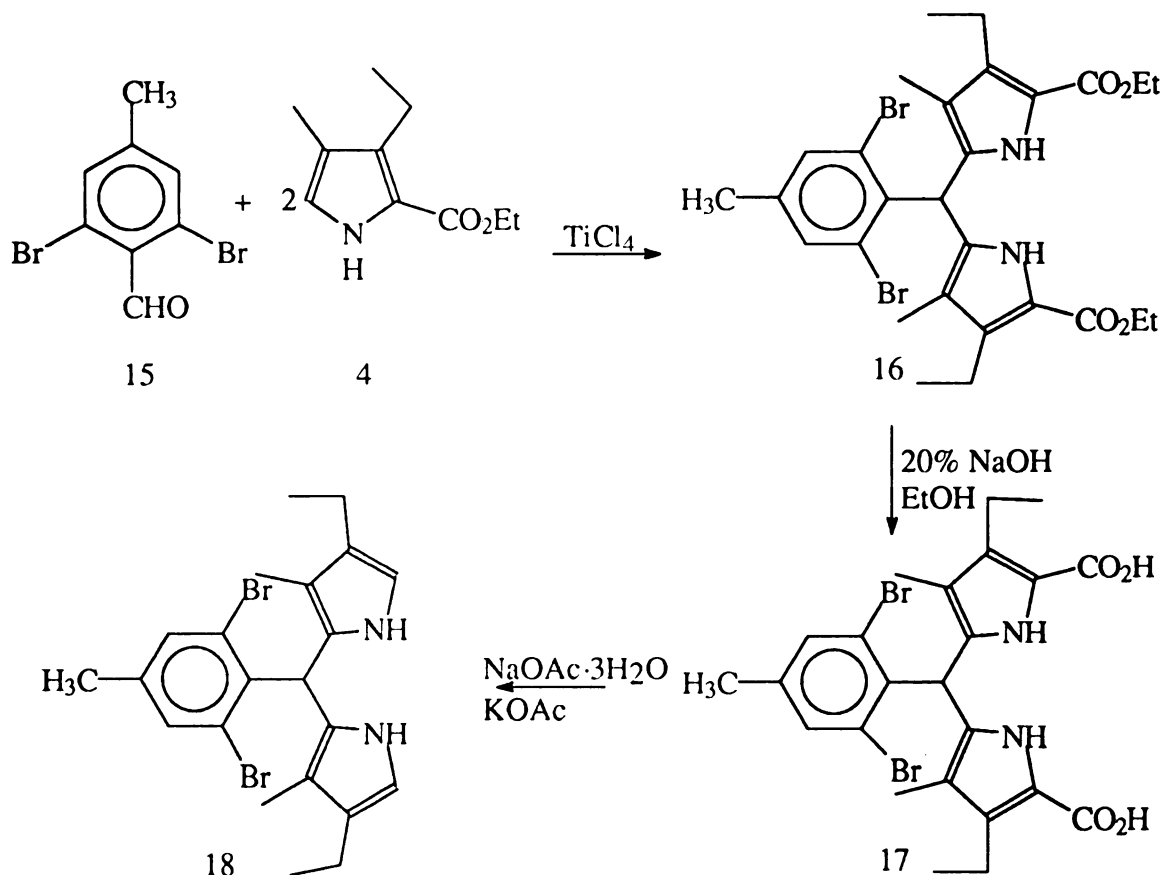
Scheme 2-5



The condensation of the benzaldehyde **15** with ethyl 3-ethyl-4-methyl-2-pyrrolicarboxylate **4** was first carried in refluxing ethanol with HCl catalyst, but yield was less satisfactory. So we turned to condense them in dichloromethane in presence of titanium tetrachloride³⁷ under argon atmosphere. The resulting dipyrromethane **16** was purified on silica gel column by chromatography with dichloromethane as eluent containing a trace amount of triethylamine. When we tried to carry out the hydrolysis and decarboxylation in one step by refluxing it overnight in a solution of NaOH, water and ethanol, the dipyrromethane severely decomposed. So we employed a two-step method, which gave decent yields. The dipyrromethane **16** was first hydrolyzed with 20% sodium hydroxide in refluxing ethanol for 3 hours, then melted with a 1:1 mixture of potassium acetate and sodium acetate trihydrate at 160 °C under argon atmosphere. The

crystalline alpha free dipyrromethane **17** was obtained by filtration in almost quantitative yield after salts was washed out (Scheme 2-6).

Scheme 2-6

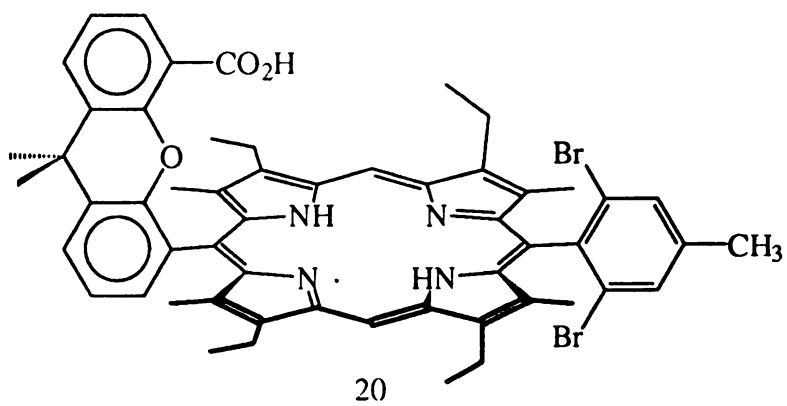
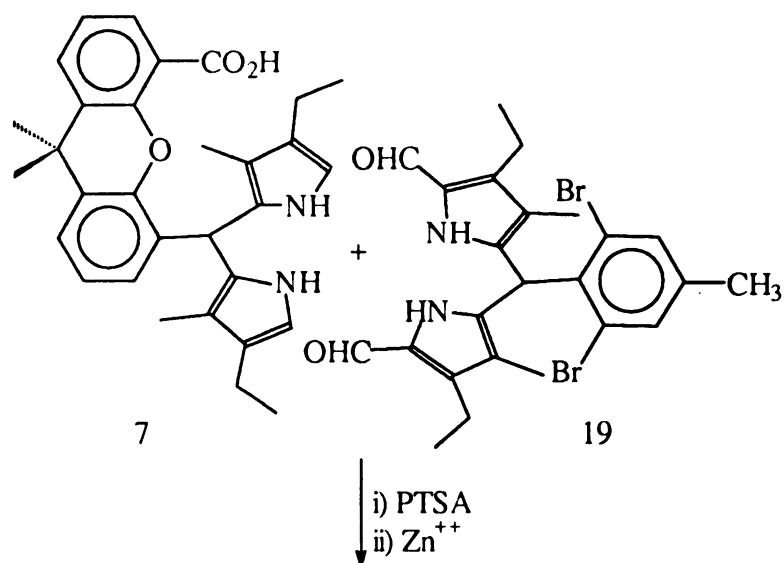
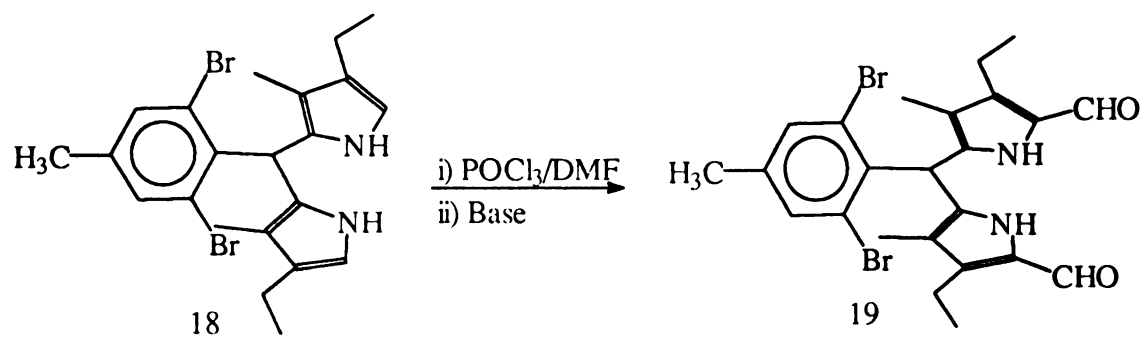


The dipyrrylmethane **18** was further converted to diformyl dipyrryl methane **19** with POCl_3 and DMF ³⁹. The crude diformyl dipyrrylmethane **19** was used to couple with the xanthene dipyrrylmethane **7** in the presence of *p*-toluenesulfonic acid followed by air oxidation facilitated with zinc acetate and sodium acetate to give the porphyrin **20**. The acid porphyrin **20** was carefully purified on silica gel column by chromatography (Scheme 2-7).

