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Synthesis of 8,12,13,17-Tetraethyl-7,18-Dimethyl-2,3-Diazaporphyrin

presented by

Michael L. Waldo

has been accepted towards fulfillment
of the requirements for

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Eugene LeGoff
Major professor

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SYNTHESIS OF 8,12,13,17-TETRAETHYL-7-18-DIMETHYL-2,3-DIAZAPORPHYRIN AND THE SYNTHESIS OF 3,5-BIS(2-PYRRYL)-1,2,4-1H-TRIAZOLE AND SUBSTITUTED ANALOGS

By

Michael Lane Waldo

A THESIS

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ABSTRACT

SYNTHESIS OF 8,12,13,17-TETRAETHYL-7-18-DIMETHYL-2,3-DIAZAPORPHYRIN
AND
THE SYNTHESIS OF 3,5-BIS(2-PYRRYL)-1,2,4-1H-TRIAZOLE AND SUBSTITUTED ANALOGS

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8,12,13,17-Tetraethyl-7-18-dimethyl-2,3-diazaporphyrin is a new class of modified porphyrin, where one of the pyrroles is replaced by a 1,2,4-triazole. It has been prepared by the acid catalyzed condensation of a 3,5-diformyl-1,2,4-1H-triazole with a tripyrrane dicarboxylic acid, followed by neutralization and oxidation with DDQ (30% yield). This diazaporphyrin has been structurally characterized by ^{1}H-NMR, ^{13}C-NMR, and single crystal X-ray diffraction analysis.

The alkyl substituted 3,5-bis(2-pyrryl)-1,2,4-1H-triazoles were prepared by condensing corresponding 2-cyanopyrroles and 2-pyrrylcarboxylic acid hydrazides in the presents of PTSA at temperatures over 200° C in moderate yields. These alkyl substituted 3,5-bis(2-pyrryl)-1,2,4-1H-triazoles are being used in the attempted formation of a triazole containing Amethyrin.

This Dissertation is Dedicated With Love to My

MA and POP,

(a.k.a. Helen and Dale Waldo)

Without their love and lots of support ($$$),

I would still be pumping gas in

a greesey old gas station

somewhere in California.

Acknowledgments

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A special thanks to the woman who I hope will be my wife, Sherry Swamba. Thank you for your love, understanding, and emotional support. Maybe someday, if you're lucky, you can love me as much as I love you.

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CHAPTER 1

INTRODUCTION

Photodynamic therapy (PDT) is a therapeutic treatment which employs the combination of light and a drug to bring about a cytotoxic or modifying effect to cancerous or otherwise unwanted tissues. The drug, a photosensitizer, with low dark toxicity is introduced into the body and accumulates preferentially in rapidly dividing cells. Once this drug reaches a desired ratio of accumulation in the diseased *verses* healthy tissue, a regulated light dose is shone into the diseased tissue. This light dose activates the drug and elicits the toxic action. The amount needs to be carefully regulated so it is large enough to cause the desired response in the tissue, but small enough to spare the surrounding healthy tissue from extensive damage. Shortly after a successful treatment, the damaged cells become necrotic, or suitably modified.

While PDT is relatively new, however, the use of drugs and light can be traced as far back as to the ancient Egyptians who used a combination of orally ingested plants (containing light-activated psoralens) and sunlight to successfully treat vitilago over 4000 years ago.[1] The use of ultraviolet light and psoralens for the treatment of psoriasis (PUVA) has been used throughout the world.[2]

In 1913 Meyer-Bets injected himself with 200 milligrams of hematoporphyrin (Hp) 1 and experienced no ill effects until he was exposed to sunlight. He suffered extreme swelling and was photosensitive for several months.[3] Twelve years later, Policard studied the ability of porphyrins to produce the phototoxic effect.[4] The most recent photoactive based drug therapies utilize porphyrin-based chromophores in combination with visible

light. Thousands of reports exploring UV light for treatments of a variety of ailments was published in a book by Gauvain[5] in 1933. The usefulness of high dose light for the treatment of auto-immune disorders and the nature of UV light in immuno-suppression is now well established.[6] In the late 1960's, Lipson[7] successfully treated a woman exhibiting breast cell metaphases with a hematoporphyrin derivative and selective light irradiation. This marked the beginning of PDT as a cancer therapy.

The basis of PDT is dependent on the longest frequency in which the drug is photoactivated. Longer wavelengths of light are known to penetrate deeper in the skin. Consequently, an effective PDT drug must be activated in the red or near infrared region.[8]

PDT therapy depends on the generation of the toxic molecular singlet oxygen by photosensitization of molecular triplet oxygen. There is still much debate on whether the molecular singlet oxygen is the species responsible for this toxic effect. However, it has been studied that PDT drugs do generate singlet oxygen.[9]

Diamagnetic porphyrins and their derivatives are the dyes of choice for PDT. It has been known for a long time that porphyrins localize selectively in rapid growing tissues such as carcinomas and sarcomas[10]. A review by Kongshaug discusses factors which may control such selectivity.[11] It is known that classic cancer chemotherapeutic agents concentrate in low density lipoprotein (LDL) serums which accumulate around LDL receptors on cancer cells.[12] The accumulation of a PDT drug in the LDL serum might be the pathway in which it is delivered.[13]

The photophysical process of the generation of singlet oxygen is shown in Figure 1. After a PDT drug has accumulated in the malignant tissue over a few days, the area of the tumor is exposed to laser light with a wave length of

625 - 635 nm (red light). The PDT drug is excited from its ground state to the first excited singlet state (route 1, Figure 1). This photosensitizer can undergo a non-radiative process of inter-system crossing (route 4). This spin-forbidden process transforms the photosensitizer to a triplet state (T_1). This excited molecule can relax from the triplet state by one of two pathways. The first is radiative by phosphorescence (route 5) and the second path is to have a spin exchange with another triplet state molecule. One such spin energy exchange is the interaction of the photosensitizer in its triplet state with triplet oxygen, $^3O_2$ (route 6). This generates the highly reactive singlet oxygen species ($^1O_2$) which has a lifetime of roughly four microseconds in water. It is this singlet oxygen that kills the cancerous cells by disrupting it biological processes by reacting with several of the cancer cells biological substrates.[14] This highly reactive, short lifetime singlet oxygen has a short range and is unlikely to escape the cell in which it is produced. Cytotoxicity is therefore restricted to the precise region of tissue absorbing the light.

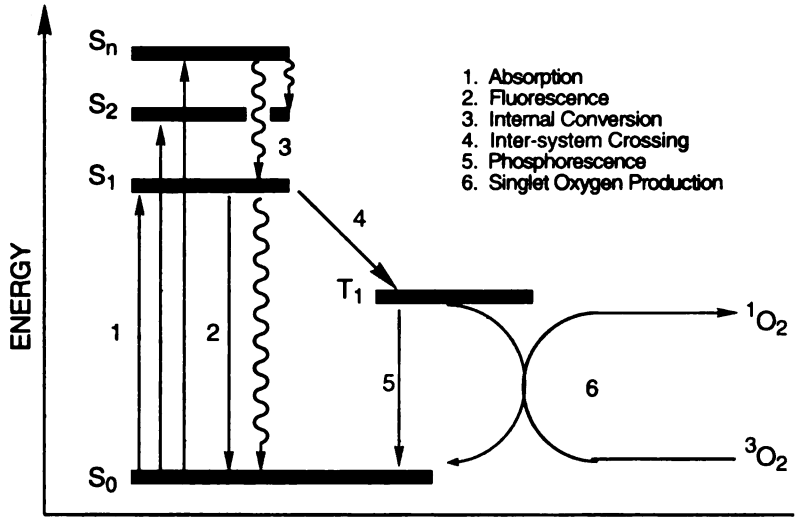

Figure 1. Modified Jablonski Diagram for the Generation of Singlet Oxygen

Since clinically used PDT drugs are closely related to the naturally occurring protoporphyrin IX, of which the iron complex is the prosthetic group of hemoglobin, new porphyrin-like molecules with this same basic framework, could be a possible candidate for novel photosensitizers. Any new PDT drugs fulfill the following requirements:

a) Strong absorption in the red part of the visible spectrum (>650 nm)

b) High quantum yield of triplet formation

c) Low dark toxicity

d) Must exhibit selectivity for the tumorous tissue over healthy tissue

There is also interest in developing new photosensitizers that could possibly be used against other diseases, including psoriasis, viral and fungal conditions.

Structurally modified and simplified porphyrins are of particular interests in PDT research. Recently there has been a growing interest in replacing one or more of the pyrrole rings in the porphyrin with other heterocyclic and non-heterocyclic subunits. Some of these hybrid porphyrinoid structures have included benzene[15], pyridine,[16] cycloalkene[17] and indecene rings[18], Figure 2.

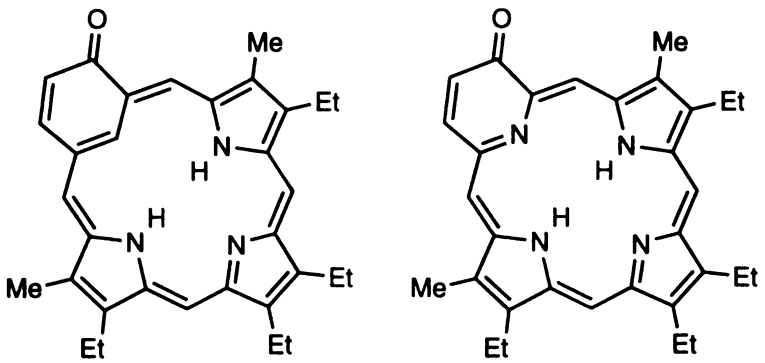

Figure 2. Some Porphyrinoid Molecules

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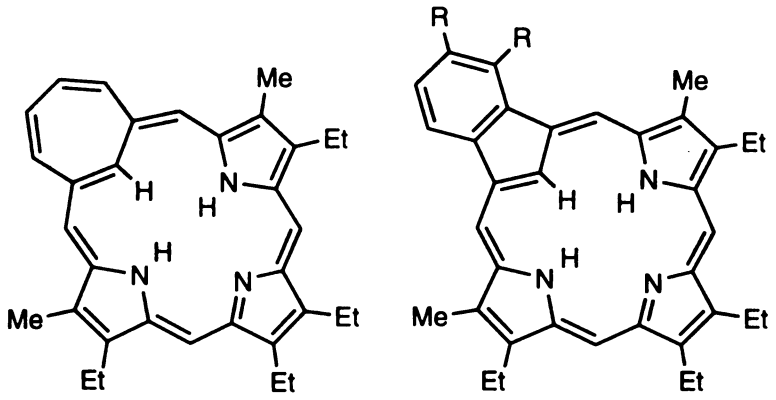


There has also been reports that having an extra nitrogen atom at the meso positions, i.e. the methine bridge of the porphyrin skeleton, had a stronger absorption then the original porphyrin in the wavelength (nearby 630 nm) of the light applied to PDT.[19] The advantage with longer wavelengths is that the light penetrates deeper into the skin. Recently a porphyrin with a nitrogen in the peripheral position has been reported.[20] This monoazaporphyrin is displayed in Figure 3. This monoazaporphyrin has an imidazole unit replacing a pyrrole in a porphyrin.

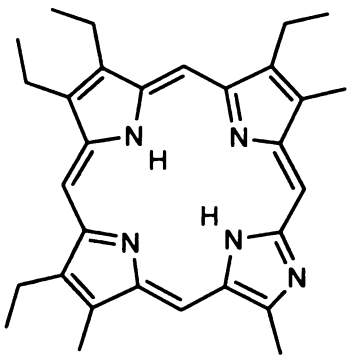
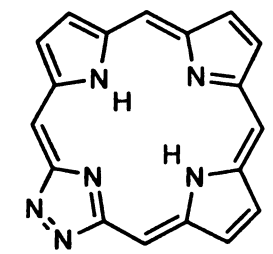
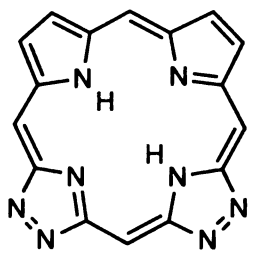


Figure 3. Masaki's Monoazaporphyrin, 2-Aza-8,12,13,17-tetraethyl-3,7,18-trimethylporphyrin

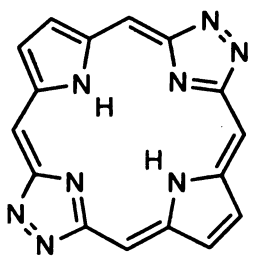
The incorporation of one 1,2,4-triazole into a porphyrin could lead to a porphyrin with two nitrogens in its periphery. This new class of porphyrinoid could give further insights to the effect of nitrogens in the porphyrin skeleton. Figure 4 displays some porphyrins with one or more 1,2,4-triazole units. Molecular orbital calculations of the electronic structure of aza-derivatives of porphyrins led to some interesting conclusions.[21] These studies on the change in the electronic structure of the porphyrin ring as a consequence of the introduction of nitrogen atoms showed a decrease in the absorption energies. By synthesizing this novel porphyrinoid with two extra nitrogens in the peripheral positions (β positions of the pyrrole ring in the porphyrin skeleton), we intend to explore the effects these nitrogens have on the electronic properties of these new porphyrin analogs. A lower absorption energy should allow for wavelengths that are more efficient for PDT use.



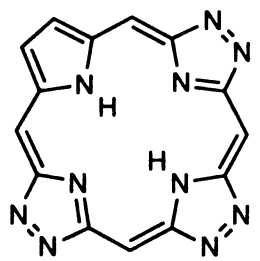
2,3-Diazaporphyrin **1**



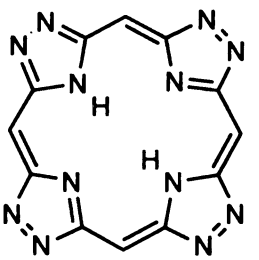
2,3,7,8-Tetraazaporphyrin **2**



2,3,12,13-Tetraazaporphyrin **3**



2,3,7,8,12,13-Hexaaza-porphyrin **4**



2,3,7,8,12,13,17,18-Octaazaporphyrin **5**

Figure 4. Five Possible 1,2,4-Triazole Containing Porphyrins

An advantage to having a 1,2,4-triazole subunit is that there will be nitrogens in the periphery of the porphyrin. Not only could these extra nitrogens improve the electronic properties and PDT potential, these peripheral nitrogens can lead to interesting magnetic and structural properties in the solid state. Disciplines such as chemistry, physics, and material science have well defined techniques to study these solid state compounds. With the increasing list of known so-called "organic metals" and "molecular superconductors", valuable information has been gathered on the strategies needed to design and synthesize better organic metals. These studies have revealed that there are several overriding features that turn a collection of organic molecules into a conduction system.[22] First, flat, conjugated molecules must be able to crystallize in segregated stacks. This allows overlap in the π-orbital system which creates an extensive pathway for electron charge transfer. This stacking forms a band structure with sizable bandwidths. The second and the most important feature of the molecular stack, is that the highest energy band must be incompletely filled. This partially filled band structure allows conduction to take place through the molecular stacks. Later studies also revealed the need for communication between the stacks, which allows the system to become two or even three dimensional.[23] This is brought about by the addition of hetero atoms to the periphery of these systems. Several solid state studies of conducting porphyrins have been carried out.[24] The addition of hetero atoms in the periphery of these porphyrins, may introduce cross stack interactions in the crystalline state and show increased conductivity in the respective metalloporphyrin.

The integration of a 1,2,4-triazole unit into a metalloporphyrin should give rise to interesting cross stack interactions. A side to side interaction could allow communication between two metalloporphyrins in neighboring stacks as shown

in Figure 5. With this type of interaction many of the metalloporphyrins in a single stack can communicate within the same stack or with other adjacent stacks in the same crystal. This interaction can allow a conducting system to become multi dimensional. Another type of interaction, as shown in Figure 6, could affect the stacking of these metalloporphyrins during crystallization. This type of interaction could disrupt the orderly stacking and possibly affect the overall conductivity. However, the substitution of another 1,2,4-triazole subunit into the macrocycle may allow this type of arrangement to show some conductivity. However, it would be expected that this type of stacking would produce materials with smaller conducting properties then those in Figure 5.

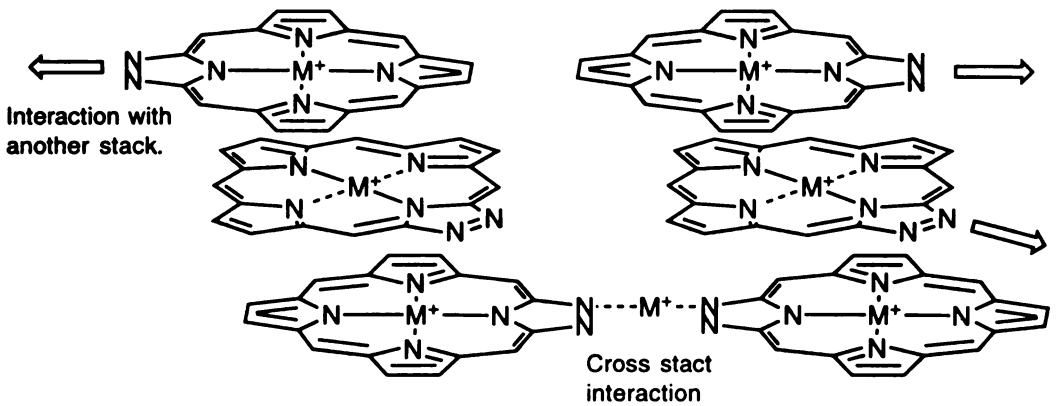


Figure 5. End to End Interactions that can occur withTriazole-Metalloporphyrins

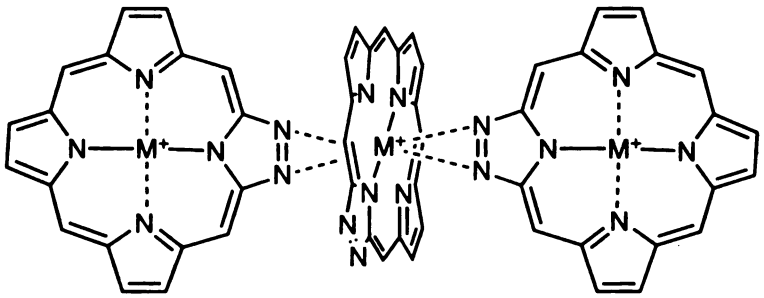


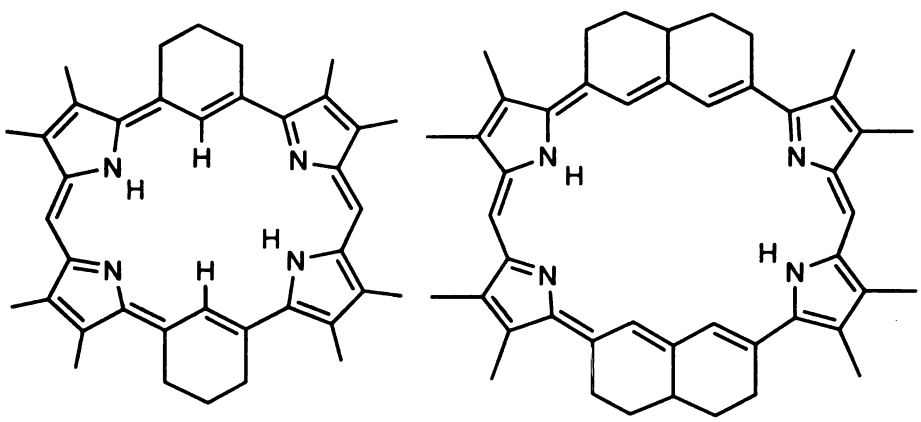
Figure 6. End to Center Interactions that can occur withTriazole-Metalloporphyrins

With the increasing interest in porphyrin modification, there has been a considerable effort devoted to the synthesis and study of larger aromatic pyrrole containing systems. These macrocycles are called "expanded porphyrins" or "platyrins"[25] (from the Greek word "platus" meaning wide). By virtue of containing a greater number of π-electrons, these larger macrocycles can exhibit aromatic or antiaromatic characteristics that can be compared with calculated resonance energies for [N]annulenes. With the increased size in the central binding core these expanded porphyrins can exhibit substantially different properties then those found for the well studied porphyrin analogs.

A considerable amount of attention has been placed on the synthesis and characterization of new expanded porphyrins. Significant effort has been devoted to exploring the use of these macrocycles as photosensitizers for PDT and as magnetic resonance imaging (MRI) contrast agents. Relatively new, MRI is a nonevasive, non-ionizing and apparently innocuous diagnostic technique used in the identification of neoplastic tissue in the early stages of development. Due to the low degree of signal enhancement of diseased *vs.* normal tissue, considerable effort is being devoted to the preparation of MRI contrast agents. Highly paramagnetic metal complexes, such as those derived from Gadolinium(III), have proved particularly efficient in clinical use. Since the

Gd(III) is too large to fit into a normal porphyrin, the expanded porphyrins offer the possibility of binding large metals in a stable porphyrin-like manner. Investigations into expanded porphyrin systems which have low toxicity, good tissue localization, and suitable core sizes, may produce Gd(III) complexes capable of acting as viable MRI contrasting agents.

The synthesis of expanded porphyrins by extending the bridging units between the pyrrole rings has been an ongoing project in this laboratory[25]. Two examples of this expansion, [1,3,1,3]platyrin and [1,5,1,5]platyrin, are shown in Figure 7. The expanded porphyrins, [1,3,1,3]platyrin and [1,5,1,5]platyrin are large enough to handle transition metal complexes.



[1,3,1,3]Platyrin [1,5,1,5]Platyrin

Figure 7. [1,3,1,3]Platyrin and [1,5,1,5]Platyrin

Other investigations into the synthesis of expanded porphyrin systems for the use as potential MRI contrast agents include the systems of pentaphyrin[26] and sapphyrin[27] and hexaphyrin[27] to name a few, Figure 8. There are many other related systems that are beyond the scope of this introduction.

As with porphyrins, there have been many successful attempts to replace one of the pyrrolic units in these expanded porphyrins with other heterocycles. Thiophenes and furans have been substituted into many macrocycles.

However, to date, a 1,2,4-triazole has not been incorporated into these porphyrin-like systems. The advantages of a 1,2,4-triazole in an expanded porphyrin are similar to those described in Figures 5 and 6. It would allow a means for cross stack interaction in the metallo-expanded porphyrins crystal stacking. This again could allow two or three dimensional conductivity. Also in PDT studies, this compound could allow for better tissue recognition or give an absorption at a higher frequency to allow better tissue penatration for a more efficient means of producing singlet oxygen.

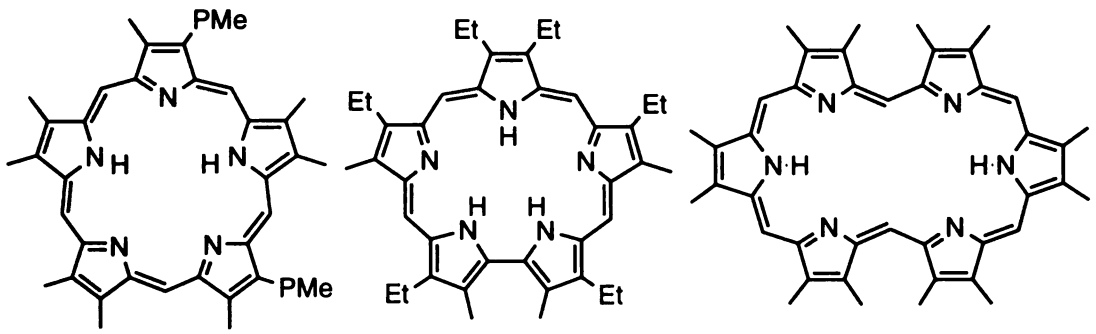


Figure 8. Pentaphyrin, Sapphyrin and Hexaphyrin

Some of the potential areas that new classes of porphyrinoids and expanded porphyrins could benefit are in photodynamic therapy and magnetic resonance imaging. With the increased core size of expanded porphyrins, applications involving metal coordination are not limited to single or transition metal ion complexation. The larger size can prove particularly useful in complexation of metals from the lanthanides and actinides series. Highly colored expanded porphyrins could also be useful as dyes. With the ever increasing numbers of new classes of macrocycles the incorporation of the 1,2,4-triazole could benefit many areas of research. Their planer nature make them a candidate for chromophores for use in liquid crystals, photo-sensors,

and complexants . One can invision linear arrays of stacked expanded triazole-porphyrins that can have unique conducting properties that could display beneficial super- or semiconducting capabilities.

Chapter 2

RESULTS AND DISCUSSION

A. Synthetic Strategies

There are two general methods for the incorporation of 1,2,4-triazole into an expanded porphyrin. The first is to start with a functionalized 1,2,4-triazole and transform it into a macrocyclic system using the substituents it possesses (method **A**, Figure 9). The second way is to use a 1,2,4-triazole as the final condensation component to complete the macrocycle (method **B**, Figure 9). Our research has utilized both of these synthetic strategies in an attempt to incorporate this heterocycle, a 1,2,4-triazole unit, into porphyrin and expanded porphyrin systems.

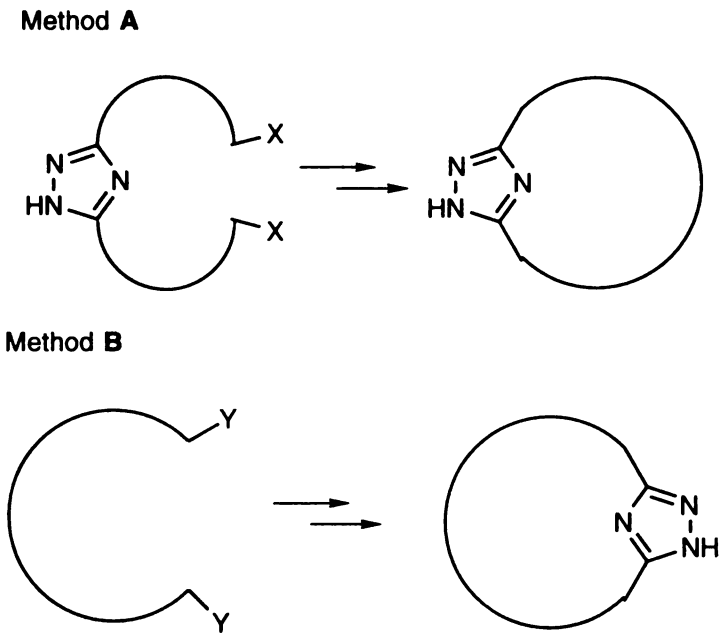


Figure 9. Two Methods of Incorporating a 1,2,4-Triazole Subunit into an Expanded Porphyrin

Since the dimensions of the 1,2,4-triazole unit closely resemble pyrrole, there are a large number of possible macrocycles in which a triazole can be incorporated. Our attention was spent on the incorporation of a triazole unit into two major macrocyclic systems. Porphyrinoid molecules where one of the pyrrolic units in a porphyrin was replaced with a heterocycle, including triazole, was the first system investigated. Figure 4 displays one tautomeric form of each of the five possible 1,2,4-triazole containing porphyrins. The second macrocyclic system resembled the extended porphyrin amethyrin[28] (Figure 10). The three possible oxidation states of tetraazaamethyrin are shown in Figure 11. The synthetic strategies for these macrocycles will be explained separately in the following sections.

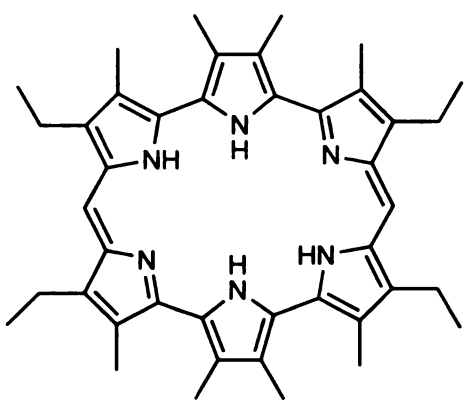


Figure 10. Amethyrin

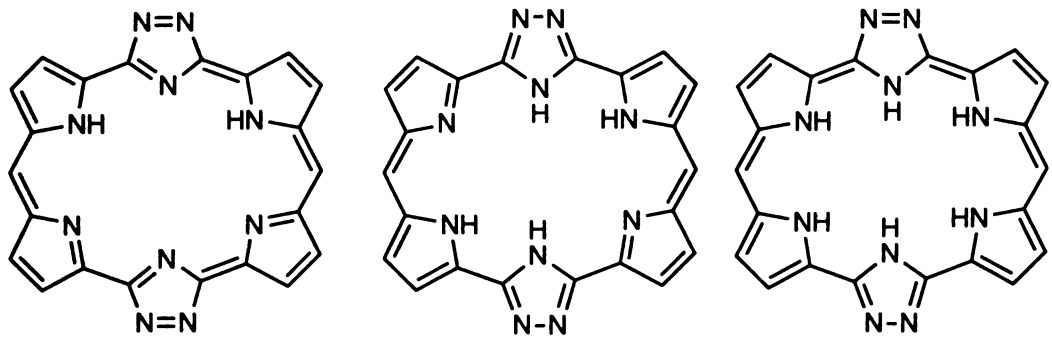


Figure 11. Three Possible Oxidation States for Tetraazaamethyrin

B. Progress Towards the Synthesis of Triazole Containing Porphyrinoids

1. Possible Triazole Containing Porphyrinoids

The first macrocycle system investigated was a class of porphyrins in which one or more of the core pyrrolic groups was replaced by a nonpyrrolic heterocycle. The substitution of one or more of the pyrrolic segments with a 1,2,4-triazole unit could lead to porphyrinoids with interesting and unique physical properties. The addition of each 1,2,4-triazole into a porphyrin places two nitrogen atoms in the periphery of each macrocycle, which could lead to interesting solid state interactions (Figures 5 and 6). There are five possible porphyrinoids which contain triazole units (Figure 4). Each of these porphyrinoids also have several tautomers. The porphyrinoid where one pyrrolic unit is replaced with a triazole is the diazaporphyrin **1**. There are two isomeric porphyrinoids where two pyrrolic units are replaced which are, **2** and **3**. The last two porphyrinoids are the hexaazaporphyrin **4** with three triazole units and the octaazaporphyrin **5** where all the four pyrrolic units have been replaced with triazoles. Most of our attention was focused on the compounds **1**

and **3**. Fortunately, there were numerous synthetic strategies available in the design of these porphyrinoids.[29]

2. Retro Synthetic Analysis of Triazole Containing Porphyrinoids **1** and **3**, Diazaporphyrin **1** and Tetraazaporphyrin **3**.

