DISSERTATION

STUDIES TOWARD THE TOTAL SYNTHESIS OF FUSARIN C

Submitted by

Christopher Sean Esslinger

Department of Chemistry

In partial Fulfillment of the requirements

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY CHRISTOPHER SEAN ESSLINGER ENTITLED STUDIES TOWARD THE TOTAL SYNTHESIS OF FUSARIN C BE ACCEPTED AS FULFILLING IN PART THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION

STUDIES TOWARD THE TOTAL SYNTHESIS OF FUSARIN C

The development of the synthesis of the heterocyclic proposed pharmacaphore of the natural mutagenic fungal metabolite fusarin C is discussed with the result of a short and elegant synthesis for this portion of the molecule. The structural integrity of this compound was studied giving rise to a method of diastereomeric preference. Studies to further the synthesis of the natural product are discussed which result in successful alkylation of the heterocycle. The alkylation procedure then produced two new non-natural products which when tested for mutagenic activity along with the heterocycle, may provide information as to the function of the penta-ene side chain of fusarin C in regard to mutagenic activity.

Christopher Sean Esslinger
Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523
Summer 1996

ACKNOWLEDGEMENTS

I would especially like to thank Professor Robert M. Williams for allowing me to perform my research independently, as this was a great learning experience. I would also like to thank him for putting up with me when I went the wrong way, both synthetically and personally.

I would also like to thank the fellow Williams' Group criminals. Not only were they open toward discussions, they helped make the lab an experience in itself.

Finally, I would like to thank my family and friends for all the advice (good or bad) and support during the ups and downs of graduate school.

DEDICATION

"Who has more fun than chemists?" - J. K. Stilli

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Chapter One

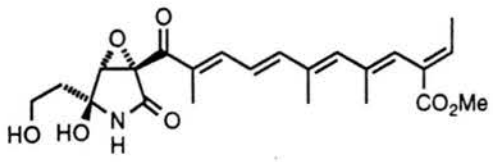
Introduction

The Fusarins

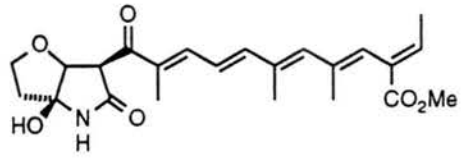
Fusarium monoliforme Sheldon is a pathogenic fungus found worldwide, infecting mostly corn but is also found on sugar cane and other crops.[1] An isolate of this fungus has shown to be highly toxic, thought to induce leukoencephalomalacia in horses,[2] and to be mutagenic.[3] The mutagen identified as fusarin C **1** (Appendix 1) was a major component of the fungal metabolic isolates. It has been found that several other species of *Fusarium* also produce fusarin C,[4] all of which are also cereal crop infecting pathogens. Fusarin C was found to be mutagenic by the Ames *Salmonella* mutagenicity assay,[5] however the compound lacks carcinogenic activity.[6]

Fusarium monoliforme produces several different secondary metabolites. Of these isolates, five fusarins have been reported as being natural products: fusarin C (**1**),[7,8a] fusarin A (**2**),[8a,b] fusarin D (**3**)[8a,] recently fusarin F (**4**),[9] and fusarin B (**5**)[10] (Figure 1).

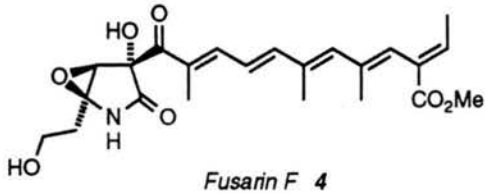
Fusarins A and D, which are structurally similar to fusarin C (Appendix B) and have an identical side chain, lack mutagenic activity.[11] Thus the pharmacaphore of fusarin C is believed to arise from C-13, C-14 epoxide moiety that is not contained in fusarins A and D. Byproducts of fusarin C resulting from double bond isomerization by UV irradiation, compounds **5** (fusarin B), **6**, and **7** (which contain the epoxy lactam of fusarin C), all possess



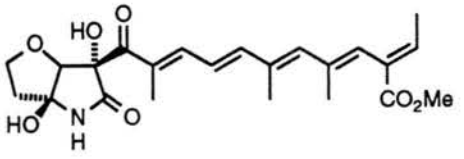
Fusarin C ***1***



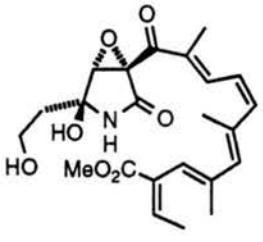
Fusarin A ***2***



Fusarin F ***4***



Fusarin D ***3***



Fusarin B ***5***

Figure 1

mutagenic activity[12] (Figure 2). This suggests that the pentaene chain is not directly responsible for mutagenic activity but may serve as a transport vehicle for passage through membranes, or acts as a possible intercalator in the minor groove binding domain to DNA delivering the reactive species proximal to the DNA bases. The carboxylic acid derivative of fusarin C (**8**) is also mutagenic, but to a lesser extent.[11] This again supports the hypothesis that the penta-ene chain is but a lipophilic portion to aid in transmembrane diffusion and the epoxy lactam is responsible for mutagenic activity.

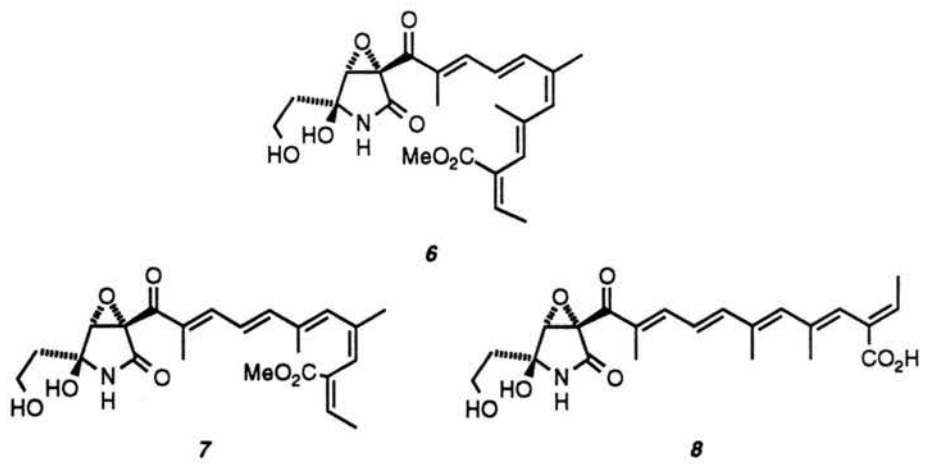


Figure 2

Fusarin F (**4**), an isomer of fusarin C (Appendix B) that presumably results from C-15 hydroxyl attack on the C-14 epoxide carbon, lacks mutagenic activity.[12] This result points to the C-13 C-14 epoxide in fusarin C as being crucial for mutagenic activity. To illustrate further the structural specificity required for activity, epi-fusarin C (compound **9**) containing the C-15 hydroxyl and the C-13 C-14 epoxide *cis*, is inactive[12]. This again suggests that the C-13 C-14 epoxy C-15 *trans* hydroxy γ lactam (**10**) is responsible for the pharmacological effects (Figure 3).

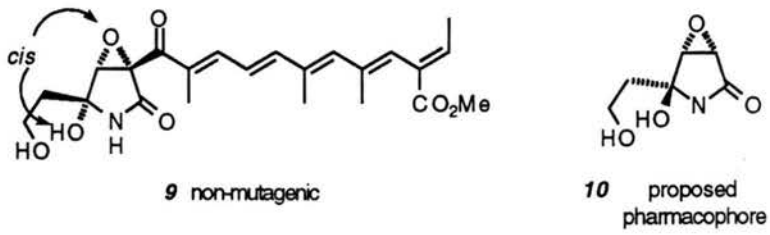
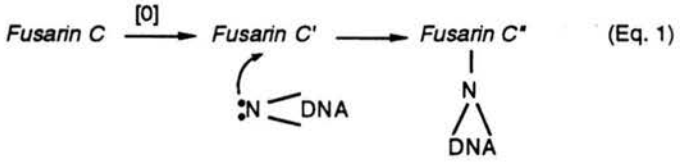


Figure 3

Fusarin C, however, is not mutagenic itself. The compound must first be activated by the complete monooxygenase system to a highly reactive intermediate of undetermined structure.[12] After incubation with liver fraction S-9 containing the complete monooxygenase system, fusarin C shows mutagenic activity over a wide range of concentrations when tested against

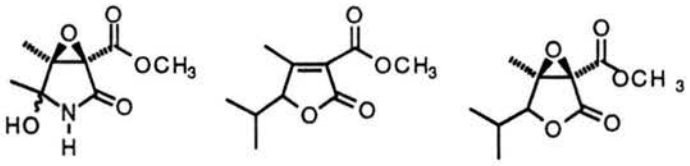
the base substitution strain *Salmonella tryphimurium* TA100 in the Ames mutagenic assay. Fusarin C was only weakly mutagenic against the frame shift tester strain *Salmonella tryphimurium* TA98 after S-9 incubation.[13] In the absence of liver fraction oxidation, fusarin C lacked mutagenic activity with the tester strains in the Ames assay. From these results, it was hypothesized that a reactive intermediate forms a covalent bond with DNA. A precursor of specific structure (fusarin C) is oxidized to a more electrophilic compound of unknown structure. This intermediate is then attacked by a nucleophilic nitrogen lone pair on a DNA base giving a DNA-fusarin C adduct also of unknown structure. This adduct then interferes with normal DNA replication (Eq. 1).



(Eq. 1)

The only previously reported synthetic work performed on fusarin C by Bjeldanes and Kim did not succeed in forming the heterocyclic diol of the natural product, but did produce compounds to probe the mutagenicity requirements of the heterocyclic portion of fusarin C.[13] Of the compounds tested, three were substantially mutagenic against the tester strain TA100 after S-9 fraction incubation (although less mutagenic than fusarin C); two α,β-epoxy lactones and the α,β-unsaturated lactone shown in Figure 4. Of the epoxy lactams tested, only weak mutagenic activity was observed. The significance of these findings as they relate to the mutagenic requirements of fusarin C is unclear. However, some speculation can be put forth; all three compounds contain a five-membered heterocycle with a 1,3-dicarbonyl moiety, reactive functionality is present in the α,β positions of the heterocycle,

and the penta-ene side chain may have a significant role in the mutagenic activity.



Synthetic mutagenic compounds

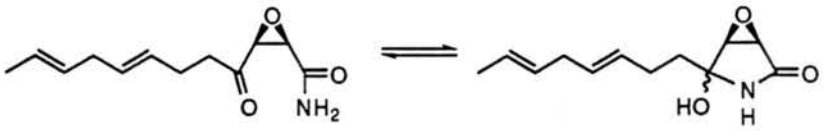
Figure 4

Since it is essential for pre-oxidation of the natural product to a more reactive form, a less obvious functionality may play a crucial role in the mechanism of mutagenesis and DNA interaction. As mentioned earlier, the unsaturated side chain may aid in bringing the reactive intermediate to the DNA *via* lipophilic interactions of the polyunsaturated side chain with the minor groove of DNA. The unsaturation (or other functionality) may undergo oxidation which, in conjunction with the *trans* hydroxy epoxide, forms the reactive intermediate. In the total synthesis of fusarin C, some of the required functionality for mutagenesis and the structural integrity of the molecule can be investigated. This may supply insight as to the nature of DNA-fusarin C interactions.

Cerulenin

A structurally related compound, cerulenin **I**, contains the epoxy-lactam moiety similar to that of the fusarin C. This compound exists as the open ring form in aprotic media, and as the lactam form in protic media[14, 23]. Cerulenin, also a fungal metabolite (isolated from the culture filtrate of *Cephalosporium caerulens*), has attracted considerable attention due to the biological activity it possesses. Cerulenin is an antifungal antibiotic and has also been shown to inhibit lipid biosynthesis in *E. coli* by irreversibly binding β-ketoacyl

synthetase, the enzyme responsible for acylating a malonyl thioester in preparation for the chain lengthening reaction in fatty acid synthesis. The irreversible binding is thought to occur between the C-2 epoxy carbon of cerulenin and the cysteine SH of the enzyme in the active site.

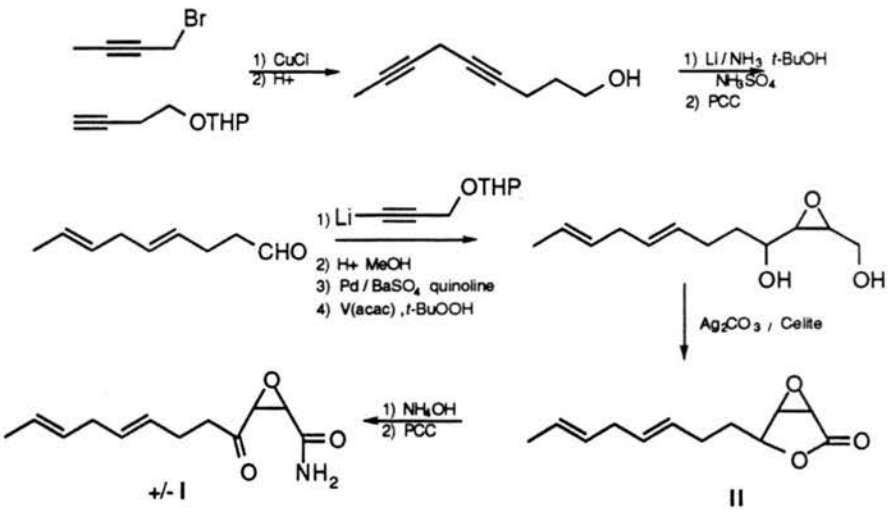


Aprotic media ⟷ Protic media

Cerulenin I

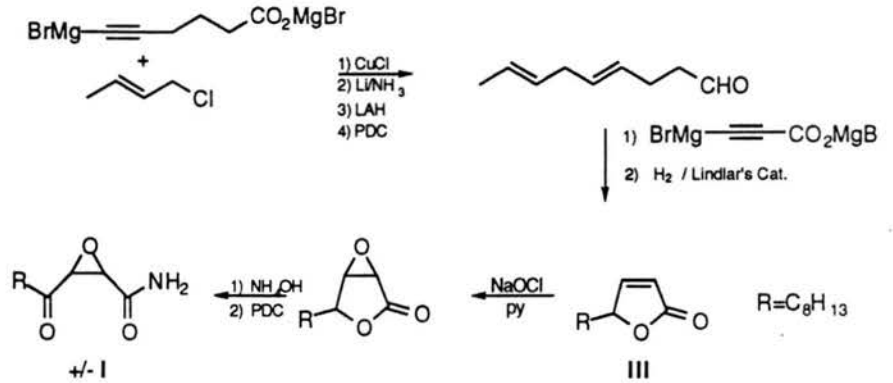
Cerulenin has been the subject of several synthetic studies as the 1,4-dicarbonyl-2,3-epoxy moiety represents a significant synthetic challenge, as well as to aid in structural identification and study of the biological properties of the compound.

The first total synthesis[15] of racemic cerulenin involved an aldol condensation between the acetylenic anion and diene aldehyde followed by *cis*-reduction and epoxidation *en route* to the epoxy lactone **II** (Scheme **A**). This epoxy lactone (a common intermediate in these syntheses) was then subject to ammonolysis followed by hydroxyl oxidation to the ketone to yield racemic cerulenin **I**.



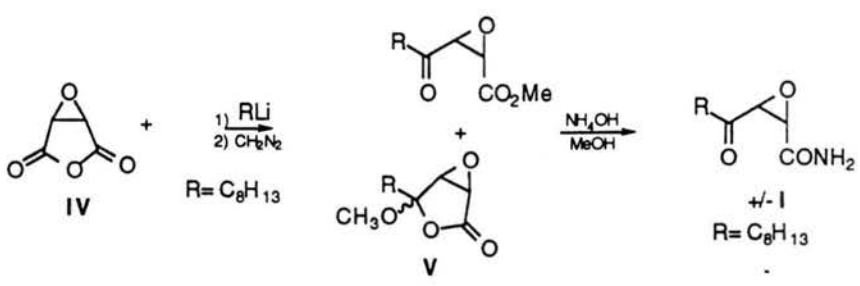
Scheme **A**

Shortly afterward a second racemic synthesis was published using the butenolide **III** as the key intermediate[16]. This approach was developed in order to control the stereochemistry of epoxidation to yield the epoxy lactone **II**, which was then carried on to cerulenin (Scheme **B**).



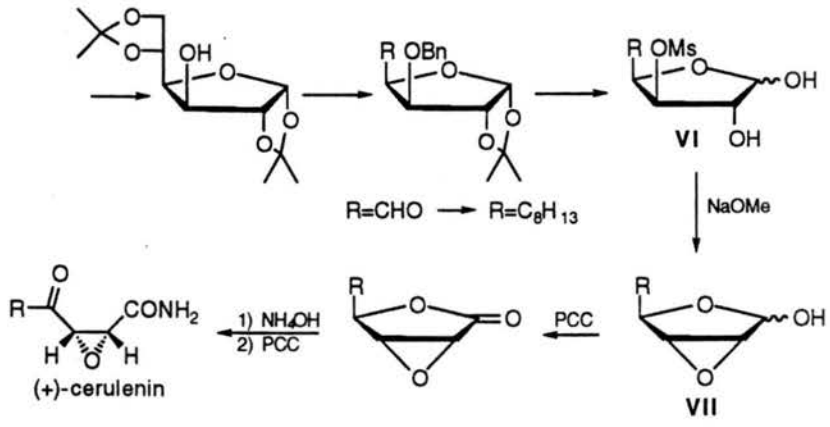
Scheme **B**

A convergent synthesis of racemic cerulenin was published about the same time in which the diene chain was condensed with the epoxy anhydride **IV** to give, after esterification, the ester and pseudolactone **V**. These two products were then converted to cerulenin in a similar manner as performed previously[17]. This synthetic method was amendable to the synthesis of ^{14}C labled cerulenin starting with labled maleic anhydride (Scheme **C**).

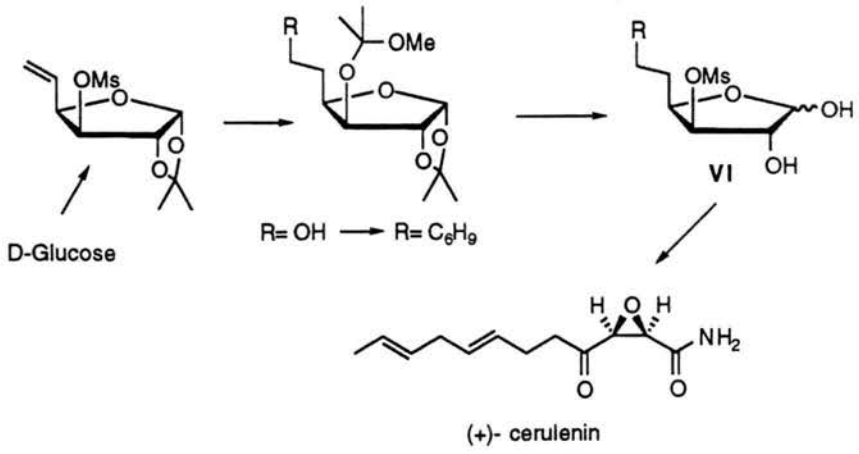


Scheme **C**

Two stereoselective syntheses of (+)-cerulenin were then performed, both starting with D-glucose[18, 19]. These syntheses are similar in that chemical manipulation of the glucose ring gave the alkylated *trans*-hydroxy mesylate **VI** which, upon base treatment, yielded the epoxy-lactol **VII** of desired configuration (Scheme **D** and Scheme **E**). Ammonolysis of the lactol followed by oxidation to the ketone yielded chiral cerulenin **I**.

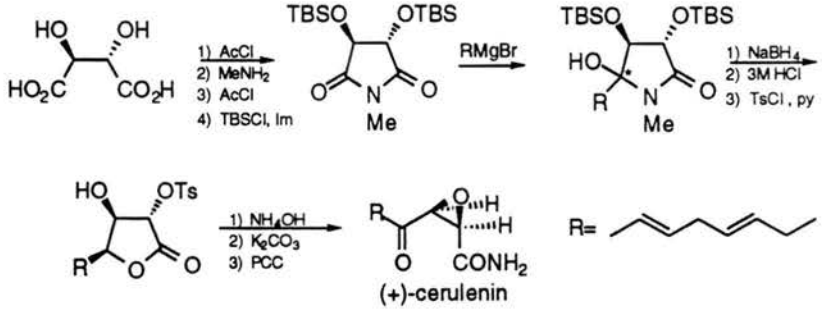


Scheme **D**



Scheme **E**

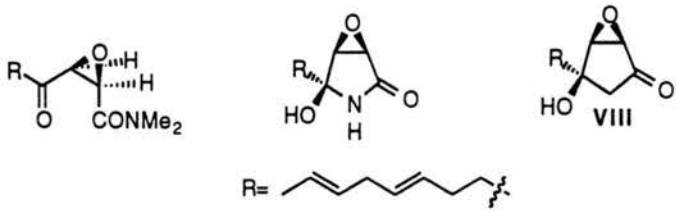
Further studies of cerulenin involved a chiral synthesis utilizing Sharpless' asymmetric epoxidation[20] as the key step, and a stereoselective synthesis starting from D-tartaric acid (Scheme **G**)[21]. In this synthesis the C_2 symmetric imide is alkylated with the diene side chain with subsequent tosylation of a later intermediate at the less hindered hydroxyl Ammonolysis of the hydroxy-tosyl lactone followed by epoxide formation and hydroxyl oxidation afforded chiral (+)-cerulenin **I**.



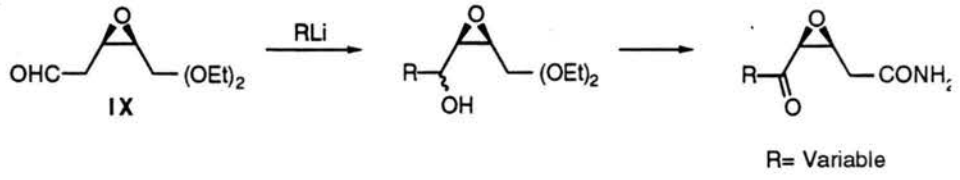
Scheme **G**

One study altered the 4-keto-2,3-epoxy-amide portion of the molecule[22]. It was found that the (2R,3S) stereochemistry of the 2,3-epoxide is crucial for biological activity. Substituting alkyl groups at the amide nitrogen retained mild activity, however, reduction of the C-4 ketone to the alcohol eliminated all activity. It was then hypothesized that the bioactive form of

cerulenin may be the hydroxy-lactam structure of the molecule, and a carbocyclic analogue replacing the nitrogen with a methylene was synthesized[22]. This cyclic compound **VIII** did exhibit biological activity, but at a much lesser extent than that of natural cerulenin.



Recently a series of chiral cerulenin analogues have been synthesized by connecting the chiral epoxyaldehyde **IX** to a number of organolithium nucleophiles[23] (Scheme **H**). In this manner a variety of cerulenin analogues containing side chains of varying lengths and degrees of saturation were synthesized to explore the contribution the side chain has on the biological activity of the molecule.



Scheme **H**

Chapter Two

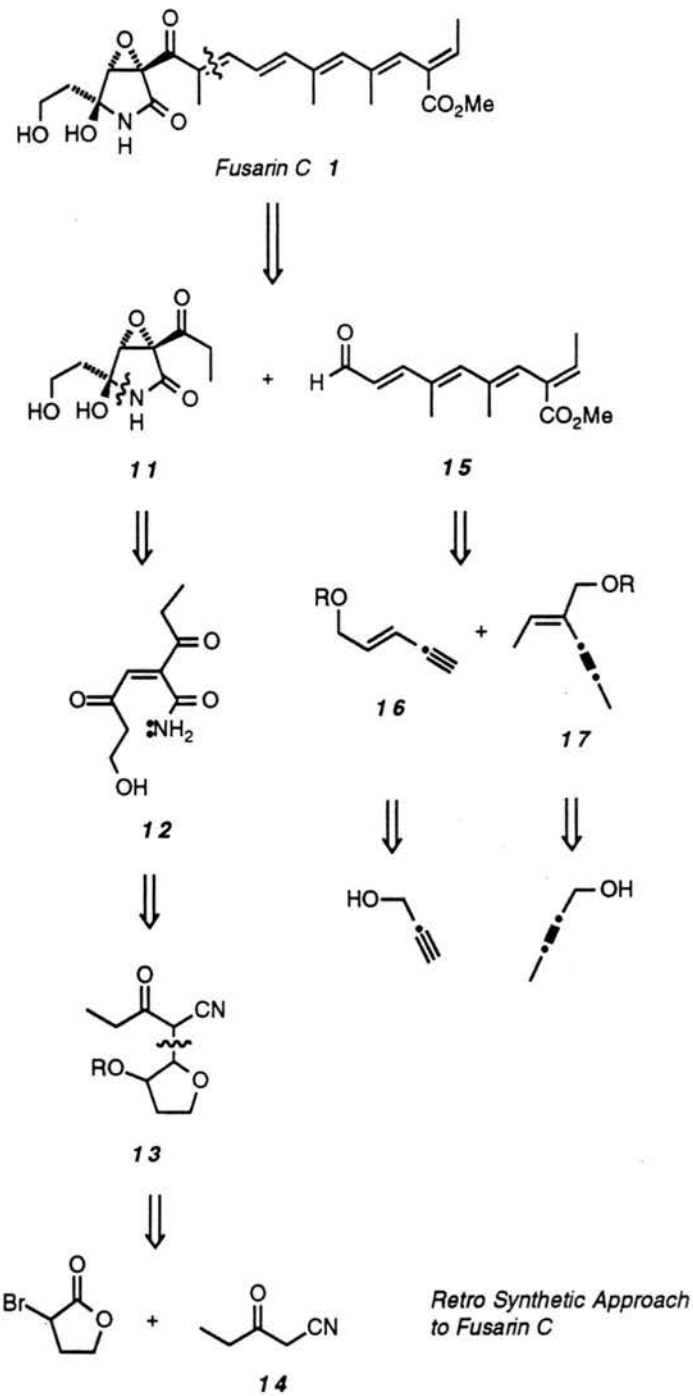
Studies Toward the Total Synthesis of Fusarin C

Retrosynthetic Analysis of Fusarin C

On examination of the structure of fusarin C **1**, the molecule can be seen as being comprised of two major pieces which can be joined in an aldol condensation/dehydration at the disconnection shown (Scheme 1).

The proposed pharmacophore (heterocycle **11**) may be envisioned as coming from (before epoxidation) a ring opened ene-dione-amide **12**. The ene-dione-amide could be synthesized using the β-keto nitrile furan derivative **13** arising from α-bromo-γ-butyrolactone and β-keto nitrile **14**.

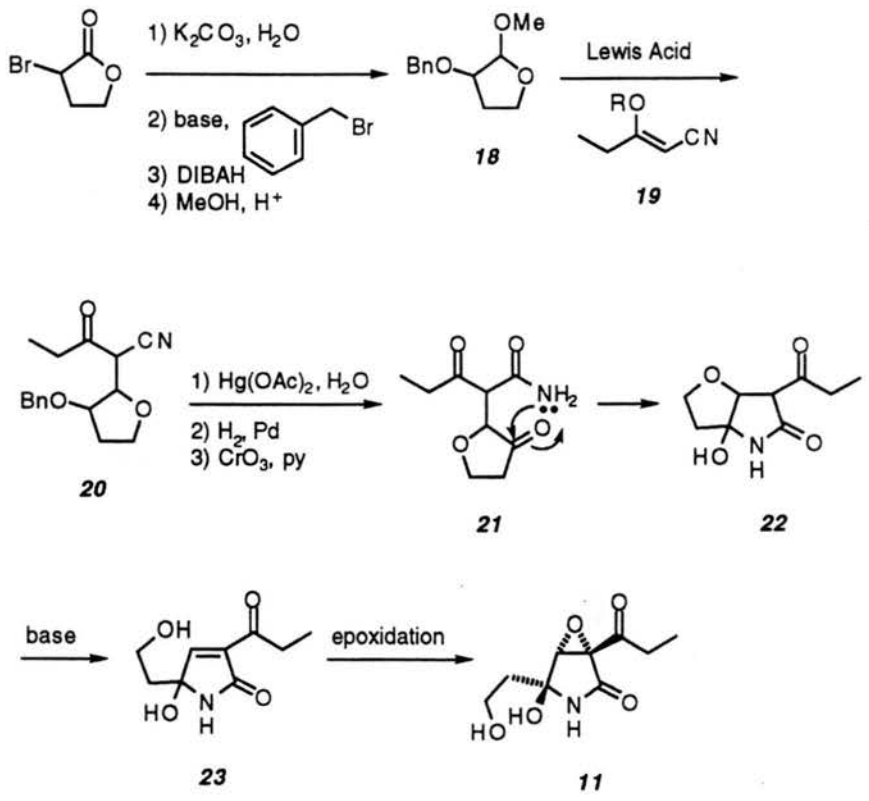
The tetraeneal ester **15** can be disconnected *via* organometallic transformations. The two pieces resulting from the retrosynthetic step are easily formed ene-ynes **16** and **17** from the starting alkynes propargyl alcohol and 2-butyne-1-ol.


Fusarin C 1
11
15
16
17
12
13
14
Retro Synthetic Approach
to Fusarin C

Scheme 1

Proposed Synthesis of Fusarin C

The actual proposed chemical steps to carry out the convergent synthesis are as follows (Scheme 2). Commercially available α-bromo-γ-butyrolactone was to be converted to the hydroxy lactone[24] followed by benzyl protection. Subsequent reduction of the lactone to the lactol[25] followed by methylation would provide the cyclic acetal **18**. Lewis Acid mediated coupling[26] of enol ether **19** and acetal **18** would afford the intermediate furan derivative **20**. Hydrolysis of the nitrile to the primary amide followed by deprotection of the hydroxyl and oxidation to the ketone would give the diketo furan amide **21** which may spontaneously cyclize[27] to the bicyclic furan pyrrolindine-one system **22**. Treatment of this bicyclic system with base should afford the double bond with furan ring opening to give pyrroline-one diol **23**. Epoxidation of the double bond will then afford the heterocyclic portion of fusarin C **11**.



Proposed Synthesis of Pharmacophore 11

Scheme 2

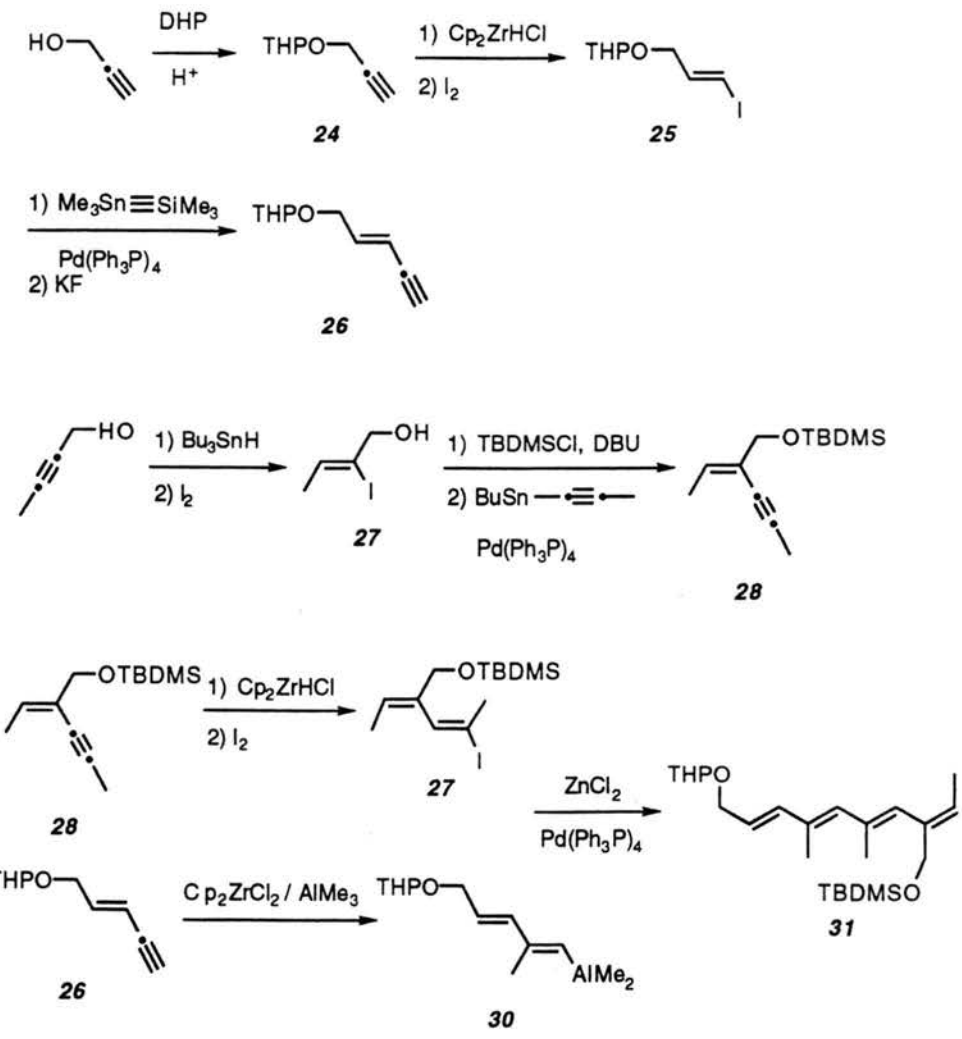
The polyene chain synthesis was planned using existing organometallic methodology (Scheme 3). The convergent synthesis would start from propargyl alcohol on one side and 2-butyne-ol from the other side. Starting with propargyl alcohol, the hydroxyl would be protected *via* acid catalyzed addition of dihydropyran[28] to give the tetrahydropyranyl ether **24**. Hydrozirconation[29] of the alkyne to the vinyl zirconate followed by halogen metal exchange would yield the E-vinyl iodide **25**. Coupling of this vinyl iodide with trimethylsilyl trimethystannyl acetylene using the Stille coupling conditions[30] (catalytic palladium(0)) followed by desilylation should produce the ene-yne **26**.

Taking 2-butyne-ol from the other side of the chain, the alkyne, after treatment with tributyltin hydride followed by halogen metal exchange[31] would

afford the Z vinyl iodide **27**. Protection of the vinyl iodide **27** followed by Stille coupling[30] with 1-tributylstannyl propyne in the presence of catalytic palladium(0) would produce the ene-yne **28**.

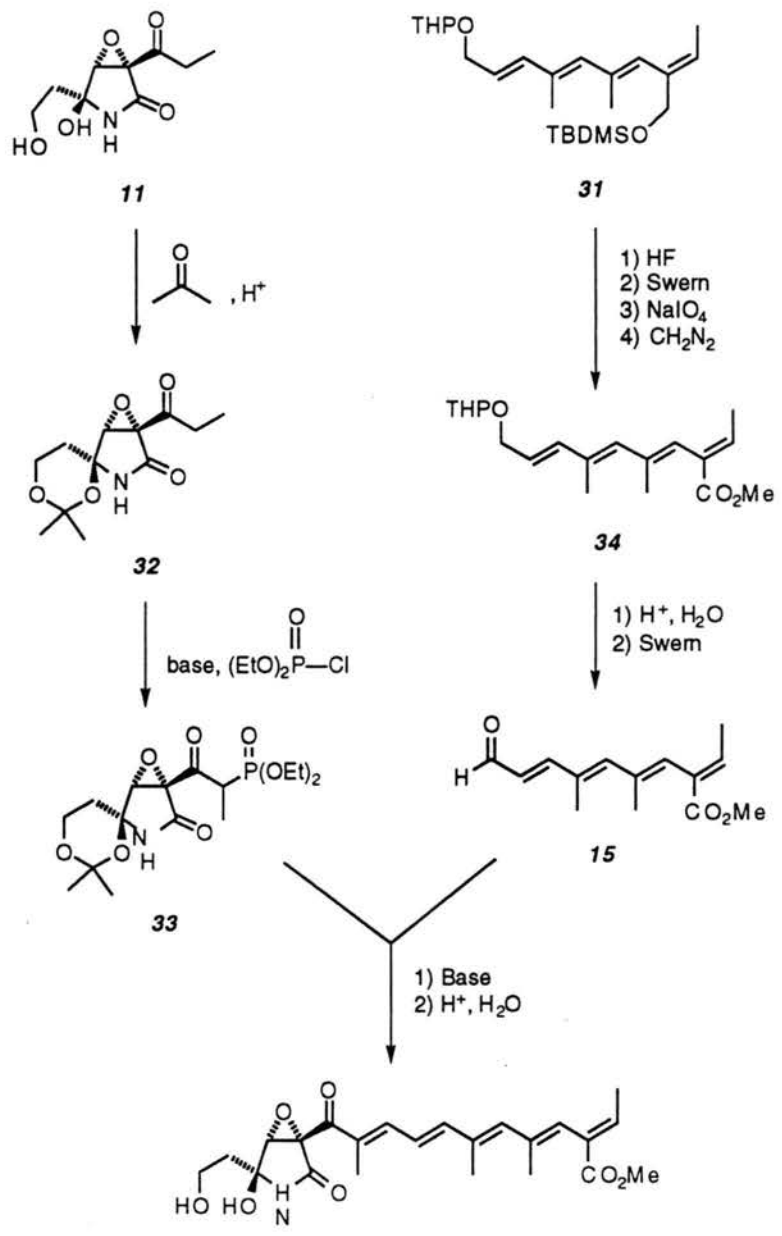
On treatment of ene-yne **28** with zirconocene hydrochloride followed by iodine-zirconium exchange yielding E-E vinyliodo diene **29**,[29] and carbometalation of ene-yne **26** to give E-E vinyl aluminum diene **30**,[32] the palladium catalyzed coupling[33] of the two dienes should give the diether tetra-ene **31** in the all E configuration.

Further manipulation of both the heterocycle **11** and tetraene **31** should afford the precursors to the final coupling of the two pieces (Scheme 4). The heterocycle is to be protected as the acetonide[34] **32** followed by conversion to the phosphonate[35] **33**. The silyl ether on the tetra-ene would be deprotected with subsequent oxidation[36] and esterification to afford the tetra-ene methyl ester **34**. Deprotection of the tetrahydropyranyl ether followed by Swern oxidation[37] of the resulting primary alcohol would give the tetra-ene-al ester **15**. Emmons-Wadsworth coupling[38] of phosphonate **33** with aldehyde **15** followed by deprotection of the acetonide[34] would yield the target compound fusarin C **1**.



Proposed Synthesis of Tetra-ene
31

Scheme 3



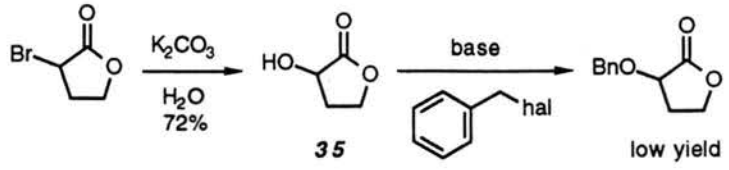
Scheme 4

The synthetic plan is highly convergent, which aids in obtaining the target compound in the case of a low yielding reaction along the synthetic pathway. Most transformations involved in the synthesis are well established, and on examination the synthetic scheme, appears to be a reasonable plan of attack to the total synthesis of fusarin C.

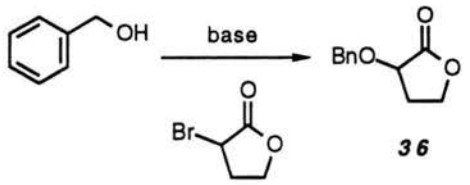
Results and Discussion

As the synthetic approach to the polyene chain is fairly well established, efforts to synthesize the pharmacaphore of fusarin C (the epoxy pyrrolidine-one diol **11**) was first pursued. Thus, the initial target became the acetal **18**.

Commercially available α-bromo-γ-butyrolactone was converted to α-hydroxy-γ-butyrolactone **35** in fair yield.[24] Benzylation of the hydroxyl proved to be more difficult. Various attempts at alkylating the hydroxy anion gave only trace amounts of product **36** (Eq. 2, Table 1). Reversing the role of nucleophile and electrophile using various conditions[39] (Eq. 3), also gave



(Eq. 2)

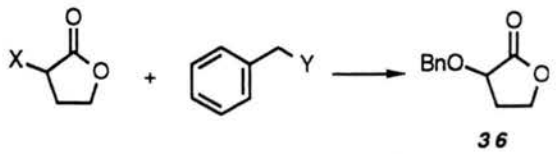


(Eq. 3)

only small amounts of product **36** (Table 1). As a starting point for a total synthesis, the low yields were unacceptable. At this point a different approach to acetal **18** was needed.

An alternative route to obtaining the α-benzyloxy-γ-butyrolactone **36** was designed (Eq. 4), which was equally unsuccessful in forming the product.

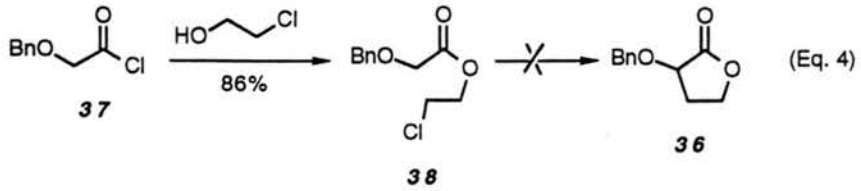
Table 1. Synthetic Efforts Toward α-benzyloxy-γ-butyrolactone ***36*** *via* Lactone and Benzyl Groups



36

X	Y	Conditions	Yield (% ***36***)
OH	Br	KH, neat, R.T.	---
OH	Br	KH, THF/DMF, R.T.	1
OH	Cl	NaH, THF, R.T.	---
OH	Cl	KH, neat, R.T.	---
Br	OH	NaH, DMSO, R.T.	---
Br	OH	NaH, Et_2O, R.T.	1
Br	OH	NaH, Et_2O, reflux	3
Br	OH	NaH, KI, DMF, Δ	4
Br	OH	Ag_2O, neat, Δ	6

--- = no product observed



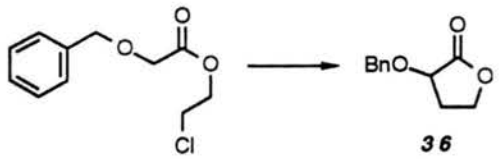
37 ***38*** ***36*** (Eq. 4)

The intermediate chloroester **38** was synthesized in modest yield by esterification of the acid chloride **37** with chloroethanol. However, attempts to cyclize *via* intramolecular alkylation to produce the lactone **36** failed (Table 2).

Again, an alternative route to acetal **18** (or α-benzyloxy-γ-butyrolactone **36**) was sought. Starting with benzyloxy acetic acid, the ethyl ester **39** was formed in good yield. Alkylation *via* Lewis Acid assistance then afforded the hydroxy ester **40**, which suffered subsequent ring closure to give the desired α-benzyloxy-γ-butyrolactone **36** (Scheme 5). Reduction of the lactone to

lactol[25] **41** followed by methanol displacement of the hydroxyl group afforded the desired acetal **18**. The five step sequence produces the acetal from

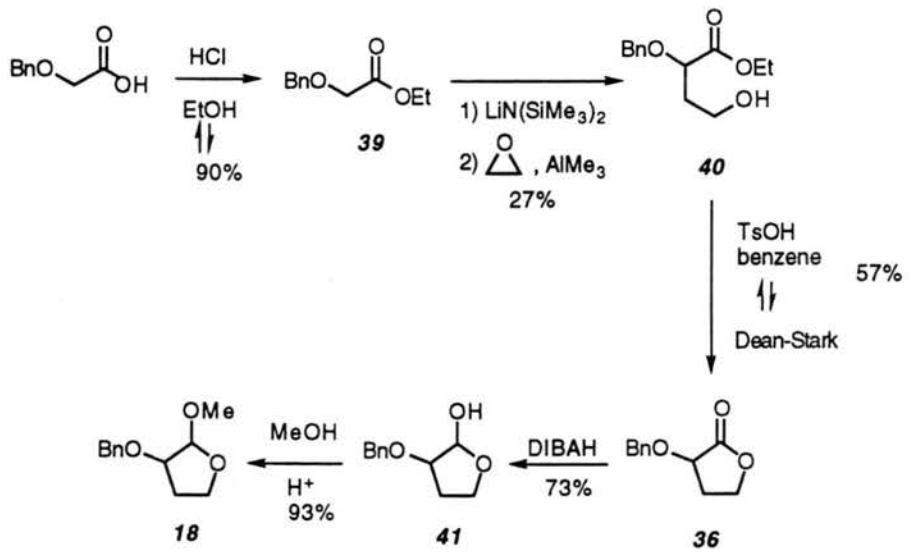
Table 2. Synthetic Efforts Toward α-Benzyloxy-γ-butyrolactone ***36*** *via* Chloroethyl Ester ***38***



38 ***36***

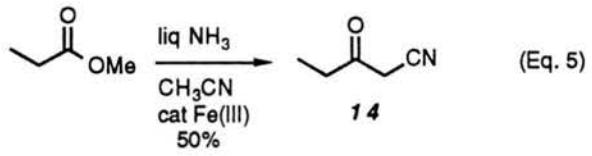
Conditions	Yield
NaH, DMF, 0°C	---
KH, DMF, 0°C	---
$LiN(SiMe_3)_2$, THF, -78°C	---
KH, THF, 0°C	---
LDA, THF, -78°C	---
LDA, THF/HMPA, -78°C	---

--- = no product observed

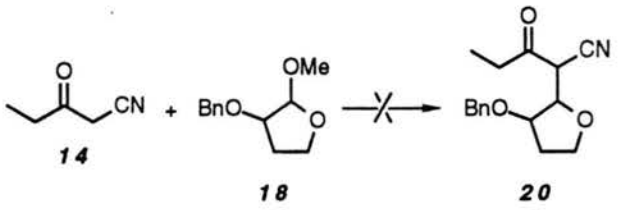


Scheme 5

benzyloxyacetic acid in 9% overall yield. The β-keto nitrile **14** must now be formed in order to carry out the proposed titanium mediated coupling. Methyl propionate was treated with acetonitrile in the presence of sodium amide to give the desired compound in fair yield (Eq. 5).[40] Attempts to couple the β-keto nitrile **14** to acetal **18** (Eq. 6) were met with defeat as no coupled product **20** was found using a variety of conditions (Table 3).



(Eq. 5)

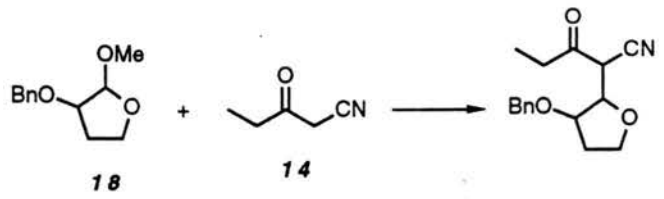


(Eq. 6)

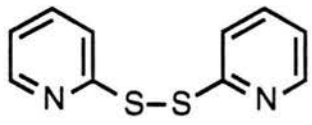
After this synthetic scheme proved unfruitful, an alternative route to obtain the intermediate **12** was devised. In this manner the heterocyclic pharmacophore may still be reached from compounds previously synthesized. The benzyloxy hydroxy ester **40** was protected as the silyl ether **42** and subsequently reduced to the benzyloxy siloxy aldehyde **43**.[25] The aldol coupled product **44** obtained from aldehyde **43** and β-keto nitrile **14** (Scheme 6) could then be advanced to the desired epoxy-pyrrolidine-one as proposed in Scheme 2. Efforts to produce the aldol product **49** unfortunately were met with failure.

The common factor with the previous coupling reaction attempts was the β-keto nitrile, possibly being too unreactive. Treating the β-keto nitrile with

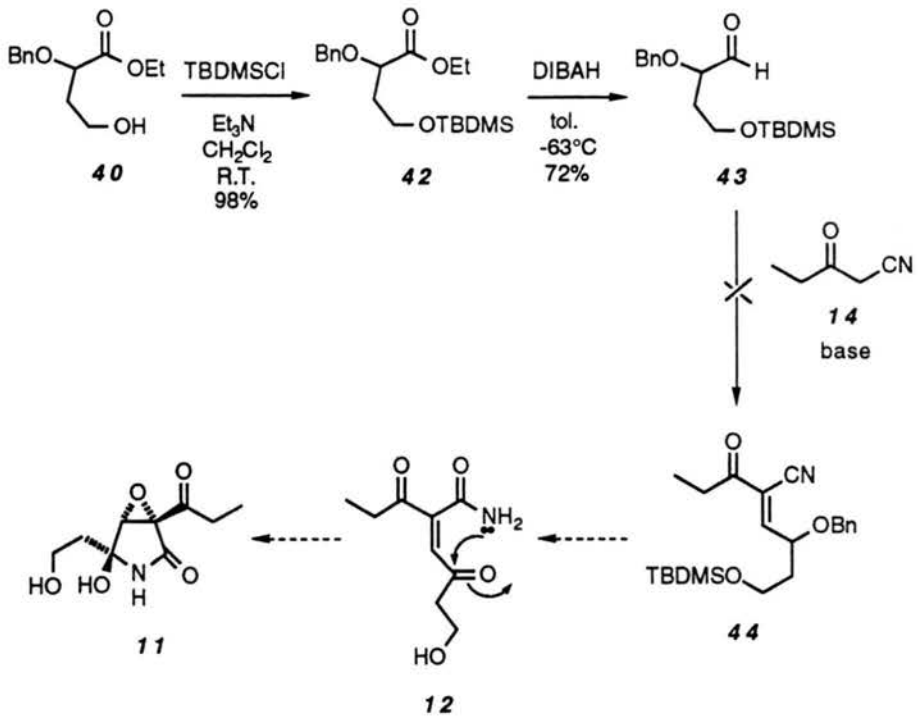
Table 3. Synthetic Efforts Toward Product ***20*** *via* Lactol ***18*** and β-ketonitrile ***14***



18 ***14***

Conditions	Yield
TsOH xylene reflux	---
TMSOTf CH_2Cl_2 -78°C	---
1) ***14*** + TMSOTf / Et_3N 2) TMSOTf	---
1) ***41*** +  / Bu_3P	---
2) AgOTf / CH_2Cl_2 / 0°C	
$TiCl_4$ / CH_2Cl_2 / 0°C	---
$TiCl_4$ / CH_2Cl_2 / Et_3N / 0°C	---
$TiCl_4$ / CH_2Cl_2 / -78°C	---
1) ***14*** + TBDMSCl / Et_3N / CH_2Cl_2 / 0°C 2) $TiCl_4$ / CH_2Cl_2 / -78°C	---

--- = no product observed



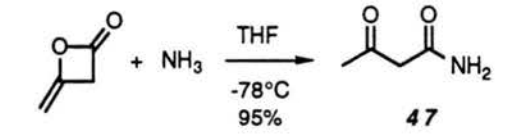
Proposed Salvage Pathway for Synthesis of Pharmacaphore ***11***

Scheme 6

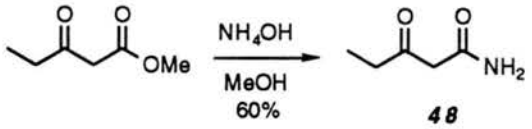
base followed by methyl iodide did not yield the α-methyl β-keto nitrile. As a control, ethyl acetoacetate was subjected to the same methylating conditions and did yield the methylated product. The β-keto nitrile approach was then abandoned.

As the β-keto nitrile proved unreactive, a β-keto amide was then needed for a similar coupling. Diketene was treated with ammonia to give acetoacetamide **47** in excellent yield (Eq. 7). Since the β-keto amide lacks a carbon as in Scheme 2, this easily accessible compound was used as a model for reactivity and product determination in the coupling with acetal **18**. The required propionyl acetamide **48** was synthesized in fair yield by reaction of methyl propionylacetate with ammonium hydroxide (Eq. 8).

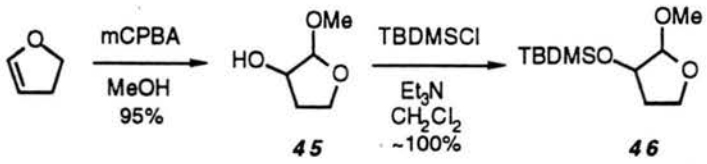
As the synthesis of acetal **18** was relatively long and low yielding for a key starting material, an alternative synthesis was sought. 2,3-Dihydrofuran was treated with *m*-chloroperbenzoic acid in the presence of methanol to afford the hydroxy acetal **45** in excellent yield.[41] Subsequent protection of the hydroxyl as the *t*-butyldimethyl silyl ether[42] gave the protected methoxy acetal **46** in a two step sequence in 95% overall yield (Eq. 9).



47 (Eq. 7)

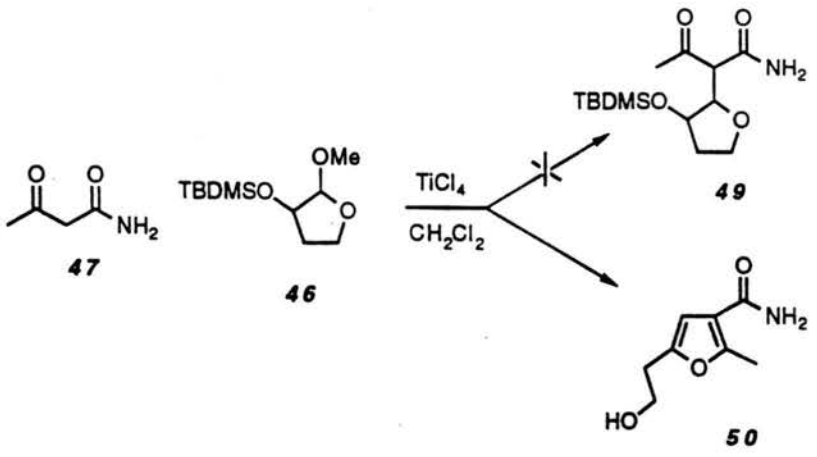


48 (Eq. 8)



45 **46** (Eq. 9)

Titanium couplings using methoxy acetals are well established.[26] The acetal **46** was coupled with β-keto amide **47** *via* titanium tetrachloride mediation in order to give the expected adduct **49** (Eq. 10). This was not the case however; extensive structural analysis including x-ray crystallography showed that the product of the reaction was the unexpected furan **50** (Figure 5 and Appendix C).



(Eq. 10)

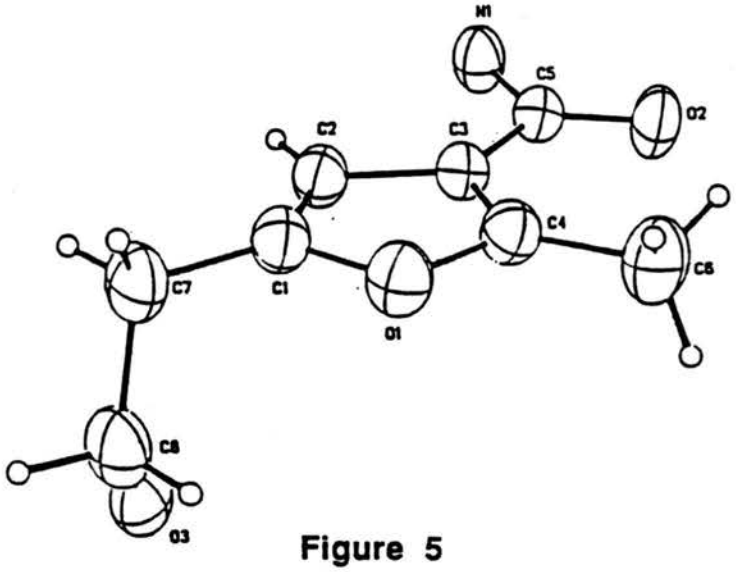
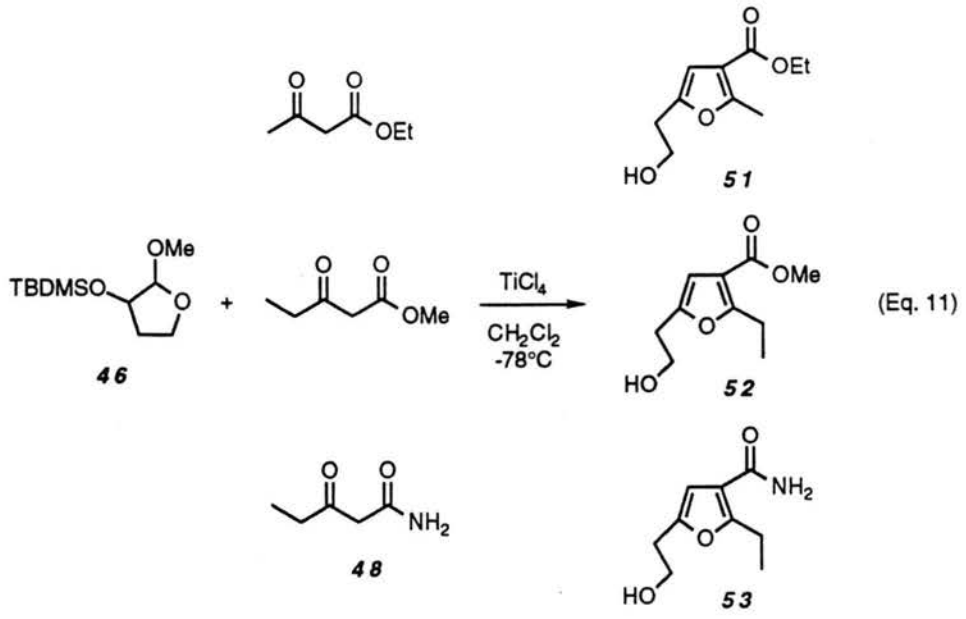


Figure 5

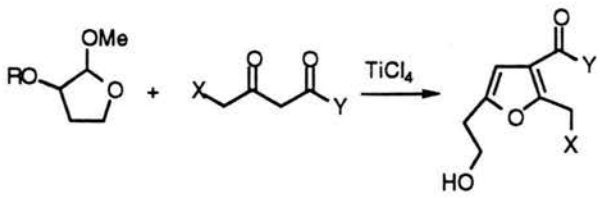
To further investigate the utility of this reaction, ethyl acetoacetate, methyl propionylacetate, and propionylacetamide **48** were coupled to siloxy acetal **46** to give the corresponding furans **51**, **52**, and **53** (Eq. 11). Using

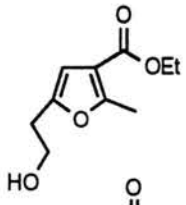
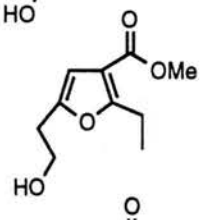
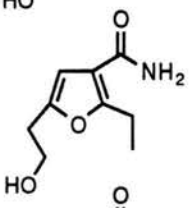
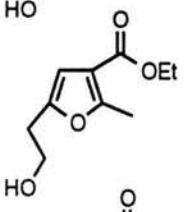
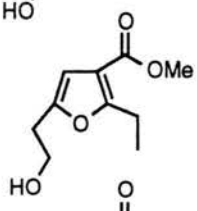
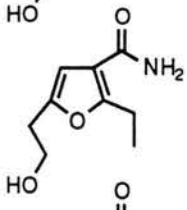
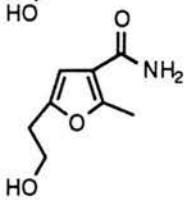


(Eq. 11)

hydroxy acetal **45** in the coupling reaction with the four β-keto carbonyl compounds also gave the corresponding furans but in varying yields (Table 4). It was found that the unprotected hydroxy acetal **45** gave better yields of

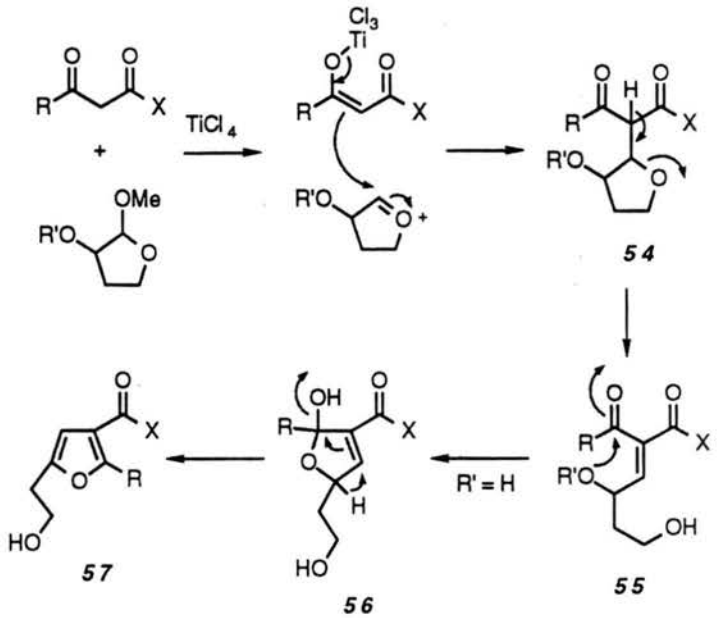
Table 4. Trisubstituted Furan Formation



R	X	Y	Product	Yield (%)
H	H	OEt		87
H	CH_3	OMe		76
H	CH_3	NH_2		---
TBDMS	H	OEt		50
TBDMS	CH_3	OMe		<10
TBDMS	CH_3	NH_2		84
TBDMS	H	NH_2		80

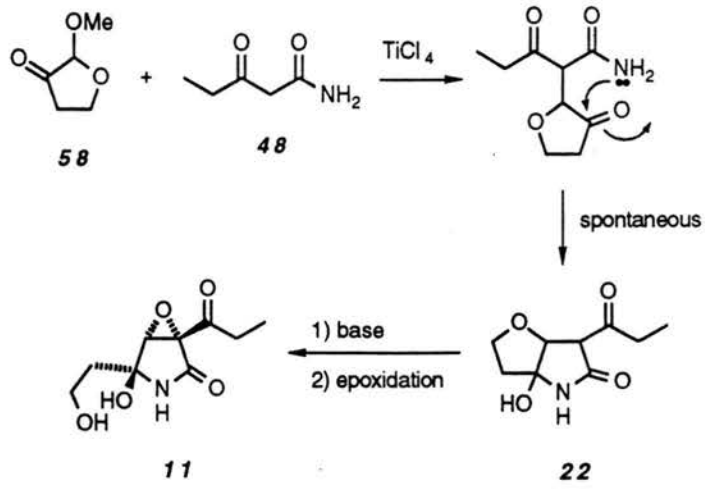
trisubstituted furans using the β-keto esters, but the siloxy acetal **46** produced the trisubstituted furans in higher yields using the β-keto amides. The reason for this preference is unclear.

