SYNTHESIS OF IPOMEAMARONE VIA THE [2+3] DIHYDROFURAN ANNULATION.

by

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in

Chemistry

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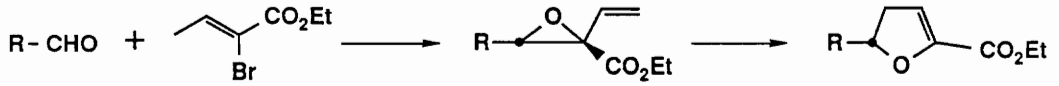
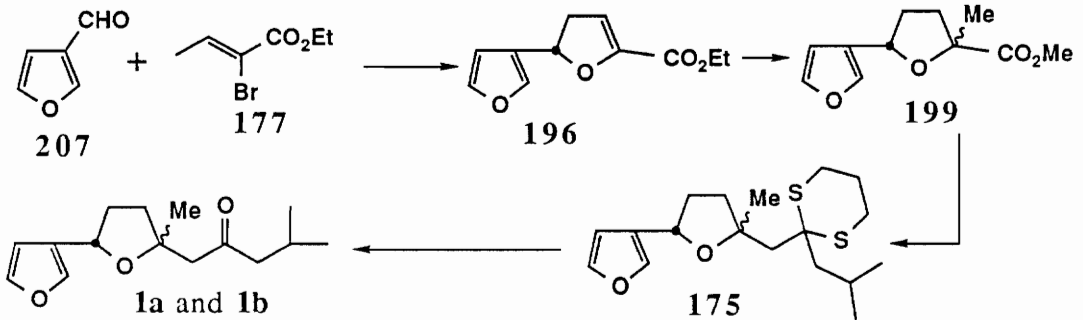
(ABSTRACT)

The synthesis of several dihydrofurans of type **179** was accomplished by the flash vacuum pyrolysis of vinyloxiranes of type **178** obtained from the addition of the dienolate of ethyl-2-bromocrotonate (**177**) to various aldehydes (**176**). Thus, dihydrofurans were prepared from aldehydes in an overall intermolecular [2+3] dihydrofuran annulation.



176 **177** **178** **179**

The utility of this new [2+3] dihydrofuran annulation was demonstrated by its application to the synthesis of ipomeamarone (**1**). The key steps in this synthesis featured the preparation and further elaboration of esters **196** to dithioketals **175** which were converted to ipomeamarone **1a** and epiipomeamarone **1b**.



207 **177** **196** **199** **175** **1a** and **1b**

To my mother and father, Landon and Helen Lovelace

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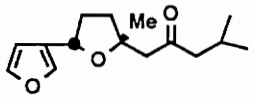
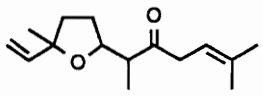
I. INTRODUCTION

Many natural products possess, within their structures, tetrahydrofuran rings of various substitution. Monensin (**3**), nigericin (**4**), davanone (**2**), and ipomeamarone (**1a**) are just a few examples of natural products containing the tetrahydrofuran moiety (Scheme 1). **3** and **4** belong to a class of compounds known as polyether antibiotics[1]. These systems have been found to possess a wide variety of properties of biological importance,[2] some of which include:

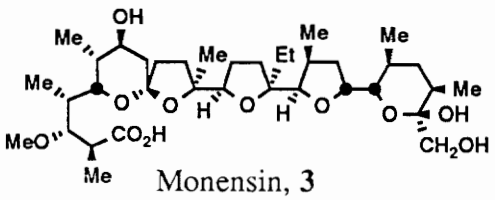
1. Polyether antibiotics possess the ability to transport metal ions across lipid bilayers.[3]
2. Polyether antibiotics are antimicrobial agents, and cause growth promotion in ruminants.[4]
3. Some polyether antibiotics are known to produce cardiovascular responses.[5]



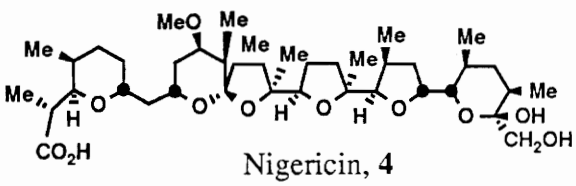
Ipomeamarone, **1a**



Davanone, **2**



Monensin, **3**



Nigericin, **4**

Scheme 1.

Ipomeamarone (**1a**) is a furanosesquiterpene which also has the tetrahydrofuran moiety present in **3** and **4**. The synthesis of these tetrahydrofuran systems may be approached from two general directions. The most direct method is to synthesize the tetrahydrofuran moiety directly with the desired substituents in place,[1] or they may be synthesized via formation of the dihydrofuran. The latter method allows for introduction of substituents after ring formation. What follows is a discussion of methods for the

synthesis of dihydrofurans, including our new approach as well as a demonstration of this new approach in an application to the formal synthesis of ipomeamarone **1a**.

II. HISTORICAL

II.1. Introduction

The history of furan chemistry[6] began in 1780 when Scheele prepared 2-furancarboxcylic acid by the dry distillation of mucic acid. Furan, was not discovered until 1870, when Limpricht heated barium furoate with soda lime.[7] Limpricht assigned the structure of furan as a hydroxy derivative of tetrol (cyclobutadiene) and named it "tetraphenol" (**6**).

5 **6**

Scheme 2

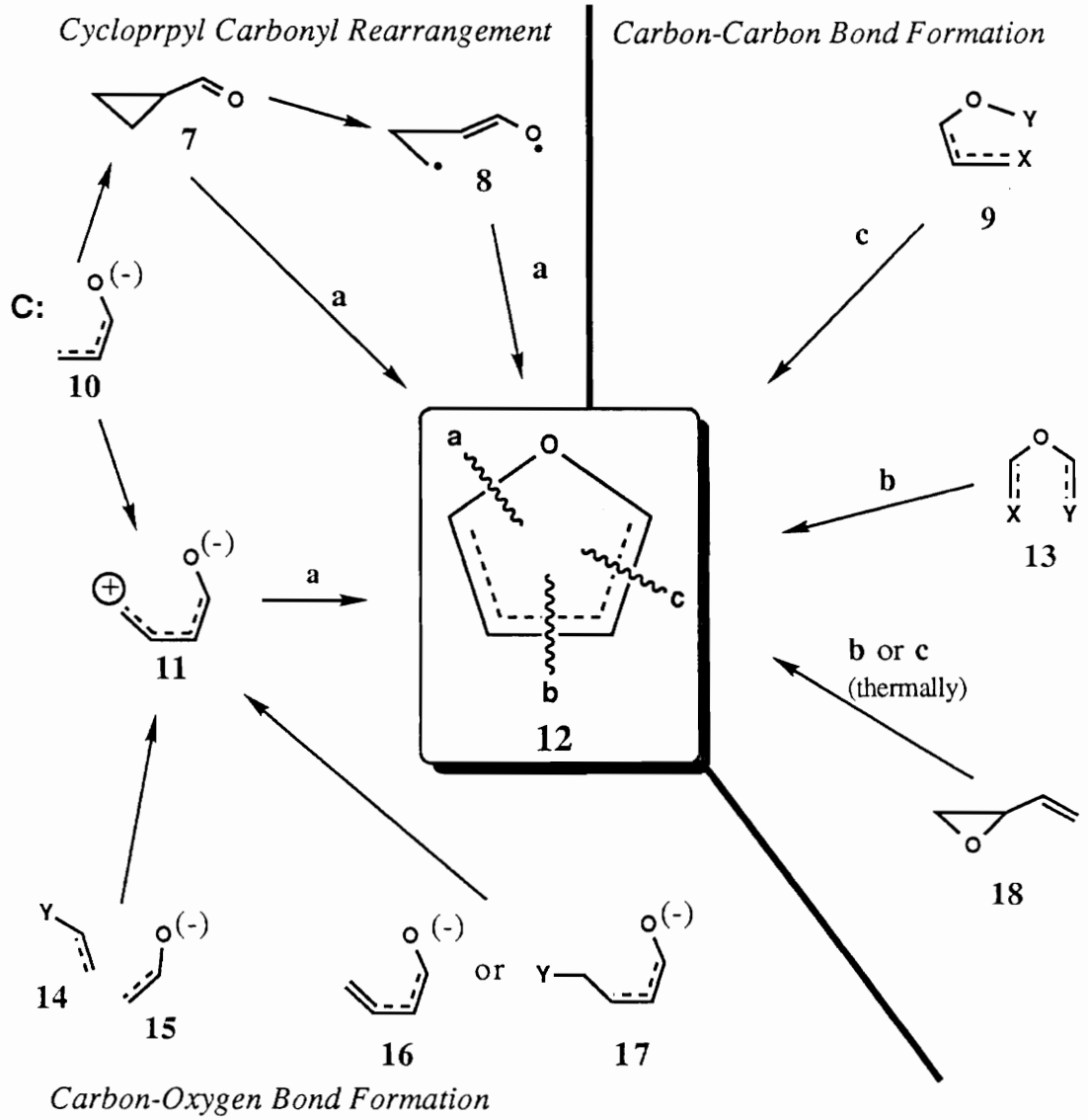
In 1887, the work of Marckwald[8] indicated that the actual structure of furan was **5**. This was supported by Harries'[9] synthesis of furan (**5**) by refluxing an aqueous solution of succinaldehyde.

The first dihydrofuran was reported in 1886, when Henninger[10] prepared 2,5-dihydrofuran by heating erythritol with formic acid. In 1891, Marshall and Perkin[11] identified 5-methyl-2,3-dihydrofuran which they synthesized from ethyl acetoacetate and ethylene bromide. In 1910, Purdie and Arup published the synthesis of 2,2,5,5-tetraphenyl-2,5-dihydrofuran which was prepared from the reaction of magnesium phenyl bromide with methyl methoxysuccinate.[12]

Dihydrofuran synthesis may be achieved through several pathways. These topics are covered in the next section. A separate section follows, and addresses the rearrangement of vinyloxiranes to dihydrofurans and dihydrooxepines. The last section will give information on the isolation, identification, biogenisis, and synthesis of ipomeamarone (**1a**).

II.2. Review of Methods for the Synthesis of Dihydrofurans

Dihydrofuran formations can be separated into two general categories according to the bond formed during the cyclization (Scheme 3). (The dotted lines in Scheme 3 represent a double bond in either position, not a resonance structure. $O^{(-)}$ refers to either a hydroxy group, a ketone, or an oxygen anion.)

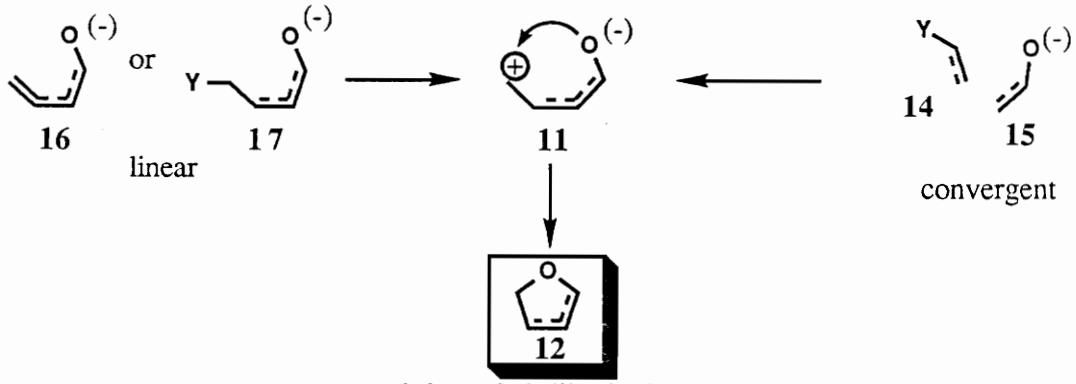


Scheme 3.

The dihydrofuran ring may result from the formation of a bond between a carbon and an oxygen which share a 1,5-disposition. A special case of this category is the rearrangement of cyclopropyl carbonyl compounds. The second category of ring closure involves formation of a bond between two carbons on a chain which are in a 1,5-disposition and are separated by an oxygen in the chain. Included in this second category is the formation of dihydrofurans by thermal rearrangement of vinyloxiranes. Since vinyloxiranes and cyclopropyl carbonyl compounds are topological equivalents, their rearrangements to dihydrofurans will be discussed separately.

II.2.1. Carbon-oxygen bond formation.

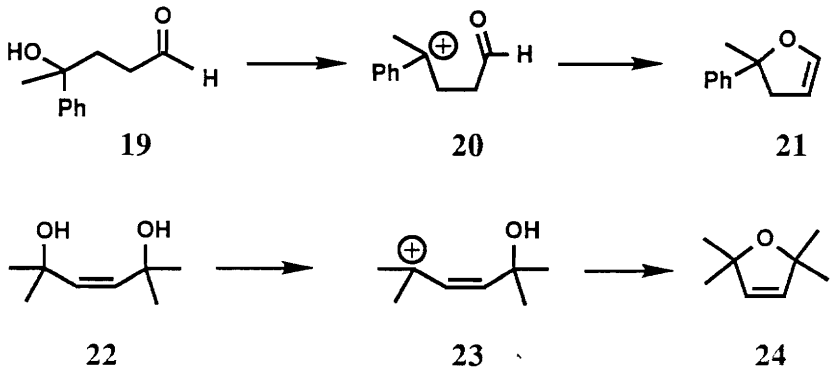
The syntheses of dihydrofurans through carbon-oxygen bond formation proceed through intermediate **11** which may be prepared by one of two methods (Scheme 4). The first method involves intramolecular cyclization of compounds of type **16** or **17**. The second method is the convergent synthesis of intermediate **11** employing systems similar to **14** and **15**.



Scheme 4.

Some intramolecular cyclizations involve the attack of an oxygen nucleophile on a carbocation derived from an alcohol. In this manner Helferich and Gehrke[13] prepared 2-methyl-2-phenyl-2,3-dihydrofuran (**21**) from 4-methyl-4-phenylpentanal (**19**). When **19** was heated to 185 °C, carbocation **20** formed followed by attack of the carbonyl and loss of H^+ to give **21** (Scheme 5).

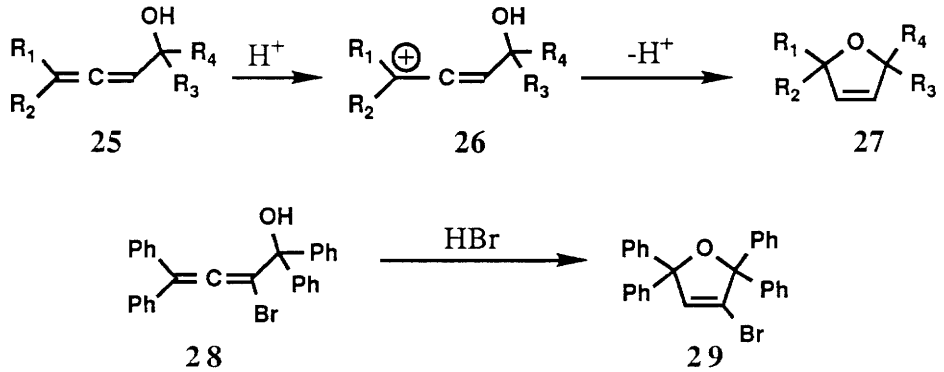
Salkind[14] was able to affect a similar transformation by cyclodehydration of 2,5-dimethyl-2,5-hex-3-enediol (**22**) to form 2,2,5,5-tetramethyl-2,5-dihydrofuran (**24**)(Scheme 5). This occurred during the reduction of the corresponding acetylene derivative of **22**. Later in 1955, Brace[15] reported the synthesis of 2,5-dihydrofuran from *cis*-2-butene-1,4-diol by thermal dehydration using activated alumina as a catalyst.



Scheme 5.

Botteghi[16] has prepared 2,3-dihydrofurans from allylic alcohols via hydroformylation using *trans*-bis(triphenylphosphine)carbonylchlororhodium(I) as a catalyst. The resulting γ-hydroxyaldehydes were dehydrated to form dihydrofurans. Using this method of aldehyde formation has allowed for the synthesis of some optically active dihydrofurans.[17]

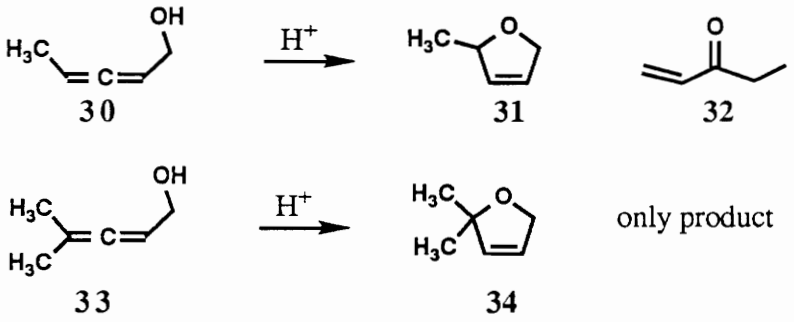
Other intramolecular cyclizations rely on substituted α-allenic alcohols as starting material. In this case, an oxygen nucleophile is attacking a carbocation derived from one double bond of the allene. When these α-allenic alcohols are of type **25** (Scheme 6), carbocation **26** is formed and loss of H^+ leads to dihydrofurans of type **27**. Toda[18] was able to prepare **34** from **33** using catalytic amounts of HBr in acetone.



Scheme 6.

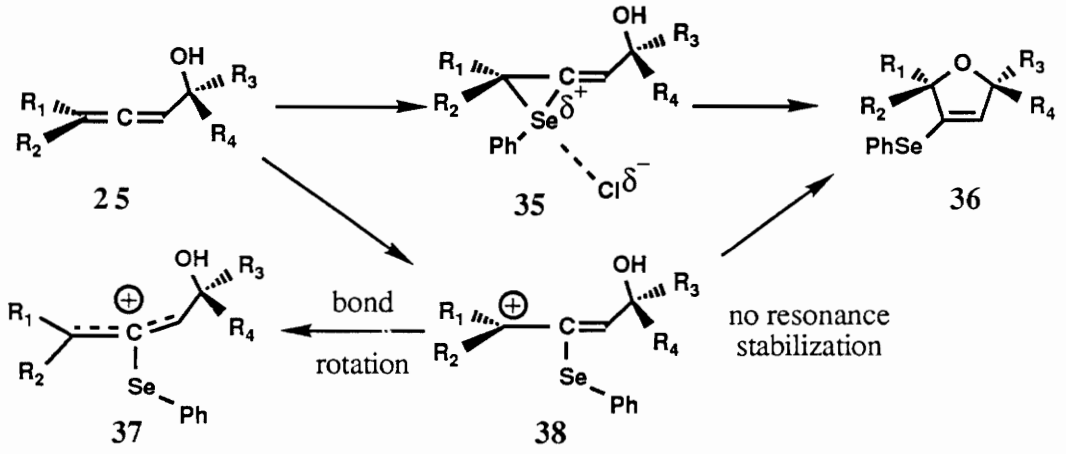
Gelin[19] *et al* reported the effects of substitution on these systems in regard to cation formation (Scheme 7). Unsubstituted or α-substituted α-allenic alcohols gave only

conjugated ketones. β-substituents led to mixtures of aldehydes and ketones. Monosubstitution at the δ-position (**30**) gave mixtures of ketone **32** and dihydrofuran **31** were obtained. Further substitution on the δ-position of **33** led exclusively to dihydrofuran **34**.



Scheme 7.

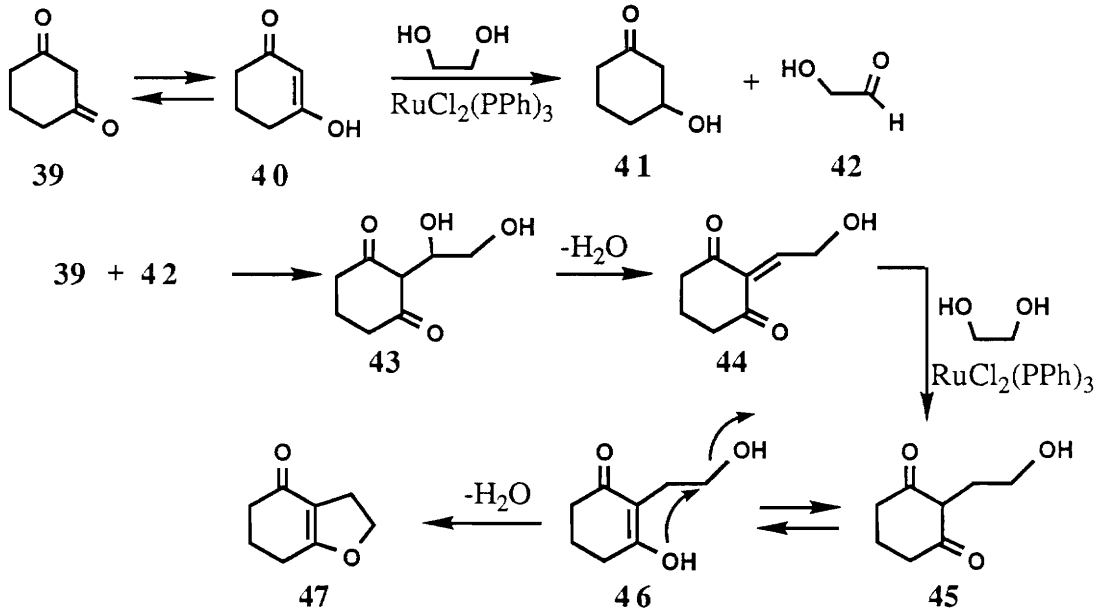
Olsson and Claesson[20] were able to form exclusively dihydrofurans of type **34**, regardless of substitution pattern, through the use of catalytic amounts of silver tetrafluoroborate in chloroform at room temperature (Scheme 7).



Scheme 8.

Beaulieu[21] *et al* achieved a stereoselective synthesis of dihydrofurans from α-allenic alcohols using selenenyl halides as shown in Scheme 8. The proposed mechanism involves the formation of either cyclic intermediate **35** or **38** followed by attack of the

oxygen to form **36**. In the case of **38**, oxygen attack must be faster than bond rotation (leading to resonance stabilized **37**). Formation of **37** would lead to a mixture of products. This reaction was carried out using a variety of substituents with yields ranging from 70 to 98%.



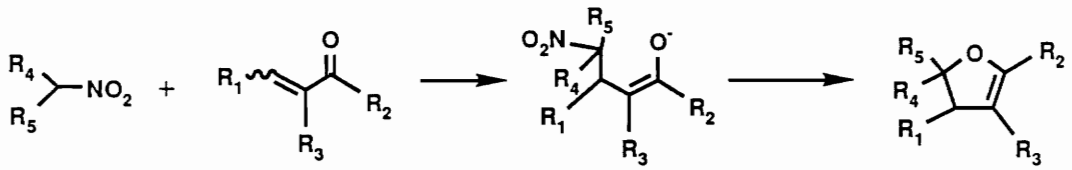
39 **40** **41** **42** **43** **44** **45** **46** **47**

Scheme 9.

Convergent synthesis of intermediate **11** is another method for dihydrofuran synthesis. An excellent example of intermolecular formation of an intermediate similar to **11**, which was reported by Blum,[22] for the synthesis of tetrahydrobenzofuranones. This one pot sequence involved the use of $RuCl_2(PPh_3)_3$ as a catalyst to hydrogenate the double bond of **40** using ethylene glycol as a source of hydrogen (Scheme 9). This led to the formation of **41** and **42**. Aldehyde **42** reacted with another molecule of **39** which, after loss of water was hydrogenated to give **45** and another molecule of **42**. Dehydrocyclization occurs to give **47**. Enol **46** represents **11**. The primary hydroxyl group is the leaving group which is attacked by the enol hydroxy group to form the dihydrofuran.

Several other methods for preparing intermediates similar to **11** have been established. One of these methods is the introduction of methylene to conjugated enones.

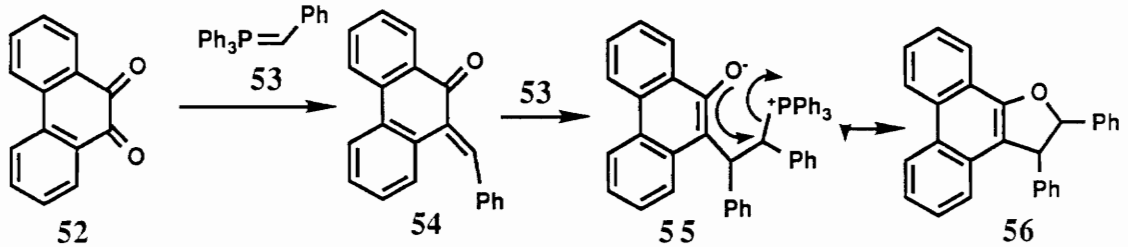
Foucaud[23] found that methylene addition could be carried out using nitroalkanes (Scheme 10.). The reaction was carried out in the presence of alumina supported potassium fluoride with acetonitrile as the solvent. Addition of **48** to **49** led to Michael adduct **50** which closed immediately to **51**. No cyclopropane intermediates were detected by ^{1}H-NMR.



48 49 50 51

Scheme 10.

The introduction of two methylenes in the formation of a intermediate similar to **11** has been performed. In 1969, Sullivan[24] and coworkers reacted 2 eq. of benzylidenetriphenylphosphorane (**53**) with 9,10-phenanthrenequinone (**52**) to yield dihydrofuran **56** (Scheme 11). The first equivalent of **53** reacts with **52** to form **54**. Michael addition of the second equivalent of **53** on **54** followed by O-alkylation with expulsion of triphenylphosphine leads to **56**. The use of *p*-bromobenzylidenetriphenylphosphorane led to the corresponding dibromide.

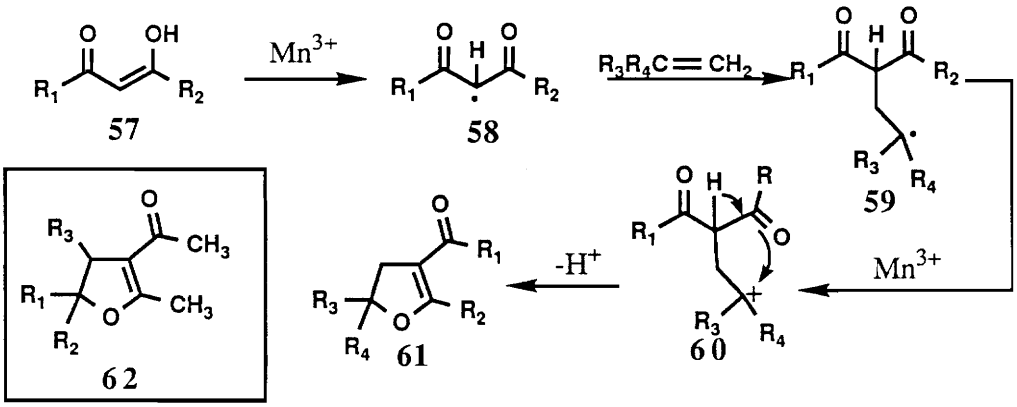


52 54 55 56

Scheme 11.

Another method for the construction of intermediate **11** involved the addition of an

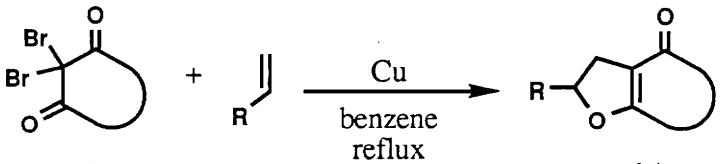
olefin α to a ketone. Heiba[25] and Dessau used manganic acetate with 1,3-dicarbonyl compounds and terminal olefins to form dihydrofurans via a free-radical mechanism as shown in Scheme 12. Oxidation of **57** followed by the addition of the olefin led to radical **59** which underwent further oxidation to yield cation **60**. Loss of H^+ resulted in cyclization to dihydrofuran **61**. This reaction was carried out using both alkyl and aryl substiuents for R_{1-4} with yields ranging from 10 to 100%. Nishino[26] prepared **62** (R_1=R_2=CH_3) by the reaction of **58** with substituted olefins.



57 58 59 60 61 62

Scheme 12.

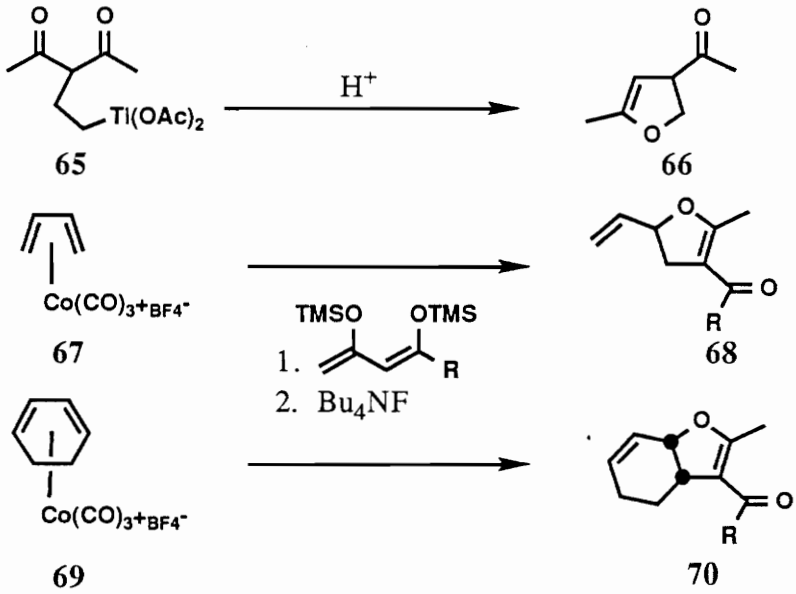
Kawabata[27,28] has reported the synthesis of 2,3-dihydrofurans by reductive debromination of **63** using copper powder to form the diketo carbene intermediate (Scheme 13). This intermediate acts as a diradical and adds to the olefin to give a freely rotating diradical intermediate which cyclizes at the carbonyl oxygen to form dihydrofuran **64**. This sequence was carried out using different olefins and 2,2-dibromo-1,3-diketones with yields ranging from 26 to 96%.



63 64

Scheme 13.

Ichikawa[29] prepared **66** (Scheme 14) by the reaction of acetylacetone and the oxythallate of ethylene. The initially formed diketone **65**, upon protonation, cyclized to **66** via one of two pathways. Either S_N2 displacement of the thallate by the hydroxy oxygen (from the enol form) would lead directly to **66** or by a second possible mechanism, the formation of a primary carbocation from the loss of AcOH and TlOAc, followed by ring closure. Ichikawa also prepared dihydrofurans using palladium-olefin[30] and lead-olefin[31] complexes.



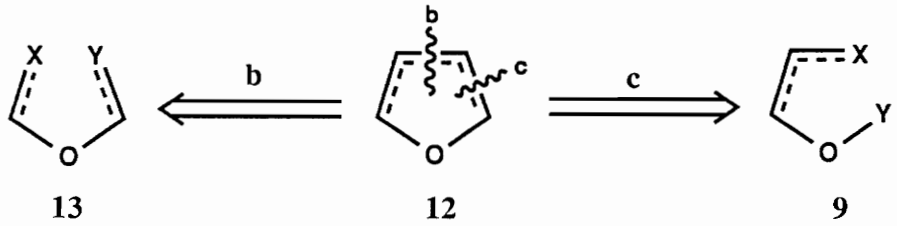
Scheme 14.

Barinelli and Nicholas[32] prepared both dihydrofurans (**68**) and tetrahydrobenzofurans (**70**) by the reaction of 1,3-bis(siloxy) dienes with π–complexes **67** and **69** respectively (Scheme 14.).

The synthesis of dihydrofurans through the formation of a carbon-oxygen bond has been exploited for many years. The linear synthesis of compounds leading to intermediates of type **11** was the earliest method. Later, convergent syntheses for the formation of **11** became available. At the same time, syntheses of dihydrofurans through the formation of carbon-carbon bonds began to emerge.

II.2.2. Carbon-carbon bond formation.

Dihydrofuran synthesis via ring closure between two carbons can be carried out in two ways as shown in Scheme 15. (Again, The dotted double bonds are intended to show possible positions of the double bond, not resonance structures.) **12** may be opened retrosynthetically by cleavage through pathway **b** or **c**. Cleavage through pathway **b** would result in **13** where either **X** is a carbon possessing a negative charge and **Y** possesses a positive charge (or visa versa, depending on substitution pattern). Attack of **X** on **Y** (or visa versa) would form a bond β to the oxygen in the dihydrofuran ring. Cleavage through pathway **c** would lead to **9** where **X** and **Y** now close to form a bond α to the oxygen in the dihydrofuran ring.



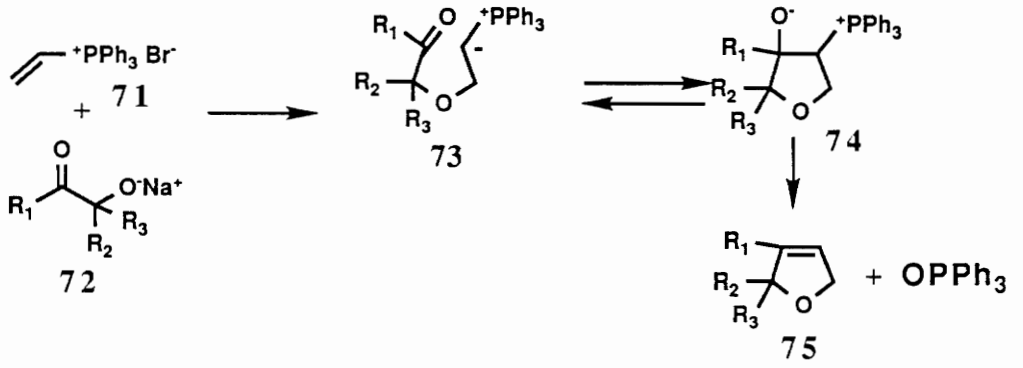
13 **12** **9**

Scheme 15.

The conversion of vinyloxiranes to dihydrofurans by thermolysis generally proceed through pathway **c**. Examples of this rearrangement will be presented in Section II.3 (p. 21). Non-thermolytic syntheses of dihydrofurans through pathway **b** or **c** are presented here.

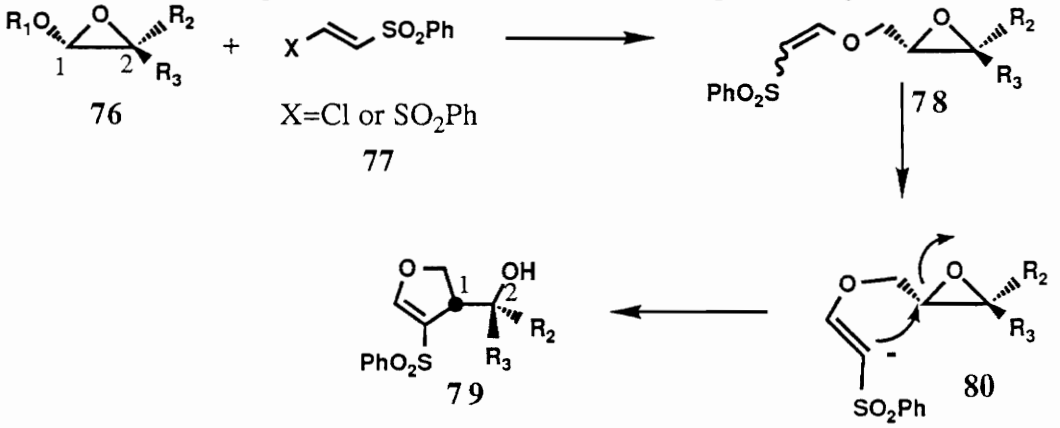
Schweizer reported the synthesis of several 2,5-dihydrofurans by the reaction of α-hydroxy ketones with vinyltriphenylphosphoniumbromide (**71**) as shown in Scheme 16.[34] This is an example of ring closure by pathway **a**. The sodium salt of **72** was prepared by the reaction with sodium hydride in anhydrous ether. **71** was added in dimethylformamide, and the reaction stirred at room temperature or with heating. Intermediate **73** contains a carbon with a negative charge which attacks the carbon with a

leaving group (a formal positive charge on the carbon). The double bond is formed when the oxygen anion and the triphenylphosphine cation are expelled as neutral triphenylphosphine oxide. Several systems were examined and the yields ranged from 7 to 71%.



Scheme 16.

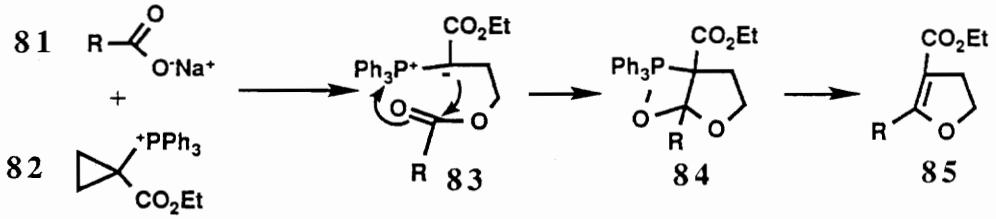
McCombie[35] prepared dihydrofurans of type **79** (by pathway **a**) using vinyl anions of 3-(phenylsulfonyl)vinyl ethers of 2,3-epoxyalcohols (**78**) with good yields. This reaction was found to be stereospecific with inversion at C-2 of the epoxide ring.



Scheme 17.

Dauben's synthesis of dihydrofurans proceeds via an intramolecular wittig reaction with carboxcylic salts via pathway **b** (Scheme 18).[36] Reaction of sodium salt **81** with **82** leads to the formation of ylide **83** which further rearranges to **85**. This reaction was

carried out using a variety of substituents and the yields were generally good. Intermediate **83** contains a carbon anion which attacks the carbonyl to close the ring. This mechanism is the same as that presented in Scheme 16, however, ring closure occurs α to the oxygen in the ring.



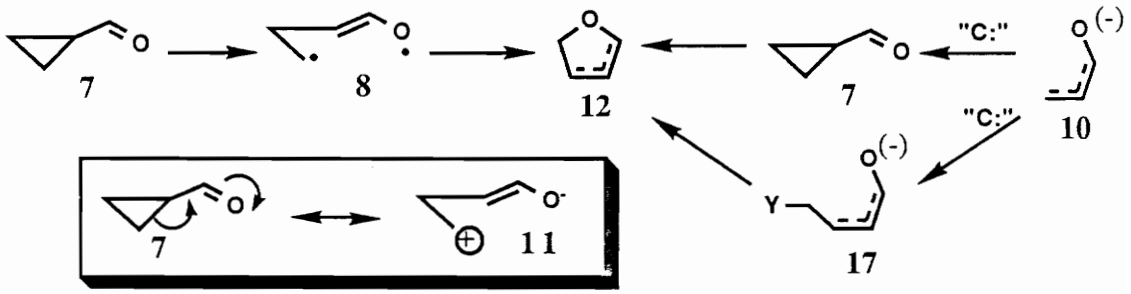
56 to 93% when R=H,CH_3,Ph,PhCH=CH

Scheme 18.

Le Corre also found that ylides of type **83** underwent dihydrofuran formation (pathway **b**) in yields comparable to those published by Dauben.[37] Alternatively, when these ylides were treated with *t*-BuOK in *t*-BuOH, cyclopropyl ketones were formed.

II.2.3. Rearrangement of Cyclopropyl Carbonyl Compounds.

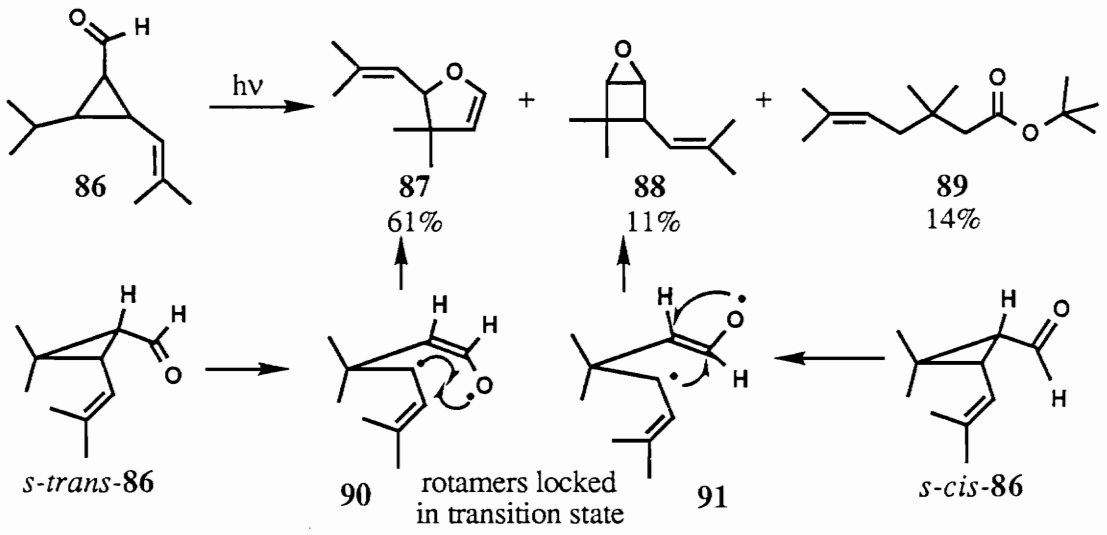
Dihydrofuran synthesis from cyclopropyl carbonyl compounds may proceed through either a biradical or a nonradical intermediate. The nonradical intermediates possible are **7** and **17** which are both equivalent to **11**. Structures **7** and **11** are equivalent through resonance. **17** is equivalent to **11** because of the formal positive charge on the carbon bearing **Y** (a leaving group).