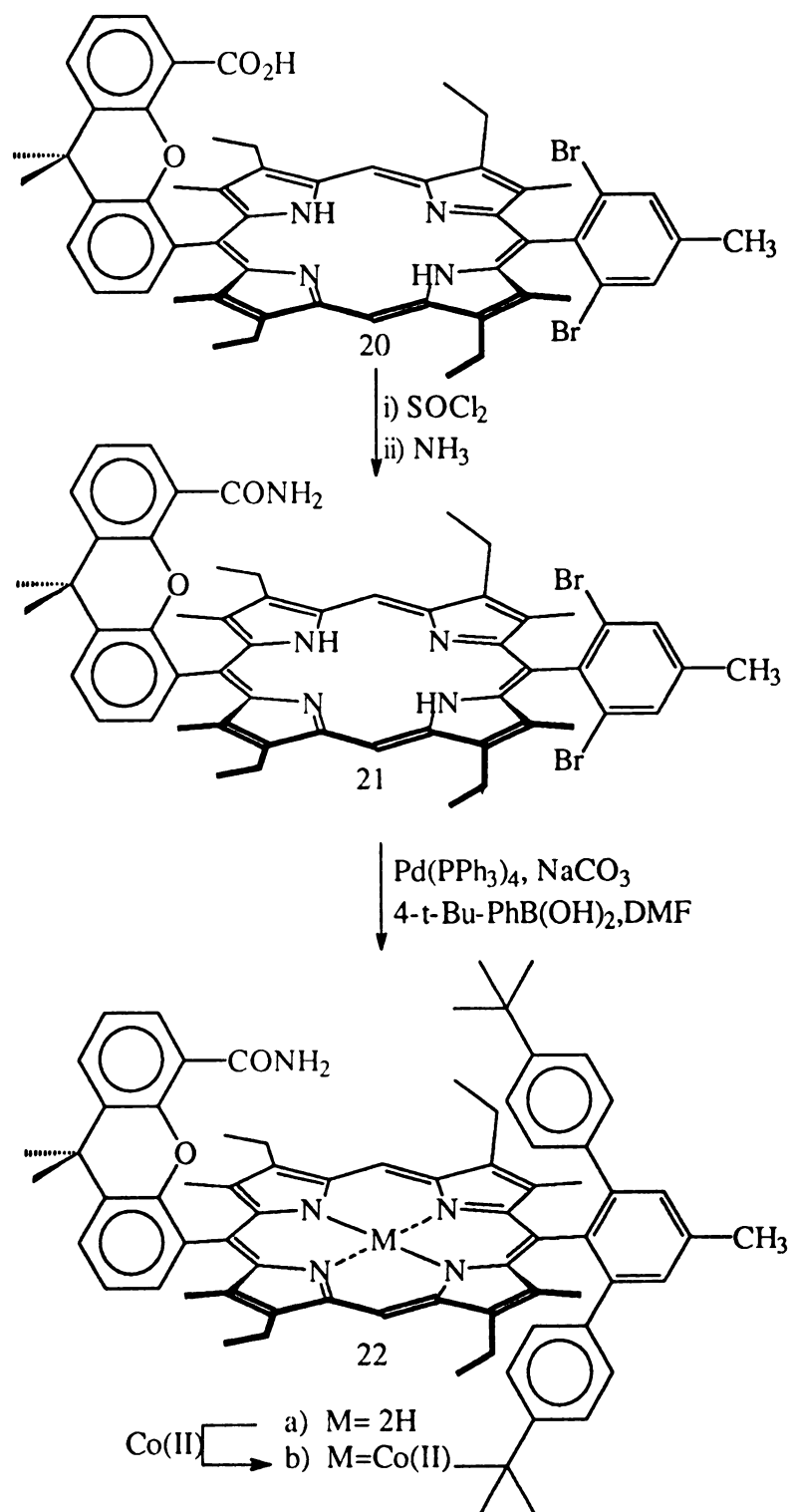
Before replacing the bromo group of **20** with 4-*t*-butylphenyl, we decided to converted it to carboxamide porphyrin **21** first. The porphyrin **20** was reacted

with thionyl chloride in refluxing dry dichloromethane for 1 hour before the excess reagent and solvent were pumped dry. After the acid chloride was redissolved in dry dichloromethane, ammonia gas was passed through the solution. The resultant product is a pure single compound—porphyrin carboxamide **21** in quantitative yield. This amide was then heated with 10 equivalents of 4-*t*-butylphenyl boronic acid³⁸ in the presence of Pd(PPh₃)₄ catalyst in DMF under argon atmosphere to give the terphenyl shielded porphyrin **22a** (Scheme 2-8). The excessive amount of boronic acid seems advantageous. An early run of this coupling with 3 equivalents of boronic acid and less palladium catalyst showed an incomplete reaction.

Scheme 2-7



Scheme 2-8

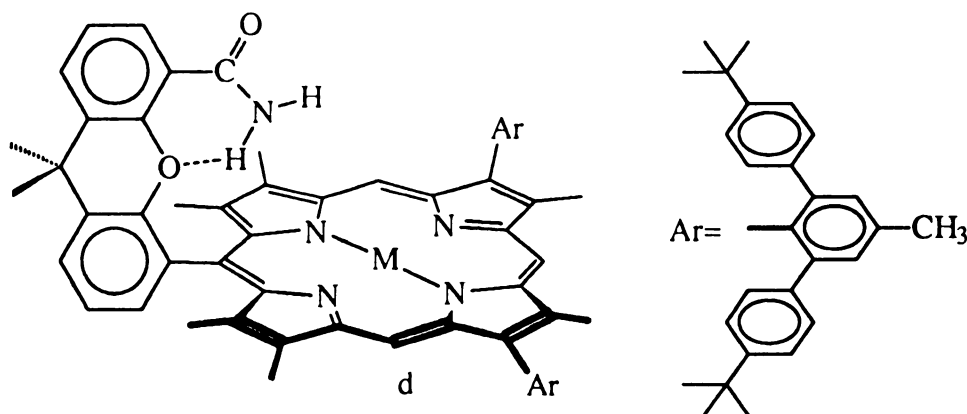


III. Synthesis of Porphyrin with Double Terphenyl Shielding Wings:

To further protect the porphyrin metal center, we designed and synthesized the porphyrin **d** (Figure 2-6). The porphyrin **d** has two terphenyl shields on the beta-pyrrole positions in addition to a xanthene amide at meso position. As the two rather large shields are totally blocking the metal center, this model may give a stable metal porphyrin oxygen complex and provided us a chance to study chemical reaction with the heme-O₂ complex at manageable conditions where most previous models failed to survive.

Figure 2-6

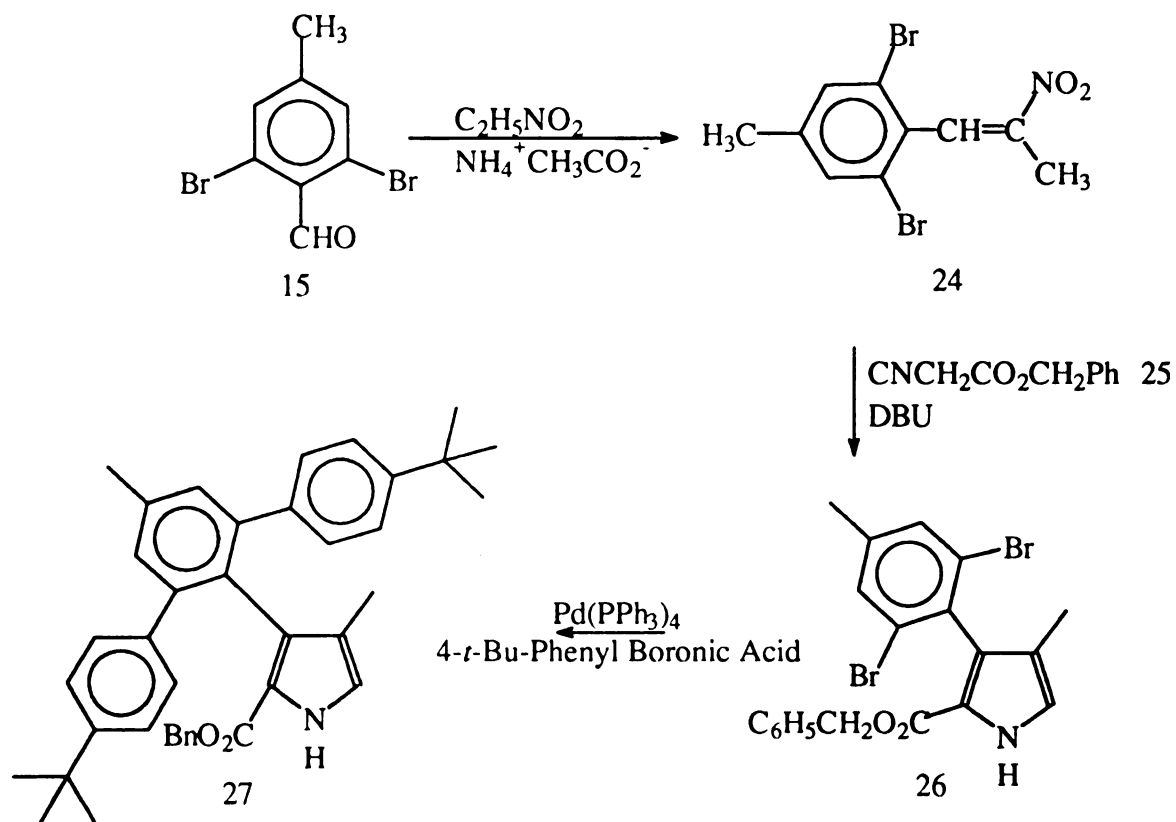
Porphyrin with double terphenyl shields



For synthesis, the key building block is the 3-terphenyl pyrrole **27**. We started to make **27** from 2,6-dibromo-4-methylbenzaldehyde **15**. A mixture of aldehyde **15** and NH₄OAc was brought to reflux in excess nitroethane to yield the nitropropene **24** in 95% yield after removal of the excess nitroethane and chromatography. **24** was then reacted with isocyanoacetate **25** in dry THF in presence of two equivalents of DBU at room temperature. After 24hr the reaction mixture was poured into 10% HCl to precipitate the dibromo aryl pyrrole **26**. The precipitate was collected by filtration and purified on silica gel column to

give a pure dibromo pyrrole⁴⁰ **26** in 62% yield. The dibromo pyrrole **26** was coupled with 4-*t*-butylphenyl boronic acid to give the terphenyl pyrrole **27** in 66% yield as light yellow solid after flash chromatography (Scheme 2-9).