The proposed mechanism for the formation of the trisubstituted furans is shown in Scheme 7. The initial adduct **54** spontaneously ring opens to the ene-diol **55** (or silyl ether). On methanol quench, silyl deprotection occurs[28b] followed by ring closer *via* the free hydroxyl attack on the ketone to give the intermediate hemi acetal **56**. Elimination of water then gives the furan **57**.



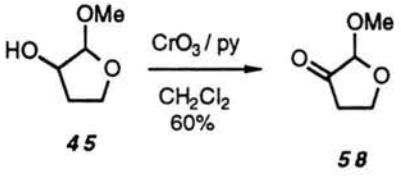
Scheme 7

The unexpected furan product appeared to be a blockade toward the target epoxy pyrrolidine-one **11**. It was envisioned that prior oxidation of the hydroxy acetal **45** to the keto acetal **58** may lead to intermediate **22** on titanium coupling with propionylacetamide (Scheme 8). This compound could then be carried on to the target as proposed in Scheme 2. The keto acetal **58** was formed in fair yield by Collins oxidation[36b] of the hydroxy

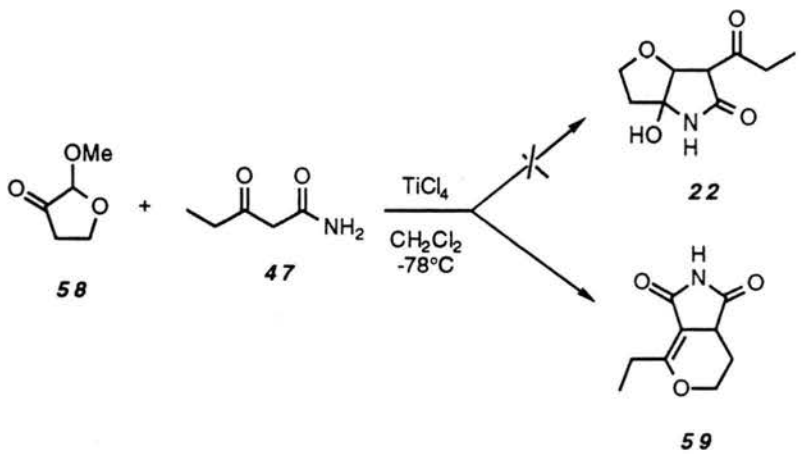


Scheme 8

acetal **45** (Eq.12). The coupling reaction gave, however, the highly unexpected succinimide derivative **59** (Eq. 13); the structure of which was determined by x-ray crystallography (Figure 6 and Appendix C). This compound could be converted in no obvious manner to the target **11** and was considered to be a dead end. The mechanism of the formation of imide **59** was not investigated.



(Eq. 12)



(Eq. 13)

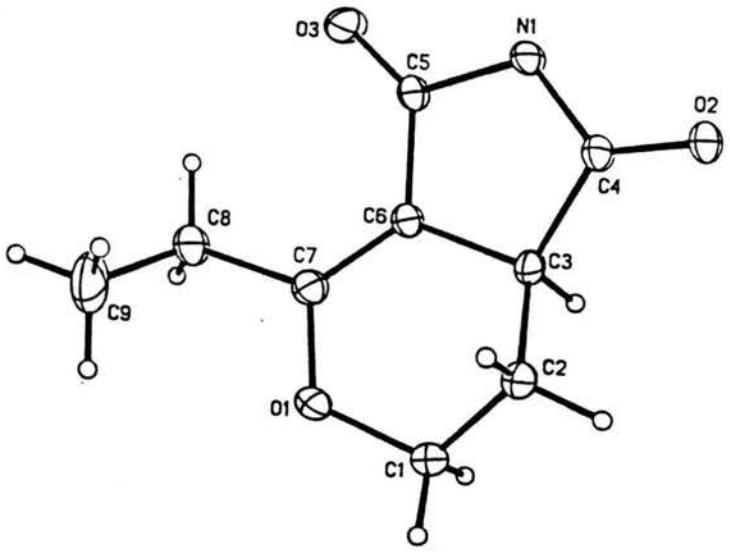
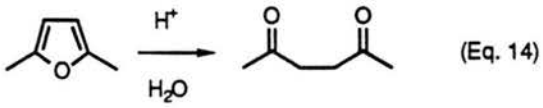
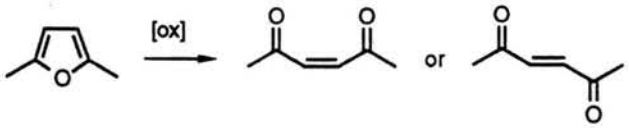


Figure 6

On examination of the structure of the furan amide **53**, it was noted that this compound has the correct number of carbons to proceed with the synthesis of heterocycle **11**. It is known that furans on acidic hydrolysis give 1,4-diones[43] (Eq. 14) and on oxidation give ene-diones[44] (Eq. 15). Using

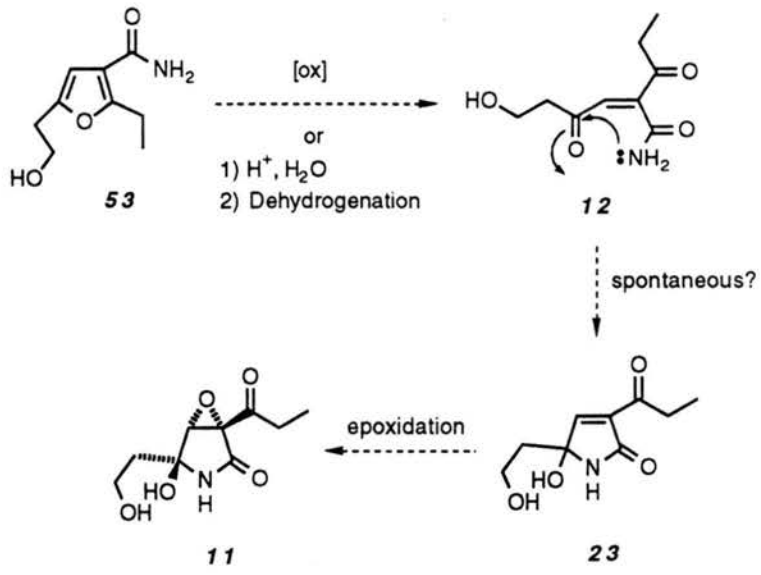


(Eq. 14)



(Eq. 15)

furan **53**, it was envisioned that proper oxidation to the *trans* ene-dione[44b,f] would be followed by amide attack on the newly formed ketone to give the pyrroline-one **23**. Epoxidation can then produce the pharmacophore of fusarin C **11** (Scheme 9).



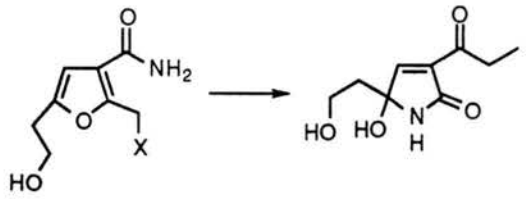
Scheme 9

Several attempts to oxidize the furan to the *trans* ene-dione **12** (and thus the pyrroline-one **23**) were performed (Table 5). Of these experiments only the singlet oxygen oxidation[45] gave a potential product (Scheme 10). However, silica gel column chromatography appeared to decompose this product and positive identification of the desired pyrroline-one **23** was not accomplished. Acid hydrolysis produced no products of recognizable structure. Oxidation gave aldehyde products resulting from primary alcohol oxidation with subsequent reaction to give complex mixtures of unknown products.

The free hydroxyl of furan **53** appeared to be the cause of some problems in the oxidation reactions. It became necessary to protect this hydroxyl, and the *t*-butyldimethylsilyl ether protection proceeded in excellent yield (Eq. 16).

A similar reaction was then performed using *meta*-chloroperbenzoic acid. This oxidant is known to give *cis* ene-diones[44e,g] in an electrocyclic ring opening fashion (Eq. 17). In the presence of light, the *cis* ene-dione **62** formed from amido furan **61** should isomerize to the *trans* ene-dione **63**.[46] This

Table 5. Oxidation Attempts of Furan ***53*** to Pyrroline-one ***23***

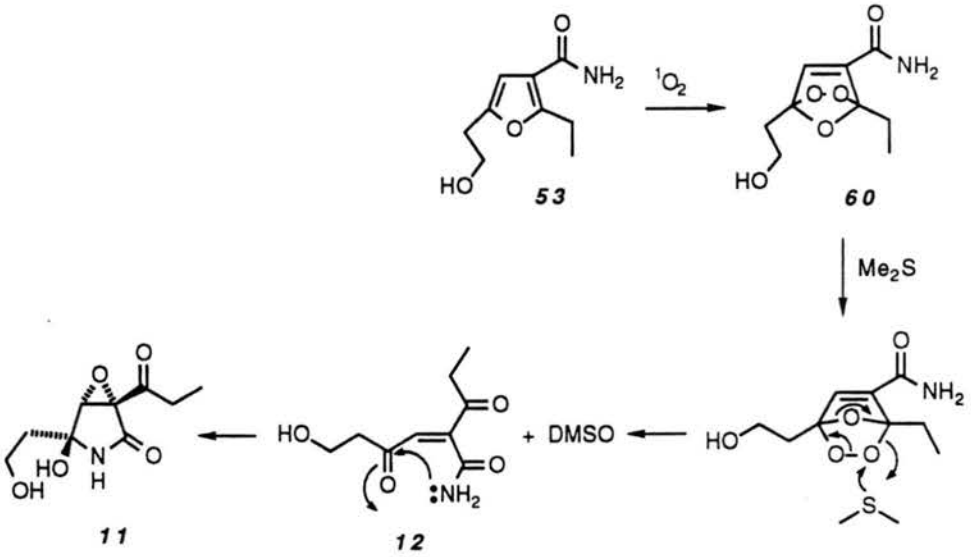


Conditions	Result
1N HCl (DDQ)	---
PCC	Aldehydes
1) TBDMSCl, Im DMF 2) PCC	---
1) $^1O_2$, CH_2Cl_2 2) Me_2S	*
1) $^1O_2$, CH_2Cl_2 2) MeOH, Ph_3P	---
1) Ac_2O, py 2) $^1O_2$, CH_2Cl_2 3) Ph_3P	
H_2O_2 / NaOCl, MeOH	---
1) Br_2 / MeOh, Et_2O, -35°C 2) H^+	---
1) Ac_2O, py 2) H^+ (DDQ)	
CAN, H_2O, CH_3CN	---
mCPBA, CH_2Cl_2	*

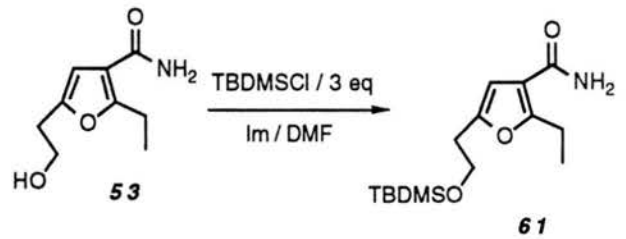
* = product observed in crude, decomposition on purification

--- = no product observed

should then ring close to give the pyrroline-one **64** (Eq. 18). Using one equivalent of peracid gave a reaction, but again the pyrroline-one product could not be isolated. Surprisingly, using two equivalents of peracid, the initially formed pyrroline-one is epoxidized to give in one step from silyl protected hydroxy amido furan **61** the epoxy pyrrolidine-one **65** in fair yield (Eq. 19). This result supports the high reactivity of the initial pyrroline-one adduct **64**; since *m*-chloroperbenzoic acid is an electrophilic reagent and should not epoxidize the highly electron deficient double bond.

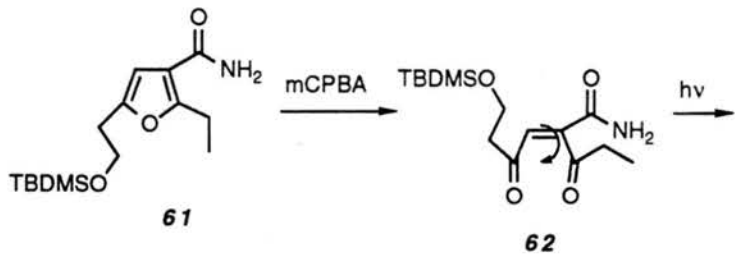


Scheme 10

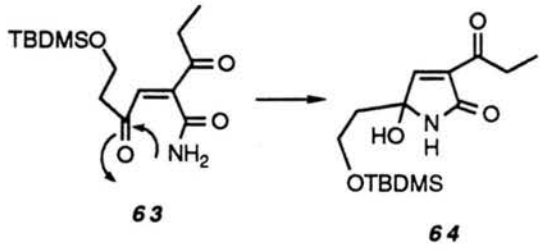


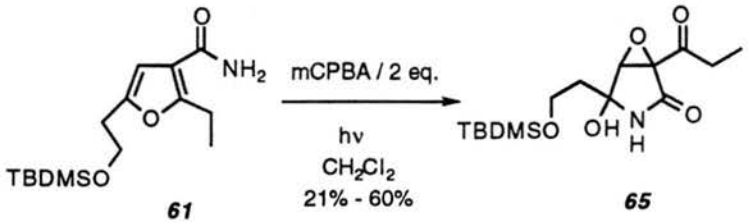
(Eq. 16)

(Eq. 17)



(Eq. 18)

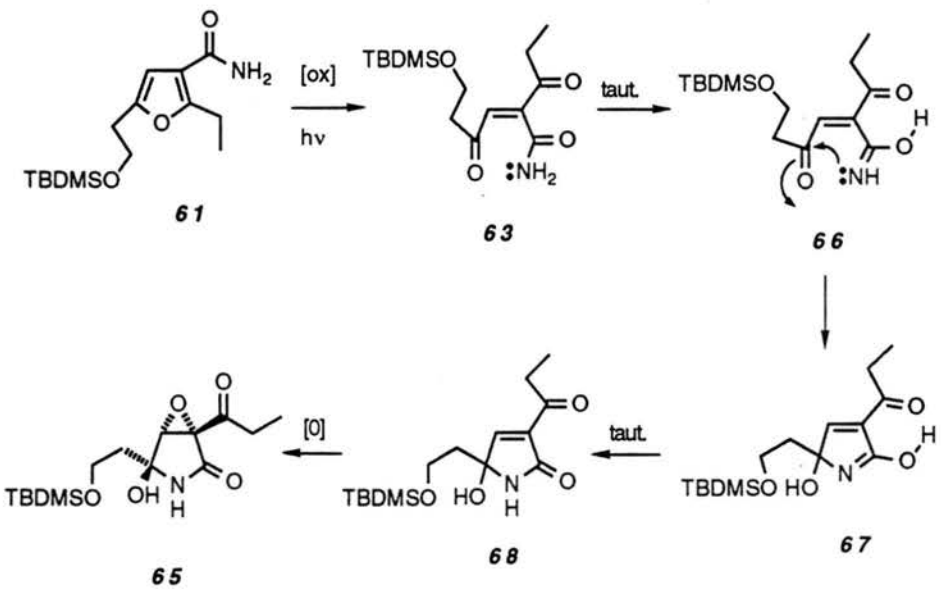




(Eq. 19)

This key reaction of oxidative ring opening of the furan, isomerization of the double bond followed by ring closure, and subsequent epoxidation was further studied. The product **64** was formed consistently in 21% yield after 30 min. in the presence of light. No desired product was found with similar conditions excluding light, supporting the need for light induced isomerization of the double bond. On longer reaction time of 24 h the yield increased to 60%. Crude proton NMR of the 30 min. reaction showed a considerable amount of compound resembling furan **61**, but the vinyl peak moved downfield to δ 7.0 from δ 6.1. This could be the intermediate pyrroline-one **64**. These results suggest the oxidation of the furan to the ene-dione **62** with subsequent isomerization of the double bond being relatively fast, while the epoxidation of the pyrroline-one is slow. It is unknown whether ring closure occurs before epoxidation or after, but the ring closure itself is interesting.

Amides do not usually act as nucleophiles because of the nitrogen lone pair being utilized in carbonyl resonance. The β-ketone may play a crucial role in increasing the nucleophilicity of the amide lone pair. The ene-dione amide **63** may undergo tautomerization to the ene-dione imine-ol **66**. This imine-ol can form a six membered ring *via* hydrogen bonding to stabilize this imine form. The lone pair on the nitrogen imine is no longer in resonance leaving it free to participate in nucleophilic attack on the carbonyl giving the pyrroline-imine **67**. Tautomerization to the pyrroline-one **68** followed by epoxidation (or epoxidation occurring at a previous point) would give the desired epoxy hemi-amidal pyrrolidine-one **65** (Scheme 11). The deoxo ene-one amide was not applied to the reaction in order to test this hypothesis.



Scheme 11

The reaction gives all four possible diastereomers of **65**. Of these, two pairs of enantiomers are present to produce two sets of diastereomers (Figure 7), one pair with the epoxide and hydroxyl moieties *trans*, and one pair with these two moieties *cis*. The diastereomers produced were separable by chromatography in a two to one ratio. NOE data gave, using the methine

proton and hydroxyl proton, 4% enhancement on the major diastereomer versus a .01% enhancement on the minor diastereomer (Figure 8).

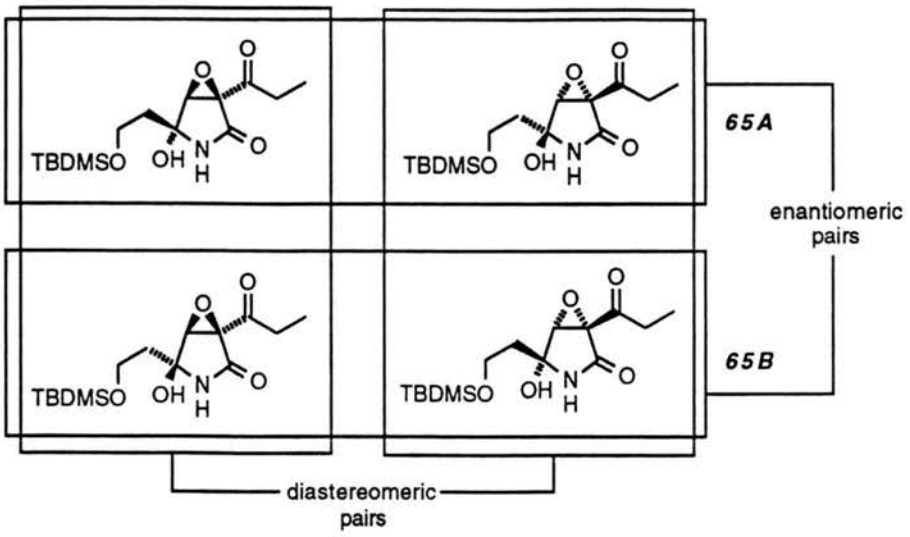


Figure 7

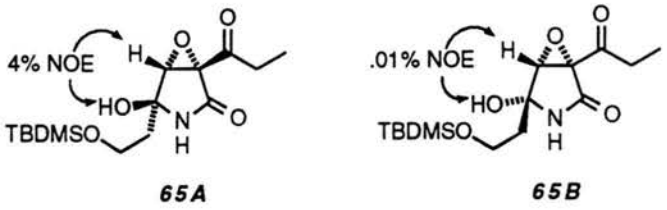
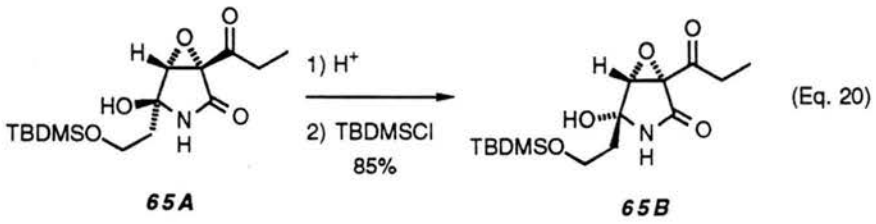
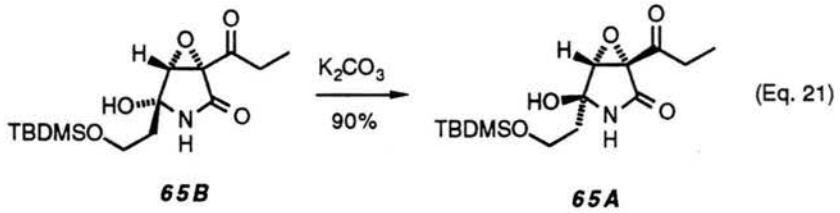


Figure 8

Further studies of the epoxy hemi-amido pyrrolidine-one ethyl ketone product were performed to investigate the structure and structural integrity of the highly functionalized heterocycle. On treatment of the major diastereomer, diastereomer **65a**, (where the epoxide and hydroxyl moieties are *trans*) with acid followed by resilylation gave almost exclusively the minor diastereomer **65b**, in which the epoxide and hydroxyl moieties are *cis* (Eq. 20). Alternatively, treatment of the *cis* diastereomer **65b** with aqueous carbonate gave the *trans* diastereomer **65a** (Eq. 21).

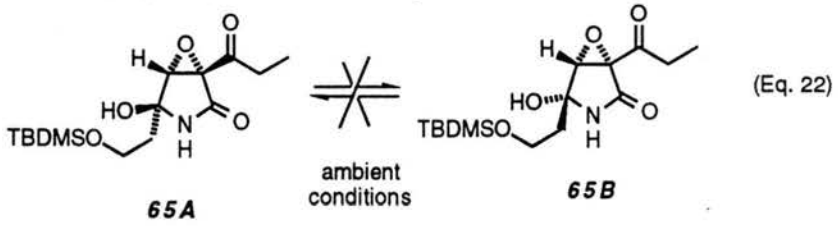


(Eq. 20)



(Eq. 21)

These results (along with the fact that the diastereomers are separable) suggest that the equilibrium between the two *cis* and *trans* forms of heterocycle **65** (Eq. 22) is extremely slow at ambient non-aqueous

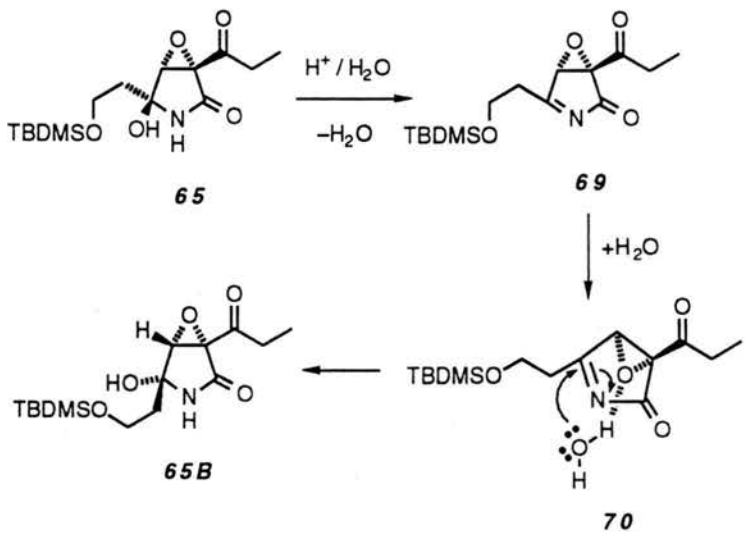


(Eq. 22)

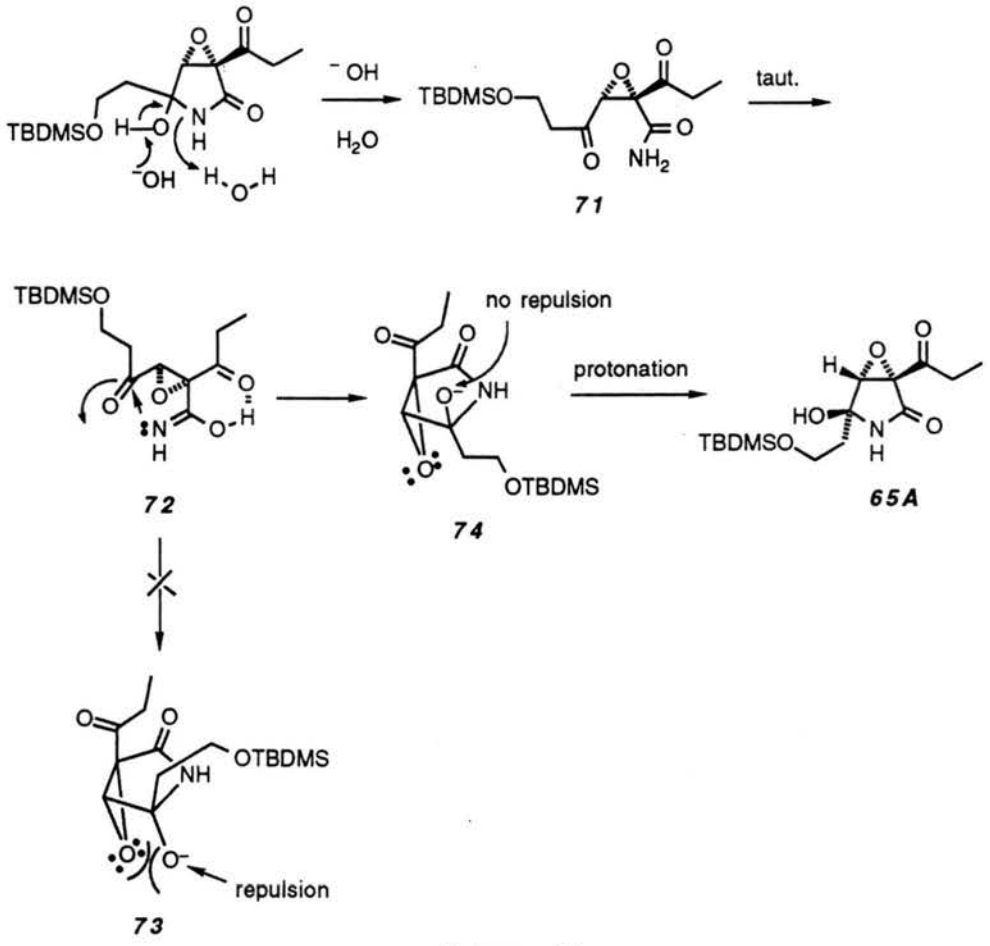
conditions. This stability may arise from hydrogen bonding of the hemi-amidal hydroxyl hydrogen to the hydroxyethyl (or siloxyethyl) oxygen. However, the epimerization at the hemi-amidal carbon in aqueous media is facile, resulting in an equilibrium mixture of the two diasteriomers. It is interesting to note that the differing conditions above result in two different compounds that are involved in the equilibria. The acidic conditions cleave the silyl group to give the diol, which then equilibrates to the more stable *cis* diastereomer. On the other hand, the silyl ether undergoes equilibration to afford the more stable *trans* diastereomer when exposed to aqueous media. In contrast to the more stable *cis* diol, the natural diol fusarin C, containing the pentaene side chain, is observed in the *trans* configuration. This would suggest a favorable

interaction between the side chain and the heterocycle to result in a more stable *trans* isomer of the natural product.

It is also very likely that this equilibrium between the *cis* and *trans* forms of the epoxy hemi-amidal is pH sensitive. This pH sensitivity becomes more clear on examining a feasible mechanism for the epimerization of the hemi-amidal carbon in both acidic media and basic media. In acidic media, the hydroxy pyrrolidine-one **65** loses water to give the imidate **69**. On rehydration, the epoxide oxygen assists the delivery through hydrogen bonding and possible general base catalysis to give the *cis* diastereomer **65b** *via* the intermediate **70** (Scheme 12). Basic media, however, would first give the keto-amide **72**. Ring closure would then proceed *via* attack on the carbonyl face to give the electronically less sterically congested intermediate **74**. The negative charge on the resulting hydroxyl would exert less electronic repulsion on the epoxide oxygen lone pairs in the *trans* intermediate **74** than in the *cis* intermediate **73** (Scheme 13).



Scheme 12



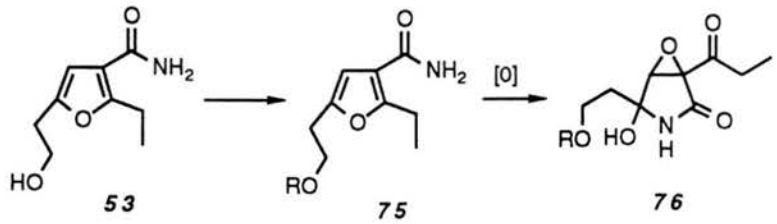
Scheme 13

Extensive NMR studies were performed on the product epoxy hemi-amidal pyrrolidine-one ethyl ketone **65**. Two-dimensional proton and two-dimensional proton-carbon spectra, along with proton decoupling, coupled carbon, and DEPT experiments gave data that match well with the structure assigned to **65**, the *t*-butyldimethylsilyl ether of the heterocyclic pharmacophore of fusarin C (Table 6 and Appendix B).

Table 6. NMR Data of Synthetic Epoxy Hemi-Amidal Ethyl-Keto pyrrolidine-one ***65*** Compared to NMR Data of Fusarin C

Carbon atom	δC/ppm	J(^{13}CH)/Hz	δH/ppm	J(HH)/Hz	Lit	δC/ppm	J(^{13}CH)/Hz	δH/ppm	J(HH)/Hz
17	168.47Sd	—	—	—		170.27S	—	—	—
13	60.70Sd	—	—	—		62.17Sd	—	—	—
14	65.56Dd	199.9	4.071d	2.5		64.15Dd	197.1	4.061d	2.1
15	84.65Sm	—	—	—		85.92S	—	—	—
18	36.27Ts	127.8	2.042ddd	14.5, 5.0, 4.0		36.27T	128.5	2.113ddd	14.6, 8.3, 4.1
			1.945ddd	14.5, 6.0, 4.5				2.059ddd	14.6, 6.0, 3.7
19	59.01Ts	143.5	3.985ddd	11.5, 6.0, 4.0		58.77Tt	144.0	4.050ddd	11.1, 8.3, 3.7
			3.891ddd	11.5, 5.0, 4.5				3.935ddd	11.1, 6.0, 4.1
12	201.32Sd	—	—	—		190.17Sm	—	—	—
11	32.90Td	126.0	2.576q	7.2		133.90S	—	—	—
24	6.66Qd	124.5	1.035t	7.2		11.55Qd	128.6	1.981d	1.3

The product **65** gave a crystalline solid, but not of x-ray quality (even after varying several recrystallization solvents and techniques). To obtain a crystal of x-ray quality, it was thought that varying the protecting group on the hydroxyethyl oxygen should be a convenient handle to prepare a crystalline solid of x-ray quality. In order to carry out this substitution to obtain the desired heterocyclic epoxide moiety, it was necessary to functionalize the hydroxy furan **53** with the desired protecting group with subsequent oxidation. Several different groups were attached to the furan followed by oxidation of the furan **75** to the epoxy hemi-amidal pyrrolidine-one ethyl ketone **76** (Eq. 23). The yields of the two transformations varied as shown in Table 7. Of the product epoxy heterocycles synthesized, none produced x-ray quality crystals.



(Eq. 23)

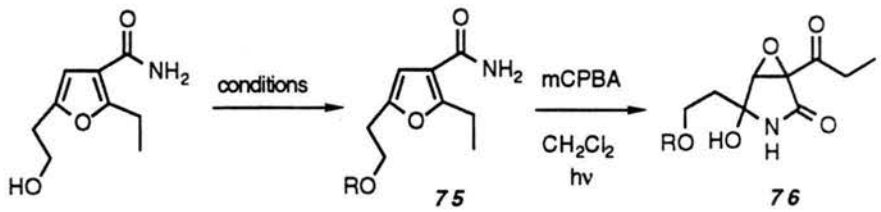
As the synthesis of the heterocyclic portion of fusarin C was completed in the five step sequence in 47% overall yield from dihydrofuran (summarized

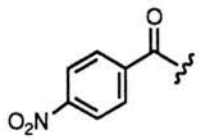
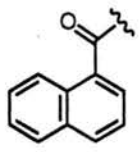
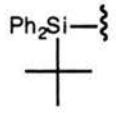
in Scheme 14), and the structure well established *via* spectroscopic techniques, the synthesis of fusarin C was continued.

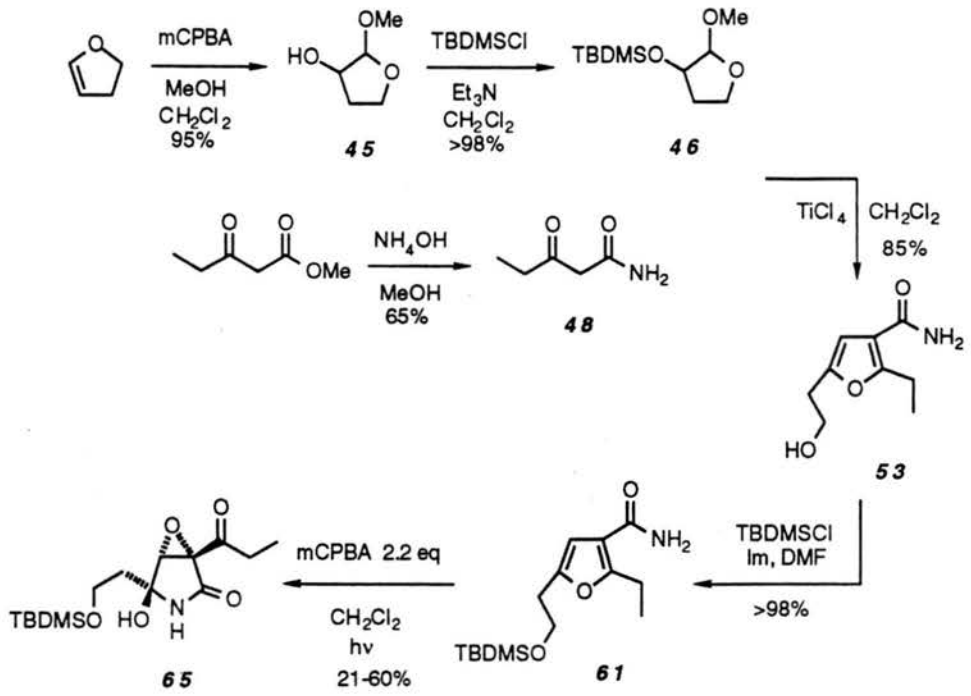
The next step in the synthesis was to functionalize the methylene of the ethyl ketone moiety of the heterocycle. The plan from this point was to convert the heterocycle **65** to the phosphonate ester **77**. The phosphonate ester could then be coupled *via* the Wadsworth-Emmons[38,54] reaction with the tetra-ene aldehyde ester **15** to give, on deprotection, fusarin C (Scheme 15).

An extensive variety of conditions were used to synthesize the

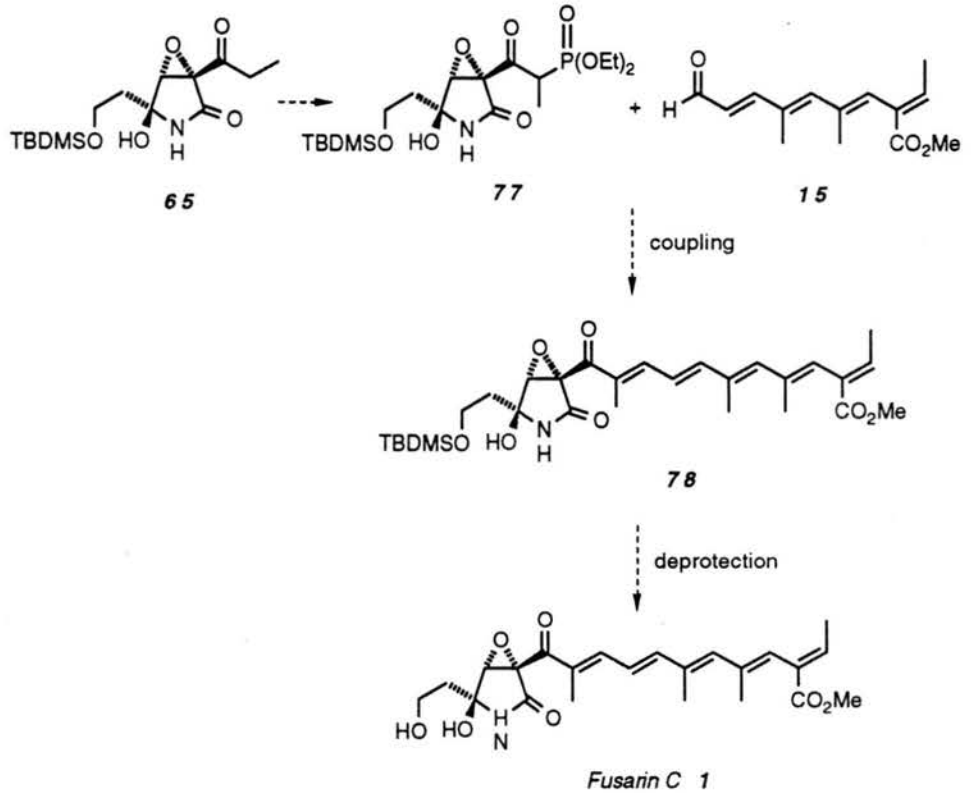
Table 7. Efforts to Synthesize X-Ray Quality Crystals of Epoxy-Pyrrolidine-One ***76***



B	B	Conditions	Yield (%75)	Yield (%76)
75A		R–Cl / py / CH_2Cl_2	15	20
75B		R–Cl / py	40	37
75C		R–Cl, Im, DMF	50	30

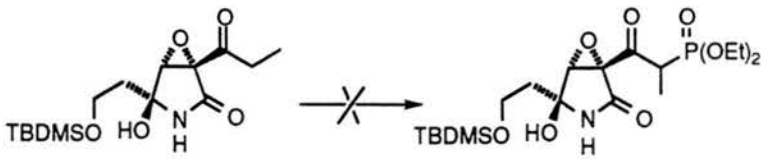


Scheme 14



Scheme 15

Table 8. Efforts to Synthesize Epoxy-pyrrolidine-one Phosphonate ***77*** *via* Ethyl Ketone ***65***



65 ***77***

Conditions

1) NBS / CCl_4 / reflux
2) $(EtO)_3P$ / THF / R.T.

1) NBS / CCl_4 / reflux
2) $(EtO)_3P$ (neut) / R.T.

1) NBS / CCl_4 / reflux
2) $(EtO)_3P$

1) NaOH / Br_2 / MeOH
2) $(EtO)_3P$ / THF / reflux

1) NaOH / I_2 / MeOH
2) $(EtO)_3P$ (neut) / Δ

$NaN(SiMe_3)_2$ / tol / 0°C / $(EtO)_2P(O)Cl$

$KN(SiMe_3)_2$ / THF / -78°C / $(EtO)_2P(O)Cl$

$Li(SiMe_3)_2$ / THF / -78°C - -40°C / $(EtO)_2P(O)Cl$

$K(SiMe_3)_2$ / THF / 0°C / $(EtO)_2P(O)Cl$

1) TMSCl / Et_2N / CH_2Cl_2
2) $(EtO)_2P(O)Cl$

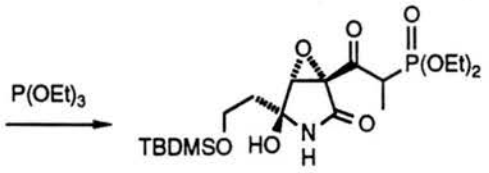
1) I_2 / NaOH / MeOH
2) $P(OEt)_3$ / THF / R.T.

NaH / THF / $(EtO)_2P(O)Cl$

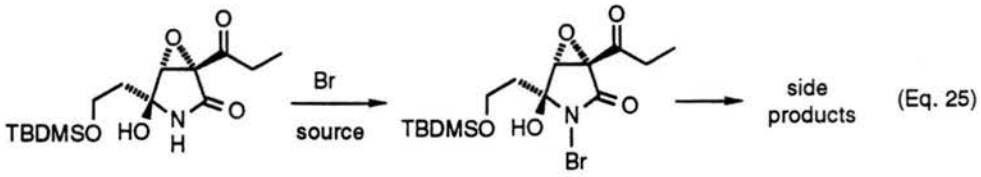
halogenation of the α-ketone position followed by the Arbuzov reaction using triethyl phosphite would afford the desired phosphonate **77** (Eq. 24). Many problems existed in this approach. The amide nitrogen could be halogenated causing subsequent difficulties[47] (Eq. 25). In radical reactions epoxides are

65

(Eq. 24)



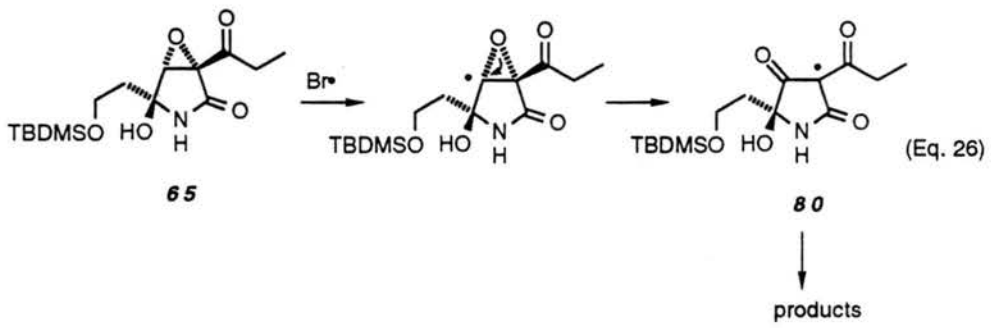
77



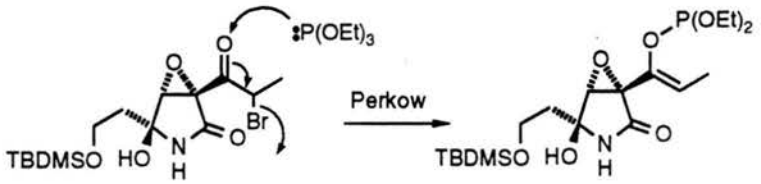
65 *79*

(Eq. 25)

prone to undergo rearrangement to ketones[48] (Eq. 26). α-Halogenated ketones are shown to undergo the Perkow reaction[49] to give enol phosphates rather than the Arbuzov reaction to result in the desired phosphonate ester (Eq. 27). The sum of these possible side reactions proved adequate for a lack of success in synthesizing the phosphonate ester **77**, as no desired product was observed.

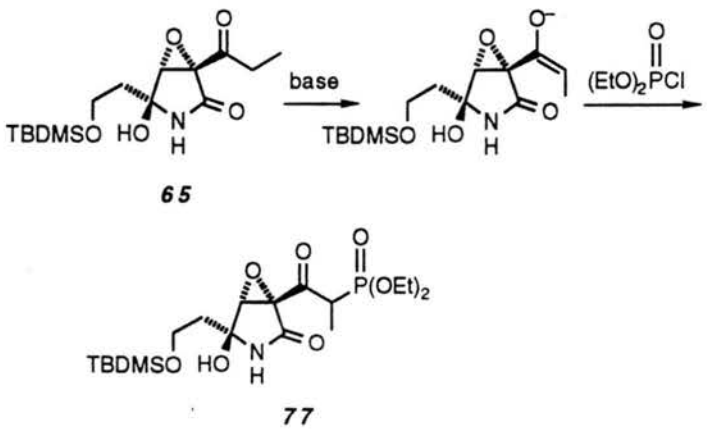


65 80 (Eq. 26)



78 81 (Eq. 27)

A different approach from the epoxy hemi-amido pyrrolidine-one ethyl ketone was investigated to form the desired phosphonate ester **77**. It was envisioned that base induced enolate formation of the ketone moiety followed by quenching of the enolate with a chlorophosphate[35] should produce the desired phosphonate ester **77** (Eq. 28). Again, no product was identified (Table 8).

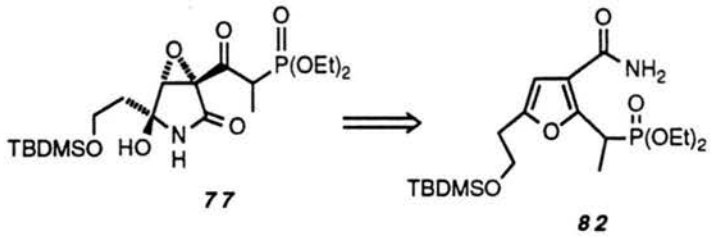


65 (Eq. 28)

77

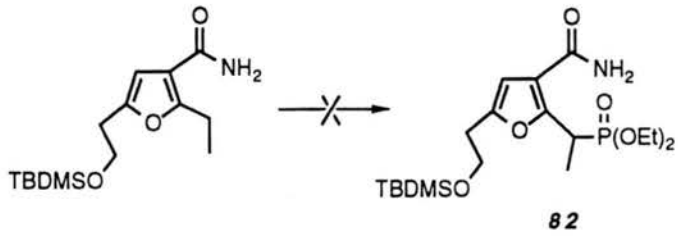
The desired phosphonate ester **77** was then sought *via* an alternative synthetic route. Conceivably, the phosphonate ester **77** can be formed from the precursor phosphonate ester furan **82** *via* the oxidative procedure

established (Eq. 29). The desired position for functionalization is similar to a benzylic position,[50] and may react similarly.

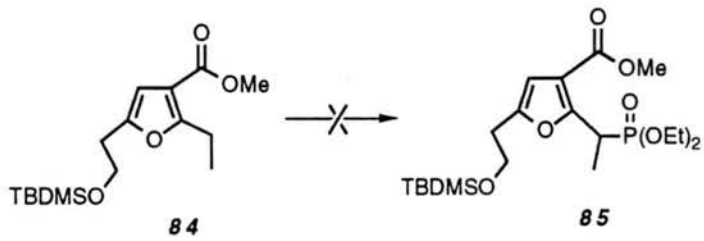


(Eq. 29)

Various conditions were utilized in the attempt to synthesize the phosphonate ester furan **82** (Table 9). Using the amido furan as the compound for phosphonate connection resulted in no product identified. This may be due to the added reactivity of the primary amide (Eq. 30). A step further back to the ester furan **84** was then the target for phosphonate functionalization (Eq. 31). This phosphonate ester furan **85** would then be



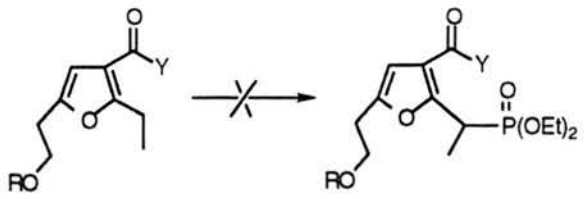
(Eq. 30)



(Eq. 31)

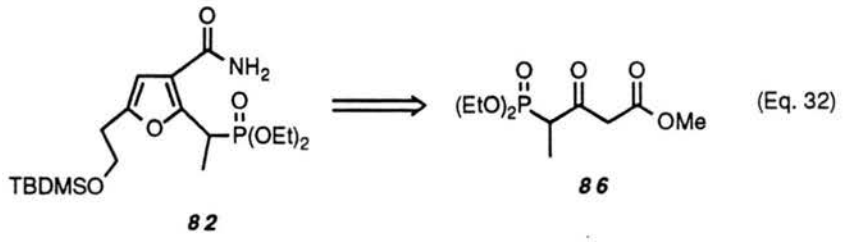
converted to the amide **82** and oxidized. Again, no desired product **85** was isolated (Table 9).

Table 9. Efforts to Synthesize Phosphonate Ester Furans ***82*** and ***85***

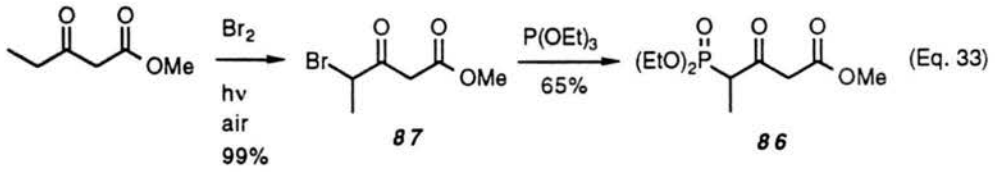


Y	R	Conditions
NH_2	TBDMS	$LiN(SiMe_3)_2$ / THF / -78°C / $(EtO)_2P(O)Cl$
NH_2	TBDMS	tBuLi / THF / -78°C / $(EtO)_2P(O)Cl$
NH_2	TBDMS	NBS / CCl_4 / reflux (Arbuzov)
NH_2	Ac	NBS / CCl_4 / reflux (Arbuzov)
OMe	H	NBS / CCl_4 / reflux (Arbuzov)
OMe	Ac	NBS / CCl_4 / reflux (Arbuzov)
OMe	TBDMS	nBuLi / THF / -78°C / $(EtO)_2P(O)Cl$
OMe	TBDMS	nBuLi / THF / R.T./ $(EtO)_2P(O)Cl$

Another step back along the proposed synthetic pathway was taken, to the β-keto amido and β-keto ester, at which point the compound will be functionalized as the phosphonate ester. The γ-phosphonate β-keto ester (or amide) would then be coupled to the acetal to give the corresponding furans (Eq. 32). The γ-phosphonate β-keto ester **86** was formed in two steps *via* bromination at the γ position[51] followed by a successful Arbuzov reaction[52] using triethyl phosphite in acidic media (Eq. 33).

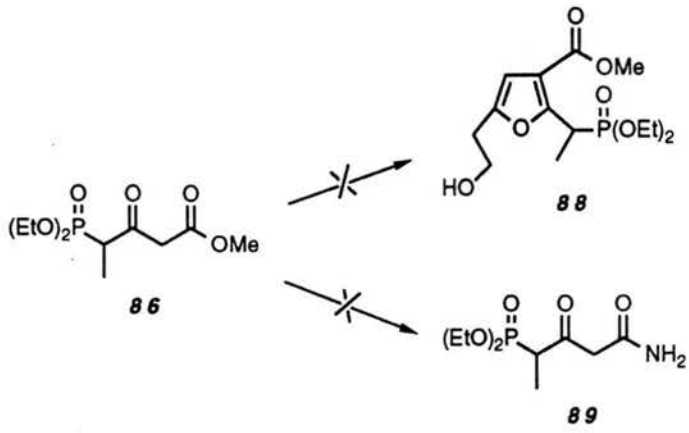


82 ***86*** (Eq. 32)



(Eq. 33)

Conversion of the γ-phosphonate β-keto ester **86** to neither the furan **88** nor the amide **89** were successful (Eq. 34, Table 10). It is believed that the



(Eq. 34)

titanium enolate of the phosphonate **90** either does not form or is not nucleophilic enough (a result of enolate delocalization) to attack the oxonium before oxonium decomposition (Figure 9), and no furan **88** is formed from the initial adduct. Various degrees of phosphoramide **91** may have been formed on treatment with ammonia which then could have reacted further (Eq. 35). From this result, the α-phosphonate ester epoxy hemi-amido pyrrolidine-one **77** approach to mediate coupling of the polyene chain was abandoned.

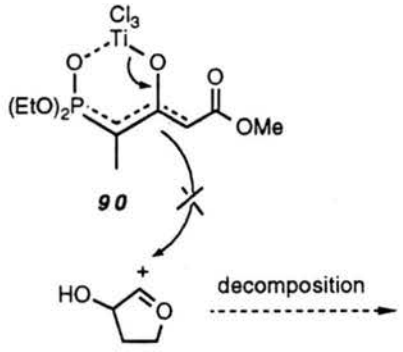
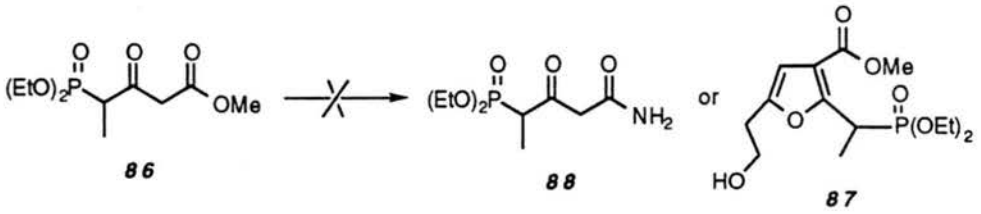
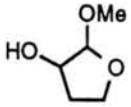
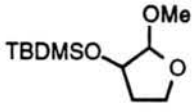
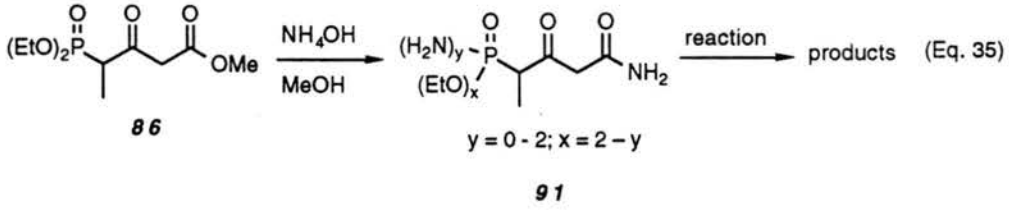


Figure 9

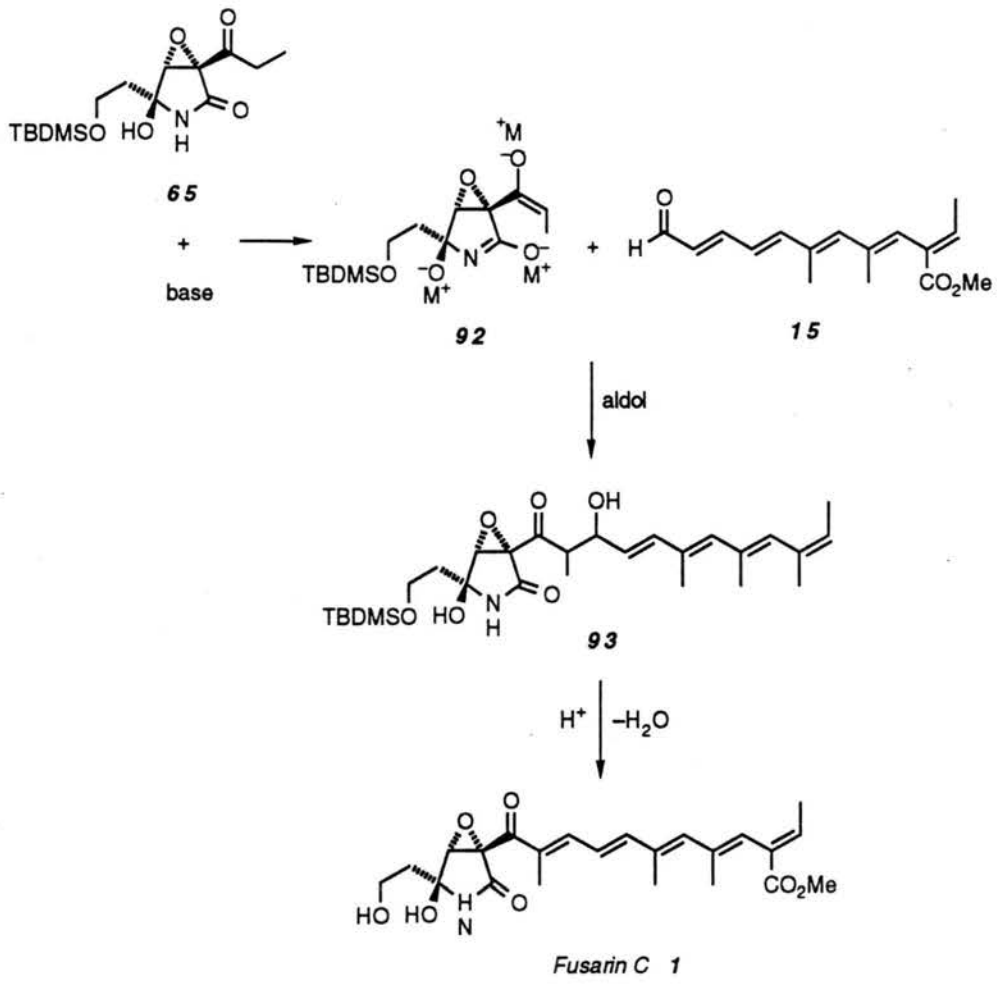
Table 10. Efforts to Incorporate Nitrogen in Phosphonate Ester ***86*** to Form Furan ***87***



Conditions	Desired Product
NH_4 / MeOH	***88***
 / 1.2 eq $TiCl_4$ / -78°C / CH_2Cl_2	***87***
▪ / 2.0 eq $TiCl_4$ / -78°C - R.T. / CH_2Cl_2	***87***
▪ / 3.0 eq $TiCl_4$ / 0°C - R.T. / CH_2Cl_2	***87***
▪ / 2.0 eq $TiCl_4$ / R.T. / CH_2Cl_2	***87***
 / 1.5 eq $TiCl_4$ / -78°C - R.T. / CH_2Cl_2	***87***

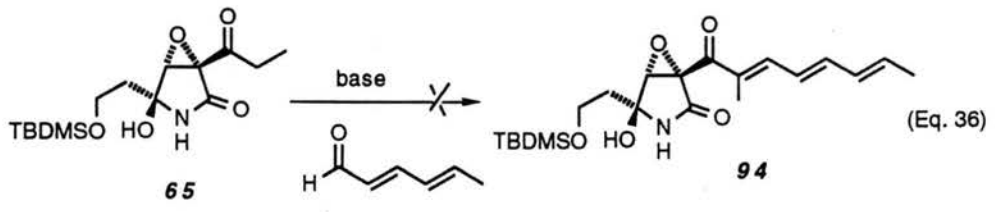


Attention was then again directed toward the epoxy hemi-amido pyrrolidine-one **65** in an alternate approach to the coupling of the two pieces of fusarin C; the aldol condensation.[53] Since efforts to protect the hemi-amidal alcohol failed, it was deemed necessary (Scheme 16) to form the di- or trianion of the ketone **92** in order to obtain the enolate. A multitude of conditions were applied using hexadieneal as a model for the final coupling (Table 11). The



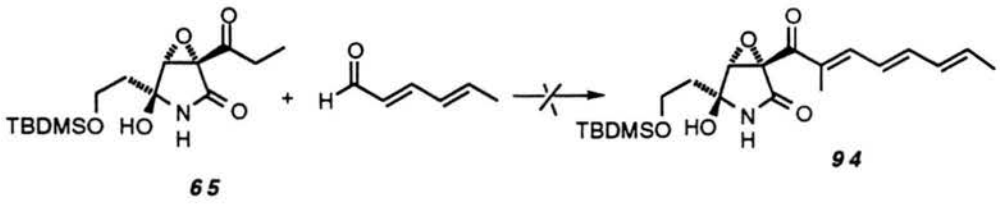
Scheme 16

desired triene **94** was not isolated (Eq. 36), nor was the initial hydroxyl intermediate.



The rationale for the failure of this aldol condensation approach is that a second acid-base reaction occurs between the di- or trianion and the unsaturated aldehyde. This would create the enolate of the aldehyde **95**

Table 11. Aldol Condensation Efforts Using Epoxy-pyrrolidine-one ***65*** and Hexadiene-al



65 ***94***

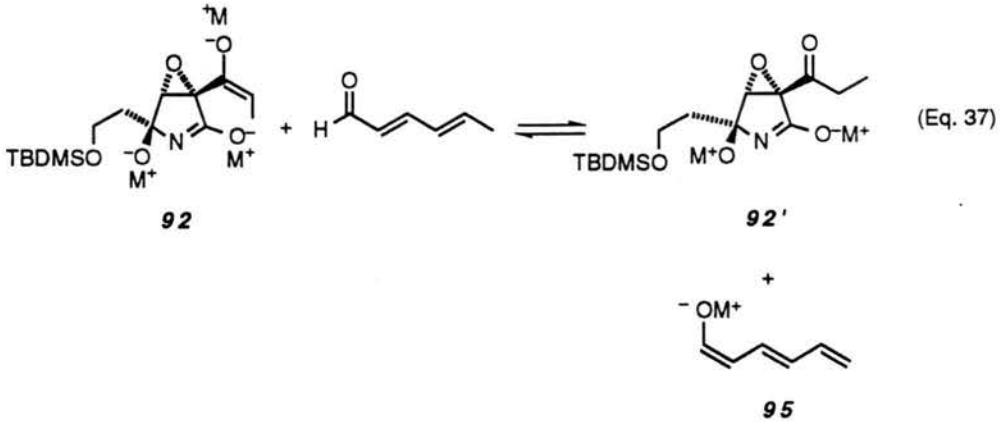
Conditions

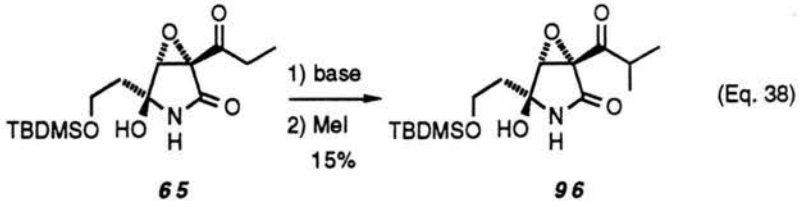
$NaN(SiMe_3)_2$ / THF / 0°C
$KN(SiMe_3)_2$ / THF / 0°C
MeONa / MeOH / 0°C / $CeCl_3$
$KN(SiMe_3)_2$ / THF / 0°C / $ZnCl_2$
9BBN–OTf / CH_2Cl_2 / Et_3N
$LiN(SiMe_3)_2$ / THF / -78°C
$LiN(SiMe_3)_2$ / THF / 0°C / $ZnCl_2$
LDA / THF / -78°C
LDA / THF / -78°C - 0°C / $ZnCl_2$
$NaN(SiMe_3)_2$ / THF / -78°C - 0°C / $ZnCl_2$
$NaN(SiMe_3)_2$ / THF–HMPA / 0°C / $CeCl_3$
tol / TsOH / R.T.
tBuOK / THF / R.T.
$NaN(SiMe_3)_2$ / THF / -78°C / $TiCl_4$
$NaN(SiMe_3)_2$ / DMF / -23°C
$NaN(SiMe_3)_2$ / tol / 0°C

which would not be electrophilic toward enolate **92**, and thus take the aldehyde out of the sphere of the reaction (Eq. 37).