Scheme 19.

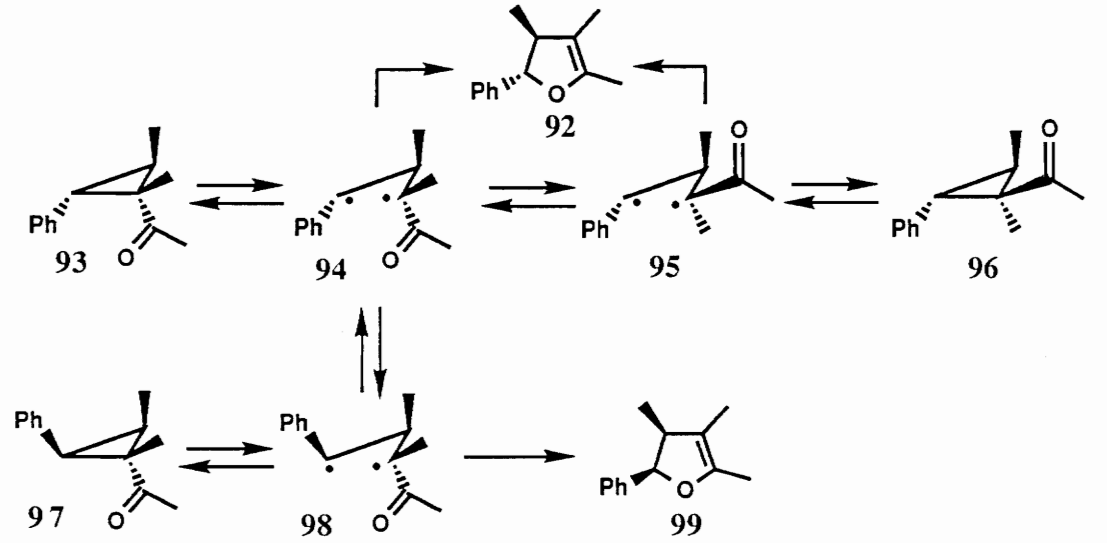
The thermal or photochemical conversion of cyclopropyl carbonyl compounds to dihydrofurans is thought to proceed by a biradical intermediate such as **8**. In 1947, Wilson[38] established that thermal interconversion of cyclopropane aldehyde and 2,3-dihydrofuran could be carried out, however the equilibrium lies toward the formation of the aldehyde.

Dauben and Shaffer[39] found that cyclopropane **86**, upon photolysis in *t*-butanol, rearranged to **87**, **88**, and **89** (Scheme 20). They reasoned that the cyclopropane ring would be cleaved to give the more stable allylic radical which could rearrange to either **90** or **91**, depending on stereochemistry, and close to either **87** or **88** respectively.



Scheme 20.

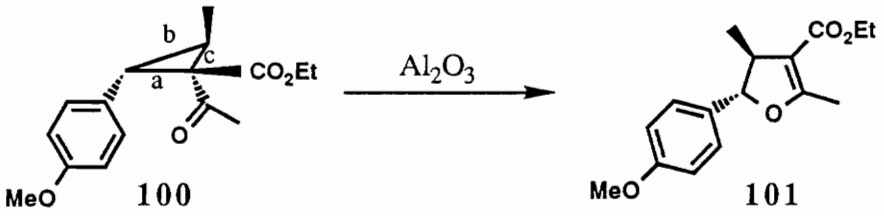
McGreer and McKinley[40] later published the details of the conversion of **93**, **97**, and **96** to both **99** and **92** using either photolytic or thermal conditions. They propose that these interconversions proceed by ring cleavage followed by isomerization and then ring closure to either a cyclopropane or dihydrofuran as shown in Scheme 21.



Scheme 21.

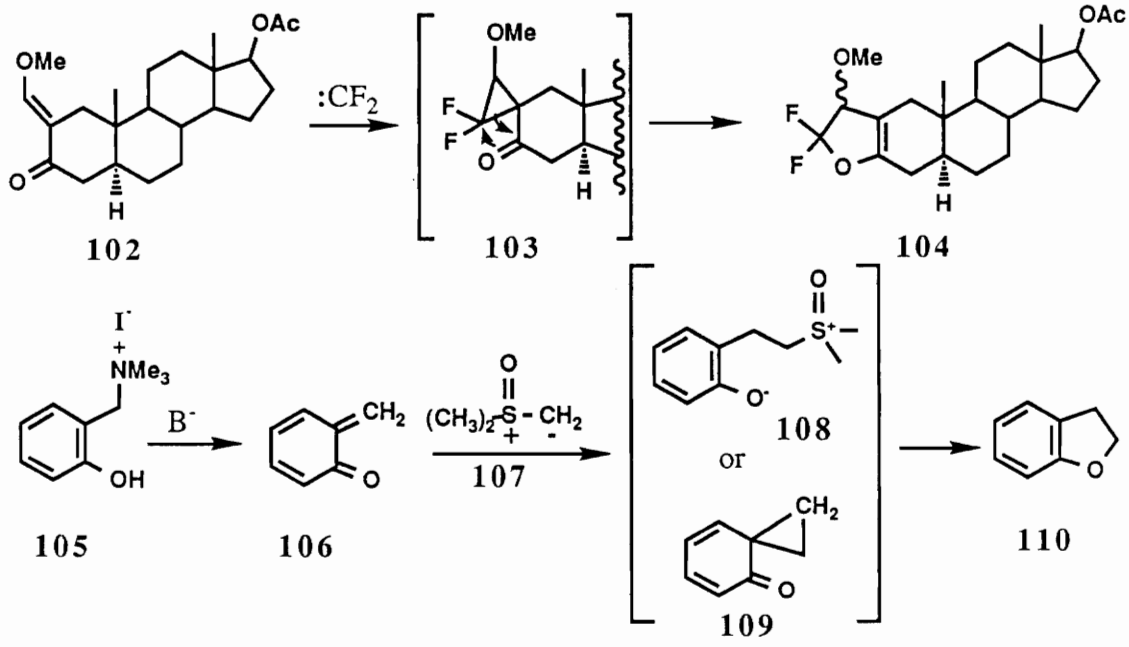
In 1980, Alonso and Morales[41] published the first Lewis acid assisted rearrangement of cyclopropyl ketones to dihydrofurans. This transformation was also found to be

stereospecific with retention of the cyclopropane configuration, indicating cleavage of bond **a**. Using this procedure, they were able to prepare **101** from **100** stereospecifically as shown in Scheme 22.



Scheme 22.

Hodge[42] reported the synthesis of 2,3-dihydrofurans via the reaction of "difluoromethylene" with conjugated enones. **102** was treated with twelve equivalents of "difluoromethylene" (generated by thermal decomposition of sodium chlorodifluoroacetate) in refluxing diglyme to afford **104** in a 70% yield as a mixture of diastereomers (Scheme 23). Based on work by Beard[43,44] in which "difluoromethylene" was added to

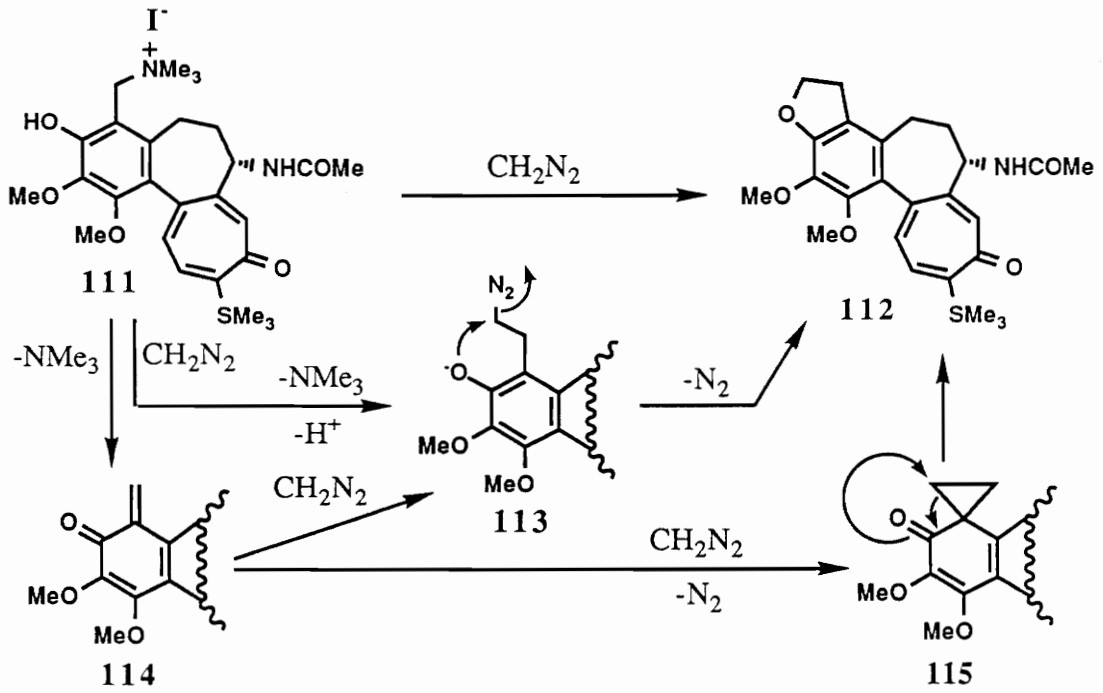


Scheme 23.

enones and dienones to give cyclopropanes, it seems reasonable that this reaction proceeds

through intermediate **103**. Attack of the carbonyl oxygen on the cyclopropyl ring causes ring cleavage to lead to dihydrofuran **104**.

Breuer[45] performed a similar transformation by the treatment of *o*-benzoquinone methide (**106**) (prepared *in situ* from *o*-hydroxy benzyltrimethylammonium iodide (**105**)) with dimethyl sulfoxonium methylide (**107**) to yield **110** in a 42% yield (Scheme 23). Breuer suggested that this reaction proceeds by intermediate **108**, however, he had no data to rule out **109**.



Scheme 24.

Blade-Font[46] reacted diazomethane with the Mannich methiodide of 3-demethylthiocolchicine (**111**) and was able to prepare dihydrofuran **112**. Three mechanisms were proposed for this reaction as shown in Scheme 24. Diazomethane can react with **111** in two ways. First, S_N2 displacement of the trimethylamine group followed by loss of H^+ would lead to **113**, which can cyclize if the oxygen attacks the

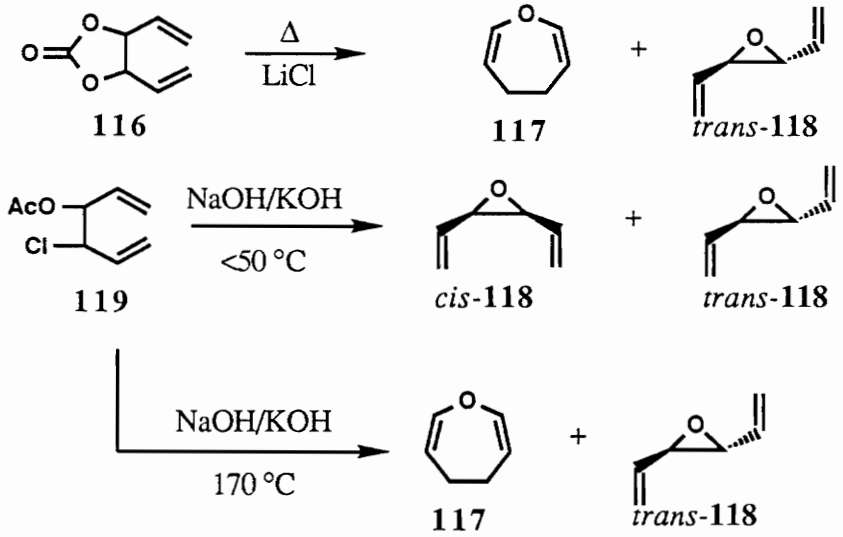
carbon bearing a leaving group, in this case, molecular nitrogen. Second, diazomethane, acting as a base, abstracts the phenolic hydrogen causing the expulsion of the trimethylamine. The addition of another molecule of diazomethane would lead to **113**, which would close to dihydrofuran **112**. Aternatively diazomethane may add to **114** to form cyclopropyl ketone **115**. Attack of the oxygen on the cyclopropyl ring followed by rearomatization of the phenyl ring would give **112**.

One other method for the synthesis of dihydrofurans through carbon-carbon bond formation exists, that is, the thermal rearrangements of vinyloxiranes.

II.3. Rearrangement of Vinyloxiranes to Dihydrofurans and Oxepines.

The synthesis of dihydrofurans by thermolysis of vinyloxiranes occurs through the cleavage of the carbon-carbon bond by pathway **c** (Scheme 15, page 13). When divinyloxiranes are subjected to thermal conditions, vinyldihydrofurans and/or dihydrooxepines are formed depending on the stereochemistry of the starting oxirane. Elucidation of the mechanism was carried out by the study of divinyloxirane rearrangement and this will be discussed first.

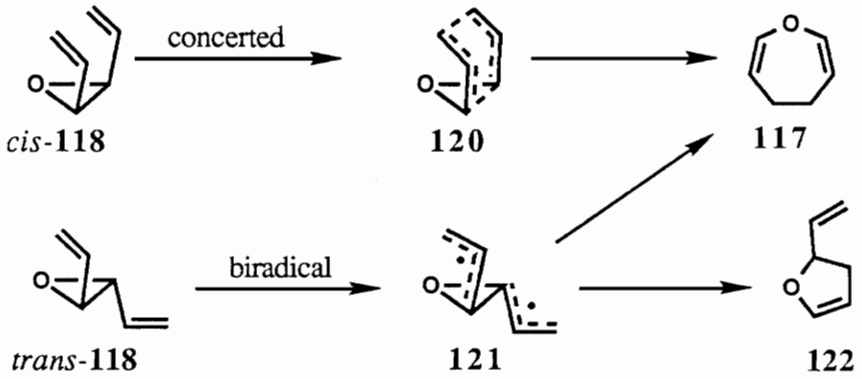
Braun[47] found that pyrolysis of **116** at 200 °C using LiCl led to the formation of **117** and *trans*-**118** (Scheme 25). Braun had expected to obtain two divinyloxiranes and reasoned that **117** arose from *cis*-**118** through a Cope rearrangement.



Scheme 25.

Stogryn[48] prepared **117**, *cis*-**118**, and *trans*-**118** by heating **119** in an aqueous solution of NaOH and KOH (Scheme 25). When the temperature was maintained below 50 °C, both divinyloxiranes were formed in a *cis:trans* ratio of 1:2. Only traces (1-2%) of **117** were observed. When the reaction was carried out at 170 °C or higher, only *trans*-**118** and **117** (2:1) were formed. When a mixture of *trans*-**118**, *cis*-**118**, and **117**

(64.4%, 27.8%, and 7.8% respectively) was heated on a steam bath overnight, *cis*-**118** rearranged to **117** while *trans*-**118** remained largely unreacted. (The composition of the product of this reaction was 61.8% *trans*-**118** and 38.2% **117**.) In addition, reaction of *trans*-**118** (93% pure) in a sealed tube at 230 °C for 17 h resulted in a mixture of starting material (48.3%) and **117** (42.9%). Under identical conditions, **117** was recovered unchanged.

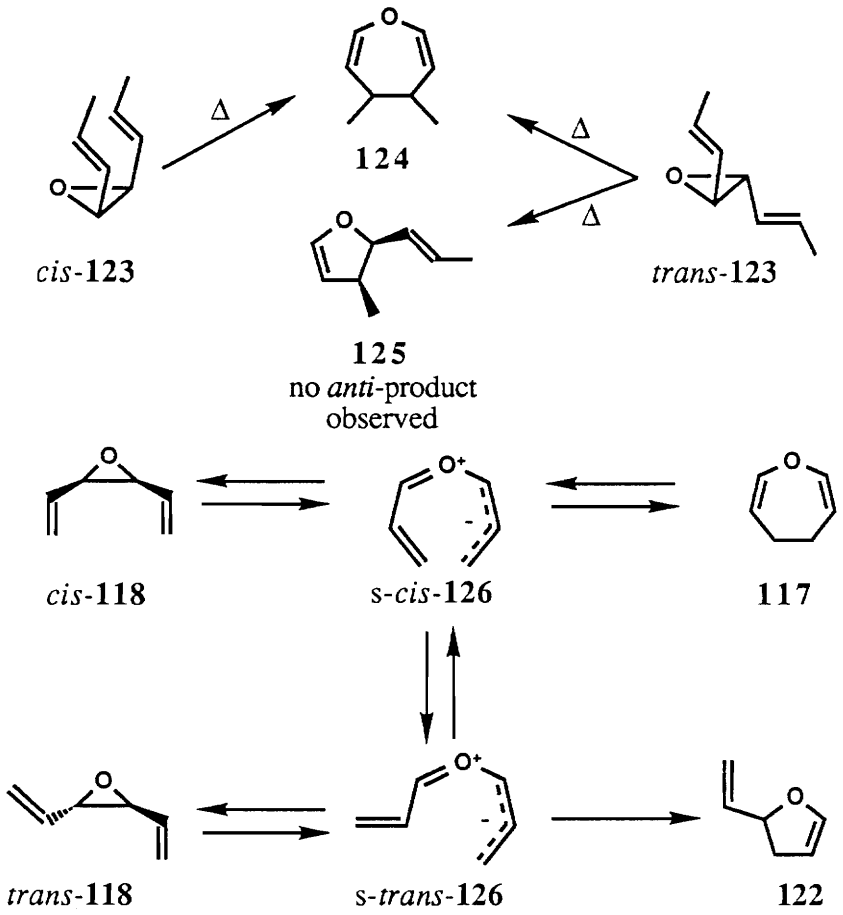


Scheme 26.

Vogel[49] studied the thermal rearrangement of *trans*-**118** and found an additional product in the reaction mixture (Scheme 26). This was identified as 2-vinyl-2,3-dihydrofuran (**122**) marking the first preparation of a dihydrofuran using this method. Vogel proposed biradical intermediate **121** because of the high isomerization temperatures and the observed branching of the reaction. Based on thermodynamic data obtained for both *cis*-**118** and *trans*-**118**, it was concluded that *cis*-**118** concerted rearrangement (through a boat transition state) while the rearrangement of *trans*-**118** proceeds by a biradical mechanism.

Pommelet *et al.*[50] subjected substituted divinyloxiranes *cis*-**123** and *trans*-**123** (Scheme 27) to thermal conditions and found that *cis*-**123** was converted to **124** at 100 °C. When *trans*-**123** was heated to 350 °C, dihydrooxepine **124** and dihydrofuran **125** were formed. No *anti*-**125** was observed, which would be expected if the mechanism involved

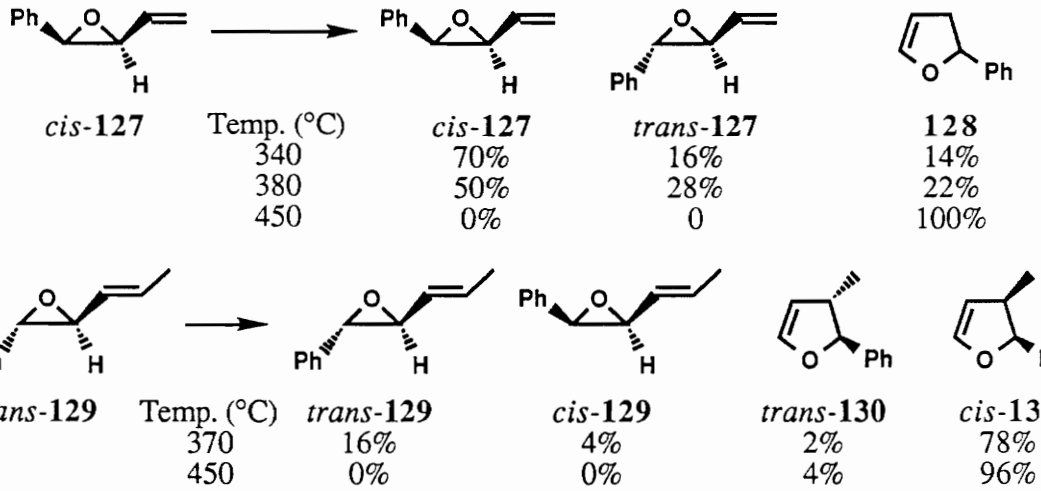
biradicals.



Scheme 27.

Further[51] study of led to the conclusion that both the *cis* and *trans*-divinyloxiranes underwent rearrangement by electrocyclic closure of ylides through the mechanism shown in Scheme 27. Oxirane *cis*-**118** would, upon cleavage of the carbon-carbon bond in the epoxide ring, form intermediate s-*cis*-**126** which was able to react in two ways. An electrocyclic ring closure (8πe) would result in **117**. Bond rotation would result in s-*trans*-**118** which was also formed by carbon-carbon bond cleavage of *trans*-**118**. s-*trans*-**126** cannot undergo an 8πe ring closure because the double bond has rotated out of place, however, a 6πe ring closure is possible which leads to **122**.

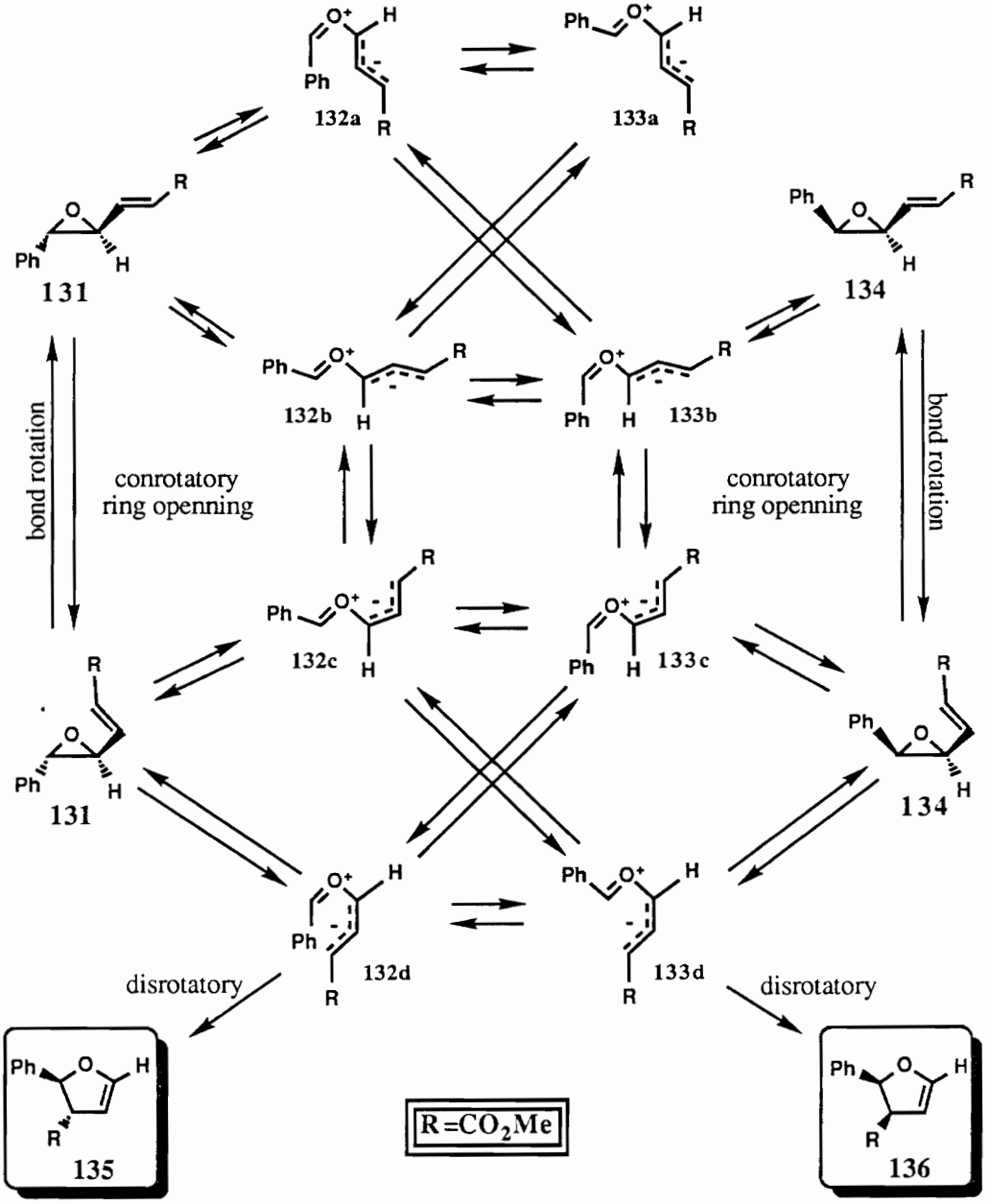
The mechanism for the thermal rearrangement of vinyloxiranes to dihydrofurans has been studied extensively.[52-55] Unlike vinylcyclopropanes or cyclopropyl carbonyl compounds which generally react by a biradical intermediate, the pathway for rearrangement of vinyloxiranes is thought to proceed through ylide intermediates. Crawford[52] found that optically pure 2-vinyloxirane underwent racemization 72 times faster than *cis-trans*-isomerization indicating that the process involves enantiomerization and not diastereomerization. He rationalized this in terms of ring opening to a carbonyl-ylide followed by reclosure. Both steps would be conrotatory leading to either the starting material or its enantiomer. A small entropy of activation (+2.1 eu) was found which is reasonable since the activation process not only involves the breaking of the carbon-carbon bond, a process expected to give a positive entropy of activation, but also involves the loss of rotation about the vinyl bond by allylic resonance.



Scheme 28.

Chuche[56] studied the rearrangement of **127** and **129** during gas phase thermolysis (Scheme 28). At lower temperatures, *cis*-**127** underwent isomerization and rearrangement. At higher temperatures only rearrangement occurred. Thermolysis of *trans*-**129** led to a 96:4 mixture of dihydrofurans at either temperature with a small amount of isomerization of

trans-**129** occurring at lower temperatures. Thermolysis of *cis*-**129** yielded both *cis*-**130** and *trans*-**130** in a 95.5:4.5 ratio respectively.

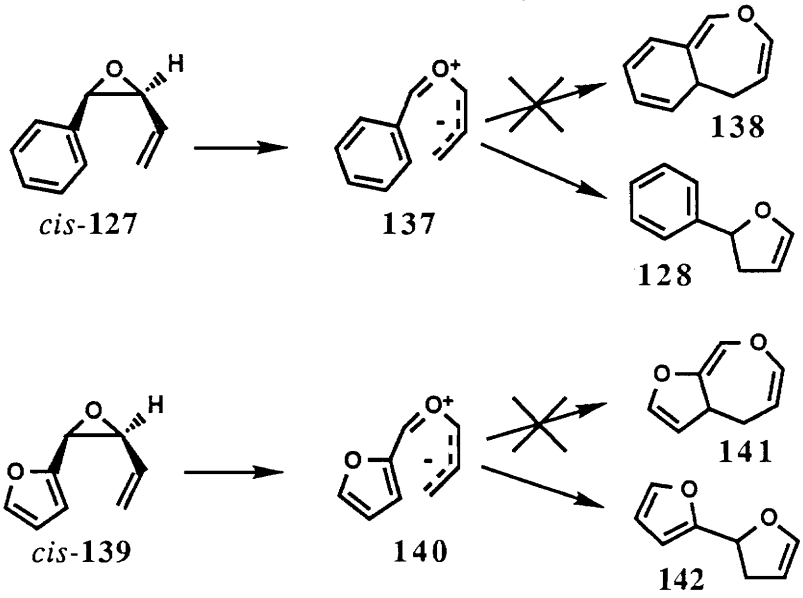


Scheme 29.

An example of the proposed mechanism is shown in Scheme 29.[53] Both **131** and

134 can adopt two conformations. Thermal ring opening (4πe, conrotatory) would result in intermediates **132a-d** and **133a-d.** These intermediates can interconvert through a series of bond rotations to **131** or **134**, however, only **132d** and **133d** possess the proper conformation to undergo ring closure (6πe, disrotatory) to dihydrofurans **136** and **135.**

Chuche[57] also examined the use of vinyloxiranes such as **127** and **139** in the preparation of dihydrooxepines (Scheme 30 showing *cis*-oxiranes only). In both cases, *cis*/*trans* isomerisation of the oxiranes and dihydrofuran formation were the only events observed. Additional substitution on the double bond gave similar results.



Scheme 30.

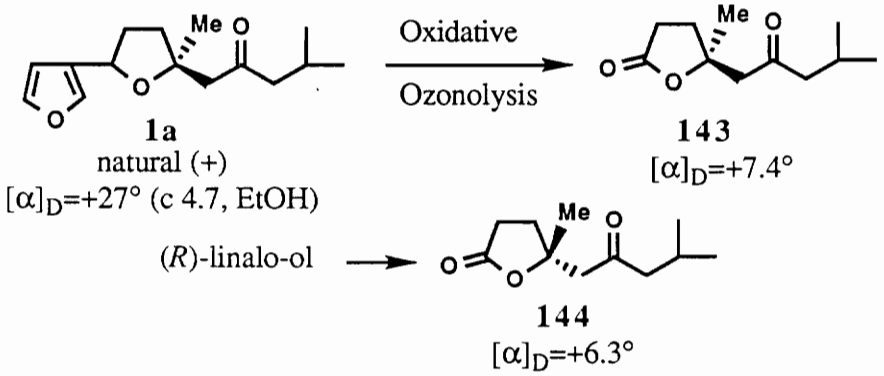
II.4. Ipomeamarone

II.4.1. Isolation and structure

(+)-Ipomeamarone was first isolated by Hiura in 1943 from the sweet potato *Ipomea batatas*.[58] Its enantiomer, (-)-ngaione, was first isolated from the leaves of the Ngaio tree (*Myoporum loetum*) in 1961.[59] (-)-Ngaione was also isolated from several varieties of the shrub *Myoporum deserti*.[60]

In 1956, Kubota and Marsuura[61] determined the structure and relative stereochemistry of **1a** by total synthesis (See Section II.4.2., p 29). At this time, Kubota concluded that ipomeamarone and ngaione were enantiomers by the comparison of both natural samples (and semicarbazones) with the synthesized racemate.

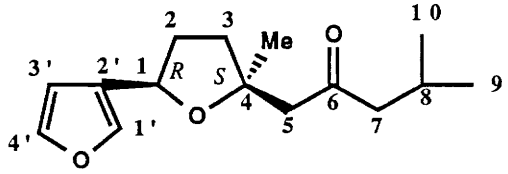
Kubota *et al* [62] later assigned C-4 as *R* by oxidative ozonolysis to afford ipomolactone (**143**)([α]$_D$=+7.4°)(Scheme 31). This conclusion was made after the rotation of **144** prepared from (*R*)-linalo-ol was found to be positive also ([α]$_D$=+6.3°). Accordingly, C-4 was assigned the *R* configuration. In view of the *trans*-relationship of the furyl and methyl substituents, Kubota concluded that **1a** had a 1*S*,4*R* chirality.



Scheme 31.

However, Sutherland[63] rejected Kubota's findings when oxidative ozonolysis resulted in a racemic mixture of lactone **143** ([α]$_D$=-0.05°). Sutherland attributed the optical

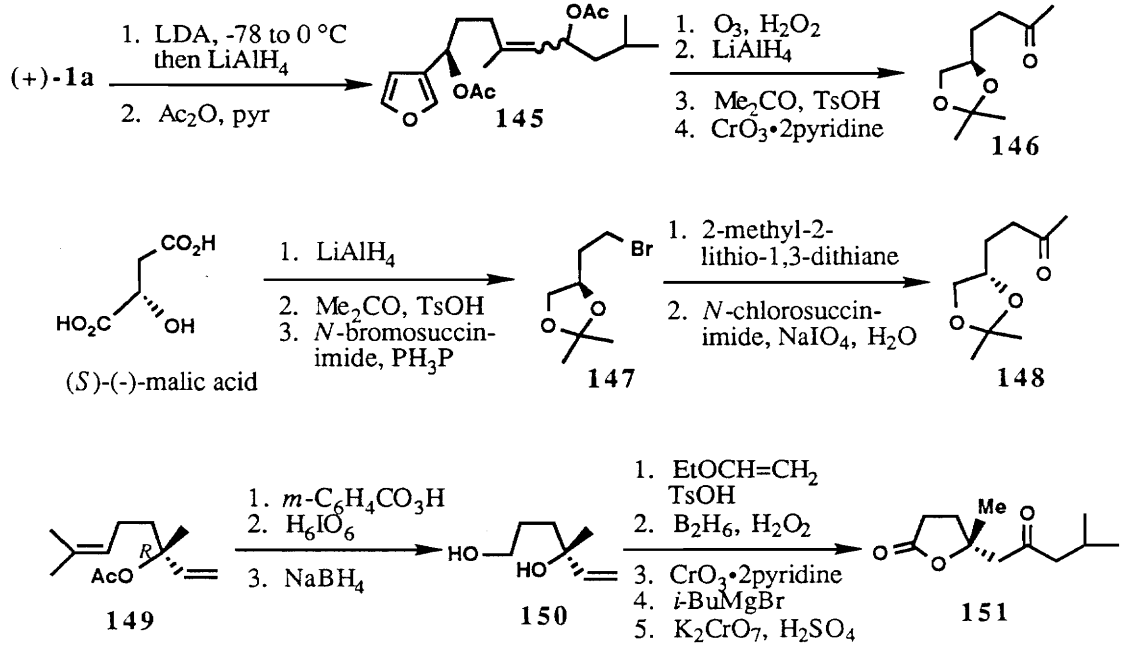
rotation found by Kubota to the presence of an optically active impurity.



(+)-1a

Scheme 32.

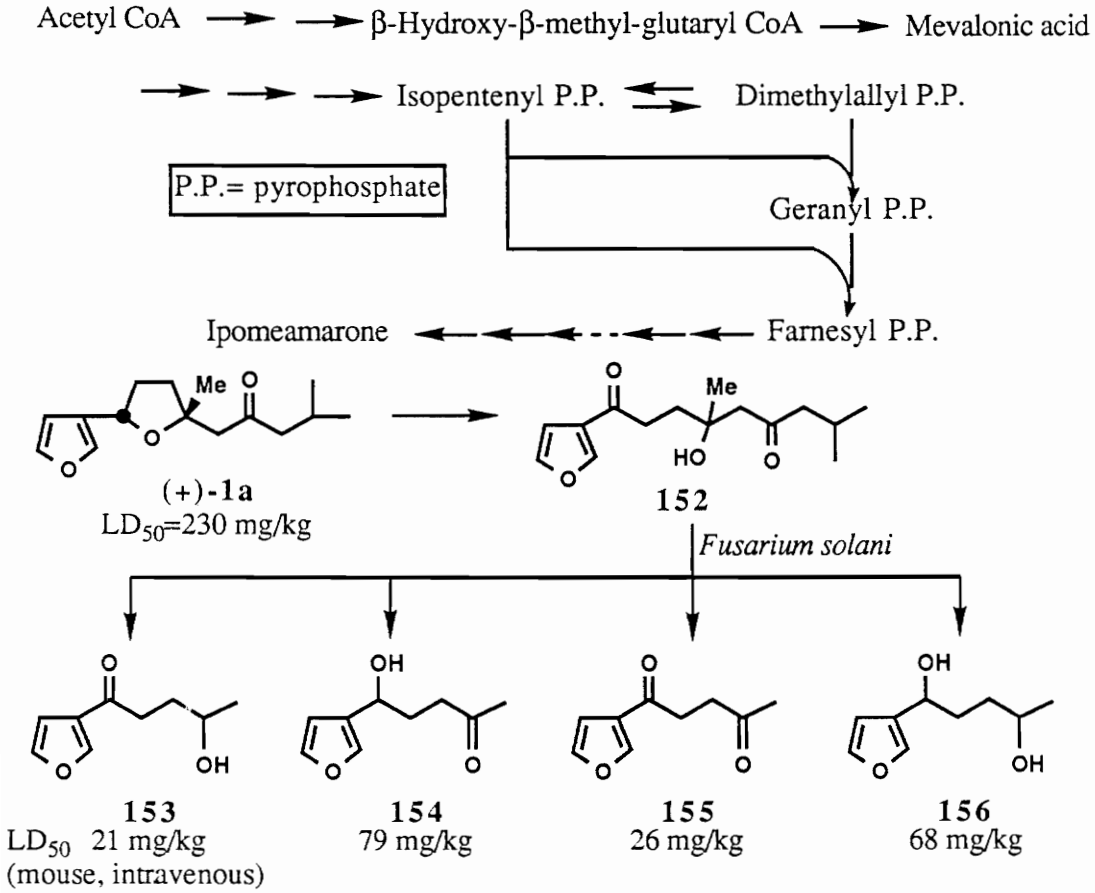
The absolute configuration was unambiguously determined to be 1*R*-4*S* by Nakanishi in 1983[64] as shown in Scheme 32. The absolute stereochemistry at the C-1 center was established by the synthesis of **146** ($[\alpha]_D$=+3.2°) from natural **1a** and **148** ($[\alpha]_D$=-2.8°) from (*S*)-(-)-malic acid (Scheme 33). The absolute stereochemistry of the C-4 center was determined by the synthesis of **144** ($[\alpha]_D$=-5.4°) from (*R*)-(-)-linalyl acetate (**148**) and comparison with **143** ($[\alpha]_D$=+5.0°) derived from the oxidative ozonolysis of natural **1a**. The optical rotation of **143** obtained by Nakanishi agrees with that of Kubota.[62]



Scheme 33.

II.4.2. Biogenesis

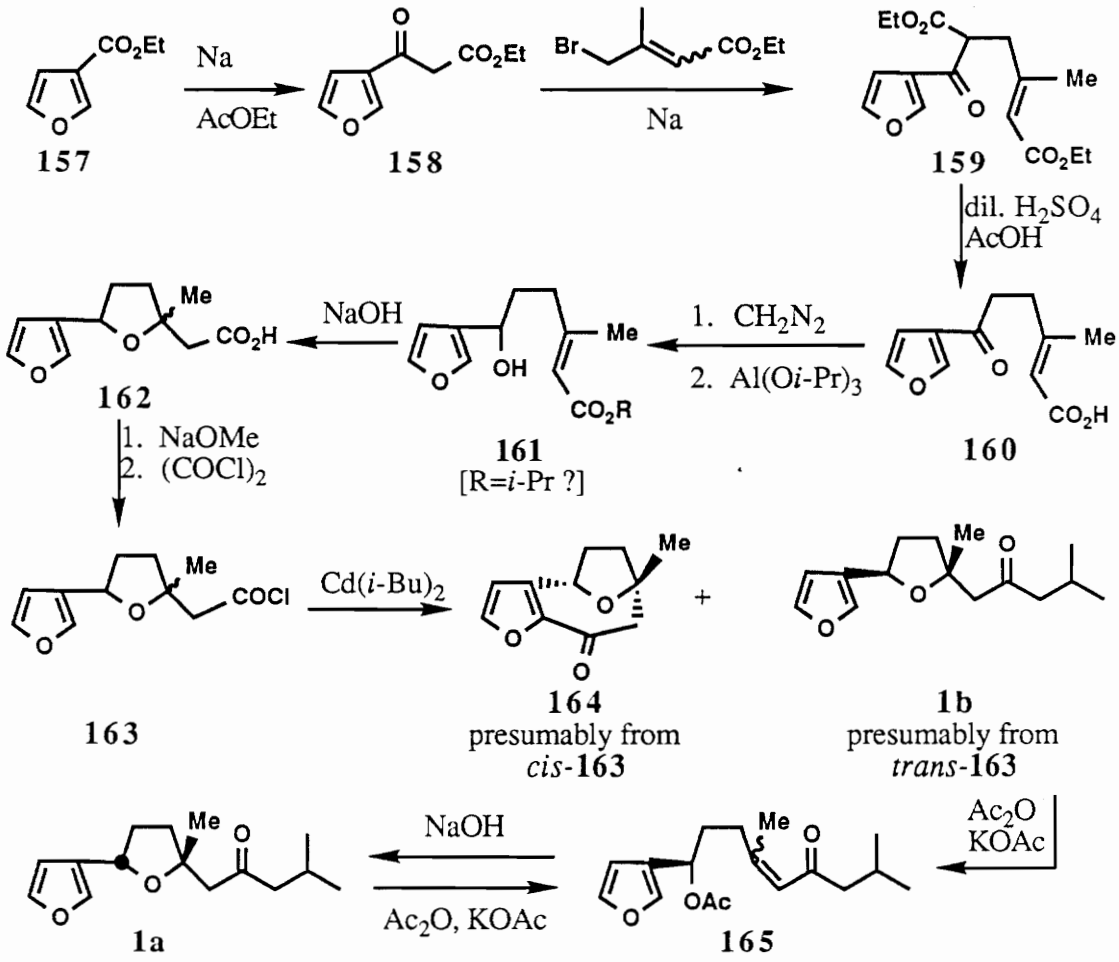
Uritani and coworkers have studied the biosynthesis of ipomeamarone extensively.[65] They concluded that **1a** is synthesized by the sweet potato root (in response to infection of *Ceratocystis fimbrata*) from both acetyl CoA and leucine via a connected pathway (Scheme 34).[66] Evidence supporting this pathway include the incorporation of: Acetate-2-^{14}C;[67] Mevalonate-2-^{14}C;[68] Farnesol-2-^{14}C;[66] and, Leucine-U-^{14}C[65] into **1a**. The study[65] involving Leucine-U-^{14}C showed that incorporation took place by both directly, and by incorporation of Leucine-U-14C through acetyl CoA. Burka and Kuhnert[69] found that **1a** was further metabolized to 4-hydroxymyoporone (**152**) which is a precursor to several lung toxins[70] shown in Scheme 34.