As stated, there were many different porphyrin methodologies that could be used in the synthesis of the porphyriniods **1** and **3**. Two of the routes possible are MacDonald's "2 + 2" and Johnson's "3 + 1" condensation. In the "2 + 2" method, a dipyrrylmethane with the alpha positions unsubstituted (or a dipyrrylmethane with a carboxylic acid on the alphs carbons) is condensed with a 5,5'-diformyl dipyrrylmethane in the presence of an acid catalyst to give a porphyrinogen which is then oxidized to afford the related porphyrin, Figure 12. The major limitation in the "2 + 2" methodology is that one of the condensing units must be symmetrical or two isomeric products will be produced. The second synthetic route is the "3 + 1" methodology. This method initially involves the condensation of a tripyrrane with a 2,5-diformylheterocycle (Figure 13). This methodology has been used extensively by Lash and others in the synthesis of modified porphyrins (Figure 2 and 3). Figure 13 shows the "3 + 1" method that Johnson and coworkers used in synthesizing oxa- and thiaporphyrins.

Using the "3 + 1" methodology, the retro synthetic analysis of **1** is shown in Scheme 1. Diazaporphyrin **1** can be assembled by two different routes. The first procedure (path 1) would be to condense a tripyrrane **6** with the 1,3-dialdehyde **7**. The second route (path 2) would condense a diazatripyrrane **9** with a 2,5-diformyl pyrrole **8**. There are a few different tripyrranes that are available, however the 3,5-diformyl triazole **7** was not readily available. There are two ways to synthesize **7** (Scheme 2). Oxidation of the hydroxymethyl

groups of compound **10** would represent the method **A** type approach discussed in Figure 9. Condensing the glyoxylic acid derivative **11** with hydrazine hydrate would correspond to method **B**.

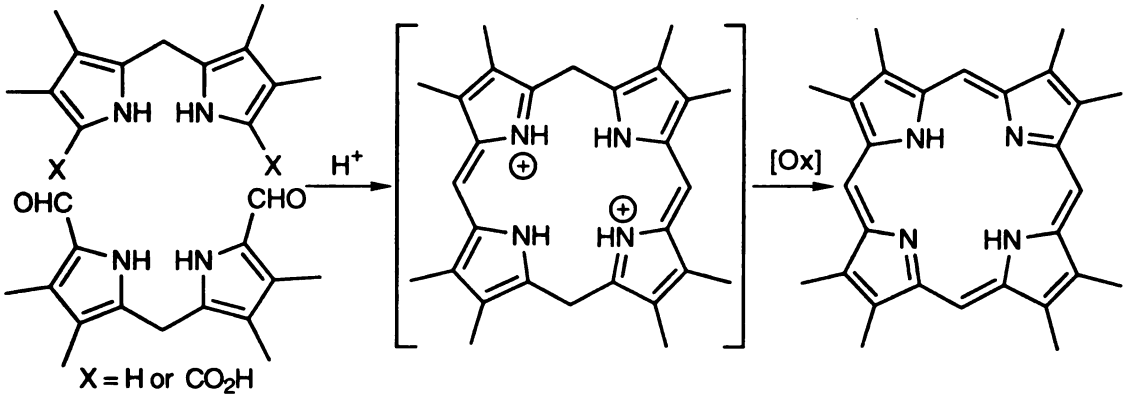


Figure 12. MacDonald's "2 + 2" Condensation

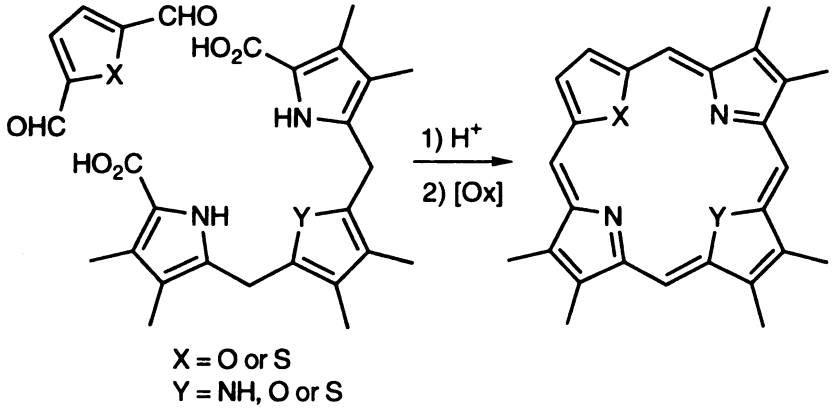
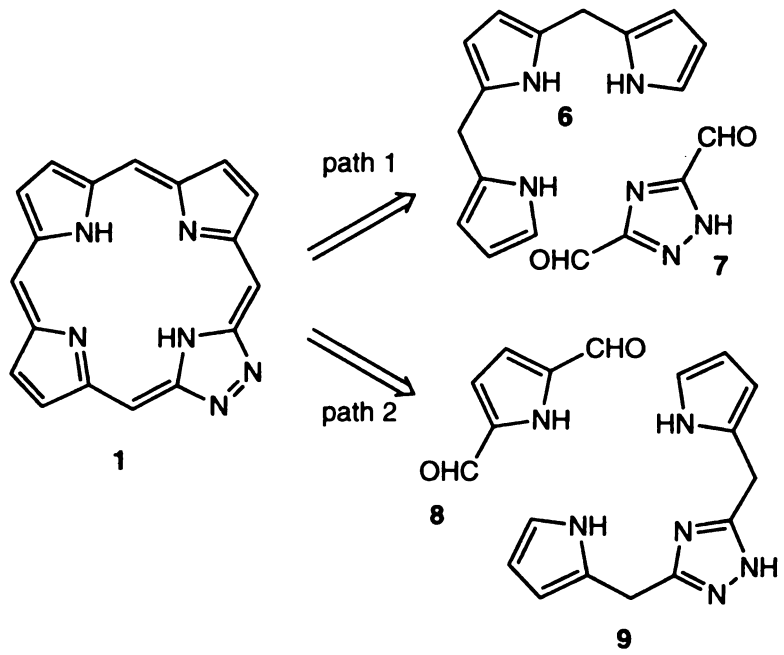
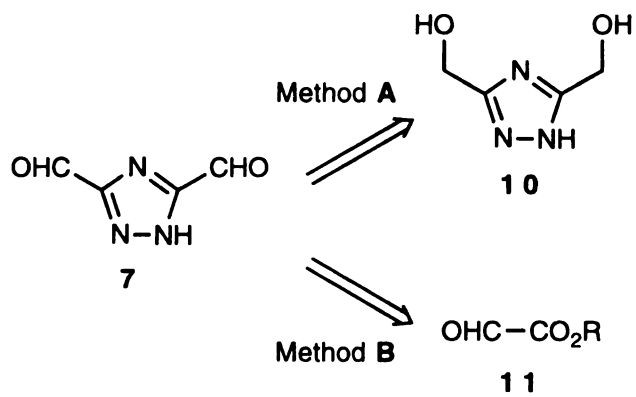


Figure 13. Johnson's "3 + 1" Synthesis of Oxa- and Thiaporphyrins

Scheme 1. Retro Synthetic Analysis of **1**

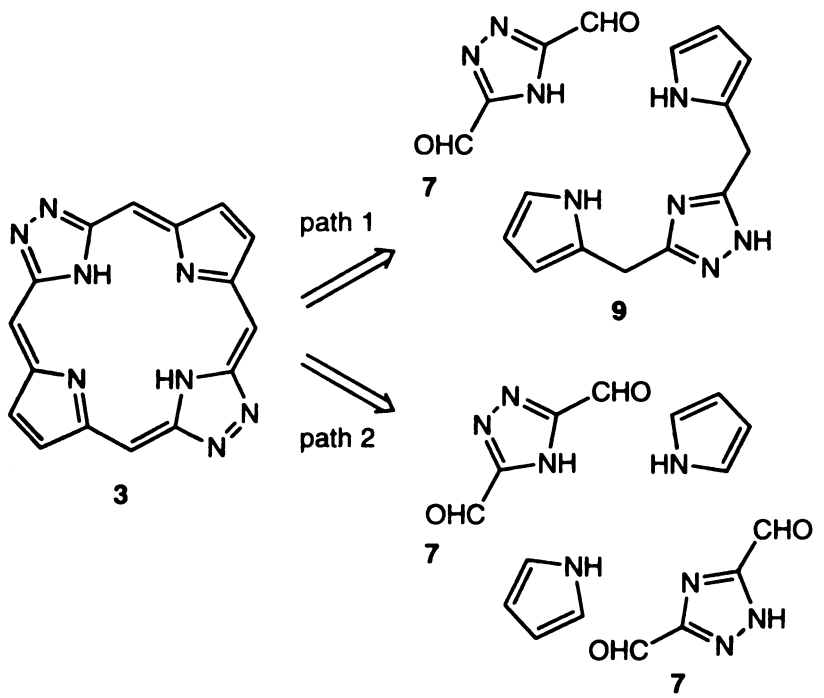


Scheme 2. Retro Synthetic analysis of **7**



The "3 + 1" methodology can also be utilized to produce **3** , as shown in path 1 of Scheme 3. In this procedure bis(dipyrrylmethyl) triazole **9** would be condensed with the 3,5-diformyl triazole **7**. Path 2 displays an alternate method to assemble the tetraazaporphyrin **3** by a one pot reaction of pyrrole and 3,5-diformyl triazole **7**. Both of the desired triazole porphyrins **1** and **3** require compound **7** and (or) **9** in the "3 + 1" type synthesis.

Scheme 3. Retro Synthetic Analysis of **3**



3. Progress Towards the Synthesis of Triazole Containing Porphyrinoids, Diazaporphyrin **1** and Tetraazaporphyrin **3**

The retro synthetic analysis of compounds **1** and **3**, revealed the need for dialdehyde **7**. There have been only a few literature examples of monoaldehyde triazoles.[30] A variety of reagents have been used in the

conversion of other functionalities into monoaldehyde triazoles. For example, lead tetraacetate has been used to oxidize 3-(hydroxymethyl)-1,2,4-triazole into 1,2,4-triazole-3-carboxaldehyde.[31] We thought it should be possible to apply the oxidation of hydroxymethyl groups to the synthesis of diformyl triazoles, since it was shown to be successful in the synthesis of monoformyl triazoles (Scheme 2). However, the oxidation of **10** using pyridium chlorochromate (PCC), Swern conditions (oxalyl chloride and dimethyl sulfoxide), and N-bromosuccinimide (NBS) led to insoluble oils which showed no aldehyde peaks in their IR or ^{1}H-NMR spectras (Scheme 4). This could be due to polymerization of the dialdehyde initially formed (Figure 14). It is known that 3-formyl-1,2,4-triazoles dimerize in some solutions, which may explain why **7** could form insoluble oils.[32] Since there is more then one aldehyde on each triazole, polymerization could occur as shown in Figure 14. This possibility of complex polymerization showed the need to control the conditions during and after the oxidation of **10**.

Torres described a convenient method in which **7** can be prepared from a glyoxylic acid derivative (method **B**, Scheme 2).[33] This was accomplished by the condensation of methyl dimethoxyacetate **12** with hydrazine hydrate to produce the aminotriazole **13** (Scheme 5). Oxidative deamination of **13** afforded the 1H-triazole **15**. Hydrolysis of **15** with dilute sulfuric acid yielded the dialdehyde **7**. The isolation of **7** was very difficult due to its insolubility and hydroscopic nature. The temperatures had to be kept below 22°C during the hydrolysis step or the aldehyde would polymerize and result in an unreactive oil.

Scheme 4. Possible Oxidation Route of **10**

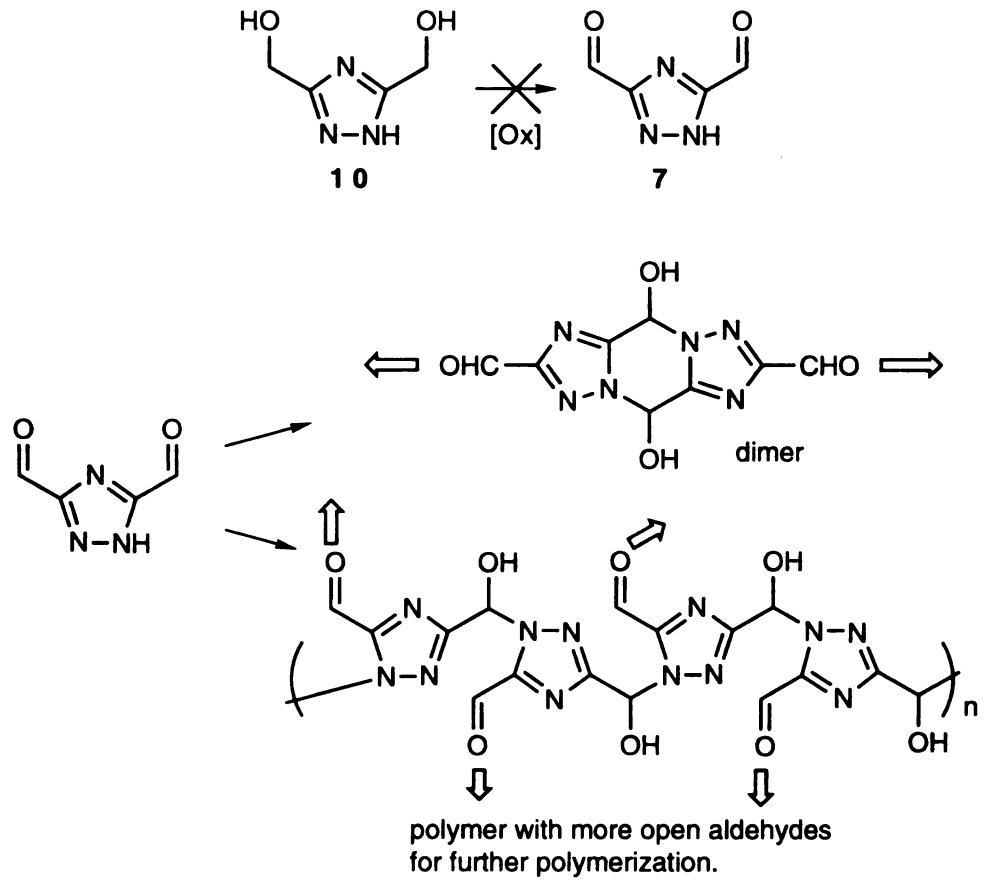
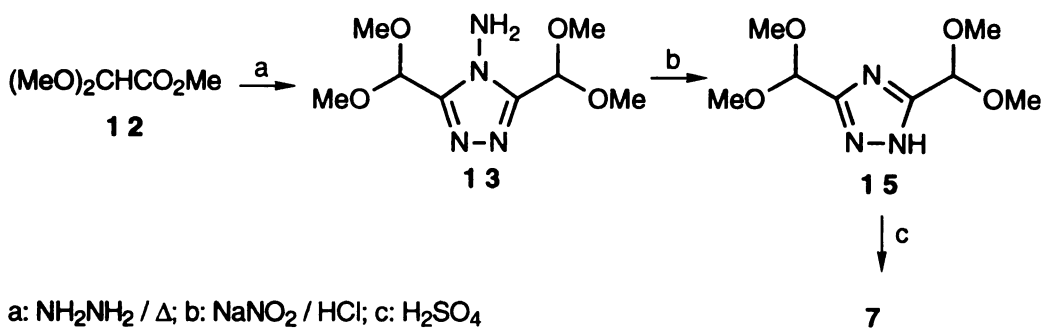


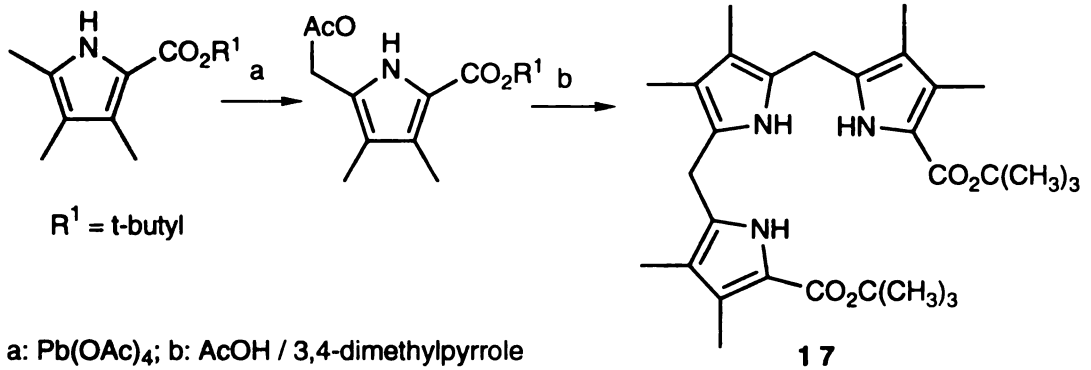
Figure 14. Dimerization and Polymerization Possibilities of **7**

Scheme 5. Synthesis of 3,5-Diformyl-1H-1,2,4-triazole **7**



To use the diformy triazole **7** in the "3 + 1" method described in path 1 of Scheme 3, a tripyrrane **6** was needed. The first tripyrrane utilized was hexamethyl tripyrrane **16,** which was produced i*n situ* from di-*tert*-butyl ester **17** (Scheme 6). Using conditions reported by Lash,[34] diester **17** was dissolved in TFA to give tripyrrane **16**. After liberation of carbon dioxide, compound **16** was then diluted with methylene chloride and condensed with **7**. After one hour the reaction mixture was neutralized with triethylamine and oxidized with 2,3-dichloro-5,6-dicyano-1,4- benzoquinone (DDQ). After work up, the only isolatable product was octamethylporphyrin **18** (Scheme 7). Longer reaction times only produced a trace amount of **19** which was detected in the mass spectral analysis of **18**. The isolation of **19** could have been hindered by its poor solubility.

Scheme 6. Synthesis of Di-*tert*- butyl 3,3',3",4,4',4"-Hexamethyltripyrraln-2',2"-dicarboxylate **17**

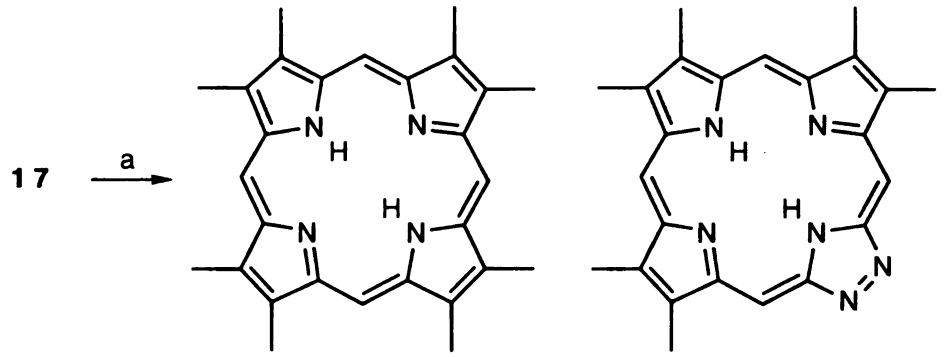


R^1 = t-butyl

a: $Pb(OAc)_4$; b: AcOH / 3,4-dimethylpyrrole

17

Scheme 7. Cyclization of **17** and **7** Using Lash Conditions



18, Major product **19**, No product formed.

a: 1) TFA; 2) **7**; 3) TEA; 4) DDQ

The presents of **18** as a major product could be due to the possible fragmentation of the tripyrrane into a 5-(methyl-2-pyrryl)-2-pyrrylcarbinyl cation.[34g] This 5-(methyl-2-pyrryl)-2-pyrrylcarbinyl cation could do a "2 + 2" cyclizaton to give the hexamethylporphyrin **18** (Figure 15). In this case, the fragmentation of the tripyrrane was a competing reaction in the formation of the diazaporphyrin **19**.

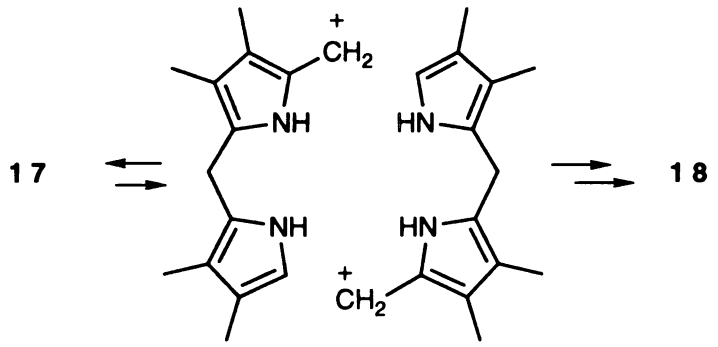
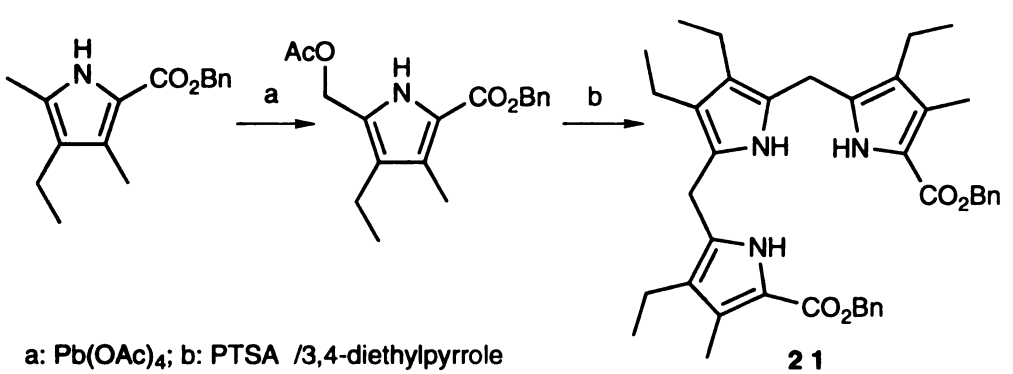


Figure 15. Possible Route of the Formation of **18**

We then decided to try a different tripyrrane in hopes of synthesizing a macrocycle with reasonable solubility. Tripyrrane **20** was created from the PTSA catalyzed condensation of 3,4-diethylpyrrole and benzyl 5-(acetoxymethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (Scheme 8). This tripyrrane dibenzyl ester **21** was hydrogenated to produce the tripyrrane diacid **20** which was decarboxylated in the presence of triflouoroacetic acid. It was then diluted with methylene chloride and was allowed to react with diformyl triazole **7** for 2 hours (Scheme 9). The reaction mixture was neutralized with triethylamine and oxidized with DDQ. After work-up, the crude product was purified by chromatography on basic alumina. The first solvent used was methylene chloride, this isolated porphyrin **22**. After porphyrin **22** was removed the solvent was changed to chloroform and a dark green fraction was isolated as the diazaporphyrin **23** in 29% yield. This diazaporphyrin **23** formed deep violet solutions in chloroform and methylene chloride. Crystallization from chloroform-hexane gave the **23** as violet needles.

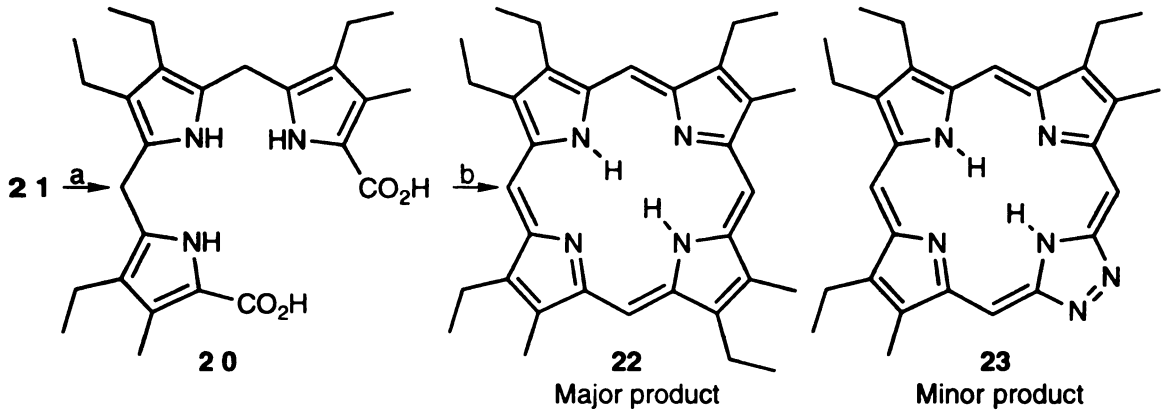
Scheme 8. Synthesis of **21**



a: $Pb(OAc)_4$; b: PTSA /3,4-diethylpyrrole

21

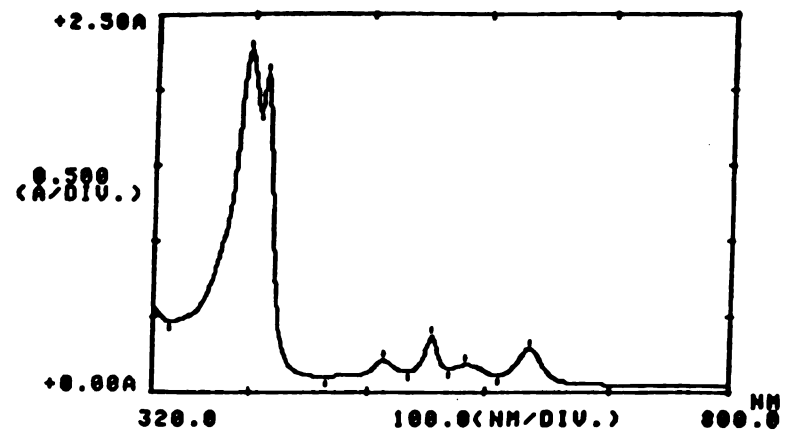
Scheme 9. Synthesis of **23**



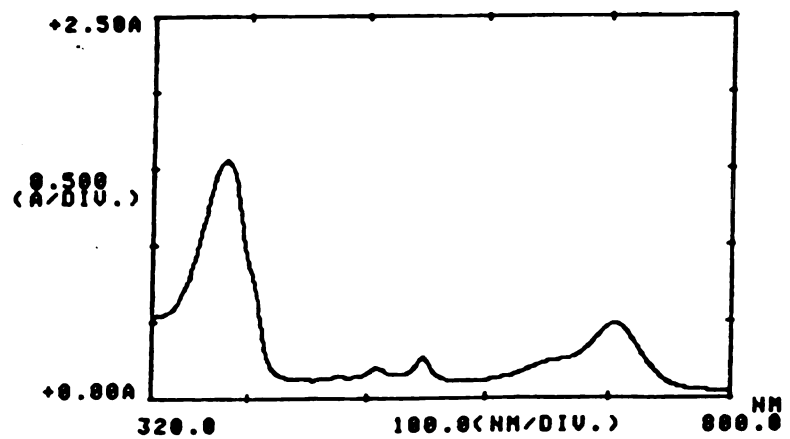
a: H_2 / Pd/c; b: 1) TFA; 2) **7**; 3) TEA; 4) DDQ

Structure determination of this dark purple compound revealed some interesting physical properties. The 70 eV electron impact mass spectrum gave the anticipated strong molecular ion at m/z 452. However, the UV-Vis spectrum of **23** in methylene chloride showed strong Soret-like bands at 398.0 (ε = 92300) and 412.0 nm (ε = 81800) (Figure 16) which showed that there was porphyrin-like aromaticity in **23**. The free-base **23** was treated with TFA and the UV-Vis spectrum of **23** (in methylene chloride and TFA) gave a single strong absorption at 374.0 nm (ε = 59000). After the acidic sample was neutralized with triethylamine, the resulting UV-Vis spectrum returned to the same profile as the spectrum of the free-base. The two strong absorptions were still present. It is possible that **23** could have two strong absorptions or there are two tautomers that have similar stability in solution at room temperature. Figure 17 shows six of the possible tautomers of **23** and their delocalization pathways are shown in bold for each tautomer. Four of these six have an 18 π-electron delocalization pathway, **23a-d**. If an equilibrium does exist between these tautomers, **23a-d**, the delocalization pathway for **23a** involves two more nitrogens then **23c** and **23d**. Since it has been predicted that the addition of

nitrogens to a porphyrin structure causes the single electron energy level transitions to lower,[21] tautomer **23a** should show a shift to longer wavelengths in its UV-Vis spectrum. This tautomer **23a** could explain the second strong absorption at 412 nm, which is very close to the strong absorption at 398 nm. The extinction coefficients for the Soret band in porphyrins are around 150,000 to about 200,000.[21] The extinction coefficients for the Soret-like bands of **23** are approximately half as intense as the ones reported for porphyrins. The extinction coefficient for Masaki's monoazaporphyrn in Figure 3 was reported to be 220,000 at 400 nm.[35] Comparing the UV-Vis absorptions of **23** to the ones from Masaki's monoazaporphyrin shows that the absorptions of **23** are approximately at the same wavelength and extinction coefficients except for the two Soret-like bands. Since the addition of the second nitrogen into a porphyrin ring gives rise to tautomers that have different delocalization pathways that involve the added nitrogens, there is a possibility that another Soret-like absorption can occur. One would have to compare the spectrum of **23** to the one from Masaki's monoazaporphyrin. If the Soret-like band for this monoazaporphyrin has a shoulder that represents an unresolved peak, this could help prove the concept of a second Soret-like absorption with the addition of a two nitrogens in the periphery of a porphyrin.



UV-Vis spectrum of **23** in methylene chloride.



UV-Vis spectrum of **23** in methylene chloride with 0.1% TFA.