Enolate formation of the heterocycle was then studied. Using methyl iodide as the electrophile, various conditions were used to form the enolate with subsequent methylation to give the isopropyl ketone derivative **96** (Eq.

38). Some hypotheses resulted from this study. One is that it appears that the trianion is indeed formed as the reaction shows considerable rate increase





with three equivalents of base. Another hypothesis is that in ethereal solvents, especially using lithium bases, a solvent cage is formed around the trianion, blocking attack of electrophiles (Figure 10). This was manifested in a slow

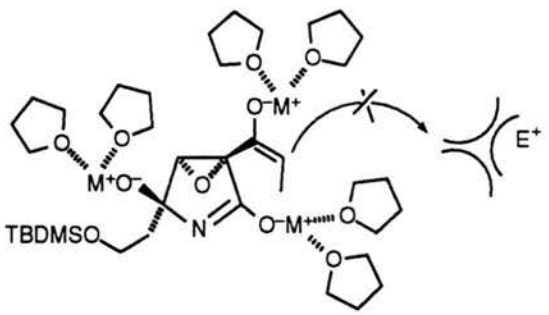
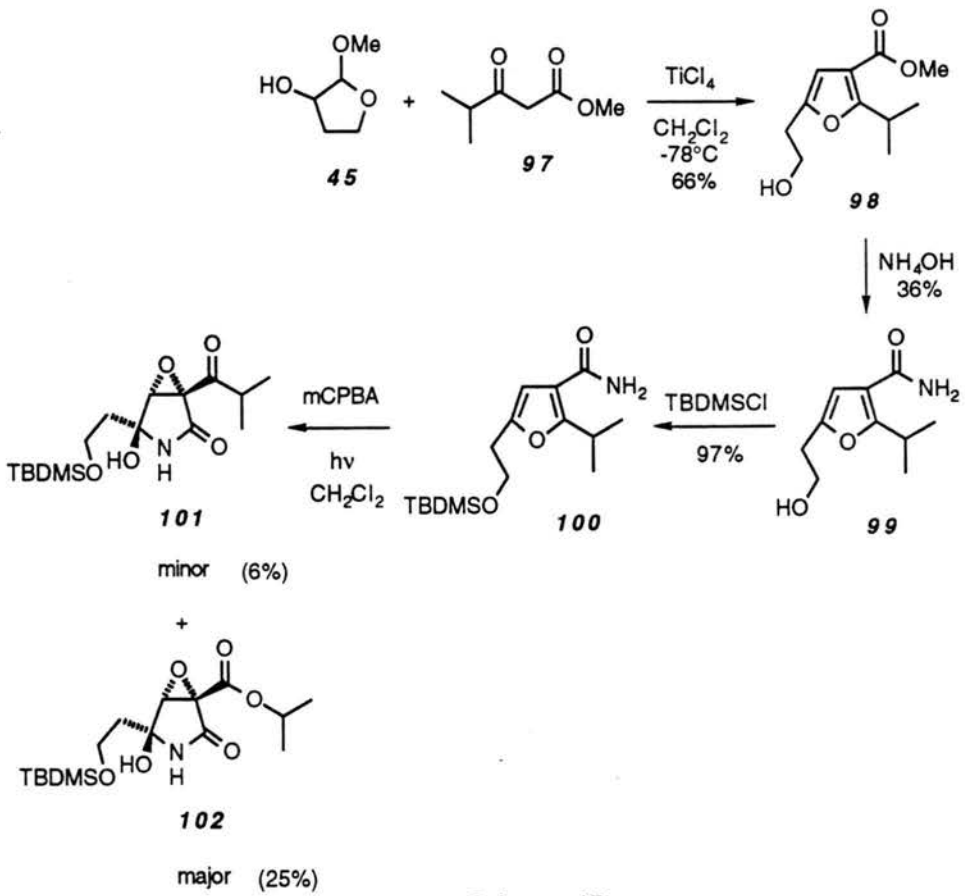


Figure 10

reaction rate in diethyl ether or tetrahydrofuran versus other solvents such as toluene (a weak coordinating solvent) or dimethyl formamide (a solvent which separates charge to aid in "naked"[55] enolate formation). An observation from these experiments was the relatively high temperatures required to generate

reactive enolate **92**. Quantitative recovery of the epoxy ketone **65** occurred at low (-78°C) temperature, while at intermediate temperature (-23°C) reaction occurred slowly and at high temperature (0°C) reaction occurred faster. At higher temperatures (>0°C) decomposition of the trianion became a major competing reaction.

To help support the methylated structure **96** from the enolate alkylation the compound was synthesized *via* an alternative route (Scheme 17).



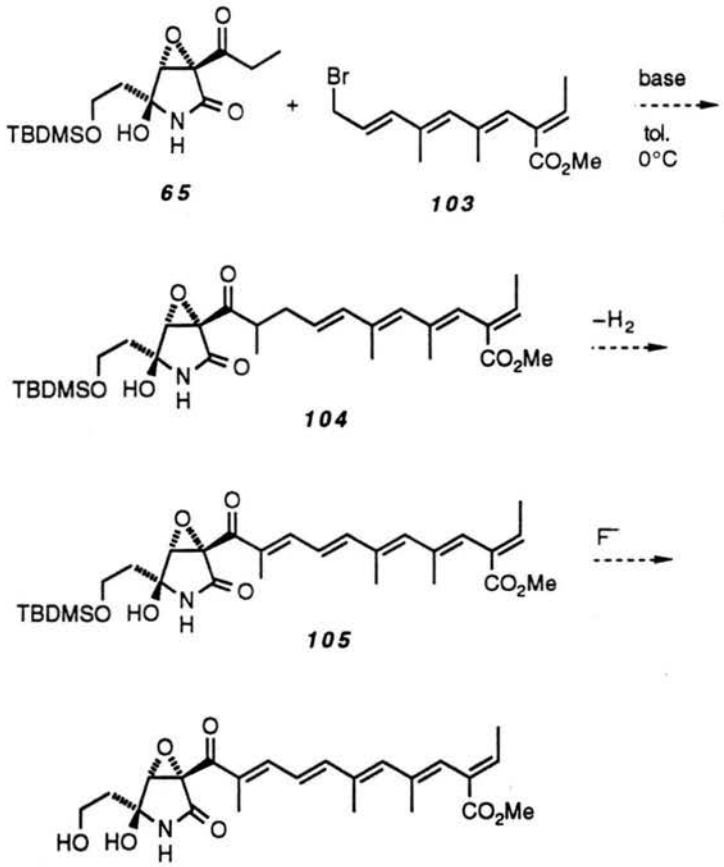
Scheme 17

Coupling of the β-keto ester **97** with ketal **45** gave the isopropyl furan ester **98**. Conversion of this ester to the amide **99**, followed by hydroxyl protection and subsequent oxidation gave the corresponding isopropyl keto epoxy hemi-amidal pyrrolidine-one **101** in low yield. Interestingly, the major product of the oxidation reaction was the ester product **102** resulting from Baeyer-Villager

oxidation[56] of the ketone. The higher substitution of the α-keto position enhances the reactivity toward the Baeyer-Villager oxidation considerably,[57,53b] and this reaction pathway becomes a significant factor in product determination.

Compounds **96** from alkylation and **101** from furan oxidation/rearrangement should be the same compound. On examining the spectra of each (see Appendix A), it is clear they are not identical. However, the spectra are similar and these compounds could easily be another pair of diastereomers. Because of the differences in reaction conditions (and in aqueous pH on work-up), these two compounds should be the *cis* and *trans* isomers of the same structure. Extensive structural proof was not performed to determine which compound contains the hydroxyl epoxide *cis*. and which compound is *trans*.

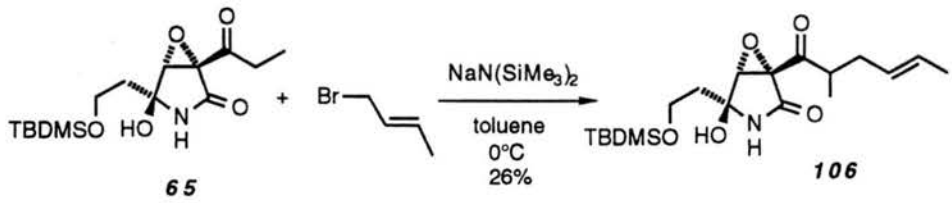
As the α-keto position on the epoxy hemi-amido pyrrolidine-one **65** can be alkylated, an alternative approach to fusarin C was devised. The ethyl ketone moiety could be alkylated with the corresponding allylic bromo tetra-ene **103** followed by dehydrogenation to give the penta-ene of fusarin C (Scheme 18).



Fusarin C **1**

Scheme 18

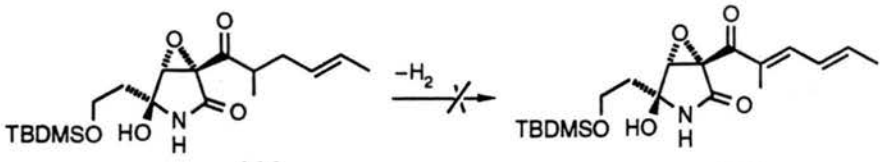
A model system beginning with readily available 2-butene was used for this study. Alkylation of the heterocycle proceeded in low yield (but exciting in the fact that product was isolated and characterized) to give the pentenyl methyl keto epoxy hemi-amidal pyrrolidine-one **106** (Eq. 39).



(Eq. 39)

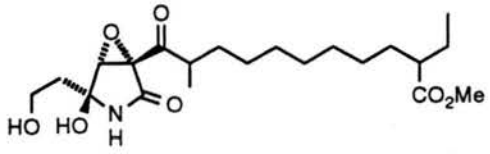
Extensive efforts to dehydrogenate[58] the α,β-keto positions of **106** to give diene **107** (Table 12) resulted in failure (Eq. 40). Oxidation *via* dicyanodichloroquinone at elevated temlperatures for extended periods of

time may have produced minute quantities of desired diene **107**, but the product was not fully characterized for lack of material and thus the reaction was not synthetically useful.



106 *107* (Eq. 40)

At this point it appeared that fusarin C was an unattainable target in the time available, and an alternative target was sought: decahydrodidemethyl fusarin C **108** (Figure 11). Upon completion of the synthesis of the saturated analogue of fusarin C, mutagenicity testing should reveal some

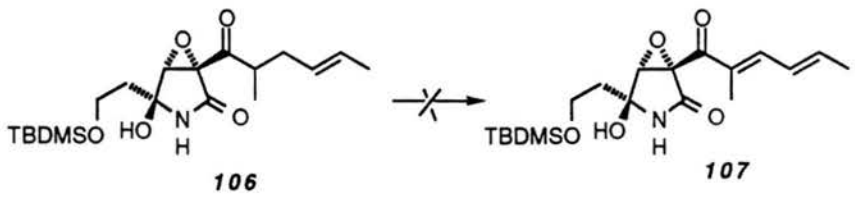


decahydro didemethyl fusarin C

108

Figure 11

Table 12. Dehydrogenation Efforts



106 *107*

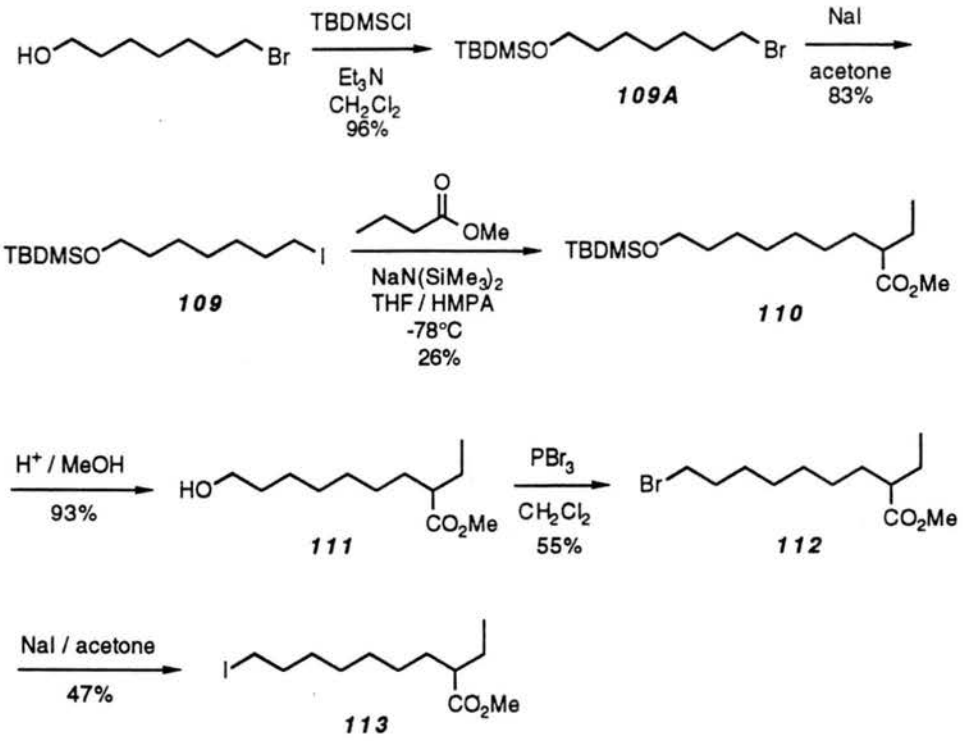
Conditions

DDQ / benzene / R.T.
PhSeCl / EtOAc / R.T.
$(PhSe–)_2$ / $NaN(SiMe_3)_2$ / THF / -23°C / HO_2
$(PhSe–)_2$ / $NaN(SiMe_3)_2$ / DMF / -23°C / H_2O_2
DDQ / Pd–carbon / EtOH / R.T.
DDQ / Pd–carbon / EtOH / reflux
Br_2 / THF / -78°C - DBU
$(PhSe–)_2$ / KH / DMF / R.T.
NBS / $CHCl_3$ / R.T. / hν - py
TMSOTf / Et_3N / CH_2Cl_2 - Pd(II)
DDQ / THF / HOAc / R.T.
DDQ / dioxane / reflux
DDQ / benzene / HOAc / R.T. - reflux
$FeCl_3$ / CH_2Cl_2 / R.T.
$PdCl_2$ / tBuOH / cat. HCl / 80°C
DDQ / dioxane / HOAc / reflux
SeO_2 / silica gel / EtOH / reflux
MnO_2 / CH_2Cl_2 / R.T.
$PdCl_2(CH_3CN)$ / $Pd(OAc)_2$ / dioxane / R.T.
nBuLi / THF / 0°C / DDQ
nBuLi / THF / 0°C / PhSe–pthalimide
NBS / CCl_4 / reflux–DBU

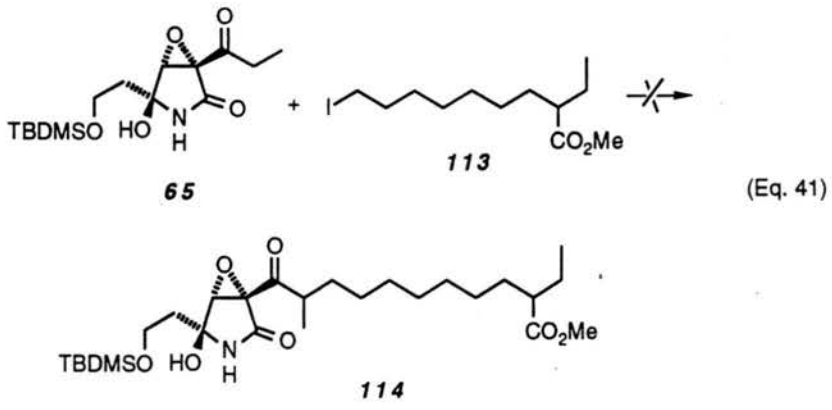
insight as to the function of the polyene chain of fusarin C. If the side chain is merely a transport vehicle, the saturated analogue should exhibit similar mutagenic characteristics to those of fusarin C. In the case of the side chain of fusarin C associating with DNA to aid in docking the heterocycle to react with DNA, the saturated analogue should exhibit a reduced mutagenic activity, as the structural rigidity of the unsaturated chain is lost in the saturated chain.

The saturated chain was synthesized in the following manner. Methyl butyrate was alkylated with 7-*tert*-butyldimethylsiloxy-1-iodoheptane **109** (formed from silylation of the bromo alcohol followed by halogen exchange) to give the decane methyl ester silyl ether **110**. The hydroxyl was deprotected to alcohol **111**, followed by bromination to give the primary bromide **112**. The bromide **112**, however, did not undergo alkylation with the epoxy hemi-amidal ketone **65**, thus the iodide **113** was formed using the Finkelstein reaction (Scheme 19).

Although the methylation of heterocycle **65** proceeded in fair yields, the saturated chain **113** did not couple as readily. Several different attempts were performed in order to obtain characterizable amounts of the target **114** (Table 13). The successful reaction conditions to give the silylated target **114** (Eq. 41) were not found, as no product was isolated in useful yields.



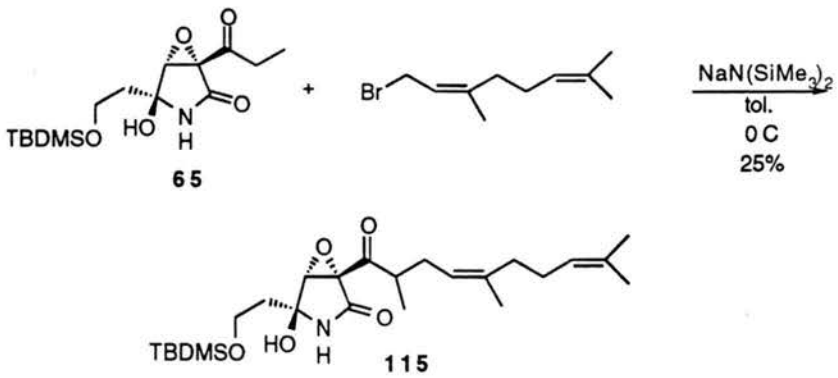
Scheme 19



The explanation for the lack of productive reaction is the difference in reactivity of the electrophile. Even though both methyl iodide and the allylic bromide did successfully alkylate the heterocycle using the same reaction conditions as the iododecane ester **113** (albeit in low yields), no product was observed when the aliphatic iodide was the substrate. This is a result of the difference in reactivity of the alkyl halides (and thus reaction rate). There is an

approximate 100 fold decrease in reaction rate[59] from the allylic bromide to the decyl-iodo ester. As the rate of alkylation became overwhelmingly slow, decomposition of the trianion became the only observed reaction.

With this result, it became apparent that a productive coupling between the heterocyclic epoxide and an alkyl chain required an allylic halide. A model for an aliphatic side chain to represent a non-rigid functionality capable of aiding passage through membranes was then chosen. Geranyl bromide, a ten carbon unit, eight carbons long, contains the allylic halide moiety required for productive coupling. This chain should contain the rotational freedom in order to test the function of the polyene chain of fusarin C while being lipophilic enough to aid in membrane transport. The coupling proceeded in low yield using the reaction conditions previously found (Eq. 42).



(Eq. 42)

With the formation of the C-12 chain ketone **115**, this gave three silated compounds with distinctly different chain lengths containing the proposed pharmacaphore of fusarin C (Figure 12). These three compounds were then desilated to give the corresponding diols. Using tetrabutylammonium fluoride as the desilating agent, the diols were produced in modest yields. The

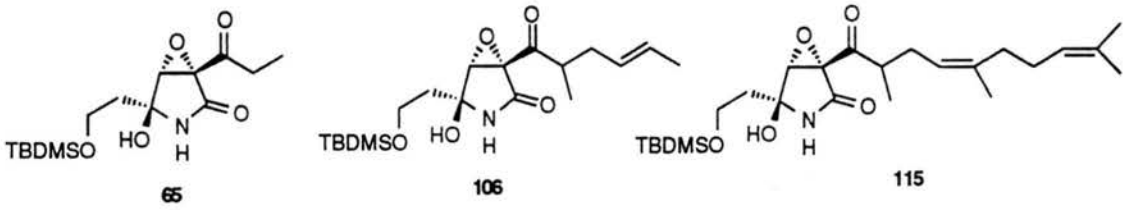
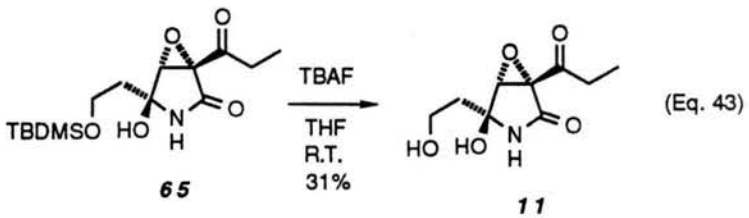
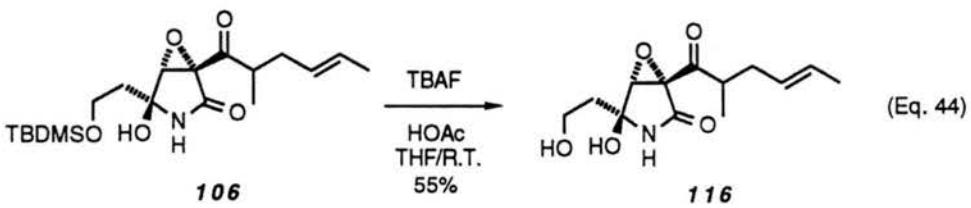


Figure 12

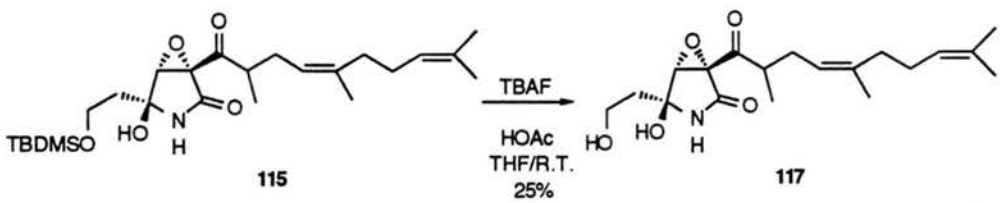
requirement for acetic acid addition in the cases of compounds **106** and **115** containing the alkene moieties is unclear, but it appeared that there was transfer of the silyl group to the double bond in the absence of the mild acid (Eqs. 43, 44, and 45).



(Eq. 43)



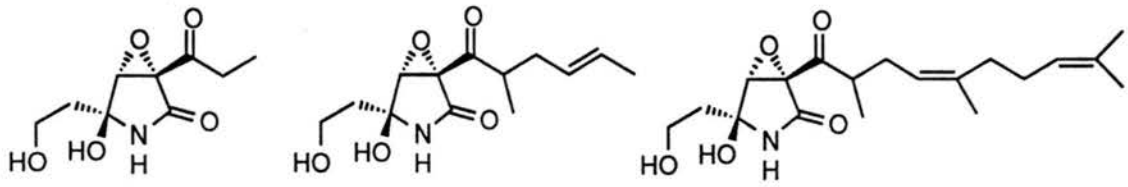
(Eq. 44)



(Eq. 45)

Conclusion

This research developed a short and elegant synthesis of the proposed pharmacaphore of fusarin C (summarized in Scheme 14). The synthesis is not stereoselective but has the potential for diastereoselective outcome. Although the crucial α,β-unsaturated ketone was not formed (thus preventing the total synthesis of the natural fungal metabolite fusarin C), three distinct non-natural analogues of fusarin C (Figure 13) were produced. These compounds contain



Synthetic Fusarin C Analogues

Figure 13

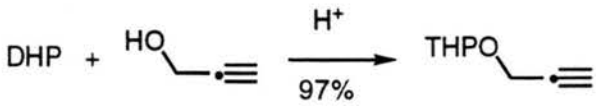
different side chains which should give the compounds varying degrees of hydrophobicity. The mutagenicity testing of these compounds may give insight to the function of the polyene chain of fusarin C as related to biological activity.

Chapter Three

Further Studies of Fusarin C and Other Heterocycles

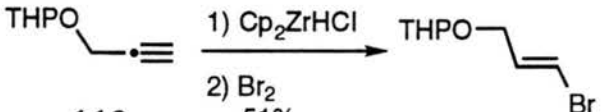
Efforts Toward the Synthesis of the Polyene Chain of Fusarin C

As in the case of the heterocyclic portion of fusarin C, the synthesis of polyene chain began with the synthetic plan shown in Scheme 3. Propargyl alcohol was first protected as the tetrahydropyranyl ether in excellent yield (Eq. 46). This THP-propargyl ether **118** was then converted to the E-vinyl bromide **119** by treatment with zirconocene hydrochloride followed by bromide-zirconium exchange (Eq. 47).



(Eq. 46)

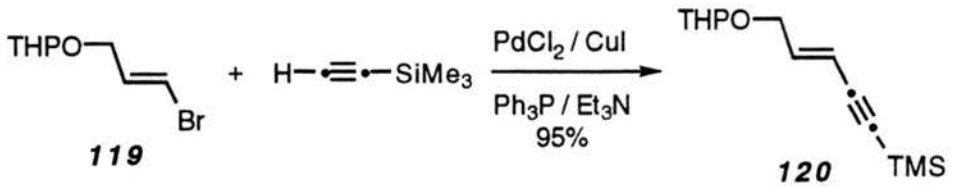
118



(Eq. 47)

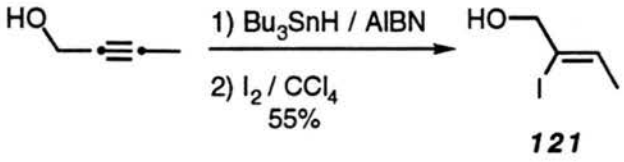
118 ***119***

The E-vinyl bromide was then treated with trimethyl silyl acetylene in the presence of palladium(II) and copper(I) to give the ene-yne **120** (Eq. 48). This forms the ene-yne of one half of the poly-ene chain.

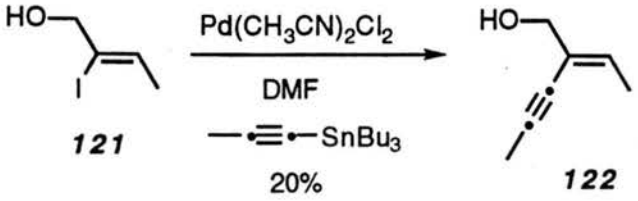


(Eq. 48)

The other half of the poly-ene chain synthesis proceeded as follows. 2-Butyne-ol was treated with tributyltin hydride followed by iodine-tin exchange (Eq. 49). The hydroxy Z-iodo olefin was then coupled to the alkynyltin to give the other ene-yne **122** (Eq. 50), using catalytic palladium coupling conditions.



(Eq. 49)

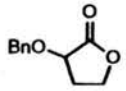
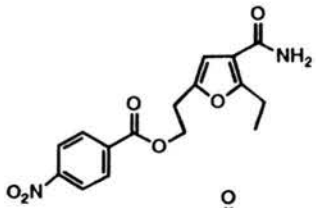
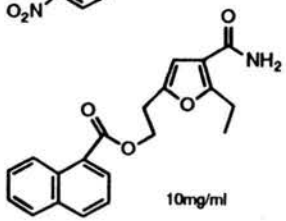
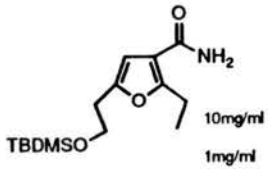


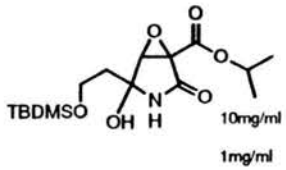
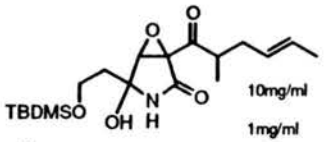
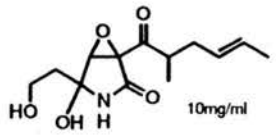
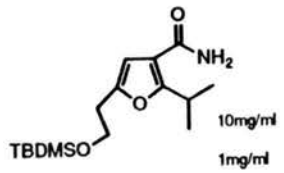
(Eq. 50)

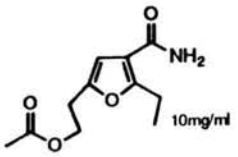
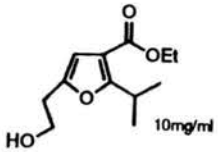
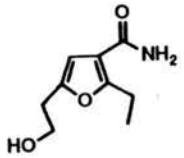
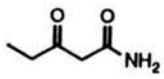
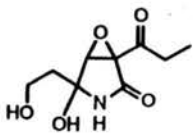
Further work to couple the two ene-ynes was not done. It was feared that the resulting tetra-ene would be unstable over time, and conditions were sought to first couple a model system to the heterocyclic portion of fusarin C. As the conclusion mentioned, conditions were not found for a successful coupling to produce the required α,β-unsaturated ketone.

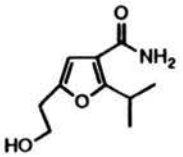
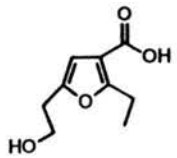
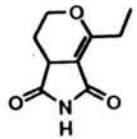
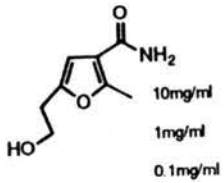
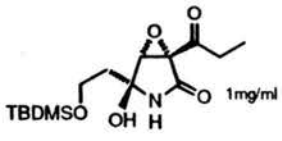
Antibacterial / Antifungal Activity of Synthesized Compounds

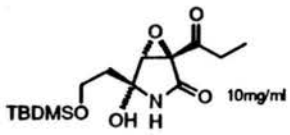
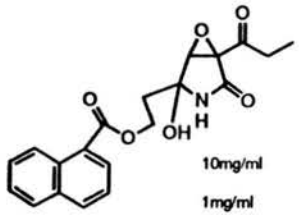
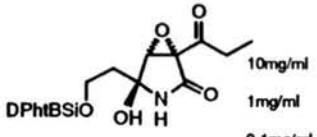
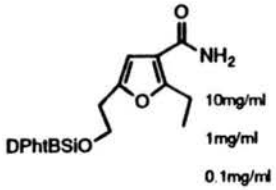
The microbial tests were carried out on agar plates on which the microbe grow. Paper disks 7 mm in diameter with compound, applied by one drop of a solution of varying concentrations, was placed on the agar on initiation of growth. Zones of inhibition (in millimeters) is a representative number of the effectiveness of the compound to act as an antimicrobial agent; the larger the number the more effective the compound. The microbes are classified into gram positive bacteria (G^+), gram negative bacteria (G^-), and yeast representing fungi. My thanks to Rene Gallegos for performing these tests.

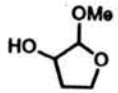
Compound	Microorganisms								
	G+			Yeast		G−			
	Bacillus subtilus	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—
 10mg/ml	10mm	12mm	—	8mm	—	—	—	—	—
 10mg/ml 1mg/ml	14mm 7.5mm	13mm 8mm	12mm —	—	—	8mm	—	—	—

Compound	G+			Yeast		G−			
	Bacillus subtilus	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
	15mm	*17mm	14mm	—	—	8mm	—	—	—
	9mm	*10mm	7.5mm	—	—	—	—	—	—
	9mm	NT	—	—	—	—	—	—	—
	8mm	NT	—	—	—	—	—	—	—
	10mm	NT	—	—	NT	—	NT	—	—
	10mm	7.5mm	10mm	—	—	—	—	—	—
	8.5mm	—	7.5mm	—	—	—	—	—	—

Compound	G+			Yeast		G−			
	Bacillus subtilus	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
 10mg/ml	10mm	11mm	8mm	—	—	—	7.5mm	—	—
 10mg/ml	15mm	14mm	12mm	—	—	11mm	—	—	—
	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—
	10mm	12mm	—	—	—	—	13mm	11mm	—

Compound	G+			Yeast		G−			
	Bacillus subtilus	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—
 10mg/ml 1mg/ml 0.1mg/ml	— — —	14mm 10mm 8mm	— — —	— — —	— — —	— — —	— — —	— — —	— — —
 1mg/ml	9mm	8mm	—	—	—	—	—	—	—

Compound		G+			Yeast		G−			
		Bacillus subtilus	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
	10mg/ml	14mm	16mm	12mm	—	—	—	8mm	—	—
	10mg/ml	18mm	20mm	16mm	—	—	—	16mm	—	—
	1mg/ml	10mm	12mm	8mm	—	—	—	12mm	—	—
	10mg/ml	18mm	—	12mm	—	—	—	—	—	—
	1mg/ml	14mm	—	10mm	—	—	—	—	—	—
	0.1mg/ml	10mm	—	9mm	—	—	—	—	—	—
	10mg/ml	12mm	9mm	12mm	—	—	—	—	—	—
	1mg/ml	10mm	7.5mm	9mm	—	—	—	—	—	—
	0.1mg/ml	8mm	—	7.5mm	—	—	—	—	—	—

Compound	*Bacillus subtilus*	*Staphylococcus aureus*	*Micrococcus luteus*	*Candida albicans*	*Saccharomyces cerevisiae*	*E. coli 22*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Pseudomonas aeruginosa*
	—	—	—	—	—	—	—	—	—

* - reduced growth
--- - resistant
NT - not tested

Controls									
Streptomycin (10 µg)	—	—	—	—	—	15±5mm	15±5mm	10±5mm	10±5mm
Penicillin (10 µg)	30±5mm	30±5mm	50±10mm	—	—	—	—	—	—
Nystatin 100	—	—	—	20±5mm	20±5mm	—	—	—	—

Chapter Four

Experimental Section

General. ^{1}H NMR and ^{13}C NMR were obtained on the following instruments: Bruker WP-270SY 270 MHz Spectrometer or Bruker AC300P NMR Spectrometer. Chemical shifts are reported in parts per million relative to residual $CHCl_3$ in $CDCl_3$ at δ 7.24 for ^{1}H, and 77.0 for $CDCl_3$ for ^{13}C.

Infrared spectra were obtained on Perkin-Elmer 1600 Series FTIR.

Low resolution mass spectra were obtained on a V.G. Micromass Ltd. Model 16F Spectrometer.

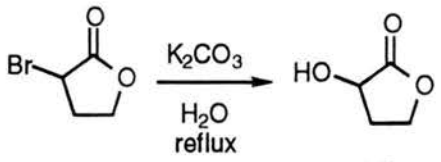
High resolution mass spectra were performed by Midwest Center for Mass Spectrometry, Lincoln, Nebraska.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, and by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Uncorrected melting points were determined in an open-ended capillary tube on a "Mel-Temp" apparatus.

Chromatography was performed using Merck silica gel grade 60, 230-400 mesh, 60Å, or 0.25 mm E. Merck precoated silica gel glass plates.

Reagents and solvents were of commercial grade and used as supplied with the following exceptions. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone. Carbon tetrachloride was freshly distilled over calcium hydride. Dimethylformamide, benzene, and toluene were dried over 4Å molecular sieves.



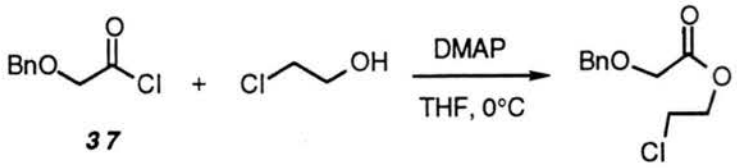
35

α-Hydroxy-γ-butyrolactone 35. α-Bromo-γ-butyrolactone (1.0 g, 6.1 mmol, 1 eq) and potassium carbonate (1.2 g, 8.7 mmol, 1.4 eq) in water (20 ml) was refluxed for 1 h, at which time the mixture was concentrated to half volume and acidified with 10N hydrochloric acid to pH 5. The mixture was taken up in ethanol and distilled to a residue. The residue was purified by bulb-to-bulb distillation to give α-hydroxy-γ-butyrolactone **35** (0.44 g, 72%) as a clear colorless oil. IR matched that reported in the literature.

^{1}H NMR (300 MHz, $CDCl_3$/MeOD) δ 4.25 (m, 1H), 4.03 (m, 2H), 2.36 (m, 1H), 2.00 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$/MeOD) δ 178.0, 66.7, 53.9, 30.8.

IR (NaCl, neat) ν 3380, 1760, 1000 cm^{-1}.



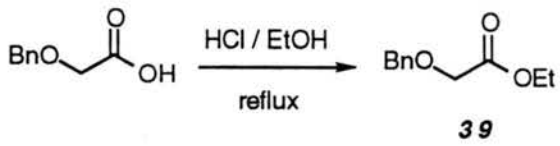
37 *38*

2-Chloroethyl benzyloxyacetate 38. To a solution of benzyloxyacetylchloride (200 mg, 1.08 mmol, 60 eq) and 2-chloroethanol (90 mg, 1.11 mol, 1.03 eq) in dry tetrahydrofuran (10 ml) at 0°C was added dimethylaminopyridine (134 mg, 1.10 mmol, 1.02 eq). After 15 min the reaction was diluted with methylene chloride (20 ml), washed with water, saturated sodium chloride solution, dried ($MgSO_4$) and concentrated to give **38** (213 mg, 86%) as a yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.62 (s, 2H), 4.39 (t, J = 5.5Hz, 2H), 4.13 (s, 2H), 3.67 (t, J = 5.5Hz, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 136.8, 128.4, 128.0, 73.2, 66.8, 64.1, 41.3.

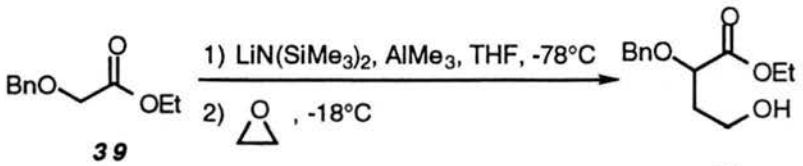
IR (NaCl, neat) ν 3064, 3032, 2951, 1760, 1605, 1955, 1269, 1190, 1128 cm^{-1}.



39

Ethyl benzyloxyacetate 39. Benzyloxy acetic acid (2.1 g, 12.6 mmol) was dissolved in 1M hydrochloric acid in ethanol (30 ml) and refluxed for 4.5 h. The crude reaction was concentrated to an oil filtered through a plug of silica gel followed by methylene chloride (50 ml) and concentrated to give **39** (2.2 g, 90%) as a clear colorless oil.

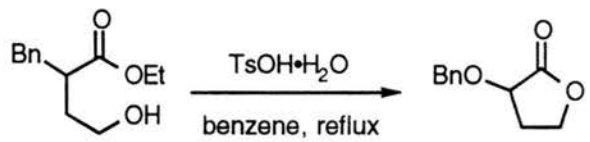
^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.64 (s, 2H), 4.23 (q, J = 6.9Hz, 2H), 4.10 (s, 2H), 1.38 (t, J = 6.9Hz, 3H).



39 *40*

Ethyl (α-benzyloxy-4-hydroxy)-butanoate 40. To a solution of ethyl benzyloxyacetate **39** (102 mg, 0.53 mmol, 1 eq) in tetrahydrofuran (5 ml) at -78°C under argon atmosphere was added trimethyl aluminum (0.6 ml, 2M in hexane, 1.2 mmol, 2.3 eq) and lithium bistrimethylsilyl amide (0.6 ml, 0.6 mmol, 1.1 eq). After 15 min ethylene oxide (470 mg, 10.7 mmol, 20.3 eq) in tetrahydrofuran (4 ml) was added and kept at -18°C for 10 h. The reaction was quenched with saturated ammonium chloride solution, extracted with diethyl ether, dried ($MgSO_4$), and concentrated. The crude oil was then chromatographed on a silica gel column (3:2 hexane/ethyl acetate) to give **40** (33 mg, 27%) as a colorless oil.

IR (NaCl, neat) ν 3440, 3020, 2960, 1750, 1580, 1440 cm^{-1}.

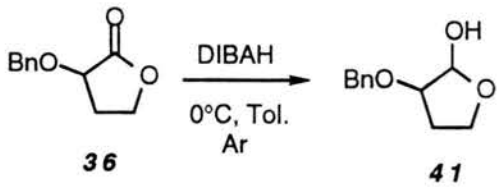


40 *36*

α-Benzyloxy-γ-butyrolactone 36. To ethyl (α-benzyloxy,4-hydroxy)butanoate **40** (12 mg, 0.05 mmol) in benzene (10 ml) was added *p*-toluene sulfonic acid monohydrate (2 mg, 0.001 mmol) and refluxed under Dean-Stark apparatus until 3 ml reaction mixture remained. The reaction was concentrated, taken up in diethyl ether, washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated to give **36** (5.5 mg, 57%) as a clear colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.83 (dd, 2H), 4.38, 4.17 (m, 3H), 2.45 (m, 1H), 2.29 (m, 1H).

IR (neat, NaCl) ν 1775 cm^{-1}.

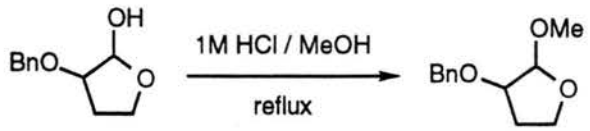


36 **41**

α-Benzyloxy-γ-butyrolactol 41. To dry toluene (5 ml) was added benzyloxy-γ-lactone **36** (76 mg, 0.40 mmol, 1.0 eq) and chilled to 0°C under argon atmosphere. Diisobutylaluminum hydride (0.5 ml of 1M toluene solution, 0.5 mmol, 1.25 eq) was added *via* syringe and stirred for 20 min. The reaction was quenched with saturated ammonium chloride solution (3 ml), diluted with diethyl ether (10 ml), and washed with 1N hydrochloric acid (5 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give **41** (56 mg, 73%) as a clear colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.42 (s, 1H), 4.58 (s, 2H), 4.08 (m, 2H), 3.79 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 1.26 (br s, 1H, D_2O exch.).

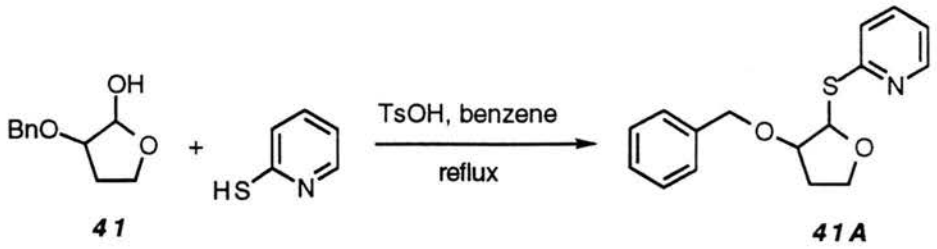
IR (NaCl, neat) ν 3400, 3025, 2920, 1600, 1452 cm^{-1}.



41 *18*

1-Methoxy-2-benzyloxytetrahydrofuran 18. To the benzyloxy γ-lactol **41** (68 mg, 0.353 mmol) was added 1M hydrochloric acid in methanol (5 ml) and refluxed for 2 h. The reaction was then concentrated to give methoxy benzyloxy acetal **18** (68 mg, 93%) as a light yellow oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.78 (s, 1H), 4.55 (s, 2H), 4.20-3.85 (m, 3H), 3.33 (s, 3H), 2.30-1.87 (m, 2H).

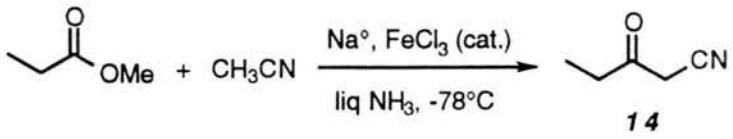


41 *41A*

1-Thiopyridyl-2-benzyloxytetrahydrofuran **41A.** To benzyloxy lactol **41** (24 mg, 0.12 mmol, 1 eq) and mercaptopyridine (25 mg, 0.22 mmol, 1.8 eq) was added dry benzene (10 ml) and *p*-toluenesulfonic acid (2 mg, 0.001 mmol). The mixture was refluxed under Dean-Stark apparatus for 8 h at which time the crude reaction was concentrated and chromatographed (3:2 hexane/ethyl acetate) to give benzyloxy thioacetal **41A** (22 mg and 12 mg, 97%) and a mixture of diastereomers.

^{1}H NMR (270 MHz, $CDCl_3$) δ 8.42 (m, 1H), 7.52 (m, 1H), 7.31 (m, 5H), 7.02 (m, 1H), 5.01 (s, 1H), 4.65 (m, 2H), 4.31 (m, 1H), 4.13 (m, 2H), 2.28 (m, 1H), 2.08 (m, 1H).

m/e (NH_3Cl) 288 (M+1), 219, 194, 175.



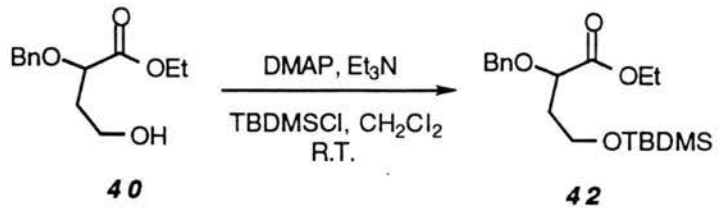
14

1-Cyano-2-butanone **14.** To 100 ml liquid ammonia at -78°C under nitrogen was added sodium metal (4.6 g, 200 mmol, 2.0 eq) and iron trichloride (100 mg, 0.60 mmol, 6 x 10^{-3} eq) followed by dry acetonitrile (10.4 ml, 200 mmol, 2.0 eq) in 10.4 ml dry diethyl ether dropwise. After 5 min methyl propionate (8.8 g, 100 mmol, 1.0 eq) was added in diethyl ether (9.5 ml) dropwise and stirred for 1 h. Diethyl ether (100 ml) was added, the ammonia was allowed to evaporate, and the reaction mixture was poured over 500 g ice. The mixture was filtered through Celite, acidified with 6N HCl to neutrality, and extracted with diethyl ether (2 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give 4.6 g (50%) orange oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 3.5 (s, 2H), 2.7 (q, J = 7.2Hz, 2H), 1.15 (t, J = 7.2Hz, 3H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 198.8, 114.2, 35.5, 31.6, 7.4.

IR (NaCl, neat) ν 2240, 1750 cm^{-1}.

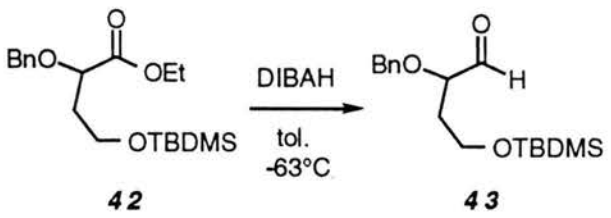


40 *42*

Ethyl α-Benzyloxy(4-*tert*-butyldimethylsiloxy)butyrate 42. To dry methylene chloride (20 ml) was added ethyl benzyloxy 4-hydroxy butanoate **40** (290 mg, 1.22 mmol, 1.0 eq) followed by dimethylamino pyridine (10 mg, 0.08 mmol, 0.07 eq), triethylamine (160 mg, 1.58 mmol, 1.3 eq), and t-butyldimethylsilyl chloride (2.37 mg, 1.58 mmol, 1.3 eq). The mixture was stirred at room temperature for 20 h, diluted with diethyl ether (15 ml), washed with water (1 x 10 ml) and saturated sodium chloride solution (1 x 10 ml), dried ($MgSO_4$) and concentrated to give ethyl 2-benzyloxy 4-siloxy butanoate **42** (471 mg, >98%) as an orange oil.

^1H NMR (270 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.55 (dd, 2H), 4.20 (q, J = 6.9Hz, 2H), 4.13 (m, 1H), 3.70 (m, 2H), 1.90 (m, 2H), 1.30 (t, J = 6.9Hz, 3H), 0.90 (s, 9H), 0.02 (s, 6H).

IR (NaCl, neat) ν 3100, 2940, 1740, 1590 cm^{-1}.



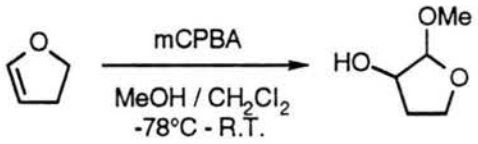
42 *43*

α-Benzyloxy-(4-*tert*-butyldimethylsiloxy)butyraldehyde 43.

To ethyl 2-benzyloxy-4-siloxybutanoate **42** (429 mg, 1.22 mmol, 1.0 eq) was added dry toluene (50 ml) and chilled to -63°C (Dry ice/chloroform slurry) under argon atmosphere. Diisobutylaluminum hydride (1.8 ml of 1M toluene solution, 1.8 mmol, 1.5 eq) was added dropwise *via* syringe and stirred at -63°C for 30 min at which time methanol (5 ml) was added followed by addition of saturated ammonium chloride solution (5 ml). The reaction was warmed to room temperature and filtered through a plug of Celite, extracted with diethyl ether, dried ($MgSO_4$) and concentrated to give 2-benzyloxy 4-siloxybutanal **43** (263 mg, 72%) as a yellow oil.

^1H NMR (270 MHz, $CDCl_3$) δ 9.70 (d, J = 1.9Hz, 1H), 7.34 (m, 5H), 4.60 (dd, J = 11.6, 27.8Hz, 2H), 4.00 (m, 1H), 3.70 (m, 2H), 2.80 (m, 2H), 0.90 (s, 9H), 0.01 (s, 6H).

IR (NaCl, neat) ν 3100, 2940, 2840, 1725, 1450 cm^{-1}.



45

1-Methoxy-2-hydroxytetrahydrofuran **45**. To dihydrofuran (2.5 g, 36.7 mmol, 1.5 eq) in dry methylene chloride (60 ml) was added methanol (35 ml) and chilled to -78°C. A slurry of *m*-chloroperbenzoate acid in methylene chloride (100 ml) was added to the stirred solution and allowed to slowly warm to room temperature. At 14 h the reaction was concentrated at 50°C on rotovap, taken up in methylene chloride (40 ml), and chilled to 0°C. The mixture was filtered and the solid washed with methylene chloride (20 ml) at 0°C. The organic solution was washed with 10% sodium carbonate (40 ml), the aqueous wash saturated with sodium chloride and extracted with methylene chloride (3 x 40 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude oil was chromatographed (3:2 hexane/ethyl acetate) to give acetate **45** (2.85 g, 95%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.07 (m, 1H), 3.97 (m, 1H), 3.83 (m, 1H), 3.55 (br s, 1H, D_2O exch.), 3.21 (s, 3H), 2.09 (m, 1H), 1.72 (m, 1H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 108.8, 74.9, 66.2, 54.2, 31.9.

IR (NaCl, neat) ν 3422, 2902, 1104, 1037 cm^{-1}.

45 **46**

1-Methoxy-2-*tert*-butyldimethylsiloxytetrahydrofuran 46. To acetal **45** (4.02 g, 34.1 mmol, 1.0 eq) in dry methylene chloride (50 ml) was added *tert*-butyldimethylsilyl chloride (6.13 g, 40.9 mmol, 1.2 eq) followed by triethylamine (5.16 g, 51.1 mmol, 1.5 eq) and dimethylaminopyridine (20 mg, catalytic amount). The mixture was stirred for 80 h at which time water (20 ml) was added and separated. The organic layer was washed with 0.05N hydrochloric acid (10 ml), saturated sodium bicarbonate solution (10 ml), dried (Na_2SO_4), and concentrated. The crude oil was chromatographed (3:2 hexane/ethyl acetate) to give silyl acetal **46** (6.90 g, ~100%) as a clear colorless oil.

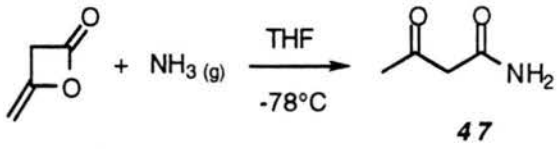
^1H NMR (270 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.16 (m, 1H), 4.07 (m, 1H), 3.91 (m, 1H), 3.29 (s, 3H), 2.07 (m, 1H), 1.71 (m, 1H), 0.85 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 109.8, 76.6, 66.7, 54.4, 33.3, 25.8, 18.1, -4.8.

IR (NaCl, neat) ν 2930, 1472, 1124, 1051, 837 cm^{-1}.

m/e (NH_3Cl) 250, 233 (M+1), 218, 201.

Elem. Anal. calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.57; H, 10.52.



47

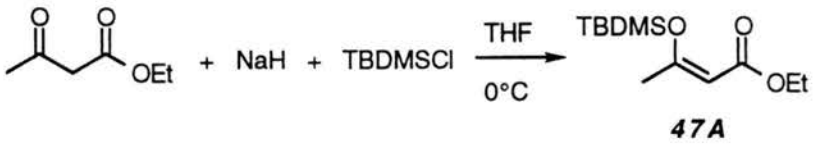
Acetyl acetamide 47. To a stirred solution of diketene (50 mg, 0.6 mmol) in dry THF (5 ml) under argon atmosphere at -78°C was added ammonia gas (2 l). After 2 h of stirring while warming to room temperature, the reaction was concentrated to give acetoacetamide **47** (55 mg, 95%) as an orange oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.04 (br s, 1H, D_2O exch.), 6.44 (br s, 1H, D_2O exch.), 3.36 (s, 2H), 2.19 (s, 3H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 204.2, 168.8, 49.8, 30.8.

IR (NaCl, neat) ν 3430, 3320, 1700, 1615, 1555, 1275, 1032 cm^{-1}.

m/e (NH_3Cl) 119, 102, 101 (M+), 86.



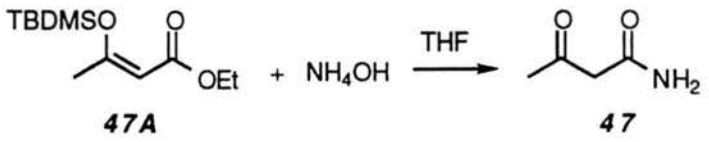
47A

Ethyl 3-*tert*-butyldimethylsiloxybutyrate-2-ene 47A. To a stirred solution of ethyl acetoacetate (1.48 g, 11.38 mmol, 1.0 eq) in 50 ml THF at 0°C under argon was added sodium hydride [600 mg, (50% in oil), 12.52 mmol, 1.1 eq] in 15 ml dry THF. The mixture was allowed to stir for 10 min followed by the addition of *tert*-butyldimethylsilyl chloride (1.85 g, 12.3 mmol, 1.1 eq) and stirred for 2 h while warming to room temperature. The mixture was filtered through Celite, concentrated, and chromatographed (2:1 hexane/ethyl acetate) to give the silyl enol ether **47A** (1.68 g, 60%) as a clear colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.04 (q, J = 6.9Hz, 2H), 2.20 (s, 3H), 1.17 (t, J = 6.9Hz, 3H), 0.85 (s, 9H), 0.14 (s, 6H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 169.5, 167.8, 100.4, 59.2, 25.6, 20.6, 18.1, 14.5, -4.4.

m/e (NH_3Cl) 244 (M^+) 186, 159.



47A *47*

Acetyl acetamide 47. To the silyl enol ether **47A** (796 mg, 3.26 mmol) was added 0.5 ml concentrated ammonium hydroxide and stirred at room temperature for 4 days. The mixture was extracted with diethyl ether (3 x 20 ml), dried ($MgSO_4$), concentrated, and chromatographed (2:1, hexane/ethyl acetate) to give acetoacetamide **47** (250 mg, 75%) as an orange oil.

^1H NMR (270 MHz, $CDCl_3$) δ 6.45 (br s, 1H, D_2O exch.), 5.23 (br s, 1H, D_2O exch.), 3.35 (s, 2H), 2.18 (s, 3H).

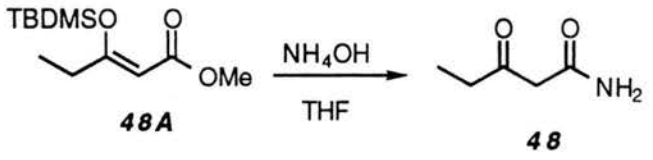
^{13}C NMR (67.9 MHz, $CDCl_3$) δ 204, 169, 50, 30.

IR (NaCl, neat) ν 3400, 3200, 1725, 1650, 1540, 116 cm^{-1}.

48A

Methyl 3-*tert*-butyldimethylsiloxypentanoate-2-ene 48A. To methyl propionylacetate (1.38 g, 10.61 mmol, 1.0 eq) in dry THF (50 ml) at 0°C under argon was added sodium hydride [611 mg (50% in oil), 12.74 mmol, 1.2 eq] in THF (10 ml) and stirred for 10 min. *tert*-Butyldimethylsilyl chloride (1.75 g, 11.67 mmol, 1.1 eq) was then added and the mixture was allowed to stir while warming to room temperature for 2.5 h. The mixture was filtered through a plug of silica gel and concentrated to give the silyl enol ether **48A** (2.3 g, 88%) as a clear colorless oil.

^1H NMR (270 MHz, $CDCl_3$) δ 5.00 (s, 1H), 3.60 (s, 3H), 2.68 (q, J = 7.5Hz, 2H), 1.04 (t, J = 7.5Hz, 3H), 0.89 (s, 9H), 0.18 (s, 6H).



48A 48

Propionylacetamide 48. To the silyl enol ether **48A** (244 mg, 1 mmol) was added concentrated ammonium hydroxide (5 ml) in THF (1 ml) and stirred at room temperature for 24 h. The mixture was then concentrated and chromatographed (EtOAc) to give propionyl acetamide **48** (86 mg, 75%) as a white crystalline solid.

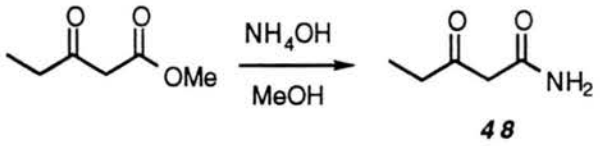
^{1}H NMR (270 MHz, $CDCl_3$) δ 7.09 (br s, 1H, D_2O exch.), 6.40 (br s, 1H, D_2O exch.), 3.36 (s, 2H), 2.50 (q, J = 9.2Hz, 2H), 1.05 (t, J = 9.2Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.6, 168.8, 48.7, 36.7, 7.2.

m/e (NH_3Cl) 133, 116, 115 (M+), 100, 74.

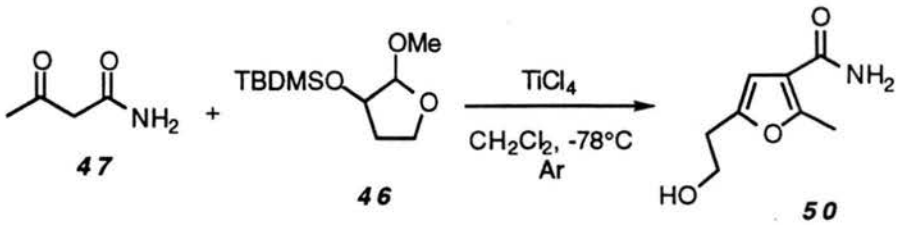
m.p. 64-67°C

Elem. Anal. calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.94; H, 7.90; N, 12.22.



48

Propionylacetamide 48. To methyl propionyl acetate (5.0 g, 38.5 mmol) was added methanol (10 ml) followed by concentrated ammonium hydroxide (200 ml). The mixture was covered by a septum and stirred for 4 days. The mixture was concentrated and chromatographed (ethyl acetate) to give propionyl acetamide **48** (2.65 g, 60%) as a white solid. Spectral analysis matched that reported earlier for propionyl acetamide **48**.



47 46 50

2-Methyl-3-amido-5-(2-hydroxy)ethyl furan 50. To acetoacetamide **47** (625 mg, 6.19 mmol, 1.6 eq) and silyl acetal **46** (810 mg, 3.97 mmol, 1.0 eq) in 25 ml dry methylene chloride at -78°C under argon was added titanium tetrachloride (905 mg, 4.76 mmol, 1.2 eq) in 2.5 ml dry methylene chloride over 5 min dropwise. The mixture was stirred at -78°C for 1 h then allowed to warm to room temperature over 2 h. The reaction was quenched with 25 ml methanol, concentrated, taken up in ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed on silica gel (3:1:4, ethyl acetate/methanol/methylene chloride) to give furan **50** (530 mg, 80%) as a white crystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ 6.14 (s, 1H), 3.74 (t, J = 6.7Hz, 2H), 2.72 (t, J = 6.7Hz, 2H), 2.44 (s, 3H); (d_6 DMSO) δ 7.36 (br s, 1H), 7.00 (br s, 1H), 4.72 (br s, 1H).

^{13}C NMR (67.9 MHz, CD_3OD) δ 169, 157, 152, 117, 106, 61, 32, 13.

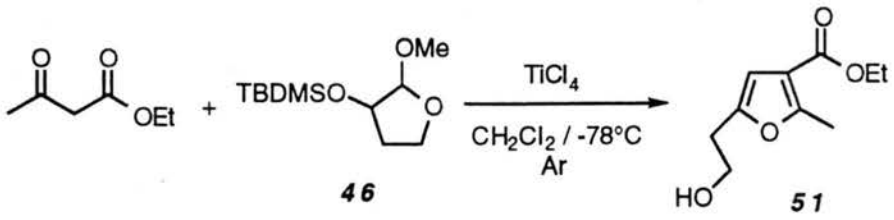
IR (KBr) ν 3370, 3292, 3188, 3102, 2961, 1669, 1608, 1584, 1235, 1051 cm^{-1}.

m/e (NH_3Cl)186, 169 (M+), 151, 138.

UV (MeOH) λ_{max} 207, 247 nm

m.p. 167-169°C

Elem. Anal. calcd for $C_8H_{11}NO_3$: C, 56.86; H, 6.56; N, 8.28. Found: C, 56.83; H, 6.84; N, 8.59.



46 51

Ethyl 2-methyl-5-(2-hydroxyethyl)-3-furanoate 51. To silyl acetal **46** (500 mg, 2.45 mmol, 1.0 eq) and ethyl acetoacetate (644 mg, 3.19 mmol, 1.3 eq) in 50 ml dry methylene chloride at -78°C under argon was added titanium tetrachloride (600 mg, 3.19 mmol, 1.3 eq) neat *via* syringe and stirred at -78°C for 2 h. The mixture was allowed to warm to room temperature over 2 h followed by the addition of methanol (20 ml). The mixture was concentrated, taken up in ethyl acetate and water, and separated. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (3:2, hexane/ethyl acetate) to give furan **51** (243 mg, 50%) as a clear colorless oil.

