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# Synthesis of analogs of aflatoxin B2 and glycinoeclepin A

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# Synthesis of analogs of aflatoxin $B_2$ and glycinoeclepin A

by

Beth Ellen Johnston

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1992

# DEDICATION

This dissertation is dedicated to my family, whose love, support, and faith in me made it possible.

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# ABBREVIATIONS

The following abbreviations are used in this dissertation:

| | |
|---|---|
| Ar | aryl |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| BPS | tert-butyldiphenylsilyl |
| Bu | butyl |
| t-Bu | tert-butyl |
| Bz | benzoyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | diisobutylaluminum hydride |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| Et | ethyl |
| g | gram |
| h | hour(s) |
| HMDS | hexamethyldisilazane |
| HMPA | hexamethylphosphoric triamide |
| LDA | lithium diisopropylamide |
| LTA | lead tetraacetate |
| *m*-CPBA | *m*-chloroperoxybenzoic acid |

| | |
|---|---|
| Me | methyl |
| MEM | (2-methoxyethoxy)methyl |
| min | minute(s) |
| mmol | millimole(s) |
| MMC | methyl methoxymagnesium carbonate |
| MMPP | monoperoxyphthalic acid, magnesium salt |
| MOM | methoxymethyl |
| Ms | methanesulfonyl (mesyl) |
| MVK | methyl vinyl ketone |
| NBS | N-bromosuccinimide |
| PCC | pyridium chlorochromate |
| Ph | phenyl |
| PM | Phenylmenthyl |
| PPTS | pyridium p-toluenesulfonate |
| i-Pr | isopropyl |
| PTSA | p-tolunesulfonic acid |
| $R_F$ | retention factor |
| TBDMS | tert-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Tr | triphenylmethyl (trityl) |
| Ts | p-toluenesulfonyl (tosyl) |

# GENERAL INTRODUCTION

For the synthetic organic chemist, a natural product represents challenge: the synthesis itself, as well as development and application of methodology toward that end. The synthetic chemist is also interested in the synthesis of simpler analogs of such a compound in the hope they will display improved, similar, or at least acceptable biological activity. Such analogs are useful for structure-activity studies and may be more suitable for commercial purposes than compounds obtained from a natural source. Intermediates formed in attempts at total syntheses are often suitable analogs.

The goal of the first part of this research was to explore the use of silver salts to promote radical cyclizations of appropriate substrates to form variously substituted furofuran systems and to apply this methodology to the synthesis of demethoxyaflatoxin $B_2$, an analog of aflatoxin $B_2$, a potent naturally occurring toxin. While such reactions have been reported previously, the conditions employed here are much milder and more convenient. In the second part of this research, various analogs of glycinoeclepin A, the naturally occurring hatching stimulus of the soybean cyst nematode, were prepared and tested for hatch-stimulating ability. While few of the compounds tested were active, this information shed light on which portions of the molecule were necessary for activity.

## Explanation of the Dissertation Format

This dissertation is divided into two separate papers, each in publishable format. The structures and references for each are therefore numbered independently. Each paper is preceded by an introduction. The first paper covers the synthesis of racemic demethoxyaflatoxin $B_2$. The second paper deals with the synthesis of analogs of glycinoeclepin A. A general summary of both papers will follow the second paper.

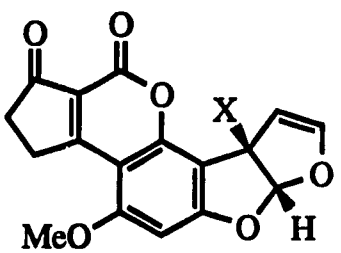
# PAPER I: TOTAL SYNTHESIS OF RACEMIC DEMETHOXYAFLATOXIN $B_2$

# INTRODUCTION

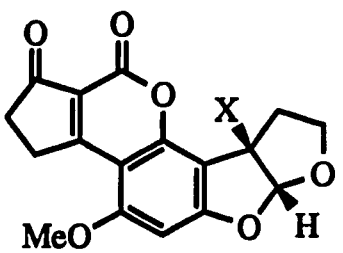
This manuscript will describe the total synthesis of racemic demethoxyaflatoxin $B_2$. The key step in the synthesis is a silver-mediated oxidative radical cyclization to form the aflatoxin $B_2$ furo[2,3-*b*]furan system. The conditions developed for this step differ from those reported for many similar methods in that they are mildly basic, rather than acidic. A second unique feature of this synthesis is that, unlike many earlier reported syntheses of aflatoxins, a von Pechmann cyclization was not employed to append the D ring.

# HISTORICAL

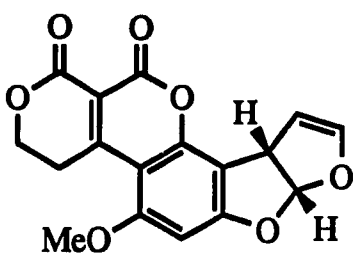
The aflatoxins are a class of mycotoxins, or toxic fungal metabolites, produced by strains of *Aspergillus flavus*, *A. parasiticus*, and *A. nomius*. Although there are numerous aflatoxins, the four major toxins are $B_1$, $B_2$, $G_1$, and $G_2$. Aflatoxins $M_1$ and $M_2$, metabolites of $B_1$



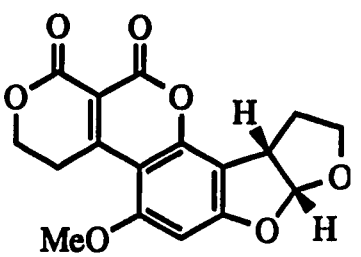
**1** $B_1$: X = H
**3** $M_1$: X = OH



**2** $B_2$: X = H
**4** $M_2$: X = OH

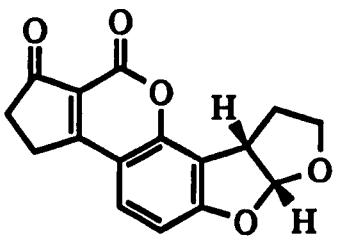


**5** $G_1$



**6** $G_2$

and $B_2$, are also biologically significant. While the aflatoxins are often considered together for toxicological purposes, this dissertation will deal primarily with aflatoxins $B_1$ and $B_2$ due to their close relationship to each other and to the target molecule.



7
Demethoxyaflatoxin $B_2$

Aflatoxins pose significant health hazards to both humans and livestock animals. They are potent liver toxins, and in differing exposure levels in animals they can cause death, liver damage or cancer, a reduction in milk and egg production, and immune suppression. Aflatoxins have also been associated with hepatic, renal, colonic, nasal, and pulmonary neoplasms in various species. Commercially, cattle, poultry, and swine are affected, and chronic, as well as acute, exposure results in serious health problems.

In humans, acute aflatoxicosis has been reported in Taiwan, Uganda, and India with numerous fatalities. A disease responsible for the deaths of several children in Thailand has been linked to aflatoxin. Chronic low-level exposure to aflatoxins is also a concern, as aflatoxins have been implicated as a possible cause of human liver cell carcinoma (LCC). Many studies, particularly in parts of Africa and Asia, have shown a link between the two. Unfortunately, other risk factors of the test populations (for example, exposure to the hepatitis B virus) and conflicting evidence from other studies have left the matter unsettled.

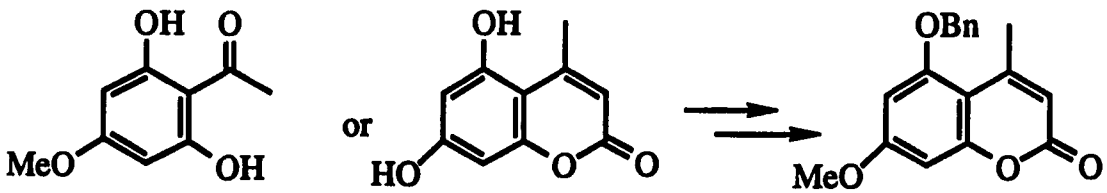
The International Agency for Research on Cancer did, however, place aflatoxin $B_1$ on its list of human carcinogens in 1988.

Aflatoxins are often found in foods and feeds in the United States. Contamination can occur on the crop in the field or during storage or transportation. Aflatoxins have been found in peanuts, corn, wheat, rice, cottonseed, copra, nuts, various foods, milk, eggs, and cheese. Although strict control of foods in the United States makes acute or chronic aflatoxicosis an insignificant problem here, long-term exposure to low levels is a concern because of the possible link to LCC. Contaminated feeds, which are less tightly regulated, can cause severe livestock health problems.

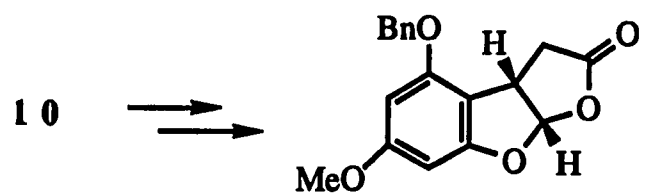
The above factors translate into economic losses. Detection of toxins, decontamination where applicable, livestock veterinary care and losses, and disposal of contaminated commodities are all costly. Improved methods of detection and analysis are needed, as are further toxicological studies and development of safe means of detoxification and decontamination.[1] Analogs of the aflatoxins could be highly useful for these applications. Toward that end, a synthetic plan for an analog of aflatoxin $B_2$ was formulated.

Many total and partial syntheses of the aflatoxins have been reported since Buchi and co-workers[2] determined the structures of aflatoxins $B_1$, $B_2$, $G_1$, and $G_2$ in the 1960's. A review by Schuda[3] summarizes the early work of the Buchi group in this area, as well as that of others.

Buchi and co-workers reported the first total synthesis of aflatoxin $B_1$.[4] Starting from phloroacetophenone-4-methyl ether (8) or dihydroxy-4-methylcoumarin (9), the key intermediate, coumarin 10,

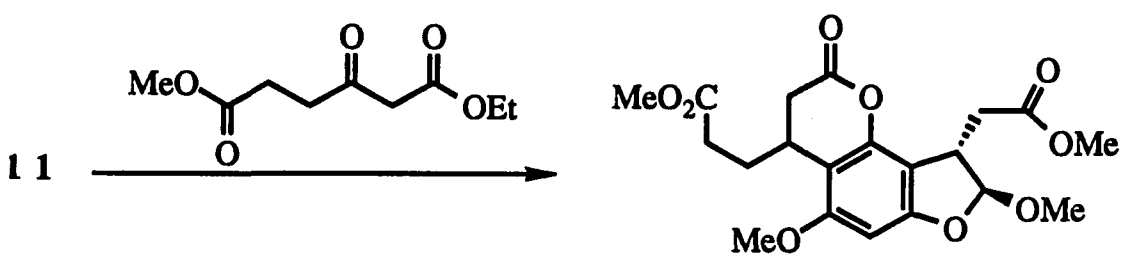



8 9 10



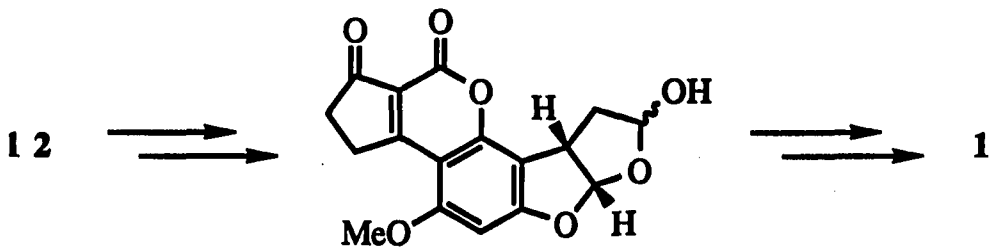

11

was prepared. Oxidation of the allylic methyl to an aldehyde and reduction of the coumarin, which also caused hydrolysis, formed an intermediate which spontaneously cyclized to lactone 11. The phenol from deprotected 11 underwent von Pechmann condensation to yield lactone 12. Hydrolysis of the esters of 12 re-formed the γ-lactone. Acid chloride formation, Lewis acid catalyzed cyclization, and reduction



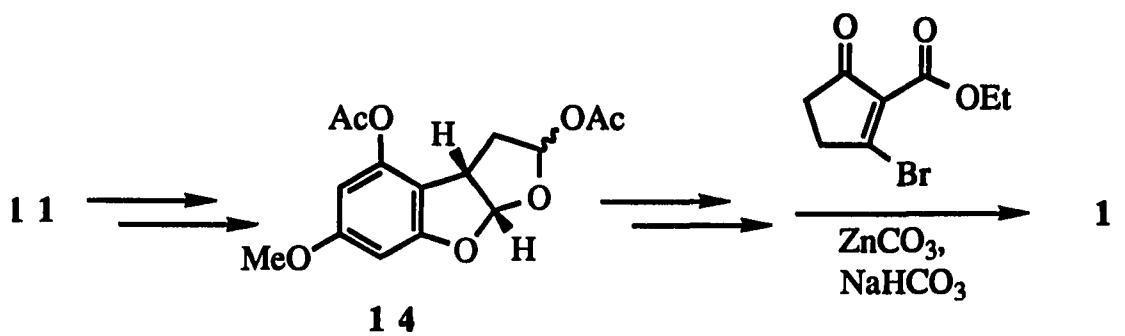

12

of the γ-lactone provided **13** (aflatoxin $B_{2a}$), whose acetate underwent pyrolysis to afford aflatoxin $B_1$.




**13**

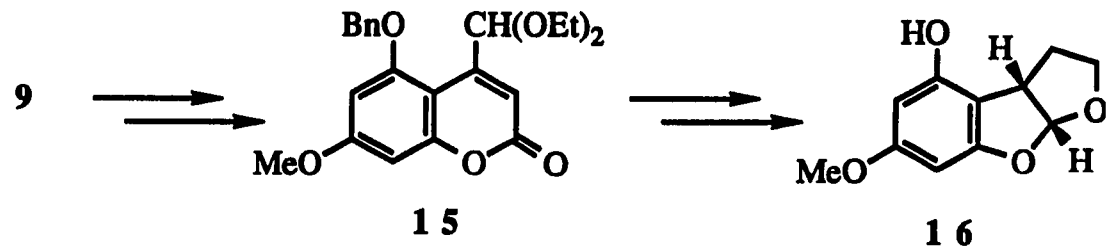
In 1971, Buchi and Weinreb[5] published an improved route to aflatoxin $B_1$ which used a milder variation of the von Pechmann condensation. Intermediate **11** was converted to diacetate **14**,



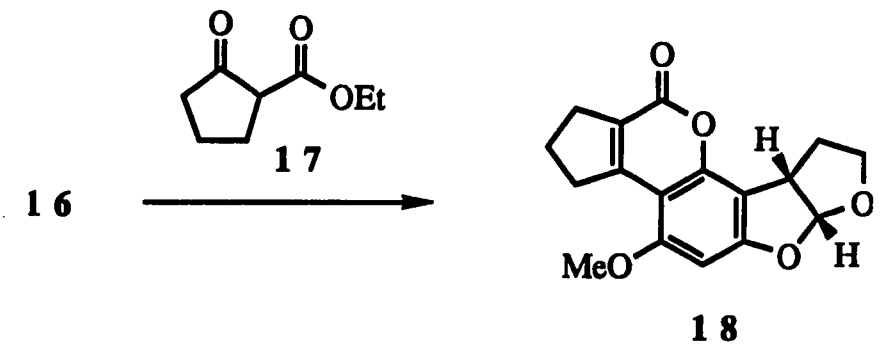

**14**

which underwent pyrolysis and deprotection to yield a phenol which in turn afforded aflatoxin $B_1$ upon von Pechmann condensation with a cyclic β-bromoenone with zinc carbonate and sodium bicarbonate.

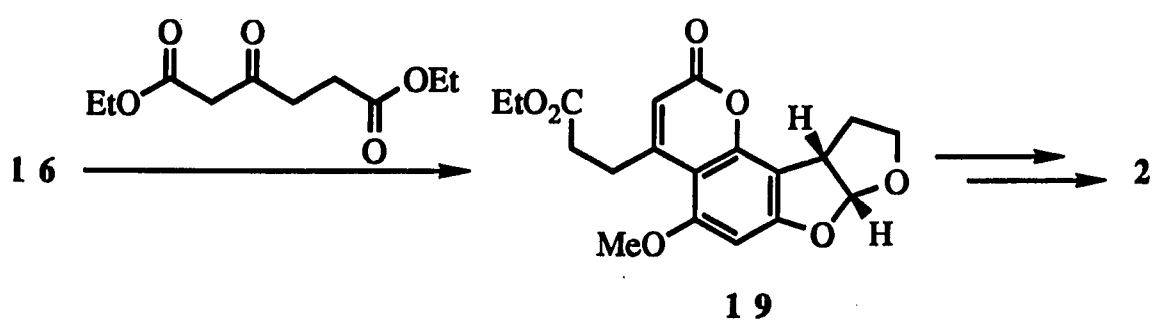
Roberts published the first synthesis of an aflatoxin $B_2$ ABC ring system.[6] Starting from **9**, coumarin **15** was prepared. Catalytic hydrogenation, acetate formation, and hydride reduction of the lactone




produced the ABC ring system **16**. Compound **16** condensed with 2-carboethoxycyclopentanone (**17**) to yield tetrahydrodeoxoaflatoxin $B_1$

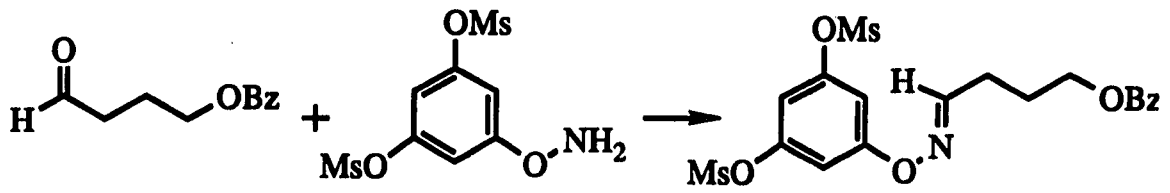



(**18**),[7] an analog of aflatoxin $B_2$. A total synthesis of aflatoxin $B_2$[7b] was realized when **16** underwent von Pechmann condensation with



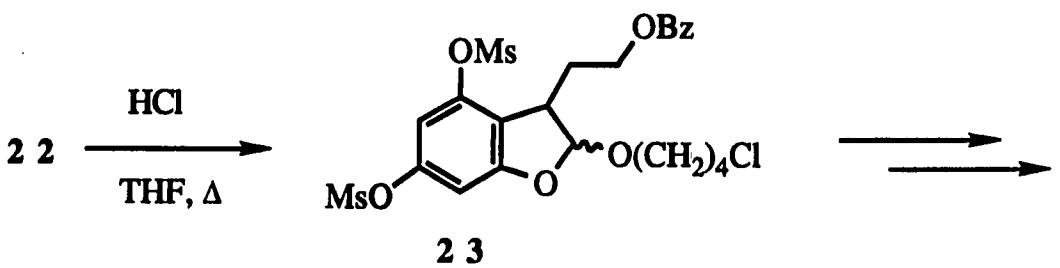

diethyl β-keto adipate to yield an ester whose acid chloride cyclized under Lewis acid conditions to afford **2**.

In 1986, Castellino and Rapoport[8] reported a new route to **16** and thus a formal total synthesis of aflatoxin $B_2$. Amine **21** reacted with an excess of aldehyde **20** to produce oxime **22** in 83% yield with an E/Z

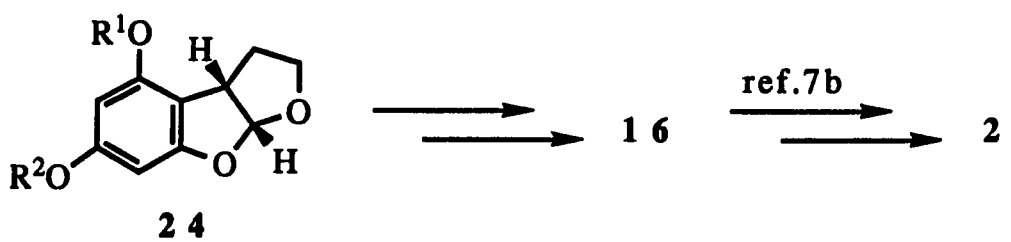



**20** **21** **22**

ratio of 18:1. Using conditions developed to avoid Beckmann rearrangement, **22** was subjected to excess anhydrous hydrochloric acid in THF at 65-70 °C in a sealed tube and 3,4-oxaza Cope product **23** resulted in 87% yield. Selective hydrolysis of **23** to a bis-mesylate was not possible; a mixture of mono-mesylates was always produced. The hydrolysis product mixture was cyclized to form the furofuran system.



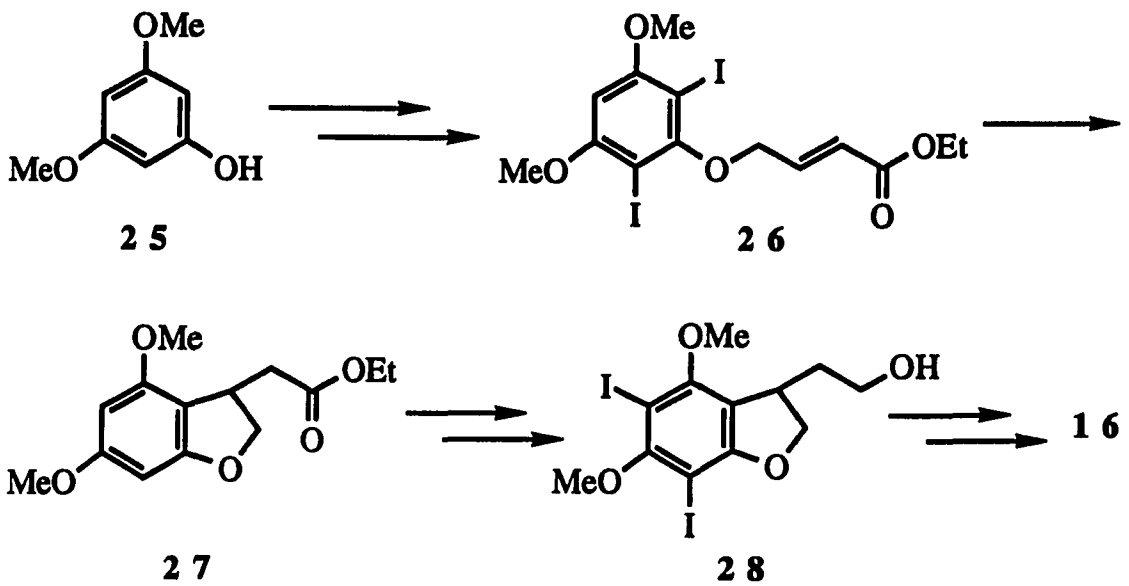

**23**




**24**

Benzylation of the phenol allowed separation of the isomers. Hydrolysis, methylation, and transfer hydrolysis then afforded the target molecule **16** in 47% overall yield.

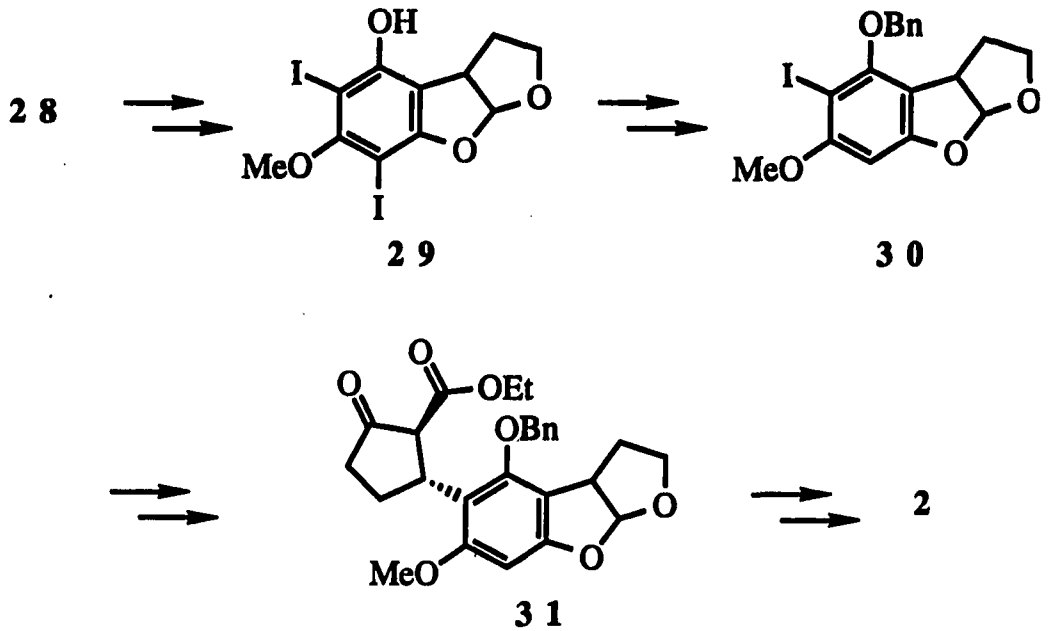
Rodrigo *et al.*[9] also published a new route to **16** which involved a lead tetraacetate-mediated cyclization of an aromatic iodide as a key step. Iodination of 3,5-dimethoxyphenol (**25**) and formation of the ether provided **26** as a substrate for LTA-iodine intramolecular conjugate addition to yield **27** after deiodination. Reduction and




iodination of **27** provided **28**. Compound **28** cyclized with LTA-$I_2$ to afford a tricyclic product which underwent deiodination and transfer hydrogenolysis to yield **16** in ca. 4% overall yield, completing the formal total synthesis of aflatoxin $B_2$.

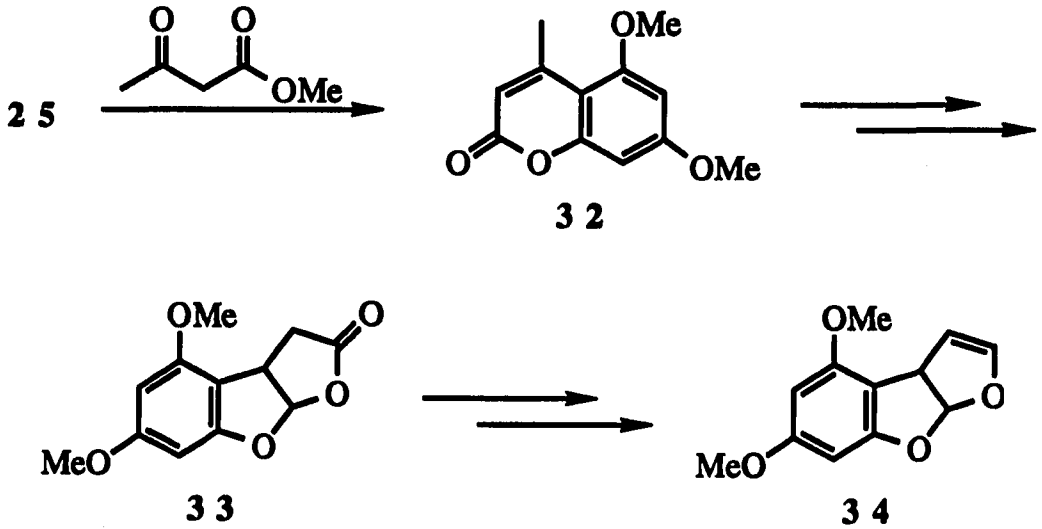
Rodrigo *et al.*[10] later used an iodide as a key intermediate in their total synthesis of aflatoxin $B_2$. Tosylation of **28**, cyclization with LTA-$I_2$,

and deprotection afforded diiodide **29**, which could also be produced by diiodination of **16**. Deiodination with one equivalent of sodium



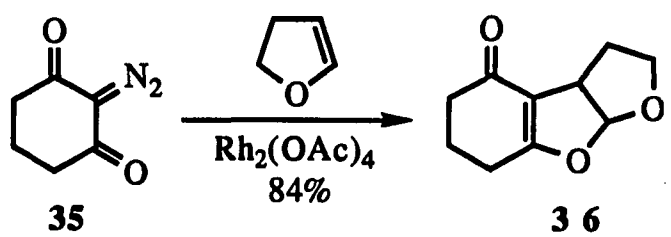

hydride followed by one equivalent of n-BuLi at -100 °C and benzylation of the phenol provided iodide **30**. Michael addition of the mixed cuprate from **30** to ethyl cyclopentenone-2-carboxylate afforded **31**. Cyclization of **31** with trifluoroacetic acid and dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided aflatoxin $B_2$ in 2.3% overall yield from 3,5-dimethoxyphenol.

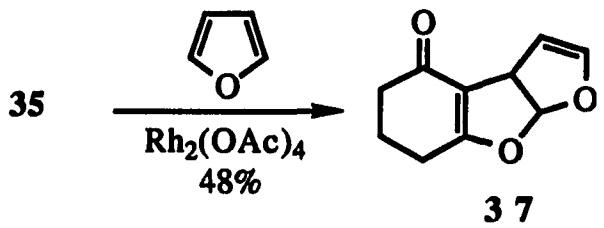
In 1991, Messeguer *et al.*[11] synthesized an aflatoxin $B_1$ model, 3a,8a-dihydro-4,6-dimethoxyfuro[2,3-*b*]benzofuran (**34**). The synthetic approach was based upon Buchi's work, and started with 3,5-dimethoxyphenol (**25**). Condensation of **25** with methylacetoacetate with methanesulfonic acid catalysis yielded coumarin **32**, which




provided an aldehyde upon allylic oxidation. When treated with zinc in acetic acid, the lactone opened and recyclized to tricyclic lactone **33**. Reduction of **33** and pyrolysis of its corresponding carbonate led to the target, **34**. Epoxidation of **34** with dimethyl dioxirane provided a compound for comparative biological testing.

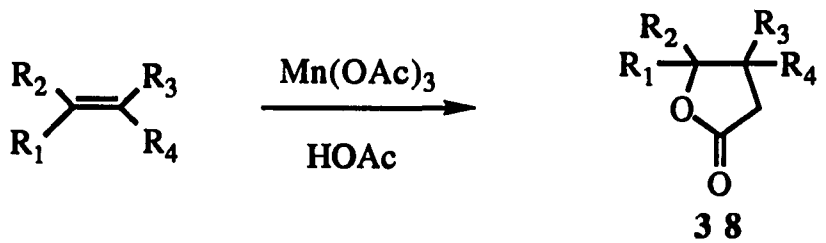
Recently, Pirrung *et al.* used the cycloaddition of cyclic rhodium carbenoids to aromatic heterocycles[12] to generate heterocyclic systems with potential as aflatoxin intermediates. Reaction of **35** with dihydrofuran or furan with rhodium acetate produced **36** and **37** respectively.






While not covered in this dissertation, syntheses of various other aflatoxins have also been reported.[3] Buchi *et al.* reported a synthesis of aflatoxin $M_1$[13] in 1981. Kraus *et al.* recently published an approach to aflatoxin $M_2$ using Type II photocyclization reactions.[14]

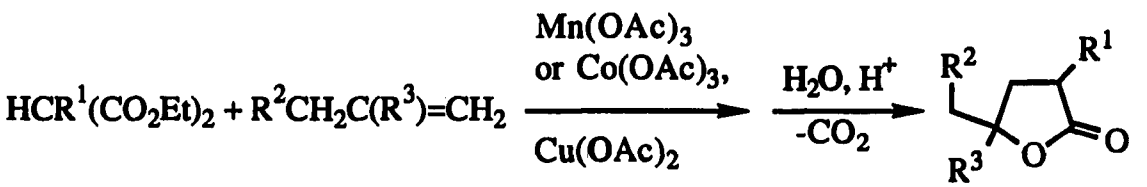
The idea of applying metal-mediated oxidative radical cyclizations to the synthesis of rings was attractive, and had an extensive history. In 1968, Bush and Finkbeiner[15] and Heiba *et al.*[16] almost simultaneously published reports that olefins and acetic acid reacted in the presence of manganese(III) acetate to produce γ-lactones. Bush




and Finkbeiner reported low to modest unoptimized yields of lactones using mono- and disubstituted olefins, $Mn(OAc)_3 \cdot 2H_2O$, and acetic anhydride in acetic acid at reflux temperature. They felt the $\cdot CH_2CO_2H$ radical was not involved, but a manganese-acid complex of some sort was. Heiba *et al.* also used mono- and disubstituted olefins, but

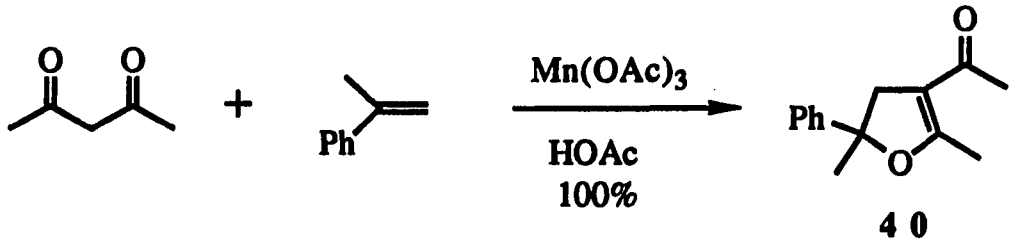
reported moderate to good yields of lactones. They employed $Mn(OAc)_3 \cdot 2H_2O$ and sodium acetate in boiling acetic acid. Propionic acid afforded lactones with an α-methyl substituent. They felt that $\cdot CH_2COOH$ radicals were produced by thermolysis of the manganic complex, and that they added to the olefins faster than they abstracted allylic protons or were oxidized.

After the publication of this pioneering work, numerous extensions, enhancements, and explanations followed. In 1973, Nikishin *et al.*[17] reported that in the presence of manganese(III) or cobalt(III) and copper(II) acetate, diethyl malonate and diethyl alkylmalonates reacted with olefins to produce diethyl alk-2-enylmalonates. These, in turn, produce γ-lactones upon acidic hydrolysis.




**39**

Heiba and Dessau extended their earlier work in 1974 to include the reaction of β-diketones and β-ketoesters[18] and then carboxylic acids[19] with olefins in the presence of manganic acetate. A wide range of yields, mostly satisfactory, were reported for both processes. In the more extensive study on the acids, it was found that various acids, including propionic and cyanoacetic, could be used, as well as high-valent metals other than manganese. Conditions were optimized

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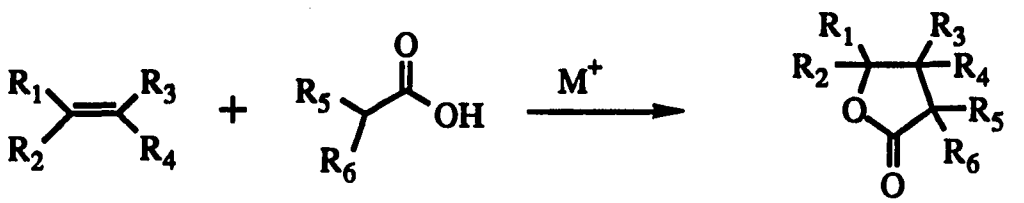


$M^+$ = Mn(III), Ce(IV), V(V)

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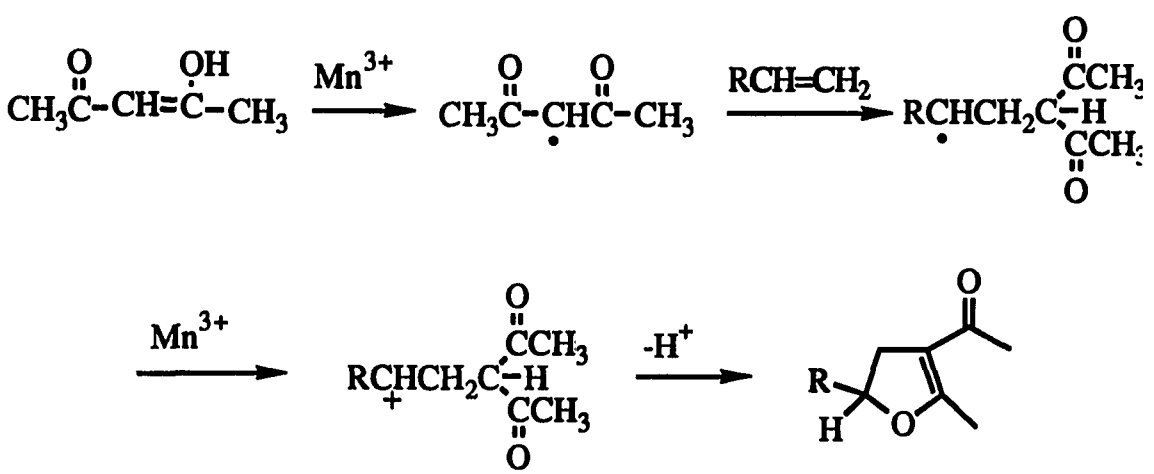
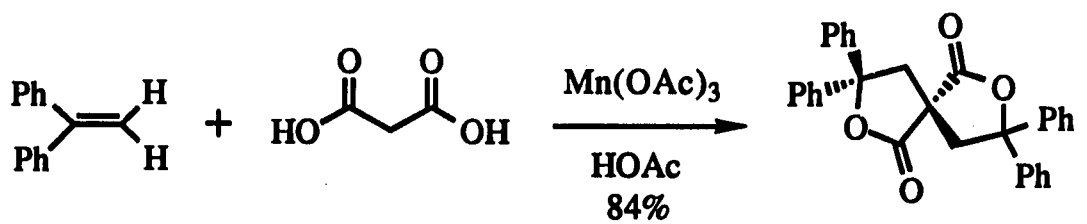
(elevated temperatures, addition of carboxylate salt, and addition of acetic anhydride to scavenge large amounts of water if the $Mn(OAc)_3$ was prepared *in situ*). A complete mechanism was also proposed:



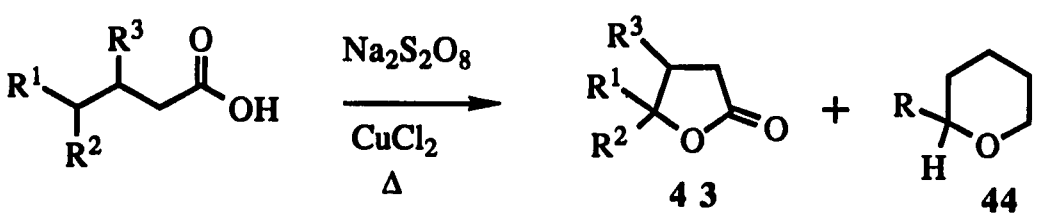
A study by Okano[20] employing acetic acid/acetic anhydride or propionic acid/propionic anhydride as a solvent system proposed that the radicals involved in the reactions were from the solvent, rather than from the manganese complex itself. The yields of lactones in this study were generally low.

