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ISBN 0-612-00613-1

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## ABSTRACT

Studies based on radical-induced ring openings of halolactones, spirocyclobutanones, and  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions of  $\alpha$ -diazoketones are described.

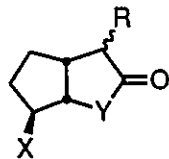
Novel ring openings and subsequent decarboxylations of iodolactone **66** and bromolactone **67** to give diene **78** were found to proceed under  $\text{SmI}_2/\text{THF}/\text{HMPA}$  (4 equiv) conditions. Upon treatment of iodothialactone **63**, iodolactone **66** or bromolactone **67** with  $\text{SmI}_2/\text{THF}/\text{HMPA}$  with "reverse addition" it was found that the ring-opened unsaturated acid **79** was obtained in good yield in each case.

The unprecedented ring opening reactions of  $\alpha$ -ketospirocyclobutanes **123** and **124** with  $\text{SmI}_2$  afforded ketones **126** and **127** in 70% and 88% yield, respectively.

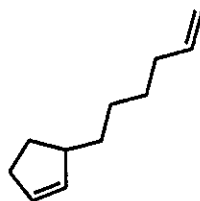
Dihydrofurans **217** and **224** were prepared from azibenzil (**210**) and  $\alpha$ -diazoketone **223**, respectively, *via*  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions with ethyl vinyl ether. The structures of **217** and **224** were rigorously established and the former assignments were corrected. These structures (**217** and **224**) were unambiguously assigned by characterization of the corresponding transketalization products **222** and **226**.

Preliminary studies towards the preparation of the novel hydrocarbon-soluble  $\text{Sm}(\text{II})$  complex **88** are presented.

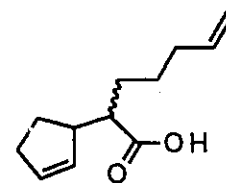
An unprecedented Grob-type fragmentation is postulated to explain the formation of benzyl alcohol from the DIBAL reduction of the donor-acceptor cyclopropane **215**. Cyclopropyl alcohol **259** was also produced from this reaction. The characterization of **259** established the intermediacy of donor-acceptor cyclopropanes in the production of dihydrofurans **217** and **224**, and suggests that this pathway is more general than the literature implies.



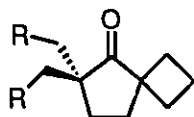
- 63 Y=S X=I R=benzyl  
 66 Y=O X=I R=4-pentenyl  
 67 Y=O X=Br R=4-pentenyl



78

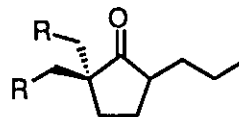


79



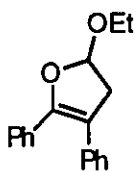
123 R=Ph

124 R=vinyl

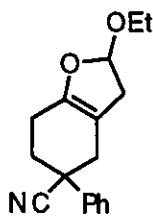


126 R=Ph

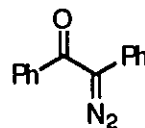
127 R=vinyl



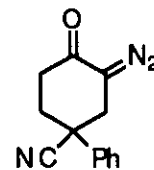
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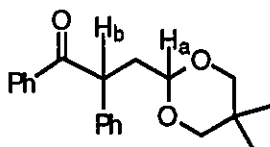
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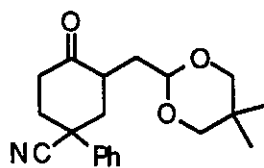
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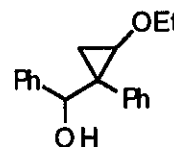
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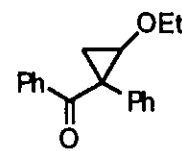
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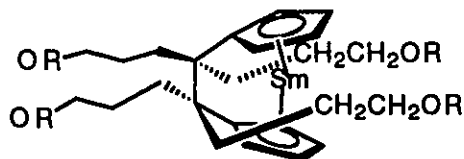
226



259



215

88 R=CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>

**To my Mother who showed me that patience  
and strength endure,**

**and my Father who proved that courage and  
determination overcome.**

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**LIST OF ABBREVIATIONS**

Ac	acetyl
AIBN	azoisobutyronitrile
aq	aqueous
Bn	benzyl
br	broad
Bu	butyl
<i>i</i> -Bu	isobutyl
<i>n</i> -Bu	primary butyl
<i>t</i> -Bu	tertiary butyl
<i>t</i> -BuOK	potassium tertiary butoxide
Bz	benzoyl
c	concentration (gmol <sup>-1</sup> )
ca.	about
calc.	calculated
cat.	catalytic
COSY	<sup>1</sup> H- <sup>1</sup> H NMR correlation spectroscopy
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Δ	heat
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminium hydride

DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	dimethylsulfoxide
E <sup>+</sup>	electrophile
equiv	equivalent(s)
eq.	equatorial
Et	ethyl
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
Et <sub>3</sub> N	triethylamine
EtOH	ethanol
<u>Exact Mass</u>	exact mass determined by high resolution mass spectroscopy
FT	Fourier Transform
g	gram(s)
<i>gem</i>	geminal
GC	gas-liquid chromatography
GC-MS	gas-liquid chromatography-mass spectroscopy
h	hour(s)
HETCOR	<sup>1</sup> H- <sup>13</sup> C heteronuclear correlation spectroscopy
HMPA	hexamethylphosphoramide
HOAc	acetic acid
Hz	hertz
i.d.	inside diameter
INADEQUATE	Incredible Natural Abundance Double-Quantum Transfer Experiment
IR	infrared
<i>J</i>	coupling constant

k	rate constant ( $\text{mol}^{-1}\text{s}^{-1}$ )
LDA	lithium diisopropylamide
lit	literature reference
m	medium for IR; multiplet for NMR
M	molar
M <sup>+</sup>	molecular ion (mass spectroscopy) or metal cation
Me	methyl
<i>m/z</i>	mass to charge ratio
MeI	methyl iodide
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mmHg	millimetres of mercury
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl-
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
<i>n</i> -	normal (primary)
NaOMe	sodium methoxide
NOESY	nuclear Overhauser enhancement spectroscopy, $^1\text{H}$ - $^1\text{H}$ NMR
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
Nu <sup>-</sup>	nucleophile
obs.	observed

PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PPTS	3-[5-(sulfophenyl)-2-pyridyl]-1,2,4-triazin-5-ylbenzenesulfonic acid, disodium salt
Pr	propyl
py	pyridine
q	quartet
R	alkyl group
R'	alkyl group other than R
rt	room temperature
RT	retention time
s	singlet
<i>sec</i>	secondary
sh	shoulder
SM	starting material
t	triplet
<i>t</i> -	tertiary
T	temperature
TBDMS	tertiary-butyldimethylsilyl
TBDMSCl	tertiary-butyldimethylsilyl chloride
<i>tert</i> -	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	<i>para</i> -toluenesulfonyl
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
TTMSS	<i>tris</i> -trimethylsilylsilane

Z	activating or electron withdrawing group
$\nu$	absorption frequency
1°	primary
2°	secondary
3°	tertiary
$\uparrow\downarrow$	reflux

## ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor, Professor Fallis, for all of the guidance and support he has given me during the course of my Ph.D. studies, as well as the infectious enthusiasm he always displays for our research and science in general.

I would also like to thank my friends, lab-mates and colleagues of the past and present for their support, suggestions, help, and fruitful discussions over the years.

All of the high-field NMR work was performed by Mr. R. Capoor and Dr. G. Facey, and their efforts are greatly appreciated.

A portion of this work was performed at the University of Windsor and I would like to thank everyone there for their kindness.

I would also like to thank the Ontario Government for their support in the form of a graduate scholarship during part of my Ph.D. studies.

A special thank-you goes to my long-distance lifeline in Salmo B.C.; without my Mother and Father just a thought away all of this would have been impossible. Thanks also to my brother Ted and his wife Theresa for always being there and letting me know they care, and to Miguel for his constant support, encouragement and many hours of help during the preparation of this thesis.

An important addition to my life has been my association with some very special people whom I have had the privilege of spending time with. With my deepest appreciation and respect I would like to thank those people who have shown me the path and have kept me on track during some difficult times in the past two years. To Bhante Viradhammo, Bhante Sugathasiri, Kelsang Tharchin Gyatso, Bhante Dhammaratana, Bhante Rahula and Sister Sucinta— Sahu dassanamariyanam sannivaso sada sukko, satam samagamo hoti yava nibbana-pattiya.

To all those I have mentioned and all of the others who made my time at the University of Ottawa so enjoyable, may you all be well, happy, and peaceful.

## INTRODUCTION

### Overview

An increasingly wide variety of reagents are available to the synthetic organic chemist which can be used to carry out transformations that were previously difficult, inefficient, or impossible. Among these, complexes of the transition metals and lanthanides have provided the largest source of these "new" reagents. The interaction of organic compounds with the metal centres in these reagents can greatly alter the reactivity of the organic moieties involved. Examples of this include the stabilization of unstable structures, and the activation of stable compounds.

Inorganic and organometallic complexes containing metals such as palladium, platinum, ruthenium, osmium and cerium have all contributed to the scope of synthetic chemistry. A testament to this fact is the large number of books and reviews that have appeared recently which deal with the application of various metals and organometallics in organic chemistry.<sup>1-10</sup>

This thesis is concerned with the application of two of these "modern" metallic reagents in a number of synthetic transformations. The work described in the following chapters investigates several different types of reactions promoted by samarium(II) iodide ( $\text{SmI}_2$ ), as well as an interesting deviation from the normal cyclopropanation reactivity of  $\alpha$ -diazoketones with ethyl vinyl ethers and rhodium carboxylate catalysts. A common feature in all of these reactions is that the synthetic transformations are based on the special properties of the metal species involved.