Figure 16. UV-Vis spectrum of **23**

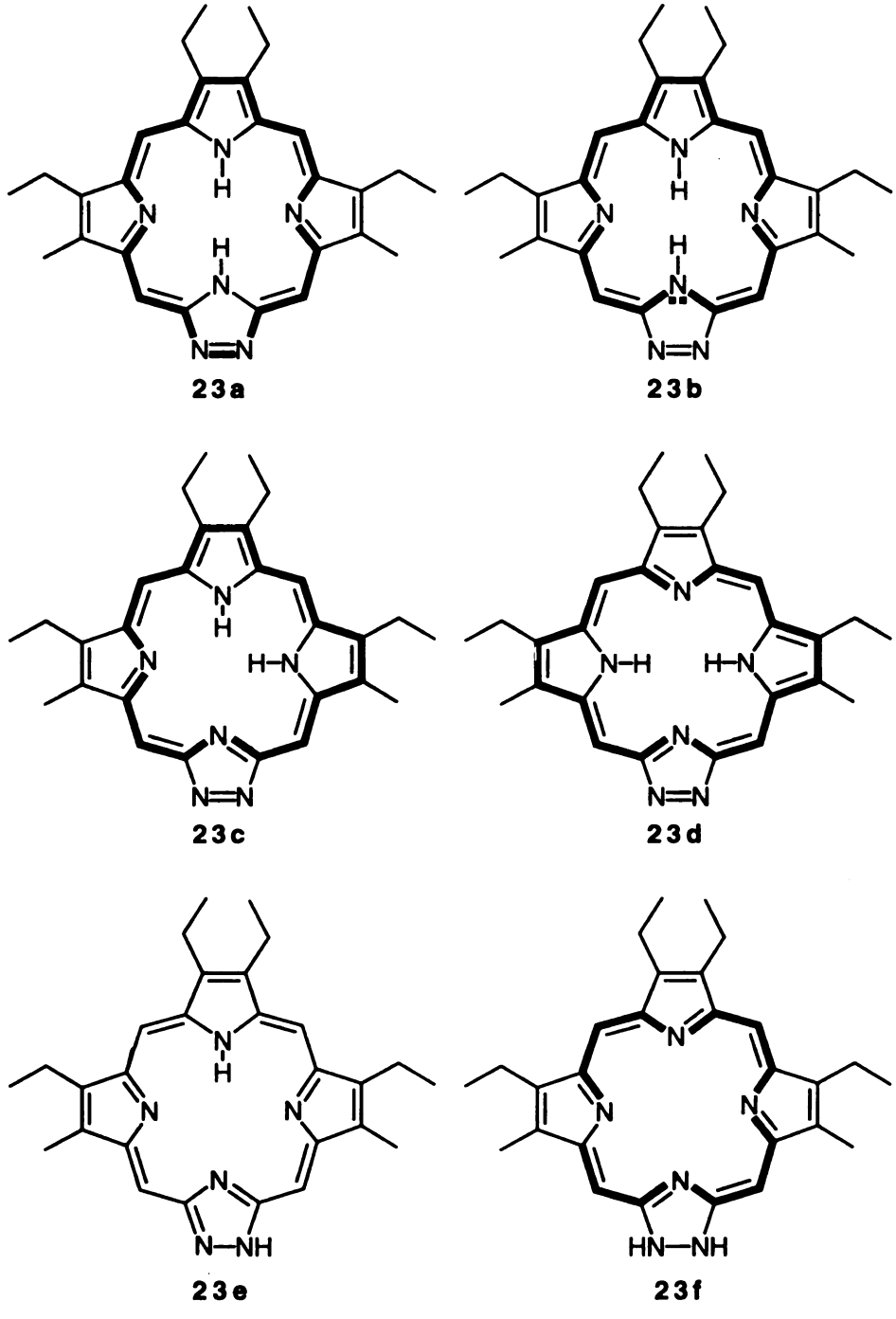


Figure 17. Six of the Possible Tautomers of **23**

The MM2 energy calculations of the six isomers from Figure 17 are displayed in Table 1. From this comparison, structure **23c** is less likely to be favored due to the increased level of steric interactions between the two internal hydrogens which leads to a higher calculated bond disassociation energy. Tautomers **23e** and **23f** are both high in calculated MM2 energy. The structure of **23e** is cross-conjugated and does not possess the aromatic-like stabilization that **23a-d** have. Tautomer **23f** is conjugated however, with 16 π-electrons, it falls under the antiaromatic category and would not be favored over the aromatic-like, 18 π-electron tautomers **23a-d**. The strong Soret-like bands in the UV-Vis spectrum also rules out **23f** . The two tautomers, **23a** and **23b** both have the same structure. The only difference is the delocalization pathway. The data displayed in Table 1 shows that **23b** is lower in energy. It would be difficult to determine which of the two would be favored over the other without more physical data. From the three remaining tautomers, **23a**, **23b** and **23d**, the actual tautomer of **23** was determined by ^{1}H NMR. The ^{1}H NMR spectrum of **23** in $CDCl_3$ (Figure A1 in appendix A) showed a single broad resonance for the two internal protons at δ = -2.6. This is consistent with the structure of **23d** in which the two internal protons are identical. The two different external *meso* -CH's were highly deshielded by the aromatic ring current and appeared as two singlets at δ = 9.2 and 10.3. These shifts for the *meso* protons fall in the average range for porphyrins.[36] The other ^{1}H NMR signals for the two different ethyl groups and the methyl group were consistent with the proposed structure of **23** and are displayed in Figure 18. When comparing the ^{1}H-NMR shifts of the methyl and ethyl groups on **23** to the same type of alkyl groups on the etioporphyrin 's I-IV,[37] the chemical shifts fall into about the same range.

Table 1. MM2 Energies Calculated for Six of the Tautomeric forms of **23**

Tautomer	MM2 energy
23a	64.54
23b	42.50
23c	165.59
23d	68.17
23e	108.10
23f	104.99

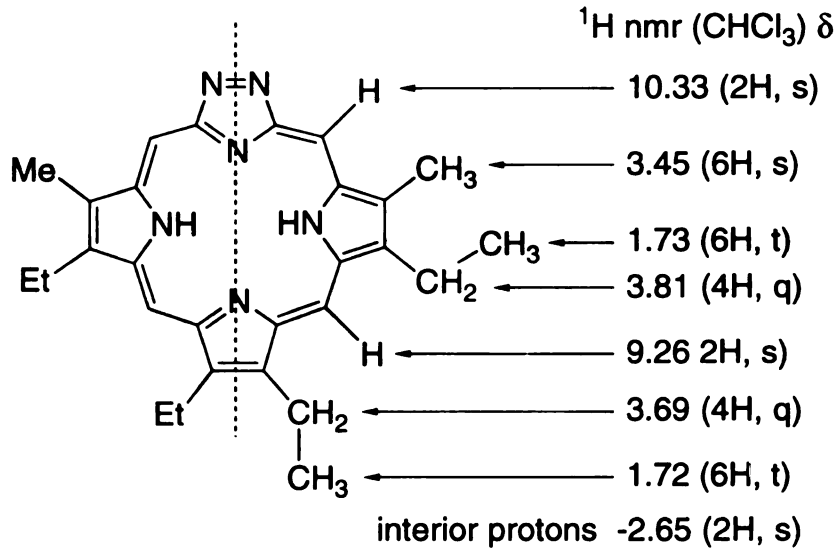


Figure 18. ^{1}H-NMR Peak Assignments for **94**

The ^{13}C NMR spectrum for **23** (Figure A2) showed thirteen of the fourteen possible carbons. Unfortunately, since the natural abundance of ^{13}C is only 1.1% that of ^{12}C, and its sensitivity is only about 1.6% that of ^{1}H, the overall sensitivity of ^{13}C-NMR is about 6000 times less then ^{1}H-NMR. With this low sensitivity, there is a requirement for larger sample sizes or increased acquisition time during ^{13}C-NMR experiments. One further limitation in ^{13}C-NMR is the long spin-lattice relaxation time for the excited ^{13}C nuclei. During a NMR experiment the sample is given a radio frequency (RF) pulse. This RF

pulse causes the ^{13}C nuclei spin axis to flip 90° (Figure 19). Then the free induction decay (FID) occurs as each nucleus relaxes back to its original spin axis. During this FID time is when data acquisition occurs. Before the next RF pulse there is a decay time (D_1) to allow all of the nuclei to completely relax. If this D_1 time is too short, the next RF pulse will flip the nuclei back to the 90° position. If this occurs then the slower relaxing nuclei will not give an adequate FID signal. These limitations could lead to the reason that there is one missing carbon signal in the ^{13}C-NMR spectrum.

There have been very few ^{13}C studies of free base porphyrins primarily because the NH tautomerization leads to severe broadening of the α-carbon resonance.[37] The structure proposed for **23** allows there to be two more sites for NH tautomerization. With the tautomerization possibility the D_1 times between acquisitions were set anywhere from 60 seconds to as much as 120 seconds. The same situation occurred in all the ^{13}C-NMR experiments with various D_1 times, only thirteen of the fourteen carbons were seen. A proton-carbon correlation experiment (HMQC) was performed on **23** to help determine which carbon was missing in the ^{13}C NMR spectrum (Figure A3). This determined that the *meso* carbon at δ = 95.2 is coupled to the *meso* proton at δ = 9.3, and *meso* carbon at δ = 101.9 is coupled to the *meso* proton at δ = 10.3. It also correlated the alkyl carbons, C^1-C^5, with the remaining proton signals. The six remaining carbon signals were assigned by running long range proton carbon correlation experiments (HMBC). The HMBC spectrum (Figure A4) helped to identify the remaining carbons, C^8-C^{13}. The missing carbon seemed to be triazole carbon, C^{14} (Figure 20). A possible reason why this carbon is not seen on the ^{13}C NMR spectrum could be due to the effects of the neighboring nitrogens. In early ^{13}C-NMR studies[38] of nitrogen containing heterocycles, problems occurred when assigning chemical shifts to carbons in pyrrole. The

carbons adjacent to the nitrogens exhibited signal broadening associated with the quadrapole relaxation involving the ^{14}N and its nonzero ^{13}C-^{14}N coupling. The missing carbon is between two nitrogens and it is in a molecule that can have several NH tautomers. These could contribute to the long relaxation times that prevents a signal entirely on the NMR time frame. Figure 20 displays the assigned carbon signals for **23**. A recent ^{13}C-NMR study of etioporphyrins I-IV by Lash[37] shows that the ^{13}C-NMR spectra taken in TFA-$CDCl_3$ can clearly distinguish each of the four isomers of etioporphyrin (I-IV). Since the ^{13}C-NMR spectrum of **23** with $CDCl_3$ only resolved thirteen of the fourteen carbons, the addition of an acid to protonate all basic nitrogens might reduce the NH tautomerism enough to detect all fourteen carbons. When **23** was protonated with small amount of TFA (<1%), the missing carbon was not resolved. When the TFA concentration was increased to 1% and the aquisition time increased to five hours, all fourteen carbons were present (Figure A6). Over the next several hours two of the carbon signals started to broaden. One of the *meso* carbons and possibly the triazole carbon.

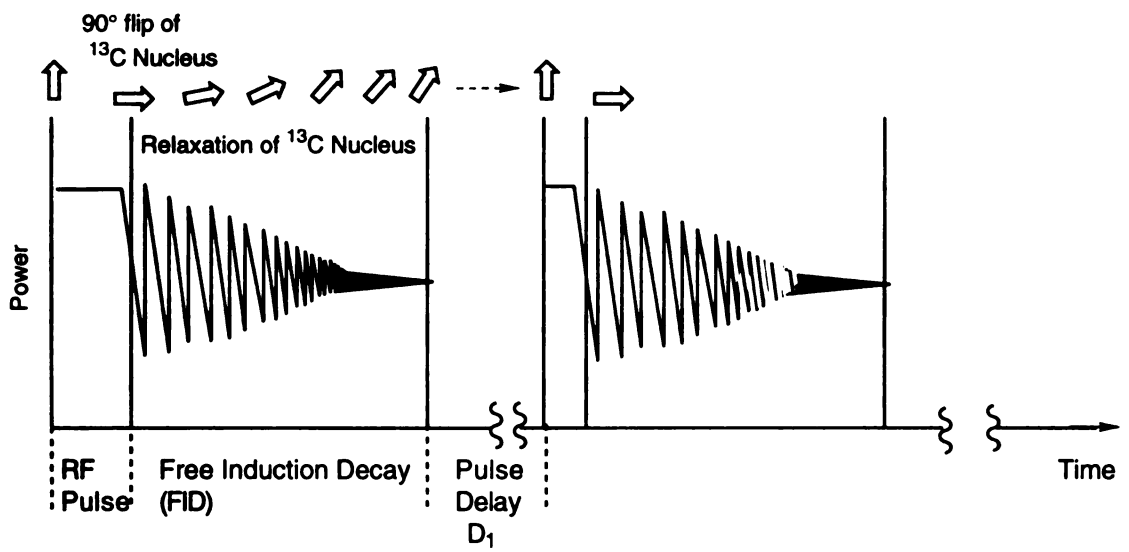
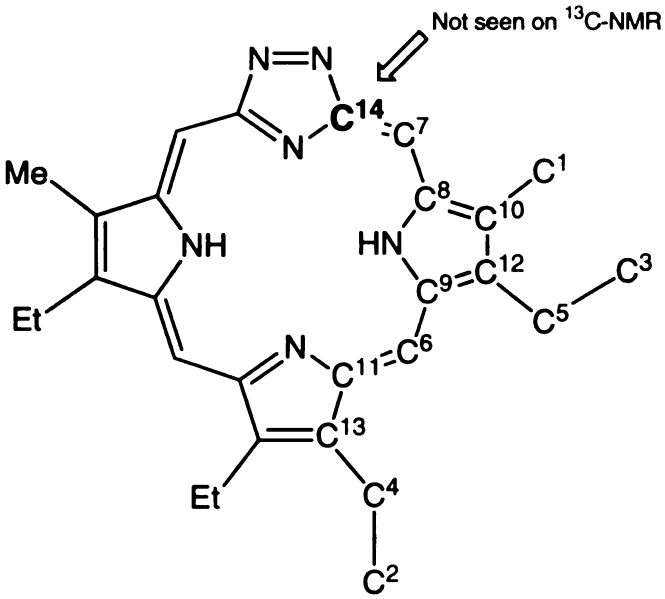


Figure 19. Schematic Representation of the Radio frequency Pulse followed by the Free Induction Decay (acquisition time) and Pulse Delay



^{13}C nmr ($CHCl_3$) δ	
C^1	11.033
C^2	17.012
C^3	18 .074
C^4	19.227
C^5	19.501
C^6	95.195
C^7	101.978
C^8	137.322
C^9	140.220
C^{10}	141.328
C^{11}	146.290
C^{12}	158.719
C^{13}	159.007

Figure 20. The ^{13}C NMR Peak Assignments for **23**

Slow recrystallization of **23** from chloroform-hexane gave the best crystals that were suitable for X-ray structure determination by D. Ward[39]. The crystals obtained from methylene chloride-hexane and methylene chloride-methanol were not suitable for X-ray structure determination. The structure was confirmed by taking a single crystal x-ray defraction spectrum of **23** (Figure 21). The crystals formed in the chloroform-hexane solution had two chloroform molecules between every diazaporphyrin. This situation most likely gave rise to the formation more uniform crystals. The methylene chloride-hexane and methylene chloride-methanol crystals did not produce crystals that had uniform unit cell dimensions. The missing triazole carbon was located and was consistent with the proposed structure of the tautomer **23d**. The internal hydrogens were resolved and are bonded to the opposing nitrogens displayed on **23d** in Figure 17. Since the X-ray crystal data was collected at a temperature of 153K, the most stable of the tautomeric must be **23d**. The R index for this structure is 43% which is within the parameters for accurate

structure determination (Table A1). Table A2 compares the MM2 calculated bond distances and bond angles of **23** with the actual crystal data obtained. The MM2 calculated bond lengths are within a few tenths of an angstrom from the actual lengths in most cases. The MM2 calculated bond angles were also within a few tenths of a degrees from the actual bond angles.

The structure **23d**, which we have named 8,12,13,17-Tetraethyl-7-18-dimethyl-2,3-diazaporphyrin, exists in a planar conformation in the solid state (Figure 21). The stacking was a herring bone pattern with the triazole units of adjacent macrocycles at opposite ends with two chloroform molecules between them (Figure 22).

This diazaporphyrin **23** readily formed both zinc and nickel(II) complexes (Scheme 10). The zinc complex **24** was obtained by refluxing the free base **23** with a solution of excess zinc acetate in methanol. The nickel(II) complexe **25** was obtained by refluxing **23** and nickel(II) acetate in N,N-dimethylformamide.[40] The mass spectra were consistent with the proposed structures of **24** and **25**. Both **24** and **25** gave absorption bands in their UV-Vis spectrum, 397.0 nm and 389.5 nm respectively (Figure 23). ^{1}H-NMR spectra for these two metallated diazaporphyrins were unclear and could not be used to confirm the site of metallation. The zinc complex of Masaki's monoazaporphyrn was also unclear on where the metal was inserted, in the ring or complexed with the external nitrogen. However, **24** had approximately the same absorptions as Masaki's zinc complex.

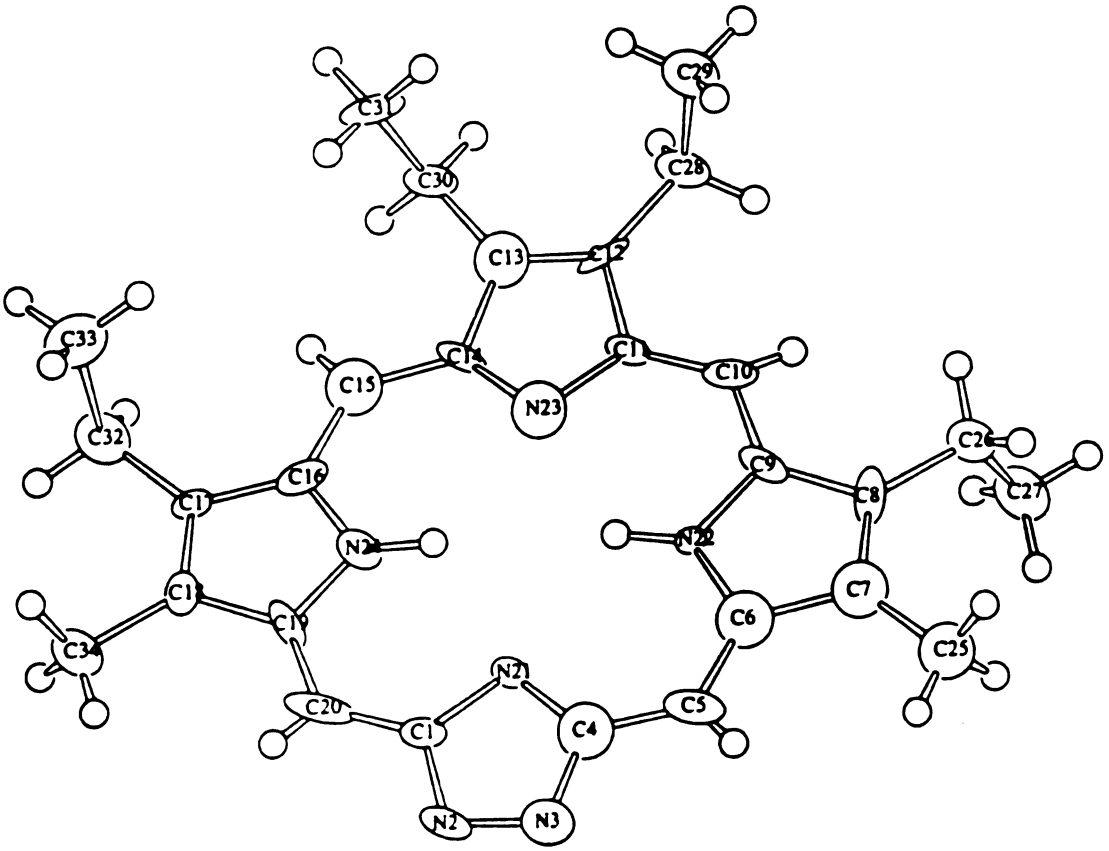


Figure 21. X-ray Structure of Diazaporphyrin **23**

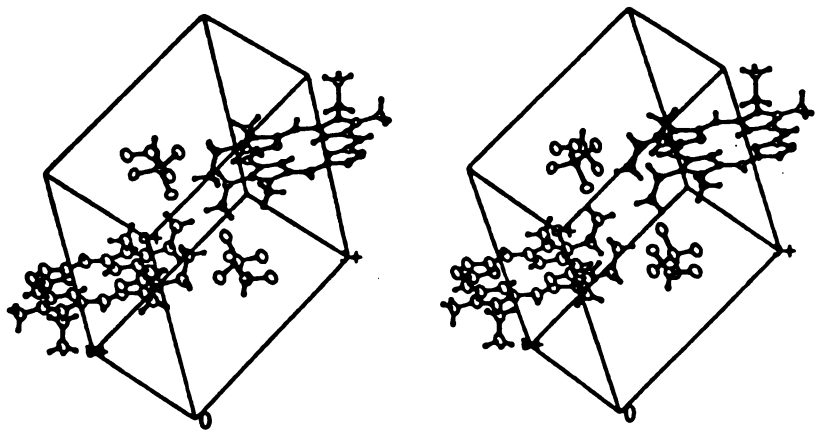
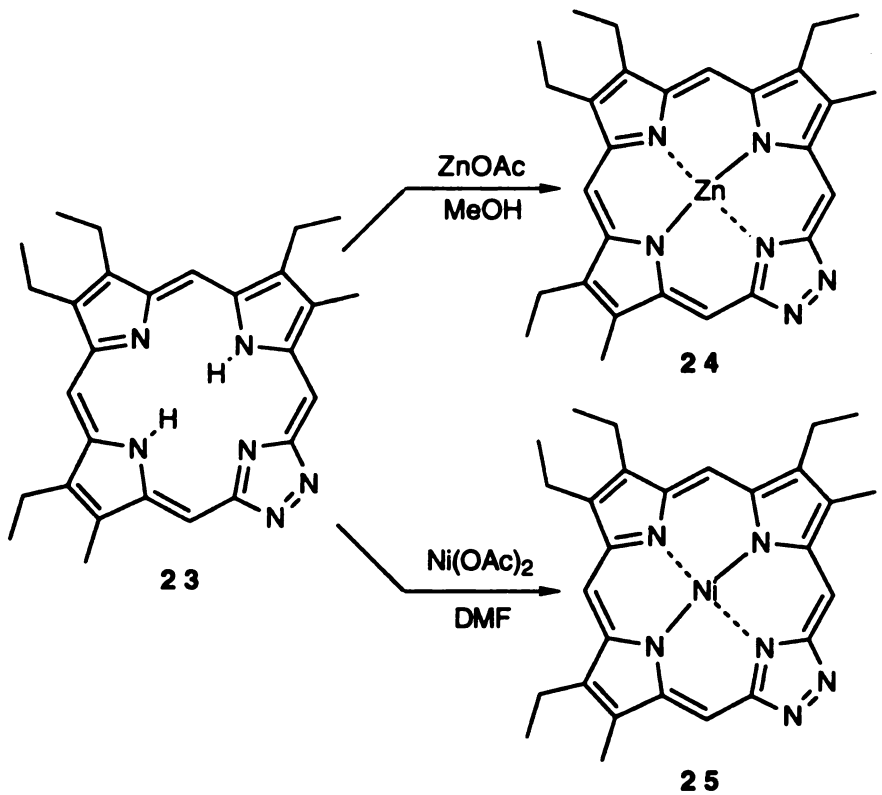
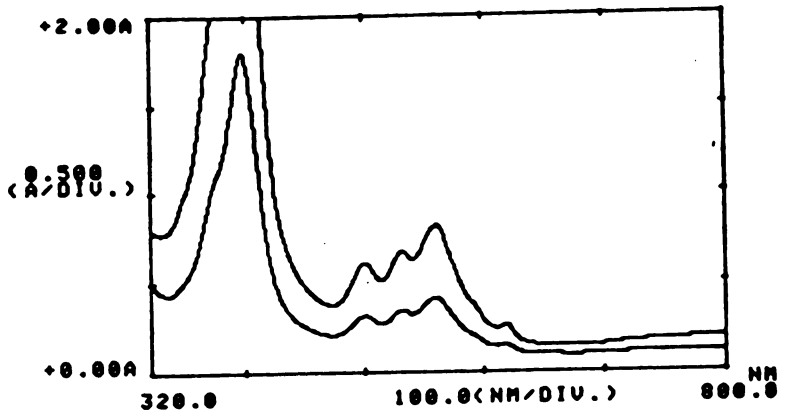


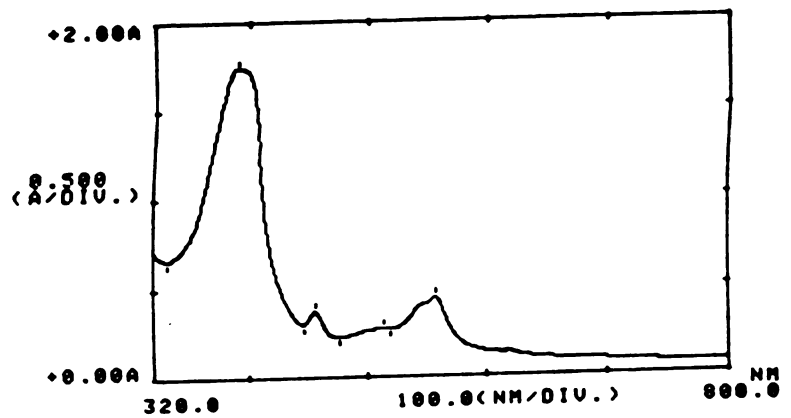
Figure 22. Crystal Stacking of Diazaporphyrin **23**

Scheme 10. Metallation of **23**





UV-Vis spectrum of **24** in methylene chloride.

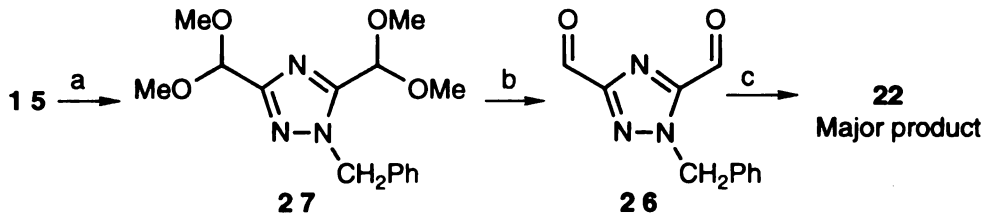


UV-Vis spectrum of **25** in methylene chloride

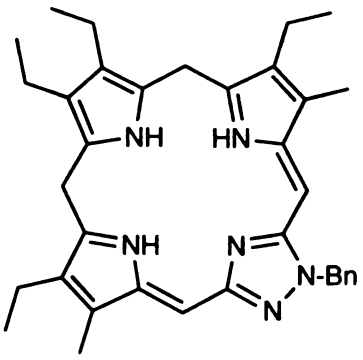
Figure 23. UV-Vis spectrum of **24** and **25**

Two other methods were attempted to synthesize **23** . One method was to react the benzyl protected triazole **26** with the tripyrrane **20**. The second attempt was to condense a bis(a-hydroxymethyl)triazole with **20**. The benzyl protected triazole **26** was produced by the benzylation of **15** under solid-liquid phase-transfer conditions to afford **27** in good yield. This diacetal **27** was hydrolyzed to give the 1-benzyl-3,5-diformly-1,2,4-triazole **26** (Scheme 11). This dialdehyde **26** was reacted with the tripyrrane **20** in the presence of TFA. The only product isolated and identified was porphyrin **22**. Several attempts to produce the benzyl porphyrin **28**, shown in Figure 24, were unsuccessful. In every case porphyrin **22** was produced.

Scheme 11. Synthesis of **26** and Its Reaction With **20**



a: Bn-Cl, K_2CO_3; b: H_2SO_4 / H_2O; c: 1) **20** / TFA 2) TEA 3) DDQ

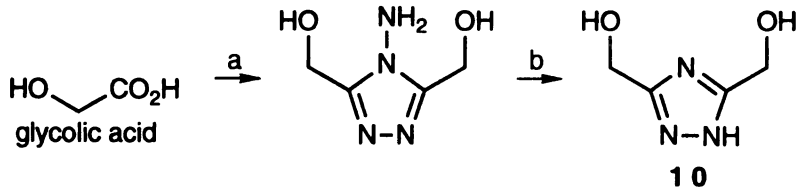


28

Figure 24. Desired Benzyl Diazaporphyrin **28**

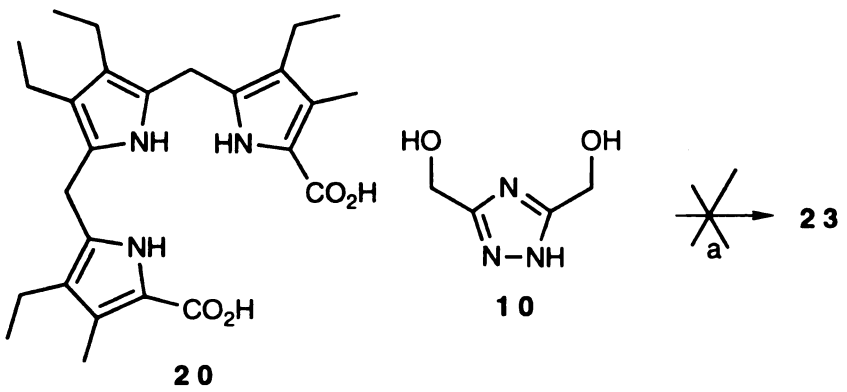
The high reactivity of 2-α-hydroxymethylated 5-membered aromatic heterocycles toward nucleophilic substitution, in the presence of acid catalysts, is well known and used in some porphyrin synthesises.[29a] It was thought that this route could be used to produce **23**, by condensing the diol **10**[41] with the tripyrrane **20** (Scheme 12). Triazole **10** was produced by the condensation of glycolic acid and hydrazine hydrate to produce the 1-amino-3,5-bis(hydroxymethyl)-1,2,4-triazole followed by deamination with $NaNO_2$ (Scheme 12). The same reaction conditions shown in Scheme 9 were carried out with **10** and **20**. Initially the diol and tripyrrane were allowed to react for 2 hours. The only isolated product, after neutralization and oxidation, was the porphyrin **22**. Longer reaction times led to the isolation of a dark green solid. This dark green compound was not the desired diazaporphyrin **23**. The UV/Vis spectrum was quite different and mass spectral analysis revealed a mass of 613. Since there wasn't a mass that corresponds to a loss of nitrogen (M^+ - N_2), there were no triazoles in the product. These by-products also showed that diol **10** was unreactive in this "3 + 1" addition reaction or that the fragmentation of the tripyrrane occurred much faster. In this case as well the reaction shown in Scheme 9, the fragmentation of the tripyrrane was a competing reaction in the formation of the diazaporphyrin **23**. Since this bis(α-hydroxymethyl) triazole 29 was relatively unreactive to the "3 + 1" conditions, a modification was needed to make it more reactive within this coupling sequence.

Scheme 12. The Synthesis of 3,5-Bis(hydroxymethyl)-1,2,4-Triazole **10**



a: $NH_2NH_2 \cdot H_2O$, Δ; b: HCl / $NaNO_2$ / 0° C

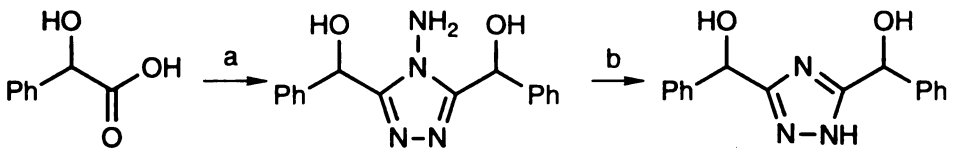
Scheme 13. Attempted Synthesis of **23** Using Diol **10** and **20**



a: 1) TFA 2) TEA 3) DDQ

One possible method to make a more reactive diol would be to synthesize the diphenyl version of **29**. This was accomplished by condensing mandelic acid with hydrazine hydrate to form the corresponding amino triazole **30** (Scheme 14). This amino triazole was deaminated with nitrous acid to yield the triazole **31**. The attempted preparation of diphenyl version of **23** was patterned after Lee's synthesis of *meso* -tetraphenylthiaporphyrins.[42] This reaction involved the acid-catalyzed condensation of a thia-tripyrrin and a 2,5-bis(α-hydroxy-α-phenylmethyl)thiophene (Scheme 15). Triazole **31** was reacted in the same manner with the tripyrrane **20,** using TFA as the catalyst (Scheme 16). The reaction failed to produce even a trace amount of the desired diphenyl diazaporphyrin **32**, and yielded only porphyrin **22.** A change in the acid catalyst, from TFA to $BF_3(OEt_2)$, did not yield any of the desired diazaporphyrin nor did it produce the by-product **22**. Thin-layer chromatography showed no trace of starting materials and only a trace of polymeric material at the origin.