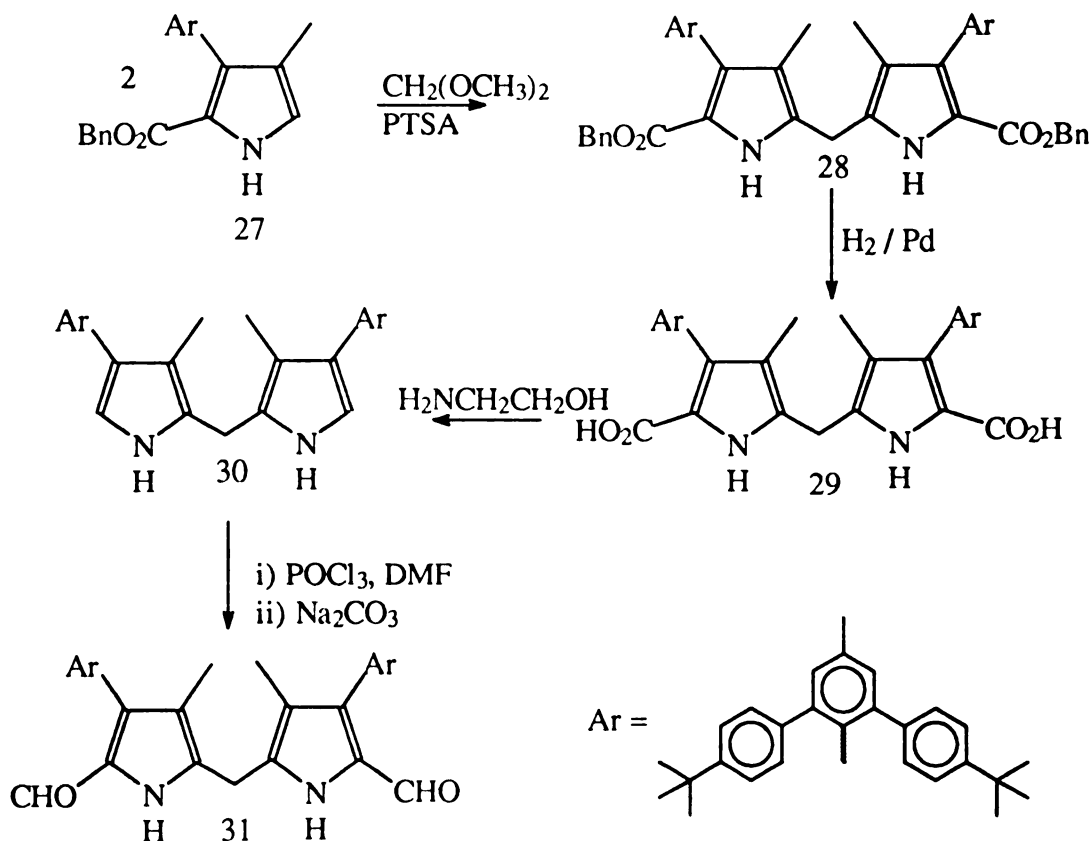
Scheme 2-9



The pyrrole **27** was reacted with methylal in refluxing chloroform in the presence of *p*-toluenesulfonic acid (PTSA) under argon atmosphere for 18 hr and the solution was extracted with dichloromethane. After purification on silica gel column, the dipyrromethane **28** was obtained in 57% yield. The dipyrromethane benzyl ester **28** was hydrogenolized in methanol with Pd-C(10%) catalyst to give the dipyrromethane di-acid **29** in 96% yield. The di-acid **29** was then decarboxylated in refluxing ethanolamine under argon atmosphere for 30 min to yield the alpha free dipyrromethane **30** in 91%. It was further reacted

with POCl_3 and dry DMF to give formyl dipyrromethane **31**, after hydrolysis (Scheme 2-10). The formyl dipyrromethane **31** was directly used for following reactions without purification.

Scheme 2-10

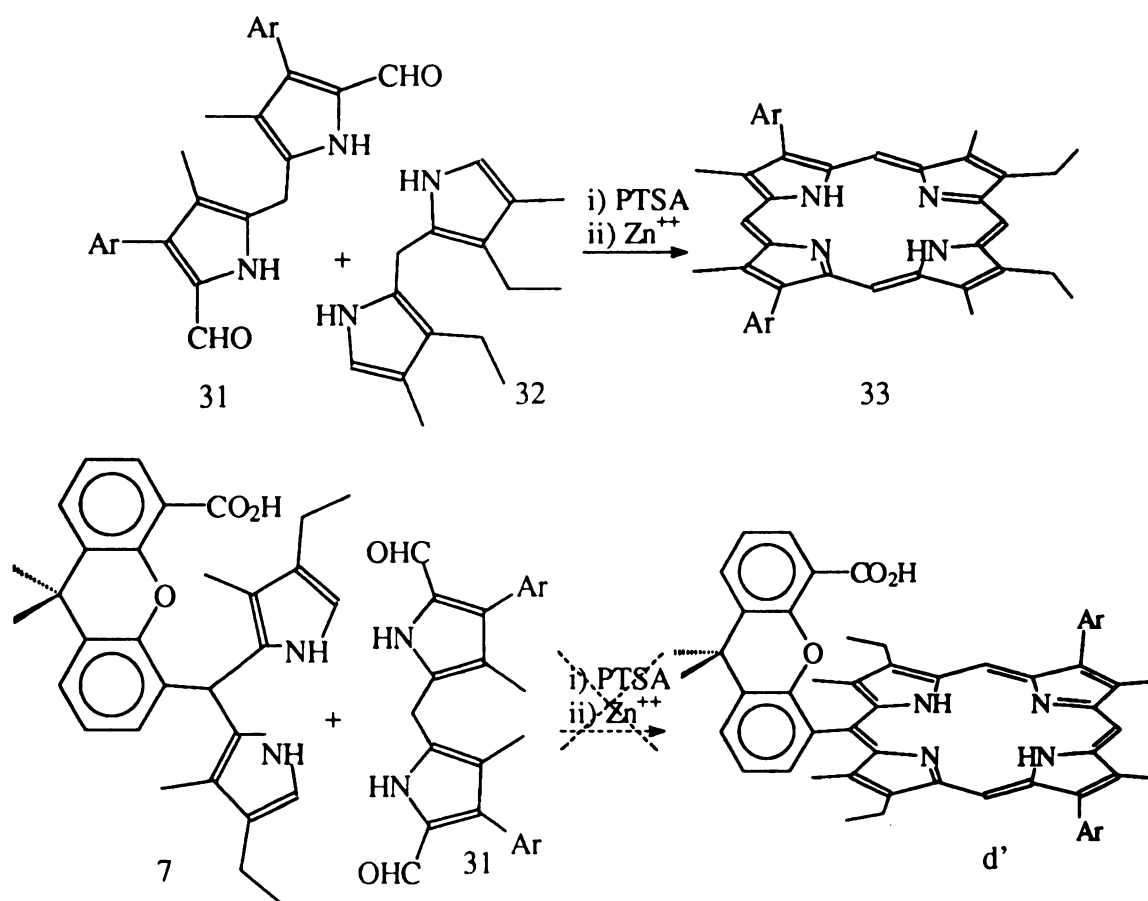


In an attempt to make our desired diaryl porphyrin **d**, we first condensed the formyl dipyrromethane **31** with a simple alpha free dipyrromethane **32**. In normal MacDonald condensation condition, the yield of the diaryl porphyrin **33** is reasonable—8%. But it did not work when we tried to couple **31** with the xanthene dipyrromethane **7**. The terphenyl substituent may be too big a steric hindrance during the coupling (Scheme 2-11).

To look for an alternative synthetic approach, we turned to a method based on tetrapyrrole biting down an aromatic aldehyde. In order to test if

diformyl xanthene **3** would work in tetrapyrrole condensation, we refluxed a methanol solution of unshielded tetrapyrrole **34** and **3** in presence of a few drops of HBr/acetic acid (30%) under argon for 24hr. The reaction gave an excellent yield (35%) of the aldehyde porphyrin **35** (Scheme 2-12).

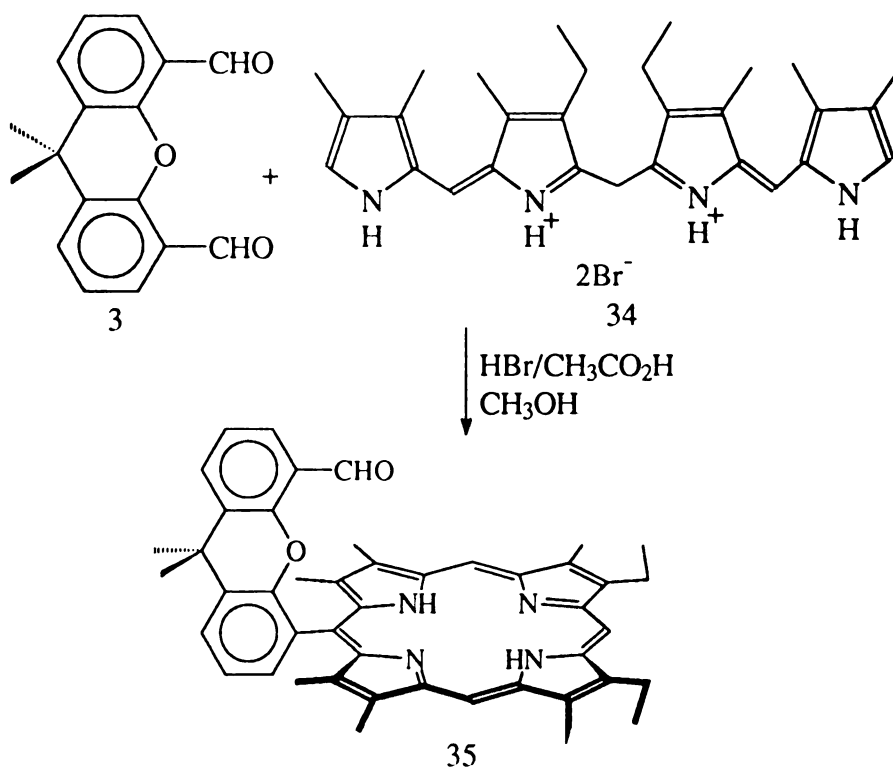
Scheme 2-11



This result suggested that this approach to our desired porphyrin **d** may be feasible. We chose to use 3,4-dimethylpyrrole **36** to make tetrapyrrole because the two relatively small methyl groups on beta positions can further reduce steric effect in both the tetrapyrrole formation and the porphyrin cyclization. The diaryl tetrapyrrole **37** was obtained by reacting dimethylpyrrole **36** with formyl dipyrromethane **31** in methanol containing HBr (48% aq.). After