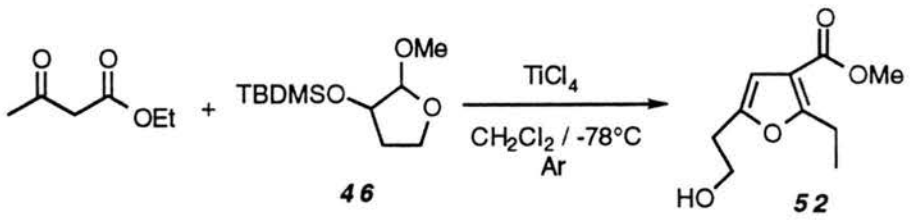
^1H NMR (270 MHz, $CDCl_3$) δ 6.40 (s, 1H), 4.26 (q, J = 6.9Hz, 2H), 3.87 (t, J = 6.2Hz, 2H), 2.84 (t, J = 6.2Hz, 2H), 2.54 (s, 3H), 1.36 (br s, 1H, D_2O exch.), 1.31 (t, J = 6.9Hz, 3H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164, 158, 150, 114, 107, 61, 60, 31, 14.5, 14.

IR (NaCl, neat) ν 3450, 3120, 1725, 1690, 1617 cm^{-1}.

m/e (NH_3Cl) 198 (M+) 167, 153, 139, 121.

Elem. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.67; H, 7.14.



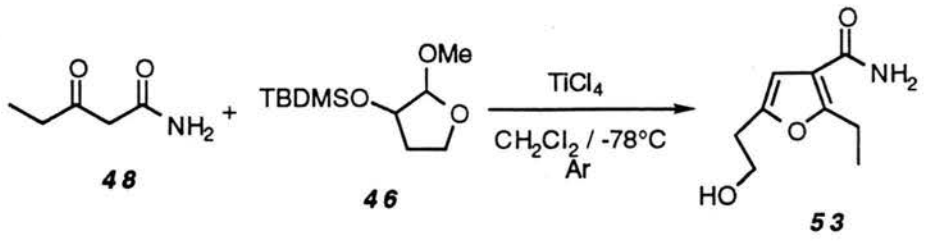
Methyl 2-ethyl-5-(2-hydroxyethyl)-3-furanoate 52. To methyl propionyl acetate (66 mg, 0.51 mmol, 1 eq) and silyl acetal **46** (120 mg, 0.51 mmol, 1 eq) in dry methylene chloride (10 ml) at -78°C under argon was added titanium tetrachloride (100 mg, 0.56 mmol, 1.1 eq) neat *via* syringe over 1 min and stirred at -78°C for 45 min. The mixture was then allowed to warm to room temperature over 1 h followed by the addition of methanol (5 ml). The mixture was stirred for 30 min, concentrated, taken up in ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (3:2, hexane/ethyl acetate) to give furan **52** (9 mg, 9%) as a colorless film.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.82 (t, J = 6.7Hz, 2H), 3.76 (s, 3H), 2.93 (q, J = 7.6Hz, 2H), 2.81 (t, J = 6.7Hz, 2H), 1.94 (br s, 1H, D_2O exch.), 1.19 (t, J = 7.6Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5, 163.3, 150.7, 112.8, 107.1, 60.7, 51.2, 31.3, 21.1, 12.2.

IR (NaCl, neat) ν 3418, 2952, 1715, 1615, 1581, 1045 cm^{-1}.

Elem. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.71; H, 7.14.



2-Ethyl-3-amido-5-(2-hydroxyethyl) furan 53. To siloxy acetal **46** (8.0 g, 34 mmol, 1.0 eq) and propionyl acetamide **48** (4.0 g, 34 mmol, 1.0 eq) in dry methylene chloride (200 ml) at -78°C under argon atmosphere was added titanium tetrachloride (7.3 g, 41 mmol, 1.2 eq) dropwise. The mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature over 2 h. Methanol (100 ml) was added and allowed to stir at room temperature for 45 min at which time the mixture was concentrated. The residue was taken up in water (100 ml) and extracted with ethyl acetate (4 x 100 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (3:1:4, ethyl acetate/methanol/methylene chloride) to give furan **53** (5.2 g, 84%) as a white solid.

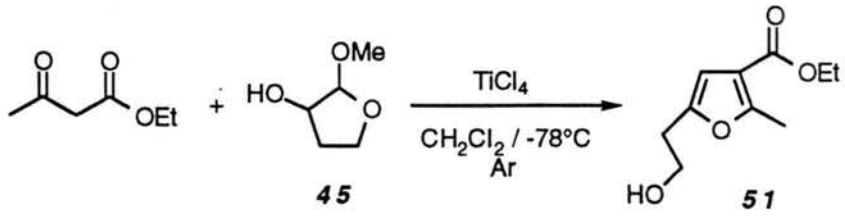
^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.45 (br s, 2H, D_2O exch.), 3.86 (t, J = 6.2Hz, 2H), 2.98 (q, J = 7.6Hz, 2H), 2.84 (t, J = 6.2Hz, 2H), 1.57 (br s, 1H, D_2O exch.), 1.22 (t, J = 7.6Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.0, 157.2, 147.8, 111.9, 102.5, 56.8, 28.4, 17.6, 9.4.

IR (NaCl, film) ν 3347, 3200, 2937, 1659, 1603, 1581, 1415, 1042 cm^{-1}.

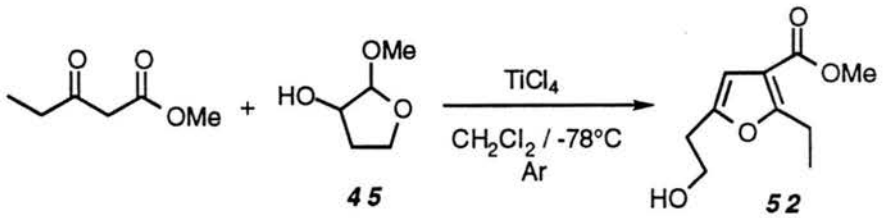
m.p. 117-118°C

Elem. Anal. calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.07, H, 7.08; N, 7.65.



45 51

Ethyl 2-methyl-5-(2-hydroxyethyl)-3-furanoate 51. To ethyl aceto acetate (69 mg, 0.53 mmol, 1.0 eq) and hydroxy acetal **45** (83 mg, 0.70 mmol, 1.3 eq) in 10 ml dry methylene chloride at -78°C under argon was dded titanium tetrachloride (110 mg, 0.60 mmol, 1.1 eq) neat *via* syringe over 1 min. The mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature over 1 h followed by the addition of water (5 ml). The mixture was separated, dried (Na_2SO_4), concentrated, and chromatographed (3:2, hexane/ethyl acetate) to give furan **51** (91 mg, 87%) as a clear colorless oil. Spectral data matched that previously reported for furan **51**.



45 52

Methyl 2-ethyl-5-(2-hydroxyethyl)-3-furanoate 52. To methyl propionyl acetate (500 mg, 3.84 mmol, 1.0 eq) and hydroxy acetal **45** (560 mg, 4.70 mmol, 1.2 eq) in 20 ml dry mthylene chloride at -78°C under argon was added titanium tetrachloride (840 mg, 4.70 mmol, 1.2 eq) neat *via* syringe over 3 min. The mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature over 4 h, at which time water (10 ml) was added. The mixture was separated, the organic layer dried (Na_2SO_4), concentrated, and

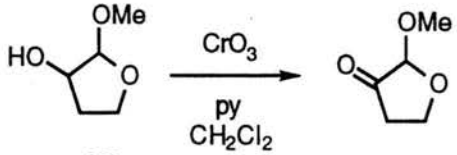
chromatographed (3:2, hexane/ethyl acetate) to give furan **52** (575 mg, 76%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.82 (t, J = 6.7Hz, 2H), 3.76 (s, 3H), 2.93 (q, J = 7.6Hz, 2H), 2.81 (t, J = 6.7Hz, 2H), 1.94 (s, 1H, D_2O exch.), 1.19 (t, J = 7.6Hz, 3H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 164.5, 163.3, 150.7, 112.8, 107.1, 60.7, 51.2, 31.3, 21.1, 12.2.

IR (NaCl, neat) ν 3418, 2952, 1715, 1615, 1581, 1045 cm^{-1}.

Elem. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.71; H, 7.14.



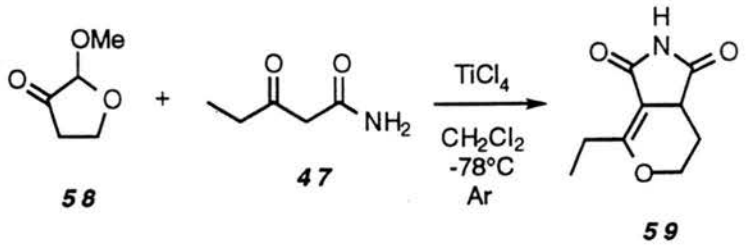
45 *58*

1-Methoxy-2-oxo-tetrahydrofuran 58. To dry methylene chloride (400 ml) at 0°C was added pyridine (28.3 g, 359 mmol, 6.2 eq) followed by solid chromium trioxide (17.3 g, 173 mmol, 6.0 eq) and stirred for 20 min. Hydroxy acetal **45** (3.4 g, 28.8 mmol, 1.0 eq) was added in dry methylene chloride (50 ml) and allowed to sit with periodic shaking for 20 h. The reaction mixture was filtered through Florisil, concentrated, and chromatographed (3:2 hexane/ethyl acetate on alumina) to give keto acetal **58** (2.07 g, 60%) as a clear colorless oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 4.53 (s, 1H), 4.25 (m, 2H), 3.37 (s, 3H), 2.43 (m, 2H).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ 207.8, 97.8, 63.8, 55.2, 33.6.

IR (NaCl, neat) ν 2950, 1770, 1060 cm^{-1}.



58 47 59

3-Ethyl-4-oxa-1,5,6-trihydrophthalimide 59. To keto acetal **58** (685 mg, 5.90 mmol, 1.0 eq) and propionyl acetamide **47** (863 mg, 7.50 mmol, 1.3 eq) in dry methylene chloride (20 ml) at -78°C under argon atmosphere was added titanium tetrachloride (1.35 g, 7.10 mmol, 1.2 eq) dropwise over 3 min. The mixture was stirred for 3 h while warming to room temperature, at which time methanol (10 ml) was added and the mixture stirred for 10 min. The mixture was concentrated, taken up in water (10 ml), and extracted with methylene chloride (4 x 10 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (3:1:4, ethyl acetate/methanol/methylene chloride) to give the succinimide derivative **59** (71 mg, 6%) as a white crystalline solid.

^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H, D_2O exch.), 4.45 (m, 1H), 4.00 (m, 1H), 3.28 (m, 1H), 2.700 (m, 2H), 2.34 (m, 1H), 1.66 (m, 1H), 1.10 (t, J = 7.5Hz, 3H).

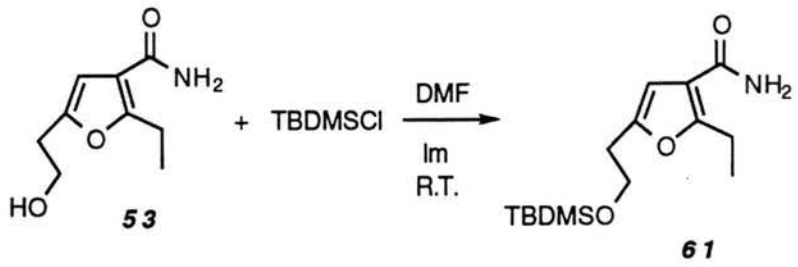
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3, 168.6, 166.8, 98.8, 67.3, 39.4, 24.1, 21.8, 11.4.

IR (NaCl, neat) ν 3199, 2974, 1730, 1703, 1643, 1449, 1343, 1233 cm^{-1}.

m/e (NH_3Cl) 199, 182 (M+1), 157.

m.p. 178-179°C

Elem. Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 5.97; N, 7.66.

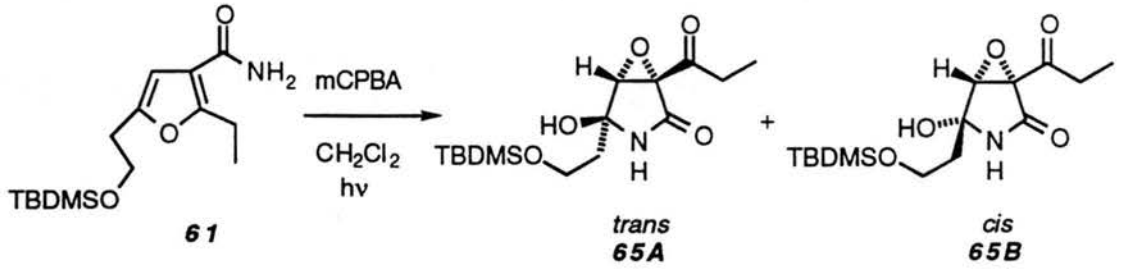


2-Ethyl-3-amido-5-(2-*tert*-butyldimethylsiloxyethyl) furan 61. To furan **53** (175 mg, 1.1 mmol, 1 eq) in dry dimethyl formamide (10 ml) at room temperature were added *tert*-butyldimethyl silyl chloride (805 mg, 5.37 mmol, 4.5 eq) and imidazole (584 mg, 8.6 mmol, 7.5 eq) as solids. The mixture was stirred at room temperature for 24 h at which time water (10 ml) was added. The mixture was extracted with diethyl ether (4 x 10 ml) and the combined organic extracts washed with water (3 x 5 ml). The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give silyl furan **61** (305 mg, 96%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.45 (s, 2H, D_2O exch.), 3.81 (t, J = 6.6Hz, 2H), 2.96 (q, J = 7.6Hz, 2H), 2.76 (t, J = 6.6Hz, 2H), 1.05 (t, J = 7.6Hz, 3H), 0.86 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.3, 161.1, 151.3, 114.3, 105.3, 61.3, 31.6, 25.8, 20.9, 18.1, 12.3, -5.5.

IR (NaCl, neat) ν 3348, 3197, 3107, 2929, 1655, 1609, 1580, 1255, 1104 cm^{-1}.



3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethyl-siloxyethyl) pyrrolidine-2-one 65. To silyl amido furan **61** (860 mg, 2.89 mmol, 1.0 eq) in dry methylene chloride (100 ml) was added solid meta-chloroperbenzoic acid [2.0 g (55%), 6.37 mmol, 2.2 eq] and irradiated with white light for 5 h. The mixture was allowed to sit at room temperature for an additional 20 h at which time 10% sodium thiosulfate (20 ml) was added followed by washing with saturated sodium bicarbonate solution (2 x 30 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give a mixture of epoxy pyrrolidine-ones **65** (2:1, A/B, 570 mg, 60%) as a white solid.

65A: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.812 (s, 1H, D_2O exch.), 5.317 (s, 1H, D_2O exch.), 4.071 (d, J = 2.5Hz, 1H), 3.985 (ddd, J = 11.5, 6.0, 4.0Hz, 1H), 3.891 (ddd, J = 11.5, 5.0, 4.5Hz, 1H), 2.576 (q, J = 7.2Hz, 2H), 2.042 (ddd, J = 14.5, 5.0, 4.0Hz, 1H), 1.945 (ddd, J = 14.5, 6.0, 4.0Hz, 1H), 1.035 (t, J = 7.2Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.3, 168.5, 84.8, 65.6, 60.7, 59.0, 36.2, 32.9, 25.8, 6.7, -5.6.

65B: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (br s, 1H, D_2O exch.), 4.79 (br s, 1H, D_2O exch.), 4.02 (m, 1H), 4.00 (d, J = 2.5Hz, 1H), 3.88 (m, 1H), 2.68 (m, 2H), 2.01 (m, 2H), 1.09 (t, J = 5.2Hz, 3H), 0.89 (m, 9H), 0.10 (s, 6H).

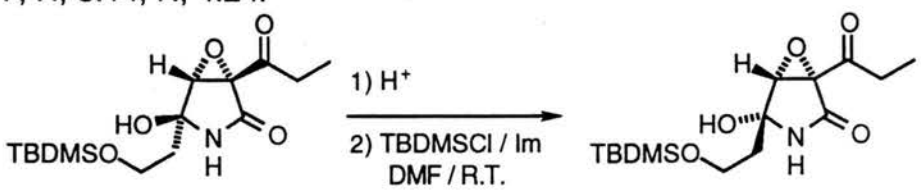
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.4, 167.9, 85.0, 65.2, 60.4, 59.4, 35.8, 33.8, 25.8, 18.0, 6.8, -5.6.

IR (NaCl, neat) ν 3328, 2930, 1739, 1697, 1407, 1256, 1096 cm^{-1}.

m/e (NH_3Cl) 330, 324, 312, 287.

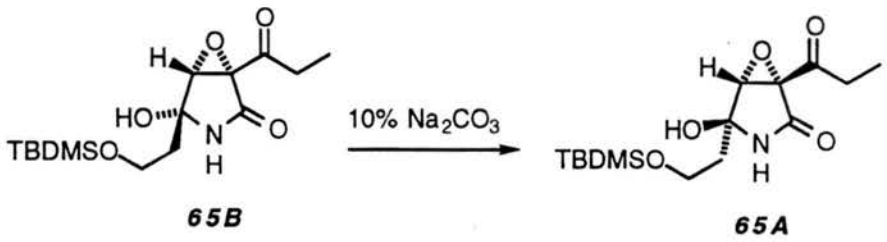
m.p. 107-109°C

Elem. Anal. calcd for $C_{15}H_{27}NO_5Si$: C, 54.68; H, 8.26; N, 4.25. Found: C, 54.77; H, 8.14; N, 4.24.



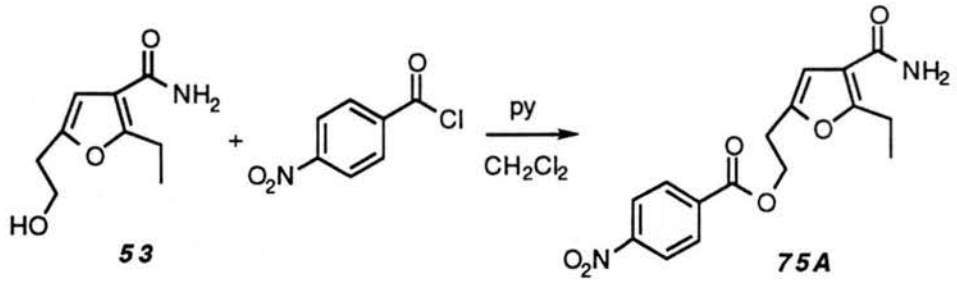
65A ***65B***

3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethyl-siloxyethyl) pyrrolidine-2-one <u>65B</u>. To epoxy-pyrrolidine-one **65A** (63 mg, 0.19 mmol) in methanol (5 ml) was added concentrated hydrochloric acid (1 drop) and stirred at room temperature for 10 min. At this time solid sodium bicarbonate (250 mg) was added and the mixture extracted with ethyl acetate (4 x 15 ml). The organic solution was dried (Na_2SO_4) and concentrated to give a yellow solid (35 mg). This solid was then taken up in dry dimethylformamide (5 ml) followed by the addition of solid *tert*-butyldimethylsilyl chloride (100 mg) and solid imidazole (100 mg) and stirred at room temperature for 48 h. To themixture was added water (5 ml) and extracted with diethyl ether (4 x 10 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (1:1 ethyl acetate/methylene chloride) to give epoxy-pyrrolidine-one **65B** (53 mg, 85%) as a white solid. ^1H NMR and TLC characteristics match that of epoxy-pyrroldine-one **65B**.



65B *65A*

3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethyl-siloxyethyl) pyrrolidine-2-one <u>65A</u>. To epoxy-pyrrolidine-one **65B** (10 mg, 0.03 mmol) in methanol (2 ml) was added 10% sodium carbonate solution (2 ml) and stirred at room temperature for 30 min at which time the mixture was extracted with ethyl acetate (4 x 10 ml). The organic solution was dried (Na_2SO_4) and concentrated to give epoxy-pyrrolidine-one **65A** (9 mg, 90%) as a white solid. ^1H NMR and TLC characteristics match that of epoxy-pyrrolidine-one **65A**.



53 *75A*

2-Ethyl-3-amido-5-(2-*para*-nitrobenzoylethyl) furan <u>75A</u>. To furan **53** (1.44 g, 7.87 mmol, 1.0 eq) in 100 ml dry methylene chloride at room temperature was added *p*-nitro benzoyl chloride (1.75 g, 9.44 mmol, 1.3 eq) followed by dry pyridine (3 ml). The mixture was stirred at room temperature for 24 h at which time was added water (20 ml) and separated. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl

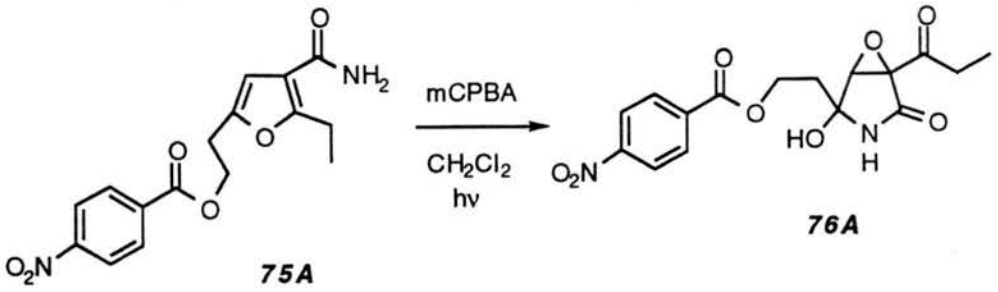
acetate/methylene chloride) to give *p*-nitro benzoate furan **75A** (400 mg, 15%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.9Hz, 2H), 8.16 (d, J = 8.9Hz, 2H), 6.16 (s, 1H), 5.73 (br s, 2H, D_2O exch.), 4.57 (t, J = 6.6Hz, 2H), 3.07 (t, J = 6.6Hz, 2H), 2.95 (q, J = 7.5Hz, 2H), 1.19 (t, J = 7.5Hz, 8H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 165.7, 164.4, 161.6, 150.6, 149.5, 135.2, 130.7, 123.5, 114.6, 105.8, 63.4, 27.5, 20.9, 12.3.

IR (NaCl, film) ν 3439, 3180, 3106, 2965, 1729, 1656, 1611, 1530, 1281, 1125 cm^{-1}.

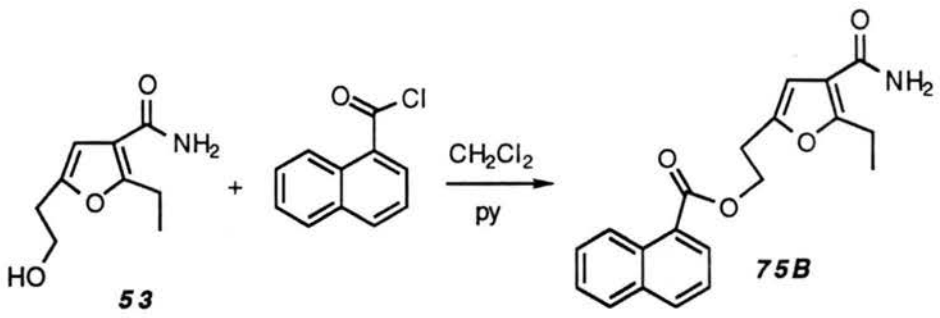
m.p. 145-145.8°C



75A *76A*

3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-*para*-nitrobenzoylethyl)-pyrrolidine-2-one **76A**. To *p*-nitro benzoyl furan **75A** (300 mg, 0.9 mmol, 1.0 eq) in methylene chloride (20 ml) at room temperature was added 55% m-chloroperbenzoic acid (1.13 g, 3.6 mmol, 4.0 eq) as a solid. The mixture was stirred at room temperature under fluorescent light for 24 h at which time it was washed with 10% sodium thiosulfate solution (1 x 10 ml), saturated sodium bicarbonate solution (3 x 10 ml) and dried (Na_2SO_4). The methylene chloride solution was concentrated and chromatographed (1:1, ethyl acetate/methylene chloride) to afford the epoxy pyrrolidine-one **75B** (70 mg, 21%) as a clear colorless glass.

^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.9Hz, 2H), 8.13 (d, J = 8.9Hz, 2H), 4.61 (m, 2H), 3.97 (s, 1H), 3.16 (m, 2H), 2.56 (m, 2H), 1.02 (m, 3H).

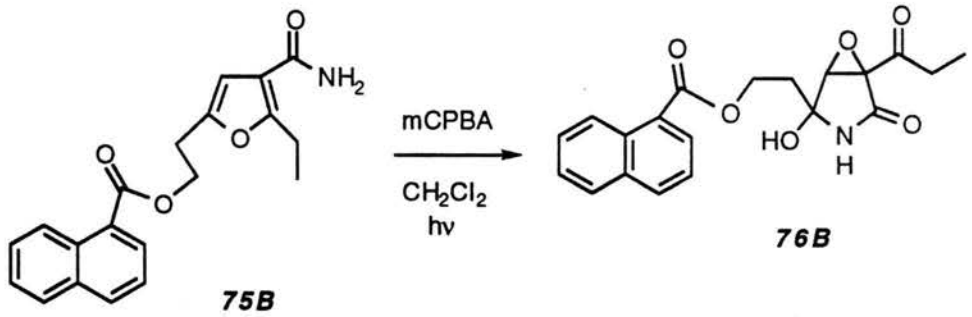


2-Ethyl-3-amido-5-(2-[1'-napthoylethyl])-furan **75B**. To 1-naphthoyl chloride (690 mg, 3.63 mmol, 1.2 eq) in dry methylene chloride (10 ml) was added amido furan **53** (550 mg, 3.03 mmol, 1.0 eq) followed by dry pyrridine (2 ml) and stirred at room temperature for 24 h. To the mixture was added water (5 ml), washed with 0.1N hydrochloric acid (1 x 5 ml) and saturated sodium bicarbonate solution (1 x 5 ml), dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give naphthoyl furan **75B** (400 mg, 40%) as a light yellow glass.

^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 8.6Hz, 1H), 8.09 (d, J = 7.3Hz, 1H), 7.93 (d, J = 8.1Hz, 1H), 7.79 (d, J = 8.1Hz, 1H), 7.51 (m, 3H), 6.60 (br s, 1H, D_2O exch.), 6.24 (s, 1H), 6.20 (br s, 1H, D_2O exch.), 4.56 (t, J = 6.4Hz, 2H), 3.00 (q, J = 7.4Hz; t, J = 6.4Hz, 4H), 1.19 (t, J = 7.4H, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.1, 166.5, 161.3, 149.6, 133.5, 133.3, 131.0, 130.1, 128.3, 127.5, 126.6, 126.0, 125.4, 124.2, 114.5, 105.7, 62.4, 27.4, 20.7, 12.1

IR (NaCl, neat) ν 3353, 3198, 3053, 2973, 1714, 1660, 1651, 1580, 1243, 1036, 782 cm^{-1}.

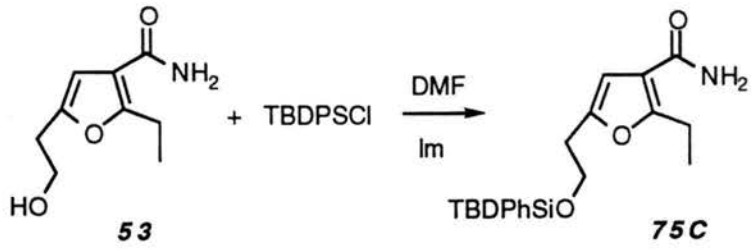


75B *76B*

3,4-Epoxy-5-hydroxy-5-(2-[1'-naphthoylethyl])-pyrrolidine-2-one 76B. To naphthoyl furan **75B** (270 mg, 0.80 mmol, 1.0 eq) in methylene chloride (20 ml) was added solid meta-chloroperbenzoic acid [600 mg (55%), 1.76 mmol, 2.2 eq] and irradiated with white light for 4 h followed by sitting at room temperature for an additional 10 h. The mixture was washed with 10% sodium thiosulfate solution (1 x 5 ml), saturated sodium bicarbonate solution (2 x 10 ml), dried ($NaSO_4$), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give naphthoyl epoxy pyrrolidine-one **76B** (114 mg, 37%) as a light yellow glass.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 8.6Hz, 1H), 8.21 (d, J = 6.8Hz, 1H), 7.98 (d, J = 8.1Hz, 1H), 7.86 (d, J = 8.1Hz, 1H), 7.48 (m, 3H), 4.63 (m, 2H), 4.26 (d, J = 2.2Hz, 1H), 2.35 (m, 4H), 0.85 (t, J = 7.1Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5, 168.9, 167.2, 133.8, 133.6, 131.3, 130.2, 128.5, 127.9, 126.9, 126.4, 125.8, 124.4, 84.0, 65.7, 61.2, 60.5, 34.2, 31.6, 6.5.

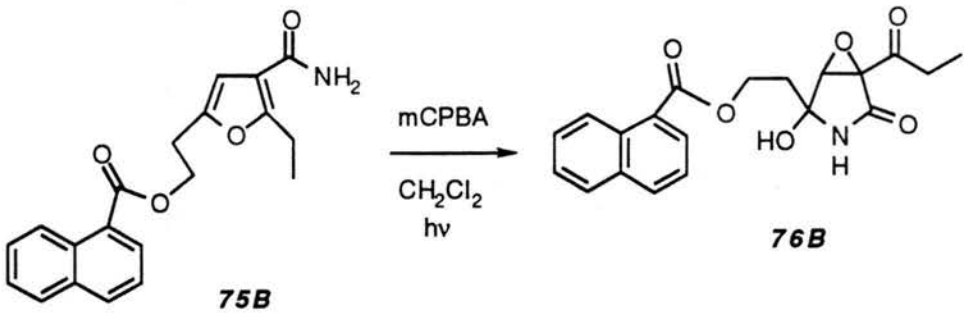


2-Ethyl-3-amido-5-(2-*tert*-butyldiphenylsiloxyethyl) furan 75C. To furan **53** (93 mg, 0.5 mmol, 1.0 eq) in 10 ml dry dimethylformamide at room temperature were added neat *tert*-butyldiphenylsilyl chloride (560 mg, 2 mmol, 4.0 eq) and imidazole (200 mg, 3 mmol, 6.0 eq). The mixture was stirred at room temperature for 48 h at which time water (10ml) was added. The solution was extracted with diethyl ether (4 x 15 ml) and the combined ethereal extracts were washed with water (3 x 10 ml). The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give silyl furan **75C** (105 mg, 50%) as a clear colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.39 (m, 6H), 6.18 (br s, 1H, D_2O exch.), 6.06 (s, 1H), 5.70 (br s, 1H, D_2O exch.), 3.89 (t, J = 6.5Hz, 2H), 2.94 (q, J = 7.6Hz, 2H), 2.83 (t, J = 6.5Hz, 2H), 1.24 (t, J = 7.6Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.3, 161.0, 151.2, 135.5, 133.5, 129.6, 127.6, 114.4, 105.3, 62.0, 31.3, 26.8, 20.9, 19.1, 12.3

IR (NaCl, neat) ν 3348, 3193, 3071, 2959, 1659, 1652, 1609, 1580, 1112, 702 cm^{-1}.

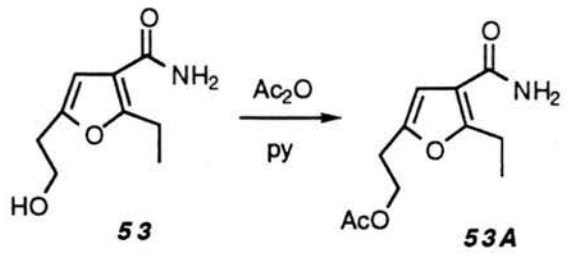


75B *76B*

3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldiphenyl-siloxyethyl)-pyrrolidine-2-one <u>76C</u>. To silyl furan **75C** (73 mg, 0.17 mmol, 1 eq) in methylene chloride (20 ml) was added *m*-chloroperbenzoic acid (215 mg, 68 mmol, 4 eq) and stirred under fluorescent lamp irradiation (hood light) for 24 h at room temperature. The mixture was washed with 10% sodium thiosulfate solution (1 x 5 ml), saturated sodium bicarbonate (3 x 10 ml), and dried (Na_2SO_4). The crude mixture was concentrated and chromatographed (1:1, ethyl acetate/methylene chloride) to give epoxy pyrrolidine-one **76C** (27 mg, 30%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.39 (m, 6H), 6.78 (br s, 1H, D_2O exch.), 5.10 (br s, 1H, D_2O exch.), 3.98 (m, 3H), 2.65 (m, 2H), 2.03 (m, 2H), 1.13 (m, 3H), 1.08 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.8, 168.5, 135.5, 130.2, 128.0, 127.8, 84.8, 65.9, 61.1, 59.4, 46.2, 34.7, 26.8, 19.1, 6.8.



1-Ethyl-2-amido-4-(2-acetylethyl)-furan <u>53A</u>. To hydroxy furan **53** (1.09 g, 5.94 mmol, 1.0 eq) in dry methylene chloride (50 ml) was added acetic anhydride (40 ml) followed by pyrridine (516 mg, 6.53 mmol, 1.1 eq) and stirred at room temperature. After 3 h the mixture was washed with water (1 x 10 ml), 0.25N hydrochloric acid (1 x 50 ml), and saturated sodium bicarbonate solution (2 x 30 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (3:1:4, ethyl acetate/methanol/methylene chloride) to give acetyl furan **53A** (1.09 g, 82%) as an orange solid.

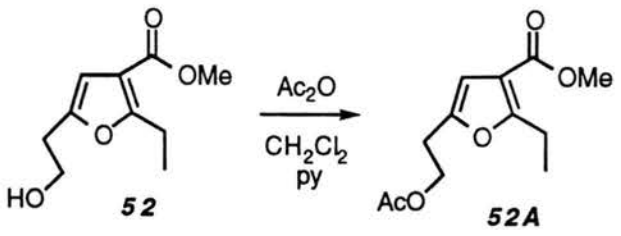
^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (br s, 1H, D_2O exch.), 6.13 (s, 1H), 5.94 (br s, 1H, D_2O exch.), 4.25 (t, J = 6.7Hz, 2H), 2.93 (q, J = 7.5Hz, 2H), 2.88 (t, J = 6.7Hz, 2H), 2.00 (s, 3H), 1.17 (t, J = 7.5Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 166.4, 161.2, 149.6, 114.5, 105.5, 61.9, 27.3, 20.8, 20.7, 12.2.

IR (NaCl, film) ν 3411, 3151, 2978, 1714, 1681, 1582, 1416, 1254, 1042 cm^{-1}.

m.p. 87°C

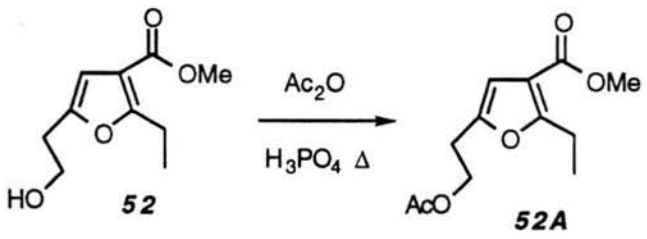
Elem. Anal. calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.11; N, 6.22. Found: C, 58.71; H, 6.76; N, 6.13.



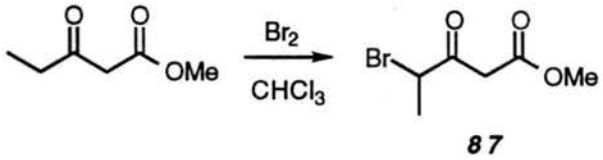
Methyl 2-ethyl-5-(2-acetylethyl)-3-furanoate 52A. To furan **52** (3.4 g, 17.2 mmol) in dry methylene chloride (10 ml) at room temperature was added acetic anhydride (5 ml, 45 mmol) followed by pyridine (1 ml) and stirred at room temperature for 2 days. Water was added to the mixture (10 ml), separated, washed with .5N HCl (1 x 5 ml), saturated sodium bicarbonate solution (2 x 10 ml), dried (Na_2SO_4), and concentrated to give acetyl furan **52A** (4.5 g, 99%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (s, 1H), 4.27 (q, J = 6.7Hz, 2H), 3.78 (s, 3H), 2.94 (q, J = 7.6Hz, 2H), 2.98 (t, J = 6.7Hz, 2H), 2.02 (s, 3H), 1.20 (t, J = 7.6Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4, 164.0, 162.9, 149.6, 112.6, 106.8, 61.6, 50.8, 27.2, 21.7, 20.5, 11.9.



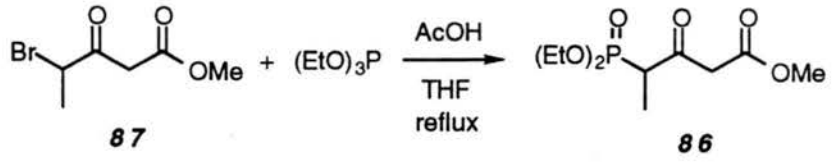
Methyl 2-ethyl-5-(2-acetylethyl)-3-furanoate 52A. To furan **52** (2.0 g, 10.1 mmol) was added acetic anhydride (5 ml, 45 mmol) followed by phosphoric acid (4 drops) and heated to 80°C for 5 min. The mixture was cooled, water (5 ml) was added followed by methylene chloride (50 ml). The organic layer was washed with saturated sodium bicarbonate solution (1 x 15 ml), dried (Na_2SO_4), and concentrated to give acetyl furan **52A** (2.4 g, 99%) as a light yellow oil.



Methyl 3-oxo-4-bromo-pentanoate 87. To methyl propionyl acetate (8.5 g, 65 mmol, 1.0 eq) in chloroform (100 ml) at room temperature was added bromine (11.5 g, 72 mmol, 1.1 eq) dropwise and the mixture stirred at room temperature for 20 h. At this time a stream of air was passed through the solution for 1.5 h, dried (Na_2SO_4) and concentrated to give bromo methylpropionyl acetate **87** (13.8 g, 99%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (q, J = 6.7Hz, 1H), 3.82 (d, J = 16.1Hz, 1H), 3.63 (d, J = 16.1Hz, 1H), 3.71 (s, 3H), 1.72 (d, J = 6.7Hz, 3H).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 196.2, 167.4, 88.9, 47.1, 44.9, 19.6.



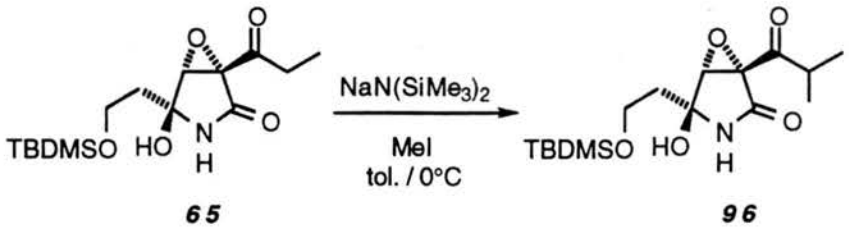
87 86

Methyl 3-oxo-4-diethylphosphono-pentanoate 86. To bromo methyl propionyl acetate **87** (900 mg, 4.28 mmol, 1.0 eq) in tetrahydrofuran (30 ml) was added triethyl phosphite (711 mg, 4.28 mmol, 1.0 eq) followed by acetic acid (2 drops) and refluxed for 30 min. The mixture was then cooled to room temperature and stirred for 8 h at which time it was concentrated and chromatographed (3:2, hexane/ethyl acetate) to give phosphonate **86** (740 mg, 65%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (q, J = 6.5Hz, 1H), 4.13 (q, J = 7.2Hz, 4H), 3.67 (s, 3H), 3.30 (s, 2H), 1.65 (d, J = 7.2Hz, 3H), 1.31 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 191.1, 113.9, 64.2, 52.0, 39.9, 15.9, 10.7.

IR (NaCl, neat) ν 3480, 2986, 1743, 1698, 1268, 1027 cm^{-1}.



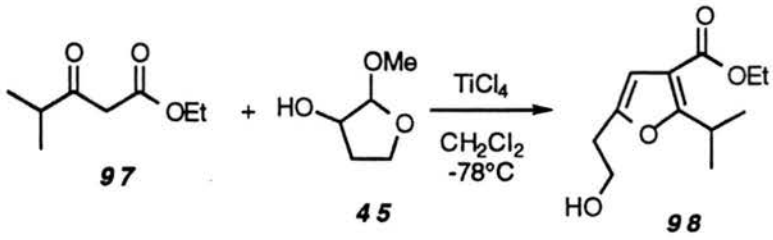
65 *96*

3-Isobutyryl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethylsiloxyethy)-pyrrolidine-2-one 96. To epoxy pyrrolidine-one ethyl ketone **65** (235 mg, 0.71 mmol, 1.0 eq) in dry toluene (12 ml) at 0°C under argon atmosphere was added 1M solution of sodium hexamethyldisilazide in tetrahydrofuran (2.2 ml, 2.2 mmol, 3.0 eq) followed by methyl iodide neat (450 mg, 3.2 mmol, 4.5 eq). The mixture was stirred at 0°C for 2.75 h at which time saturated ammonium chloride (10 ml) was added. The aqueous layer was separated and extracted with ethyl acetate (3 x 15 ml), dried (Na_2SO_4) and concentrated. The crude mixture was chromatographed (3:2 hexane/ethyl acetate) to give the epoxy pyrrolidine-one isopropyl ketone **96** (36 mg, 15%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (br s, 1H, D_2O exch.), 4.51 (s, 1H, D_2O exch.), 4.03 (m, 1H0, 3.91 (d, J = 2.3Hz, 1H), 3.89 (m, 1H), 3.08 (m, 1H), 2.03 (m, 2H), 1.21 (m, 3H), 0.89 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.2, 168.5, 84.8, 65.4, 60.7, 59.1, 36.2, 33.1, 25.8, 18.0, 6.7, -5.6.

IR (NaCl, neat) ν 3333, 2930, 1733, 1102, 1004 cm^{-1}.



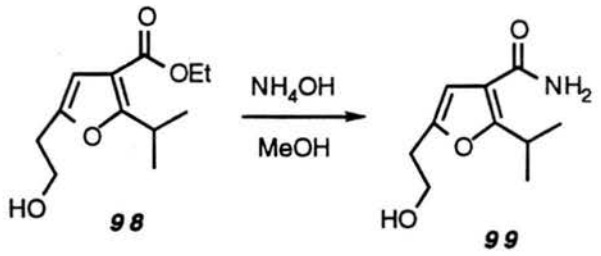
Ethyl 2-isopropyl-5-(2-hydroxyethyl)-3-furanoate 98. To ethyl isobutyryl acetate **97** (2.00 g, 12.6 mmol, 1.0 eq) and hydroxy acetal **45** (1.50 g, 12.6 mmol, 1.0 eq) in dry methylene chloride (20 ml) at -78°C under argon was added titanium tetrachloride (2.88 g, 15.2 mmol, 1.2 eq) neat. The mixture was allowed to warm to room temperature over 2 h, at which time water (10 ml) was added. The organic phase was separated and washed with saturated sodium bicarbonate solution (1 x 10 ml) and dried (Na_2SO_4). The solution was concentrated and chromatographed (3:2 hexane/ethyl acetate) to give furan **98** (1.88 g, 66%) as a clear colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.23 (q, J = 7.2Hz, 2H), 3.84 (t, J = 6.3Hz, 2H), 3.69 (heptet, J = 7.0Hz, 1H), 2.83 (t, J = 6.3Hz, 2H), 2.11 (br s, 1H, D_2O exch.), 1.30 (t, J = 7.2Hz), 1.22 (d, J = 7.0Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.1, 164.1, 150.4, 112.0, 107.0, 60.6, 59.9, 31.2, 27.1, 20.6, 14.2.

IR (NaCl, neat) ν 3436, 3123, 2974, 1715, 1614, 1577, 1237, 1062 cm^{-1}.

Elem. Anal. calcd for $C_{10}H_{16}O_4$: C, 63.70; H, 8.02. Found: C, 63.31; H, 7.93.



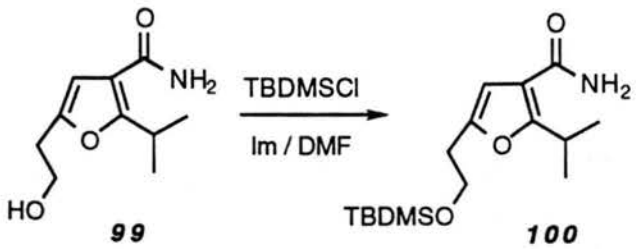
98 99

2-Isopropyl-3-amido-5-(2-hydroxyethyl)-furan 99. To ester furan **98** (1.78 g, 7.88 mmol) in methanol (20 ml) was added concentrated ammonium hydroxide (200 ml) and stirred at room temperature for 48 h. The mixture was then concentrated and chromatographed (3:1:4 ethyl acetate/methanol/methylene chloride) to give amido furan **99** (560 mg, 36%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.83 (br s, 2H, D_2O exch.), 3.85 (t, J = 6.2Hz, 2H), 3.72 (heptet, J = 6.9Hz, 1H), 2.82 (t, J = 6.2Hz, 2H), 2.62 (br s, 1H, D_2O exch.), 1.21 (d, J = 6.9Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.3, 164.7, 150.7, 113.3, 105.5, 60.5, 31.3, 26.9, 20.9.

IR (NaCl, neat) ν 3349, 3209, 2971, 1659, 1603, 1579, 1243, 1053 cm^{-1}



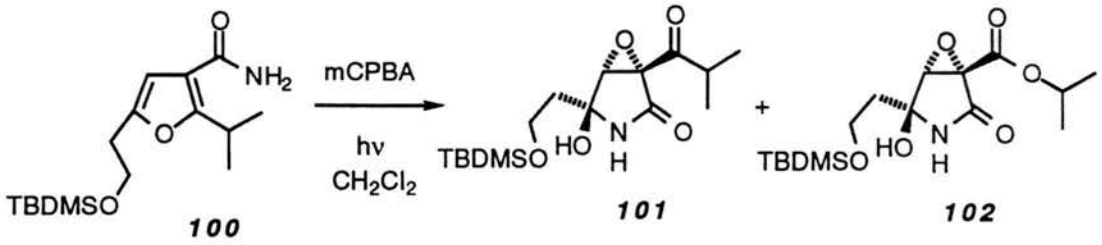
2-Isopropyl-3-amido-5-(2-*tert*-butyldimethylsiloxyethyl)-furan 100. To amido furan **99** (560 mg, 2.8 mmol, 1.0 eq) in dry dimethylformamide (5 ml) was added solid *tert*-butyldimethylsilyl chloride (1.3 g, 8.5 mmol, 3.0 eq) followed by solid imidazole (1.0 g, 14 mmol, 5.0 eq) and stirred at room temperature for 24 h. Water (5 ml) was then added and the mixture extracted with diethyl ether (3 x 20 ml). The etheral solution was dried (Na_2SO_4) and chromatographed (1:1 ethyl acetate/methylene chloride) to give silyl amido furan **100** (840 mg, 97%) as a white crystalline solid.

^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (br s, 1H, D_2O exch.), 6.06 (s, 1H), 5.97 (br s, 1H, D_2O exch.), 3.75 (t, J = 6.6Hz, 2H), 3.70 (heptet, J = 7.0Hz, 1H, 2.69 (t, J = 6.6Hz, 2H), 1.15 (d, J = 7.0Hz, 6H), 0.78 (s, 9H), -0.08 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.6, 163.8, 150.7, 113.4, 105.3, 61.1, 31.5, 26.7, 25.7, 20.8, 18.1, -5.6.

IR (NaCl, neat) ν 3351, 3195, 2957, 1651, 1608, 1580, 1104, 837 cm^{-1}.

Elem. Anal. calcd for $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50. Found: C, 61.69; H, 9.44; N, 4.50.



100 *101* *102*

3-Isobutyryl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethyl-siloxyethyl)-pyrrolidine-2-one 101 and 3-Isopropyl formate-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethylsiloxyethyl)-pyrrolidine-2-one 102. To silyl amido furan **100** (840 mg, 2.7 mmol, 1.0 eq) in methylene chloride (15 ml) was added solid m-chloroperbenzoic acid and irradiated for 3 h followed by sitting at room temperature for 8 h. The mixture was washed with saturated sodium bicarbonate solution (2 x 10 ml), dried (Na_2SO_4) and concentrated. The crude reaction mixture was then chromatographed to give epoxy ketone **101** (53 mg, 6.4%) and epoxy ester **102** (240 mg, 25%) both as light yellow oils.

101: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (br s, 1H, D_2O exch.), 4.91 (br s, 1H, D_2O exch.), 4.03, 3.88 (m, 2H), 3.96 (d, J = 2.3Hz, 1H), 3.07 (m, 1H), 2.03 (m, 2H), 1.21 (m, 3H), 0.89 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.3, 168.3, 85.2, 65.1, 60.4, 59.4, 38.1, 35.8, 25.8, 18.0, 17.7, -5.6.

IR (NaCl, neat) ν 3348, 2930, 1733, 1697, 1098 cm^{-1}.

HRMS calcd for $C_{16}H_{30}NO_5Si$ $[M+H]^+$: 344.189328

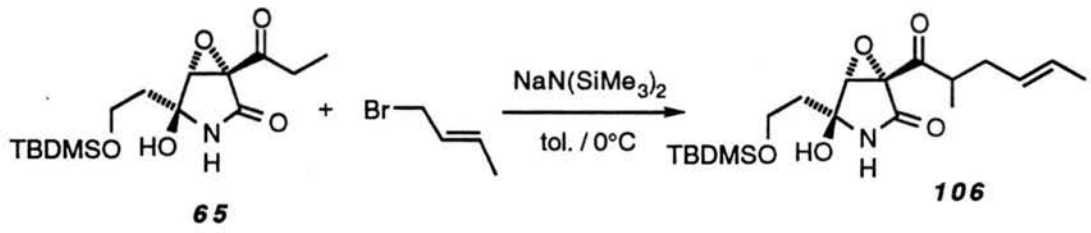
Found: 344.1882.

102: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (br s, 1H, D_2O exch.), 5.15 (heptet, J = 6.3Hz, 1H), 4.92 (br s, 1H, D_2O exch.), 4.05 (d, J = 2.6Hz, 1H), 4.02 (m, 1H), 3.89 (m, 1H), 2.01 (m, 2H), 1.30 (d, J = 6.3Hz, 6H), 0.87 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.1, 162.9, 85.0, 70.7, 64.3, 62.7, 59.3, 35.8, 25.8, 21.6, 18.1, -5.6.

IR (NaCl, neat) ν 3328, 2930, 1749, 1697, 1103, 836 cm^{-1}.

HRMS Calcd for $C_{16}H_{30}NO_6Si$ $[M+H]^+$: 360.184243 Found: 360.1833.



65 *106*

3-(2-Methylpentoyl-4-ene)-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethylsiloxyethyl)-pyrrolidine-2-one 106. To keto epoxy pyrrolidine-one **65** (107 mg, 0.32 mmol, 1.0 eq) in dry toluene (4 ml) at 0°C under argon atmosphere was added 1M solution of sodium hexamethyl disilazide in tetrahydrofuran (.97 ml, .97 mmol, 3.0 eq) followed by crotyl bromide (130 mg, .97 mmol, 3.0 eq) neat. The mixture was stirred at 0°C for 10 min at which time saturated ammonium chloride solution (5 ml) was added. The mixture was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 ml), dried (Na_2SO_4), and concentrated. The crude reaction mixture was then chromatographed (3:2, hexane/ethyl acetate) to give the isohexenyl ketone **106** (33 mg, 27%) as a mixture of diastereomers as a light yellow oil.

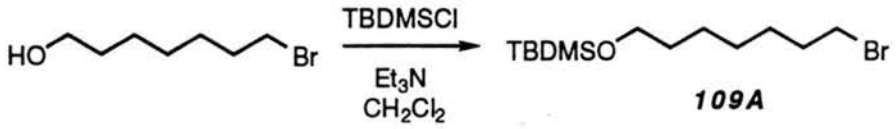
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (br s, 1H, D_2O exch.), 5.45 (m, 1H), 5.30 (m, 1H), 4.92 (br s, 1H, D_2O exch.), 3.97 (m, 3H), 2.38 (m, 3H), 2.03 (m, 2H), 1.61 (d, J = 6.1Hz, 3H), 1.06 (d, J = 6.7Hz, 3H), 0.89 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.0, 168.3, 128.4, 127.8, 85.2, 65.2, 61.2, 59.4, 43.2, 35.6, 34.2, 25.8, 18.0, 15.7, 14.0, -5.6.

IR (NaCl, neat) ν 3322, 3025, 2930, 1733, 1699, 1653, 1472, 1099, 1005 cm^{-1}.

m/e (NH_3Cl) 384 (M+1), 366, 350, 204.

Elem. Anal. calcd for $C_{19}H_{33}NO_5Si$: C, 58.89; H, 8.58; N, 3.61. Found: C, 58.70; H, 8.78; N, 3.78.

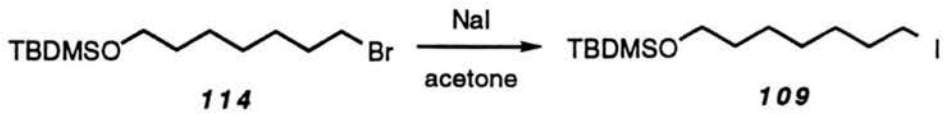


109A

7-*tert*-Butyldimethylsiloxy-1-bromoheptane <u>109A</u>. To 7-bromoheptanol (1.09 g, 5.59 mmol, 1.0 eq) in dry methylene chloride (6 ml) was added *tert*-butyl dimethyl silyl chloride (1.00 g, 6.7 mmol, 1.2 eq) followed by triethylamine (1.09 g, 10.7 mmol, 1.9 eq) and stirred at room temperature for 72 h. The reaction mixture was then quenched with water (5 ml), diluted with methylene chloride (50 ml), washed with 0.1N hydrochloric acid (10 ml) followed by saturated sodium bicarbonate (15 ml), dried (Na_2SO_4), and concentrated. The crude mixture was chromatographed (3:2 hexane/ethyl acetate) to give *tert*-butyl dimethyl silyl-bromo-heptyl ether **109A** (1.65 g, 96%) as a light orange oil.

^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (t, J = 6.5Hz, 2H), 3.32 (t, J = 6.8Hz, 2H), 1.78 (t, J = 7.6Hz, 2H), 1.35 (m, 8H), 0.82 (s, 9H), -0.03 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 62.8, 33.5, 32.5, 28.9, 28.4, 27.8, 25.6, 25.4, 18.0, -5.6.

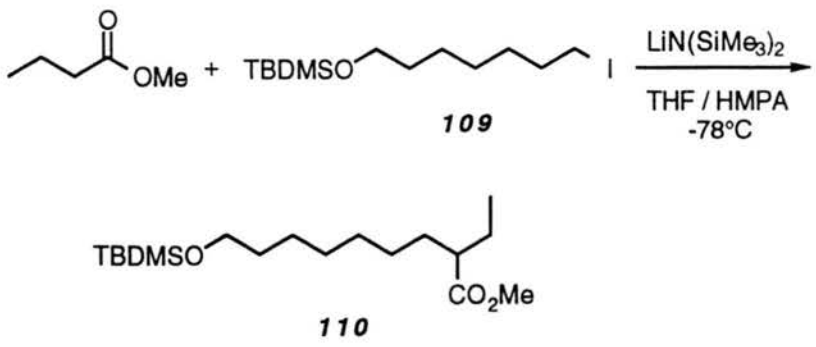


114 *109*

1-Iodo-7-(*tert*-butyldimethylsiloxy)heptane 109. To heptyl bromide **109A** (4.75 g, 15.4 mmol, 1.0 eq) in dry acetone (50 ml) was added sodium iodide (11.5 g, 77.0 mmol, 5.0 eq) and stirred at room temperature for 16 h. The mixture was concentrated, taken up in ethyl acetate, filtered through a plug of silica gel, and concentrated. The crude oil was chromatographed (20:1, hexane/ethyl acetate) to give iodo-heptane **109** (4.54 g, 83%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (t, J = 6.5Hz, 2H), 3.15 (t, J = 7.0Hz, 2H), 1.79 (m, 2H), 1.45 (m, 2H), 1.28 (m, 6H), 0.87 (s, 9H), 0.3 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.2, 33.5, 32.8, 30.4, 29.2, 28.5, 26.0, 25.7, 18.3, -5.3.

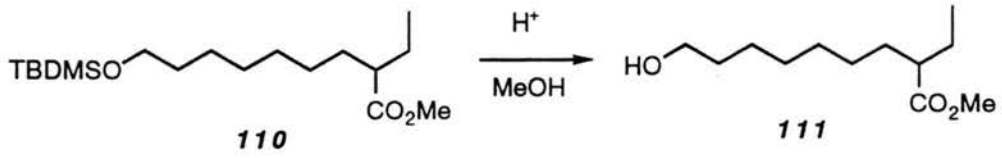


3-Carbomethoxy-10-*tert*-butyldimethylsiloxy decane 110. To methyl butyrate (240 mg, 2.3 mmol, 1.1 eq) in dry tetrahydrofuran (5 ml) under argon at -78°C was added a 1M solution of lithium hexamethyl disilazide in tetrahydrofuran (2.5 ml, 2.5 mmol, 1.2 eq) and stirred for 5 min. At this time 1-*tert*-butyldimethylsiloxy-7-iodo heptane **109** (750 mg, 2.1 mmol, 1.0 eq) was added in tetrahydrofuran (2 ml)/hexamethylphosphoramide (2 ml) mixture dropwise and stirred from -78°C to -10°C over 45 min. The mixture was quenched with saturated ammonium chloride solution (5 ml), diluted with diethyl ether (20 ml), washed with water (2 x 5 ml), dried (Na_2SO_4), and concentrated. The crude mixture was chromatographed (20:1 hexane/ethyl acetate) to give siloxy ester **110** (255 mg, 26%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.53 (t, J = 6.5Hz, 2H), 2.21 (m, 1H), 1.44 (m, 6H), 1.21 (m, 8H), 0.83 (s, 12H), -0.02 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.7, 70.9, 63.2, 51.1, 47.2, 32.8, 32.0, 29.4, 29.3, 27.4, 25.9, 25.4, 18.3, 11.8, -5.4.

IR (NaCl, neat) ν 2930, 1739, 1463, 1255, 1100 cm^{-1}.



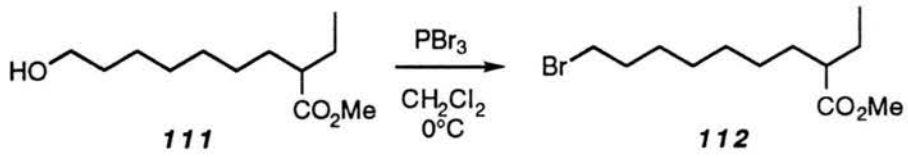
110 *111*

3-Carbomethoxy-10-hydroxy decane 111. To siloxy decane **110** (900 mg, 2.5 mmol) in 0.5M hydrochloric acid in methanol (30 ml) at room temperature was stirred for 20 min. To the mixture was added solid sodium bicarbonate until bubbling ceased, then extracted with diethyl ether (3 x 20 ml). The organic solution was dried (Na_2SO_4), and chromatographed (20:1, hexane/ethyl acetate) to give decanol ester **111** (500 mg, 93%) as a clear colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 3.55 (s, 3H), 3.43 (t, J = 6.7Hz, 2H), 3.27 (t, J = 6.7Hz, 2H), 2.86 (br s, 1H, D_2O exch.), 1.44 (m, 2H), 1.20 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.7, 62.4, 51.0, 47.1, 32.5, 31.9, 29.3, 29.2, 27.2, 25.6, 25.3, 11.6.

IR (NaCl, neat) ν 3418, 2929, 1738, 1462, 1258, 1196, 1169, 1098 cm^{-1}

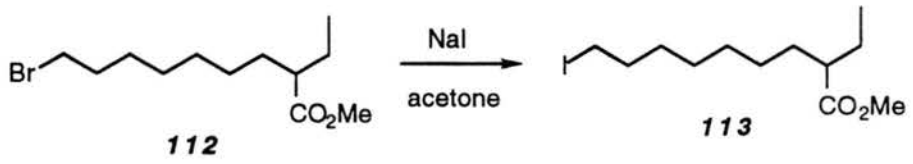


111 *112*

3-Carbomethoxy-10-bromo-decane **112**. To decanol **111** (120 mg, 0.55 mmol, 1.0 eq) in dry methylene chloride (15 ml) at 0°C was added neat phosphorous tribromide (165 mg, 0.06 mmol, 1.1 eq) and stirred for 4 h. The mixture was filtered through a plug of silica gel, washed with water (2 x 10 ml) and saturated sodium bicarbonate solution (1 x 10 ml), and dried (Na_2SO_4). The solution was concentrated and chromatographed (20:1, hexane/ethyl acetate) to give bromo-decane **112** (85 mg, 55%) as a clear colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.36 (t, J = 6.5Hz, 2H), 2.23 (m, 1H), 1.80 (m, 2H), 1.50 (m, 2H), 1.39 (m, 2H), 1.23 (m, 8H), 0.87 (t, J = 7.4Hz, 3H).

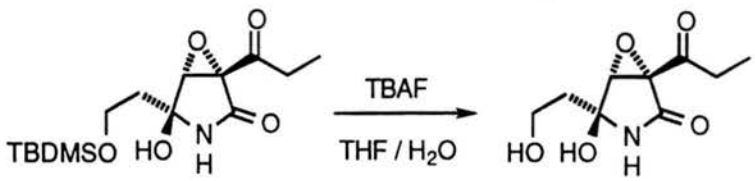
IR (NaCl, neat) ν 2930, 1738, 1461, 1168 cm^{-1}.