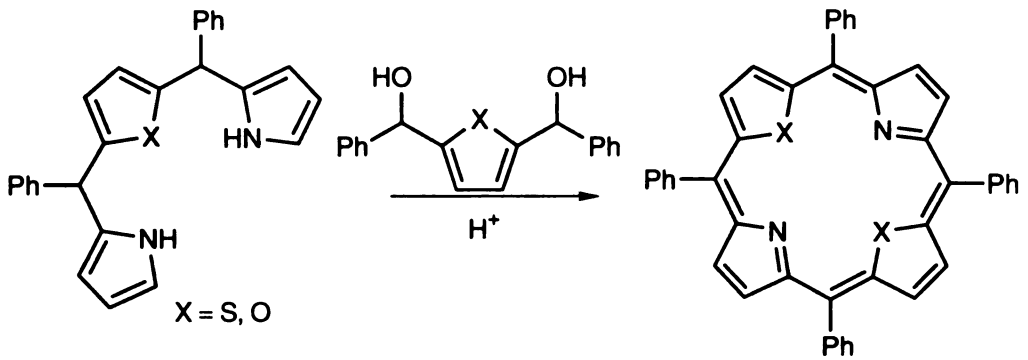
Scheme 14. Synthesis of 2,5-Bis(a-hydroxy-a-phynylmethyl)-1,2,4-triazole **31**



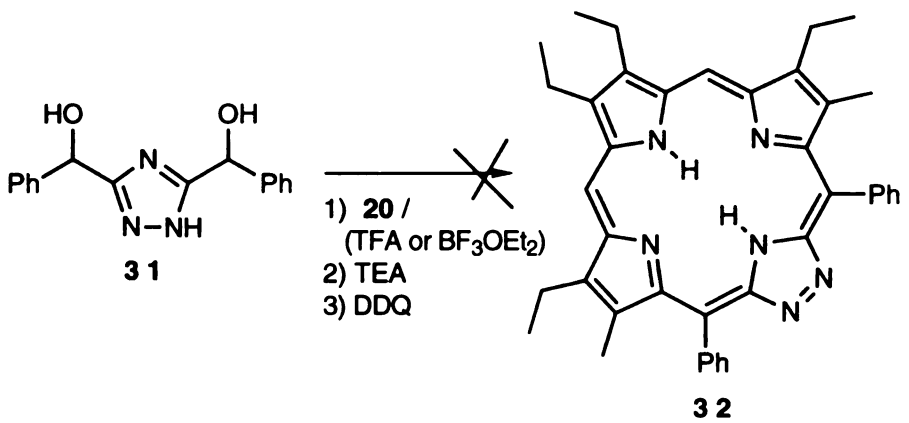
mandelic acid **30** **31**

a: $NH_2NH_2 \bullet H_2O$; b: HCl / $NaNO_2$

Scheme 15. Lee's Synthesis of *meso* -Tetraphenylthiaporphyrin



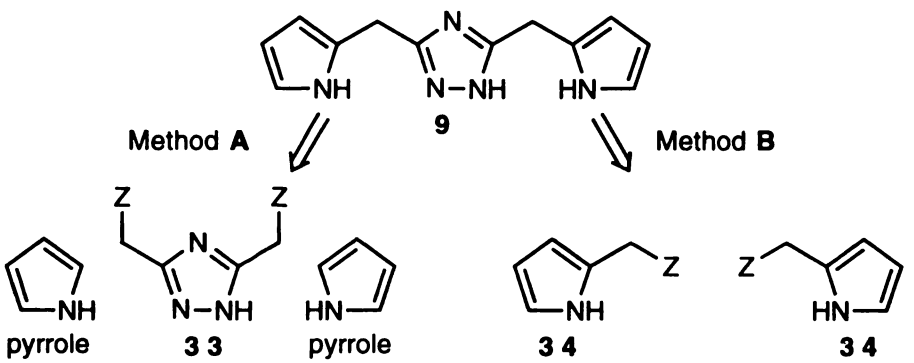
Scheme 16. Attempted Condensation of **20** and **31**



31 **32**

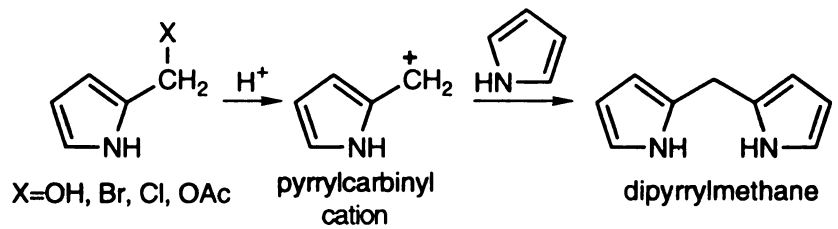
The second approach to synthesize **94** was the method shown in path 2 of Scheme 10. The diazatripyrrane **9** is an important synthon to diaziaporphyrin **1** (Scheme 1) and the tetraazaporphyrin **3** (Scheme 3). The retro synthetic analysis of **9** shows two methods in which it can be produced (Scheme 17). Method **A** would involve adding pyrrole to a functionalized triazole resembling **33**, whereas method **B** would entail the condensation of a triazole between two suitable methylene pyrroles **34** (Scheme 17). Our initial attempts followed the route outlined in method **A**.

Scheme 17. Retro Synthetic Analysis of **9**



Electrophillic aromatic substitution reactions have been used for the linkage of two pyrroles through a single bridge in the formation of dipyrrylmethanes, dipyrrylmethenes, and dipyrrylketones. For example, dipyrrylmethanes can be synthesized by the reaction of a pyrrylcarbinyl cation and an alpha free pyrrole under acidic conditions (Scheme 18). This idea was utilized in an effort to synthesize 3,5-bis(2-pyrrylmethyl)-1,2,4-triazole **9**.

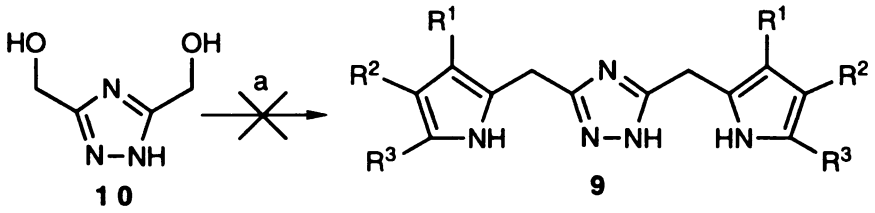
Scheme 18. Formation of Dipyrrylmethanes from Pyrrylcarbinyl Cation



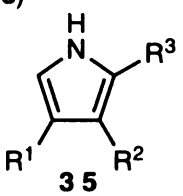
The idea was to take a difunctional triazole that resembled **33** and condense it with an alpha free pyrrole to yield a 3,5-bis(2-pyrrylmethyl)-1,2,4-triazole like **9.** The first triazole used was the 3,5-bis(hydroxymethyl)-1,2,4-triazole **10.** Compound **10** was subjected to the condensation conditions shown in Scheme 18 with five different pyrroles (**35 a-e**). However, none of these reactions produced the expected 3,5-bis(2-pyrrylmethyl)-1,2,4-triazoles (Scheme 19). Triazole **36**, which was produced by treatment of **37** with $SOCl_2$, was then reacted with compounds **35** (**a-e**). Again, there was no 3,5-bis(2-pyrrylmethyl)-1,2,4-triazoles produced. The only combination that produced any detectable amount of a diazatripyrrane is shown in Scheme 20. Here ethyl 4-ethyl-3-methyl-2-pyrrole carboxylate **38** was refluxed with **10** in an acetic acid-ethanol solution (3:1) for several hours. After workup diazatripyrrane **39** was detected by mass spectroscopy. Triazole **10** and a small amount of pyrrole **38** were the only actual isolated materials. Variation of reaction times, temperatures and the acid catalyst, produced no increase in the desired diazatripyrrane. Triazole **31** was then substituted for the triazole **10** and subjected to the same conditions (Scheme 21). This led to the similar results, diazatripyrrane **40** was detected only by mass spectroscopy. Compound **41** (prepared from **10** and acetic anhydride, Scheme 22) also failed to yield the desired product when reacted with pyrroles **35 a-e**, even though the acetoxypyrroles (X = OAc, Scheme 18) have worked well in the synthesis of

various dipyrrylmethanes.[43] In Schemes 19 - 22, a variety of acids including acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, PTSA, were tried as a catalyst along with a variety of solvents such as methanol, ethanol and acetic acid. However only intractable materials were recovered. Triazole **42**, produced by the condensation of lactic acid with hydrazine hydrate followed by deamination with nitrous acid (Scheme 24), was subjected to the same reaction conditions as **10** and gave similiar results. In view of these results another route was needed to synthesize **9**.

Scheme 19. Attempted Condensation of **10** with Several Pyrroles



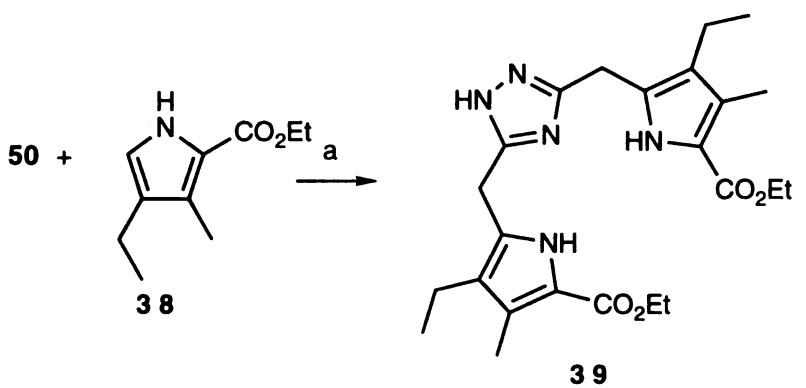
a: H^+ / **35(a - e)**



35

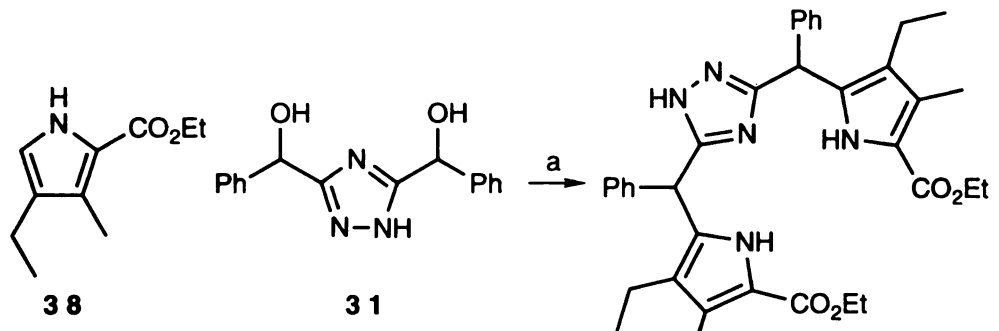
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = R^2 = R^3 = Me$
c) $R^1 = R^3 = Me$, $R^2 = H$
d) $R^1 = R^3 = Me$, $R^2 = Et$
e) $R^1 = R^2 = Me$, $R^3 = H$

Scheme 20. Attempted Synthesis of **39**



a: EtOH:AcOH (3:1), Δ

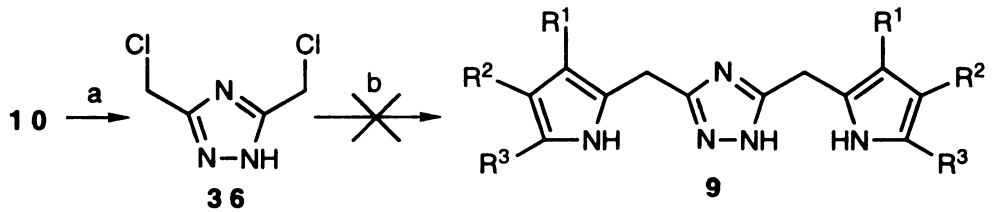
Scheme 21. Attempted Synthesis of **40**



38 **31** **40**

a: EtOH:AcOH (3:1), Δ

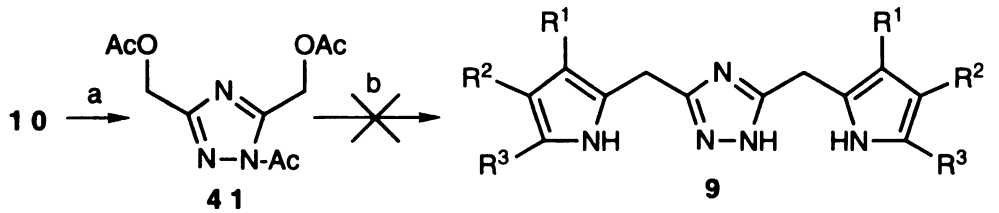
Scheme 22. Attempted Condensation of **36** with Several Pyrroles



36 **9**

a: $SOCl_2$; b) H^+ / **35(a-e)**

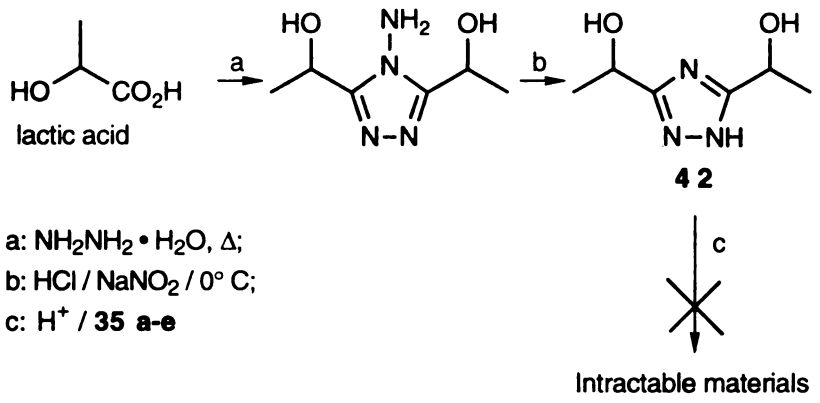
Scheme 23. Attempted Condensation of **41** with Several Pyrroles



41 **9**

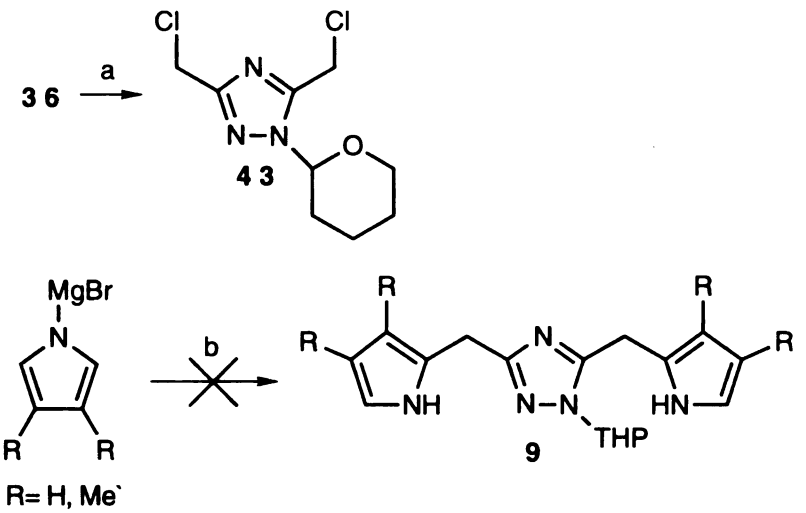
a: Ac_2O; b) H^+ / **35 (a-e)**

Scheme 24. Synthesis of **42** and Its Condensation With Several Pyrroles



Improving the nucleophilic reactivity of pyrroles by converting them into pyrryl anions was another method employed in an attempt to achieve condensation with the relatively unreactive triazole side chains. Attention was focused on the use of the pyrrylmagnesium bromide since it is possible to control the selectivity on electrophilic attack on carbon or nitrogen.[44] Since the triazole has an acidic proton, the pyrrylmagnesium bromide would be ineffective unless a protecting group was introduced into the system. Triazole **36** was the first compound that was protected. The tetrahydropyranal (THP) protecting group was chosen because of its ease of addition and removal with mild acid. Triazole **36** was reacted with dihydropyran in methylene chloride to give the THP protected triazole **43** in 74% yield[29b] (Scheme 25). The protected triazole was then treated with the pyrrylmagnesium bromide. The resulting oil showed no trace of the desired product and was thought to contain mostly polymeric products. 3,4-Dimethylpyrrole magnesiun bromide **35e** was reacted with **43** and the same results occurred. An attempt to limit the polymerization products, 2,3,4-trimethylpyrrole magnesiun bromide **35b** was used. However, only the unreacted **35b** was recovered.

Scheme 25. Synthesis of **43** and Its Reaction with Pyrrylmagnesium Bromide

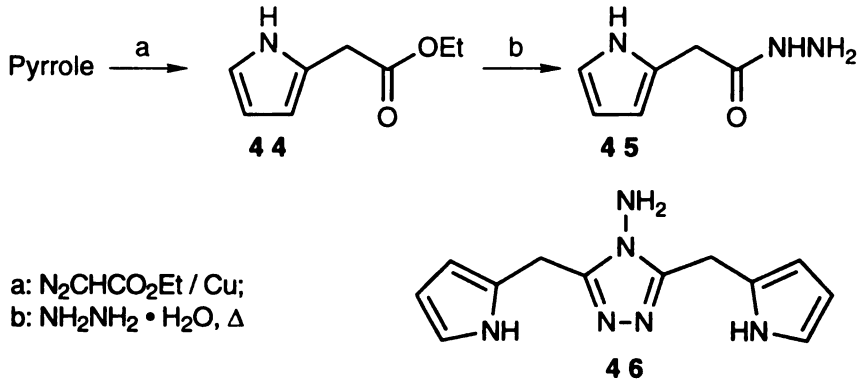


a: DHP; b) **43** / ether

Since it was not possible to produce **9** using method **A** from Scheme 17, we decided to try a reaction sequence that resembled method **B** from the same Figure. This method utilizes the condensation of two functionalized 2-methyl pyrroles to for a 1,2,4-triazole. Ethyl 2-pyrrylacetate was the first compound studied and was produced by reacting pyrrole with ethyl diazoacetate and copper dust to yield the ester compound **44**.[45] This ester was treated with 4 equivalents of hydrazine hydrate and heated in a sealed tube for eight hours at 150°C. The reaction was cooled and the heterogeneous reaction mixture was diluted with water and the solids were collected. The only product isolated was hydrazide **45** (Scheme 26). There was no detectable amount of the desired amino triazole **46**. The reaction time and temperature were increased to 12 hours at 180° C. Mass spectral analysis of compound **45** revealed small amounts of compound **46**. Ester **44** was refluxed in hydrazine hydrate for 10 hours. The water and excess hydrazine hydrate were removed by distillation and the reaction mixture was heated to 180° C. After cooling, the only product

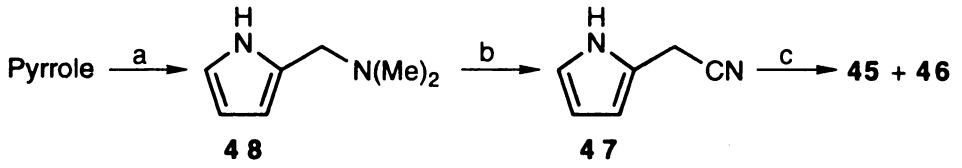
detected was hydrazide **45**. Increasing the temperature to 200 - 210° C , only led only to a decreased amounts of **45** and an increase in insoluble materials.

Scheme 26. Reaction of Hydrazine Hydrate with **44**



Nitrile **47** was then utilized in the attempted synthesis of amino triazole **46**. The nitrile was produced by first reacting pyrrole with dimethylamine hydrochloride and formaldehyde to form dimethylaminopyrrole **48** (Scheme 27). Compound **48** was then reacted with methyl iodide and heated with sodium cyanide to yield the nitrile **47**. This nitrile was then heated with one molar equivalent of hydrazine hydrate for 10 hours at 200° C in a sealed tube. This reaction only afforded a black insoluble solid which showed no signs of the starting pyrrole or any triazole products. When the reaction was repeated with an excess of hydrazine hydrate the major product isolated was hydrazide **45** and only trace amounts of aminotriazole **46**. The hydrazine hydrate condensation method of triazole production has been shown ineffective when applied to ester **44** and nitrile **47**. The only isolated product formed in these reaction was the hydrazide **45**.

Scheme 27. Formation of **47** and Its Reaction With Hydrazine Hydrate

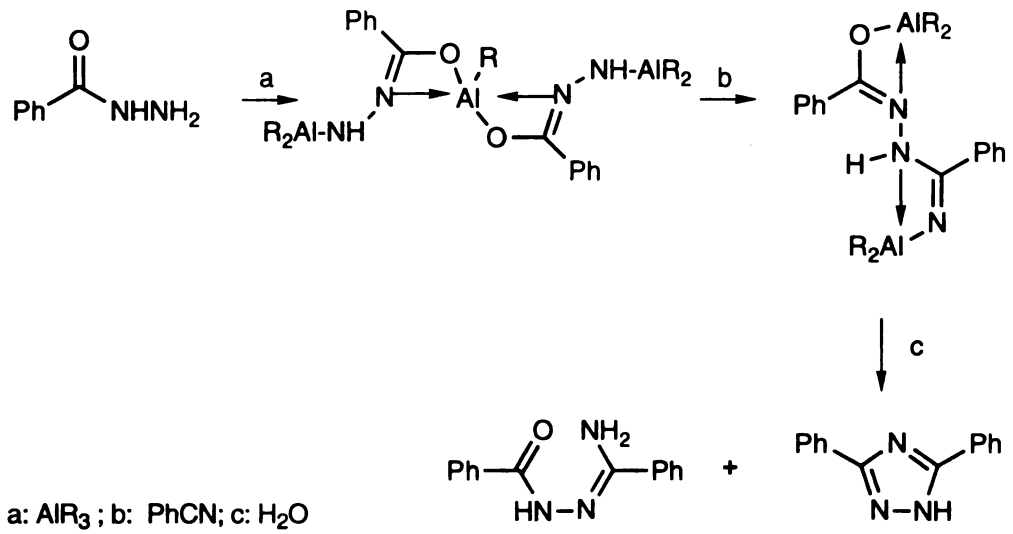


48 **47**

a: Me_2NH / HCHO / HCl; b: 1) MeI, 2) NaCN Δ c: $NH_2NH_2 \bullet H_2O$

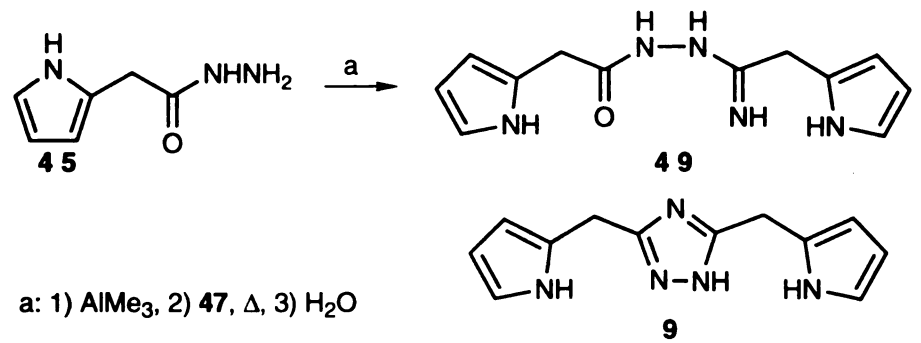
A more effective route to triazole production was a method that involves lower temperatures, developed by Kauffmann[46] in 1981. This procedure reacts a hydrazide with a trialkylaluminum, followed by the addition of a nitrile to yield an acylamidrazone. The acylamidrazone is then heated to give the cyclized triazole product (Scheme 28). When the Kauffmann triazole synthesis was employed on the hydrazide **45** and the nitrile **47**, the only product isolated was acyl amidrazone **49** (Scheme 29). The reaction times and temperatures were varied, but the only product isolated was **49**. Trace amounts of triazole **9** were detected when compound **49** was subjected to mass spectrometry. Since there is a possibility of several reactions occurring during the electron bombardment phase of mass spectrometry process, dehydration of **49** could have happened which explains the presence of the mass ion peak of **9** in the mass spectrum. Attempts to condense **49** into the triazole **9** were unsuccessful.

Scheme 28. Kauffmann Triazole Synthesis



a: AlR_3 ; b: PhCN; c: H_2O

Scheme 29. Kauffmann Triazole Synthesis Reacted with **45** and **47**



a: 1) $AlMe_3$, 2) **47**, Δ, 3) H_2O

The compound **47** has two acidic protons (Figure 25). The acidity of the methylene proton may explain why it was difficult to form a triazole from **47**. The aluminum hydradzide intermediate generated is basic and could inhibit the production of triazoles. Even with the pyrrole hydrogen protected, there is still an acidic proton that could inhibit nucleophilic attack on the nitrile.

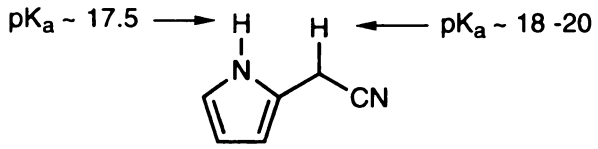
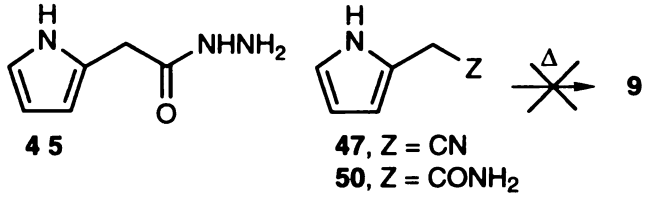


Figure 25. The Relative pK_a's of the Two Acidic Protons in **47**

The attempted condensation of the hydrazide **45** with the nitrile **47** or with the amide **50** did not produce the triazole **9** (Scheme 30). There was partial recovery of **45** in both cases and no recovery of the nitrile **47** or the amide **50**. At temperatures lower then 200° C no reaction seemed to occur and recovery of the reactants was possible. However, temperatures above 200° C, led to decomposition products.

Scheme 30. Attempted Concensation of **45** With Both **47** and **50**



4. Conclusion on the Synthesis of Diazaporphyrin **1** and Tetraazaporphyrin **3**

The 8,12,13,17-Tetraethyl-7-18-dimethyl-2,3-diazaporphyrin **23** was synthesized by the acid catalyzed condensation of tripyrrane **20** and triazole **7** using the " 3 + 1" approach. The structure was characterized by ^{1}H-NMR, ^{13}C-NMR and single crystal X-ray diffraction analysis. This represents the first triazole containing porphyrin and opens up new fields of study on porphyrins with a nitrogen atom in the peripheral position. This diazaporphyrin should be a

good candidate for PDT studies since it does possess a UV/Vis absorption around 650 nm in both the free-base (634 nm, ε = 14600) and in its protonated state (721 nm, ε = 20600).

Several attempts to produce triazole **9**, which was an important precursor for the synthesis of both the diaza and tetraazaporphyrins (**1** and **3**, respectivly), were not successful. Condensations of several triazoles with a verity of functionalized pyrroles resulted in either recovery of starting materials or an intractable mixture. The unreactive nature of the triazoles benzylic carbons towards nucleophilic attack with pyrrolic reagents might have been the major cause for the condensation reactions not to occur. Any future work on the synthesis of tetraazaporphyrin **3** should attempt to increase the reactivity at the triazoles benzylic carbon.

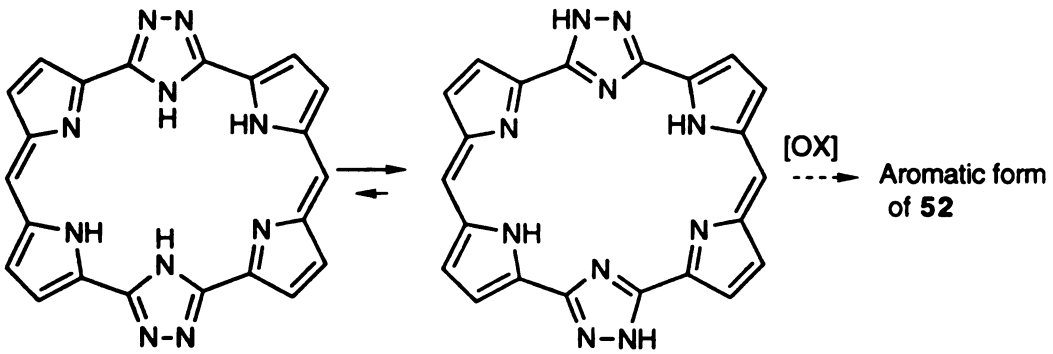
Any future work on this diazoporphyrin should focus on its potential as a sensitizers in PDT.

C. Progress Towards the Synthesis Tetraazaamethyrin

1. Retro Synthetic Analysis of Tetraazaamethyrin, **52**

The second triazole containing macrocycle studied was the tetraazaamethyrin **1** (Figure 11). As stated, Figure 11 shows the three possible oxidation states of the triazole containing amethyrin. Assuming that this macrocycle could form, further questions arise as to which oxidation state would be favored. The aromatic 22 and the 26 π-electron systems are expected to be preferred over the nonaromatic 24 π-electron system. After numerous attempts, Sessler could only get the nonaromatic form of amethyrin (Figure 10). If the synthesis of tetraamenthyrin favors the nonaromatic form, with a triazole unit incorporated into this macrocycle, there is the possibility that a tautomeric form of 24 π-electron version could be further oxidize to an aromatic form (Scheme 31). Based upon MM2 molecular modeling studies of tetraazaamethyrin **52**, the 26 π-electron form has the lowest energy of the three and is essentially planar. The space filling top view and side view models of **52** are shown in Figure 26. Core dimensions were estimated to be about 5.06 Å from top to bottom and 5.34 Å wide.

