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Synthesis of biomimetic compounds

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Synthesis of biomimetic compounds

by

Steven John Vander Louw

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: George A. Kraus

Iowa State University

Ames, Iowa

1997

Graduate College

Iowa State University

This is to certify that the Doctoral dissertation of

Steven John Vander Louw

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

Signature was redacted for privacy.

For the Graduate College

To my parents, Lyndis and John Vander Louw , for all of their love and support, and to Kaleena for always being there when I needed someone.

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GENERAL INTRODUCTION

The ultimate goal of the synthetic natural product chemist is to synthesize, in as efficient a route as possible, complex molecules that mimic the natural product's activity. At the synthetic chemist's disposal are the vast array of synthetic techniques that have been previously reported in the literature. By combining these reactions, and those discovered by the chemist, in novel combinations, the requisite transformations can be attained and produce molecules that behave in solution like those isolated from various natural sources. Synthetic chemistry relies on imagination, creativity, and knowledge of the previous work in the field combined with a mechanistic understanding of the reactions used in order to solve complex molecular puzzles.

The purpose of this research was to develop efficient syntheses to biologically interesting molecules. The three projects undertaken were the synthesis of natural light harvesting antennas, the synthesis of soybean cyst nematode hatch inhibitors, and a study towards the total synthesis of glycinoclepin A.

The first project was developed as a collaborative study between, myself, Dr. George Kraus and Dr. Walter Struve. We wished to determine if efficient light harvesting antennas could be synthesized and characterized to an extent that these antennas could be used as model systems for studying the process of photosynthesis. We envisioned three different types of antennas, based on alpha helices of a polypeptide, an arboral structure, and a polystyrene-based oligomer.

In the second project, we set out to synthesize molecules that could control the rate of proliferation of the soybean cyst nematode (SCN). In the years 1989 through 1991, SCN cost soybean producers in the North Central Region over $250 million dollars, more than any other soybean disease.[1] Over the course of our study, we developed several compounds, which are efficiently synthesized from commercially available starting materials, that effectively prevent the hatch of this devastating pest.

In the third project, we worked toward the total synthesis of glycinoclepin A, which exhibits a complementary biological activity against the soybean cyst nematode.[2] Glycinoclepin A causes premature hatch of the nematode, but is unavailable on a industrial scale for use against the SCN.[3]

Dissertation Organization

This dissertation was written so that each chapter represents a publishable article. Therefore, the numbering scheme adopted for the compounds and the references are independent for each paper. Following the last page of the last chapter is a general conclusions section which highlights the importance of the research reported.

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1. Doupnik, B. *Plant Disease* **1993**, *77*, 1170.
2. Fukuzawa, A.; Furaski, A.; Ikura, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1985**, 222.
3. Murai, A.; Ohkita, M.; Honma, T.; Hoshi, K.; Tanimoto, N.; Araki, S.; Fukuzawa, A. *Chem. Lett.* **1992**, 2103.

CHAPTER 1. A SYNTHETIC APPROACH TO ARTIFICIAL LIGHT HARVESTING ANTENNAS

A paper, a portion of which was submitted to Synlett

George A. Kraus and Steven J. Vander Louw

Introduction

The primary event in photosynthesis is the capture of sunlight by the light-harvesting antennas. These antennas absorb the sunlight and transmit the resulting singlet electronic excitation to the photochemical reaction centers.[1,2] The antenna is defined as a large-scale assembly of intensely absorbing pigments that are oriented in such a way as to permit efficient transfer of the singlet electron to the reaction center without energy loss through excited state decay or quenching. By increasing the number of pigments within an antenna, the probability of the singlet electron reaching the reaction center is greatly increased. Natural systems contain hundreds of pigments per reaction center. The time needed for the absorption of light and resultant excitation at the reaction center is very small and seldom exceeds the low tens of picoseconds in green plants.[3,4,5] Therefore, it is believed that the single-step energy transfers and other antenna processes transpire in the ultrafast (femtosecond to picosecond) time regime.[6] The probability for dipole-dipole energy transfer between antenna pigments is proportional to the fluorescence quantum yield of the donor molecule, the absorption cross section of the acceptor molecule, and the dipole-dipole orientational factor. The probability also scales with the inverse sixth power of the pigment-pigment separation.

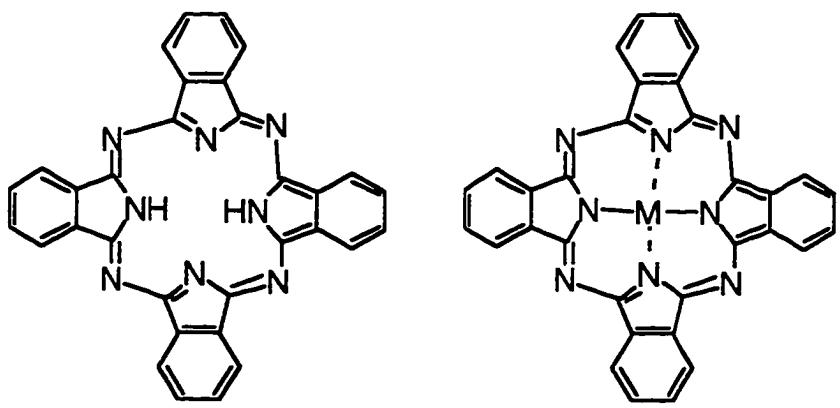
For the purposes of designing novel antennas, biodegradable pigments, such as chlorophyll and bacteriochlorophyll, are unattractive, since they are unstable outside of their protein hosts. However, phthalocyanines are extremely stable to heat, air, and light and mimic the spectral characteristics of chlorophyll *a*. Phthalocyanines also have the inherent advantage of spectral diversity based

upon the substitution of the aromatic ring. Phthalocyanines have not been used in the past because so little was known about their chemistry and they are fairly inert to aromatic substitution conditions.

History of Phthalocyanine Synthesis

The first synthesis of a phthalocyanine was accomplished by Braun and Tchneric in 1907.[7] They heated *o*-cyanobenzamide at a high temperature and isolated a blue compound in low yield, of which the structure was not determined until twenty five years later by Linstead and coworkers and determined to be metal free phthalocyanine (**1**).[8] The procedure to form metal free phthalocyanine was later improved by Linstead's group and the yield was subsequently raised to 40% upon addition of magnesium or antimony metal to the *o*-cyanobenzamide and heating to 230 °C. The resulting metallophthalocyanine **2** was demetallated with cold concentrated sulfuric acid.[9] Surprisingly, the use of substituted analogs of *o*-

Figure I



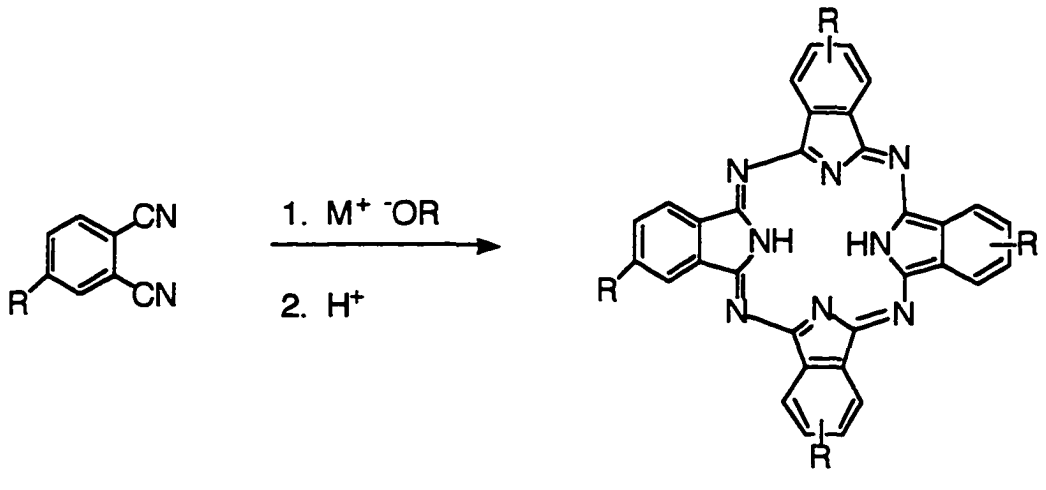
(**1**) (**2**)

cyanobenzamide to make phthalocyanine analogs has not been common.

The reagent of choice for the easy preparation of phthalocyanines is phthalonitrile (**4**). Treatment of **4** with sodium or lithium *n*-pentoxide in *n*-pentanol at 135 °C gave disodium phthalocyanine (Scheme I).[10] The resulting metal center

was removed upon treatment with concentrated sulfuric acid to give **6**. Variations of this method abound in the literature leading to substituted phthalocyanines. By using 4-phenoxyphthalonitrile (**5**) as the starting material, 2,9,16,23-tetraphenoxyphthalocyanines (**7**) can be prepared in 39% yield.[11]

Scheme I



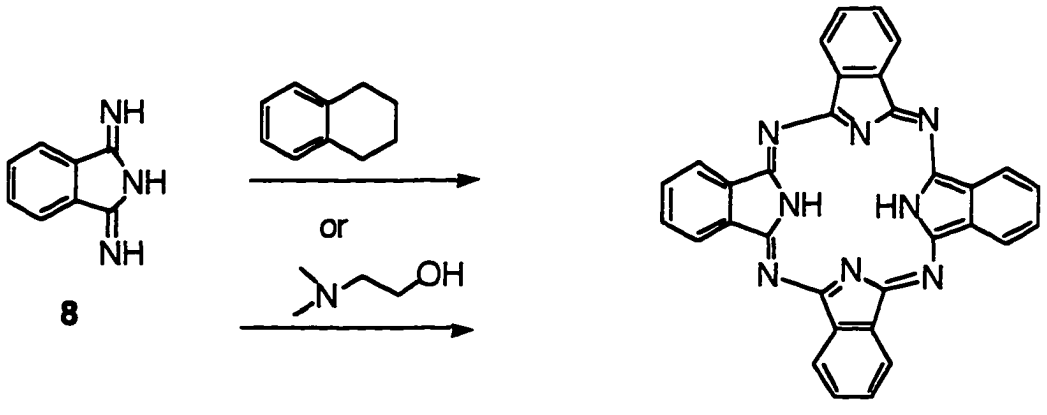
4 R = H
5 R = PhO

6 R = H
7 R = PhO

Another useful reagent for the synthesis of pthalocyanines, developed by Linstead and coworkers, is 1,3-diiminoisoindoline (**8**). Phthalonitrile can be readily converted to 1,3-diiminoisoindoline by treating a methanolic solution of **8** with gaseous ammonia and sodium methoxide at room temperature. When **8** was heated in the presence of a hydrogen donor, such as boiling tetralin, metal free phthalocyanine was formed in 45% yield.[12] Weinberg later improved the yield of metal free phthalocyanine formation to 85% by converting **8** to **1** by simply refluxing **8** in 2-*N,N*-dimethylaminoethanol (Scheme II).[13] Octasubstituted phthalocyanines have been readily formed by this method from 5,6-bis(ethoxymethyl)-1,3-diiminoisoindoline to give 2,3,9,10,16,17,23,24-octa(ethoxymethyl)-phthalocyanine in 80% yield.[14] As is the case in all symmetrically bis substituted diiminoisoindolines, all of the substituents on the

phthalocyanine ring are identical. If it was necessary to prepare phthalocyanines with different substituents, a mixed condensation could be attempted, although statistical mixtures of the inseparable compounds would result. Leznoff and

Scheme II

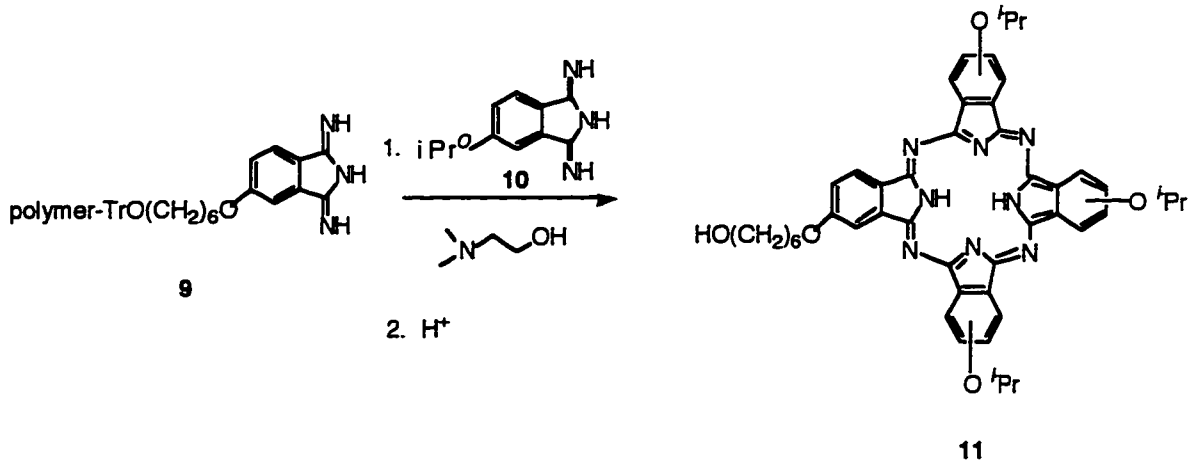


coworkers resolved this problem by attaching one of the substituted diiminoisoindolines to an insoluble polymer and reacting it with a large excess of a second diiminoisoindoline in solution. Upon completion of the reaction, the phthalocyanine is liberated from the polymer to form the unsymmetrically substituted phthalocyanine. As an example (Scheme III), a polymer bound trityloxyalkoxy-1,3-diiminoisoindoline (**9**) was condensed with 5-isopropoxy-1,3-diiminoisoindoline (**10**) in a mixed diiminoisoindoline condensation, using 2-*N,N*-dimethylaminoethanol as the solvent, to give the polymer bound phthalocyanine. Upon acid treatment, the unsymmetrically tetrasubstituted 2-(6'-hydroxyhexyloxy)-9,16,23-triisopropoxy-phthalocyanine (**11**) was isolated in 24% yield.[15] This method was later modified and used with a variety of polymer supports and diiminoisoindolines to give unsymmetrically substituted phthalocyanines.[16]

The use of phthalic anhydride (**12**) or related compounds, such as phthalic acid, phthalimide, or phthalamide, for the preparation of metallophthalocyanines, such as **2**, has been extensively reviewed.[17] In a typical procedure (Scheme IV), phthalic anhydride dissolved in nitrobenzene at 170-190 °C with urea, $CoCl_2$, and

often a catalyst such as ammonium molybdate, gave phthalocyaninato cobalt (II) (**1 4**) in high yield.[18] When perhalosubstituted phthalic anhydride **1 3** was

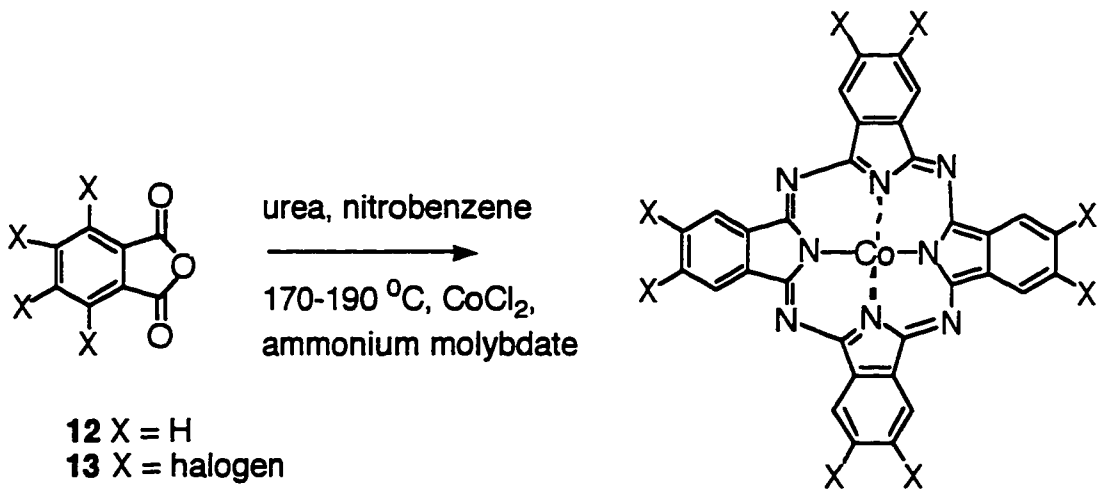
Scheme III



9

11

Scheme IV



12 X = H
13 X = halogen

14 X = H
15 X = halogen

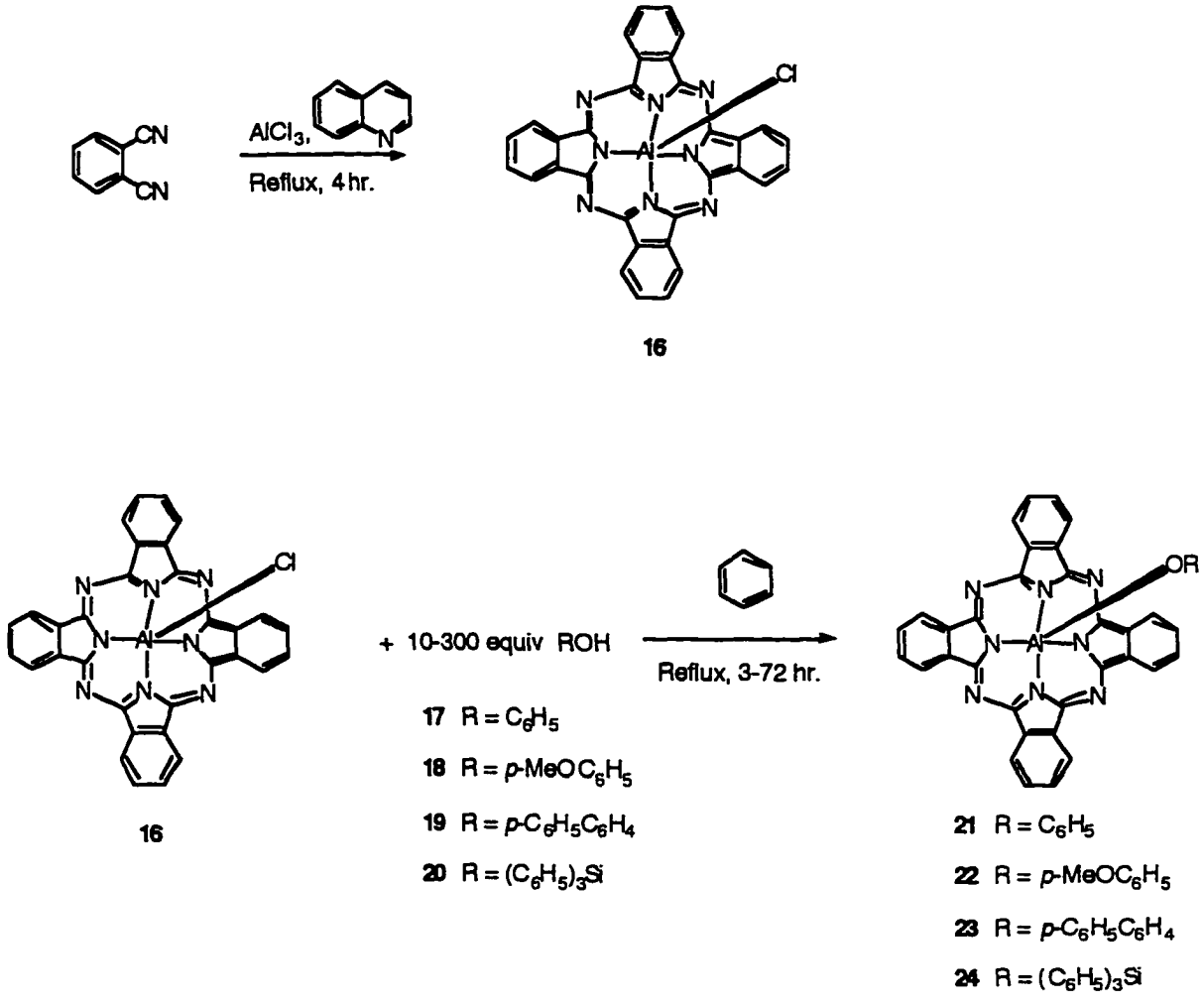
treated under similar conditions, the hexadecahalophthalocyanine **1 5** was obtained in up to 80% yield.

Of particular importance to the goals of our research project was the synthesis of metallophthalocyanines containing silicon or aluminum as the central

atom. By using these low weight metalloids as the central atoms, the chance of intersystem quenching of the excited state of the pigment was sequestered. Much of the pioneering work in aluminum and silicon phthalocyanine chemistry was done by Malcom Kenney at Case Western Reserve University in Cleveland, Ohio. His synthesis of aluminum phthalocyanine (**16**) is shown in Scheme V. He was also able to substitute the chlorine of the aluminum phthalocyanine with various alkoxy groups by reacting it with substituted alcohols. Kenney fails to report any yields for these reactions, although he does make the general comment that yields are "low".[19] These compounds are significant, because they are the first reported aluminum phthalocyanines that are monosubstituted at the central atom. Also, the reaction seems to be general in scope, as Kenney later went on to make the phthalocyaninogermanium and silicon derivatives.[20] Kenney also synthesized a variety of bridged aluminum phthalocyanines, specifically the μ-oxo bridged aluminum, silicon, and germanium phthalocyanines.[21] Aluminum phthalocyanines are clearly an important species, but they have the disadvantage of only one ligand site open for displacement on the central atom. Silicon phthalocyanines, with silicon possessing an octahedral arrangement within the phthalocyanine molecule, offered the advantage of two reactive ligand sites which could lead to polymeric species.

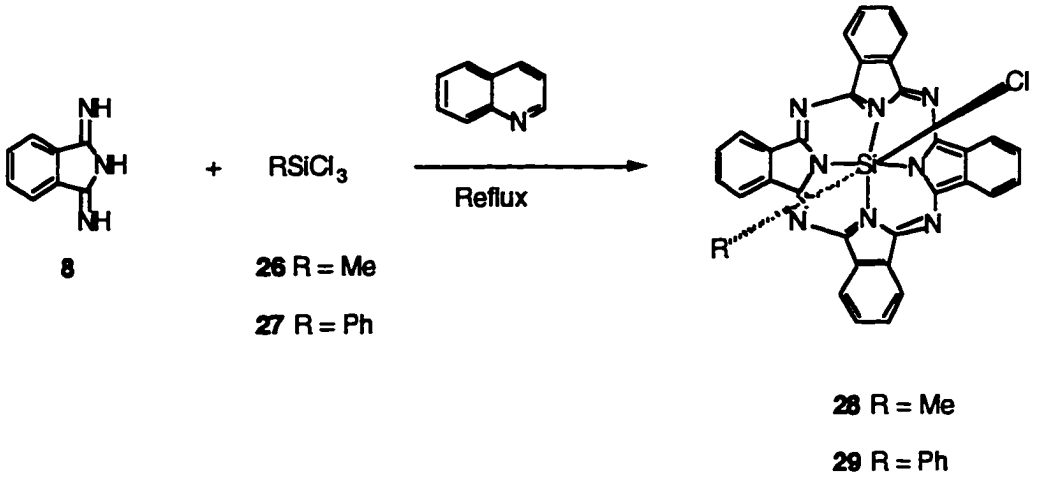
In the originally reported synthesis of dichlorosilicon phthalocyanine, *o*-phthalonitrile was allowed to react with either silicon tetrachloride or hexachlorodisiloxane in quinoline.[20b] These syntheses were experimentally inconvenient and were improved by Kenney in 1965.[22] The most convenient synthesis was based on 1,3-diiminoisoindoline (**8**), and mirrors the synthesis of metal free phthalocyanine discussed previously (Scheme VI). This method allowed for crystalline dichlorosilicon phthalocyanine to be synthesized in high yield (78%). Later it was shown that if the chlorines are replaced with different *trans* groups, the solubility of the phthalocyanine greatly increases.[23] In addition, work was carried out where one, but not both, of the *trans* groups is a methyl (**28**) or phenyl (**29**) group. Davison and Wynne took advantage of the solubility

Scheme V



properties of silicon phthalocyanines to synthesize silicon phthalocyanine monomers for incorporation into siloxane polymers.[24] Hanack took this idea one step further and looked to develop a conducting organic material based on silicon phthalocyanine.[25] Hanack was able to displace the chloride and simultaneously polymerize the metal phthalocyanine by a linear bridging ligand, such as acetylene, to give the phthalocyanine based polymer **30** (Scheme VI).

Scheme VI



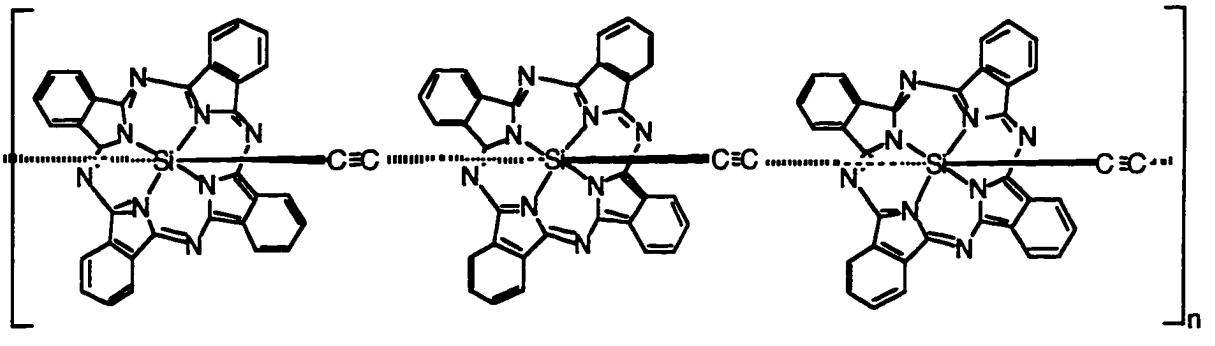
8

26 R = Me

27 R = Ph

28 R = Me

29 R = Ph



30

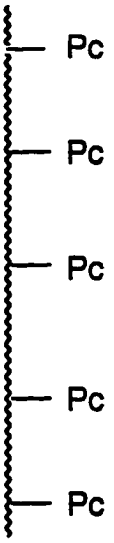
Results and Discussion

We became interested in phthalocyanines for the reasons of stability and spectroscopic properties. The challenge for the project was to create molecules that held the pigments in a proper orientation and at set, defined distances. For optimum overlap and energy transfer, a distance of 10-15 angstroms is best. We also believed that previous syntheses of substituted phthalocyanines were less than ideal and could be greatly improved upon.

Our original strategy is shown in Scheme VII, where we envisioned the phthalocyanine dyes being held at defined distances by three different systems. The first system was based on a polypeptide backbone. Urry had discovered that peptide polymers of the type VPGXG would spontaneously form alpha helices when heated to 80°C in an aqueous solution.[26] We imagined replacing the X group in the VPGXG sequence with lysine, and utilizing the ε-amino group as a handle on which to attach the pigment, giving a molecule such as **3 1**. The second idea was to attach the pigment via the central atom to a styrene moiety and then polymerize to form a polystyrene-based antenna like **3 2**. The final idea was to synthesize an arborol **3 3** and then attach pigments to the arborol at the peripheral oxygens and form a "sphere" where the pigments are tangential to the surface of this sphere.

We began our synthesis concentrating on the chemistry of the central atom of the phthalocyanine knowing that a suitable peptide could easily be synthesized by standard methods or eventually synthesized on an automated peptide synthesizer available to our department. As previously mentioned, Kenney had been able to attach a phenol to the aluminum of chloroaluminum phthalocyanine by using up to 300 equivalents of alcohol in the reaction. Thinking that there was significant room for improvement, we varied the conditions for the nucleophilic displacement of the chlorine by an alcohol. Chloroaluminum phthalocyanine was synthesized in the usual way using dicyanobenzene and aluminum chloride in refluxing quinoline. Upon recrystalization from 1-chloronapthalene, purple crystals were isolated in 80% yield. Our first idea was to try nucleophilic displacement of the chlorine with the oxygen anion of hydroquinone, hoping for a bridged phthalocyanine species (Scheme VIII). Using pyridine as a solvent, 1 equivalent of hydroquinone was added to 2.1 equivalents of **1 6**. Unfortunately, only starting material was isolated after four days. Introduction of Hunig's base (5 equivalents) and Hunig's base with excess hydroquinone also returned starting chloroaluminum phthalocyanine. Even refluxing with pyridine had no effect on the starting material. Clearly something more reactive was needed in order to cleave the aluminum-chlorine bond.