112 *113*

3-Carbomethoxy-10-iodo-decane **113**. To bromo-decane **112** (80 mg, 0.30 mmol, 1.0 eq) in dry acetone (5 ml) was added sodium iodide (215 mg, 1.50 mmol, 5.0 eq) in dry acetone (5 ml) at room temperature and stirred for 5 h. The mixture was concentrated, taken up in ethyl acetate, filtered through a plug of silica gel, and concentrated. The crude mixture was then chromatographed (20:1, hexane/ethyl acetate) to give iodo-decane **113** (46 mg, 47%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.32 (t, J = 6.6Hz, 2H), 2.21 (m, 1H), 1.73 (m, 2H), 1.53 (m, 2H), 1.19 (m, 10H), 0.82 (t, J = 7.4Hz, 3H).



65 *11*

3-Propionyl-3,4-epoxy-5-hydroxy-5-(2-hydroxyethyl)-pyrrolidine-2-one 11. To silyl epoxy pyrrolidine-one **65** (262 mg, 0.79 mmol, 1.0 eq) in tetrahydrofuran (15 ml) at room temperature was added 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.8 ml, 0.8 mmol, 1.0 eq) and of water (1 drop). The mixture was stirred at room temperature for 5 min, water (10 ml) was then added and the mixture extracted with ethyl acetate (4 x 15 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (3:1:4, ethyl acetate/methanol/methylene chloride) to give epoxy pyrrolidine-one diol **11** (53 mg, 31%) as a light yellow solid.

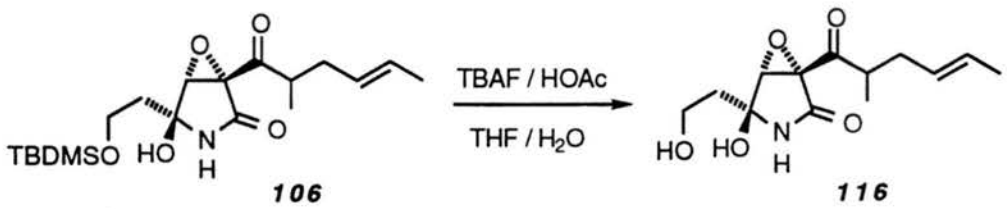
^1H NMR (300 MHz, d_4-MeOD) δ 4.19 (s, 1H), 3.80 (m, 2H), 2.62 (m, 2H), 2.16 (m, 1H), 1.96 (m, 1H), 1.04 (m, 3H).

^{13}C NMR (75.5 MHz, d_4-MeOD/$CDCl_3$) δ 200.8, 167.8, 84.4, 65.3, 60.5, 58.3, 36.4, 33.0, 6.2.

IR (NaCl, neat) ν 3302, 2920, 1718, 1697, 1457, 1090 cm^{-1}.

HRMS calcd for $C_9H_{14}NO_5$ $[M+H]^+$: 216.087199.

Found: 216.0870.



3-(2-Methyl)pentoyl(4-ene)-3,4-epoxy-5-hydroxy-5-(2-hydroxyethyl)-pyrrolidine-2-one 116. To silyl epoxy isohexene-one **106** (36 mg, 0.09 mmol, 1.0 eq) in tetrahydrofuran (3 ml) was added 1M acetic acid (1 drop) followed by 1M tetrabutyl ammonium fluoride (0.1 ml, 0.1 mmol, 1.1 eq) in tetrahydrofuran and stirred at room temperature for 48 h. To the mixture was added 10% sodium carbonate (5 ml), and extracted with ethyl acetate (4 x 10 ml). The organic solution was dried (Na_2SO_4), concentrated, and chromatographed (1:1, ethyl acetate/methylene chloride) to give epoxy diol **116** (14 mg, 55%) as a light yellow oil.

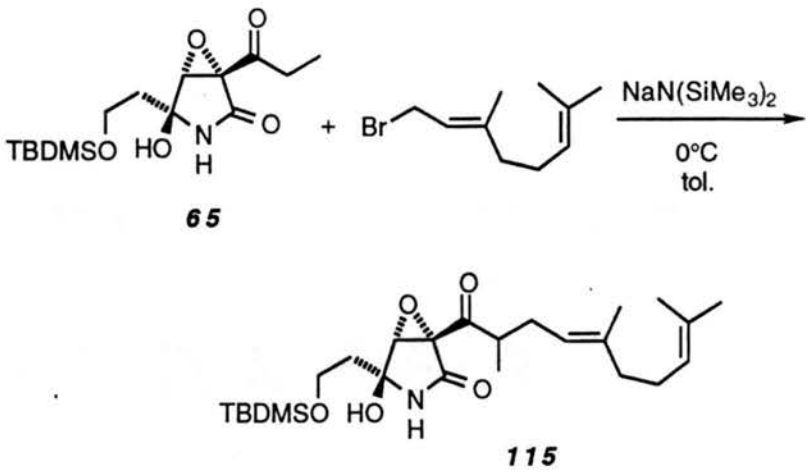
^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (br s, 1H, D_2O exch.), 5.50 (m, 1H), 5.27 (m, 2H, 1H, D_2O exch.), 4.13 (d, J = 2.1Hz, 1H), 4.04 (m, 1H), 3.89 (m, 1H), 3.03 (br s, 1H, D_2O exch.), 2.85 (m, 1H), 2.37 (m, 1H), 2.03 (m, 3H), 1.62 (d, J = 6.5Hz, 3H), 1.16 (d, J = 6.5Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.1, 169.4, 129.4, 125.5, 85.0, 64.5, 62.3, 58.1, 52.1, 39.1, 35.7, 19.7, 18.0.

IR (NaCl, neat) ν 3351, 3024, 2927, 1727, 1695, 1651, 1455, 1090, 970 cm^{-1}.

HRMS calcd for $C_{13}H_{20}NO_5$ $[M+H]^+$: 270.134149

Found: 270.1340.



3-(2,6,9-Trimethyl-2,6-di-ene)decanoyl-3,4-epoxy-5-hydroxy-5-(2-*tert*-butyldimethylsiloxyethyl)-pyrrolidine-2-one 115. To epoxy pyrrolidine-one **65** (215 mg, 0.55 mmol, 1.0 eq) in dry toluene (11 ml) at 0°C under argon was added geranyl bromide (565 mg, 2.6 mmol, 4.0 eq) followed by 1M solution of sodium hexamethyl disilazide (1.75 ml, 1.75 mmol, 3.0 eq) in tetrahydrofuran. The mixture was stirred at 0°C for 2 h, followed by the addition of saturated ammonium chloride solution (10 ml). The mixture was extracted with ethyl acetate (3 x 10 ml), dried (Na_2SO_4), and chromatographed (3:2, hexane/ethyl acetate) to give the geranyl epoxy pyrrolidine-one **115** (75 mg, 25%) as a light yellow oil.

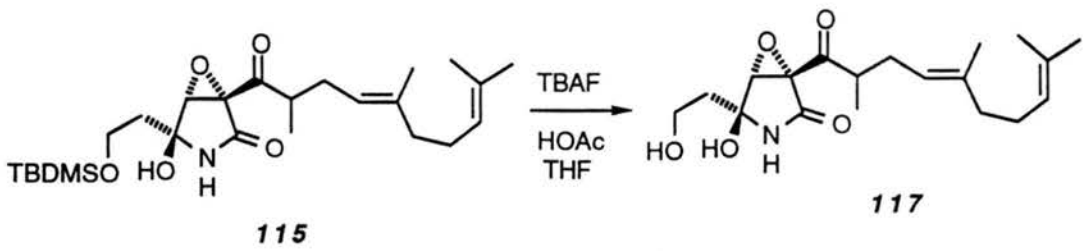
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (br s, 1H, D_2O exch.), 5.04 (m, 3H, 1H, D_2O exch.), 4.04 (m, 1H), 4.90 (m, 1H), 3.85 (d, J = 2.1Hz, 1H), 2.37 (m, 3H), 1.98 (m, 6H), 1.64 (s, 3H), 1.56 (s, 6H), 1.18 (s, 3H), 0.88 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.4, 169.1, 138.2, 131.4, 124.2, 119.2, 85.1, 69.3, 62.3, 59.2, 52.7, 39.9, 35.9, 34.2, 26.6, 25.8, 25.7, 19.6, 18.0, 17.7, 16.3, -5.6.

IR (NaCl, neat) ν 3352, 2929, 1733, 1699, 1682, 1102 cm^{-1}.

HRMS calcd for $C_{25}H_{44}NO_5Si$ $[M+H]^+$: 466.298878

Found: 466.3004.



115 *117*

3-(2,6,9-Trimethyl-2,6-diene)decanoyl-3,4-epoxy-5-hydroxy-5-(2-hydroxyethyl)-pyrrolidine-2-one 117**.** To silyl epoxy pyrrolidine-one **115** (25 mg, 0.05 mmol, 1.0 eq) in tetrahydrofuran (5 ml) at room temperature was added acetic acid (1 drop) followed by 1M solution of tetrabutyl ammonium fluoride (0.10 ml, 0.10 mmol, 2.0 eq) in tetrahydrofuran and stirred at room temperature for 12 h. To the mixture was added saturated sodium bicarbonate solution (5 ml) and was extracted with ethyl acetate (3 x 10 ml). The organic solution was dried (Na_2SO_4) and chromatographed (1:1, ethyl acetate/methylene chloride) to give diol **117** (9 mg, 48%) as a clear colorless film.

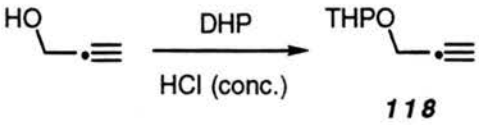
^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (br s, 1H, D_2O exch.), 5.04 (m, 3H, 1H D_2O exch.), 4.04 (m, 2H), 3.91 (m, 1H), 2.84 (m, 1H), 2.33 (m, 2H), 2.03 (m, 7H, 1H D_2O exch.), 1.65 (s, 3H), 1.57 (s, 6H), 1.03 (d, J = 6.6Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.3, 168.7, 142.4, 138.4, 124.1, 120.2, 84.9, 65.1, 60.7, 58.2, 42.8, 39.8, 30.8, 29.7, 26.5, 25.7, 17.7, 16.1, 13.9.

IR (NaCl, neat) ν 3309, 3052, 2925, 1732, 1654, 1456, 1094 cm^{-1}.

HRMS calcd for $C_{19}H_{30}NO_5$ $[M+H]^+$: 352.212399

Found: 352.2109.



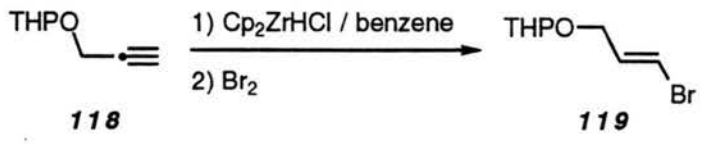
118

Tetrahydropyranyl propargyl ether 118. To dihydropyran (7.55 g, 89.9 mmol, 1.1 eq) at 0°C was added concentrated hydrochloric acid (4 drops) followed by dropwise addition of propargyl alcohol (4.57 g, 81.7 mmol, 1.0 eq). The mixture was stirred for 2 h and distilled (30-40°C/2 mm) to give the tetrahydropyranyl propargyl ether **118** (10.97 g, 96%) as a clear colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (t, J = 3.2Hz, 1H), 4.21 (dd, J = 2.4Hz, 6.8Hz, 2H), 3.79 (m, 1H), 3.47 (m, 1H), 2.37 (t, J = 2.4Hz, 1H), 1.56 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 96.7, 79.7, 73.9, 61.9, 53.9, 30.1, 25.2, 18.9.

IR (NaCl, neat) ν 3290, 2949, 2118, 1442, 1202, 1120, 1028 cm^{-1}.

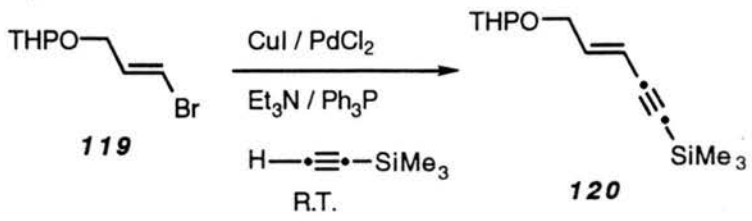


118 *119*

Tetrahydropyranyl-3-bromo-2-E-propenyl ether 119. To tetrahydropyranyl propargyl ether **118** (5.02 g, 35.8 mmol, 1.0 eq) in dry benzene (55 ml) under argon was added solid zirconocene hydrochloride (9.2 g, 35.8 mmol, 1.0 eq) and stirred at room temperature for 8 h. The light yellow solution was then chilled to 0°C followed by the dropwise addition of bromine neat (5.74 g, 35.8 mmol, 1.0 eq). After bromine addition, the resulting solid was filtered and the filtrate washed with 10% sodium thiosulfate (15 ml), saturated sodium bicarbonate (15 ml), and dried (Na_2SO_4). The crude mixture was concentrated and chromatographed (9:1 hexane/ethyl acetate) to give tetrahydropyranyl E-3-bromo-2-E-propenyl ether **119** (4.02 g, 51%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (m, 2H), 4.53 (m, 1H), 3.86 (m, 2H), 3.73 (m, 1H), 3.49 (m, 1H), 1.56 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 129.0, 128.2, 98.8, 74.3, 62.1, 30.7, 25.5, 19.4.

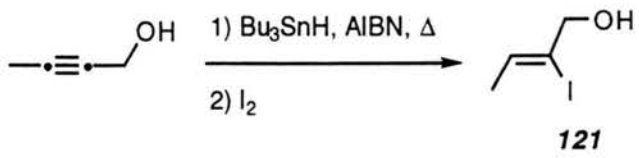


Tetrahydropyranyl-5-trimethylsilyl-pent-2-E-ene-4-yne-yl ether 120. To tetrahydropyranyl E-3-bromo-2-propenyl ether **119** (4.01 g, 18.2 mmol, 1.0 eq) and trimethyl silyl acetylene (1.80 g, 18.2 mmol, 1.0 eq) was added dry triethylamine (8.71 g, 86.2 mmol, 4.7 eq) followed by palladium(II) chloride (320 mg, 1.82 mmol, 0.10 eq), triphenylphosphine (1.00 g, 3.64 mmol, 0.20 eq), and copper(I) iodide (200 mg, catalytic amount) as solids. The rust colored mixture was stirred for 4 days at room temperature at which time water (20 ml) and diethyl ether (100 ml) were added. The mixture was separated, the aqueous washed with diethyl ether (2 x 20 ml), and the combined ethereal extracts dried (Na_2SO_4). The solution was concentrated and chromatographed (9:1 hexane/ethyl acetate) to give ene-yne **119** (5.02 g, 95%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (m, 1H), 5.72 (m, 1H), 4.57 (m, 1H), 4.20 (m, 1H), 3.98 (m, 1H), 3.78 (m, 1H), 3.45 (m, 1H), 1.52 (m, 6H), 0.14 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.6, 111.0, 103.1, 97.7, 66.3, 61.9, 53.4, 30.5, 25.3, 19.1, -0.2.

IR (NaCl, neat) ν 3032, 2954, 2134, 1687, 1037, 844 cm^{-1}.

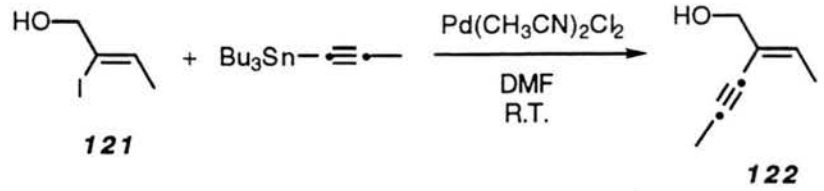


121

1-Hydroxy-2-iodo-2-Z-butene <u>121</u>. To 2-butyn-ol (2.81 g, 40.2 mmol, 1.2 eq) was added tributyltin hydride (10.0 g, 39.4 mmol, 1.0 eq) followed by azo-isobutyrylnitrile (40 mg). The mixture was heated to 85°C under argon for 2 h, then distilled under vacuum (107°C/0.2 mm). The vinyl stannane was dissolved in dry carbon tetrachloride (50 ml) followed by the addition of solid molecular iodine (10.2 g, 40.2 mmol, 1.2 eq) and stirred at room temperature for 30 min. The mixture was washed with 10% sodium thiosulfate (2 x 25 ml) and the organic solution dried (Na_2SO_4) concentrated. The crude material was taken up in acetonitrile (100 ml) and extracted with hexane (3 x 75 ml) to separate the tin salts. The acetonitrile was concentrated and chromatographed (3:2, hexane/ethyl acetate) to give iodo-butene-ol **121** (4.38 g, 55%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (q, J = 6.4Hz, 1H), 4.22 (s, 2H), 2.08 (br s, 1H, D_2O exch.), 1.77 (d, J = 6.4Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 131.6, 110.0, 71.9, 26.9.



121 *122*

1-Hydroxy-2-(1-propyne-yl)-2-E-butene **122.** To dry dimethyl formamide (8 ml) under argon was added bis-acetonitrile palladium (II) chloride (20 mg, 0.2 mmol, 0.05 eq) followed by vinyl iodide **121** (960 mg, 4.85 mmol, 1.0 eq) and propyne-yl stannane (1.59 g, 4.85 mmol, 1.0 eq) in dry methyl formamide (3 ml). The black mixture was stirred for 4 days at room temperature at which time 10% ammonium hydroxide was added (15 ml) and the mixture extracted with diethyl ether (3 x 20 ml). The ethereal mixture was washed with water (3 x 10 ml), filtered through Celite, dried (Na_2SO_4) and concentrated. The crude mixture was chromatogrpahed (3:2, hexane/ethyl acetate) to give ene-yne **122** (105 mg, 20%) as a light yellow oil.

^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (q, J = 6.7Hz, 1H), 4.02 (d, J = 6.0Hz, 2H), 1.99 (s, 3H), 1.81 (d, J = 6.7Hz, 3H), 1.76 (br s, 1H, D_2O exch.).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 131.9, 124.2, 91.6, 71.6, 66.4, 15.6, 4.4.

IR (NaCl, neat) ν 3457, 3005, 2922, 2252, 1653 cm^{-1}.

Chapter Five

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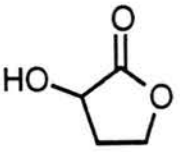
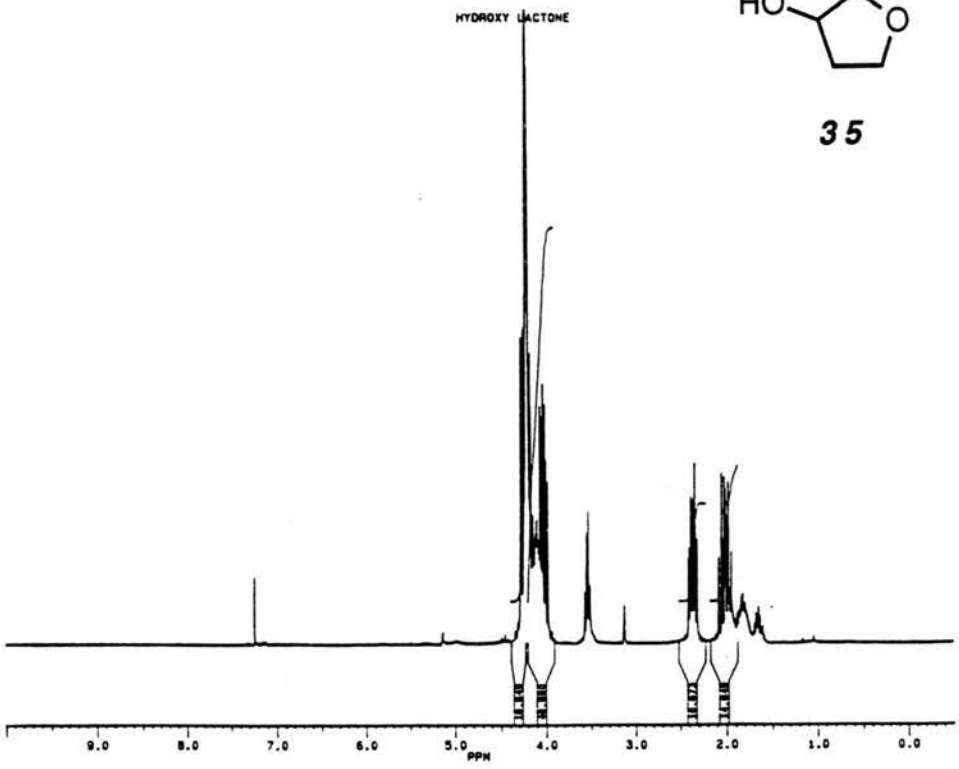
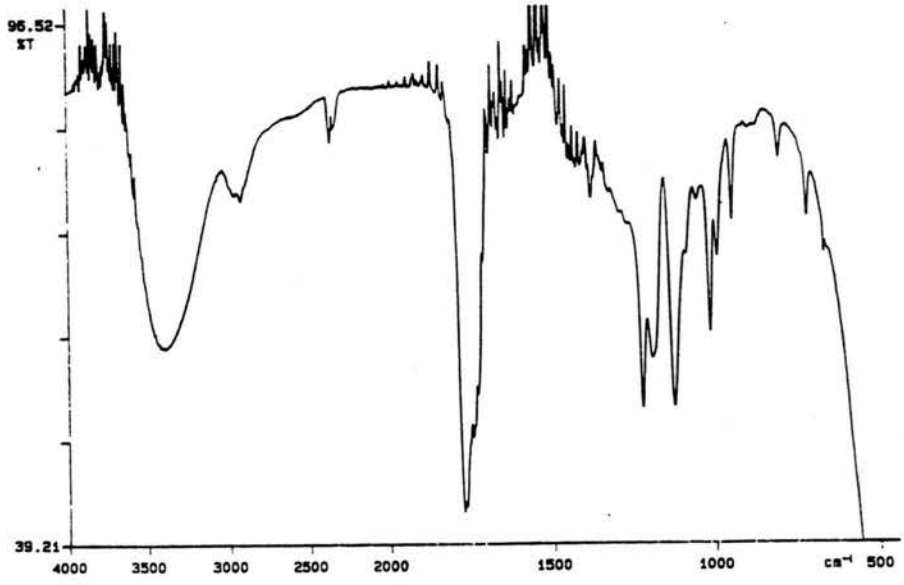
Appendix A

Spectra of Synthesized Compounds

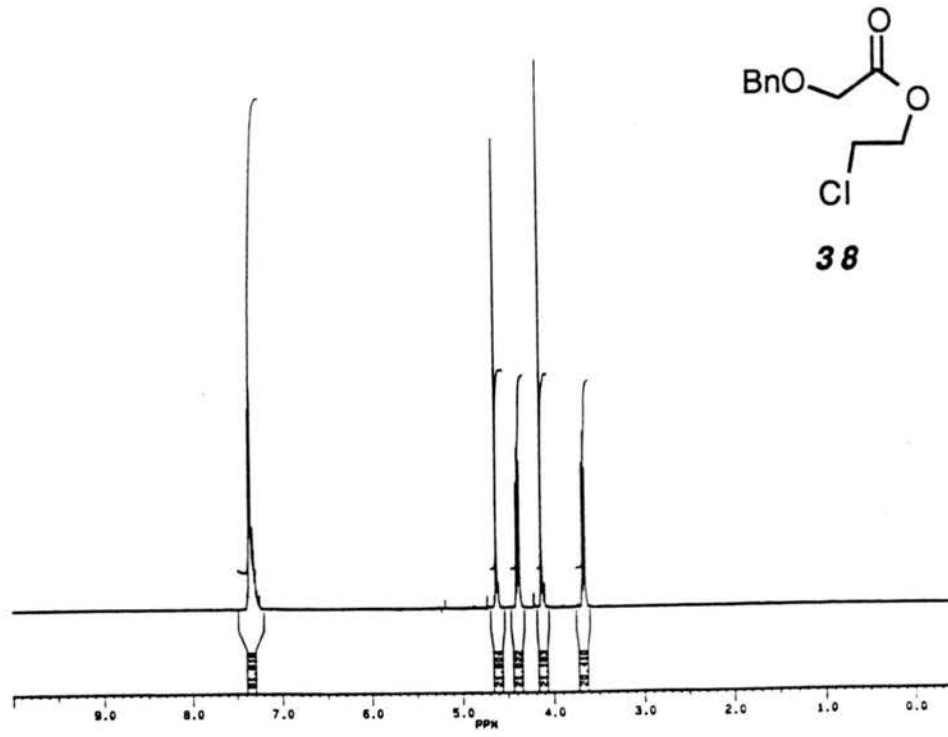


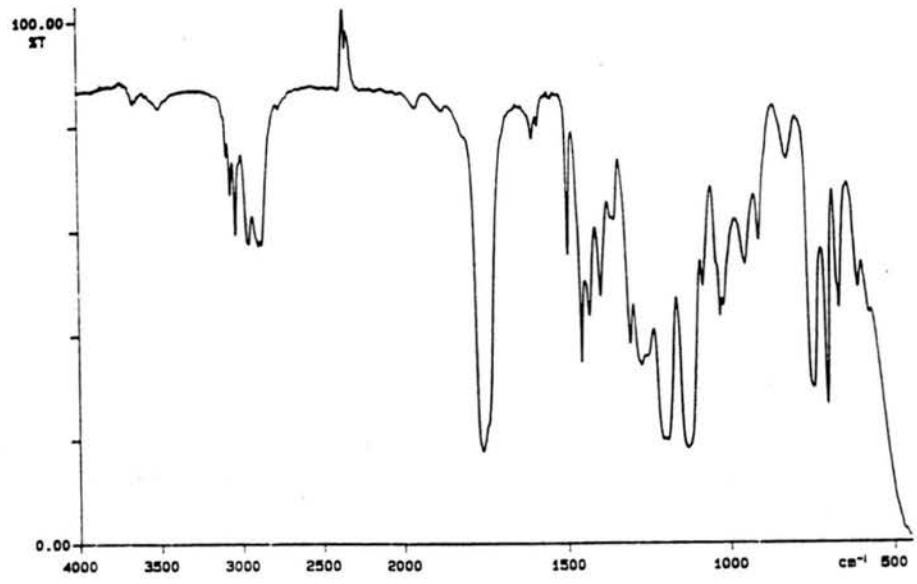
35



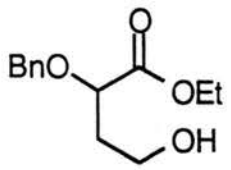


^{1}H NMR (300 MHz) and IR for compound **35**.





^{1}H NMR (300 MHz) and IR for compound **38**.



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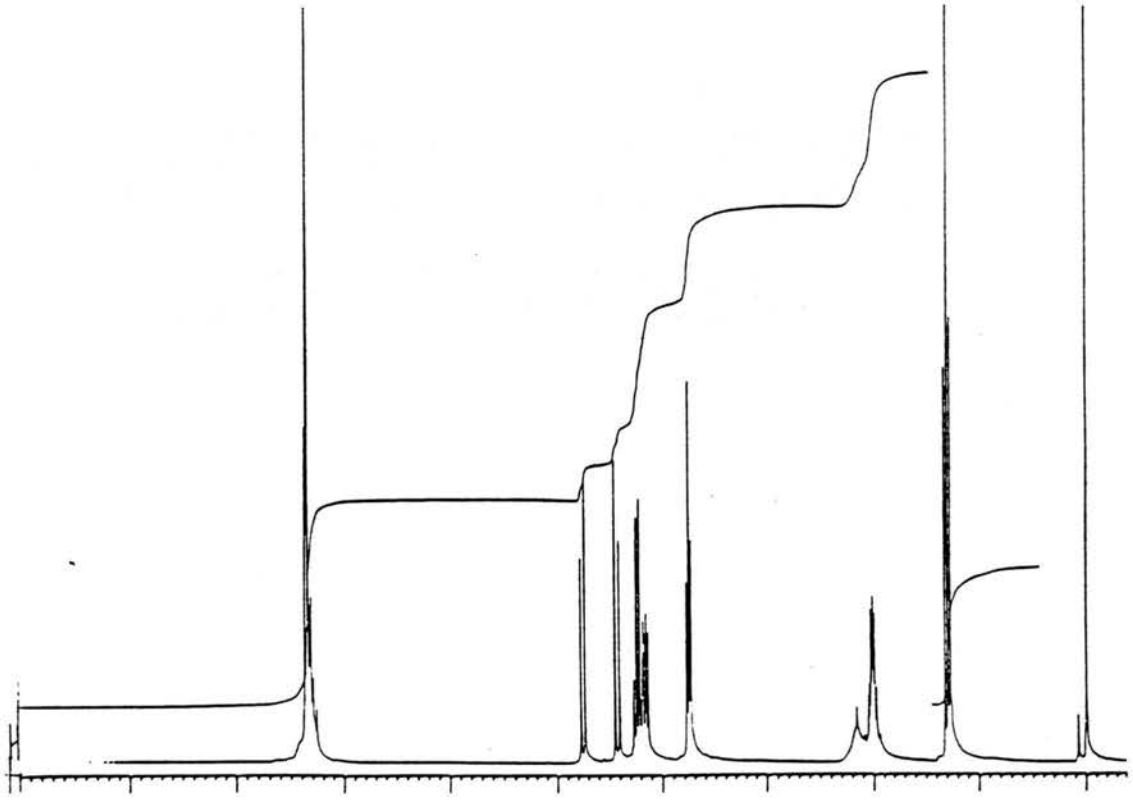
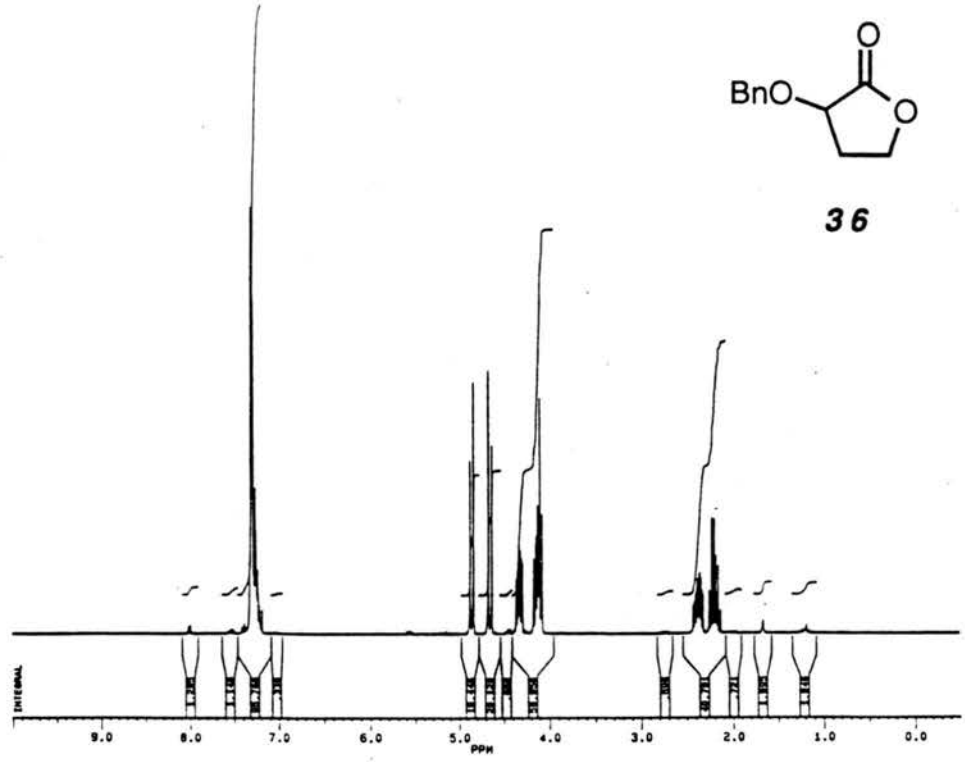
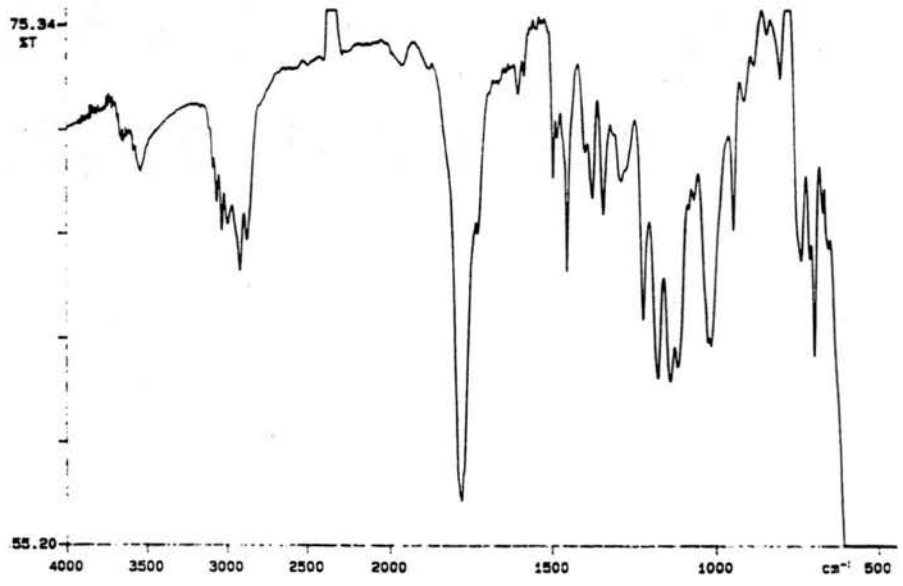
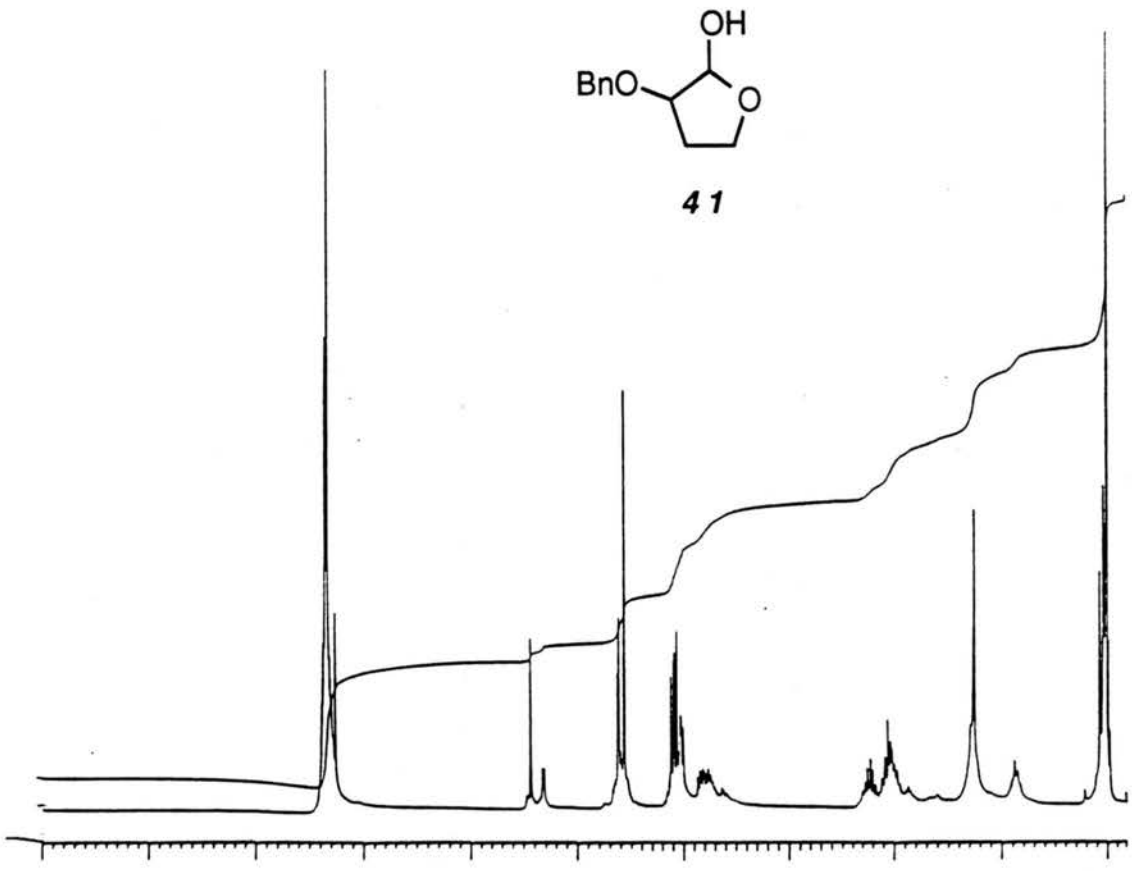


^{1}H NMR (270 MHz) for compound **40**.





^{1}H NMR (300 MHz) and IR for compound **36**.



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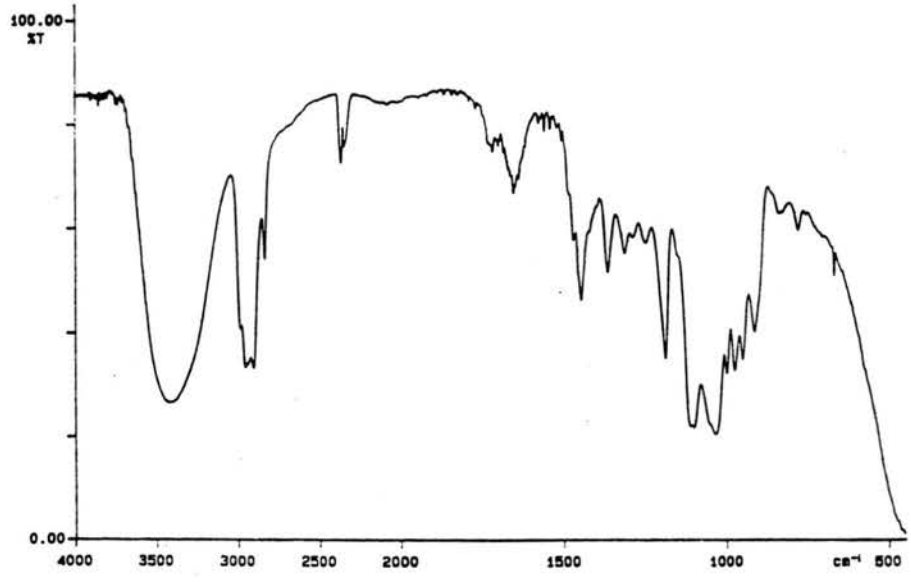

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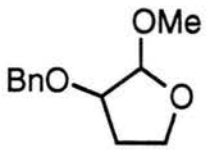

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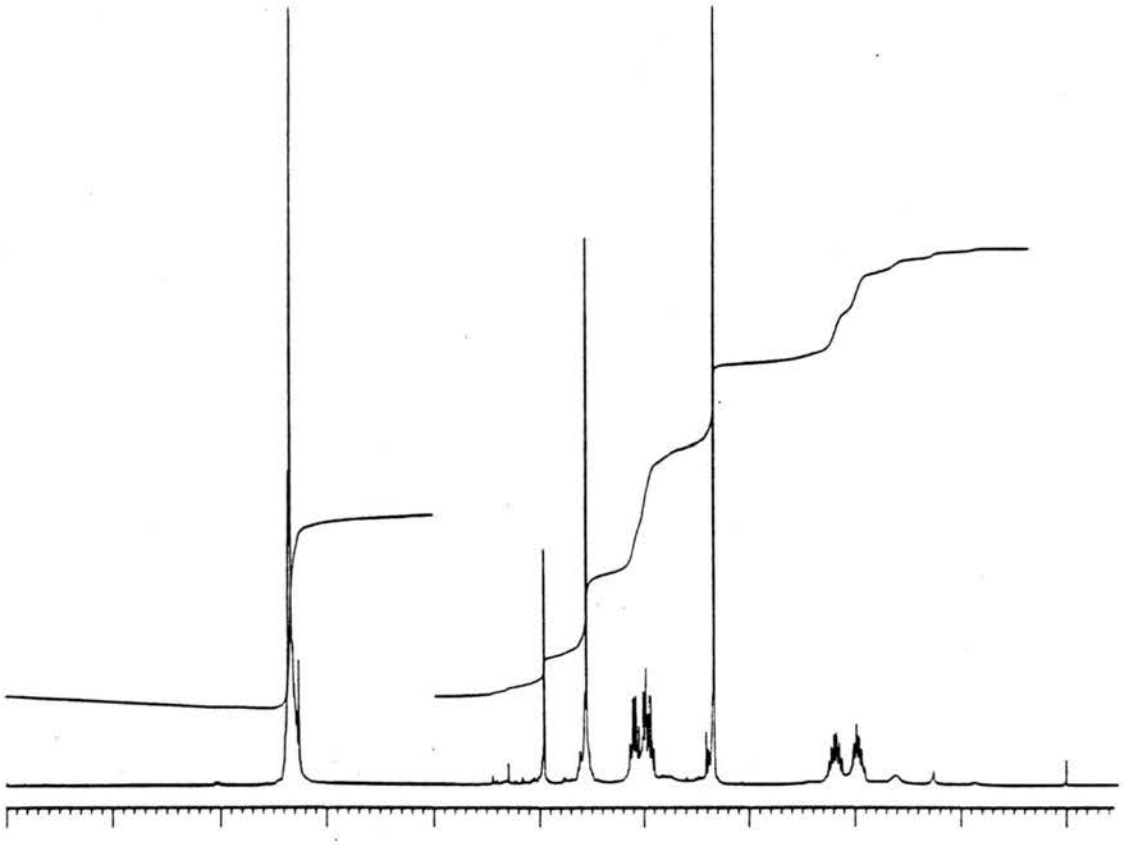
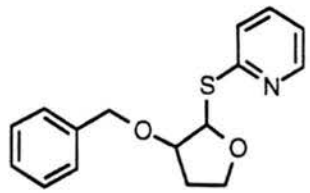
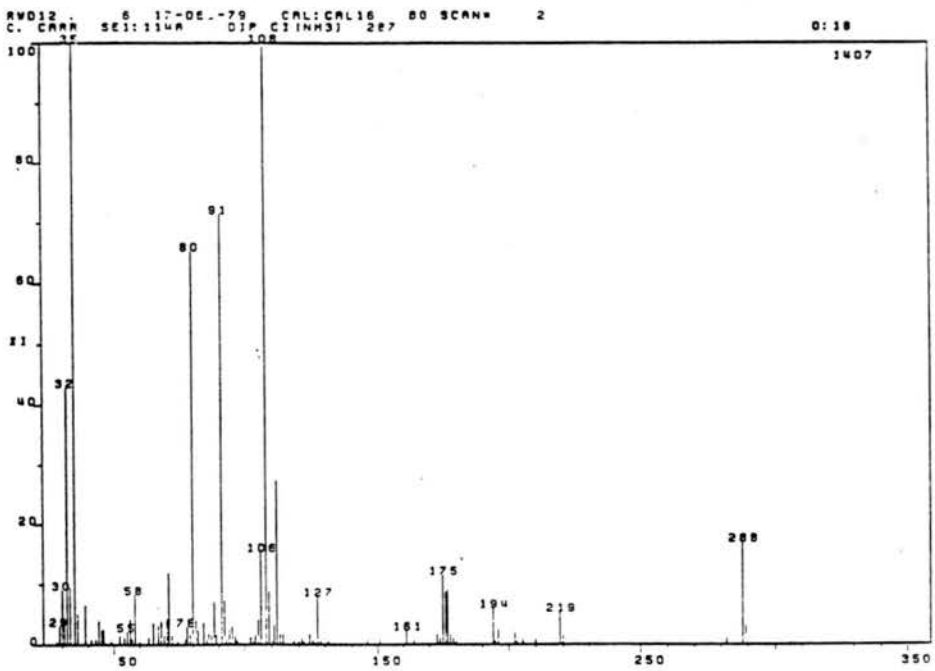


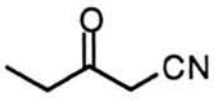
^{1}H NMR (270 MHz) for compound **18**.



41A



^{1}H NMR (270 MHz) and mass spectrum for compound **41A**.



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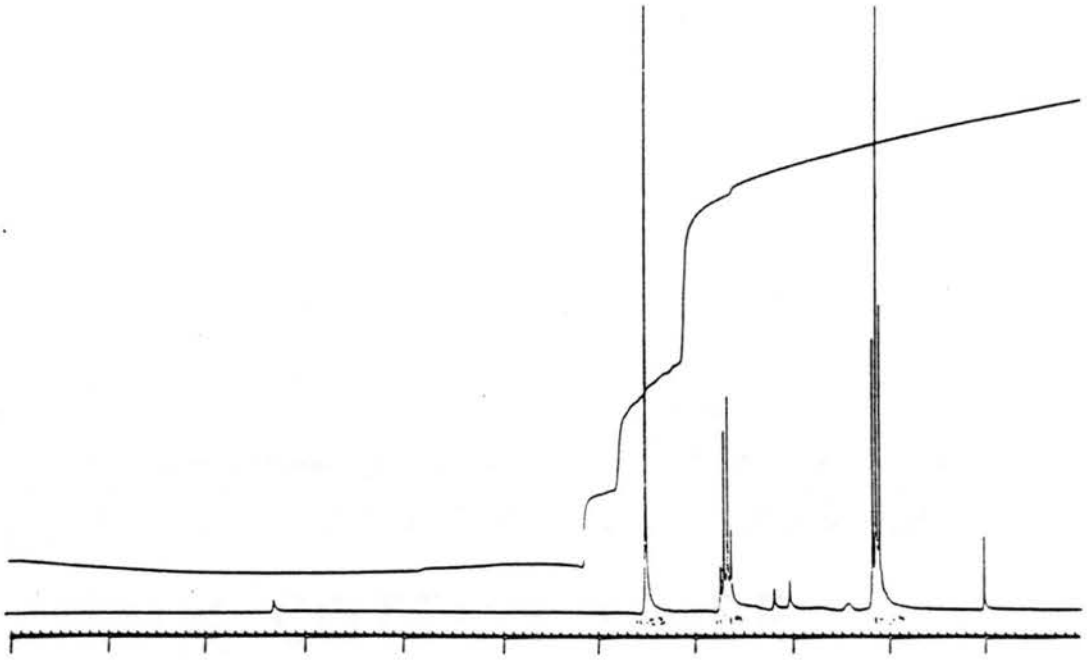
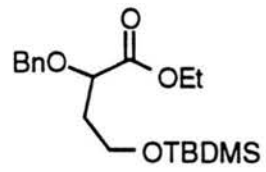


^{1}H NMR (270 MHz) of compound **14**.



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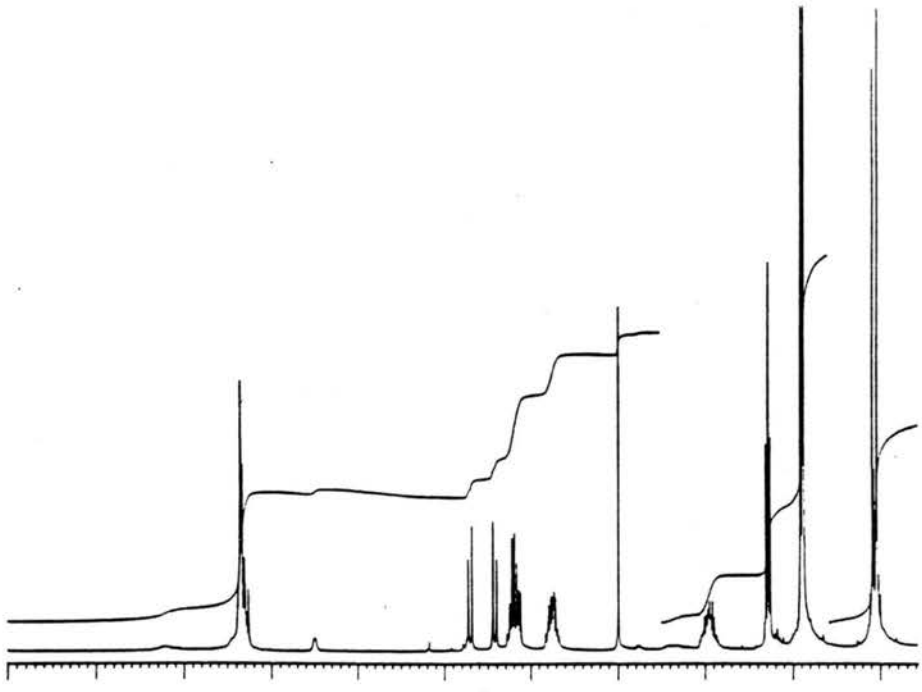

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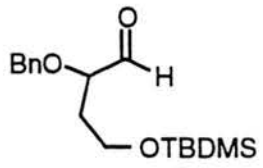

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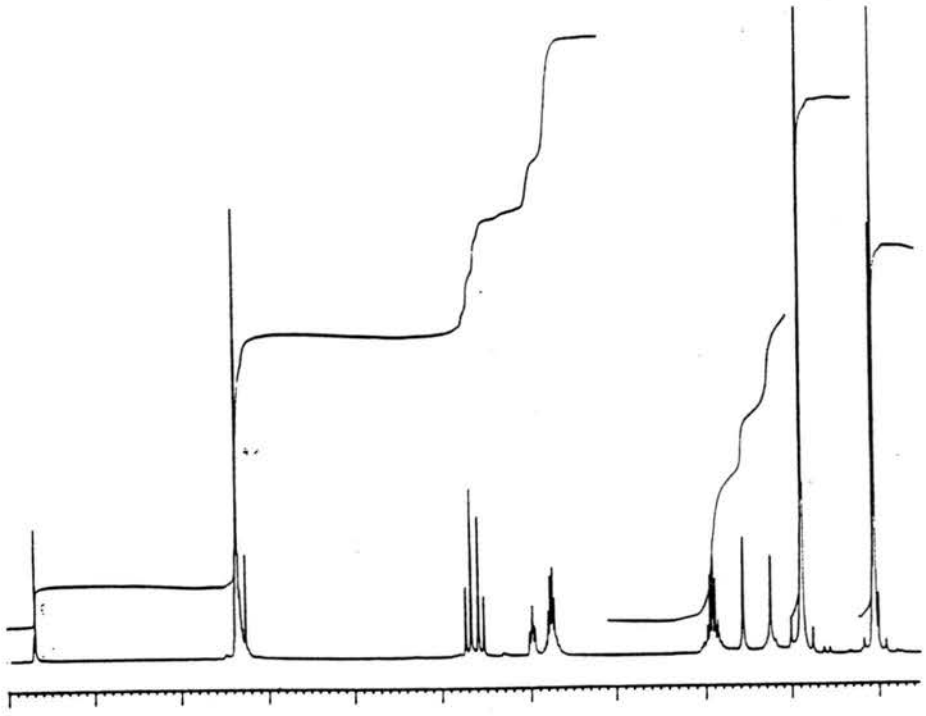

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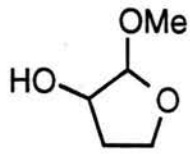

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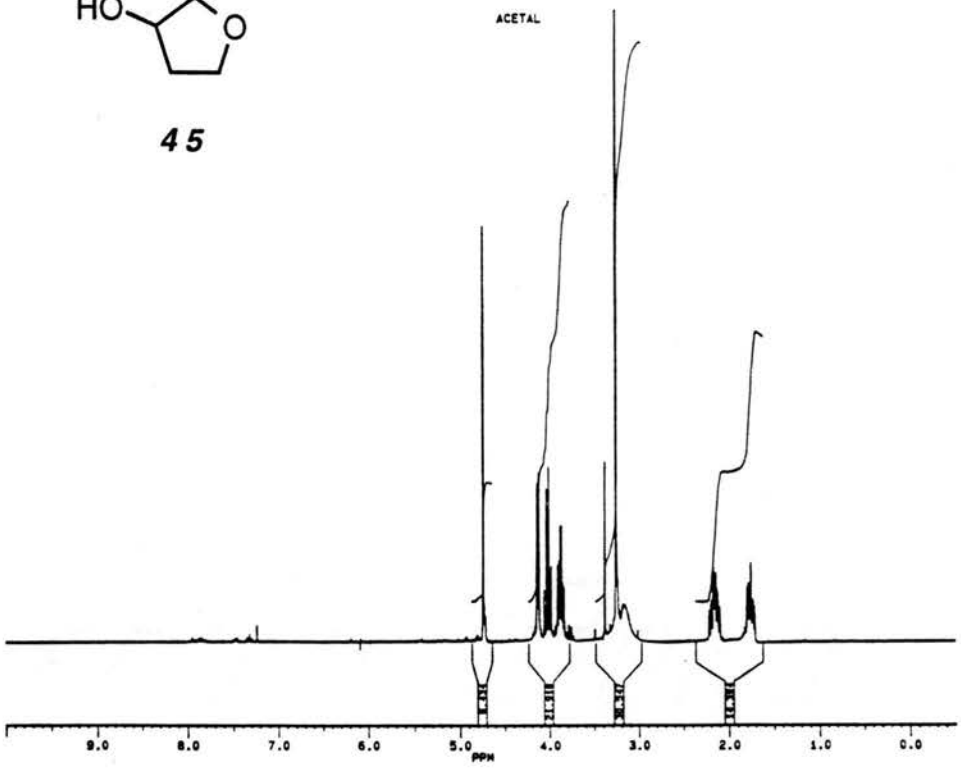
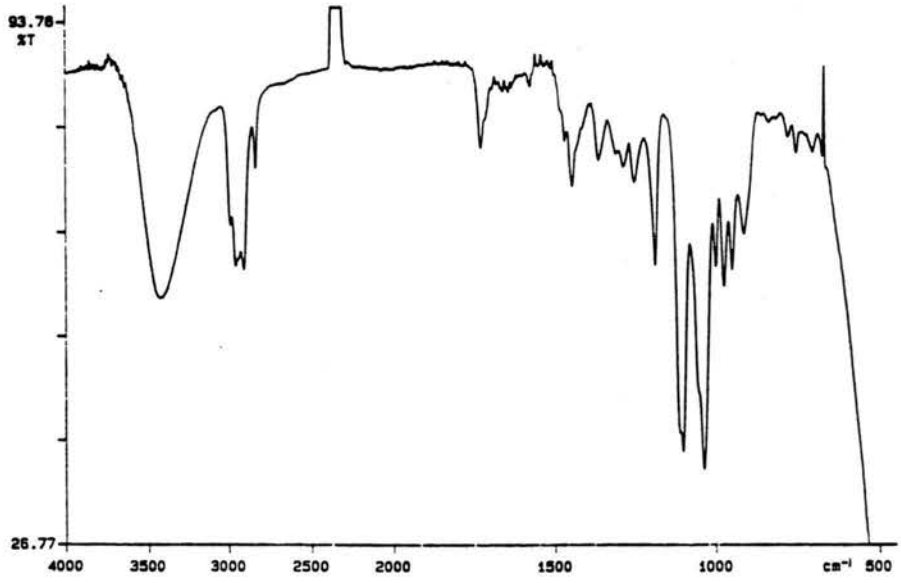
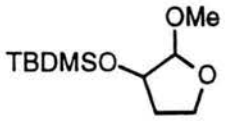
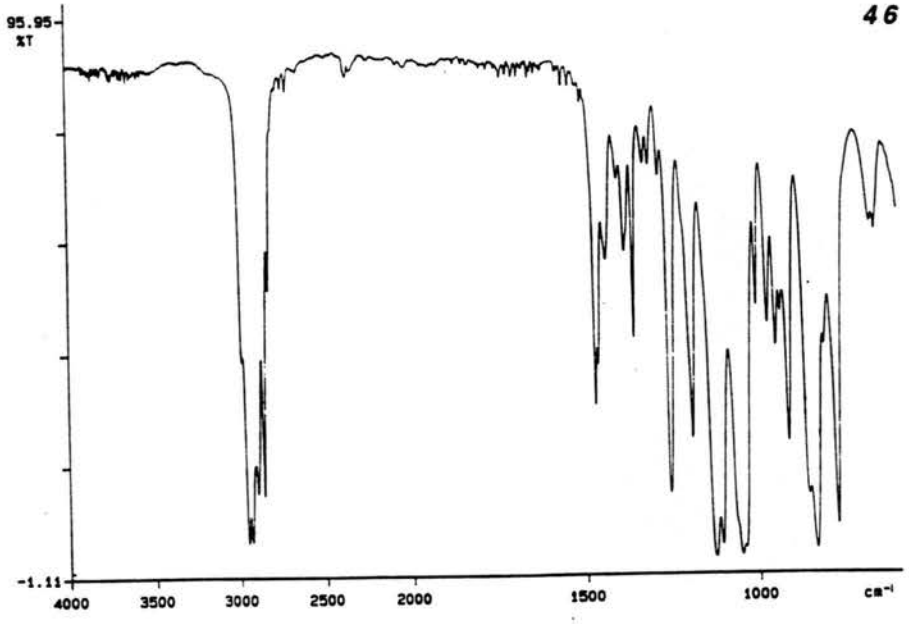


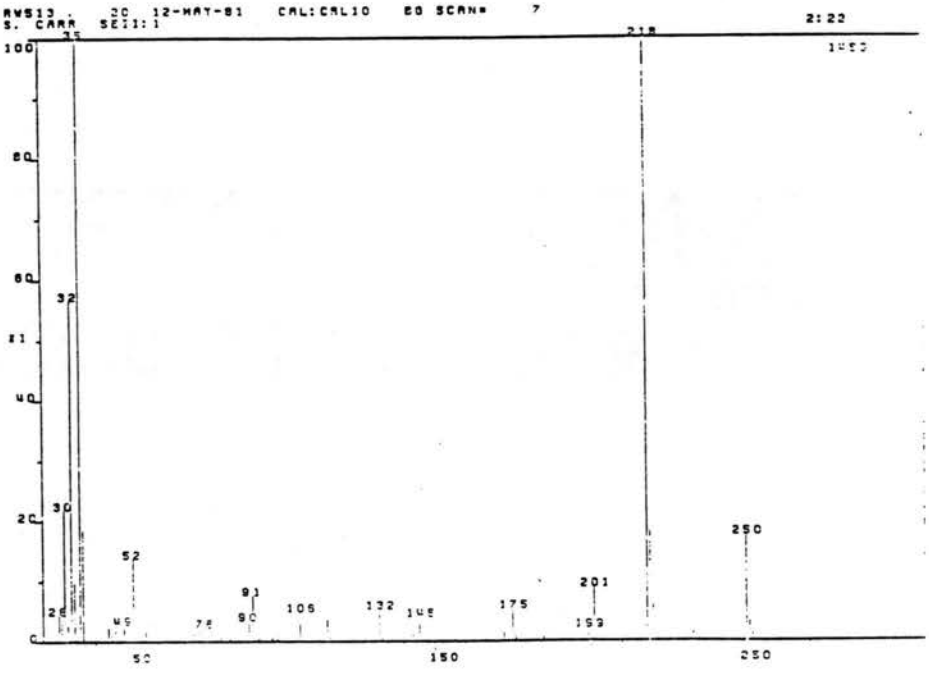


^{1}H NMR (300 MHz) and IR for compound **45**.

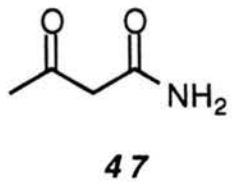


46

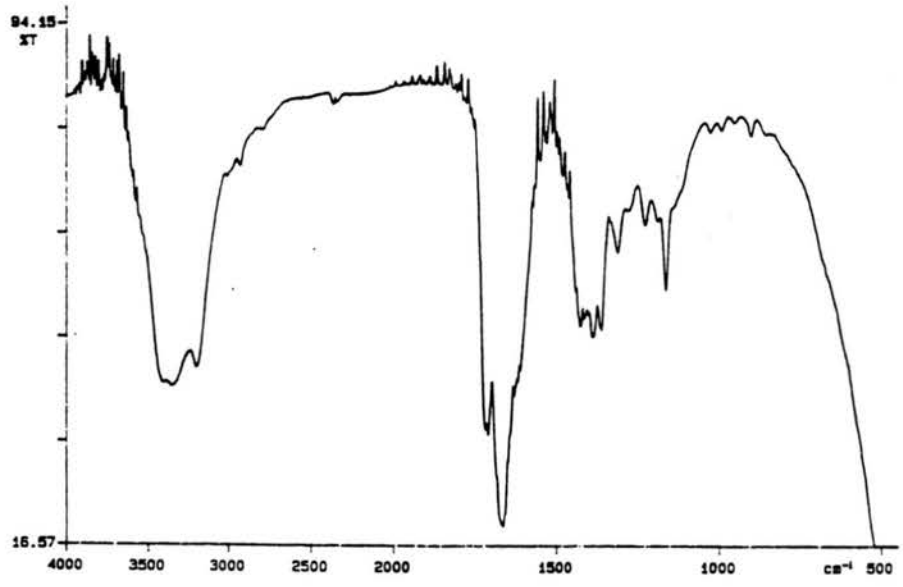




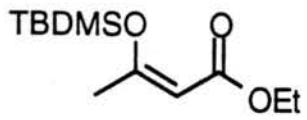
IR and mass spectrum for compound **46**.