Kurosawa *et al.*[21] found that olefins reacted with malonic acid in acetic acid in the presence of manganese(III) acetate to produce substituted 2,7-dioxaspiro[4.4]nonane-1,6-diones in variable yields.



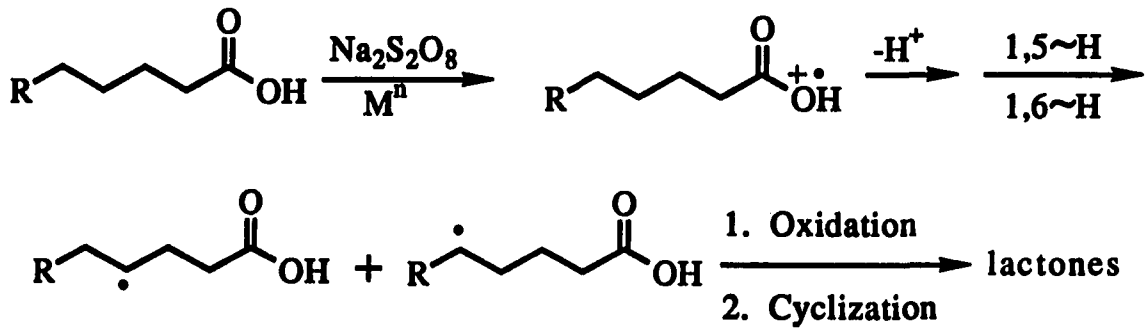

42

In 1983, Nikishin *et.al.*[21] found that saturated acids and amides could be cyclized to γ-lactones in moderate yields, along with δ-lactone by-products, using $Na_2S_2O_8$-$CuCl_2$ in aqueous media. Regioselectivity

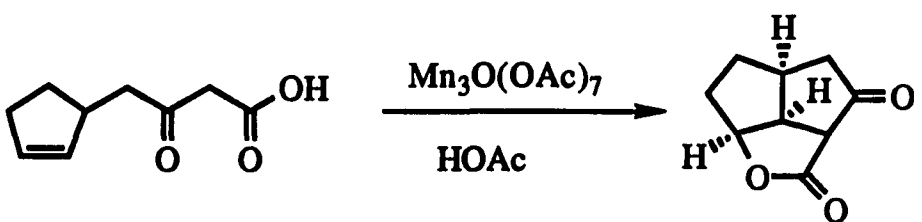



43 44

for γ– vs. δ-lactones was found to be greater for the acids. The proposed mechanism is shown:



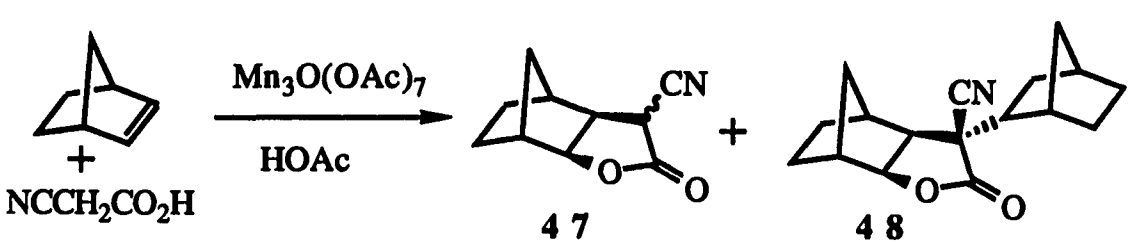

Corey and co-workers published several reports on the use of manganese(III) acetate to form heterocycles. In 1984, Corey and Kang[23] used intramolecular cyclization to produce tricyclic lactones with possible applications toward natural products such as the gingkolides.




45 46

These reactions occurred at 23-40 °C in reasonable yields.

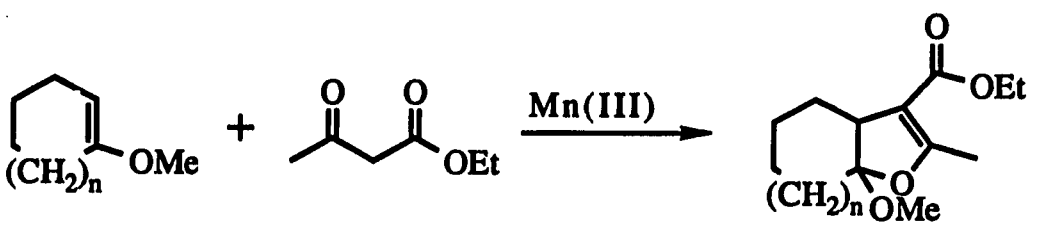
With reactive acids, such as cyanoacetic acid,[24] maximum lactone yields were achieved with short reaction times. Longer times allowed further reaction to form 48. Ethyl hydrogen malonate and ethyl




47 48

hydrogen chloromalonate[24] also gave good yields of α-substituted γ-lactones.

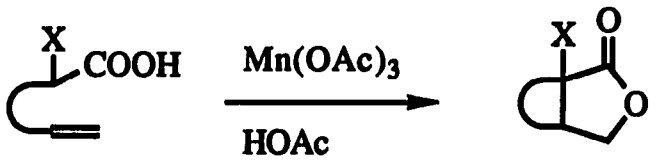
Corey and Ghosh[25] published a synthesis of furans using manganese(III)-promoted cyclizations of enol ethers with β-dicarbonyl compounds. Cyclic and acyclic enol ethers were used, and a variety of




49

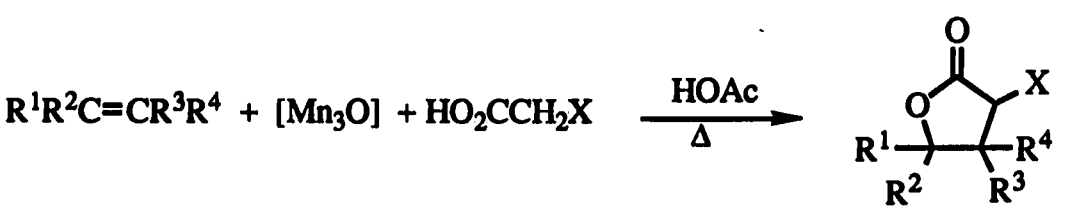
β-dicarbonyl compounds were also found to be successful. Mechanistically, Corey felt that coordination of the carbonyl with manganese formed a "radicaloid" which then attacked the olefin.

Fristad and coworkers were also active in this area of research. Fristad and Peterson[26] reported that acetic anhydride appeared to enhance reaction rates, but did so because it was oxidized more rapidly than acetic acid. Addition of the anhydride altered the product mixture; unsaturated acids were produced along with reduced amounts of lactones. Optimized reaction conditions and regio- and stereochemical outcomes were discussed. A mechanism involving a radical as part of a manganese complex was also proposed. Ernst and Fristad[27] used manganese(III) acetate to effect intramolecular cyclizations of unsaturated activated carboxylic acids to bicyclo[3.3.0]- and -[4.3.0]-lactones. Formation of 2,7-dioxaspiro[4,4]nonane-1,6-diones from




51

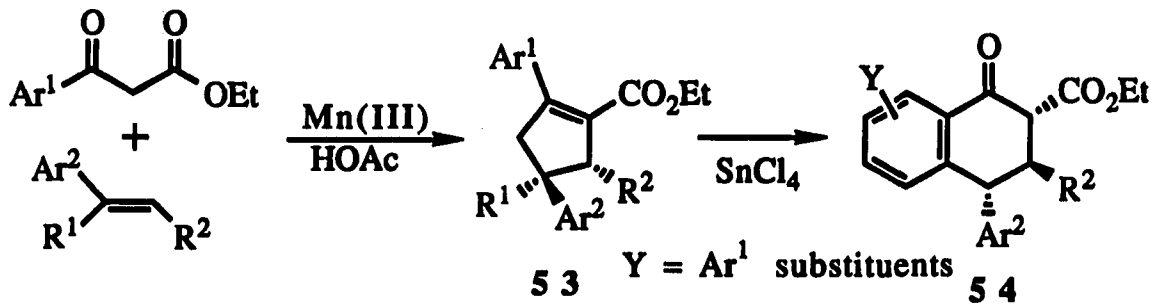
malonic acid and olefins was reported by Fristad and Hershberger,[28] with due note of essentially the same results published earlier by Kurosawa.[21] Rapid exchange with ligands in the manganese complex was proposed. Synthesis of several α–substituted-γ-lactones using substituted acetic acids was reported.[29] Although similar reactions




X = Cl, $CH_2Cl$, CN, COOMe

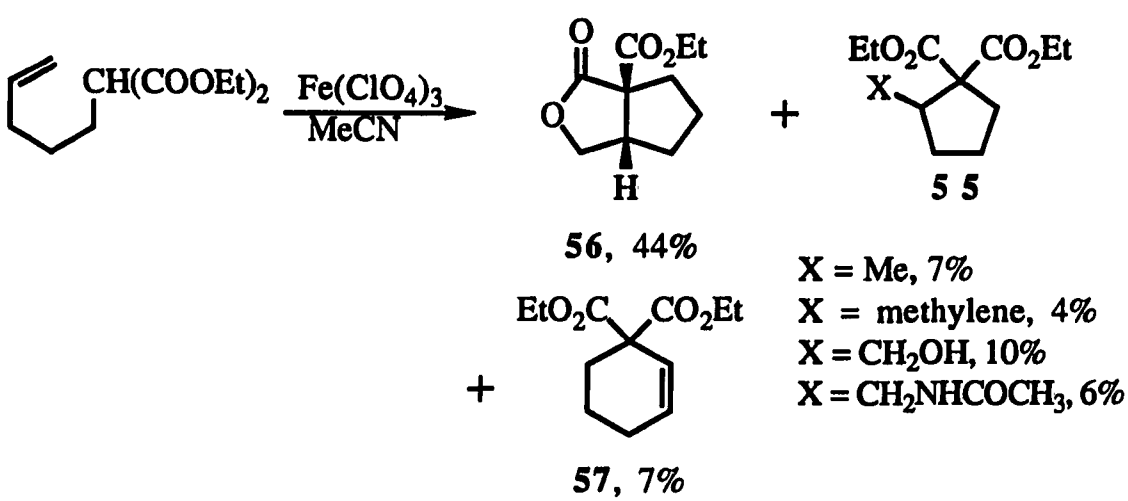
52

had been published, this report investigated more substituents (X=S(O)Ph, $SO_2Ph$, $NO_2$, $P(O)(OEt)_2$, $NMe_3^+$, and Br were also used and found unsatisfactory) and details of stereochemistry and optimal conditions were described. Use of a manganese(III) acetate mediated cyclization in a route to substituted tetralones was also reported.[30]

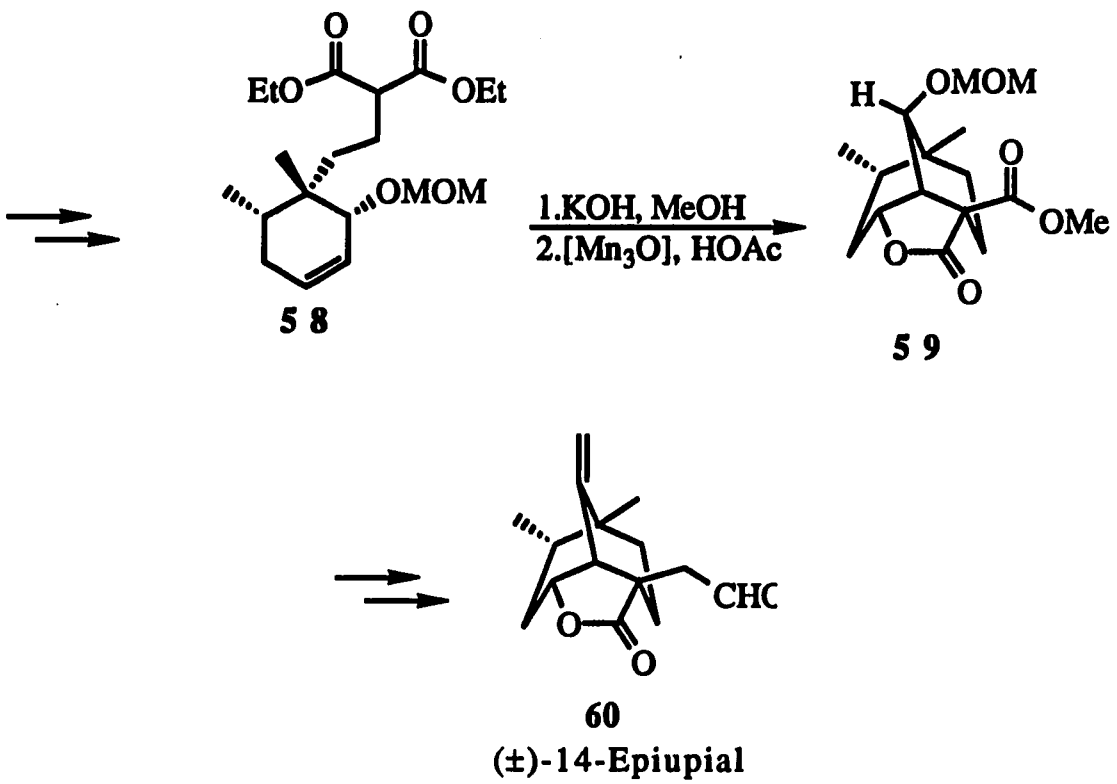



53 54

In a departure from the widely used manganese(III) acetate in acetic acid, Citterio *et al.*[31] found that oxidative deprotonation of carbonyl compounds occurred with iron(III) salts in acetonitrile or acetic anhydride. Moderate yields of γ-lactones, along with other oxidative addition products, were achieved when β-diesters reacted with olefins, inter- or intramolecularly, in the presence of iron(III) perchlorate nonahydrate in acetonitrile.




Paquette *et al.*[32] used manganese (III) mediated cyclization to produce a key intermediate in a synthesis of (±)-14-epiupial.




58

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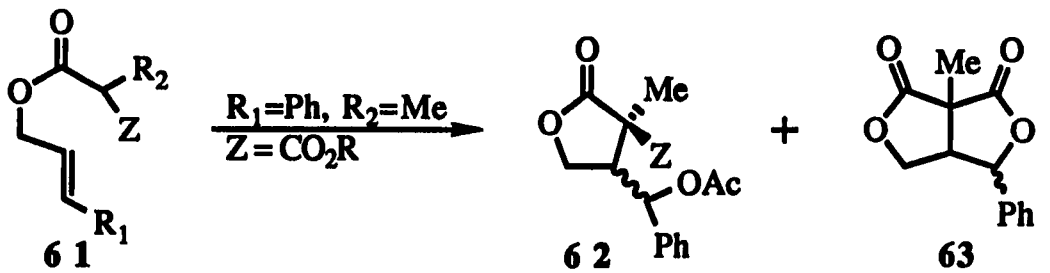
60

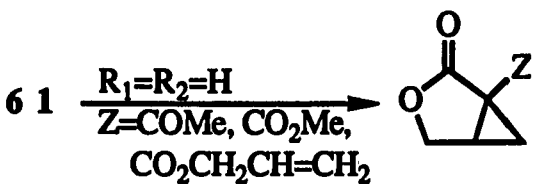
(±)-14-Epiupial

Interesingly, the epimer of **58** with the MOM group cis to the methyl group refused to cyclize. Stereogenic factors are believed to be involved, as well as possible heteroatom effects.

Surzur *et al.* investigated the reaction of allylic esters of acetoacetic acid and malonic acid with manganese(III) acetate, copper(II) acetate, and potassium acetate in acetic acid.[33] Substituted γ-lactones, bis γ-lactones, or cyclopropyl γ-lactones were produced, depending on the substitution pattern of the starting material.




61 62 63

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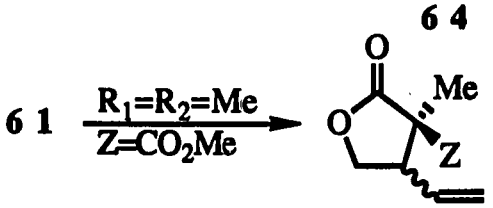
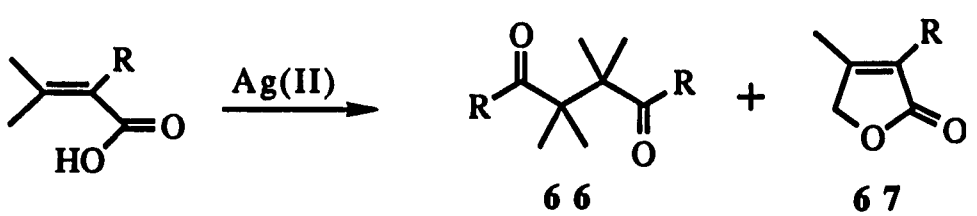
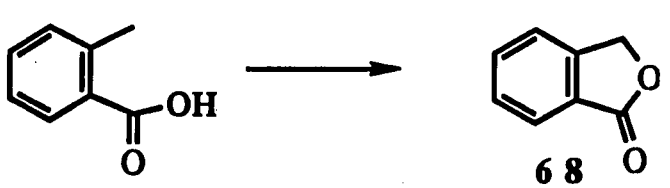



65

In a short review of lactone synthesis by electron transfer and radical chemistry, Surzur and Bertrand[34] described intramolecular cyclizations of acrylic acids in aqueous acetonitrile with $Na_2S_2O_8$ and catalytic silver nitrate and copper(II). The reaction of allylic esters of

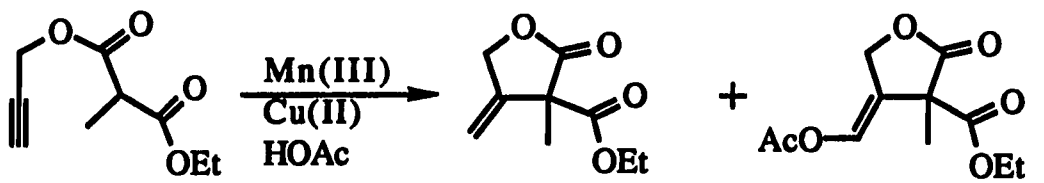



66 67



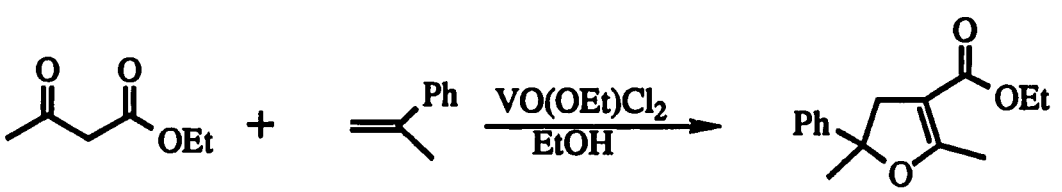

68

acetoacetic and malonic acids with manganese(III) and copper(II) to produce various lactones and bis-lactones was further explored. Propargylic esters were also found to react under the same conditions to produce γ-lactones.




69 70 71

Vanadium(V) compounds can be used for one-electron oxidations. Hirao *et al.* found that ethyl acetoacetate reacted with α-methylstyrene and $VO(OEt)Cl_2$ in ethanol to afford lactone **72** in 52% yield.[35]

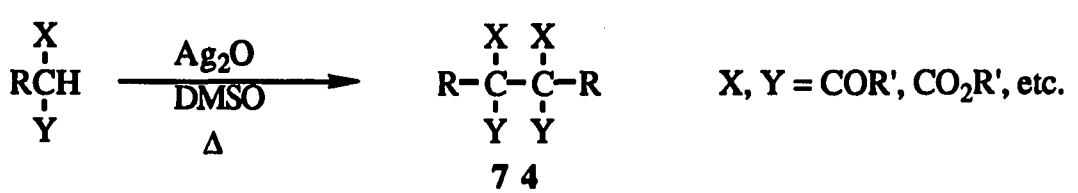



72

Snider and co-workers have been very active in the area of manganese(III)-mediated oxidative radical cyclizations.[36] As this work deals primarily with the formation of carbocycles, rather than heterocycles, it will not be detailed here. However, a recent publication detailing new, milder reaction conditions is relevant to the work to be presented. Until this work, most metal-mediated oxidative radical cyclizations were performed under rather harsh conditions: carboxylic

acid solvents, and often elevated temperatures. Ethanol[37] was recently employed as a solvent, and the results compared to cyclizations performed in acetic acid. It was found that a greater percentage of 5-exo cyclization products was produced in cyclizations in ethanol than in acetic acid. Ethanol also acted as a reducing agent for primary and vinyl radicals. If copper(II) acetate is used to oxidize primary cyclopentanemethyl radicals, alkenes are mainly produced in ethanol, while alcohols and lactones are produced preferentially in acetic acid. It should be noted, however, that products from this radical are minor overall products in the reaction in acetic acid. Products from a cyclohexyl radical predominate. Of course, the main advantage of ethanol as a solvent is that acid-sensitive substrates, such as many enol ethers, may be used in these metal-mediated radical cyclizations.

In view of the work published at the time our work on aflatoxin analogs was begun, we were drawn to a report by Saegusa *et al.* which used the relatively mild conditions of silver(I) oxide in DMSO to dimerize β-ketoesters.[38]

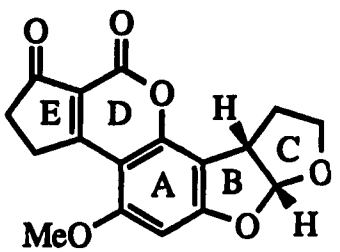



7 4

Hoping to employ these mild conditions to perform cyclizations like those described above, work was begun.

## RESULTS AND DISCUSSION

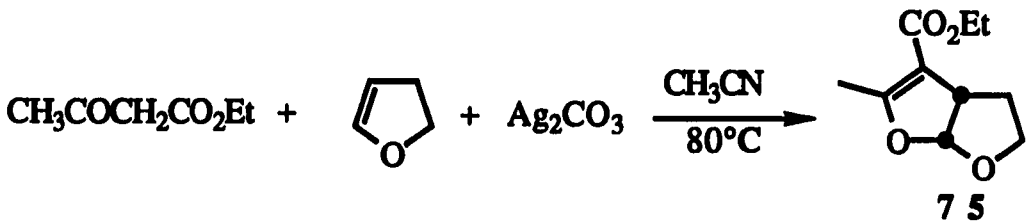
The strategy initially envisioned was to use the conditions of Saegusa[38] to form a substituted aflatoxin $B_2$[2,3-*b*]furofuran system and then continue with construction of the remaining three rings.




Aflatoxin $B_2$

Cyclizations were initially run with silver(I) oxide in DMSO. However, it was discovered that acetonitrile, with a dielectric constant similar to DMSO, could also be used successfully and more conveniently. Easily prepared[39] silver(I) carbonate was then found to work well as an oxidant. Being mildly basic and employing a readily removable solvent, silver(I) carbonate in near-boiling acetonitrile provides an attractive alternative to the widely used conditions using carboxylic acids as solvents for oxidative radical cyclizations.

Ethyl acetoacetate reacted with an excess of 2,3-dihydrofuran and silver carbonate in hot acetonitrile to afford furofuran **75** in 50% yield after chromatographic purification. It was hoped that **75** could be converted to diene **76**, which could undergo a Diels-Alder reaction to append the A ring to the system. When **75** was treated with LDA and

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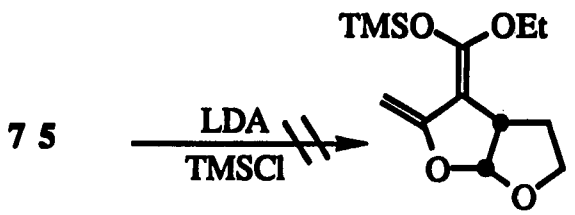
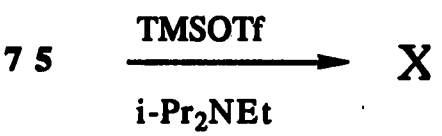


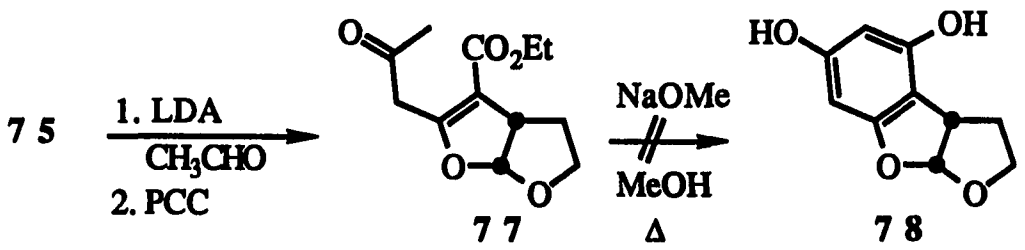

76



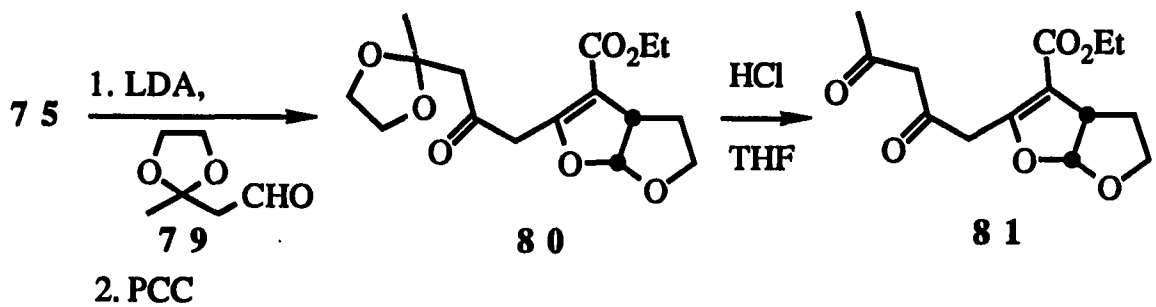

TMSCl, diene **76** did not result. It appeared that C- rather than O-silylation had occurred. Unfavorable steric interactions in an initial O-silylated product may have encouraged the transfer of the silicon to the carbon. When **75** was treated with the more reactive TMSOTf and diisopropylethylamine, it decomposed, likely due to reaction with the acetal.

An intramolecular cyclization of an appropriately substituted furofuran was next eyed to build the A ring. Compound **75** reacted with LDA and acetaldehyde to produce an alcohol, which afforded ketone **77** on oxidation with pyridinium chlorochromate (PCC). Unfortunately, attempts to cyclize **77** with sodium methoxide in

methanol at temperatures from -15 °C to 120 °C (sealed tube) failed to produce the desired benzofuran **78**. A theory for this failure is that

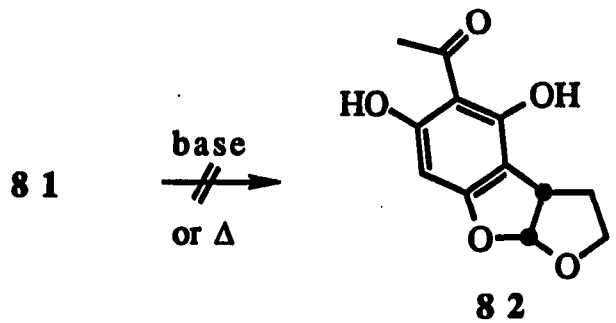



there may have been an insufficient concentration of the neccessary ketone enolate under the thermodynamic conditions employed. Compound **81** was then synthesized, with the hope its greater tendency toward enolization would facilitate cyclization. Treatment of **75** with LDA and aldehyde **79**[40] and subsequent oxidation of the alcohol produced with PCC provided ketoacetal **80**. The ketal proved more




difficult to hydrolyze than anticipated; it resisted PTSA in acetone[41] and silica gel and aqueous oxalic acid in dichloromethane.[42] Treatment with 5% HCl in THF[43] yielded diketone **81**. Numerous attempts were made to cyclize **81**: KOH in methanol or water, NaOMe/MeOH, LiH, t-BuOLi, and t-BuOMg, all at temperatures from 0 °C to 86 °C. The desired

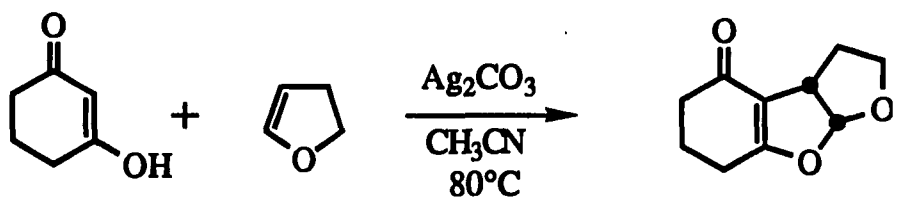
benzofurofuran was not produced. Heating at 210 °C in an open tube also failed to yield **82**. These reactions generally returned starting




**82**

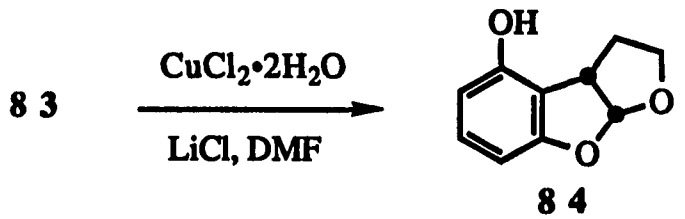
material and/or decomposition products.

At this point, a new route to the benzofurofuran was sought. Direct formation via the developed silver(II) carbonate methodology seemed appropriate. Cyclohexane-1,3-dione reacted with 2,3-dihydrofuran and silver(II) carbonate to produce the furofuran **83** in good yields (55-70%).

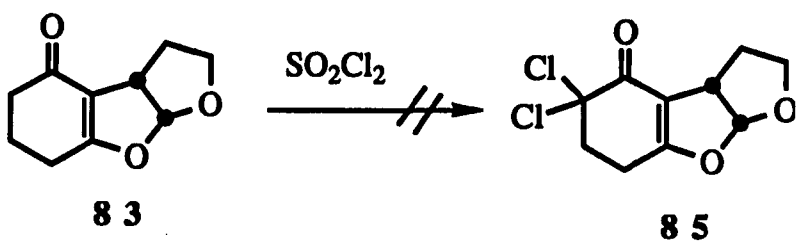


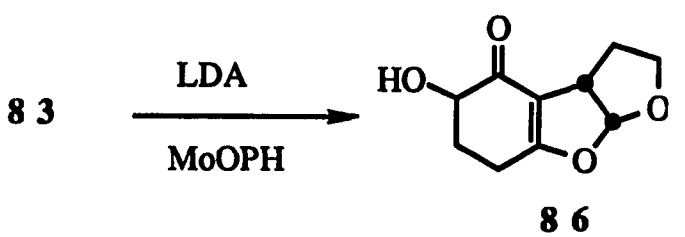

**83**

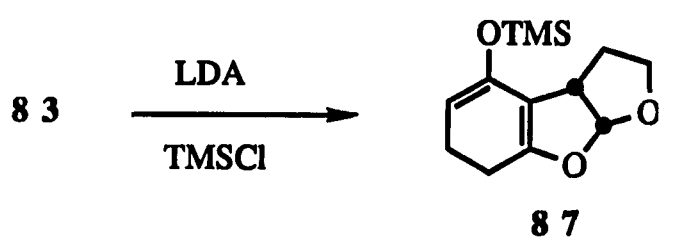
With **83** in hand, attachment of the A-ring methoxy group and "handles" upon which to build the D and E rings were necessary. Treatment of **83** with cupric chloride dihydrate and lithium chloride in



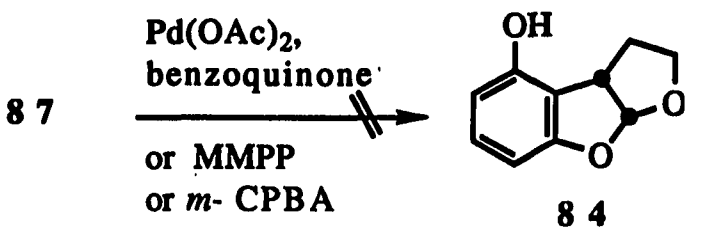

DMF[44] afforded phenol **84** in 22% yield. Unfortunately, attempts to produce a substituted phenol failed. Reaction of **83** with sulfuryl chloride[45] did not produce the α,α–dichloride. Treatment with LDA and MoOPH[46] gave a promising result, but was not pursued due to the hazards involved. While triethylamine and TMSOTf failed to produce the enol silyl ether of **83**, LDA and TMSCl was successful.



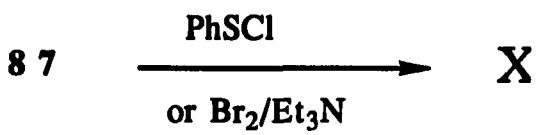



Oxidations of **87** with palladium (II) acetate[47], MMPP (monoperoxyphthalic acid, magnesium salt), or *m*-CPBA[48] all failed to yield the phenol **84**. Efforts to add PhSCl or bromine[49] to **87** were also fruitless.