Scheme VII



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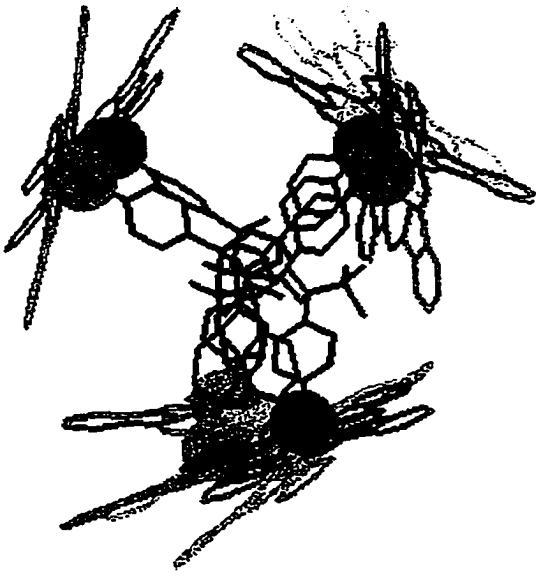

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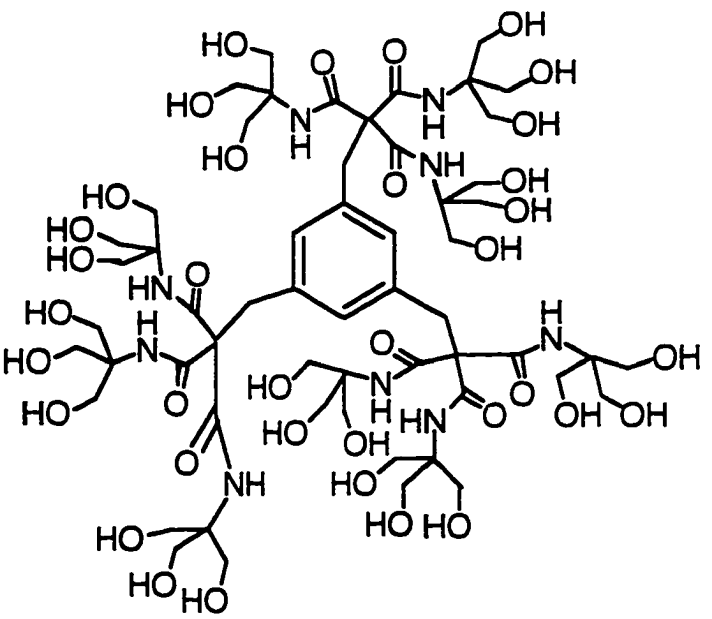
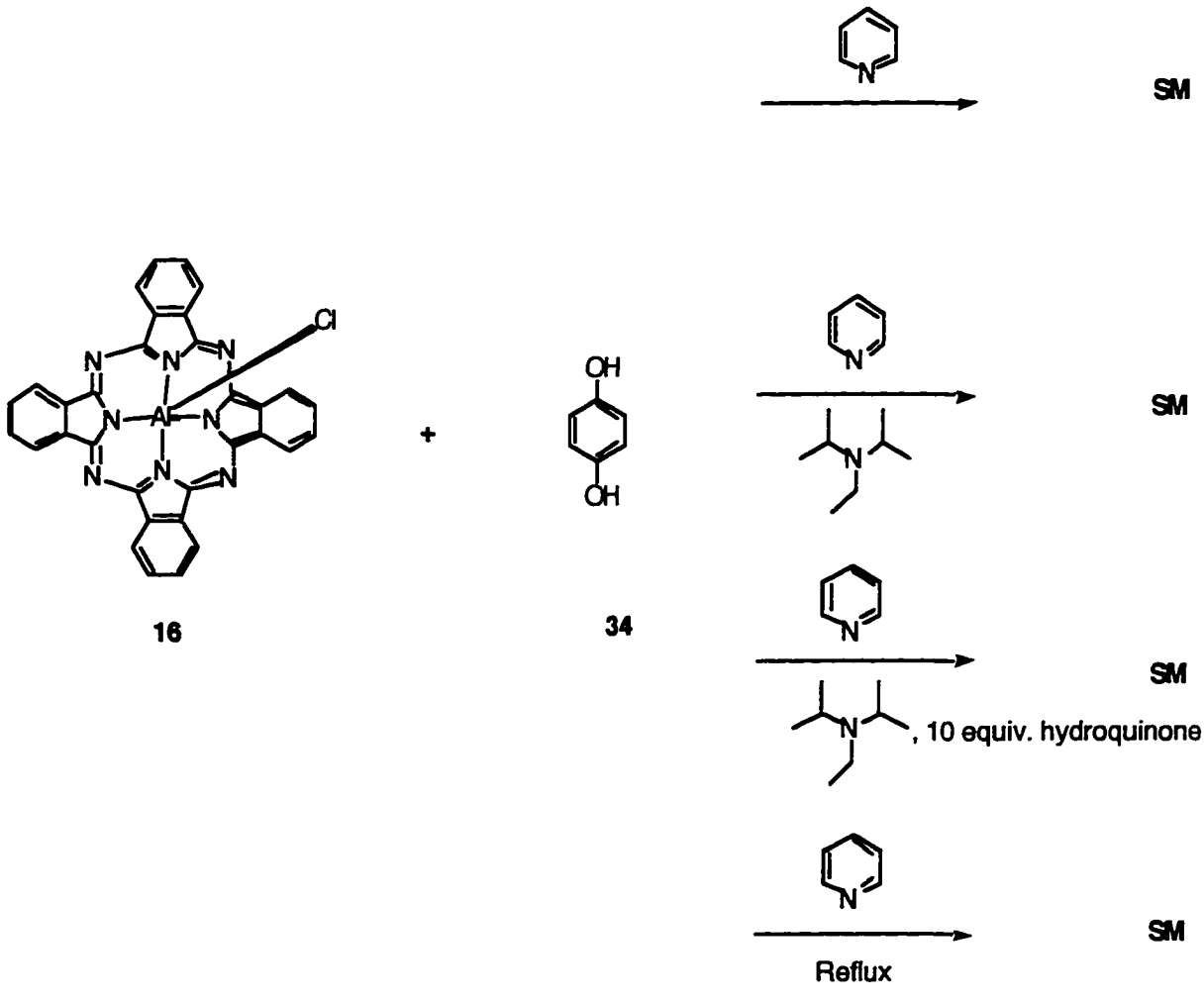


33

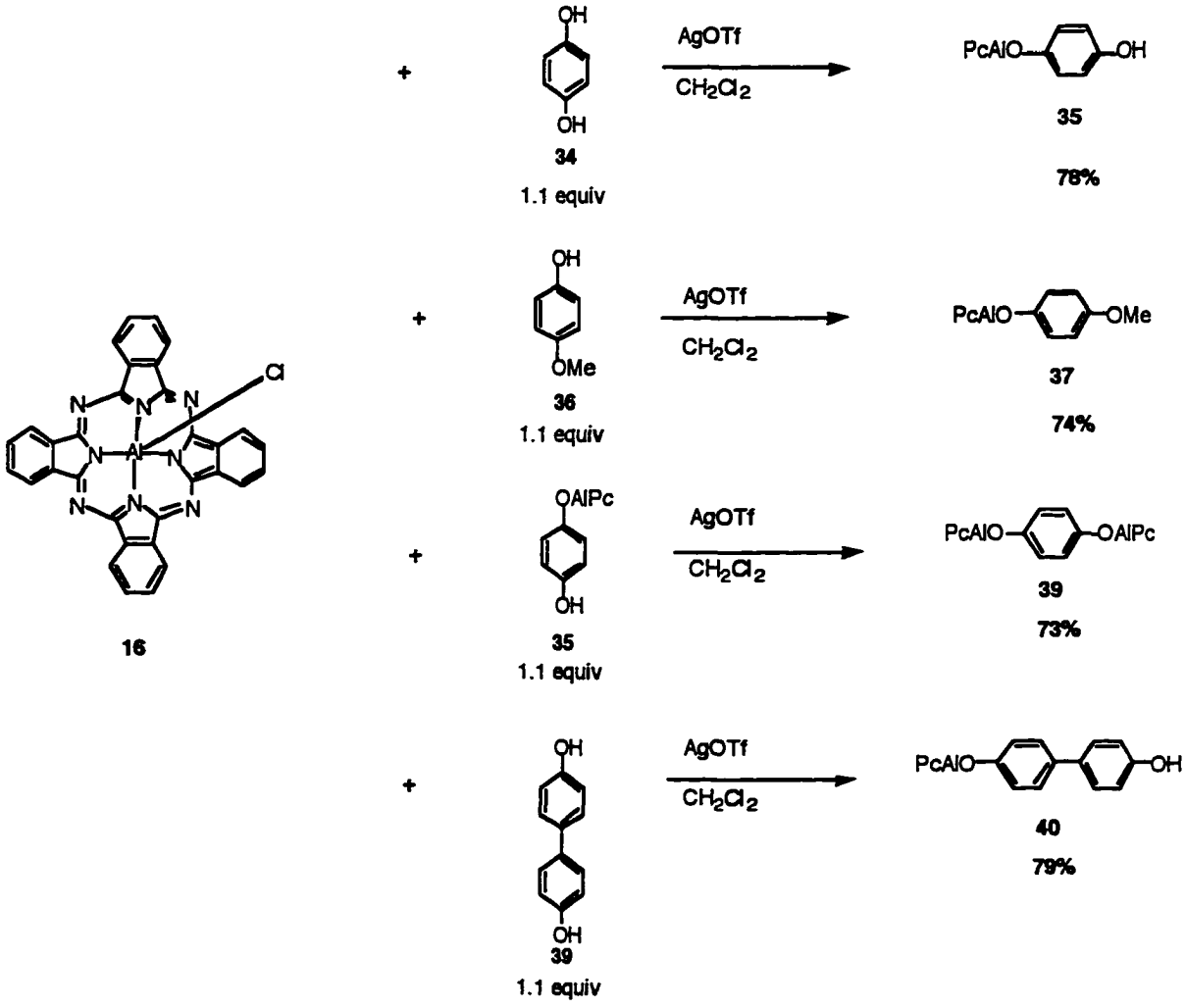
Scheme VIII



Our idea was to incorporate Ag^{+1} into the reaction in order to complex with the chlorine of the phthalocyanine in solution and facilitate the addition of the hydroquinone to the aluminum center. This was achieved by using silver trifluoromethanesulfonate (silver triflate). The phthalocyanine was dissolved in methylene chloride and 1 equivalent of silver triflate was added to the solution in the absence of light. After one hour, 1.1 equivalents of hydroquinone (**3 4**) were added and the reaction was allowed to stir overnight. Upon isolation of the reaction products, ^{1}H NMR and UV spectroscopy showed the attachment of the hydroquinone to the aluminum center to give compound **3 5** in 78% yield (Scheme IX). Reactions utilizing silver triflate in a 1:1 coupling were unprecedented in the

literature, and a number of compounds using various hydroquinone derivatives were developed. Use of *p*-methoxyphenol (**36**) under similar conditions led to **37** in 74% yield. Treatment of **16** with silver triflate and then 1.1 equivalents of **35** led to the bridged compound **38** in 78%

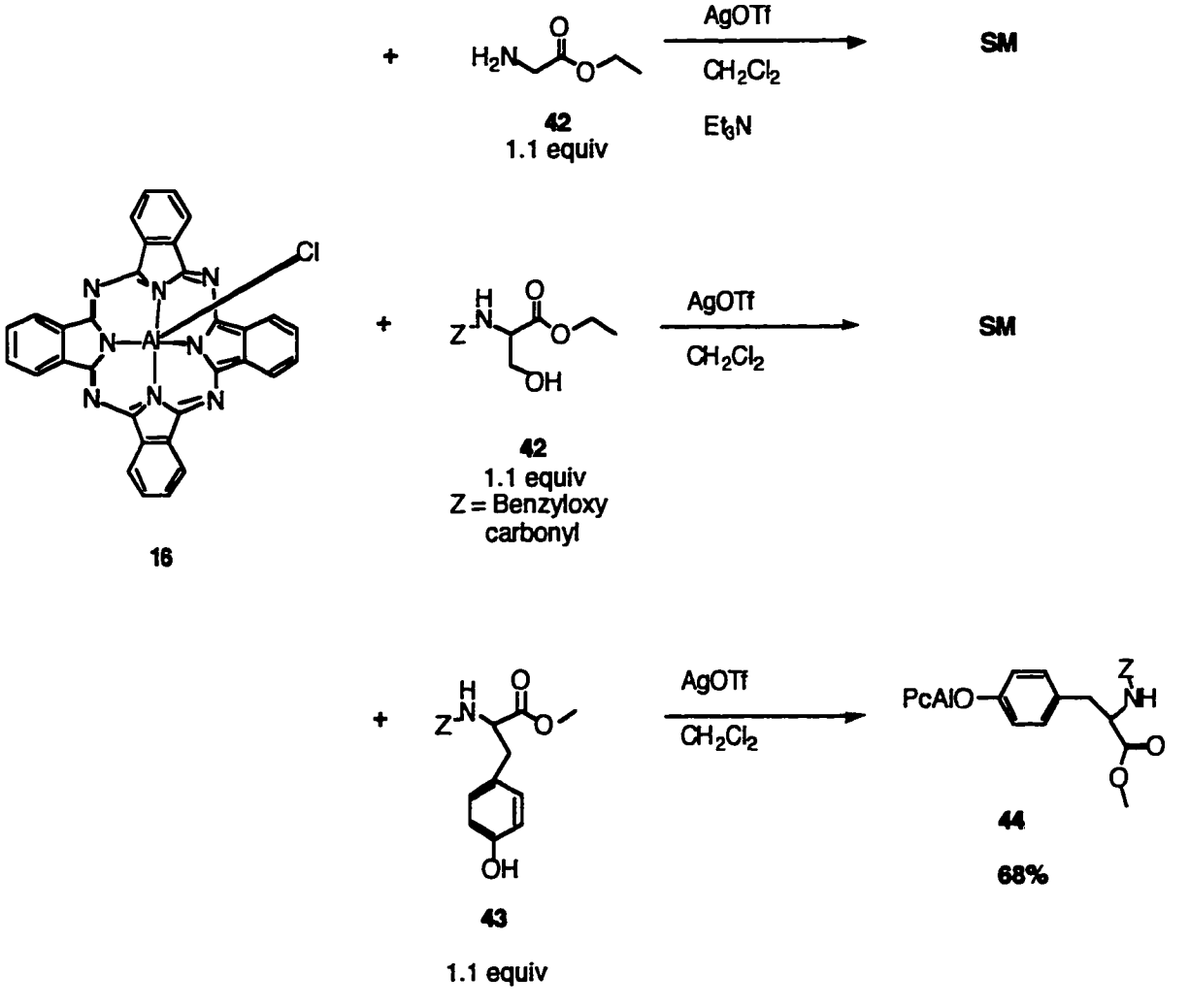
Scheme IX



yield. Finally, use of 4,4'-biphenol (**39**) as the nucleophile led to substituted phthalocyanine **40** in 79% yield. Realizing that the main goal of the project was to be able to attach phthalocyanine units to a polymer backbone at set, defined distances, we needed to elucidate the ability of the silver triflate reaction conditions

to connect a phthalocyanine to a peptide residue. To accomplish this, **1 6** was combined with the silver triflate and then 1.1 equivalents of glycine ethyl ester hydrochloride (**4 1**) and 1.1 equivalents of triethyl amine (Scheme X).

Scheme X

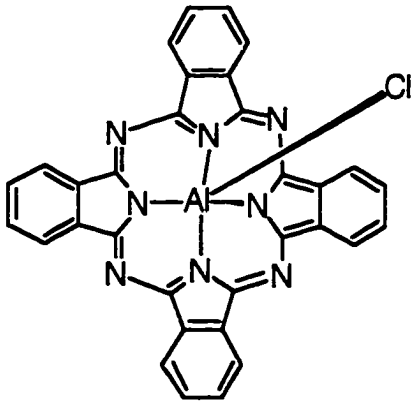


Unfortunately, only starting material was recovered. Similar results were obtained upon using the benzyloxycarbonyl protected serine ethyl ester derivative **4 2**. The serine derivative was made by reacting serine with benzyl chloroformate under pH=10 conditions at 0 °C and esterifying the resulting protected amino acid with potassium carbonate and methyl iodide.[27] To better mimic the success of our phenol conditions, we turned to tyrosine as an amino acid that would link our

polypeptide chain to the pigment. Reacting L-tyrosine methyl ester with sodium carbonate and benzyl chloroformate afforded the Z-protected tyrosine residue **43** in 81% yield.[28] Addition of the tyrosine to the chloroaluminum phthalocyanine / silver triflate reaction mixture afforded in 68% yield the tyrosine-substituted aluminum phthalocyanine **44**. This gave us the unprecedented ability to bind phthalocyanines selectively to a tyrosine residue in a polypeptide chain.

After completion of the above reactions, it was evident that the phthalocyanines could be made in high, reproducible yields. Also, monosubstitution was possible using our new silver triflate technology, provided that we use a phenol as our link. Unfortunately, these compounds tended to degrade over time, especially when placed in protic solvents, such as methanol. It was clear that the aluminum-oxygen bond was basically a salt linkage and was being destroyed in the protic solvents. We needed to find a more stable linkage. One of the advantages of phthalocyanines, upon first inspection, is that the periphery aromatic positions should be susceptible to aromatic substitution reactions. We tried various aromatic substitution reaction conditions on **16**, including nitration,[29] bromination,[30] methylation via methyl triflate,[31] and Vilsmeyer conditions (Scheme XI).[32] Nitration and bromination conditions lead to decomposition of the phthalocyanine starting material, while methyl triflate and Vilsmeyer conditions gave back starting material. Given these results, we believed that it would be advantageous to incorporate the necessary handle onto the peripheral rings prior to the phthalocyanine ring formation step. Of course, this would give us a mixture of tetra substituted phthalocyanines, but we felt it was necessary. We believed that by putting in an amino group on the phthalocyanine, we would have a suitable handle for linking to a polypeptide. Synthesis of the substituted phthalocyanine began with the nitration of phthalimide (**45**) using a 4:1 mixture of concentrated sulfuric acid and nitric acid at 0 °C (Scheme XII).[29] The resulting 5-nitro-1H-isoindole-1,3(2H)-dione (**46**) was combined with ammonium hydroxide and THF and ammonia gas bubbled through the solution for 30 minutes to give upon work up 4-nitro-1,2-benzenedicarboxamide (**47**) in 71% yield.

Scheme XI



16

HNO_3, H_2SO_4 → **X**

H_2SO_4, $KBrO_3$ → **X**

Br_2, HNO_3, H_2SO_4 → **X**

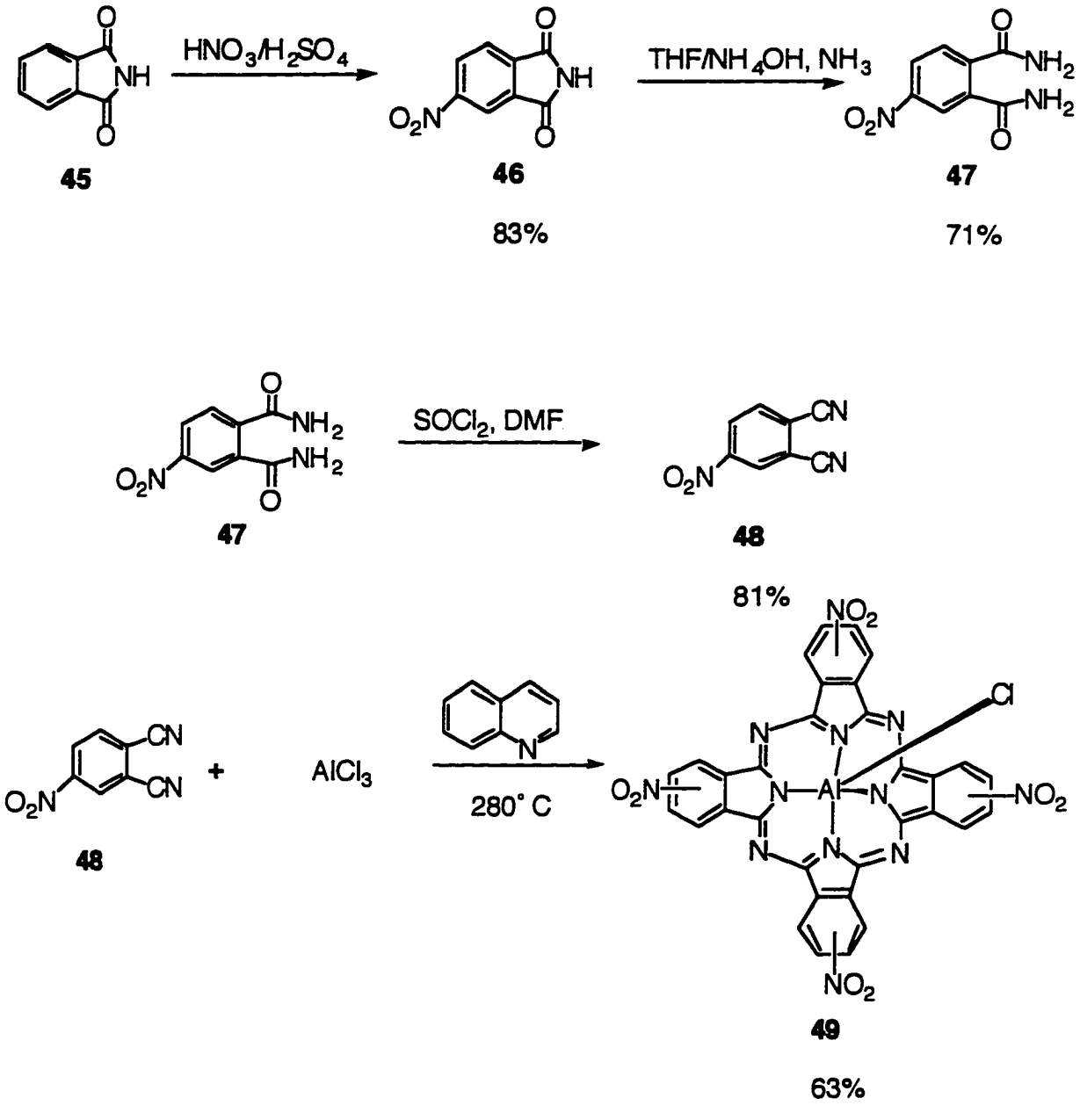
MeOTf, CH_2Cl_2 → **SM**

$POCl_3$, DMF → **SM**

Treatment of **47** with two equivalents of thionyl chloride in DMF at 0 °C, gave 4-nitro-1,2-dicyanobenzene (**48**) in 81% yield. The 4-nitro-1,2-dicyanobenzene was the combined with aluminum chloride in a sealed tube with quinoline as a solvent and heated to 280 °C for 4 hours to give the tetranitro-chloroaluminum phthalocyanine (**49**) in 63% yield.

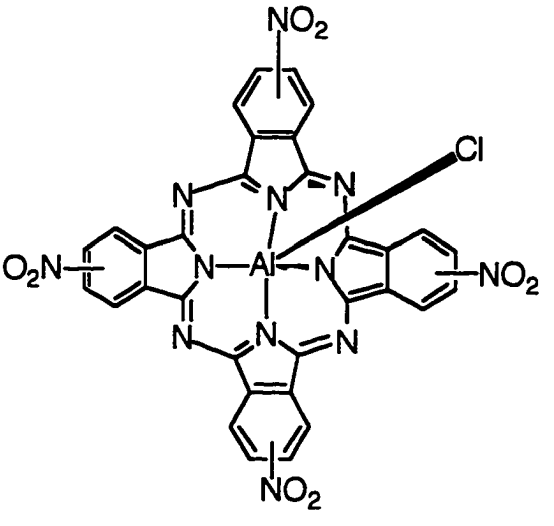
With **49** in hand, we were ready to attempt to reduce the nitro group to an amino group for the purpose of creating an attachment point for the polypeptide.

Scheme XII



Unfortunately, attempts to reduce the nitro groups via catalytic platinum / hydrogen,[33] catalytic palladium / hydrogen ,[34] Raney nickel / hydrogen,[35] iron /acidic methanol, stannous chloride / ethanol,[36] and zinc / sodium hydroxide,[37] failed (Scheme XIII). The unsuccessful attempts at reducing the nitro group of the phthalocyanine ring led us to explore replacing the nitro groups with amines or

Scheme XIII



PtO_2, H_2 → EtOH/EtOAc → **SM**

H_2, Pd/C, HCl → **SM**

H_2, Raney Ni → **SM**

Fe, HCl → **SM**

$SnCl_2$, EtOH → **SM**

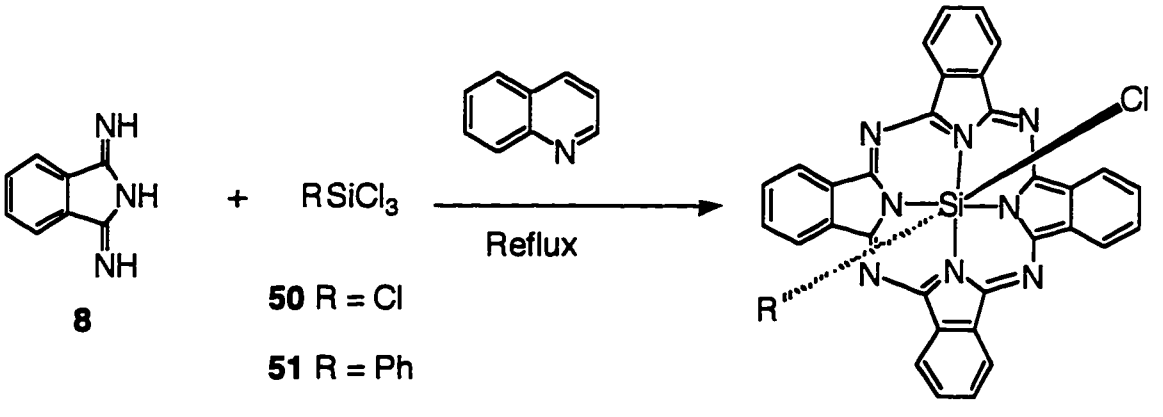
Zn, NaOH → **SM**

some other functionality (such as a thio or hydroxy group) that would allow us to attach it to the polypeptide. Unfortunately, although the starting materials were readily made from **4** **8**, any attempts to cyclize them and form a phthalocyanine were fruitless.

The attempts to make a more stable connection between chloroaluminum phthalocyanine and some sort of handle were a failure. It was apparent that further

revision of our idea was necessary and the possibility of turning to a different central atom emerged. Keeping in mind that the central atom must have a low molecular weight and be able to be functionalized readily, we turned to dichlorosilicon phthalocyanine **5 2**. Dichlorosilicon phthalocyanine has two major advantages over the aluminum analog in that it has two sites available for nucleophilic attack and the chemistry of the silicon-oxygen bond is well precedented in the literature. The synthesis of **5 2** followed that of Scheme VI; starting with 1,3-diiminoisoindoline (**8**) and silicon tetrachloride (**5 0**) in refluxing quinoline gave the dichlorosilicon phthalocyanine in 80% yield (Scheme XIV). By replacing silicon tetrachloride with phenyl trichlorosilane (**5 1**), we were able to get the unsymmetrical phenylchlorosilicon phthalocyanine (**2 9**) in 39% yield.

Scheme XIV



52 R = Cl 80%

29 R = Ph 39%

Believing that the silicon atom in phenylchlorosilicon phthalocyanine should behave like any other silicon, we attempted a classical silylation of an alcohol using imidazole and benzyl alcohol in DMF (Scheme XV).[38] Much to our surprise, these reaction conditions returned starting material. Nucleophilic displacement of the chloride with sodium benzoate in refluxing benzyl alcohol gave starting material also. Most disturbing was the fact that reactions with silver triflate and

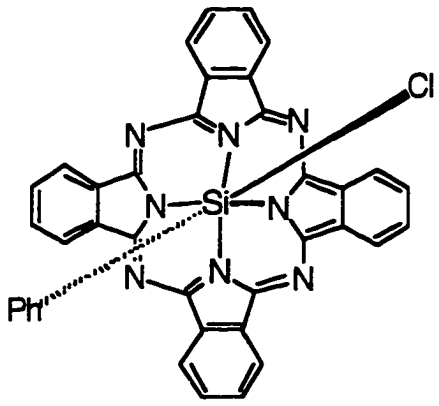
p-methoxyphenol and *p*-nitrophenol were likewise unsuccessful. Even the dianion of propargyl alcohol returned starting material after mixing with (**29**) overnight.

We were quite discouraged by this turn of events. We had assumed that the silicon-chlorine bond would be quite easily displaced in this system affording us a stable silicon-oxygen bond, which should have been able to withstand any other conditions in our reaction sequence. Clearly the silicon-chlorine bond was not acting like other silicon-chlorine bonds in other systems, such as TBDMSCl. A literature search revealed conflicting data.[39] It turns out that the silicon-chlorine bond is very unstable and readily hydrolyzes in air. This explained why the triflate chemistry was not working; we were dealing with the hydroxy compound and not the chlorine compound. To ensure that we had the hydroxy compound, **29** was reacted with excess sodium hydroxide in refluxing pyridine following the procedure of Davison and Wynne[24] to afford the hydroxy compound **53** in quantitative yield (Scheme XVI).

The use of siloxy phthalocyanines as nucleophiles is unprecedented in the literature, but our idea was to form the siloxy anion and react it with a substituted triazine. The triazine would have a free alcohol as a second attachment, affording us a substituted phthalocyanine with the proper functionality to attach to the polypeptide, polystyrene, or arborol. The synthesis of the substituted triazine began by reacting benzaldehyde with ethylene glycol in the presence of a catalytic amount of PTSA to afford acetal **55** in 89% yield (Scheme XVII).[40] Treatment of acetal **55** with four equivalents of aluminum chloride and a one equivalent of lithium aluminum hydride in ether at 0 °C led to alcohol **56** in 78% yield. Compound **56** was deprotonated with 1 equivalent of sodium hydride and added to 1 equivalent of cyanuric chloride to afford the monosubstituted triazine in 68% yield.[41]

With the monosubstituted triazine successfully synthesized, the next step was to attach the phthalocyanine and this proceeded smoothly using 1 equivalent of sodium hydride as a base to give the disubstituted triazine **58** in 71% yield

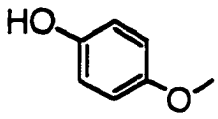
Scheme XV

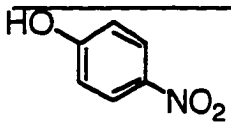


29

Imidazole, benzyl alcohol → **SM**

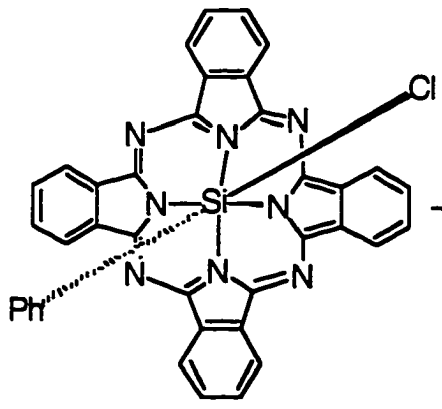
Sodium benzoate, Benzyl alcohol, reflux → **SM**

AgOTf, DMF,  → **SM**

AgOTf, DMF,  → **SM**

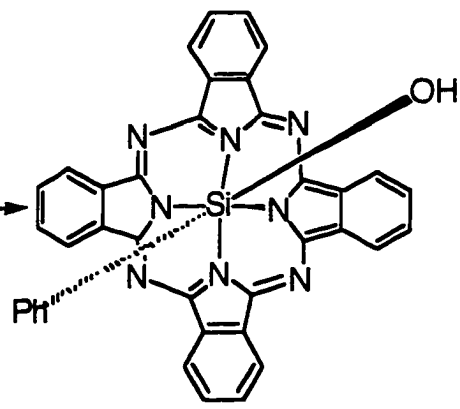
2 equiv Na, propargyl alcohol → **SM**

Scheme XVI



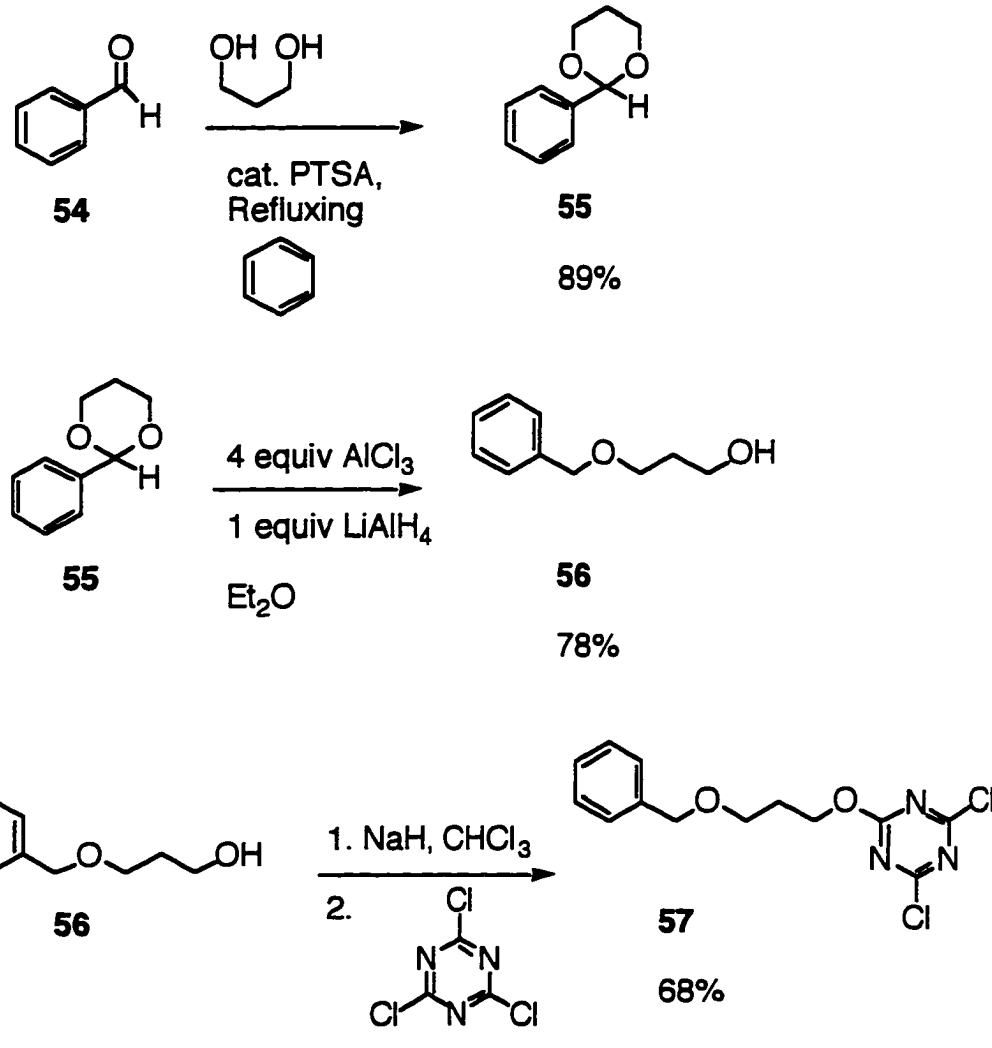
29

NaOH, Pyridine, H_2O, Reflux



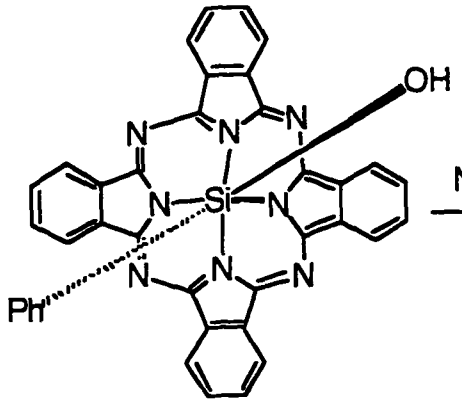
53

Scheme XVII



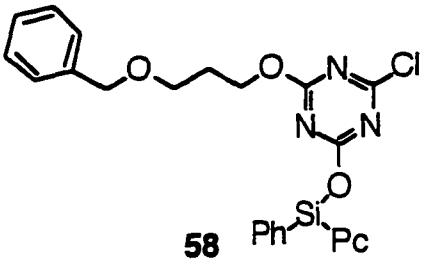
(Scheme XVIII). If another equivalent of the phthalocyanine anion was added to **5 8** and allowed to react over a four day period in refluxing chloroform, bis phthalocyanine adduct **5 9** could be formed in 54% yield. Cleavage of the benzyl protecting group was accomplished with TMSI to afford the alcohol **6 0** in quantitative yield.[42] At this point it was decided to form a small dendrimer molecule that could serve as a model compound for the spectroscopy studies to be completed by the Struve group. Upon completion and analysis of these model studies, more elaborate compounds could be made using **6 0** as the key