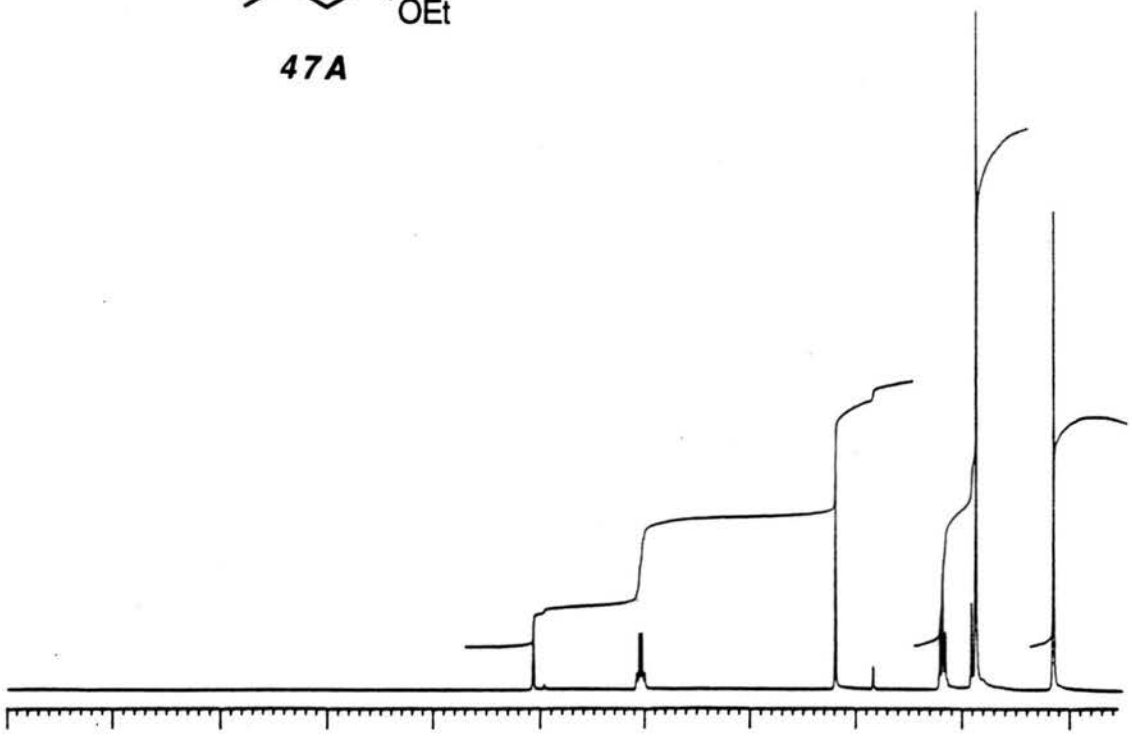
47

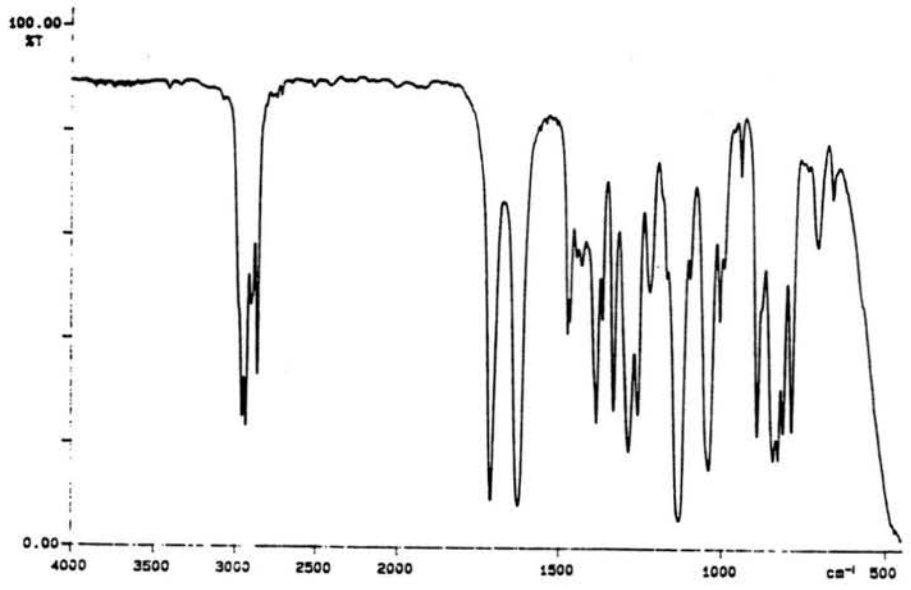


^{1}H NMR (300 MHz) and IR for compound **47**.



47A





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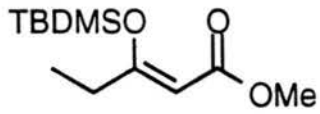
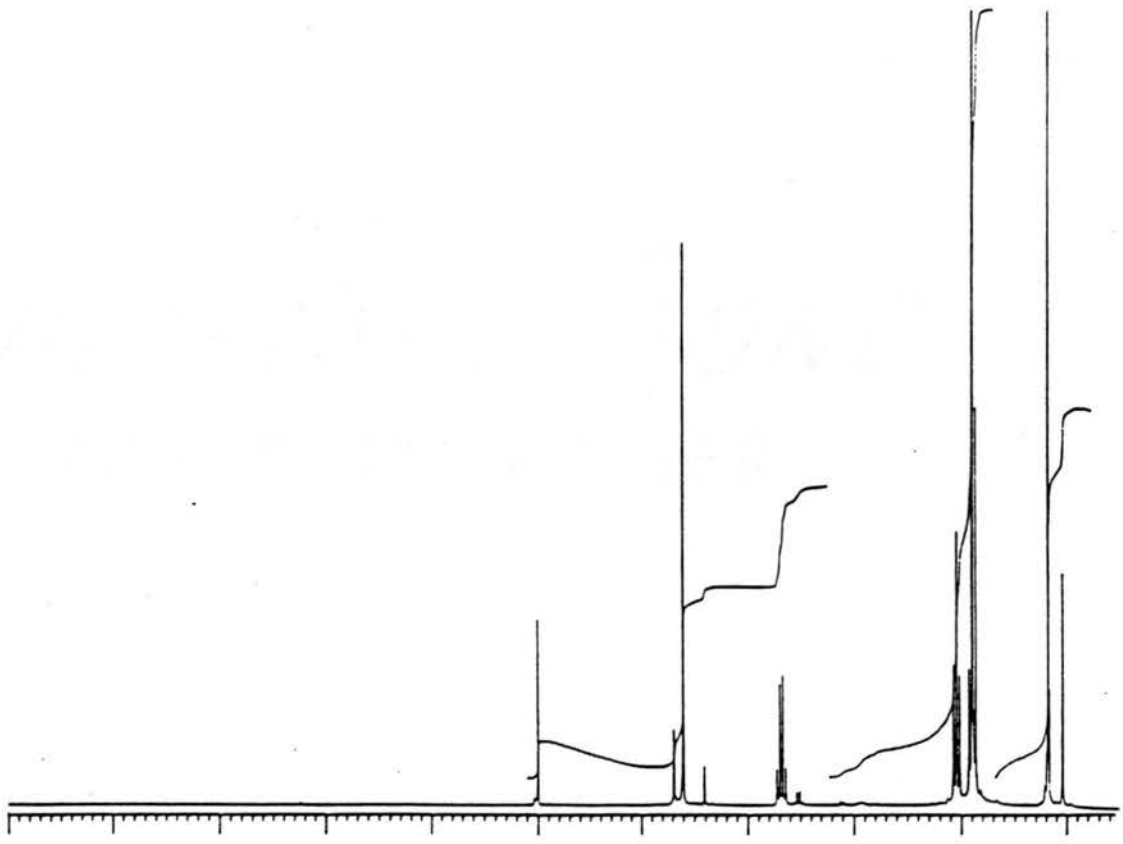
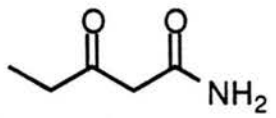


48A



^{1}H NMR (270 MHz) for compound **48A**.



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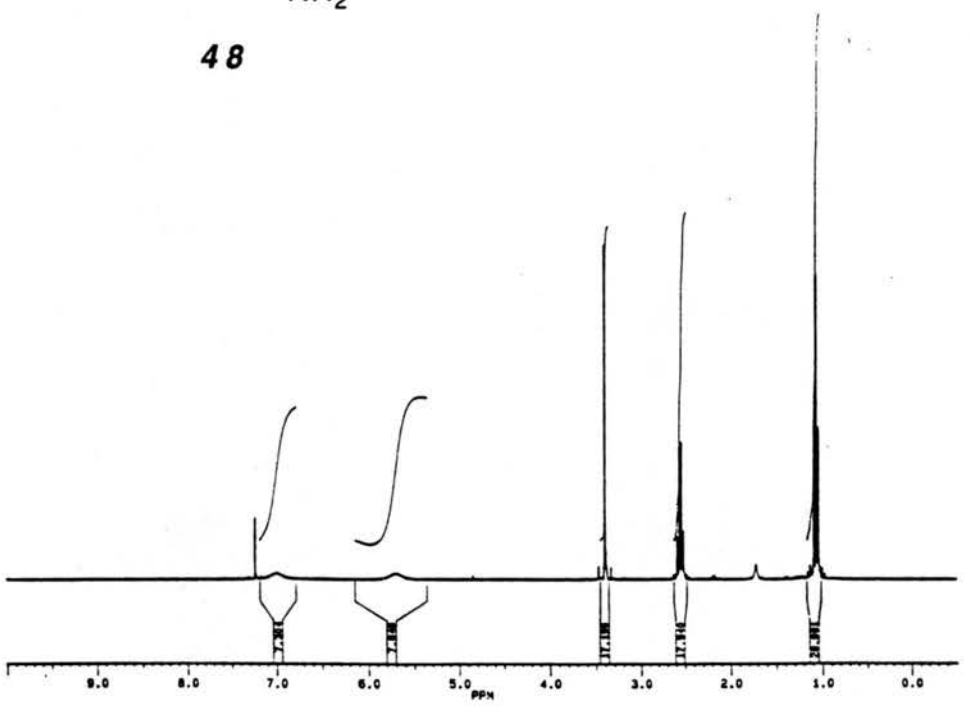
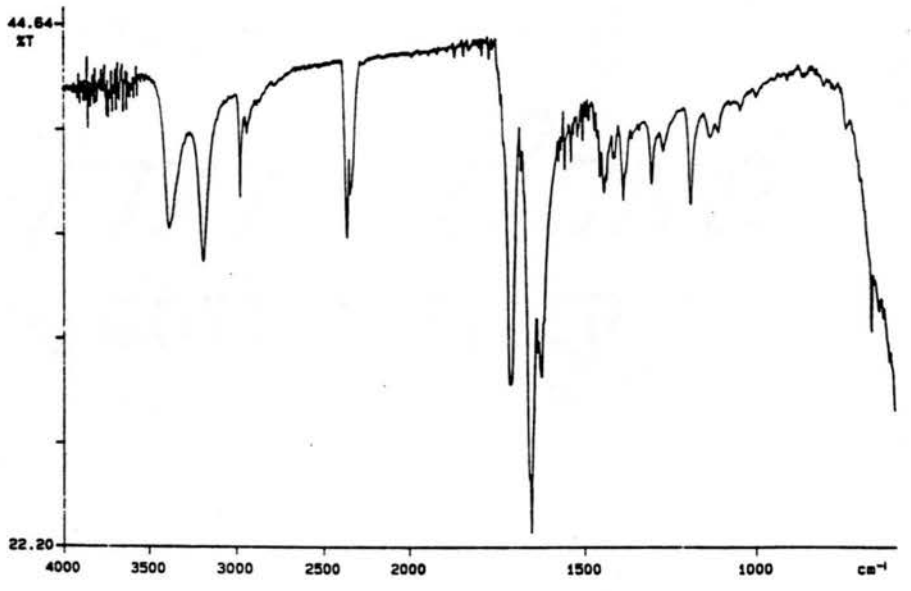
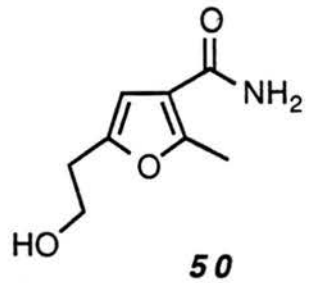




^{1}H NMR (300 MHz) and IR for compound **48**.



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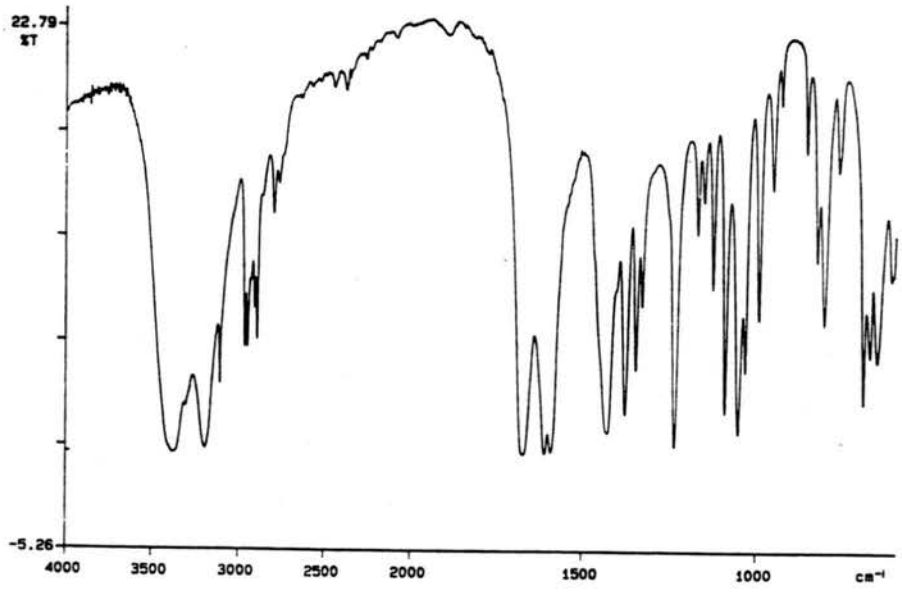

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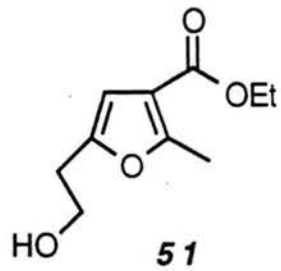
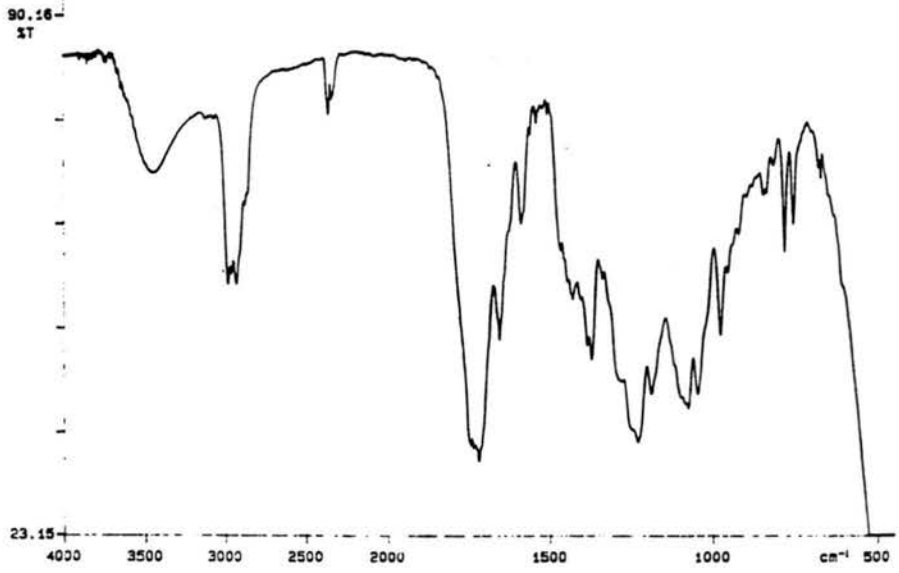
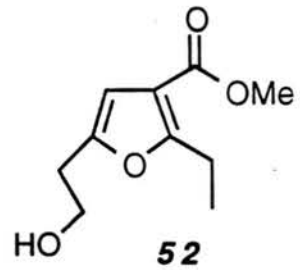


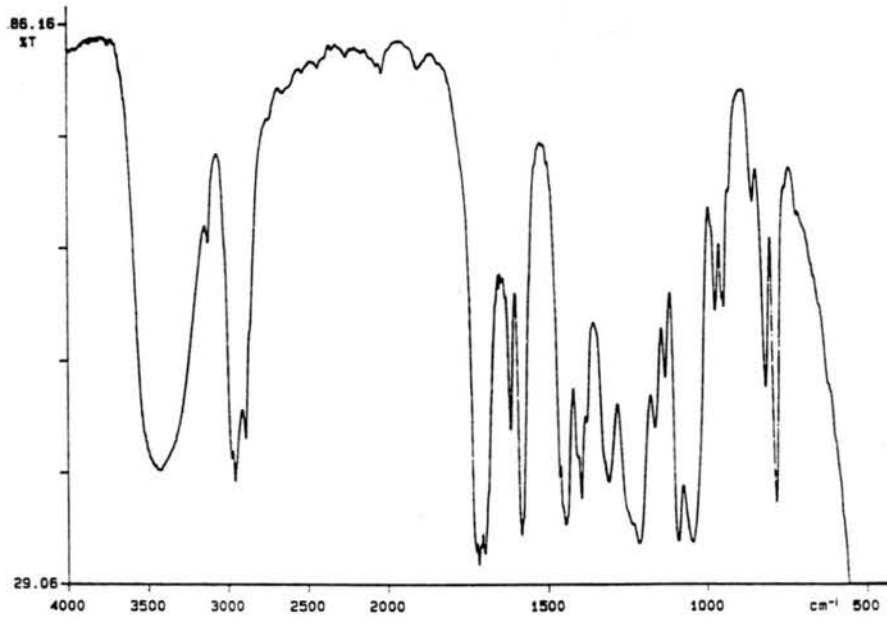
51



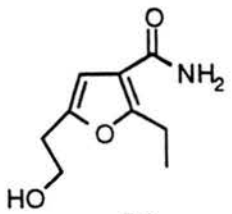
^{1}H NMR (270 MHz) and IR for compound **51**.



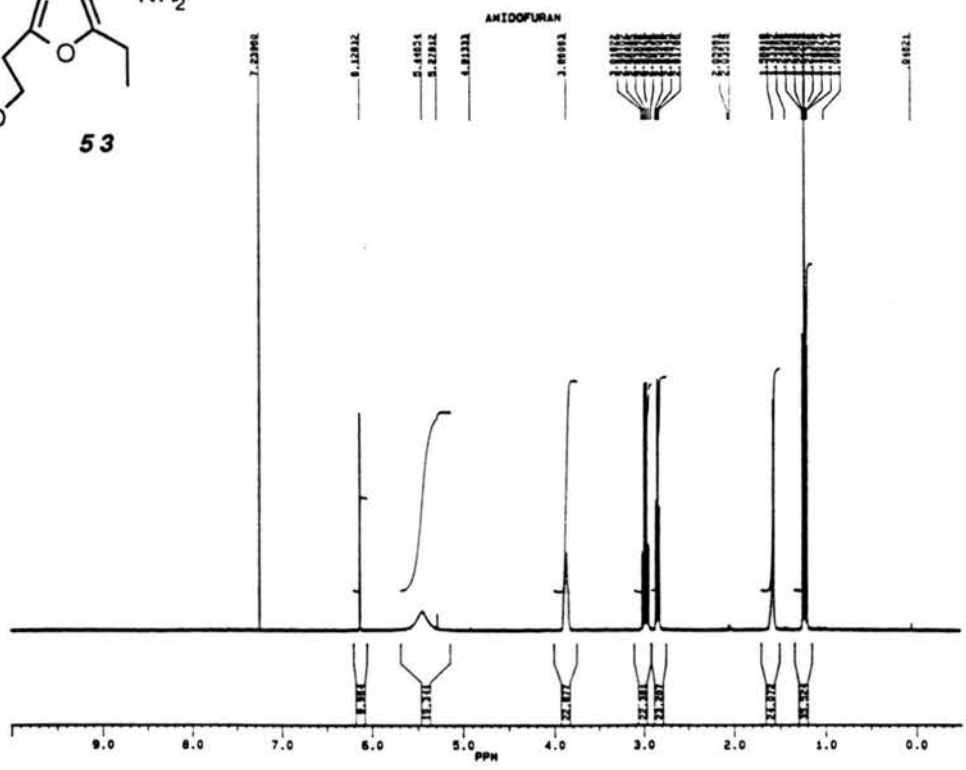
52

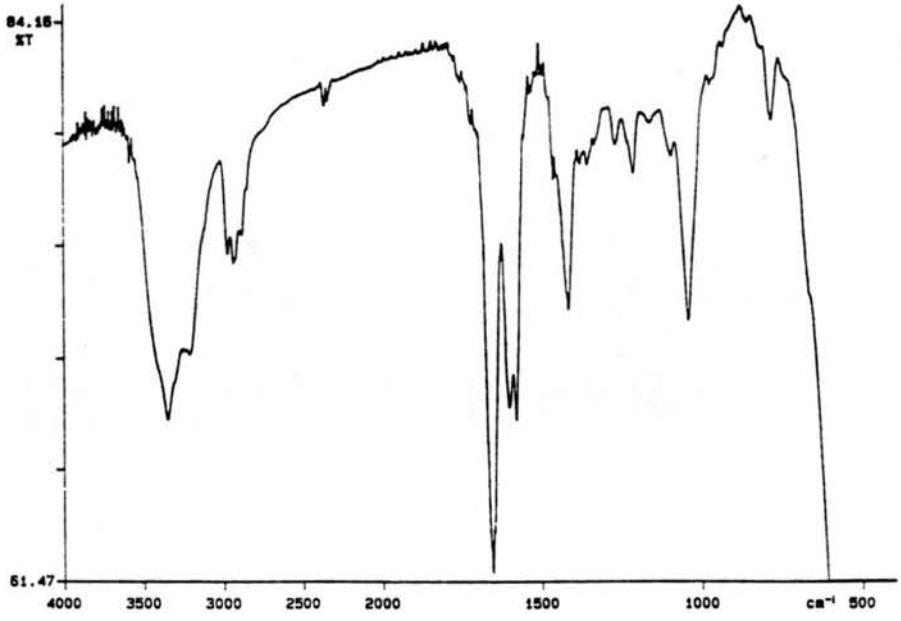


^{1}H NMR (300 MHz) and IR for compound **52**.

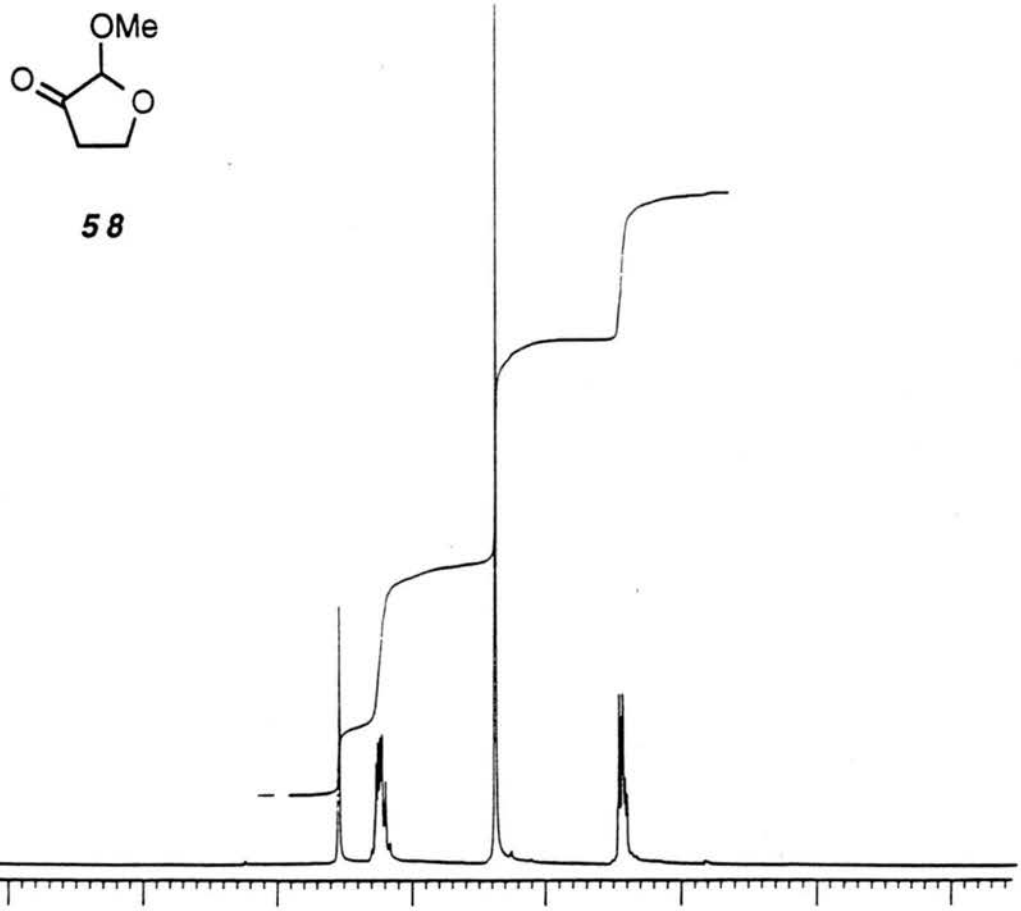


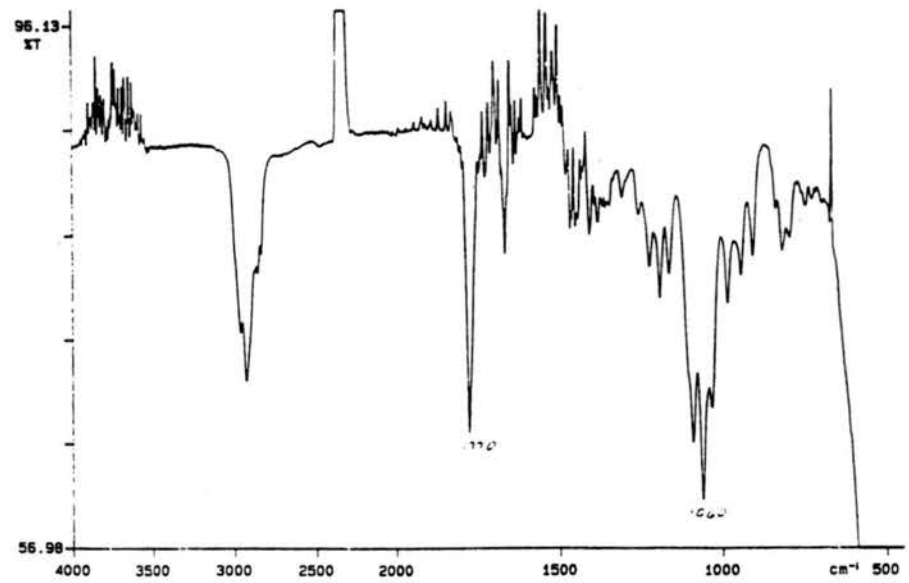
53



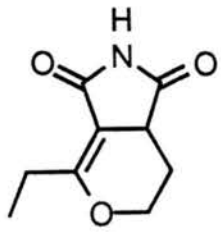


^{1}H NMR (300 MHz) and IR for compound **53**.

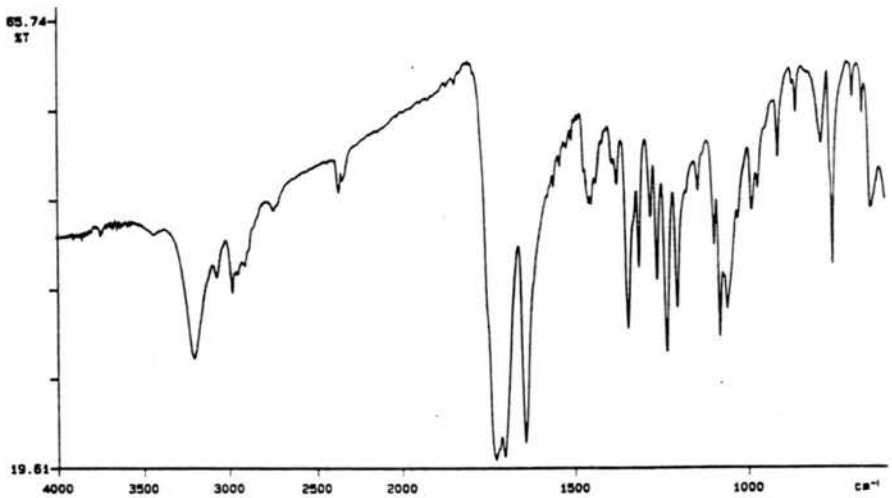




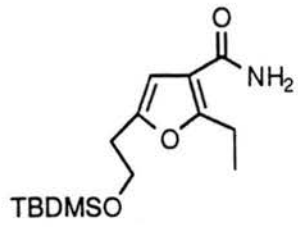
^{1}H NMR (270 MHz) and IR for compound **58**.



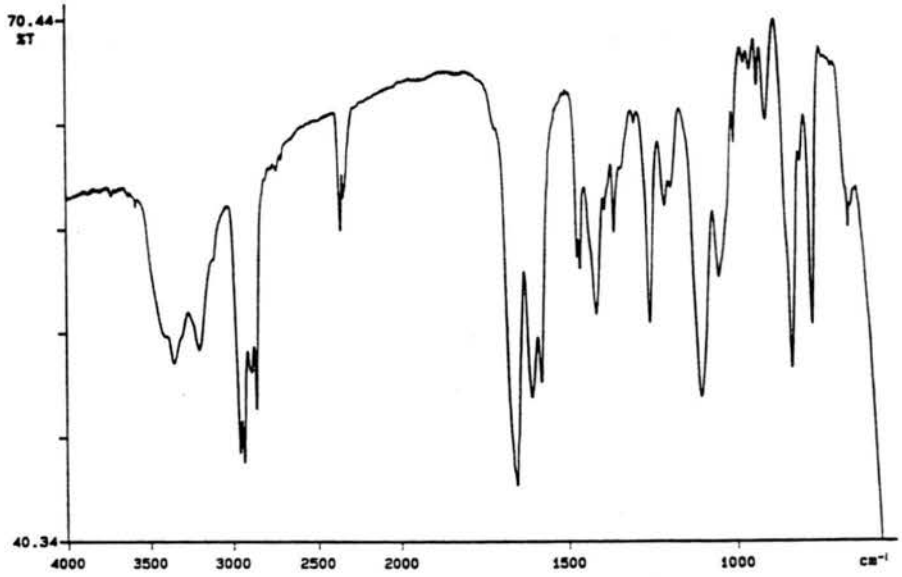
59



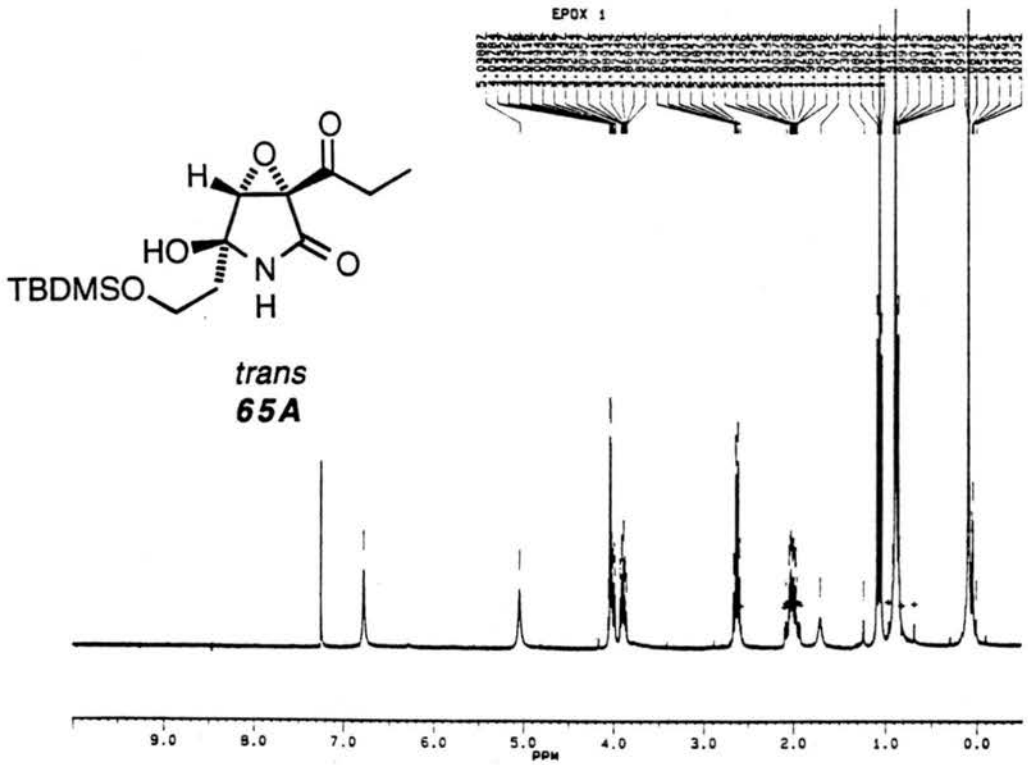
^{1}H NMR (300 MHz) and IR for compound **59**.



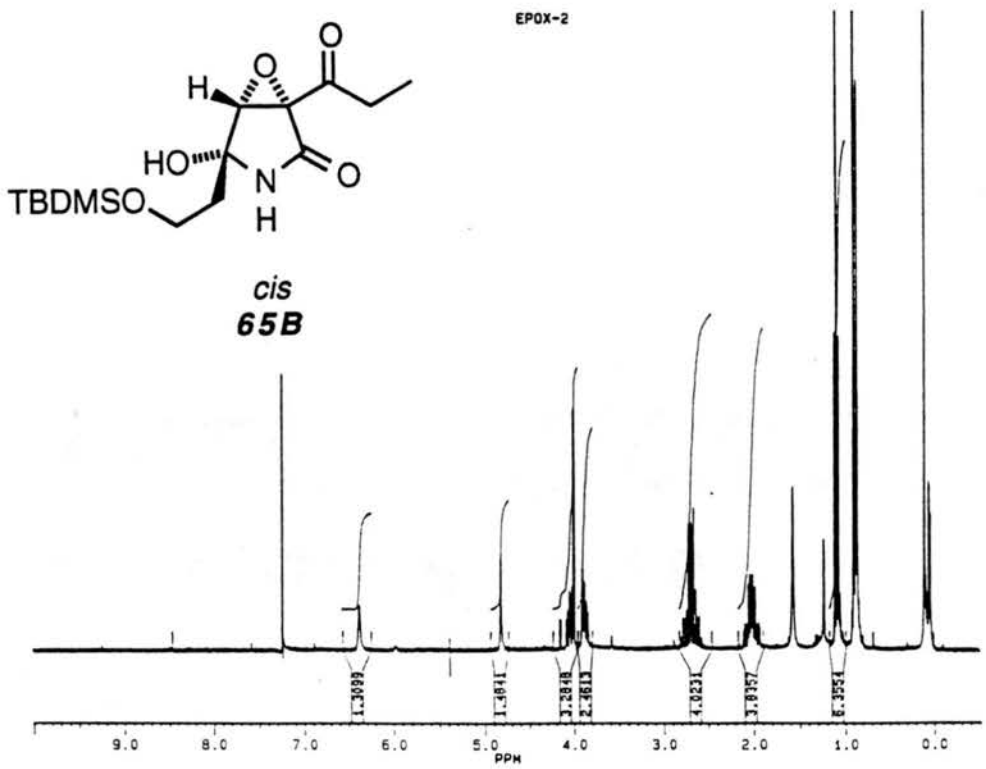
61



^{1}H NMR (300 MHz) and IR for compound **61**.

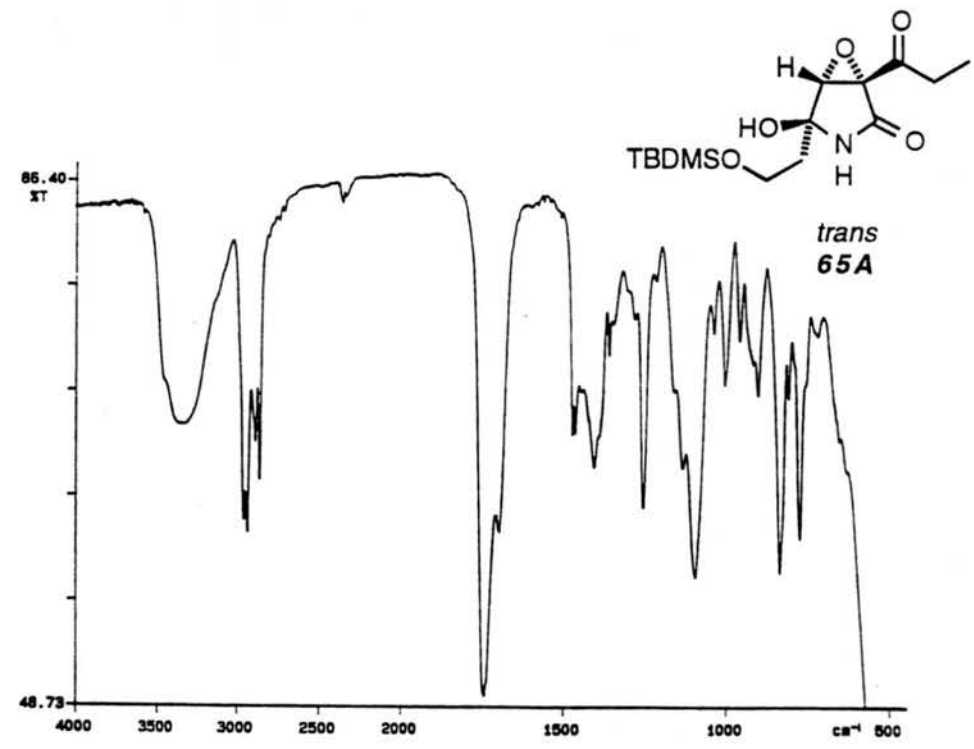


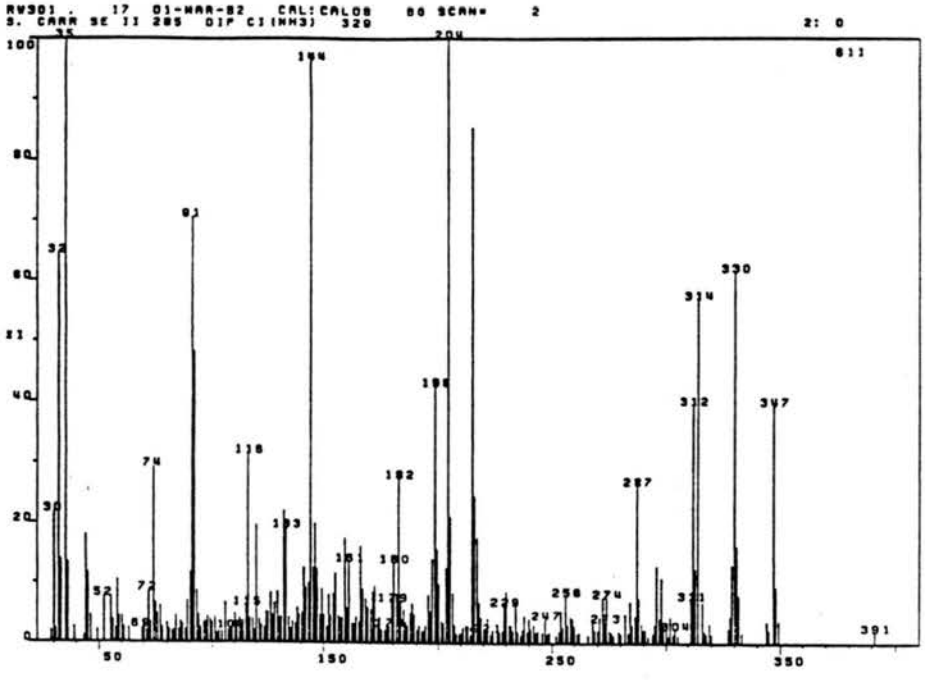
trans
65A



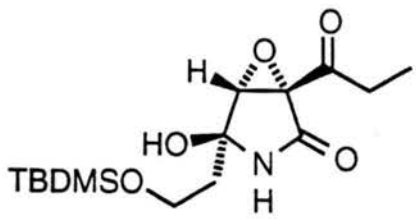
cis
65B

^{1}H NMR (300 MHz) of compound **65A** and **65B**.

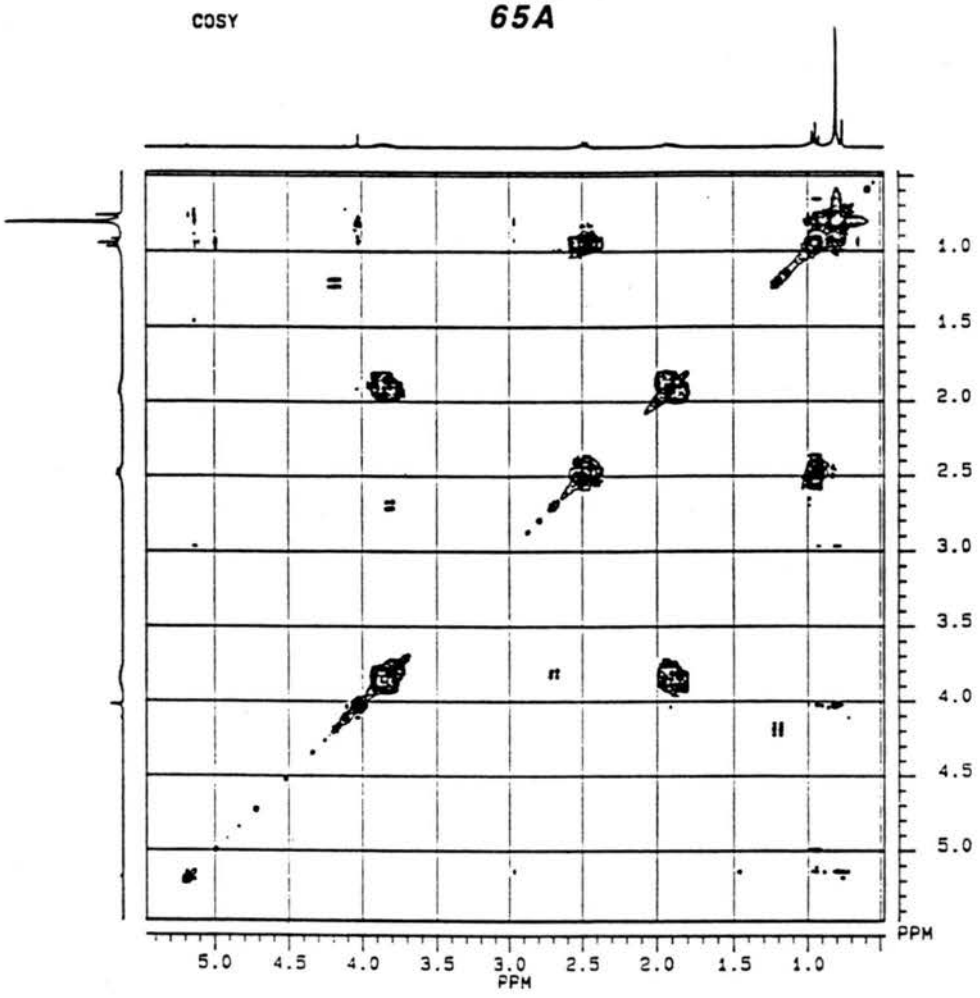




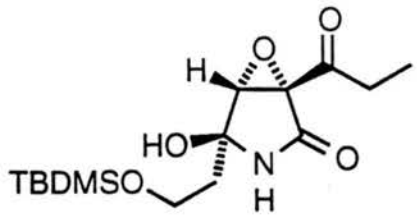
IR and mass spectrum of compound **65**.



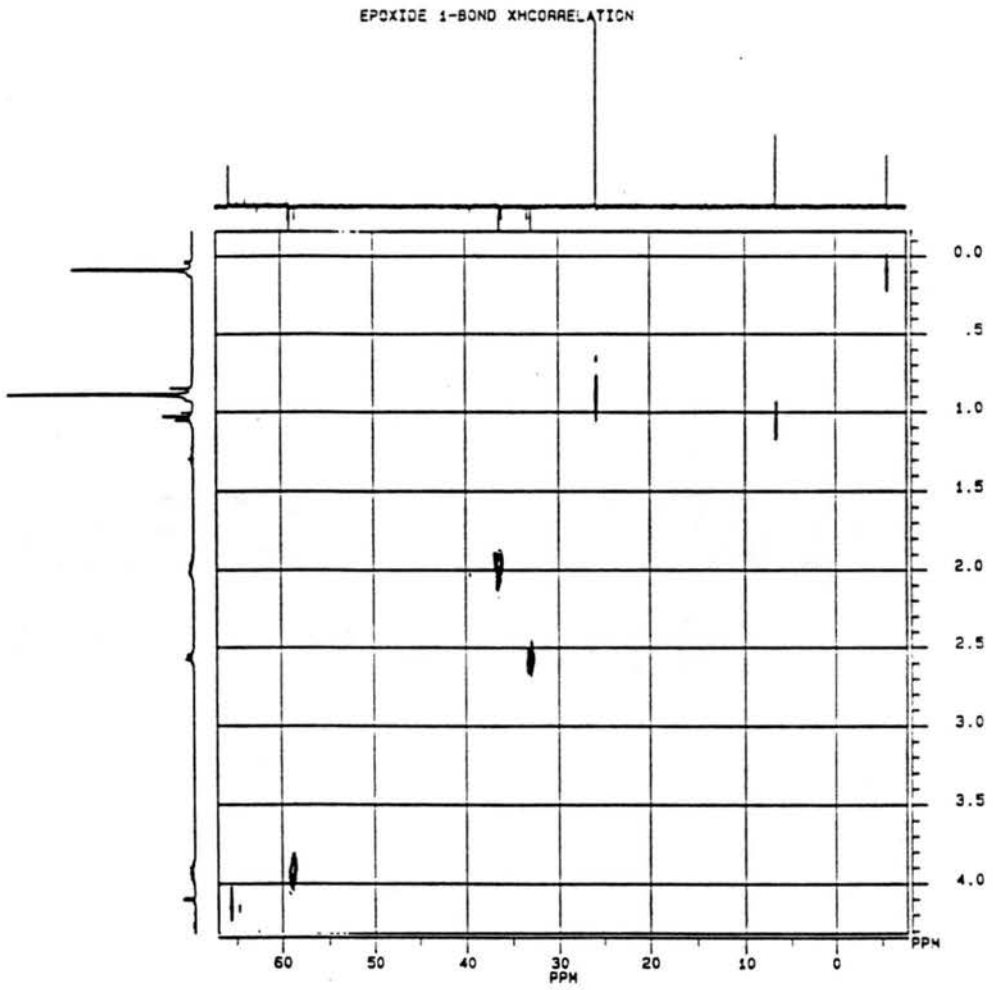
trans
65A



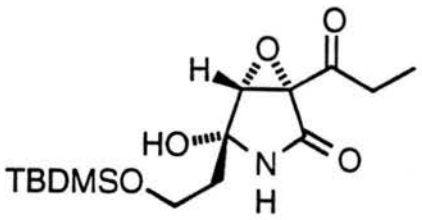
2D Homonuclear COSY for compound **65A**.



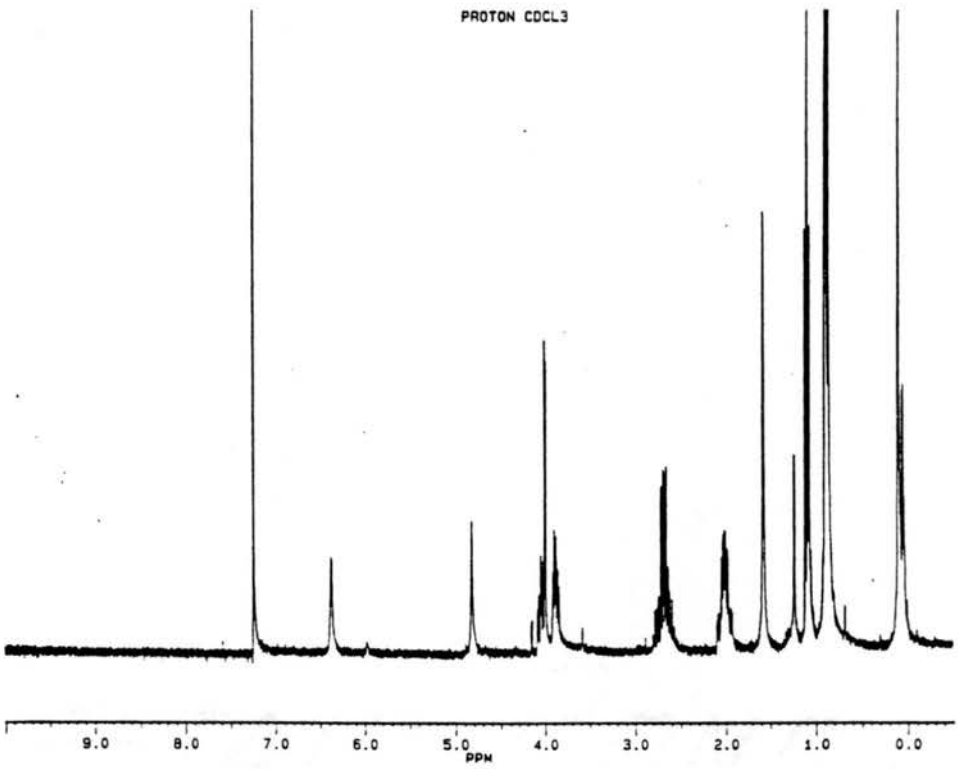
trans
65A



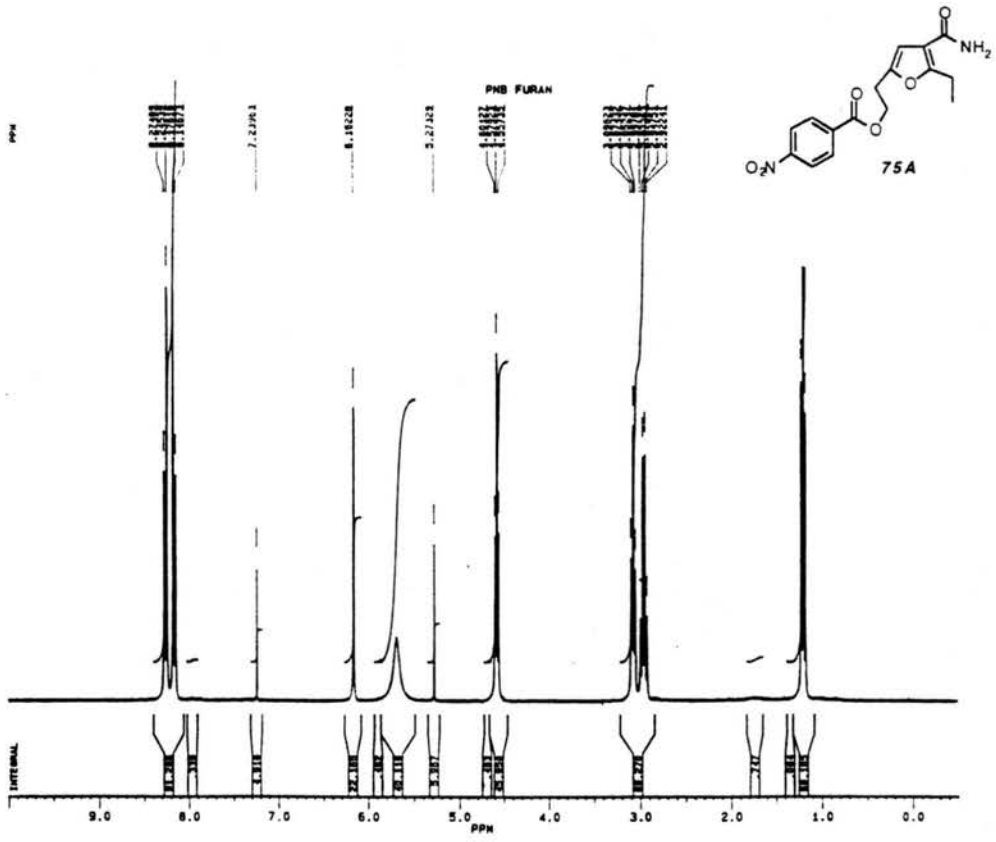
2D Heteronuclear HETCOR for compound **65A**.

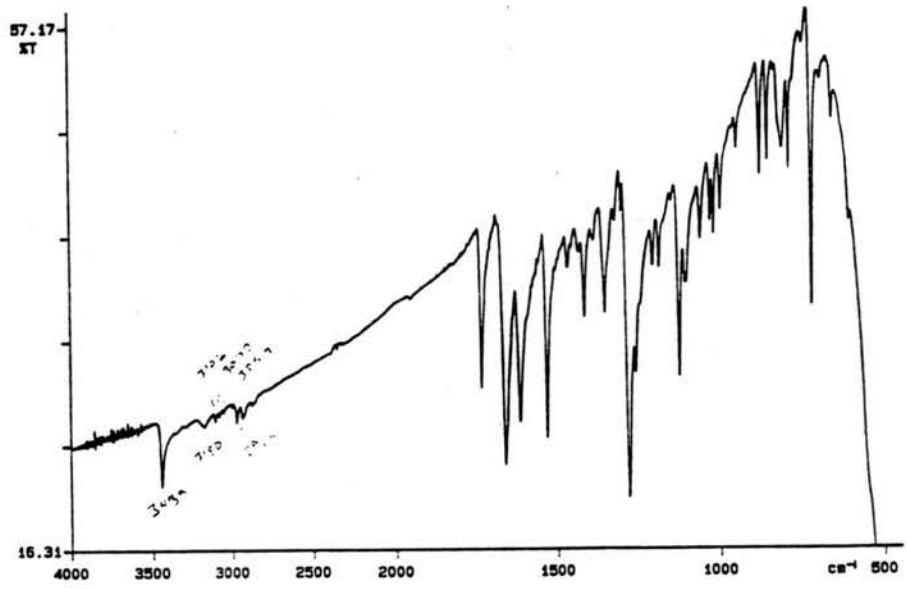


cis
65B

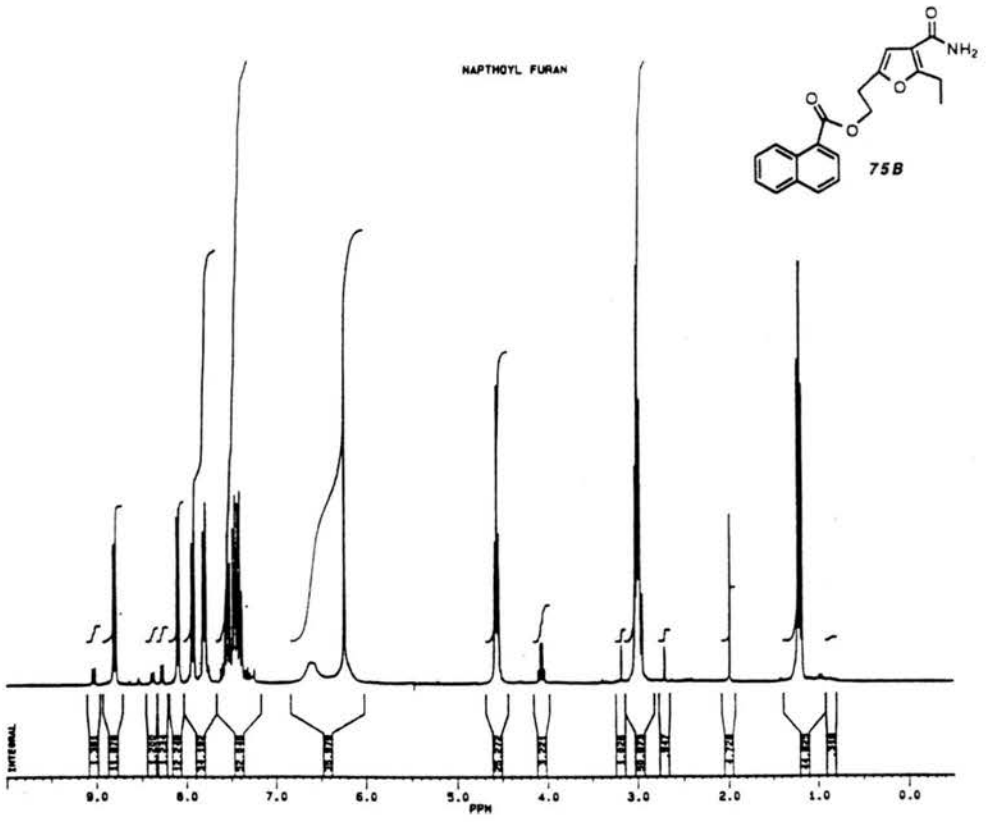


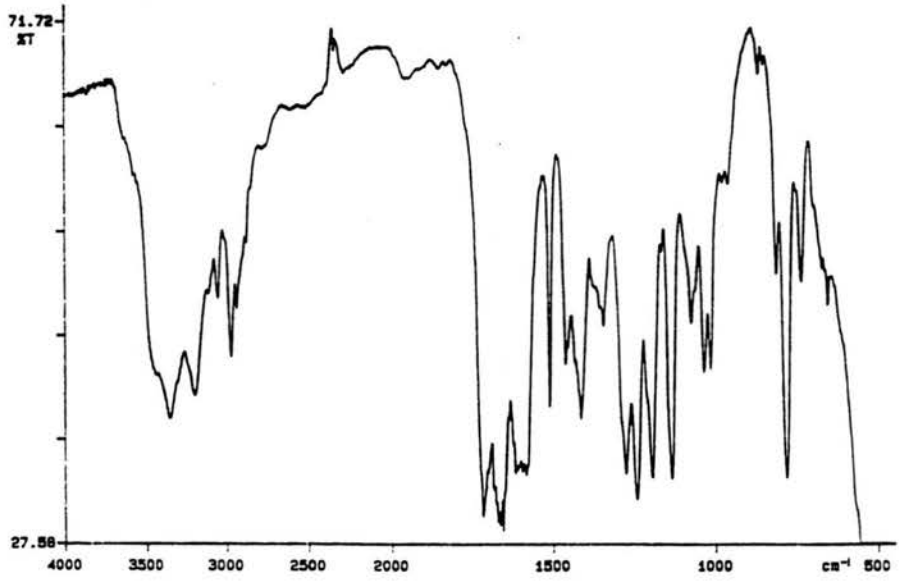
^{1}H NMR (300 MHz) for compound **65B**.



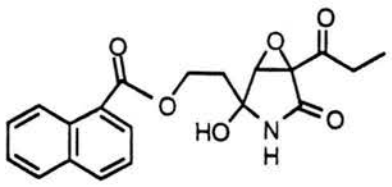


^{1}H NMR (300 MHz) and IR for compound **75A**.

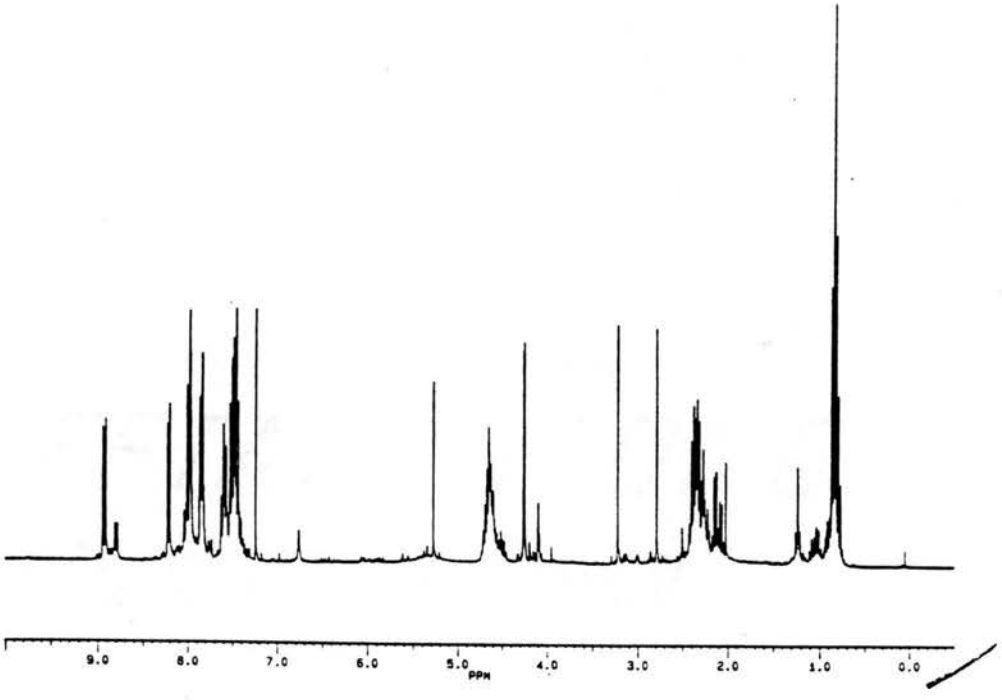




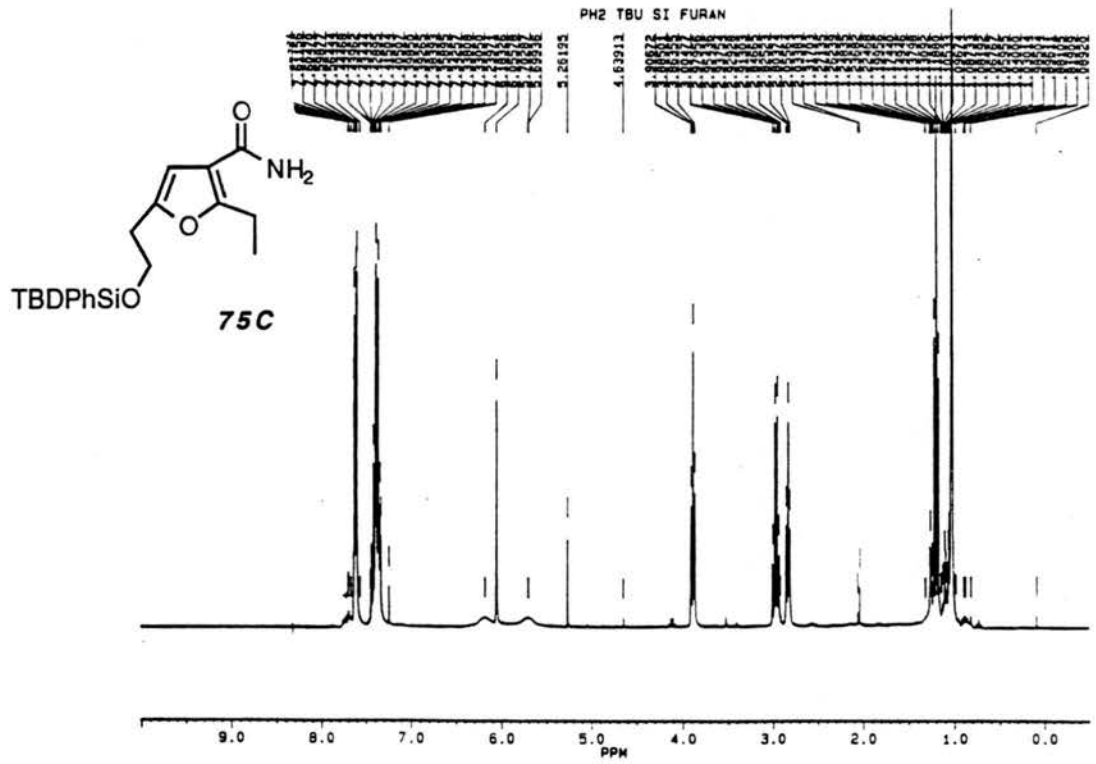
^{1}H NMR (300 MHz) and IR for compound **75B**.