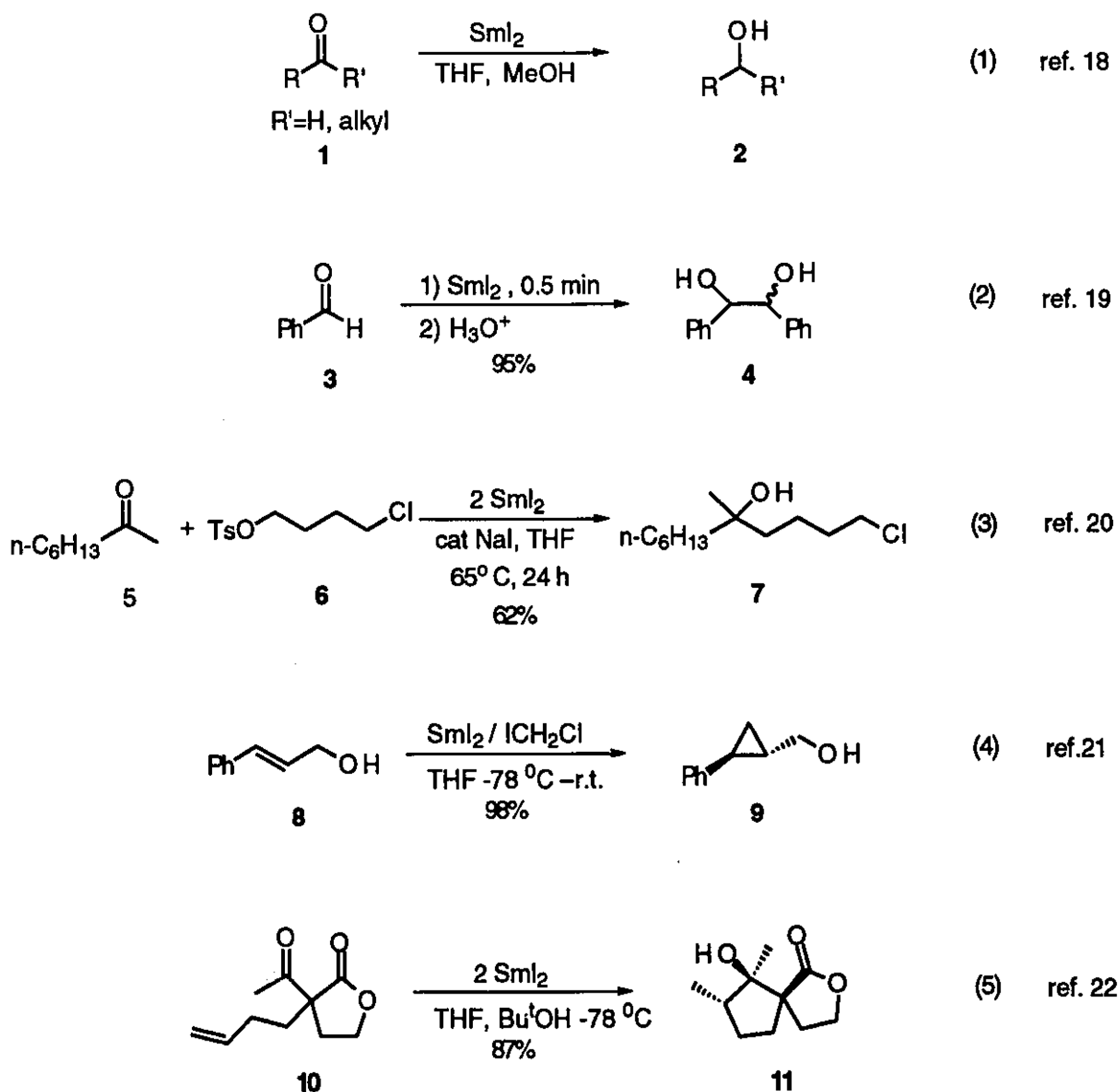
## Samarium-Promoted Ring Openings

Samarium, a lanthanide metal, has an aqueous reduction potential ( $E^\circ$ ) of  $-1.55$  V for the  $\text{Sm}^{3+}/\text{Sm}^{2+}$  couple.<sup>11</sup> This large negative  $E^\circ$  value is comparable to the redox couples of other complexes that are known to be highly effective for the reduction of organic compounds. For example, the  $\text{Ti}^{2+}/\text{Ti}^0$  redox couple has an aqueous reduction potential of  $-1.7$  V.<sup>12</sup> The facility with which samarium complexes are able to donate a single electron to a large number of electron acceptors has opened up a new avenue by which to initiate either free radical or carbanionic transformations. Anionic reactions can be viewed as occurring through a stepwise process that involves the donation of two single electrons from two equivalents of samarium, generating a net two electron reduction.<sup>13</sup>

The use of samarium(II) iodide as a reducing agent in organic chemistry began with Kagan's discovery that it could be readily prepared by the reaction of samarium powder and diiodoethane in tetrahydrofuran.<sup>14</sup> The resulting deep blue solution of  $\text{SmI}_2$  in THF can be kept for long periods provided that it is stored over a small amount of samarium metal under an inert atmosphere .

Since its introduction,  $\text{SmI}_2$  has been used to promote a large number of synthetic transformations and several reviews outlining its use in organic chemistry have appeared.<sup>12-17</sup> Some selected examples are shown below in Scheme 1. The reduction of aldehydes or ketones to alcohols (eq. 1)<sup>18</sup> or pinacols (eq. 2)<sup>19</sup> is accomplished readily when reactions are carried out under protic or aprotic conditions, respectively. Both inter- (eq. 3)<sup>20</sup> and intramolecular Barbier-type additions to ketones are known. Highly chemoselective additions such as that shown in equation 3 take advantage of the large difference in reactivity between primary tosylates and chlorides with  $\text{SmI}_2$  under Barbier-type reaction conditions.

Chemoselectivity is also important in the samarium-based Simmons-Smith reaction (eq. 4).<sup>21</sup> Unlike the traditional zinc-based protocol,  $\text{SmI}_2$  and dihalomethanes selectively cyclopropanate allylic alcohols to the complete exclusion of reaction with isolated olefins.