Scheme XVIII



53

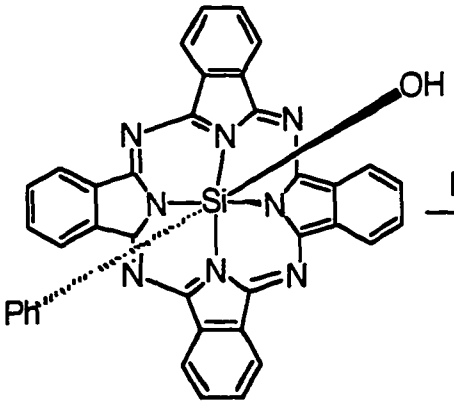
NaH, **57**



58

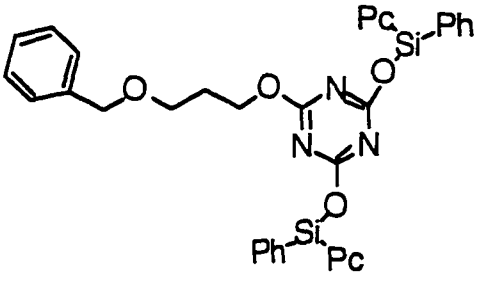
71%

Pc = Phthalocyanine



53

NaH, **58**

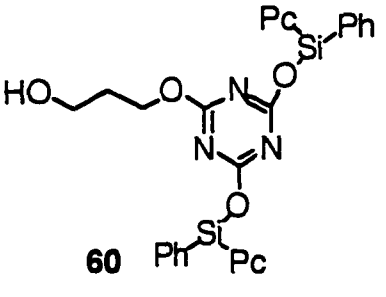


59

54%

59

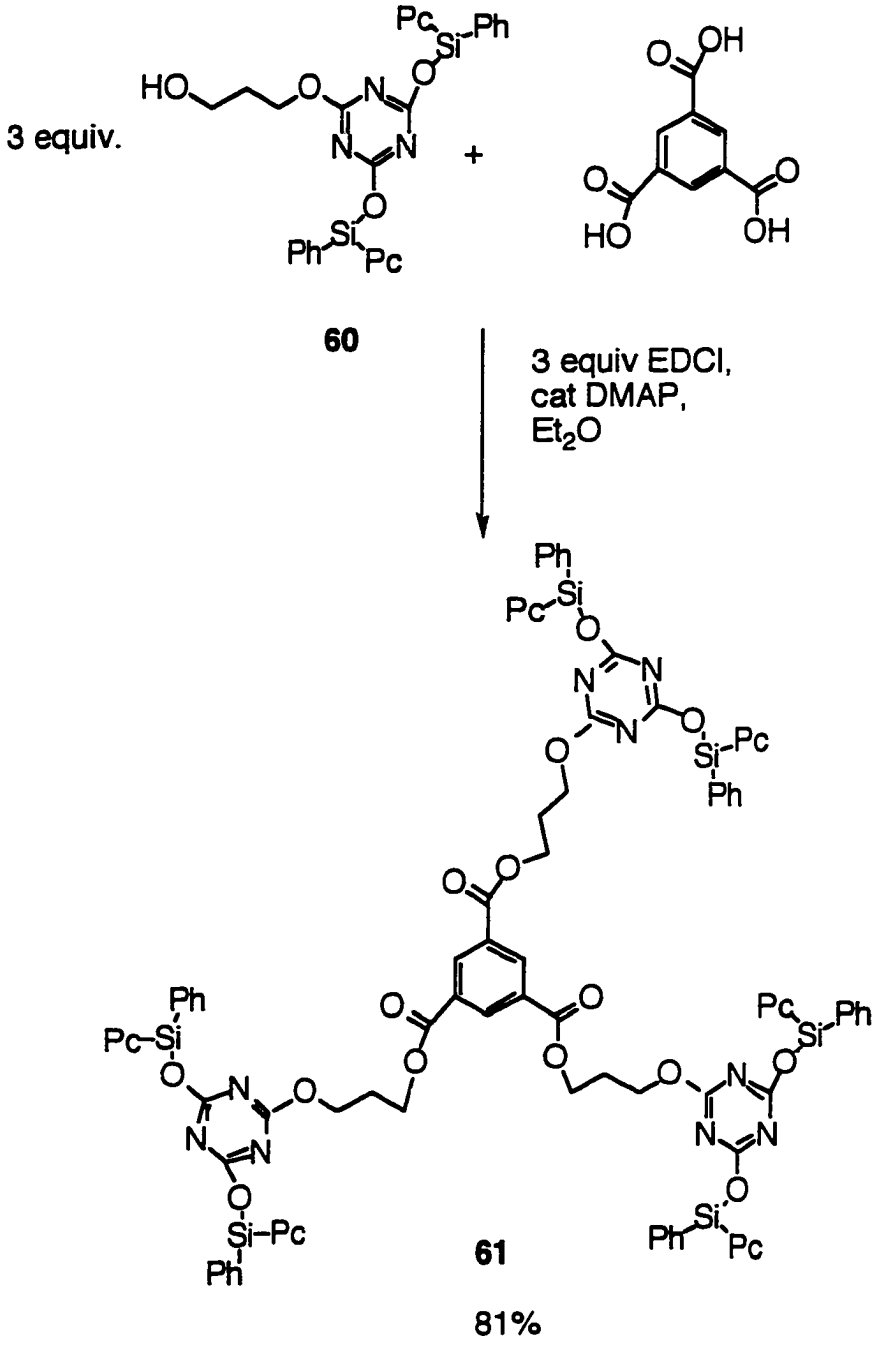
TMSI



60

Quantitative

Scheme XIX



intermediate. To form this model compound, **60** was treated with EDCI (1-(3-Dimethylaminopropyl)-3-carbodiimide hydrochloride, a water soluble carbodiimide), DMAP, and 1,3,5-tribenzoic acid to form ester **61** in 81% yield (Scheme XIX). This is the first known compound of this type with six

phthalocyanines surrounding a central core. It is hopeful that compound **60** will be useful in determining the mechanism for energy transfer in natural photosynthetic systems.

Conclusions

We have developed two methods to form substituted phthalocyanines that are bound to an organic molecule via the central atom. The new route for silicon phthalocyanines promises to open up an entire new class of interesting compounds via the common intermediate **60**. A series of dendrimers, each with an increasing number of phthalocyanine sub units, could be formed quite directly using this route. Also, alcohol **60** offers a suitable handle for esterification to an amino acid side chain as part of a larger polypeptide network. Along the way, we have also developed new methodology for the attachment of chloroaluminum phthalocyanines using silver triflate. This is a unique reaction for this system.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl

acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Varian 300 Spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Varian 300 Spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

Chloro[phthalocyaninato (2-) N^{29},N^{30}, N^{31}, N^{32}] Aluminum (16). To a solution of aluminum chloride (1.00 g, 7.5 mmol) in 25 mL of refluxing quinoline, was added 5.00 g of *o*-phthalonitrile (39.0 mmol, 5.2 equiv.). After heating for 30 min., the reaction mixture is cooled to room temperature and filtered. The remaining solid is washed consecutively with benzene, chloroform, and then acetone. The remaining solid is dried under reduced pressure at 110 °C for 3 hours to give 2.61 g (61%) of product as purple crystals. ^1H NMR ($CDCl_3$) δ 8.37-8.52 (m, 8H), 9.60-9.75 (m, 8H). IR (nujol) 1127, 1080, 1042, 907, 880, 791 cm^{-1}. Anal. Calcd. for $C_{32}H_{16}N_8AlCl$: C 66.85, H 2.81, N 19.48. Found: C 66.81, H 2.84, N 19.51.

PcSi(Ph)(Cl) (29). To a solution of 1,3-diiminoisoindoline (5.00 g, 34.4 mmol) in 12.5 mL of tri-*n*-butylamine and 40.0 mL of refluxing tetralin, was added 10.57 g of phenyltrichlorosilane (50.0 mmol, 1.45 equiv.). After heating for 4 hours, the reaction mixture is cooled to room temperature and filtered. The remaining

solid is washed with methanol. The solid is then dried under reduced pressure at 110 °C for 3 hours to give 8.75 g (39%) of product as a green powder. ^{1}H NMR (CD_3OD) δ 6.81 (s, 5H), 8.37-8.42 (m, 8H), 9.63-9.69 (m, 8H). Decomposition of compound to PcSi(Ph)(OH) limited analysis to ^{1}H NMR.

PcAl(OC_6H_4OH) (35). To a solution of chloroaluminum phthalocyanine **16** (0.300 g, 0.52 mmol) in 2.0 mL of dry methylene chloride, was added 0.154 g of silver trifluoromethanesulfonate (0.60 mmol, 1.1 equiv.) in the absence of light. After stirring for 12 hours, 66.0 mg of hydroquinone (0.60 mmol, 1.1 equiv.) was added. After stirring for 16 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and the suspension filtered. The solvent was removed in vacuo affording the crystalline phthalocyanine in 78% yield. The remaining solid was washed with methanol. ^{1}H NMR (CD_3OD) δ 6.69 (s, 4H), 8.37-8.54 (m, 8H), 9.60-9.75 (m, 8H). IR (nujol) 1125, 1084, 1029, 913, 874, 794 cm^{-1}. Anal. Calcd. for $C_{38}H_{21}AlN_8O_2$: C 70.37, H 3.26, N 17.27. Found: C 70.30, H 3.29, N 17.30.

PcAl($OC_6H_4OCH_3$) (37). To a solution of chloroaluminum phthalocyanine **16** (0.100 g, 0.20 mmol) in 2.0 mL of dry methylene chloride, was added 51.0 mg of silver trifluoromethanesulfonate (0.60 mmol, 1.1 equiv.) in the absence of light. After stirring for 12 hours, 25.0 mg of *p*-methoxyphenol (0.20 mmol, 1.1 equiv.) was added. After stirring for 16 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and the suspension filtered. The solvent was removed in vacuo affording the crystalline phthalocyanine in 74% yield. ^{1}H NMR (CD_3OD) δ 3.62 (s, 3H) 6.67 (s, 4H), 8.39-8.53 (m, 8H), 9.63-9.75 (m, 8H). IR (nujol) 1124, 1083, 1037, 903, 880, 797, 772, 737 cm^{-1}. UV (MeOH) 670 (λ max), 638, 604. MS (EI, *m/z*) 662 (M^+), 647, 538, 123. Anal. Calcd. for $C_{39}H_{23}AlN_8O_2$: C 70.69, H 3.50, N 16.91. Found: C 70.71, H 3.49, N 16.89.

PcAl(OC_6H_4OAlPc) (39). To a solution of substituted chloroaluminum phthalocyanine **35** (0.100 g, 0.15 mmol) in 2.0 mL dry methylene chloride, was added 42.3 mg of silver trifluoromethanesulfonate (0.60 mmol, 1.1 equiv.) in the absence of light. After stirring for 12 hours, 88.6 mg of chloroaluminum phthalocyanine **16** (0.15 mmol, 1 equiv.) was added. After stirring for 16 hours, the reaction mixture was concentrated in vacuo. The residue is dissolved in ethyl acetate and the suspension filtered. The solvent was removed in vacuo affording the crystalline phthalocyanine in 73% yield. ^1H NMR (CD_3OD) δ 6.67 (s, 4H), 8.37-8.55 (m, 16H), 9.60-9.75 (m, 16H). IR (nujol) 1124, 1086, 909, 885, 880, 797, 732 cm^{-1}. UV (MeOH) 673 (λ max), 640, 601. MS (EI, *m/z*) 1187 (M^+), 647, 538, 123. Anal. Calcd. for $C_{70}H_{36}Al_2N_{16}O_2$: C 70.82, H 3.06, N 18.88. Found: C 70.86, H 3.02, N 18.90.

4-Nitrophthalimide (46). To a solution of 10.0 mL of concentrated sulfuric acid and 2.50 mL of concentrated nitric acid at 15 °C, was added 2.00 g of phthalimide **45** (13.5 mmol) in portions over a 15 minute period. After stirring for 12 hours, the solution was cooled to 0 °C, and the resulting solid filtered and washed with ice cold ethanol. The solvent was removed in vacuo affording the crystalline 4-nitrophthalimide in 83% yield (mp = 194-196 °C). ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 9.1Hz, 1H), 8.45 (s, 1H), 8.60 (d, J = 9.1 Hz, 1H). IR (film) 3320, 3090, 3040, 1785, 1700, 1615 cm^{-1}. MS (CI, *m/z*) 192 (M^+), 103. ^{13}C NMR ($CDCl_3$) δ 117.9, 124.5, 130.1, 134.1, 137.3, 151.4, 167.0, 167.2

4-Nitrophthalamide (47). To a solution of 36.0 mL concentrated ammonium hydroxide and 50.0 mL of THF at 40 °C, was added 0.500 g of phthalimide **46** (2.6 mmol). After the solid had dissolved, ammonia gas was bubbled through the solution for 30 minutes. After stirring for 12 hours, the solution was cooled to 0 °C, and the resulting solid filtered and washed with ice cold ethanol. The solvent was removed in vacuo affording the crystalline 4-nitrophthalamide in 71% yield (mp =

196-197 °C).^{1}H NMR ($CDCl_3$) δ 7.65 (s, br, 1H), 7.80 (d, *J* = 9.1 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.30 (s, 1H). IR (film) 3410, 3300, 3180, 1655, 1605, 1515 cm^{-1}. MS (CI, *m/z*) 209 (M^+), 193. ^{13}C NMR ($CDCl_3$) δ 122.0, 124.1, 129.2, 137.4, 142.1, 147.3, 167.6, 168.9.

4-Nitro-1,2-benzenedicarbonitrile (48). To a solution of 0.500 g of phthalamide **47** (2.6 mmol) in 3.50 mL of DMF at 0 °C, was added 0.364 mL of thionyl chloride (5.00 mmol, 2.1 equiv.). After stirring for 12 hours, the solution was cooled to 0 °C, and the resulting solid filtered and washed with ice cold ethanol. The solvent was removed in vacuo affording the crystalline 4-nitro-1,2-benzenedicarbonitrile in 81% yield (mp = 140-142 °C). ^{1}H NMR ($CDCl_3$) δ 8.41 (d, *J* = 9.3 Hz, 1H), 8.68 (d, *J* = 9.3 Hz, 1H), 8.95 (s, 1H). IR (film) 3090, 3028, 2230, 1600, 1528 cm^{-1}. MS (CI, *m/z*) 173 (M^+), 127. HRMS m/z calculated for $C_8H_3N_3O_2$: 173.0226, measured 173.0228. ^{13}C NMR ($CDCl_3$) δ 113.7, 114.5, 117.0, 121.2, 128.3, 137.1, 150.0.

Chloro [2,9,16,23-tetranitro-29H,31H-phthalocyaninato (2-) - N^{29}, N^{30}, N^{31}, N^{32}] Aluminum (29). To a solution of aluminum chloride (1.00 g, 7.5 mmol) in 25 mL of refluxing quinoline, was added 5.00 g of 4-nitro-1,2-benzenedicarbonitrile **48** (28.9 mmol, 5.2 equiv.). After heating for 30 min., the reaction mixture was cooled to room temperature and filtered. The remaining solid was washed consecutively with benzene, chloroform, and then acetone. The remaining solid was dried under reduced pressure at 110 °C for 3 hours to give 2.64 g (63%) of product as green crystals. ^{1}H NMR ($CDCl_3$) δ 8.97-9.05 (m, 8H), 9.81-9.92 (m, 4H). UV (MeOH) 684 (λ max), 649, 612. Anal. Calcd. for $C_{32}H_{16}N_8AlCl$: C 50.98, H 1.60, N 22.28. Found: C 51.13, H 1.72, N 22.36.

Dichloro[phthalocyaninato (2-) N^{29},N^{30}, N^{31}, N^{32}] Silicon (52). To a solution of 1,3-diiminoisoindoline (5.00 g, 34.4 mmol) in 12.5 mL of tri-*n*-

butylamine and 40.0 mL of refluxing tetralin in a sealed tube, was added 5.72 mL of phenyltrichlorosilane (50.0 mmol, 1.45 equiv.). After heating for 4 hours at 265 °C, the reaction mixture was cooled to room temperature and filtered. The remaining solid was washed with methanol. The solid was then dried under reduced pressure at 110 °C for 3 hours to give 8.75 g (39%) of product as a deep blue powder. ^{1}H NMR (CD_3OD) δ 8.24-8.35 (m, 8H), 9.04-9.17 (m, 8H). Decomposition to $PcSi(OH)_2$ limited analysis to ^{1}H NMR.

PcSi(Ph)(OH) (53). To a solution of **29** (1.00 g, 1.5 mmol) in 15 mL of refluxing pyridine and 2 mL of water, was added sodium hydroxide (0.245 g, 4 equiv.). After heating for 4 hours, the reaction mixture was cooled to room temperature and filtered. The remaining solid was washed with refluxing methanol in a Soxlet extractor for 24 hours. The solid was then dried under reduced pressure at 110 °C for 3 hours to give 0.950 g (99%) of product as a green powder. ^{1}H NMR (CD_3OD) δ 6.81 (s, 5H), 8.37-8.42 (m, 8H), 9.63-9.69 (m, 8H). IR (nujol) 1077, 1072, 916, 830, 794 cm^{-1}. Anal. Calcd. for $C_{38}H_{22}N_8OSi$: C 71.91, H 3.49, N 17.65. Found: C 72.04, H 3.58, N 17.77.

2-Phenyl-1,3-dioxane (55). To a stirred solution of benzaldehyde (**54**) (8.00 mL, 78.0 mmol) in 50 mL of benzene was added ethylene glycol (4.25 mL, 0.75 equiv.) and *p*-toluenesulfonic acid (1.10 g, 0.10 equiv.). This solution was refluxed for 18 hours. Upon cooling, the solution was concentrated in vacuo and then diluted with 150 mL of ether, washed with 150 mL of 10% sodium hydroxide, and finally washed with 150 mL of brine. The organic layer was dried over sodium sulfate and then concentrated in vacuo affording 2-phenyl-1,3-dioxane in 89% yield. ^{1}H NMR ($CDCl_3$) δ 1.15-1.72 (m, 1H), 1.72-2.67 (m, 1H), 3.63-4.50 (m, 4H), 5.45 (s, 1H), 7.13-7.70 (m, 5H). IR (film) 3049, 2967, 1493, 1449, 1378, 1272 cm^{-1}. MS (CI, *m/z*) 164 (M^+), 146, 107, 57. HRMS m/z calculated for $C_{10}H_{12}O_2$: 164.0837, measured 164.0845 .

3-Benzyloxy-1-propanol (56). To 125 mL of cold diethyl ether at 0 °C was added 13.00 g of aluminum chloride (97.0 mmol, 4.0 equiv.). After the solid had completely dissolved, 0.910 g of lithium aluminum hydride (24.0 mmol, 1 equiv.) was added slowly, in portions, to the solution. The mixture was stirred at 0 °C for an additional 30 minutes. After 30 minutes, 4.00 g of 2-phenyl-1,3-dioxane (24.0 mmol, 1 equiv.) dissolved in 25 mL of diethyl ether was added dropwise via syringe. After 18 hours, 125 mL of 2N H_2SO_4 was added dropwise over one hour to the ether solution. The layers were then separated and the aqueous layer extracted with 125 mL of diethyl ether. The organic portions were combined and dried over sodium sulfate. The solvent was removed in vacuo to give 3.10 g (78%) of 3-benzyloxy-1-propanol as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.78 (qu, J = 6.2 Hz, 2H), 3.38-3.83 (m, 5H), 4.40 (s, 2H), 7.28 (s, 5H). IR (film) 3425, 3040, 2944, 2879, 1107 cm^{-1}. MS (CI, *m/z*) 166 (M^+), 107, 59. HRMS m/z calculated for $C_{10}H_{14}O_2$: 166.0994, measured 166.0999.^{13}C NMR ($CDCl_3$) δ 32.2, 61.6, 70.1, 73.2, 127.5, 127.9, 128.3, 138.1

2,4-Dichloro-6-(3-benzyloxy-1-propanoxy)-1,3,5-triazine (57). To a solution of **5 6** (1.75 g, 11.0 mmol) in 22 mL of freshly distilled chloroform was added 0.463 g sodium hydride (11.5 mmol, 1.1 equiv.). In a separate flask, 1.93 g cyanuric chloride (11.0 mmol, 1 equiv.) was dissolved in 22 mL of freshly distilled chloroform and heated to 50 °C. The sodium hydride/alcohol solution was then added dropwise with stirring to the cyanuric chloride solution over a period of 1 hour. After 4 hours of stirring, 50 mL of water was added and the layers separated. The aqueous layer was then extracted with methylene chloride and the combined organic layers dried over sodium sulfate. Removal of the solvent left 2.35 g of triazine ether **5 7** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.09-2.13 (m, 2H), 3.65 (t, J = 5 Hz, 2H), 4.53 (s, 2H), 4.61 (t, J = 5 Hz, 2H), 7.28 (s, 5H). IR (film) 3030, 2975,

1675, 1460, 1107 cm^{-1}. MS (CI, *m/z*) 318 (M^++ 4), 316 (M^++2), 314 (M^+), 166. HRMS m/z calculated for $C_{13}H_{13}O_2N_3Cl_2$: 313.0385, measured 313.0389.

Triazine Phthalocyanine ether (58). To a solution of **53** (0.100 g, 0.16 mmol) in 20 mL of freshly distilled chloroform was added 6.8 mg of sodium hydride (0.17 mmol, 1.1 equiv.). In a separate flask, 54.0 mg of **57** (0.17 mmol, 1.1 equiv.) was dissolved in 10 mL of freshly distilled chloroform and heated to 50 °C. The sodium hydride/alcohol solution was then added dropwise with stirring to the triazine solution over a period of 1 hour. After stirring overnight, 50 mL of water was added and the solution filtered. The solid was washed with hexane and methanol until the filtrate was colorless and then dried in vacuo to afford 0.103 g (71%) of **58** as a green powder. ^{1}H NMR ($CDCl_3$) δ 2.09-2.24 (m, 2H), 3.68 (t, J = 5.0 Hz, 2H), 4.59 (s, 2H), 4.64 (t, J = 5.0 Hz, 2H), 6.81 (s, 5H), 7.28 (s, 5H), 8.37-8.52 (m, 8H), 9.65-9.82 (m, 8H). Anal. Calcd. for $C_{51}H_{34}N_{11}ClO_3Si$: C 67.14, H 3.76, N 16.88. Found: C 67.01, H 3.82, N 16.96.

Triazine Bisphthalocyanine Ether (59). To a solution of **53** (63.5 mg, 0.10 mmol) in 20 mL of freshly distilled chloroform was added 4.4 mg of sodium hydride (0.11 mmol, 1.1 equiv.). In a separate flask, 0.100 g of **58** (0.11 mmol, 1.1 equiv.) was dissolved in 20 mL of freshly distilled chloroform and heated to 50 °C. The sodium hydride/alcohol solution was then added dropwise with stirring to the triazine solution over a period of 1 hour. After 4 days of stirring, 50 mL of water was added and the solution filtered. The solid was washed with hexane and methanol until the filtrate was colorless and then dried in vacuo to afford 81.5 mg (54%) of **59** as a deep green powder. ^{1}H NMR ($CDCl_3$) δ 2.09-2.24 (m, 2H), 3.68 (t, J = 5.1 Hz, 2H), 4.59 (s, 2H), 4.64 (t, J = 5.1 Hz, 2H), 6.81 (s, 10H), 7.28 (s, 5H), 8.37-8.52 (m, 16H), 9.65-9.82 (m, 16H). Anal. Calcd. for $C_{89}H_{55}N_{19}O_4Si_2$: C 70.77, H 3.67, N 17.61. Found: C 70.85, H 3.60, N 17.48.

Triazine Bisphthalocyanine Alcohol (60). To a solution of **59** (0.100 mg, 0.066 mmol) in 15 mL of freshly distilled chloroform was added 12.2 μl of iodotrimethylsilane (0.086 mmol, 1.3 equiv.). After 30 minutes of stirring, 15 mL of methanol was added and the solution filtered. The solid was washed with hexane and methanol until the filtrate was colorless and then dried in vacuo to afford 99.6 mg (quant.) of **60** as a deep green powder. ^{1}H NMR ($CDCl_3$) δ 2.07-2.28 (m, 2H), 3.67 (t, J = 5.1 Hz, 2H), 4.68 (t, J = 5.1 Hz, 2H), 6.81 (s, 10H), 8.37-8.52 (m, 16H), 9.65-9.82 (m, 16H). Anal. Calcd. for $C_{82}H_{49}N_{19}O_4Si_2$: C 69.33, H 3.47, N 18.72. Found: C 69.19, H 3.40, N 18.60.

Phthalocyanine Dendrimer (61). To a solution of 1,3,5-tribenzoic acid (48.9 mg, 0.023 mmol) in 22 mL of freshly distilled chloroform was added 13.4 mg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.07 mmol, 3.1 equiv.) and 1.4 mg of 4-dimethylaminopyridine (0.012 mmol, 0.5 equiv.) . After stirring for 10 minutes, 0.100 g of **60** (0.07 mmol, 3 equiv.) were added to the solution. After stirring for 2 days, the reaction was quenched with water and filtered. The remaining green powder was washed with water and acetone until the filtrate was colorless. The solid was then extracted in a Soxlet extractor for 48 hours using acetone as the solvent. Drying of the solid in vacuo afforded 0.254 g (81%) of **61** as a green powder. ^{1}H NMR ($CDCl_3$) δ 2.07-2.28 (m, 6H), 3.67 (t, J = 5.1 Hz, 6H), 4.68 (t, J = 5.1 Hz, 6H), 6.81 (s, 30H), 7.45 (s, 3H), 8.37-8.52 (m, 48H), 9.65-9.82 (m, 48H). Anal. Calcd. for $C_{255}H_{147}N_{57}O_{18}Si_6$: C 68.59, H 3.32, N 17.87. Found: C 68.47, H 3.23, N 17.70.

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CHAPTER 2. SYNTHETIC APPROACHES TO SOYBEAN CYST NEMATODE HATCH INHIBITORS

A paper, a portion of which was submitted to Journal of Agriculture and Food Chemistry

George A. Kraus and Steven J. Vander Louw

Introduction

Soybean cyst nematode (SCN), also known as *Heterodera glycines*, is one of the most widely distributed and economically devastating soybean pests. SCN was first reported in Japan by Hori in 1915 and first appeared in the United States in North Carolina in 1954.[1] SCN has since been confirmed in 28 states.[2] SCN was first detected in Iowa in 1978 in Winnebago County and currently 70 of 99 Iowa counties are known to be infested with SCN. It can be assumed that undetected infestations are probably present in many other counties as well.[3] The nematode now occurs in many other production areas worldwide including Canada and South American countries, such as Brazil and Colombia.[4] During the early years of soybean production in the United States, soybeans were grown for forage and green manure. In 1919, 99,000 acres of soybean were planted for production of seed. At present, soybean is planted on 60 million acres.[4] As the use of soybeans for more valuable products increased, the significance of the SCN problem has also increased. Documenting the economic impact of SCN is an arduous task at best, because detection is difficult in the early stages and the producers may attribute the loss in yields to other factors and not to SCN. If nationwide loss is conservatively estimated at 1%, SCN costs soybean producers $121 million in 1992 alone.[5] Typically the estimated percentage losses are not 1%, but rather range from 1.1- 5.8%.[5]

SCN survives in the soil as eggs contained within protective cysts. Many of the eggs contain fully developed second-stage juveniles (J2), which will hatch

under the proper conditions.[4] The hatched J2 is the only infectious stage of the nematode and will invade the root and complete its development as a sedentary endoparasite within the roots. As it establishes specialized feeding sites, the nematode draws off nutrients from the soybean for the remainder of its life cycle. The adult females continue to grow and eventually will break through the surface of the root and can be seen with the naked eye as white nodes on the root surface.[6] After fertilization, an adult female begins to deposit eggs externally and later will retain the remainder of the eggs within the body cavity. Females die upon completion of egg production and the body cavity becomes a tough protective covering for the eggs. The egg-filled body of the dead female, called the cyst, is easily dislodged from the root and encysted eggs can remain viable in the soil for eleven years or more. The cyst typically contains 200 to 400 eggs. Because of the relatively short life cycle of the SCN (24 to 30 days), under the proper conditions, three to four generations of SCN can be produced in a single growing season. This ability of the SCN to rapidly proliferate, combined with its hardiness and longevity make the SCN difficult to control.

The spread of the SCN has only added to the problem. Although the SCN can only move short distances, the spread has been continuous and has become a very serious problem for many soybean producers. The SCN is readily dispersed by the movement of infested soil through adherence to machinery, and may also be dispersed by wind, runoff water, livestock, wildlife, and migrating birds.

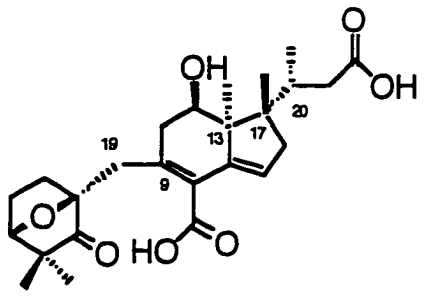
Currently, management of the SCN is achieved by incorporation of a crop rotation strategy, use of resistant soybean varieties, and the use of nematicides. Because of environmental and economic concerns, the use of nematicides has dwindled over the years.[6] In place of nematicides, crop rotation strategies have been utilized where two years of non-host crops are used followed by one year of SCN resistant soybeans. This strategy has been effective in controlling SCN population densities, but market considerations make this strategy unattractive, if not unfeasible, to producers. Also, the overuse of SCN-resistant soybean varieties

may lead to the development of SCN races which can readily reproduce on resistant soybeans.

In recent years there has been more interest in the possible development of herbicides that affect the hatch of the SCN.[7] Herbicides which stimulate or inhibit the hatch could be used to manage the SCN populations if they could cause the SCN to hatch prematurely in the absence of a host plant or completely suppress the hatch. In the absence of a host plant, the SCN would not be able to reproduce and would ultimately die from starvation, parasitism, or predation. If the SCN was found to be present during the growing season, a herbicide that surpressed hatch could be used to keep the population densities from proliferating.

Glycinoclepin A (Figure I) is a hatching stimulus capable of initiating hatch of SCN eggs at concentrations as low as 10^{-12} g/mL.[7] It is a naturally occurring compound which should be readily biodegradable. Glycinoclepin A has been isolated by extraction from kidney bean roots, but only milligram quantities were obtained from thousands of kilograms of roots.[7]

Figure I



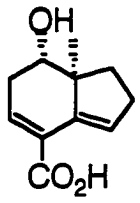
Glycinoclepin A

1

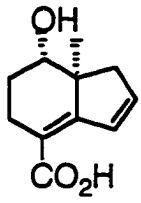
Murai and coworkers set out to determine the minimum functionality needed in order to stimulate SCN hatch. They synthesized numerous compounds and measured the minimum concentration accelerating the hatching of the larvae from half the number of eggs (ED_{50}) (Scheme I). It was determined from this study that the minimum functionality to induce hatch are the axial hydroxyl group and the two

carboxylic acids. Of significant interest, the side chain cyclohexanone functionality of **8** and also the position of the cross-conjugated system of **4-7** have little effect on the activity of the analogs.