Scheme 34.[71]

II.4.3. Synthesis

Ipomeamarone (**1a**) has been synthesized on three different occasions and in all cases, no stereoselectivity was obtained. The first synthesis was reported by Kubota and Matsuura[72] in 1956 as shown in Scheme 35. Kubota concluded the **162** was a mixture of *cis* and *trans* isomers based on the fact that the acids would not crystallize. (**161** was crystalline (m.p.=104-105 °C) and was assumed to be one isomer.)

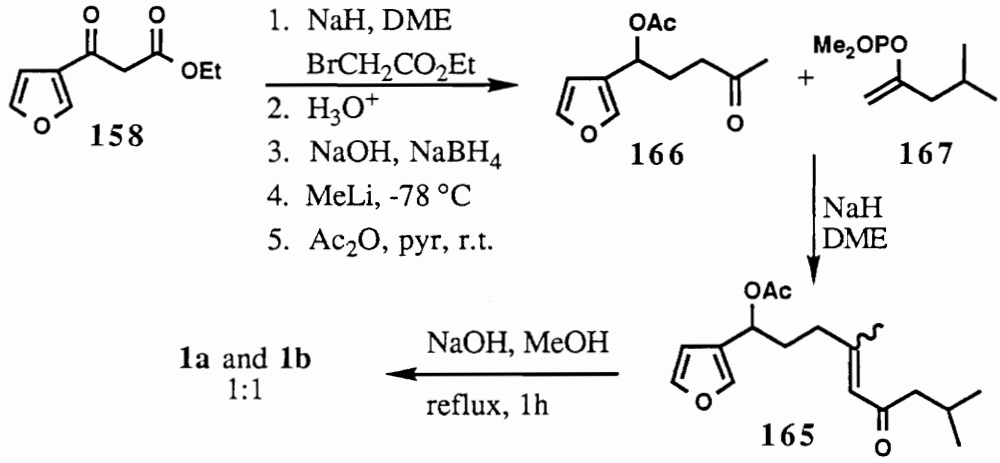


Scheme 35.

The reaction of acid chlorides **163** led to two products, **164** and **1b**, which supported this conclusion. Kubota proposed that **164** arose from *cis*-**163**. *Trans*-**163** reacted with

diisobutyl cadnium to give **1b**. The infrared spectra of **1b** did not match exactly with the natural sample, nor did the melting points of the semicarbazones. However, ring cleavage of **1b** followed by closure did lead to **1a**. This was proved by both infrared spectroscopy and mixed melting points of the free ketone and the semicarbazones. (The cis-relationship of the C-1 hydrogen and the methyl group were later confirmed by Nakanishi[64] using n.o.e. difference experiments.)

Hegarty[60] found that Kubota had in fact synthesized a 1:1 mixture of **1a** and **1b**. Kubota[72] had treated natural ipomeamarone in the same manner as he treated **1b** and assumed he would destroy both chiral centers, however, he unknowingly epimerized the C-4 center at the same time.



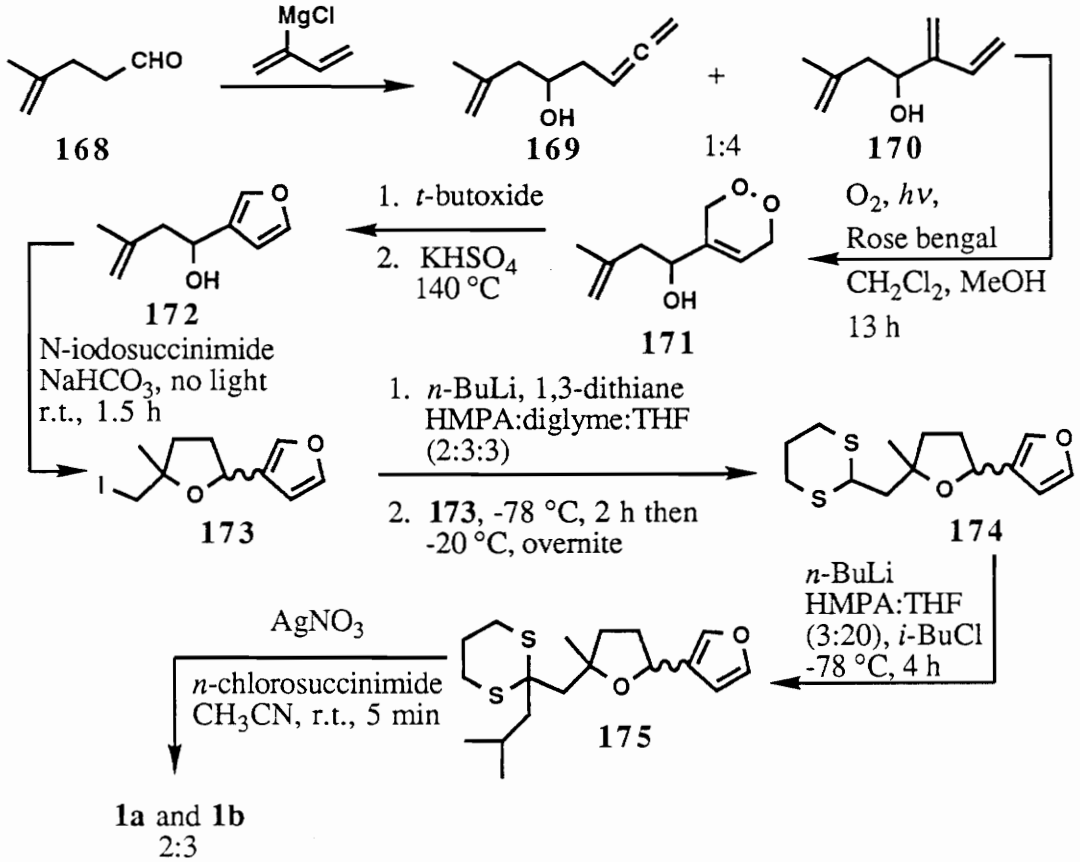
Scheme 36.

A second synthesis of **1a** and **1b** was reported in 1974 by Burka (Scheme 36).[73] This synthesis began with **158** which was prepared[71] in three steps from diethyl 3,4-furandicarboxylate. Nucleophilic attack of the enolate of **158** on ethyl bromoacetate, followed by decarboxylation, lactonization, ring opening using MeLi, and protection of the hydroxy group led to **166**. Condensation of **166** and **167** led to **165** which was the same intermediate in Kubota's synthesis. Cyclization of **165** yielded a one to one mixture of **1a** and **1b**. This synthesis is an improvement over Kubota's in that the production of tricyclic

ketone **164** is avoided.

In 1976, Kondo and Matsumoto[74] synthesized **1a** and **1b** by photooxygenation of diene **170**. Peroxide **171** was reduced to furan **172** which underwent oxidative cyclization to **173** which was a mixture of diastereomers (Scheme 37).

Attempts to add the side chain by the reaction of **173** with the carbanion of 2-isobutyl-1,3-dithiane under various conditions failed. However, the reaction of **173** with the carbanion of 1,3-dithiane did prove successful, and the addition of the anion of **174** to isobutyl chloride was carried out to yield **175**. Liberation of the ketone from **175** led to a 2:3 mixture of **1a** and **1b**. This ratio was equilibrated to 1:1 by treatment with NaOMe in methanol for 30 min.



Scheme 37.

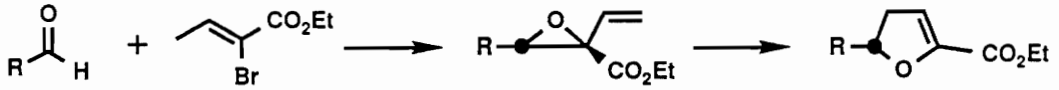
In the three syntheses of ipomeamarone (**1a**), no attempts were made to control the relative stereochemistry on the tetrahydrofuran ring. In light of the information regarding epimerization of the C-4 center, however, previous stereoselection is unnecessary. A mixture of **1a** and**1b** can be equilibrated to 1:1 using any of the three techniques[73,74,72] described, the isomers separated, and **1b** reequilibrated.

Various types of dihydrofuran synthesis have been presented in the previous sections as well as information on ipomeamarone and its synthesis. The following discussion will address the study of the [2+3] dihydrofuran annulation methodology developed in our laboratory and an application of this technique toward the synthesis of ipomeamarone.

III. DISSCUSSION

III.1. Introduction.

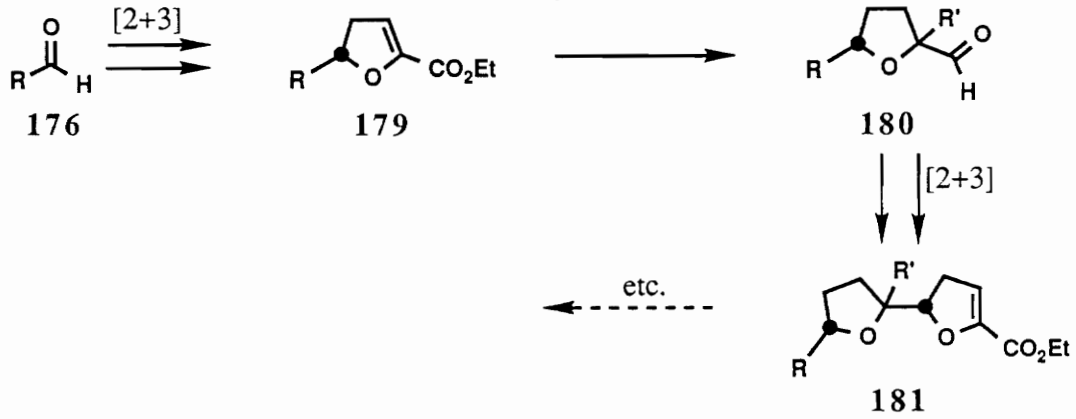
The [2+3] dihydrofuran annulation (Scheme 38) developed in our laboratory[75] offers several advantages which the methodologies reviewed earlier do not. This methodology allows for the convergent synthesis of 2,5-disubstituted-2,3-dihydrofurans from an aldehyde and ethyl-2-bromocrotonate (**177**). No other methodology has such simple starting materials.



176 **177** **178** **179**

Scheme 38.

The syntheses reviewed all lack another quality, that is, the ability to provide chains of tetrahydrofuran rings in an iterative fashion for use in the synthesis of polyether antibiotics. If the synthesis of the tetrahydrofuran moiety in **1a** were adaptable to an iterative process, it could be used to prepare polyether antibiotics such as monensin (**3**) and nigericin (**4**). Methods for the synthesis of **1a** available today do not have this versatility.



176 **179** **180** **181**

Scheme 39.

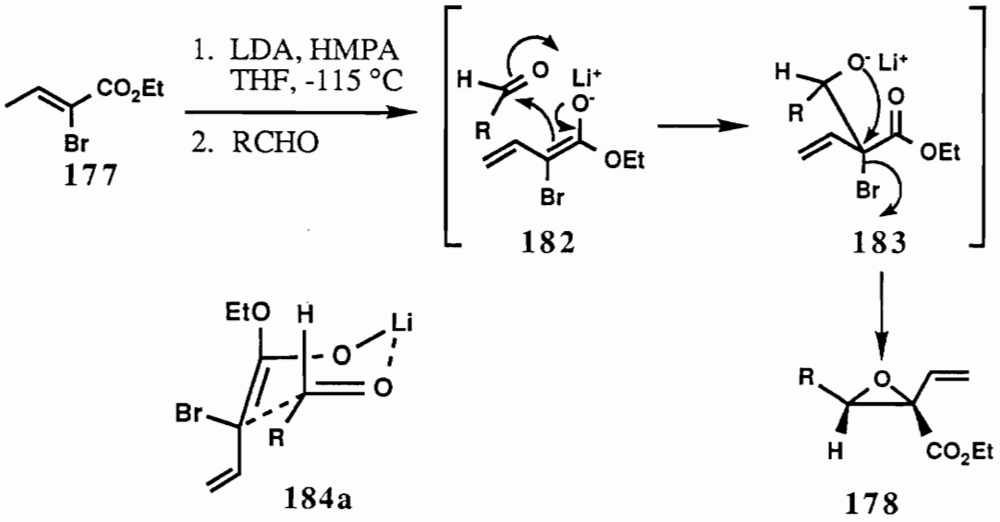
The [2+3] dihydrofuran annulation methodology developed in our laboratory could be

used in an iterative fashion as shown in Scheme 39. Reduction of ester **179** to aldehyde **180** would allow repetition of the entire process resulting in chains of tetrahydrofuran rings. An iterative methodology would greatly simplify the synthesis of compounds containing such chains (e.g. polyether anitibiotics). To illustrate the utility of the [2+3] dihydrofuran annulation methodology, we chose to pursue the synthesis of ipomeamarone (**1a**) as the simplest unit.

This discussion has been divided into four sections. The first two sections describe the development of the [2+3] dihydrofuran annulation methodology, the preparation of the vinyloxiranes from aldehydes, and the rearrangement of the vinyloxiranes to dihydrofurans by flash vacuum pyrolysis. The third section is a discussion of the vinyloxirane/dihydrooxepine rearrangement. The fourth section will describe the use of this methodology in the synthesis of **1a**.

III.2. Vinyloxiranation with Ethyl-2-Bromocrotonate

Vinyloxiranes of type **178** were prepared using a method developed in our laboratory[75] which begins with the condensation of the dienolate of ethyl-2-bromocrotonate (**177**) with an aldehyde (Scheme 40).

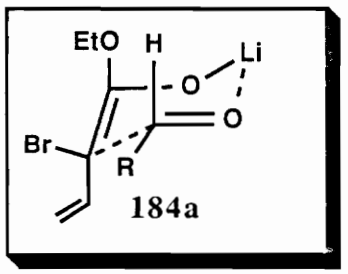


Scheme 40.

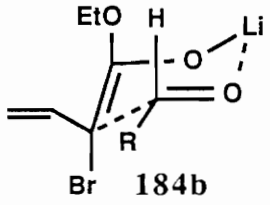
The conditions for the formation of the dienolate of **177** were found to require temperatures below -100 °C. Higher temperatures led to polymerization of **177**. Aldol attack of the dienolate on the carbonyl of the aldehyde would lead to an intermediate similar to **183**. S_N2 displacement of the bromide by the oxygen would complete the formation of **178**. We were surprised to find that only one isomer of the vinyloxirane (where the hydrogen on the epoxide ring and the ester are in a syn relationship) was formed. In order to explain this phenomenon, we adapted the aldol-chair transition state to our system. Four transition states are possible as shown in Scheme 41.

Transition states **184c** and **184d** can be ruled out since their 1,3-diaxial interactions would be greater than for **184a** or **184b**.

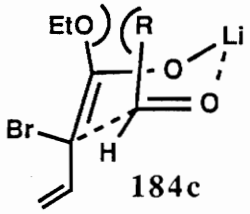
Transition state **184a** would arise from attack of the *E*-dienolate on the aldehyde. Dienolate attack on the carbonyl would lead to an intermediate where the lone pair on the oxygen and the bromide are antiperiplanar allowing for S_N2 displacement with no rotation necessary. This would lead to one isomer of **178**. Transition state **184b** would arise from attack of the *Z*-dienolate on the aldehyde. The intermediate formed must rotate in order to displace the bromide (by *anti* attack). This would lead to two diastereomers of vinyloxiranes. Based on this explanation it would seem likely that only **184a** is formed.



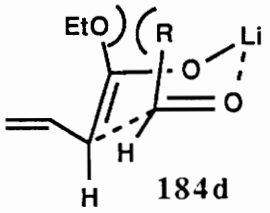
184a



184b



184c

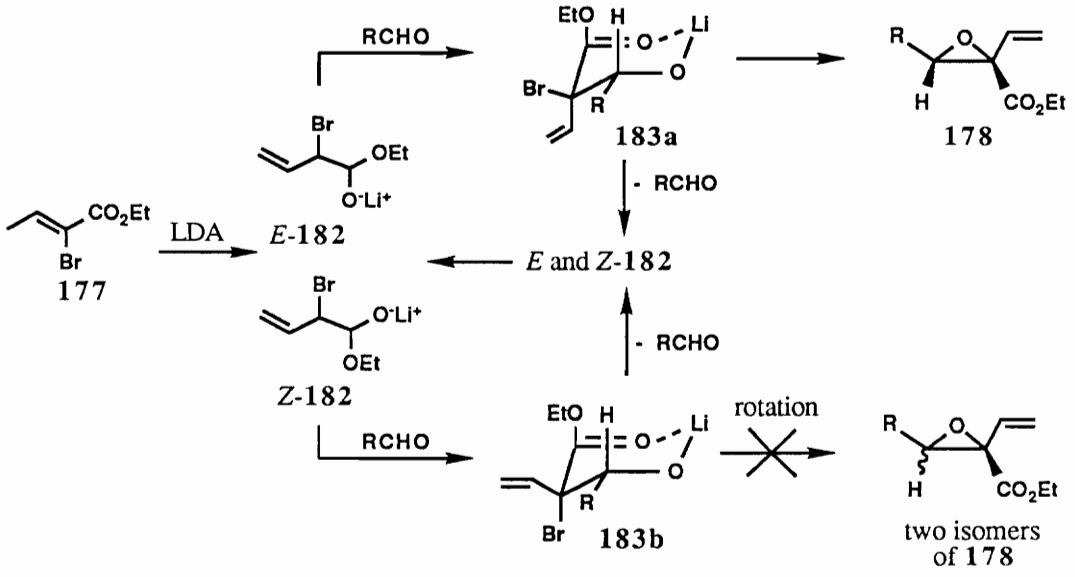


184d

Scheme 41.

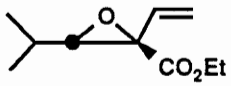
However, preliminary studies[76] indicate that in fact both the *E* and *Z* dienolates are being formed regardless of the geometry of starting crotonate (**177**). Aldol condensation of the *E*-dienolate would result in the formation of intermediate **183a** through transition state **184a** as shown in Scheme 42. Intermediate **183a** can either react as discussed above to give one isomer of **178**, or it can undergo a retro-aldol leading to a *mixture* of dienolates. The first pathway is irreversible and diminishes the *E*-dienolate. The second pathway would lead back to both dienolates.

Similarly, intermediate **183b** would arise from the *Z*-dienolate through transition state **184b** and should react by the two pathways described for **183a**. Retro-aldol would lead

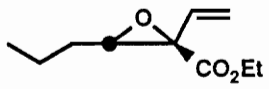


Scheme 42.

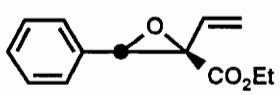
to a *mixture* of dienolates, however, as mentioned earlier S_N2 displacement cannot be accomplished without bond rotation to achieve an antiperiplanar disposition between the oxygen and the bromine. This rotation would lead to the formation of two isomers of **178**. As only one isomer of **178** is observed, it would seem likely that rotation is *not* possible and the only course left to **183b** is to undergo the retro-aldol step, thus allowing for the conversion of the *Z*-dienolate to the *E*-dienolate. In this manner, both *E* and *Z*-dienolates are consumed and only one vinyloxirane is formed.



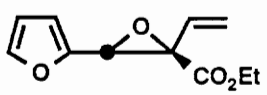
185 (49%)



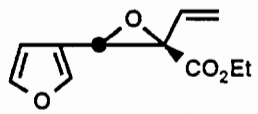
186 (47%)



187 (68%)



188 (51%)

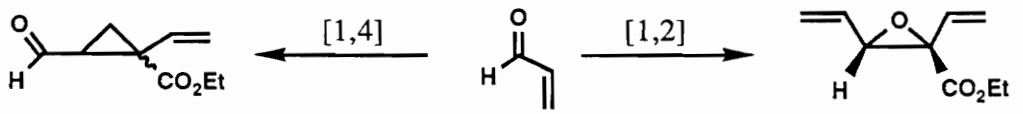


189 (70%)

Scheme 43.

Several simple aldehydes were reacted with the dienolate of **177** and the results are shown in Scheme 43. The vinyloxiranes were isolated from the crude reaction mixture by flash chromatography. In all cases, only one isomer of the vinyloxirane was obtained. The structure of the vinyloxiranes were determined using spectral data. The stereochemistry of the vinyloxiranes was determined by NOE difference experiments[77]

When acrolein (**191**) was used as a starting material (Scheme 44) *cis*-vinyloxirane **192** and a mixture of vinylcyclopropanes **190** were formed.[78] Acrolein can be viewed as both and aldehyde and an activated Michael receptor and reacts as either. The addition of the dienolate of **177** in a Michael fashion leads to the vinylcyclopropane in the same fashion as reported from our laboratory for enones.[79] Addition of the dienolate to the carbonyl leads to the cis-divinyloxirane.



190 **191** **192**

Scheme 44.

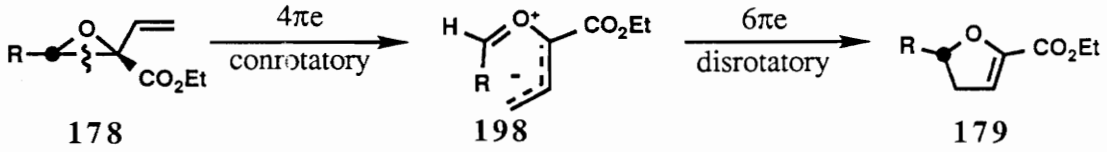
Based on the results given above, it is only fair to say that this technique for the preparation of vinyloxiranes should be applicable to a wide variety of substrates containing an aldehyde, including tetrahydrofuran complexes which have themselves been prepared by the [2+3] dihydrofuran annulation, thus allowing an iterative annulation process to be developed. Additionally, vinyloxirane **196** can be used in the synthesis of ipomeamarone (**1a**) in order to show the utility of this methodology in the synthesis of natural products.

In order complete the synthesis of **1a**, an investigation of the second step of the [2+3] dihydrofuran annulation must be performed. That second step involves the thermal rearrangement of the vinyloxiranes to dihydrofurans.

III.3. Thermolysis of Vinyloxiranes

Thermolysis of vinyloxiranes was carried out using a technique known as flash vacuum pyrolysis.[80] A sample of the vinyloxirane was placed in a flask which was attached to a quartz tube. This tube was passed through an oven capable of the required temperature and connected at the other end to a trap cooled with liquid nitrogen. The entire apparatus was kept under a vacuum of approximately 10^{-4} mm Hg attained by means of a diffusion pump. The vinyloxiranes were then evaporated into the quartz tube and collected in the trap. The dihydrofurans were isolated by flash chromatography, and their structures determined by analysis of spectral data. The vinyloxiranes that were pyrolysed and the dihydrofurans obtained are shown in Table 1.

Comparisons of the yield of aromatic dihydrofurans versus non-aromatic dihydrofurans support the mechanism proposed by others[51-74] which involves electrocyclic ring opening (4πe) of **187** to ylide **198** followed by closure (6πe) to dihydrofuran **179** as shown in Scheme 45. When **R** is an aromatic group (e.g. **186**, **188**, and **187**), resonance stabilization of the positive charge on the ylide can occur. However, if **R** is a nonaromatic group such as **185** and **186**, no such resonance can occur. This may be reflected in the low yields of **194** and **193**.



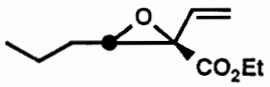
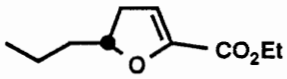
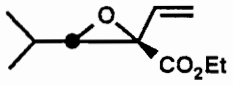
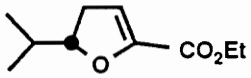
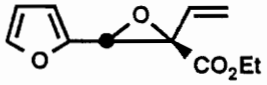
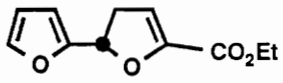
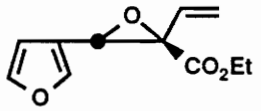
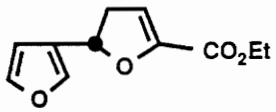
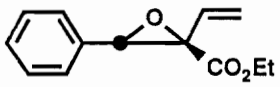
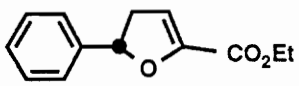
178 198 179

Scheme 45.

It should be noted that in the pyrolysis of **185** and **186** complete conversion of the vinyloxirane did not occur during the first pyrolysis. By subjecting the crude pyrolysate from oxirane **185** to a second pyrolysis, better yields of **194** were obtained. This was not

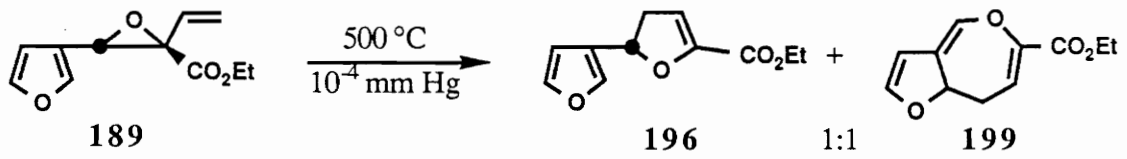
possible in the case of **193** Repeated pyrolysis did consume more oxirane (**186**), however, dihydrofuran **193** decomposed at a similar rate. When the crude pyrolysate containing **186** and **193**, was subjected to repetitive pyrolysis until no starting material was present (by tlc and NMR), dihydrofuran **193** was isolated in the same yield (10%).

Table 1.

Vinyloxirane	Conditions	Dihydrofuran (Yield)*
 **186**	500 °C 0.02 mm Hg	 **193** (10%)
 **185**	500 °C 0.02 mm Hg	 **194** (7%)
 **188**	500 °C 0.02 mm Hg	 **195** (49%)
 **189**	550 °C 10^{-4} mm Hg	 **196** (75%)
 **187**	500 °C 0.02 mm Hg	 **197** (95%)

*Isolated yield.

Vinyloxiranes **189**, **188**, and **187** did indeed give better results upon pyrolysis. This is predictable using an ylide intermediate which is now stabilized by an aromatic system. Dihydrofuran **197** was prepared in a 95% yield with no purification necessary. Dihydrofurans **196** and **195** were also prepared in good yields. (These compounds decomposed during purification leading to slightly lower isolated yields.)



189 **196** 1:1 **199**

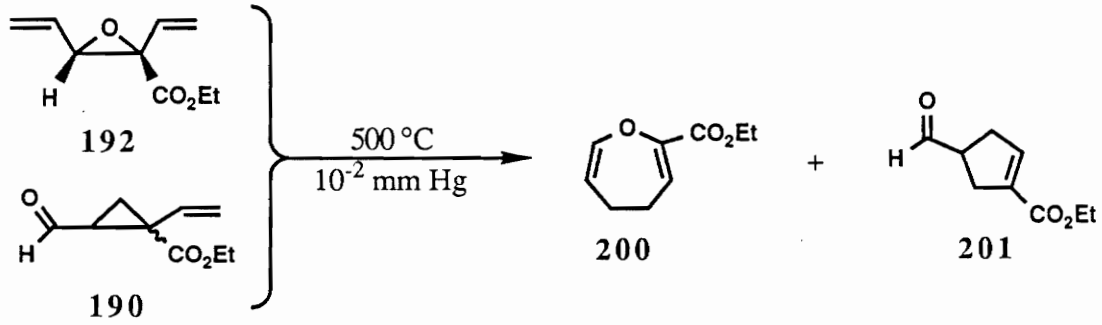
Scheme 46.

The pyrolysis of **189** (Scheme 46) at 500 °C (10^{-4} mm Hg) led to a mixture of dihydrofuran **196** and dihydrooxepine **199**. A temperature profile revealed that either oxepine **199** or dihydrofuran **196** could be prepared selectively. This information, coupled with the results from the pyrolysis of divinyloxirane **192**, attracted our interest and led to a detailed investigation of the vinyloxirane/oxepine rearrangement.

III.4. Vinyloxirane/Dihydrooxepine Rearrangement

During the investigation of the thermal rearrangement of vinyloxiranes, two interesting results appeared that prompted an investigation into the possibility for the synthesis of dihydrooxepines from those oxiranes containing a second double bond attached to the epoxide ring. These results surfaced during the experiments on the pyrolysis of the mixture from the vinyloxiranation of acrolein (**190** and **192**), and the pyrolysis of oxirane **189** in which the second double bond is contained in an aromatic system (i.e. a furan ring).

As discussed earlier (Section III.2, p. 36), when acrolein was subjected to the conditions of vinyloxiranation, *cis*-divinyloxirane **192** and vinylcyclopropanes **190** were isolated as mixture. When this mixture was subjected to pyrolysis at 500 °C (10^{-2} mm Hg), two products were obtained as shown in Scheme 47. Due to the lability of divinyloxiranes to rearrangement, **192** was isolated as oxepine **200**. Vinylcyclopropanes **190** were isolated as a mixture in pure form. Upon pyrolysis of **190** at 500 °C (10^{-4} mmHg), cyclopentene **201** was formed in a 95% yield as expected.[79]

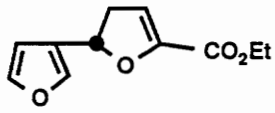
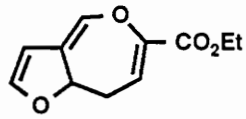


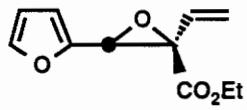
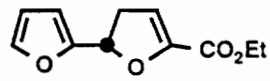
Scheme 47.

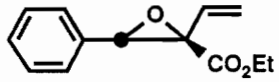
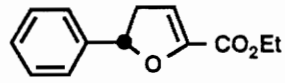
The interesting result to note, however, is the fact that when the mixture of **190** and **192** was subjected to thermal conditions ranging from 50 to 500 °C, no vinyldihydrofuran was observed. Even when this mixture was pyrolysed at 600 °C (10^{-2} mmHg) the only products were **200** and **201**. Based on Chuche's results[51] concerning the thermal

rearrangement of divinyloxiranes **118** ((Section II.3. p. 21) in which *cis*-**118** led to

Table 2.

Temperature (10^{-4} mm Hg)	 **196**	 **199**
400 °C	5	95
450 °C	11	89
500 °C	70	30
550 °C	77	23
600 °C	80	0
650 °C	56	0

(10^{-4} mm Hg)	 **188**	 **195**
350 °C	100	0
400 °C	21.5	57
450 °C	0	100

(10^{-4} mm Hg)	 **187**	 **197**
300 °C	100	0
350 °C	97	3
400 °C	63	18
450 °C	10	70
500 °C	0	100

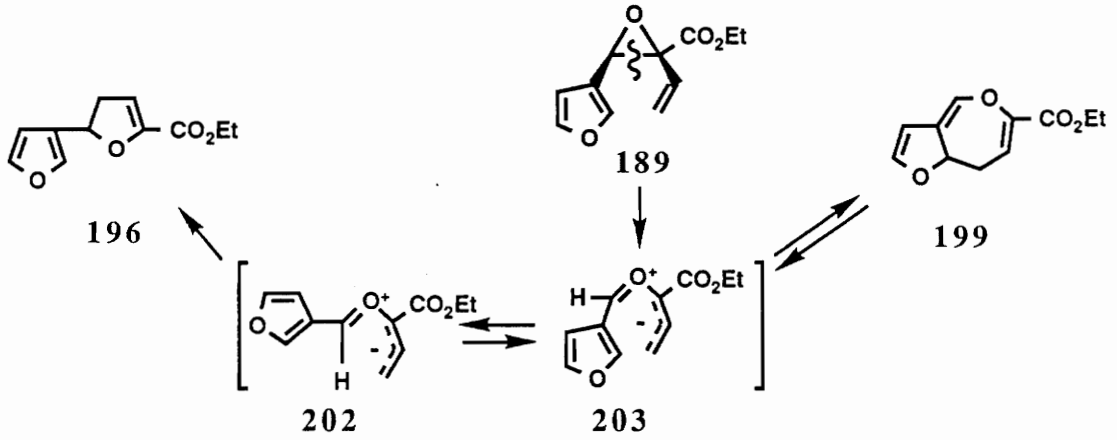
exclusively oxepine **117** while *trans*-**118** led to both the oxepine and dihydrofuran **122**),

and the fact that all other vinyloxiranes prepared using the [2+3] dihydrofuran annulation gave only *syn*-vinyloxiranes, it is reasonable to assume that the vinyloxiranation of acrolein results in only the *cis*-divinyloxirane **192** and therefore no dihydrofuran can be prepared.

The pyrolysis of oxirane **189** at different temperatures allowed the selective preparation of **196** and **199** to be achieved (Table 2). Additionally, When oxepine **199** was pyrolysed at 550 °C, dihydrofuran **196** was obtained, indicating that the oxepine is formed by a reversible ring closure.

In order to complete the study of oxepine formation, temperature profiles were performed on oxiranes **187** and **188** (Table 2). In both cases, no oxepine formation was observed. These results are in agreement with Chuche's findings[57] on the thermal rearrangement of **127** and **139** (Scheme 30. p. 26).

The results of the thermal rearrangement of both vinyloxiranes and divinyloxiranes support the mechanism shown in Scheme 45 (p. 40). This mechanism can be adapted to include oxepine formation as shown in Scheme 48.



Scheme 48.

Cleavage of the carbon-carbon bond on the epoxide ring of **189** leads directly to ylide **203**. This ylide can either undergo an electrocyclic ring closure (8πe) to form oxepine **199**, which is a reversible step, or ylide **203** can be converted to **202** through a bond

rotation. This step is also reversible. Ylide **202** does not have the proper conformation to undergo the 8πe ring closure, however, it can undergo a 6πe ring closure to form dihydrofuran **196**. This step, however, is not reversible.

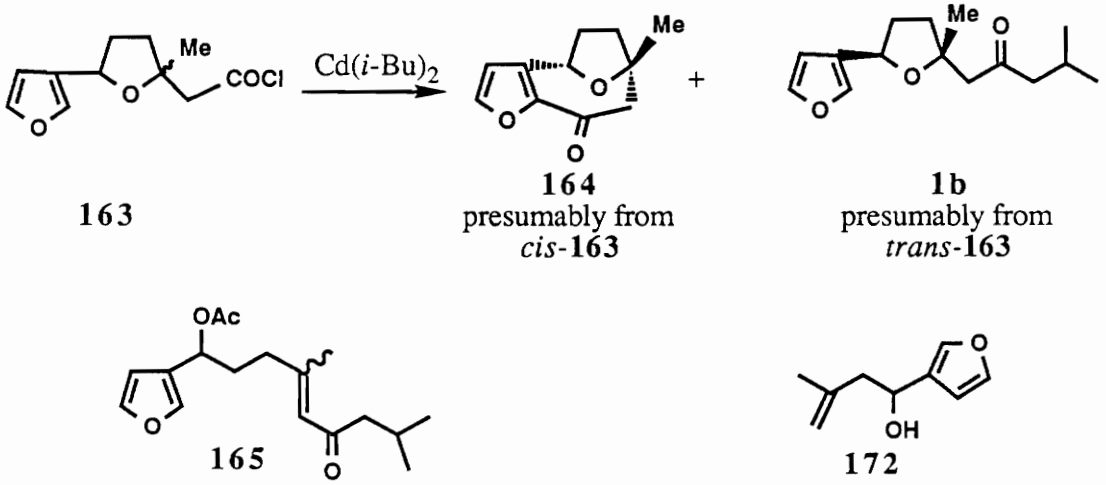
A second possible mechanism for the conversion of oxirane **189** to oxepine **199** would involve a Cope rearrangement (formally a 3,3-sigmatropic shift), however this mechanism does not explain the formation of dihydrofuran **196** directly from the oxepine. In order for this event to occur, the vinyloxirane **189** would have to be an intermediate, in which case some *cis*/*trans*-isomerization should be observed at intermediate temperatures, however no isomerization was observed at any temperature (^{1}H NMR).

The investigation of the [2+3] dihydrofuran annulation has led to several interesting results. First, this method for the synthesis of vinyloxiranes was found to be stereospecific. Second, condensation of acrolein with the dienolate of **177** led to both *cis*-vinyloxirane **192** and to vinylcyclopropanes **190**. Third, the study of the thermal rearrangement of vinyloxiranes to oxepines indicate reaction by way of ylide intermediates, and finally, vinyloxirane **189** was found to undergo thermal rearrangement selectively to form either dihydrofuran **196** or oxepine **199**.

The final step in the investigation of the [2+3] dihydrofuran annulation was to show its utility by an application to the synthesis of a natural product, and ipomeamarone (**1a**) was chosen as the target.

III.5. Synthesis of Ipomeamarone

The key intermediates (**165** and **172**) in the previous syntheses[72,73,74] of ipomeamarone (**1a**) are shown in Scheme 49. None of these syntheses were stereoselective. Kubota's synthesis[72] has an additional flaw in the transformation of acid chloride **163** using the cadmium reagent (Scheme 49). He loses half of his material in the form of ketone **164**. (the yield of this reaction was 16% **164** and 13% **1b**). Furthermore, epimerization of **1b** through acetate **165** led to a mixture of **1a,b** which Kubota incorrectly assumed was only one diastereomer, that is, **1a**.



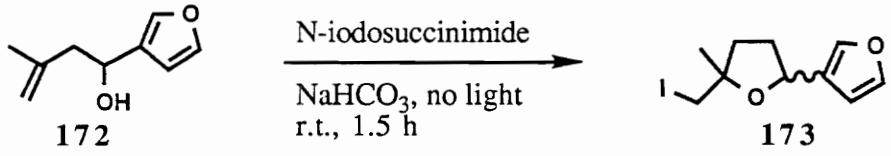
Scheme 49.

He drew this conclusion based on the conclusion that treatment of natural (+)-ipomeamarone with KOAc (to give **165**) followed by ring closure (alkaline hydrolysis) would destroy both asymmetric centers thereby creating racemic ipomeamarone. Additionally, the melting point of this racemate (as the semicarbazone) was identical to the melting point of a 1:1 mixture of the semicarbazones of (+)-ipomeamarone and (-)-Ngaione (the enantiomer of **1a**). The IR spectra were also identical. Consequently, when Kubota's synthetic ipomeamarone was found to be identical to the racemate prepared from the natural sample, he concluded that the epimerization of **1b** had been complete.

However, treatment of (+)-ipomeamarone with base can only epimerise the C-4 center, thereby creating a mixture of ipomeamarone and epi-ipomeamarone as two diastereomers. In order to destroy the C-1 center it would be necessary to treat the compounds with acid.

Burka's[73] synthesis of **1** converged with Kubota's at acetate **165**, rendering the synthesis nonstereoselective. This synthesis was an improvement over Kubota's since Burka avoided the cadnium reaction.

The third synthesis of **1** proceeds through intermediate **172**. Oxidative cyclization afforded **173** as a mixture of diastereomers. Subsequent addition of the anion of dithiane followed by alkylation with isobutyl chloride and hydrolysis of the thioketal gave a mixture of **1a** and **1b** (2:3)which was epimerized (NaOMe, MeOH) to a 1:1 mixture. Here again, the possibility of stereoselection is ruled out.



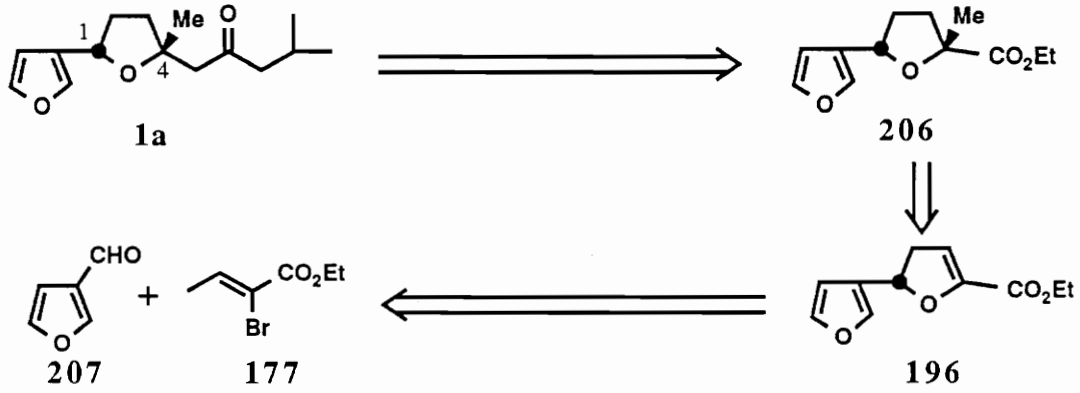
172 **173**

Scheme 50.

The synthesis of ipomeamarone using the [2+3] dihydrofuran annulation will have one advantage over these previous syntheses. Using this method will allow control of stereochemistry at C-4 to take place *after* ring formation as shown in the retrosynthetic analysis in Scheme 51. If stereoselection is not possible, epimerization and separation of the **1a** can be performed. In addition, this synthesis should be shorter than the previous syntheses in that the majority of the molecule will be formed in the two steps of the [2+3] dihydrofuran annulation.

The actual synthesis of ipomeamarone **1a** can be divided into three sections: first, the preparation of dihydrofuran **196**; second, the introduction of the methyl group at C-4; and finally, transformation of the ester in **206** to the ketone in **1a**.