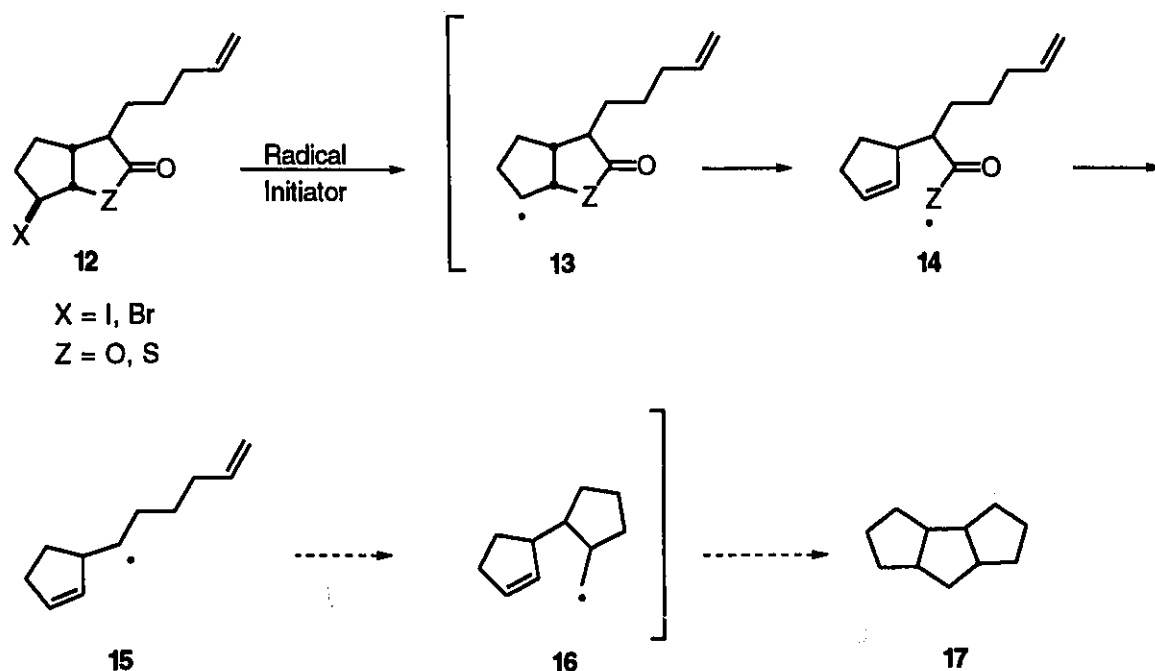


Scheme 1 Selected Examples of SmI<sub>2</sub>-Promoted Reactions

A representative example of the synthetic potential of samarium-ketyl alkene cross-coupling reactions is given in equation 5.<sup>22</sup> By taking advantage of chelation to Sm<sup>3+</sup>, (revealing the cation's ability to act as a Lewis acid), the relative stereochemistry at the developing hydroxy and carboxylate stereocentres can be controlled in this type of system. Additional control at the third stereocentre is obtained through favourable secondary orbital interactions between the developing methyl radical and the alkyl group attached to the ketyl.<sup>15</sup>

The initiation of radical reactions by the reduction of organohalides to alkyl or aryl radicals is a growing area of samarium(II) iodide chemistry that has only begun to be explored. Reactions promoted by  $\text{SmI}_2$  provide significant advantages over traditional procedures which generally involve the use of toxic tin reagents. Workup procedures are often easier with  $\text{SmI}_2$ -initiated reactions as the separation of tin byproducts from a reaction mixture often poses a significant problem during product isolation.

Our investigations of  $\text{SmI}_2$ -initiated radical ring opening reactions have contributed to this growing field of lanthanide promoted radical reactions. The first chapter of this thesis deals with the ring opening and decarboxylation of halolactones. Our initial goal (Scheme 2) was to investigate the feasibility of generating an alkyl radical **13** alpha to the



Scheme 2 Proposed Radical Cascade Reaction

heteroatom of a cyclic halolactone that would undergo  $\beta$ -elimination to produce an acyloxy radical **14** ( $\text{Z}=\text{O}$ ) that should decarboxylate to give the secondary alkyl radical **15**. A

tandem radical cyclization is possible from this intermediate as it is set up to undergo a 5-*exo* cyclization to give **16**, which may cyclize again in a 5-*exo* fashion to give the linear triquinane-type structure **17**. Successful implementation of this scheme would facilitate the construction of complex natural product skeletons in a direct, stereocontrolled manner.

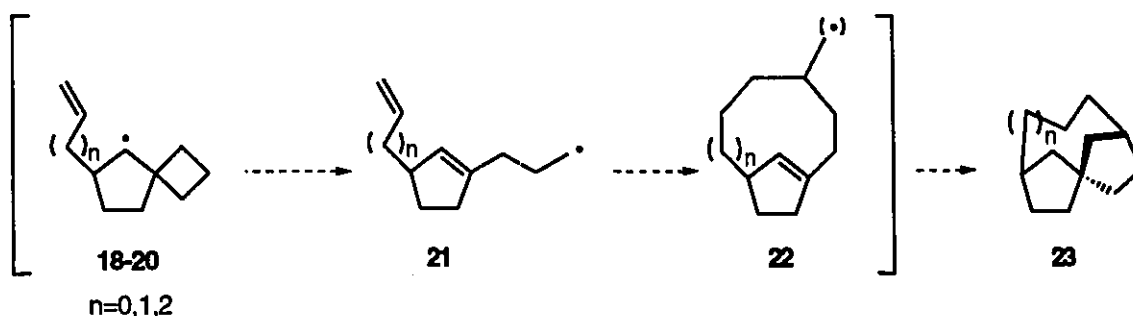
A number of critical factors will determine the success of the proposed radical cascade shown in Scheme 2. After the initial generation of an alkyl radical by a suitable initiator, the facility of the C-Z bond cleavage and subsequent loss of CO<sub>2</sub> or COS are of primary importance. Carbon-sulfur bond cleavage is known to occur *via*  $\beta$ -scission under radical conditions.<sup>23-25</sup> It was hoped that if the lactone failed to open, the weaker C-S bond in the thialactone would promote the desired transformation. Oxidation of the thialactone sulfur might further encourage elimination as the strength of the C-Z bond of a sulfoxide would be reduced to an even greater extent. Other crucial factors include the lifetimes and rates of cyclization of the newly formed alkyl radicals which will ultimately determine the extent of the ring formation (steps **15-16-17**). To address the issue of bond cleavage and to evaluate the relative ease of elimination depending on the heteroatom present, a model system was developed. Results obtained from these model studies led to experiments on a number of cyclic halolactones.

### **Radical-Promoted Ring Opening of Spirocyclobutanes**

Chapter 2 describes experiments involving the ring opening of substituted  $\alpha$ -keto-spirocyclobutanes. We wished to investigate the possibility of generating a ring-opened alkyl radical **21** (Scheme 3) from a substituted spirocyclobutane **18-20**, which might be capable of undergoing further cyclizations to generate bicyclic (**22**) or polycyclic (**23**) systems.