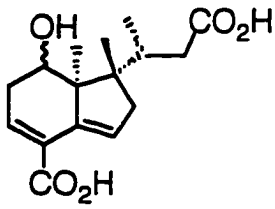
Scheme I



2 5×10^{-6} g/ml

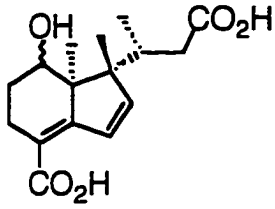


3 5×10^{-6} g/ml



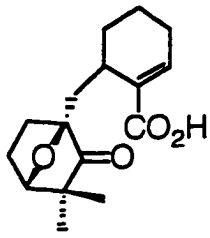
4 α-OH, 10^{-6} g/ml

5 β-OH, 10^{-7} g/ml

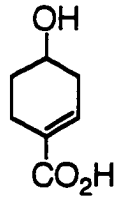


6 α-OH, 10^{-6} g/ml

7 β-OH, 10^{-7} g/ml



8 10^{-6} g/ml



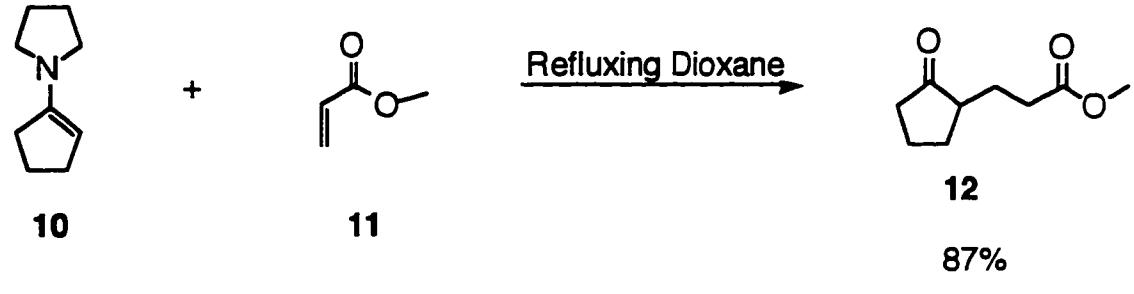
9 10^{-5} g/ml

The structure activity relationship was invaluable in determining the course of our project. We wished to develop a series of small molecules that would allow us to imitate the activity of glycinoclepin A. Of particular importance was that these molecules should be synthetically accessible in the fewest number of steps possible and be made from readily available starting materials. With these two goals in mind, we set out to discover new and potent compounds to control the proliferation of the soybean cyst nematode.

Results and Discussion

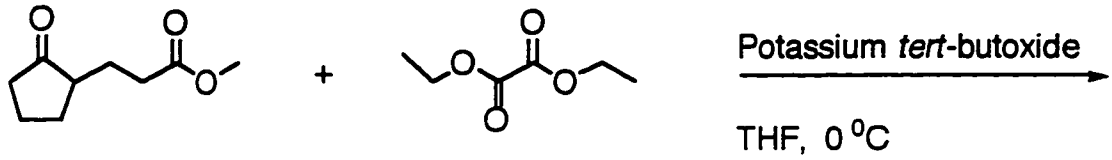
The synthesis of the analogs began with a plan to create a molecule that has as many of the necessary active groups as possible. Our first approach used a procedure by Bonadies and Scarpati as the key step in forming an unsaturated

Scheme II

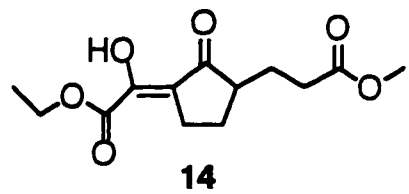


10 **11** **12**

87%



12 **13**



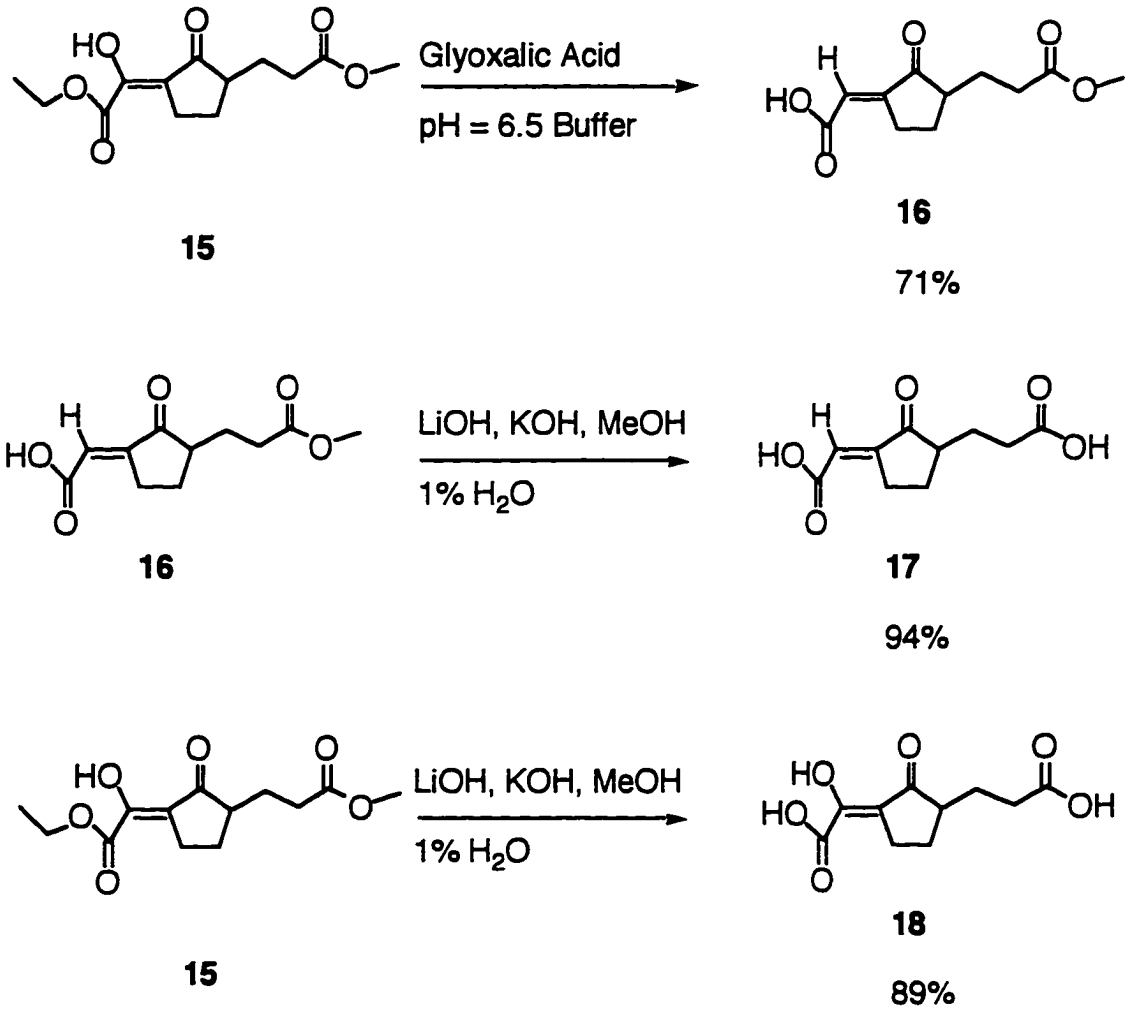
14

83%

acid from a enolic diketone.[8] The synthesis began with 1-pyrrolidino-1-cyclopentene (**1 0**) and methyl acrylate (**1 1**) in an enamine condensation developed by Stork (Scheme II).[9] This gave, upon acidic workup, the substituted cyclopentanone **1 2** in 87% yield. Treatment of **1 2** with 1 equivalent of potassium

tert-butoxide and an equivalent of diethyl oxalate (**13**) in THF at 0 °C gave the bis ester **14** in 83% yield. Compound **14** was a key intermediate in the synthesis and prepared us for the crucial reaction. Treatment of **14** with one equivalent of glyoxylic acid (**15**) at pH 6.5 in an aqueous phosphate buffer solution following the

Scheme III

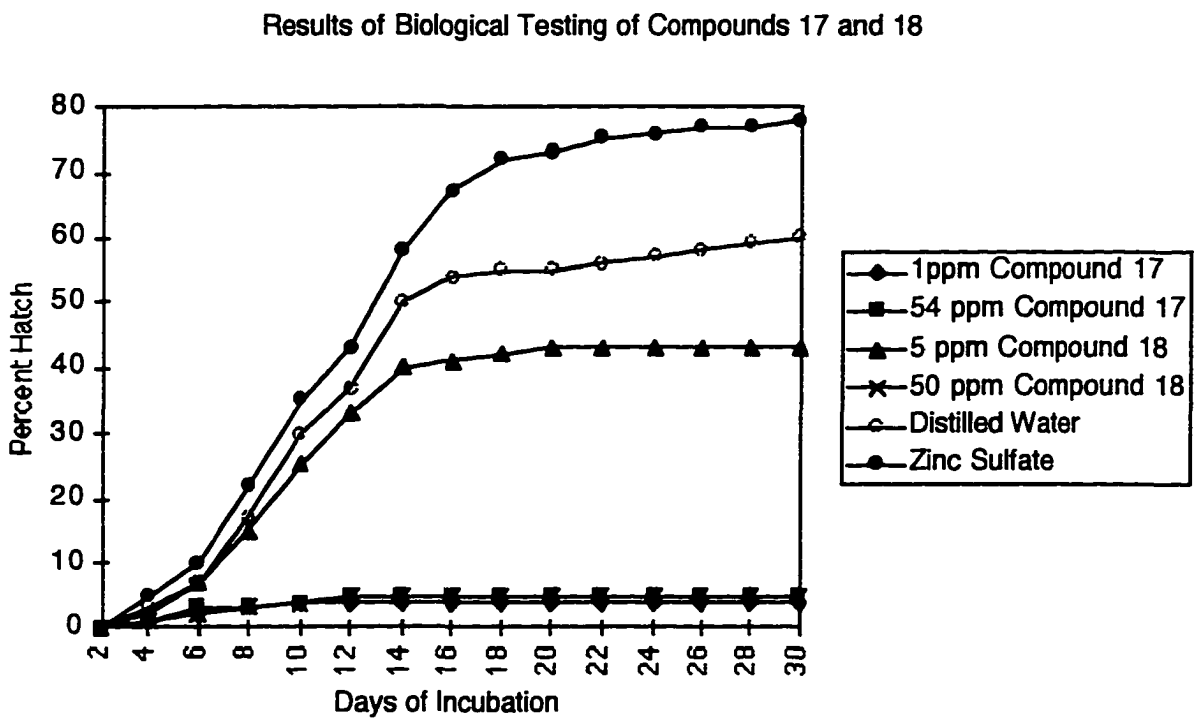


conditions given by Scarpati gave the unsaturated acid **16** in 71% yield (Scheme III). This reaction proved to be very difficult to reproduce at first until it was determined that the reaction is very pH dependent. Hydrolysis of the remaining ester using four equivalents of lithium hydroxide and two equivalents of potassium hydroxide in methanol / 1% water afforded the diacid **17** in 94 % yield. This

compound was then given to Dr. Greg Tylka of the Iowa State University Plant Pathology Department for testing as a hatch promoter of the soybean cyst nematode.

With the problems that we were having reproducing the glyoxylic acid reaction, we turned to key intermediate **15** as a possible alternative. Hydrolysis of **15** under the same conditions as used for **16** afforded diacid **18** in 89% yield. This compound was also submitted for testing. The results of the testing can be seen in Figure II.

Figure II

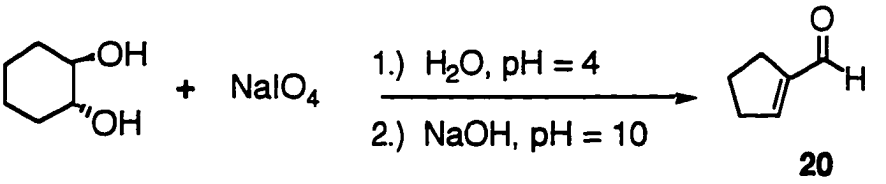


The compounds were tested using distilled water as a control and zinc sulfate, a known hatch stimulator, as a standard for comparison. The results of the screening surprised us. Unlike glycinoclepin A and zinc sulfate, compounds **17** and **18** were not hatch stimulators but rather hatch suppressers. In addition,

compounds **17** and **18** were also extremely potent, with **17** inhibiting the hatch at the 1 ppm level. It is also worth noting that if the compounds were washed away after 30 days and the eggs placed in water or zinc sulfate, the hatch profile resumed its normal curve. Therefore, clearly compounds **17** and **18** were not killing the SCN, but were repressing hatch by some unknown mechanism. This result was clearly unexpected and we set out to see if we could synthesize other analogs with even more potent activity or the opposite activity.

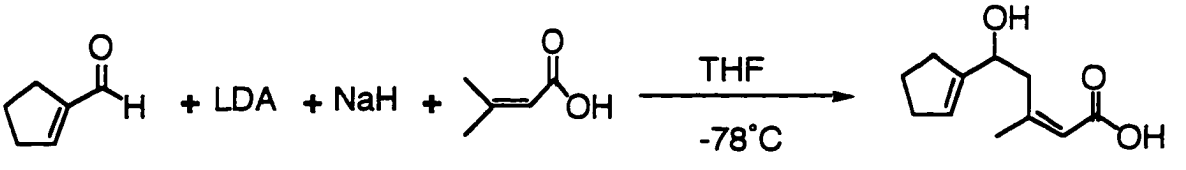
Our next step in the synthesis of the analogs involved combining the acid functionality that was so effective in **17** and **18** with a hydroxyl group somewhere in the molecule, and preferably an axial hydroxyl group. The synthesis began with the periodate oxidation of *trans*- 1,2-cyclohexanediol according to the procedure of Brown (Scheme IV).[10] The addition of 1.2 equivalents of sodium periodate to *trans*-

Scheme IV



20

79%



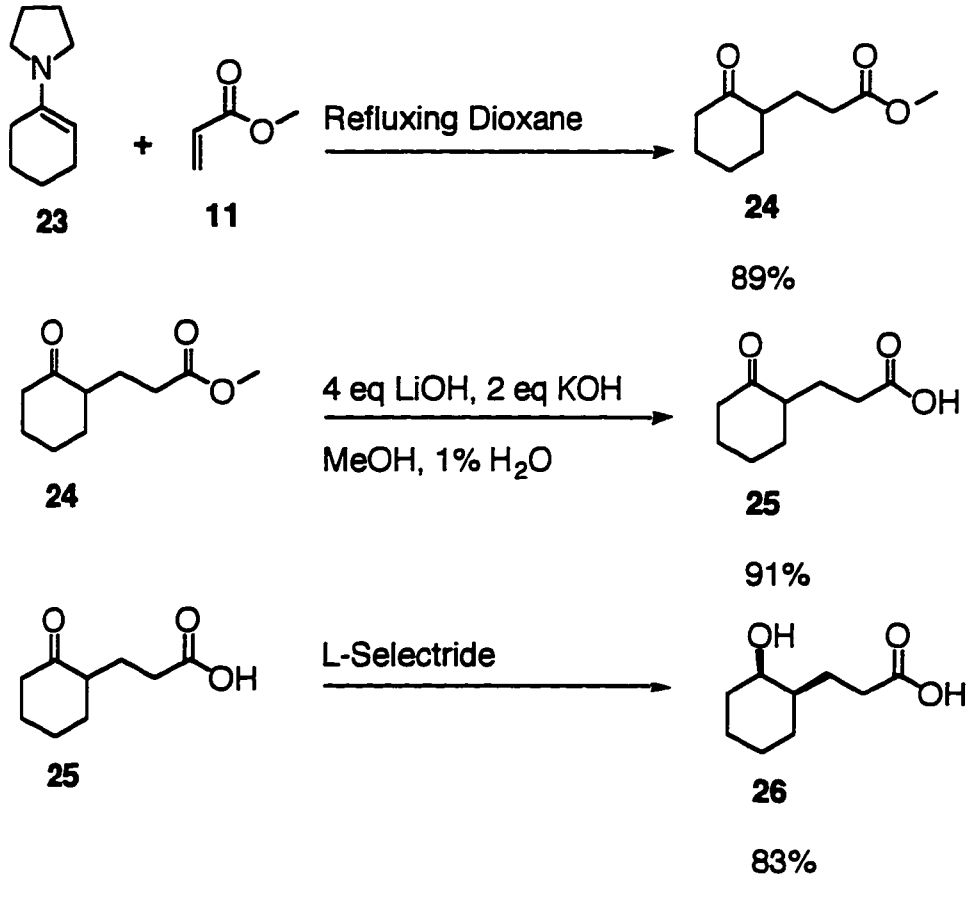
22

75%

1,2-cyclohexanediol at pH 4 followed by the addition of base led to 1-cyclopentene-1-carboxaldehyde (**20**) in 79% yield. Treatment of **20** with the dianion of 3-methyl-2-butenoic acid at -78 °C led to the hydroxy acid **22** in 75% yield.

In order to test the effectiveness of an axial alcohol combined with an acid moiety, we set out to make a six membered ring analog. This was accomplished using reactions that had already proven successful in our project. Treatment of 1-pyrrolidinone-1-cyclohexene (**23**) with methyl acrylate (**11**) gave the keto ester **24** in 89% yield (Scheme V). Hydrolysis of **24** under the standard lithium hydroxide and potassium hydroxide conditions gave the keto acid **25** in 91% yield.

Scheme V



23 **11** **24** 89%

24 **25** 91%

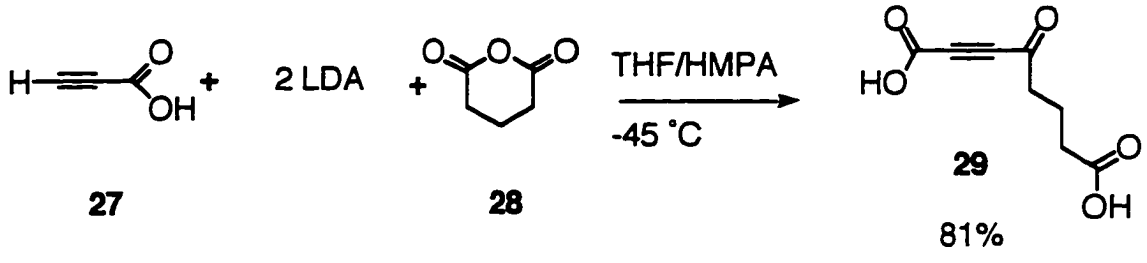
25 **26** 83%

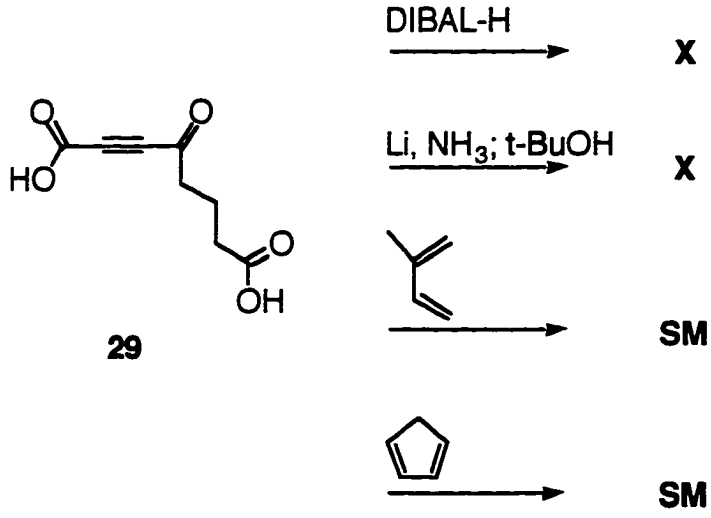
Reduction of the ketone using L-selectride gave the axial hydroxy acid **26** in 83% yield.[11] Compounds **22** and **26** were submitted for testing, but unfortunately they did not exhibit hatch stimulus properties; they were again hatch inhibitors, but marginal inhibitors at best.

Our next objective was to determine what effect, if any, the five membered ring had on the hatch suppressing activity. Our first attempt was to create a acyclic diacid with an acetylene moiety. Our thought was that the diacid acetylene could be used as a key intermediate to synthesize several other interesting compounds by a Diels-Alder reaction or reduction. Starting with propiolic acid (**27**), the dianion was formed with 2 equivalents of LDA in a 1:1 mixture of THF and HMPA at -45 °C. After the addition of 1 equivalent of glutaric anhydride (**28**), the reaction was allowed to warm to room temperature to afford the diacid **29**, upon protic workup, in 81% yield (Scheme VI). Attempted reduction of **29** with DIBAL or lithium in liquid ammonia led to degradation of the staring material. Also, attempted Diels Alder reactions with cyclopentadiene or isoprene similarly failed, returning the starting material, even at elevated temperatures in a sealed tube. Compound **29** was submitted for testing without further synthetic elaboration. Realizing that our best hatch inhibitors contained an enolic diketone and wanting to test the effect of the six member ring upon activity, an acyclic and six membered ring analog were synthesized and tested (Scheme VII). The acyclic analog was synthesized by reacting 4-acetylbutyric acid (**30**) with two equivalents of potassium *tert*-butoxide and one equivalent of diethyl oxalate (**13**) to afford the keto acid ester **31** in 91% yield. Hydrolysis of the remaining ester with lithium hydroxide and potassium hydroxide gave the keto diacid **32** in 95% yield . The cyclohexanone derivative was made by reacting previously synthesized **24** with potassium *tert*-butoxide in THF at 0 °C to give diester **33** in 90% yield. Subsequent hydrolysis afforded the diacid **34** in 97% yield.

Compounds **32** and **34** showed significant hatch suppression activity, but were not as effective as **17** and **18**, as a higher concentration of **32** and **34** were needed in order to achieve the same level of activity. With this new information, we decided to temporarily change the goal of the project slightly and instead of finding a hatch stimulator, we decided to investigate what the most economical route was to a hatch suppresser of superior activity. We wanted this hatch-inhibiting compound to contain the minimum functionality required to limit hatch activity and

Scheme VI

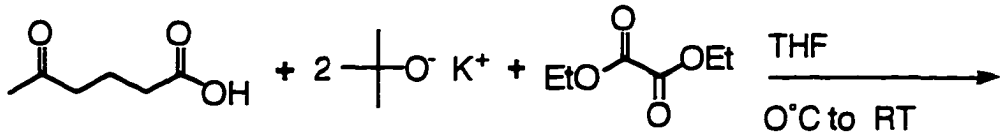




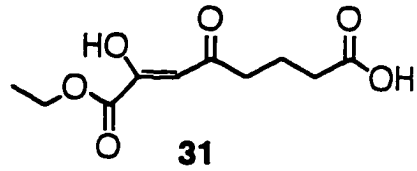
also be able to be synthesized in relatively few steps from commercially available materials. We felt that success in this area could greatly extend the current technology available to control the SCN.

Analyzing our results, we determined that of the compounds that are active in suppressing SCN hatch, they all had one of two common functional groups; the enolic dicarbonyl or the diacid. By incorporating these simple functional groups into our molecule, we hoped to have similar activity. The study began by testing our hypothesis that the enolic dicarbonyl was crucial to the activity of the analogs.

Scheme VII

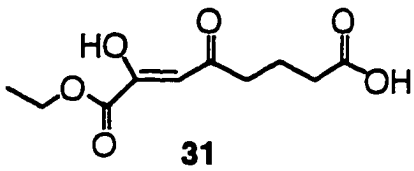


13

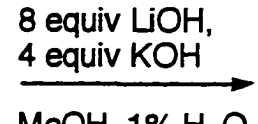


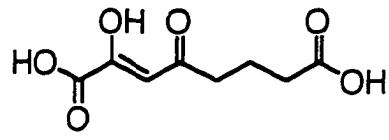
31

91%



31





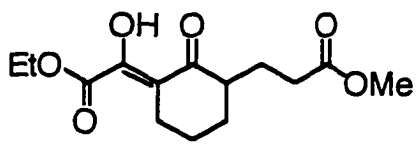
32

93%

13

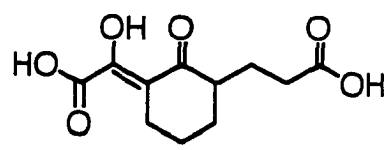
33

90%



33

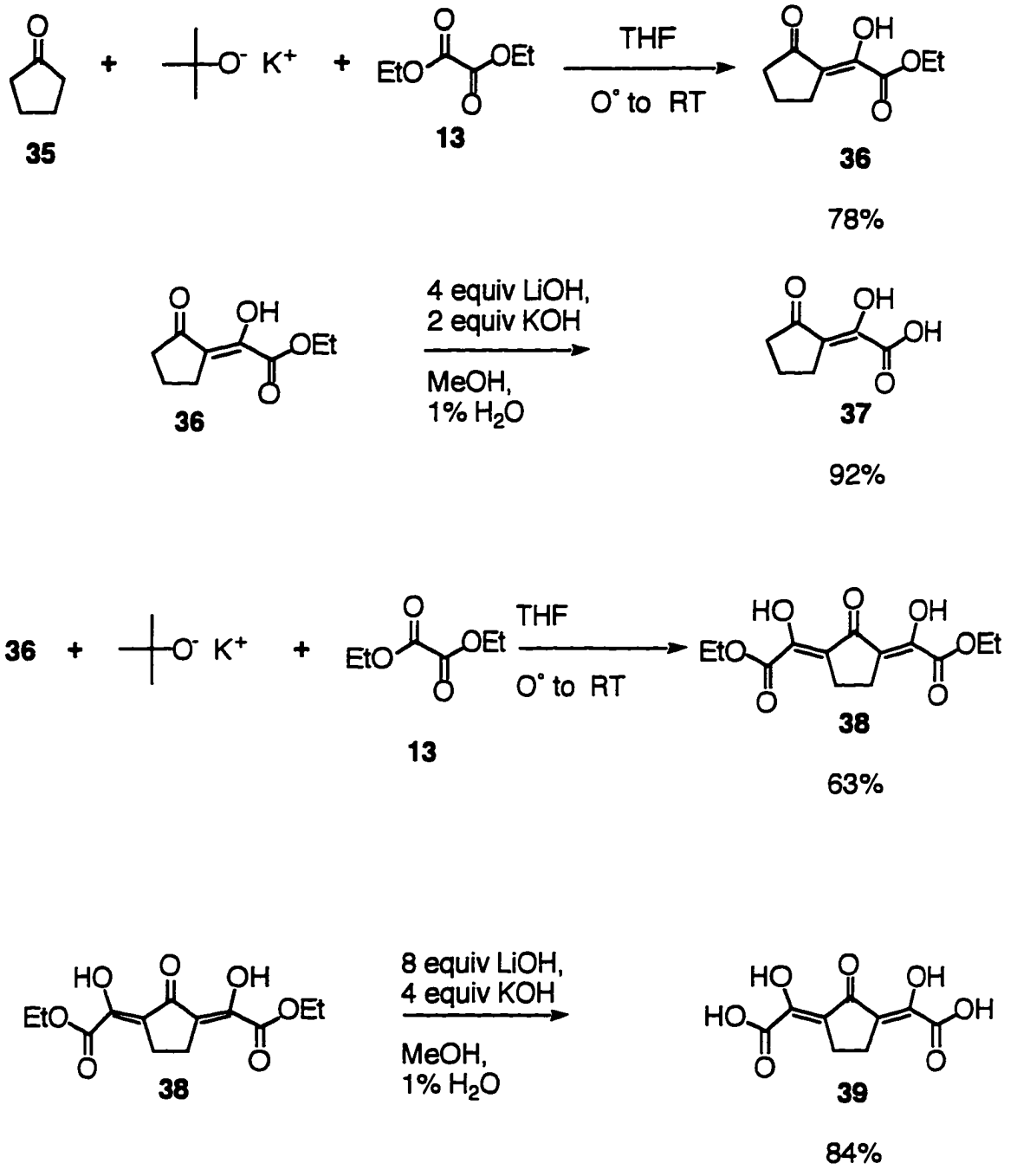
90%



34

97%

Scheme VIII



Therefore, cyclopentanone **35** was treated with one equivalent of potassium *tert*-butoxide and diethyl oxalate (**13**) to give the keto ester **36** in 78% yield. (Scheme VIII). Compound **36** was then hydrolyzed with lithium hydroxide and potassium hydroxide to give the keto acid **37** in 92% yield. Compound **36** was also

resubmitted to the basic conditions and another equivalent of diethyl oxalate (**13**) to form the diester **38** in 63% yield. Solubility problems dictated that **37** besynthesized stepwise from **36** instead of in one pot from cyclopentanone (**35**).

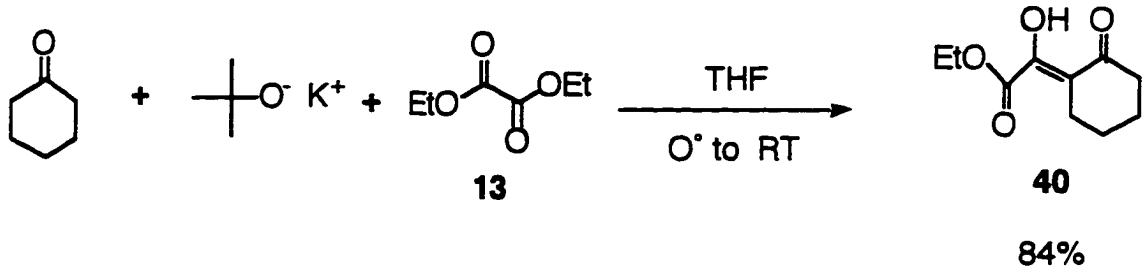
Compounds **36**, **37**, **38**, and **39** were all submitted for testing and the results were encouraging. It seems as though it is the enolic portion of the molecule that is producing the desired hatch suppression. There was significant hatch suppression by **36** and **37**, but the difference between the two was minimal. This demonstrated to us that the acid functionality was not needed for hatch inhibition, only the enolic dicarbonyl. Similar results were found with **38** and **39**. This was a very exciting development, because now it was possible to synthesize compounds in one step (from readily available and inexpensive starting materials) that effectively contained the hatch of the SCN. We felt it was worth our time to determine if ring size had anything to do with the activity. We synthesized the six and seven membered ring analogs **40-43** by similar methods and tested them for activity (Scheme IX). The results were similar to the five member ring analogs, with the ester being just as active as the acid, but overall the larger ring size seems to diminish activity slightly.

The final set of experiments to determine the minimum functionality required for hatch inhibition were centered around determining if the ester group of the enolic dicarbonyl was necessary for activity or if a simple enolic carbonyl was just as effective. To accomplish this, we chose to condense cyclopentanone with ethyl formate (**44**) to form the enolic derivative **45** (Scheme X). This compound was as active as any other in hatch inhibition.

We also wished to determine if a side chain acid group would enhance the activity of an enolic compound such as **45**. Therefore, keto ester **12** was condensed with ethyl formate (**44**) to form the enolic keto ester **46.** Compound **46** was then hydrolyzed to form the acid **47**.