Dihydrofuran **196** was prepared by the [2+3] dihydrofuran annulation as described earlier. It was found that this sequence of reactions could be carried out on large scale (30 g of **196**) with relative ease. The reactions were further simplified by distilling vinyloxirane **189** directly from the crude reaction mixture (after workup) into the pyrolysis tube. Dihydrofuran **196** was then purified by filtration through a short flash column. The overall yield of this two-pot sequence was 56% from 3-furaldehyde (**207**).

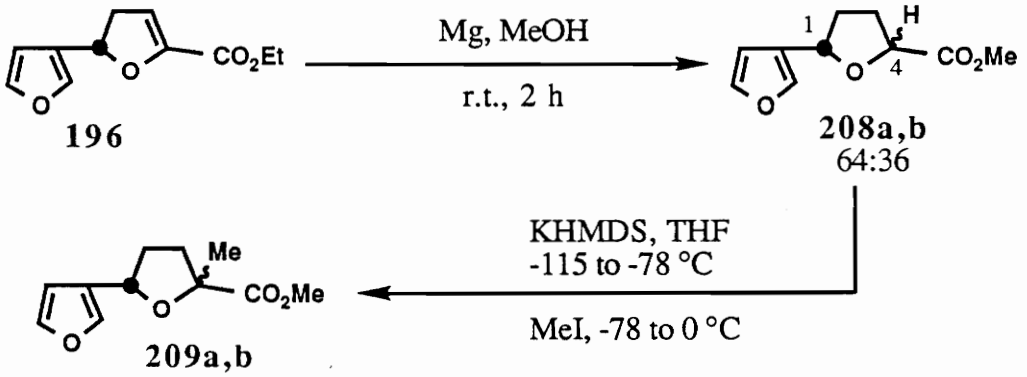


Scheme 51.

Introduction of the methyl group at the C-4 position was carried out by reduction of the double bond in dihydrofuran **196** followed by alkylation with MeI as shown in Scheme 52. The reduction of the double bond in dihydrofuran **196** was carried out using a methodology developed in our laboratory for the selective reduction of a double bond in α,β–unsaturated esters.[81] Dihydrofuran **196** was dissolved in anhydrous MeOH followed by the slow addition of dry Mg. The mixture was stirred at r.t. for 2 h. When this reaction was run on larger scale, cooling became necessary in order to slow the reaction.

In addition to reduction of the double bond, transesterification was observed. An aliquot taken during the reaction and analysed by G.C. revealed six peaks, indicating that reduction and transesterification were taking place simultaneously. Consequently, the

products of this reaction were the reduced methyl esters **208a** and **208b**. The ratio of diastereomers was found to be 36:64 respectively, however, alkylation of the C-4 center required the formation of an enolate which would destroy the stereochemistry.



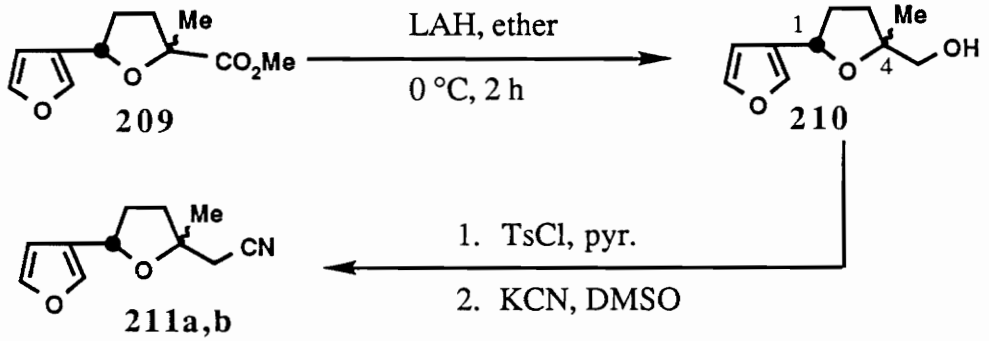
Scheme 52.

Alkylation at the C-4 center was first carried out using LDA to generate the enolate, however, this led to poor yields of **209** (25%) even at -115 °C. The use of potassium hexamethyldisilazane (KHMDS) gave better results. Thus, **208** was dissolved in THF and cooled to -115 °C. KHMDS precooled and added via canula to **208**. The temperature was raised to -78 °C and stirred for 2-8 h depending on scale. At this point neat MeI was injected and the mixture warmed to 0 °C over 2 h affording (after workup) **209a** and **209b** as an inseparable mixture in 88% isolated yield. **208a,b** was also recovered (10%) and could be recycled without further purification. No stereoselection was observed. Attempts to control the stereochemistry using HMPA, 18-crown-6, or transmetalation failed. (In all cases, a 1:1 mixture of **209a** and **209b** was observed.)

Tetrahydrofuran **209** has been prepared in a 40% overall yield in 4 steps from 3-furaldehyde (**207**). The final step(s) in this synthesis involved the transformation of the ester in **209** to the ketone side chain of **1**.

The most straightforward method for this transformation would be homologation of the ester in **209** to give Kubota's acid (**162**). This however would lead to the same loss of

material that Kubota experienced when he reacted acid chloride **163** with diisobutyl cadmium.[72] In order to avoid this problem, we chose a different route for the homologation which would result in nitrile **211a,b** as shown in Scheme 53.



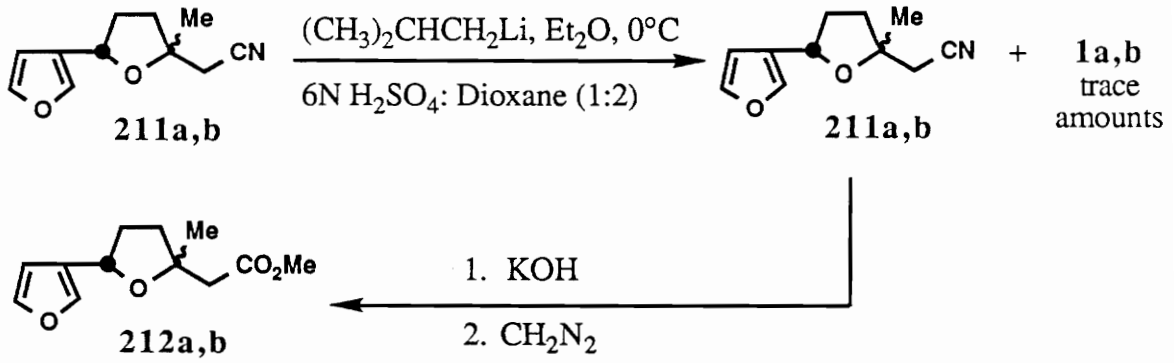
Scheme 53.

Reduction of ester **209** was accomplished using lithium aluminum hydride (LAH) in ether to afford quantitatively alcohols **210a** and **210b** which were separable by flash chromatography. At this point the relative stereochemistry of each diastereomer was made based on NOE difference experiments. **210b** showed enhancement of the furan protons upon irradiation of the methyl protons on C-4 indicating that these groups were on the same side of the tetrahydrofuran ring. **210a** showed no such enhancement, however the proton on C-1 was enhanced. Therefore, we assigned **210a** as having the correct stereochemistry for the synthesis of ipomeamarone **1a**. Further reactions were carried out on mixtures of the two isomers as well as each isomer separately in order to obtain both **1a** and **1b**, for the epimerization studies.

Alcohols **210** were transformed to nitriles **211** via tosylate **214** (prepared quantitatively from the alcohol using tosyl chloride and pyridine). The displacement of **214** by cyanide required drastic conditions (KCN, DMSO, 18-crown-6, 100 °C), and the yield was low (50%). Additionally, when either diastereomer of **214** was reacted, it appeared (from initial analysis of spectral data) that epimerization had taken place resulting

in both diastereomers of nitrile **211**.

Addition of an isobutyl group to alleged nitriles **211a,b** followed by hydrolysis of the resulting imines would lead directly to ipomeamarone **1a** (and **1b**), thus avoiding Kubota's tricyclic ketone **164**. This was first attempted using isobutyllithium as shown in Scheme 54.



Scheme 54

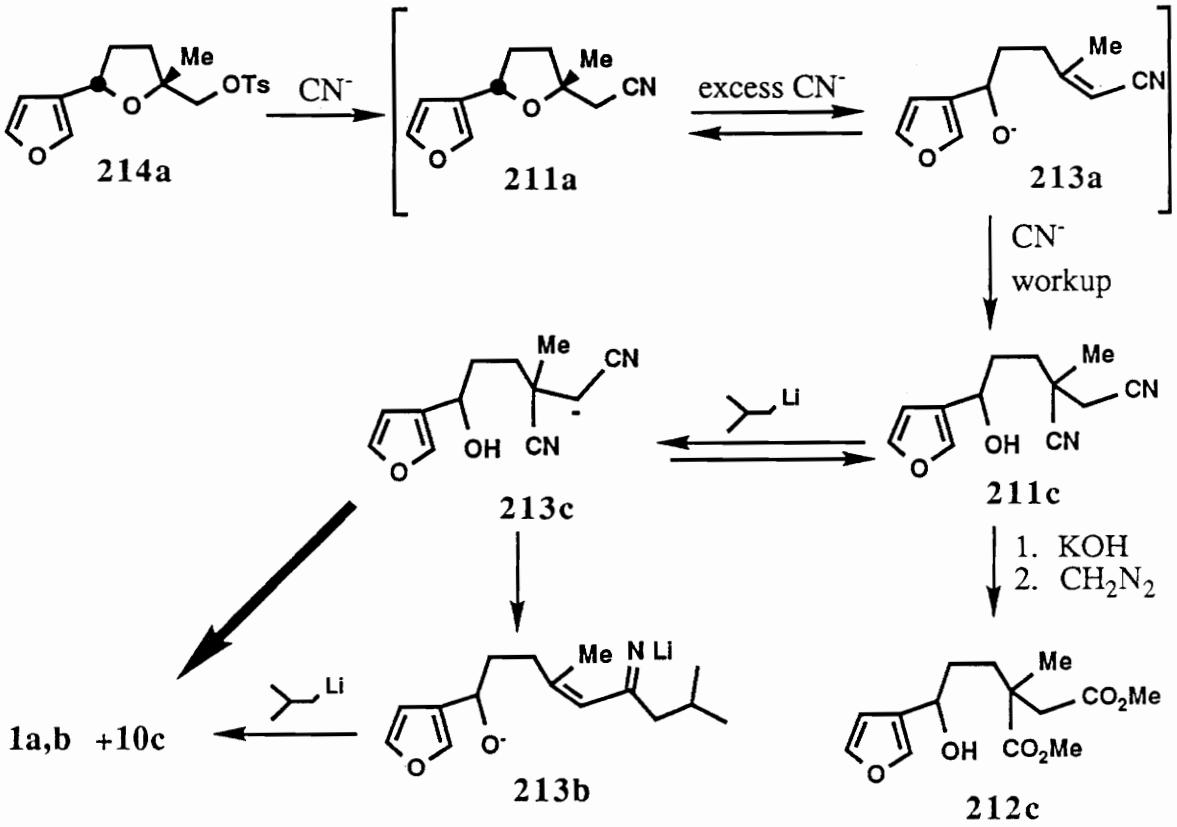
The reaction of isobutyllithium with **211** followed by hydrolysis led to trace amounts of **1**, however, the majority of the reaction mixture was nitrile **211**. When the reaction mixture was quenched with D_2O before hydrolysis, it was found that the isobutyllithium was abstracting the α-proton from **211** in preference to addition. (^{1}H-NMR showed a marked decrease in the signal corresponding to the α-CH_2, indicating deuterium incorporation into **211**.) This route was thought to still be useful in that hydrolysis of **211** to the acid would intercept Kubota's synthesis[72] of **1**.

Full characterization of nitriles **211a,b** showed two anomalies, specifically, an infrared absorption corresponding to an OH group, and an extra proton in the NMR spectra which also behaved as a hydroxy proton. These were first attributed to the formation of a hydrate.

Purification of nitriles **211a,b** also seemed to be difficult. Combustion analysis results were off to a large degree, and derivatization seemed to be the best alternative. Thus the nitriles were hydrolysed to its acid and the crude reaction mixture esterified with

ethereal diazomethane. The ^{1}H-NMR spectra of the resulting ester (**212a,b**) showed that, in fact, two methoxy groups were present relative to one set of furan protons. Additionally, the infrared spectrum of **212** showed that a hydroxy group was also present. After careful analysis of all spectral data, it was determined that the actual structures of **211a,b** and **212a,b** were that of dinitrile **211c** and diester **212c** respectively (Scheme 55).

Not only did these structures explain all of the anomalies in the spectral data, they also explain the chemistry of the reaction of dinitrile **211c** with isobutyllithium. The mechanistic rationale is shown in Scheme 55.



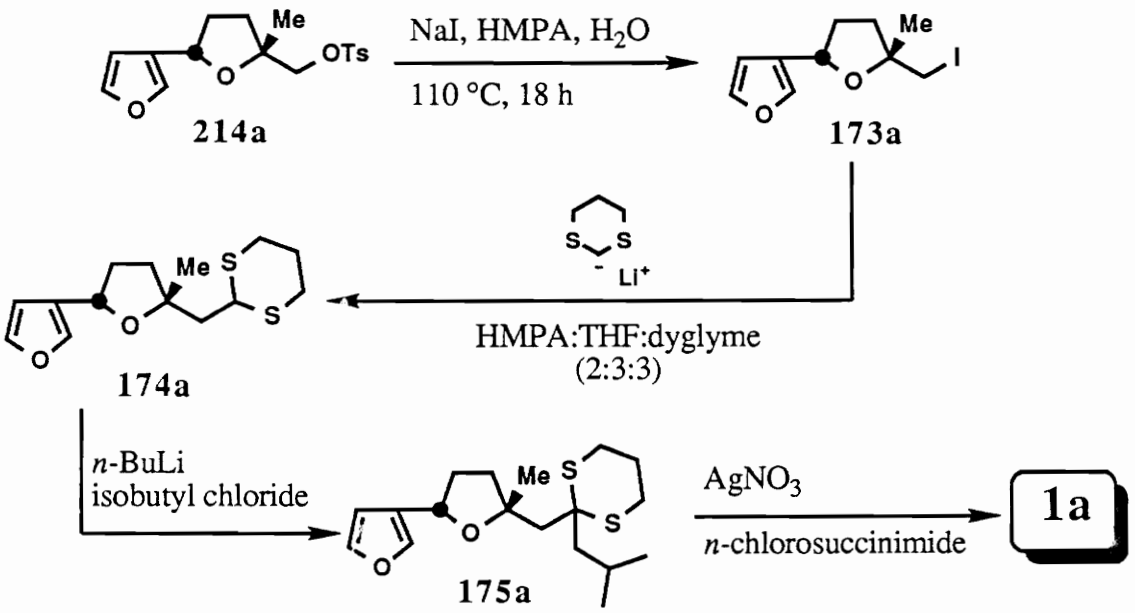
Scheme 55.

Reaction of tosylate **214a** (or **214b**) would lead first to **211a** (or **211b**). The drastic conditions required for reaction to occur required the use of excess KCN allowing ring

opening to followed by the addition of a second cyanide anion. Aqueous workup would then lead to **211c**.

The reaction of **211c** with isobutyllithium leads to mainly starting material with a small amount of **1a,b**. The first step of this reaction is the abstraction of the proton α to both nitriles leading to anion **213c** which can undergo elimination and ring closure followed by the addition of isobutyllithium to the remaining nitrile (leading to **1a,b**). According to the deuterium experiment, however, the favored pathway of anion **213c** is to remain an anion until hydrolysis. This anion should be stable in that it can resonate between the two nitrile groups.

The preparation of **212a,b** would have intercepted Kubota's[72] synthesis of ipomeamarone but is seemed unlikely that **212c** could be reverted to **212a,b**. A more efficient synthesis of ipomeamarone was provided by the interception of Kondo's[74] at the stage of iodide **173**.



Scheme 56.

Accordingly, iodide **173** was prepared[82] from tosylate **214** (Scheme 56) using NaI in HMPA with approximately 1% H_2O added. The reaction proceeded smoothly to give iodide **173** in a 59% yield. (Since the overall yield of the transformation from alcohol **210** to iodide **173** was comparable to methods for direct displacement of alcohols with iodide,[83] no attempt was made to prepare **173** directly from **210**.)

Iodide **173** was treated with the anion of 1,3-dithiane to afford **174**. Further lithiation, followed by the addition of isobutyl chloride led to the thioketal which upon hydrolysis gave, at last, ipomeamarone (**1a**). The spectral data from **1a** proved to be identical to that of natural ipomeamarone, indicating that earlier predictions of the relative stereochemistry of alcohols **210a** and **210b** had been correct. Iodide **173b** was also treated in a similar fashion, to furnish epiipomeamarone (**1b**).

A sample of epiipomeamarone (**1b**) was epimerized to a 1:1 mixture of **1a** and **1b** following Kondo's procedure.[74]

The overall yield of this ipomeamarone synthesis was 0.63% from 3-furaldehyde. This yield does not include epimerization, nor does it take into account the fact that the dithiane reactions were not optimized. (These reactions were carried out a total of six times.)

IV. CONCLUSIONS

The synthesis of ipomeamarone concludes the investigation of the [2+3] dihydrofuran annulation. It has been shown that this methodology offers several advantages over alternative methods for the synthesis of dihydrofurans. The utility of this methodology has been demonstrated in the synthesis of ipomeamarone. This synthesis has also given insight into the manipulation of side chains on the tetrahydrofuran ring.

The [2+3] dihydrofuran annulation would make the synthesis of several polyether antibiotics somewhat easier for two reasons. First, the preparation of the tetrahydrofuran rings would require only a suitable substrate containing an aldehyde, and the appropriately substituted version of ethyl 2-bromocrotonate (**177**). Second the resulting dihydrofuran would already contain an ester in the proper position for introduction of the next tetrahydrofuran ring (after reduction to the aldehyde). Further investigation of this methodology will include the use of more highly substituted forms of **177**.

V. EXPERIMENTALS

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried. THF, ether, diglyme, and benzene were distilled from benzophenone ketyl, HMPA and diisopropyl amine from calcium hydride.

Analytical TLC was performed on silica gel 60F-254 plates (EM Science). Flash chromatography was performed on Kieselgel 60 (EM Science, 230-400 mesh). Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double focusing DuPont 21-110C or VGT instrument (exact mass). Infrared spectra were recorded on neat samples (NaCl plates) on a Perkin Elmer 283B, 710B, or a FT-IR instrument. ^{1}H-NMR spectra were obtained from a Bruker WP-200 or WP-270 instrument. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard (0.00 ppm). ^{13}C-NMR spectra were obtained from a Bruker NR-80, WP-200 or WP-270 instrument. Chemical shifts are reported in ppm relative to the center line of $CDCl_3$ triplet (77.0 ppm) and the multiplicity is indicated by CH_3, CH_2, CH, or C (INEPT experiments).

General Procedure for Pyrolysis of Vinyloxiranes. A sample of the vinyloxirane was evaporated at the specified temperature (T_e) and pressure through a horizontally situated quartz tube (41 cm, 5 mm i.d.) heated to the specified temperature (T_p). The pyrolysate was condensed in a liquid-nitrogen-cooled trap and the apparatus rinsed with CH_2Cl_2. The solvent was evaporated to give the crude oxalene.

5-*n*-Propyl-2-carbethoxy-2-oxolene (193). 186 (117 mg, 0.64 mmol) was pyrolysed (T_e=45 °C, 0.02 mm, T_p=500 °C) to give **193** in a 33% crude yield (GC) and 50% of **186**. The crude material was chromatographed on 9 g of silica gel with 95%

hexane:5% ether as eluant to give 12 mg (10%) of **193**.

193: R_f=0.52 (70% hexane, 30% ether); **IR** (neat): 2950, 1735, 1630, 1310, 1120 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.92 (t, 3H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz), 1.25-1.63 (m, 3H), 1.71-1.86 (m, 1H), 2.41 (ddd, 1H, J_1=17.2 Hz, J_2=8.6 Hz, J_3=3.0 Hz), 2.80 (ddd, 1H, J_1=17.2 Hz, J_2=10.2 Hz, J_3=3.0 Hz), 4.23 (q, 2H,.J=7.2 Hz). 4.64-4.75 (m, 1H), 5.85 (t, 1H, J=3.0 Hz); **^{13}C-NMR** ($CDCl_3$) δ 13.9 (CH_3), 14.2 (CH_3), 18.3 (CH_2), 35.8 (CH_2), 38.1 (CH_2), 60.9 (CH_2), 82.9 (CH), 110.2 (CH), 148.2 (C), 160.5 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 184 (M^+, 12), 149 (72), 99 (53), 82 (21), 69 (42), 55 (100). **HRMS Calc'd for** $C_{10}H_{16}O_3$: 184.1099 **Found:** 184.1116.

5-isopropyl-2-carbethoxy-2-oxolene (194). 185 (155 mg, 0.84 mmol) was pyrolysed (T_e=45 °C, 0.02 mm, T_p=500 °C). The crude material was pyrolysed two more times (whereupon TLC indicated no starting material) to give 80 mg of a yellow oil. A pure sample of the **194** (11 mg, 7%) was obtained by preparative TLC (Whatman PKGF, silica gel, 500 μm, 20x20 cm; 2% ethyl acetate, 98% hexane; three elutions).

194: R_f=0.35 (90% hexane, 10% ethyl acetate); **IR** (neat): 2920, 1735, 1630, 1257 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.89 (d, 3H, J=6.8 Hz), 0.95 (d, 3H, J=6.8 Hz), 1.29 (t, 3H, J=7.1 Hz), 1.87-1.99 (m, 1H), 2.48 (ddd, 1H, J_1=17.4 Hz, J_2=9.3 Hz, J_3=3.0 Hz), 2.71 (ddd, 1H, J_1=17.4 Hz, J_2=9.3 Hz, J_3=3.0 Hz), 4.23 (q, 2H,.J=7.3 Hz). 4.45 (ddd, 1H, J_1=10.2 Hz, J_2=9.4 Hz, J_3=6.4 Hz), 5.83 (t, 1H, J=3.0 Hz); **^{13}C-NMR** ($CDCl_3$) δ 11.6 (CH_3), 14.2 (CH_3), 17.1 (CH_3), 32.8 (double intensity, CH_2, CH), 60.9 (CH_2), 87.9 (CH), 110.3 (CH), 148.4 (C), 160.5 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 184 (M^+, 3.7), 171 (3.3), 157 (5.3), 149 (39), 81 (43), 69 (100), 55 (51). **HRMS Calc'd for** $C_{10}H_{16}O_3$: 184.1099 **Found:** 184.1105.

5-(2'-Furyl)-2-carbethoxy-2-oxolene (195). 188 (98 mg, 0.47 mmol 71% pure by GC) was pyrolysed (T_e=45 °C, 0.02 mm, T_p=500 °C) give 86.5 mg of a yellow oil which by GC was 89% **195**. A pure sample of the **195** was obtained by flash chromatography on 15 g of silica gel. Elution with hexane/ethyl acetate (95:5, 90:10, 85:15) gave pure **195** (48 mg, 69%).

195: R_f=0.17 (90% hexane, 10% ethyl acetate); **IR** (neat): 3110, 2975, 1720, 1630 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 3.05 (dd, 1H, J_1=3.0 Hz, J_2=1.0 Hz), 3.08 (d, 1H, J=3.0 Hz), 4.24 (qd, 2H, J_1=7.1 Hz, J_2=2.2 Hz), 5.65 (t, 1H, J=9.9 Hz), 5.98 (t, 1H, J=3.0 Hz), 6.33 (dd, 1H, J_1=3.2 Hz, J_2=1.9 Hz), 6.37 (d, 1H, J=3.2 Hz). 7.4 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 13.9 (CH_3), 34.4 (CH_2), 60.8 (CH_2), 76.5 (CH), 108.3 (CH), 110.1 (CH, double intensity), 142.8 (CH), 147.5 (C), 152.3 (C), 159.7 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 208 (M^+, 9), 134 (13), 107 (28), 86 (67), 84 (100). **HRMS Calc'd for** $C_{11}H_{12}O_4$: 208.0736 **Found:** 208.0729.

5-(3'-Furyl)-2-carbethoxy-2-oxolene (196). 189 (1.19 g, 5.7 mmol) was pyrolysed (T_e=235 °C, 10^{-4} mm, T_p=550 °C) to give 1.07 g of a yellow oil which was filtered through 5 g of silica gel using CH_2Cl_2 as eluant to give **196** (1.07 g, 83% pure). An analytical sample was obtained by flash chromatography (silica gel) with hexane/ether (9:1) as eluant.

196: R_f=0.33 (70% hexane, 30% ether); **IR** (neat): 3200, 3025, 1740, 1625, 1130, 1040 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.28 (t, 3H, J=7.0 Hz), 2.76 (ddd, 1H, J_1=17.3 Hz, J_2=8.6 Hz, J_3=3.0 Hz), 3.10 (ddd, 1H, J_1=17.3 Hz, J_2=10.4 Hz, J_3=3.0 Hz), 4.23 (qd, 2H, J_1=7.0 Hz, J_2=1.3 Hz), 5.63 (dd, 1H, J_1=10.4 Hz, J_2=8.6 Hz), 5.95 (t, 1H, J=3.0 Hz), 6.42 (m, 1H), 7.37 (m, 1H), 7.43 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 14.3 (CH_3), 37.4 (CH_2), 61.2 (CH_2), 77.0 (CH),108.7 (CH), 110.2 (CH), 126.1 (C), 139.9 (CH),

143.8 (CH), 148.3 (C), 160.3 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 208 (M^+, 8), 123 (32), 107 (55), 95 (84), 79 (93), 67 (100), 55 (62). **HRMS Calc'd for** $C_{11}H_{12}O_4$: 208.0736 **Found:** 208.0772.

2-Carbethoxy-[5,6,b]-4,5-dihydrofurano-2,6-oxepine (199). 189 (0.5 g, 2.40 mmol) was pyrolysed (T_e=235 °C, 10^{-4} mm, T_p=400 °C) to afford 0.50 g of a mixture of **199** and **189** (0.5 g)which was separated by flash chromatography using 90% hexane:5% ether as eluant to give **199** (0.44 g, 88%) as a white crystalline solid (m.p., 58.5-60.5) and **189** (0.11 g, 12%).

199: R_f=0.50 (70% hexane, 30% ether); **IR** (neat, hot NaCl plates): 3030, 2960, 1744, 1665, 1592, 1272, 1180 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 2.40 (ddd, 1H, J_1=15.3 Hz, J_2=9.2 Hz, J_3=3.0 Hz), 2.98 (ddd, 1H, J_1=15.9 Hz, J_2=9.3 Hz, J_3=3.4 Hz), 4.21 (q, 2H, J=7.1 Hz), 5.10 (dt, 1H, J_1=10.0 Hz, J_2=3.4 Hz), 5.40 (d, 1H, J=3.0 Hz), 6.18 (dd, 1H, J_1=9.2 Hz, J_2=3.4 Hz), 6.46 (s, 1H); **^{13}C-NMR** ($CDCl_3$) δ 14.1 (CH_3), 33.0 (CH_2), 61.5 (CH_2), 79.5 (CH), 101.7 (CH), 109.4 (CH), 120.2 (C), 128.6 (CH), 143.7 (C), 149.2 (CH), 162.9 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 208 (M^+, 13), 135 (51), 125 (85), 107 (85), 79 (100), 55 (95). **HRMS Calc'd for** $C_{11}H_{12}O_4$: 208.0736 **Found:** 208.0701.

5-Phenyl-2-carbethoxy-2-oxolene (197). 187 (100 mg, 0.46 mmol,) was pyrolysed (T_e=50 °C, 0.02 mm, T_p=500 °C) to give pure **197** (95 mg, 95%).

189: R_f=0.42 (90% hexane, 10% ethyl acetate); **IR** (neat): 2970, 1735, 1730, 1637, 1257, 1230, 1120 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.31 (t, 3H, J=7.3 Hz), 2.77 (ddd, 1H, J_1=17.5 Hz, J_2=8.8 Hz, J_3=3.0 Hz), 3.21 (ddd, 1H, J_1=17.5 Hz, J_2=10.8 Hz, J_3=3.0 Hz), 4.28 (q, 2H, J=7.3 Hz), 5.67 (dd, 1H, J_1=10.8 Hz, J_2=8.8 Hz), 5.96 (t, 1H, J=3.0

Hz), 7.30 (m, 5H); **^{13}C-NMR** ($CDCl_3$) δ 14.0 (CH_3), 38.6 (CH_2), 60.8 (CH_2), 83.4 (CH),110.0 (CH), 125.5 (CH), 127.7 (CH), 128.3 (CH), 141.6 (C), 148.0 (C), 159.9 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 218 (M^+, 79), 160 (27), 145 (96), 127 (52), 117 (100), 105 (41), 91 (31), 77 (42). **Anal. Calc'd for** $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; **Found:** C, 70.33; H, 6.55.

2-Carbethoxy-2,6-oxepine (200) and 2-Carbethoxy-2-ethenyl-1-cyclopropylcarboxaldehyde and its isomer (190). To a stirred solution of lithium diisopropylamide (30.6 mmol), prepared from diisopropylamine (4.2 mL) and *n*-butyllithium (12.03 mL, 2.5 M in hexane), in 50 mL THF and 5.23 mL of HMPA at -110 °C was added a solution of ethyl 2-bromobut-2-enoate (3.2 g, 27.8 mmol), in 38 mL of THF, cooled to -105 °C, while maintaining the temperature of the reaction at or below -100 °C. After the addition was complete, the reaction mixture was stirred for 15 min and then treated with a solution of acrolein (1.75 mL, 26.1 mmol) in 30 mL of THF cooled to -105 °C. This addition was also carried out at such that the temperature of the reaction remained at or below -100 °C. Stirring was continued at -100 °C or less for 0.5 h and at -78 °C for 1 h whereupon the temperature was raised to -50 °C and diluted with saturated NH_4Cl solution, and diluted with ether. The ether layer was washed with 3N HCl (1x15 mL), water (3x15 mL), brine, and dried over Na_2SO_4. The solvent was removed to give a dark brown oil which was filtered through Fluricil (80% hexanes, 20% ethyl acetate) leaveing 1.52 g of a clear yellow oil containing of a mixture of **192** (304 mg, 20%) and **190** (288 mg, 19%) which was separated by TLC (80% hexane, 20% ethyl acetate)into two fractions which were identified as a mixture of **192** and**200**, and **190**. Pyrolysis(400 °C, 10^{-4} mm Hg) of the mixture containing **192** and**200** gave exclusively **200** (95%).

200: R_f=0.49 (70% hexane, 30% ether); **IR** (neat): 3050, 2980, 2940, 1722, 1650,

1255, 1125 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.26 (t, 3H, J=7.2 Hz), 2.27 (m, 2H), 2.42 (m, 2H), 4.19 (q, 2H, J=7.2 Hz), 4.88 (dt, 1H, J_1=7.4 Hz, J_2=5.6 Hz), 6.26 (d, 1H, J=7.4 Hz), 6.42 (t, 1H, J=6.5Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.1 (CH_3), 25.2 (CH_2), 26.2 (CH_2), 61.2 (CH_2),109.4 (CH), 142.3 (CH), 144.8 (C), 163.1 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 168 (M^+, 40), 95 (51), 85 (61), 67 (70), 55 (100). **HRMS Calc'd for** $C_9H_{12}O_3$: 168.0786; **Found:** 168.0801.

190: This was found to be a mixture of vinylcyclopropanes (7:1) **R_f**=0.39 (80% hexane, 20% ethyl acetate). The major isomer exhibited the following spectral data.**^{1}H-NMR** ($CDCl_3$) δ 1.25 (t, 3H, J=7.1 Hz), 1.67 (dd, 1H, J_1=5.1 Hz, J_2=8.5 Hz), 2.05 (m, 1H), 2.23 (m, 1H), 4.18 (t, 1H, J=7.3 Hz), 5.06 (m, 2H), 6.28 (dd, 1H, J_1=17.1 Hz, J_2=10.6 Hz), 9.29 (d, 1H, J=6.1 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.1, 19.4, 35.8, 38.9, 61.8, 114.9, 134.6, 169.9, 198.3.

1-Carboethoxy-4-formylcyclopent-1-ene (201). 190 (40 mg, as a 7:1 mixture of isomers) was pyrolysed (T_e=200 °C, 10^{-4} mm, T_p=500 °C) to give a yellow oil which was filtered through 5 g of silica gel using CH_2Cl_2 as eluant to give **201** (38 mg, 95%). An analytical sample was obtained by flash chromatography (silica gel) with hexane/ether (9:1) as eluant.

201: **R_f**=0.17 (70% hexane, 30% ether); **IR** (neat): 2980, 2930, 2710, 1745, 1725, 1650 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.26 (t, 3H, J=7.1 Hz), 2.61-2.79 (m, 1H), 2.8-2.98 (m, 3H), 3.13-3.23 (m, 1H), 4.17 (q, 2H, J=7.1 Hz), 6.66 (m, 1H), 9.66 (d, 1H, J=1.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 14.2 (CH_3), 31.8 (CH_2), 33.1 (CH_2), 48.8 (CH),60.3 (CH_2), 140.9 (CH), 143.0 (C), 164.5 (C), 201.5 (CH); **Mass Spectrum** (70 eV, m/e (rel. int.)): 168 (M^+, 2), 161 (40), 133 (70), 105 (85), 79 (88), 77 (89), 67 (97), 55 (100).

3-(3'-Furyl)-2-carbethoxy-2-ethenyloxirane (189). To a stirred solution of lithium diisopropylamide (5.2 mmol), prepared from diisopropylamine (0.73 mL) and *n*-butyllithium (2.09 mL, 2.5 M in hexane), in 8 mL THF and 1.0 mL of HMPA at -110 °C was added a solution of ethyl 2-bromo-2-butenoate (0.965 g, 5.0 mmol), in 17 mL of THF, cooled to -105 °C, over a period of 25 min, while maintaining the temperature of the reaction at or below -100 °C. After the addition was complete, the reaction mixture was stirred for 15 min and then treated with a solution of 3-furaldehyde (0.43 mL, 5.0 mmol) in 7 mL of THF cooled to -105 °C. This addition took about 5 min and was also carried out at such a rate that the temperature of the reaction remained at or below -100 °C. Stirring was continued at -100 °C or less for 0.5 h and at -78 °C for 1 h whereupon the temperature was raised to -50 °C. The reaction was quenched with saturated NH_4Cl solution, and diluted with ether. The ether layer was washed with 3N HCl (1x15 mL), water (3x15 mL), brine, and dried over Na_2SO_4. The solvent was removed in vacuo, to give 1.04 g of a 6:1 mixture of **189** and starting material. The residue was filtered through silica gel (10% deactivated with H_2O), with hexane/ether (95:5) as eluant to give pure **189** (730 mg, 70%).

189: R_f=0.44 (80% hexane, 20% ethyl acetate); **IR** (neat): 3145, 2980, 1730, 1640, 1595, 1045, 1025 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.31 (t, 3H, J=7.2 Hz), 4.22 (s, 1H), 4.26 (qd, 2H, J_1=7.1 Hz, J_2=1.5 Hz), 5.37 (dd, 1H, J_1=10.8 Hz, J_2=1.5 Hz), 5.45 (dd, 1H, J_1=17.2 Hz, J_2=1.5 Hz), 6.09 (dd, 1H, J_1=17.2 Hz, J_2=10.8 Hz), 6.32 (m, 1H), 7.32 (m, 1H), 7.37 (m, 1H); **^{13}C-NMR** ($CDCl_3$) δ 13.7 (CH_3), 58.4 (CH), 61.5 (CH_2), 62.5 (C),109.4 (CH), 118.3 (C), 119.8 (CH_2), 127.5 (CH), 141.6 (CH), 142.6 (CH), 168.6 (C); **Mass Spectrum** (70 eV, m/e (rel. int.)): 208 ($M^{+\cdot}$, 3), 125 (100), 107 (28), 97 (55), 55 (59). **HRMS Calc'd for** $C_{11}H_{12}O_4$: 208.0736 **Found:** 208.0744. **Anal. Calc'd**

for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81; **Found:** C, 63.34; H, 5.82.

5-(3'-furyl)-2-carbomethoxyoxolane (208b) and its isomer (208a). To a solution of **196** (211 mg, 1.01 mmol) in methanol (10 mL) was added dry Mg (0.25 g, 10.1 mmol). The reaction was stirred for 2 h at room temperature, whereupon it was diluted with ether, and 3N HCl was added (with cooling) to dissolve the unreacted Mg. The aqueous layer was separated and extracted with ether (3x10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent yielded a yellow oil (198 mg) which was filtered through silica gel (95% hexane, 10% ether) to give an inseparable mixture of **208b** and **208a** (174 mg, 82%, 64:36). The spectral data was obtained on the mixture of epimers.

208b and **208a**: R_f=0.58 (70% hexane, 30% ethyl acetate); **IR** (neat): 3160, 2960, 1743, 1605, 1503, 1083 cm^{-1}.

208b: **^{1}H-NMR** ($CDCl_3$) δ 1..81-2.45 (m, 4H), 3.74 (s, 3H), 4.63 (dd, 1H, J_1=8.0 Hz, J_2=6.0 Hz), 5.13 (dd, 1H, J=6.9 Hz), 6.36 (bs, 1H), 7.36 (bs, 1H), 7.38 (bs, 1H); **^{13}C-NMR** ($CDCl_3$) δ 30.6 (CH_2), 32.7 (CH_2), 52.0 (CH_3), 75.0 (CH), 76.8 (CH), 100.5 (C), 109.0 (CH), 139.4 (CH), 143.4 (CH), 176.5 (C).

208a: **^{1}H-NMR** ($CDCl_3$) δ 1..81-2.45 (m, 4H), 3.74 (s, 3H), 4.54 (dd, 1H, J_1=8.3 Hz, J_2=4.6 Hz), 4.99 (m, 1H,), 6.48 (bs, 1H), 7.36 (bs, 1H), 7.46 (bs, 1H); **^{13}C-NMR** ($CDCl_3$) δ 30.2 (CH_2), 32.4 (CH_2), 52.0 (CH_3), 75.7 (CH), 77.2 (CH), 98.0 (C), 108.7 (CH), 139.9 (CH), 143.3 (CH), 176.5 (C).

5α-(3'-furyl)-2α-carbomethoxy-2methyloxolane (209a) and **5α-(3'-furyl)-2β-carbomethoxy-2methyloxolane (209b).** To a stirred 0.2M solution of potassium hexamethyldisilazane (KHMDS, 12.76 mmol, 25.5 mL, 0.5 M solution in

toluene, 40 mL THF) at -110 °C was added a mixture of **208a** and **208b** (1.0 g, 5.1 mmol) in 31 mL THF (0.5 M, precooled to -110°C). The resulting solution was warmed to -78 °C over 1 h and stirred at that temperature for an additional 3.5 h. Methyl iodide (8 mL, 127 mmol) was added neat and the reaction slowly warmed to room temperature. The reaction was quenched with sat. NH_4Cl and diluted with ether. The aqueous layer was extracted with ether (4x20 mL). The combined ether layers were washed with 3 N HCl (1x20 mL, pH<7), water (4x15 mL), brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give 955 mg of a pale yellow oil which was purified by flash chromatography on silica gel (90% hexane, 10% ethyl acetate) to yield **209a** and **209b** (50:50, 589 mg, 55%) as well as **208a** and **208b** (160 mg, 27%).

The spectral data was obtained from a mixture of both epimers: R_f=0.34 (70% hexane, 30% ether); **IR** (neat): 3160, 2960, 1740, 1600, 1060 cm^{-1}. **Anal. Calc'd for** $C_{11}H_{14}0_4$: C, 62.85; H, 6.71; **Found:** C, 62.78; H, 6.71.

209a: ^{1}**H-NMR** ($CDCl_3$) δ 1.50 (s, 3H), 1.90-2.53 (series of multiplets, 4H), 3.72 (s, 3H), 5.6 (m, 1H), 6.44 (bs, 1H), 7.38 (bs, 1H), 7.42 (bs, 1H).

209b: ^{1}**H-NMR** ($CDCl_3$) δ 1.53 (s, 3H), 1.9-2.53 (series of multiplets, 4H), 3.74 (s, 3H), 5.6 (m, 1H), 6.36 (bs, 1H), 7.36 (bs, 1H), 7.38 (bs, 1H).

5α-(3'-furyl)-2α-hydroxymethyl-2β-methyloxolane (210a) and **5α-(3'-furyl)-2β-hydroxymethyl-2α-methyloxolane (210b)**. To a suspension of lithium aluminum hydride (327 mg, 8.6 mmol) in ether (20 mL) was added a mixture of **209b** and **209a** (905 mg, 4.31 mmol) in 15 mL ether at 0 °C. After 2 h, 327 μL of H_2O, 981 μL of KOH (10% w/w in H_2O), and 327 μl of H_2O were added in succession. The solution was stirred for 0.5 h. Na_2SO_4 was added, and the mixture filtered. The solvent was removed in vacuo to give 775 mg (98%) of a mixture of **210a** and **210b** (50:50) as a clear oil. The

two diastereomers were separated on a flash silica column (70% hexane, 30% ethyl acetate).