Suitable radical precursors were prepared in order to generate either alkyl or ketyl

radicals at the position alpha to the spirocyclobutane from the corresponding halide or ketone, respectively. The opening of spirocyclopropanes under free radical conditions has been well documented.<sup>26,27</sup> The radical-promoted opening of spirocyclobutane systems has received much less attention as the kinetics are less favourable. Rate constants

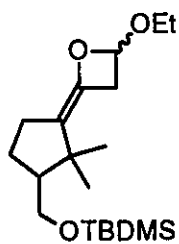
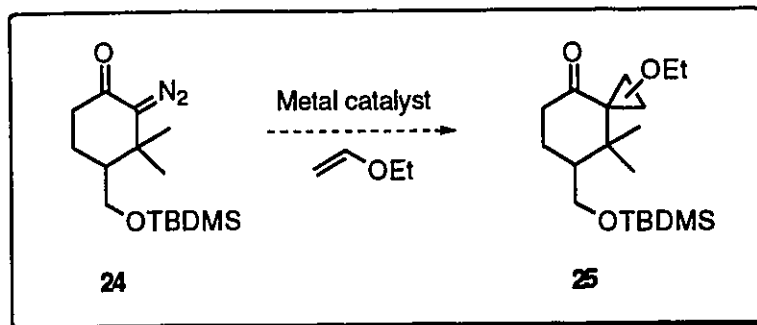


Scheme 3 Proposed Ring Opening of Substituted Spirocyclobutanes

have been measured for the opening of simple systems such as methylcyclobutane ( $k = 1 \times 10^3$ ).<sup>28</sup> Our preliminary investigations into the preparation and ring opening of the spirocyclobutane will be described.

### Rhodium Catalyzed Cyclopropanation-Rearrangement Reactions

The results presented in the final chapter of this thesis arose as a result of investigations into the cyclopropanation of an  $\alpha$ -diazoketone (**24**, Scheme 4) with ethyl vinyl ether under rhodium(II) acetate-catalyzed conditions. The expected cyclopropane **25** was not obtained. A compound was isolated from the reaction that was tentatively identified as oxetane **26**. The characterization and isolation of the actual reaction product, a rearranged donor-acceptor cyclopropane, will be discussed in Chapter 3.

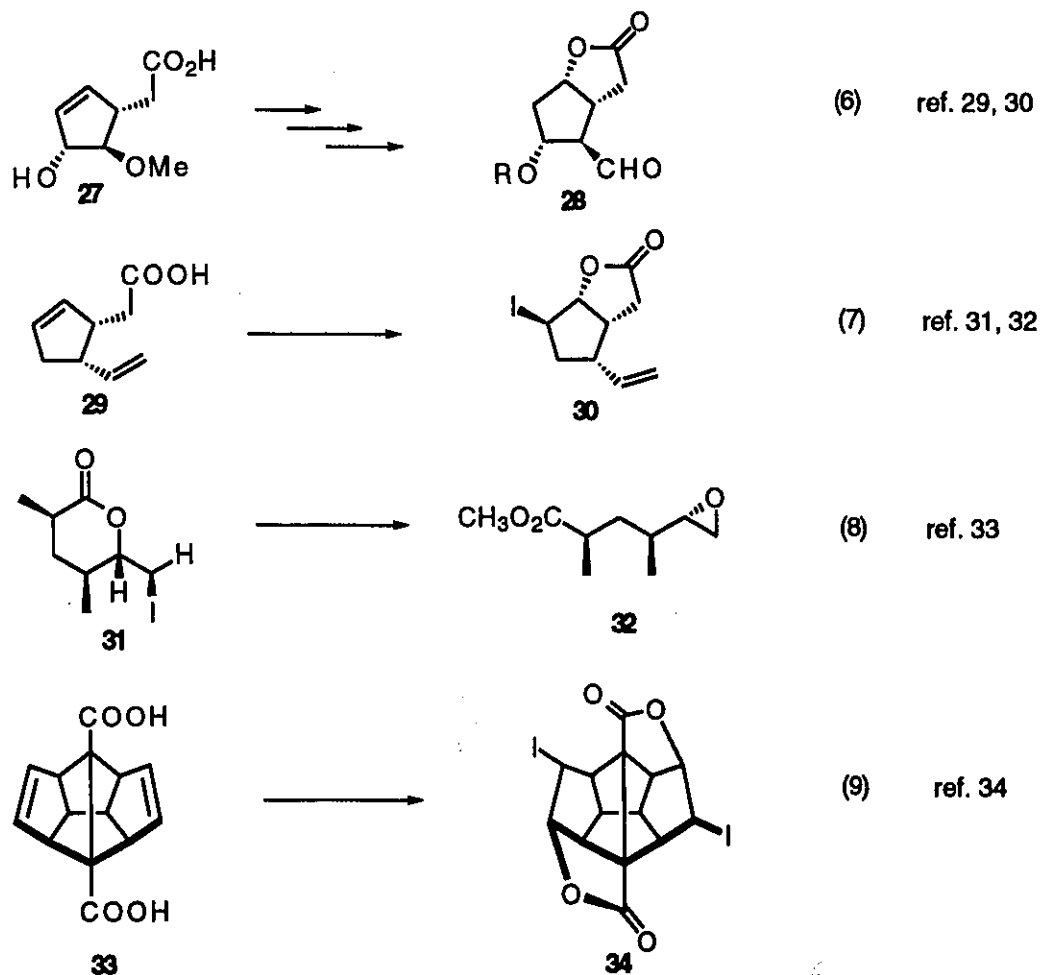
**26**Scheme 4 Attempted Cyclopropanation of  $\alpha$ -Diazoketone **24**

## CHAPTER 1

### HALOLACTONE RING OPENING REACTIONS

#### 1.1 Introduction

Halolactones have proven to be extremely useful synthetic intermediates in the total synthesis of natural products. A well known example of this is found in the total synthesis of prostaglandins. Iodolactonization of **27**, followed by further transformations generated aldehydolactone **28** (eq. 6, Scheme 5), which was first prepared independently by Corey<sup>29</sup>