All four compounds were tested. The results show that there is no significant difference between the simple enol **45** and the enolic dicarbonyl **36**. This proves that the active portion of the molecule is centered around the interaction of the enol

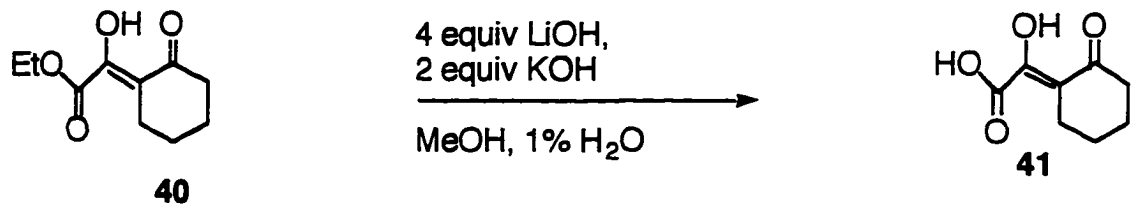
Scheme IX



13

40

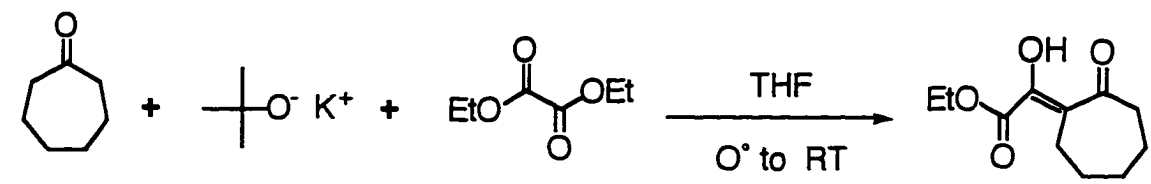
84%



40

41

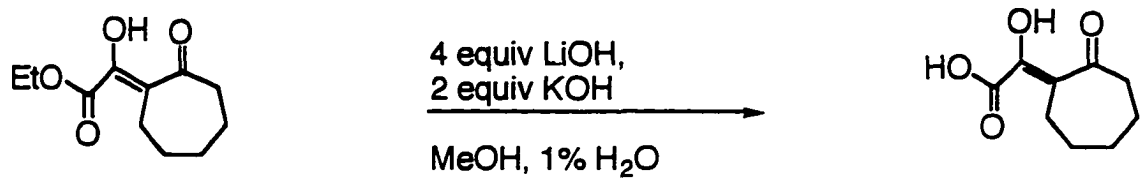
89%



13

42

84%

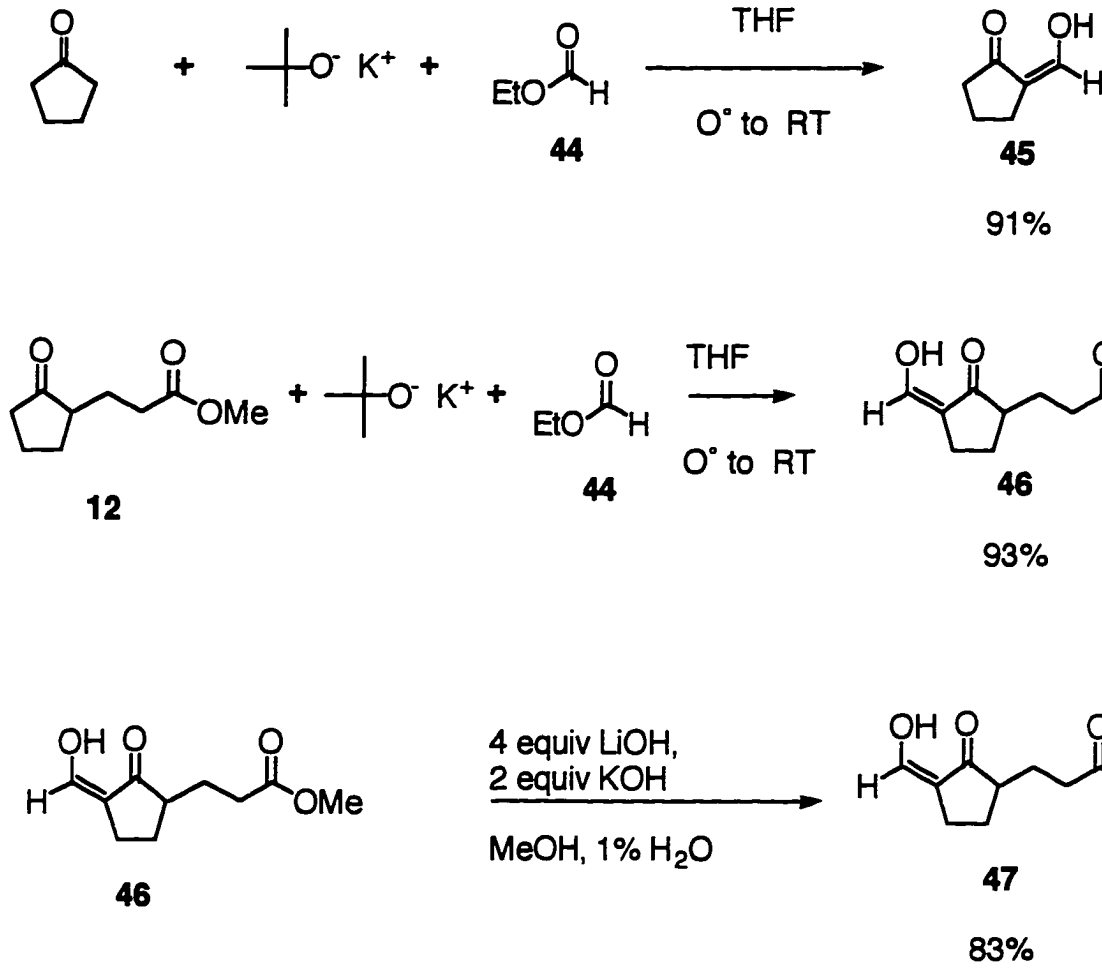


42

43

87%

Scheme X



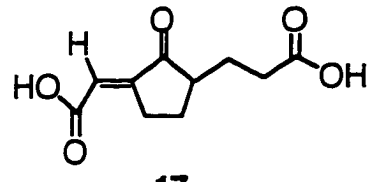
with the SCN (pure cyclopentanone had no activity). The addition of the side chain ester or acid offered no enhancement of activity.

Conclusions

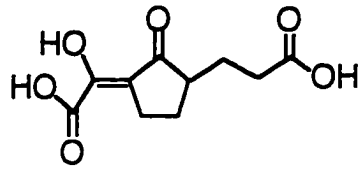
During this investigation we have come across some surprising, yet advantageous, results. Although our idea when we began this study was to develop small molecules that causes premature hatch of the SCN, we have synthesized nine compounds (**17**, **18**, **32**, **34**, **36**, **37**, **45**, **46**, and **47**) that effectively inhibit the hatch of the SCN (Figure III). These compounds have been submitted for two separate patents. During the course of the study we have ascertained that the minimum functionality for activity is the enolic dicarbonyl. Also,

we have discovered that the five membered ring analogs are more effective than the related six and seven membered ring analogs at inhibiting hatch. We have

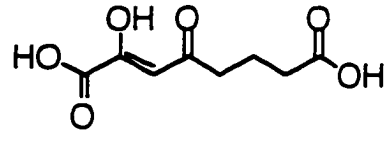
Figure III



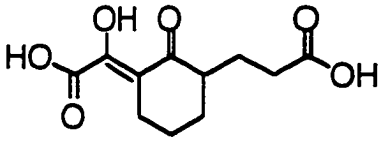
17



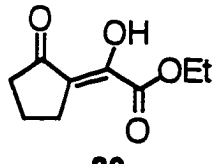
18



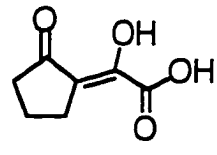
32



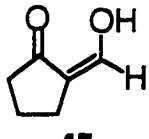
34



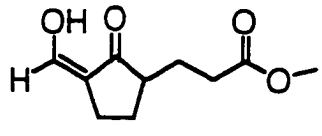
36



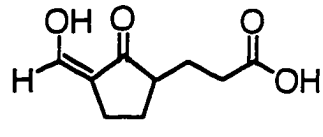
37



45



46



47

therefore developed nine compounds that are synthesized from readily available and inexpensive starting materials that will help to control the proliferation of the soybean cyst nematode.[12]

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium

aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Varian 300 Spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Varian 300 Spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

General Procedure For Enamine Synthesis: To a stirred solution of 5.28 mL of 1-pyrrolidino-1-cyclopentene (36 mmol) (**1 6**) in 36 mL of dry, refluxing dioxane was added 4.84 mL of methyl acrylate (52 mmol, 1.44 equiv.). After 24

hours, 6 mL of water was added and the solution refluxed for an additional 6 hours. The layers were separated and washed with a 1:1 solution of 1N HCl and diethyl ether. The combined organic layers were dried over sodium sulfate and then concentrated in vacuo. Purification with 4:1 H:EA gave methyl (2-oxocyclopentyl)-propionate (**1 2**) (R_f = 0.36) in 87% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.55-1.62 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.90 (m, 2H), 2.10-2.22 (m, 1H), 2.30-2.45 (m, 2H), 2.45 (t, *J* = 5.8 Hz, 2H), 3.67 (s, 3H). IR (neat) 2960, 2854, 1734, 1710, 1416 cm^{-1}. MS (CI, *m/z*) 170 (M^+), 155, 152, 59. HRMS m/z calculated for $C_9H_{14}O_3$: 170.0943, measured 170.1045. ^{13}C NMR ($CDCl_3$) δ 22.9, 26.4, 37.1, 37.6, 38.4, 39.8, 51.8, 172.4, 217.6.

Methyl (2-oxocyclohexyl)-propionate (24): ^{1}H NMR ($CDCl_3$) δ 1.50-1.63 (m, 4H), 1.65-1.78 (m, 2H), 1.81-2.04 (m, 4H), 2.15 (t, *J* = 9.1 Hz, 2H), 2.18-2.29 (m, 1H), 3.60 (s, 3H). IR (neat) 2968, 2856, 1730, 1716, 1416 cm^{-1}. MS (CI, *m/z*) 184 (M^+), 169, 59. HRMS m/z calculated for $C_{10}H_{16}O_3$: 184.1099, measured 184.1104. ^{13}C NMR ($CDCl_3$) δ 24.3, 25.2, 26.4, 27.9, 28.2, 40.1, 42.4, 52.1, 173.1, 210.4.

General Procedure for Diethyl Oxalate Condensation: To a solution of methyl (2-oxocyclopentyl)-propionate (**1 2**) (1.55 g, 9.0 mmol) at 0 °C was added 1.20 mL ethyl oxalate (9.0 mmol, 1 equiv.). In a separate flask, 1.53 g of potassium *tert*-butoxide (9.9 mmol, 1.1 equiv.) was suspended in 10 mL of dry THF and cooled to 0 °C. The methyl (2-oxocyclopentyl)-propionate / diethyl oxalate mixture was added dropwise over 10 minutes via a syringe to the stirring THF solution. The reaction mixture was allowed to stir overnight and then acidified with 6N HCl to pH 2. The solution was diluted with 10 mL of water and extracted three times with 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel, eluting with *n*-hexane/ethyl acetate (3:1) gave 2.236 g (83%) of (3-methoxy-3-oxopropyl)-α-

hydroxy-2-oxopentylidene acetic acid, ethyl ester (**1 4**) (R_f = 0.41). ^{1}H NMR ($CDCl_3$) δ 1.47 (t, *J* = 8.1Hz, 3H), 1.55-1.62 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.90 (m,2H), 2.10-2.22 (m,1H), 2.50 (t, *J* = 6.1 Hz, 2H), 3.67 (s, 3H), 4.12 (q, *J* = 8.1Hz, 2H), 15.37 (s, 1H). IR (neat) 3114, 2954, 2881, 1738, 1730, 1714, 1448 cm^{-1}. MS (CI, *m/z*) 270 (M^+), 255, 239, 225. HRMS m/z calculated for $C_{13}H_{18}O_6$: 270.1103, measured 270.1108. ^{13}C NMR ($CDCl_3$) δ 13.8, 23.2, 26.4, 37.7, 38.3, 39.6, 50.7, 62.1, 105.8, 163.7, 172.4, 192.4, 218.8.

2,4-Dioxo-1,8-octanedioic acid, mono ethyl ester (31): ^{1}H NMR ($CDCl_3$) δ 1.49 (t, *J* = 8.1 Hz, 3H), 1.85-1.95 (m, 2H), 2.15 (s,1H), 2.40 (t, *J* = 8.2 Hz, 2H), 2.55 (t, *J* = 8.2 Hz, 2H), 4.18 (q, *J* = 8.1 Hz, 2H), 15.37 (s, 1H). IR (neat) 3118, 2972, 2842, 1749, 1738, 1715, 1709 cm^{-1}. MS (CI, *m/z*) 230 (M^+), 215, 185. HRMS m/z calculated for $C_{13}H_{18}O_6$: 230.0790, measured 230.0795. ^{13}C NMR ($CDCl_3$) δ 14.9, 28.9, 34.7, 38.1, 60.8, 62.1, 168.4, 178.4, 197.2, 204.1.

3-[(3-Methoxy-3-oxopropyl)-2-oxocyclohexylidene]-hydroxy-acetic acid, ethyl ester (33): ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* = 8.3 Hz, 3H), 1.50-1.68 (m, 4H), 1.68-1.78 (m, 2H), 1.81-2.04 (m, 4H), 2.10-2.24 (m,1H), 3.65 (s, 3H), 4.21 (q, *J* = 8.3Hz, 2H), 15.81 (s, 1H). IR (neat) 3150, 2950, 2817, 1737, 1729, 1711 cm^{-1}. MS (CI, *m/z*) 284 (M^+), 269, 239. HRMS m/z calculated for $C_{14}H_{20}O_6$: 284.1260, measured 284.1263. ^{13}C NMR ($CDCl_3$) δ 15.4, 25.9, 26.3, 27.2, 27.8, 40.7, 42.9, 51.8, 61.7, 103.2, 165.1, 174.3, 194.1, 201.3. R_f = 0.27 (4:1, H:EA)

Hydroxy-(2-oxocyclopentylidene) acetic acid, ethyl ester (36): ^{1}H NMR ($CDCl_3$) δ 1.47 (t, *J* = 8.1 Hz, 3H), 1.96 (t, *J* = 8.7 Hz, 2H), 2.00-2.05 (m, 2H), 2.10 (t, *J* = 8.7 Hz, 2H), 4.21 (q, *J* = 8.3 Hz, 2H), 15.39 (s, 1H). IR (neat) 3304, 2982, 1732, 1709, 1471 cm^{-1}. MS (CI, *m/z*) 184 (M^+), 139. HRMS m/z calculated for

$C_9H_{12}O_4$: 184.0735, measured 184.0738. ^{13}C NMR ($CDCl_3$) δ 14.5, 21.4, 28.3, 38.1, 60.7, 105.6, 165.3, 190.4, 220.7 R_f = 0.41 (4:1, H:EA)

Bis-hydroxy-(2-oxocyclopentylidene) acetic acid, diethyl ester (38): ^1H NMR ($CDCl_3$) δ 1.42 (t, *J* = 7.9 Hz, 3H), 1.89 (s, 2H), 4.01 (q, *J* = 7.9 Hz, 2H), 15.21 (s, 1H) . IR (neat) 3201, 2932, 1732, 1710 cm^{-1}. MS (CI, *m/z*) 284 (M^+), 239, 194. HRMS m/z calculated for $C_{15}H_{16}O_7$: 284.0896, measured 284.0901. ^{13}C NMR ($CDCl_3$) δ 14.5, 26.8, 61.4, 104.3, 163.2, 191.2, 219.2.

Hydroxy-(2-oxocyclohexylidene) acetic acid, ethyl ester (40): ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.8 Hz, 3H), 1.63-1.78 (m, 6H), 2.24 (t, *J* = 9.7 Hz, 2H), 4.08 (q, *J* = 7.8 Hz, 2H), 15.52 (s, 1H) . IR (neat) 3210, 2859, 1737, 1715, 1471 cm^{-1}. MS (CI, *m/z*) 198 (M^+), 153. HRMS m/z calculated for $C_{10}H_{14}O_4$: 198.0892, measured 198.0899. ^{13}C NMR ($CDCl_3$) δ 12.7, 24.7, 26.8, 27.2, 42.7, 61.8, 103.2, 167.2, 191.8, 211.4. R_f = 0.55 (2:1, H:EA).

Hydroxy-(2-oxocycloheptylidene) acetic acid, ethyl ester (42): ^1H NMR ($CDCl_3$) δ 1.41 (t, *J* = 8.0 Hz, 3H), 1.76-2.10 (m, 8H), 2.39 (t, *J* = 7.4 Hz, 2H), 4.12 (q, *J* = 8.0 Hz, 2H), 15.56 (s, 1H) . IR (neat) 3184, 2869, 1733, 1718 cm^{-1}. MS (CI, *m/z*) 212 (M^+), 167. HRMS m/z calculated for $C_{11}H_{16}O_4$: 212.1048, measured 212.1052. ^{13}C NMR ($CDCl_3$) δ 13.1, 24.5, 26.2, 30.8, 31.9, 44.2, 62.1, 104.0, 166.4, 192.1, 215.4. R_f = 0.39 (3:1, H:EA)

General Procedure for Ethyl Formate Condensation: To a solution of cyclopentanone (**29**) (1.00 g, 11.8 mmol) at 0 °C was added ethyl formate (0.969 g, 13.0 mmol). In a separate flask, 1.46 g of potassium *tert*-butoxide (13.0 mmol, 1.1 equiv.) was suspended in 120 mL of dry THF and cooled to 0 °C. The cyclopentanone / ethyl formate mixture was added dropwise over 10 minutes via a

syringe to the stirring THF solution. The reaction mixture was allowed to stir overnight and then acidified with 6N HCl to pH 2. The solution was diluted with 120 mL of water and extracted three times with 120 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel, eluting with *n*-hexane/ethyl acetate (4:1) gave 1.27 g (96%) of 2-(hydroxymethylene)cyclopentanone (**45**) : ^{1}H NMR ($CDCl_3$) δ 1.97 (t, J = 7.1 Hz, 2H), 2.02 (m, 2H), 2.07 (t, J = 7.2 Hz, 2H), 7.21 (s, 1H), 15.07 (s, 1H). IR (neat) 3151, 2958, 1710, 1398, 1361, 1191, 1015, 835 cm^{-1}. MS (CI) m/z 112 (M^+), 84, 70. HRMS m/z calculated for $C_6H_8O_2$: 112.0524, measured 112.0522. ^{13}C NMR ($CDCl_3$) δ 22.7, 26.8, 37.9, 59.1, 103.4, 190.7, 194.3, 218.2. R_f = 0.37 (4:1, H:EA).

5-(3-Methoxy-3-oxopropyl)-2-(hydroxymethylene)-cyclopentanone (46): ^{1}H NMR ($CDCl_3$) δ 1.45-1.62 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.90 (m, 2 H), 1.97 (t, J = 8.6 Hz, 2H), 2.10-2.22 (m, 1H), 3.67 (s, 3H) 7.21 (s, 1H), 15.37 (s, 1H). IR (neat) 3158, 2961, 1738, 1709, 1394, 1359 cm^{-1}. MS (CI) m/z 198 (M^+), 167. HRMS m/z calculated for $C_{10}H_{14}O_4$: 198.0892, measured 198.0987. ^{13}C NMR ($CDCl_3$) δ 22.8, 26.1, 36.9, 38.2, 39.7, 51.7, 105.4, 169.2, 191.4, 217.4. R_f = 0.37 (4:1, H:EA)

General Procedure for Acid Hydrolysis: To a stirred solution of **16** (0.300 g, 1.05 mmol) in 2.20 mL of methanol and 0.22 mL of water was added 0.101 g of lithium hydroxide (4.22 mmol, 4.2 equiv.) and 0.118 g of potassium hydroxide (2.11 mmol, 2.1 equiv.). The reaction mixture was allowed to stir overnight and then acidified to pH = 2 with 2N HCl. The mixture was washed with 15 mL of a 1:1 mixture of CH_2Cl_2 and water and the combined organic layers dried over sodium sulfate. The solvent was removed in vacuo affording (3-methoxy-3-oxopropyl)-2-oxocyclopentylidene acetic acid (**18**) in 89% yield. ^{1}H NMR ($CDCl_3$) δ 1.55-1.62 (m, 2H), 1.65-1.73 (m, 2H), 1.75-1.90 (m, 2 H), 2.10-2.22 (m, 2H), 2.5 (t, J = 5Hz, 2H), 11.27 (br, s, 1H), 15.39 (s, 1H). IR (neat) 3100, 2876, 1755, 1714, 1454

cm^{-1}. MS (CI) m/z 228 (M^+), 183, 138. HRMS m/z calculated for $C_{10}H_{12}O_6$: 228.0634, measured 228.0640. ^{13}C NMR ($CDCl_3$) δ 23.1, 26.9, 37.2, 38.1, 39.4, 105.6, 171.4, 179.1, 190.7, 217.6.

Vinyl Acid (17): ^1H NMR ($CDCl_3$) δ 1.50-1.82 (m, 4H), 2.00-2.38 (m, 3H), 2.50 (t, J = 8.3 Hz, 2H), 6.65 (s, 1H), 11.16 (br, s, 1H), 11.47 (br, s, 1H). IR (neat) 3105, 2976, 2879, 1756, 1750, 1711, 1462 cm^{-1}. MS (CI) m/z 212 (M^+), 167, 122. HRMS m/z calculated for $C_{10}H_{12}O_5$: 212.0684, measured 212.0690. ^{13}C NMR ($CDCl_3$) δ 26.8, 37.6, 38.7, 39.1, 51.7, 108.9, 127.4, 171.4, 179.4, 218.1.

3-(2-Oxocyclohexyl)propiolic acid (25): ^1H NMR ($CDCl_3$) δ 1.50-1.68 (m, 4H), 1.65-1.78 (m, 2H), 1.83-2.08 (m, 4H), 2.13 (t, J = 9.2 Hz, 2H) 2.18-2.32 (m, 1H), 11.14 (br, s, 1H) . IR (neat) 3121, 2972, 1751, 1712, 1471 cm^{-1}. MS (CI, *m/z*) 170 (M^+), 125. HRMS m/z calculated for $C_9H_{14}O_3$: 170.0943, measured 170.0950. ^{13}C NMR ($CDCl_3$) δ 23.9, 25.4, 26.1, 26.9, 28.1, 40.1, 42.4, 178.9, 209.8.

4-Oxo-2-octyn-1,8-dioic acid (29): ^1H NMR ($CDCl_3$) δ 1.72-1.82 (m, 2H), 2.31 (t, J = 7.9 Hz, 2H), 2.51 (t, J = 7.9 Hz, 2H), 11.24 (br, s, 2H) . IR (neat) 3127, 2971, 1758, 1749, 1711 cm^{-1}. MS (CI, *m/z*) 184 (M^+), 139. HRMS m/z calculated for $C_8H_8O_5$: 184.0371, measured 184.0374.

2,4-Dioxo-1,8-octanedioic acid (32): ^1H NMR ($CDCl_3$) δ 1.85-1.95 (m, 2H), 2.15 (s, 2H), 2.40 (t, J = 8.2 Hz, 2H), 2.55 (t, J = 8.2Hz, 2H), 11.01 (br, s, 2H) . IR (neat) 3098, 2963, 2874, 1755, 1751, 1719, 1714 cm^{-1}. MS (CI, *m/z*) 202 (M^+), 157, 112. HRMS m/z calculated for $C_8H_{10}O_6$: 202.0477, measured 202.0478. ^{13}C NMR ($CDCl_3$) δ 29.1, 34.3, 37.1, 61.4, 169.3, 177.1, 197.2, 203.7.

(3-Oxopropyl)-α-hydroxy-2-(oxocyclohexylidene) acetic acid (34): ^{1}H NMR ($CDCl_3$) δ 1.50-1.68 (m, 4H), 1.68-1.78 (m, 2H), 1.81-2.04 (m, 4H), 2.10-2.24 (m, 1H) 11.62 (br, s, 2H), 15.72 (s, 1H) . IR (neat) 3075, 2962, 1751, 1747, 1718 cm^{-1}. MS (CI, *m/z*) 242 (M^+), 197, 152. HRMS m/z calculated for $C_{11}H_{14}O_6$: 242.0790, measured 242.0795. ^{13}C NMR ($CDCl_3$) δ 24.9, 26.4, 26.8, 27.3, 40.8, 42.1, 104.1, 170.9, 179.2, 193.2, 204.7.

Hydroxy-(2-oxocyclopentylidene)acetic acid (37): ^{1}H NMR ($CDCl_3$) δ 1.96 (t, J = 8.7 Hz, 2H), 2.01-2.04 (m, 2H), 2.07 (t, J = 8.7 Hz, 2H), 11.21 (br, s, 1H), 15.41 (s, 1H). IR (neat) 3256, 2979, 1735, 1707, 1454 cm^{-1}. MS (CI, *m/z*) 156 (M^+), 111. HRMS m/z calculated for $C_7H_8O_4$: 156.0422, measured 156.0423. ^{13}C NMR ($CDCl_3$) δ 21.7, 28.3, 38.4, 105.6, 172.4, 193.1, 218.4.

Bis-hydroxy-(2-oxocyclopentylidene)acetic acid (39): ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 1H), 11.01(br, s, 1H), 15.21 (s, 1H) . IR (neat) 3178, 2964, 1762, 1708 cm^{-1}. MS (CI, *m/z*) 228 (M^+), 183, 138. HRMS m/z calculated for $C_9H_8O_7$: 228.0270, measured 228.0279. ^{13}C NMR ($CDCl_3$) δ 27.2, 103.8, 172.4, 189.7, 218.9.

Hydroxy-(2-oxocyclohexylidene)acetic acid (41): ^{1}H NMR ($CDCl_3$) δ 1.68-1.78 (m, 6H), 2.24 (t, J = 9.7 Hz, 2H), 11.71 (br,s,1H), 15.52 (s, 1H) . IR (neat) 3100, 2972, 1750, 1714 cm^{-1}. MS (CI, *m/z*) 170 (M^+), 125. HRMS m/z calculated for $C_8H_{10}O_4$: 170.0579, measured 170.0586. ^{13}C NMR ($CDCl_3$) δ 24.9, 26.3, 27.0, 43.0, 103.2, 173.5, 192.4, 210.8.

Hydroxy-(2-oxocycloheptylidene) acetic acid, ethyl ester (42): ^{1}H NMR ($CDCl_3$) δ 1.78-1.93 (m, 8H), 2.39 (t, J = 7.4 Hz, 2H), 11.56 (br, s, 1H), 15.56 (s, 1H) . IR (neat) 3098, 2936, 1753, 1717 cm^{-1}. MS (CI, *m/z*) 184 (M^+), 149.

HRMS m/z calculated for $C_9H_{12}O_4$: 184.0735, measured 184.0741. ^{13}C NMR ($CDCl_3$) δ, 24.5, 26.2, 30.8, 31.9, 44.2, 104.0, 172.4, 192.1, 215.4.

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CHAPTER 3. STUDIES TOWARD THE SYNTHESIS OF GLYCINOCLEPIN A

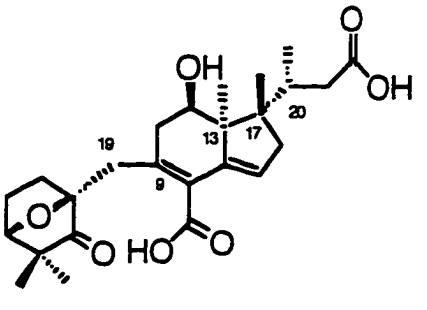
A paper, a portion of which is to be submitted to the Journal of Agriculture and Food Chemistry

George A. Kraus and Steven J. Vander Louw

Introduction

The isolation[1] and structural elucidation[2] of glycinoclepin A (**1**) has revealed a compound possessing a complex structure and significant biological activity (Figure 1). Glycinoclepin A is a degraded triterpenoid isolated from kidney bean roots as a semiochemical effective on soybean cyst nematode. Its unusual structure makes it an attractive target for synthetic chemists. To date, there have

Figure I



Glycinoclepin A

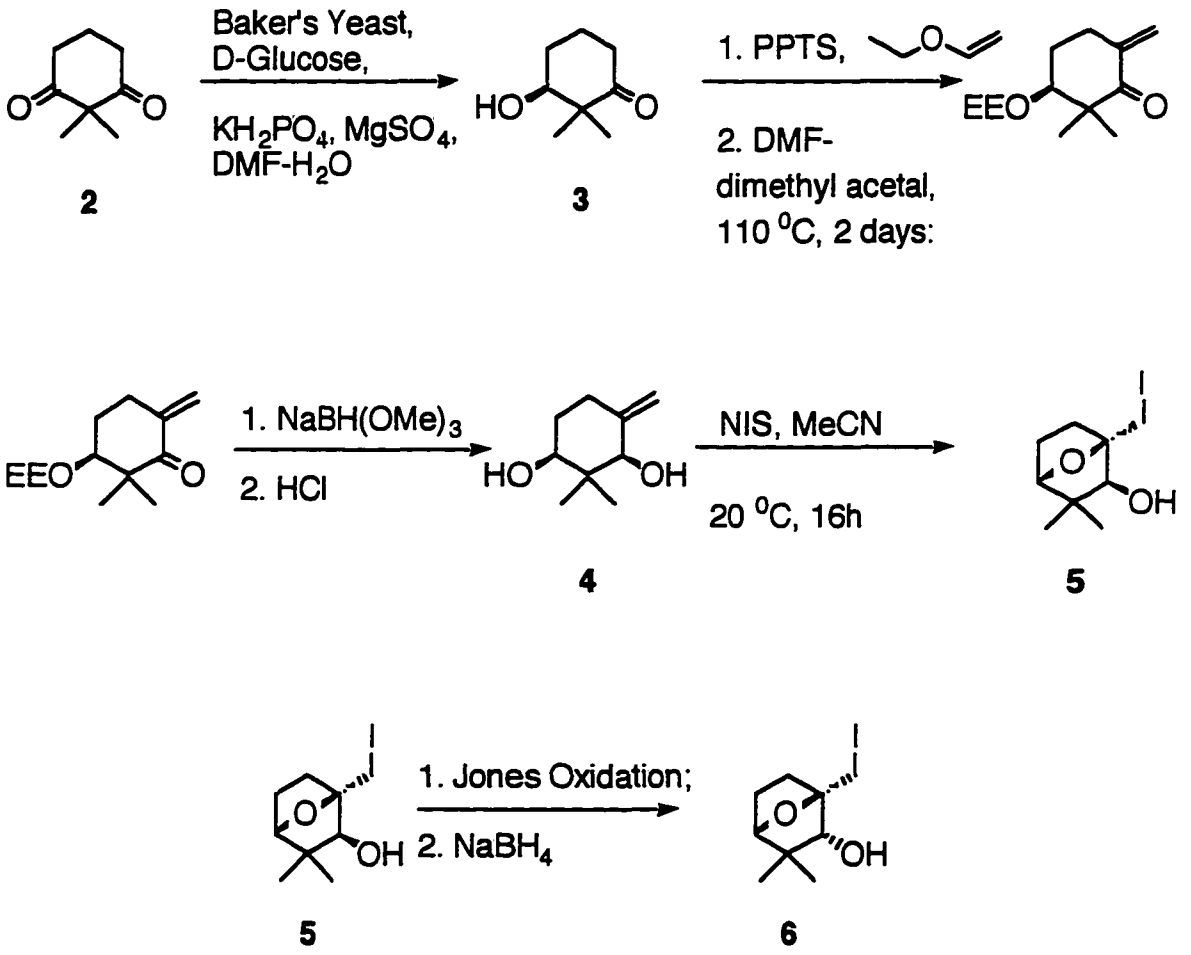
1

been three total syntheses of glycinoclepin A, each possessing a minimum of 22 steps.

The first synthesis of **1** was completed by Murai and coworkers in 1988.[3] Murai's synthesis gave **1** in 27 steps starting from 2,2-dimethylcyclohexane-1,3-

dione (**2**). Baker's yeast reduction[4] of **2** gave (*S*)-2,2-dimethyl-3-hydroxycyclohexan-1-one (**3**) in 94% ee and 67% yield (Scheme I). Keto alcohol **3** was converted into an olefinic *cis*-glycol **4** by first treating it with ethyl vinyl ether and PPTS to afford the protected alcohol in 97% yield. Treatment of the resulting ketone with DMF-dimethyl acetal at 110 °C for 2 days, followed by DIBAL reduction, gave the intermediate unsaturated ketone. The unsaturated ketone was then

Scheme I



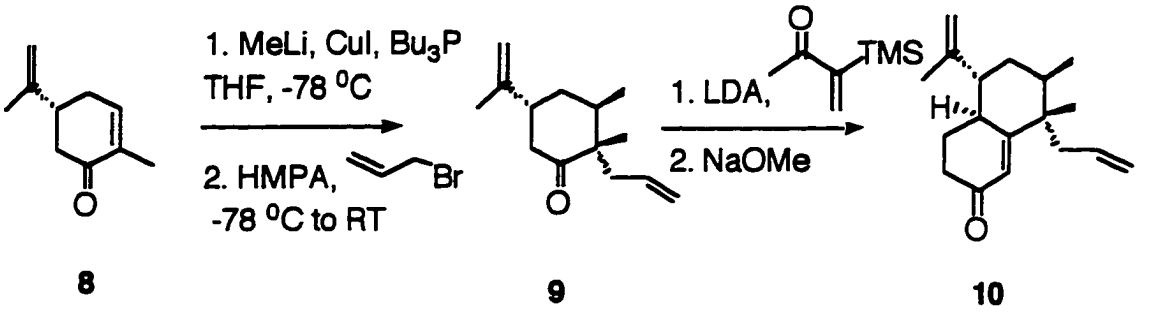
reduced with $NaBH(OMe)_3$ and treated with HCl to give **4** in a 52% overall yield from **3**.[5] Compound **4** was then treated with *N*-iodosuccinimide in acetonitrile to achieve the halocyclization product **5** in 79% yield and 100% ee. Jones oxidation followed by reduction with sodium borohydride afforded the isomeric (2*R*) alcohol **6**

as the only product. Compound **6** was introduced later in the synthesis as the cyclohexanone side chain moiety.