Scheme 31. Tautomeric Form of **52** that may Oxidize to an Aromatic Form



24 π-electron system

tautomeric form of the 24 π-electron system

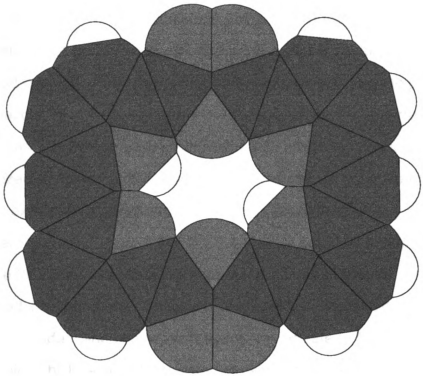


Figure 26. The Three Dimensional and Space-Filling Views and The Calculated Lowest Energy Core Size of **1**

Retrosynthetic analysis of **52** shows that there are three important precursors that could lead to a successful synthesis (Figure 27). The formyl dipyrryl triazole **54** and the diformyl dipyrryl triazole **55** could both be synthesized from **53**. Referring to Figure 9, there are two ways to produce the dipyrryl triazole **53**. Method **A** would involve the addition of a pyrrole to a functionalized 1,2,4-triazole whereas method **B** entails the condensation of two functionalized pyrroles. Method **B** was the route chosen because of the numerous examples of functionalized pyrroles available.[47]

There are several ways that a 1,2,4-triazole could be incorporated into **53**. Figure 28 outlines some of the common methods of triazole synthesis.[48] One method involves the condensation of a carboxylic acid derivative (esters, hydrazides, amides, and nitriles) with hydrazine hydrate to form the 4- amino-1,2,4-triazole, which is then deaminated to give the 1,2,4-triazole. The other involves the condensation of an amide or a nitrile with a hydrazine hydrate to directly produce a 1,2,4-triazole. The are other less common, more complex methods that will be described later.

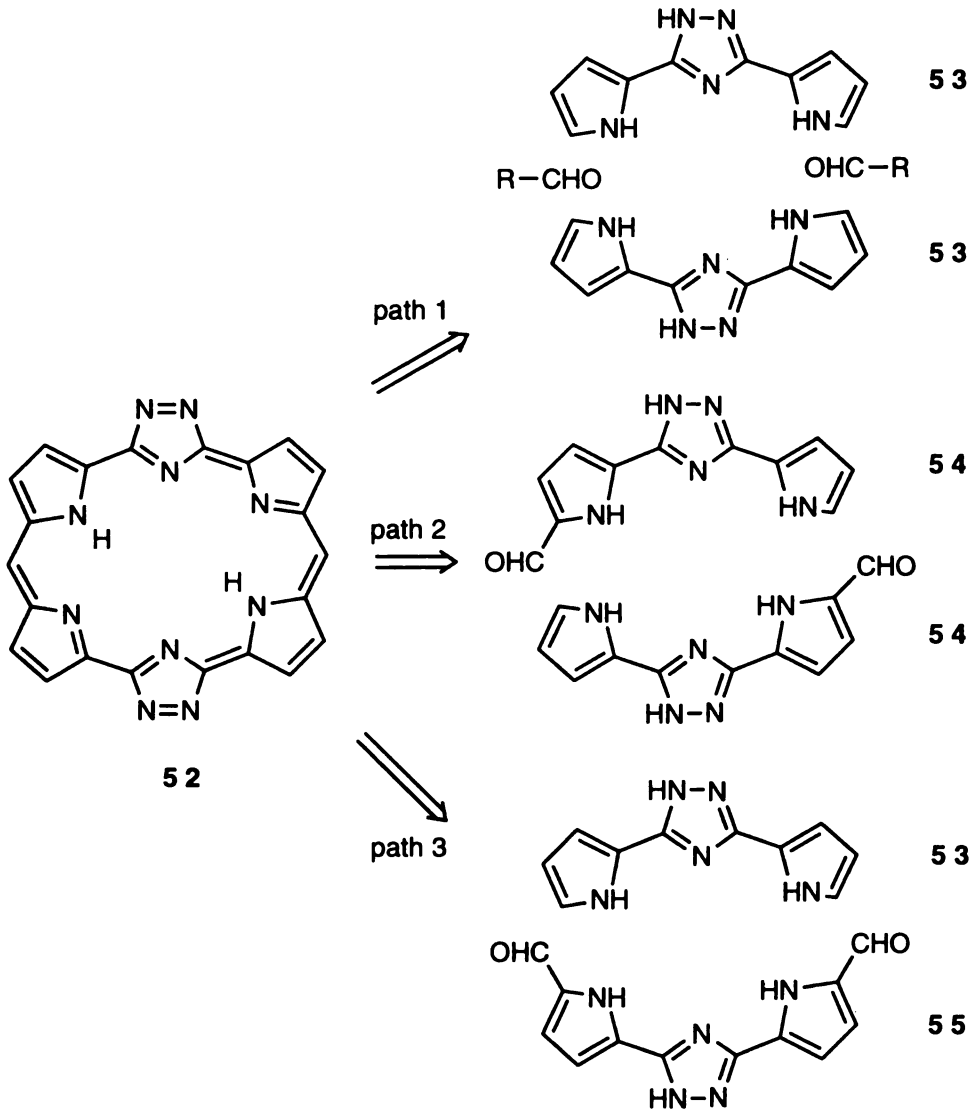


Figure 27. Retrosynthetic Analysis of Tetraazaamethyrin **52**

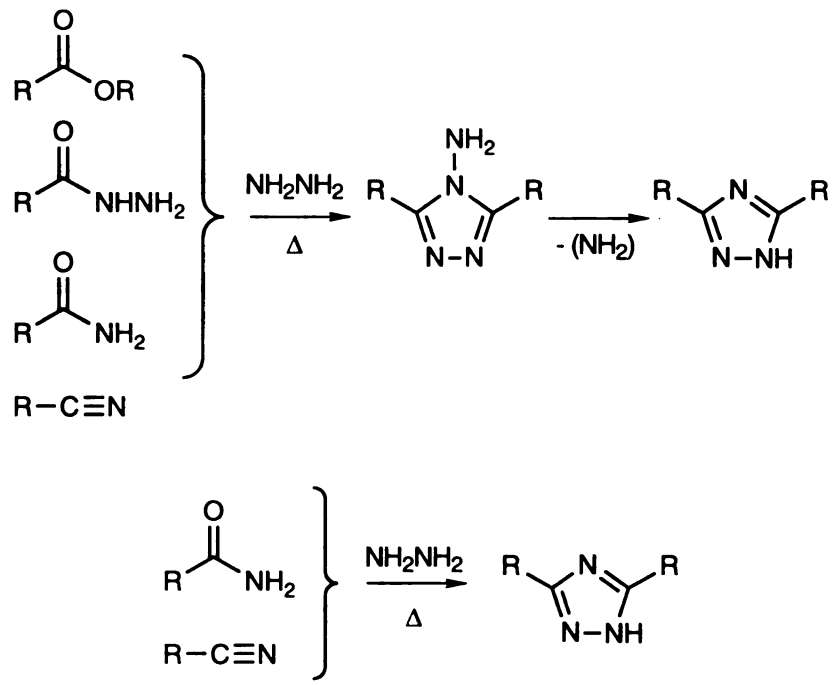


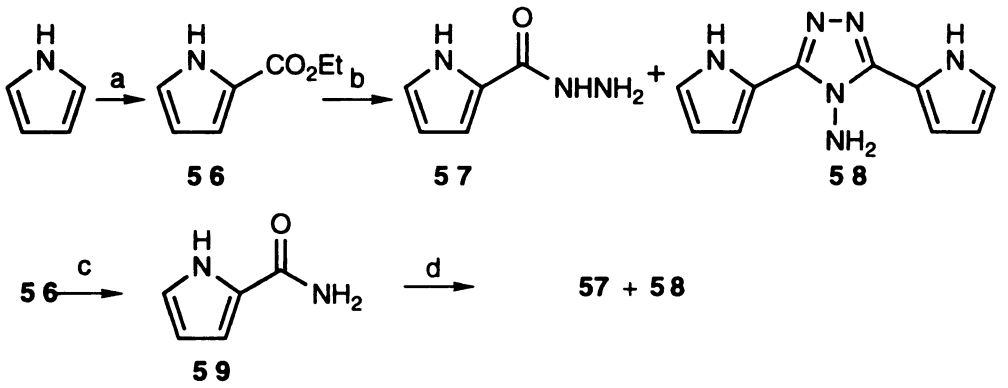
Figure 28 Common Methods of Producing a 1,2,4-Triazoles

2. Progress Towards the Synthesis of Tetraazaamethyrin, **52**

Initial attempts at synthesizing **1** involved the condensation of two functionalized pyrroles with hydrazine hydrate to yield the 4-amino-dipyrryl triazole. Heating ethyl 2-pyrrolecarboxylate **56**[49] in a sealed tube with hydrazine hydrate at 150° C, produced only hydrazide **57**[50] (~78% yield, Scheme 32). Increasing the temperature to 200° C still resulted in hydrazide **57** as the major product. However, a small amount of the amino triazole **58** was detected in the mass spectrum analysis of **57** In hopes of producing compound **58** pyrryl hydrazide **57** was heated with hydrazine hydrate at 200° C. As before, only a small amount of the amino triazole **58** was seen. It was then determined that a different precursor would be necessary for the successful synthesis of **58**. These reaction conditions also proved

unsuccessful for other precursors as well. Heating amide **59**[51], which was prepared by heating ester **56** in a saturated ammonium chloride solution, with hydrazine hydrate under the above conditions again gave hydrazide **57** as the major product (Scheme 32).

Scheme 32. Condensation of Ethyl 2- Pyrrolecarboxylate **57** and 2-pyrrolecarboxamide **59** with Hydrazine Hydrate

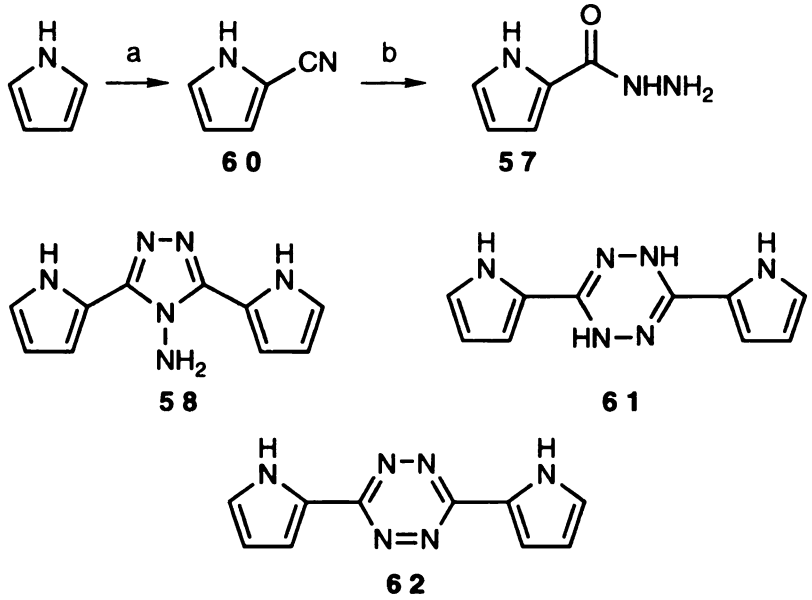


a: 1) BrMgEt, 2) $CO(OEt)_2$; b: NH_2NH_2, sealed tube c: NH_4Cl

When the pyrryl nitrile **60** was heated with excess hydrazine hydrate in a sealed tube, at 200° C, four products were formed (Scheme 33). The major product was the dipyrryl tetrazine **62**. A small amount of the amino triazole **58** and the hydrazide **57** were also detected. This tetrazine **62** was an insoluble brick red solid that had a very high melting point (>300 C). A similar product distribution was reported[52] when 2-cyanofuran was heated with excess hydrazine hydrate, with the di(furan-2-yl) tetrazine being the major product. Nitrile **60** was then heated with one equivalent of hydrazine hydrate which resulted in the formation of hydrazide **62** (Scheme 34). Heating **63** in a sealed tube at 200° C with and without an acid catalyst, failed to produce the triazole ring . Refluxing **63** in a concentrated solution of zinc chloride in water also failed to give the desired triazole **53**. When **63** was heated with hydrazine

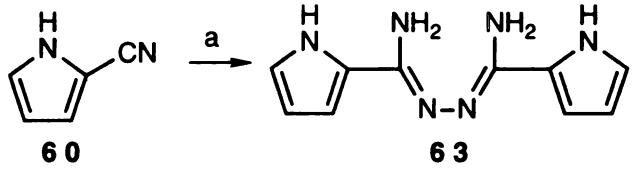
hydrate, tetrazine **62** was produced. It became apparent that another method was needed to synthesize **53** because of the difficulty in controlling the amount of hydrazine hydrate used to obtain pure and acceptable quantities of the desired triazole **58**.

Scheme 33 Reaction of 2-Cyanopyrrole with Excess Hydrazine Hydrate



a: 1) BrMgEt, 2) EtSCN or CSI DMF;
b: NH_2NH_2, sealed tube

Scheme 34. Reaction of 2-Cyanopyrrole with One Equivalent of Hydrazine Hydrate

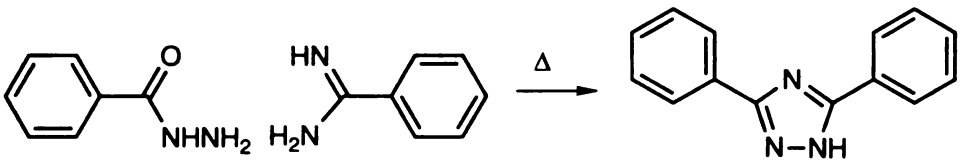


a: 1 eq. NH_2NH_2, sealed tube

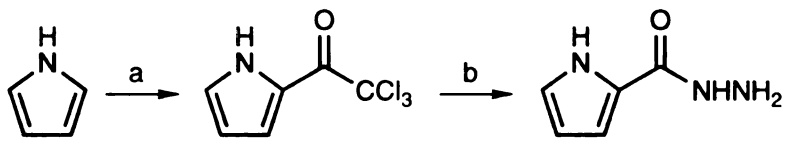
Another route to synthesize substituted 1,2,4-triazoles, which bypasses the need to control the amount of hydrazine hydrate, was reported by Anisworth

and Jones.[53] Their synthesis involved the condensation of an amidine and a hydrazide to produce a triazole (Scheme 35). To utilize this methodology, we required gram quantities of compound **57** and the amidine of compound **60**. Hydrazide **57** can be obtained by the condensation of the ester **56** with hydrazine hydrate. However, **56** proved time consuming to synthesize. An alternative method was used to make large quantities of hydrazide **57**. Pyrrole was reacted with trichloroacetyl chloride to form the trichloromethyl 2-pyrrole ketone **64**. This ketone was dissolved in ether and hydrazine hydrate was added dropwise to this homogenous solution which caused hydrazide **57** to precipitate out of solution in good yield (Scheme 36).

Scheme 35. Anisworth - Jones Triazole Condensation



Scheme 36. Synthesis of 2-pyrrolecarboxylic Acid Hydrazide **57**

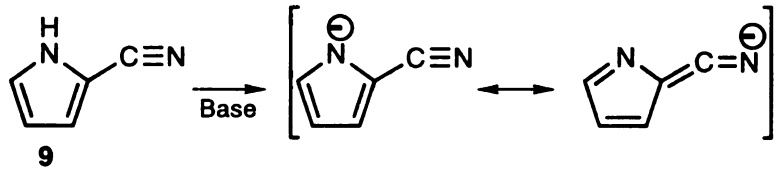


64 **57**

a: Cl_3CCOCl; b: $NH_2NH_2 \cdot H_2O$

The amidine of compound **60** proved more challenging to produce. There are a several ways to produce amidines. One involves the nucleophilic attack on a nitrile with sodium amide. This approach was unsuccessful when applied to **60** and resulted in the recovery of starting material. The recovery of the starting material is caused in part by the acidic N-H proton. When this

proton is abstracted it generates a negatively charged pyrrole compound which inhibits the attack of sodium amide on the nitrile. Figure 29 shows the resonance contributors to **60**'s anion. Garigipati designed a convenient method for the direct, one step, conversion of a nitrile to an amidine.[54] This method employed the Weinreb's methylchloroaluminum amide to convert carboxylic esters into carboxamides in one step.[55] However, when nitrile **60** was subjected to methylchloroaluminum amide only a small amount of the amidine was isolated. This low yield can be attributed to the acidic proton that **60** possess.

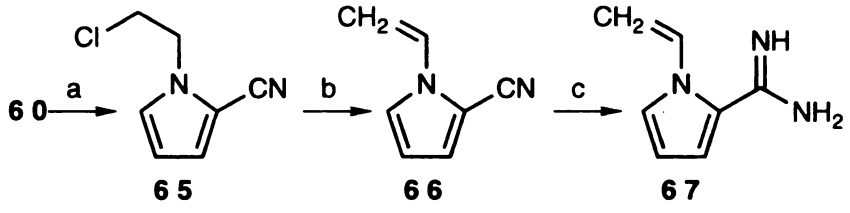


9

Figure 29. Anion **60**'s Resonance Contributors

It was determined that a protected version of **60** was needed to remove the acidic proton from the system. Several protecting groups were considered and due to the reaction conditions, this protecting group would have to survive a strong basic environment and could be removed with out decomposing the desired product. The vinyl protecting group was chosen to protect **60** because of its ease of introduction and when it's removed the acidic conditions required should not react adversly to to the remaining triazole. Compound **60** was reacted with sodium hydride followed by 1,2-dichloroethane to yield 1-(2-chloroethyl)-2-cyanopyrrole, **65** (Scheme 37). This protected nitrile was again treated with sodium hydride to produce the elimination product, 1-vinyl-2-cyanopyrrole, **65**. This vinyl protected nitrile was then treated with methylchloroaluminum amide to afford the amidine **67** , abeit in low yield.

Scheme 37. Protection of 2-Cyanopyrrole **60** and the Formation of it's Amidine **67**



a: 1) NaH, 2) $ClCH_2CH_2Cl$; b: NaH; c: $MeAl(Cl)NH_2$

Amidine **67** and the hydrazide **57** were heated together in an attempt to produce a substituted triazole as described by Anisworth and Jones. This was unsuccessful and only the hydrazide **57** was recovered.

A modified version of this condensation was reported using the amidate ester in the place of the amidine.[56] This strategy requires the amidate ester of the nitrile **60**. Hydrochloric acid was bubbled through a solution of nitrile **60** in anhydrous ethanol for fifteen minutes and left to react in an attempt to produce the required amidate ester. However, after 48 hours the nitrile **60** was recovered quantitatively. Nitrile **60** was unreactive to acid catalyzed amidine esterification due to the low basicity of the nitriles and the pyrrole nitrogen's resonance ability to stabilize the protonated nitrile (Figure 30).

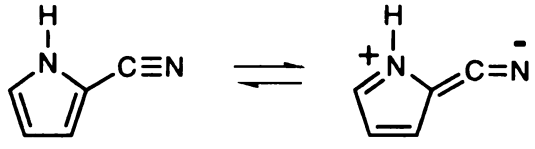
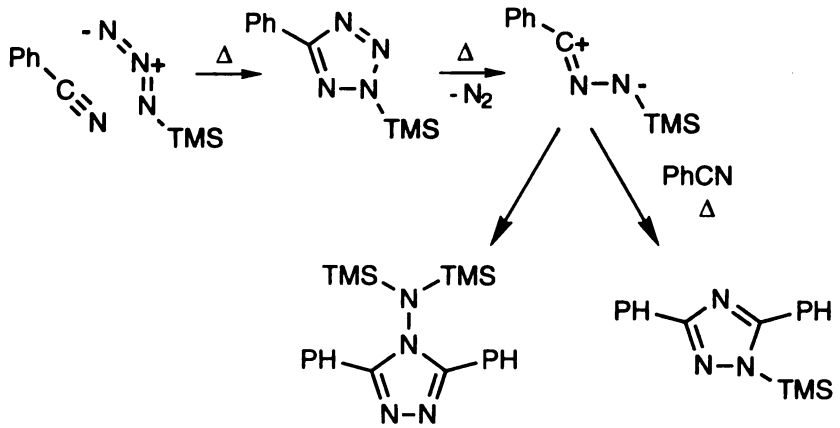


Figure 30. The Resonance Contributors to the Stability of 2-Cyanopyrrole **60**

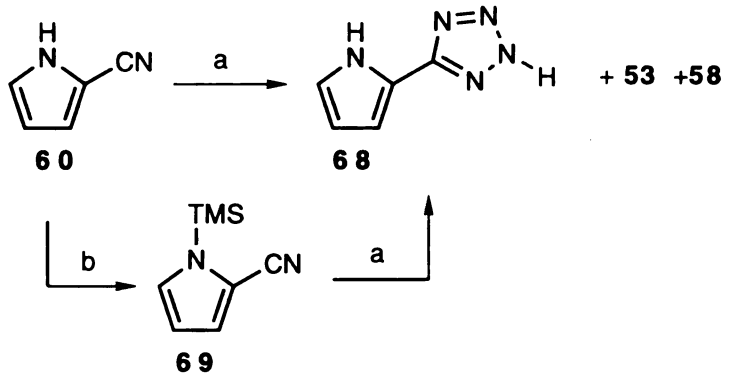
Rühlmann developed a more efficient method to synthesize triazoles and amino triazoles by reacting a nitrile with trimethylsilylazide[57] (Scheme 38). The first species produced is the trimethylsilyl tetrazole. Heating this tetrazole

further eliminates nitrogen (N_2) and forms a very reactive trimethylsilyl diazo intermediate. This intermediate can dimerize to form the N,N-ditrimethylsilyl -4-amino-disubstituted 1,2,4-triazole or it can be condensed with another nitrile to give a disubstituted 1,2,4-triazole. Nitrile **60** was heated in a sealed tube with trimethylsilylazide, which resulted in a mixture of products (Scheme 39). The major product was the pyrryl tetrazole **68.** Triazole **2** and the amino triazole **58** were only detected in trace amounts by mass spectrometry. Also, there was no signs of the trimethylsilyl groups surviving the reaction. The reaction was repeated at a lower temperature and the major product again was the tetrazole **68.** As before, the trimethylsilyl group did not survive. Due the insoluibility of this tetrazole, methanol was required to isolate the product and this process caused the removal of the trimethylsilyl groups.

Scheme 38. Rühlmann Triazole Reaction



Scheme 39. Rühlmann Triazole Reaction With 2-Cyanopyrrole **60**



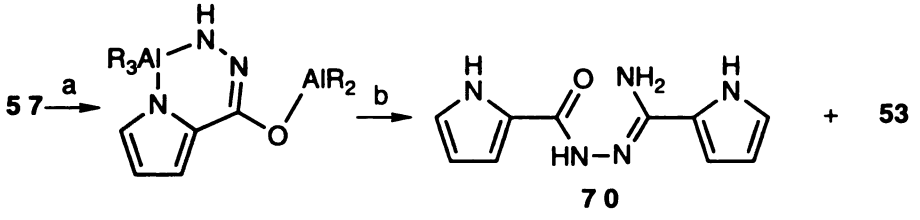
a: $TMSN_3$, Δ b: $(TMS)_2NH$

In an attempt to increase the solubility of the products of the reaction described in Scheme 39, nitrile **60** was refluxed in hexamethyl-disilazane to give the 1-trimethylsilyl-2-cyanopyrrole **69**. This protected nitrile **69** was reacted in a sealed tube with trimethylsilylazide. Unfortunately, the solubility of the product was not improved and the tetrazole **68** was again produced as the major product. The protected triazole **65** was also subjected to the same conditions, but none of the expected products were detected. A more effective route to triazole production was required

The Kauffmann[46] triazole synthesis (Scheme 28), was employed on **57** and **60**. Hydrazide **57** was treated with trimethylaluminun in dry toluene and allowed to react until the liberation of methane subsided. Nitrile **60** was added to this solution and allowed to react for 6 hours at room temperature. The reaction mixture was then carefully quenched with ice and the resulting solid was filtered and washed with hot ethyl acetate to yield the acyl amidrazone **70**, as the only isolated product (Scheme 40). The reaction was repeated in the same manner except that after the addition of the nitrile the reaction mixture was heated at 80° C for 5 hours before quenching. This resulted in the detection of

a small amount of dipyrryltriazole **53** in the reaction mixtures by mass spectrometry. These results were promising and it was decided to further increase the reaction temperature. After the introduction of nitrile **60** to the reaction mixture, the solution was allowed to reflux for 10 hours. These conditions resulted in a small amount (10 mg) of **53** being isolated after column chromatography. The H-NMR spectrum of **53** was ambiguous due to the tautomeric nature of the triazole but the mass spectrum showed the correct mass for the expected structure. This dipyrryl triazole **53** was very insoluble in common organic solvents but soluble in methanol and ethanol. However, when this dipyrryl triazole is dissolved to alcohols it turns black and is unrecoverable from the alcohol solution. These conditions were successful in producing the dipyrryl triazole **53** in small quantities, but the insolubility of this heterocycle hindered its isolation.

Scheme 40 Kauffmann Triazole Reaction with the **57** and **60**



70

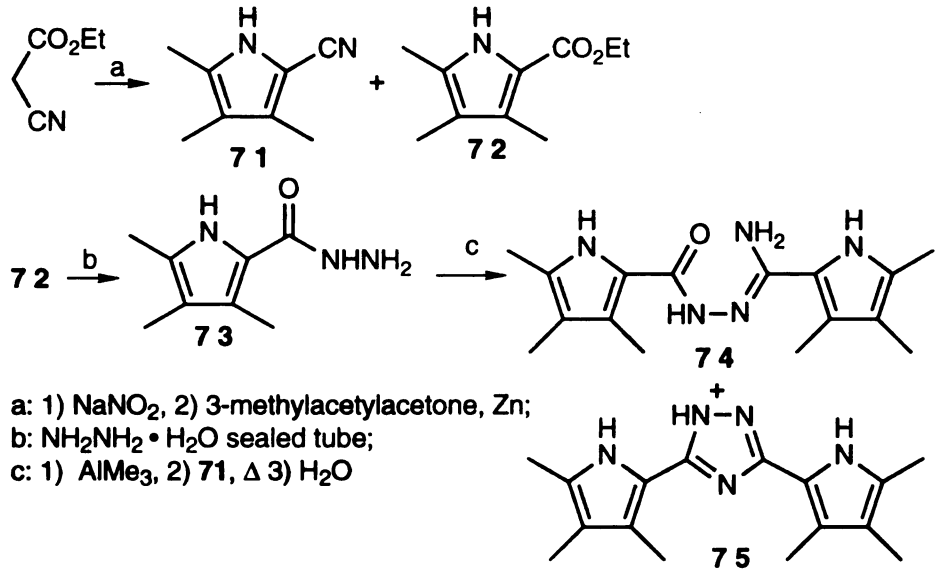
a: $AlMe_3$, b: 1) **60**, Δ; 2) H_2O

It has been reported in this laboratory that terpyrroles[58] and systems that closely resemble them,[59] have very low solubility in organic solvents. To increase the solubility and possibly improve the overall yield of the formation of these dipyrryl triazoles, alkylated versions of the nitrile **60** and the hydrazide **57**were employed. The 3,4,5-trimethyl-2-cyanopyrrole **71** and ethyl 3,4,5-trimethyl-2-pyrrolecarboxylate **72** were both synthesized from the condensation

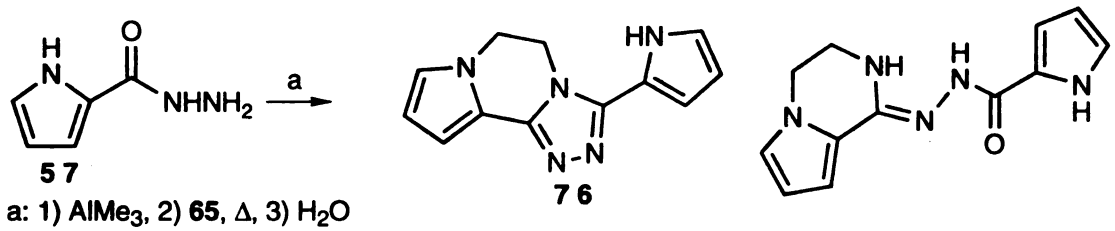
of the oxime of ethyl cyanoacetate and 3-methylacetoacetate, using Knorr conditions as shown in Scheme 41.[60] Hydrazide **73** was produced by reacting ester **72** with hydrazine hydrate in a sealed tube at 150° C. This hydrazide was treated with trimethylaluminum, nitrile **71** was introduced into the reaction mixture and the solution was refluxed for 10 hours. A small amount of the acyl amidrazone **74** was produced along with a 70 % recovery of the starting hydrazide **73**. When the hydrazide to nitrile ratio was increased to four molar equivalents of the hydrazide to each equivalent of nitrile (4:1 ratio), the yield of the acyl amidrazone **74** was increased and a small quantity of the triazole **75** was detected by mass spectrometry. Attempts to condense this acyl amidrazone **74** by heating it in a sealed tube failed to produce the triazole **75**. Refluxing the acyl amidrazone in concentrated aqueous zinc chloride also failed to give the triazole **75**. Since the trimethylaluminum hydrazide intermediate is slightly basic, the acidic proton on the nitriles **60** and **71** may inhibit coupling and thus reduce the yield.

Reacting the hydrazide **57** with trimethylaluminum followed by the addition of the protected nitrile **65** gave an acyl amidrazone and the triazole, as shown in Scheme 42. This triazole method proved unsuccessful in the formation of the desired dipyrryl triazoles. However, another route was reported to be more successful in the production of 3,5-disubstituted 1,2,4-triazoles. This method developed by Potts, involves the ρ-toluenesulfonic acid (PTSA) catalyzed condensation of a hydrazide and a nitrile (Scheme 43).[61]

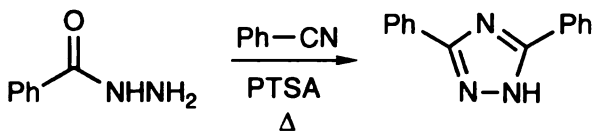
Scheme 41. Synthesis of 3,4,5-Trimethyl-2-pyrrole carboxylic acid hydrazide **73** and its Kauffmann Triazole Reaction with 3,4,5-Trimethyl-2-cyanopyrrole **71**



Scheme 42. Kauffmann Triazole Reaction With **57** and **65**



Scheme 43. Potts Triazole Synthesis

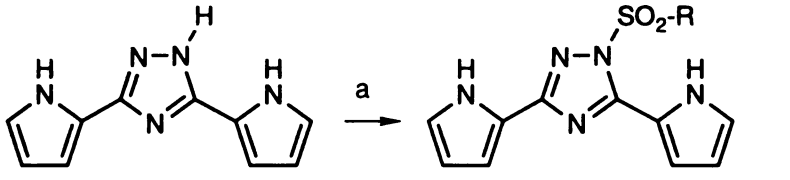


The Potts method was carried out using hydrazide **57** and nitrile **60** First hydrazide **57** was dissolved in warm ethanol and one molar equivalent of PTSA was added and the solvent was evaporated to give the PTSA-hydrazide salt of **57**. This hydrazide salt was added to the nitrile **60** and heated under

nitrogen at 200° C for 2 hours. The cooled reaction melt was extracted with 10% sodium hydroxide and the resulting homogenous solution was neutralized with concentrated hydrochloric acid. The triazole precipitated out of solution and was collected to give the bis-3,5-(2-pyrryl)-1,2,4-triazole **53** in 15% yield. The mass spectrum was consistent with the proposed structure of **53** (M^+ = 199) and the ^{1}H-NMR spectrum revealed that the triazole was isolated as the PTSA salt.