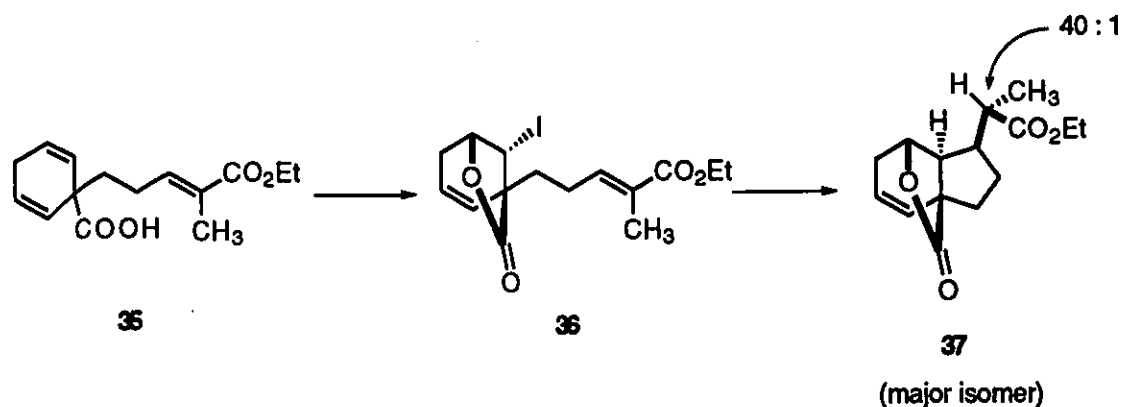


Scheme 5 Halolactones as Intermediates in the Total Synthesis of Natural Products

and Sutherland<sup>30</sup>. This intermediate can be functionalized with appropriate sidechains using conventional Wittig chemistry, and further converted into a number of the primary prostaglandins. Paquette has also developed a synthetic approach that "provides a preparatively useful route to a wide selection of prostanoid hormones from the simplest of achiral conjugated dienes".<sup>31,32</sup> This approach is based upon the successful construction of iodolactone **30** (eq.7) from butadiene.

Bartlett's group prepared epoxy ester **32** from the methanolysis of iodolactone **31** and used this as a key intermediate in the total synthesis of the insect sex attractant multistriatin (eq.8).<sup>33</sup> The first synthesis of dodecahedrane involved a diiodolactonization of **33** to produce an important "cross-corner" functionalized intermediate **34** (eq.9, Scheme 5) that was difficult to prepare by other procedures.<sup>34</sup>

In a recent total synthesis of *dl*-pleurotin,<sup>35</sup> the combination of iodolactonization and subsequent radical cyclization allowed Hart's group to prepare the perhydroindane nucleus **37** in an efficient and stereoselective manner from the unsaturated acid **35** (Scheme 6). This example illustrates the possibility of generating a free radical from an iodolactone which can be used to further transform the substrate of interest.

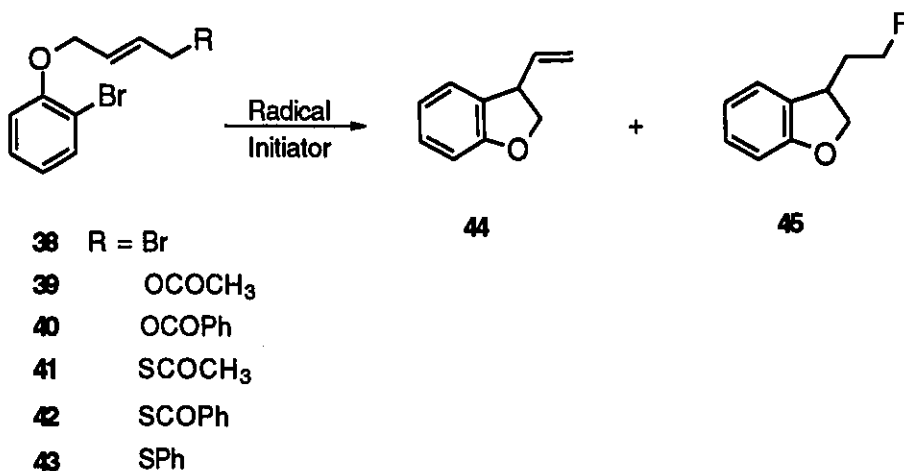


Scheme 6 Lactonization and Cyclization to Form Perhydroindane Nucleus **37**<sup>35</sup>

Our goal at the outset of this project (see Scheme 2 in the Introduction) was to investigate the possibility of generating a free radical from a halolactone followed by  $\beta$ -elimination to produce an acyloxy radical **14** ( $Z=O$ ) which would then decarboxylate to give a secondary alkyl radical **15**. Tandem radical cyclization of this intermediate would produce the linear triquinane-type structure **17**. The critical factors that would in turn determine the success of our proposal were briefly outlined in the introduction.

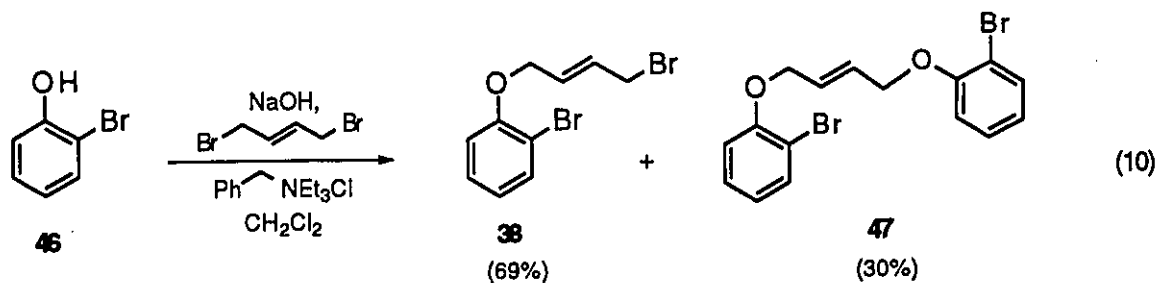
## 1.2 A Model System

A central feature of our scheme involves the opening of a cyclic halolactone via  $\beta$ -elimination of the adjacent alkyl radical. In order to address this issue and to evaluate the relative ease of bond cleavage a model system was developed (Scheme 7). One important requirement for the model system was that derivatives bearing a range of potential leaving