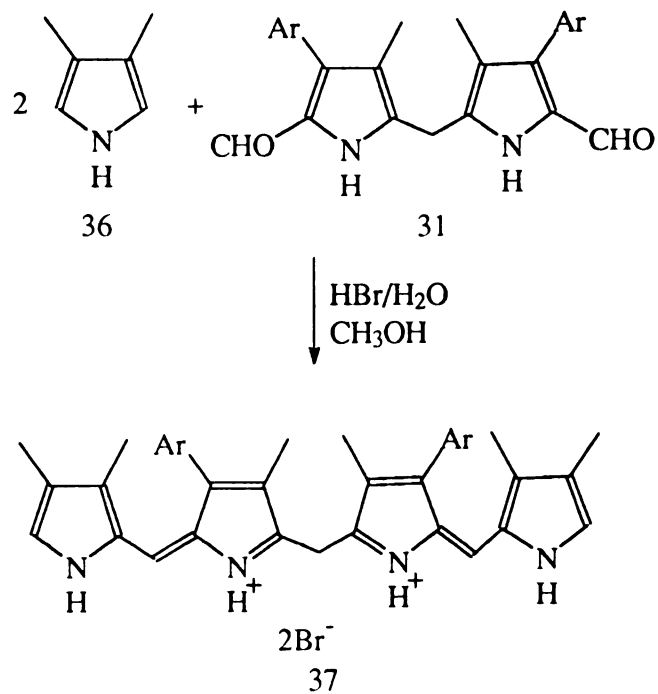
the mixture was heated on steam bath for 3 min followed by standing at room temperature for 2 hr, it was cooled in a refrigerator to help precipitate the product. The brown diaryl tetrapyrrole **37** was collected by filtration and washed with methanol containing a small amount of HBr. It was used for next step without further purification (Scheme 2-13).

Scheme 2-12

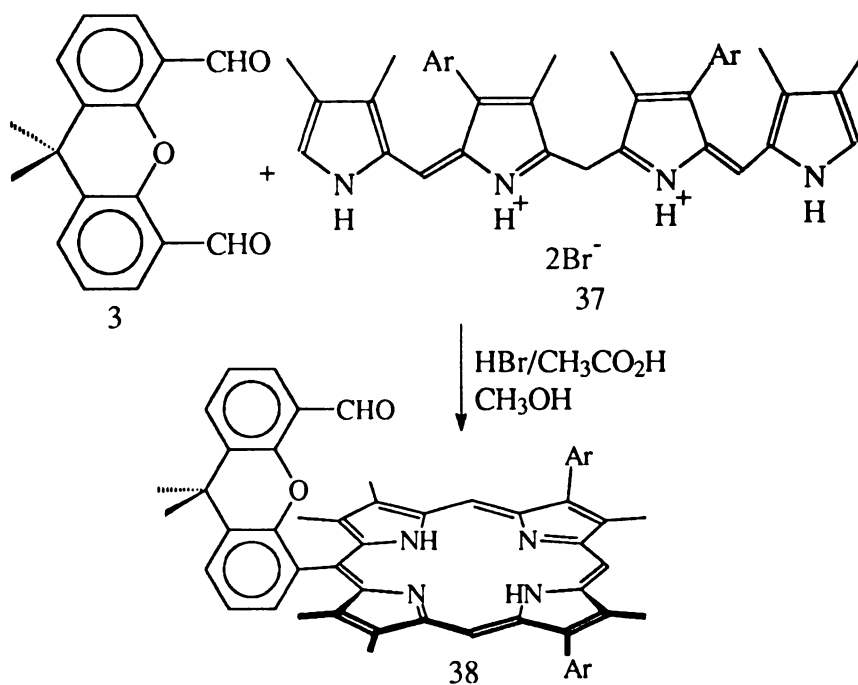


The tetrapyrrole **37** was coupled with diformyl xanthene **3** in refluxing methanol in presence of a few drops of HBr/acetic acid (30%) for 24hr. The major compound we got is the desired xanthene diaryl porphyrin **38**. The porphyrin **38** was carefully purified on silica gel by chromatography (Scheme 2-14).

Scheme 2-13



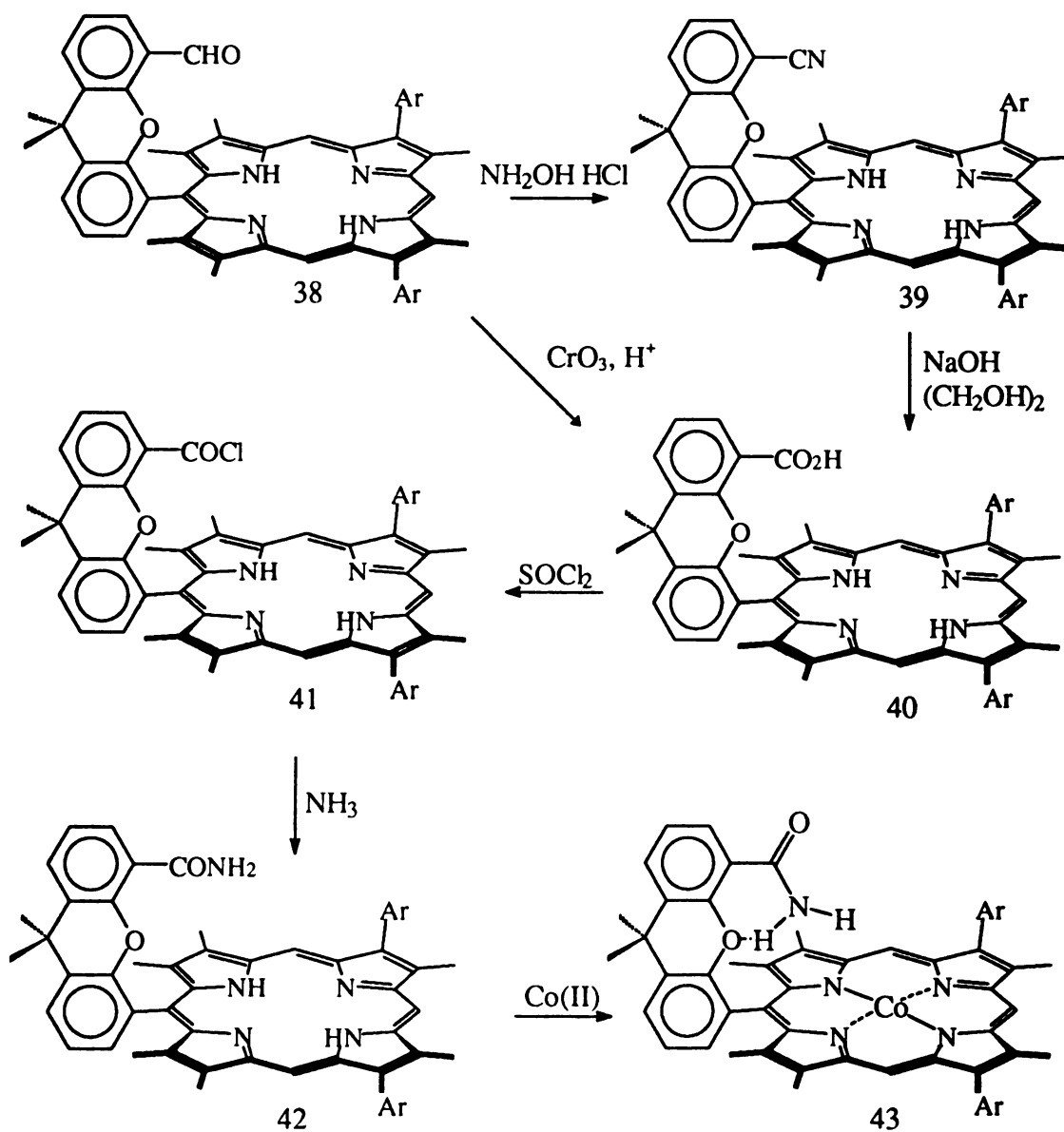
Scheme 2-14



Converting the aldehyde group to nitrile **39** was achieved by refluxing **38** with excess $\text{NH}_2\text{OH}\cdot\text{HCl}$ in formic acid overnight under argon atmosphere. The hydrolysis of the nitrile to carboxylic acid was proved to be troublesome. We first tried to reflux it with formic acid, HCl and 20% water for a day, but it did not give any hydrolyzed product. We then turned to alkaline hydrolysis. A mixture of porphyrin, NaOH, Pyridine and 10% water was refluxed for 24 hours, but only a trace amount of hydrolyzed product was detected on TLC. It seems a stronger condition was needed. The hydrolysis was finally successful when porphyrin **39** was refluxed with a large excess of NaOH in pure ethylene glycol at 198 °C for 1 day under argon atmosphere. The product—porphyrin **40** was purified on silica gel plate with dichloromethane containing 2% methanol as the eluent. The amide porphyrin **42** was obtained following the regular acid chloride-anhydrous ammonia route. Cobalt complexes of both **22a** and **43** were prepared and they will be used for O_2 binding study.