An attempt to make the benzenesulfonate derivative of **53** using phase transfer conditions failed. The reason for this failure could be due to the stability of the deprotonated triazole. The benzenesulfonate was successfully produced by treating **53** with benzenesulfonyl chloride and triethylamine (TEA), in acetonitrile for 48 hours as shown in Scheme 44. This benzenesulfonyl triazole **77** gave a complex mixture of aromatic proton signals in the ^{1}H-NMR spectrum. The benzene proton signals were found to overlap with the pyrrole hydrogens signals, which made peak interpretation difficult. However the ^{13}C-NMR spectrum revealed the proper number of carbons. The tosylated triazole **78** was produced in the same manner as **77** (Scheme 44). The tosylated triazole **78** gave a clear ^{1}H-NMR spectrum where the two aromatic doublets from the tosyl group did not overlap with the pyrrole hydrogens. The ^{13}C-NMR spectrum was also consistent with structure **78**.

Scheme 44. Arylsulfonation of Bis-3,5-(2-pyrryl)-1,2,4-triazole **53**



53

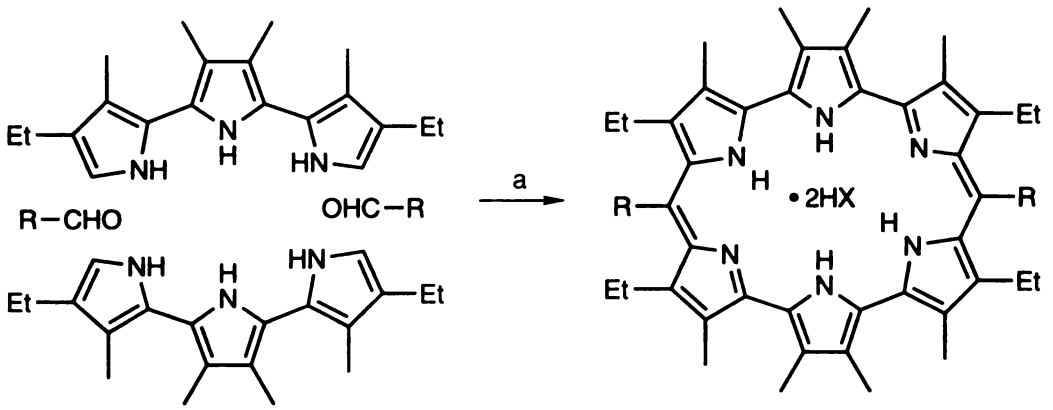
77, R = Ph
78, R = $C_6H_4CH_3$

a: TEA, R-SO_2Cl

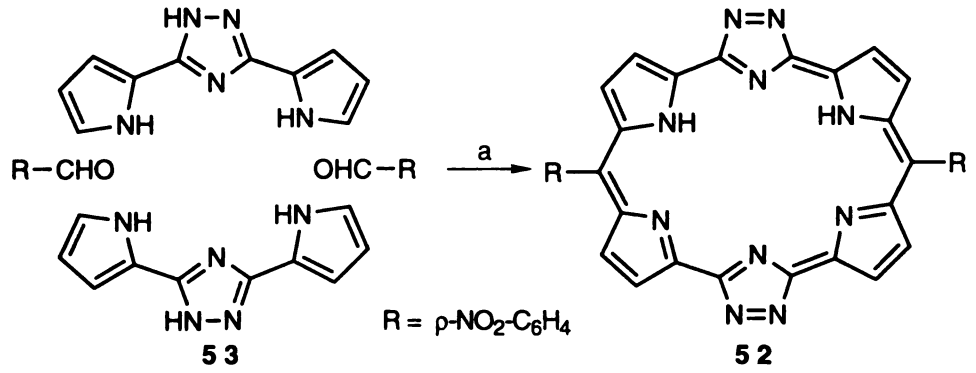
The dipyrryl triazole **53** is one of the possible precursors of the tetraazaamethyrin **52** as shown in path 1 of Figure 27. This pathway resembled Sessler's cyclization of amethyrin which is displayed in Scheme 45. This cyclization method was employed on the dipyrryl triazole **53**. A mixture of **53** and ρ-nitrobenzaldehyde was dissolved in methylene chloride (with 10% methanol) and a catalytic amount of TFA was added and stirred for four hours. After oxidation no macrocyclic products were detected by TLC or by its UV/Vis spectrum. The same reaction was repeated and allowed to react for seven days and the same results occurred after oxidation. Changing the reaction solvent to a 75:25 methylene chloride / ethanol mixture and refluxing the solution for several days, there were no trace of macrocyclic products formed within ten days (Scheme 46). However, after two weeks interesting products were isolated after column chromatography. One of these products was a dark green solid with interesting UV-vis properties. It showed an absorption at 397.0 nm and several smaller absorptions at 497.0 nm, 530.5 nm, 566.0 nm and 619.0 nm. Analysis by mass spectrometry revealed that the mass is consistent with the 22 π-electron macrocycle after the loss of nitrogen (N_2). One of the characteristic mass signals of a compound which possess a 1,2,4-triazole is the one associated with the loss of nitrogen. The ^{1}H-NMR spectrum of this compound seemed unclear on which oxidation state this macorcycle occupies. There was a broad peak at -2.4 ppm and a peak that is at 10.1 ppm. The broad peak at -2.4 ppm indicates the possibility of an aromatic molecule. However the peak that shows up at 10.1 ppm indicates that this compound is nonaromatic. This type of macrocycle seems to have a low solubility. When it was isolated from an alumina chromatography column, it had to be removed by flushing the column with ethyl acetate with 10% methanol. There could be the reason that

there is two oxidation states of the same compound. Changing the aldehyde in this reaction from ρ-nitrobenzaldehyde to benzaldehyde or formaldehyde did not produce similar results.

Scheme 45. Sessler's Cyclization of Amethyrin



Scheme 46. Condensation of **53** with ρ-Nitrobenzaldehyde

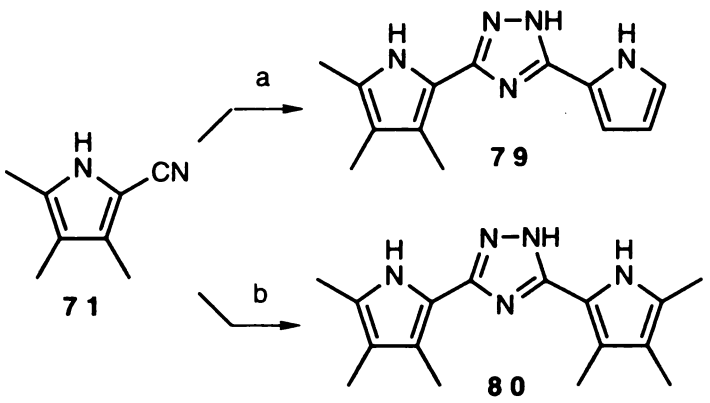


The initial attempt to formylate the bispyrryl triazole **53** with $POCl_3$ and N,N-dimethylformamide, created an intractable oil. The need for a dipyrryl triazole that would lead to a macrocyclic product that is more soluible and has the nessessary functional groups in the alpha positions that can be converted to

formyl groups. The first was attempted by the condensation of the PTSA salt of **57** and the 3,4,5-trimethyl-2-cyanopyrrole **71** at 250° C for four hours. Unsymmetrical dipyrryl triazole **79** was isolated in 33% yield (Scheme 47). This reaction required a higher temperature and a longer reaction time to produce this new triazole. The PTSA salt of the hydrazide **73** was also condensed with the nitrile **71**, to produce the dipyrryl triazole **80** in 30% yield. This triazole required a temperature of 300-320° C for the condensation to occur. Temperatures between 200-280° C produced only a trace of the desired triazole with recovered **57**. The black viscous reaction melt of **80** could not be extracted with 10% sodium hydroxide. The reaction melt was first dissolved in THF then the 10% sodium hydroxide solution was added. The THF was removed under reduced pressure and this heterogeneous aqueous solution was cooled in an ice bath and the insoluble solids were removed by vacuum filtration and the remaining homogenous solution was acidified with concentrated hydrochloric acid until the pH was slightly acidic (~pH 6) to produce **80** (30% yield). With the alpha positions occupied by methyl groups, **80** was not suitable for a Sessler type condensation to produce an expanded porphyrin.

In an attempt to transform **80** into an usable precursor, the methyls in the alpha positions needed to be modified. The triazole **80** was subjected to sulfuryl chloride (SO_2Cl_2) in an attempt to oxidize the alpha methyl groups of the pyrroles to carboxylic acids. There was no detectable dicarboxylic acid of the dipyrryl triazole nor was there any **80** recovered. The mass spectrum of the reaction products did not show any mass above 200, which may mean a ring opening reaction could have occurred during the sulfuryl chloride treatment. Attempted oxidation with lead tetraacetate also failed to produce the acetoxy product.

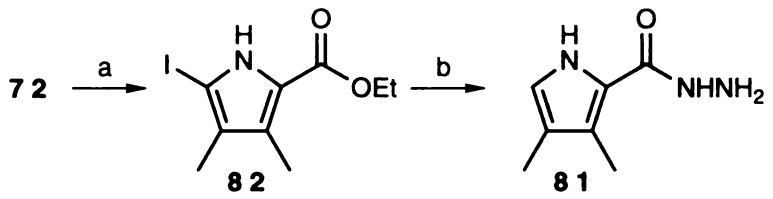
Scheme 47. Synthesis of Dipyrryl Triazoles **79** and **80**



a: PTSA, **57**, Δ; b: PTSA, **73**, Δ

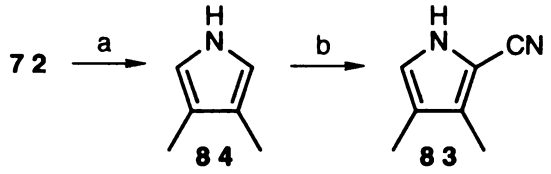
Since the hexamethyl dipyrryl triazole **80** could not be transformed into the diformyl analog, a dipyrryl triazole with the alpha positions free was needed. This required the 3,4-dimethyl-2-pyrrole carboxylic acid hydrazide **81** and the 3,4-dimethyl-2-cyanopyrrole for use in the Potts triazole reaction. Hydrazide **81** was produced by oxidizing the ester **21** with sulfuryl chloride followed by treatment with iodine and potassium iodide to give the ethyl 5-iodo-3,4-dimethyl-2-pyrrolecarboxylate[52] **82** . This iodo pyrrole **82** was heated in a sealed tube with excess hydrazine hydrate at 150° C for eight hours to convert the ethyl ester to a hydrazide and reduce off the iodine to produce the 3,4-dimethyl-2-pyrrole carboxylic acid hydrazide **30** in 96% yield (Scheme 48). Next, the 3,4-dimethyl-2-cyanopyrrole **83** was produced by taking ester **72** and transforming it into 3,4-dimethylpyrrole **84**. Compound **84** was treated with chlorosulfonylisocyanoate to produce the desired nitrile **83** (Scheme 49).

Scheme 48. Synthesis of 3,4-Dimethyl-2-pyrrolecarboxylic acid hydrazide **81**



a: 1) SO_2Cl_2, 2) H_2O/acetone, 3) KI, I_2 Na HCO_3
b: $NH_2NH_2 \bullet H_2O$

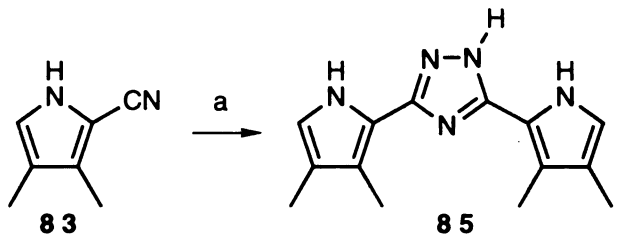
Scheme 49. Synthesis of 3,4-Dimethyl-2-cyanopyrrole **83**



a: 1) SO_2Cl_2, 2) H_2O/acetone,
3) NaOH, 4) NaOAc / KOAc
b: CSI

The PTSA salt of the hydrazide **81** and the nitrile **83** were heated at 320° C for four hours and cooled, Scheme 50. These reactions conditions yielded the dipyrryl triazole **85** in less them 1% yield. Dipyrryl triazole **85** was isolated in the same manner as **80**. The reaction temperature was raised to 380 - 410° C but, the yield increased to only 3%. The mass spectrum gave the correct mass (M^+ = 255) and the ^1H and ^{13}C NMR's were also consistent with the structure of the dipyrryl triazole **85**. This triazole could now be used in a Sessler type cyclization.

Scheme 50 Synthesis of Bis-3,5-(3,4-dimethyl-2-pyrryl)-1,2,4-triazole **85**

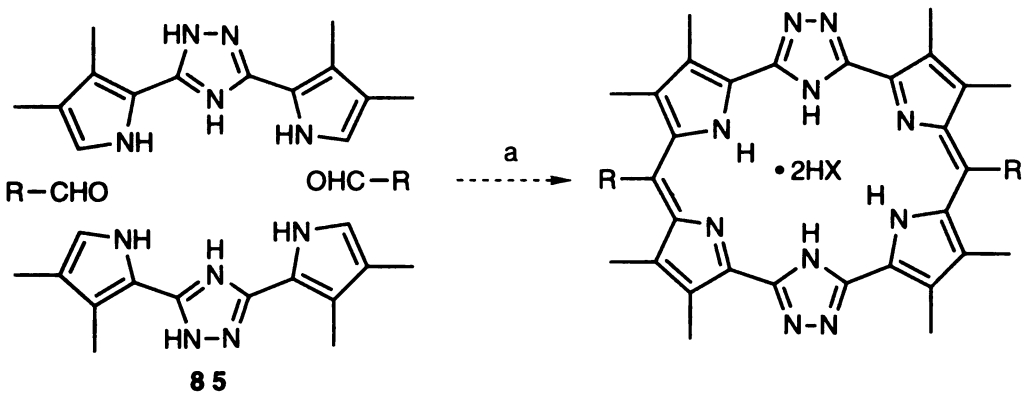


83 **85**

a: PTSA, **81**, Δ

The cyclization of **34** with benzaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, and formaldehyde was attempted using the same conditions as **53** in Scheme 46. However, in all cases there was no evidence of any cyclized products (Scheme 51). There was partial recovery of the dipyrryl triazole **85** in every instance. The unreactivity could be due to the basicity of the triazole portion of **85.** This could be forming a salt in the acidic media that would inhibit the addition of the aldehyde on the pyrrole portion of **85**.

Scheme 51. Attempted Cyclization of the dipyrryl triazole **85**

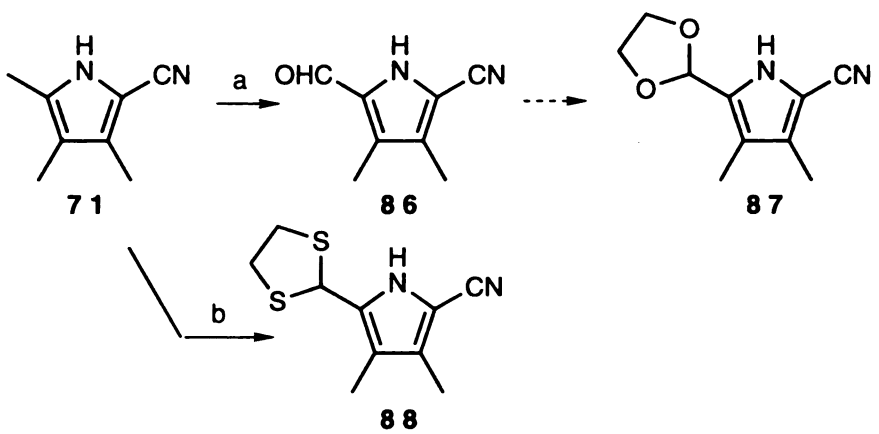


85

a: 1) TFA / R-CHO 2) DDQ

One way to possibly promote the cyclization to tetraazaamethyrin **52**, would be to produce the monoformyl substituted dipyrryl triazole version of **54** (path 2 from Figure 27). The two ways to accomplish this would be to functionalize a nitrile with a suitable group that would produce the desired monoformyl dipyrrole triazole when condensed with the PTSA salt of **81** or to monoformylate **85** using Vilsmeier conditions . The first attempt was to produce a nitrile that could be condensed with **81**. Oxidation of nitrile **71** with SO_2Cl_2 gave aldehyde **86** (Scheme 52). Since the aldehyde was susceptible to attack from the hydrazide, it needed to be protected. The first attempt at protection was to treat **86** with ethylene glycol and sulfuric acid to give the acetal **87**. However, the acetal **87** was isolated as an unstable oil which quickly hydrolyzed from the moisture in the air back to the aldehyde **86**. This was unsuitable because the acetal would hydrolyze by the water generated in the triazole condensation reaction. The thioacetal was then chosen because it was more stable then the acetal. This thioacetal **88** was easily produced from the treatment of **71** with two molar equivalents of SO_2Cl_2 to give the intermediate dichloromethyl pyrrole. This intermediate was then reacted with ethylene dithiol and a catalytic amount of HCl to yield the thioacetal **88** in 71% yield (Scheme 52).

Scheme 52. Synthesis of the Thioacetal **88**

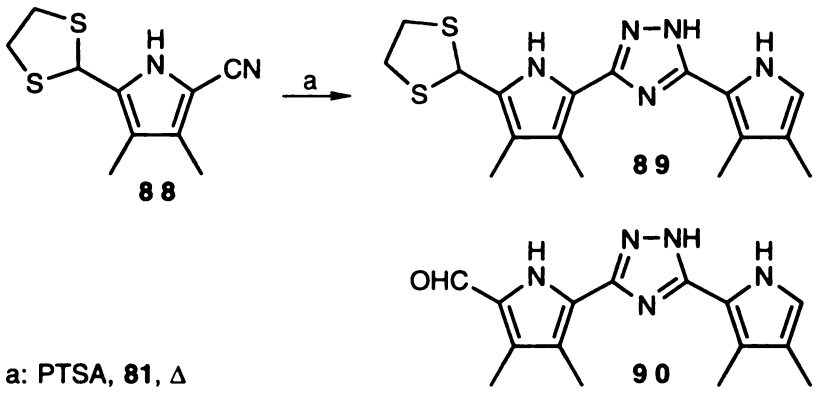


a: 1) SO_2Cl_2 ,2) H_2O; b:1) SO_2Cl_2 ,2) $HSCH_2CH_2SH$ / HCl

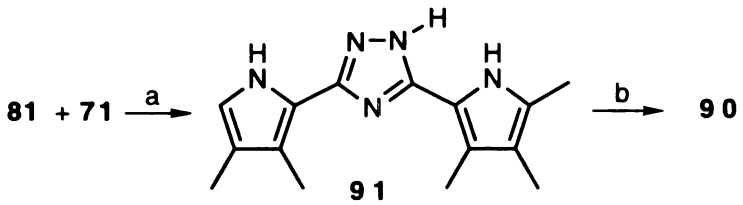
This thioacetal **88** was condensed with the PTSA salt of hydrazide **81** at 280 - 300° C for four hours but only yielded a trace amount of thioacetal dipyrryl triazole **89** (Scheme 53). When the temperature was increased to 380 - 400° C, a larger amount of the product was extracted from the reaction melt. The mass spectral analysis revealed the mass for both the thioacetal **89** and the aldehyde **90**. The ^{1}H-NMR spectrum was consistent with compound **89** as it showed a characteristic peak for the protected aldehyde but no peak for the aldehyde itself. It was speculated that the protecting was partially removed in the mass spectrometer. An attempt to remove the thioacetal protecting group with $HgCl_2$ and with boron trifloride etherate led to the destruction of most of triazole **89** with out producing **90.** This method of producing a formyl dipyrryl triazole was not a viable method due to the high reaction temperature and acidic work-up. A less destructive method was needed to produce the formylated triazole **90**. Another possible method to produce **90** is by oxidizing an alpha methyl group with ceric ammonium nitrate (CAN). The utility of CAN has been demonstrated in the conversion of alpha methyl to formyl groups in

pyrroles and dipyrrylmethanes.[62] Triazole **91**, which was produced by the condensation of **71** and **81** with PTSA, was subjectred to CAN and allowed to react at room temperature for three days and after work-up produced a detectable amount of **90** (Scheme 54). However, **90** was unable to be purified for further use.

Scheme 53. Potts Reaction With **88** and **81**



Scheme 54. Production of **90** by way of Ceric Ammonium Nitrate



Another method of producing the monoformylatied version of **85** is to subject **85** to Vilsmeier formylation conditions. Treating **85** with a ten to fifteen fold excess of Clezy's modified Vilsmeier reagent at room temperature, did not result in the desired formylated product (Figure 24).[63] The treatment of **85** with a 15 molar excess of the Vilsmeier-Haack reagent, followed by hydrolization with 10% sodium hydroxide to remove any triazole nitrogen formulations, also

failed to produce monoformylated product. However, it did give the diformylated triazole **92** in less then 2% (Scheme 55). The diformyl triazole was dissolved in methylene chloride (with 1% methanol) and reacted with **85** using a catalytic amount of triflouroacetic acid (Scheme 56). After 12 hours the reaction was oxidized, but mass spectral analysis of the reaction mixture failed to detect any of the desired macrocycle. Only unreacted starting materials were seen.

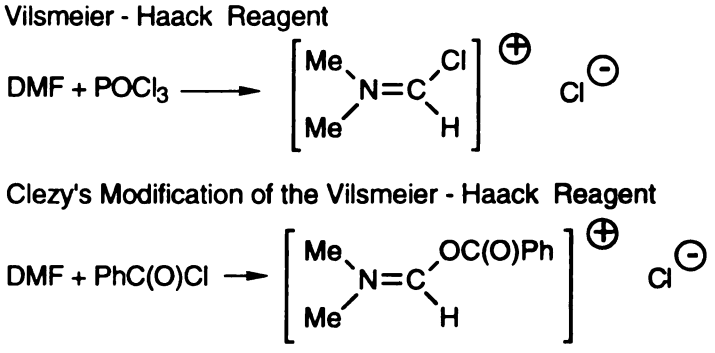
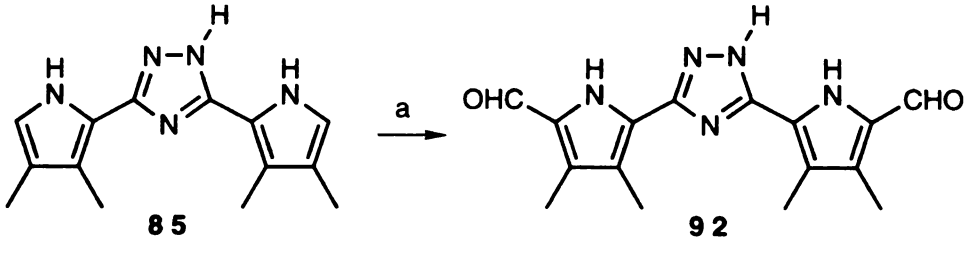


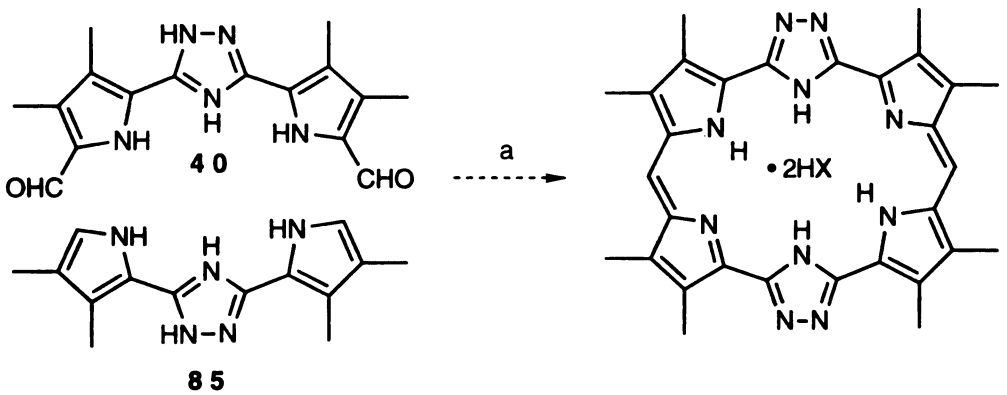
Figure 31. Vilsmeier - Haack Reagent and Clezy's Modified Vilsmeier Reagent

Scheme 55. Vilsmeier Formylation of **85**



a: 1) DMF / (15 eq) $POCl_3$; 2) NaOH; 3) HCl

Scheme 56. Attempted Cyclization of **92** and **85** using Sessler Conditions



a: 1) TFA 2) DDQ

3. Conclusions on the Attempts to Synthesize Tetraazaamethyrin **52**

A variety of bis(2-pyrryl)-1,2,4-triazoles have been synthesized, resulting in a series of new compounds that can be used in the creation of new class of expanded porphyrins that contain 1,2,4-triazole units. The use of these bis(2-pyrryl)-1,2,4-triazoles in cyclization reactions was limited by solubility and separability. Attempted synthesis of tetraazaamethyrin **52** led to the conclusion that the triazole portion of the dipyrryl triazole might have hindered the final cyclization step. Because of the possibility of protonating the triazole during the acidic reaction sequence, the nucleophilic nature of the pyrroles could have been inhibited. It was found that conditions strong enough to initiate cyclization only produced trace amounts that were detected by mass spectrometry.

Any future work on the synthesis of diazaamethyrin or tetraazaamethyrin should attempt to increase the solubility by the incorporation of different alkyl groups.

Chapter 3

EXPERIMENTAL

General: Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) were obtained using a Varian Gemini (300 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) using either the residual solvent proton resonance (chloroform, δ 7.24), or tetramethyl silane as internal standard (δ 0.00). ^{1}H-NMR data are reported as the chemical shift, chemical shift multiplicity (s for singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet) and number of hydrogens. ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectra were obtained using a Varian Gemini (75.4 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) using the residual solvent resonance as internal reference (chloroform, δ 77.0). Ultraviolet (UV) spectra were obtained using a Shimadzu UV-16 spectrometer. Electron impact mass spectra (EI-MS) were obtained using either a Finnegan 400 mass spectrometer or a VG Instruments Trio-1 mass spectrometer. Flash chromatography was performed according to the method of Still, Kahn, and Mitra.[64] Trimethylaluminum solutions, n-butyllithium solutions, anhydrous tetrahydrofuran, diethyl ether, dimethyl acetamide, and dimethyl formamide were purchased from the Aldrich Chemical Company, Milwaukee, WI and used as received. Dichloromethane and triethylamine were distilled from calcium hydride. Toluene was distilled from sodium-benzophenone ketyl. Ethanol was dried by distillation from magnesium. Chloroform was washed with water, predried with magnesium sulfate, and distilled from phosphorous pentoxide. All reactions were performed under an argon or nitrogen atmosphere unless otherwise mentioned.

3,5-Diformyl-1,2,4-1H-triazole 7:

3,5-Bis(dimethoxymethyl)-1H-1,2,4-triazole **15** (90 mg, 0.414 mmol) was stirred at room temperature in 1N H_2SO_4 (5 mL) for 3 days then neutralized with K_2CO_3 (5%). The water was evaporated under reduced pressure without heating. The residue was extracted with ethanol (100 mL) and filtered, the solvent was evaporated with out heating to give an oil (41 mg, 80%)[33] which was used in the next step with purification.

3,5-Di(hydroxymethyl)-1,2,4-triazole, 10:

4-Amino-3,5-(hydroxymethyl)-1,2,4-triazole (2.88 g, 0.02 mole) was dissolved in water (10 mL) and hydrochloric acid (10 mL of 12N) and cooled to 0° C. To this mixture sodium nitrite (1.93 g, 0.028 mole) in water (30mL) was slowly added keeping the reaction temperature below 10° C. After addition, the mixture was allowed to stir for 2 hours. The solution was neutralized with sodium bicarbonate to pH 7 and the solvent was evaporated over a steam bath. The crude triazole was recrystallized from acetonitrile to yield 1.23 g (48 %) of 3,5-(hydroxymethyl)-1,2,4-triazole, m.p. 142 - 143° C (lit.[65] mp145° C).

4-Amino-3,5-(hydroxymethyl)-1,2,4-triazole:

Glycolic acid (80 g, 1.05 mole) and hydrazine hydrate (100 g, 2.0 mole) were heated to 100° C for 6 hours. The temperature was allowed to rise to 165° C over a 3 hour period by distilling the excess hydrazine and water. The internal temperature was maintained at 165° C for 3 hours and then was allowed to rise by distillation to 190° C then removed from the heat. The crude triazole was recrystallized from water to give 45.4 g (63%) of 4-amino-3,5-(hydroxymethyl)-1,2,4-triazole, m.p. 206 - 209° C (lit.[66] mp 207 - 209°C).

3,5-Bis(dimethoxymethyl)-4-amino-1,2,4-triazole 13:

Methyl dimethoxyacetate (18 g, 0.135 mmol) was heated with hydrazine hydrate (20 mL) in a sealed tube at 250° C for 48 hr. The reaction mixture was cooled to room temperature and the 3,5-bis(dimethoxymethyl)-4-amino-1,2,4-triazole percipitated and was collected, 5.9 g, 38%, mp 67 - 69°C (lit.[33] mp 65 - 68°C).

3,5-Bis(dimethoxymethyl)-1H-1,2,4-triazole 15 :

A solution of 3,5-bis(dimethoxymethyl)-4-amino-1,2,4-triazole **13** (5.9 g, 0.025 mol) in 5 N HCl (20 mL) was cooled to 0°C. To this stirred solution, $NaNO_2$ (1.70 g, 0.024 mol) in H_2O (15 mL) was added dropwise keeping the temperature below 5° C. After the addition was complete, the mixture was stirred for 3h at room temperature, and then neutralized with NH_4OH(conc.) and extracted with $CHCl_3$ (5 x 50 mL). the combined organic layers were dried ($NaSO_4$) and evaporated to give an oil, which was purified by flash chromatography (CH_2Cl_2/ MeOH, 20:1) to give 4.1 g of 3,5-bis(dimethoxymethyl)-1H-1,2,4-triazole, mp 99 - 100° C (it.[33] mp 96 - 100°C) in 73% yield.