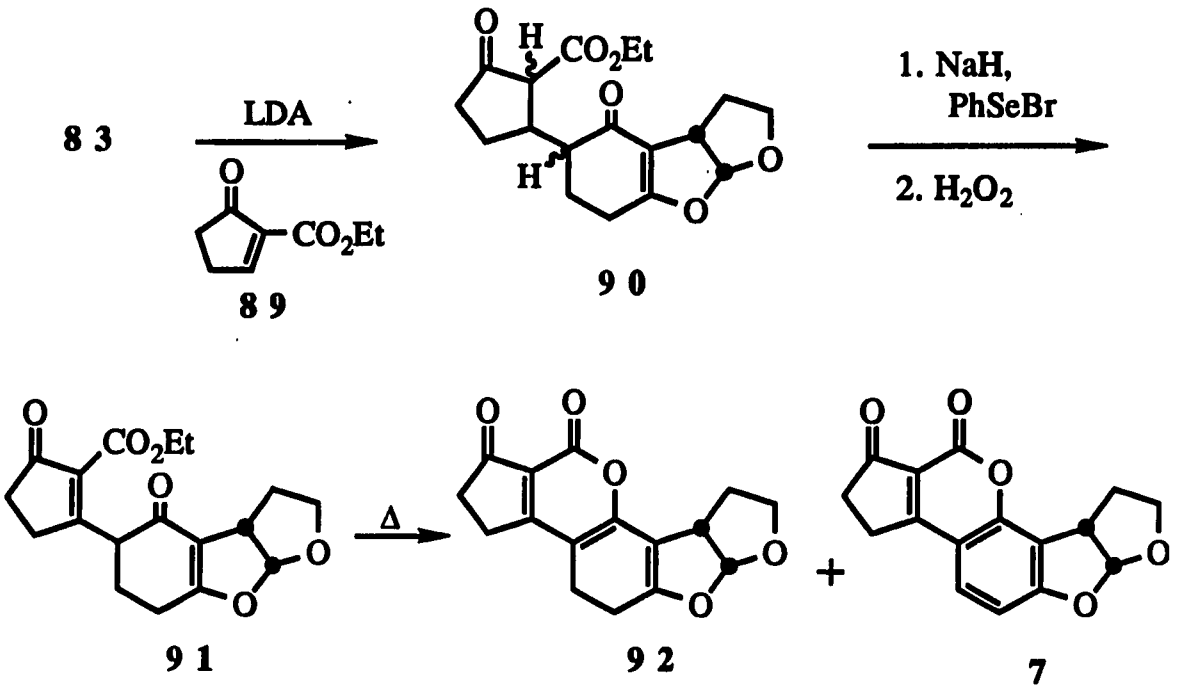



**84**

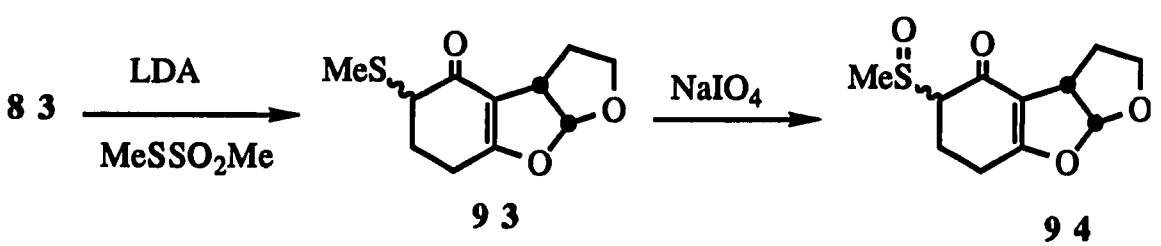


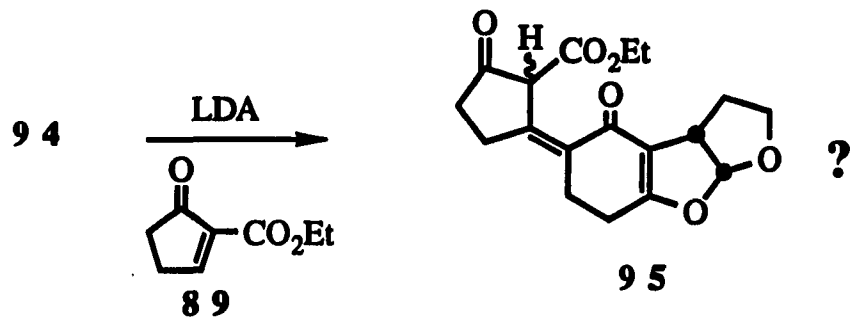

As LDA had successfully generated the enolate of **83** in the formation of its enol silyl ether, use of the enolate was further explored. As addition to acetaldehyde was also promising, Michael addition to an appropriate Michael acceptor seemed attractive.

Treatment of **83** with LDA and ketoester **89**[50] produced Michael adduct **90**, which in turn led to enone **91** after formation of the selenide and oxidation.[50] Reaction of DBU or PTSA with **91** failed to produce a cyclized product. Heating at ~200 °C in toluene in a sealed tube produced some cyclized product as well as the aromatic target molecule **7**. Treatment of **92** with DDQ produced **7** in 50% yield. A selenide of **91** could also be prepared and eliminated to an aromatic product, but this route was not pursued.

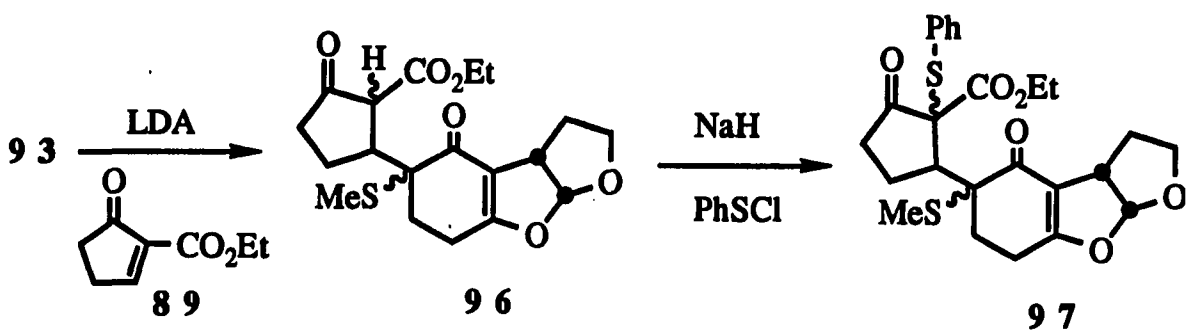



While this route showed promise and did produce small amounts of demethoxyaflatoxin $B_2$, the thermal cyclization was unreliable and yields were quite low, so improvements were sought. Compound **83** reacted with LDA and $MeSSO_2Me$[51] to produce sulfide **93** in 84% yield. Oxidation of **93**[52] produced sulfoxide **94**. Attempts to react the lithium enolate of **94** with **89** produced what appeared to be an exo-eliminated

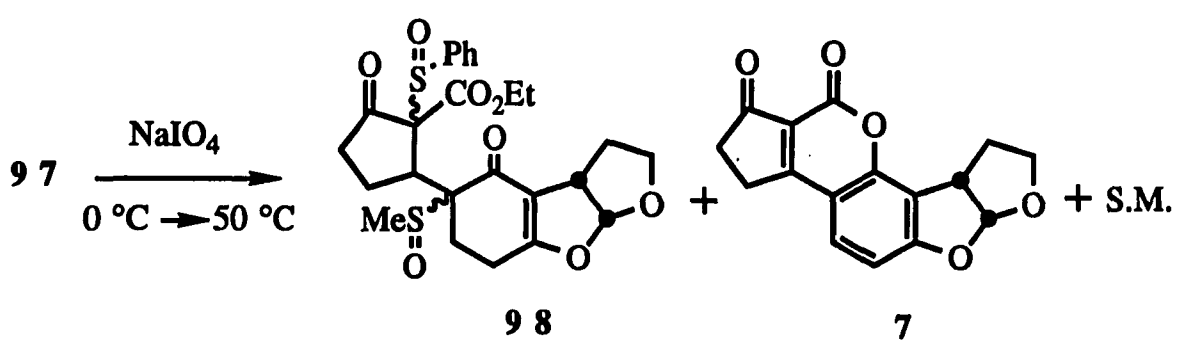





product. Michael addition using **93** was successful (78-84%). Conversion of **96** to **97**[53] was accomplished in excellent yields (83-98%).




Formation of a phenyl selenide was unsuccessful. Oxidation of **97** produced bis-sulfoxide **98** plus starting material and a 16% yield of



$$\text{Crude product mixture} \xrightarrow{150^{\circ}C} 7$$

demethoxyaflatoxin $B_2$. Heating the unpurified oxidation reaction mixture from **97** at 150 °C in toluene in a sealed tube for seven hours afforded 27% of **7** (from **97**) after purification.

This improved route to demethoxyaflatoxin $B_2$ requires only six steps and proceeds in approximately 11% overall yield.

# CONCLUSION

The total synthesis of racemic demethoxyaflatoxin $B_2$ is described. The key step in the synthesis is a silver-mediated oxidative radical cyclization to form the aflatoxin $B_2$ benzofuro[2,3-b]furan system. The conditions developed for this step differ from, and are complementary to, those reported for many similar methods in that they are mildly basic, rather than acidic. A sequence of Michael addition to an E-ring precursor by the ABC ring system, phenyl sulfenylation, oxidation, and cyclization of the D ring completed the synthesis in a concise manner.

# EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or dried in a 150 °C oven for 12 h and cooled under a stream of nitrogen or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography 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. The abbreviation sg represents silica gel. 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 Nicolet Magnetics Corporation NT-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), ABq (AB quartet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR spectra (75.47 MHz) were obtained on a Varian Associates VXR-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). High

resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was determined to be >90% by 300 MHz proton NMR and/or elemental analysis.

**General Procedure for the Radical Cyclization:** A suspension of dicarbonyl compound (1 equiv), vinyl ether (10 equiv) and freshly prepared silver(I) carbonate (2 equiv) in dry MeCN (3 mL/mmol of dicarbonyl compound) was heated at reflux under nitrogen until TLC analysis indicated that no dicarbonyl compound remained. The mixture was cooled, filtered through Celite and concentrated in vacuo. The residue was purified by sg chromatography using H:EA.

**75**: $^1$H NMR ($CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 2.00-2.11 (m, 2H), 2.23 (d, J = 1.8 Hz, 3H), 3.62-3.79 (m, 2H), 4.00-4.08 (m, 1H), 4.10-4.28 (m, 2H), 6.07 (d, J = 6.3 Hz, 1H); IR (NaCl, neat) 2980, 1690, 1640 $cm^{-1}$; HRMS: *m/e* for $C_{10}H_{14}O_4$, calcd. 198.08921, measured 198.08866; CMR ($CDCl_3$) δ 13.72, 14.09, 31.31, 46.72, 59.13, 66.55, 103.13, 109.25, 164.92, 168.09; m.p.: 41.5 °C-45.5 °C; TLC (4:1 H:EA) $R_F$ = 0.35.

**83**: light yellow oil. $^1$H NMR ($CDCl_3$) δ 2.00-2.18 (m, 4H), 2.30-2.40 (t, J = 6.6 Hz, 2H), 2.40-2.55 (m, 2H), 3.59-3.68 (m, 1H), 3.68-3.80 (m, 1H), 4.09 (td, J = 8.1, 0.6 Hz, 1H), 6.24 (d, J = 5.7 Hz, 1H); IR ($CDCl_3$) 2980, 1765 (w), 1720 (w), 1630 (br) $cm^{-1}$; HRMS: *m/e* for $C_{10}H_{12}O_3$

calcd. 180.07864, measured 180.07877. Anal. Calcd: C, 66.65; H, 6.71. Found: C, 65.18; H, 6.82. TLC (1:2 H:EA) $R_F$ = 0.23.

**Ethyl 2-(2,4-dioxopentyl)-furo[2,3-b]furan-3-carboxylate (81):** To a solution of LDA (1.2 mmol, prepared from diisopropylamine and n-BuLi at 0°C) in 0.5 mL of THF at -78 °C was added ester **75** (0.198 g, 1.00 mmol) in 1.5 mL of THF over 2 min. The solution was stirred at -78 °C for 30 min. Aldehyde **79** (0.200 g, 1.5 mmol) in 1.5 mL of THF was added dropwise and the solution was allowed to warm to 0 °C. The solution was cooled to -78°C, quenched with 0.13 mL of acetic acid and diluted with water. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried and concentrated in vacuo. The residue ($R_F$ (1:1 H:EA) = 0.25) was immediately oxidized.

To a suspension of PCC (0.289 g, 1.3 mmol) and Florisil (0.57 g) in $CH_2Cl_2$ (3 mL) was added the above alcohol (0.220 g, 0.67 mmol). After TLC showed that no alcohol remained, the suspension was poured into 40 mL of ether and filtered through Celite. The residue was dissolved in 1.1 mL of THF and 1.1 mL of 5% HCl and the solution was stirred for 22 h. After the usual workup, the residue was purified by sg chromatography using 2:1 H:EA to afford 0.18 g (100% yield) of **9**. Compound **77** was prepared from ester **75** and acetaldehyde by the first two steps of this procedure.

**77:** $^1$H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 2.00-2.19 (m, 2H), 2.23 (s, 3H), 3.76-3.83 (m, 2H), 3.80 (dd, J = 17.0, 42.2 Hz, 2H), 4.02-4.12

(m, 1H), 4.12-4.25 (m, 2H), 6.45 (d, J = 6 Hz, 1H); IR (NaCl, neat) 2985, 2885, 1735, 1690, 1640 $cm^{-1}$; TLC (1:1 H:EA) $R_F$ = 0.43.

**81**: $^1H$ NMR ($CDCl_3$) δ 1.28 (td, J = 7.1, 1.2 Hz, 3H), 2.04 (s, 3H), 2.05-2.17 (m, 2H), 2.25 (s, 1H), 3.65-3.85 (m, 4H), 4.02-4.12 (m, 1H), 4.12-4.25 (m, 2H), 5.56 (s, 1H), 6.15 (d, J = 6 Hz, 1H); IR (NaCl, neat) 2980, 2880, 1695, 1640, 1610 $cm^{-1}$; HRMS: *m/e* for $C_{14}H_{18}O_6$ calcd. 282.11034, measured 282.11069; TLC (2:1 H:EA) $R_F$ = 0.35.

**2,3,3a,4,5,6,7,8a-Octahydro-5-methylthio-[2,3-b]-benzofuran-4-one (93):** To a stirred solution of LDA [4.27 mmol, prepared from distilled diisopropylamine (4.66 mmol, 0.65 mL) and n-BuLi (4.27 mmol)] in 2 mL dry THF at -78 °C under nitrogen was added dropwise ketone **83** (0.70 g, 3.88 mmol) in 7.8 mL dry THF. After 30 min at -78 °C, $MeSSO_2Me$ (4.66 mmol, 0.48 mL) was added dropwise and the reaction mixture stirred while warming to to 0 °C. When the reaction appeared to be done by TLC, the mixture was recooled to -78 °C, quenched with 30 mL of a pH 7 buffer, the cooling bath was removed, and the solution pH adjusted to 6. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organics washed with brine, dried over $Na_2SO_4$, and concentrated. The crude sulfide (1.01 g) was purified by flash chromatography on sg (1:4 H:EA) to yield the keto-sulfide **93** (0.74 g, 3.27 mmol) in 84% yield. Compound **93** was a light yellow oil: $^1H$ NMR ($CDCl_3$) δ 2.04-2.08 (m, 2H), 2.09-2.14 (m, 1H), 2.17 and 2.20 (s, 3H), 2.31-2.49 (m, 2H), 2.60-2.82 (m, 1H), 3.26 (t, J = 4.1 Hz, 1H), 3.60-3.78 (m, 2H), 6.23 and 6.27 (d, J = 5.7 Hz, 1H); IR (film) 2980, 1733, 1635, 1405 $cm^{-1}$; TLC (1:4 H:EA) $R_F$ = 0.53.

**2,3,3a,4,5,6,7,8a-Octahydro-5-methylthio-5-(3-oxo-2-(1-oxo-2-oxabutyl)-cyclopentyl)furo-[2,3-b]benzofuran-4-one (96):** To a solution of LDA (0.484 mmol, prepared from n-BuLi (0.484 mmol) and diisopropylamine (0.52 mmol) in 0.2 mL of THF at -78 °C) was added a solution of ketone **93** (0.100 g, 0.44 mmol) in 1 mL of THF over 2 min. The solution was stirred at -78 °C for 30 min. Ketoester **89** (0.0746 g, 0.48 mmol) in 1 mL of THF was added dropwise and the solution was stirred at -78°C for 30 min. Acetic acid was added to quench the reaction; water was added and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried and concentrated. The residue was purified by chromatography using 1:1 H:EA to afford 0.14 g (84% yield) of **96**. Compound **96** was a light yellow oil: $^1$H NMR ($CDCl_3$) δ 1.25-1.32 (m, 3 H), 1.55-1.86 (m, 1 H), 1.90 and 1.98 (s, 3 H), 2.01-2.08 (m, 2 H), 2.10-2.14 (m, 1 H), 2.19 (d, J = 5.7 Hz, 1 H), 2.20-2.40 (m, 1 H), 2.41-2.48 (m, 2 H), 2.70-2.95 (m, 1 H), 3.15-3.29 (m, 1 H), 3.46-3.50 (m, 1 H), 3.55-3.80 (m, 3 H), 4.06-4.14 (m, 1 H), 4.14-4.25 (m, 2 H), 6.24 and 6.28 (br d, J = 6 Hz, 1 H); IR (film) 2980, 1750, 1720, 1635 $cm^{-1}$; TLC (1:4 H:EA) $R_F$ = 0.55.

**Demethoxyaflatoxin $B_2$ (7):** To a stirred suspension of NaH (0.0098g, 0.41 mmol) (washed three times with hexanes and dried with $N_2$) in 2 mL of THF at 0 °C under $N_2$ was added the diketoester **96** in 1 mL of THF. After 30 min at 0 °C, PhSCl was added (0.0684 g, 0.47 mmol), the solution was stirred for 5 min, the ice bath was removed, and the mixture was stirred at room temperature. TLC after 80 min and 140 min showed starting material, and after stirring overnight

showed little change. The reaction mixture was added dropwise to 10 mL each of ether, pentane, and saturated aqueous sodium bicarbonate, plus ice. The aqueous layer was extracted with 10 mL of 1:1 ether: pentane. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The material was purified by flash sg column to remove the PhSSPh (1:1 H:EA) to yield 0.13 g crude material.

The bis-sulfide (0.13 g) was taken up in acetonitrile, cooled in an ice/salt bath, and 0.5 M aqueous $NaIO_4$ (1.06 mmol, 2.13 mL) was added dropwise. After stirring at ice/salt temperature for 1 h, the mixture was stored in a refrigerator overnight. The flask was then removed from the refrigerator and the mixture was stirred at room temperature for 24 h, during which time a white precipitate formed. The mixture was filtered, extracted with $CH_2Cl_2$, and the combined organic layers washed with brine, dried over $Na_2SO_4$, and concentrated to yield 0.10 g of the crude bis-sulfoxide.

The crude bis-sulfoxide was dissolved in 12 mL of dry toluene. The solution was degassed with argon for 10 min and then heated at 150 °C in a sealed tube for 7 h. The mixture was diluted with water. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers was dried over $Na_2SO_4$ and concentrated. Purification by flash chromatography on sg (1:4 H:EA) yielded 0.0207 g (18 % yield from **93**) of the aflatoxin analog **7**. Compound **7** was a beige solid: $^1$H NMR ($CDCl_3$) δ 2.27-2.37 (m, 2H), 2.70-2.77 (m, 2H), 3.16-3.22 (m, 2H), 3.62 (q, $J_{AB}$ = 9, 17Hz, 1H), 4.12-4.26 (m, 2H), 6.50 (d, J = 6 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H); IR ($CH_2Cl_2$) 3045, 1765, 1697, 1610

$cm^{-1}$; MS: *m/e* 284; HRMS: calcd. 284.06847, measured 284.06826; CMR ($CDCl_3$) δ 24.50, 31.50, 34.90, 44.18, 67.80, 107.65, 112.38, 113.46, 114.82, 118.84, 127.35, 153.05, 155.11, 166.41, 176.54, 200.67; TLC (1:4 H:EA) $R_F$ = 0.16; mp (decomposed).

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# PAPER II: SYNTHETIC APPROACHES TOWARD ANALOGS OF GLYCINOECLEPIN A

# INTRODUCTION

This manuscript will describe the syntheses of various analogs of glycinoeclepin A, the natural hatching stimulus for the soybean cyst nematode. While a total synthesis of the molecule was not achieved, analogs including modified C and D rings and modified A, B, and C rings have been synthesized and tested for hatch-stimulating activity.

For the sake of simplicity, many of the compounds described here have been shown without stereochemistry. Unless stereochemistry is explicitly detailed, these compounds should be considered to be mixtures of isomers.

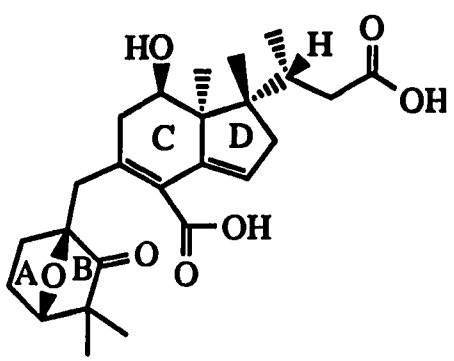
# HISTORICAL

Nematodes of various types have troubled agriculturalists for centuries. Because nematodes generally have a very narrow host plant range, crop rotations of host and non-host plants generally provide effective pest management. Chemical nematicides have also been used, but most effective ones have been deemed environmentally unsafe. Resistant plant varieties can also be used, but are often lower yielding than susceptible cultivars. Over time, nematodes can also adapt to resistant varieties.

In recent years, the soybean cyst nematode (SCN) has become an increasing problem for soybean growers in the United States. Infestation is particularly widespread in Missouri and other southern bean-growing states, but is spreading rapidly to the north. Many regions in the area of infestation, or in its path, depend heavily on soybeans, and the multiyear crop rotations necessary to reduce SCN populations to a non-damaging level are not economically feasible. With chemical control environmentally unsound and resistant plant cultivars often not satisfactory for various reasons, an effective, safe, economical means of SCN control is clearly needed.

SCN overwinters in eggs encased in protective cysts in the soil. The eggs can remain viable for years within the cysts, hatching when conditions become favorable. Among these conditions are pH, moisture, temperature, chemicals in the soil, root diffusates, and chemical

hatching factors. We believed that if conditions could be modified to stimulate SCN egg hatching at a time when no host plants were available, the juveniles would die, leaving fields safe for planting at the appropriate time. Most of the conditions required for hatching are beyond the farmer's control. However, the hatching stimulus for SCN, glycinoeclepin A, is known, and if it (or a sufficiently active analog) could be prepared in adequate quantities, we believe it could be used to trigger non-seasonal hatching of the encysted eggs. Glycinoeclepin A stimulates hatching at extremely low concentrations and is released during the normal growth cycle of soybeans. Thus, its use should be both economically and environmentally sound.

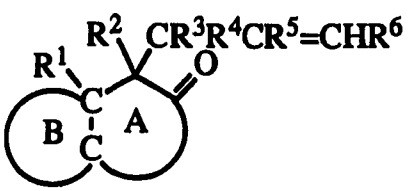



1 Glycinoeclepin A

Glycinoeclepin A (1) was first isolated[1] in microgram quantities from 113 kg dried 'Hon-kintoke' kidney bean roots and was found to be active at $10^{-11}$ to ~$10^{-12}$ g/ml. Its structure was determined[2] in 1985 using various spectral means and X-ray crystallography, all on the derived bis(p-bromophenacyl) ester.

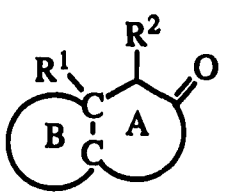
As only 1.25 mg of the diester of glycinoeclepin A could be isolated from approximately a ton of bean root,[2] it was obvious that an alternate source of glycinoeclepin A was needed. Since 1986, several researchers have reported syntheses of glycinoeclepin A or analogs of it. Analogs are an attractive option to glycinoeclepin A, for even if they are only partially as active as the highly active parent, they could still posess sufficient activity to be commercially useful.

Sakakibara applied for a Japanese patent in 1986 for several highly substituted multicyclic carbonyl compounds, which he intended as intermediates for glycinoeclepin A synthesis.[3] In 1987, he followed

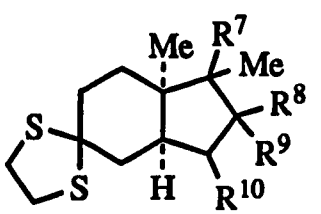



2

$R^{1-6}$ = alkyl



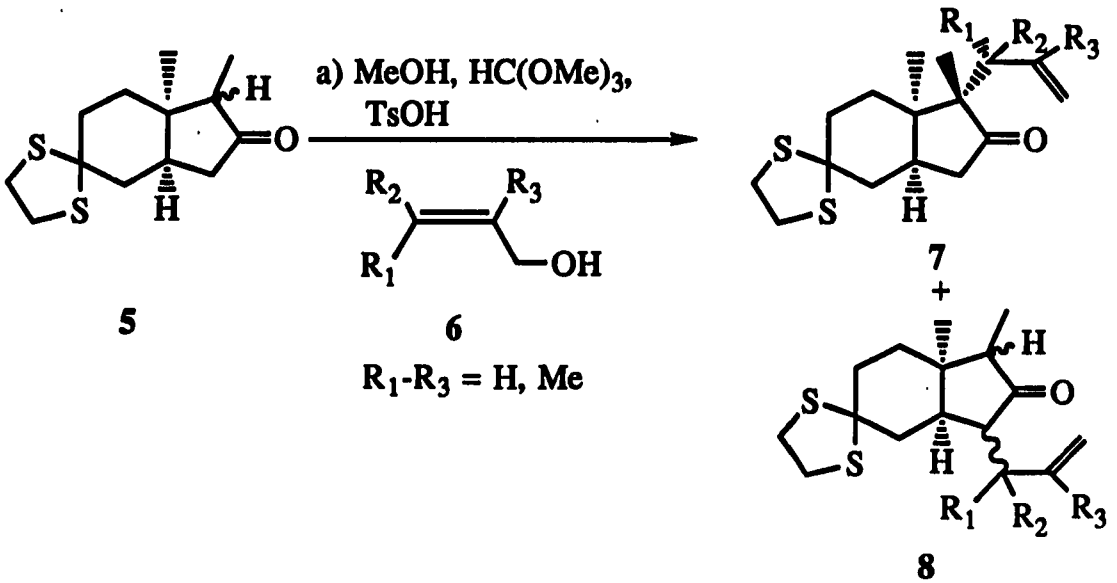

3




4

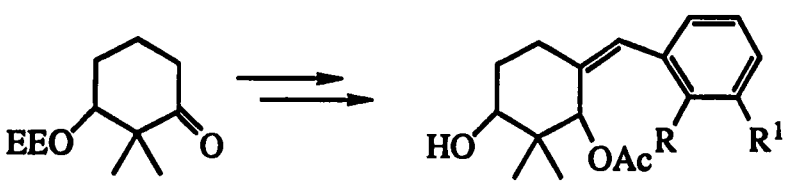
$R^7, R^{10}$ = H, $R^8R^9$ = O;
$R^7 = CH_2CMe{=}CH_2$, $R^8R^9$ = O
$R^{10}$ = H; $R^7$ = H, $R^8R^9$ = O
$R^{10} = CH_2CMe{=}CH_2$

this work with an approach to glycinoeclepin A's side chain which involved a Claisen rearrangement.[4] Although the acid moiety was never placed on the side chain, the terminal double bond was seen as a ready "handle" for doing so. Also in 1987, Sakakibara published a synthesis of two active glycinoeclepin A analogs.[5] Having noticed that four of the

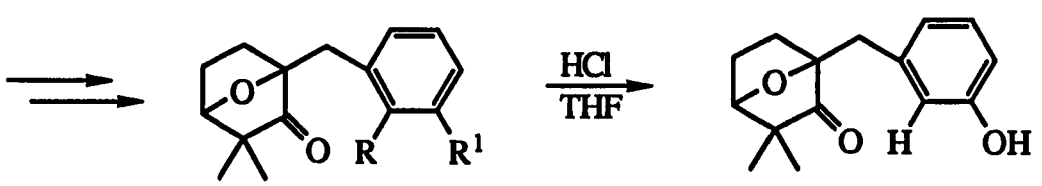



5 6 7 + 8

molecule's five oxygen-containing functional groups appeared to form a space appropriate for a "guest," structures containing the appropriate partial structures were constructed. A key step in the synthesis was



9 10 a: R = $CH_2OAc$, $R^1$ = H
b: R = H, $R^1$ = OMOM

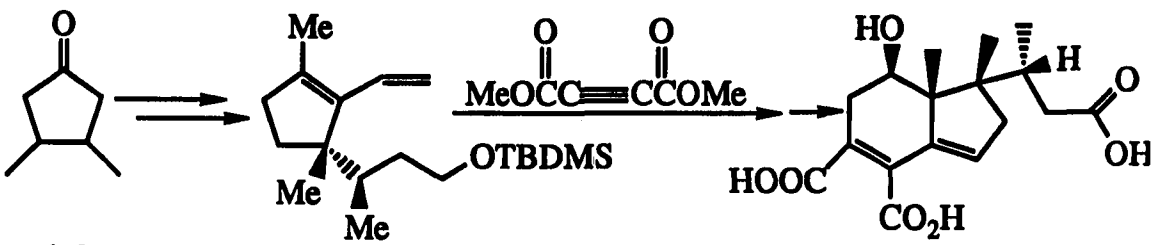



11 a: R = $CO_2H$, $R^1$ = H
b: R = H, $R^1$ = OMOM

12 (from 11b)

the halocyclization to form the precursor to the AB ring system. Compound **11a** was accompanied by a lactone which could be converted back to **11a**. Both **11a** and **12** exhibited approximately 50% hatching stimulation at $10^{-5}$ g/ml.

Sasai *et al.*[6] synthesized an analog of the CD ring system of glycinoeclepin A. The diene **14** underwent a Diels-Alder reaction

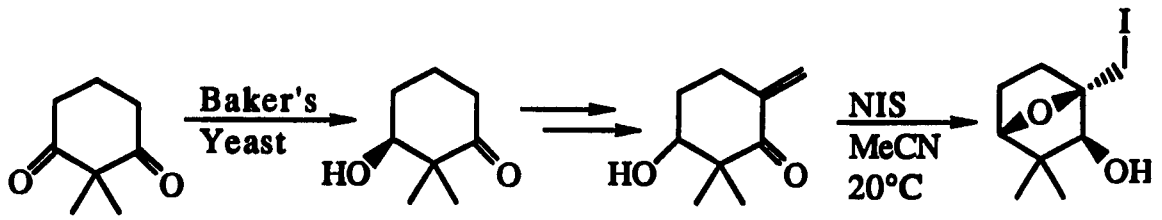



**13** **14** **15**

with dimethyl acetylene dicarboxylate to form a bicyclic adduct. Further transformations yielded the diacid **15**, which showed hatching activity at $10^{-9}$ g/ml.

In 1988, Murai *et al.* published the first total synthesis[7] of glycinoeclepin A. A convergent route was followed, in which the AB ring system was constructed and joined to the C ring, followed by a final cyclization to yield the D ring. Functionalization and opening of a 6-membered ring was used to set the stereochemistry of the D-ring side chain during construction of the C ring.

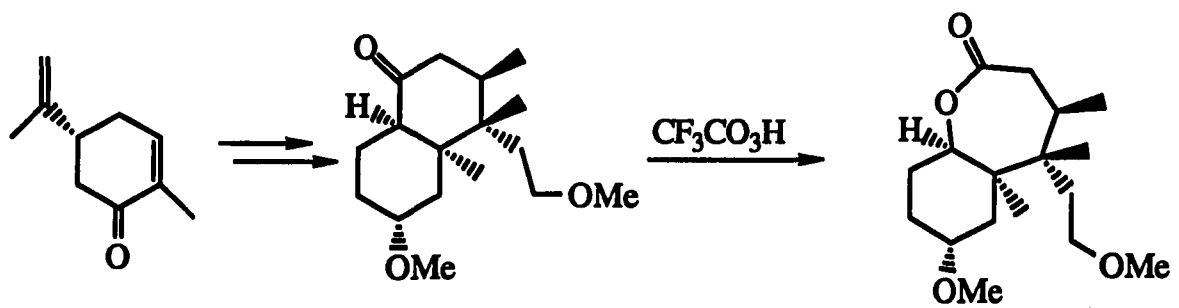
A Baker's yeast reduction of 2,2-dimethylcyclohexane-1,3-dione yielded an optically active keto alcohol. Formation of the exo methylene group allowed for halocyclization to form the AB ring system, as in



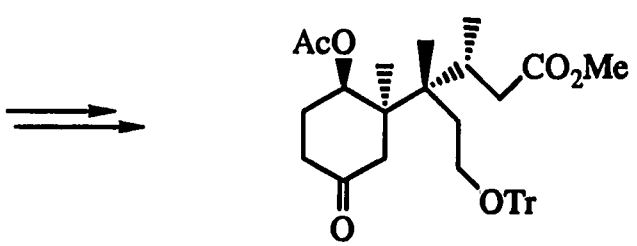

16 17 18

Sakakibara's work.

Construction of the C and D rings began with R-(-)-carvone. The molecule was manipulated to produce a functionalized bicyclic system,



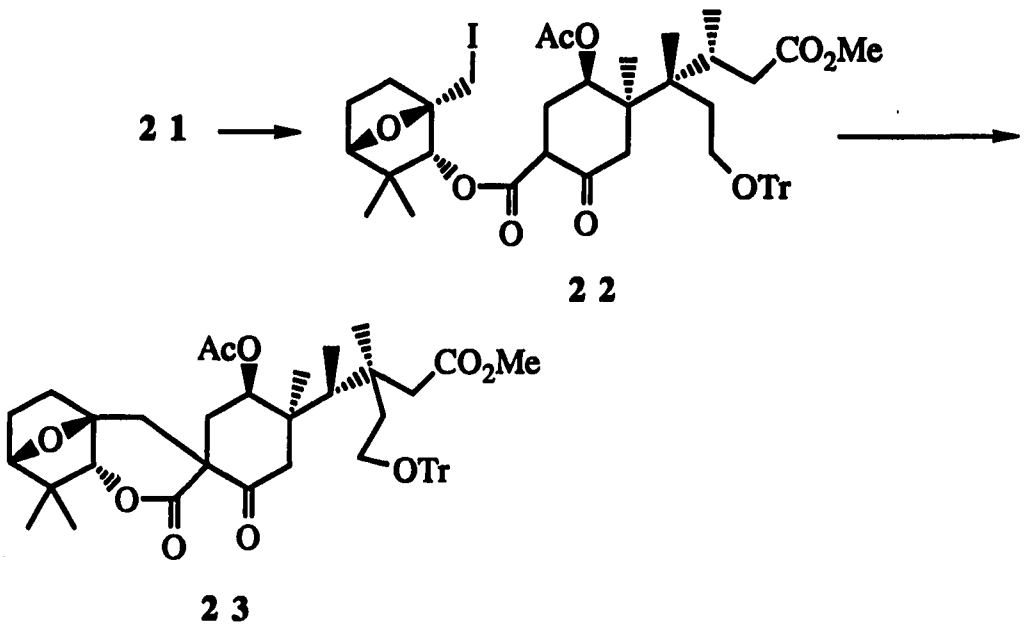

19 20



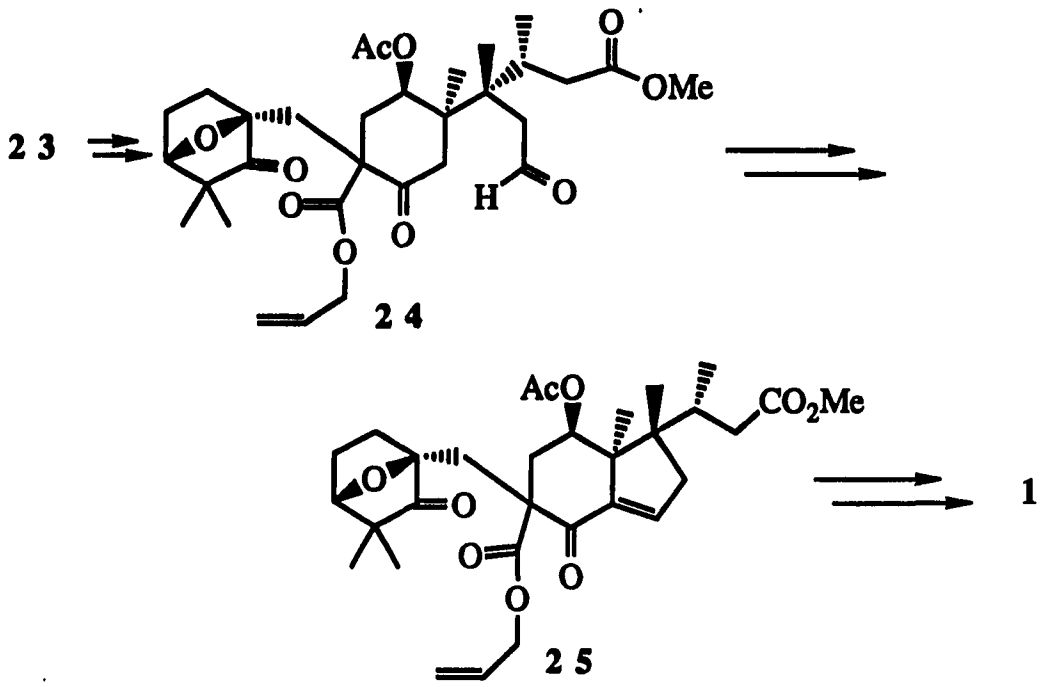

21

one ring of which was oxidized to a lactone and then opened with base to reveal a handle for the formation of the D ring, with its side chain already in place.