To avoid the troublesome hydrolysis of **39**, we developed an alternative method to convert the porphyrin **38** to acid **40** directly by oxidation. While many conventional oxidation methods are available in converting aldehyde to acid, few has been applied to porphyrinic aldehyde. The oxidation condition proved to be tricky since degradation of the porphyrin often occurred. However, we discovered that the best condition is the Jones's reagent in ice bath for 1.5 hr and then followed by room temperature for 1.5 hr under argon atmosphere. This gave us the optimum yield on converting porphyrin **38** to **40** in one step without the going through the difficult cyanide hydrolysis.

Scheme 2-15



IV. Conclusion:

In this research, we have demonstrated the effectiveness of a xanthene amide group as an intramolecular proton donor in heme models. When incorporated onto a porphyrin meso position, the xanthene oxygen bridge uniquely anchors one amide proton and renders the other amide proton pointing toward the porphyrin metal center. As such, it may serve as an excellent model for the distal H-bonding effect in heme enzymes. Replacing the amide by a hydrazide group, however, resulted in a stable metal-to-hydrazido nitrogen bond.

We have also explored new strategies of introducing steric shielding to heme model compounds. We have synthesized shielded porphyrins with either a single meso attached or two beta-connected terphenyl groups having further substituents at the flanking wings of the terphenyl. These exceedingly bulky superstructures were made through the use of Suzuki cross-coupling reactions. The combination of intramolecular proton donor (from xanthene amide) and steric protections should allow the realization of stable heme-dioxygen complex even at room temperature.

Chapter III

EXPERIMENTAL

Materials and measurements Reagents and solvents for synthesis were used as received unless otherwise stated. ^1H NMR spectra were recorded on Varian Gemini-300 in 99.9% CDCl_3 with residual CHCl_3 as the internal standard set at 7.24 ppm. Mass spectra were measured on a VG Trio-1 mass spectrometer for M/Z less than 1000 or on JEOL HX-110 HF double focusing spectrometer in the FAB-MS positive ion detection mode for M/Z over 1000. UV-Visible spectra were measured on a Shimadzu 160 spectrometer. Infrared spectra were measured on a Nicolet IR/42 spectrometer.

4,5-Diformyl-9,9-dimethylxanthene (3): 9,9-Dimethylxanthene (3 g, 14 mmol) and tetramethylethylenediamine (TMEDA) (5.72 ml) in dry heptane (150 ml) was degassed by passing argon through for 5 min. To this solution butyl lithium (21.45 ml, 1.6 M hexane solution) was added dropwise in a 30 min period, this resulting solution was refluxed for 10 min and cooled to 0 $^\circ\text{C}$. After dry DMF (6 ml) was added, the solution was slowly warmed up to room temperature and stirred for 15 min. The solution was poured into water (500 ml), and the precipitated product **3** was collected by filtration. Yield: 80%. MS: m/z = 266.0 for $\text{C}_{17}\text{H}_{14}\text{O}_3$. ^1H NMR (300 MHz, CDCl_3): δ = 10.69 (2H, s, CHO), 7.82 (2H, d), 7.71 (2H, d), 7.21 (2H, d), 1.71 (6H, s).

5-Formyl-4-[[5,5'-bis(ethoxycarbonyl)-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrryl]methyl]-(9,9-dimethyl)xanthene (5): 4,5-Diformyl-9,9-dimethylxanthene (522 mg, 2 mmol) was dissolved in anhydrous ethanol (20 ml) at room temperature in presence of concentrated HCl (0.5 ml) under argon

atmosphere. To this solution was added ethyl 3-ethyl-4-methyl-2-pyrrole carboxylate (742 mg, 4.1 mmol) in three portions over a period of 15 min. The solution mixture was refluxed for 45 min under argon atmosphere. The deep colored solution was then kept in refrigerator for 4 h and the light yellow crystalline solid was collected by filtration. The filtrate was concentrated and then diluted with water. The solid product was filtered and thoroughly washed with water to give yellow crystals of **5**. The combined yield was 987 mg (81%) : mp 104-106 °C; MS: $m/z = 610$ for $C_{37}H_{42}N_2O_6$; 1H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.12 (1H, s, CHO), 8.30 (2H, br, NH), 7.65 (2H, t), 7.39 (1H, d), 7.17-7.06 (2H, m), 6.79 (1H, d), 5.99 (1H, s, methane CH), 4.21 (4H, q), 2.69 (4H, q), 1.80 (6H, s), 1.64 (6H, s), 1.26 (6H, t), 1.08 (6H, t).

5-Cyano-4-[[5,5'-bis(ethoxycarbonyl)-4,4'-diehyl-3,3'-dimethyl-2,2'-dipyrryl]methyl]-(9,9-dimethyl)xanthene (6): The aldehyde **5** (610 mg, 1 mmol) was dissolved in 99% formic acid (8 ml) and hydroxylamine hydrochloride (75 mg, 1.1 mmol) was added to the mixture. The resulting mixture was refluxed for 1 h before being poured onto ice. After the solution was neutralized with 5% NaOH solution, the brown solid was collected by filtration to afford 590 mg (97%) of **6**. MS: $m/z = 607.4$ for $C_{37}H_{41}N_3O_5$; IR ν_{C-N} 2236 cm^{-1} , 1H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.19 (2H, br, NH), 7.66-7.51 (2H, m), 7.40 (1H, d), 7.27-6.95 (2H, m), 6.68 (1H, d), 5.70 (1H, s, methane CH), 4.22 (4H, q), 2.70 (4H, q), 1.81 (6H, s), 1.54 (6H, s), 1.28 (6H, t), 1.07 (6H, t).

5-[5-Carboxylic acid-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylpophinato Zinc(II) (9a): The diester dipyrlylmethane **6** (500 mg, 0.82 mmol) was decarboxylated and the cyano group was simultaneously hydrolyzed by refluxing for overnight in ethylene glycol (20 ml) containing NaOH solution (5 ml, 20%) at argon atmosphere. The dark color solution was poured into ice water and the resulting yellowish-brown solid was collected by filtration.

This decarboxylated dipyrromethane **7** and 5,5'-diformyl-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (230 mg, 0.81 mmol) was dissolved in dry methanol (60 ml) under argon atmosphere. To this mixture 70% perchloric acid (0.5 ml) was added and the solution was stirred at room temperature under argon atmosphere with exclusion of light for 16 h. Then a solution of NaOAc (0.5 g) in methanol (10 ml) was added, followed by another solution of *o*-chloranil (180 mg) in methanol (5 ml). After 1 h, the solvent was removed and the residue was taken up in dichloromethane (20 ml) and a solution of zinc acetate (300 mg) in methanol (5 ml) was added. After being stirred for 3 h, the solvent was evaporated and the residue was purified by chromatography (silica gel, dichloromethane) to give 182 mg (29%) pure product of **9a**. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 406 (0.668), 536 (0.033), 570 (0.032); MS: m/z = 792.7 for $\text{C}_{48}\text{H}_{48}\text{N}_4\text{O}_3\text{Zn}$; ^1H NMR (300 MHz, CDCl_3): δ = 10.15 (2H, s, meso), 10.06 (1H, s, meso), 7.93 (2H, m), 7.72-7.58 (3H, m), 7.08 (1H, t), 4.09 (8H, q), 3.65 (6H, s), 2.50 (6H, s), 1.94 (12H, m), 1.76 (6H, t).

5-[5-Carboxylic acid-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin (9b): The Zinc porphyrin **9a** was demetalated by washing with 10% HCl in dichloromethane to afford **9b** in quantitative yield. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 403 (0.868), 501 (0.114), 534 (0.070), 571 (0.053), 622 (0.022); MS: m/z = 730.5 for $\text{C}_{48}\text{H}_{50}\text{N}_4\text{O}_3$; ^1H NMR (300 MHz, CDCl_3): δ = 10.14 (2H, s, meso), 9.96 (1H, s, meso), 7.93 (1H, d), 7.78 (1H, d), 7.71 (1H, d), 7.64 (1H, d), 7.59 (1H, t), 7.11 (1H, t), 4.08-3.92 (8H, m), 3.62 (6H, s), 2.47 (6H, s), 1.93 (6H, s), 1.86 (6H, t), 1.71 (6H, t), -3.26 (2H, br, NH).

5-[5-Carboxylic acid-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylpophinato Copper(II) (9c): A mixture of porphyrin **9b** (25 mg, 0.03 mmol) in chloroform (20 ml) and copper acetate (80 mg, 0.4 mmol) in methanol (5 ml) was refluxed for 45 min before the solvent was removed. The residue was

dissolved in dichloromethane and the crude product was chromatographed on silica gel eluting with dichloromethane to give 26 mg (96%) of **9c**. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 402 (1.035), 527 (0.043), 564 (0.061), MS: m/z = 790.9 for $\text{C}_{48}\text{H}_{48}\text{N}_4\text{O}_3\text{Cu}$.

5-[5-Carboxamide-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin (11a): To porphyrin **9b** (25 mg, 0.03 mmol) in dry dichloromethane (10 ml) was added SOCl_2 (0.5 ml) and the solution was refluxed for 1 h under argon atmosphere before the solvent was removed. The residue was dissolved in dry dichloromethane and NH_3 gas was bubbled through the solution for 2 min. The solution was washed with water and evaporated to afford a purple solid of **11a** (25 mg, 98%). UV-Vis (dichloromethane): λ_{max} (rel. int.) = 402 (1.134), 502 (0.119), 535 (0.071), 570 (0.066), 623 (0.038); MS: m/z = 729.5 for $\text{C}_{48}\text{H}_{51}\text{N}_5\text{O}_2$; ^1H NMR (300 MHz, CDCl_3): δ = 10.16 (2H, s, meso), 10.00 (1H, s, meso), 7.94-7.88 (2H, m), 7.65-7.57 (3H, m), 7.03 (1H, t), 4.29 (2H, br, amide NH) 4.12-3.93 (8H, m), 3.64 (6H, s), 2.51 (6H, s), 1.90 (6H, s), 1.85 (6H, t), 1.72 (6H, t), -3.24 (2H, br, NH).