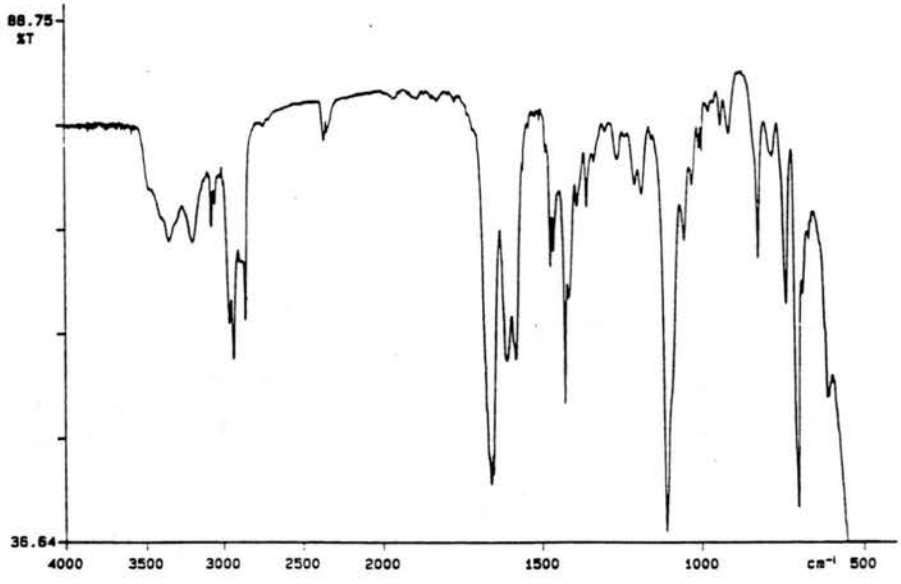


76B

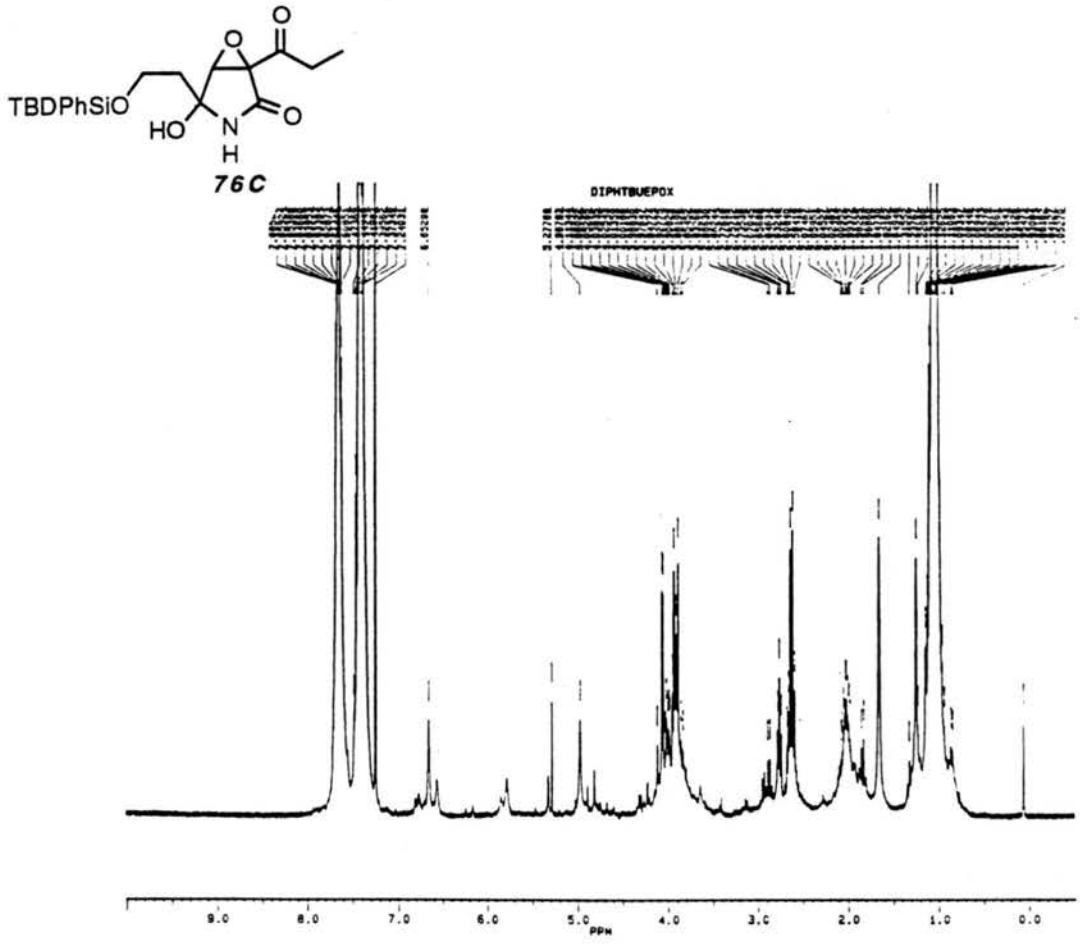


^{1}H NMR (300 MHz) for compound **76B**.

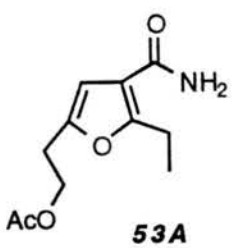




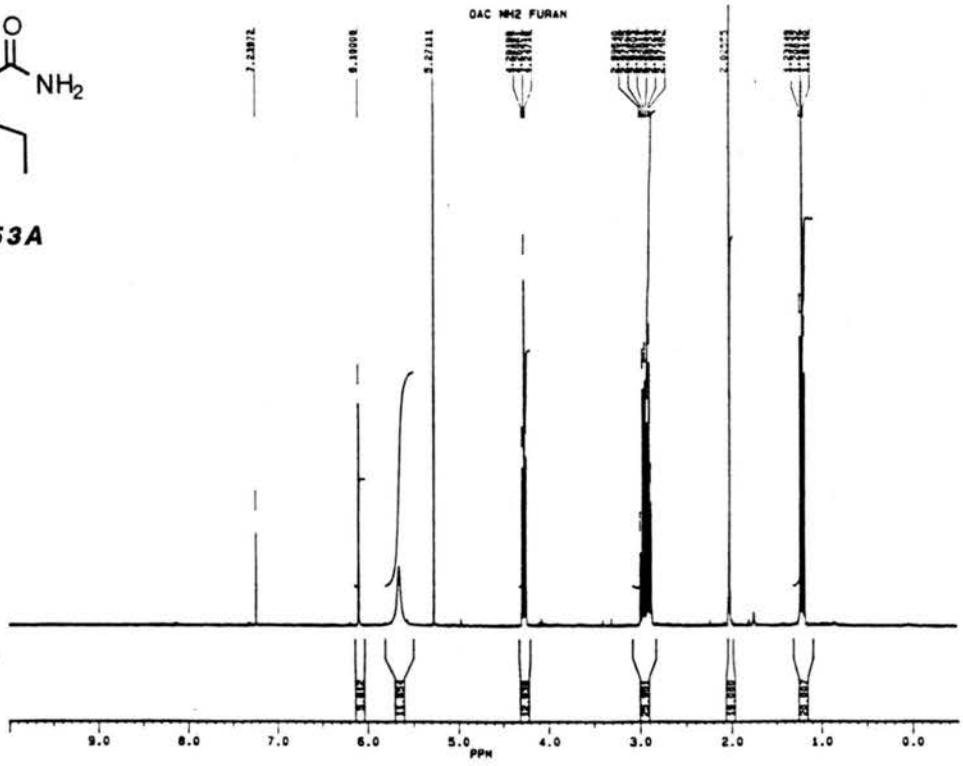
^{1}H NMR (300 MHz) and IR for compound **75C**.

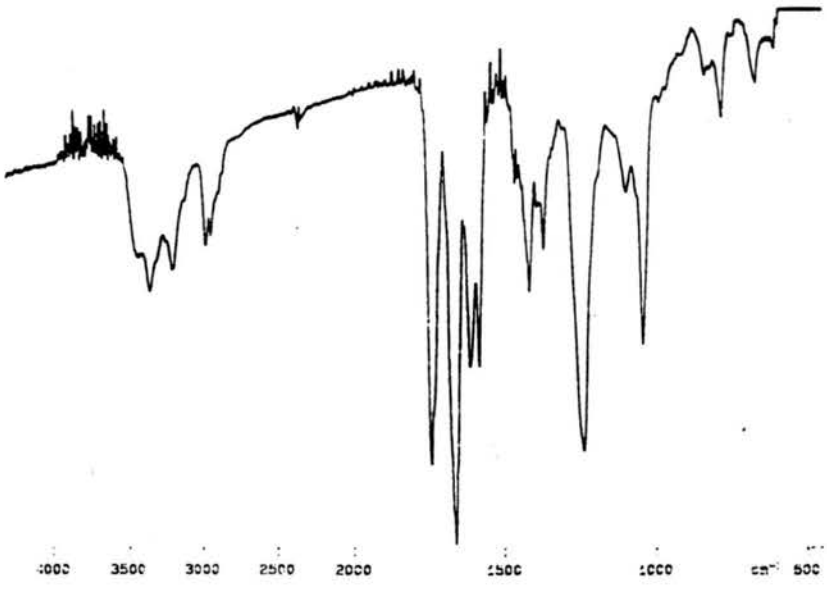


^{1}H NMR (300 MHz) for compound **76C**.

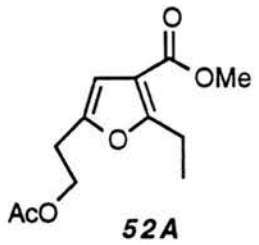


53A

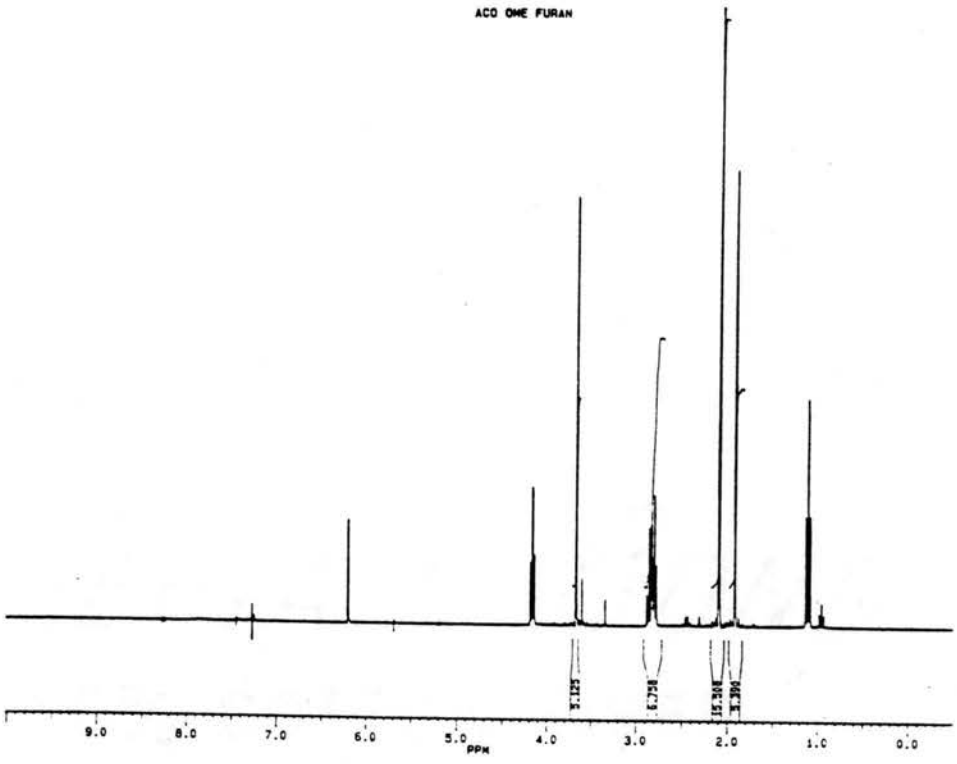




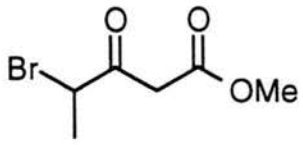
^{1}H NMR (300 MHz) and IR for compound **53A**.



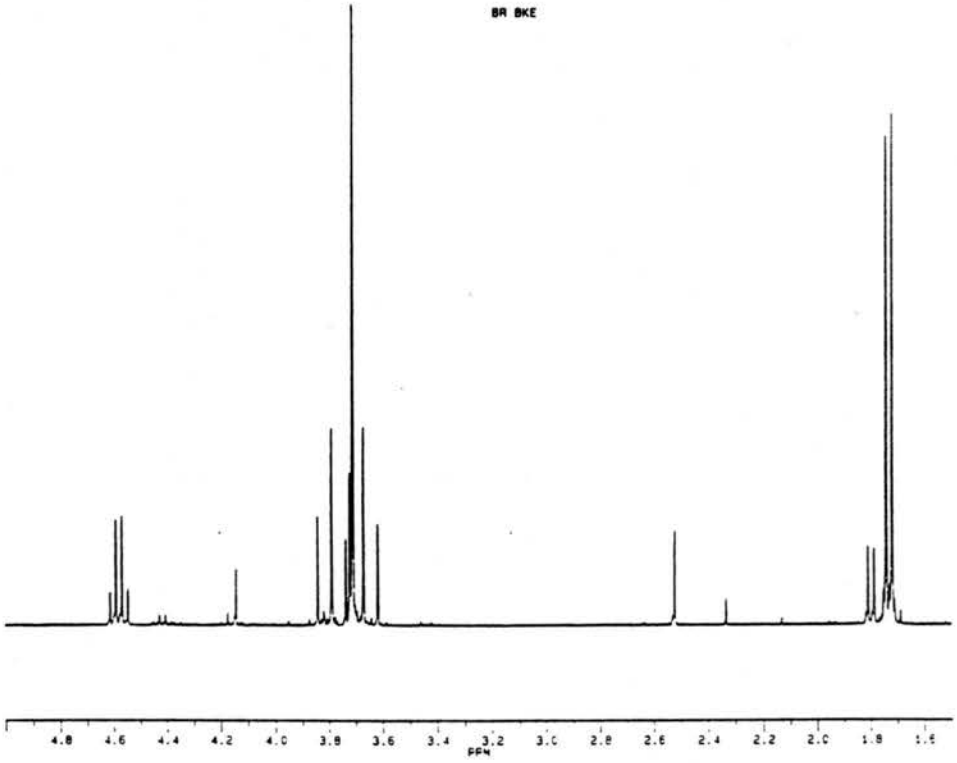
52A



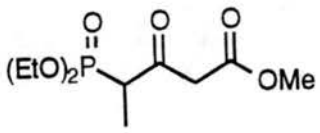
^{1}H NMR (300 MHz) for compound **52A**.



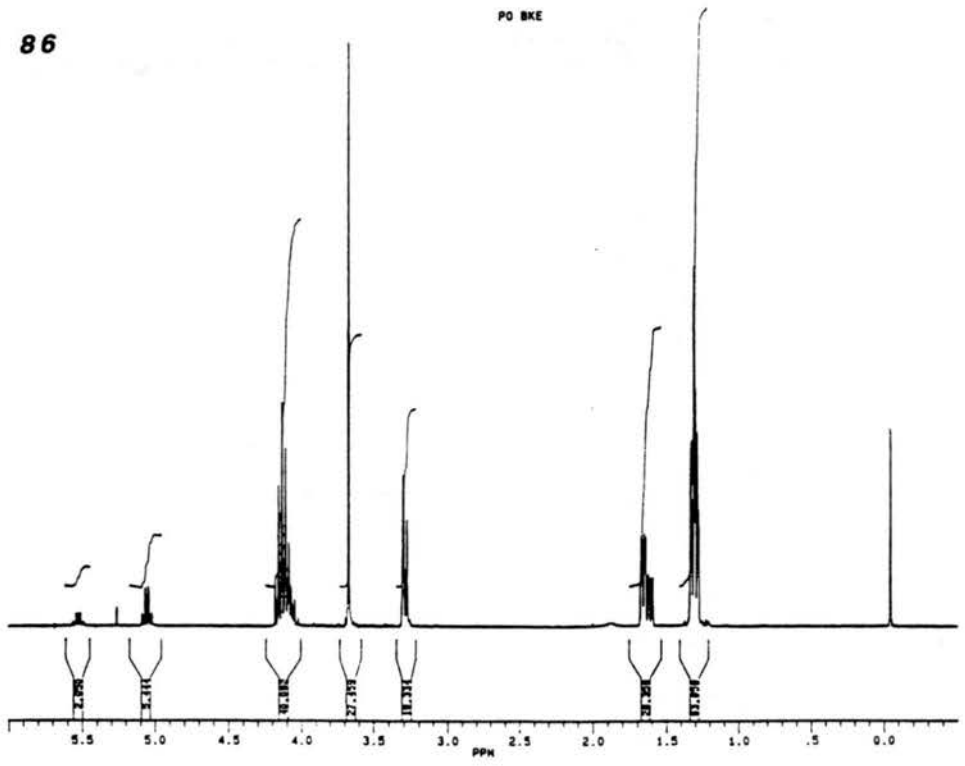
87

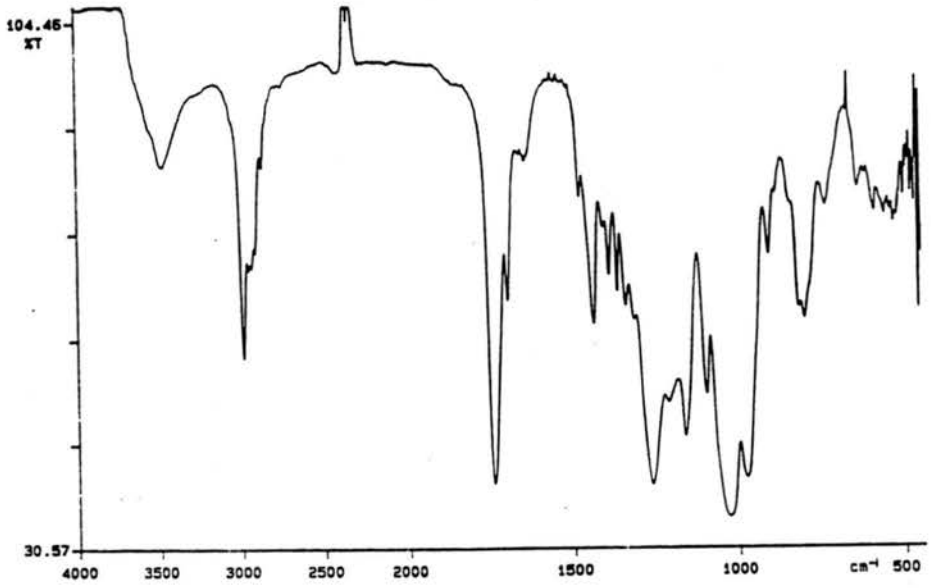


^{1}H NMR (300 MHz) for compound **87**.

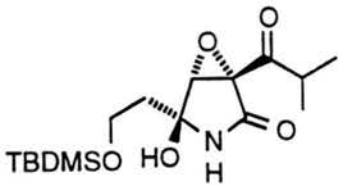


86

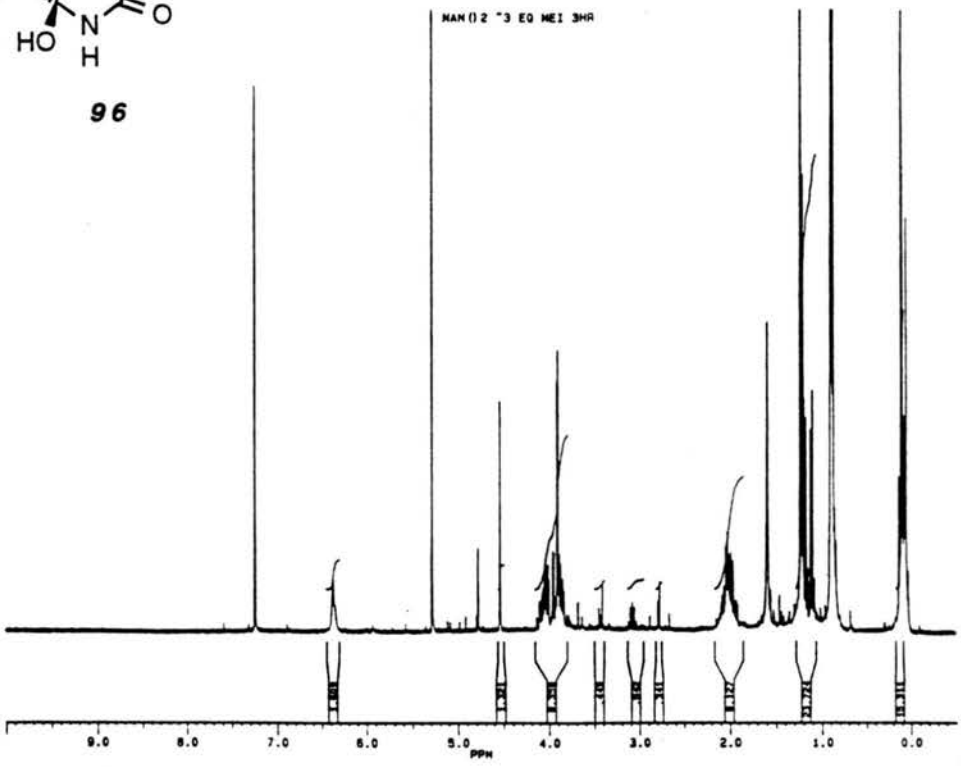


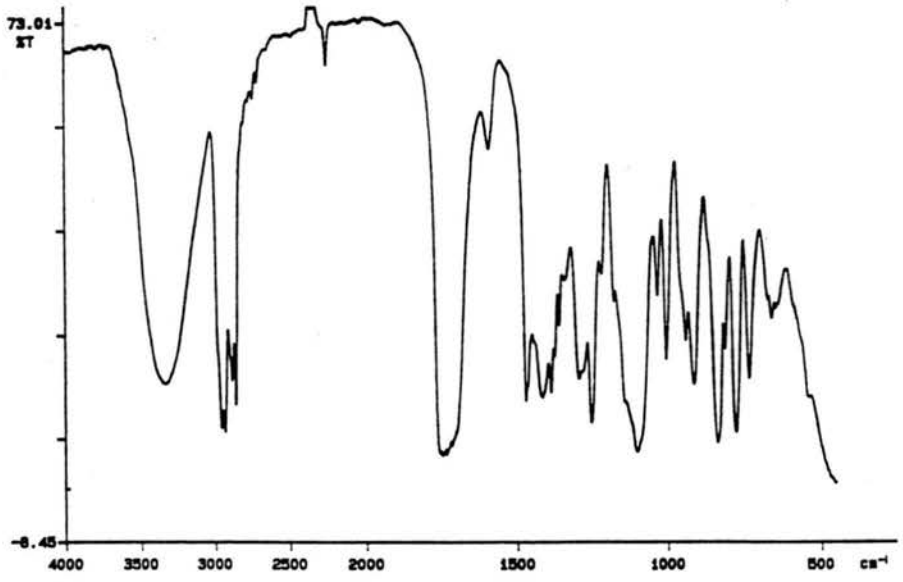


^{1}H NMR (300 MHz) and IR for compound **86**.

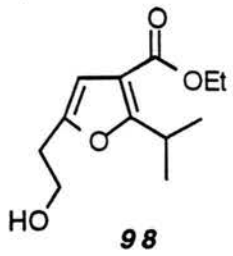


96

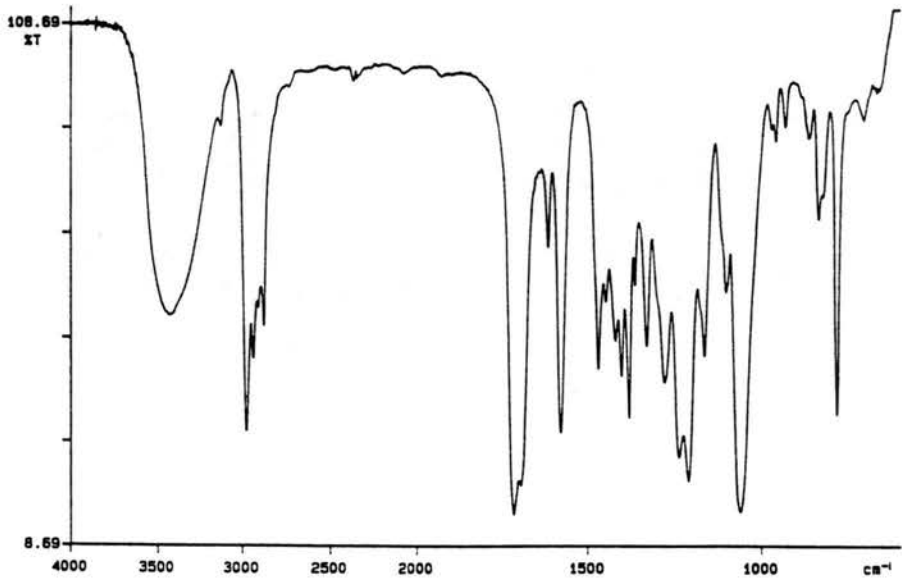




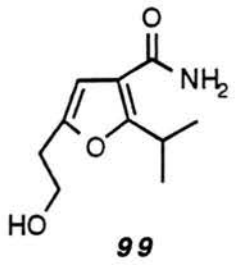
^{1}H NMR (300 MHz) and IR for compound **96**.



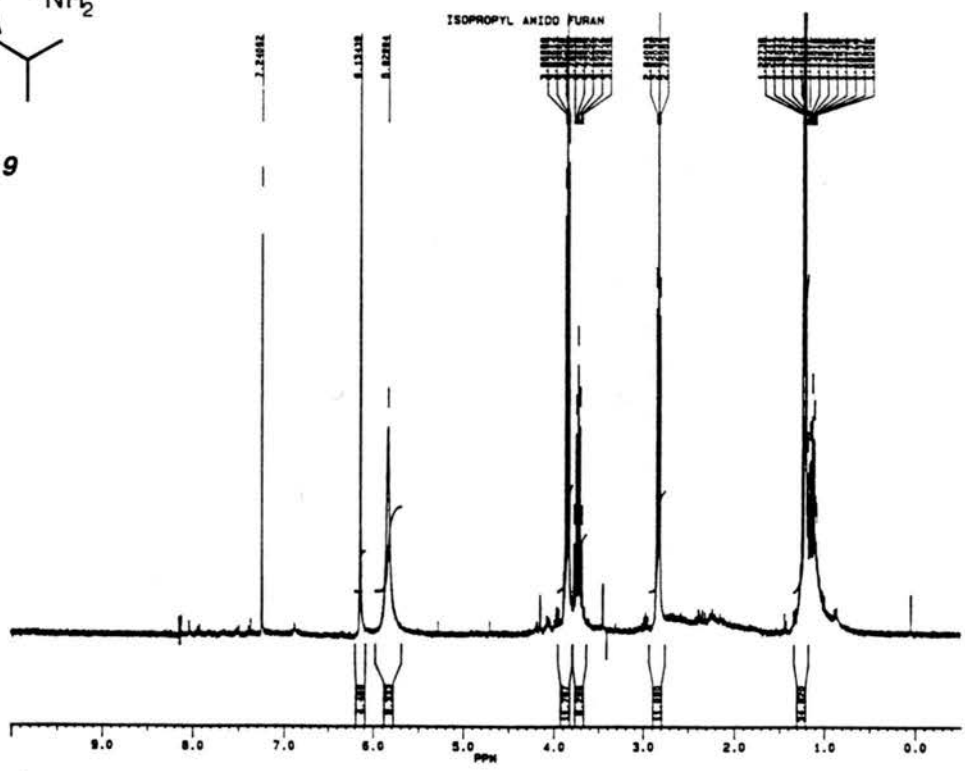
98

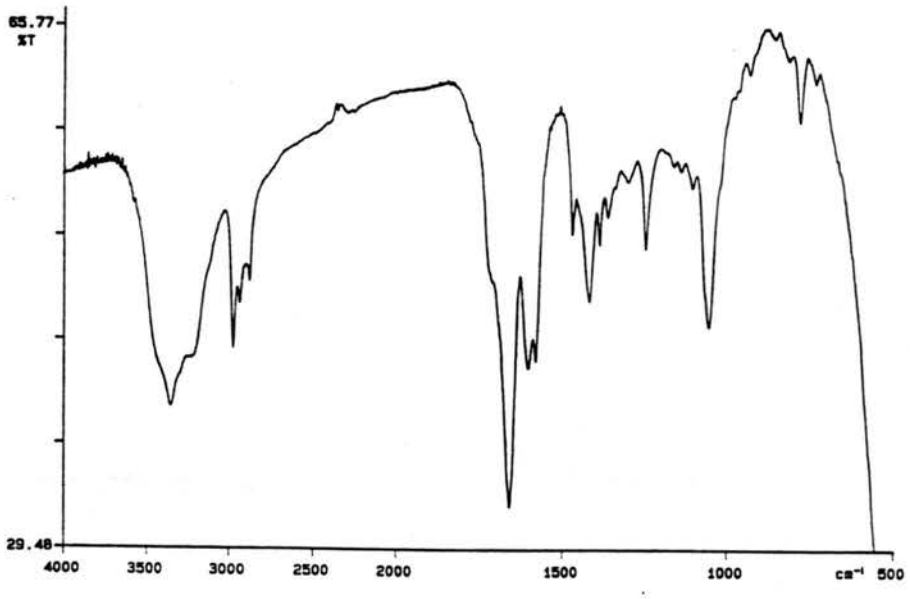


^{1}H NMR (300 MHz) and IR for compound **98**.

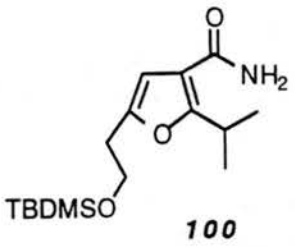


99

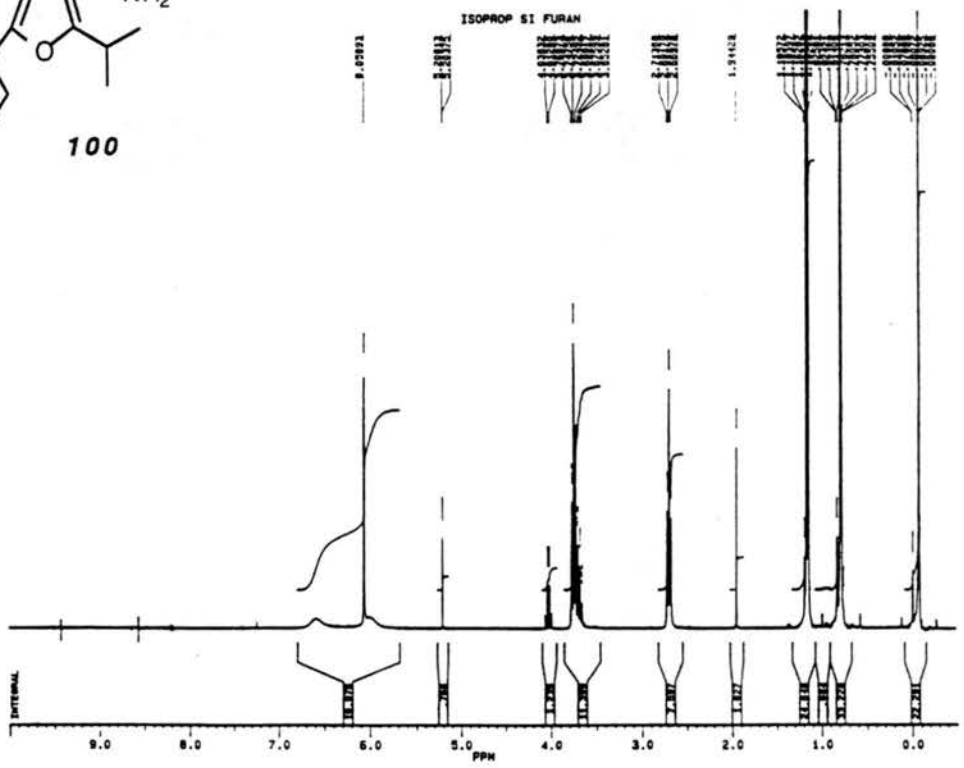


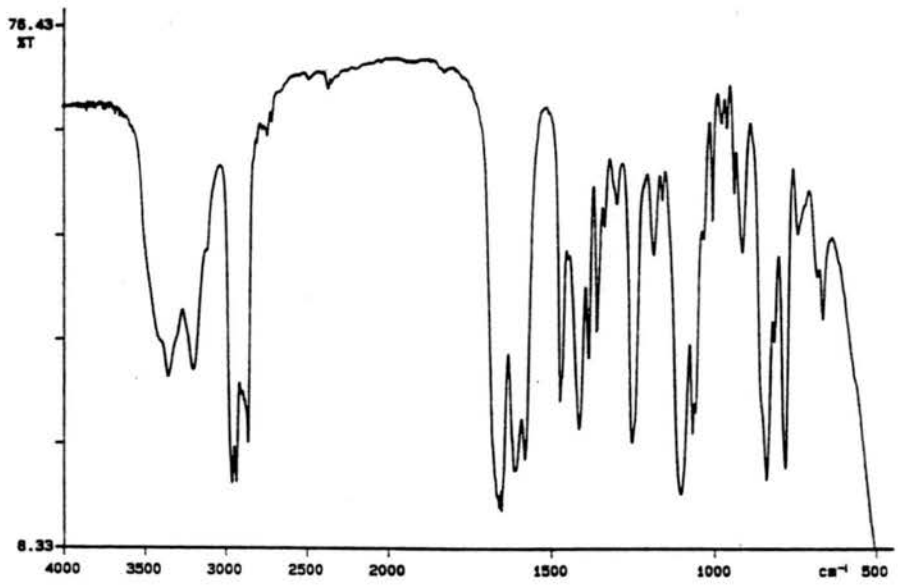


^{1}H NMR (300 MHz) and IR for compound **99**.

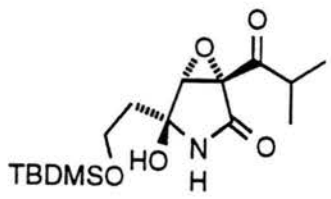


100

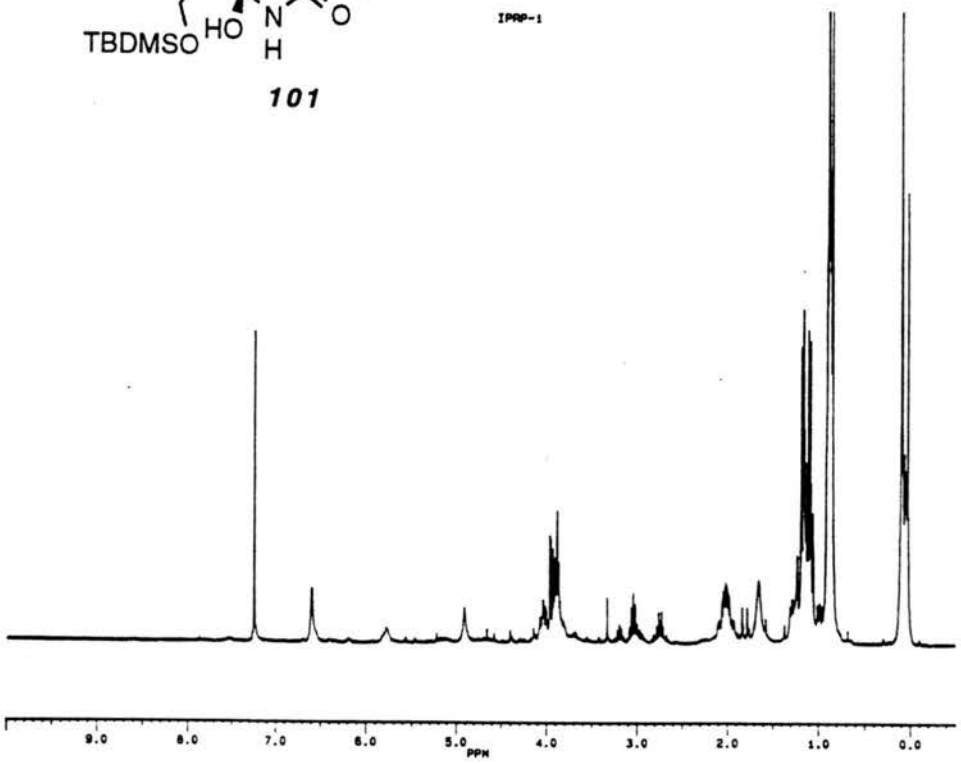


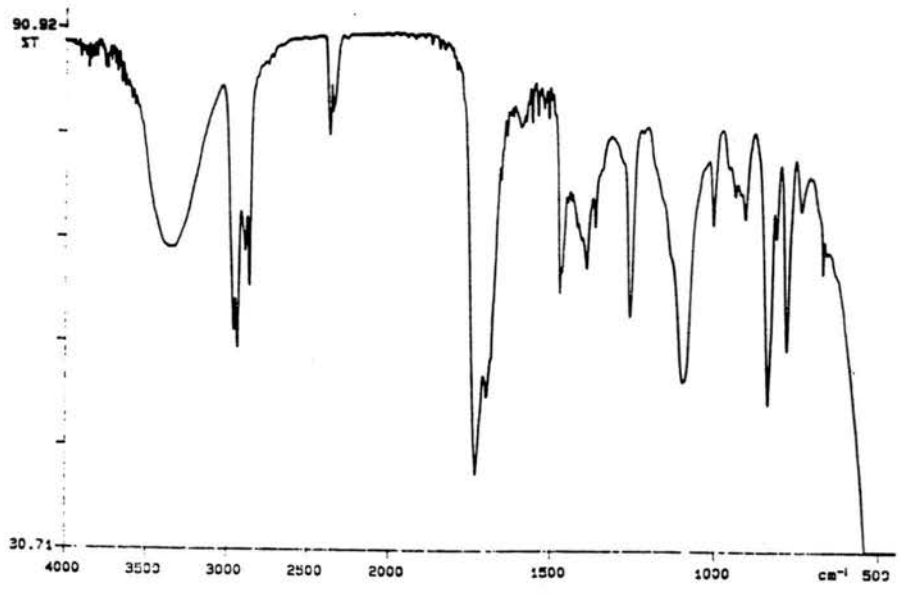


^{1}H NMR (300 MHz) and IR for compound **100**.

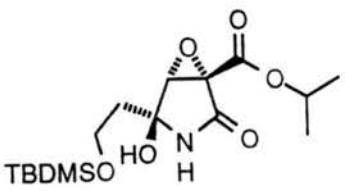


101

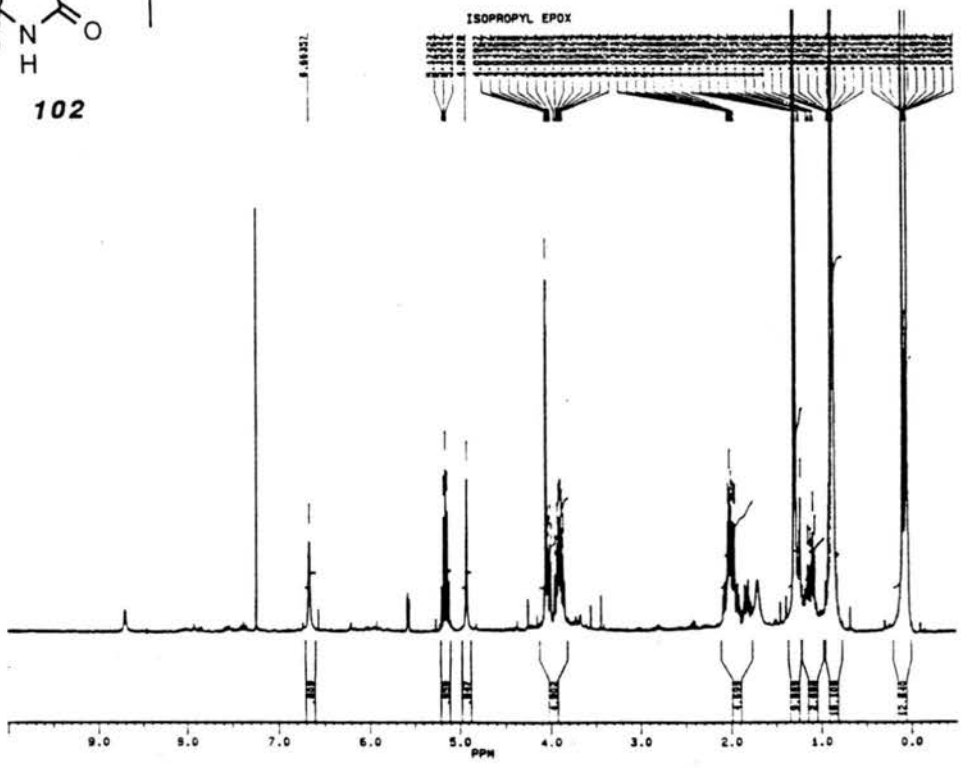


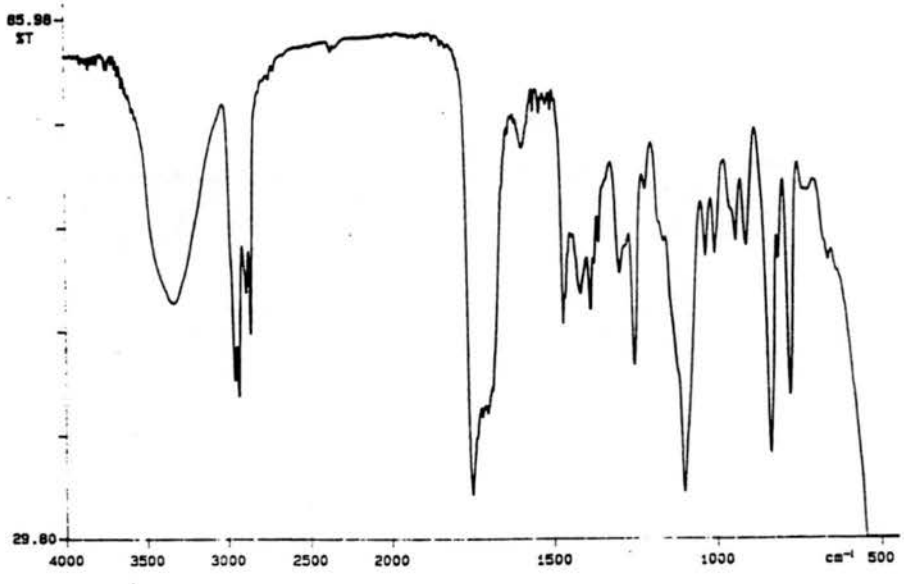


^{1}H NMR (300 MHz) and IR for compound **101**.

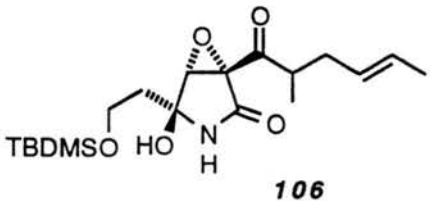


102

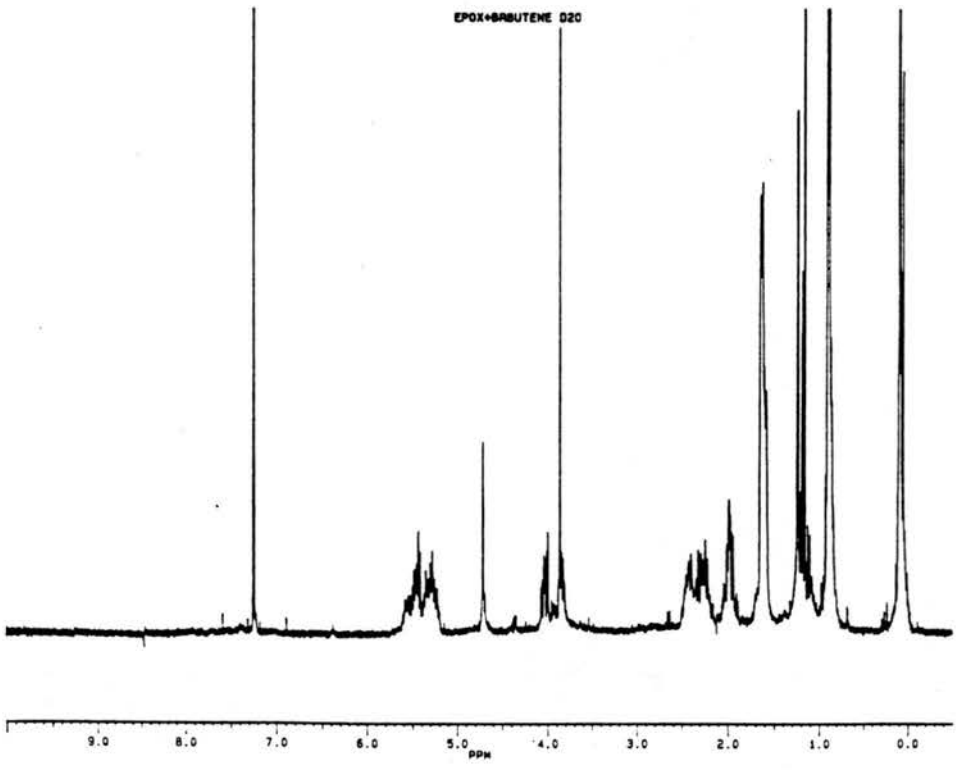




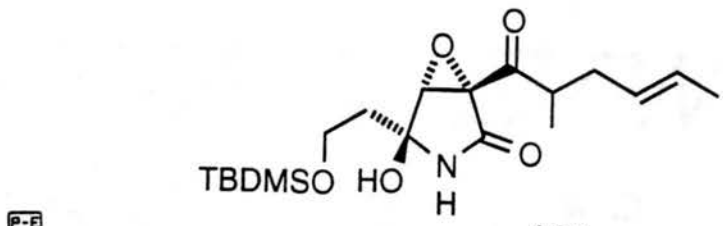
^{1}H NMR (300 MHz) and IR for compound **102**.

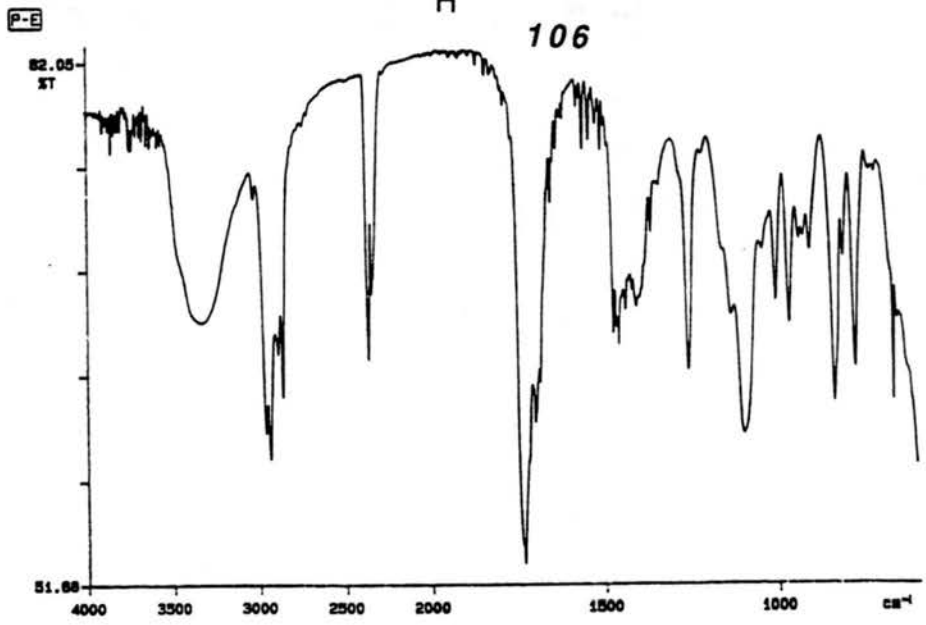


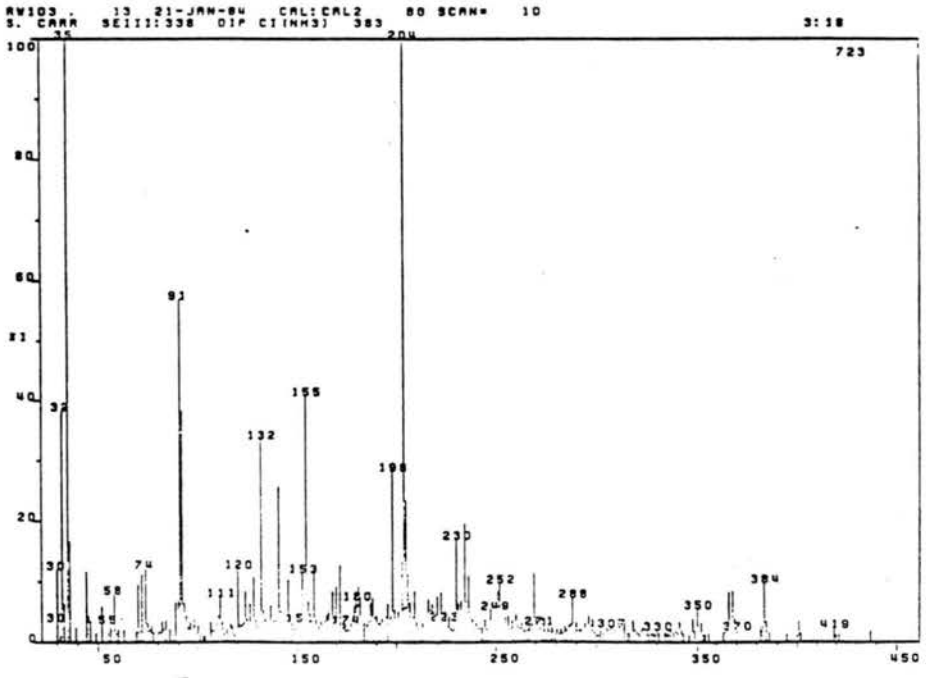
106



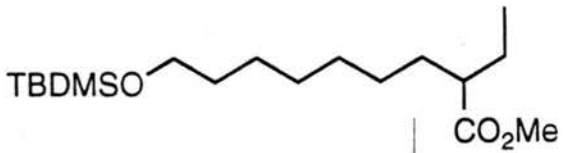
^{1}H NMR (300 MHz) for compound **106**.



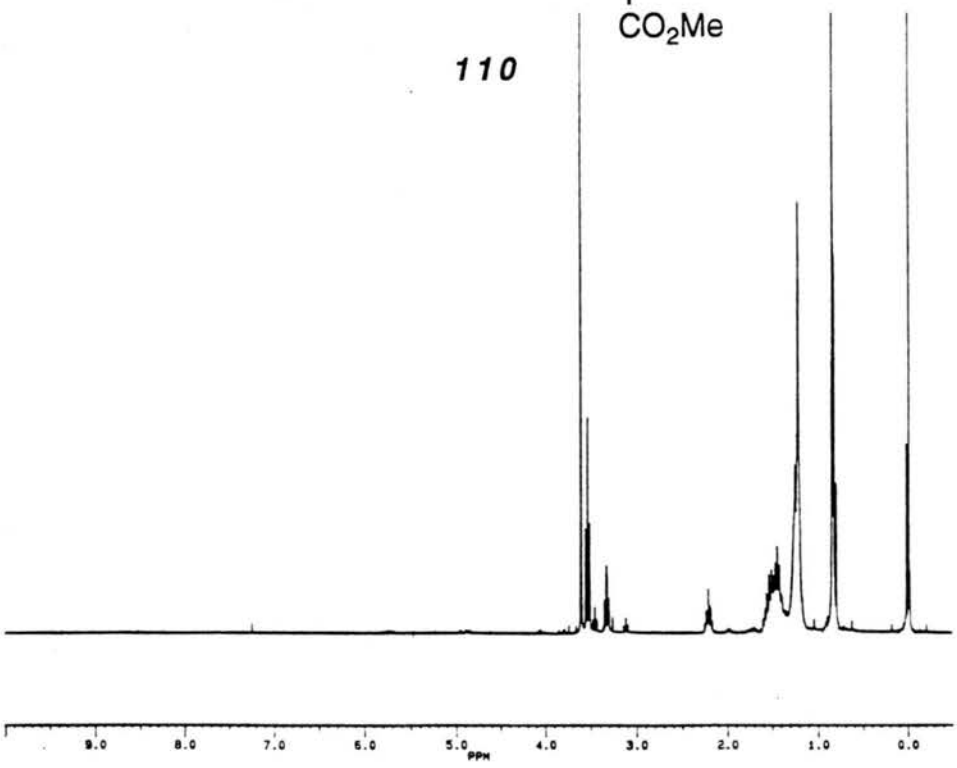


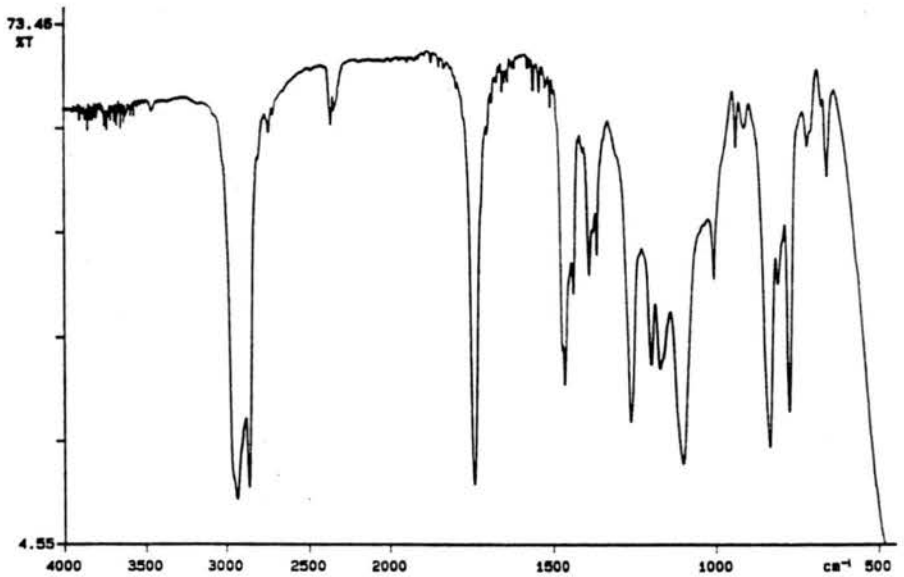


IR and mass spectrum for compound **106**.



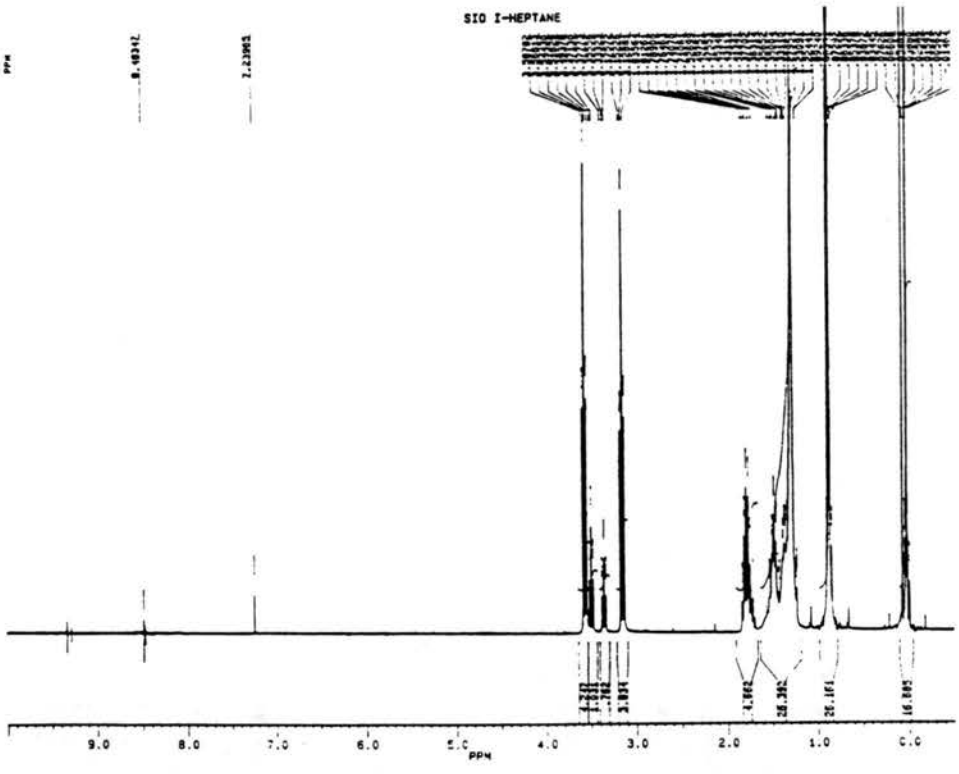
110



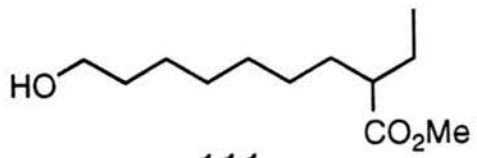


^{1}H NMR (300 MHz) and IR for compound **110**.

109



^{1}H NMR (300 MHz) for compound **109**.



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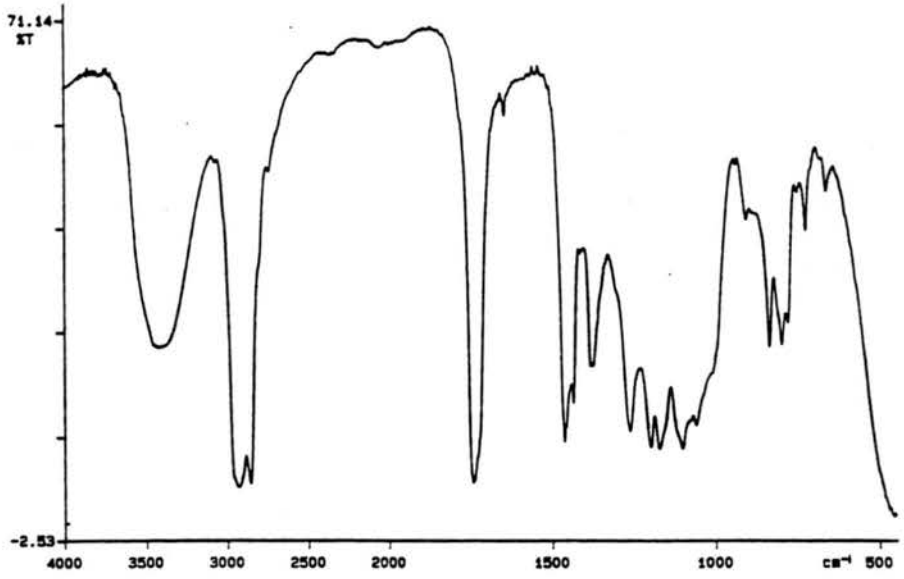
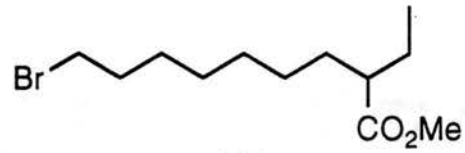
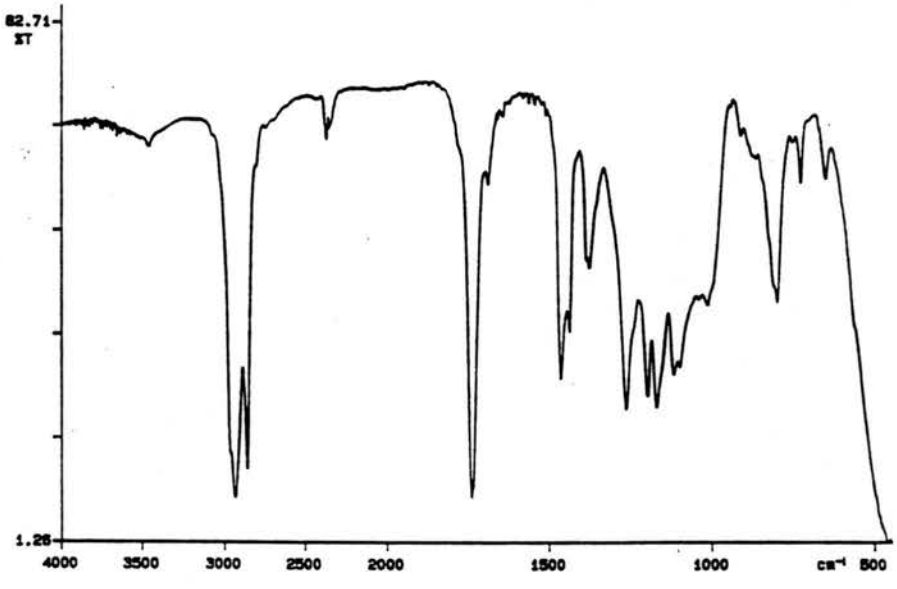


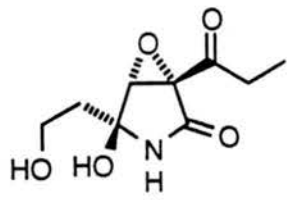
IR for compound **111**.