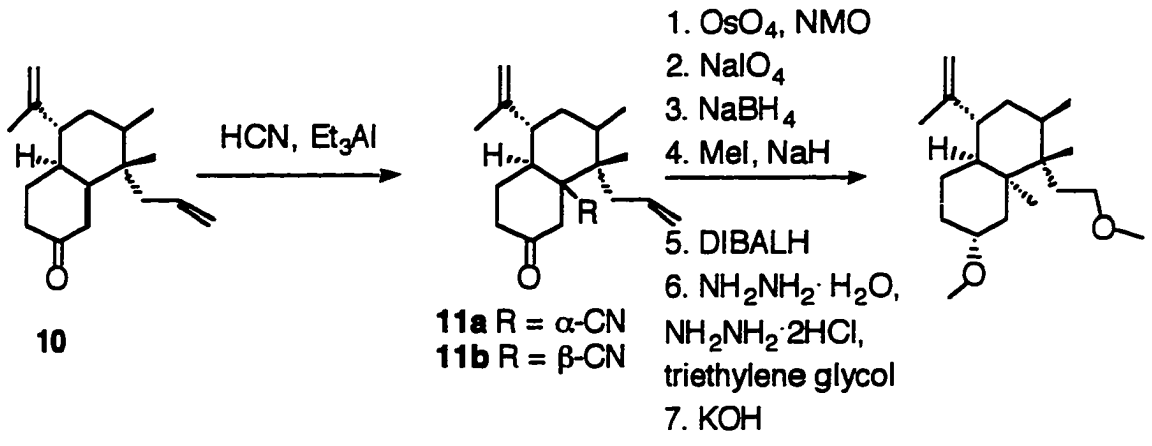
The synthesis continued with the construction of key intermediate **7**, the C and D ring fragment of **1** (Scheme II). Starting with (*R*)-carvone, Murai introduced four chiral centers in a key synthetic sequence. Addition of dimethyl cuprate to enone **8** and trapping the resulting anion with allyl bromide led to **9** in 78% yield.[6] Subjection of **9** to annulation conditions using 2-(trimethylsilyl)-3-butene-2-one and sodium methoxide yielded the α, β-unsaturated octalone **10** in 74% yield.[7] Compound **10** was treated with hydrogen cyanide and triethylaluminum under kinetic conditions to form predominantly the *cis*-cyano ketone **11a** in 63% yield and its trans isomer **11b** in 30% yield.[8] With the four stereogenic centers now in place, the synthesis continued with osmylation and reduction to provide **12** in 40% yield from **11** over five steps. Oxidation of **12** with peroxytrifluoroacetic acid gave ε-caprolactone **13** in 72% yield. Lactone opening was achieved by saponification of **13** with KOH followed by treatment of the resulting acid with diazomethane and protection of the alcohol as the acetate. Cleavage of the methoxy groups of **14** with aluminum chloride and sodium iodide in acetonitrile according to a procedure developed by Fuji gave monoacetate **15** in 85% yield.[9] Tritylation and oxidation of **15** afforded acetoxycyclohexanone trityl ether **7** in 91% yield.

The next phase of the synthesis was to connect **6** and **7**. Murai achieved the intramolecular coupling by treating **7** with bromomagnesium thioureide-carbon dioxide complex to afford the β-ketocarboxylic acid which was immediately reacted with **6** in the presence of dicyclohexylcarbodiimide to afford keto ester **16** (Scheme III).[10] Treatment of **16** with potassium fluoride in acetonitrile in the presence of 18-crown-6 at 65 °C coupled C(9) to C(19) and gave the lactone **17** in 94% yield.[11] Attempted intramolecular cyclization of the corresponding isomeric keto ester (prepared from **5**) and **7** was unsuccessful. Lactone **17** was treated with sodium allyloxide and then Swern oxidation conditions to give keto ester **18**.[12]

Scheme II

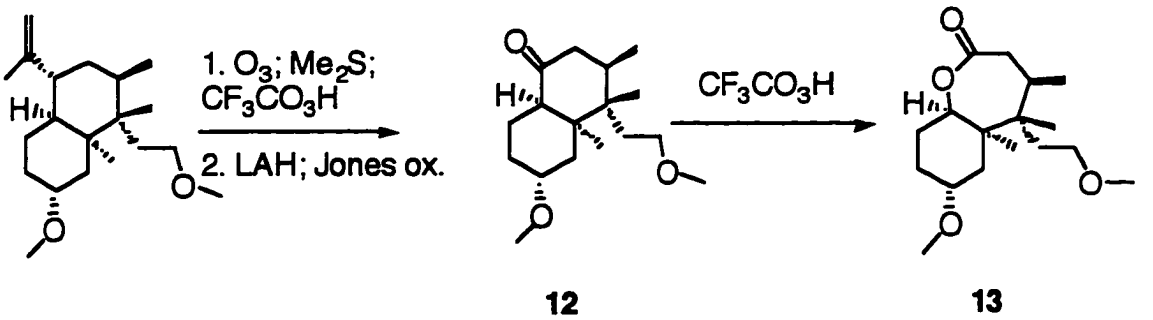


8 **9** **10**

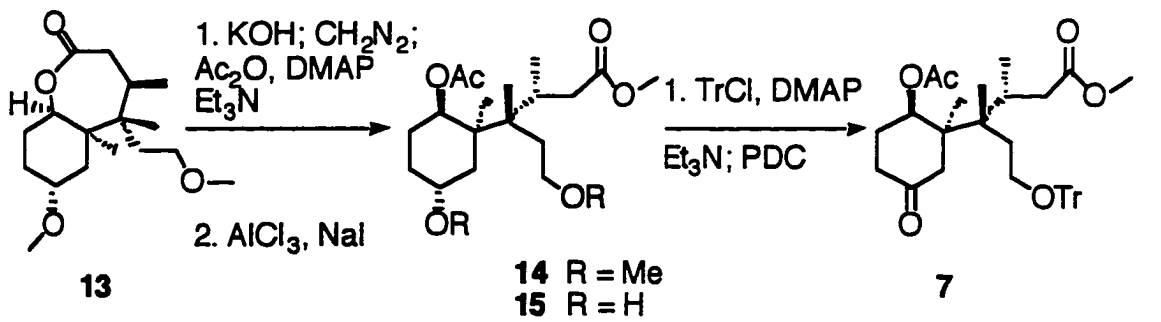


10

11a R = α-CN
11b R = β-CN



12 **13**

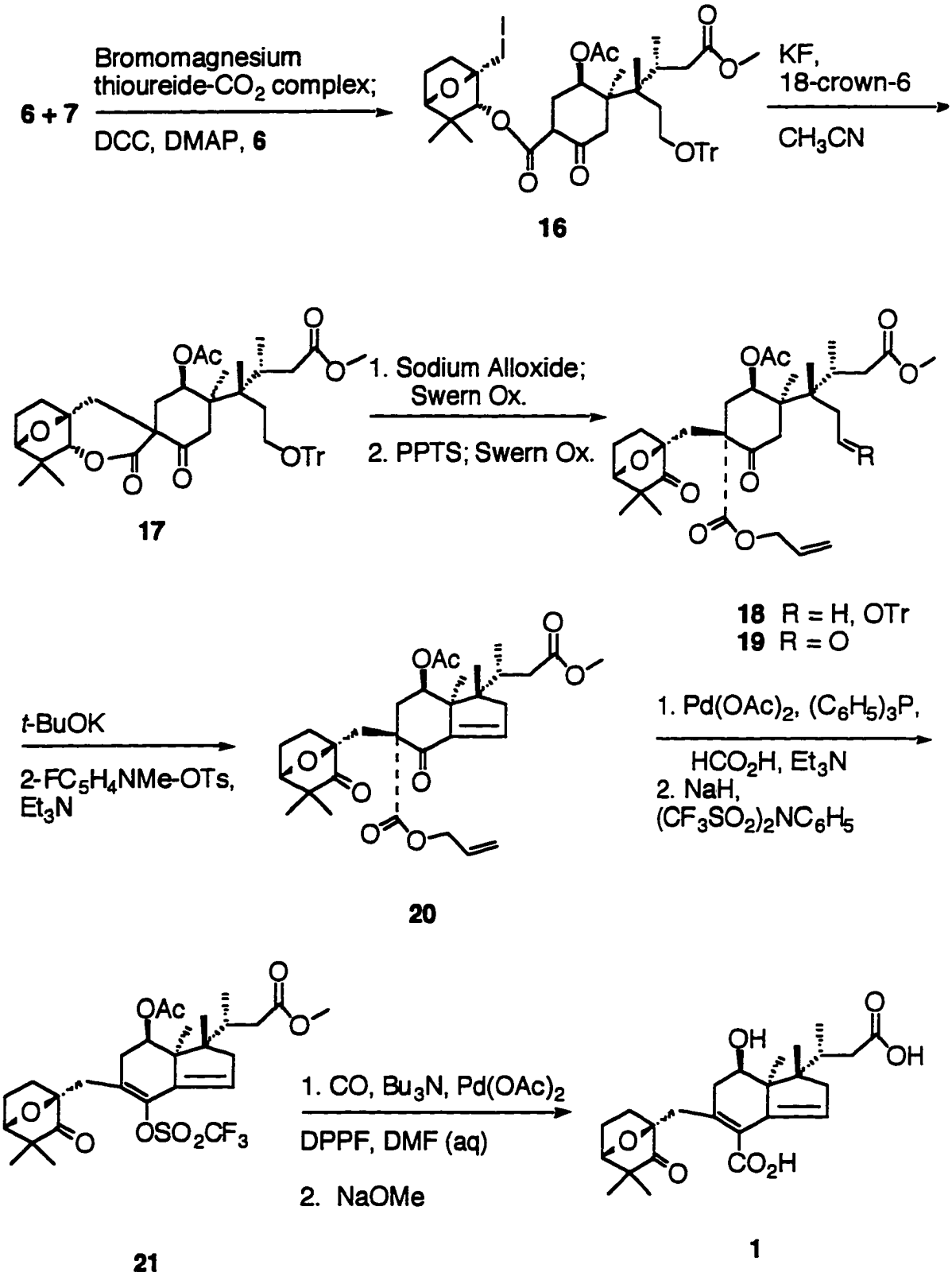


13

14 R = Me
15 R = H

7

Scheme III


6 + 7
Bromomagnesium thioureide-CO_2 complex;
DCC, DMAP, 6
KF, 18-crown-6
CH_3CN
16
1. Sodium Alloxide; Swern Ox.
2. PPTS; Swern Ox.
17
18 R = H, OTr
19 R = O
t-BuOK
2-FC_5H_4NMe-OTs, Et_3N
1. $Pd(OAc)_2$, $(C_6H_5)_3P$, HCO_2H, Et_3N
2. NaH, $(CF_3SO_2)_2NC_6H_5$
20
1. CO, Bu_3N, $Pd(OAc)_2$
DPPF, DMF (aq)
2. NaOMe
21
1

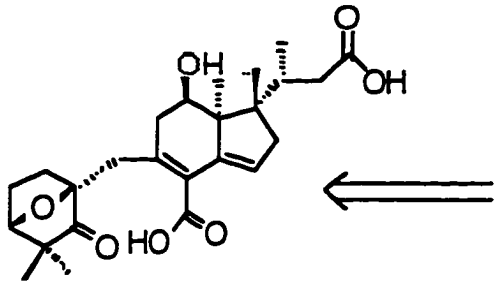
Compound **18** was submitted to detritylation with acid and Swern oxidation to afford aldehyde ketone **19**.[12] Treatment of **19** with potassium *tert*-butoxide gave the aldol product, which was immediately dehydrated with 2-fluoropyridinium tosylate to afford methoxycarbonyl enone **20**.[13] The allyloxycarbonyl group was removed according to a procedure by Tsuji,[14] to give the dienol, which was treated with sodium hydride and phenyl triflimide[15] to yield the corresponding dienyl triflate **21**. A modification of the methodology developed by Ortar [16] led to the incorporation of the remaining one-carbon unit at the C(8) position. Compound **21** was treated with tributylamine, palladium acetate, and 1,1'-bis(diphenylphosphino)ferrocene in aqueous DMF under a carbon monoxide balloon to afford the acetoxyl dicarboxylic acid which upon removal of the acetoxy group with sodium methoxide yielded **1**.

Murai's synthesis is worth noting primarily because it was the first synthesis of glycinoclepin A. However, it is an inefficient synthesis and could be greatly improved upon.

The second synthesis of glycinoclepin A was done by Kenji Mori in 1989.[17] Mori's synthetic scheme was based upon the two chiral synthons **25** and **28**, which come from the baker's yeast reduction of starting materials **26** and **29** (Scheme IV). Further elaboration of **25** and **28** leads to key intermediates **24** and **27**. An aldol condensation between **24** and **27** yields **23**. Introduction of a two carbon unit then leads to **22** and reductive fission of the lactone carbon-oxygen bond followed by nucleophilic addition of the ester carbanion to the carbonyl group generates the six-membered C-ring and completes the synthesis of **1**.

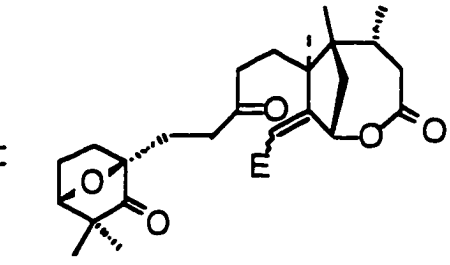
The two key intermediates **24** and **27** were prepared as shown in Scheme V. For the synthesis of **24**, the (*S*)-hydroxy ketone **3** was first converted to the *tert*-butyldimethylsilyl ether using imidazole and TBDMSCl. It was then subjected to an aldol condensation using acetaldehyde and LDA, followed by mesylation with mesyl chloride and triethylamine to afford **30**. Reduction of **30** with sodium borohydride, followed by protection of the new hydroxyl group with ethyl vinyl ether

Scheme IV



Glycinoclepin A

1



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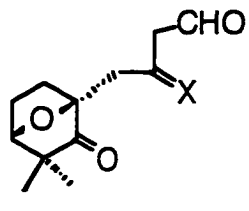

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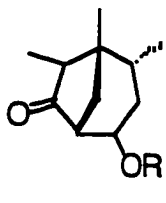

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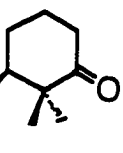

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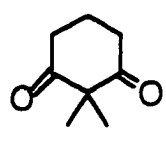

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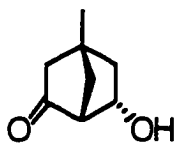

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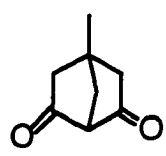

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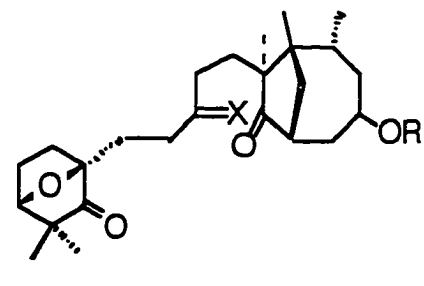

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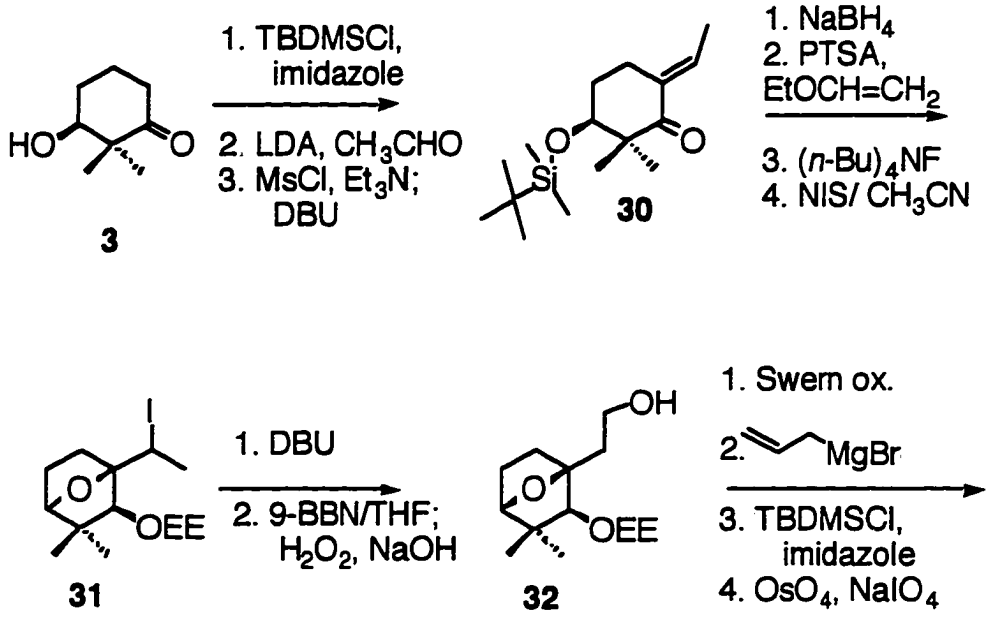
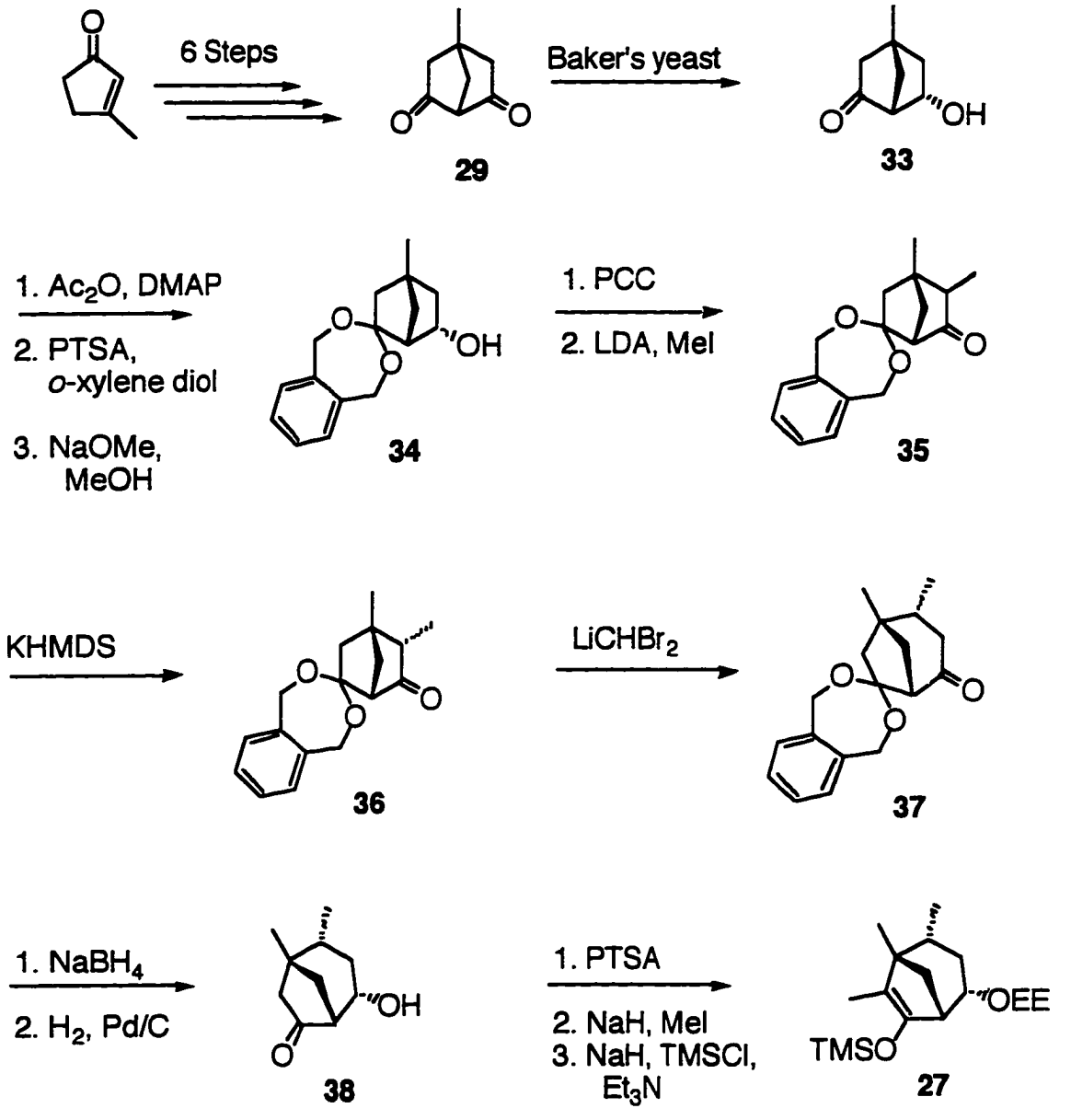
Scheme V



and PTSA, and subsequent iodocyclization gave **31** in 57% yield from **30**. Treatment of **31** with DBU gave the olefin, and hydroboration/oxidation gave **32**. Swern oxidation of **32**, followed by treatment with allylmagnesium bromide and trapping the resulting alcohol with TBDMSCl gave the protected alcohol. Osmylation of the terminal olefin with osmium tetroxide and sodium periodate afforded key intermediate **24** in 62% yield from **32** and in 32% overall yield from **3**.

The synthesis of **27** started from **29**, which was made in 6 steps from 3-methyl -2-cyclopenten-1-one (Scheme VI). Reduction of **29** with baker's yeast gave **33** in 55% yield and 80% ee. Compound **33** was purified to 100% ee by

Scheme VI



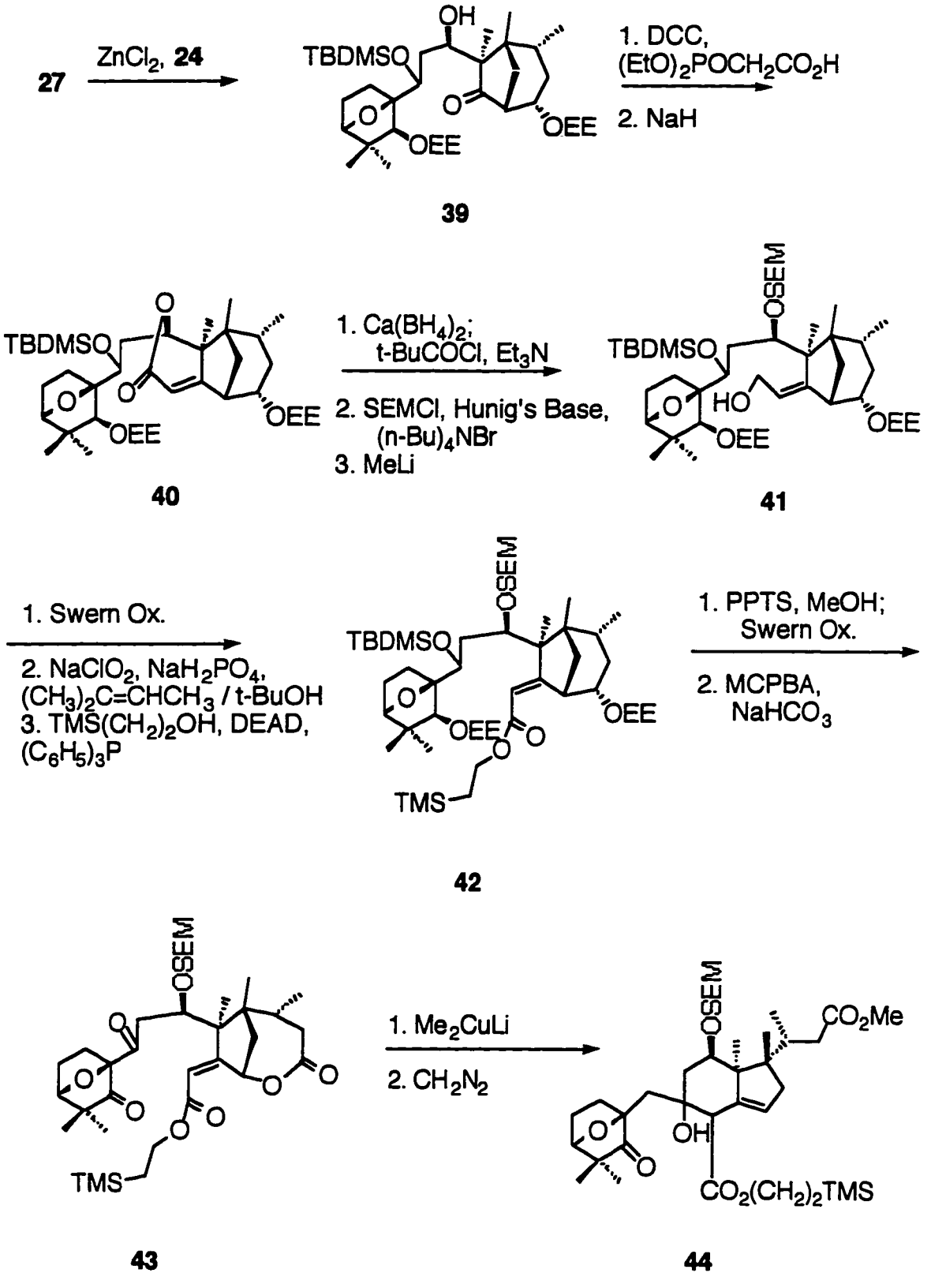
recrystalization of the corresponding ketal **3 4**. Oxidation of **3 4** with PCC to the ketone followed by methylation with LDA and methyl iodide gave **3 5** in 94% yield. Enolization of **3 5** with potassium bis(trimethylsilyl)amide gave **3 6** in 97% yield. Ring expansion of **3 6** was done via Nozaki's method[18] using lithium dibromomethide, followed by treatment with one equivalent of methyl lithium and one equivalent of *n*-butyl lithium, to give **3 7** in 50% yield. Reduction of **3 7** using

sodium borohydride proceeded smoothly and following removal of the acetal via hydrogenolysis gave **38** in 98% yield. Finally, treatment of **38** with ethyl vinyl ether and PTSA protected the alcohol, sodium hydride and methyl iodide introduced the requisite methyl group, and then enolization with sodium hydride and triethylamine, followed by trapping with TMSCl, afforded the key intermediate **27**.

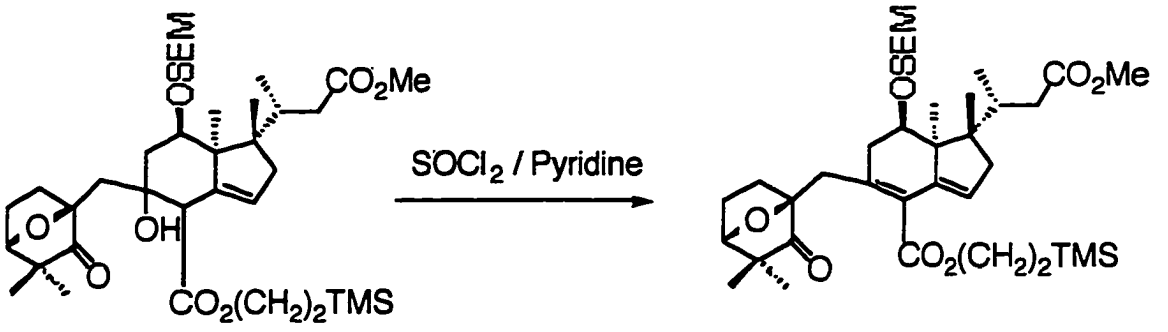
With the two key intermediates in hand, Mori attempted the aldol condensation of **27** and **24** (Scheme VII). Treatment of **27** with zinc chloride,[19] followed by the addition of **24**, led to an unstable aldol **39**, which was immediately converted to the corresponding diethyl phosphonoacetate (Scheme VII). Treatment of the phosphonoacetate with sodium hydride gave lactone **40** by an intramolecular olefination reaction. Lactone **40** was reduced with calcium borohydride to give a diol, which upon protection and deprotection yielded allylic alcohol **41**. Compound **41** was first converted to ester **42** by Swern oxidation followed by sodium chlorite oxidation, and finally esterification using Mitsunobu reaction conditions.[20] Removal of the ethyl vinyl ether and *tert*-butyl dimethylsilyl groups lead to the triol, which was oxidized via Swern conditions. Baeyer-Villager oxidation of the triketone was selective to give the desired diketo lactone **43** as the only product. Reduction cyclization using lithium dimethyl cuprate as a reducing agent [21] afforded the cyclized product **44** after esterification with diazomethane. Dehydration of **44** with thionyl chloride and pyridine afforded **45**, which upon deprotection with lithium hydroxide and tetra-*n*-butylammonium hydroxide followed by tetra-*n*-butylammonium fluoride provided glycinoclepin A.

Mori's synthesis was not much of an improvement over Murai's and was also less than ideal due to its length and complexity. These problems are significant when one bears in mind the difficulty of isolating a useful amount of glycinoclepin A. Corey threw his hat into the ring in 1990 with a new synthesis of glycinoclepin A that revolved around a Diels-Alder reaction and an interesting 1,2 methyl shift.[22] Corey's synthesis involved a coupling of mono and bicarbocyclic moieties and began with the enantioselective establishment of the C(17)-C(20)

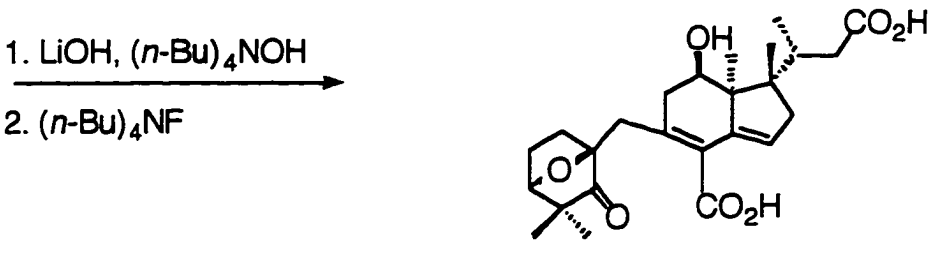
Scheme VII


27
ZnCl2, 24
TBDMSO
OH
O
OEE
OEE
1. DCC,
(EtO)2POCH2CO2H
2. NaH
39
TBDMSO
O
OEE
OEE
40
1. Ca(BH4)2;
t-BuCOCl, Et3N
2. SEMCl, Hunig's Base,
(n-Bu)4NBr
3. MeLi
OSEM
TBDMSO
HO
OEE
OEE
41
1. Swern Ox.
2. NaClO2, NaH2PO4,
(CH3)2C=CHCH3 / t-BuOH
3. TMS(CH2)2OH, DEAD,
(C6H5)3P
OSEM
TBDMSO
OEE
OEE
TMS
42
1. PPTS, MeOH;
Swern Ox.
2. MCPBA,
NaHCO3
OSEM
TMS
43
1. Me2CuLi
2. CH2N2
OSEM
CO2Me
OH
CO2(CH2)2TMS
44

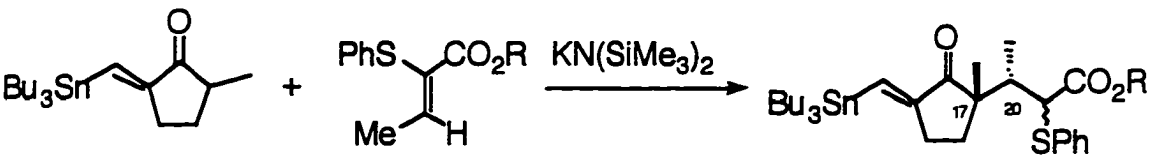
Scheme VII Continued



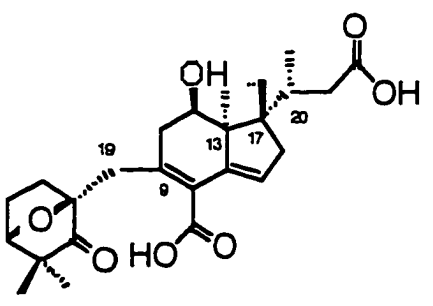
44 **45**



Scheme VIII

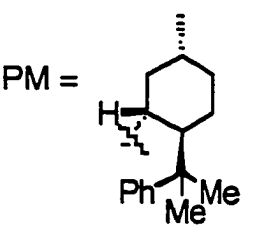


46 **47a** R = PM **48a** R = PM
47b R = Me **48b** R = Me



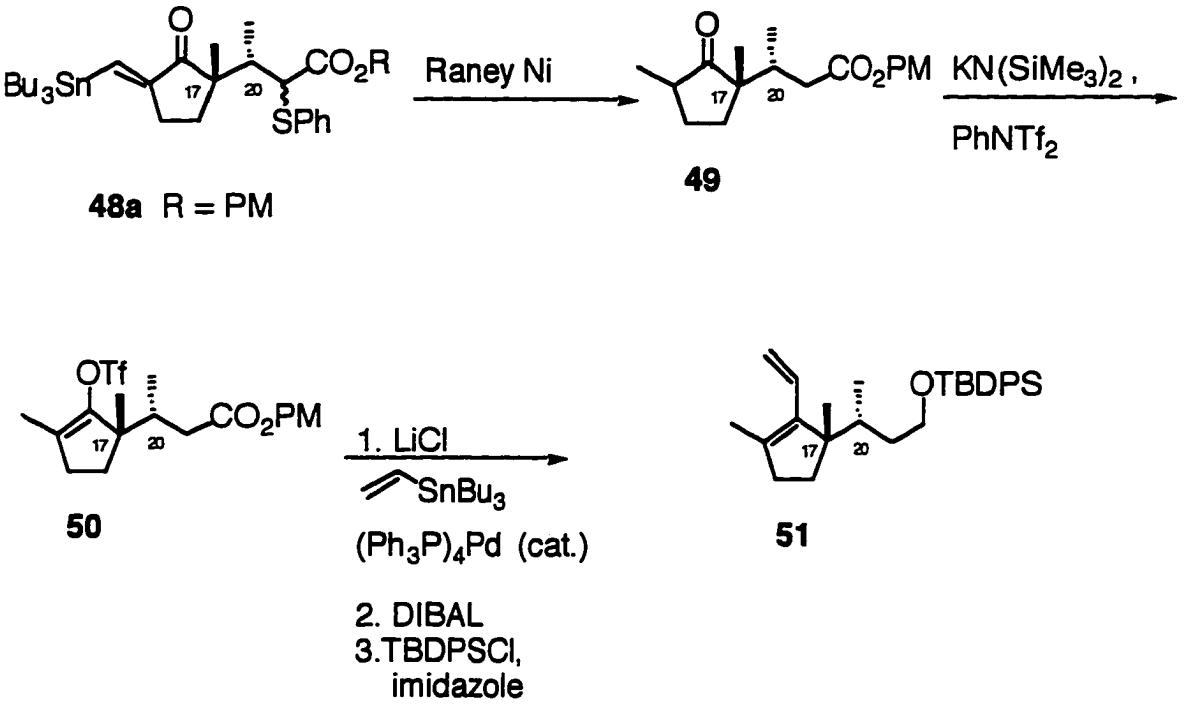
Glycinoclepin A

1



stereocenters (Scheme VIII). Cyclopentanone **46**[23] was converted to the potassium enolate and allowed to react at -100 °C with the ester **47a**[24] to give the major product **48a** with 95:5 enantioselectivity and 5:1 C(17)-C(20) diastereoselectivity (89% yield). The corresponding reaction of potassium enolate **46** with **47b** gave (±) **48b** in 82% yield with 97:3 C(17)-C(20) diastereoselectivity. Treatment of **48a** with Raney nickel in ethanol gave the keto ester **49** in 85% yield. Enolization was achieved with potassium bis(trimethylsilyl)amide and then the enol was trapped with *N*-phenylbistrifluoromethanesulfonamide to form enol triflate **50** in 84% yield (Scheme IX) Vinylation[25] of **50** with vinyltributyltin-LiCl in the

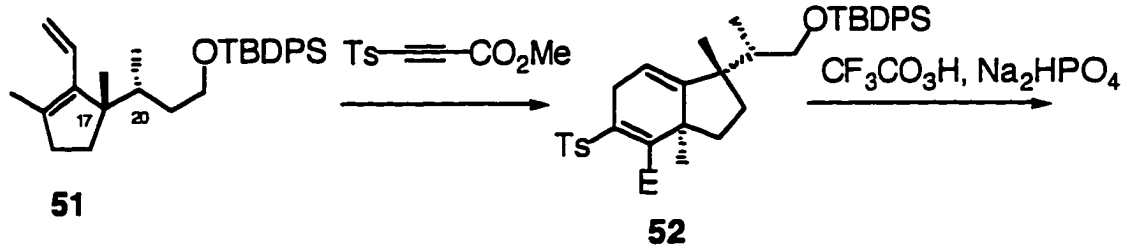
Scheme IX



presence of 0.07 equivalents of $(Ph_3P)_4Pd$ at 65 °C afforded the desired diene ester (87%) which was reduced with DIBAL and protected with TBDPSCl to give diene **51**.