5-[5-Carboxamide-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetra ethyl-3,7,12,18-tetramethylporphinato Iron(III) chloride (11b): Iron was inserted into the porphyrin core **11a** by the usual FeSO_4 method. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 385 (0.928), 503 (0.088), 534 (0.077), 639 (0.036); MS: m/z = 783.1 [$\text{M}^+ - \text{Cl}$] for $\text{C}_{48}\text{H}_{49}\text{N}_5\text{O}_2\text{ClFe}$.

5-[5-Carboxhydrazide-4-(9,9-dimethyl)xanthene]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin (12a): To porphyrin **9a** (25 mg, 0.03 mmol) in dry dichloromethane (10 ml) was added SOCl_2 (0.5 ml) and the solution was refluxed for 1 h under argon atmosphere before the solvent was removed. The residue was dissolved in dry dichloromethane and an excess of anhydrous

hydrazine (10 ml, 0.29 mmol) was added. The solution was stirred for 10 min before being washed with water. The solvent was evaporated to afford a purple solid (25 mg, 98%) of **12a**. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 404 (1.003), 503 (0.082), 536 (0.045), 570 (0.044), 623 (0.019); MS: m/z = 744.2 for $\text{C}_{48}\text{H}_{52}\text{N}_6\text{O}_2$; ^1H NMR (300 MHz, CDCl_3): δ = 10.17 (2H, s, meso), 9.99 (1H, s, meso), 7.93 (2H, d), 7.59 (3H, m), 7.05 (1H, t), 5.23 (1H, br, hydrazide NH) 4.04 (8H, m), 3.64 (6H, s), 2.49 (6H, s), 1.89 (6H, s), 1.88 (6H, t), 1.73 (6H, t), -0.91 (2H, hydrazide NH), -3.18 (1H, br, NH), -3.23 (1H, br, NH).

5-[5-Carboxhydrazide-4-(9,9-dimethyl)xanthyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphinato Zinc(II) (12b): A mixture of porphyrin **12a** (25 mg, 0.03 mmol) in chloroform (20 ml) and zinc acetate (75 mg, 0.34 mmol) in methanol (5 ml) was refluxed for 45 min before being washed with water. The solvent was evaporated to give 26.5 mg (98%) of **12b**. UV-Vis (dichloromethane): λ_{max} (rel. int.) = 415 (1.055), 543 (0.056), 580 (0.033); MS: m/z = 808.1 for $\text{C}_{48}\text{H}_{50}\text{N}_6\text{O}_2\text{Zn}$; ^1H NMR (300 MHz, CDCl_3): δ = 10.06 (2H, s, meso), 10.01 (1H, s, meso), 8.69 (1H, d), 7.85 (1H, d), 7.71 (1H, t), 7.35 (1H, d), 7.03 (1H, d), 6.70 (1H, t), 4.10 (6H, m), 3.85 (2H, q), 3.62 (6H, s), 2.56 (6H, s), 2.48 (1H, br, hydrazide NH), 1.91 (6H, t), 1.74 (6H, s), 1.73 (6H, t), -1.91 (2H, br, hydrazide NH).

2,6-Dibromo-4-methylbenzonitrile (14): Sodium nitrite (75.9 mg, 11 mmol) was added portionwise to a stirred concentrated sulfuric acid (10 g) at 0 °C. The resulting solution was allowed to warm up to 55 °C and then held at room temperature for 15 min. This nitrosyl sulfuric acid solution was then added dropwise to a stirred solution of 2,6-dibromo-4-methylaniline (2.65 g) in acetic acid (10 ml) at 20 °C. After standing 1 h at room temperature, the diazonium solution was carefully added to a vigorously stirred 100 ml aqueous solution of KCN (3.7 g, 55 mmol), CuCN (1.35 g, 15 mmol) and Na_2CO_3 (12.7 g, 120 mmol)

at 0 °C. After completing the addition, the resulting mixture was stirred at room temperature for 1 h. The crude product was precipitated, filtered, thoroughly washed with water and dried. This crude product was dissolved in benzene and the insoluble inorganic material was removed by filtration. The filtrate was chromatographed (silica gel, hexane-dichloromethane) to give benzonitrile **14** as light yellow solid (2.29 g, 83.3%) . mp:149-150°C. MS, m/z =274.8 for C₈H₅Br₂N. ¹H NMR (300 MHz, CDCl₃): δ=2.37 (3H, s), 7.44 (2H, s).

2,6-Dibromo-4-methyl-benzaldehyde (15): 2,6-dibromo-4-methyl-benzonitrile **14** (2.75 g, 10 mmol) in dry heptane (20ml) was dissolved at 0 °C under argon atmosphere. To this solution diisobutyl aluminum hydride (DIBAL) (12 ml, 12mmol, 1 M hexane solution) was added dropwise, and the resulting solution was stirred at 0°C for 30 min, at room temperature for 2 h, and then was refluxed for 5min. After cooled to room temperature, this solution was poured into HCl (60 ml, 6 N) with crushed ice. After stirred for 1 h, the mixture was extracted with dichloromethane (50 ml x 2). The organic layer was combined, washed with saturated aqueous NaHCO₃ solution, and concentrated. The residue was chromatographed (silica gel, hexane-dichloromethane) to give light yellow solid benzaldehyde **15** (1.57 g, 56.7%). mp:96-97 °C. MS, m/z =277.9 for C₈H₆Br₂O. ¹H NMR (300 MHz, CDCl₃): δ=2.35 (3H, s), 7.45 (2H, s), 10.22 (1H, s).

2,6-Dibromo-1-[[5,5'-bis(ethoxycarbonyl)-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrryl]methyl]-4-methylbenzene (16): **15** (1.0 g, 3.6 mmol) and ethyl 3-ethyl-4-methyl-2-pyrrolicarboxylate (1.3 g, 7.2 mmol) in dry dichloromethane (100 ml) was degassed by passing argon through for 15 min. After TiCl₄ (1.5 ml) was added, the resulting solution was stirred for 24 h at room temperature. The reaction solution was thoroughly washed with water and chromatographed (silica gel, dichloromethane) to afford light yellow solid **16** (2.0 g, 89%). MS, m/z =622.1 for C₂₈H₃₄N₂Br₂. ¹H NMR (300 MHz, CDCl₃): δ= 1.15 (6H, t), 1.31 (6H, t),

1.77 (6H, s), 2.30 (3H, s), 2.65-2.69 (4H, m), 4.23-4.34 (4H, m), 6.31 (1H, s, methane CH), 7.43 (2H, s), 7.76 (2H, br).

2,6-Dibromo-1-[[4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrryl]methyl]-4-methylbenzene (18): **16** (1.0 g, 1.6 mmol), NaOH (1.0 g in 5 ml water) and ethanol (15 ml) were refluxed for 3 h under argon atmosphere. After it was cooled to room temperature, the reaction solution was poured into ice water (50 ml) and neutralized with 10% HCl to give pink solid **17** (0.90 g, 99%). The diacid **17** was mixed with NaOAc·3H₂O (5 g) and KOAc (5g), heated to melt at 160 °C under argon atmosphere, and then cooled to room temperature. To the reaction mixture water (50ml) was added, and the yellow precipitate was filtered, washed with water to give **18** (0.68 g, 81%). MS, m/z=478.1 for C₂₂H₂₆N₂Br₂. ¹H NMR (300 MHz, CDCl₃): δ= 1.16 (6H, t), 1.78 (6H, s), 2.26 (3H, s), 2.41 (4H, q), 6.33 (1H, s, methane CH), 6.40 (2H, d, α-H), 7.39 (2H, s), 7.76 (2H, s).

2,6-Dibromo-1-[[5,5'-diformyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrryl]methyl]-4-methylbenzene (19): To a solution of **18** (1 g, 2.1 mmol) in dry DMF (7 ml) immersed in an ice bath was added POCl₃ (0.5 ml) in ice bath and the resulting solution was stirred for 10 min in ice bath and held at room temperature for 2 h. After the excess DMF was removed, the residue was hydrolyzed with saturated sodium carbonate aqueous solution at 60°C for 5 min. The yellow precipitate was collected by filtration, washed thoroughly with water and gave crude product **19** (1g). **19** was used directly for the following step without further purification. MS, m/z=534.2 for C₂₄H₂₆N₂O₂Br₂.

5-(5-Carboxylic acid-9,9-dimethyl-4-xanthyl)- 15-(4-Methyl-2,6-dibromophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (20): Formyl dipyrrylmethane **19** (267 mg, 0.5 mmol) and dipyrrylmethane **7** (241 mg, 0.5 mmol) were dissolved in dichloromethane (150 ml). To this solution, p-toluenesulfonic acid (475 mg, 2.5 mmol) in methanol (5 ml) was added. The

resulting solution was stirred for 12 h, before a solution of $\text{Zn}(\text{OAc})_2$ (200 mg) and NaOAc (800 mg) in methanol (15 ml) was added and stirred overnight. After the solution was washed with water (100 ml), HCl (50 ml, 10%), and water (100 ml), it was dried with sodium sulfate and concentrated. Porphyrin **20** was chromatographed (silica gel, methanol-dichloromethane). Yield: 48 mg (10%). MS, $m/z = 978.8$ for $\text{C}_{55}\text{H}_{54}\text{Br}_2\text{O}_3\text{N}_4$.