210a: R_f=0.29 (70% hexane, 30% ethyl acetate); **IR** (neat): 3436, 3175, 2970, 1050 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.20 (s, 3H), 1.60-1.75 (m, 1H), 1.80-1.95 (m, 1H), 2.00-2.15 (m, 1H), 2.17-2.25 (m, 1H), 2.35 (bs, 1H), 2.35 (bs, 1H), 3.38 (m, 2H), 4.92 (dd, 1H, J_1=8.1 Hz, J_2=6.2 Hz), 6.34 (bs, 1H), 7.33 (m, 2H); **^{13}C-NMR** ($CDCl_3$) δ 23.4 (CH_3), 33.4 (CH_2), 34.1 (CH_2), 69.0 (CH_2),73.1 (CH), 83.5 (C), 108.6 (CH), 126.9 (C), 139.2 (CH), 143.3 (CH); **Mass Spectrum** (CI, m/e (rel. int.)): 183 (25, M^++1), 181 (70), 165 (100), 151 (15), 137 (10), 115 (10). **HRMS Calc'd for** $C_{10}H_{15}O_3$: 183.1021 **Found:** 183.1011

210b: R_f=0.23 (70% hexane, 30% ethyl acetate); **IR** (neat): 3431, 3180, 2970, 1029 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.12 (s, 3H), 1.65-1.80 (m, 1H), 1.90-2.10 (m, 2H), 2.11-2.25 (m, 2H), 3.47 (d, 2H, J=6.3 Hz), 4.89 (dd, 1H, J_1=10.6 Hz, J_2=8.7 Hz), 6.36 (d, 1H, J=1 Hz), 7.36 (bs, 2H); **^{13}C-NMR**($CDCl_3$): δ 23.5 (CH_3), 33.4 (CH_2), 34.2 (CH_2), 69.0 (CH_2), 73.1 (CH), 83.6 (C), 108.7 (CH), 127.0 (C), 139.2 (CH), 143.4 (CH); **Mass Spectrum** (CI, m/e (rel. int.)): 183 (25, M^++1), 181 (55), 165 (100), 151 (20), 137 (15), 115 (15). **HRMS Calc'd for** $C_{10}H_{15}O_3$: 183.1021 **Found:** 183.1003.

5α-(3'-furyl)-2α-[(toluenesulfonyl)methoxy-2β-methyloxolane (214a). Alcohol **210a** (998 mg, 5.48 mmol) was added to 27 mL of pyridine and cooled with stirring to 0 °C. *p*-toluenesulfonyl chloride (3.14 g, 16.45 mmol) was added and the flask was stoppered and placed in the refrigerator overnight. The mixture was then warmed to room temperature and poured over 10 mL ice water. The aqueous solution was extracted with ether (3x10 mL). The ether layers were combined and washed with 3N HCl (1x5 mL), sat. $CuSO_4$ (4x5 mL), sat. NaCl (2x5 mL), and dried over Na_2SO_4. The solvent

was removed in vacuo to give pure **214a** (1.75 g, 95%).

214a: mp. 68.5-69.5 °C; R_f=0.35 (80% hexane, 20% ethyl acetate); **IR** (neat): 3146, 2975, 1359, 1120 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.23 (s, 3H), 1.7-2.0 (m, 2H), 2.10-2.25 (m, 3H), 2.43 (s, 3H), 3.87 (dd, 2H, J_1=17.4 Hz, J_2=9.5 Hz), 4.91 (dd, 1H, J_1=8.5 Hz, J_2=5.4 Hz), 6.31 (d, 1H, J=1.5 Hz), 7.28 (m, 2H), 7.33 (m, 2H), 7.74, (d, 2H, J=8.3 Hz); **^{13}C-NMR**($CDCl_3$): δ 21.5 (CH_3), 24.2 (CH_3), 33.4 (CH_2), 35.1 (CH_2), 73.9 (CH), 74.7 (CH_2), 81.1 (C), 108.7 (CH), 126.6 (C), 127.9 (CH, double intensity), 129.8 (CH, double intensity), 133.2 (C), 139.4 (CH), 143.3 (CH), 144.7 (C); **Anal. Calc'd for** $C_{17}H_{20}O_5S$: C, 60.69; H, 5.99; **Found:** C, 60.61; H, 6.02.

5α-(3'-furyl)-2β-[(toluenesulfonyl)methoxy-2α-methyloxolane (214b). Treatment of alcohol **210b** (180 mg, 0.99 mmol) in a similar fashion gave 318 mg (96%) of tosylate **214b** as a clear yellow oil.

214b: R_f=0.42 (80% hexane, 20% ethyl acetate); **IR** (neat): 3146, 2975, 1358, 1097 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.23 (s, 3H), 1.70-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.00-2.15 (m, 1H), 2.15-2.30 (m, 1H), 2.42 (s, 3H), 3.88 (dd, 1H, J_1=12.8 Hz, J_2=9.5 Hz), 6.30 (m, 1H), 7.33 (m, 4H), 7.80 (m, 2H); **^{13}C-NMR**($CDCl_3$): δ 21.5 (CH_3), 24.6 (CH_3), 33.2 (CH_2), 34.3 (CH_2), 74.5 (CH), 74.6 (CH_2), 81.0 (C), 108.6 (CH), 127.0 (C), 127.9 (double intensity, CH), 129.7 (double intensity, CH), 133.2 (C), 139.1 (CH), 143.2 (CH), 144.7 (C).

5α-(3'-furyl)-2α-(iodomethyl)-2β–methyloxolane (173a). To a stirred solution of HMPA (30 mL) containing 30 drops of H_2O and NaI (3.68 g, 24.5 mmol) was added tosylate **214a** (2.39 g, 7.11 mmol). The mixture was stirred at 120 °C overnight. The reaction was allowed to cool to room temperature, diluted with H_2O (30 mL), and extracted with Et_2O (5 x 50 mL). The organic layers were combined and washed with H_2O (6 x 20

mL) and brine (2 x 20 mL). Filtration and solvent evaporation gave a brown oil (1.47 g) which was purified by flash chromatography on silica gel (95% hexane, 5% ethyl acetate) to yield **173a** (1.34 g, 59%) as a clear liquid.

173 a: b.p. 50 °C (0.05mm Hg, kugelrohr); R_f=0.35 (95% hexane, 5% ethyl acetate); **IR** (neat): 3140, 2970, 2870, 1208, 1024 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.46 (s, 3H), 1.80-2.35 (m, 4H), 3.30 (m, 2H), 5.00 (m, 1H), 6.43 (m, 1H), 7.37 (m, 1H), 7.40 (m, 1H); **^{13}C-NMR**($CDCl_3$): δ 17.5 (CH_2), 26.3 (CH_3), 33.9 (CH_2), 37.2 (CH_2), 74.2 (CH), 81.6 (C), 108.8 (CH), 127.1 (C), 139.3 (CH), 143.3 (CH); **Anal. Calc'd for** $C_{10}H_{13}O_2$: C, 41.11; H, 4.48; **Found:** C, 41.00; H, 4.43.

5α-(3'-furyl)-2β-(iodomethyl)-2α–methyloxolane (173b). Tosylate **214b** (2.06 g, 6.13 mmol) was treated in a similar fashion to give, after purification, **173b** (1.33 g, 58%).

173 b: b.p. 50 °C (0.05mm Hg, kugelrohr); R_f=0.39 (95% hexane, 5% ethyl acetate); **IR** (neat): 3143, 2970, 2869, 1205, 1028 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.47 (s, 3H), 1.90-2.35 (m, 4H), 3.32 (m, 2H), 5.02 (m, 1H), 6.35 (m, 1H), 7.36 (m, 2H); **^{13}C-NMR**($CDCl_3$): δ 17.6 (CH_2), 26.7 (CH_3), 33.9 (CH_2), 37.3 (CH_2), 74.4 (CH), 81.7 (C), 108.6 (CH), 126.9 (C), 139.3 (CH), 143.3 (CH).

Bis-1,3-propane dithioketal of 5α-(3'-furyl)-2α-((formyl)methyl)-2β–methyloxolane (174a). 1,3-Dithiane (226 mg. 1.88 mmol) was dissolved in THF (9.4 mL, 0.2M) and cooled to -40 °C. *n*-BuLi (0.94 mL, 2.2M in hexanes) was added dropwise. The temperature was raised to -20 °C and stirring continued for 2 h. Iodide **173a** (500 mg, 1.71 mmol) was dissolved in a mixed solvent (3.4 mL, 0.5M) composed of HMPA, diglyme, and THF (2:3:3), and cooled to -78 °C. The lithiated dithiane was added dropwise and stirring continued for 2 h at -78 °C and then 12 h at -20 °C. The

reaction was warmed to room temperature, diluted with aq. NH_4Cl and extracted with Et_2O (3 x 15 mL). The organic layers were combined, washed with H_2O (4 x 5 mL) and brine (2 x 5 mL), and dried over Na_2SO_4. This was filtered, and the solvent evaporated to give 598 mg of a yellow oil. Purification by flash chromatography on silica gel (95% hexane, 5% ethyl acetate) yielded 240 mg of **173a** and 104 mg of **174a** (41% based on recovered starting material).

174a: R_f=0.56 (80% hexane, 20% ethyl acetate); **IR** (neat): 3133, 2965, 2898, 1244, 1024 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.50 (s, 3H), 1.70-1.95 (m, 5H), 2.00-2.15 (m, 2H), 2.15-2.30 (m, 1H), 2.75 (dt, 2H, J_1=14.0 Hz, J_2=3.9 Hz), 2.84-2.96 (m, 2H), 4.17 (t, 1H, J=5.9 Hz), 4.94 (t, 1H, J=6.8 Hz), 6.38 (d, 1H, J=1.6 Hz), 7.34 (t, 1H, J=1.7 Hz), 7.39 (t, 1H, J=0.7 Hz); **^{13}C-NMR**($CDCl_3$): δ 25.5 (CH_2), 26.5 (CH_3), 31.1 (CH_2), 31.2 (CH_2), 33.6 (CH_2), 38.2 (CH_2), 43.2 (CH), 48.0 (CH_2), 73.3 (CH), 82.6 (C), 108.9 (CH), 127.0 (C), 139.2 (CH), 143.2 (CH); **Anal. Calc'd for** $C_{14}H_{20}O_2S_2$: C, 59.12; H, 7.09; **Found:** C, 59.08; H, 7.09.

Bis-1,3-propane dithioketal of 5α-(3'-furyl)-2β-((formyl)methyl)-2α-methyloxolane (174b). In a similar fashion **173b** (500 mg, 1.88 mmol) was treated with the lithium anion of dithiane (prepared from 1,3-dithiane (226 mg, 1.88 mmol) and *n*-BuLi (0.94 mL, 2.2M in hexanes) to give, after purification, **173b** (138 mg) and **174b** (120 mg, 33% based on recovered starting material).

174b: R_f=0.61 (80% hexane, 20% ethyl acetate); **IR** (neat): 3137, 2967, 2930, 1276, 1027 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.36 (s, 3H), 1.70-2.15 (m, 6H), 2.15-2.25 (m, 2H), 2.70-2.85 (m, 2H), 2.90-3.05 (m, 2H), 4.19 (t, 1H, J=6.0 Hz), 4.94 (t, 1H, J=6.8 Hz), 6.35 (d, 1H, J=0.8 Hz), 7.34 (d, 1H, J=2.2 Hz), &.35 (d, 1H, J=2.2Hz); **^{13}C-NMR**($CDCl_3$): δ 25.5 (CH_2), 27.4 (CH_3), 31.1 (double intensity, CH_2), 33.5 (CH_2), 38.2 (CH_2), 43.1 (CH), 46.9 (CH_2), 73.4 (CH), 82.6 (C), 108.8 (CH), 127.8 (C), 139.3

(CH), 143.2 (CH).

Bis-1,3-propane dithioketal of cis-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3'-bifuran]-5-yl)-2-pentanone (175a). 174a (60 mg, 0.211 mmol) was dissolved in THF (0.92 mL) and cooled to -40 °C. *n*-BuLi (0.14 mL, 2.2M in hexanes) was added dropwise and the mixture stirred for 7 h at -20 °C. The mixture was cooled to -78 °C and HMPA (0.14 mL) was added. After 5 min, isobutyl chloride (0.1 mL, 0.633 mmol) was added dropwise and the reaction stirred overnight, allowed to warm to room temperature, and the solvent evaporated. The residue was diluted with H_2O and extracted with Et_2O (4 x 10 mL). The organic layers were comnbined, washed with H_2O (3 x 5 mL) and brine (2 x 5 mL), dried over Na_2SO_4, filtered, and the solvent evaporated to give 53 mg of a brown oil. Purification by flash chromatography on silica gel (95% hexane, 5% ethyl acetate) gave 22 mg (41%) of **175a** as a clear oil.

175a: R_f=0.64 (80% hexane, 20% ethyl acetate); **IR** (neat): 3115, 2953, 1160, 1026 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.96 (d, 3H, J=3.7 Hz), 0.98 (d, 3H, J=3.7 Hz), 1.47 (s, 3H), 1.75-2.05 (m, 7H), 2.05-2.30 (m, 4H), 2.70-2.90 (m, 4H), 4.93 (m, 1H), 6.37 (d, 1H, J=1.4 Hz), 7.33 (t, 1H, J=1.7 Hz), 7.37 (d, 1H, J=0.7 Hz); **^{13}C-NMR**($CDCl_3$): δ 25.0 (triple intensity, CH_2, CH_3, CH_3), 25.5 (CH), 26.9 (double intensity, CH_2), 27.3 (CH_3), 33.1 (CH_2), 39.0 (CH_2), 49.0 (CH_2), 50.3 (CH_2), 53.0 (CH), 72.3 (CH), 84.2 (C), 109.1 (CH), 127.7 (C), 139.3 (CH), 143.0 (CH); **Mass Spectrum** (70 eV, m/e (rel. int.)): 340 (M^+, 16), 189 (17), 175 (7), 152 (10), 151 (100), 107 (5).

Bis-1,3-propane dithioketal of trans-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3'-bifuran]-5-yl)-2-pentanone (175b). In a similar fashion, **174b** (85 mg, .299 mmol) was lithiated (0.25 mL *n*-BuLi, 2.2M in hexanes), and condensed with

isobutyl chloride (0.11 mL, 1.09 mmol) to give after purification, 72 mg (71%) of **175b** as a clear oil.

175b: R_f=0.71 (80% hexane, 20% ethyl acetate); **IR** (neat): 3139, 2952, 1238, 1027 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.01 (t, 6H, J=6.4 Hz), 1.45 (s, 3H), 1.80-2.00 (m, 7H), 2.10-2.45 (m, 4H), 2.70-2.90 (m, 4H), 4.94 (dd, 1H, J_1=8.6 Hz, J_2=5.8 Hz), 6.35 (m, 1H), 7.34 (m, 1H); **^{13}C-NMR**($CDCl_3$): δ 25.1 (triple intensity, CH_2, CH_3, CH_3), 25.6 (CH), 26.9 (CH_2), 29.5 (CH_3), 33.8 (CH_2), 39.0 (CH_2), 48.6 (CH_2), 49.1 (double intensity, CH_2), 53.0 (C), 73.2 (CH), 84.0 (C), 108.8 (CH), 127.9 (C), 139.2 (CH), 143.1 (CH); **Mass Spectrum** (70 eV, m/e (rel. int.)): 340 (M^+, 19), 189 (18), 175 (8), 152 (10), 151 (100), 107 (7).

Cis-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3'-bifuran]-5-yl)-2-pentanone (1a). $AgNO_3$ (36 mg, 0.212 mmol) and *n*-chlorosuccinimide (25 mg, 0.188 mmol) were dissolved in a mixed solvent (composed of CH_3CN and H_2O (2.5:1)) and cooled to 0 °C. **175a** (16 mg, 0.047 mmol) was added in CH_3CN (0.5 mL). After 5 min, DMSO (0.1 mL) was added and the mixture warmed to room temperature. Filtration through a small pad of silica gel removed the inorganic salts. The filtrate was diluted with H_2O and extracted with $CHCl_3$ (3 x 5 mL). The extracts were washed with aqueous ammonium acetate. The ammonium acetate layer was back-extracted with $CHCl_3$ (3 x 5 mL). All organic layers were combined, washed with H_2O and brine, dried over Na_2SO_4, filtered and the solvent evaporated to give 10 mg of a yellow-brown oil. Purification by flash chromatography on silica gel (90% hexane, 10% ethyl acetate) gave 4 mg (34%) of **1a** as a clear oil.

1a: R_f=0.60 (80% hexane, 20% ethyl acetate); **IR** (neat): 3142, 2958, 1710, 1026 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.85 (d, 3H, J=3.4 Hz), 0.88 (d, 3H, J=3.4 Hz), 1.31 (s, 3H),

1.80-1.95 (m, 2H), 2.05-2.20 (m, 2H), 2.20-2.30 (m, 1H), 2.30 (d, 2H, J=6.6 Hz), 2.66 (dd, 2H, J_1=26.7 Hz, J_2=5.0 Hz), 4.89 (t, 1H, J=7.1 Hz), 6.34 (s, 1H), 7.35 (s, 2H); **^{13}C-NMR**($CDCl_3$): δ 22.5 (double intensity, CH_3), 24.4 (CH), 26.7 (CH_3), 33.0 (CH_2), 37.0 (CH_2), 53.6 (CH_2), 54.2 (CH_2), 72.5 (CH), 81.7 (C), 108.8 (CH), 139.2 (CH), 143.3 (CH), 209.4 (C).

Trans-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3'-bifuran]-5-yl)-2-pentanone (1b). In a similar fashion, **175b** (44 mg, 0.129 mmol) was treated with $AgNO_3$ (99 mg, 0.581 mmol) and *n*-chlorosuccinimide (69 mg, 0.518 mmol) in aqueous CH_3CN (2 mL) to give, after purification 12 mg (37%) of **1b**.

1b: **R_f**=0.63 (80% hexane, 20% ethyl acetate); **IR** (neat): 3144, 2958, 1709, 1028 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 0.89 (d, 6H, J=6.6 Hz), 1.31 (s, 3H), 1.90-2.05 (m, 2H), 2.05-2.25 (m, 3H), 2.33 (d, 2H, J=6.9 Hz), 2.67 (m, 2H), 4.89 (m, 1H), 6.34 (d, 1H, J=1.2 Hz), 7.35 (d, 2H, J=1.2 Hz); **^{13}C-NMR**($CDCl_3$): δ 22.5 (double intensity, CH_3), 24.4 (CH), 26.6 (CH_3), 33.0 (CH_2), 37.1 (CH_2), 53.7 (CH_2), 54.3 (CH_2), 72.6 (CH), 81.7 (C), 108.8 (CH), 127.3 (C), 139.1 (CH), 143.2 (CH), 209.1 (C).

3-cyano-6-(3'-furyl)-3-methylhexanitrile (210c). Tosylate **214a** (3.30 g, 9.82 mmol) was dissolved in DMSO (19.64 mL) and added drowise to a mixture of KCN (2.55 g, 39.28 mmol) and 18-Crown-6 (1.35 g, 4.91 mmol) in DMSO (5 mL) and heated to 130 °C. After stirring at 130 °C for 1.5 h the reaction was allowed to cool to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (5 x 50 mL). The organic layers were combined and washed with H_2O (4 x 25 mL) and brine (2 x 25 mL). The aqueous washes were back-extracted with EtOAc (3 x 10 mL). The back-extracts were washed with H_2O (1 x 10 mL) and brine (1 x 10 mL). All organic layers were then combined, dried over

Na_2SO_4,filtered, and the solvent evaporated to give 2.13 g of a dark brown oil. Purification by flash chromatography on silica gel (50% hexanes, 50% ethyl acetate) gave **210c** (580 mg, 31%).

210c: R_f=0.28 (50% hexane, 50% ethyl acetate); **IR** (neat): 3478, 3146, 2935, 2869, 2249, 1270, 1059 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.50 (s, 3H), 1.60-2.10 (m, 5H), 2.67 (m, 2H), 4.70 (m, 1H), 6.38 (s, 1H), 7.38 (m, 2H); **^{13}C-NMR** ($CDCl_3$): δ 23.5 (CH_3), 27.7 (CH_2), 32.6 (CH_2), 34.1 (CH_2), 34.5 (CH_2), 65.4 (CH), 108.1 (CH), 115.3 (C), 121.1 (C), 128.1 (C), 138.8 (CH), 143.2 (CH);**Mass Spectrum** (70 meV, m/e (rel. int.)): 218 (15, M^+), 200 (5), 165 (100), 160 (10), 122 (30), 97 (100), 69 (100). **HRMS Calc'd for** $C_{12}H_{14}O_2N_2$: 218.1055 **Found:** 183.1043; **Anal. Calc'd for** $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.46; **Found:** C, 65.17; H, 6.52.

Methyl 3-carbomethoxy-6-(3'-furyl)-3-methylhexanoate (19). Dinitrile **210c** (297 mg, 1.55 mmol) was dissolved in a mixed solvent system (5 mL, composed of 25% aqueous KOH and EtOH (2:1)) and heated to reflux for 2 h. The reaction was allowed to cool to room temperature, acidified with 3N HCl, and extracted with EtOAc (6 x 20 mL). The organic layers were combined, washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered, and the solvent evaporated. The residue was diluted with THF, cooled to 0 °C, and ethereal diazomethane added until a bright yellow color persisted. 30 min after the addition was complete, diazomethane was removed by gentle heating with a heat gun. The remaining solution was dried over Na_2SO_4, filtered, and the solvent evaporated to give 323 mg of a yellow oil. Purification by flash chromatography on silica gel (60% hexane, 40% ethyl acetate) gave **19** (178 mg, 51%) as a clear oil.

19: R_f=0.14 (70% hexane, 30% ethyl acetate); **IR** (neat): 3469, 3145, 2952, 1732, 1022 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 1.23 (s, 3H), 1.55-1.85 (m, 6H), 2.42 (d, 1H, J=15.8),

2.73 (d, 1H, J=15.8), 3.62 (s, 3H), 3.66 (s,3H), 4.60 (m, 1H), 6.35 (s, 1H), 7.35 (m, 2H); **^{13}C-NMR** ($CDCl_3$): δ 21.6 (CH_3), 32.5 (CH_2), 35.0 (CH_2), 42.5 (CH_2), 43.9 (C), 51.4 (CH_3), 51.8 (CH_3), 66.7 (CH), 108.3 (CH), 128.8 (C), 139.1 (CH), 143.3 (CH), 171.5 (C), 176.4 (C);**Mass Spectrum** (70 eV, m/e (rel. int.)): 284 (10, M^+), 252 (25), 160 (30), 128 (90), 110 (40), 94 (100), 69 (40). **HRMS Calc'd for** $C_{14}H_{20}0_6$: 284.1260 **Found:** 284.1269; **Anal. Calc'd for** $C_{12}H_{14}0_2N_2$: C, 59.14; H, 7.09; **Found:** C, 58.44; H, 7.12.

VI. REFERENCES

1. Boivin, T.L.B. *Tetrahedron* **1987**, *43*, 3309.
2. See for example: Painter, G.R.; Pressman, B.C. Top. Curr. Chem. 1982, 101, 83; Westley, J.W. Annu. Rev. Med. Chem. 1975, 10, 246; Ruff, M.D. Polyether Antibiotics: Naturally Occurring Acid Ionophores (Westley, J.W., ed.), Vol I, Ch. 6. Marcel Dekker, New York, 1982.
3. Westley, J.W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores* Vols. I and II. Marcel Dekker, New York, 1982.; Painter, G.R.; Pressman, B.C. *Top. Curr. Chem.* **1982**, *101*, 83.
4. Ruff, M.D. *Polyether Antibiotics: Naturally Occurring Acid Ionophores* (Westley, J.W., ed.), Vol I, Ch. 6, Marcel Dekker, New York, 1982.
5. Hanley, H.G.; Slack, J.D. *Polyether Antibiotics: Naturally Occurring Acid Ionophores* (Westley, J.W., ed.), Ch. 8, Marcel Dekker, New York, 1982; Reed, P.W.; Bokoch, G.M.; *ibid.*, Ch. 9; Osborne, M.W.; Wenger, J.; Zanko, M.; Kovzelove, F.; Cohen, M.R.; *ibid.*, Ch. 10.
6. Dunlop, A.P.; Peters, F.N. *The Furans.* Reinhold, New York 1953.
7. Limpricht, H. *Ann.* **1873**, *165*, 253.
8. Marckwald, W. *Berichte* **1887**, *20*, 2811.
9. Harries, C. *Berichte* **1901**, *34*, 1488.
10. Henninger *Ann. Chim.* **1886**, [vi] *7*, 216.
11. Marshall, T.R.; Perkin, W.H. *J. Chem Soc.* **1891**, 853.
12. Purdie, T.; Arup, P.S. *J. Chem. Soc.* **1910**, *97*, 3210.
13. Helferich, B.; Gehrke, M. *Berichte* **1921**, *54*, 2640.
14. Salkind, J *Berichte* **1923**, *56*, 187.

15. Brace N.O. *J. Am. Chem. Soc.* **1955**, *77*, 4157.

16. Botteghi, C.; Consiglio, G.; Ceccarelli, G. Stefani, A. *J. Org. Chem* **1972**, *37*, 1835.

17. Botteghi, C. *Gazz. Chim. Italiana* **1975**, *105* , 233.

18. Toda, F.; Komoda, T.; Akagi, K. *Bull. Chem. Soc., Japan* **1968**, *41*, 1493.

19. Gelin, R.; Gelin, S.; Albrand, M. *Bull. Chem. Soc., France* **1972**, 720.

20. Olsson, L.; Claesson, A. *Synthesis* **1979**, 743.

21. Beaulieu, P.L.; Morisset, V.M.; Garratt, D.G. *Tetrahedron Letters* **1980**, 129.

22. Albin, P.; Blum, J.; Dunkelblum, E.; Sassoon, Y. *J. Org. Chem.* **1975**, *40*, 2402.

23. Melot, J.M.; Texier-Boullet, F.; Foucaud, A. *Tetrahedron* **1988**, *44*, 2215.

24. Sullivan, W.W.; Ullman, D.; Shecter, H. *Tetrahedron Lett.* **1969**, 457.

25. Heiba, E.I.; Dessau, R.M. *J. Org. Chem.* **1974**, *39*, 3456.

26. Nishino, H. *Bull. Chem. Soc., Japan* **1985**, *58*, 1922.

27. Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *Tetrahedron Lett.* **1984**, *25*, 2817.

28. Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *J. Org. Chem.* **1985**, *50*, 3467.

29. Ichikawa, K.; Uemura, S.; Sugita, T. *Tetrahedron* **1966**, *22*, 407.

30. Uemura, S.; Ichikawa, K. *Bull. Chem. Soc., Japan* **1967**, *40*, 1016.

31. Ichikawa, K.; Uemura, S. *J. Org. Chem* **1967**, *32*, 1493.

32. Barinelli, L.S.; Nicholas, K.M. *J.Org. Chem.* **1988**, *53*, 2114.

34. Schweizer, E.E.; Liehr, J.G. *J. Org. Chem.* **1968**, *33*, 583.

35. McCombie, S.W.; Shankar, B.B.; Ganguly, A.K. *Tetrahedron Lett.* **1985**, *26*, 6301.

36. Dauben, W.G.; Hart, D.J. *Tetrahedron Lett.* **1978**, 4353.

37. Hercouet, A.; Le Corre,* M. *Tetrahedron* **1981**, *37*, 2855.

38. Wilson, C.L. *J. Am. Chem. Soc.* **1947**, *69*, 3002.

39. Dauben, W.G.; Shaffer, G.W. *J. Org. Chem.* **1969**, *34*, 2301.

40. McGreer, D.E.; McKinley, J.W. *Can. J. Chem.* **1973**, *51*, 1487.

41. Alonso, M.E.; Morales, A. *J. Org. Chem.* **1980**, *45*, 4530.

42. Hodge, P.; Edwards, J.A.; Fried, J.H. *Tetrahedron Lett.* **1966**, 5175.

43. Beard, C.; Dyson, N.H.; Fried, J.H. *Tetrahedron Lett.* **1966**, 3281.

44. Beard, C.; Harrison, I.T.; Kirkham, L.; Fried, J.H. *Tetrahedron Lett.* **1966**, 3287.

45. Breuer, E.; Melumad, D. *Tetrahedron Lett.* **1969**, 1875.

46. Blade-Font, A. *Tetrahedron Lett.* **1969**, 3607.

47. Braun, R.A. *J. Org. Chem.* **1963**, *28*, 1383.

48. Stogryn, E.L.; Gianni, M.H.; Passannante, A.J. *J. Org. Chem.* **1964**, *29*, 1275.

49. Vogel, E.; Günther, H. *Ang. Chem. Internat. Edit.* **1967**, *6*, 385.

50. Pommelet, J.; Manisse, N.; Chuche, J. *C.R. Acad. Sc. Paris, Ser. C* **1970**, *270*, 1894.

51. Pommelet, J.C.; Manisse, N.; Chuche, J. *Tetrahedron* **1972**, *28*, 3929.

52. Crawford, R.J.; Lutener, S.B.; Cockcroft, R.D. *Can. J. Chem.* **1976**, *54*, 3364.

55. Eberbach, W.; Seiler, W.; Fritz, H. *Chem. Ber.* **1980**, *113*, 875.

56. Paladini, J.C.; Chuche, J. *Tetrahedron Lett.* **1971**, 4383.

57. Paladini, J.C.; Chuche, J. *Bull. Soc. Chim. France* **1974**, 197.

58. Hiura, M., *Rep. Gifu. Agric. Coll.* **1943**, *50*, 1.

59. Denz, F.A.; Hanger, W.G. *J. Path. Bact.* **1961**, *81*, 91.

60. Hegarty, B.F; Kelly, J.R.; Park, R.J; Sutherland, M.D. *Aust. J. Chem.* **1970**, *23*, 107.

61. Kubota, T.; Matsuura, T. *Chem. Ind. London* **1956**, 521.

62. Kubota, T. in *Cyclopentanoid Terpene Derivatives*, eds. W.I. Taylor and A.R. Battersby, Marcel Dekker, New York, 1969, p. 312; Matsuura, T.; Nakajima, R.; Kubota, T. *Abstr. 8th Symp. Nat. Prod. Japan* **1964**, 59.

63. Hamilton, W.D.; Park, R.J.; Perry, G.J.; Sutherland, M.D. *Aust. J. Chem.* **1973**, *26*, 375.

64. Schneider, J.A.; Yoshihara, K.; Nakanishi, K.* *J. Chem Soc., Chem Commun.* **1983**, *7*, 352.

65. Oshima-Oba, K.; Sugiura, I.; Uritani, I. *Agr. Biol. Chem.* **1969**, *33*, 586. See also references 3-9 of this paper.

66. Oguni, I.; Uritani, I. *Plant & Cell Physiol.* **1971**, *12*, 507.

67. Akazawa, T.; Uritani, I.; Akazawa, Y. *Arch. Biochem. Biophys.* **1962**, *99*, 52.

68. Akazawa, T.; Uritani, I. *Agr. Biol. Chem.* **1962**, *26*, 131.

69. Burka, L.T.; Kuhnert, L. *Phytochemistry* **1977**, *16*, 2022.

70. Burka, L.T., Kuhnert, L.; Wilson, B.J.; Harris, T.M. *J. Am. Chem. Soc.* **1977**, *99*, 2302.

71. Boyd, M.R.; Burka, L.T.; Harris, T.M.; Wilson, B.J. *Biochimica et Biophysica Acta* **1974**, *337*, 184.

72. ref. 61; Kubota, T.; Matsuura, T. *J. Chem. Soc.* **1958**, 3667.

73. Burka, L.T.; Wilson, B.J.; Harris T.M. *J. Org. Chem.* **1974**, *39*, 2212.

74. Kondo, K.; Matsumoto, M. *Tetrahedron Lett.* **1976**, 4363.

75. Hudlicky, T.;* Fleming, A.; Lovelace, T.C. *Tetrahedron*, **1989**, *45*, 3021.

76. unpublished results by Hudlicky, T. and Barbieri, G.

77. Fleming, A; Research Dissertation, V.P.I. & S.U., Blacksburg, VA, 1990.

78. Hudlicky, T.; Maxwell, M.; Lovelace, T.C., manuscript in preparation.

79. Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691.

80. For a complete description of several pyrolytic methods as well as flash vacuum pyrolysis, see: Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry* Academic Press, New York, 1980.

81. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M.G. *Tetrahedron Lett.* **1987**, *28*, 5287; Youn, I.K.; Yon, C.S.; Pak, G. H. *Tetrahedron Lett.* **1986**, *27*, 2409.

82. Stephenson, B.; Solladie, G.; Mosher, H.S. *J. Am. Chem. Soc.* **1972**, *94*, 4184.

83. a. Jung, M.E.; Ornstein, P.L.; *Tetrahedron Lett.* **1977**, 2659. b. Haynes, R.K.; Holden, M. *Aust. J Chem.* **1982**, *35*, 517.

VII. APPENDIX: SELECTED SPECTRA

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Trans-4-methyl-1-(2,3,4,5-tetrahydro-5-methyl[2,3'-bifuran]-5-yl)-2-pentanone (1b).....113

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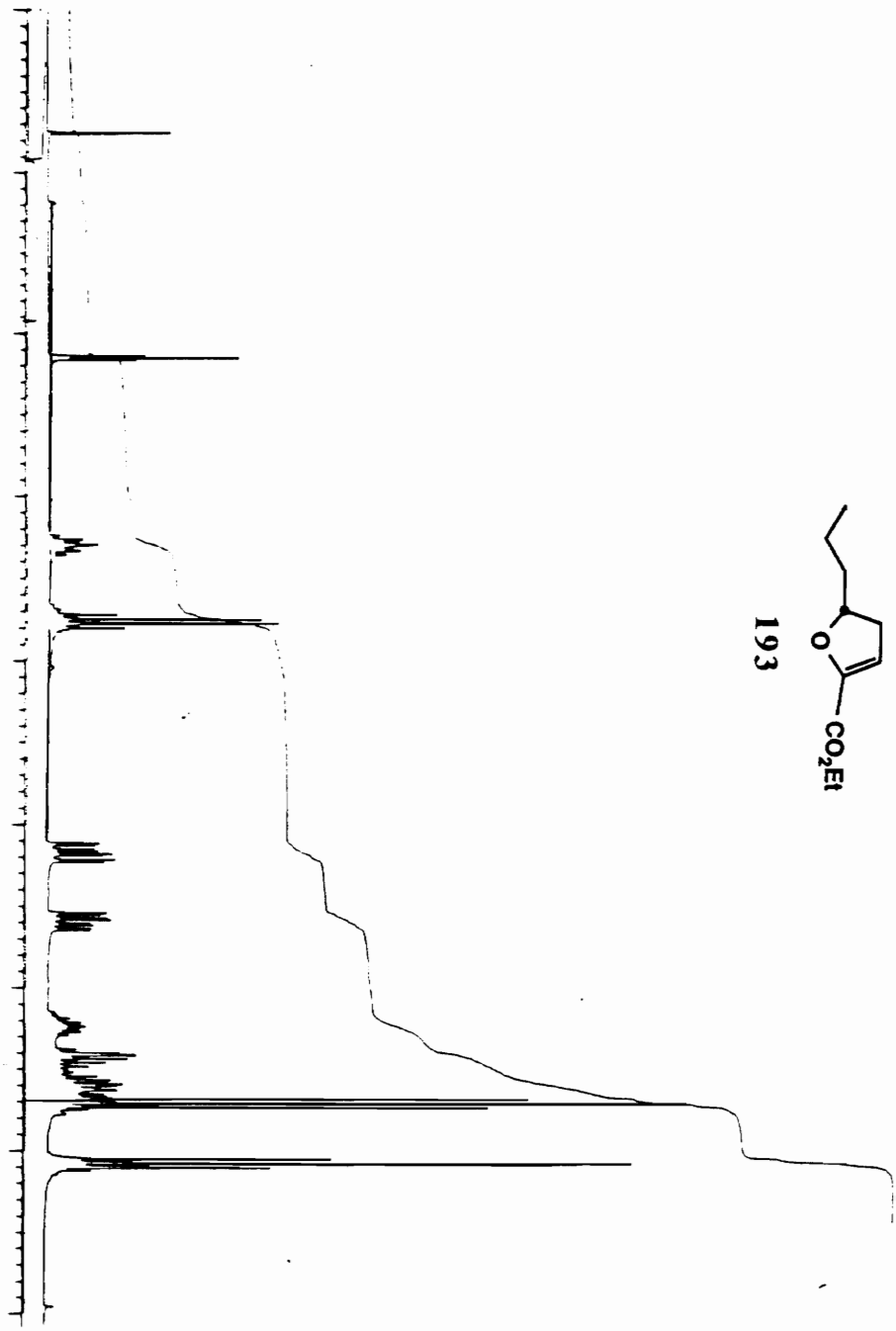

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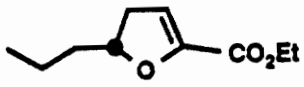

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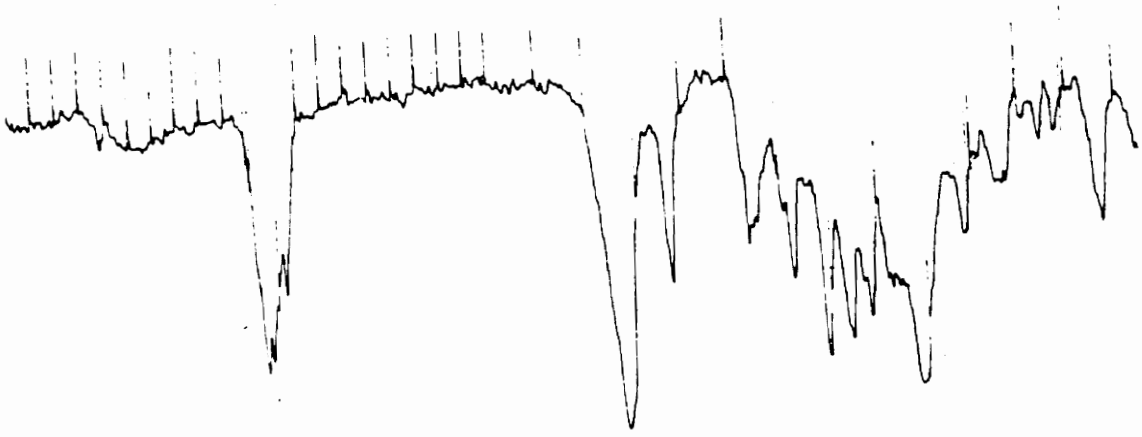