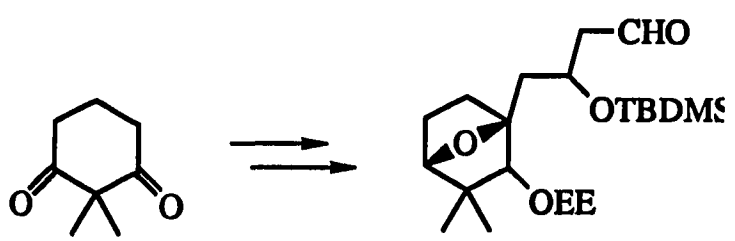
The AB and C ring moieties were first joined with a lactone linkage. The desired C-C bond between the AB and C rings




was established using KF/18-crown-6. Opening of the lactone ring and functional group manipulation set the stage for cyclization to form the D ring. Further functional group manipulation led to glycinoeclepin A.

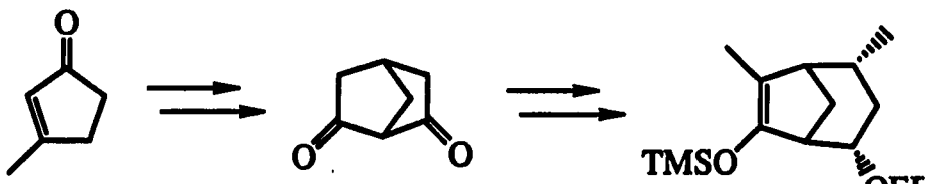



Mori and Watanabe[8] reported a total synthesis of glycinoeclepin A in 1989. They employed many strategies similar to those of previous workers, but used a unique method of forming the C ring. The synthesis began with a Baker's yeast reduction of 2,2-dimethyl-1,3-cyclohexanedione, followed by functionalizations and a halocyclization to form the AB ring system with a "handle." To form the D ring and its



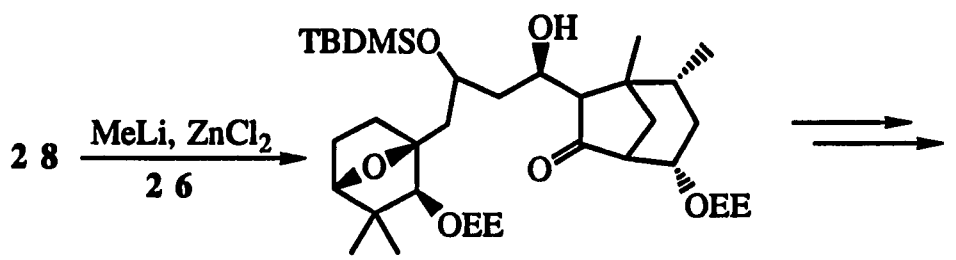

26

side chain, the bicyclic dione **27** was prepared from 3-methyl-2-cyclopentenone and reduced with Baker's yeast. Functionalization and ring expansion yielded compound **28**. Compound **28** was condensed with **26** in the presence of methyl lithium and zinc chloride.

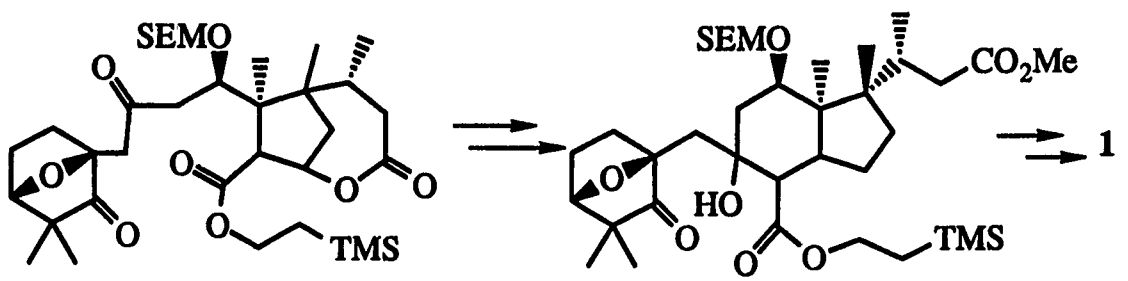



**27** **28**

Functionalization of the tetracyclic system led to compound **30**, which underwent reductive cyclization upon treatment with lithium dimethylcuprate. Simultaneous opening of the lactone ring freed the D-ring side chain. Final functional group manipulation led to



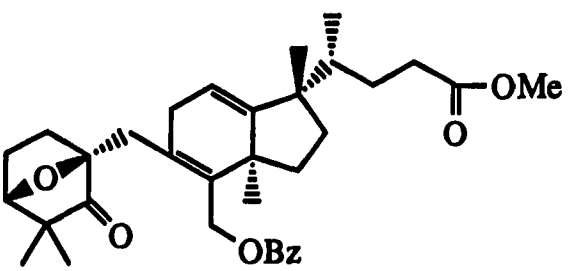

**29**




**30** **31**

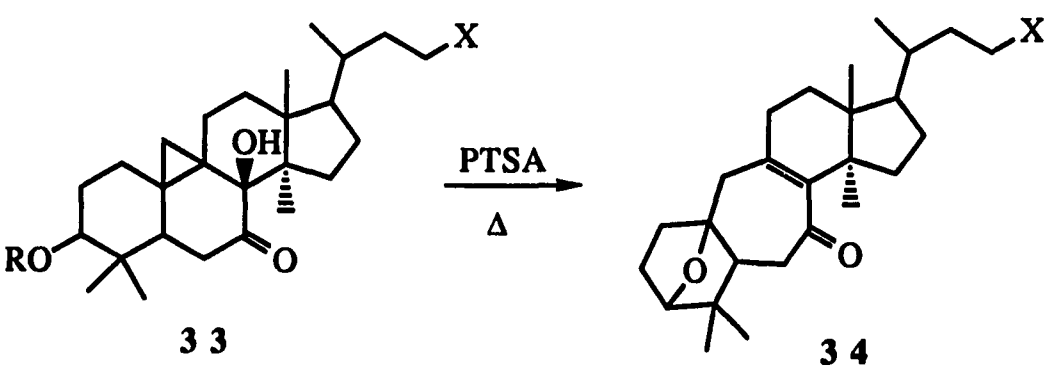
glycinoeclepin A. A second total synthesis of glycinoeclepin A published by Mori and Watanabe[9] in 1991 was nearly identical, but used much more efficient means of final ester cleavage and hydroxyl deprotection than the previous work.

Fukuzawa *et al.*[10] used biomimetic methods to prepare glycinoeclepin A analog **32.**




**32**

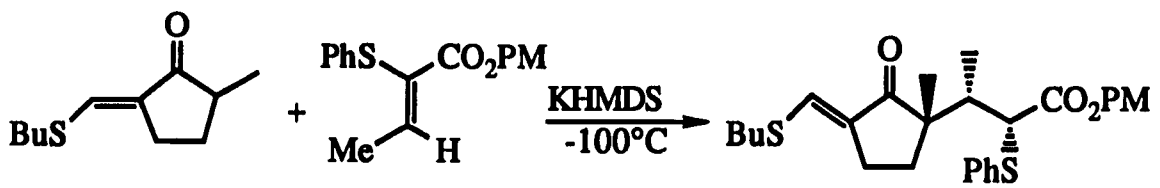
9,10-Seco-cycloartanes were prepared by Sakamaki *et al.* as intermediates for glycinoeclepins.[11]




**33** **34**

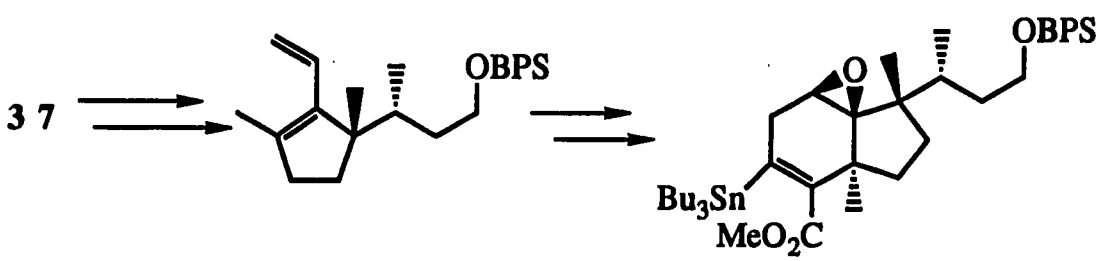
X = lower alkyl, alkylidene, haloalkyl, hydroxyalkyl, $CO_2H$, alkoxycarbonyl
R = H, pyranyl, methoxymethyl, ethoxyethyl

In 1990 Corey and Houpis[12] reported a total synthesis of glycinoeclepin A. This synthesis was quite different than those previously reported in that it began at the D ring and built the other rings on in turn, and it used intramolecular oxymercuration rather than halocyclization to form the AB ring system. Reaction of the potassium enolate of cyclopentanone **35** with ester **36** (prepared from the acid and (-)8-phenylmenthol) yielded a product with 95:5 enantioselectivity and 5:1 diastereoselectivity for C-17 to C-20. The corresponding



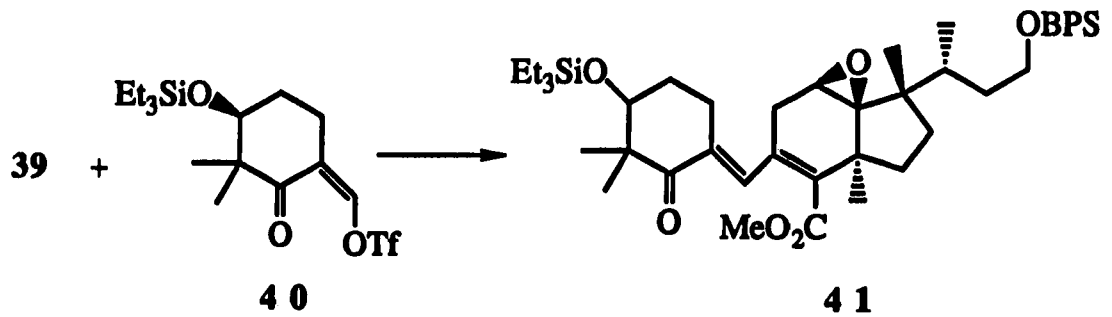

**35** **36** **37**

methyl ester gave a racemic product. Further transformations of **37** led to diene **38**, which underwent a Diels-Alder reaction with 3-(p-toluenesulfonyl)propiolic acid and further functionalization to afford compound **39**. Coupling of **39** with triflate **40** (prepared



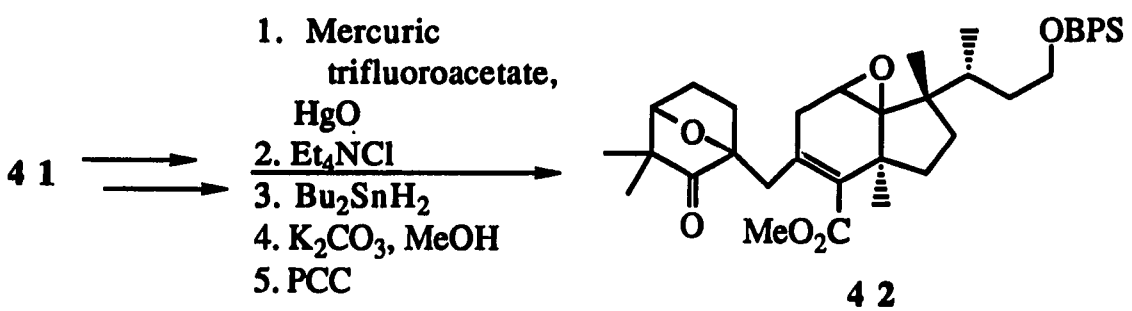

**38** **39**

enantioselectively from 2,2-dimethylcyclohexane-1,3-dione *via* Baker's yeast reduction and appropriate functionalization) yielded compound



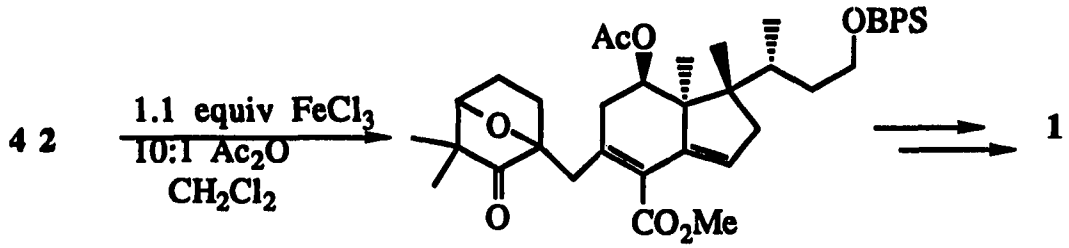

40 41

**41**. Once the ketone in **41** was reduced and chloroacetylated and the silyl protecting group was removed, intramolecular oxymercuration/ demercuration formed the ether linkage of the AB ring system.



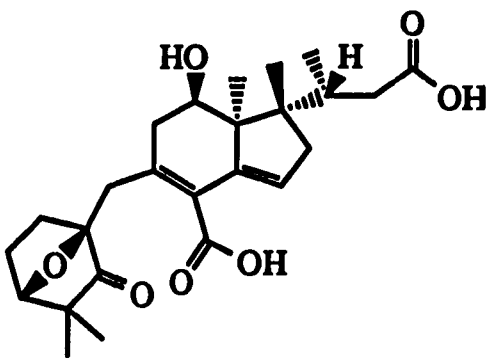

42

Compound **42** underwent rearrangement with $FeCl_3$ in acetic anhydride to give compound **43**, which was converted to glycinoeclepin A in five steps. The p-bromophenacyl ester was identical to that of an authentic sample by HPLC, MS, IR, 500 MHz proton NMR, and optical rotation. This total synthesis is the most simple and brief of those reported to date.




43

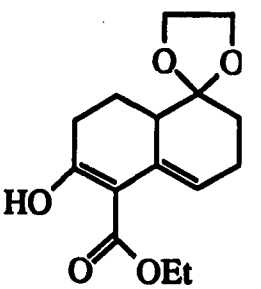
## RESULTS AND DISCUSSION




1 Glycinoeclepin A

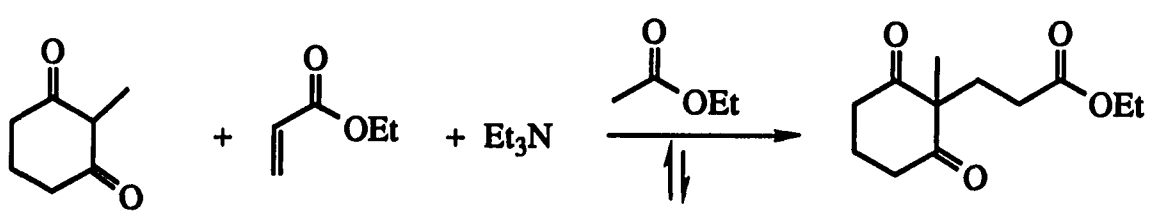
Upon brief inspection, glycinoeclepin A appears to be a relatively straightforward synthetic target, its four contiguous stereogenic centers providing the greatest challenge. Synthesis of the two bicyclic units and connection of them seemed a reasonable strategy. Unfortunately, synthesis of the AB system in particular proved much more difficult than anticipated. In light of our primary goal of synthesizing field-usable compounds with SCN hatching activity, simple analogs appeared more attractive than glycinoeclepin A itself. In order to determine which functionalities were necessary for biolgical activity, many analogs were prepared and tested. Variations included the presence or absence of various functional groups, the number and size of rings, and the length of the side chain. We postulated initially that the acid moieties were important, the hydroxyl group less important or unimportant, and the methyl groups unimportant. Based on these ideas, syntheses were begun.

Compound 44[13] looked like a good precursor to an analog of glycinoeclepin A's CD ring system. Although it was a hexahydro-naphthalene, rather than a hexahydroindane, it had appropriate double bonds, a carboxyl functionality in the correct C-ring position, a hydroxyl for functionalization toward the AB system, and a ketal which could be opened to approximate the side chain. Unfortunately, the literature reports were not reproducible, and 44 itself was not synthesized.




44

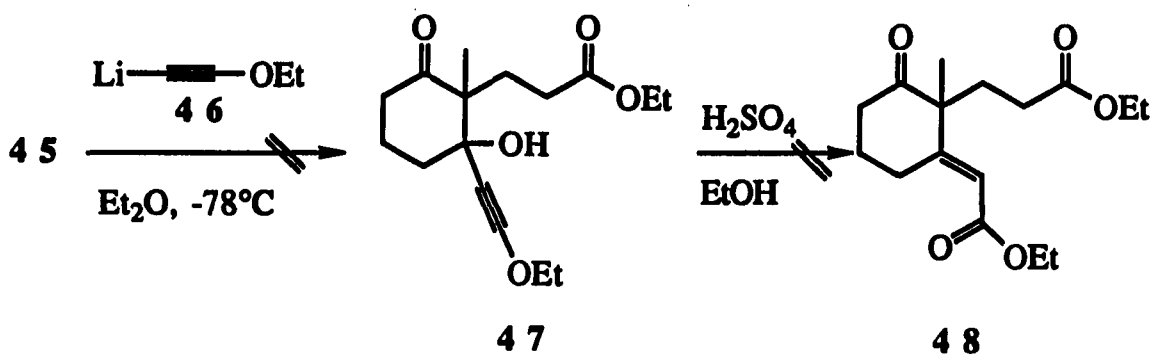
2-Methyl-1,3-cyclohexanedione reacted with ethyl acrylate (methyl acrylate was also used successfully later) in the presence of triethylamine in boiling ethyl acetate to produce the ester 45[14] in




45

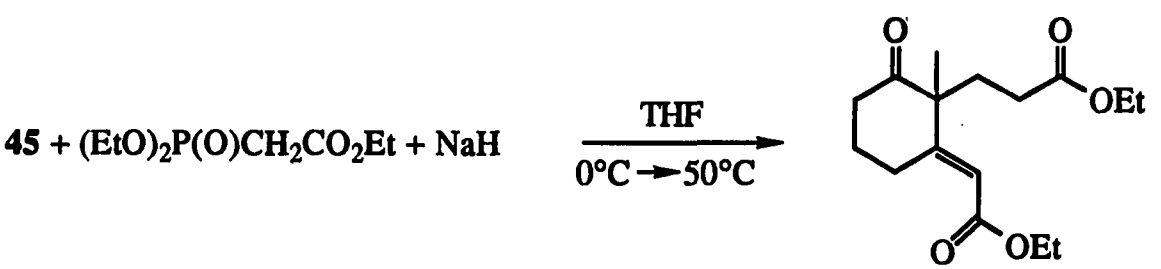
approximately 75% purified yield. The next step was to be addition of lithioacetylenylethyl ether to the dione with subsequent dehydration

and ester formation using sulfuric acid in ethanol.[12] Unfortunately, the anion addition did not work well, and only traces of the desired product were ever formed. The corresponding addition to benzaldehyde was




47 48

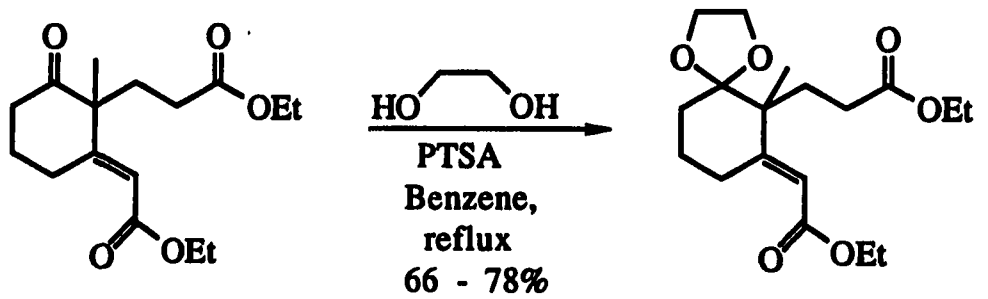
successful, so the failure to produce **47** was attributed to peculiarities of the molecule and a new method was selected. The Horner-Emmons[15] modification of the Wittig reaction seemed a logical choice. Treatment of triethylphosphonoacetate with sodium hydride and **45** gave a 66-




**48**

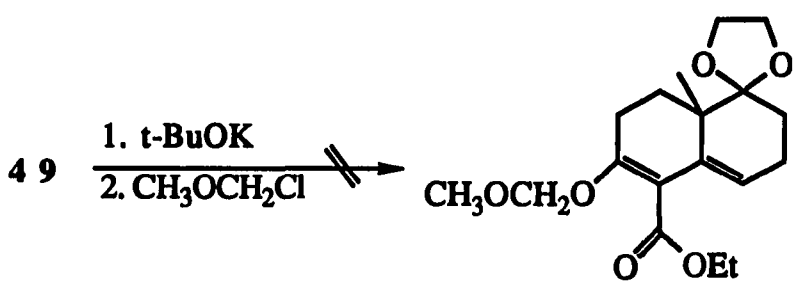
70% yield of **48** after flash column chromatography on silica gel. Before attempting the intramolecular cyclization of the diester, transformation of the ketone moiety was undertaken. Reaction of **48** with ethylene

glycol and p-toluenesulfonic acid in boiling benzene[13] gave acceptable yields of ketal **49**.



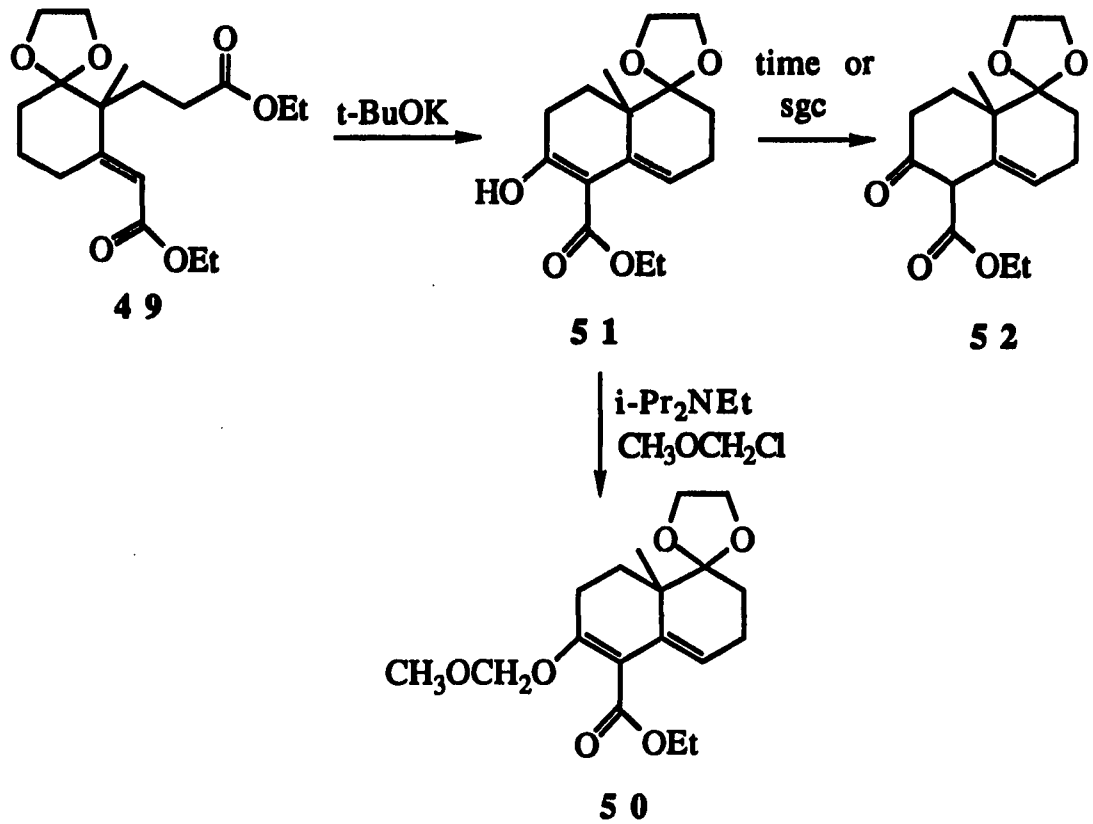

**48** **49**

Initial attempts to cyclize **49** were not as successful as those reported in the literature.[13,16] Direct trapping of the enolate failed.




**49** **50**

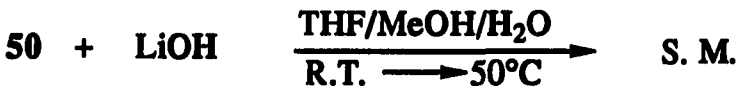
to give satisfactory results. If no trapping agent was added, the enol could be isolated,[13] but it rearranged within 24 h to the enone. The methoxymethyl protected enol could be made from the freshly prepared enol and chloromethylmethyl ether with diisopropylethylamine in moderate to good yields.




49 51 52

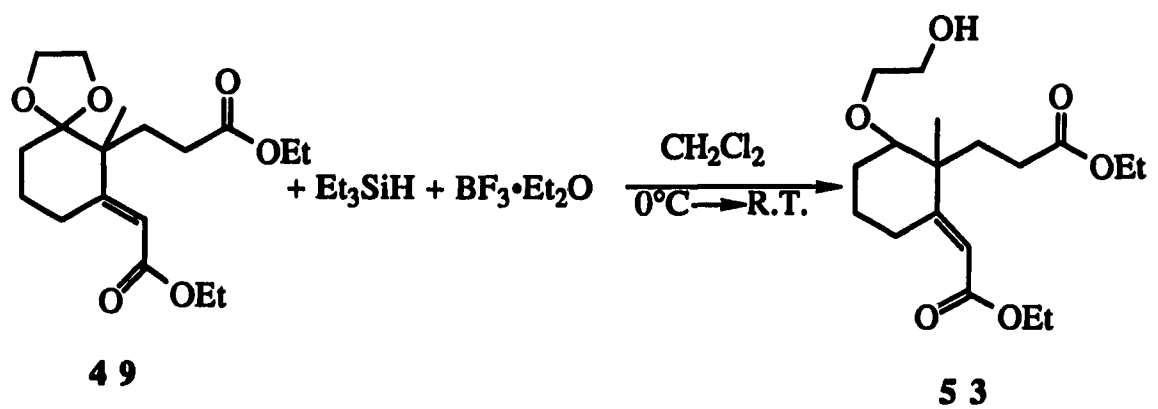
50

In order to free the acid moiety and produce an analog suitable for testing, attempts were made to hydrolyze the ester. Treatment of **50** with lithium hydroxide in THF/methanol/water simply returned starting material. BuSLi in HMPA[17] also failed to cleave the ester. These difficulties, coupled with the discovery that **50** decomposed slowly upon storage, led to alterations in the target molecule.

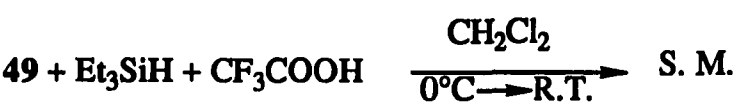




As **49** was stable and readily accessible, it was used as a convenient starting point. In order to approximate the D-ring side chain, the acetal of **49** was opened using triethylsilane and

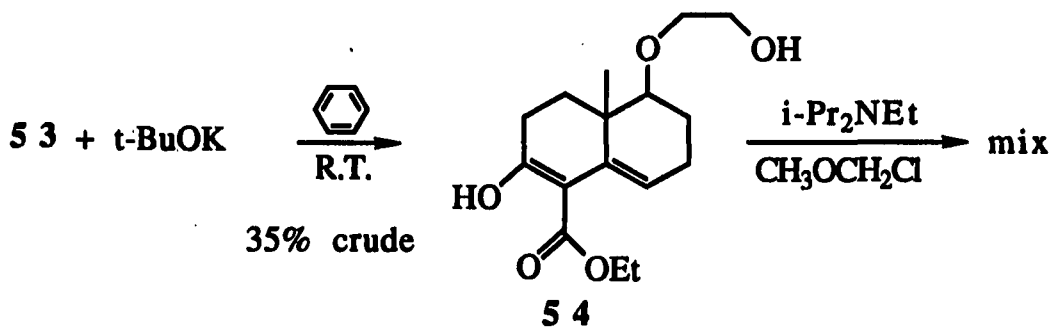



**49** **53**




borontrifluoride etherate[18] to afford the alcohol in 61-80% yield. Triethylsilane with trifluoroacetic acid failed to open the acetal. Cyclization of the diester with *in situ* trapping of the enolate was next attempted. Treatment of **53** with potassium tert-butoxide in benzene

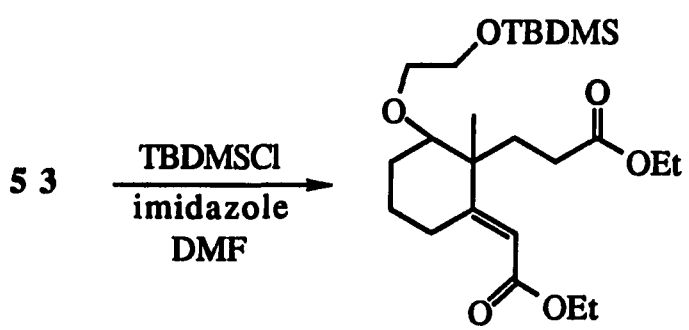

at room temperature, followed by addition of chlorotrimethylsilane, led to an unsatisfactory mixture of products. Cyclization of **53** with potassium tert-butoxide, followed by quenching of the enolate with $H_2O$, gave a promising result by proton NMR, albeit in relatively low yield.




**5 4**

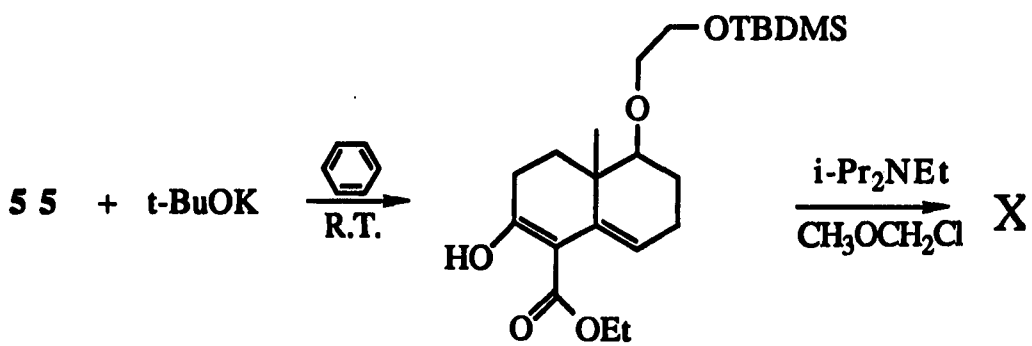
Unfortunately, an attempt to form the methoxymethyl protected enol resulted in a large number of product spots by TLC and low mass return.

Concerned that the free alcohol group in **53** might be one of the




**5 5**

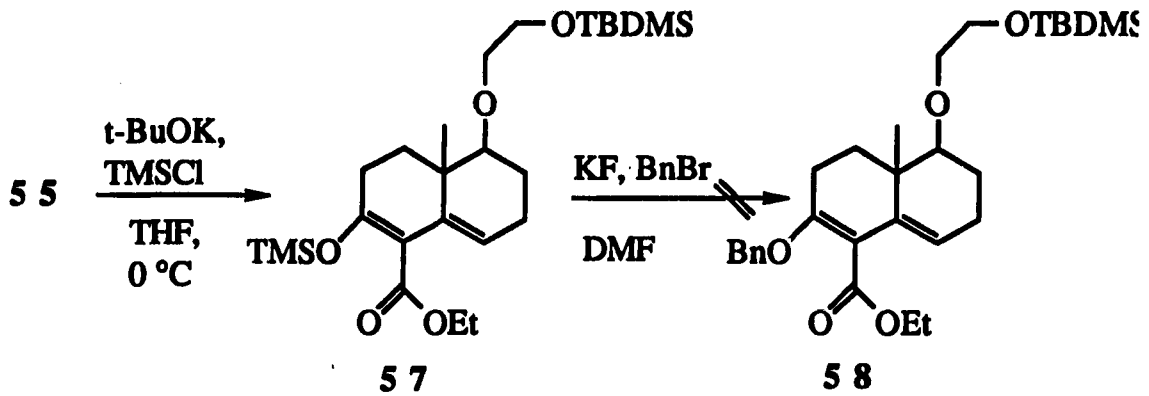
problems in the above work, it was protected as a tert-butyl-dimethylsilyl ether.[19] Cyclization of **55** with potassium tert-butoxide showed promise, but an attempt to protect the enol as a methoxy-methyl ether did not proceed cleanly. Cyclization with *in situ* trapping of the enolate with chloromethylmethyl ether failed. Cyclization and *in situ* trapping using THF as the solvent at room temperature gave a very similar TLC profile, and the product proved difficult to purify by



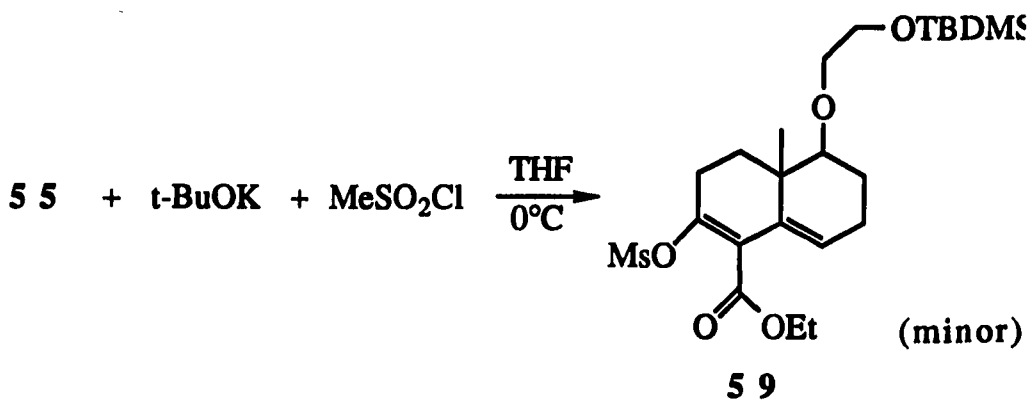

**56**

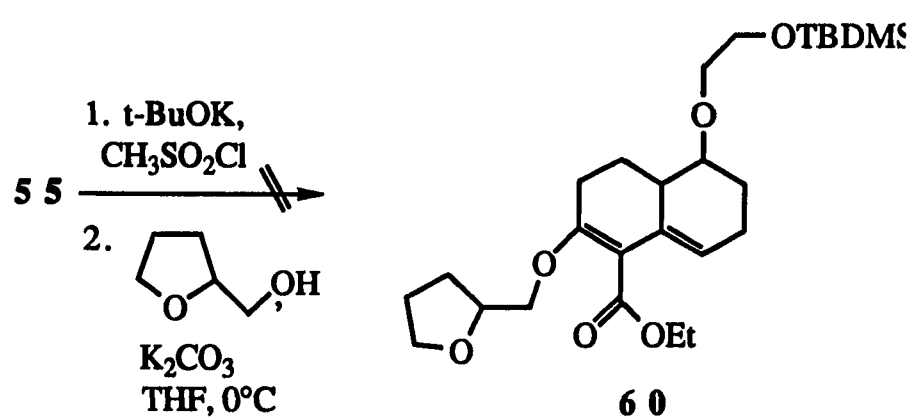
chromatgraphy. Similar attempts to cyclize **55** (THF, 0 °C) and trap the enolate with benzoyl chloride or methyl iodide proved unsatisfactory.

When **55** was treated with potassium tert-butoxide in THF at 0 °C, the cyclized enolate could be trapped with chlorotrimethylsilane to yield enol silyl ether **57** in 75-85% yield. Treatment of **57** with potassium fluoride and benzyl bromide failed to produce the desired benzyl compound **58**.