8,12,13,17-Tetraethyl-7-18-dimethyl-2,3-diazaporphyrin 23:

The tripyrrane **20** (150 mg, 0.331 mmol) was stirred in TFA (3 mL) under nitrogen for 10 minutes. Methylene chloride (38 mL) was added followed immediately by 3,5-diformyl-1H-1,2,4-triazole **7** (41 mg, 0.331 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was neutralized with Et_3N, then DDQ (150 mg) was added and stirred for an additional 1 h. The mixture was washed with water and purified by chromatography on neutral Grade III alumina eluting first with methylene

chloride and then with chloroform. The dark violet fraction was collected and recrystallized from chloroform-hexane to give 45 mg (30%) of dark violet crystals, mp > 300° C; UV/Vis ($CHCl_3$): λ_{max} (ε) = 399 (123000), 414 (109000), 515 (13600), 555 (21900), 587 (12800), 637 (17700); UV/Vis ($CHCl_3$ / >1% TFA): λ_{max} (ε) = 388 (78300), 479 (7840), 510 (12400), 550 (16000), 697 (23600); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 634 (15600), 585 (12400), 554 (18,700), 513 (13800),412 (80,200) 397 nm (90,015); UV/Vis (CH_2Cl_2/ >1% TFA): λ_{max} (ε) = 721 (20600), 548 (12800), 507 (11300), 374 (59000); ^1H NMR (300 MHz, $CDCl_3$): δ = -2.65 (2H, s), 1.72 (6H,t), 1.73 (6H, t), 3.45 (6H, s), 3.69 (4H, q), 3.81 (4H, q), 9.26 (2H, s), 10.33 (2H, s); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ= 11.03, 17.01. 18.07, 19.23, 19.50, 95.20, 101.98, 137.32, 140.22, 141.33, 146.29, 158.72, 159.01; ^1H NMR (500 MHz, $CDCl_3$-TFA): δ = 1.62 (6H,t), 1.66 (6H, t), 3.21 (6H, s), 3.58 (8H, m), 8.85 (2H, s), 9.68 (2H, s); ^{13}C NMR (75.46 MHz, $CDCl_3$-TFA): δ= 10.6, 15.3, 16.0, 18.9, 19.3, 97.1, 107.3, 143.7, 144.6, 145.7, 149.5, 151.3, 153.8, 156.7; MS (EI, 70 eV) m/z (%) 454 (13), 453 (21) 452 (58) [M^+], 424 (100) [M^+ - N2].

Crystal Structure Determination and Refinement for 23.[39]

Data was collected at 153 K on a Siemens CCD diffractometer using Mo Ka radiation (l = 0.71073 Å). Data was collected as 90 second frames in a hemisphere of reciprocal space. Final unit cell parameters were obtained by least-squares refinement of accurately centered reflections obtained from 60 frames of collected data. SMART was employed to obtain a unit cell and SAINT was utilized to intergrate the collected frames. SADABS was then used to apply absorption corrections to the data. The structures were solved using SHELXL-86. Atomic coordinates and thermal parameters were refined using the full-matrix least-squares program, SHELXL-97, and calculations were based on F^2

data. All non-hydrogen atoms were refined using anisotropic thermal parameters. All crystallographic computations were performed on Silicon Graphics Indigo computers.

3,5-Di(chloromethyl)-1,2,4-triazole, 36:

3,5-(Hydroxymethyl)-1,2,4-triazole **10** (1.6 g, 0.013 mole) was placed in a flask and thionyl chloride (10 mL) was slowly added and then refluxed for 1.5 hours. The reaction mixture was allowed to stand at room temperature for 8 hours. The percipitated crude triazole was collected by filtration and recrystillized from acetonitrile to give 2.4 g (96 %) of 3,5-(chloromethyl)-1,2,4-triazole as the hydrochloride salt, m.p. 112 - 114° C (lit.[65] mp 113 - 114° C).

1-Tetrahydropyranal-3,5-di(chloromethyl)-1,2,4-triazole, 43:

3,5-(Chloromethyl)-1,2,4-triazole hydrochloride, **36** (5 g, 0.025 mole) and dihydropyran (6 mL) were stirred in methylene chloride (130 mL) for 5 hours. The reaction mixture was then washed with saturated sodium bicarbonate and dried over sodium sulfate. The solvent was removed under vacuum and the crude oil was recrystallized from hexane to yield 3 g (59 %) of 1-tetrahydropyranal-3,5-(chloromethyl)-1,2,4-triazole, m.p. 79 - 80° C (lit.[65] mp 82° C).

1-Tetrahydropyranyl-3,5-di(Iodomethyl)-1,2,4-triazole:

1-Tetrahydro-pyranyl-3,5-di(chloromethyl)-1,2,4-triazole, **43** (0.5 g, 0.002 mole) and potassium iodide (2 g) were dissolved in acetone (10 ml) and refluxed for 8 hours. The cooled solution was filtered to remove the the insoluble salts and the acetone was removed under vacuum and crude solid was recrystallized from hexane to give 0.6 g (70%) of 1-tetrohydropyranyl-3,5-di(Iodomethyl)-

1,2,4-triazole, m.p. 89 - 90° C. ^{1}H-NMR ($CDCl_3$) δ 5.36 (dd, 1H), 4.49 (dd, 2H), 4.31 (s, 2H), 3.95 (m, 1H), 3.65 (m, 1H), 2.25 (m, 2H), 2.05 (m, 2H), 1.66 (m, 2H).

Ethyl 2-pyrrylacetate, 44:

Pyrrole (50 g, 0.75 mole) and copper dust (4 g) were heated to 90° C and slowly charged with ethyl diazoacetate (35.8 g, 0.31 mole) at such a rate that the reaction temperature was kept between 95 - 105° C. The reaction was held at 100° C for 3 hours then cooled to room temperature. The solution was filtered and distilled to give 21.7 g (46 %) of ethyl 2-pyrrylacetate, bp. 98 - 115° C (1.5 mm), lit bp. 76° C (0.2 mm)[67]. ^{1}H-NMR ($CDCl_3$) δ 8.84 (s, 1H), 6.78 (s, 1H) 6.16 (s, 1H), 6.05 (s, 1H), 4.20 (q, 2H), 3.69 (s, 2H), 1.30 (t, 3H).

Bis-3,5-(2-pyrryl)-1H-1,2,4-triazole, 53:

2-Pyrrole carboxylic acid hydrazide, **57** (0.7g, 5.6 mmole) was dissolved in a minimum amount of warm ethanol (75 ml). To this solution p-toluenesulfonic acid hydrate (1.2g, 6.3 mmole) was slowly added and was heated for 15 minutes. The pale yellow solution was cooled to room temperature and the ethanol was evaporated *in vacuo*. The hydrazide PTSA salt (mp 238-240°C) was then heated with 2-cyanopyrrole **60** (0.5g, 5.6 mmole) to 200° for 4 hrs. After cooling the reaction mixture was dissolved in 10% sodium hydroxide (100 mL) and the insoluible material was removed by filtration. The basic solution was neutralized with conc. hydrochloric acid until a tan precipitate was formed. The solid was collected and dried to yield 0.25g (15%) of the dipyrryltriazole, mp > 295 C°. ^{1}H-NMR (DMSO-d_6) δ 11.71 (s, 2H), 7.00 (s, 2H), 6.83 (s, 2H), 6.22 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ 148.9, 122.8, 117.5, 111.4, 109.7.

2-Pyrrole carboxylic acid hydrazide, 57:

To a stirred solution of 2-trichloroacetylpyrrole, **64** (10 g., 0.047 mole) and diethyl ether (100 mL), hydrazine hydrate (15 mL, 0.3 mole) was added dropwise. The heterogenous solution was stirred for 1 hour and the tan percipitate was collected by filtration and recrystallized from ethanol to yield 4.1 g. (70%) of the hydrazide, m.p. 231 - 233°C (lit.[68]. mp 227 - 228°C)

2-Cyanopyrrole, 60:

Method 1: A solution of 5.0 M ethyl magnesium bromide (50 mL)in ether was slowly added to a magnetically stirred solution of pyrrole (15.4 g, 0.23 mole) in dry ether (25 mL) and was refluxed for 1 hour. This pyrrylmagnesium bromide solution was cooled to 0° C and slowly charged with ethyl thiocyanate (10.0 g, 0.115 mole) and then was refluxed for 4 hours and allowed to set at room temperature for 10 hours. This heterogenous solution was hydrolized with 40 mL of 10% NH_4Cl then washed with 2N H_2SO_4 (2 X 40 mL). The organic extracts were then washed with water and dried with $MgSO_4$ and concentrated under reduced pressure. The product was distilled through a six inch vacuum-jacketed Vigreux column, yielding 5 g (47%) of 2-cyanopyrrole, b.p. 85 - 91, 1.5 mm (lit[69] bp 89 -90° C, 1.5 mm)

.

Method 2: Pyrrole (5.0 g, 0.075 mole) was dissolved in a mixture of acetonitrile (25 mL) and DMF (25 mL) and the solution was cooled in a dry ice / acetone bath. Chlorosulfonyl isocyanate (11.7 g, 0.082 mole) in acetonitrile (30 mL) was added dropwise to the stirred solution over a twenty minute period and the reaction mixture was allowed to warm up to 5° C over about 1hour. The mixture was poured into aqueous NaOH (3M. 27 mL), 5% $NaCO_3$ solution (150 mL), and ice (100 g). The aqueous mixture was extracted with

dichloromethane. The organic extracts were washed with water and dried with K_2CO_3, then concentrated under reduced pressure to leave an oily residue. The oily product was distilled (80 - 88°C, 1.5 mm) yielding 3.8 g (55 %) of 2-cyanopyrrole.

1-Benzenesulfonyl-2-cyanopyrrole:

2-Cyanopyrrole **60** (1 g, 0.011 mole) and benzenesulfonyl chloride (2.88 g, 0.016 mole) were dissolved in methylene chloride (20 mL). To this solution 2N sodium hydroxide (10 mL) and tetrabutylammonium bromide (0.2 g) were added and the heterogeneous mixture was refluxed for 48 hours. The solution was washed with water, dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography (methylene chloride eluent, Rf .70) gave 2.2 g (86%) of 1-benzenesulfonyl-2-cyanopyrrole, m.p. 86 - 87° C (lit[70]. mp 95.4 - 95° C) ^{1}H-NMR ($CDCl_3$) δ 8.02 (d, 2H), 7.67 (t, 1H), 7.56 (7, 2H), 7.46 (dd, 1H), 6.94 (dd, 1H), 6.31 (t, 1H).

2-Trichloroacetylpyrrole, 64:

Trichloroacetyl chloride (16.3 g, .09 mole) and diethyl ether (20 mL) were placed into a dropping funnel and slowly added to a solution of pyrrole (5.5 g, .08 mole) in ether (25 mL). After addition the solution was stirred for 1 hour. K_2CO_3 (5.3 g) in water (25 mL) was slowly added. The mixture was extracted with ether, dried with magnesium sulfate then treated with Norit (1 g). The solvent was removed under reduced pressure and the residue was recrystallized from hexane yielding 9.6 g (55%) of 2-trichloroacetylpyrrole, mp. 72-75°C (lit[71] mp 73-75°C).

1-(2-Chloroethyl)-2-cyanopyrrole, 64:

2-Cyanopyrrole **60** (0.48 g, 5.26 mmole) was dissolved in 1,2-dichloroethane (10 mL) and added to 50% aqueous sodium hydroxide (5 mL). Tetrabutylammonium iodide (1.9 g, 5.26 mmole) was added to the heterogeneous reaction mixture and stirred at room temperature. A minimum amount of water was added dropwise to remove the clumps of tetrabutylammonium iodide. The resulting solution was refluxed for 1 hour, cooled then diluted with water (15 mL). The mixture was washed with 2N hydrochloric acid (15 mL) then washed with water. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure to give 0.9 g (74%) of 1-(2-chloroethyl)-2-cyanopyrrole as a pale yellow oil (bp 89 - 91°C, 1.5 mm). ^{1}H-NMR ($CDCl_3$) δ 6.89 (dd, 1H), 6.75 (dd, 1H), 6.13 (dd, 1H), 4.29 (t, 2H), 3.74 (t, 2H); ^{13}C-NMR ($CDCl_3$) δ 127.2, 120.3, 113.2, 109.5, 103.2, 43.4, 43.0; MS (EI, 70 eV) m/z (%) 156 (M^++2, 10.5), 154 (M^+, 35.4), 105 (100.0).

1-Vinyl-2-cyanopyrrole, 66:

Sodium hydride (0.68 g , 0.0143 mole) was washed with hexanes (3 X 10 mL) decanted then was diluted methylene chloride (30 mL). 1-(2-Chloroethyl)-2-cyanopyrrole (2 g, 0.013 mole) was added to the solution and refluxed for 6 hours. The reaction solution was cooled and washed with water, dried over magnesium sulfate and the solvent was removed under vacuum to leave a yellow oil residue. The oil was distilled to yield 1.1 g (72%) of 1-vinyl-2-cyanopyrrole (bp 85 - 88°C, 1.5 mm).

1-Trimethylsilyl-2-cyanopyrrole, 69:

2-Cyanopyrrole, **60** (2 g, 0.022 mole) and hexamethyldisilylazane (5 mL) were heated together with ammonium sulfate (0.02 g) for 6 hours at 150° C. The reaction mixture was cooled and distilled to yield 2 g (55 %) of 1-trimethylsilyl-2-cyanopyrrole (bp 60°C, 20 mm). ^{1}H-NMR ($CDCl_3$) δ 6.91 (m, 2H), 6.23 (t, 1H), 0.51 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 129.29, 124.10, 115.53, 111.20, 105.00, 0.48.

3,4,5-Trimethyl-2-cyanopyrrole, 71:

Ethyl cyanoacetate (113 g., 1 mole) was dissolved in acetic acid (200 mL) and cooled in an ice bath. A solution of sodium nitrite (207 g, 3 mole) in water (300 mL) was added dropwise over a 1 hour period keeping the temperature below 10° C. After complete addition the reaction mixture stirred at room temperature for 4 hours. The solution was then extracted with ether (3 X 200 mL) and the combined organic extracts were dried over magnesium sulfate and condensed under vacuum to give an oily oxime which solidified. The solid was triturated with benzene and collected by filtration yielding 57 g (40%), m.p. 128 - 129° C (lit.[72] m.p. 129 - 130°·C) This oxime was dissolved in acetic acid (60 mL) and water (30 mL) and was added dropwise into a solution of 3-methyl-2,4-pentanedione (45.8 g., 0.40 mole) in acetic acid (150 mL) at 90° C. During the addition of the oxime a mixture of zinc (208 g.) and sodium acetate (110 g.) was added in small portions. The reaction temperature was kept between 95 - 105° C during the additions. After the addition was complete the reaction mixture was stirred for an hour at 90° C then the hot solution was poured into ice water (500 g) and allowed to percipitate. The crude pyrrole was collected by filtration and taken up in dichloromethane (100 mL) and dried over magnesium sulfate. The solvent was removed under vacuum to gave 21.2 g. of crude pyrrole. Column chromatography of the crude product (500 g of neutral alumina, 50 mm

column, CH_2Cl_2) provided 8.2 g (15%) of 3,4,5-trimethyl-2-cyanopyrrole, **71** (m.p. 135 - 137° C, lit.[73], m.p. 139 - 140° C) and 12.5 g (17%) of 3,4,5-trimethyl-2-pyrrolecarboxylate, **72** (mp 124 - 126° C).

3-Methyl-2,4-pentanedione:

2,4-pentanedione (200mL, 1.95 mole), methyl iodide (312 g., 2.20 mole), and potassium carbonate (240 g) were placed in acetone (300 mL) and refluxed for 18 hours. The carbonate salts were removed by filtration and the remaining solution was distilled to give 191 g (86%) of 3-methyl-2,4-pentanedione, b.p 174 -180°C (lit.[74] b.p. 186 - 190°C).

Ethyl 3,4,5-trimethyl-2-pyrrolecarboxylate, 72:

Diethyl malonate (216.8 g., 1.40 mole) was dissolved in acetic acid (200 mL) and was placed in an ice bath. To this solution sodium nitrite (280 g.,4.05 mole, dissolved in 200 mL water) was added dropwise while stirring vigerously with a mechanical stirrer. The reaction temperature was kept below 10° C. during the addition. After complete addition the oxime solution was stirred for an hour. In a separate flask, 3-methyl-2,4-pentanedione (152 g, 1.34 mole) was dissolved in acetic acid (300 mL). The oxime solution was added dropwise to the dione solution while keeping the reaction temperature below 90° C. During the addition of the oxime solution, zinc (708 g.) and sodium acetate (222 g.) were added in small portions. After complete addition of all the reactants the mixture was refluxed for 2 hours. The hot solution was then poured over ice (500 g.). After 3 hours the crude pyrrole precipitated and was collected by filtration, washed with water and recrystallized from ethanol to yield 128 g. (53%) of ethyl 3,4,5-trimethyl-2-pyrrolecarboxylate, m.p. 125 - 127°C (lit.[75] mp 125 - 126°C)

3,4,5-Trimethyl-2-pyrrolecarboxylic acid hydrazide, 73:

Ethyl 3,4,5-trimethyl-2-pyrrolecarboxylate, **72** (3.0 g, 0.017 mole) and hydrazine hydrate (5 mL) were placed in a sealed tube and heated to 150° C for 8 hours then slowly cooled to room temperature. The sealed tube was then placed in an ice bath and cooled to ~ 0 ° C before opening. The precipitate was collected by filtration and washed with water then washed with dicholoromethane. The crude hydrazide was recrystallized from ethanol to yield 2.3 g (82%) of 3,4,5-trimethyl-2-pyrrole carboxylic acid hydrazide, mp. 231 - 234° C (lit.[68] mp. 236° C).

3,5-Bis(3,4,5-trimethyl-2-pyrryl)-1H-1,2,4-triazole, 75:

3,4,5-Trimethyl-2-pyrrole carboxylic acid hydrazide, **73** (0.5 g, 0.003 mole) and 3,4,5-trimethyl-2-cyanopyrrole **71** (0.4 g, 0.003 mole) were heated with p-toluenesulfonic acid (0.6 g 0.003 mole) at 280° C for 4 hours. The reaction melt was cooled and dissolved a methanol and10% sodium hydroxide aqueous solution (200 ml, 75% methanol in 10% NaOH). The basic solution was acidified with conc. hydrochloric acid until a violet precipitate formed. The solid was collected and washed with water (2 X 20 ml) and dried to yield 0.5 g (30%), m.p. >300° C. ^{1}H-NMR (DMSO-d_6) δ 11.07 (br s, 1H), 2.24 (s, 6H), 2.17 (s, 6H), 1.89 (s, 6H).

Bis-3,5-(2-pyrryl)-1-benzenesulfonyl-1H-1,2,4-triazole, 77:

Benzenesulfonyl chloride (0.44g, 2.4 mmole), triethylamine (0.3g, 2.8 mmole), and bis-3,5-(2-pyrryl)-1H-1,2,4-triazole, **53**(0.5, 2.5 mmole) were dissolved in acetonitrile (30 mL) and magnetically stirred at room temperature for 48 hr. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with water (3 X 25 mL), then dried with $MgSO_4$ and evaporated *in vacuo*. Flash column

chromatography of the crude product (10g of 230-400 mesh silica gel, 20 mm od column, CH_2Cl_2, R_f 0.48) yielded 0.16g (19%) of bis-3,5-(2-pyrryl)-1-benzenesulfonyl-1H-1,2,4-triazole, mp 165°C. ^{1}H-NMR ($CDCl_3$) δ 10.07 (br s, 1H), 9.38 (br s, 1H), 7.90 (d, 1H), 7.87 (d, 1H) 7.56 (m, 1H),7.39 (m, 3H), 7.02 (m, 1H), 6.82 (m, 2H) 6.357 (q, 1H) 6.27 (q, 1H); ^{13}C-NMR ($CDCl_3$) δ 156.7, 151.8, 136.6, 135.2, 134.9, 129.6, 126.4, 127.8, 126.9, 123.2, 121.5,120.7, 118.1, 116.7, 110.9, 110.1;

Bis-3,5-(2-pyrryl)-1-toluenesulfonyl-1H-1,2,4-triazole, 78:

Bis-3,5-(2-pyrryl)-1H-1,2,4-triazole, **53** (0.3g, 1.5 mmole), toluenesulfonyl chloride (0.32g, 1.6 mmole) and triethylamine(0.17g, 1.6 mmole) were reacted in the same general procedure for the sulfonation **77**. Flash column chromatography of the crude product (10g of 230-400 mesh silica gel, 20 mm column, CH_2Cl_2, R_f 0.49) yielded 0.10g (20%) of bis-3,5-(2-pyrryl)-1-toluenesulfonyl-1H-1,2,4-triazole, mp 173°C. ^{1}H-NMR ($CDCl_3$) δ 10.1 (br s, 1H), 9.37 (br s 1H), 7.78 (d, 2H), 7.40 (s, 1H), 7.22 (d, 2H), 7.05 (s, 1H), 6.86 (s, 2H), 6.38 (s, 1H), 6.25 (s,1H), 2.36 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 156.6, 151.7, 146.4, 133.7, 130.0, 127.9, 123.1, 121.7, 120.7, 118.2, 116.6, 110.9, 110.7, 110.1, 21.7.

3,4-Dimethyl-2-pyrrole carboxcylic acid hydrazide , 81:

In a sealed tube ethyl 5-iodo-3,4-dimethyl-2-pyrrolecarboxylate, **82** (1.0 g, 0.0034 mole) and hydrazine hydrate (10.0 g, 0.17 mole) were heated at 220°C for 48 hours. After cooling the solid was collected and washed with water (2 X 10 ml) and CH_2Cl_2 (2 X 10 ml). The crude hydrazide was recrystallized from ethanol to give 0.5 g (96%) of 3,4-dimethyl-2-pyrrole carboxhydrazide, m.p. 205 - 210°C. ^{1}H-NMR (DMSO-d_6) δ 10.64 (br s, 1H), 8.54 (s, 1H), 6.58 (d, 2H), 4.29

(s, 2H), 2.14 (s, 3H), 1.89 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 162.4, 121.3, 121.0, 118.3, 118.0, 10.2, 9.9.

5-Ethoxycarbonyl-3,4-dimethypyrrole-2-carboxylic acid.

Ethyl 3,4,5-trimethyl-2-pyrrolecarboxylate, **72** (10g, 0.056 mole.) was dissolved in ether (90 mL) and dichloromethane (50 mL). To this solution sulfuryl chloride (24.6g.,0.182 mole) in dichloromethane (40 mL) was added rapidly. After final addition the reaction mixture was stirred for 1h at room temperature. The solvent was removed under reduced pressure. The oily residue was dissolved in an acetone (67 mL) and water (23 mL), then refluxed for 30 minutes. The solution was cooled and the crude pyrrole acid was collected by filtration and dissolved in hot ethanol (90 mL). Saturated sodium bicarbonate (30 mL) was added slowly, then ethanol solution was heated over a steam bath for 15 minutes. The cooled solution was filtered through a cotton plugged funnel to remove the oily insoluble materials. The filtered solution was cooled in an ice bath and was acidified with concentrated hydrochloric acid. The pure acid pyrrole, percipitating out as an off white powder, was collected, washed with water, and air dried to yield 10.9g. (93 %) of 5-ethoxycarbonyl-3,4-dimethypyrrole-2-carboxylic acid, m.p.166 - 168°C
(lit.[76] mp 168 - 170°C).

Ethyl 3,4-dimethyl-5-iodopyrrole-2-carboxylate, 82:

5-Ethoxycarbonyl-3,4-dimethypyrrole-2-carboxylic acid, (7.7g, 0.036 mole) and sodium bicarbonate (9.2 g) in ethanol (30 mL) and water (50 mL) was stirred at 75°. A solution of iodine (10 g) and potassium iodide (15 g) in water (100 mL) was added as fast as it was decolorized (25 min.). The percipitate was collected and washed with water, dried at 80° C. Recrystallized from ethanol

gave 8.6 g. (81%) of ethyl 3,4-dimethyl-5-iodopyrrole-2-carboxylate, mp 133 - 136°C (lit.[77] mp134 -136° C)

3,4-Dimethyl-2-cyanopyrrole, 83:

3,4-Dimethylpyrrole, **84** (0.7 g, 0.007 mole) was dissolved in a mixture of acetonitrile (10 mL) and DMF (10 mL) and the solution was cooled in a dry ice / acetone bath. Chlorosulfonyl isocyanate (1.15 g, 0.008 mole) in acetonitrile (30 mL) was added dropwise to the stirred solution over a twenty minute period and the reaction mixture was allowed to warm up to 5° C over about 1h. The mixture was poured into aqueous NaOH (3M. 15 mL), 5% $NaCO_3$ solution (75 mL), and ice (100 g). The aqueous mixture was extracted with dichloromethane. The organic extracts were washed with water and dried with magnesium sulfate, and concentrated under reduced pressure to leave a dark oily solid. The solid was recrystallized from aqueous ethanol to give 1.2 g. (46 %) of 3,4-dimethyl-2-cyanopyrrole, m.p. 123 - 124°C (lit.[78] mp 119 - 120° C).

3,4-Dimethyl-2,5-pyrroledicarboxylic acid:

5-Ethoxycarbonyl-3,4-dimethypyrrole-2-carboxylic acid, (45 g., 0.21 mole) was was dissolved in ethanol (300 mL) and water (50 mL). Potassium hydroxide (20 g) was added and refluxed for 10 hours. The reaction mixture was cooled and most of the solvent was removed under reduced pressure. The remaining solution was diluted with water (150 mL) and cooled in ice and acidified with cold acetic acid until all of the diacid percipitated out. The product was collected by filtration, washed with water and air dried to yield 22.5 g. (59%) of 3,4-dimethyl-2,5-pyrroledicarboxylic acid, m.p.165-168°C (lit.[77] mp 168 - 170°C).

3,4-Dimethylpyrrole, 84:

3,4-Dimethyl-2,5-pyrroledicarboxylic acid, (13 g., 0.06 mole), sodium acetate trihydrate (10 g.), and potassium acetate (10 g.) was ground together until a uniform mixture was achieved. This mixture was placed into a round bottom flask and heated to 140° C. The mixture melted and was removed from the heat when the evolution of CO_2 subsided in approximately 30 minutes. The reaction solution was allowed to cool and diluted with water and extracted with dichloromethane, dried over magnesium sulfate. The solvent was removed under reduced pressure and the dark oil was allowed to solidify producing 1.3 g. (23 %) of crude 3,4-dimethylpyrrole[79]. The crude product was used without further purification. NMR ($CDCl_3$) δ 7.75 (br s 1H), 6.50 (d, 2H), 2.02 (s, 6H).

3,5-Bis(3,4-dimethyl-2-pyrryl)-1,2,4-1H-triazole, 85:

3,4-Dimethyl-2-pyrrole carboxylic acid hydrazide **81** (1.5 g, 9.8 mmole) was dissolved in hot ethanol (100 mL) and p-toluenesulfonic acid (2.0 g, 10.8 mmole) was added and the solvent was removed *in vacuo* to give the crude PTSA-hydrazide salt. To this solid, 3,4-dimethyl-2-cyanopyrrole **83** (1.2 g, 9.8 mmole) was added and the solid mixture was heated to 380-410°C for 4 hours. The reaction melt was cooled and dissolved in THF (50 mL) and methanol (20 mL). To this solution an aqueous solution of 10% sodium hydroxide (200 ml) was added. The basic solution was acidified with conc. hydrochloric acid until a violet percipitate formed. The solid was collected and dried to yield 75 mg (3 %), m.p. >300° C.

5-(1,3-Dithiolan-2-yl)-3,4-dimethyl-2-cyanopyrrole, 88.

To a stirred solution of 3,4,5-trimethyl-2-cyanopyrrole, **71** (3.0 g, 0.022 mole) in dry CH_2Cl_2 (100 ml), sulfuryl chloride (6.3 g, 0.047 mole) was added dropwise. After addition was complete, the red solution was refluxed for 10 minutes, evaporated to dryness and diluted with warm aqueous acetone (100 ml of 75% acetone in water). This solution was refluxed for 20 minutes and cooled. The crude aldehyde was then dissolved in ethanol (50 ml) and heated over a steam bath with ethylene dithiol (2.1g, 0.022 mole) and conc. hydrochloric acid (0.5 ml) for 1 hr. The solution was then poured into ice (50 g). After the ice was melted the crude product was collected and washed with water (3 X 25 ml) and recrystallized from aqueous ethanol to give 3.5 g (71%)of 5-(1,3-dithiolan-2-yl)-3,4-dimethyl-2-cyanopyrrole, m.p.. 174-176°C. ^{1}H-NMR ($CDCl_3$) δ 8.80 (br s 1H), 5.69 (s, 1H), 3.41 (m, 2H), 3.35 (m, 2H), 2.10 (s, 3H), 1.97 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 131.9, 131.7, 116.8, 114.6, 98.3,46.5, 39.7, 9.9, 8.7.