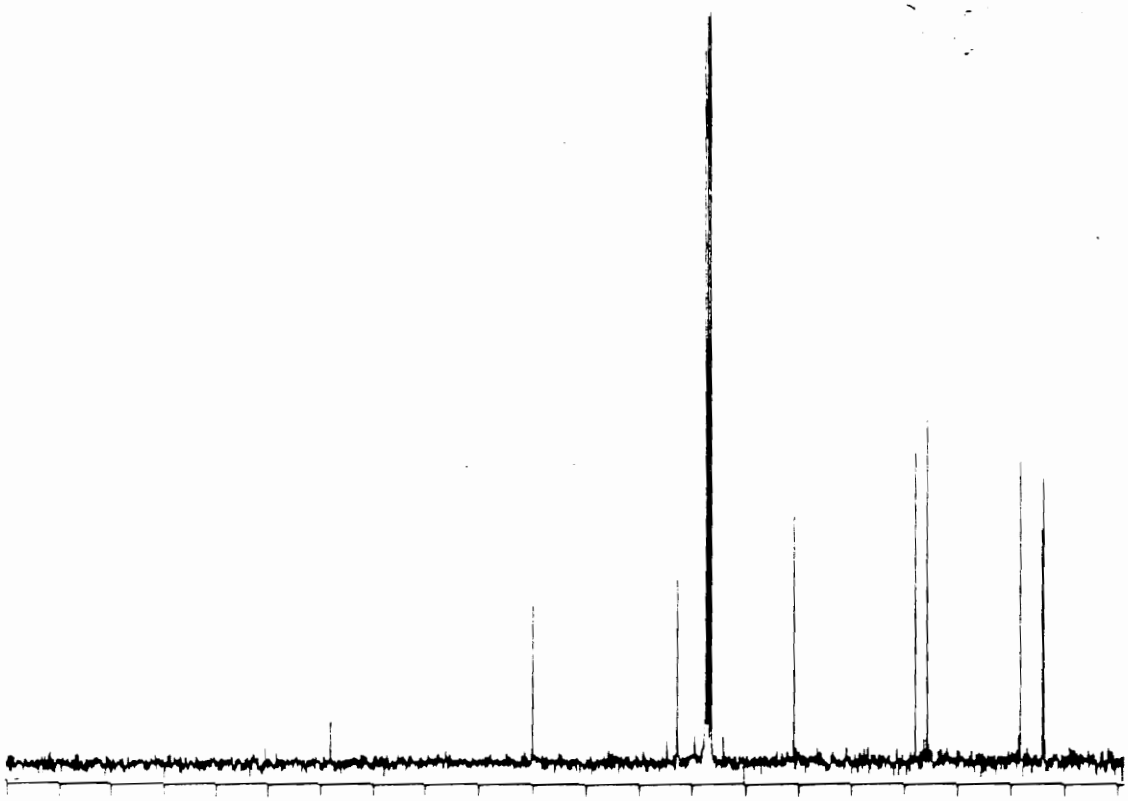

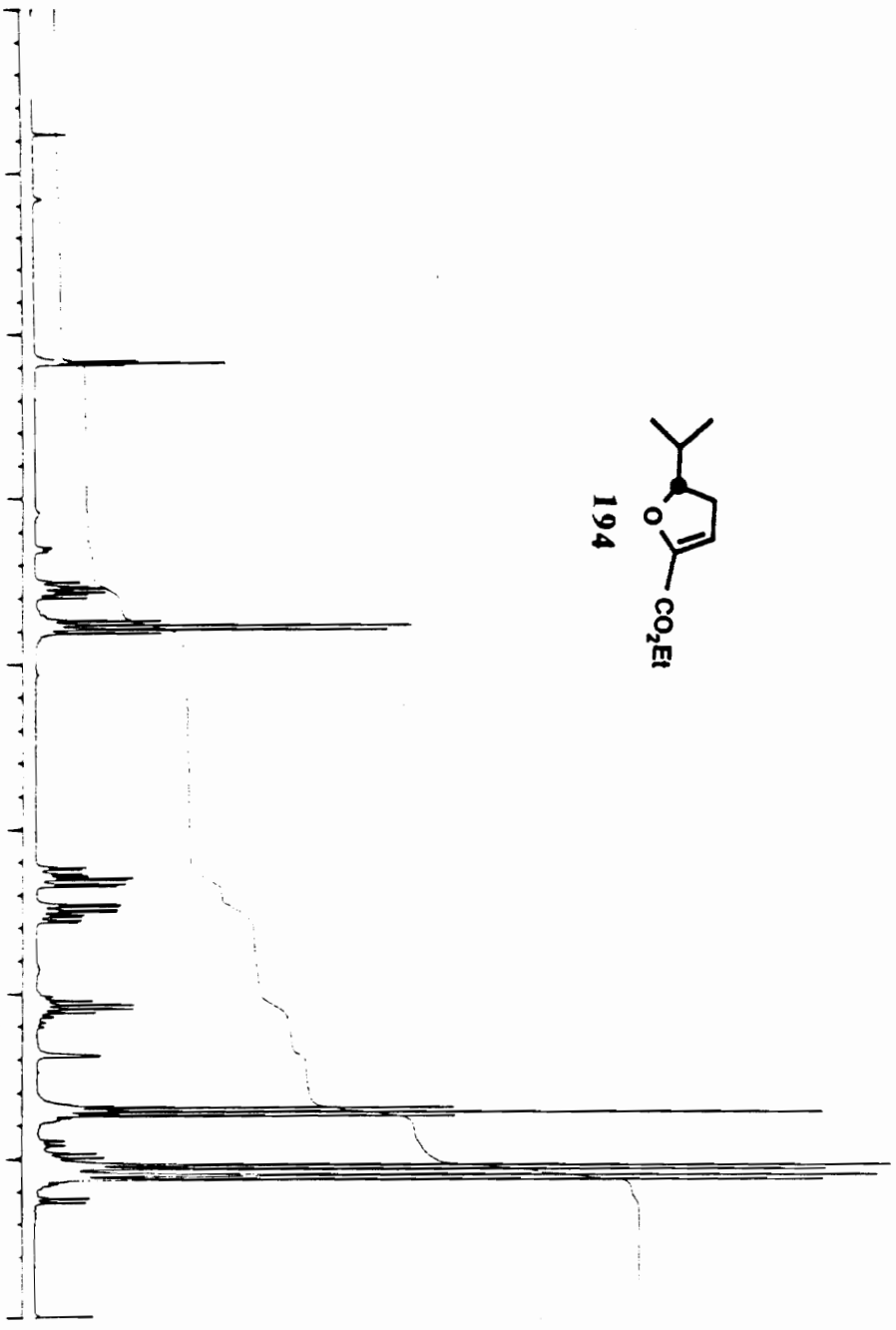

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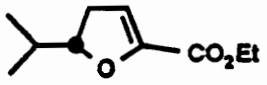

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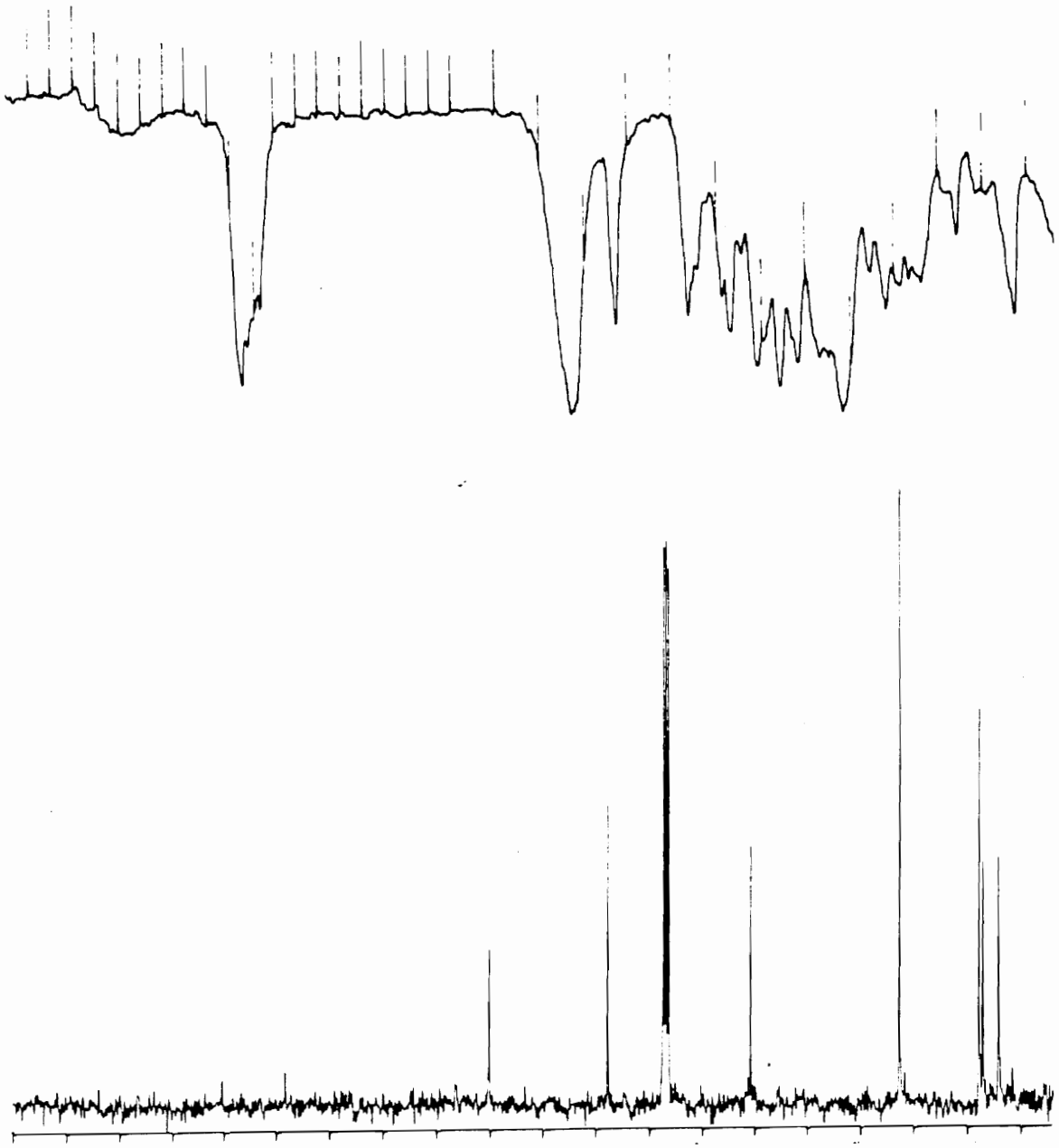

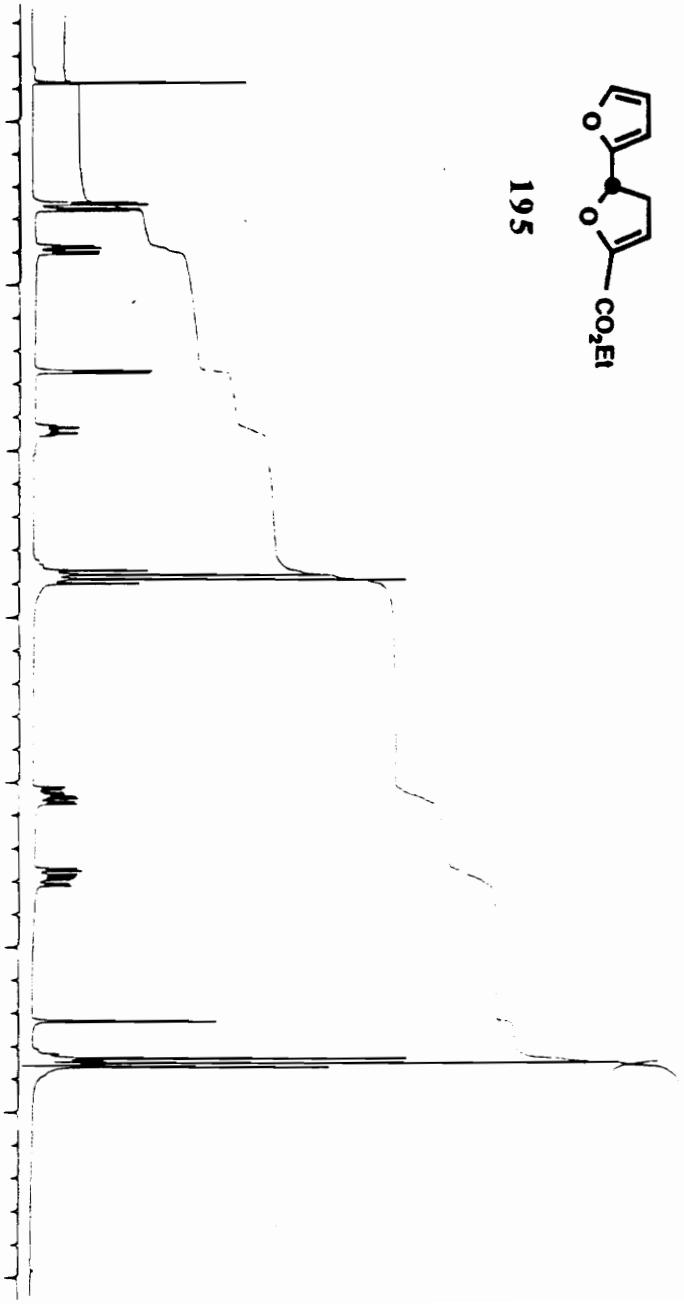

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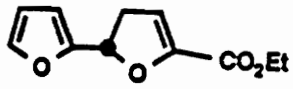

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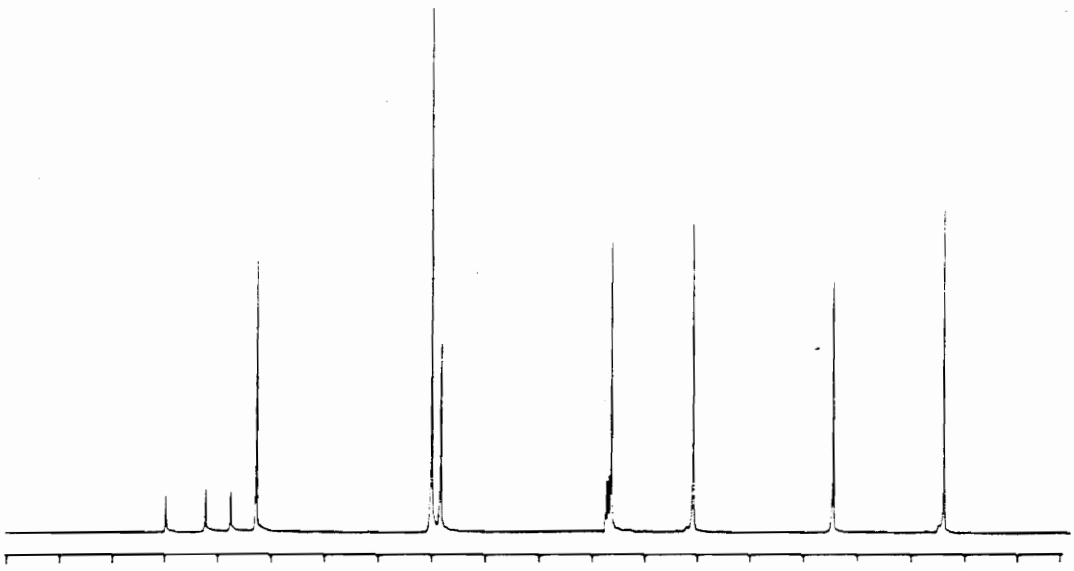

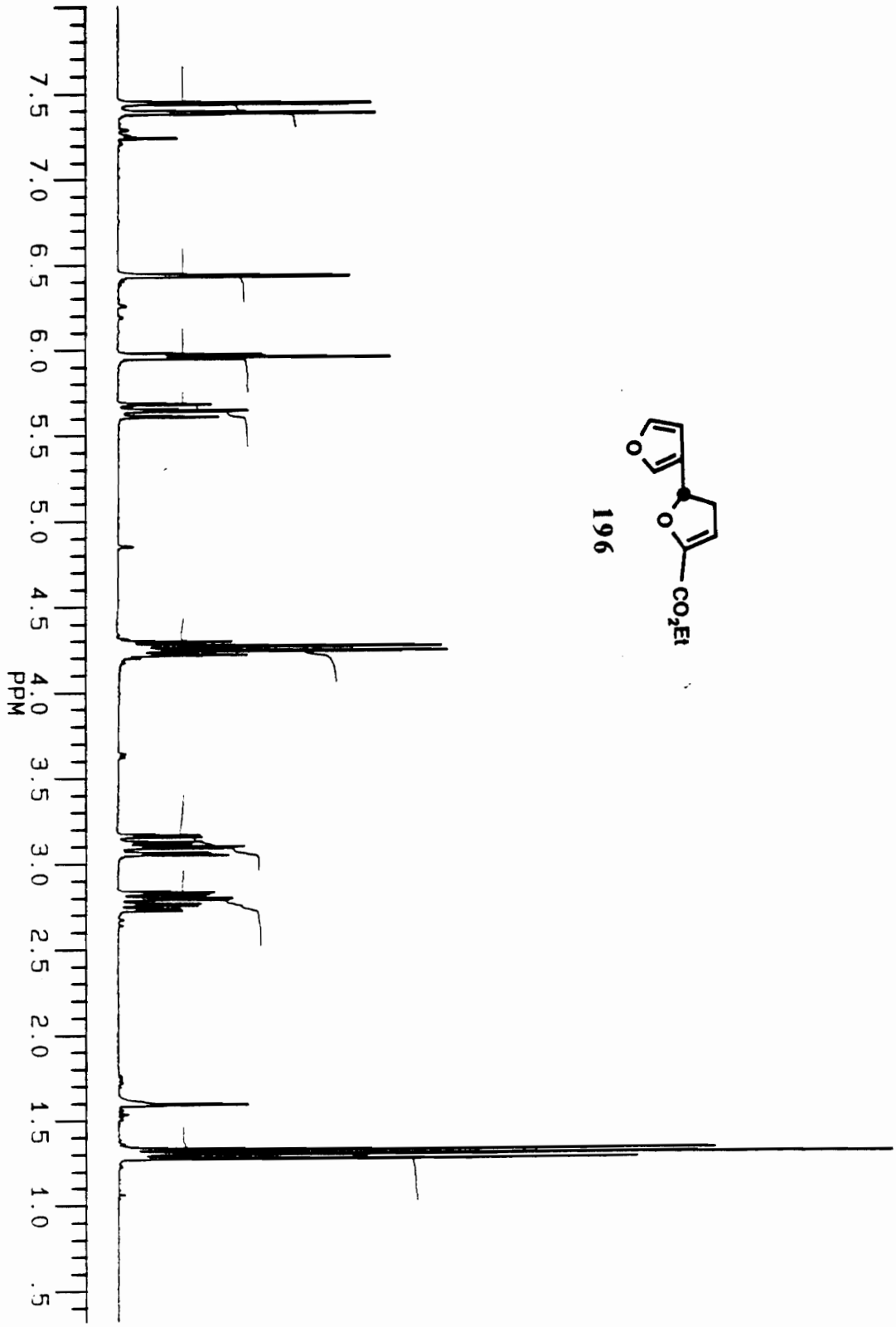

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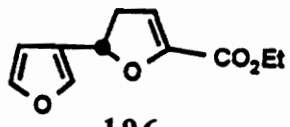

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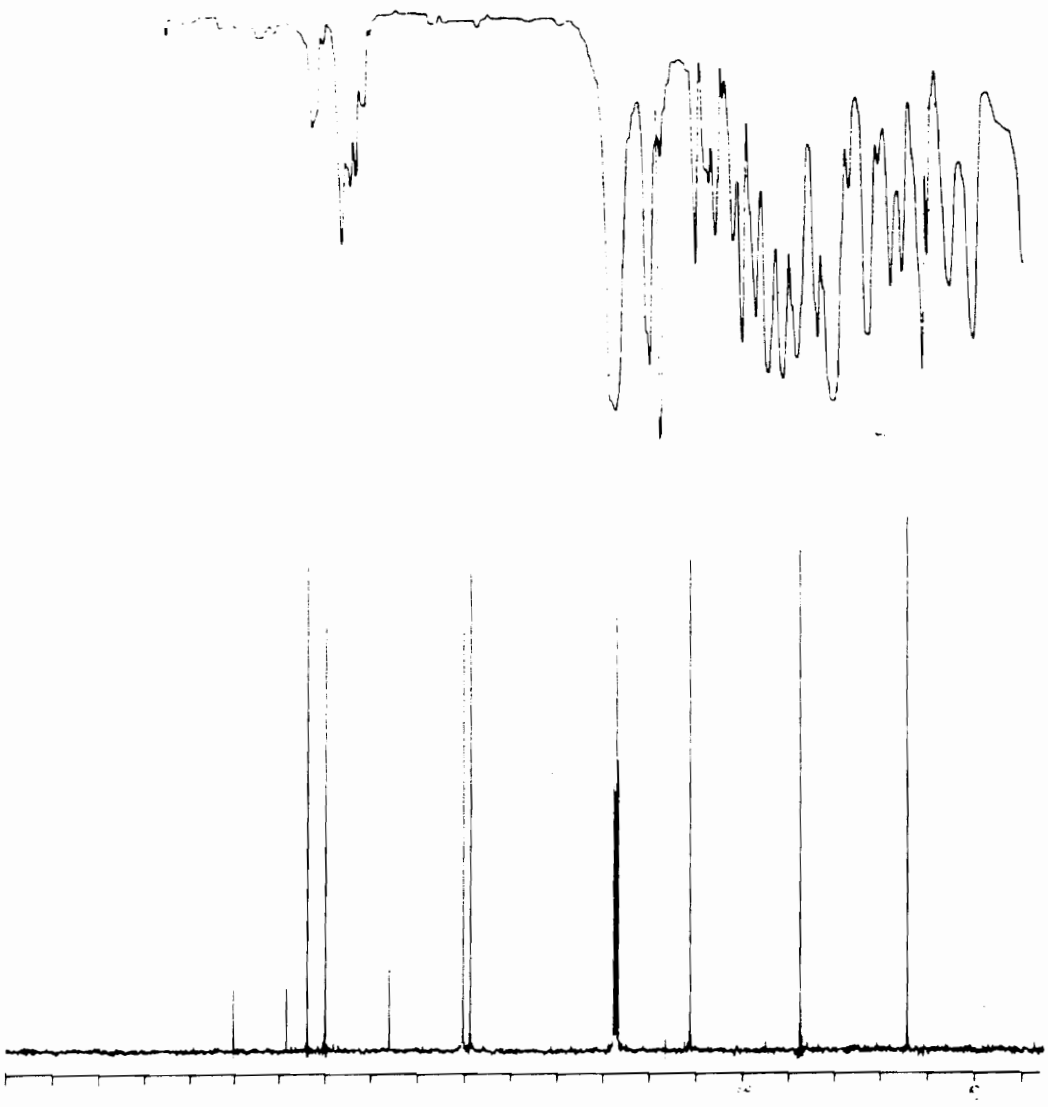

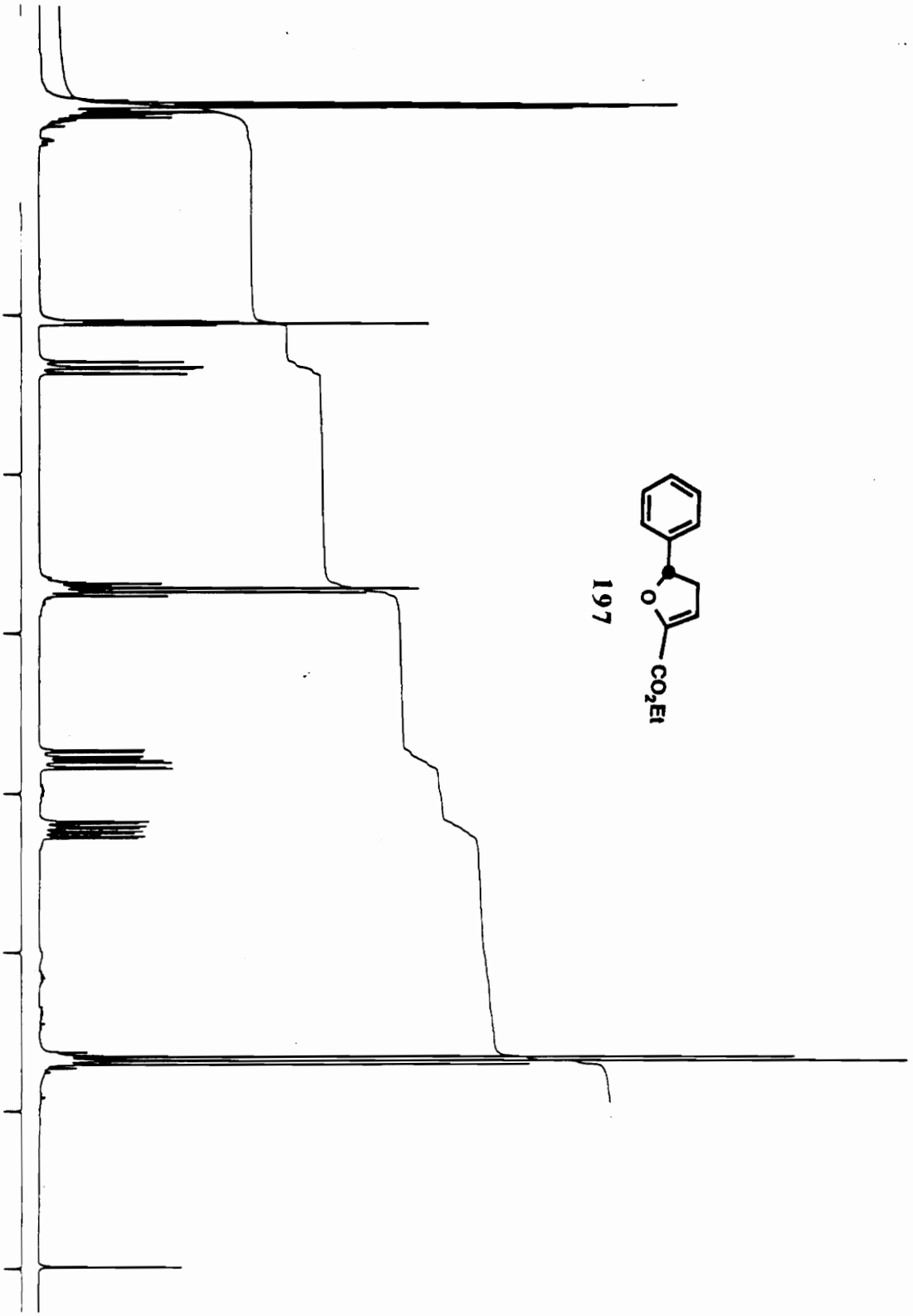

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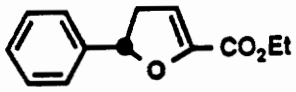

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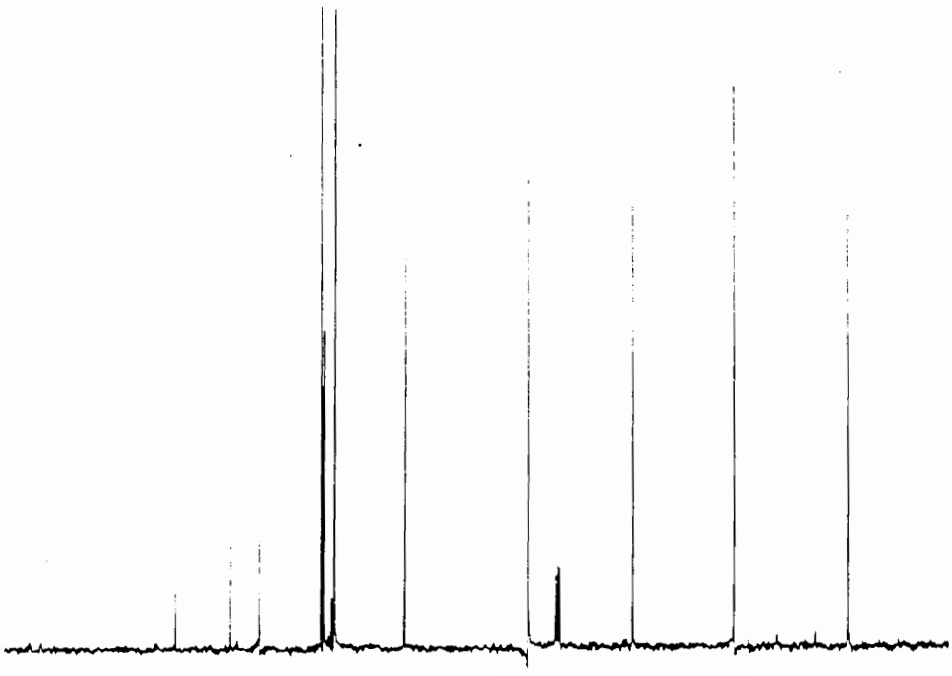

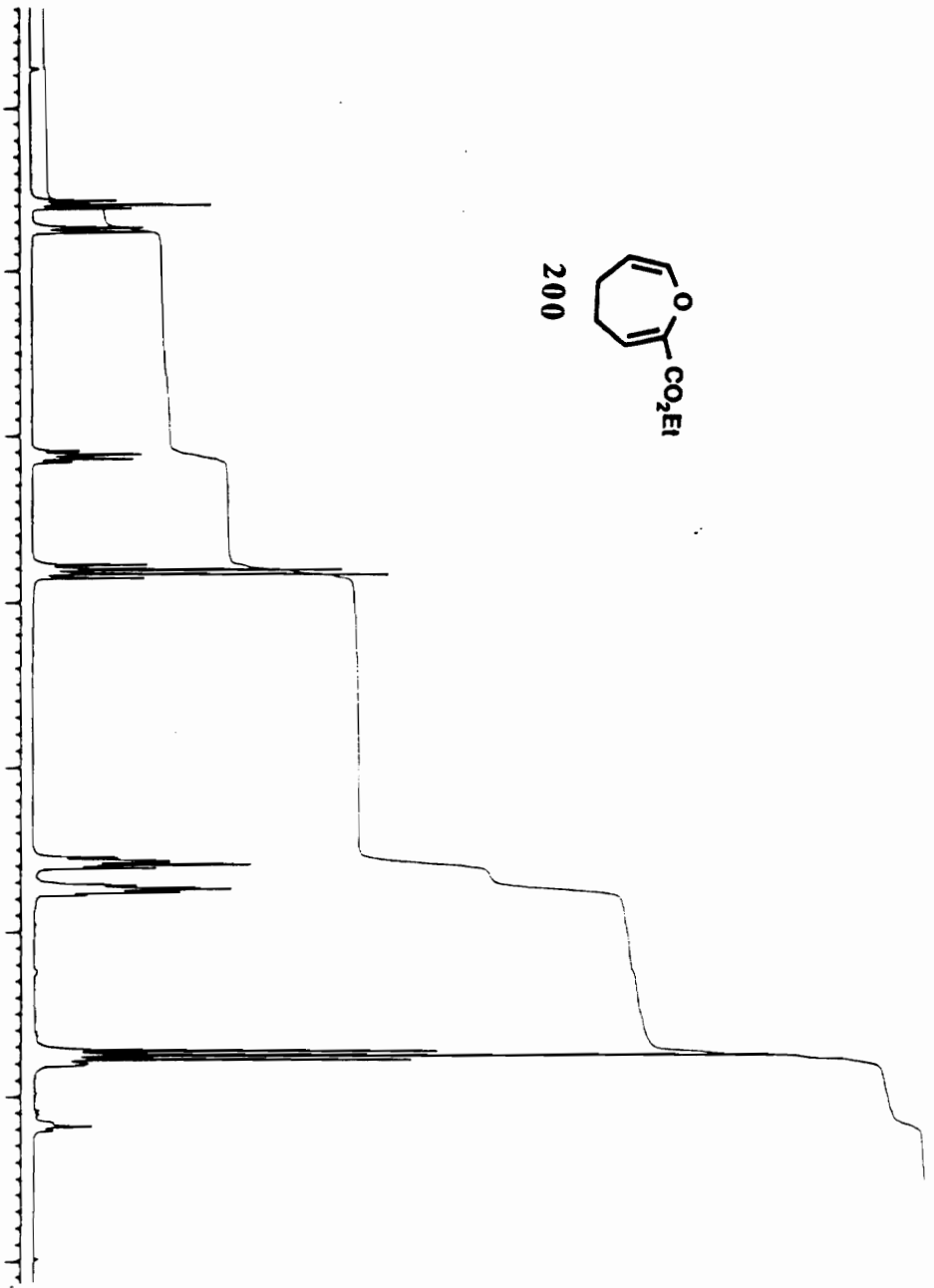

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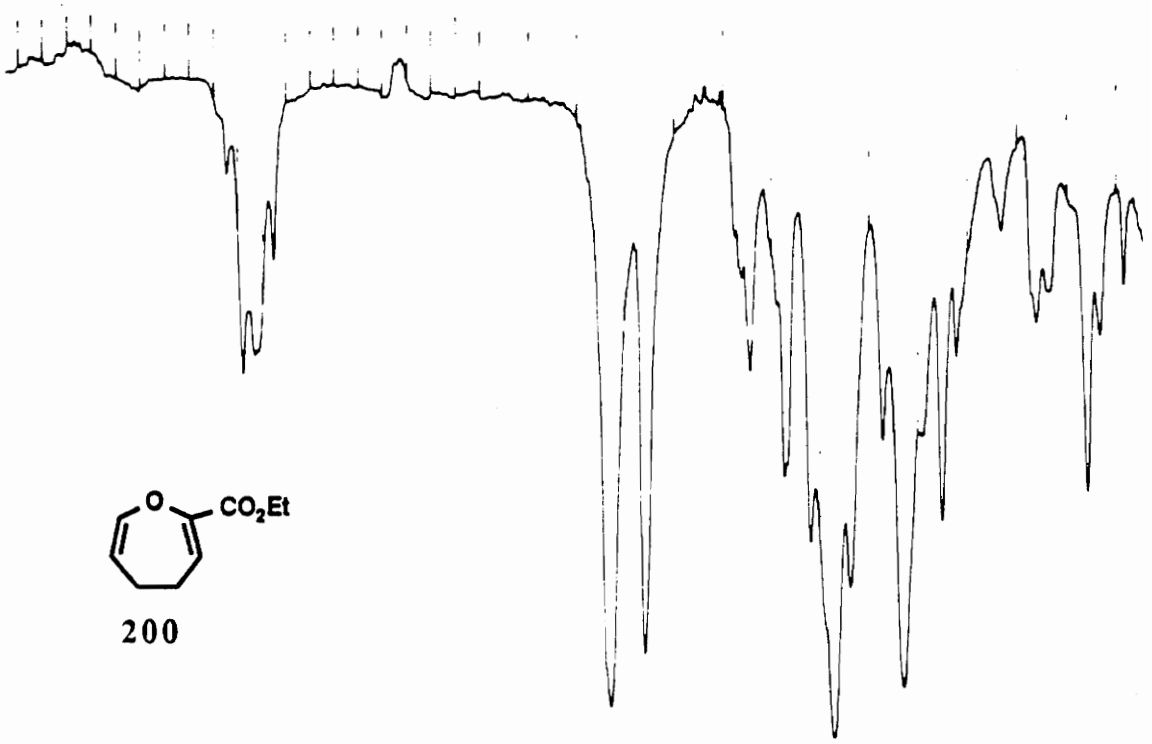

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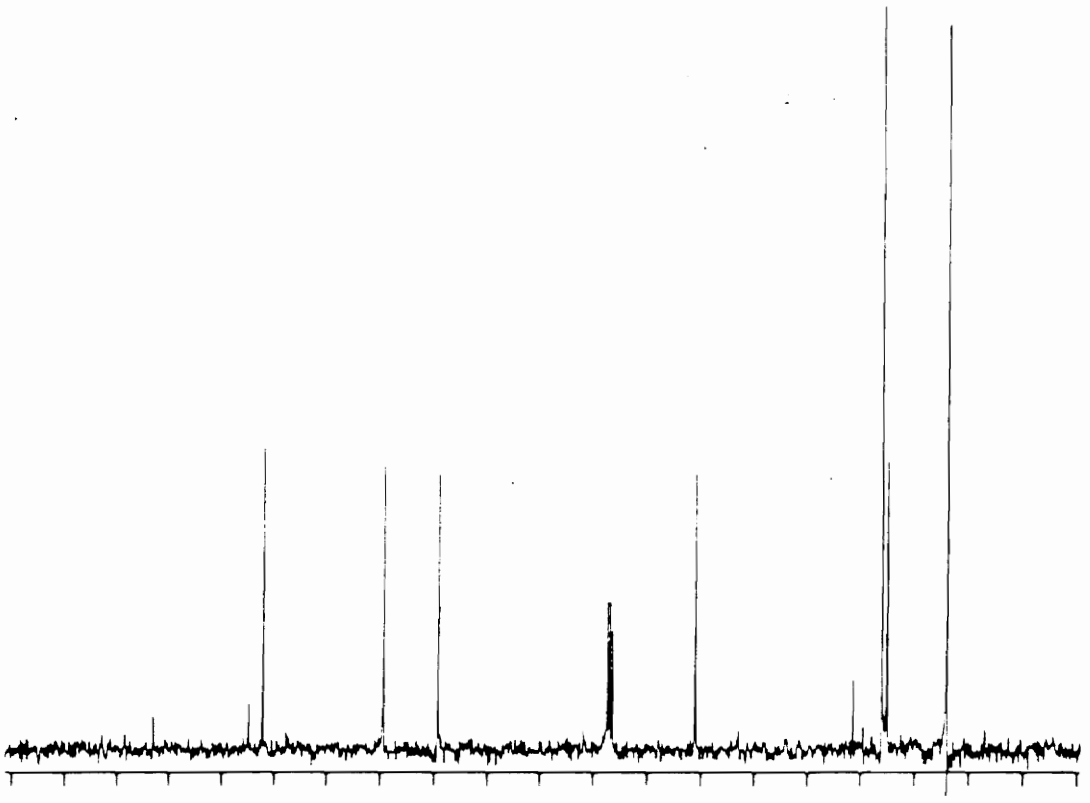

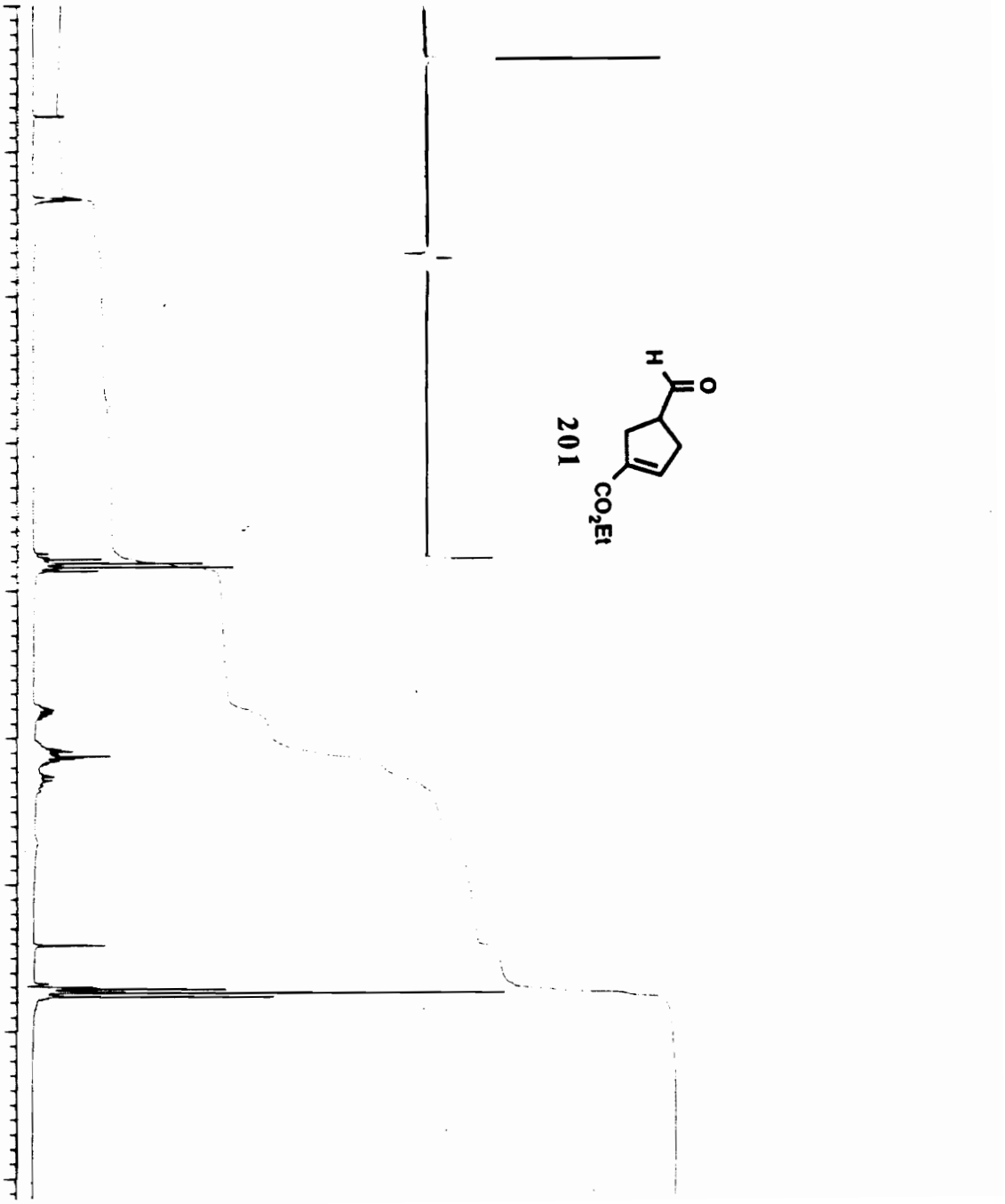

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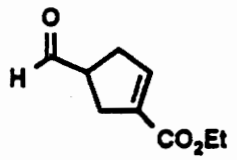
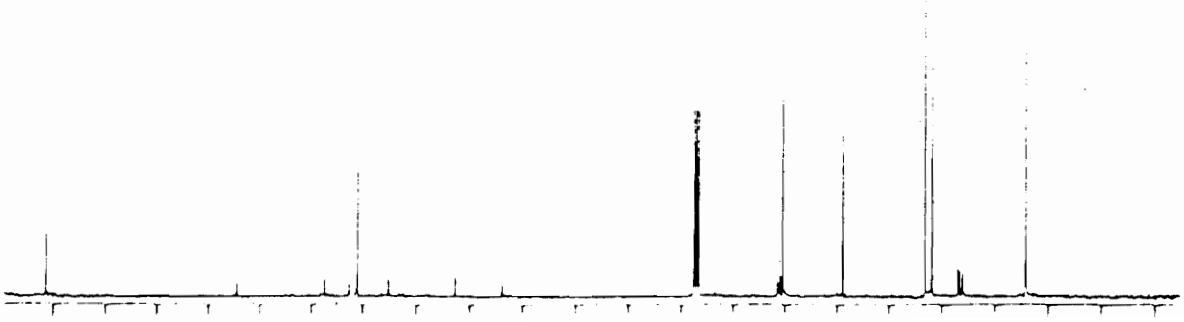
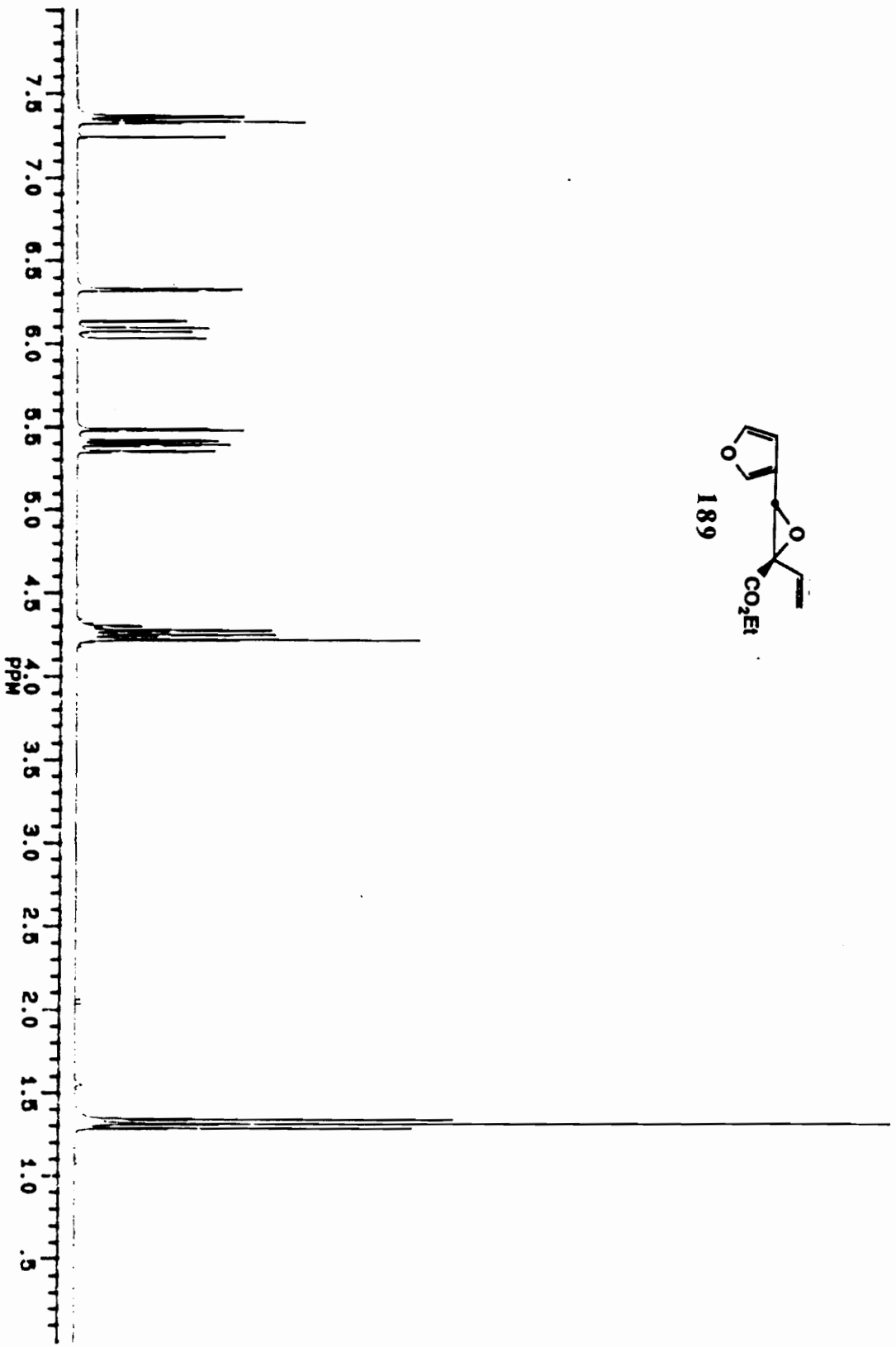