5-(5-Carboxamide-9,9-dimethyl-4-xanthyl)- 15-(4-Methyl-2,6-dibromo phenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (21): To a solution of porphyrin **20** (25 mg, 0.03 mmol) in dry dichloromethane (10 ml) was added SOCl_2 (0.5 ml) and this resulting solution was refluxed for 1 h under argon atmosphere before the solvent was removed. The residue was dissolved in dry dichloromethane and NH_3 gas was bubbled through the solution for 2 min. The solution was washed with water and evaporated to afford a purple color solid of porphyrin **21** (25 mg, 98%). MS: $m/z = 977.6$ for $\text{C}_{55}\text{H}_{55}\text{N}_5\text{O}_2\text{Br}_2$; ^1H NMR (300 MHz, CDCl_3): $\delta = 10.21$ (2H, s, meso), 7.94-7.84 (2H, m), 7.65-7.57 (3H, m), 7.03 (1H, t), 4.45 (2H, br, amide NH) 4.12-3.93 (8H, m), 2.68 (3H, s), 2.63(6H,s), 2.52 (6H, s), 1.91 (6H, s), 1.80 (6H, t), 1.72 (6H, t), 1.54 (6H,s), -2.40 (2H, br, NH).

5-(5-Carboxamide-9,9-dimethyl-4-xanthyl)-15-[4-methyl-2,6-bis(4- *tert*-butylphenyl)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (22a): Porphyrin **21** (30mg, 0.031 mmol) was dissolved in DMF (5 ml) and was degassed by passing argon through the solution for 15 min. To this solution, $\text{Pd}(\text{PPh}_3)_4$ (30 mg) was added and followed by sodium carbonate (30 mg in a minimum amount of water) and 4-*tert*-butylphenyl boronic acid (88 mg). The mixture was refluxed for 48hr under argon atmosphere before it was diluted with dichloromethane (30 ml) and washed with water. The dichloromethane solution was then dried with sodium sulfate and concentrated and the residue was chromatographed (silica gel plate, 1% methanol in dichloromethane) to give

purple solid porphyrin **22** (18 mg, 54%) . UV-Vis (dichloromethane): λ_{max} (rel. int.) = 412.5 (2.147), 510.5 (0.205), 543.5 (0.105), 578.5 (0.138), 629.0 (0.072). MS: m/z = 1083.6390 for $\text{C}_{75}\text{H}_{81}\text{N}_5\text{O}_2$. ^1H NMR (300 MHz, CDCl_3): δ = 10.06 (2H, s, meso), 7.93 (1H, d), 7.78(1H, d), 7.71 (1H, d), 7.64 (1H, d), 7.59 (1H, t), 7.11 (1H, t), 6.87 (2H, d), 6.62 (2H, d), 6.44 (2H, d), 6.23 (2H, d), 4.90 (4H, m), 3.92 (4H, m), 2.76 (3H, s), 2.71 (6H, s), 2.49 (6H, s), 2.02 (6H, t), 1.92 (6H, s), 1.70 (6H, t), 0.65 (9H, s), 0.56 (9H, s), -2.41 (2H, br, NH).

5-(5-Carboxamide-9,9-dimethyl-4-xanthyl)-15-[4-methyl-2,6-bis(4- *tert*-butyl phenyl)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphinato Cobalt (22b): A solution of porphyrin **22a** (2 mg) in chloroform (15 ml) and $\text{Co}(\text{OAc})_2$ (10 mg) in methanol (2 ml) was refluxed for 2 h under argon atmosphere. After solvents were removed, the porphyrin cobalt complex was obtained in quantitative yield.

1-(2,6-Dibromo-4-Methylphenyl)-2-nitropropene (24): benzaldehyde **15** (2.78 g, 10 mmol) and NH_4OAc (1.1 g, 14mmol) in nitroethane (12 ml) were refluxed for 12 h. The excess nitroethane was removed under vacuum at 70 °C and the residue was chromatographed (silica gel, hexane-dichloromethane) to afford colorless liquid nitropropene **24** (3.20 g, 95.5%). MS, m/z = 334.99 for $\text{C}_{10}\text{H}_9\text{Br}_2\text{O}_2\text{N}$. ^1H NMR (300 MHz, CDCl_3): δ = 2.07(3H, s), 2.33 (3H, s), 7.40 (2H, s), 7.77(1H, s).

Benzyl 4-methyl-3-(2,6-dibromo-4-methylphenyl)-2-pyrrolecarboxylate (26): To nitropropene **24** (3.35 g, 10 mmol) and benzyl isocyanoacetate **25** (2.0g, 11.5 mmol) in 30 ml dry THF was added dropwise DBU (3.05 g, 20 mmol in 10 ml dry THF) in ice bath and the solution was stirred for 24h at room temperature. Then the solution was poured into HCl (250 ml, 10%) and stirred for 15min. The precipitate was filtered, washed with water and chromatographed (silica gel, hexane-dichloromethane) to give light yellow solid **26** (2.88 g, 62.6%). MS, m/z =

462.9 for $C_{20}H_{17}Br_2O_2N$. 1H NMR (300 MHz, $CDCl_3$): δ =1.85 (3H, s), 2.26 (3H, s), 5.08 (2H, s), 6.83 (1H, d), 7.02 (2H, m), 7.22 (3H, m), 7.31 (2H, s), 9.08 (1H, s).

Benzyl 4-methyl-3-[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-2-pyrrole-carboxylate (27): A solution of **26** (1 g, 2.16 mmol) in DMF (25 ml) was degassed by passing argon through it for 15 min. Then $Pd(PPh_3)_4$ (200 mg), Na_2CO_3 (1.06 g in minimum amount of water) and 4-*t*-butylphenylboronic acid (1.04 g, 5.89 mmol) were added to the solution in sequence, and the resulting mixture was refluxed for 48 h under argon atmosphere before it was cooled to room temperature. The mixture was diluted with dichloromethane (30 ml), filtered, washed with saturated aqueous NaCl solution (50 ml $\times$ 3) and dried with Na_2SO_4 . After solvents were removed, the residue was chromatographed (silica gel, hexane-dichloromethane) to give light yellow solid **27** (0.81 g, 66%). MS, m/z = 569.4 for $C_{40}H_{43}O_2N$. 1H NMR (300 MHz, $CDCl_3$): δ =1.27 (18H, s), 1.57 (3H, s), 2.46 (3H, s), 5.06 (2H, s), 6.47 (1H, d), 6.88-7.01 (5H, m), 7.11-7.28 (10H, m), 8.60 (1H, s).

Dibenzyl 5,5'-di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-2,2'-dimethyl-5,5'-dipyrromethanedicarboxylate (28): **27** (569 mg, 1 mmol), methylal (46 mg, 0.6 mmol) and *p*-toluenesulfonic acid (171 mg, 0.9 mmol) in chloroform (30 ml) were refluxed for 18 h under argon atmosphere. The reaction mixture was then diluted with equal volume of dichloromethane and washed with water twice. The organic layer was separated, dried with Na_2SO_4 and concentrated. The residue was chromatographed (silica gel, dichloromethane) to give yellow solid dipyrromethane **28** (329 mg, 57.2%). MS, m/z = 1150.6 for $C_{81}H_{86}O_4N_2$. 1H NMR (300 MHz, $CDCl_3$): δ =1.19 (42H, s), 2.43 (6H, s), 3.50 (2H, s), 5.01 (4H, s), 6.88-7.01 (10H, m), 7.11-7.28 (20H, m), 8.82 (2H, s).

5,5'-Di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-2,2'-dimethyl-5,5'-dipyrromethanedicarboxylic acid (29): Dipyrromethane **28** (2.15 g, 1.87

mmol) and Pd-C (250 mg, 10%) in methanol (100 ml) was degassed and filled with H₂ three times under vacuum and stirred for 48 hr with H₂ (1 atm). The mixture was filtered and concentrated to give light yellow solid dipyrromethane **29** (1.75 g, 96.55). MS, m/z = 970.8 for C₆₇H₇₄O₄N₂. ¹H NMR (300 MHz, CDCl₃): δ=1.13 (42H, s), 2.38 (6H, s), 3.49 (2H, s), 6.94 (8H, m), 7.05 (8H, m), 7.13 (4H, s), 9.34-9.64 (2H, s).

5,5'-Di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-2,2'-dipyrromethane (30): Dipyrromethane **29** (1.75 g, 1.80 mmol) in ethanolamine (40 ml) was refluxed under argon atmosphere for 30min before it was cooled to room temperature. After it was poured into water (200 ml), the precipitate was filtered, washed with water and dried to give white solid dipyrromethane **30** (1.45 g, 91.1%). MS, m/z = 882.7 for C₆₅H₇₄N₂. ¹H NMR (300 MHz, CDCl₃): δ=1.25 (36H, s), 1.29 (6H, s), 2.44 (6H, s), 3.45 (2H, s), 5.93 (2H, d), 6.92 (2H, b), 7.11 (8H, m), 7.15 (8H, m), 7.22 (4H, s).

5,5'-Di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-2,2'-dimethyl-5,5'-diformyl dipyrromethane (31): Dipyrromethane **30** (250 mg, 0.28 mmol) in dry DMF (5 ml) was added dropwise distilled POCl₃ (0.5 ml) in ice bath. The resulting solution was stirred at 0°C for 10 min and at room temperature for 2 h before the excess DMF was removed. The residue was hydrolyzed with saturated sodium carbonate aqueous solution (30ml) at 60 °C for 5min. The yellow precipitate was collected by filtration and washed with water to give the crude formyl dipyrromethane **31**. It was used for the next step without further purification. MS m/z = 938.6 for C₆₇H₇₄O₂N₂.