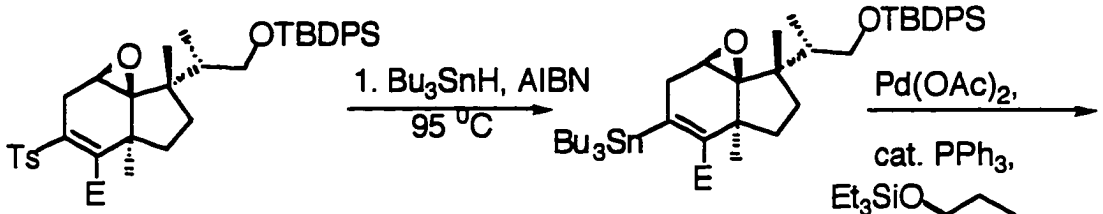
The Diels Alder reaction of **51** with 3-(*p*-toluenesulfonyl)propiolic acid[26] proceeded with specificity to give **52** in >95% yield and a 3:1 ratio of C(14)

Scheme X

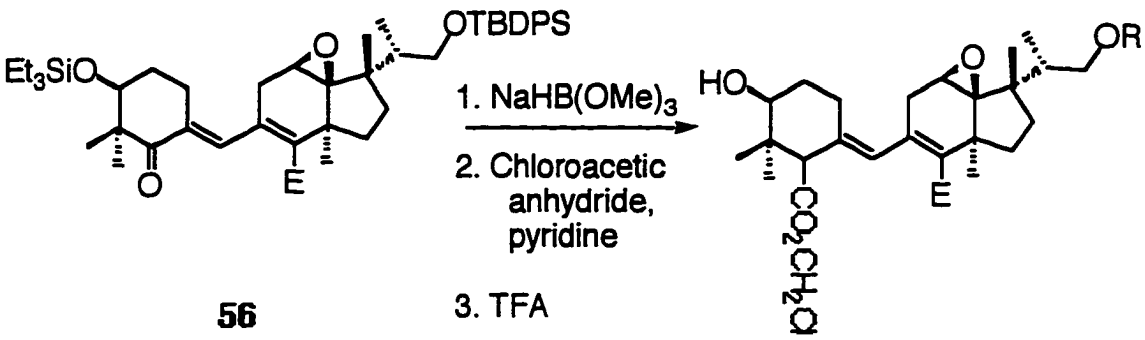


51 **52**

E= Methyl Ester



53 **54** **55**

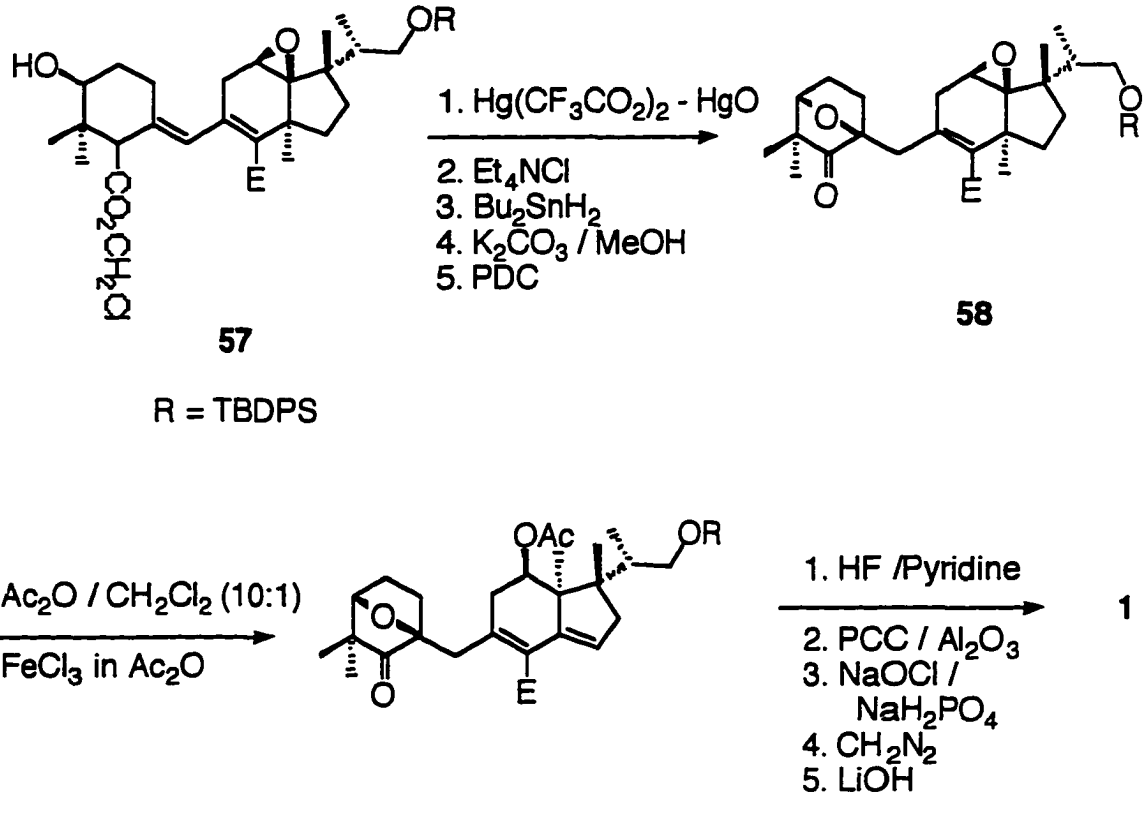


56 **57**

R = TBDPS

diastereomers (Scheme X). The mixture was epoxidized with anhydrous CF_3CO_3H to give the pure epoxide **5 3** in 65% overall yield from diene **51.** The *p* -toluenesulfonyl group of **5 3** was replaced by tributylstannyl by heating with three equivalents of tri-*n*-butyltin hydride with a catalytic amount of AIBN in toluene at 95 °C to afford **5 4** in 84% yield. Vinyl triflate **55** was coupled to **5 4** using $Pd(OAc)_2$ and catalytic triphenylphosphine to give key intermediate **5 6** in 66% yield. Reduction of the carbonyl in **5 6** was accomplished using $NaBH(OMe)_3$ and the

Scheme XI



57

R = TBDPS

58

59

resulting alcohol protected with chloroacetic anhydride and pyridine. Desilylation using trichloroacetic acid finished the transformation of **5 6** into hydroxy diene **5 7** in 82% overall yield from **5 6**.

With **57** in hand, Corey set out to finish his synthesis (Scheme XI). Reaction of **57** with mercuric trifluoroacetate-HgO in acetonitrile, followed by treatment with triethylammonium chloride, provided internal oxymercuration to give a single bridged ether which was demercurated with dibutyltin hydride. Chloroacetate cleavage with potassium carbonate followed by oxidation with PDC, gave keto ether **58** in 58% yield from **57**. Reaction of **58** in 10:1 acetic anhydride / methylene chloride with 1.1 equivalents of anhydrous ferric chloride in acetic anhydride at -78°C gave a single rearranged acetate **59** in 83% yield. Other Lewis acids, such as diethyl aluminum chloride, borontrifluoroetherate, or even ferric chloride in ether led to the isomeric ketone by rearrangement of a hydrogen instead of carbon. The successful rearrangement is probably initiated by transfer of CH_3CO^+ to the epoxide oxygen of **58.** Completion of the synthesis is achieved by treating **58** with HF in acetonitrile, followed by oxidation of the primary hydroxyl group to a formyl group by PCC, oxidation of the formyl group to carboxyl by sodium chlorite - NaH_2PO_4, and esterification of the resulting acid. Finally, the hydrolysis of the ester and acetyl groups with lithium hydroxide led to pure **1**.

Of the three syntheses of glycinoclepin A, Corey's is by far the most direct, with noteworthy conversion of **51** to **52** *via* the Diels Alder reaction and **58** to **59** via the 1, 2 methyl shift. Although it is more direct, at over 20 steps, there is room for improvement. It is precisely for this reason that we set out to construct a synthesis of glycinoclepin A.

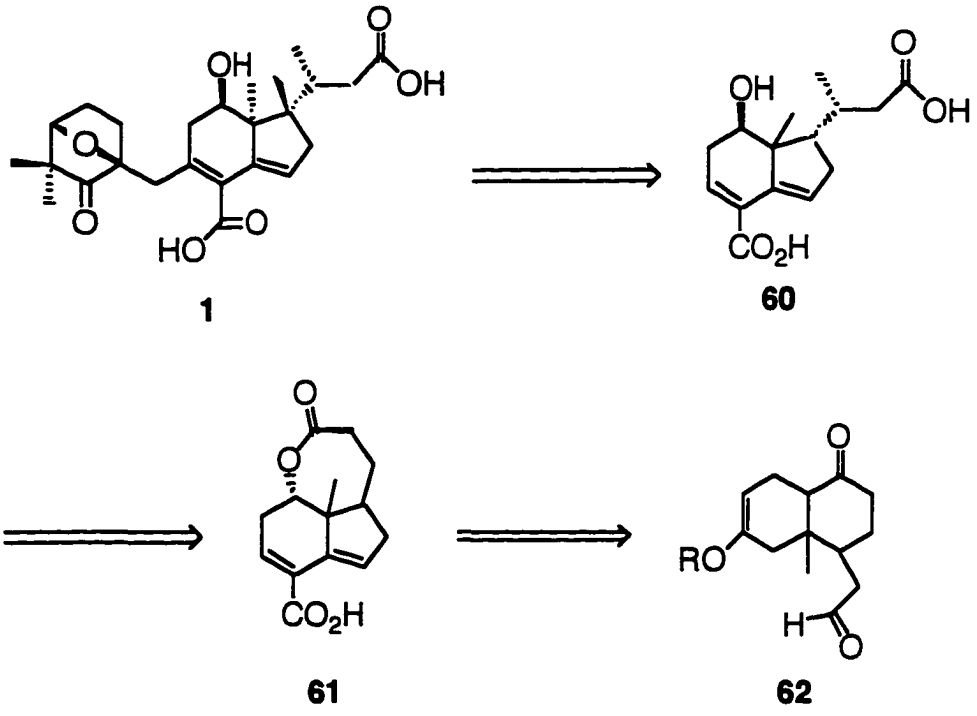
Results and Discussion

Our retrosynthetic analysis for glycinoclepin A can be seen in Scheme XII. We envisioned constructing the bicyclic **62** *via* a Diels Alder reaction with a substituted cyclohexenone and 2-methoxy-1,3-butadiene. Deprotection of the vinyl ether to a ketone, subsequent aldol reaction, conversion of the enone to a diene and Baeyer-Villager oxidation would lead to **61**. Opening of the lactone **61** would lead to key intermediate **60** after isomerization of the alcohol and introduction of

the methyl group. Finally, attachment of the side chain cyclohexanone would lead to **1**.

The first step in the synthesis was to construct the bicyclic keto aldehyde **62**. Treatment of 1,3-cyclohexanedione (**63**) with a catalytic amount of PTSA and one equivalent of trimethyl orthoformate (**64**) in refluxing benzene / methanol led to 3-methoxy-2-cyclohexen-1-one (**65**) in 83% yield as a pure white solid (Scheme XIII).[27] The anion of **65** was formed with 1.1 equivalents of LDA and then

Scheme XII

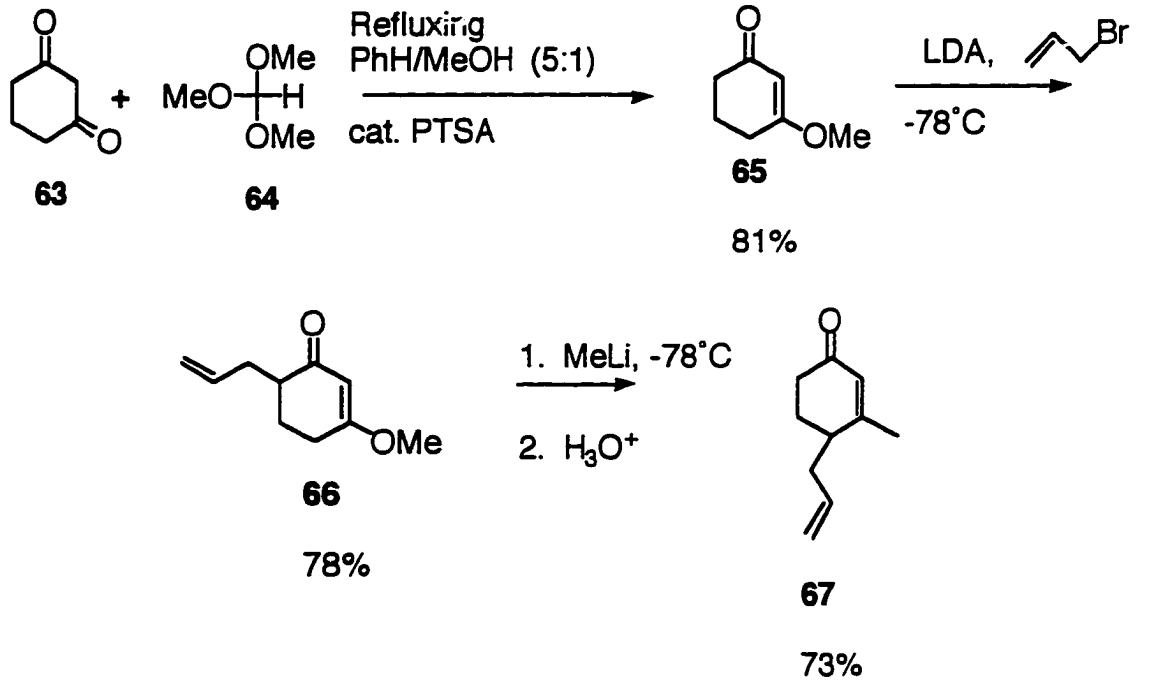


quenched with allyl bromide to afford the substituted enone **66** in 84% yield. Addition of one equivalent of methyl lithium to enone **66**, followed by acidic workup, led to the rearranged enone **67** in 73% yield. Compound **67** was the key intermediate to be used for the Diels Alder reaction.

Compound **67** was combined with three equivalents of 2-methoxy-1,3-butadiene using acetonitrile as the solvent at 40 °C in an attempt to form the bicyclic compound **62** (Scheme XIV). Unfortunately, these conditions returned

only starting material. Addition of borontrifluoroetherate at 0 °C and also at -45 °C led to degradation of the starting materials. We then switched to toluene as the solvent and elevated the temperature to 150 °C and then 210 °C in a sealed tube, but on both occasions, only starting material was returned. Switching to Danishefsky's diene did not change the outcome of the reaction, even after the addition of Lewis acids. It was possible that the methyl group in enone **6 7** was hindering the reaction. In fact, upon review of the literature, we could not find any

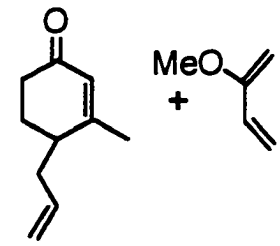
Scheme XIII



examples of successful Diels Alder reactions of cyclohexenones with a substituent in the 3 position.

To alleviate this problem, we simply returned to **6 6** and reduced the ketone to the allylic alcohol, and upon acidic workup, isolated the rearranged enone **7 0** in high yield (Scheme XV). Compound **7 0** was then subjected to Diels Alder conditions, but again, no successful conditions were found even when 1-trimethylsiloxy-1,3-butadiene (**7 1**) was used. Attempted cyclization using lithium perchlorate in ether as a solvent according to a procedure by Grieco[28] was

Scheme XIV



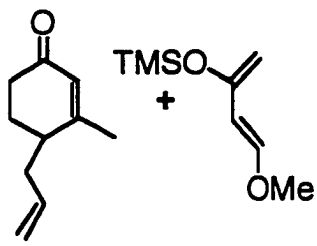
67 68

2M CH_3CN
Sealed Tube,
100 °C
→ SM

$PhCH_3$, Sealed Tube
$BF_3 \cdot OEt_2$, 0 °C to 210 °C
→ X

2M CH_3CN, Sealed Tube
$BF_3 \cdot OEt_2$, -45 °C to 0 °C
to 135 °C
→ X

$PhCH_3$, Sealed tube
210 °C
→ SM



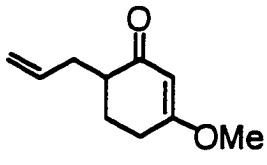
67 69

CH_3CN, Sealed Tube
$AlCl_3$, 0 °C to 130 °C
→ SM

2M CH_3CN, Sealed Tube
135 °C
→ SM

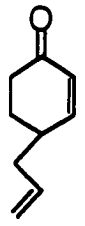
$PhCH_3$, Sealed tube
210 °C
→ X

Scheme XV



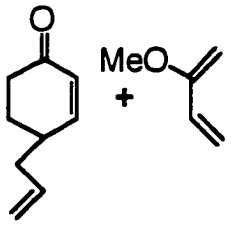
1. $LiAlH_4$, Et_2O

2. H_3O^+



70

93%



70 **68**

2M CH_3CN, Sealed Tube, 135 °C — **SM**

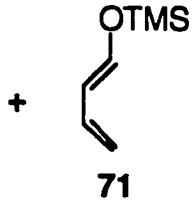
2M CH_3CN, Sealed Tube, $BF_3 \cdot OEt_2$, 0 °C to 135 °C — **SM**

2M CH_3CN, Sealed Tube, 135 °C — **SM**

2M CH_3CN, Sealed Tube, $AlCl_3$, 0 °C to 135 °C — **X**

Neat, Sealed Tube, 100 °C — **X**

Neat, Sealed Tube, 130 °C, BHT (1equiv) — **SM**



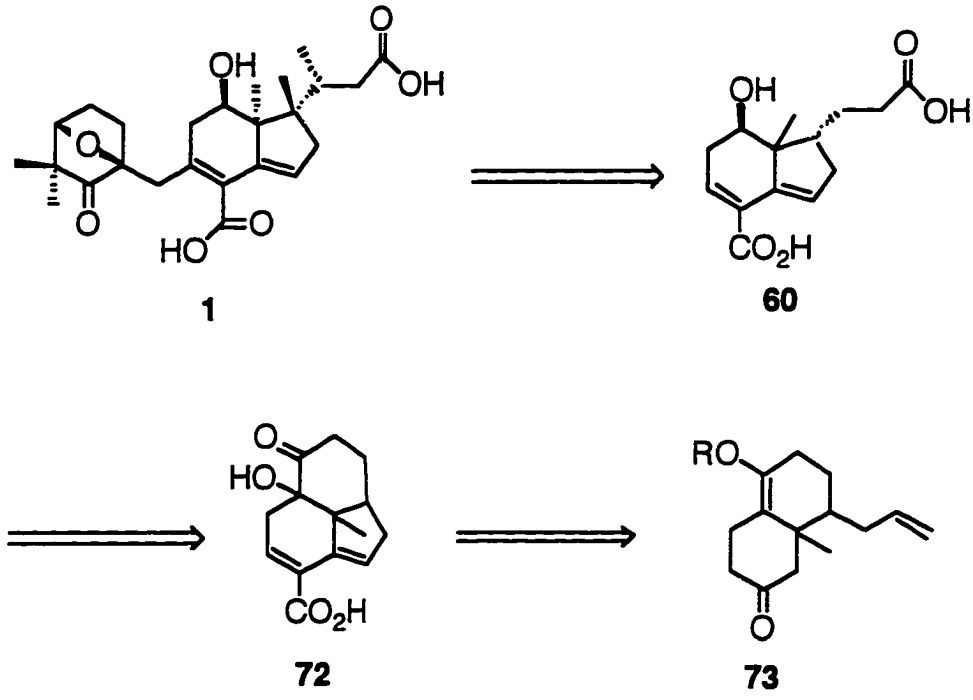
71

2M CH_3CN, Sealed Tube, 135 °C — **SM**

similarly fruitless. The idea behind the perchlorate reaction was to increase the pressure on a molecular level by using a very polar solvent to squeeze the relatively non polar starting materials together.

Upon analysis of the Diels Alder experiments, we decide to change our plan and approach the molecule from a different angle. The revised retrosynthetic analysis can be see in Scheme XVI. Key intermediate **7 3** could be seen coming

Scheme XVI

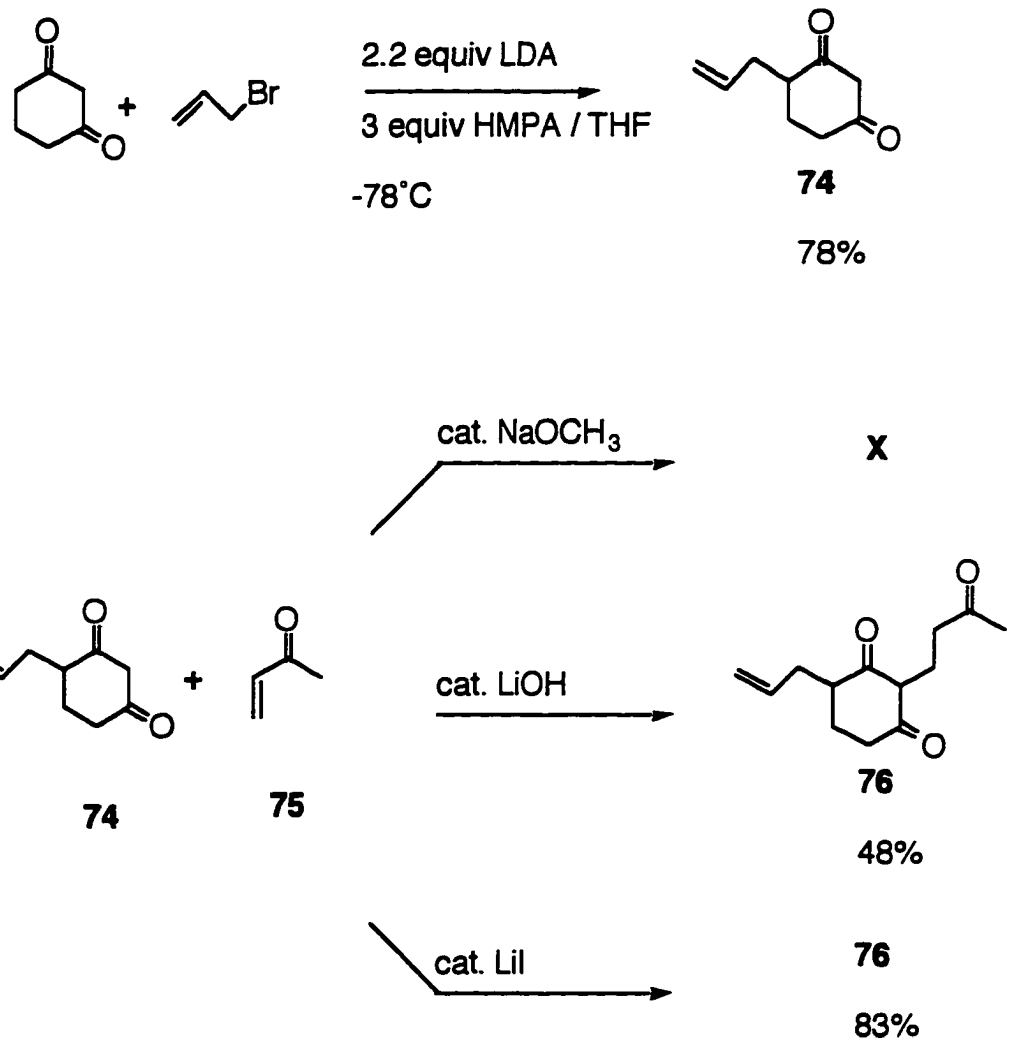


from a Robinson type annulation on a substituted cyclohexanone. Liberation of an aldehyde from the terminal double bond, followed by aldol condensation, transformation of the ketone to an unsaturated carboxylic acid, and formation of the hydroxy ketone from the vinyl ether would lead to **7 2**. Cleavage of the hydroxy ketone and subsequent reduction would give us key intermediate **6 0**.

The synthesis began with the formation of the 4-substituted-1,3-dione **7 4** (Scheme XVII). Treatment of cyclohexane-1,3-dione with 2.2 equivalents of LDA in HMPA / THF at -78 °C gave the dione **7 4** in 78% yield.[29] Compound **7 4** was

combined with methyl vinyl ketone (MVK) (**75**) and a catalytic amount of sodium methoxide in an unsuccessful attempt to promote 1,4-addition. Switching the base to lithium hydroxide in dimethoxyethane (DME) afforded the 1,4-product **76** in 48 %

Scheme XVII

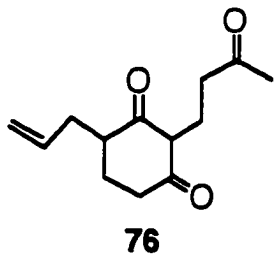


yield. The yield was further improved by using a catalytic amount of lithium iodide in place of lithium hydroxide using DME again as the solvent to give **76** in 83% yield.[30]

The next step in the synthesis was to try to selectively form one of the two possible enones. As can be seen in Scheme XVIII, little selectivity was observed

for a variety of systems. Treatment of **7 6** with diazomethane was finally chosen as the best system because of the ease and speed of the reaction and also because the isomers could be separated and **7 8** hydrolyzed with acid to recycle the starting material. With **7 7** in hand, treatment of the methyl ketone with potassium metal in *tert*-butyl alcohol and benzene (4:1) led to the conjugated enone **7 9** in 51% yield (Scheme XIX). Treatment of enone **7 9** with simple dimethyl cuprate led to **8 0**.[31]

Scheme XVIII

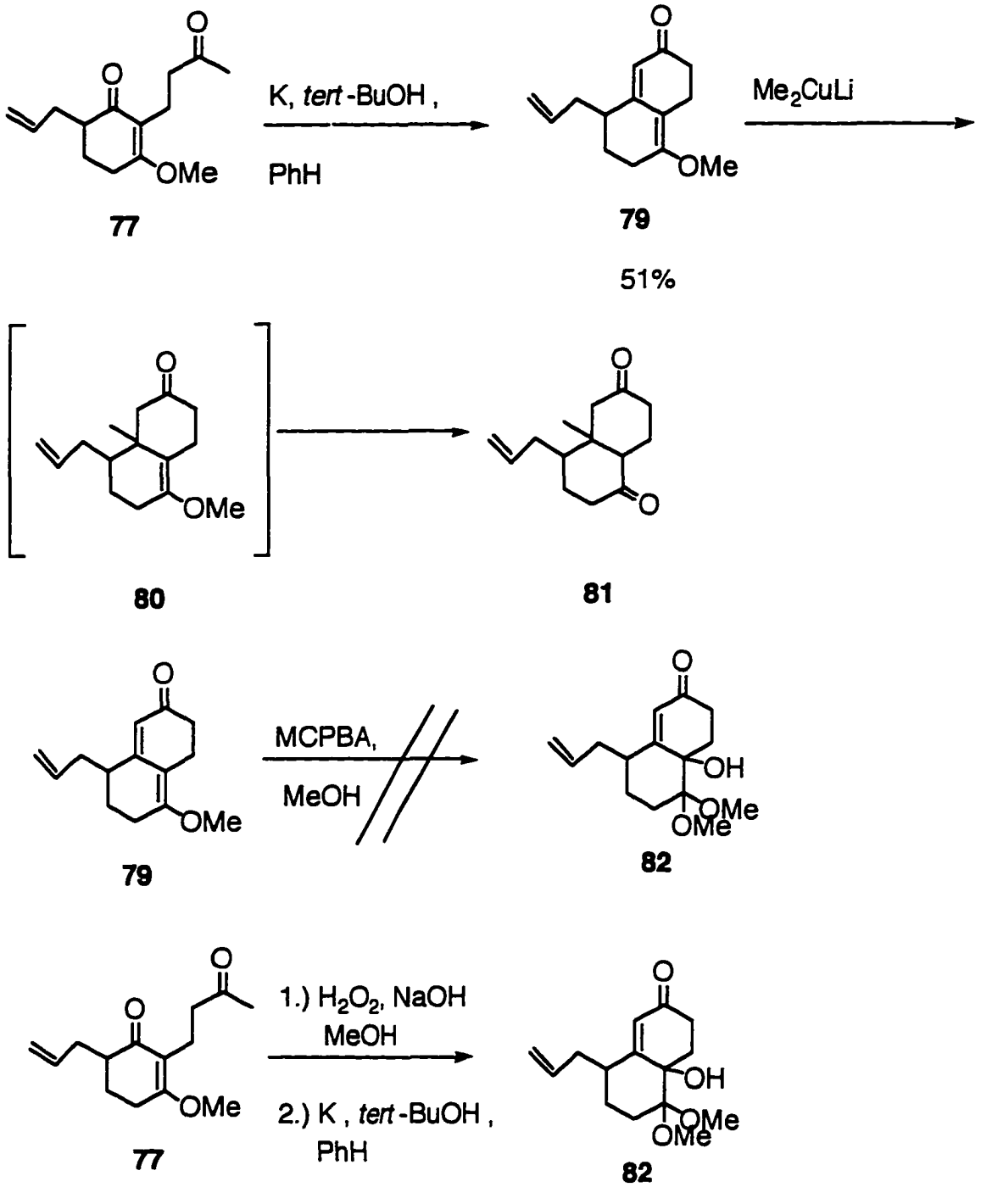


76

	77	**78**
TBDMSCl, Imidazole, DMF	44%	40%
Diphenyldiazomethane	45%	39%
NaH, MeI	35%	36%
Diazomethane	48%	47%