201





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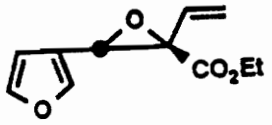

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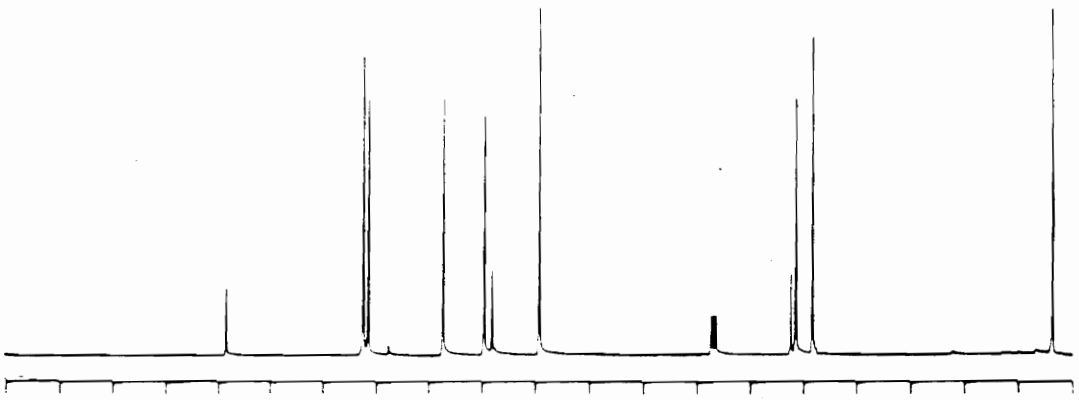

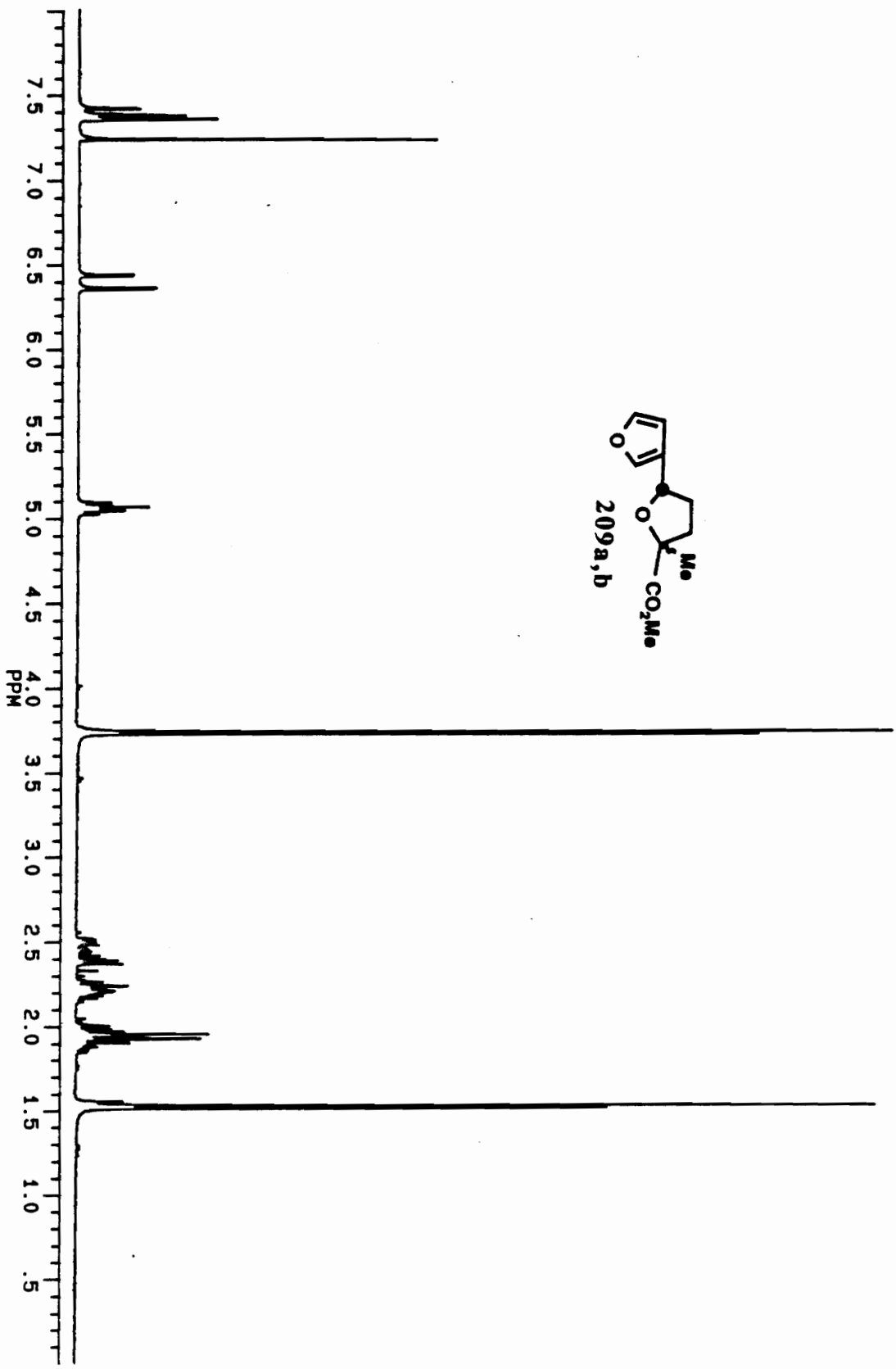
7.5
7.0
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5.0
4.5
4.0
PPM
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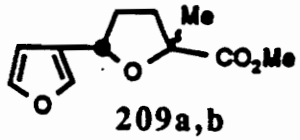
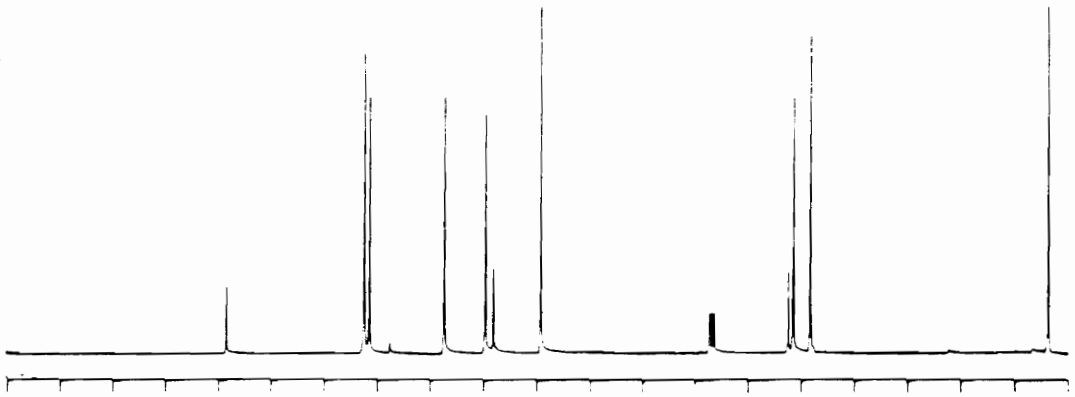
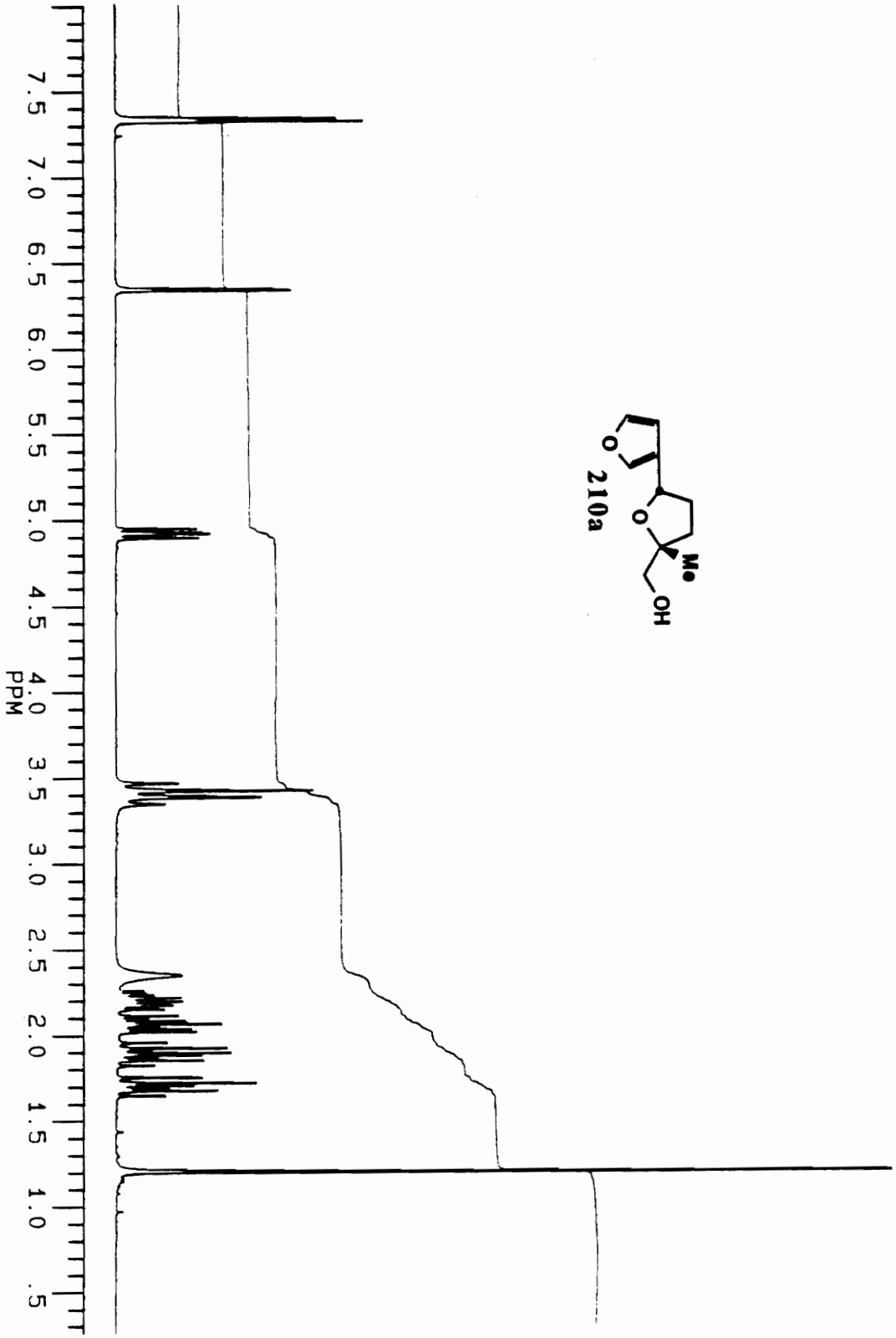
1.5
1.0
.5
O
O
Me
CO2Me
209a,b

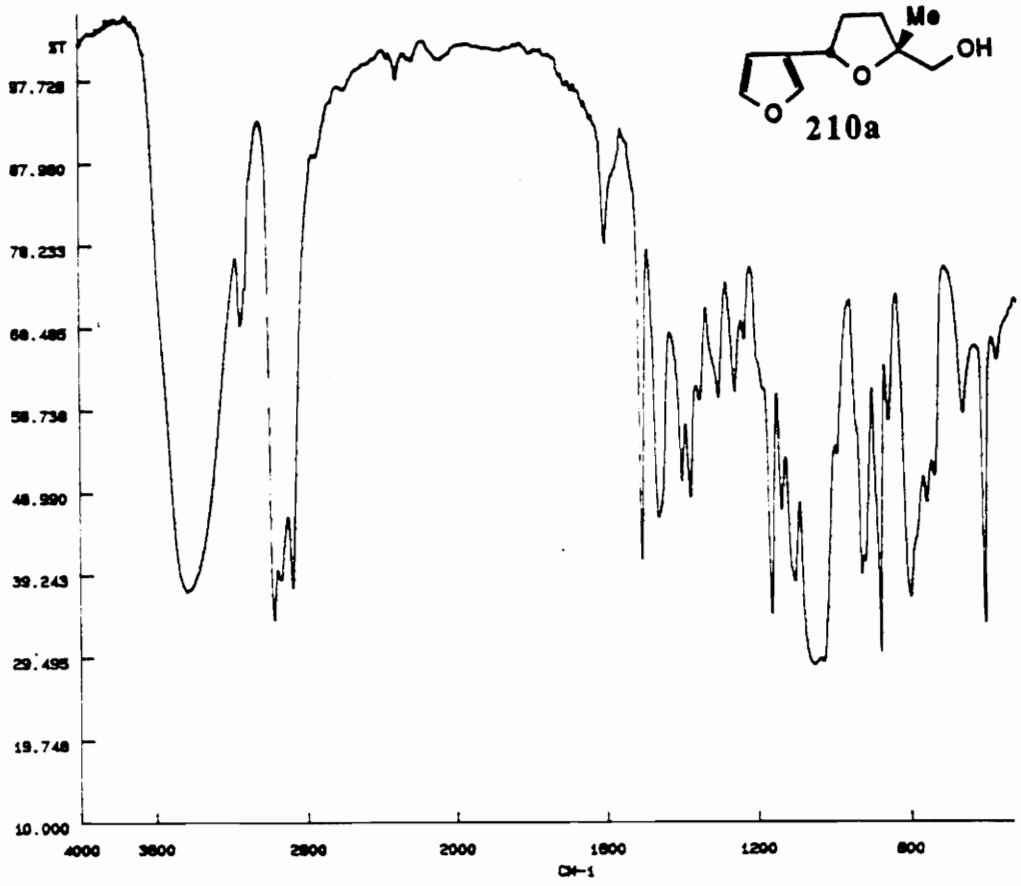


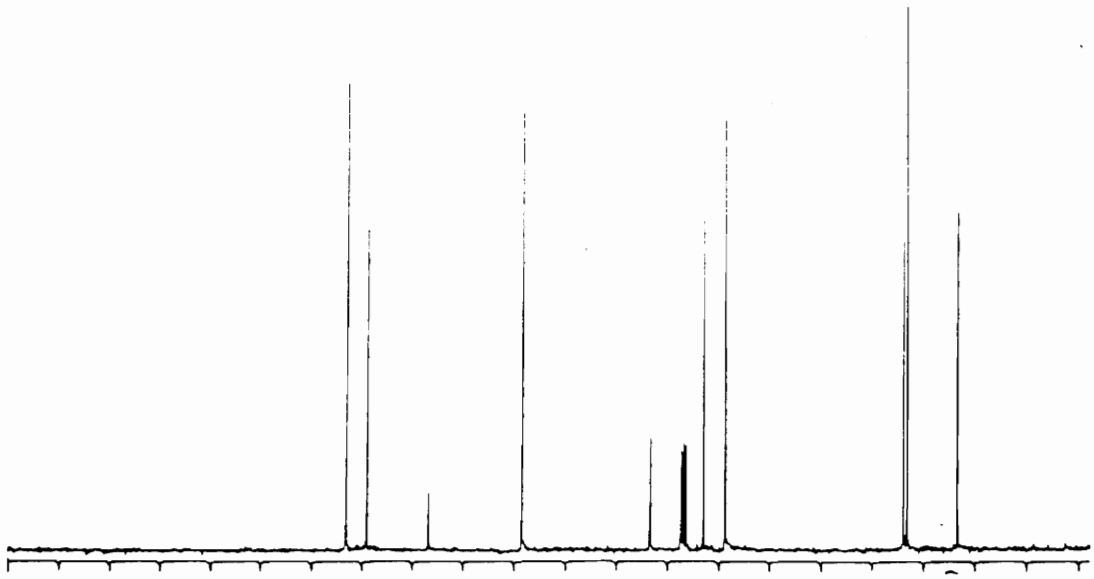
209a,b

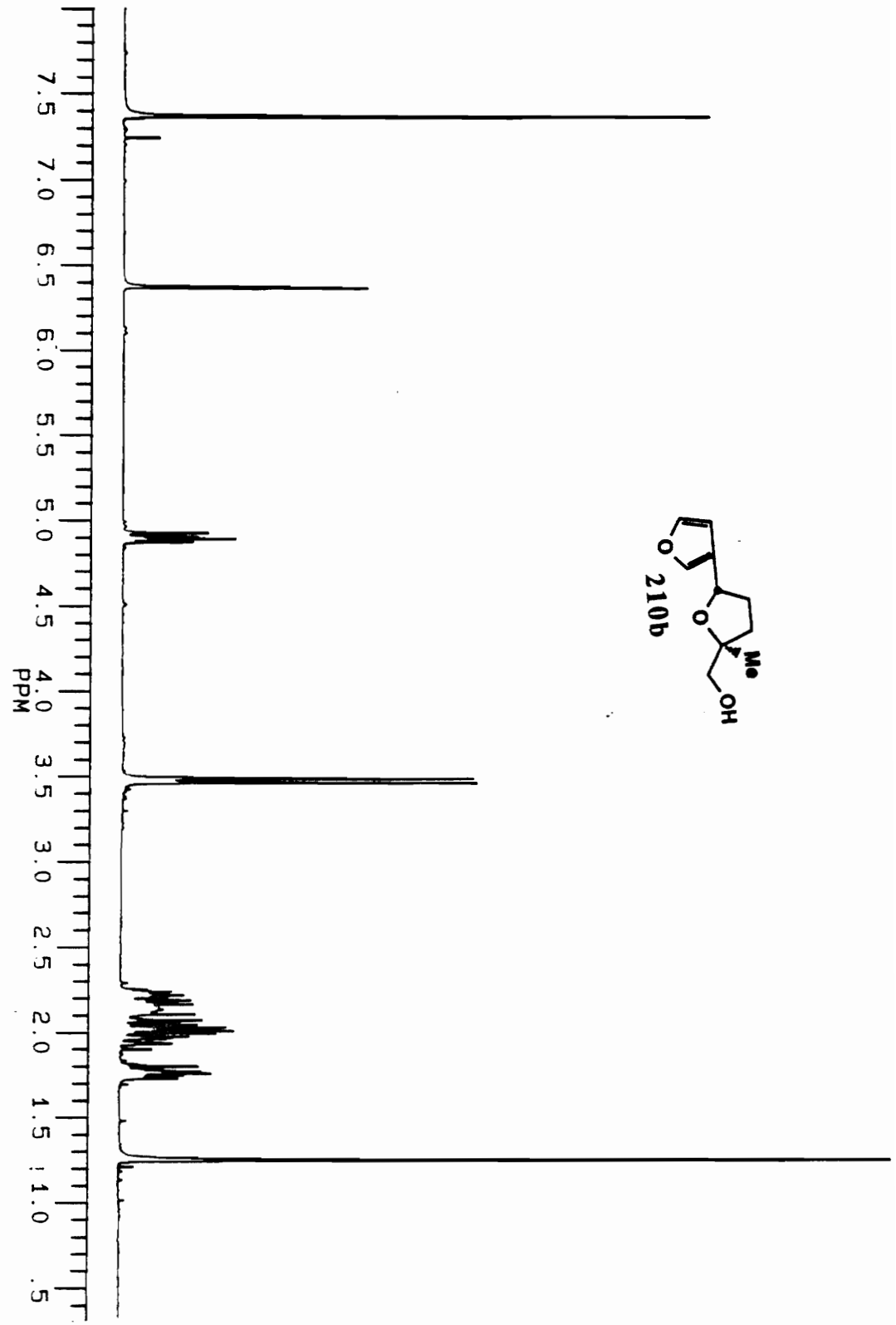




210a


%T
97.728
87.980
78.233
68.485
58.738
48.990
39.243
29.495
19.748
10.000
4000
3600
2800
2000
1600
1200
800
CM-1
Me
OH
O
O
210a

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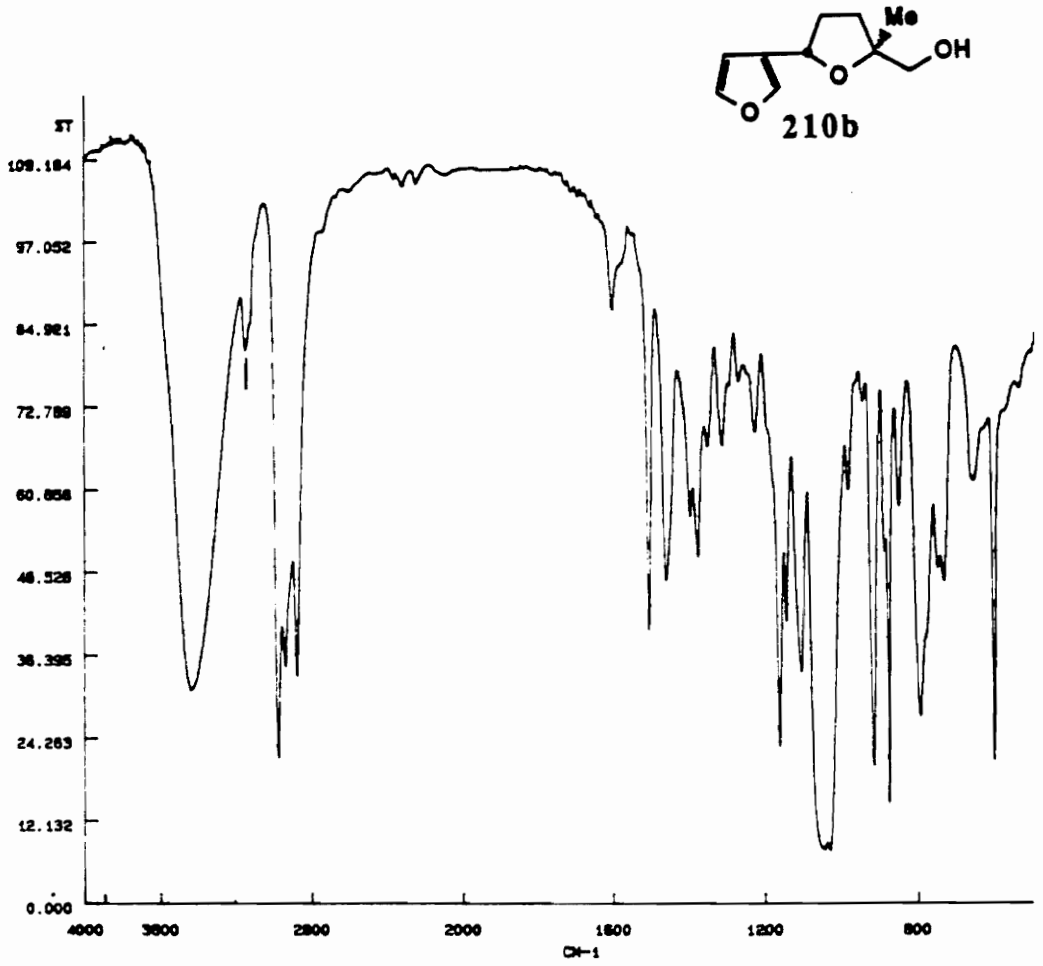
3.0
2.5
2.0
1.5
1.0
.5
PPM
O
O
Me
OH
210b


Me
OH
O
O
210b
%T
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97.052
84.921
72.789
60.656
48.528
36.395
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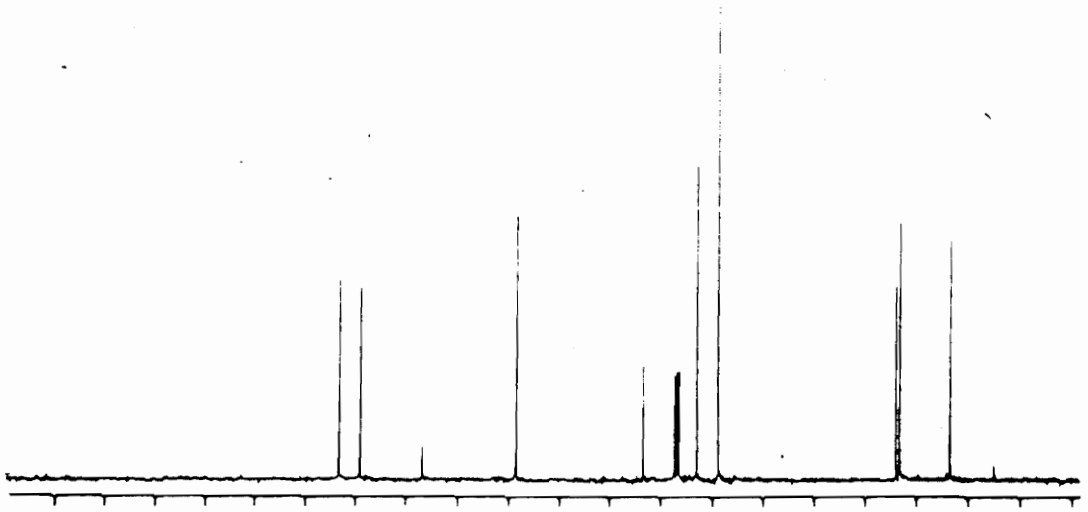
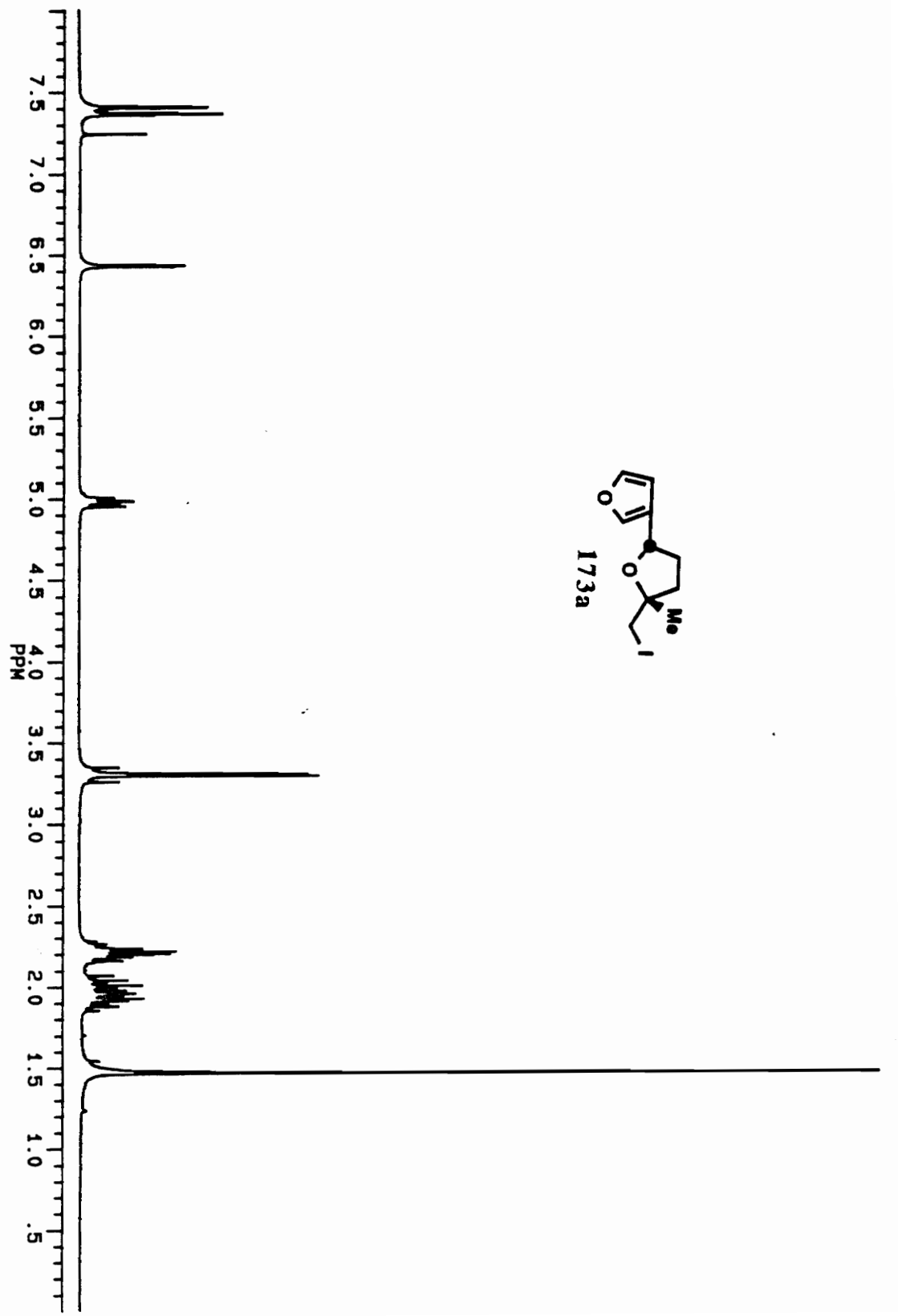
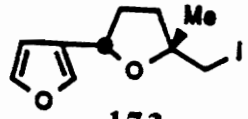
4000
3600
2800
2000
1600
1200
800
CH-1