2,8-Di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl]-13,17-diethyl-3,7,12,18-tetramethyl-porphyrin (33): Dipyrromethane **31** (260 mg, 0.28 mmol), 3,3'-diethyl-4,4'-dimethyldipyrromethane **32** (63 mg 0.28 mmol) in dichloromethane

(150 ml) and 230 mg (1.21 mmol) p-toluenesulfonic acid in methanol (2 ml) was stirred overnight, before a solution of zinc acetate (200 mg) and sodium acetate (800 mg) in methanol (10 ml) was added and stirred for 12 h. After the solution was washed with water, dried with sodium sulfate and concentrated, the residue was chromatographed (silica gel, dichloromethane:hexane=1:3) to give the zinc (II) porphyrin. It was demetalated by washing with 10% HCl to give porphyrin **33** (25 mg, 8%). UV-Vis (dichloromethane): λ_{max} (rel. int.) = 407.0 (2.405), 503.5 (0.269), 539.0 (0.221), 571.5 (0.157), 625.5 (0.114). MS, m/z = 1130.5 for $\text{C}_{82}\text{H}_{90}\text{N}_4$. ^1H NMR (300 MHz, CDCl_3): δ = -3.97 (2H, s), 0.71 (36H, s), 1.76 (6H, t), 2.71 (6H, s), 3.03 (6H, s), 3.40 (6H, s), 4.00 (2H, q), 6.56 (8H, d), 7.09 (8H, d), 7.60 (4H, s), 9.61 (2H, s), 9.63 (1H, s), 9.89 (1H, s).

13,17-Diethyl-5-(5-formyl-9,9-dimethyl-4-xanthyl)-2,3,7,8,12,18-hexamethyl porphyrin (35): The solution of **3** (162 mg, 0.54 mmol), biladiene **34** (100 mg, 0.17 mmol) and saturated hydrobromic acid acetic acid solution (5 drops) in methanol (25 ml) was refluxed for 24 h under argon atmosphere and then cooled to room temperature. The solution was extracted with dichloromethane (30 ml x 3) and washed with water. After the combined dichloromethane solution was washed with sodium bicarbonate aqueous solution and water, dried with sodium sulfate and concentrated, the dark residue was chromatographed (silica gel, dichloromethane) to give porphyrin **35** (40 mg, 35%). UV-Vis (dichloromethane): λ_{max} (rel. int.) = 402.5 (2.171), 501.5 (0.217), 533.5 (0.125), 570.0 (0.120), 623.0 (0.068). MS, m/z = 686.4 for $\text{C}_{46}\text{H}_{46}\text{N}_4\text{O}_2$. ^1H NMR (300 MHz, CDCl_3): δ = -3.22 (1H, br), -2.99 (1H, br), 1.02 (6H, s), 1.92 (12H, m), 2.56 (6H, s), 3.52 (6H, s), 3.66 (6H, s), 4.10 (4H, q), 7.00 (2H, t), 7.45-7.53 (3H, m), 7.69 (1H, d), 7.90 (1H, d), 10.01 (1H, s, meso), 10.17 (2H, s, meso).

1,19-Dideoxy-2,3,8,12,17,18-hexamethyl-7,13-di[2,6-bis(4-*tert*-butylphenyl)-4-methylphenyl] biladiene-a,c- dihydrobromide (37): Dipyrromethane **31**

(200 mg, 0.21 mmol) and 3,4-dimethylpyrrole **36** (40.5 mg, 0.426 mmol) in methanol (15 ml) containing HBr (1.5 ml, 48% aqueous solution) was first heated for 3 min on steam bath and then stirred for 2 h at room temperature. After it was cooled in refrigerator, the brown precipitate **37** was collected by filtration and washed with 10 ml cold methanol containing a trace amount of hydrobromic acid. Yield: 58%. MS, $m/z = 1252.55$ for $C_{79}H_{90}N_4Br_2$.

12,18-Di[4-methyl-2,6-bis(4-*tert*-butylphenyl)phenyl]-5-(5-formyl-9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethylporphyrin (38): **3** (146 mg, 0.55 mmol) and biladiene **37** (70 mg, 0.055 mmol) and saturated hydrobromic acid acetic acid solution (7 drops) in methanol (30 ml) was refluxed for 24 h under argon atmosphere and then cooled to room temperature. The solution was extracted with dichloromethane (30 ml x 3). After the combined dichloromethane solution was washed with sodium bicarbonate aqueous solution and water, dried with sodium sulfate, and concentrated, the dark residue was chromatographed (silica gel, dichloromethane) to give porphyrin **38** (6 mg). UV-Vis (dichloromethane): λ_{max} (rel. int.) = 412.5 (1.339), 507.5 (0.145), 542.0 (0.103), 574.5 (0.095), 628.5 (0.058). MS, m/z for $C_{96}H_{98}N_4O_2$ 1338.76. 1H NMR (300 MHz, $CDCl_3$): δ = -3.42 (1H, br), -3.30 (1H, br), 0.65 (18H, s), 0.81 (18H, s), 1.87 (6H, s), 2.40 (6H, s), 2.69 (6H, s), 3.03 (6H, s), 3.23 (6H, s), 6.46 (4H, d), 6.69 (4H, d), 6.96-7.19 (10H, m), 7.39-7.46 (6H, m), 7.57(2H, d), 9.53 (1H, s, meso), 9.67 (2H, s, meso), 10.72 (1H, s, $\underline{CHO}$).

12,18-Di[4-methyl-2,6-bis(4-*tert*-butylphenyl)phenyl]-5-(5-cyano-9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethylporphyrin (39): Porphyrin **38** (15 mg), hydroxylamine hydrochloride (10 mg) in 5 ml of 98% formic acid was refluxed overnight under argon atmosphere before cooled to room temperature. After the solution was poured into ice water (80 ml) and neutralized with 10 % sodium hydroxide solution, precipitated porphyrin **39** was collected by filtration (90%). MS, $m/z = 1135.76$ for $C_{96}H_{97}N_5O$. IR ν_{C-N} 2233.85 cm^{-1} .

12,18-Di[4-methyl-2,6-bis(4- *tert*-butylphenyl)phenyl]-5-(5- carboxylic acid - 9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethylporphyrin (40): Porphyrin **38** (25 mg) in acetone (30 ml) was cooled in ice bath under argon atmosphere. To this solution the Jone's reagent (3 ml, prepared by dissolving CrO_3 (6.7 g) in H_2SO_4 (98%, 6 ml) and then diluted with water (50 ml)) was carefully added. The reaction was kept in ice bath for 1.5 hr and then at room temperature for 1.5 hr under carefully monitoring by TLC. After the reaction was completed, the solution was diluted with water (50 ml) and extracted with dichloromethane (20 ml x 3). The organic solution was dried with sodium sulfate and concentrated. The porphyrin **40** was obtained in 47.4% (12 mg) yield by chromatography (silica gel plate, dichloromethane). MS, $m/z = 1354.76$ for $\text{C}_{96}\text{H}_{98}\text{N}_4\text{O}_3$.

12,18-Di[4-methyl-2,6-bis(4- *tert*-butylphenyl)phenyl]-5-(5- Carboxamide -9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethylporphyrin (42): Porphyrin **39** (13.5 mg) and sodium hydroxide (50 mg) in ethylene glycol (30 ml) was refluxed for 24 h under argon before cooled to room temperature. After the solution was poured into ice water (200 ml), neutralized with 10% hydrochloric acid and extracted with dichloromethane (30 ml x 3), the combined dichloromethane solution was dried with sodium sulfate and concentrated at reduced pressure to give the crude carboxylic acid porphyrin **40**. The crude porphyrin **40** and thionyl chloride (0.25 ml) in dry dichloromethane (10ml) were refluxed for 1 h under argon atmosphere before the solvent and the excess thionyl chloride were removed at reduced pressure. The dark residue was redissolved in dry dichloromethane (10 ml) and ammonia gas was passed through the solution for 1 min. After the solution was diluted with dichloromethane (20 ml), washed with water (15 ml x 2) and dried with sodium sulfate, It was chromatographed (silica gel, 1% methanol/dichloromethane) to give porphyrin **43** (7 mg). UV-Vis (dichloromethane): λ_{max} . (rel. int.) = 413.0 (1.952), 509.5 (0.207), 544.0 (0.134), 577.0 (0.117), 630.5 (0.071). MS, $m/z = 1353.7800$ for $\text{C}_{96}\text{H}_{99}\text{N}_5\text{O}_2$. ^1H NMR

(300 MHz, CDCl₃): δ = -3.33 (2H, br, ring NH), 0.64 (18H, s, t-butyl), 0.83 (18H, s, t-butyl), 1.87 (6H, s), 2.34 (6H, s), 2.68 (6H, s), 2.98 (6H, s), 3.23 (6H, s), 5.92 (2H, br, NH), 6.48 (4H, d), 6.69 (4H, d), 7.05-7.22 (10H, m), 7.39 (2H, m), 7.43-7.46 (1H, m), 7.54-7.60 (4H, m), 7.69-7.72 (1H, m), 7.79-7.83 (1H, m), 8.06-8.09 (1H, m), 9.48 (1H, s, meso), 9.65 (2H, s, meso).

12,18-Di[4-methyl-2,6-bis(4-*tert*-butylphenyl)phenyl]-5-(5- Carboxamide -9,9-dimethyl-4-xanthyl)-2,3,7,8,13,17-hexamethylporphyrinato Cobalt (43):

Porphyrin **42** (2 mg) in chloroform (15 ml) and Co(OAc)₂ (10 mg) in methanol were refluxed for 2 h under argon atmosphere. After the solvents were removed, the porphyrin cobalt complex was obtained in quantitative yield.

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