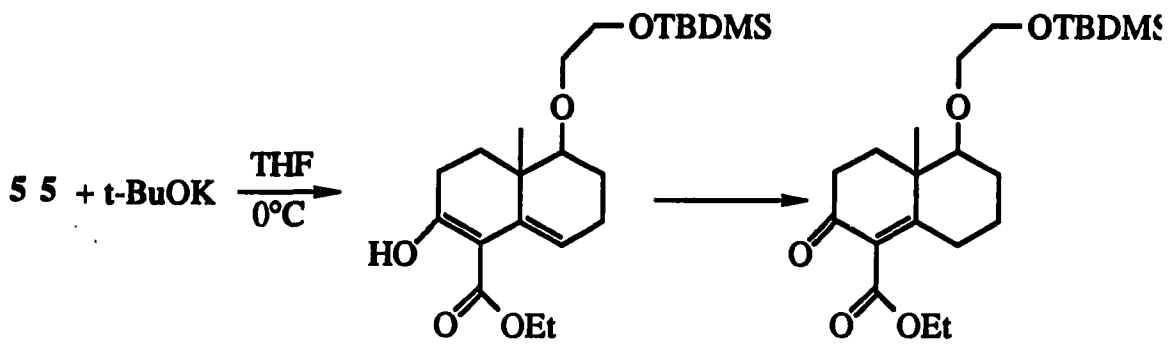

Based on the initial positive result, other trapping experiments were examined. Treatment of **55** with potassium tert-butoxide followed by methanesulfonyl chloride gave a small amount of the

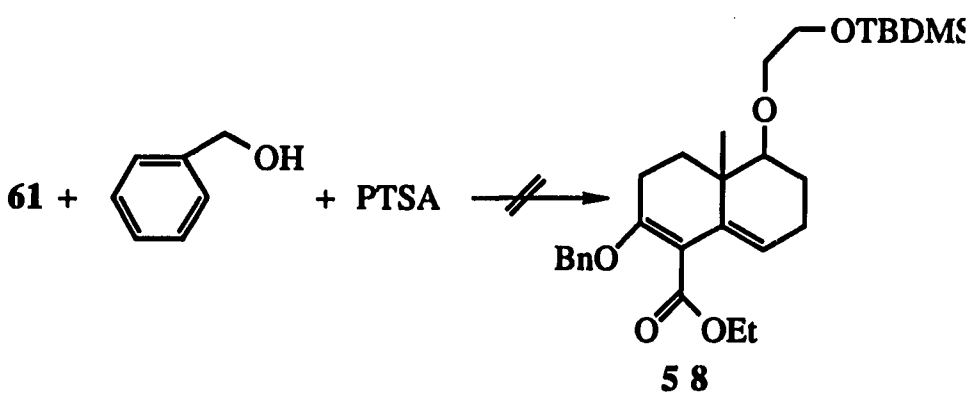


desired mesylate, but the reaction mixture was a multitude of spots by TLC analysis. An attempt to generate the mesylate and allow it to react *in situ* with tetrahydrofurfuryl alcohol also gave an unclear result. A later attempt to trap the enolate with benzyl bromide also gave several products.

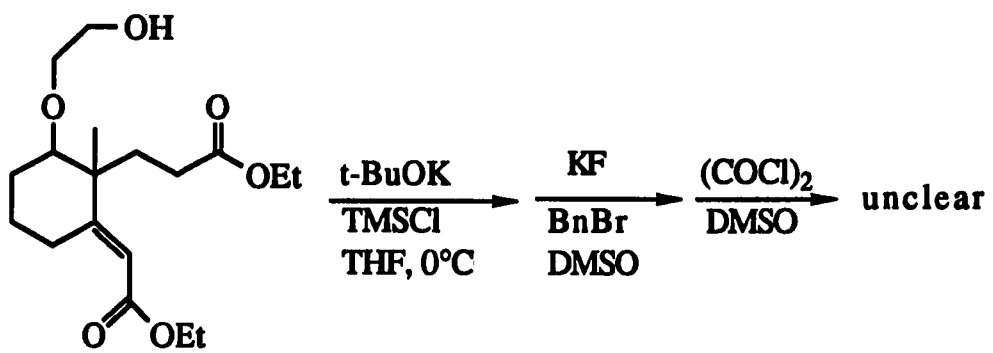
Treatment of **55** with potassium tert-butoxide followed by careful aqueous workup gave enol **56** which converted to enone **61** with time or with silica gel chromatography. Treatment of **61** with benzyl alcohol and p-toluenesulfonic acid failed to give the desired unsaturated benzyl



ether, which would have very roughly approximated the AB system of glycinoeclepin A. Unfortunately, **61** proved unstable, decomposing within days at 0 °C. Therefore, this route was dismissed as a feasible path to analogs.

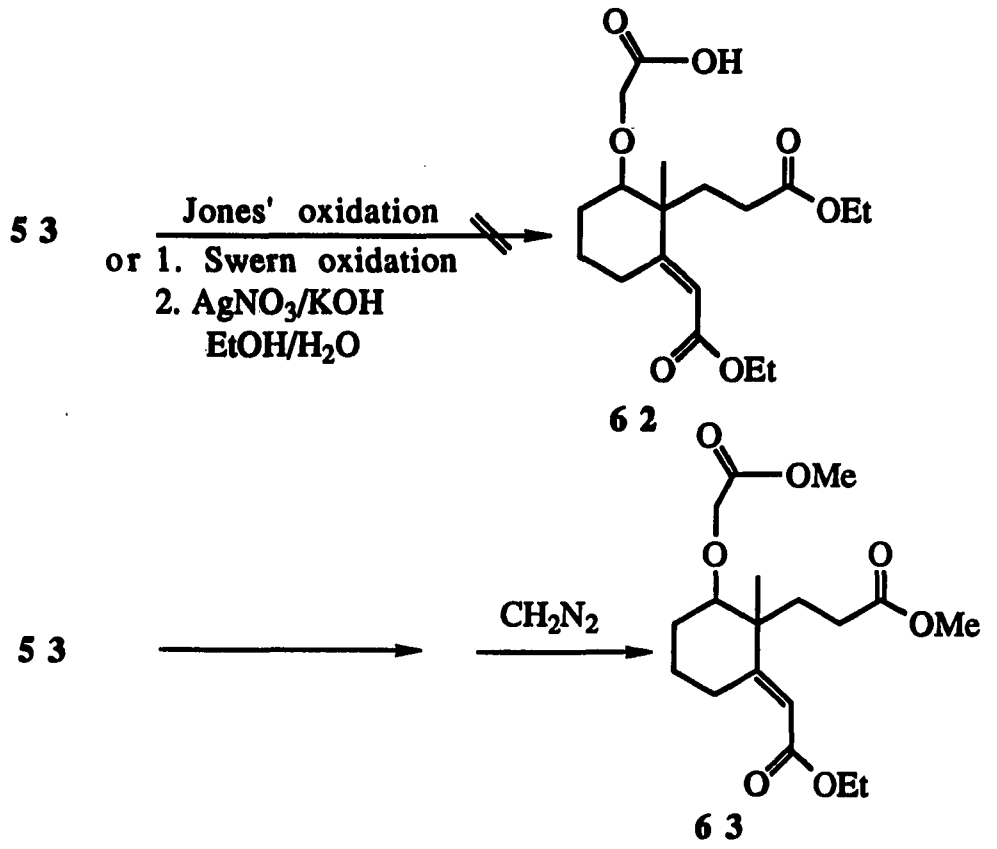
At this point, interest in compound **53** was renewed. A second attempt was made to cyclize **53** with potassium tert-butoxide using THF at 0 °C and *in situ* trapping of the enolate with chlorotrimethylsilane. Treatment of the presumed bicyclic enol silyl ether with potassium fluoride and benzyl bromide in dimethylformamide yielded what




**53**

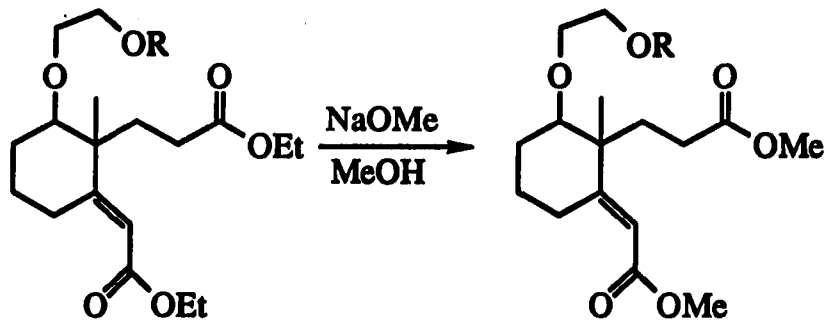
appeared to be a benzyl ester/benzylvinyl ether. While Swern oxidation of this product did produce an aldehyde, this path was abandoned as more promising paths arose.

Treatment of alcohol **53** with Jones' reagent[20] produced an acid, but in low yields. A two step oxidation of this alcohol involving a Swern oxidation[21] to the aldehyde followed by a silver oxide oxidation[22] to the




acid proved much more effective, with yields up to 86%. Initially, the product of both oxidations was believed to be the monoacid **62**. Integration of the ester region in the proton NMR spectrum did not support this structure. Treatment of the oxidation product with diazomethane[23] yielded a product with two new methyl ester peaks. The proton NMR and infrared spectrum supported triester **63**.

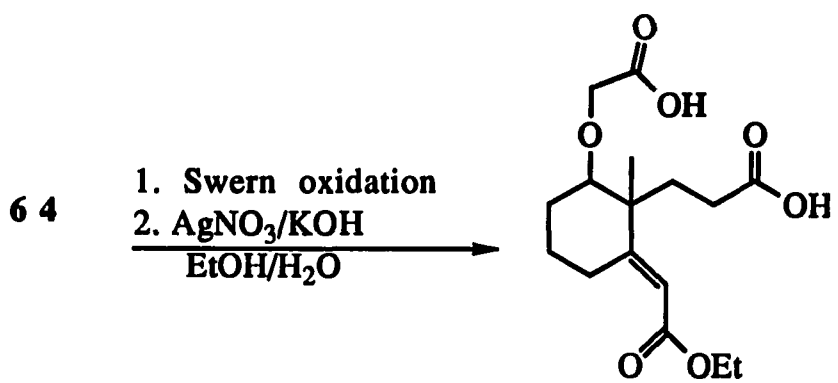
In an earlier attempt to cyclize **55** with sodium methoxide in methanol, transesterification resulted. This transesterification was also successful on unprotected alcohol/diester **53**. In an effort to simplify




**53** : R = H
**55** : R = TBDMS

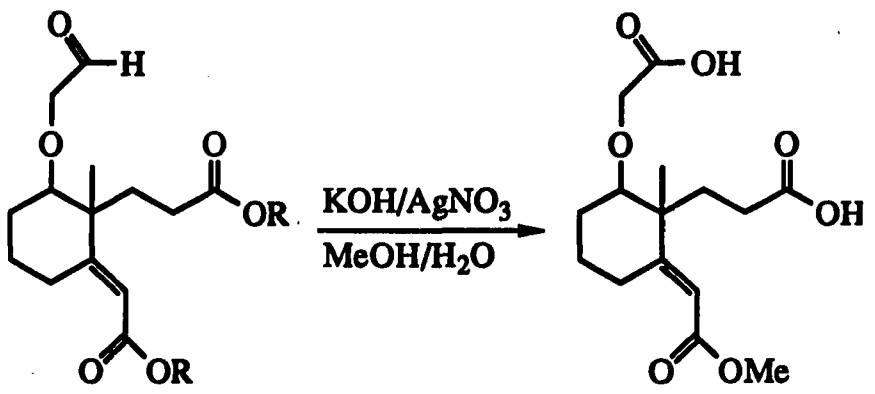
**64** : R = H
**65** : R = OTBDMS

spectra, bis-methyl ester **64** was prepared in > 95% yield. Compound **64** underwent Swern oxidation in quantitative yield, but upon further oxidation with silver oxide in aqueous ethanol product **66** resulted and resisted a third transesterification attempt. Based on these results,




**6 6**

oxidation of aldehyde **67** (from Swern oxidation of **64**) was performed using aqueous methanol and diacid **68** resulted. It was ultimately discovered that both the bis-methyl and bis-ethyl ester gave the same

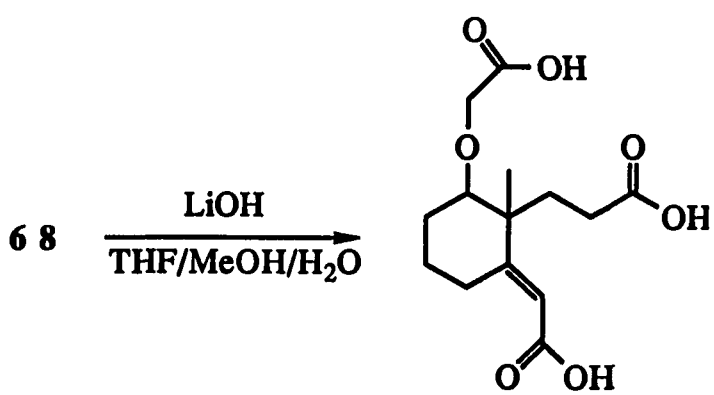



67 a: R = Me
b: R = Et

68

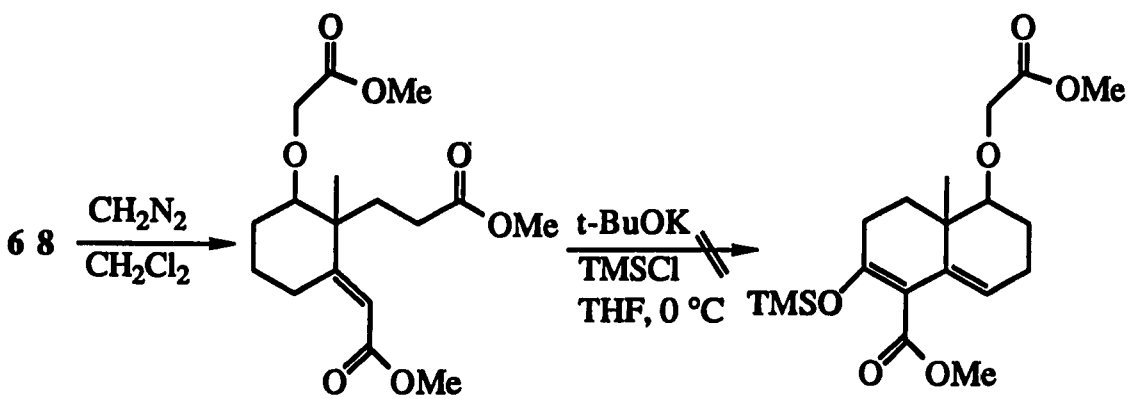
oxidation product when methanol was used as the solvent. Thus, prior transesterification was unnecessary.

As compound **68** contained approximations of glycinoeclepin A's D-ring side chain, B-ring "acid" (masked as an ester), and further oxygen-containing functionality, it was submitted as an analog for biological testing. Results to date are inconclusive Lithium hydroxide hydrolysis to the triacid **69** afforded a second analog for testing. Compound **69** has not yet been tested.



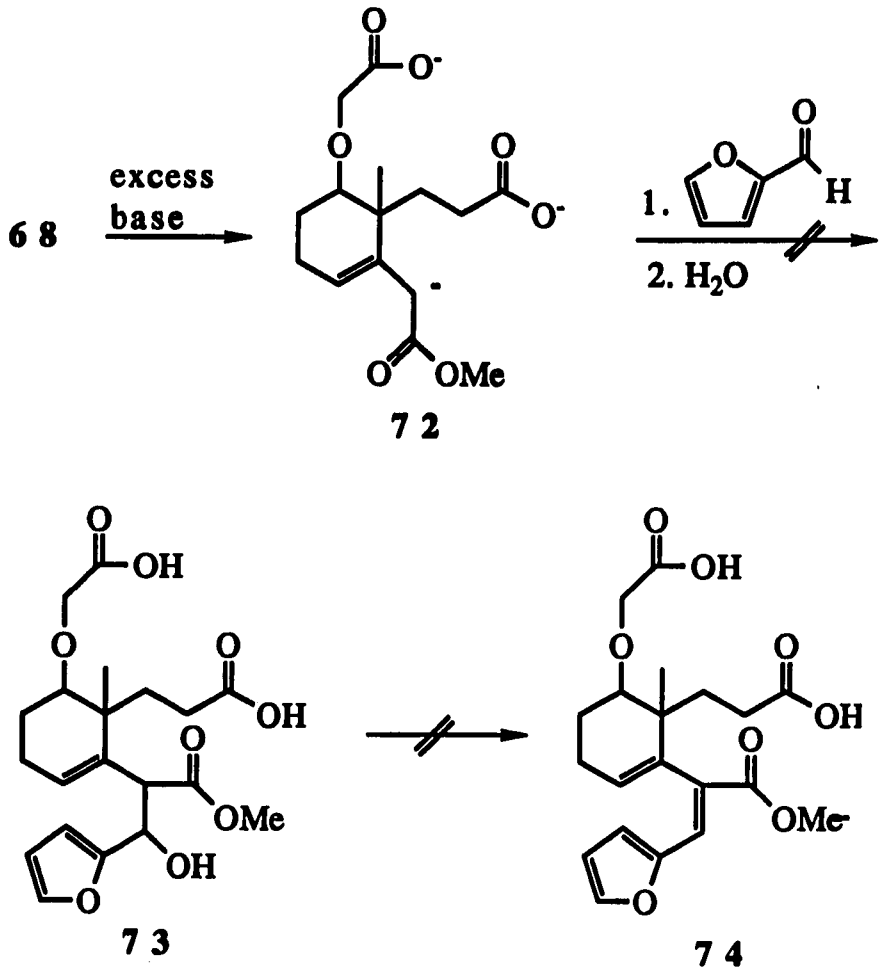

69

Attempts were then made to produce closer glycinoeclepin A analogs from **68**. Treatment of **68** with diazomethane in dichloromethane yielded triester **70**. When subjected to potassium tert-butoxide and chlorotrimethylsilane in THF at 0 °C, compound **70** failed to produce the desired bicyclic enol silyl ether **71**.

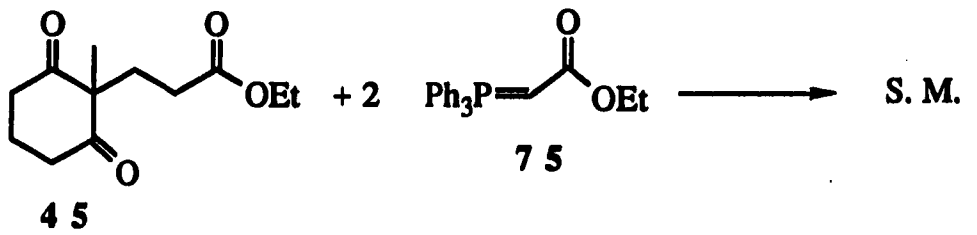



**70** **71**

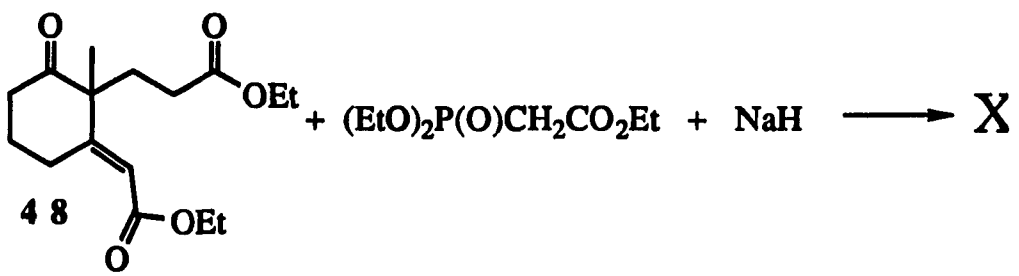
It was hoped that treatment of **68** with strong base would produce an anion which quench $\alpha$-to the ester, allowing the introduction of an A ring approximation. 2-Furaldehyde was chosen as the electrophile because of its ring size and ring oxygen. It was hoped that the alcohol produced could be eliminated to form the unsaturated furan. Unfortunately, treatment of **68** with various bases failed to yield the addition product **73**. Conditions used included three, four, or five equivalents of lithium diisopropylamide, three equivalents of potassium hydride, and five equivalents of potassium tert-butoxide in THF, DMF, or DMSO.




Bis-Wittig products from a precursor of **68** were also seen as potential analogs, but their synthesis proved elusive. Treatment of **45** with two equivalents of the Wittig reagent **75** returned starting material, while treatment with two equivalents of sodium hydride and two equivalents of triethylphosphonoacetate also failed to yield the desired product. Resubmission of the mono-Wittig product did not produce the bis-product.

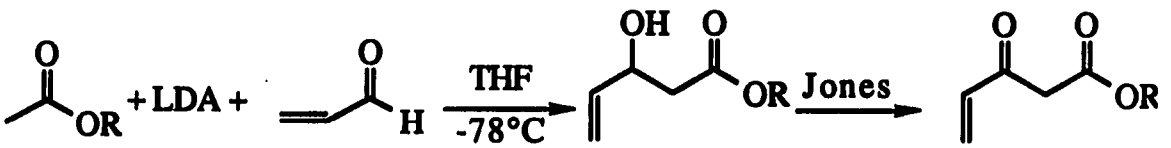



45 + 2 $(EtO)_2P(O)CH_2CO_2Et$ + NaH ⟶ X




Pursuit of analogs along this line was halted at this point and new pathways explored. The method of Mukaiyama[24] for coupling enol silyl ethers and $\alpha,\beta$-unsaturated carbonyl compounds seemed a likely starting point.

It was hoped that **77** or **78** would couple with an appropriate enol ether under Mukaiyama's conditions and that the resulting adduct could be cyclized to give a CD ring system analog with a masked acid moiety and a handle upon which to build the D-ring side chain. Treatment of ethyl or benzyl acetate with LDA followed by addition of acrolein produced the unsaturated alcohols **75** and **76** in greater than 71% yield. Jones oxidation[20] afforded the dicarbonyl compounds. The coupling was attempted first on a model system, and gave promising

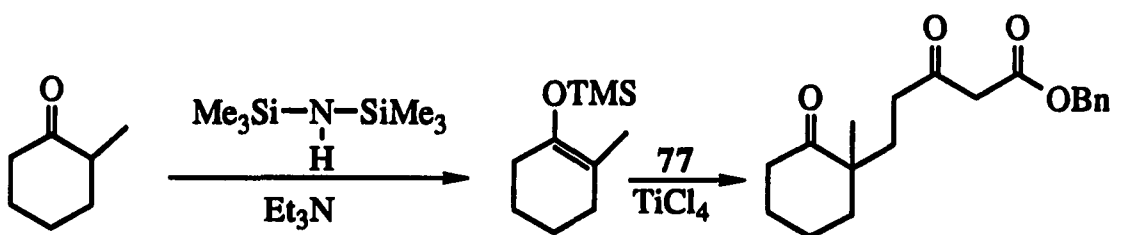



R = benzyl or ethyl

**75** R = Bn
**76** R = Et

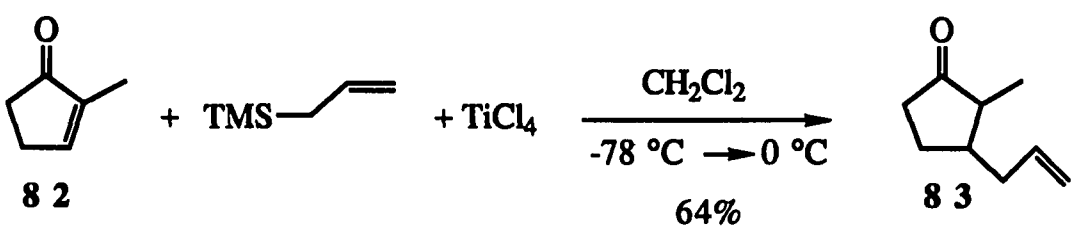
**77** R = Bn
**78** R = Et

results by proton NMR. Based on this result, a cyclic ketone for the desired analog was prepared.[25]



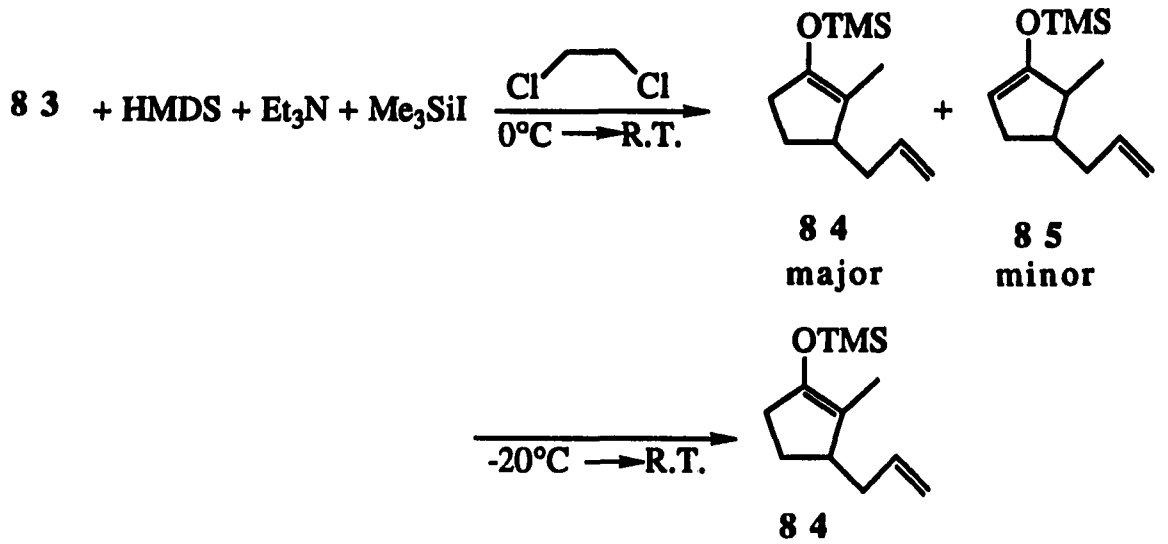

**79** **80** **81**

Treatment of 2-methyl-2-cyclopenten-1-one with titanium(IV) chloride and allyltrimethylsilane afforded moderately good yields of **83**



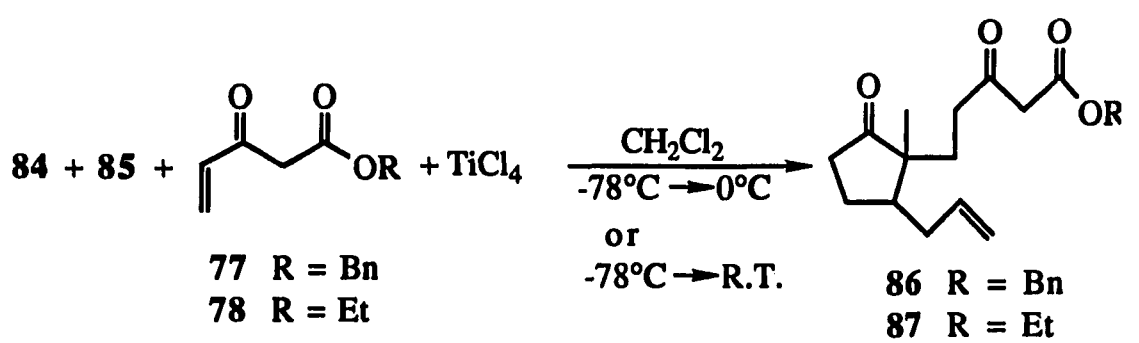

**82** **83**

after purification. Formation of the enol silyl ether using HMDS, $Et_3N$, and TMSI at 0 °C invariably led to a product mixture containing some of the kinetic product, as well as the desired thermodynamic product. It

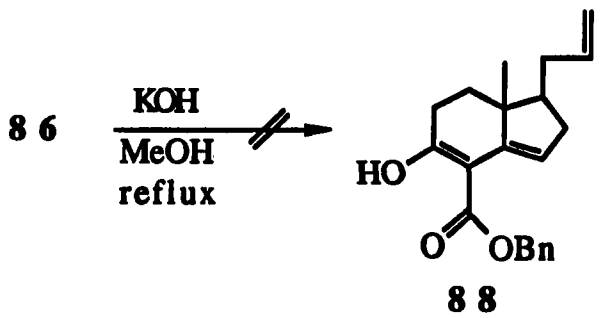



was later discovered that this problem could be overcome by starting the reaction at a lower temperature.[26]

Reaction of a mixture of **84** and **85** with **77** in the presence of titanium (IV) chloride afforded an initially promising crude mixture.

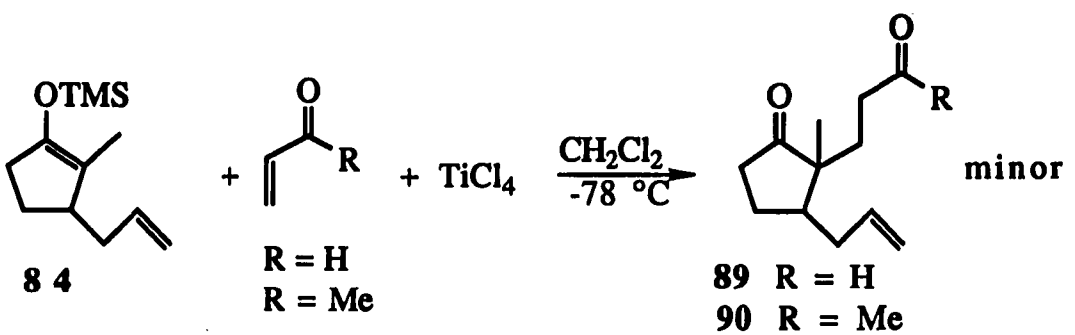


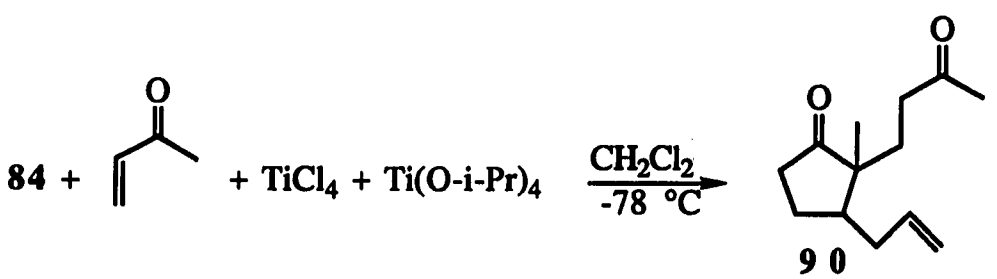

Silica gel chromatography failed to yield the desired product definitively and attempted cyclization of the tentatively identified product gave unclear results. Allowing the coupling reaction to warm to

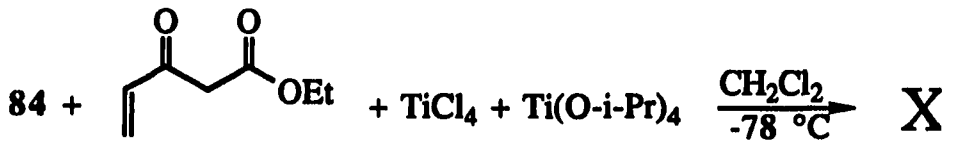



room temperature did not appear to improve the results. Use of the ethyl ester, rather than the benzyl ester, also failed to produce the desired product cleanly.

Attempts to couple **84** with acrolein in the presence of titanium(IV) chloride failed to produce appreciable amounts of the coupled aldehyde. Methylvinyl ketone (MVK) also failed to produce

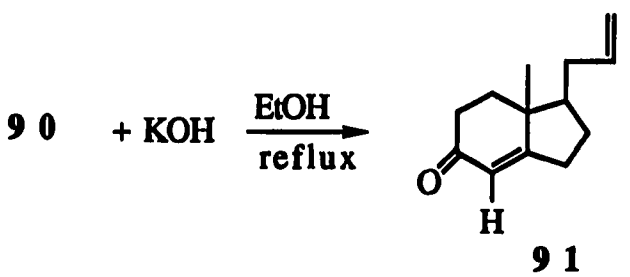




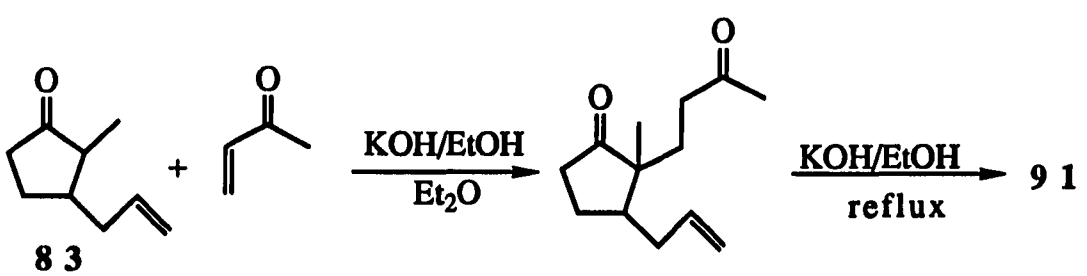

satisfactory results. A combination of titanium(IV) chloride and titanium(IV) isopropoxide[27] served to couple **84** and MVK, albeit in low yield. Extension to the unsaturated $\beta$-ketoester was not promising.

The dicarbonyl compound **90** could be cyclized to the desired bicyclic compound **91** using potassium hydroxide in boiling ethanol.




**91**

However, it was discovered that **91** could be produced much more efficiently (approximately 50% yield) by a two step process[28] in which **84** reacted with MVK in the presence of catalytic potassium hydroxide

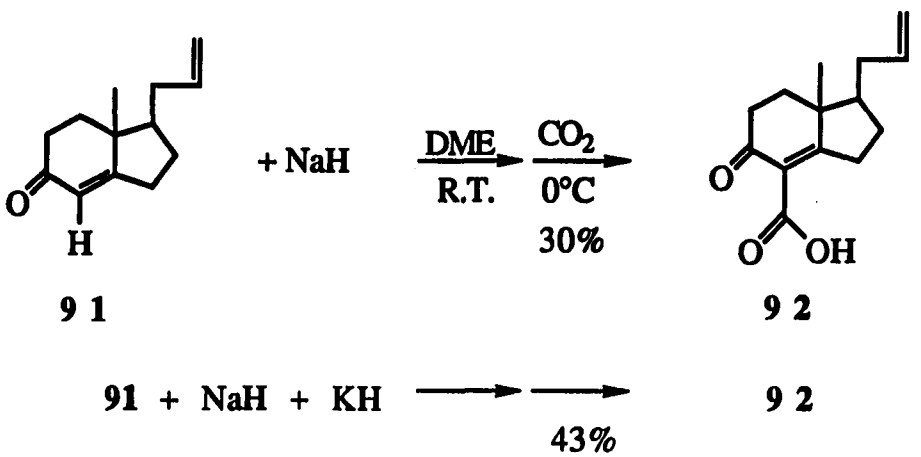



**83**

+ cyclized

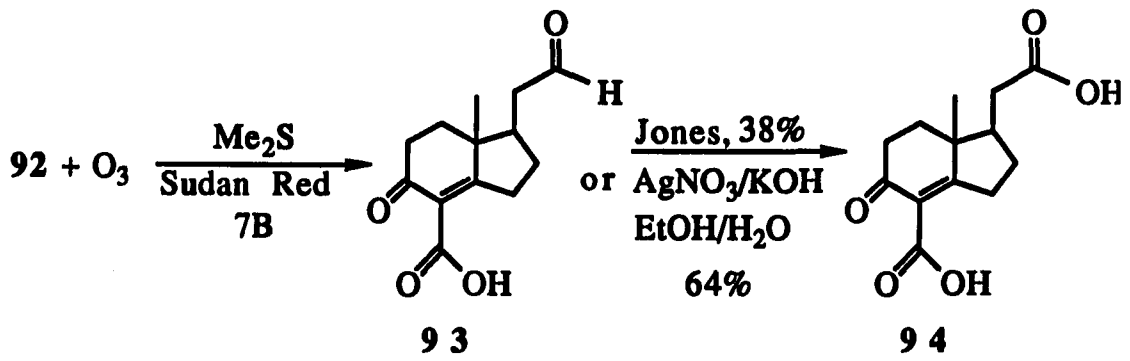
in ether. When the unpurified reaction mixture was heated with excess potassium hydroxide, **91** was formed.

As **91** contained the bicyclic system of glycinoeclepin A, a precursor for its side chain, and an enone capable of undergoing further functionalization, it was used as a precursor for several analogs. Treatment of **91** with sodium hydride, followed by bubbling carbon dioxide gas through the reaction mixture,[29] afforded carboxylic acid **92** in 30% yield. Addition of a catalytic amount of potassium hydride increased the yield to 43%. A sample of **92** was submitted for biological



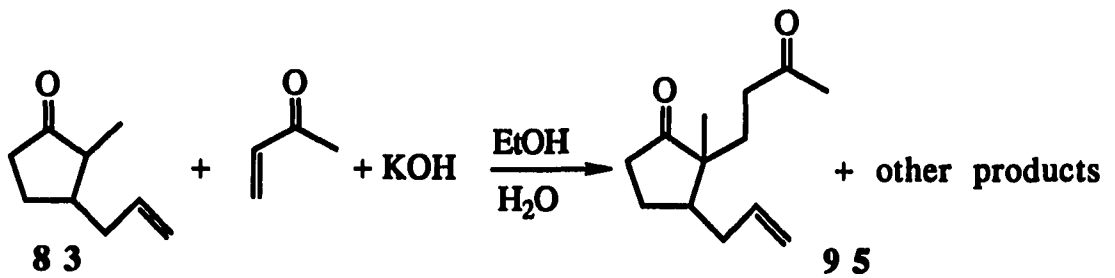

testing and was found to be inactive.