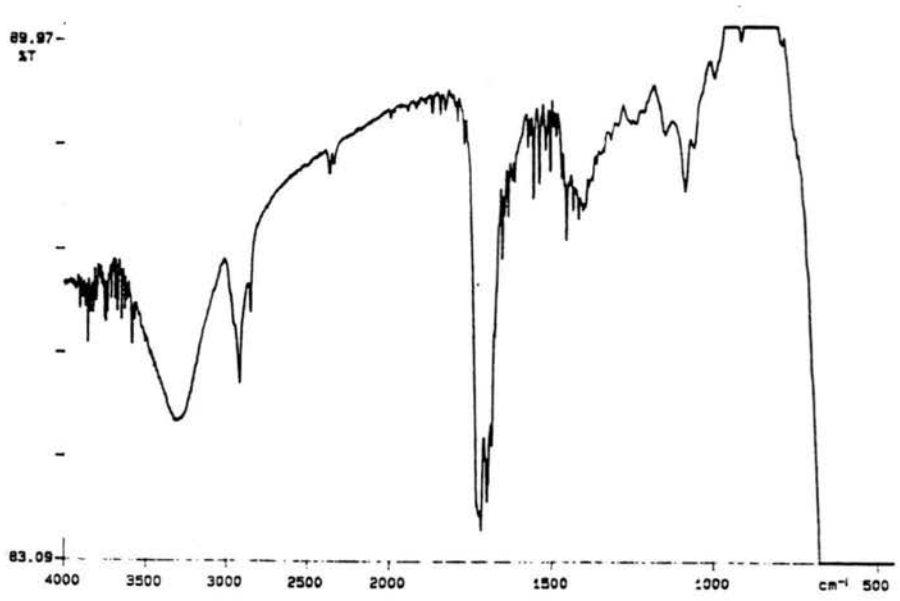
112



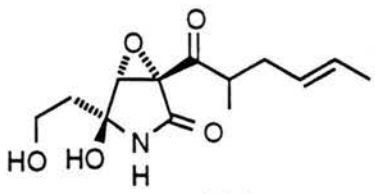
IR for compound **112.**



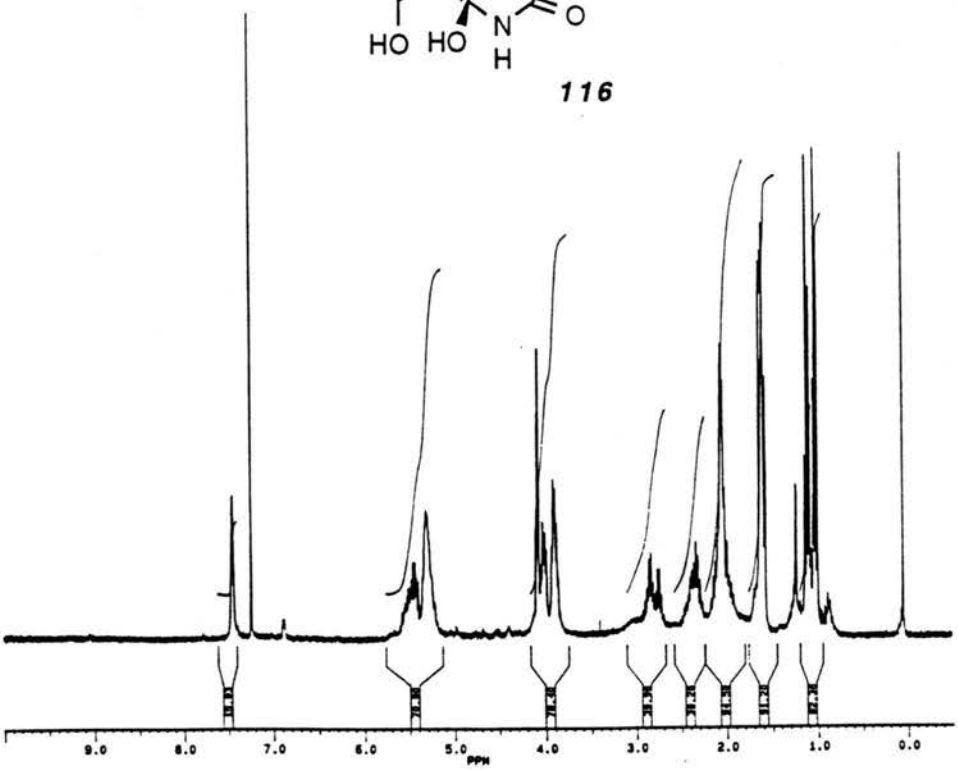
11

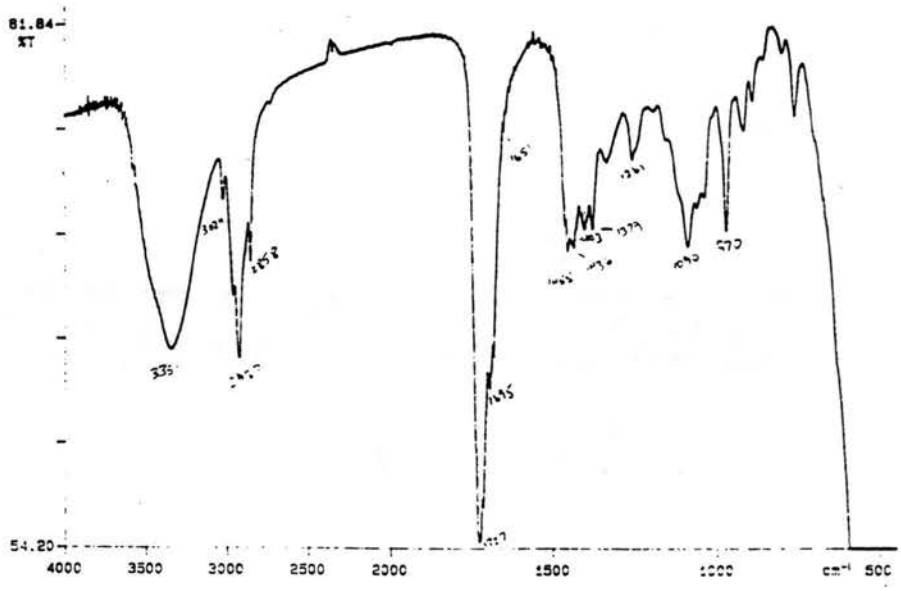


^{1}H NMR (300 MHz) and IR for compound **11**.

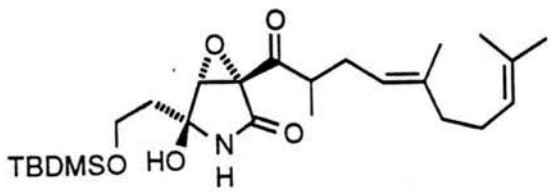


116





^{1}H NMR (300 MHz) and IR for compound **116**.



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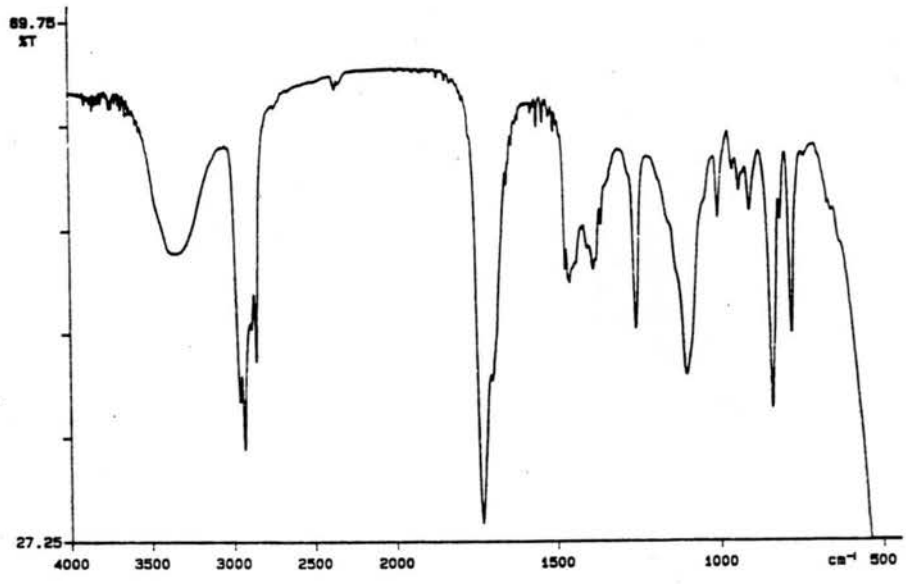
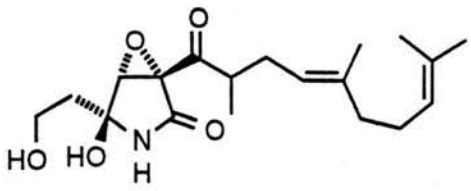
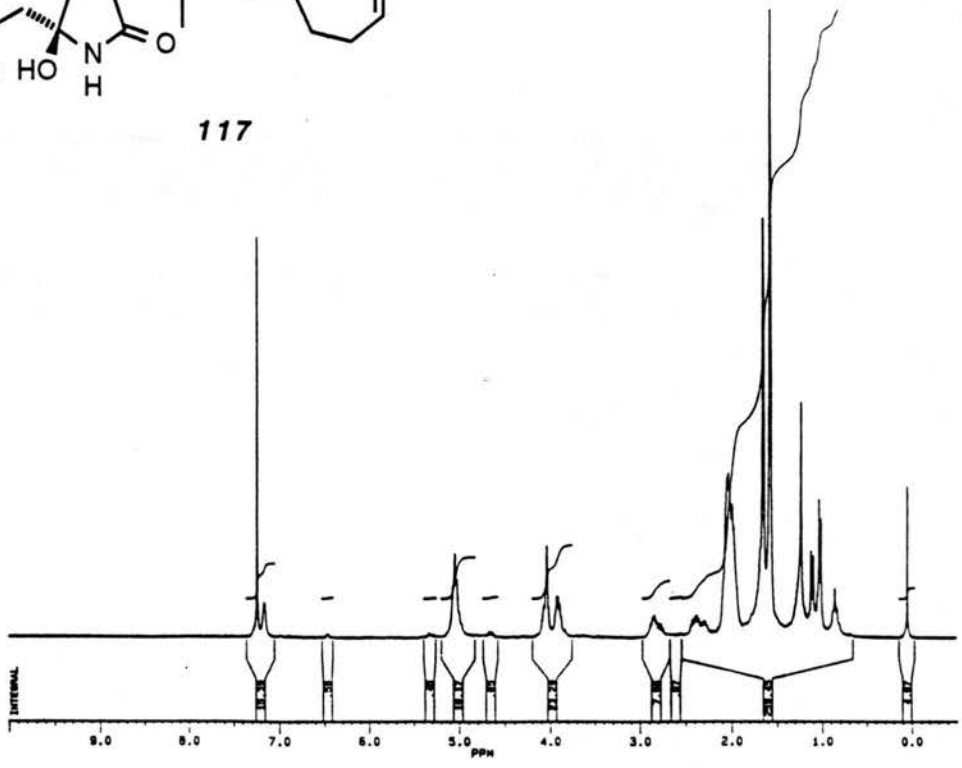
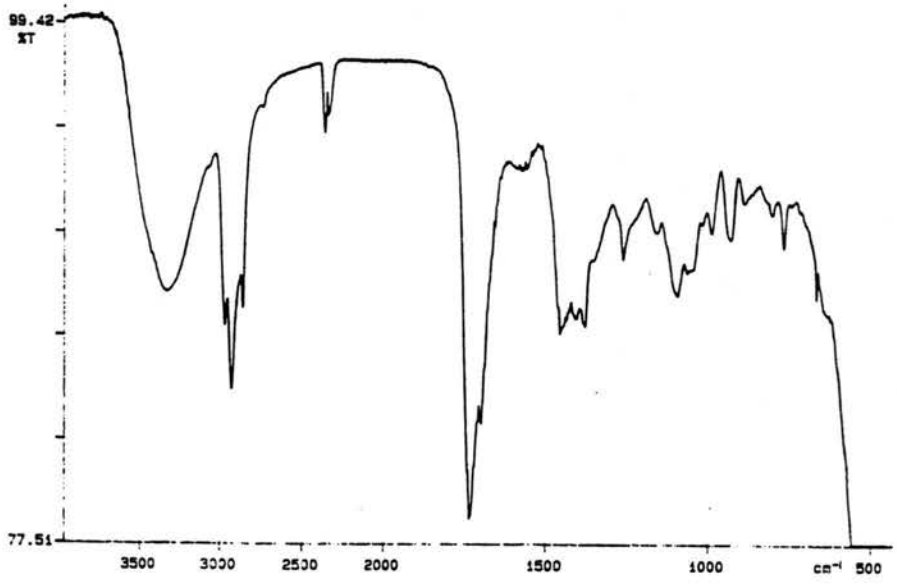


^{1}H NMR (300 MHz) and IR for compound **115**.

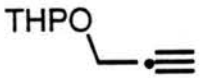


117

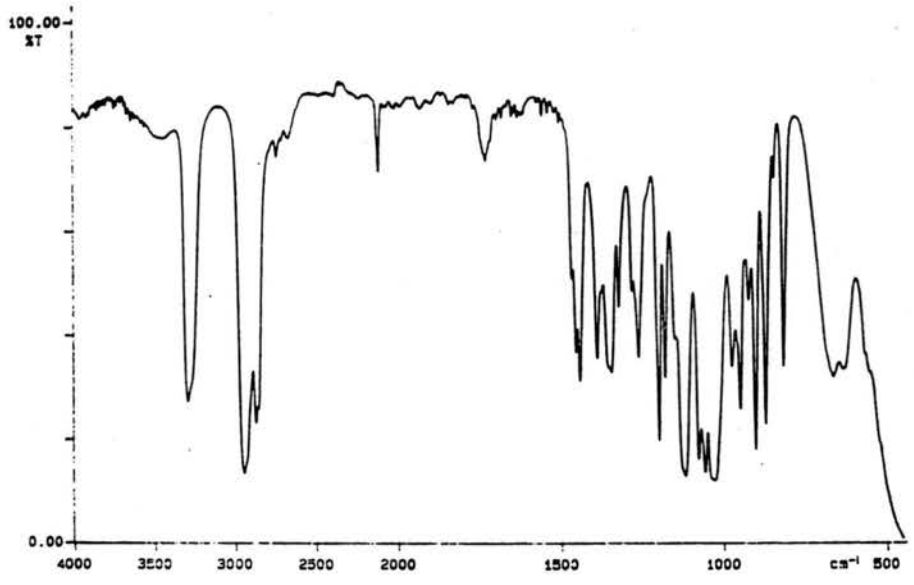




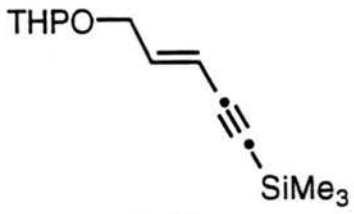
^{1}H NMR (300 MHz) and IR for compound **117**.



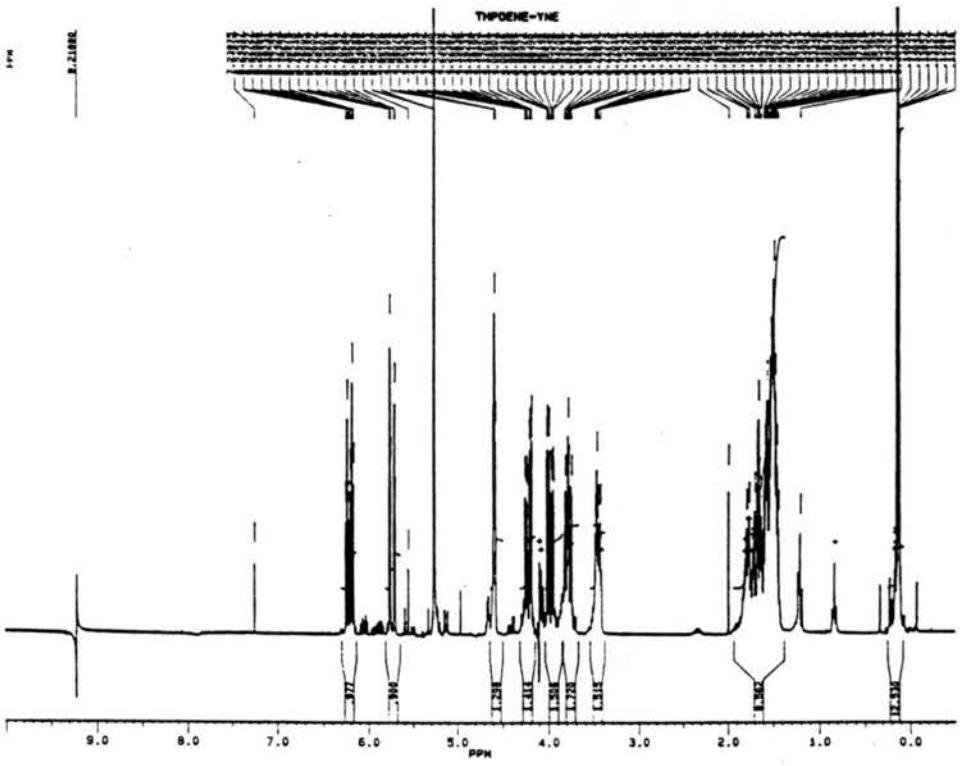
118



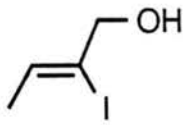
^{1}H NMR (300 MHz) and IR for compound **118**.



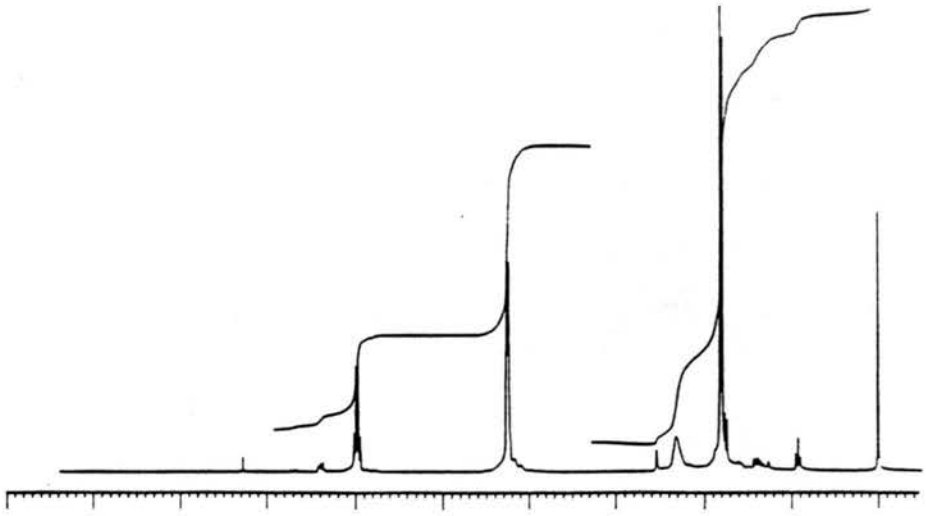
120



^{1}H NMR (300 MHz) for compound **120**.



121

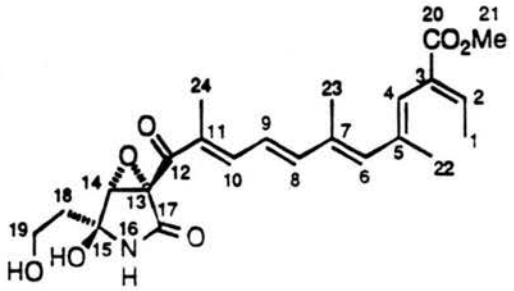


^{1}H NMR (270 MHz) for compound **121**.

Appendix B

The Fusarins: Spectral Data

Fusarin C has been assigned different absolute stereochemistries in the epoxy-lactam portion of the molecule. From the numbering of fusarin C (Figure A1), the C-13, C-14 epoxide and the C-15 hydroxyl are opposite in the two representations. The adopted absolute stereochemistry in this paper complies with that shown from the perspective drawing of the crystalline C-8, C-9 Z isomer (names fusarin B) from which an x-ray diffraction pattern was obtained.



Fusarin C **1**

Figure A1

According to homonuclear nuclear Overhauser enhancement, fusarin C exists in solution as an equilibrium between the s-*cis* and s-*trans* isomers from rotation of the C-5-C-6 single bond (Figure A2). Further NMR data of fusarins C **1**, A **2**, and F **4** are given in Tables A1 (proton NMR) and A2 (carbon NMR). Other spectroscopic data collected on these compounds are given in Table A3.

A biosynthetic study was performed on Fusarium moniliforme metabolites. By the addition of both [1,2-$^{13}C_2$] acetate and (2S)-[methy-^{13}C] methionine, ^{13}C NMR data of fusarin A **2** suggest the carbon framework

derived from these two compounds as shown in Figure A3. These results suggest a C_{14}-polyketide chain formed (C-1, C-13, C-17), starting with C-1, C-2, from acetate units with subsequent methylation at the C-2 of the acetate by methionine methyl addition. The origin of the heterocyclic structure of fusarin A (and fusarin C) is unknown. This biosynthetic hypothesis should also apply to the same portion of fusarin C.

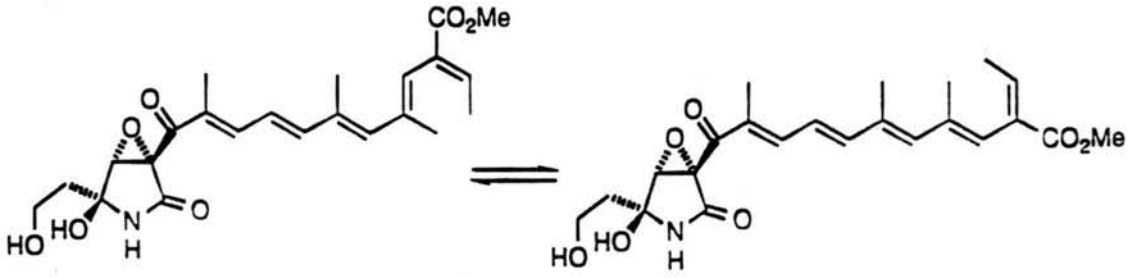


Figure A2

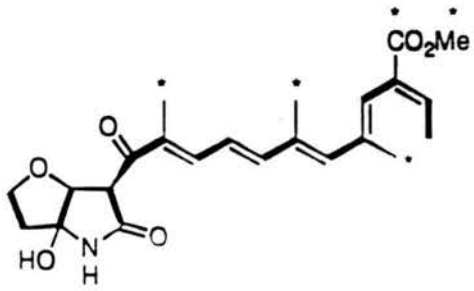


Figure A3

Intact acetate units in Fusarin A • -derived from (2S)-[methyl-^{13}C] methionine

Table A1. Proton NMR of Fusarins C, A, and F

	Fusarin C				Fusarin A		Fusarin F	
C	$CDCl_3$	J(Hz)	CD_2Cl_2	J(Hz)	CD_2Cl_2	J(Hz)	$CDCl_3$	J(Hz)
1	1.79d	7.2	1.773dd	7.2, 1.4	1.779dd	7.2, 1.5	1.77dd	7.2, 1.4
2	6.99q	7.2	6.957qd	7.2, 1.1	6.960qd	7.2, 1.2	6.96q	7.2
4	6.08s		6.071qd	1.4, 1.1	6.085m		6.06bs	
6	6.29s		6.302sbr		6.328sbr		6.27bs	
8	6.80d	15.0	6.790d	15.0	6.880d	15.0	6.76d	15
9	6.61dd	12.0, 15.0	6.670dd	15.0, 11.0	6.684dd	15.0, 11.0	6.62dd	15, 11.5
10	7.52d	12.0	7.492dbr	11.0	7.512dq	11.0, 1.1	7.47d	11.7
14	4.02d	2.7	4.061d	2.1	4.351s	1.2	4.11d	2.4
					4.223d			
18	2.08m		2.059ddd	14.6, 6.0, 3.7	2.365ddd	12.8, 8.9, 8.6	2.22m	
			2.113ddd	14.6, 8.3, 4.1	2.260ddd	12.8, 6.5, 3.9	2.09m	
19	4.0m		4.050ddd	11.1, 8.3, 3.7	4.084ddd	8.9, 8.6, 3.9		
					3.992ddd	8.9, 8.9, 6.5	3.99m	
							3.92m	
21	3.75s		3.715s		3.717s		3.73s	
22	1.72s		1.729d	1.4	1.740d	1.4	1.72d	1.4
23	2.0s		2.091d	1.3	2.108d	1.3	2.07s	
24	2.09s		1.981d	1.3	1.970d	1.2	1.97s	

Table A2. ^{13}C NMR Data for Fusarins C, A, and F

	Fusarin C				Fusarin A		Fusarin F
C	$CDCl_3$	J(Hz)	CD_2Cl_2	J(Hz)	CD_2Cl_2	J(Hz)	$CDCl_3$
1	16.04q	110	16.15q	127.3	16.12q	126.6	15.9
2	140.23d	155	140.33d	157.5	140.27d	157.3	140.1
3	130.29s		130.81s		130.86s		130.4
4	126.20d	134	126.67d	157.5	126.63d	158.1	126.2
5	137.41s		137.81s		137.79s		137.4
6	140.95d	151	140.99d	151.3	140.96d	151.7	140.9
7	134.85s		135.42s		135.41s		134.8
8	149.37d	132	149.15d	157.0	149.16d	152.9	149.2
9	123.29d	134	123.79d	154.4	124.01d	152.6	123.4
10	146.41d	128	145.73d	154.6	146.13ds	152.7	146.5
11	133.38s		133.90s		134.44s		133.5
12	190.36s		190.17s		197.70s		189.5
13	61.93s		62.17s		57.19d	141.0	64.2
14	64.75d	175	64.15d	197.1	86.23d	160.1	62.4
15	85.43s		85.92s		94.95s		84.8
17	170.36s		170.27s		171.08s		168.2
18	35.97t	135	36.27t	128.5	37.89t	133.2	39.2
19	58.05t	127	58.77t	144.0	68.85t	148.4	57.6
20	167.65s		167.77s		167.73s		167.6
21	51.95q	125	52.07q	146.7	52.05q		51.9
22	18.79q	110	18.91q	1271.1	18.92q	18.7	
23	14.09q	110	14.28q	127.5	14.31q		14.1
24	11.45q	110	11.55q	128.6	11.77q		11.3

Table A3. Spectroscopic Data of Fusarins C, A, and F

	Fusarin C	Fusarin A	Fusarin F
hrms	431.1953 ($C_{23}H_{29}NO_7$)	415.1993 ($C_{23}H_{29}NO_6$)	431.1933 ($C_{23}H_{29}NO_7$)
λ_{max}	358 nm (MeOH)	352 nm (MeOH)	370 nm ($CHCl_3$)
IR cm^{-1}	($CHCl_3$) 1720	($CHCl_3$) 3410	3300
	1630	1710	3000
	1590	1625	2350
	3300-3600	1600	1710
	1735	1580	1580
	1725		1400
	1665		1250
			1200
			1030
			895
			840
$[\alpha]^{23}$	+47.04 (2.0% MeOH)		
R_f			
*i*PrOH:$CHCl_3$ (1:9)	0.38	0.56	0.30

Mutagenicity tests performed on *Salmonella typhimurium* TAIDO using fusarin C showed that fusarin C was non-mutagenic (compared to the controls) without oxidative activation (Table A4). In the presence of phenobarbitol

induced S9 liver fractions (PS9), the mutagenic activity of fusarin C greatly increased as histidine revertants (resulting from DNA mutation).

Table A4. Mutagenic Activity of Fusarin C using *S. typhimurium* TA100

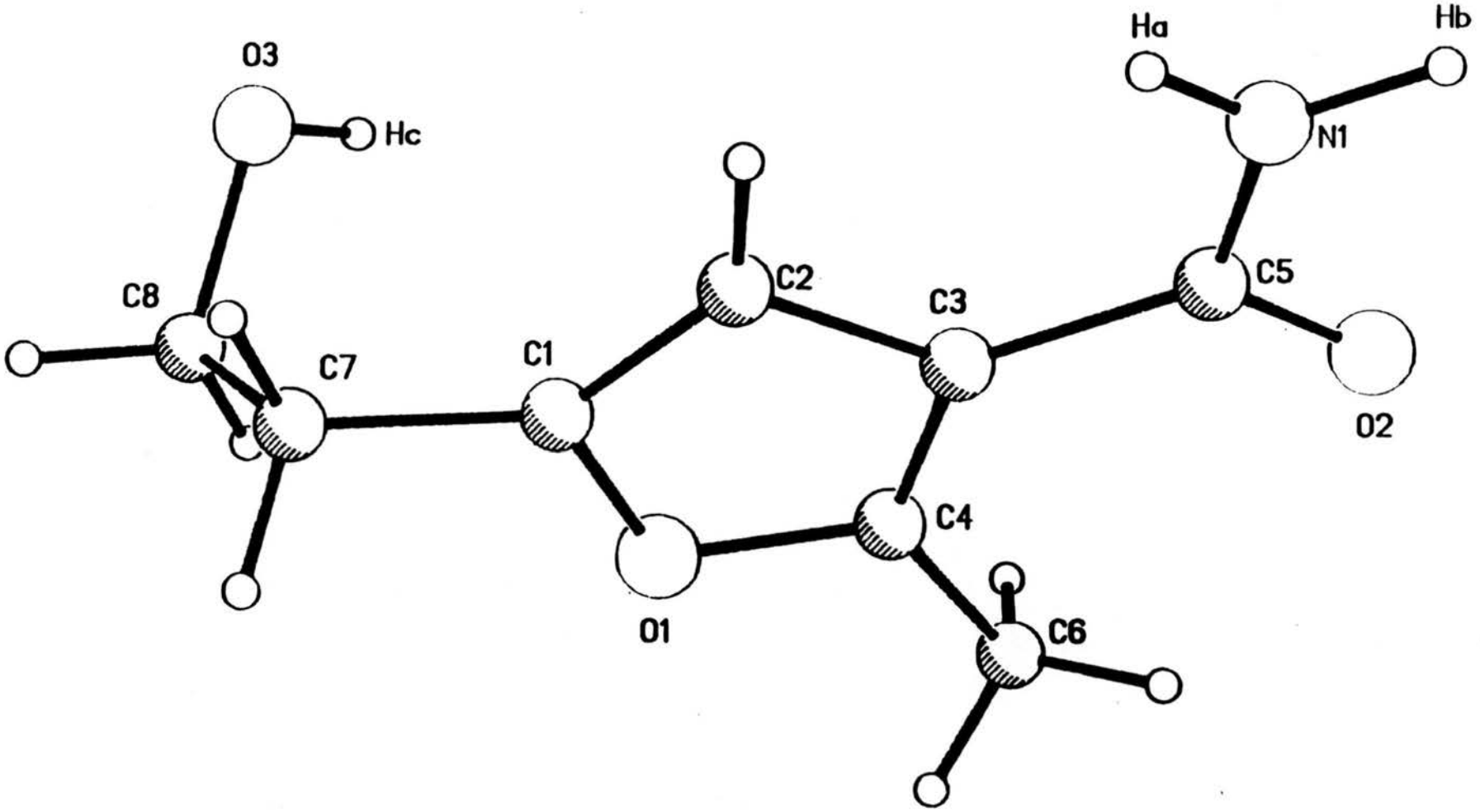
Mutagen System	Histidin Revertants/Plate
control	157 ± 10
PS9	179 ± 1
DMSO	100 ± 8
*Fusarin C	279 ± 3
* Fusarin C + PS9	1123 ± 49

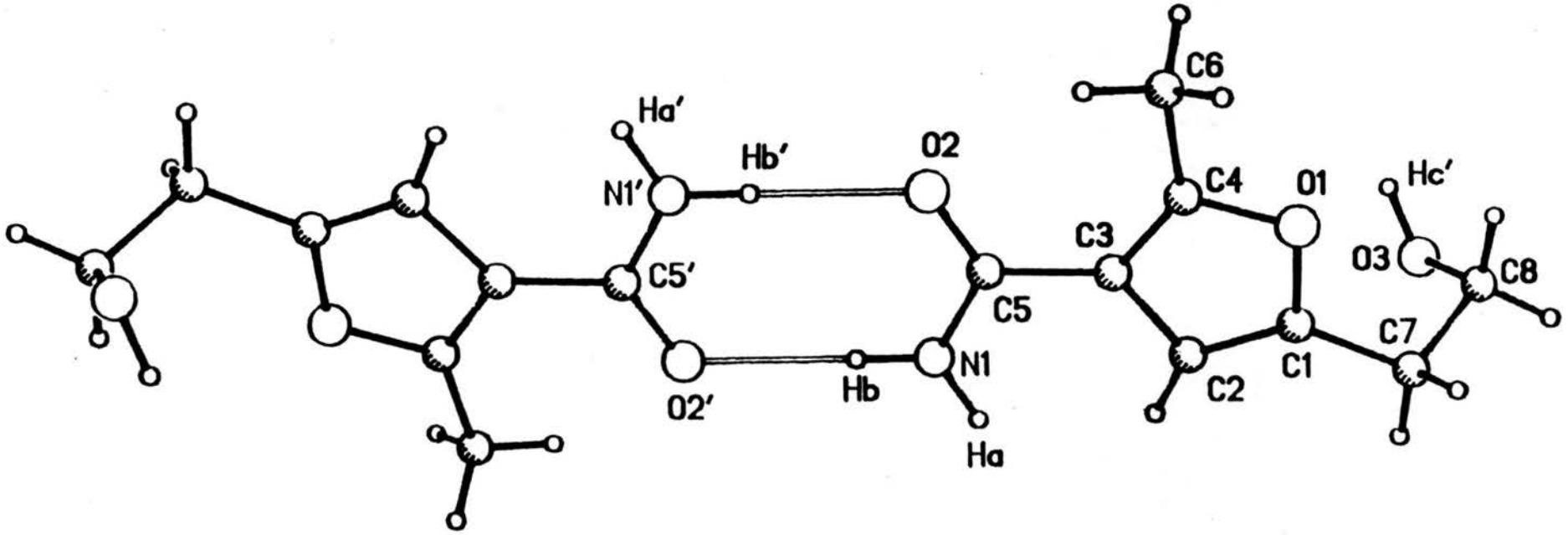
* Fusarin C concentration at 46 nmol/plate

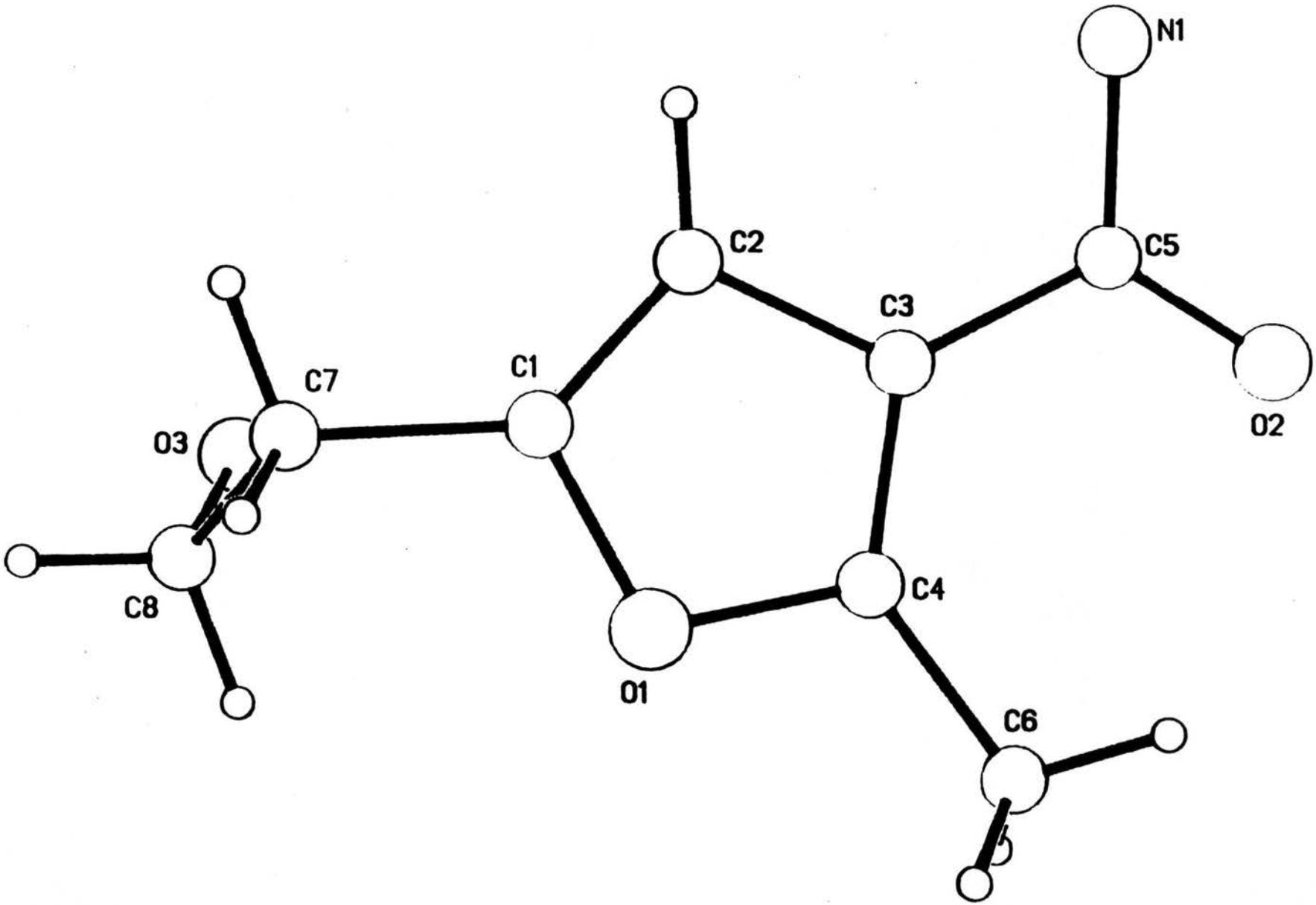
APPENDIX C

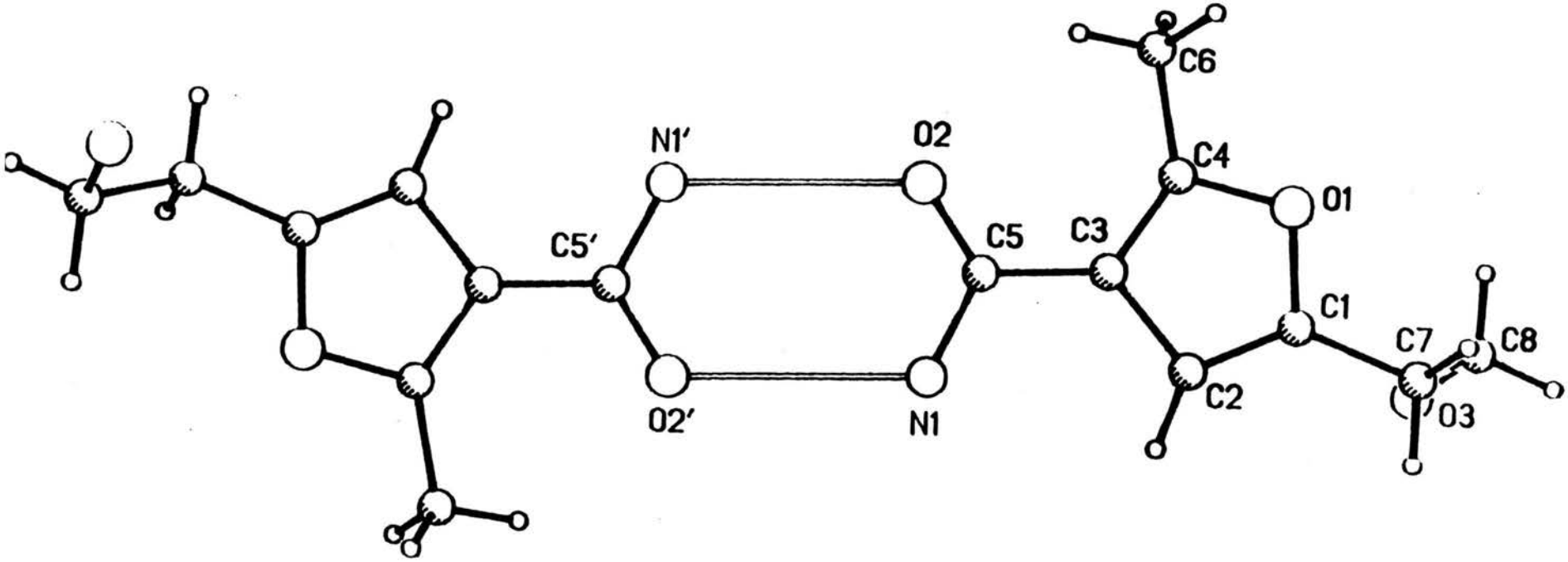
Crystallographic Data for Compound 50

Mol formula	$C_8H_{11}NO_3$
Formula wt	169
Crystal system	Treclinic
Space group	PT
Lattice constants	
a, Å	7.3820(10)
b, Å	7.6801(10)
c, Å	8.4691(21)
α, deg	77.655(16)
β, deg	71.174(16)
γ, deg	66.660(10)
V, Å^3	415.2
Temperature, °C	22
Z	2
F (000)	180
ρ (observed, g cm^{-3})	---
ρ (calculated, g cm^{-3}	1.35
Crystal dimensions, mm	0.18x0.19x0.28
Radiation	MoKα (λ = 0.7107 Å)
Monochromator	graphite
μ, cm^{-1}	1.0
Scan type	Wyckoff
Geometry	Bisecting
Scan speed, deg min^{-1}	variable 2 to 30
2Θ range, deg	4 to 50
Index restrictions	$0 \le h \le 9$, $-10 \le k \le 10$, $-11 \le l \le 11$
Total no. of reflections	1571
No. of unique, observed reflections	1257
Observed reflection criterion	$\|F_o\| \ge 2.5\ \alpha\ (\|F_o\|)$
No. of least squares parameters	124
Data/parameter ratio	10.14
R	0.043
R_w	0.048
GOF	1.65
g (refined)	0.00053
Slope, normal probability plot	1.414


O3
Hc
C8
C7
C1
C2
C3
C5
Ha
Hb
N1
O2
C4
O1
C6


Ha'
Hb'
O2
C6
N1'
C4
O1
Hc'
C3
O3
C8
C5'
C5
C7
N1
C2
C1
O2'
Hb
Ha


N1
C2
C5
C3
O2
C1
C7
O3
C8
O1
C4
C6


C6
N1′
O2
C4
O1
C5′
C5
C3
C1
C7
C8
O2′
N1
C2
O3

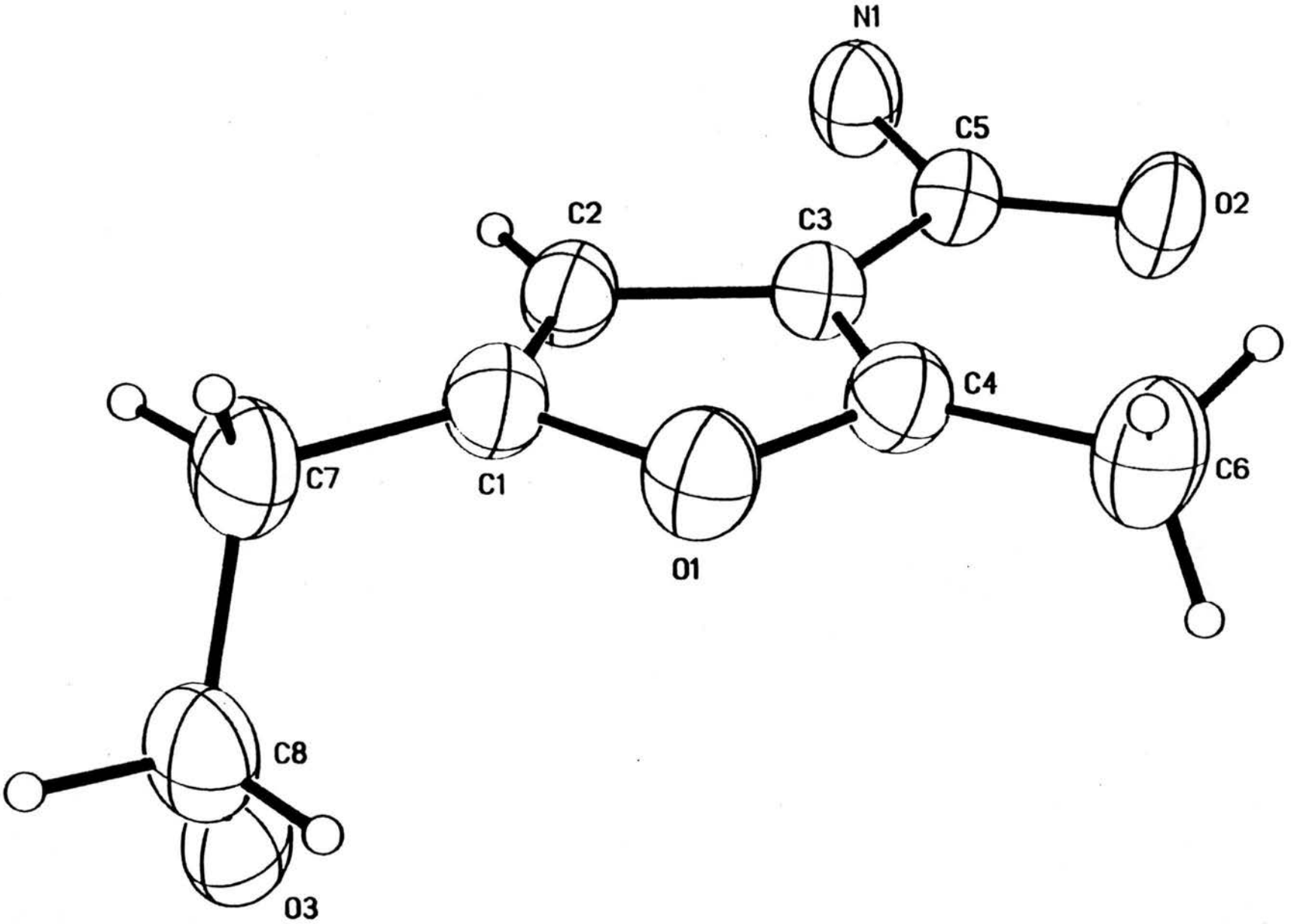

N1
C5
O2
C2
C3
C4
C6
C7
C1
O1
C8
O3

TABLE 1 Atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($Å^2 \times 10^3$)[a] for $C_8H_{11}NO_3$ (RW20 WILLIAMS/CARR

atom	x	y	z	U^b_{iso}
N1	3939(3)	11850(2)	6493(2)	47(1)*
O1	1632(2)	10147(2)	12102(2)	45(1)*
O2	4038(2)	8841(2)	7056(2)	51(1)*
O3	-2991(2)	14128(2)	13148(2)	49(1)*
C1	1400(3)	12056(3)	11753(2)	41(1)*
C2	2038(3)	12458(3)	10099(2)	39(1)*
C3	2716(3)	10711(2)	9344(2)	35(1)*
C4	2439(3)	9364(3)	10618(2)	40(1)*
C5	3604(3)	10400(3)	7564(2)	37(1)*
C6	2837(4)	7307(3)	10737(3)	55(1)*
C7	522(3)	13171(3)	13222(3)	50(1)*
C8	-1627(3)	13247(3)	14182(2)	50(1)*

(a) Estimated standard deviations in the least significant digits are given in parentheses.

(b) For values with asterisks, the equivalent isotropic U is defined as 1/3 of the trace of the U_{ij} tensor.

TABLE 2 Bond lengths (Å)[a] for $C_8H_{11}NO_3$ (RW20 WILLIAMS/CARR

N1-HA	0.891(28)	N1-HB	0.934(24)
N1-C5	1.329(2)	O1-C1	1.384(2)
O1-C4	1.361(2)	O2-C5	1.244(3)
O3-HC	0.848(34)	O3-C8	1.419(3)
C1-C2	1.336(3)	C1-C7	1.481(3)
C2-C3	1.445(3)	C3-C4	1.350(2)
C3-C5	1.467(3)	C4-C6	1.475(3)
C7-C8	1.515(3)		

(a) Estimated standard deviations in the least significant digits are given in parentheses.

TABLE 3 Bond angles (deg)[a] for $C_8H_{11}NO_3$ (RWZ0 WILLIAMS/CARR

HA-N1-HB	119.1(21)	HA-N1-C5	121.3(14)
HB-N1-C5	119.3(15)	C1-O1-C4	107.6(1)
HC-O3-C8	107.7(17)	O1-C1-C2	109.3(2)
O1-C1-C7	115.8(2)	C2-C1-C7	134.8(2)
C1-C2-C3	107.0(2)	C2-C3-C4	106.3(2)
C2-C3-C5	127.9(2)	C4-C3-C5	125.7(2)
O1-C4-C3	109.8(2)	O1-C4-C6	115.6(2)
C3-C4-C6	134.6(2)	N1-C5-O2	120.5(2)
N1-C5-C3	117.6(2)	O2-C5-C3	121.9(2)
C1-C7-C8	113.5(2)	O3-C8-C7	110.9(2)

(a) Estimated standard deviations in the least significant digits are given in parentheses.

TABLE 4 Anisotropic thermal parameters ($Å^2 \times 10^3$)[a,b] for $C_8H_{11}NO_3$ (RW20 WILLIAMS/CARR

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	63(1)	38(1)	36(1)	-8(1)	-2(1)	-22(1)
O1	57(1)	43(1)	36(1)	-3(1)	-11(1)	-19(1)
O2	70(1)	41(1)	45(1)	-13(1)	-3(1)	-28(1)
O3	60(1)	36(1)	54(1)	-6(1)	-13(1)	-19(1)
C1	45(1)	40(1)	40(1)	-8(1)	-10(1)	-18(1)
C2	42(1)	36(1)	38(1)	-6(1)	-9(1)	-15(1)
C3	36(1)	33(1)	37(1)	-6(1)	-8(1)	-13(1)
C4	42(1)	39(1)	40(1)	-7(1)	-11(1)	-14(1)
C5	37(1)	35(1)	40(1)	-8(1)	-9(1)	-13(1)
C6	73(1)	38(1)	53(1)	1(1)	-18(1)	-22(1)
C7	62(1)	53(1)	41(1)	-12(1)	-13(1)	-22(1)
C8	67(1)	48(1)	32(1)	-7(1)	-4(1)	-23(1)

(a) Estimated standard deviations in the least significant digits are given in parentheses.

(b) The anisotropic thermal parameter exponent takes the form:

$$-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+ \ldots +2hka^*b^*U_{12})$$

TABLE 5 Hydrogen coordinates ($\times 10^4$) and thermal parameters ($Å^2 \times 10^3$) for $C_8H_{11}NO_3$ (RW20 WILLIAMS/CARR

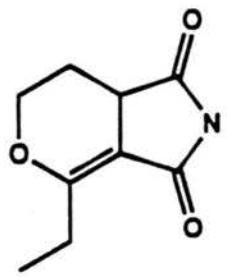
atom	x	y	z	U_{iso}
HA	3722(33)	12945(34)	6850(27)	51(6)
HB	4543(34)	11677(31)	5358(30)	60(6)
HC	-3183(38)	13254(37)	12832(32)	67(7)
--	2122	13591	9383	48
H6A	3943	6732	9816	67
H6B	1644	7065	10770	67
H6C	3216	6775	11767	67
H7A	1388	12592	13968	62
H7B	497	14449	12840	62
H8A	-2091	13972	15121	61
H8B	-1615	11975	14578	61

The Structure of 3-ethyl-4-oxa-1,5,6-trihydrophthalimide

Kevin A. Andersen and Oren P. Anderson*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Abstract. $C_9H_{11}NO_3$; M_r = 181.19, monoclinic, $P2_1/c$, a = 12.262 (3) Å, b = 8.027 (2) Å, c = 8.596 (1) Å, β = 92.36 (2)°, V = 845.4 (3) Å^3, Z = 4, D_x = 1.42 g cm^{-3}, λ(Mo Kα) = 0.7107 Å, μ = 1.2 cm^{-1}, F(000) = 384, T = −108 °C, R = 0.050 (wR = 0.075) for 1365 unique, observed reflections. The compound is a derivative of phthalimide substituted in the six-membered ring by an ether oxygen and an ethyl group.



1

Experimental. Crystals (colorless prisms) of $C_9H_{11}NO_3$ (hereafter **1**) obtained from a ethyl acetate/hexane solution by Sean Esslinger and Professor Robert M. Williams (Colorado State University). Crystal size 0.47 × 0.60 × 0.44

mm. Nicolet *R*3*m* diffractometer, unit cell constants from least squares fit of setting angles for 25 reflections ($2\theta_{av}$ = 31.40°). Data collected ($\theta/2\theta$ scans) to $(\sin\theta)/\lambda$ = 0.5947 Å, $-11 \le h \le 11$, $0 \le k \le 10$, $0 \le l \le 15$. Three standard reflections (400, 020, 005) every 97, no trend in intensity observed; Lorentz and polarization corrections; no absorption correction applied due to low absorption coefficient; 1623 unique reflections, 1365 reflections with $F_o > 4.0\sigma(F_o)$ observed.

Structure solved by direct methods (SOLV); block diagonal (max. 103 parameters/block, 125 parameters total, data/parameters = 10.9) weighted [$w = (\sigma^2(F) + gF^2)^{-1}$, $g = 1.37 \times 10^{-3}$] least-squares refinement on *F*. H atoms in idealized positions (C–H = 0.96 Å, $U(H) = 1.2 \times U_{iso}(C)$) with exception of H atom on N(1) (located in difference map and refined with isotropic thermal parameters). Non-H atoms refined with anisotropic thermal parameters. At convergence ($(\Delta/\sigma)_{max}$ = 0.036, $(\Delta/\sigma)_{mean}$ = 0.011 for last 2 cycles) *R* = 0.050, *wR* = 0.075, *S* = 1.81, slope of normal probability plot = 1.56, $(\Delta\rho)_{max}$ = 0.40 e Å^{-3}, $(\Delta\rho)_{min}$ = –0.32 e Å^{-3}. Neutral atom scattering factors and anomalous dispersion corrections used (*International Tables for X-Ray Crystallography*, 1974); all calculations performed using SHELXTL program library (Sheldrick, 1983). Table 1 gives atomic coordinates, Tables 2 and 3 give bond lengths and angles, respectively.* Fig. 1 shows the structure of **1**, as well as the numbering scheme used.

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* Lists of anisotropic thermal parameters, H coordinates, and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP _____ (11 pp). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Related literature. Phthalimide and five derivatives of phthalimide have been previously studied: phthalimide (Matzat, 1972), 5-methyl-1,3,4,6-tetraoxaperhydropyrrolo(3,4-c)pyridine (Amorese, 1982), 4-(4'-N-diethylaminophenylazo)phthalimide (Golinski, 1985), 1,2,3,6-tetrahydrophthalimide (Ki, 1976), pyromellitic di-imide (Bulgarovskaya, 1976), 3,4,5,6-tetrahydrophthalimide (Ki, 1975).

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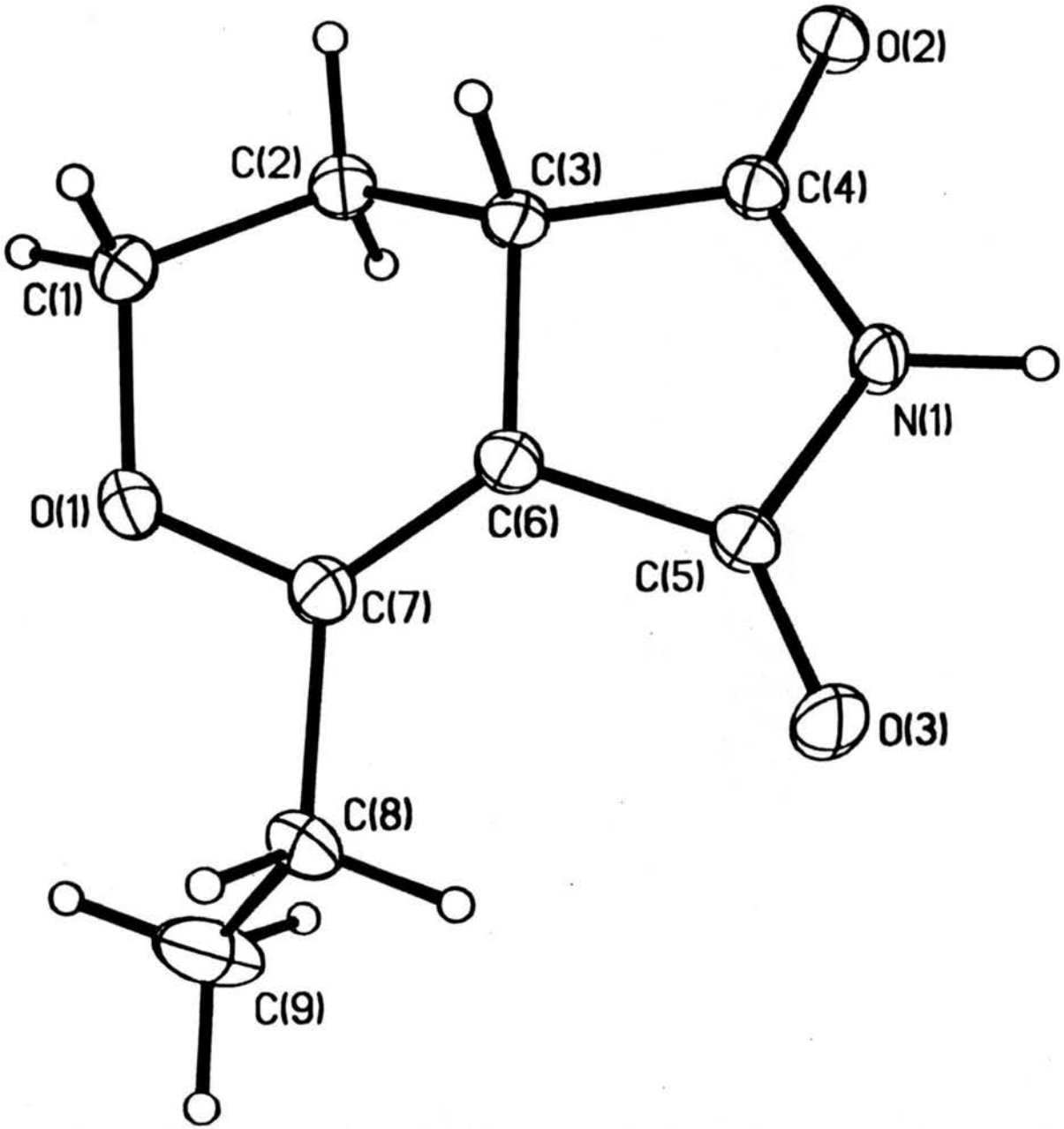
O(2)
C(2)
C(3)
C(4)
C(1)
N(1)
O(1)
C(6)
C(5)
C(7)
O(3)
C(8)
C(9)

Table 1. Atomic coordinates and isotropic thermal parameters ($Å^2 x 10^3$) for 1

	x	y	z	U
O(1)	0.8387(1)	0.0476(2)	0.1339(2)	25(1)*
O(2)	0.4994(1)	0.1669(1)	-0.2315(1)	20(1)*
O(3)	0.7062(1)	0.5532(1)	0.0324(2)	28(1)*
N(1)	0.5860(1)	0.3846(2)	-0.1072(2)	18(1)*
HN(1)	0.5482(2)	0.4697(3)	-0.1693(3)	37(6)
C(1)	0.7610(1)	-0.0827(2)	0.0872(2)	22(1)*
C(2)	0.6892(1)	-0.0350(2)	-0.0535(2)	20(1)*
C(3)	0.6292(1)	0.1226(2)	-0.0094(2)	17(1)*
C(4)	0.5644(1)	0.2199(2)	-0.1312(2)	16(1)*
C(5)	0.6734(1)	0.4145(2)	0.0012(2)	17(1)*
C(6)	0.7096(1)	0.2496(2)	0.0534(2)	17(1)*
C(7)	0.8086(1)	0.2071(2)	0.1150(2)	19(1)*
C(8)	0.8971(1)	0.3259(2)	0.1676(2)	24(1)*
C(9)	1.0078(2)	0.2849(3)	0.1055(3)	37(1)*

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

TABLE 2. Bond lengths (Å)[a] for 1

O(1)-C(1)	1.459(2)	O(1)-C(7)	1.340(2)
O(2)-C(4)	1.227(2)	O(3)-C(5)	1.210(2)
N(1)-HN(1)	0.972(23)	N(1)-C(4)	1.363(2)
N(1)-C(5)	1.412(2)	C(1)-C(2)	1.515(2)
C(2)-C(3)	1.519(2)	C(3)-C(4)	1.507(2)
C(3)-C(6)	1.503(2)	C(5)-C(6)	1.460(2)
C(6)-C(7)	1.348(2)	C(7)-C(8)	1.501(2)
C(8)-C(9)	1.515(3)		

(a) Estimated standard deviations in the least significant digits are given in parentheses.

TABLE 3. Bond angles (deg)[a] for 1

C(1)-O(1)-C(7)	118.5(1)	HN(1)-N(1)-C(4)	120.9(14)
HN(1)-N(1)-C(5)	125.1(14)	C(4)-N(1)-C(5)	113.7(1)
O(1)-C(1)-C(2)	112.9(1)	C(1)-C(2)-C(3)	106.4(1)
C(2)-C(3)-C(4)	120.3(1)	C(2)-C(3)-C(6)	109.7(1)
C(4)-C(3)-C(6)	102.6(1)	O(2)-C(4)-N(1)	124.0(1)
O(2)-C(4)-C(3)	128.2(1)	N(1)-C(4)-C(3)	107.7(1)
O(3)-C(5)-N(1)	122.6(1)	O(3)-C(5)-C(6)	132.2(2)
N(1)-C(5)-C(6)	105.2(1)	C(3)-C(6)-C(5)	108.6(1)
C(3)-C(6)-C(7)	122.4(1)	C(5)-C(6)-C(7)	127.4(2)
O(1)-C(7)-C(6)	121.9(1)	O(1)-C(7)-C(8)	112.2(1)
C(6)-C(7)-C(8)	125.9(2)	C(7)-C(8)-C(9)	113.8(2)

(a) Estimated standard deviations in the least significant digits are given in parentheses.