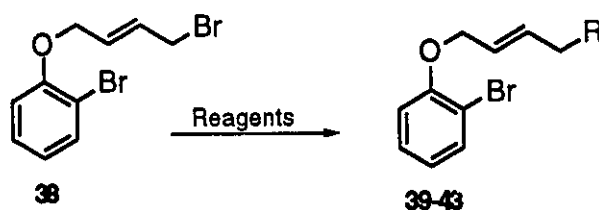


Scheme 7 Model System

groups could be readily prepared. Dibromide **38** was chosen as a precursor in which the allylic bromide could easily be replaced with a variety of substituents to generate the required series of model compounds (**39-43**). Dibromide **38** was obtained in 69% yield



upon treatment of *ortho*-bromophenol with 1,4-dibromo-2-butene under phase transfer catalysis conditions (eq.10). The dialkylated dibromide **47**, was isolated in 30% yield as a side product. Substitution of the allylic bromide in compound **38** with the appropriate nucleophile provided compounds **39-43** in moderate to good yields (Table 1).



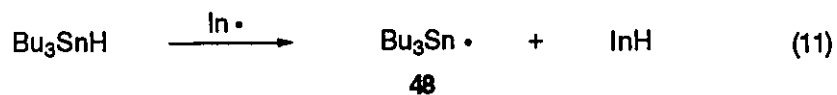
Product	Reagents	R	Yield
<b>39</b>	AgOAc, AcOH, H <sub>2</sub> O, r.t.	OCOCH <sub>3</sub>	87%
<b>40</b>	PhCO <sub>2</sub> H, NaOH, BnNBu <sub>3</sub> Br, H <sub>2</sub> O/CH <sub>2</sub> Cl <sub>2</sub> , r.t.	OCOPh	52%
<b>41</b>	NaH, CH <sub>3</sub> COSH, THF, 0 °C	SCOCH <sub>3</sub>	89%
<b>42</b>	NaH, PhCOSH, THF, 0 °C	SCOPh	51%
<b>43</b>	NaH, PhSH, THF, 0 °C	SPh	80%

Table 1 Preparation of Model Compounds

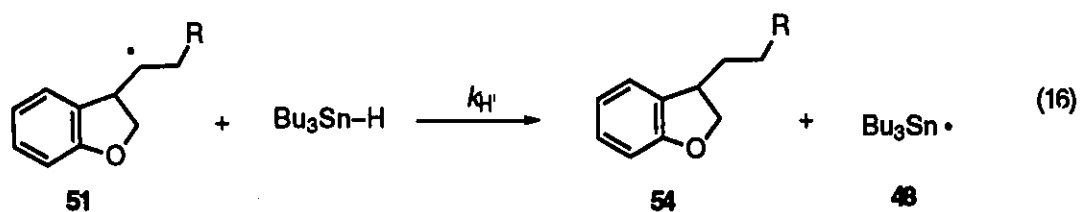
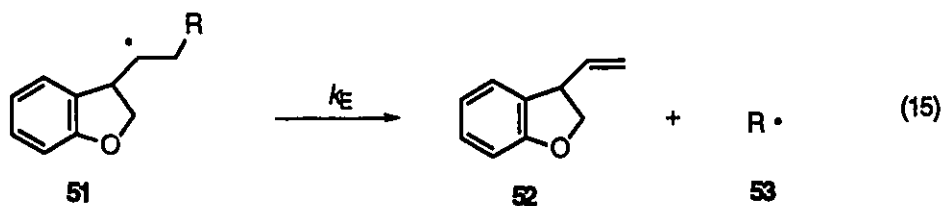
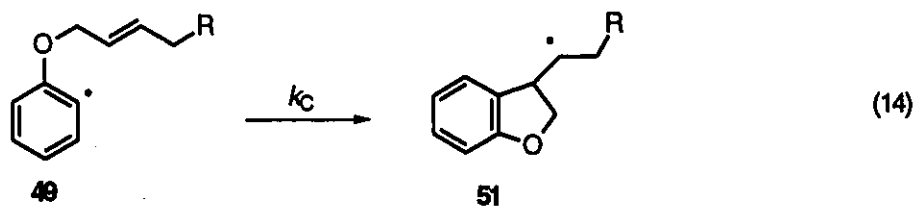
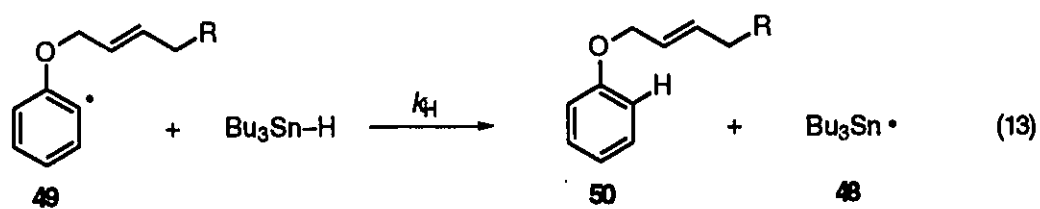
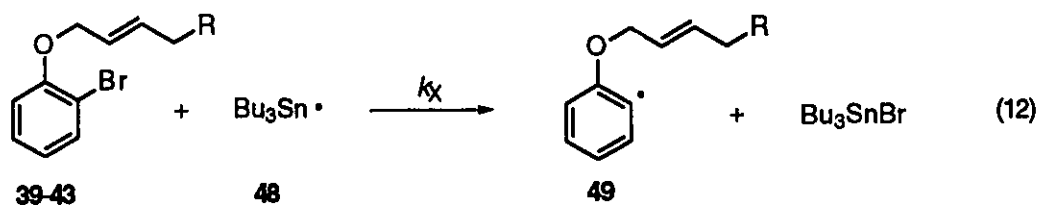
In order to examine the effect of different chain transfer agents and radical initiators, aryl radicals were generated from the corresponding bromides using three different methods. The first method, generally referred to as the "tin hydride method"<sup>36</sup> is the most common method of carrying out radical reactions in organic synthesis. Using this method tributyltin radicals are generated in an initiation step from tin hydride (Scheme 8) and an initiator (In) such as azobisisobutyronitrile (AIBN). Thermal decomposition of AIBN generates an alkyl radical (In•) which readily abstracts a hydrogen atom from the tin hydride (eq.11). The tributyltin radical **48** begins the propagation sequence by abstracting a halogen (bromine in this case, however a variety of atoms or groups can be used) from the organohalide **39-43** to provide the aryl radical **49** and tributyltin bromide (eq.12). The reduced product **50** is formed if aryl radical **49** abstracts a hydrogen atom in a second-order reaction, regenerating the chain carrier tributyltin radical **48** in the process (eq.13). Alternatively, **49** may cyclize in a 5-*exo* or 6-*exo* (much slower)<sup>28</sup> fashion to produce, in the first instance, the alkyl radical **51** in an irreversible first-order reaction (eq.14). In the next step (eq.15),  $\beta$ -elimination of R• from **51** generates olefin **52**. Hydrogen abstraction from Bu<sub>3</sub>SnH is also possible for **51** which generates the reduced cyclized product **54** and the tributyltin radical once again in another chain transfer step (eq.16).