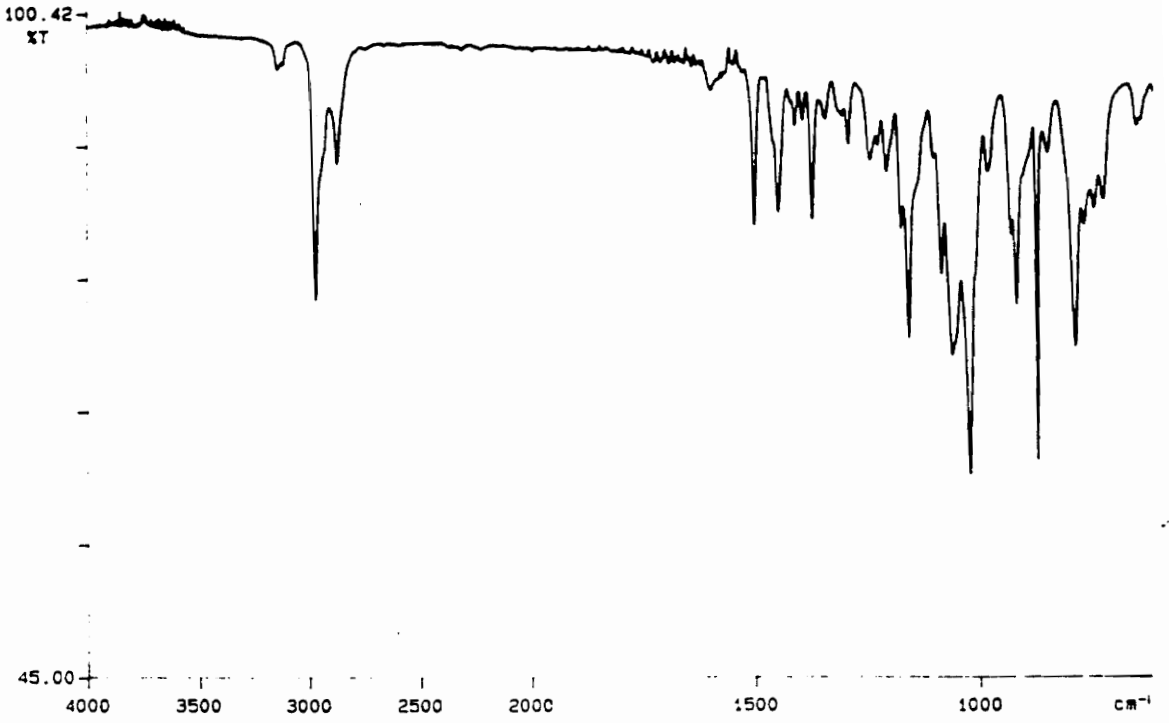


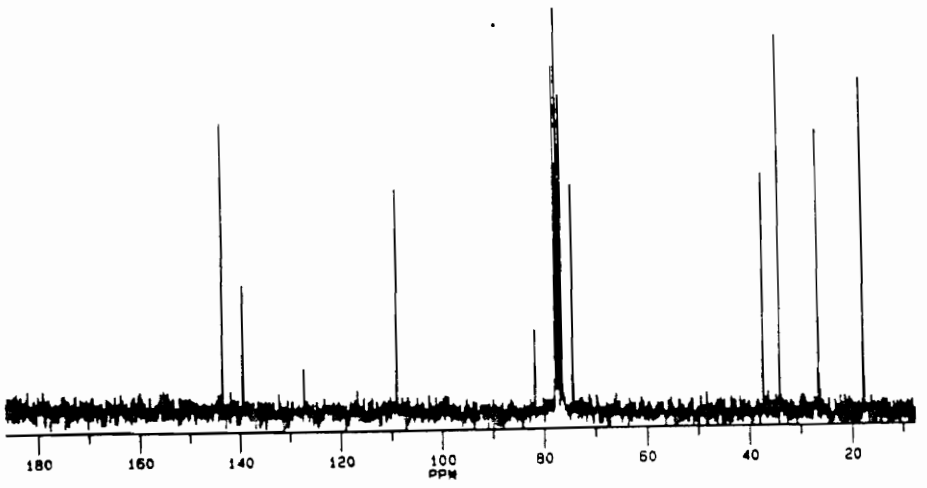


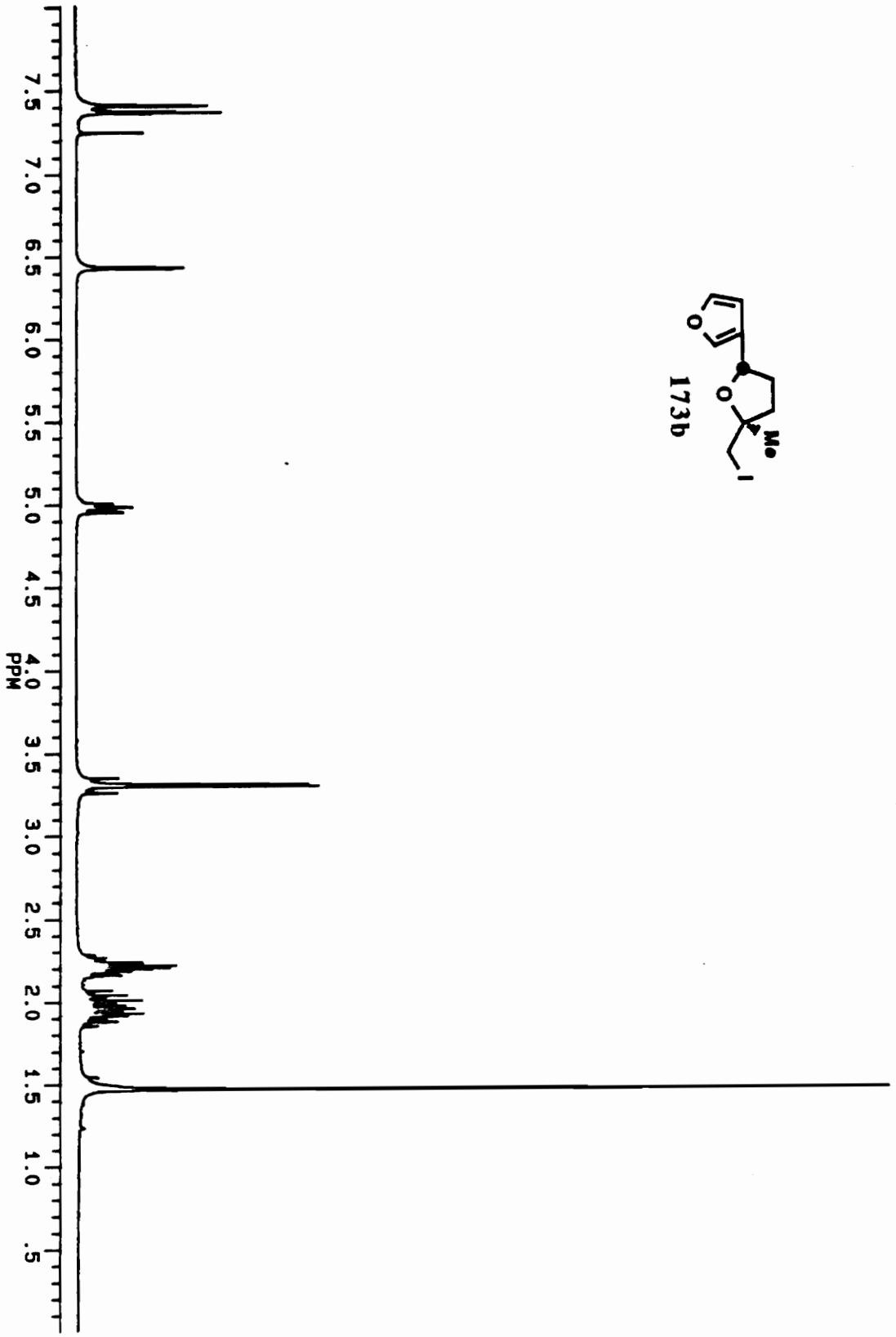
173a


Me
I
O
O

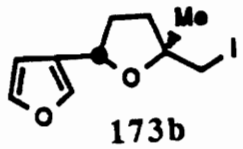
173a


100.42
%T
45.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

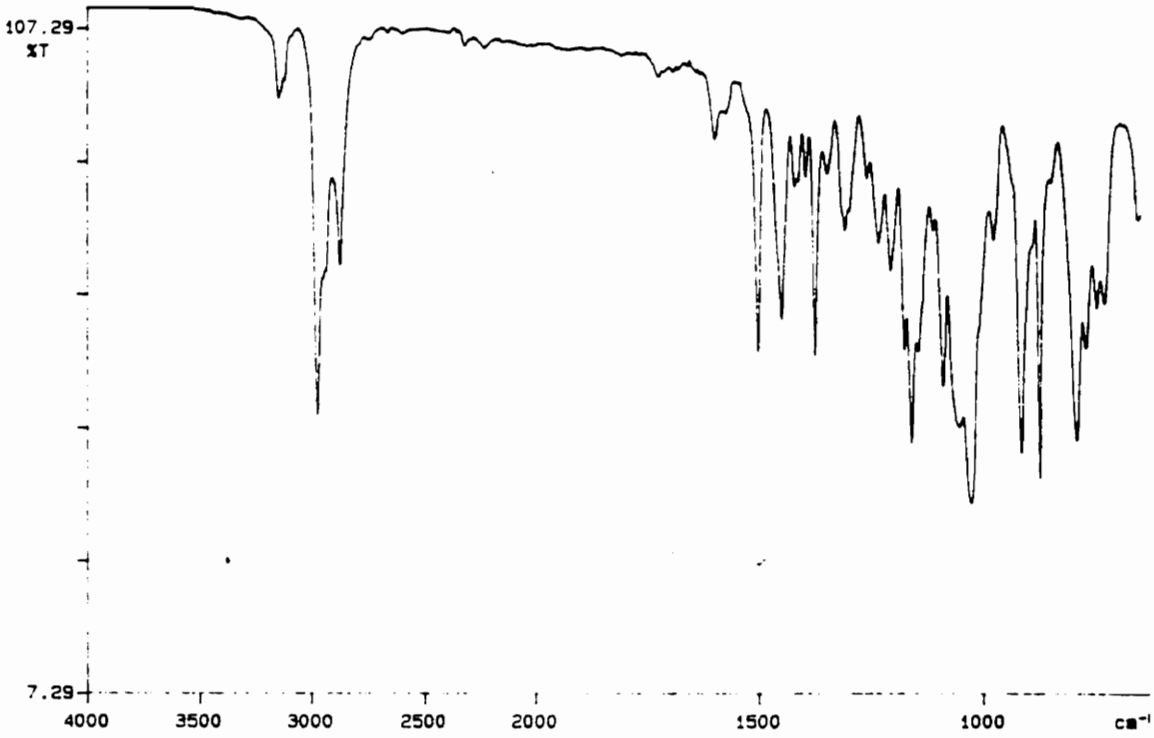

180
160
140
120
100
80
60
40
20
ppm

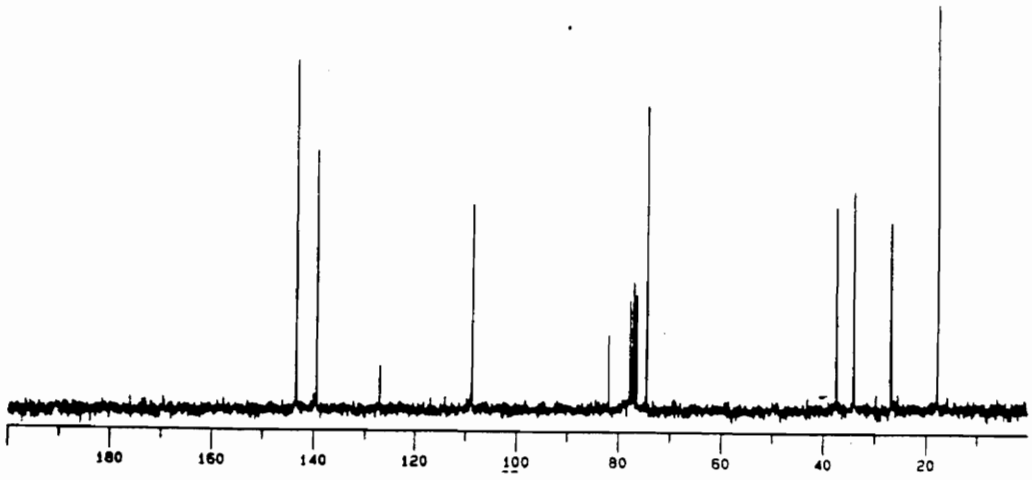


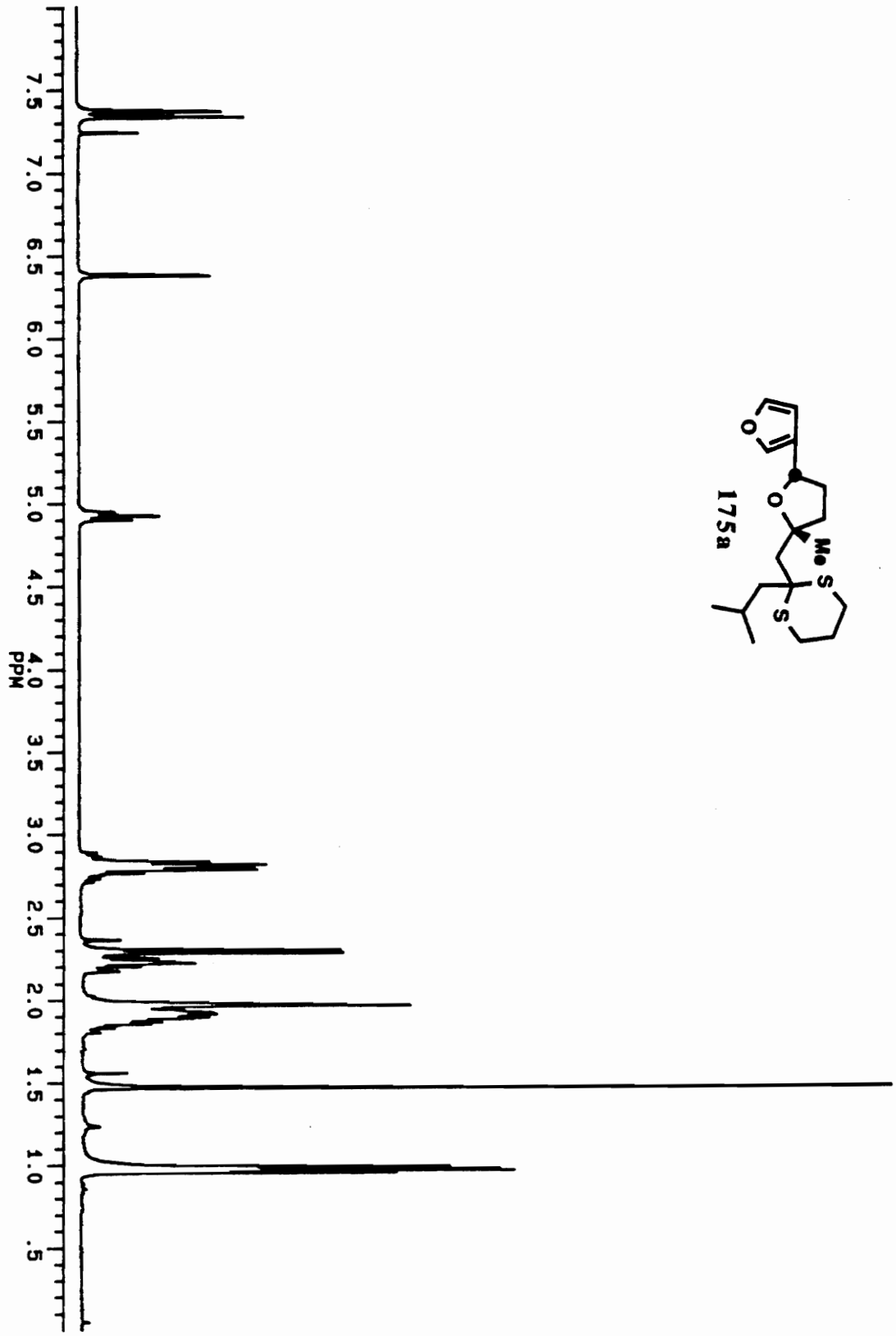
173b


Me
I
O
O

173b


107.29
%T
7.29
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


180
160
140
120
100
80
60
40
20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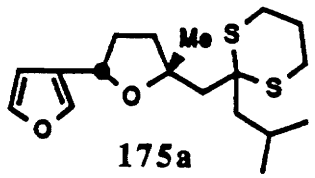
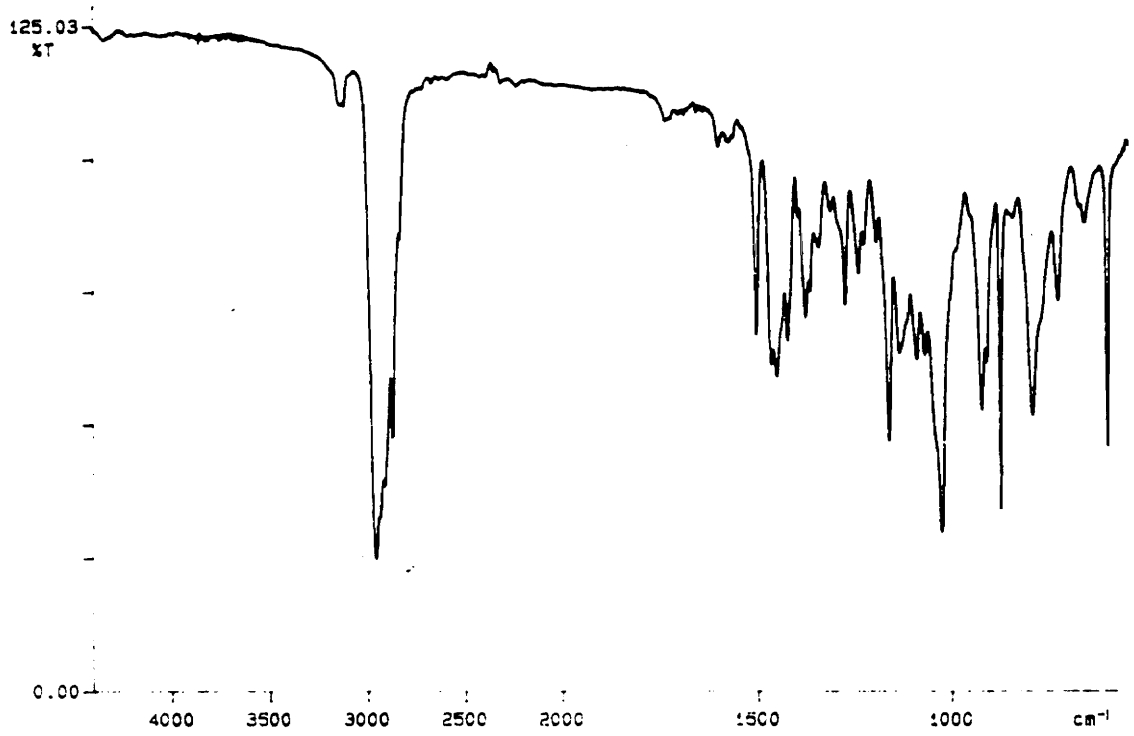
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM
O
O
Mo
S
S
175a


Me
S
O
S
O

175a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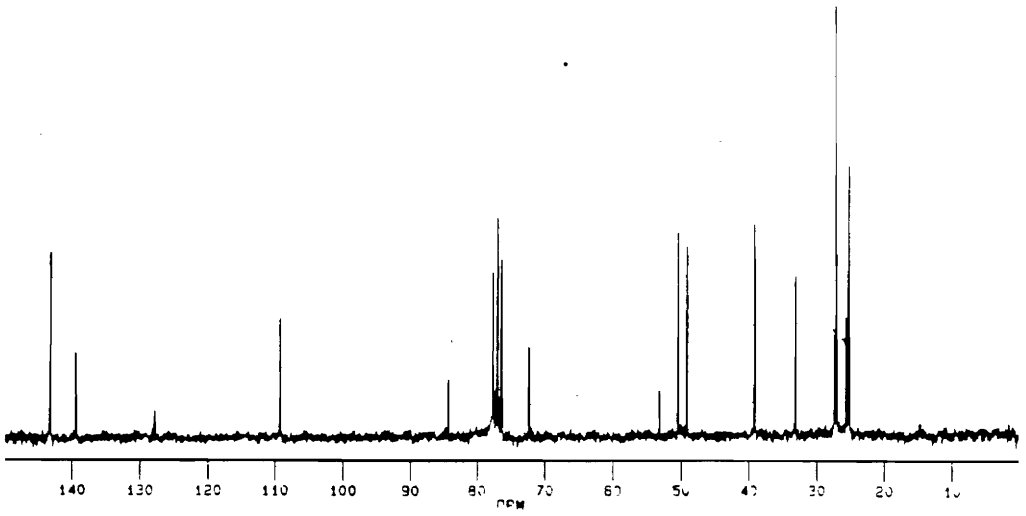
2500
2000
1500
1000
cm-1


140
130
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110
100
90
80
70
60
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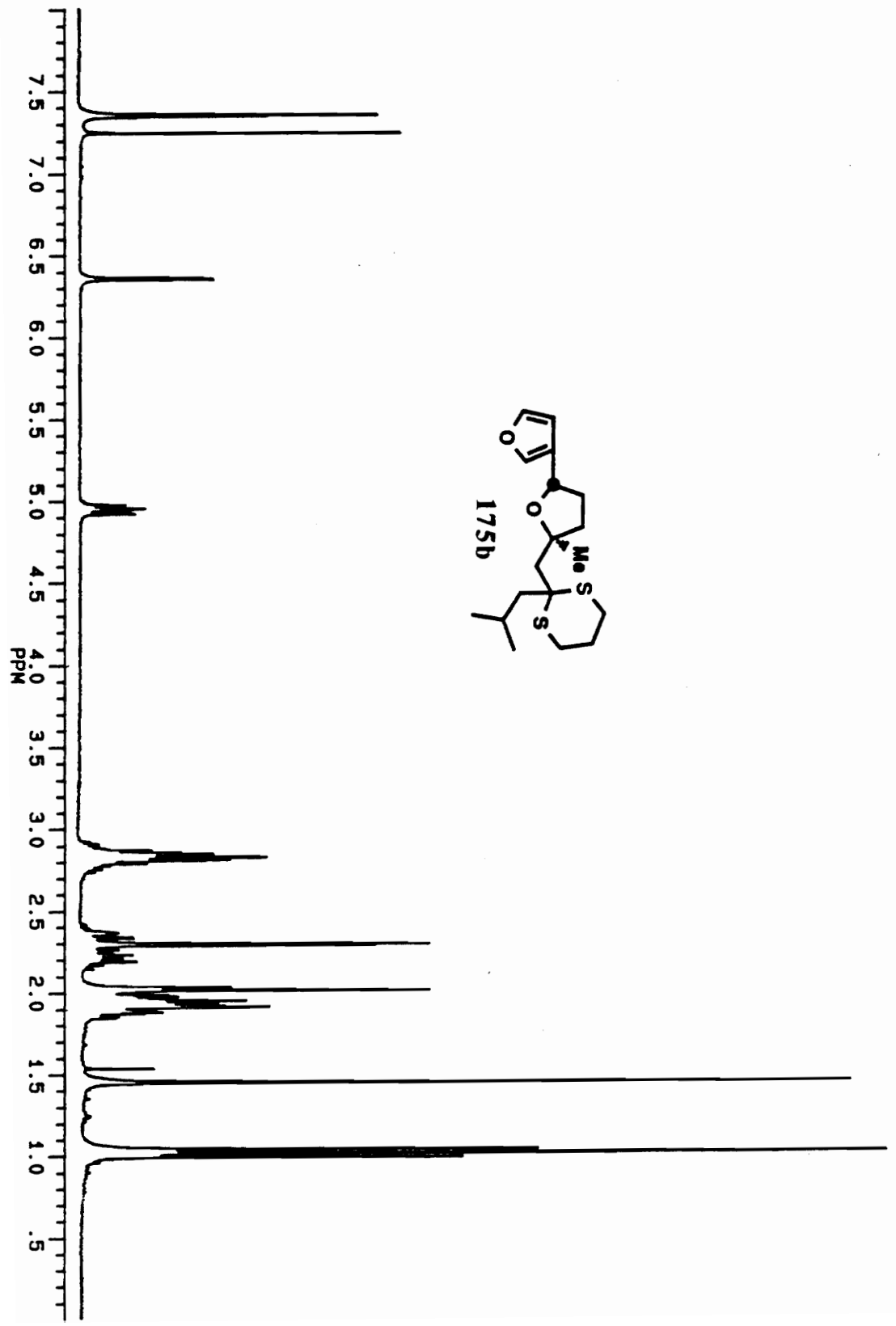
30
20
10
ppm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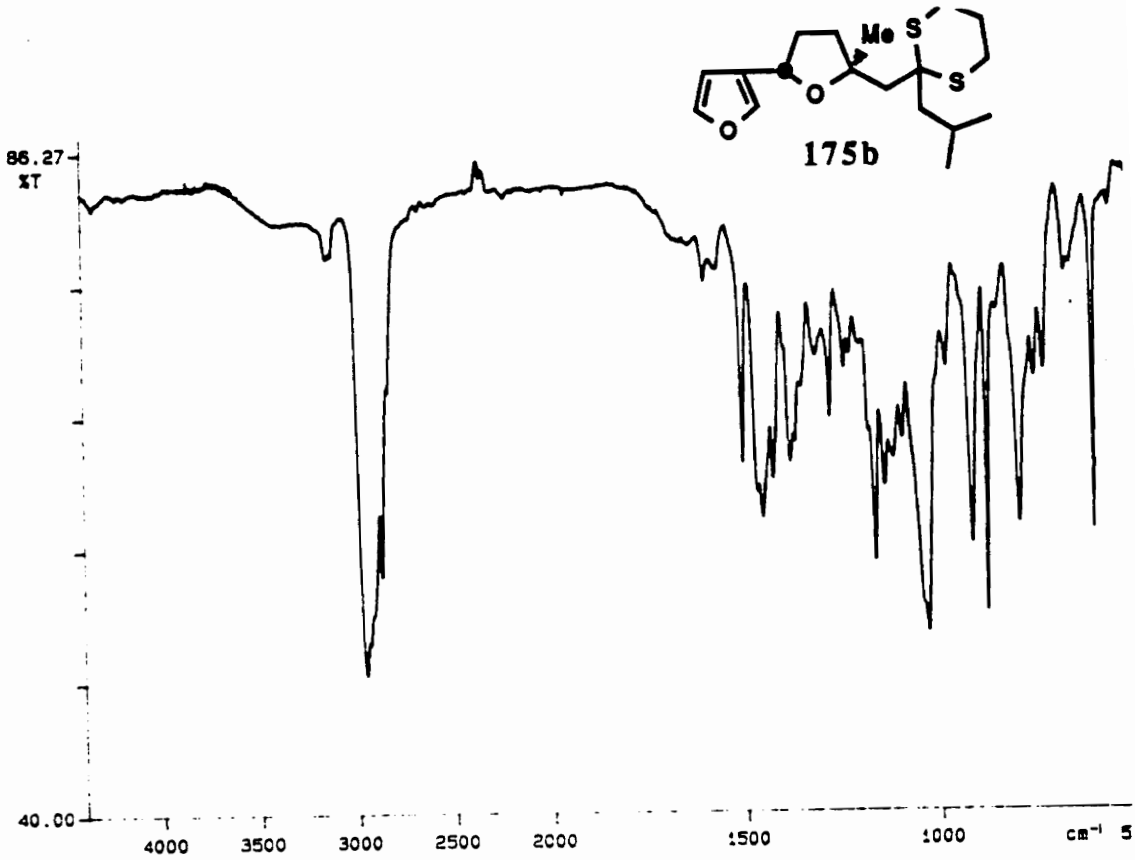
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
.5
O
O
Mo
S
S
175b


Me
S
S
O
O
175b
86.27
%T
40.00
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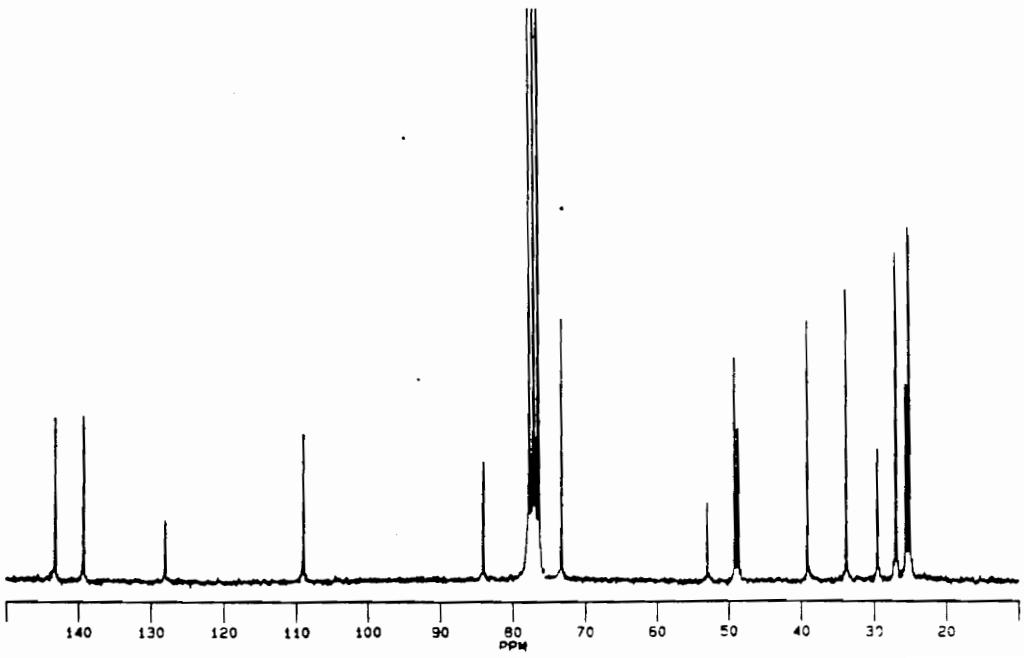
3500
3000
2500
2000
1500
1000
cm⁻¹


140
130
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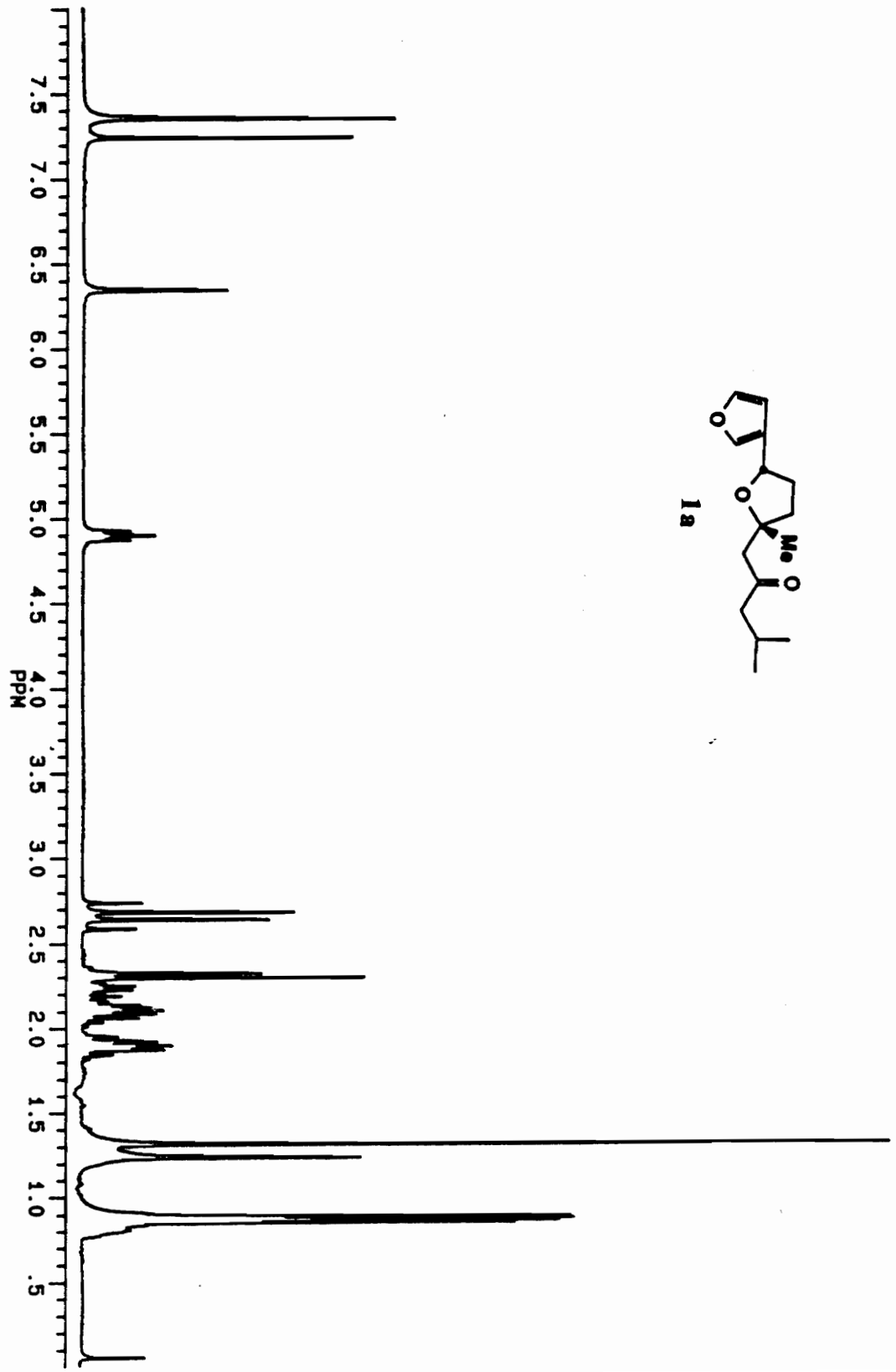
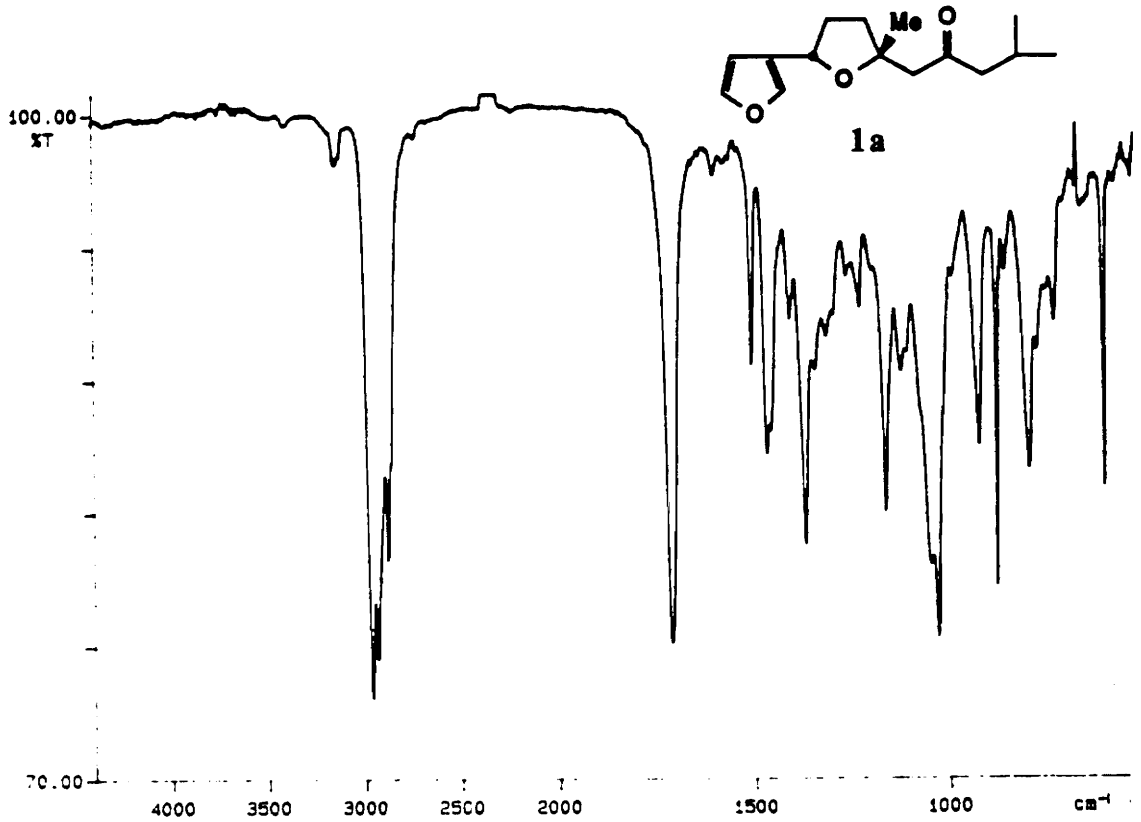
110
100
90
80
70
60
50
40
30
20
ppm



1a


Me
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%T
70.00
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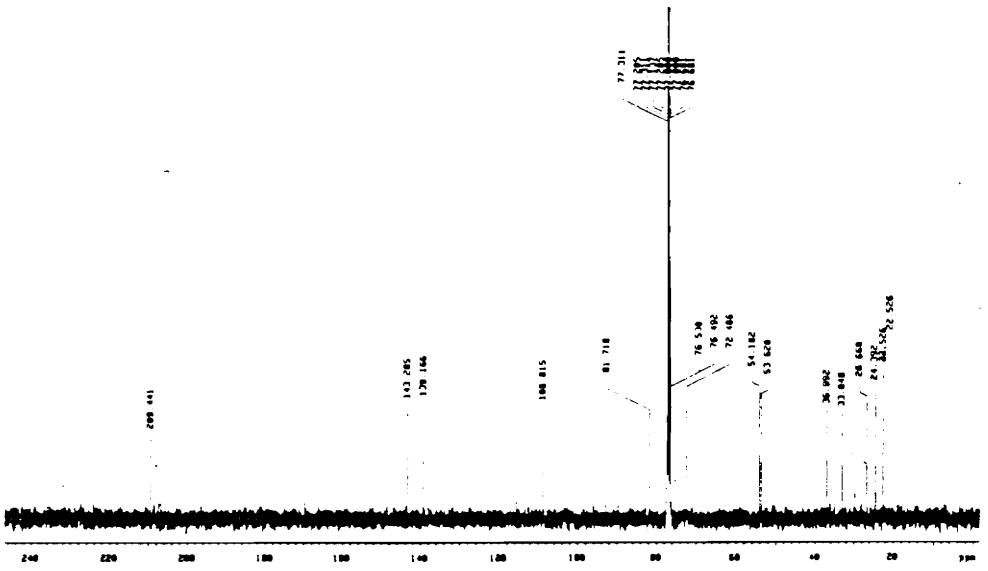
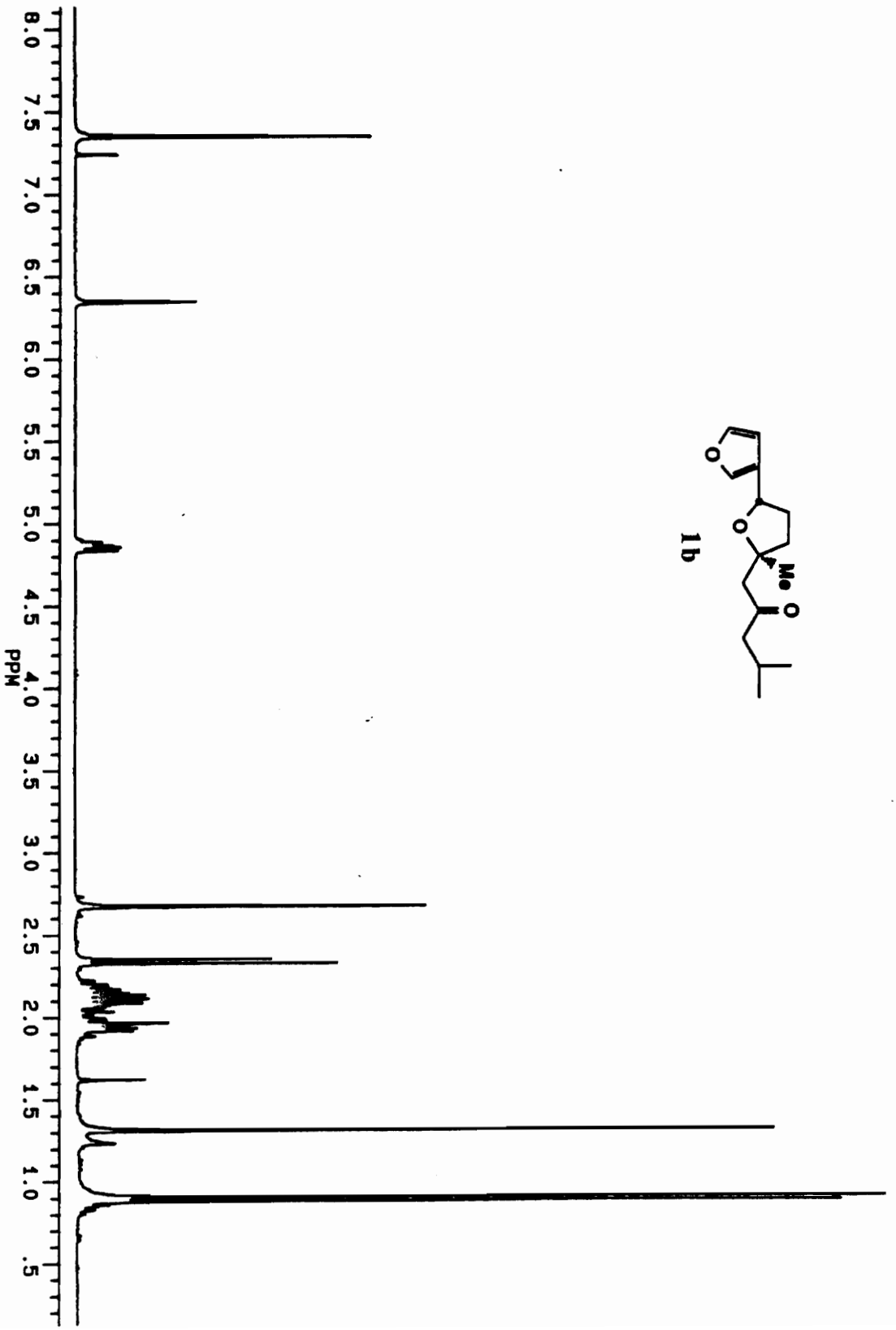
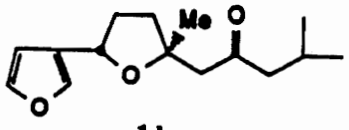
3500
3000
2500
2000
1500
1000
cm-1

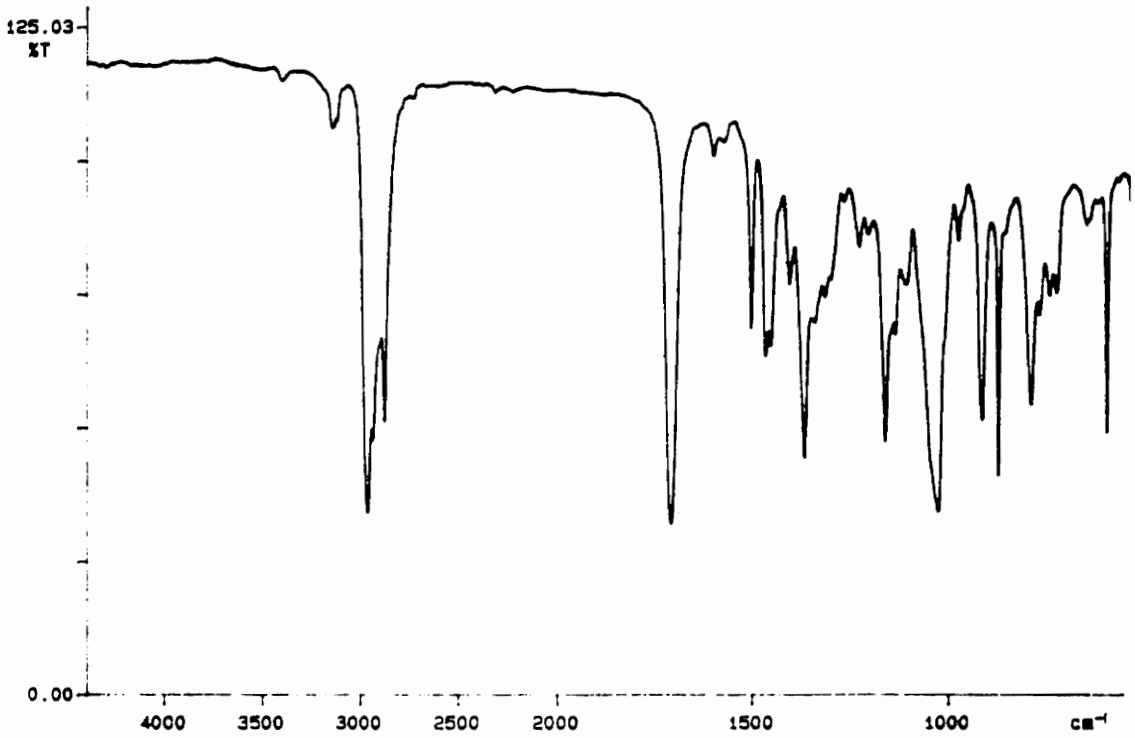


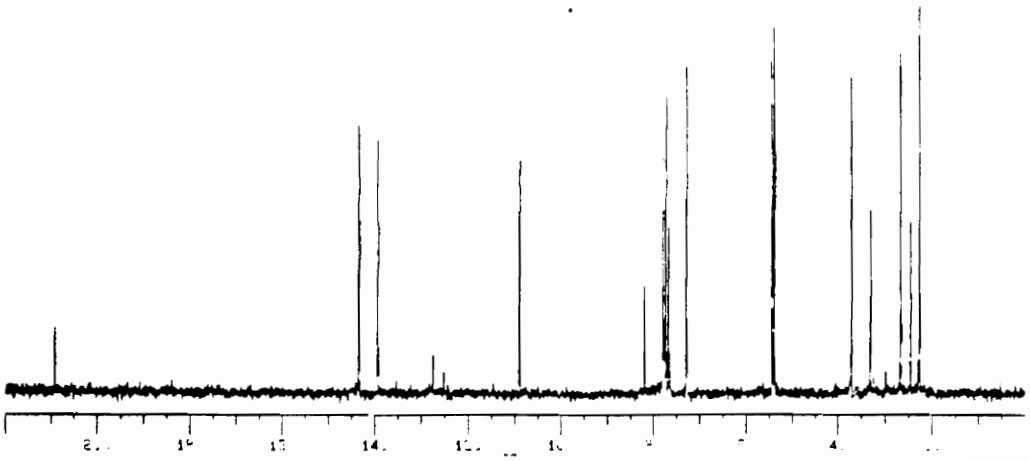


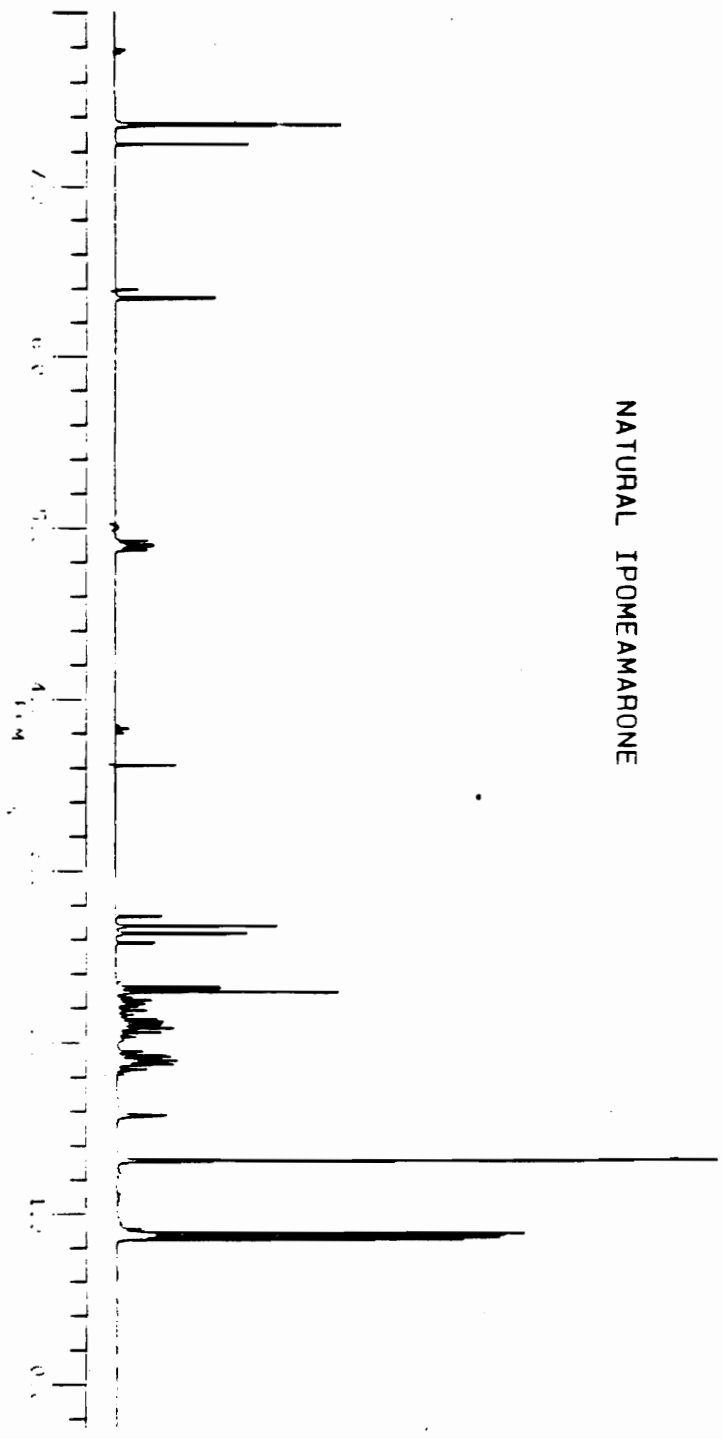
1b



1b







NATURAL IPOMEAMARONE

VIII. VITA

Thomas Claiborne Lovelace was born in Roanoke, Virginia on March 11, 1960. He graduated from Cave Spring High School (Roanoke) in 1978, and entered Virginia Tech the following year. During the later stages of his education Thomas was married to Deana A. Morrow. In the spring of 1988 he earned his Bachelor of Science degree in chemistry . Thomas continued his study of chemistry at Virginia Tech under the advisement of Dr. Tomas Hudlicky in the pursuit of a Master's degree in Organic Synthesis. During this time he and Deana were blessed with the birth of their son, Matthew Claiborne.