Further functionalization of the side chain was the next goal. Toward this end, a selective ozonolysis of **92** using Sudan Red 7B as an indicator[30] was performed, and an aldehyde resulted. The aldehyde could be further oxidized using either Jones' reagent or silver oxide in aqueous ethanol, with the latter affording greater yields. Unfortunately, the ozonolysis proved somewhat unreliable, failing in some cases to go



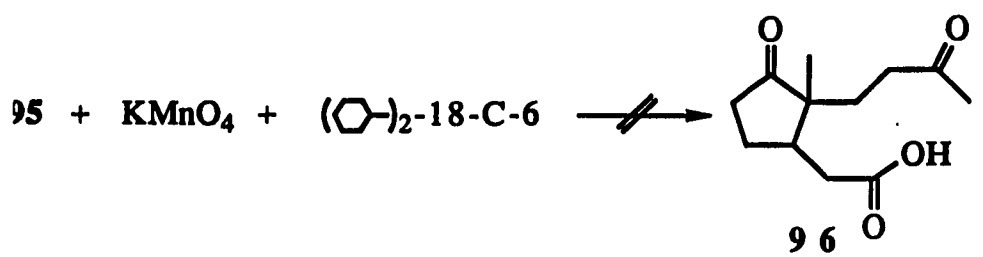

to completion. In other cases, the ozonolysis intermediate failed to decompose completely to the aldehyde. Model systems, including carvone and heptene, were employed to test reaction conditions. Solvents used were methanol, dichloromethane, and 2:1 dichloromethane/ethanol. Sudan Red 7B, Solvent Red 23, and Sudan III were used in different cases, and dimethylsulfide (or triphenylphosphine) was used to decompose the intermediates. No suitable conditions were found, so the route was abandoned.

As functionalization of the side chain in **91** was not readily achieved by ozonolysis, it was hoped that it could be performed before cyclization. Ozonolysis of the unpurified product mixture from the reaction of **83**, MVK, and potassium hydroxide in aqueous ethanol was only marginally successful. Oxidation with silver oxide produced an acid, as evidenced by the infrared spectrum. Cyclization of the unpurified mixture with potassium hydroxide in boiling ethanol was tentatively promising by proton NMR, but the ester produced by reaction with diazomethane did not appear promising by proton NMR.

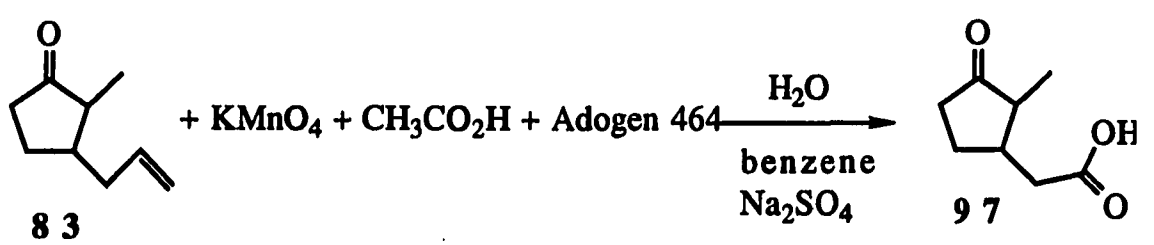


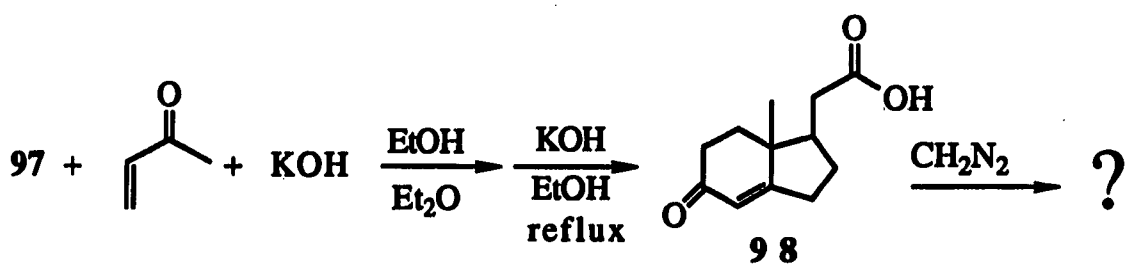


Treatment of **95** with potassium permanganate and dicyclohexyl-18-crown-6[31] failed to produce the desired acid.




Use of the unpurified reaction mixture **95** made determination of results difficult, so further attempts at oxidation were made on **83**. Treatment of **83** with potassium permanganate, acetic acid, and Adogen 464[32] afforded acid **97** in 71-78% yield. Reaction of **97** with MVK and

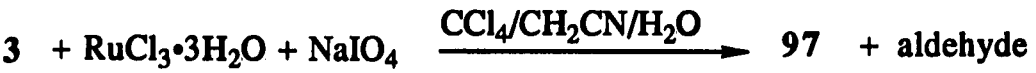




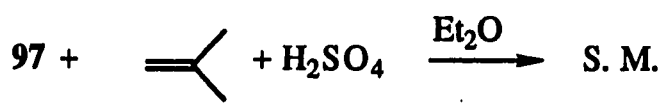

98

potassium hydroxide in $EtOH/Et_2O$ and heating the unpurified reaction mixture with potassium hydroxide in ethanol appeared to yield the enone **98**; however, after reaction of **98** with diazomethane the results were unclear.

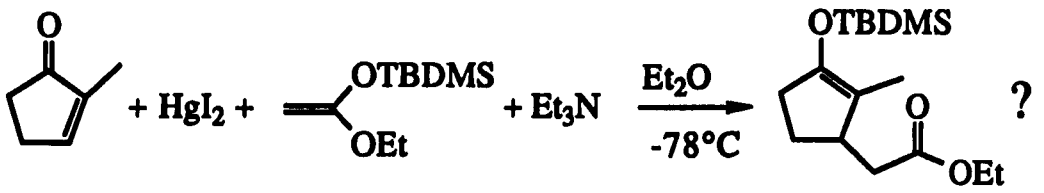
Treatment of **83** with ruthenium(III) chloride trihydrate and sodium periodate[33] afforded **97**, accompanied by a trace of the corresponding aldehyde.




It was hoped that a tert-butyl ester of **97** would cyclize more readily than **97**, and be readily cleaved to the desired acid once cyclization was achieved. Toward that end, **97** was treated with isobutylene and sulfuric acid in ether. Unfortunately, the reaction primarily returned starting material.

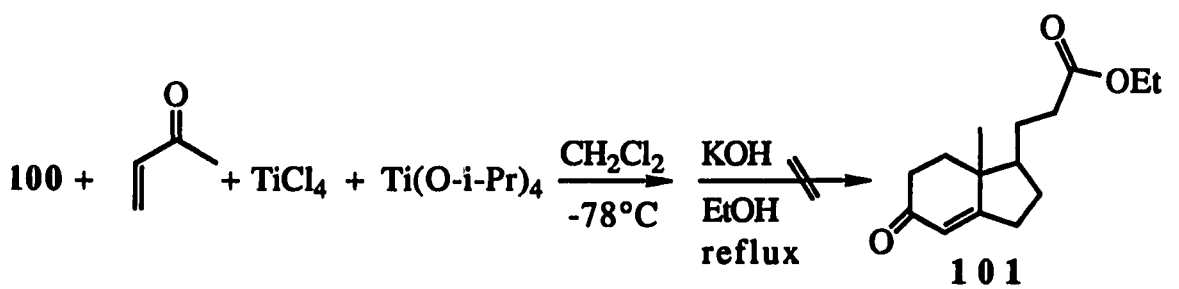


An attempt was also made to react 2-methylcyclopent-2-ene-1-one with the tert-butyldimethylsilyl enol ether of ethyl acetate in the presence of mercury(II) iodide and triethylamine.[34] While the starting material was consumed, the product was not clean and defied



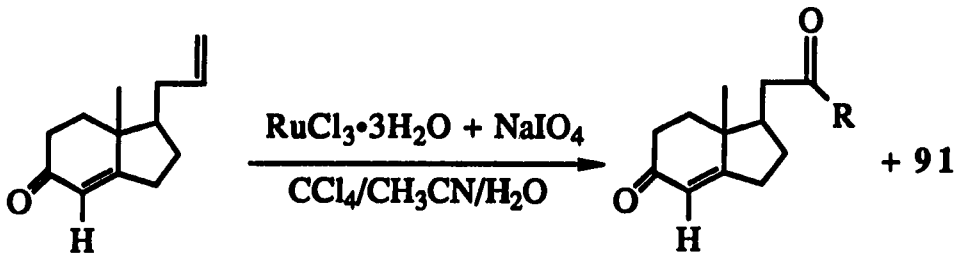

**100**

purification by chromatography. An attempt to couple **100** with MVK using titanium(IV) chloride and titanium(IV) isopropoxide[27] gave an unclear result. Attempted cyclization of the unpurified reaction mixture did not afford the desired bicyclic compound.




**101**

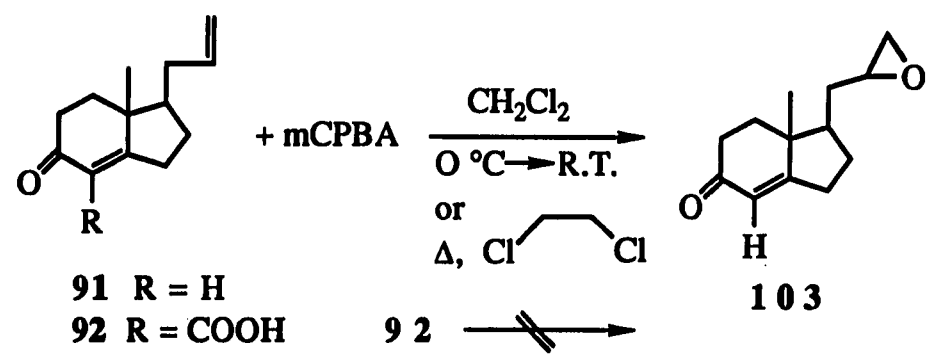
At this point, a return to the bicyclic intermediate seemed prudent. Treatment of **92** with ruthenium(III) chloride and sodium periodate afforded a mixture of starting material, aldehyde, and acid, as determined by infrared spectra and proton NMR.




**91**

**102** R = H
**98** R = OH

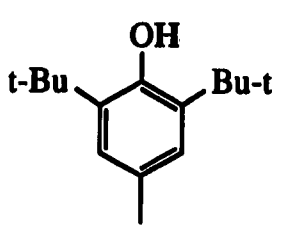
A sidechain epoxide appeared to be a desirable intermediate. With the hope that epoxidation would occur preferentially at the more electron rich double bond, **91** was treated with *m*-chloroperoxybenzoic acid to yield epoxide **103** in 28-30%. Addition of butylated hydroxytoluene (BHT, **104**) to the reaction mixture as a radical inhibitor and raising the temperature increased yields to 38%. Use of the sulfide inhibitor **105**[35] and higher temperatures increased yields to 42%.



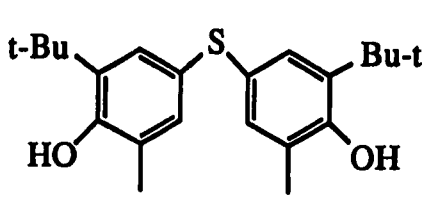

**91** R = H
**92** R = COOH

**92**

**103**



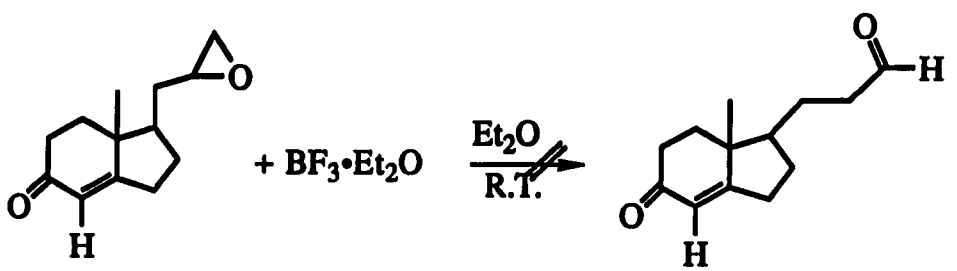
**104**



**105**

An attempt to epoxidize acid **92** was not satisfactory.

Various methods were employed in an effort to open the epoxide ring. Treatment of **103** with boron trifluoride etherate[36] did not give a clear result. Aluminum trichloride in dioxane[37] did effect opening to




**103** **106**

**103** + $AlCl_3$ or $Et_2AlCl$ → (1. dioxane; 2. HCl; R.T. or ~12 °C) → **106** (minor)

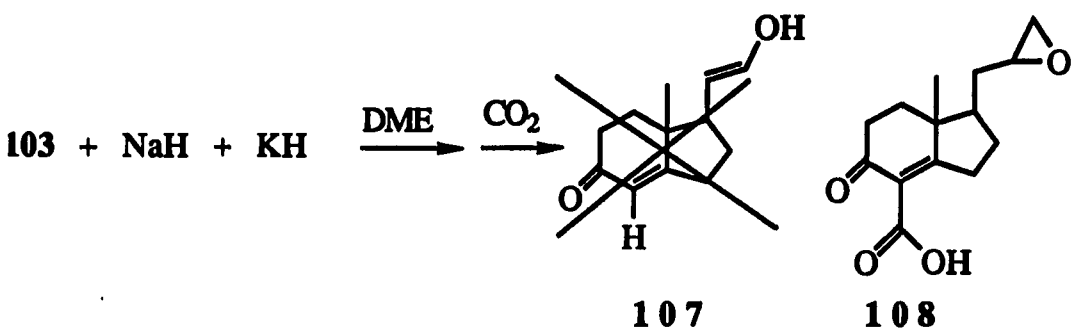
**103** + $Et_2AlCl$ → (1. $CH_2Cl_2$; 2. $NaHCO_3$; -78 °C → 0 °C; 0 °C → R.T.) → **106**

**103** + $AlCl_3$ → (1. $CH_2Cl_2$; 2. HCl) → **106** (trace)

the aldehyde, as did diethylaluminum chloride in dioxane. The latter afforded better yields. Diethylaluminum chloride in dichloromethane with an aqueous sodium bicarbonate quench[38] failed to produce the aldehyde at temperatures from -78 °C to room temperature. Aluminum

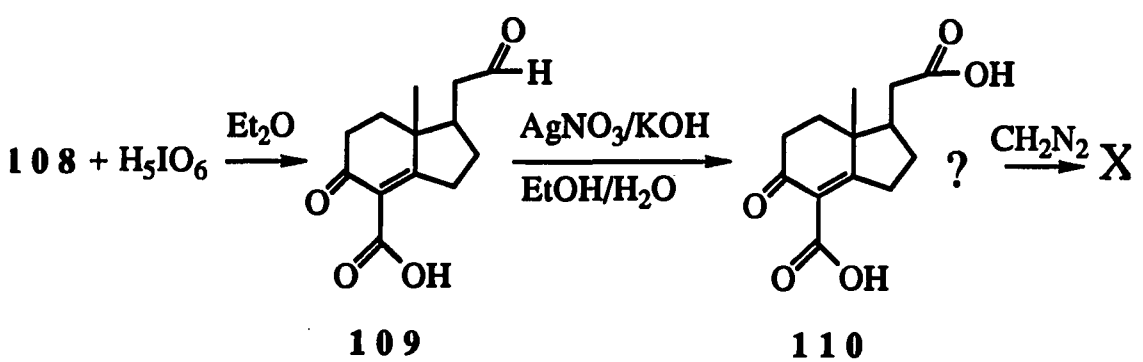
trichloride in dichloromethane with an acidic aqueous workup yielded only a trace of the desired aldehyde.

Epoxide **103** was next treated with sodium hydride, catalytic potassium hydride, and carbon dioxide in the hopes that the epoxide would open, either during the reaction or during the basic workup.




**107** **108**

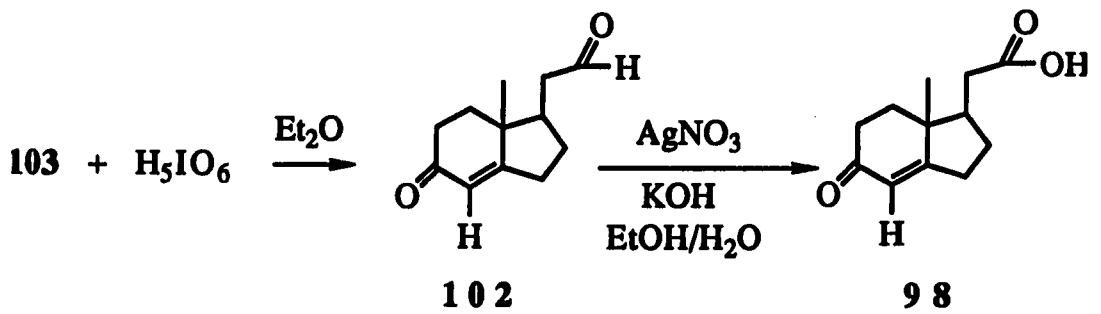
While the epoxide did not open to form **107**, acid **108** was produced in 66% yield. Treatment of **108** with periodic acid[39] afforded an aldehyde.




**109** **110**

The product of silver oxide oxidation of **109** was difficult to identify by proton NMR, but treatment of the unpurified reaction mixture with diazomethane showed it to be several products with none dominant.

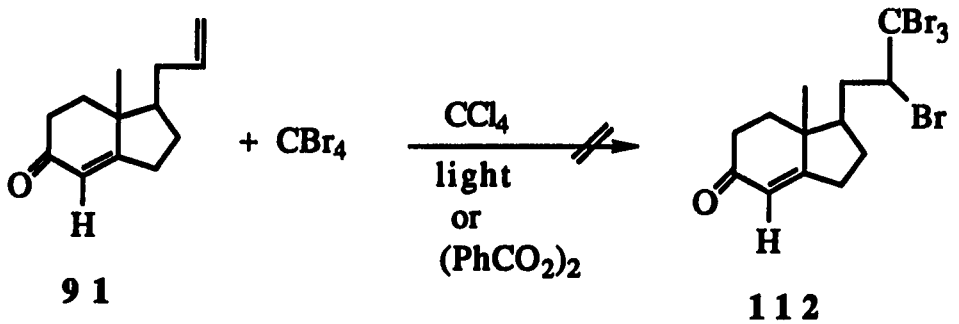
Treatment of **103** with periodic acid[39] afforded aldehyde **102**. An attempt to purify **102** by chromatography failed and the material began to decompose when concentrated in vacuo. Treatment of **102** with silver oxide initially gave unclear results, but acid **98** was




**102** **98**

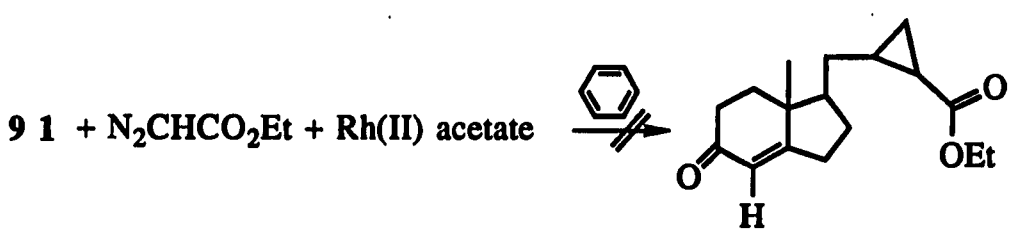
produced when the reaction was repeated on a larger scale. A sample of **98** was sent for biological testing to determine whether its short side chain had an effect on biological activity. The test results were inconclusive.

Further modifications of the side chain were sought. Attempts to add carbon tetrabromide to olefin **91** using light or benzoyl peroxide and heat[40] failed. Treatment of **91** with ethyl diazoacetate[41]



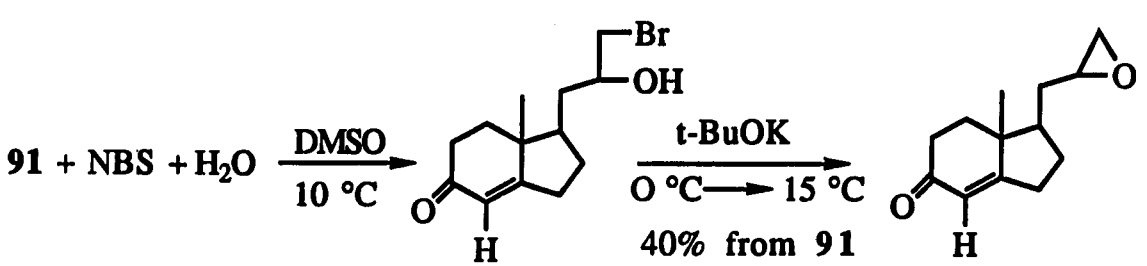

**91** **112**

produced only small amounts of a possible ester along with returned starting material and several other products. Compound **91** reacted

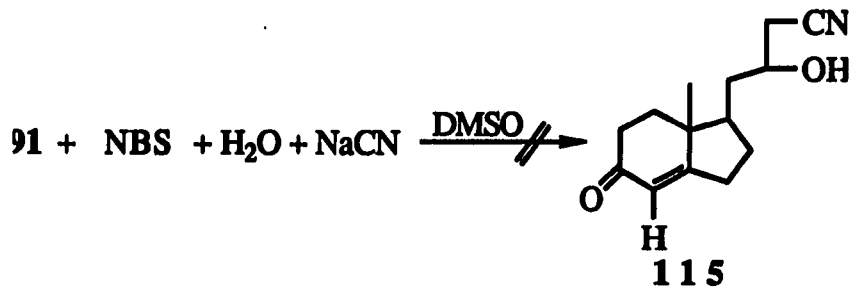



**113**

with N-bromosuccinimide and water[42] to produce bromohydrin **114**, which in turn produced epoxide **103** in 40% yield over the two steps.



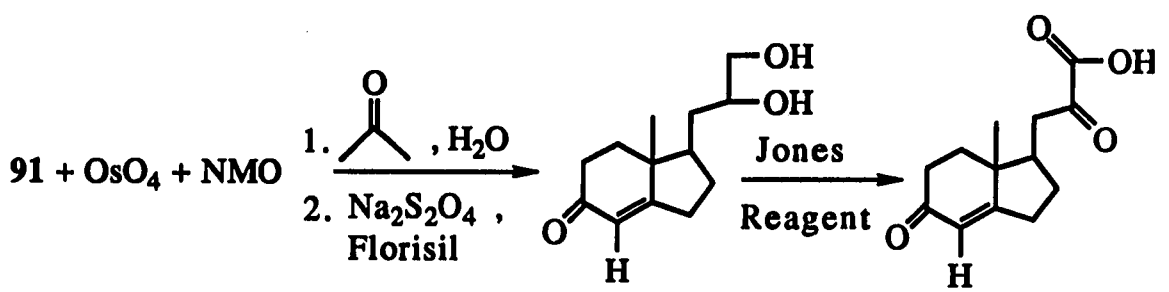

**103**




115

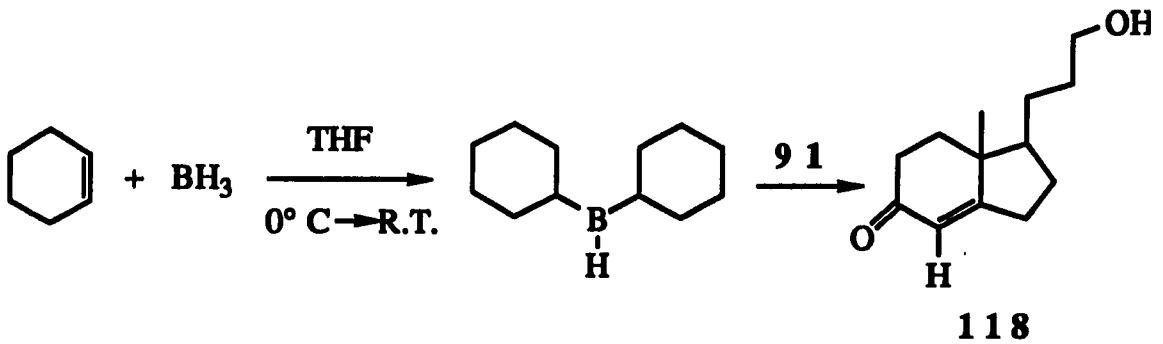
An attempt to use this method to produce the hydroxy nitrile failed, affording instead the bromohydrin and the epoxide.

Osmylation[43] of **91** afforded diol **116** in 76-85% yield. Oxidation of the diol with the Jones' reagent produced the $\alpha$-ketoacid **117**.

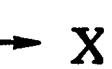



116 117

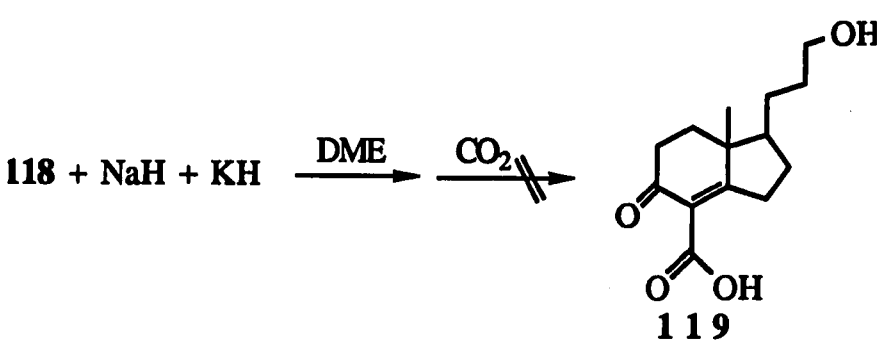
Selective hydroborations were next examined. Treatment with dicyclohexylborane (prepared *in situ*)[44] afforded the desired alcohol **118** in 63-79% yield. 9-Borabicyclo[3.3.1]nonane (9-BBN)[45] failed to produce **118** from **91**.



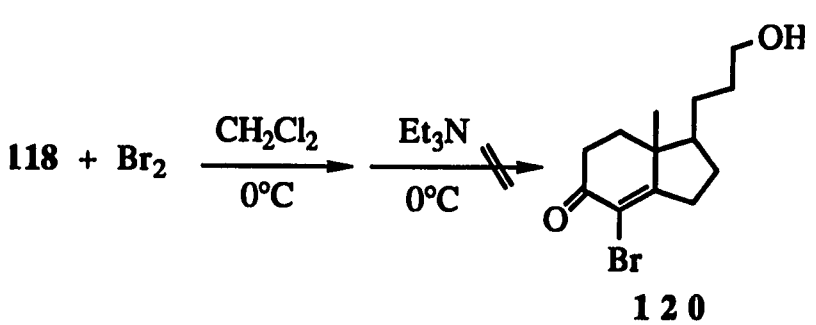

118




An attempt to produce α,β-unsaturated acid **119** from **118** · failed, as did an attempt to produce bromide **120**.

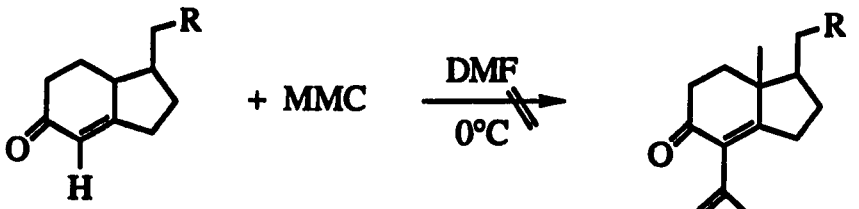



119




120

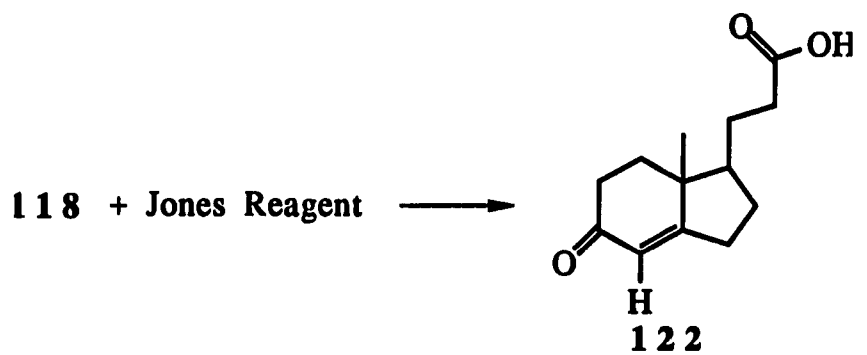
Treatment of **118** or its precursor **91** with methyl methoxy-magnesium carbonate[46] did not yield the desired acid **121**.



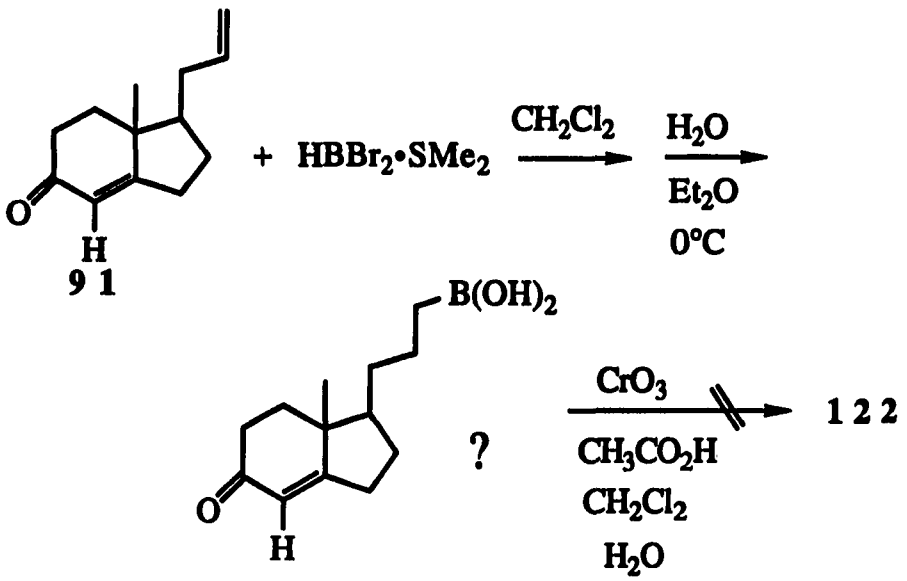

**91**: R = C≡C
**118**: R = $CH_2CH_2OH$

**121**

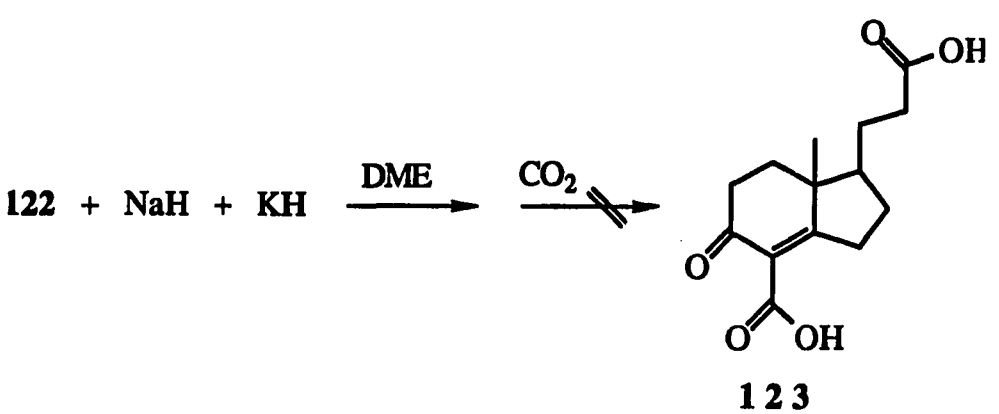
Oxidation of **118** with Jones' reagent produced acid **122** in excellent yield. A sample of **122** was sent for biological testing, with inconclusive results. An attempt to produce **122** from the olefin[47] via a boronic acid[48] was not successful.

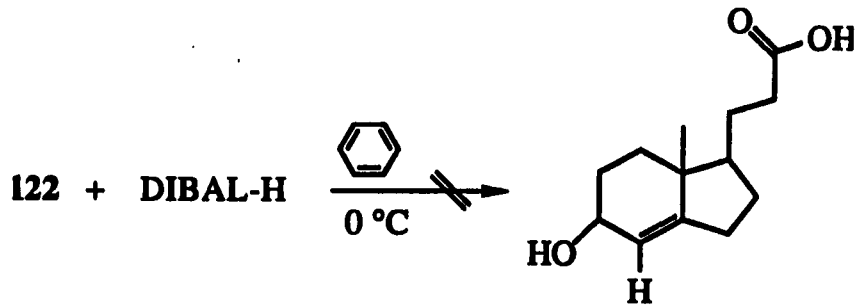



**122**



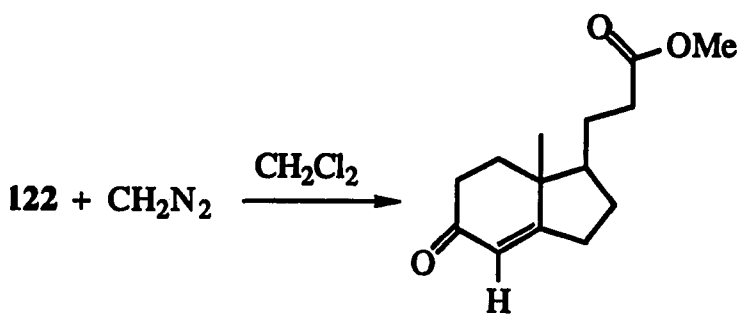

As with **118**, the α,β-unsaturated acid was not formed when **122** was treated with base and $CO_2$. An attempt to reduce the enone to the alcohol with diisobutylaluminum hydride (DIBAL-H)[49] also failed.






124

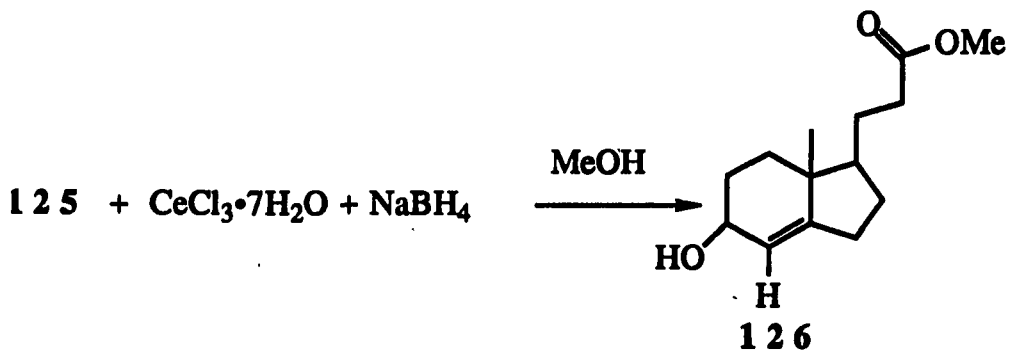
To help confirm the identity of **122**, its methyl ester **125** was prepared using diazomethane. Due to its superior solubility




125

properties and greater ease of handling compared to the acid, it was seen as a valuable intermediate for further analog synthesis. The ester could be hydrolyzed after the desired compounds were made.

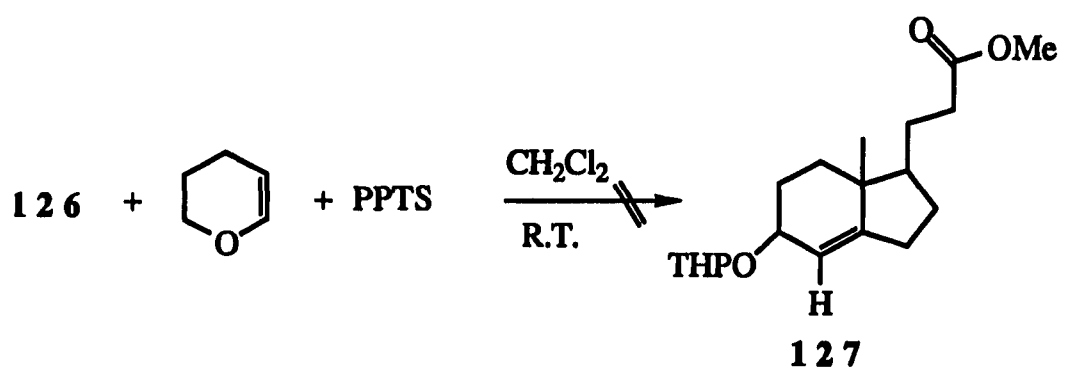
Enol ethers of **125** were seen as potential analogs. Toward that end both **122** and **125** were treated with cerium trichloride heptahydrate and sodium borohyride in methanol.[50] While




**126**

the acid produced an unsatisfactory product mixture, the ester afforded good yields of the alcohol after purification.