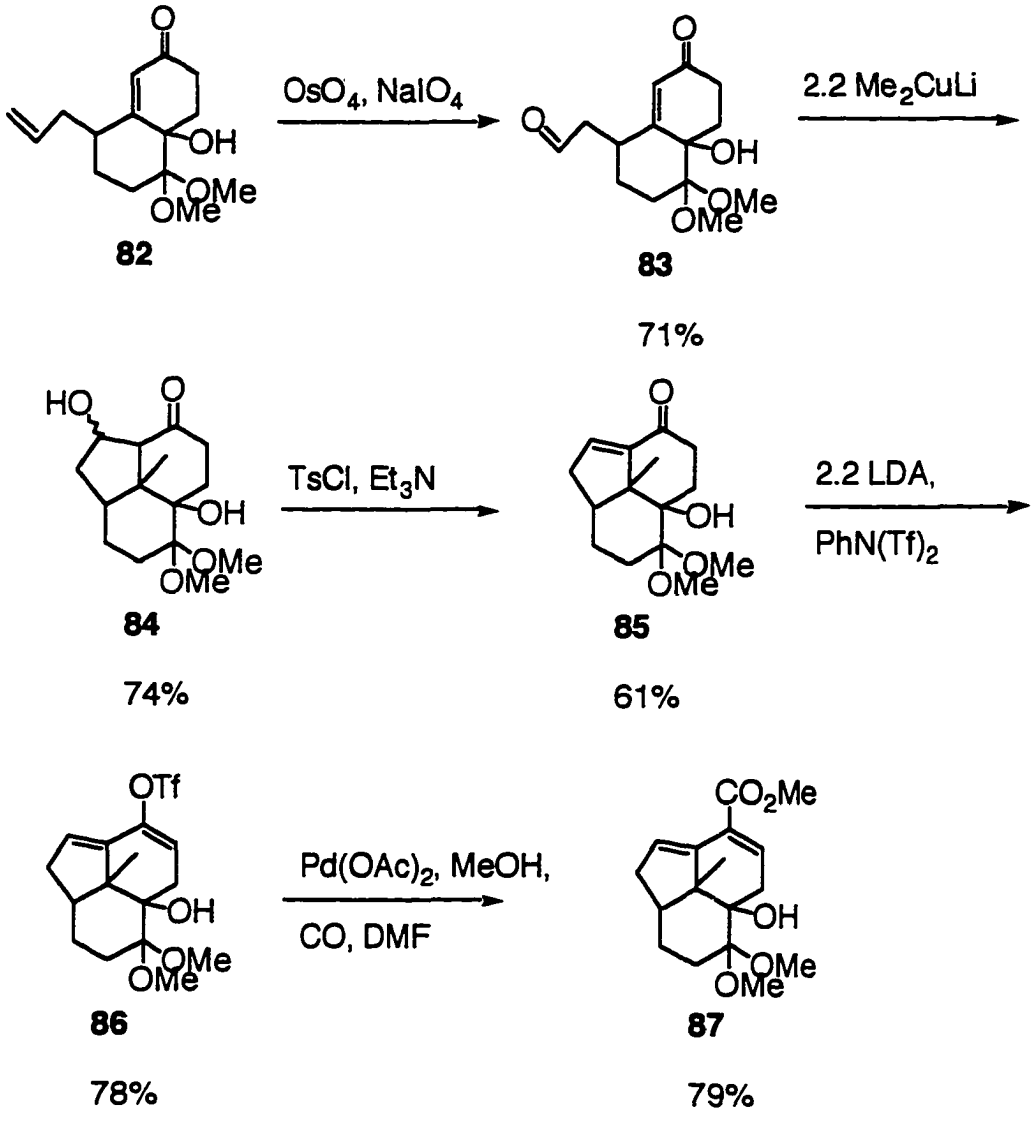
Unfortunately, **8 0** was not stable and easily hydrolyzed to form the diketone **8 1**, no matter how much care was given to keep it away from any acids. We therefore returned to **7 9** and tried to selectively epoxidate the vinyl ether using MCPBA to try to form the hydroxy ketal **8 2**. All attempts at this reaction similarly failed. Realizing that the conjugated double bond of enone **7 7** was also limiting

Scheme XIX


K, tert-BuOH,
PhH
Me2CuLi
OMe
77
79
51%
80
81
MCPBA,
MeOH
OH
OMe
82
1.) H2O2, NaOH
MeOH
2.) K, tert-BuOH,
PhH

our yields in the aldol reaction, we attempted to epoxidate the enone using alkaline hydrogen peroxide. This procedure worked smoothly in 68% yield to form the hydroxy ketal.[32] The condensation reaction proceeded to give us enone **8 2** in a

Scheme XX



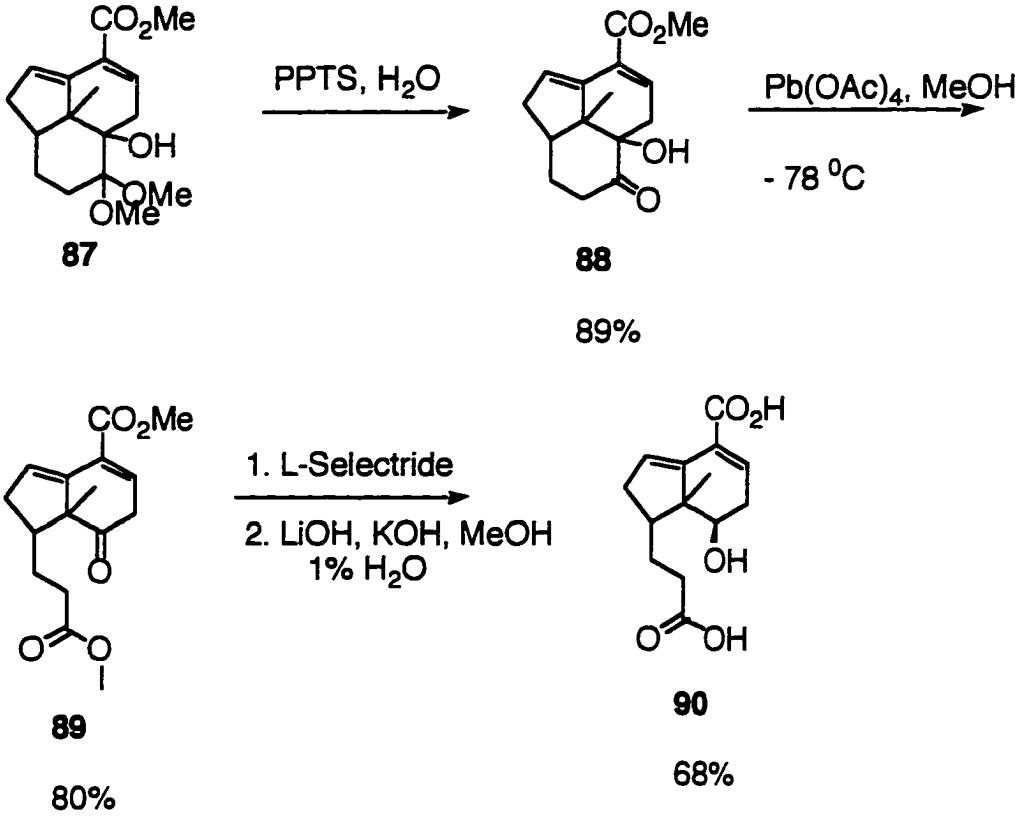
higher yield (67%) under the same reaction conditions used for **7 9**.

Compound **8 2** was then subjected to osmylation conditions to liberate the aldehyde **8 3** in 71% yield (Scheme XX). Cuprate addition (2.2 equivalents) proceeded smoothly to give the tricyclic diol **8 4** in 74% yield. Selective

dehydration using tosyl chloride and triethylamine was achieved to form enone **85** in 61% yield.[33] The next phase of the synthesis was to convert the enone to an unsaturated acid. This was accomplished by treating **85** with 2.2 equivalents of LDA and 1 equivalent of *N*-phenylbistrifluoromethanesulfonamide to give the vinyl triflate **86** in 78% yield. Formation of the acid **87** was accomplished using a modification of Ortar's method to form the acid in 79% yield.[34]

The final steps of the synthesis involve cleavage of the hydroxy ketal, reduction of the resulting ketone, and hydrolysis of the esters(Scheme XXI). First,

Scheme XXI



87 was treated with PPTS in water to liberate the hydroxy ketone in 89% yield. Cleavage of the hydroxy ketone **88** proved difficult at first, with degradation of the starting material being the most common result with sodium periodate or lead tetraacetate at room temperature. If **88** was cooled to -78 °C in methanol and

benzene, and a solution of lead tetraacetate in methanol was added dropwise over 1 hour, keto ester **89** could be isolated in 80% yield.[35] Reduction with L-selectride followed by alkaline hydrolysis lead to **90** in 68% yield over the two steps.

Compound **90** has been submitted for testing with Dr. Greg Tylka's lab and the efficacy of **90** as a hatch stimulus has not been ascertained at the time of printing.

Conclusions

Compound **90** is an important precursor to glycinoclepin A. It is hopeful that this route can be used in the near future for a total synthesis of **1**. Unlike Mori's and Murai's total synthesis, **90** is made in relatively high yield from commercially available starting materials. It is hoped that **90** will be a potent hatch stimulator.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2), and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-

Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Varian 300 Spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Varian 300 Spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

3-Methoxy-2-cyclohexen-1-one (65): To a stirred solution of 10.6 g of 1,3-cyclohexanedione (95 mmol) (**63**) in 180 mL of dry, refluxing benzene was added 0.460 g of *p*-toluenesulfonic acid (2.5 mmol, 0.25 equiv.), 36.0 mL of methanol (271 mmol, 2.85 equiv.) and 11.0 mL of trimethyl orthoformate (100 mmol, 1.05 equiv.). After 24 hours, the mixture was cooled and washed with 180 mL of 10 % aq NaOH saturated with brine. The organic layer was dried over sodium sulfate and the solvent removed in vacuo to give the 9.10 g (81%) of product, which was purified by distillation, bp = 52-53 °C at 0.7 mm Hg. ^1H NMR ($CDCl_3$) δ 1.80-1.90 (m, 2H), 1.98 (t, J = 9.6 Hz, 2H), 2.18 (t. J = 9.3 Hz, 2H), 3.70 (s, 3H), 5.81 (s, 1H). IR (neat) 3084, 2975, 2842, 1681, 1610 cm^{-1}. MS (CI, *m/z*) 126 (M^+). HRMS m/z calculated for $C_7H_{10}O_2$: 126.0681, measured 126.0683. ^{13}C NMR ($CDCl_3$) δ 27.8, 30.1, 42.7, 53.7, 128.6, 158.9, 201.4.

3-Methoxy-6-(prop-2-enyl)-cyclohex-2-en-1-one (66) : To a 50 mL flask containing 15 mL of dry THF at -78 °C was added 1.14 mL of diisopropylamine (8.7 mmol, 1.1 equiv.) and 3.70 mL of a 2.36 M solution of *n*-butyl

lithium in THF (8.7 mmol, 1.1 equiv.). This solution was stirred for one hour and then added dropwise to a stirred solution of 1.00 g of 3-methoxy-2-cyclohexen-1-one (7.9 mmol, 1 equiv.) (**65**) in 15 mL of dry THF at -78 °C. After one hour, 0.754 mL of allyl bromide (8.7 mmol, 1.1 equiv.) was added dropwise over one minute. The solution was allowed to warm to room temperature and then was quenched with 150 mL of brine and extracted three times with 50 mL of diethyl ether. The organic layers were combined and dried over sodium sulfate. Removal of the solvent in vacuo left 1.03 g (78%) of **66** after purification by sgc (4:1 H:EA , R_f = 0.37) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.78-1.90 (m, 2H), 1.98 (t, J = 9.6 Hz, 2H), 2.15-2.68 (m, 3H), 3.70 (s, 3H), 4.98-5.10 (m, 2H), 5.65-5.91 (m, 2H). IR (neat) 3097, 2968, 2856, 1683, 1610 cm^{-1}. MS (CI, *m/z*) 166 (M^+), 124. HRMS m/z calculated for $C_{10}H_{14}O_2$: 166.0994, measured 166.1001. ^{13}C NMR ($CDCl_3$) δ 18.6, 27.8, 30.1, 42.9, 53.9, 114.1, 128.6, 141.7, 158.6, 201.3.

3-Methyl-4-(prop-2-enyl)-2-cyclohexen-1-one (67): To a stirred solution of 1.00 g of **66** (6.0 mmol) in 12 mL of THF at -78 °C was added 4.73 mL of a 1.4 M methyl lithium (6.6 mmol, 1.1 equiv.). After allowing the solution to warm to room temperature, the reaction was quenched with water and 12 mL of 1N H_2SO_4 was added and allowed to react overnight. The reaction mixture was taken up in 75 mL of a 1:1 solution of ether and water and extracted. The aqueous layer was further extracted 3 times with 35 mL of ether, and the organic layers combined and dried over sodium sulfate. The solvent was removed in vacuo and afforded 0.657 g (73%) of **67** after purification by sgc (3:1 H:EA, R_f = 0.42) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H), 1.80-1.94 (m, 2H), 2.08-2.32 (m, 5H), 4.97-5.12 (m, 2H), 5.65-5.90 (m, 1H), 5.93 (s, 1H). IR (neat) 3084, 2941, 2799, 1676 cm^{-1}. MS (CI, *m/z*) 150 (M^+), 108. HRMS m/z calculated for $C_{10}H_{14}O$: 150.1045, measured 150.1048. ^{13}C NMR ($CDCl_3$) δ 18.9, 21.4, 28.1, 32.8, 41.9, 114.3, 128.4, 142.1, 158.1, 201.5.

4-(Prop-2-enyl)-2-cyclohexen-1-one (67): A solution of 1.00 g of **66** (6.0 mmol) in 12 mL of diethyl ether was added dropwise to a stirring solution of 56 mg of lithium aluminum hydride (0.15 mmol, 0.25 equiv.) in 12 mL of diethyl ether at -78 °C. After allowing the solution to warm to room temperature, the reaction was quenched with water and 12 mL of 1N H_2SO_4 was added slowly and allowed to react overnight. The reaction mixture was taken up in 75 mL of a 1:1 solution of ether and water and extracted. The aqueous layer was further extracted 3 times with 35 mL of ether, and the organic layers combined and dried over sodium sulfate. The solvent was removed in vacuo to afford 0.758 g (93%) of **70** after purification by sgc (3:1 H:EA, R_f = 0.41) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.81-1.92 (m, 2H), 2.08-2.33 (m, 5H), 4.94-5.09 (m, 2H), 5.65-5.88 (m, 1H), 5.92 (d, *J* = 10.1 Hz, 1H), 6.87 (m, 1H). IR (neat) 3072, 2965, 2794, 1673 cm^{-1}. MS (CI, *m/z*) 136 (M^+), 94. HRMS m/z calculated for $C_9H_{12}O$: 136.0888, measured 136.0893. ^{13}C NMR ($CDCl_3$) δ 19.1, 28.4, 31.7, 41.8, 115.1, 128.3, 142.2, 157.9, 201.2.

4-(Prop-2-enyl)-1,3-cyclohexanedione (74) : To a 50 mL flask containing 18 mL of dry THF at -78 °C was added 2.56 mL of diisopropylamine (19.6 mmol, 2.2 equiv.) and 8.30 mL of a 2.36 M solution of *n*-butyl lithium in THF (19.6 mmol, 2.2 equiv.). This solution was stirred for one hour and then added dropwise to a stirred solution of 1.00 g of 1,3-cyclohexanedione (9.0 mmol, 1equiv.) and 4.65 mL of HMPA (26.8 mmol, 3 equiv.) in 15 mL of dry THF at -78 °C. After one hour, 0.848 mL of allyl bromide (9.8 mmol, 1.1 equiv.) was added dropwise over five minutes. The solution was allowed to warm to room temperature and then was quenched with 150 mL of brine and extracted three times with 50 mL of diethyl ether. The organic layers were combined and dried over sodium sulfate. Removal of the solvent in vacuo left 1.06 g (78%) of **74** after purification by sgc (1:1 H:EA , R_f = 0.27) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.51-1.67 (m, 0.5H), 1.72-1.86 (m, 0.5H), 2.08-2.24 (m, 2H), 2.32-2.49 (m, 1H), 2.51-2.76 (m, 3H), 3.42 (d, *J* = 17.0 Hz,

0.5 H), 3.48 (d, J = 17.0 Hz, 0.5H), 5.04-5.15 (m, 2H), 5.47 (s, 0.5H), 5.71-5.88 (m, 1H). IR (neat) 3201, 3072, 2985, 1720, 1650, 1615 cm^{-1}. MS (CI, *m/z*) 152 (M^+), 110, 95. HRMS m/z calculated for $C_9H_{12}O_2$: 152.0837, measured 152.0843.

2-(3-Oxo-butyl)-4-(prop-2-enyl)-1,3-cyclohexanedione (76): To a stirred solution of 1.00 g of **74** (6.6 mmol) in 15 mL of 1,2-dimethoxyethane was added 44 mg of lithium iodide (0.33 mmol, 0.05 equiv.) and 0.604 mL of methyl vinyl ketone (7.3mmol, 1.1equiv.). After refluxing for two days, the solution as cooled and 15 mL of 1N HCl solution was added and the solution was refluxed for an additional hour. After cooling, the layers were separated and the aqueous layer was further extracted three times with 50 mL of diethyl ether. The organic layers were combined and dried over sodium sulfate. The solvent was removed in vacuo and 1.21 g (83%) of **7 6** was obtained after vacuum distillation (bp = 154-156 °C at 0.1mm Hg). ^1H NMR ($CDCl_3$) δ 1.55-1.80 (m, 1H), 2.04-2.24 (m, 5H), 2.40-2.63 (m, 8H), 3.40-3.52 (m, 1H), 4.99-5.14 (m, 2H), 5.72-5.86 (m, 1H). IR (neat) 3146, 3098, 2954, 1718, 1714, 1650, 1615 cm^{-1}. MS (CI, *m/z*) 222 (M^+), 180, 137. HRMS m/z calculated for $C_{13}H_{18}O_3$: 222.1256, measured 222.1258.

2-(3-oxo-butyl)-3-methoxy-6-(prop-2-enyl)-2-cyclohexen-1-one (77): To an unstirred solution of 1.00 g of **76** (4.5 mmol) in 20 mL of diethyl ether at 0 °C was added an ethereal solution of diazomethane dropwise until nitrogen no longer evolved from the reaction mixture. Nitrogen gas was then gently bubbled through the solution for 30 minutes and the solvent was removed in vacuo. The isomers were purified by sgc (EA, R_f = 0.72) and 0.510 g (96% yield on 51% conversion) of **7 7** was obtained. ^1H NMR ($CDCl_3$) δ 1.60-1.80 (m, 1H), 2.05-2.25 (m, 6H), 2.47-2.71 (m, 8H), 3.80 (s, 3H), 4.99-5.10 (m, 2H), 5.72-5.86 (m, 1H). IR (neat) 3086, 2975, 2842, 1716, 1683, 1611 cm^{-1}. MS (CI, *m/z*) 236 (M^+), 194, 151. HRMS m/z calculated for $C_{14}H_{20}O_3$: 236.1412, measured 236.1418. ^{13}C NMR

($CDCl_3$) δ 18.4, 19.6, 27.4, 30.7, 31.9, 35.4, 42.7, 53.4, 114.1, 129.4, 141.6, 158.7, 201.6, 206.8.

4,4-Dimethoxy-10-hydroxy-8-(prop-2-enyl)-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (82): To a stirred solution of 1.00 g of **77** (4.0 mmol) in 25 mL of methanol at 20 °C was added 1.36 mL of a 30% solution of hydrogen peroxide (12.0 mmol, 3 equiv.). 1.00 mL of 2N NaOH (2.0 mmol, 0.5 equiv.) was then added dropwise via syringe pump over 1 hour. The solution was quenched with water and extracted 3 times with 25 mL of diethyl ether. In a separate flask, 0.156 g of potassium metal (4.0 mmol, 1.0 equiv.) was dissolved in 1.53 mL of *t*-butanol (16.0 mmol, 4.0 equiv.). The crude product was then dissolved in 4.0 mL of benzene and added dropwise to the freshly prepared *t*-butanol / potassium solution and reacted for four hours. The reaction was then quenched with water and extracted 3 times with 50 mL of benzene. The combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to yield 0.485g (45%) of **82** as a bright yellow oil after sgc purification (3:1 H:EA, R_f = 0.35) .^{1}H NMR ($CDCl_3$) δ 1.92-2.32 (m, 4H), 2.41-2.72 (m, 8H), 3.68 (s, 6H), 4.99-5.10 (m, 2H), 5.69-5.80 (m, 1H), 5.89 (s, 1H). IR (neat) 3156, 3072, 2968, 2841, 1676 cm^{-1}. MS (CI, *m/z*) 266 (M^+), 234, 224, 202. HRMS m/z calculated for $C_{15}H_{22}O_4$: 266.1518, measured 266.1521. ^{13}C NMR ($CDCl_3$) δ 18.5, 27.2, 27.8, 28.8, 31.9, 42.3, 53.9, 71.4, 91.4, 114.3, 132.4, 141.4, 161.0, 199.8.

4,4-Dimethoxy-10-hydroxy-8-(3-oxo-propyl)-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (83): To a stirred solution of 1.00 g of **82** (3.8 mmol) in 11.5 mL of diethyl ether at 25 °C was added 9.65 mL of a 0.005 g/mL solution of osmium tetroxide in water (0.19 mmol, 0.05 equiv.) and 1.60 g of sodium periodate (7.5 mmol, 2 equiv.). The reaction was stirred overnight and then was

quenched with water, filtered, and the filtrate extracted 3 times with 25 mL of diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to yield 0.723g (71%) of **8 3** as a yellow oil after sgc purification (1:1 H:EA, $R_f = 0.46$) .^{1}H NMR ($CDCl_3$) δ 1.94-2.29 (m, 4H), 2.41-2.78 (m, 8H), 3.67 (s, 6H), 5.89 (s, 1H), 9.98 (s, 1H). IR (neat) 3167, 3048, 2914, 2867, 1727, 1674 cm^{-1}. MS (CI, *m/z*) 268 (M^+), 250, 236, 204. HRMS m/z calculated for $C_{14}H_{20}O_5$: 268.1311, measured 268.1309. ^{13}C NMR ($CDCl_3$) δ 27.0, 27.3, 29.1, 31.7, 42.4, 46.7, 53.7, 71.5, 91.3, 132.1, 161.3, 194.2, 200.2.

Keto-Diol 84: To a stirred solution of 1.55 g of copper(I) iodide (8.1 mmol, 2.2 equiv.) in 8.0 mL of diethyl ether at 0 °C was added 10.26 mL of a 1.6 M solution of methyllithium in diethyl ether (16.4 mmol, 4.4 equiv.). In a separate flask, 1.00 g of **8 3** was dissolved in 8.0 mL of diethyl ether and cooled to 0 °C . After the copper iodide / methyllithium solution had turned colorless again, it was added dropwise to the enone solution. After 1 hour, the reaction was quenched with water and washed with a saturated ammonium chloride solution, followed by washing with an aqueous ammonium hydroxide solution. The organic layer was dried over sodium sulfate and the solvent removed in vacuo to yield 0.778 g (74%) of **8 4** as a pale yellow oil after sgc purification (1:1 H:EA, $R_f = 0.42$) .^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.78-2.41 (m, 8H), 2.45-2.63 (m, 7H), 3.68 (s, 6H). IR (neat) 3164, 2972, 2833, 1718 cm^{-1}. MS (CI, *m/z*) 284 (M^+), 267, 236. HRMS m/z calculated for $C_{15}H_{24}O_5$: 284.1624, measured 284.1620. Anal. Calcd. for $C_{15}H_{24}O_5$: C 63.36, H 8.51. Found: C 63.42, H 8.45.

Hydroxy ketal enone 85: To a stirred solution of 1.00 g of **84** (3.5 mmol) in 11.5 mL of THF at 0 °C was added 0.536 mL of triethylamine (3.8 mmol, 1.1 equiv.) and 0.671 g of *p*-toluenesulfonyl chloride (3.8 mmol, 1.1 equiv.). The

reaction was stirred overnight and then an additional 0.536 mL of triethylamine was added to the reaction. After the reaction was determined to be complete by TLC, it was quenched with water and extracted 3 times with 25 mL of diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to yield 0.568g (61%) of **85** as a yellow oil after sgc purification (1:1 H:EA, $R_f = 0.17$) . ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.81-2.27 (m, 8H), 2.31-2.53 (m, 4H), 3.69 (s, 6H), 5.66 (br s, 1H). IR (neat) 3118, 3071, 2941, 2816, 1676, 1609 cm^{-1}. MS (CI, *m/z*) 266 (M^+), 249, 235, 204. HRMS m/z calculated for $C_{15}H_{22}O_4$: 266.1518, measured 266.1511. ^{13}C NMR ($CDCl_3$) δ 15.7, 22.4, 27.1, 28.7, 32.3, 34.3, 43.1, 51.2, 53.8, 71.6, 91.5, 133.4, 168.2, 202.1.

Vinyl Triflate 86 : To a 50 mL flask containing 18 mL of dry THF at -78 °C was added 1.08 mL of diisopropylamine (8.2 mmol, 2.2 equiv.) and 3.5 mL of a 2.36 M solution of *n*-butyl lithium in THF (8.2 mmol, 2.2 equiv.). This solution was stirred for one hour and then added dropwise to a stirred solution of 1.00 g of **85** (3.7 mmol, 1 equiv.). After one hour, 1.34 g of *N*-phenyltrifluoromethanesulfonamide (3.7 mmol, 1.0 equiv.) was added portion wise over five minutes. The solution was allowed to warm to room temperature and then was quenched with 150 mL of brine and extracted three times with 50 mL of diethyl ether. The organic layers were combined and dried over sodium sulfate. Removal of the solvent in vacuo left 1.16 g (78%) of **86** after purification by sgc (1:1 H:EA , $R_f = 0.21$) as a bright yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.80-2.24 (m, 8H), 2.31-2.45 (m, 2H), 3.69 (s, 6H), 5.91 (br s, 1H), 6.83 (m, 1H). IR (neat) 3142, 3071, 2979, 2834, 1369 cm^{-1}. MS (CI, *m/z*) 398 (M^+), 383, 329. HRMS m/z calculated for $C_{16}H_{21}O_6F_3S$: 398.1011, measured 398.1017.

Hydroxy ketal ester 87: A mixture of 1.00g of **86** (2.5 mmol), 0.697 mL triethylamine (5.0 mmol, 2 equiv.), 17 mg of palladium acetate (0.08 mmol, 0.03

equiv.), 39 mg of triphenylphosphine (0.15 mmol, 0.06 equiv.) and 4.05 mL of methanol (100 mmol, 40 equiv.) in 10 mL DMF was purged with carbon monoxide for 5 minutes and stirred under a CO balloon at room temperature for three hours. The reaction was quenched with 25 mL water and extracted 3 times with 50 mL of diethyl ether. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed in vacuo and gave 0.605 g (79%) of 87 after purification by sgc (1:1 H:EA , R_f = 0.29). ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.81-2.23 (m, 8H), 2.30-2.46 (m, 2H), 3.49 (s, 3H), 3.69 (s, 6H), 5.91 (br s, 1H), 6.68 (m, 1H). IR (neat) 3116, 3074, 2918, 2879, 1723 cm^{-1}. MS (CI, *m/z*) 308 (M^+), 291, 277. HRMS m/z calculated for $C_{17}H_{24}O_5$: 308.1624, measured 308.1628. Anal. Calcd. for $C_{17}H_{24}O_5$: C 66.21, H 7.84. Found: C 66.30, H 7.91.

Hydroxy keto ester 88: To a stirred solution of 1.00 g of **87** (3.3 mmol) in 13.0 mL of water at 25 °C was added 0.122 g of pyridinium *p*-toluenesulfonate (0.5 mmol, 0.15 equiv.). The reaction was stirred overnight and then diluted with diethyl ether and extracted 3 times with 25 mL of diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to yield 0.757 g (89%) of **8 8** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.80-2.20 (m, 6H), 2.29-2.45 (m, 4H), 3.49 (s, 3H), 5.92 (br s, 1H), 6.65 (m, 1H). IR (neat) 3184, 3078, 2932, 2843, 1724, 1714 cm^{-1}. MS (CI, *m/z*) 262 (M^+), 244, 231. HRMS m/z calculated for $C_{15}H_{18}O_4$: 262.1205, measured 262.1201. Anal. Calcd. for $C_{15}H_{18}O_4$: C 68.69, H 6.92. Found: C 66.58, H 6.87.

Keto bis-ester 89: To a stirred solution of 1.00 g **88** (3.8 mmol) in 20 mL of absolute methanol and 20 mL of dry benzene was added 2.03 g of lead tetraacetate (4.6 mmol, 1.2 equiv.) dissolved in 20 mL of absolute methanol dropwise over 1 hour via syringe pump at -78 °C. After 18 hours, the reaction was

quenched with 25 mL of water and the layers separated. The aqueous phase was further extracted 3 times with 50 mL of diethyl ether and the organic layers combined, dried over sodium sulfate and the solvent removed in vacuo to afford 0.892g (80%) of **8 9** after purification by sgc (1:1 H:EA, R_f=0.34). ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.56-1.98 (m, 5H), 2.11-2.45 (m, 4H), 3.49 (s, 3H), 3.64 (s, 3H), 5.92 (br s, 1H), 6.65 (t, *J* = 7.1 Hz, 1H). IR (neat) 3054, 2968, 2816, 1738, 1721, 1713 cm^{-1}. MS (CI, *m/z*) 292 (M^+), 261, 230. HRMS m/z calculated for $C_{16}H_{20}O_5$: 292.1311, measured 292.1304.

Hydroxy bis-acid 90: To a stirred solution of 1.00 g of **89** (3.4 mmol) in 13.5 mL of THF at -78 ^{0}C was added 3.77 mL of L-Selectride (3.8 mmol, 1.1 equiv.). The reaction was stirred for one hour and then warmed to room temperature and quenched with water. The reaction mixture was extracted 3 times with 25 mL of diethyl ether, the organic layers dried over sodium sulfate, and the solvent removed in vacuo. The crude product was then dissolved in 15 mL of methanol and 0.655 g of lithium hydroxide (27.4 mmol, 8 equiv.) and 0.767 g of potassium hydroxide (13.7 mmol, 4 equiv.) were added and the reaction stirred overnight. The reaction was then acidified with 2N HCl and then diluted with diethyl ether and extracted 3 times with 25 mL of diethyl ether. The combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to yield 0.618 g (68%) of **9 0** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 2.10-2.21 (m, 4H), 2.45-2.60 (m, 6H), 5.66 (br s, 1H), 6.65 (t, *J* = 7.1 Hz, 1H). IR (neat) 3334, 2918, 1758, 1410 cm^{-1}. MS (CI, *m/z*) 266 (M^+), 222, 178. HRMS m/z calculated for $C_{14}H_{18}O_5$: 266.1154, measured 2666.1150. Anal. Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.81. Found: C 63.21, H 6.89. ^{13}C NMR ($CDCl_3$) δ 18.4, 21.4, 29.2, 30.8, 31.3, 32.6, 33.8, 69.4, 125.2, 128.6, 131.4, 142.9, 174.1, 178.5.

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GENERAL CONCLUSIONS

It is the duty of the synthetic chemist to incorporate all disciplines of organic chemistry into his or her intellectual arsenal. The task of building complex natural products demands that he or she use all of his or her skills to finish the project quickly and efficiently. It is this quest that motivates the synthetic chemist to continually challenge that which is known and strive to explore the unknown.

In conclusion, we have developed pathways to a number of different biomimetic compounds and several biologically interesting analogs. In the first project, we developed a pathway to the development of novel photosynthetic antennas. We have synthesized the first arborol type molecule with a central core and six peripheral phthalocyanines.

In the second project, we developed analogs of glycinoclepin A which will be used to control the spread of the SCN. All of the analogs synthesized were hatch inhibitors, not hatch initiators. These analogs have been patented and we hope are new weapons in the fight against SCN proliferation.

Finally, in the third project, we have developed a synthetic pathway to the core structure of glycinoclepin A. Hopefully, a total synthesis based on this work will be completed in the near future.

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