Appendix A

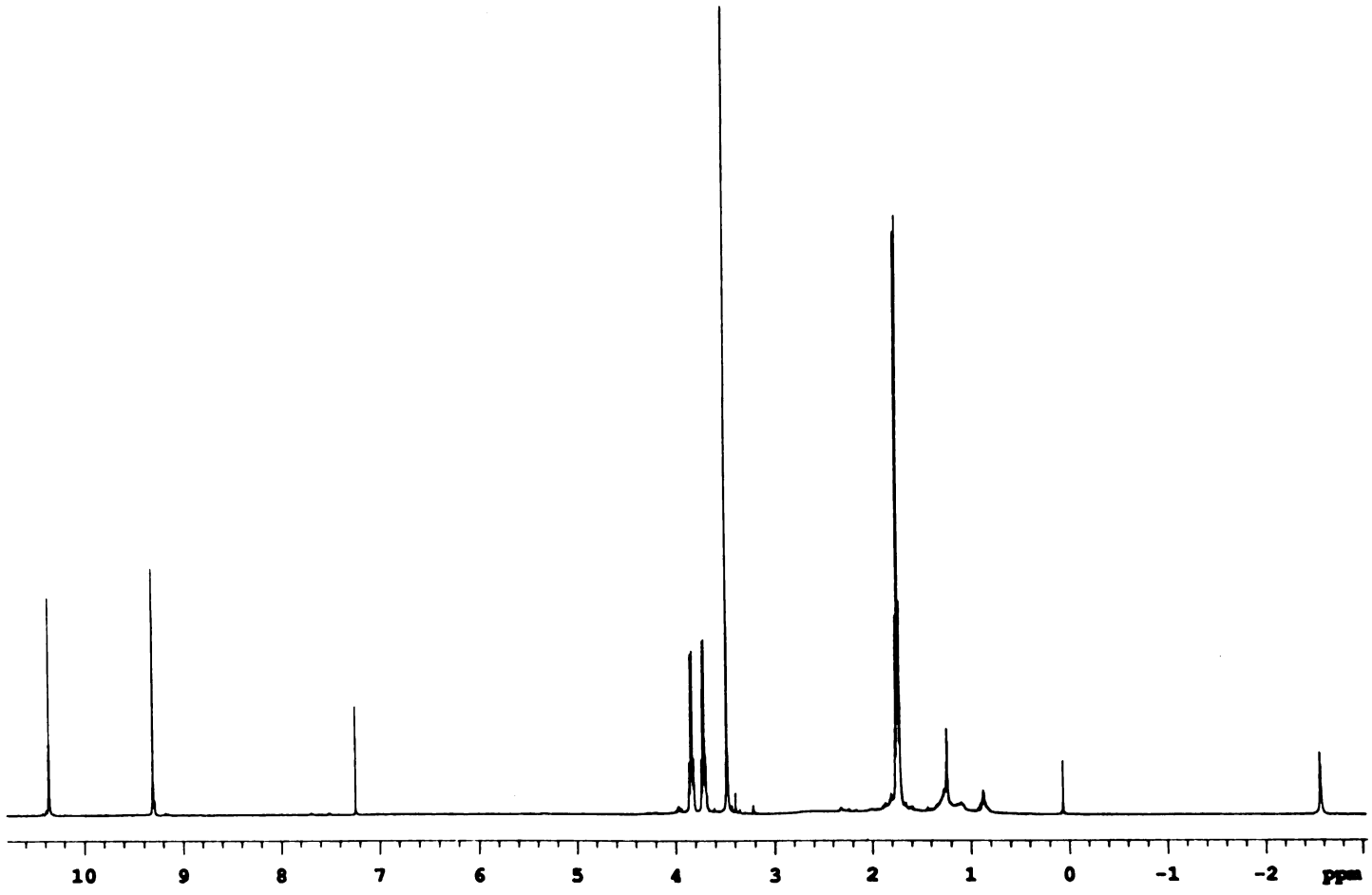


Figure A1. 1H-NMR (CDCl3) of **23**

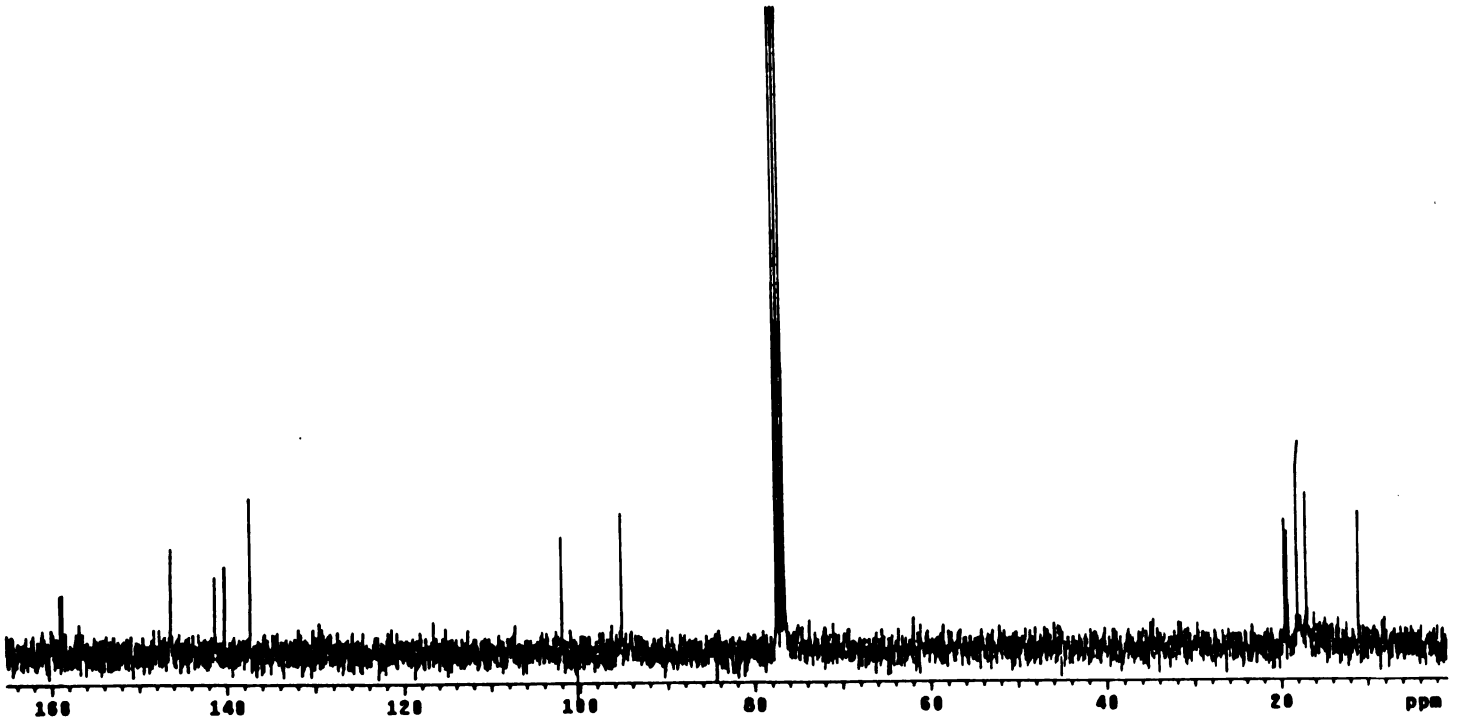


Figure A2. 13C-NMR (CDCl3) of **23**

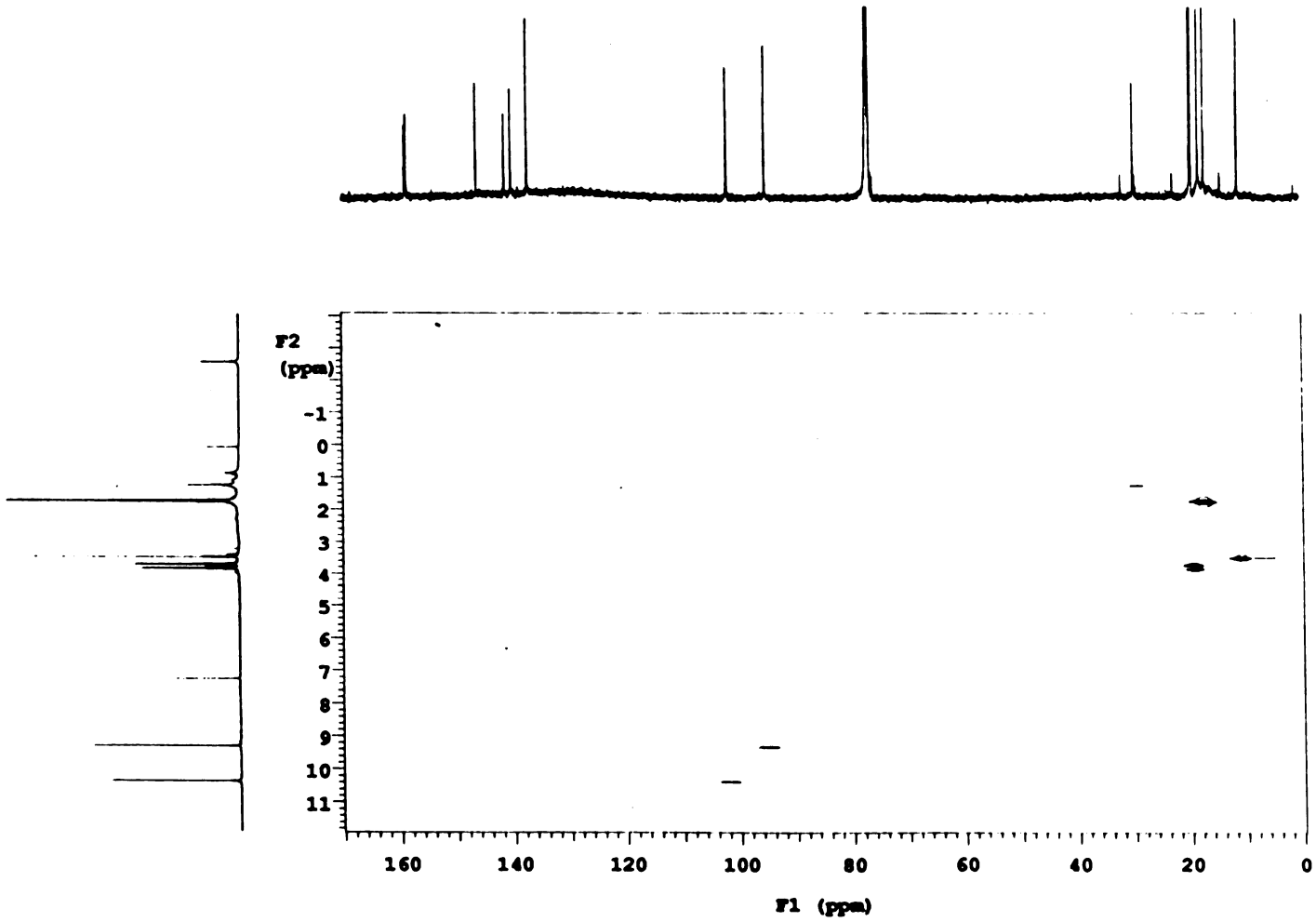


Figure A3. HMQC (CDCl3) of **23**

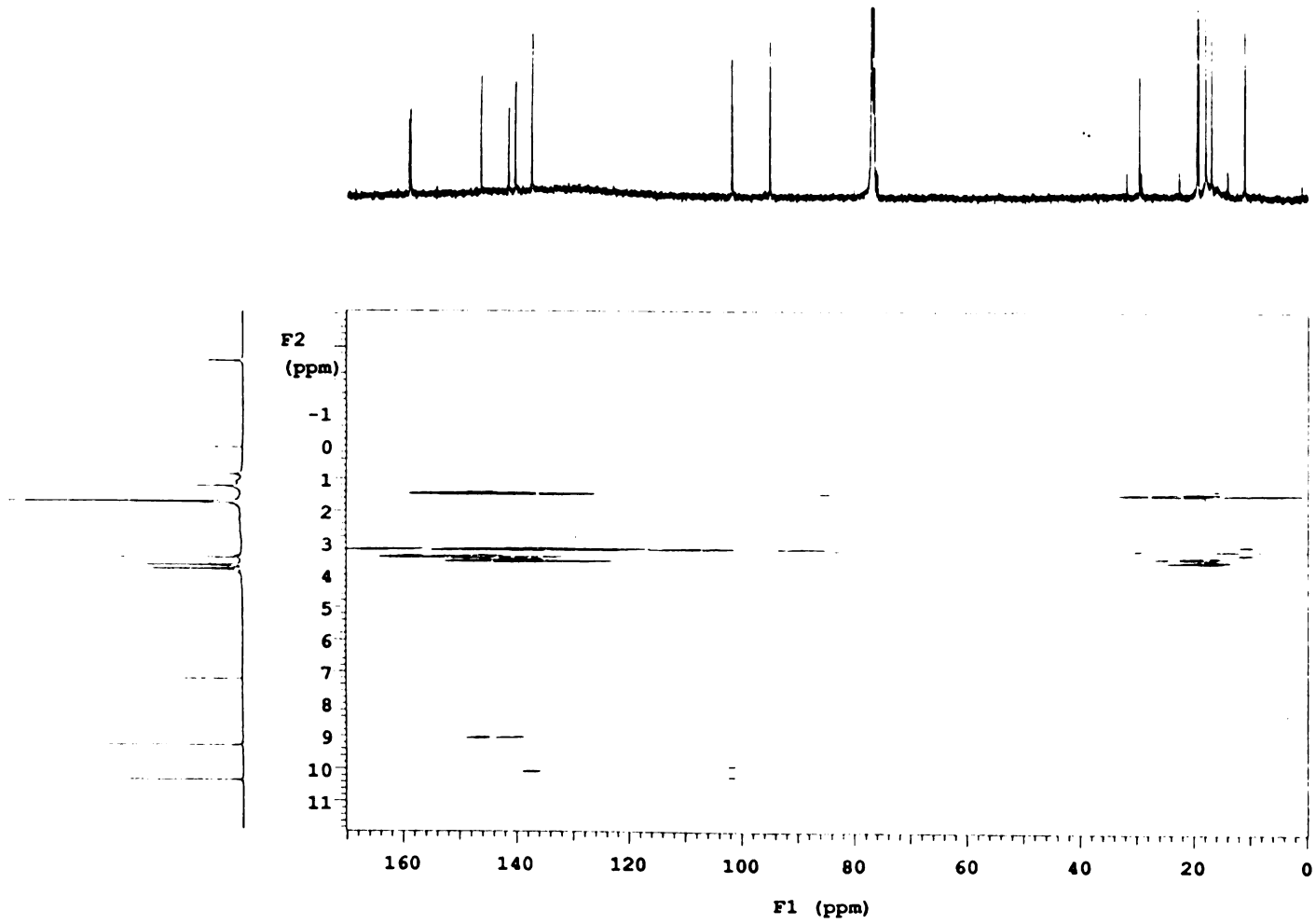


Figure A4. HMBC (CDCl3) of **23**

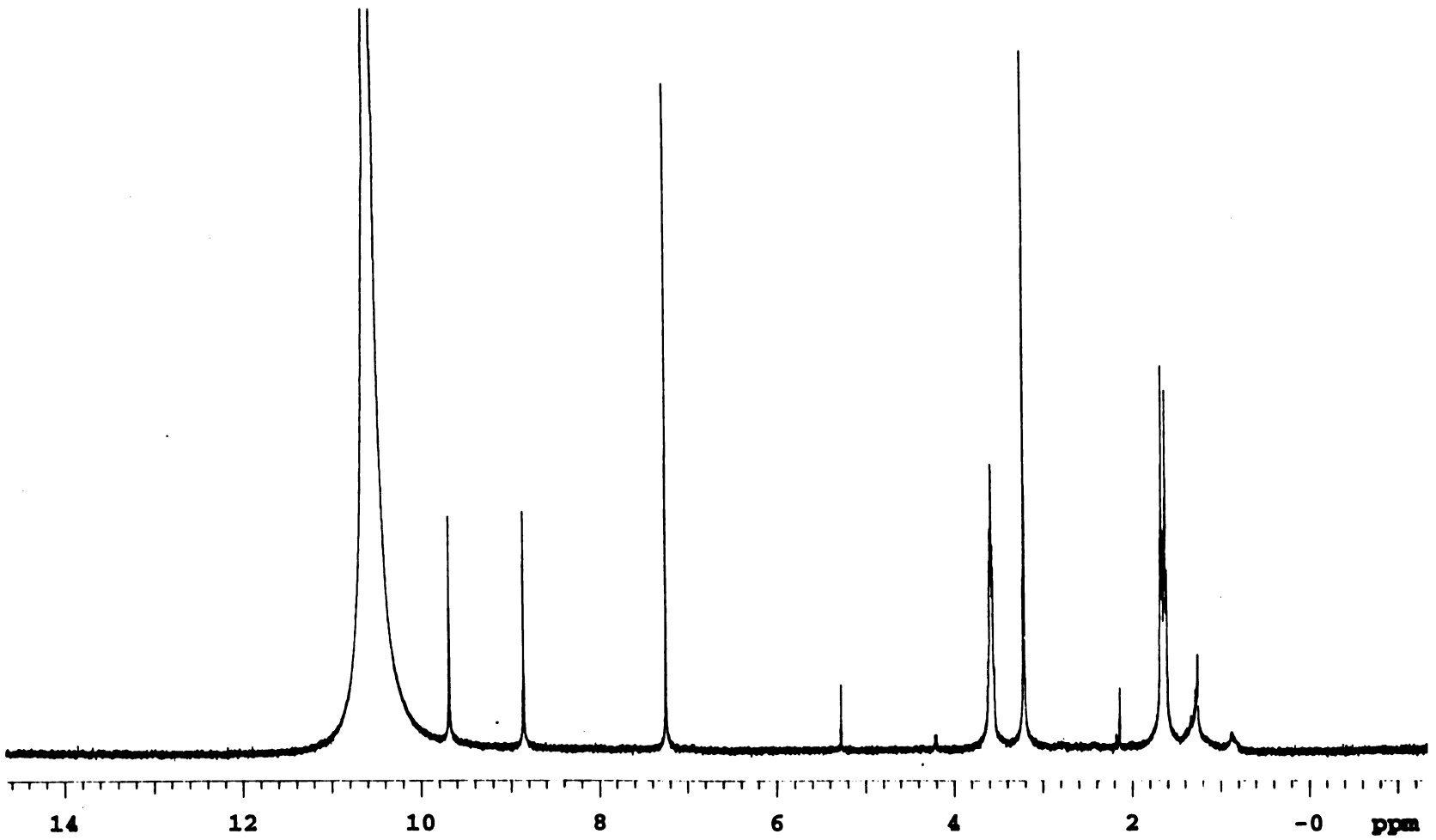


Figure A5. 1H-NMR (CDCl3-1% TFA) of **23**

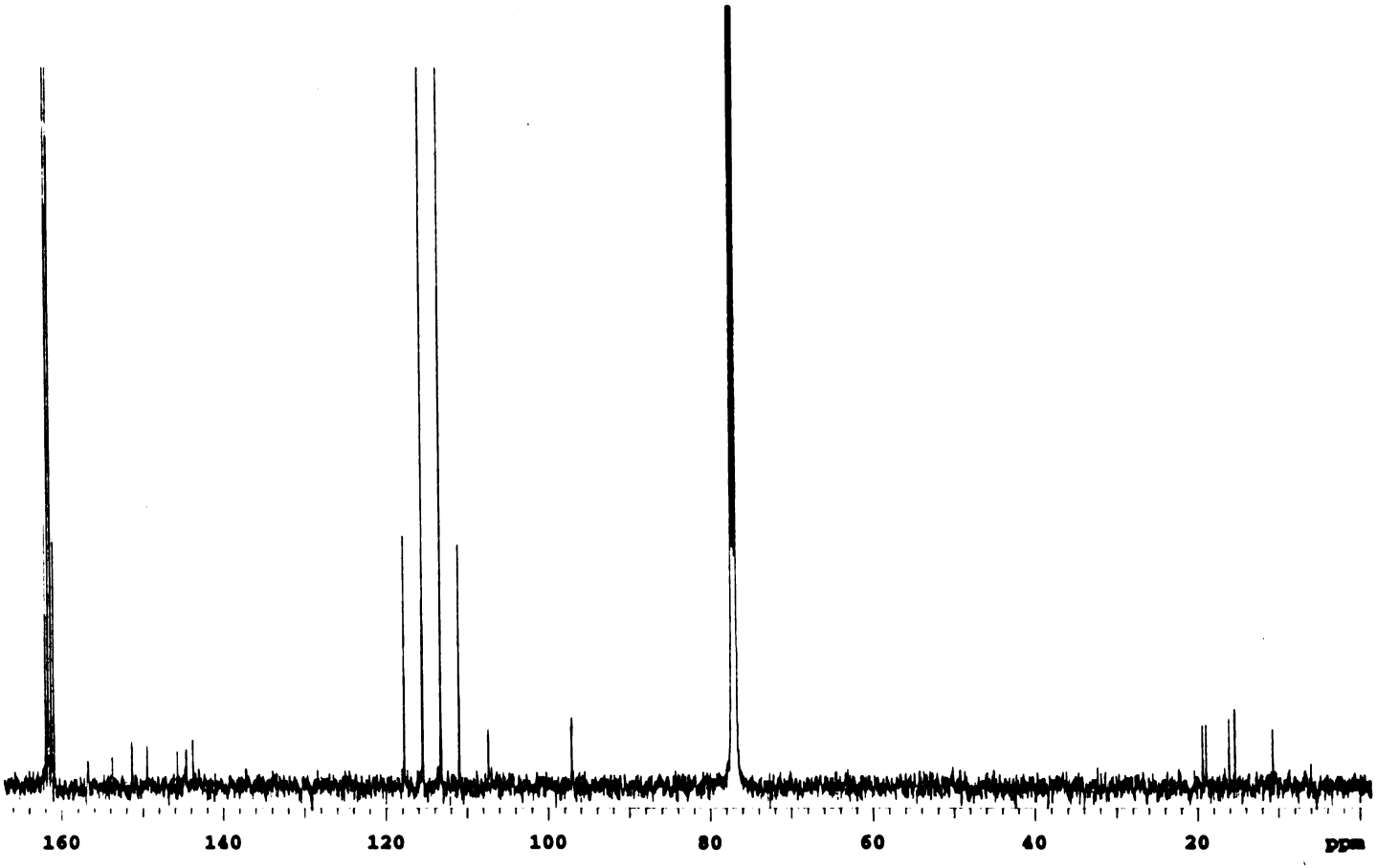


Figure A6. 13C-NMR (CDCl3-TFA) of **23**

Table A1. Crystal Data and Conditions for Crystallographic Data Collection and Structure Refinement

Formula	$C_{28}H_{32}N_6 \cdot 2CHCl_3$
Formula weight	691.33
Temperature	-120° C
Waveleingth	0.71073 Å
Space group	Triclinic P-1 (#2)
Unit cell dimensions	
a(Å)	9.354(2)
b(Å)	13.387(3)
c(Å)	13.773(3)
α (°)	75.58(3)
β (°)	88.35(3)
γ (°)	82.70(3)
Volume ($Å^3$)	1656.8(6)
Z	2
Density (Mg / m^3)	1.386
Absorption coefficient (mm^{-1})	0.549
F(000)	716
Crystal size (mm)	0.47x 0.05 x 0.03
Theta range for data collection (°)	1.53 to 28.42
Index ranges	$-12 \le h \le 12$, $-17 \le k \le 17$, $-18 \le l \le 18$
Reflections collected	17000
Independant reflections	7514 [R(int) = 0.2302]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7514 / 0 / 404
Goodness-of-fit on F^2	1.014
Final R indices [I > 2sigma (I)]	$R_1 = 0.1879$, $wR_2 = 0.2809$
R indices (all data)	$R_1 = 0.4344$, $wR_2 = 0.3832$
Extinction coefficient	0.007(2)
Largest diff. peak and hole ($Å^{-3}$)	0.499 and -0.534 e

Table A2. MM2 calculated and Actual Bond Lengths (Å) and Angles (°) for **94**.

Bond Lengths (Å)	Calc	Actual
C(1) - N(21)	1.34	1.357
C(1) - N(2)	1.28	1.365
C(1) - C(20)	1.40	1.39
N(2) - N(3)	1.26	1.315
N(3) - C(4)	1.28	1.371
C(4) - N(21)	1.35	1.355
C(4) - C(5)	1.40	1.37
C(5) - C(6)	1.41	1.38
C(6) - N(22)	1.37	1.389
C(6) - C(7)	1.41	1.457
C(7) - C(8)	1.41	1.38
C(7) - C(25)	1.50	1.49
C(8) - C(9)	1.41	1.42
C(8) - C(26)	1.50	1.48
C(9) - C(10)	1.41	1.370
C(10) - C(11)	1.40	1.44
C(11) - N(23)	1.37	1.353
C(11) - C(12)	1.35	1.47
C(12) - C(13)	1.35	1.31
C(12) - C(28)	1.51	1.53
C(13) - C(14)	1.35	1.47
C(13) - C(30)	1.51	1.53
C(14) - N(23)	1.34	1.338
C(14) - C(15)	1.41	1.39
C(15) - C(16)	1.40	1.43
C(16) - N(24)	1.36	1.343
C(16) - C(17)	1.41	1.39
C(17) - C(18)	1.41	1.35
C(17) - C(32)	1.51	1.51
C(18) - C(19)	1.41	1.419
C(18) - C(34)	1.50	1.526
C(19) - C(20)	1.40	1.35
C(19) - N(24)	1.37	1.385
C(26) - C(27)	1.53	1.51
C(28) - C(29)	1.53	1.52
C(30) - C(31)	1.53	1.506
C(32) - C(33)	1.53	1.52

Bond Angles (°)	Calc	Actual
N(21) - C(1) - N(2)	106.8	113.2
N(21) - C(1) - C(20)	127.5	124.4
N(2) - C(1) - C(20)	125.7	122.5
N(3) - N(2) - C(1)	110.4	107.0
N(2) - N(3) - C(4)	110.3	105.6

Table A2 (cont.).

Bond Angles (°)	Calc	Actual
N(21) - C(4) - N(3)	106.8	113.8
N(21) - C(4) - C(5)	127.3	126.9
N(3) - C(4) - C(5)	125.9	119.3
C(6) - C(5) - C(4)	124.3	125.7
C(6) - C(5) - N(22)	126.9	124.3
C(5) - C(6) - C(7)	126.4	130.2
N(22) - C(6) - C(7)	106.8	105.5
C(8) - C(7) - C(6)	107.5	108.1
C(8) - C(7) - C(25)	126.3	127.4
C(6) - C(7) - C(25)	126.3	124.4
C(7) - C(8) - C(9)	107.6	107.8
C(7) - C(8) - C(26)	125.8	126.3
C(9) - C(8) - C(26)	126.6	125.8
N(22) - C(9) - C(8)	106.8	107.7
N(22) - C(9) - C(10)	127.1	122.8
C(8) - C(9) - C(10)	126.2	129.4
C(11) - C(10) - C(9)	126.7	127.4
N(23) - C(11) - C(10)	126.0	126.2
N(23) - C(11) - C(12)	107.3	111.1
C(10) - C(11) - C(12)	126.6	122.7
C(13) - C(12) - C(11)	108.5	106.0
C(13) - C(12) - C(29)	128.3	126.6
C(11) - C(12) - C(28)	123.3	127.2
C(12) - C(13) - C(14)	107.6	106.6
C(12) - C(13) - C(30)	130.7	130.0
C(14) - C(13) - C(30)	121.7	123.4
N(23) - C(14) - C(15)	126.1	126.7
N(23) - C(14) - C(13)	107.9	111.2
C(15) - C(14) - C(13)	126.1	122.1
C(14) - C(15) - C(16)	127.5	128.3
N(24) - C(16) - C(17)	107.2	110.0
N(24) - C(16) - C(15)	126.7	121.2
C(17) - C(16) - C(15)	126.2	128.8
C(18) - C(17) - C(16)	107.1	107.2
C(18) - C(17) - C(32)	129.1	127.9
C(16) - C(17) - C(32)	123.9	124.7
C(17) - C(18) - C(19)	107.7	108.2
C(17) - C(18) - C(34)	126.7	127.4
C(19) - C(18) - C(34)	125.6	124.5
C(20) - C(19) - N(24)	126.1	122.5
C(20) - C(19) - C(18)	127.1	130.8
N(24) - C(19) - C(18)	106.8	106.7
C(19) - C(20) - C(1)	124.9	128.0
C(4) - N(21) - C(1)	105.7	100.4

Table A2 (cont.).

Bond Angles (°)	Calc	Actual
C(9) - N(22) - C(6)	111.4	110.8
C(14) - N(23) - C(11)	108.7	105.1
C(16) - N(24) - C(19)	111.3	108.0
C(8) - C(26) - C(27)	111.1	112.3
C(29) - C(28) - C(12)	111.3	111.6
C(31) - C(30) - C(13)	122.1	112.4
C(17) - C(32) - C(33)	118.6	111.4

Table A3. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Paramerter (A^2 x 10^3) for **94**

	x	y	z	U(eq)	Occ.
Cl (1)	4976 (4)	9751 (3)	2246 (3)	71 (1)	1
Cl (2)	3682 (6)	9699 (4)	4167 (3)	103 (2)	1
Cl (3)	2014 (4)	9405 (4)	2558 (4)	91 (2)	1
C (35)	3387 (5)	10031 (10)	2871 (9)	47 (4)	1
Cl (4)	2114 (5)	4024 (3)	4724 (3)	93 (2)	1
Cl (5)	2555 (5)	1854 (3)	5563 (3)	95 (2)	1
C (6)	-231 (5)	2944 (5)	5586 (4)	125 (2)	1
C (36)	1355 (14)	2888 (12)	4892 (11)	59 (5)	1
C (1)	2819 (11)	-6958 (9)	11374 (8)	24 (3)	1
N (2)	2339 (12)	-7540 (7)	12253 (7)	33 (3)	1
N (3)	1279 (11)	-6955 (8)	12567 (7)	39 (3)	1
C (4)	1147 (12)	-6021 (9)	11865 (9)	24 (3)	1
C (5)	99 (15)	-5242 (11)	11982 (9)	40 (4)	1
C (6)	-149 (10)	-4266 (9)	11346 (8)	24 (3)	1
C (7)	-1174 (12)	-3373 (9)	11421 (9)	33 (3)	1
C (8)	-960 (12)	-2557 (9)	10615 (10)	34 (3)	1
C (9)	143 (13)	-2922 (9)	10007 (9)	35 (3)	1
C (10)	756 (13)	-2374 (9)	9092 (9)	30 (3)	1
C (11)	1863 (13)	-2738 (9)	8566 (8)	29 (3)	1
C (12)	2412 (14)	-2100 (10)	7634 (8)	38 (3)	1
C (13)	3485 (13)	-2691 (10)	7347 (8)	31 (3)	1
C (14)	3630 (12)	-3690 (9)	8106 (9)	32 (3)	1
C (15)	4679 (12)	-4510 (10)	8038 (8)	29 (3)	1
C (16)	4912 (13)	-5527 (10)	8692 (9)	30 (3)	1
C (17)	5904 (12)	-6365 (10)	8605 (8)	31 (3)	1
C (18)	5682 (11)	-7173 (9)	9383 (9)	28 (3)	1
C (19)	4555 (11)	-6828 (8)	9980 (9)	28 (3)	1
C (20)	3949 (15)	-7337 (10)	10833 (11)	43 (4)	1
N (21)	2100 (10)	-5984 (7)	11100 (7)	29 (2)	1
N (22)	620 (10)	-3935 (7)	10471 (6)	22 (2)	1
N (23)	2637 (9)	-3690 (6)	8825 (6)	21 (2)	1
N (24)	4106 (9)	-5798 (8)	9516 (7)	29 (2)	1
C (25)	-2240 (12)	-3372 (10)	12242 (8)	41 (3)	1
C (26)	-1717 (12)	-1482 (8)	10424 (9)	34 (3)	1
C (27)	1065 (15)	-835 (9)	11006 (10)	54 (4)	1
C (28)	1828 (14)	-987 (9)	7093 (9)	42 (3)	1
C (29)	715 (13)	-964 (10)	6300 (9)	51 (4)	1
C (30)	4413 (12)	-2477 (9)	6406 (8)	37 (3)	1
C (31)	3955 (13)	-2978 (10)	5620 (8)	47 (4)	1
C (32)	6937 (12)	-6363 (10)	7740 (9)	44 (4)	1
C (33)	6185 (13)	-6500 (11)	6824 (9)	56 (4)	1
C (34)	6474 (12)	-8275 (9)	9607 (9)	38 (3)	1

(U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor).

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