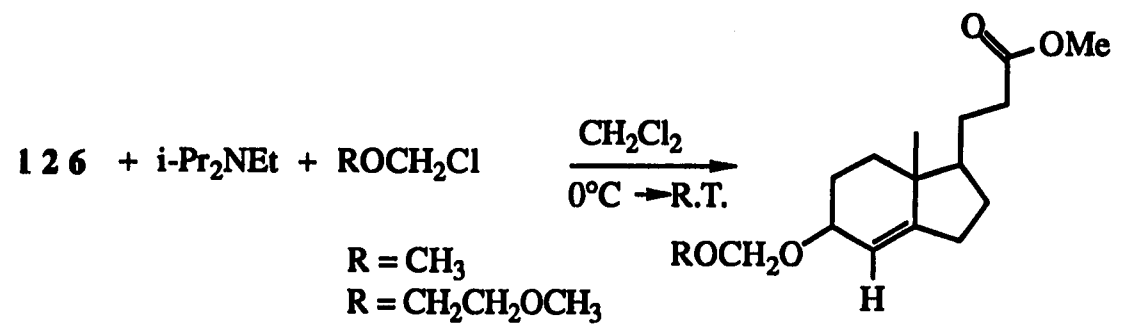
Using an oxygen, rather than a methylene, to link the analog AB and C rings did not seem significant, and a tetrahydropyranyl ether seemed a good starting approximation of the glycinoeclepin A A ring.




**127**

Treatment of **126** with dihydropyran and pyridinium-p-toluenesulfonate (PPTS)[51] unfortunately did not produce the desired ether **127**.

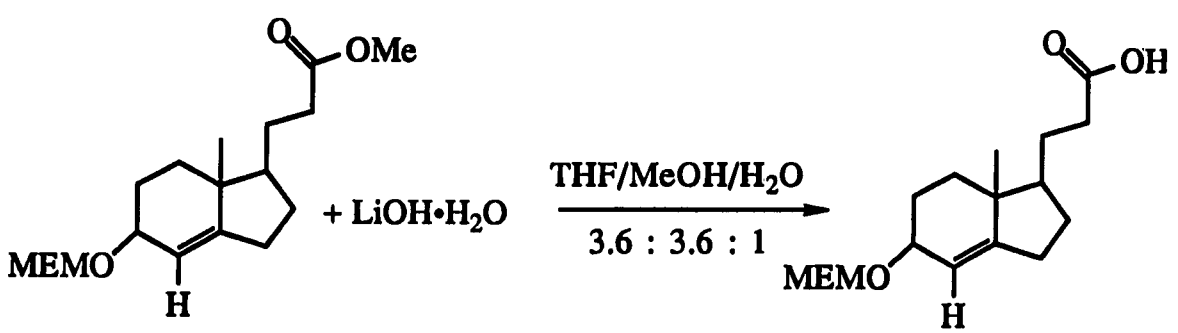
Hoping to introduce further oxygen functionality for an analog, **126** was treated with diisopropylethylamine and chloromethyl methyl ether to afford ether **128** in good yields. The methoxy ethyl ether




**128** R =$CH_3$
**129** R = $CH_2CH_2OCH_3$

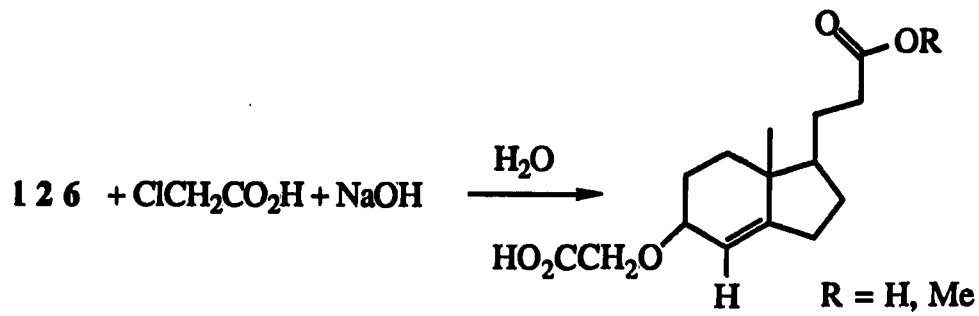
was produced similarly in excellent yield, and contained an additional oxygen to help create a "host" area for an analog.

Hydrolysis of **129** with lithium hydroxide afforded acid **130** on a small scale.



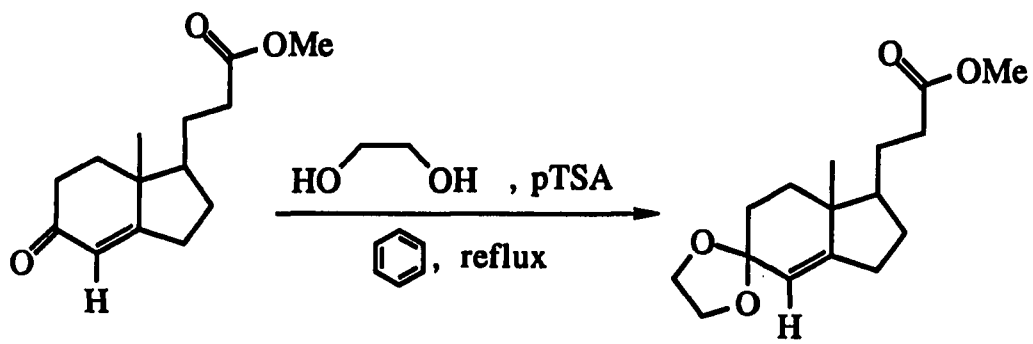

**129** **130**

Treatment of **126** with sodium hydroxide and chloroacetic acid[52] in water was initially promising, with possible hydrolysis of the ester, but this avenue was not further pursued, as more promising routes were found.




**131**

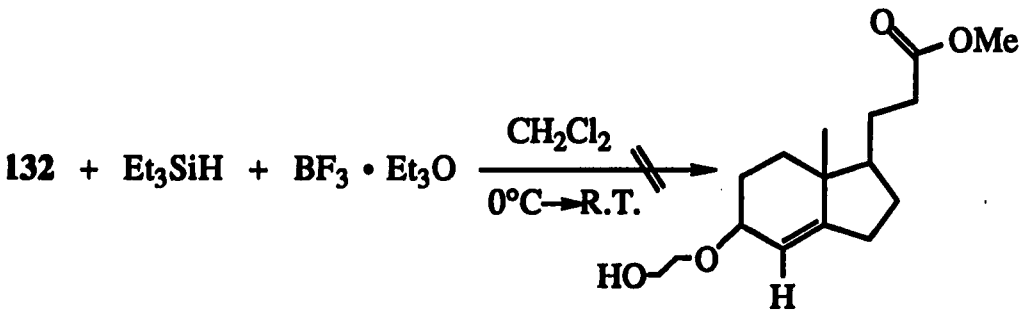
At this point, attention was once again focused on the enone. Treatment of **125** with ethylene glycol and PTSA produced ketal **132** in



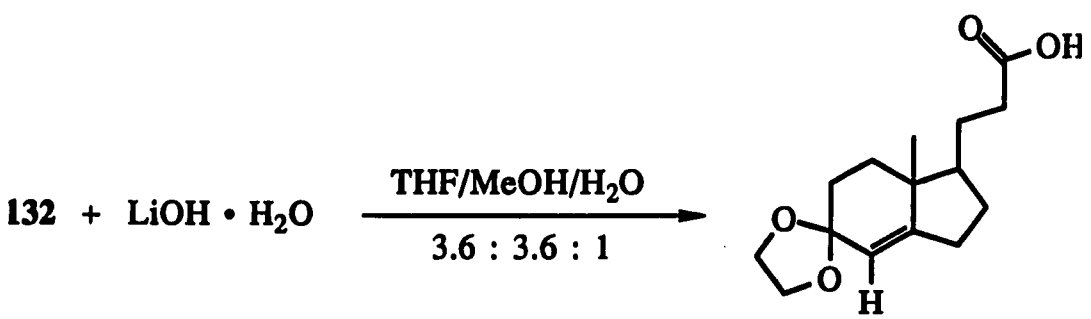

**125** **132**

47% yield. While reaction of **132** with triethylsilane and boron trifluoride etherate failed to open the ketal, hydrolysis of the ester with

lithium hydroxide afforded acid **134**, which was sent for biological testing. The test results were inconclusive.

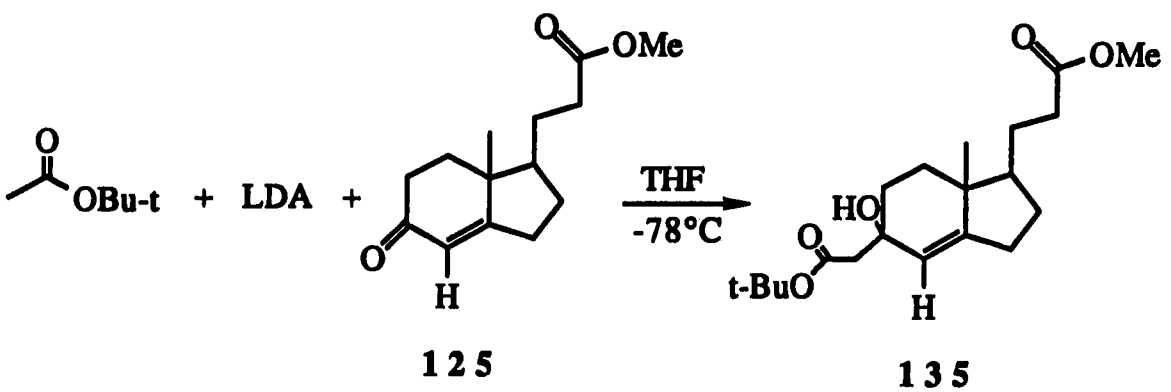



**133**

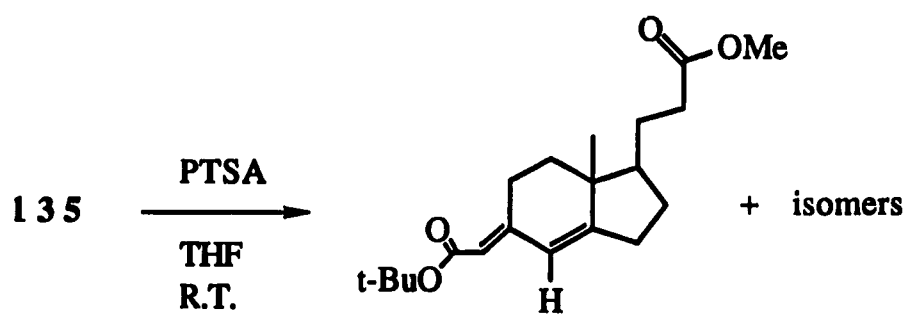



**134**

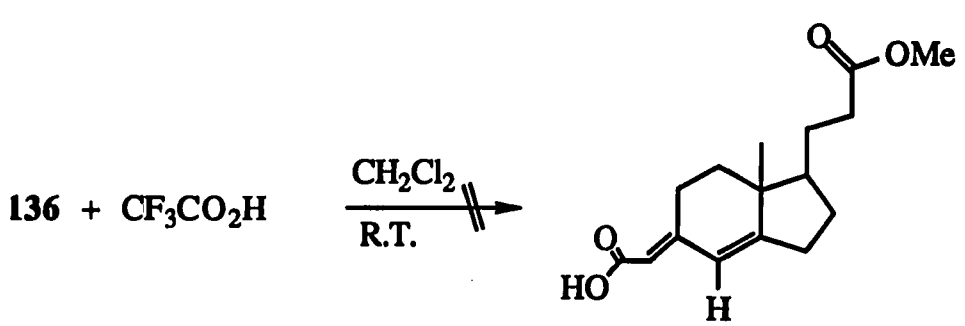
Lithio tert-butylacetate reacted with **125** to produce alcohol **135**, which underwent elimination to yield unsaturated ester **136** plus isomers with acid catalysis. Unfortunately, cleavage of the tert-butyl ester proved difficult. Both trifluoroacetic acid[53] and iodotrimethylsilane[54] failed to produce the desired acid **137** cleanly.



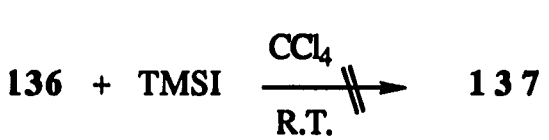

125 135



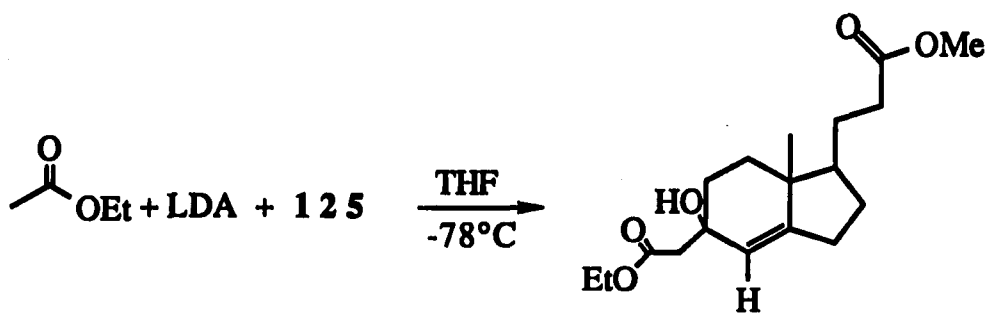

136



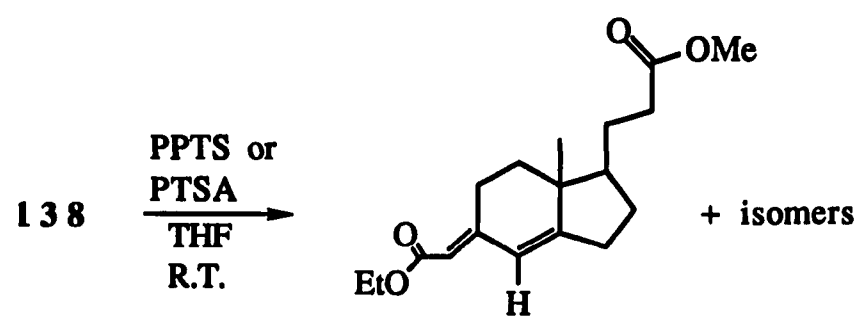

137



Lithio ethylacetate also reacted with **125** to produce an alcohol, which afforded the unsaturated ester and its isomers with PTSA or

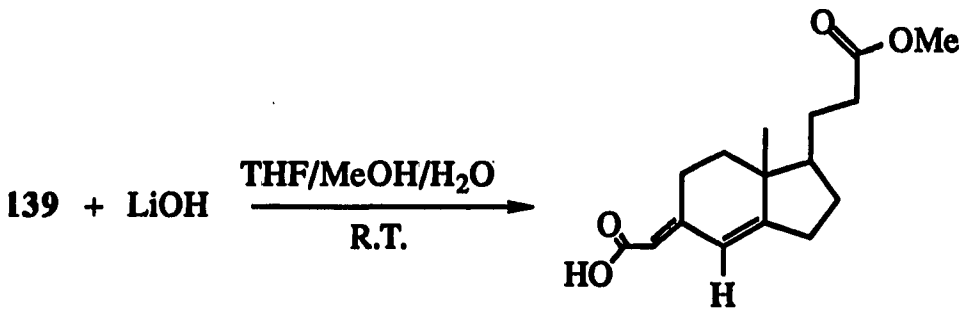



**138**

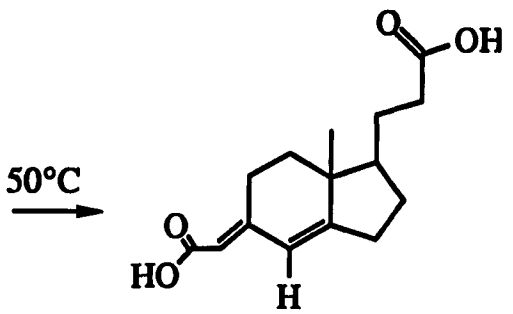



**139**

PPTS. The initial attempt to hydrolyze **139** with lithium hydroxide succeeded only in cleaving the ethyl ester. At 50 °C, the desired diacid was produced.

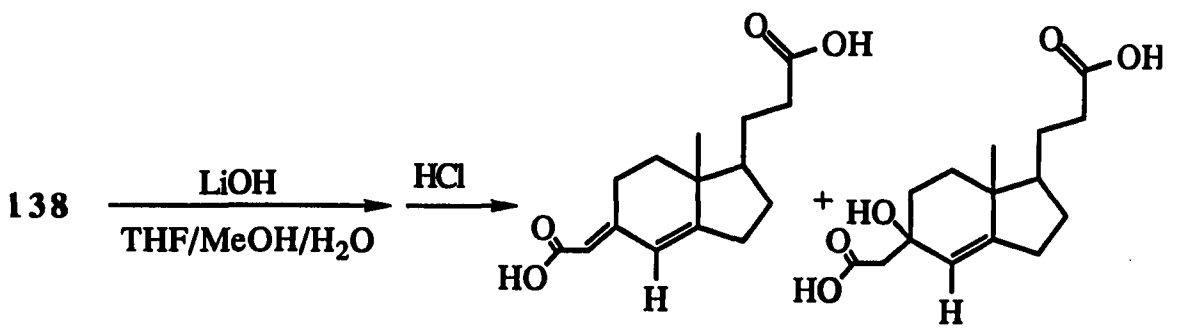



140



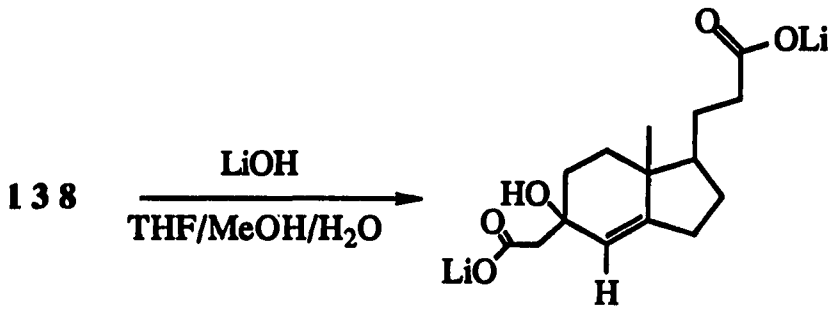

141

The hydroxy diacid was desired as an analog. Treatment of **138** with lithium hydroxide over several days served to cleave the esters, but some elimination occurred during the acidic workup. In order to avoid this problem, the reaction was repeated, the reaction mixture



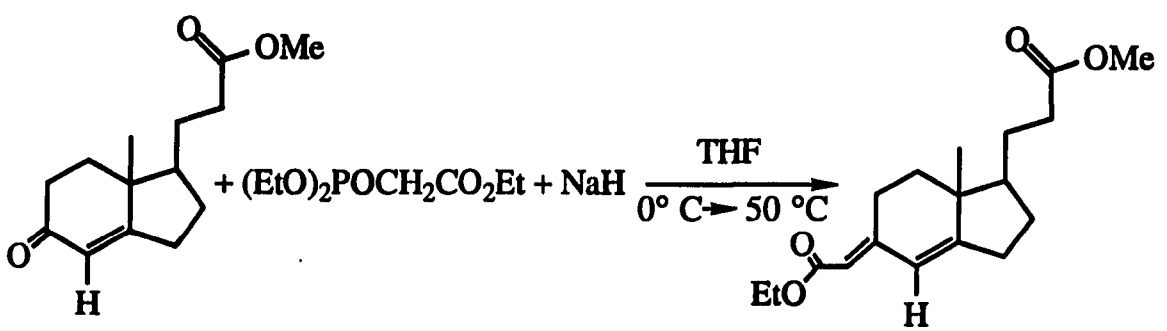

142 + isomers 143

neutralized, and the solvents removed. The salt **144** was sent for biological testing, with inconclusive results.




**144**

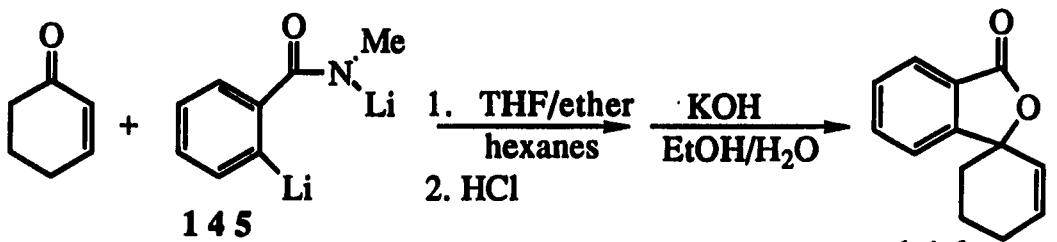
A Horner-Emmons reaction between **125** and triethyl-phosphonoacetate led to **139**, but in lower yield than the route described above. Trimethylphosphonoacetate showed little promise.




**125** **139**

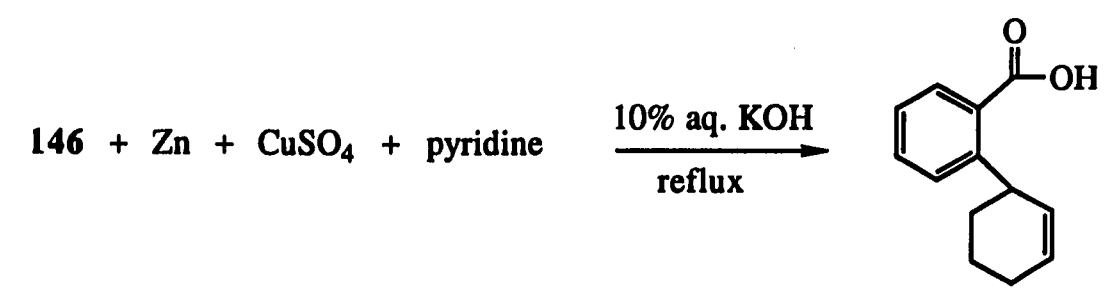
An effort was then made to produce analogs with better representations of the AB ring system. Dilithio-N-methylbenzamide was known to react with some carbonyl compounds. Phthalides could be produced from these initial adducts.[55] Armed with this knowledge,

a model system was studied. Reaction of cyclohexenone with dilithio-N-methylbenzamide (prepared *in situ*) followed by treatment of the unpurified adduct with potassium hydroxide in boiling aqueous ethanol produced phthalide **146** in moderate yield.



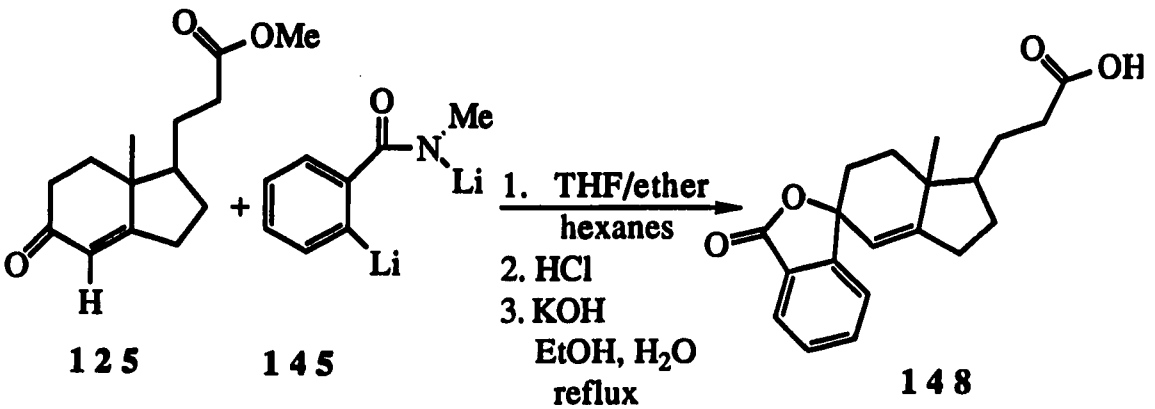

**145** **146**

With the phthalide in hand, numerous attempts were made to open it to the corresponding acid. Treatment of **146** with PTSA, boron trifluoride etherate, trifluoroacetic acid, lithium hydroxide, or activated zinc in aqueous formic acid[56] returned starting material. Treatment with iodotrimethylsilane[54] was not promising. Reaction with activated zinc, catalytic copper(II) sulfate, and pyridine in boiling aqueous potassium hydroxide[56] did produce an acid of undetermined purity.

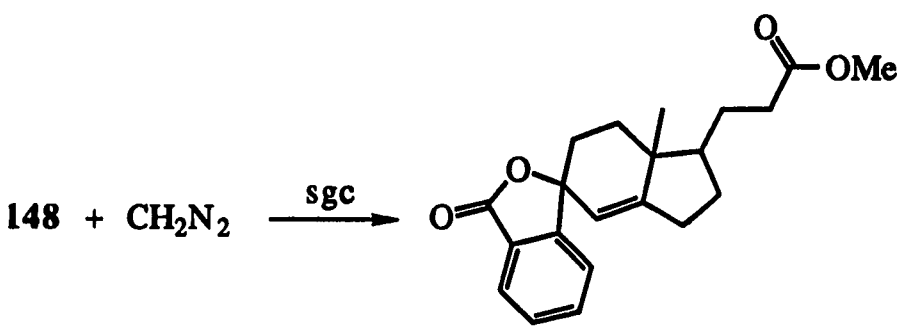



**147**

Treatment of the analog precursor **125** with dilithio-N-methylbenzamide as in the model system was tentatively promising, although the methyl ester appeared to be cleaved during the KOH step. Re-




**125** **145** **148**

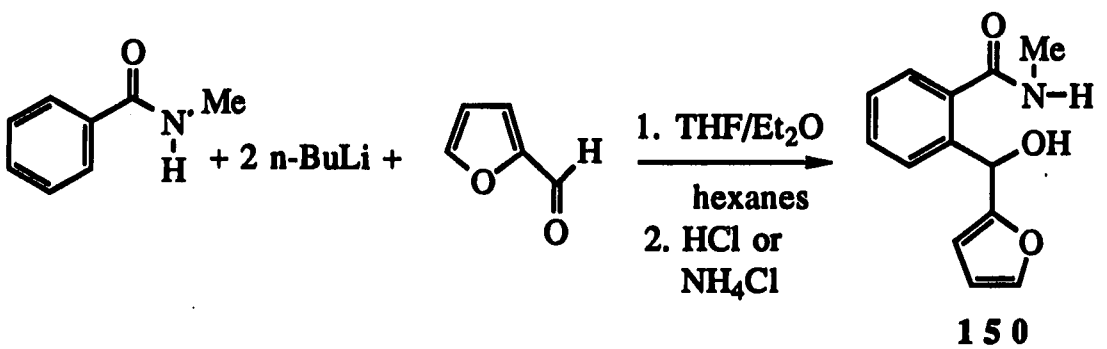



**149** < 20%

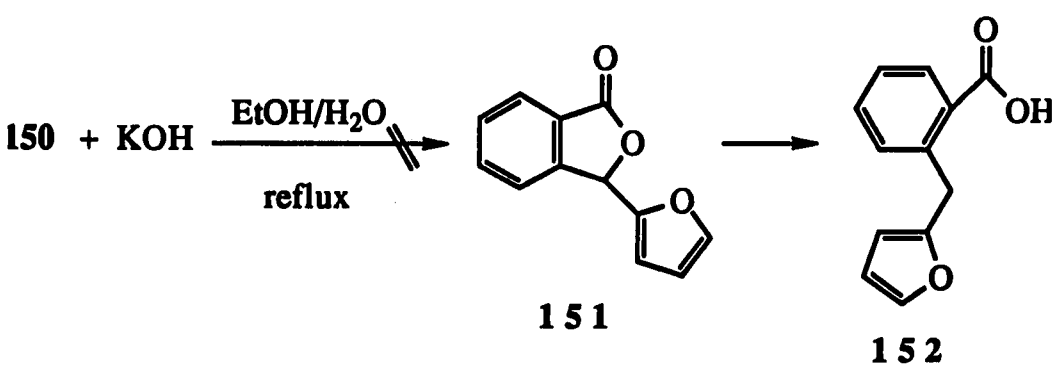
formation of the ester with diazomethane allowed for purification. This delivered what appeared to be the desired phthalide, but in low yield. At this point, this route was abandoned to seek more promising ones.

Treatment of N-methylbenzamide with two equivalents of n-butyllithium and 2-furaldehyde afforded alcohol **150**. It was hoped that **150** could be cyclized to the phthalide and later opened to yield

the desired acid **152**. Unfortunately, reaction of **150** with potassium hydroxide in boiling aqueous ethanol failed to yield the phthalide **151**.

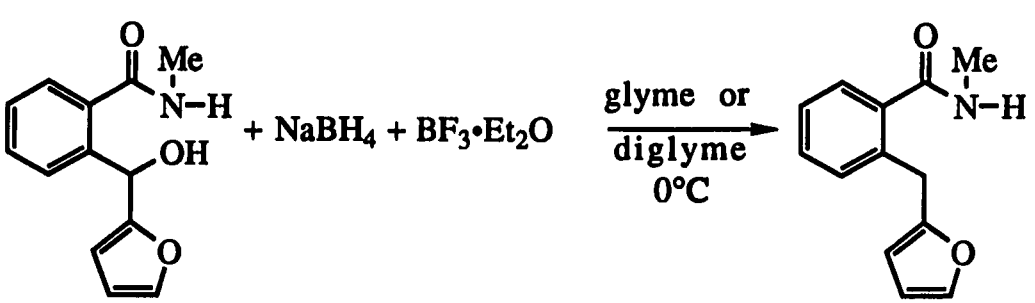



**150**




**151** **152**

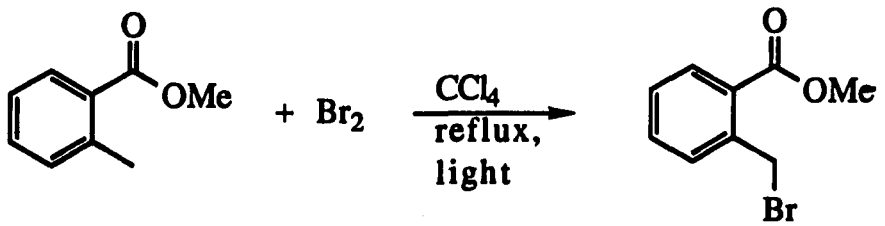
An attempt was then made to remove the hydroxyl functionality to produce an amide which could be converted to an acid. Treatment of




**150** **153**

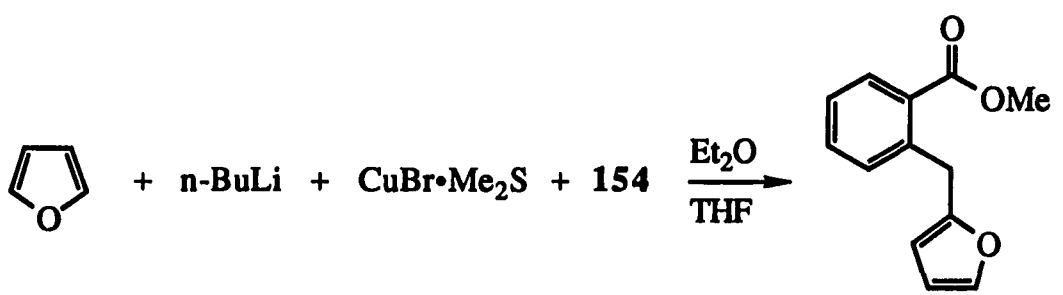
**150** with sodium borohydride and boron trifluoride etherate in glyme or diglyme[57] failed to completely remove the hydroxyl functionality. Flash silica gel chromatography yielded a small amount of the desired product. A different route to **152** was then sought.

Treatment of methyl-*o*-toluate (prepared from *o*-toluic acid and methanol) with bromine and sunlamp irradiation[58] afforded bromide **154** in good yield. Although some starting material remained, the

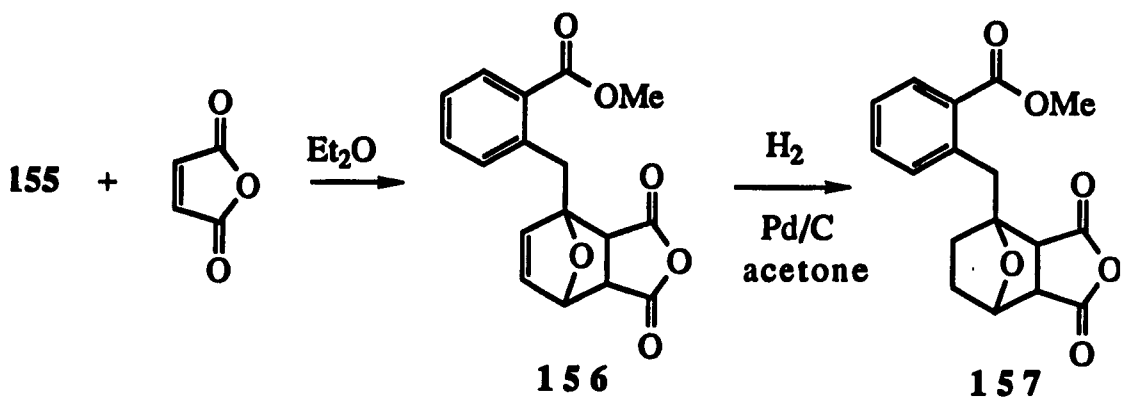



**154**

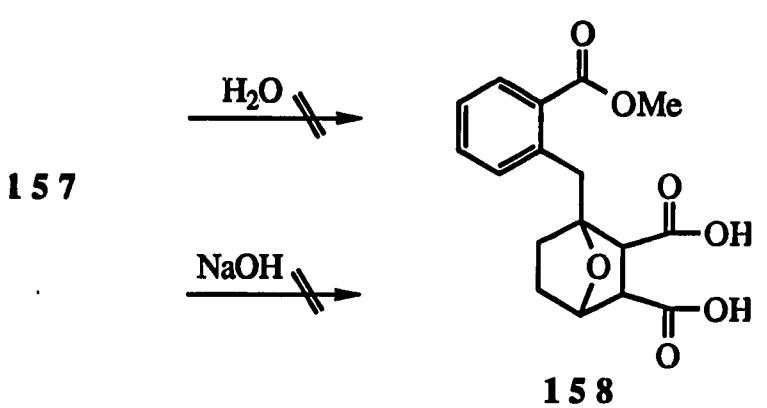
product was pure enough to carry on. Treatment of **154** with difuryl-cuprate[58] yielded furan **155** in 28-49% yield after chromatography. Compound **155** underwent a Diels-Alder[59] reaction with maleic



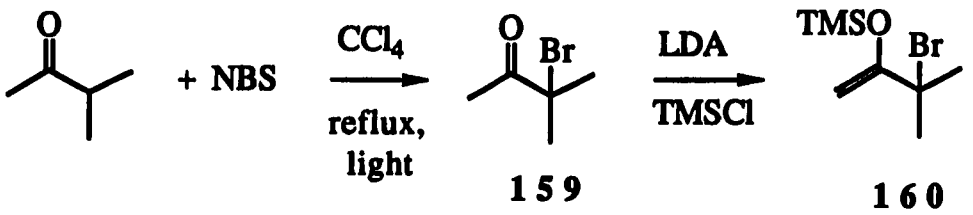

**155**



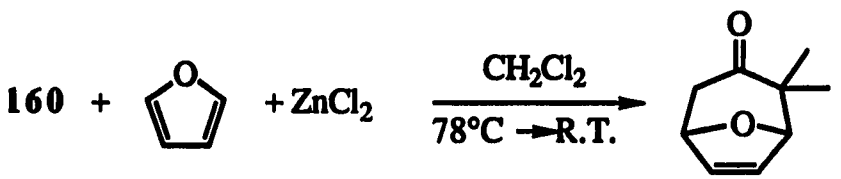

anhydride to afford adduct **156** in moderate yield. Hydrogenation of the adduct produced anhydride **157**. Treatment of **157** with water did not appear to produce the desired diacid. Reaction with sodium hydroxide decomposed the starting material. As a more promising route was found, this one was abandoned.




A [4+3] cycloaddition to furan **155** was next explored. Bromination of 3-methyl-2-butanone[60] afforded bromide **159** in good yield. In a model system, the enol silyl ether of **159** reacted with furan and zinc chloride to produce the cyclized compound **161**.[61] After this



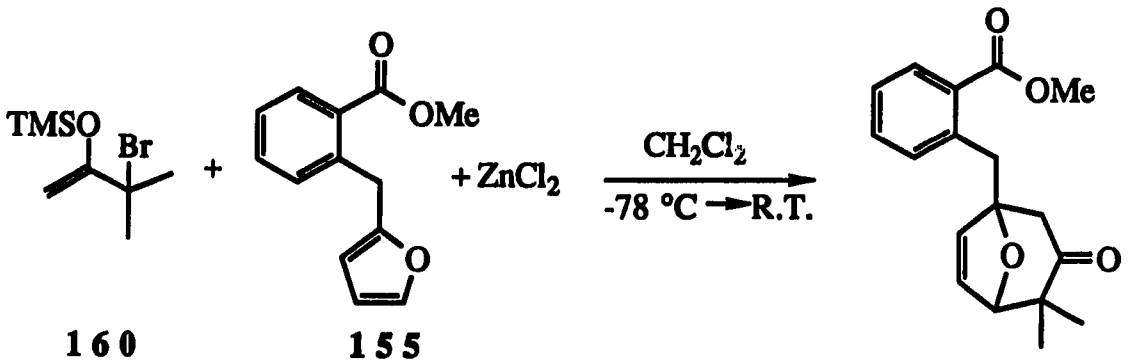

159 160




161

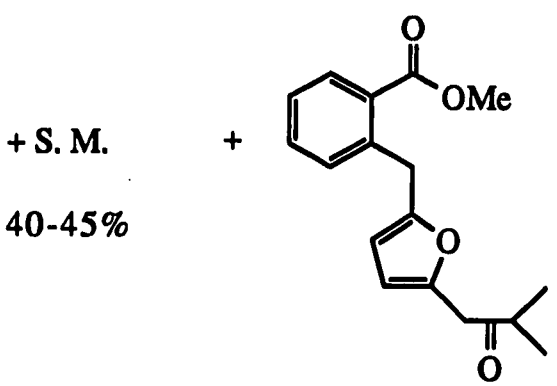
positive result, **155** and **160** were combined in the presence of zinc chloride. Chromatography of the reaction mixture yielded starting material, the desired cycloadduct **162**, and an uncyclized addition product **163**. Boron trifluoride etherate did not effect cyclization when used in place of zinc chloride.

Hydrolysis of **162** with lithium hydroxide required several days at room temperature and did not reach completion. However, the acid was produced in 81-84% yield, and was submitted for biological testing. Acid **164** has not yet been tested.

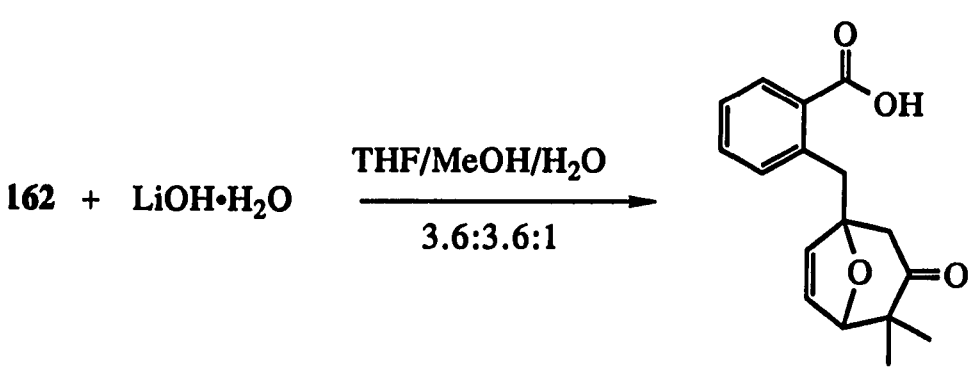



160 155

13-20% 162




15-16% 163




164

# CONCLUSION

Several analogs of glycinoeclepin A were synthesized and submitted for testing of their hatch-stimulating ability. The analogs possessed a variety of the functional groups found in glycinoeclepin A and were constructed using a variety of synthetic methods. While only one of the analogs tested to date (compound **68**) has shown any activity, this information is valuable in the determination of which functionalities are critical for stimulation of soybean cyst nematode hatching.

# EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or dried in a 150°C oven for 12 h and cooled under a stream of nitrogen or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography 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. The abbreviation sg represents silica gel. 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 Nicolet Magnetics Corporation NT-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), ABq (AB quartet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR spectra were obtained on a Varian Associates VXR-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). High resolution

mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was determined to be >90% by 300 MHz proton NMR and/or elemental analysis.

**Ethyl 2-[(ethoxycarbonyl)methylene]-1-methyl-6-oxocyclohexane propionate (48):** To a stirred suspension of NaH (1.27 g of a 60% mull in mineral oil, 31.8 mmol,washed three times with hexanes and dried with $N_2$) in 64 mL dry THF at 0 °C under $N_2$ was added dropwise triethylphosphonoacetate (7.13 g, 31.8 mmol) in 25 mL THF . After 45 min at 0 °C, dione **45**[14] (6.00 g, 26.5 mmol) in 27 mL THF was added dropwise. The mixture was allowed to warm to room temperature with stirring, then heated to 50 °C in an oil bath. The reaction was monitored by TLC. When starting material was still present after two days, the mixture was heated to reflux and stirred for three h. The mixture was cooled to room temperature, 200 mL water was added, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by sg chromatography using 3:1 H:EA to yield **48** (5.93 g, 76%) as a pale oil. (Large quantities of **48** were purified by high vacuum distillation, collecting the material distilling from 137 °C to 150 °C at 30-33 μm Hg.)

**48**: $^1$H NMR ($CDCl_3$) δ 1.25 (d, J = 0.6 Hz, 3H), 1.22-1.32 (m, 6H), 1.61-1.79 (m, 1H), 1.85-2.09 (m, 2H), 2.13-2.35 (m, 3H), 2.39-2.71 (m, 3H), 3.65 (dt, J = 13.8, 4.5 Hz, 1H), 4.07-4.20 (m, 4H), 5.75 (s, 1H); IR (Neat) 2975, 2935, 2900, 2870, 1720 (Broad), 1630 cm$^{-1}$; MS (CI-$NH_3$) *m/e* 297 (M+H), 314 (M+$NH_4$); TLC (3:1 H:EA) $R_F$ = 0.38.

**General Procedure for Ketalization:** A mixture of the ketone (1 equiv), ethylene glycol (2 equiv), and PTSA (0.12 equiv) in dry benzene (0.14 M in the ketone) was heated to reflux in dry benzene under nitrogen in a flask fitted with a Dean-Stark trap and a reflux condenser. Reflux was maintained until TLC indicated the reaction to be complete. If necessary, activated molecular sieves and/or additional PTSA was added to the reaction flask to drive the reaction to completion. The reaction mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$, water, and brine, dried over $Na_2SO_4$, and concentrated in vacuo. The crude product was purified by sg chromatography using H:EA.

**Ethyl 2-[(ethoxycarbonyl)methylene]-6,6-(ethylenedioxy)-1-methylcyclohexane propionate (49)**: $^1$H NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.49 (dt, J = 13.2, 4.2 Hz, 1H), 1.60-1.72 (m, 2H), 1.72-1.85 (m, 1H), 1.86-2.05 (m, 4H), 2.11-2.22 (m, 2H), 3.83-4.00 (m, 4H), 4.05-4.17 (m, 4H), 5.66 (s, 1H); IR (Neat) 2975, 2950, 2880, 1730, 1715, 1635 cm$^{-1}$; MS (CI-$NH_3$) *m/e* 295, 317, 334, 341 (M+H), 358 (M+$NH_4$); TLC (3:1 H:EA) $R_F$ = 0.41.

**1',2',3',6',7',7'a-Hexahydro-1-[3-(hydroxycarbonyl) ethyl]-7'a-methyl-spiro[1,3-dioxolane-2,5'-[5H]indene] (132):** $^1$H NMR ($CDCl_3$) δ 0.91 and 1.12 (s, 3 H), 1.28-2.03 (m, 9 H), 2.21-2.40 (m, 4 H), 3.67 (s, 3 H), 3.88-3.98 (m, 4 H), 5.26 and 5.31 (br s, 1 H); IR (Neat) 2950, 2880, 1735; TLC (5:1 H:EA) $R_F$ = 0.26.

**Ethyl 2-[(ethoxycarbonyl)methylene]-6-(2-hydroxy-ethoxy)-1-methylcyclohexane propionate (53):** To a solution of **49** (9.57 g, 28.1 mmol) in 100 mL dry methylene chloride at 0 °C under nitrogen was added triethylsilane (4.90 g, 42.2 mmol) dropwise. $BF_3$•$Et_2O$ was then added dropwise and the solution allowed to stir while warming to room temperature overnight. TLC indicated that starting material remained; thus 50% more triethylsilane was added, the mixture cooled to 0 °C, 50% more $BF_3$•$Et_2O$ was added, and the mixture was stirred at room temperature and monitored by TLC. After four h, the mixture was heated to reflux and again monitored by TLC. After five h at reflux, heating was ceased and the mixture stirred while cooling to room temperature overnight. TLC then indicated the reaction to be essentially complete. The mixture was washed with 70 mL saturated aqueous $NaHCO_3$, 500 mL ether was added, the organics washed with 100 mL saturated aqueous $NaHCO_3$ and 100 mL brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification of the crude alcohol by flash sg chromatography (3:1 H:EA) afforded **53** (7.45 g, 77%) as a pale oil: $^1$H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3H), 1.59-2.26 (m, 9H), 3.01 (dd, J = 4.4, 10.7 Hz, 1H), 3.38-

3.43 (m, 1H), 3.57-3.73 (m, 4H), 4.07-4.18 (m, 4H), 5.69 (s, 1H); IR (Neat) 3480 (broad), 2980, 2935, 2865, 1730, 1715, 1630 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 360 ($M+NH_4$); TLC (1:1 H:EA) $R_F$ = 0.36.

**Ethyl 2-[(ethoxycarbonyl)methylene]-6-(2-hydroxyethoxy)-1-methylcyclohexane propionate (67b):** To a solution of DMSO (0.66g, 8.41 mmol) in 21 mL dry methylene chloride at -78 °C under $N_2$ was added dropwise oxalyl chloride ( 0.80 g, 6.31 mmol). After 10 min at -78 °C, **53** ( 1.44 g, 4.21 mmole) in 4.2 mL dry methylene chloride was added dropwise along with a 1 mL rinse. The mixture was stirred at -78 °C for one h, during which a white precipitate formed. Triethylamine was then added dropwise, the mixture was stirred while warming to 0 °C, and stirred at 0 °C for 10 min. The mixture was then poured into 20 mL saturated aqueous $NH_4Cl$ and 120 mL ether, the organics washed with water and brine, dried over $Na_2SO_4$, and concentrated in vacuo. The crude aldehyde was obtained as a yellow oil in nearly quantitative yield (1.43 g, > 99% crude): $^1H$ NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.22-1.31 (m, 6H), 1.61-2.32 (m, 9H), 3.05 (dd, J = 4.2, 10.8 Hz, 1H), 3.64-3.74 (m, 1H), 3.93-4.18 (m, 6H), 5.71 (s 1H), 9.73 (s, 1H); IR (Neat) 3445 (broad), 2975, 2955, 2865, 1733 (broad), 1710 (broad), 1630 $cm^{-1}$; TLC (1:1 H:EA) $R_F$ = 0.40.

The bis-methyl ester was prepared analogously:

**Methyl 2-[(methoxycarbonyl)methylene]-6-(2-hydroxyethoxy)-1-methylcyclohexane propionate (67a):** $^1H$ NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.63-2.25 (m, 10H), 3.00-3.12 (m, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.94-4.15 (m(ABq?), 2H), 5.72 (s, 1H), 9.73 and 9.73

(s, 1H); IR (Neat) 3450 (broad), 2940, 2860, 1732, 1717, 1642 $cm^{-1}$; TLC (1:1 H:EA) $R_F = 0.40$.

**General Procedure for Silver Oxide Oxidation:** To a 0.2 M solution of the aldehyde (1 equiv) in absolute ethanol or methanol was added dropwise a 4.67 M aqueous solution of silver nitrate (2.33 equiv). A 1.07 M aqueous solution of potassium hydroxide (5.35 equiv) was then added dropwise (a black ppt formed), and the mixture stirred at room temperature for 2.5-4.5 h. When TLC indicated the reaction to be complete, the silver salts were filtered on a fritted funnel and washed with water. The aqueous layer was washed with ether, acidified to pH = 3, and extracted with methylene chloride and ether. The organic layers from the second extraction were dried over $Na_2SO_4$ and concentrated in vacuo.

**2-[(Methoxycarbonyl)methylene]-6-(3-hydroxy-1-oxa-3-oxopropyl)-1-methylcyclohexane propionic acid (68):** Viscous yellow oil which became a pale yellow foam when placed under vacuum for several hours; $^1H$ NMR ($CDCl_3$) $\delta$ 1.21 (s, 3H), 1.65-2.35 (m, 9H), 3.11-3.16 (m, 1H), 3.55-3.65 (m, 1H), 3.70 (s, 3H), 4.04-4.21 (m(ABq?), 2H), 5.72 and 5.73 and 5.76 (br s, 1H); IR ($CDCl_3$) 3400-3000 (-OH), 2970, 2940, 2865, 1720, 1710 (broad), 1630 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 244, 258, 274, 288, 304, 318, 332 ($M+NH_4$), 346 ($M+NH_4$ for residual ethyl ester).

**1,2,3,6,7,7a-Hexahydro-7a-methyl-5-oxo-1-[5H]indene acetic acid (98):** Yellow oil; $^1H$ NMR ($CDCl_3$) $\delta$ 1.06 (s, 3H), 1.20-1.45 (m, 1H), 1.72-1.93 (m, 1H), 1.93-2.21 (m, 1H), 2.21-2.75 (m, 8H), 5.80

and 5.86 (br s, 1H); IR (Neat) 3600-3080 (-OH), 2940, 2920, 1725, 1705, 1660, 1645 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 226 (M+$NH_4$), 243 (M+$NH_4$+$NH_3$), 434 (2M+$NH_4$).

**General Procedure for Lithium Hydroxide Hydrolysis:** To a 0.13 M solution of the ester (1 equiv) in 3.6:3.6:1 THF:MeOH:$H_2O$ at room temperature under $N_2$ was added LiOH•$H_2O$ in one portion. The reaction flask was briefly flushed with $N_2$, and the mixture stirred at room temperature or 50°C until TLC showed the reaction to be complete. The mixture was then cooled to room temperature, concentrated to remove THF and MeOH, the residue taken up in water, the aqueous extracted with ether and methylene chloride, acidified to pH = 3, extracted with ether, the organic layers from the second extraction washed with a small portion of brine, dried over $Na_2SO_4$, and concentrated in vacuo.

**2-[Hydroxycarbonyl)methylene]-1-methyl-6-(3-hydroxy-1-oxa-3-oxopropyl) cyclohexane propionic acid (69):** white foam; $^1H$ NMR (Acetone D-6) δ 1.26 (s, 3H), 1.65-2.30 (m, 9H), 3.22 (dd, J = 4.4, 10.7 Hz, 1H), 3.62-3.75 (m, 1H), 4.10-4.23 (m(ABq?), 2H), 5.76 (s, 1H), 10.61 (br s); IR (Film) 3500-3000 (-OH), 2940, 2871, 2679, 2575, 1740, 1701, 1686, 1630 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 242, 318 (M+$NH_4$); TLC (6:3:1 $CHCl_3$:MeOH:AcOH) $R_F$ = 0.67; mp = 171-176 °C.

**1',2',3',6',7',7'a-Hexahydro-1-[3-(methoxycarbonyl)-ethyl]-7'a-methyl-spiro[1,3-dioxolane-2,5'-[5H]indene] (134):** white solid; $^1H$ NMR ($CDCl_3$) δ 0.92 and 1.13 (s, 3H), 1.32-2.03 (m, 9H), 2.33-2.42 (m, 4H), 3.89-3.98 (m, 4H), 5.26 and 5.31 (br s, 1H); IR ($CDCl_3$)

3450-3100 (-OH), 2956, 2934, 2892, 1707 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 267 (M+H), 284 (M+$NH_4$), 301 (M+$NH_4$+$NH_3$); TLC (6:3:1 $CHCl_3$:MeOH:AcOH) $R_F$ = 0.80; mp = 102-105 °C.

**Lithium 5-[2-lithiumoxycarbonyl)ethyl]-1,2,3,6,7,7a-hexahydro-5-hydroxy-7a-methyl-1-[5H]indene-3-propionate (144):** The lithium carboxylate was prepared by the above method without acidic workup. The reaction mixture was neutralized and concentrated to afford a tan powder: $^1H$ NMR ($D_2O$) δ 0.73 and 0.93 (s, 3H), 1.07-1.35 (m, 5H), 1.42-1.82 (m, 6H), 1.87-2.10 (m, 2H), 3.18 (s, 2H), 5.01 and 5.81 (br s, 1H).

**1-[2-(Hydroxycarbonyl)benzyl]-4,4-dimethyl-8-oxa-3-oxobicyclo[3.2.1]octene (164):** light orange powder; $^1H$ NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.23 (s, 3H), 2.40 (d, J = 16.2 Hz, 1H), 2.71 (d, J = 15.9 Hz, 1H), 3.52-3.63 (m (ABq?), 2H), 4.43 (s, 1H), 6.10-6.16 (m 2H), 7.30-7.52 (m, 3H), 7.98 (d, J = 7.8 Hz, 1H); IR (Film) 3130 (broad), 3074, 2967, 2928, 1709, 1696 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 287 (M+H), 304 (M+$NH_4$); HRMS *m/e* for $C_{17}H_{18}O_4$, calcd 286.12051, measured 286.12010; mp = 131-142 °C.

**2-Methyl-3-(2-propenyl)-cyclopentan-1-one (83):** To a solution of 2-methyl-2-cyclopenten-1-one (9.23 g, 96 mmol) in 128 mL of dry methylene chloride at -78 °C under $N_2$ was added $TiCl_4$ (36.42g, 192 mmole) dropwise over 12 minutes. After 20 minutes' stirring at -78°C, allyl trimethylsilane (27.42 g, 240 mmol) was added dropwise over 20 min. The dark purple mixture was stirred at -78 °C for two h, the cold bath exchanged for a normal ice bath, and the mixture stirred

an additional two h. It was then re-cooled to -78 °C, quenched with 160 mL water, the aqueous extracted with methylene chloride, and the organics washed with water and brine, dried over $Na_2SO_4$, and concentrated. Distillation of the crude yellow oil at 5 mm Hg and collecting the material distilling from 67-100 °C yielded **83** as a colorless liquid (9.11g, 69%): $^1H$ NMR ($CDCl_3$) δ 1.01 and 1.08 (d, J = 7.2 Hz, d, J = 6.6 Hz, 3H), 1.33-1.51 (m, 1H), 1.67-2.01, (m, 2H), 2.01-2.15 (m, 2H), 2.15-2.26 (m, 1H), 2.26-2.49 (m, 2H), 5.00-5.13 (m, 2H), 5.69-5.91 (m, 1H); IR (Neat) 3070, 2960, 2925, 2870, 1735, 1635 $cm^{-1}$; TLC (9:1 H:EA) $R_F$ = 0.32.

**1,2,3,6,7,7a-Hexahydro-7a-methyl-5-oxo-1-(2-propenyl)-[5H]indene (91):** To 43 mL dry ether at room temperature under $N_2$ was added 4.29 mL 2.5 M ethanolic potassium hydroxide. The mixture was cooled in an ice/salt bath and **83** (8.32 g, 60.2 mmol) was added dropwise (neat + 2 - 1.0 mL ether rinses). Methyl vinyl ketone (4.22 g, 60.2 mmol) in 10.72 mL dry ether was then added slowly dropwise with the bath temperature maintained at -6° to -7 °C. and the mixture stirred at -7 °C for 45 min. The ice bath was removed and the mixture stirred an additional 45 minutes at room temperature, after which it was poured into 43 mL 10% aqueous HCl. The aqueous layer was saturated with NaCl and extracted with ether, and the organics dried over $Na_2SO_4$ and concentrated in vacuo. The crude amber oil was checked by $^1H$ NMR then taken up in 43 mL 10% ethanolic potassium hydroxide and heated to reflux, where the mixture was stirred for 30 min. The cooled mixture was neutralized with glacial

acetic acid to pH = 6, concentrated, and the residue taken up in 200 mL water. The aqueous layer was extracted with ether, the organics washed with brine, dried over $Na_2SO_4$, and concentrated to yield an amber oil. Purification by sg chromatography provided **91** as a light yellow oil (6.68 g, 58 % over two steps): $^1H$ NMR ($CDCl_3$) δ 1.04 and 1.25 (s, 3H), 1.44-1.79 (m, 3H), 1.89-2.15 (m, 3H), 2.17-2.73 (m, 5H), 4.93-5.10 (m, 2H), 5.64-5.88 (m, 2H); IR (Neat) 3065, 2960, 2940, 2920, 2865, 1665, 1635 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 191 (M+H), 208 (M+$NH_4$), 381 (2M+H); TLC (4:1 H:EA) $R_F$ = 0.34.

**1,2,3,6,7,7a-Hezhydro-4-hydroxycarbonyl-7a-methyl5-oxo-1-(2-propenyl)-[5H]indene (92):** To a suspension of NaH (0.30 g of a 60% mull in mineral oil, 7.39 mmol) and KH (two small drops of a 35% dispersion in mineral oil) in 14.7 mL dry dimethoxy-ethane (DME) at room temperature was added rapidly enone **91** (1.58 g, 8.30 mmole) in 2.1 mL DME. The mixture was stirred at room temperature overnight. The dark mixture was then cooled to 0 °C and $CO_2$ (passed through a $CaCl_2$ drying tube) was bubbled through it for 75 min. 14.8 mL 10% aqueous NaOH was added and the mixture stirred at 0 °C for 15 min. The aqueous layer was extracted with ether, acidified to pH = 2-3, stirred for 30 min, and extracted with ether. The combined organics from the second extraction were dried over $Na_2SO_4$ and concentrated to afford a yellow oil which began to crystallize upon cooling: $^1H$ NMR ($CDCl_3$) δ 1.13 and 1.34 (s, 3H), 1.52-1.95 (m, 3H), 1.99-2.33 (m, 4H), 2.54-2.93 (m, 2H) 3.27 (dd, J = 5.3, 9.5 Hz, 2H), 4.98-5.14 (m, 2H), 5.61-5.87 (m, 1H); IR (Neat) 3500-3100 (-OH), 3065, 2965,

2925, 2760, 1740, 1620, 1593 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 235 (M+H), 252 (M+$NH_4$), 486 (2M+$NH_4$); TLC (3:1 H:EA) $R_F$ = 0.06 (streak).

**1,2,3,6,7,7a-Hexahydro-7a-methyl-1-(oxiranylmethyl)-5-oxo-[5H]indene (103):** To a solution of **91** (0.57 g, 3.00 mmol) in 15 mL dry dichloroethane at room temperature under $N_2$ was added 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide (5.7 mg, 0.016 mmol) then m-chloroperoxybenzoic acid (0.93 g of 67%, 3.59 mmol). The mixture was heated to 90 °C and stirred at that temperature for one h. TLC showed starting material was still present and starch iodide paper tested negative for peroxides. 4.2 mg inhibitor and 0.47 g *m*-CPBA were added and heating resumed for one h. TLC indicated the reaction was complete. The mixture was diluted with methylene chloride, washed with aqueous $NaHSO_3$ and aqueous $NaHCO_3$, and the aqueous extracted with methylene chloride. The organics were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification of the residue by sg chromatography provided **103** as a pale yellow oil: $^1H$ NMR ($CDCl_3$) δ 1.03 and 1.26 (s, 3H), 1.60-1.87 (m, 4H), 1.96-2.20 (m, 3H), 2.30-2.84 (m, 6H), 2.87-2.97 (m, 1H), 5.78 and 5.83 (br s, 1H); IR (Neat) 3040, 2980, 2945, 2925, 2865, 1700, 1665 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 207 (M+H), 224 (M+$NH_4$), 241 (2M+$NH_4$+$NH_3$), 413 (2M+H), 430 (2M+$NH_4$); TLC (1:1 H:EA) $R_F$ = 0.30.

**1,2,3,6,7,7a-Hexahydro-7a-methyl-5-oxo-1-(2-oxoethyl)-[5H]indene (102):** To a suspension of periodic acid (0.28 g, 1.23 mmol) in 17.5 mL dry ether at room temperature under $N_2$ was added rapidly dropwise epoxide **103** (0.25 g, 1.23 mmol) in 4.9 mL dry ether.

A precipitate began to form immediately, and the mixture was stirred vigorously at room temperature for three h. TLC showed starting material to be present, so 0.08 g periodic acid (27%) was added. The mixture was stirred until TLC showed it to be complete (2.5 h). The mixture was filtered through Celite, washed with saturated aqueous $NaHCO_3$ until no more orange color appeared in the aqueous layer, washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. An attempt to purify the aldehyde from another experiment had led to partial decomposition; thus the product, a yellow oil (0.14 g, 59%), was carried on unpurified; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05 and 1.29 (s, 3H), 1.68-1.85 (m, 1H), 1.91-2.03 (m, 1H), 2.03-2.22 (m, 1H), 2.30-2.78 (m, 8H), 5.78 and 5.80 and 5.84 (br s, 1H), 9.79-9.83 (m, 1H); IR (Neat) 2960, 2920, 2860, 1720, 1663 (broad) $cm^{-1}$; TLC (20:10:1 ether: hexane: ethanol) $R_F$ = 0.20.

**1,2,3,6,7,7a-Hexahydro-1-(3-hydroxypropyl)-7a-methyl-5-oxo-[5H]indene (118):** To a 1.0 M solution of borane in THF (17.34 mL, 17.34 mmol) at 0 °C under $N_2$ was added dropwise cyclohexene (2.85 g, 34.68 mmol) in dry THF. The ice bath was removed and the mixture stirred for 30 min at room temperature, during which time a white precipitate formed. The mixture was re-cooled to 0 °C, and allyl compound **91** (3.00 g, 15.8 mmol) in 7.9 mL dry THF was added dropwise. The mixture was allowed to stir with no further addition of ice to the cooling bath. TLC showed the reaction to be complete after 2.5 h. 10.4 mL ethanol, 3.48 mL 6 N NaOH, and 6.95 mL 30% $H_2O_2$ were added sequentially; this mixture was heated at 50 °C

for one h, and cooled to room temperature. The aqueous material was absorbed by $Na_2SO_4$, the $Na_2SO_4$ rinsed well with ether, the organics washed with brine, the brine back-extracted with ether, and the combined organics dried over $Na_2SO_4$ and concentrated. Compound **118** was obtained as a pale oil (2.60 g, 79%) after sg chromatography: $^1H$ NMR ($CDCl_3$) δ 1.02 and 1.24 (s, 3H), 1.24-1.37 (m, 1H), 1.41-1.79 (m, 6H), 1.95-2.13 (m, 2H), 2.29-2.80 (m, 5H), 3.64-3.70 (m, 2H), 5.76 and 5.81 (br s, 1H); IR (Neat) 3420 (broad), 2930, 2855, 1650 (broad); TLC (1:4 H:EA) $R_F$ = 0.27.

**1,2,3,6,7,7a-Hexahydro-7a-methyl-5-oxo-1-[5H]indene-3-propionic acid (122):** Alcohol **118** was taken up in reagent grade acetone and cooled to 0 °C. Jones reagent was added dropwise until a red color persisted. The mixture was stirred at 0 °C for three h, when TLC indicated the reaction to be complete. 2-Propanol was added until a green color persisted and the quenched mixture stirred at 0 °C for 20 min. Enough brine was added to dissolve the sticky blue-green residue and the aqueous layer was saturated with NaCl and extracted with ether and methylene chloride. The combined organic layers were washed with brine, the brine back-extracted with ether, and the organics dried over $Na_2SO_4$ and concentrated in vacuo. Base extraction with cold 1 N NaOH and ether afforded 0.74 g (87%) of **122** as a yellow oil: $^1H$ NMR ($CDCl_3$) δ 1.04 and 1.24 (s, 3H), 1.42-1.63 (m, 2H), 1.63-1.92 (m, 2H), 1.92-2.12 (m, 2H), 2.28-2.77 (m, 7H), 5.77 and 5.83 (br s, 1H); IR (Neat) 3500-3000 (-OH), 2940, 2860, 1730, 1705, 1660, 1635 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 223 (M+H), 240 ($M+NH_4$) TLC (1:4 H:EA) $R_F$ = 0.11 (streak).

**Methyl 1,2,3,6,7,7a-Hexahydro-7a-methyl-5-oxo-1-[5H]indene-3-propionate (125):** A solution of diazomethane in ether was added *via* disposable pipet without stirring to a solution of acid **122** (0.56 g, 2.52 mmol) in methylene chloride in an Erlenmeyer flask until a bright yellow color persisted. The mixture was allowed to stand at room temperature for one h, $N_2$ was bubbled through the solution for 45 min (the yellow color dispersed), and the solvent was removed in vacuo. Sg chromatography (2:1 H:EA) yielded 0.52 g (87%) of **125** as a pale yellow oil: $^1$H NMR ($CDCl_3$) δ 1.04 and 1.24 (s, 3H), 1.48-1.56 (m, 1 H), 1.65-1.89 (m, 2H), 1.93-2.10 (m, 2H), 2.24-2.75 (m, 8H), 3.69 (s, 3H), 5.76 and 5.82 (br s, 1H); IR (Neat) 2949, 2868, 1734, 1669 (broad) cm$^{-1}$; MS (CI-$NH_3$) *m/e* 237 (M+H), 254 (M+$NH_4$), 473 (2M+H); HRMS calcd. for $C_{14}H_{20}O_3$ 236.14124, measured 236.14123; TLC (2:1 H:EA) $R_F$ = 0.24.

**Methyl 5-[2-(ethoxycarbonyl)ethyl]-1,2,3,6,7,7a-hexahydro-5-hydroxy-7a-methyl-1-[5H]indene-3-propionate (138):** To a 1 M solution of LDA (prepared at 0 °C from diisopropylamine (0.15 g, 1.52 mmol) in 0.50 mL dry THF and n-BuLi (0.685 mL in hexane, 1.40 mmol)) at -78 °C under $N_2$ was added ethyl acetate (0.12 g, 1.40 mmol) in 1.26 mL dry THF. The mixture was stirred at -78 °C for 90 min, and enone **125** (0.30 g, 1.27 mmol) in 1.27 mL dry THF was added dropwise. TLC showed the reaction to be essentially complete after 3.5 h. The mixture was quenched with 10% acetic acid in methylene chloride, stirred at -78 °C for 10 minutes, water was added, and the cooling bath removed. The mixture was stirred while warming

to room temperature, the pH adjusted to 7, the aqueous layer extracted with methylene chloride, and the organics washed with water and brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification by sg chromatography (2:1 H:EA) afforded 0.18 g (45%) of **138** as a pale yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 0.91 and 1.11 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.31-1.53 (m, 1H), 1.68-2.02 (m, 5H), 2.02-2.48 (m, 3H), 2.52 (s, 2H), 3.68 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 5.21 and 5.30 (br s, 1H); IR (Neat) 3510, 2950, 2865, 1747, 1728 $cm^{-1}$; TLC (2:1 H:EA) $R_F$ = 0.37.

**Methyl 2-(2-furylmethyl)benzoate (155):** To a solution of furan (4.82 g, 70.8 mmol) in 29 mL dry ether at 0 °C under $N_2$ was added n-BuLi (2.10 M in hexane, 32.48 mL, 68.2 mmol) dropwise. The ice bath was removed and the mixture stirred at room temperature protected from light for 70 min. 19.7 mL dry THF was added to dissolve the precipate which formed, and the amber solution transferred over 20 min via canula to a suspension of copper(I) bromide•dimethyl sulfide complex (7.11 g, 34.6 mmol) in 44 mL dry THF at -45 °C under $N_2$. 5 mL additional THF was required to dissolve precipitate which fell back out of solution. After 45 min at -45 °C, bromoester **154**[58] in 29 mL dry ether was added dropwise *via* canula, and the mixture allowed to stir while warming to room temperature, protected from light, in the ice bath overnight. The mixture was poured into saturated aqueous $NH_4Cl$, the aqueous extracted with ether, the organics washed with brine, dried over $Na_2SO_4$, filtered through Celite on a fritted funnel, and concentrated. Purification of the brown oil by sg chromatography provided **155** as a yellow oil (1.67g, 39%): $^1H$ NMR

($CDCl_3$) δ 3.86 (s, 3H), 4.39 (s, 2H), 5.95-5.96 (m, 1H), 6.27 (dd, J = 1.8,3.0 Hz, 1H), 7.23-7.32 (m, 3H), 7.40 (td, J = 7.5, 1.2 Hz, 1H), 7.91 (dd, J = 1.2, 7.8 Hz, 1 H); IR (Neat) 3067, 2950, 1719, 1601 $cm^{-1}$; MS (CI-$NH_3$) *m/e* 217 (M+H), 234 (M+$NH_4$); HRMS *m/e* for $C_{13}H_{12}O_3$ calcd. 216.07864, measured 216.07857; TLC (30:1 H:EA) $R_F$ = 0.26.

**1-(2-Methoxycarbonylbenzyl)-4,4-dimethyl-8-oxa-3-oxo-bicyclo[3.2.1]octene (162):** Zinc chloride (0.47 g, 3.47 mmol) was fused under vacuum in the reaction flask. Furan **155** (0.50 g, 2.31 mmol) in 2.31 mL dry methylene chloride was added and the mixture cooled to -78 °C. Enol silyl ether **160**[61] in dry methylene chloride was added dropwise and the mixture stirred at -78 °C for one h. TLC showed no product being formed, so the mixture was warmed to -3 °C over 75 min. TLC showed no change, so the ice bath was removed. TLC after 30 min showed product, with no change after 30 more min. The mixture was poured into water, the organics washed with water, the aqueous extracted with methylene chloride, and the organics washed with brine, dried over $Na_2SO_4$, and concentrated. **162** was obtained as a yellow oil (0.14 g, 20%) after sg chromatography of the crude brown oil: $^1H$ NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.24 (s, 3H), 2.64 (d, J = 15.9 Hz, 1H), 3.33 (d, J = 15.9 Hz, 1H), 3.55 (s, 2H), 3.89 (s, 3H), 4.39 (d, J = 1.5 Hz, 1H), 6.03-6.13 (m, 2H), 7.26-7.31 (m, 1H), 7.37-7.47 (m, 2H), 7.86 (dd, J = 1.2, 7.8 Hz, 1H); IR (Neat) 3072, 2952, 2927, 2869, 1717, 1702 $cm^{-1}$; MS (CI-$NH_3$) 301 (M+H), 318 (M+$NH_4$); HRMS *m/e* for $C_{18}H_{20}O_4$ calcd. 300.13616, measured 300.13643; TLC (10:1 H:EA) $R_F$ = 0.15.

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# APPENDIX: BIOLOGICAL TESTING

For the purpose of biological testing, zinc sulfate is the standard for SCN hatching activity to which synthetic compounds are compared. If a compound's activity is significantly less than that of $ZnSO_4$, it is considered inactive. If its activity is greater than or equal to that of $ZnSO_4$, it is considered active. To date, compounds **68**, **92**, **98**, **122**, **134**, and **144** have been tested. **68** was active on its first test, negative on its second, and positive on its third. Unfortunately, the standard exhibited aberrant behavior on the third trial, and more testing has been ordered. Compound **92** tested negative. Compounds **98**, **122**, **134**, and **144** all gave inconclusive test results due to unusual behavior of the standard. Compounds **69** and **164** have not yet been tested.

# GENERAL SUMMARY

This dissertation has shown the value of the application of synthetic organic chemistry to other disciplines. Analogs of compounds which have potential as toxins or as agricultural aids have been synthesized. Demethoxyaflatoxin $B_2$ could be useful in structure/activity studies of the aflatoxins, as well as in studies on their mode of toxic action and means of detoxifying them. The synthetic methodology developed for the synthesis of the aflatoxin furofuran ring system complements the existing methods of radical oxidative cyclization in that mildly basic, rather than acidic conditions are used.

Analogs of glycinoeclepin A hold great potential as a safe and economical means of control of the soybean cyst nematode. Although only one of the analogs submitted for testing has shown hatch-stimulating activity to date, the negative tests shed light on the portions of the molecule necessary for biological activity.

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