Propagation steps of radical reactions generally have low enthalpies of activation and the rates of reaction are very fast. The extent to which each of the various products are formed depends on the rates of the various competing reactions. Accurate rate constants are available for many elementary processes.<sup>37</sup> The effect of varying the substituents at the radical centre has also been studied. Appropriate reaction conditions including temperatures and concentrations can therefore be predicted. Generally the cyclization steps are desired and suitable modifications are made to favour the rates of cyclization over those of reduction.

Initiation:



Propagation:



Scheme 8 The Tin Hydride Method

The rate of quenching is dependent on the concentration of tin hydride and it is therefore beneficial to keep the concentration as low as possible. Syringe pump techniques and *in situ* generation of  $\text{SnBu}_3\text{H}$  from the reaction of a catalytic amount of  $\text{SnBu}_3\text{X}$  and a reducing agent such as  $\text{NaCNBH}_4$  are often employed in preparative procedures.<sup>38,39</sup> There is a limit to this dilution factor due to the fact that if the rates of the propagation steps involving tin hydride fall to a sufficient extent, the chain could collapse.

Other radical-radical or radical-molecule reactions can also compete with the desired chain propagation steps. Hydrogen atom abstraction from the solvent, for example, often competes favourably with propagation steps. For this reason radical reactions are often carried out in benzene which does not contain any hydrogen atoms that are easily abstracted.

A significant drawback to using the tin hydride method, besides the known toxicity of organotin compounds, is the difficulty that is often encountered in attempting to separate the tin residues from the reaction products. This becomes especially difficult when the reaction products are non-polar.

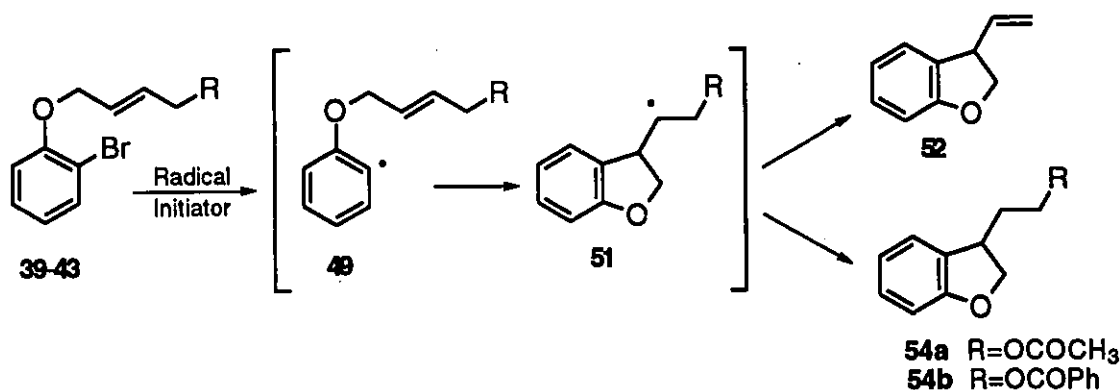
Tris(trimethylsilyl)silane (TTMSS) is the second method that was used to generate radicals in our model systems. Although most silicon-hydrogen bonds are too strong to donate hydrogen at a rate sufficient to propagate a chain reaction, TTMSS has a Si-H bond strength that is significantly lower than most alkyl silanes (BDE for Si-H in TTMSS is  $79 \text{ kcal mol}^{-1}$  ( $330 \text{ kJmol}^{-1}$ ) cf. that of  $\text{Et}_3\text{SiH}$  at  $90 \text{ kcalmol}^{-1}$  ( $377 \text{ kJmol}^{-1}$ )).<sup>40</sup> The Si-H bond strength of TTMSS ( $79 \text{ kcal mol}^{-1}$ ) compares favourably with that of  $n\text{Bu}_3\text{SnH}$  (BDE for Sn-H is  $71 \text{ kcalmol}^{-1}$  ( $266 \text{ kJmol}^{-1}$ )), thus, TTMSS is a sufficiently good hydrogen donor that it is capable of sustaining a radical chain reduction of an alkyl halide analogous to the tin method shown in Scheme 8.<sup>41</sup>

The final method that was used to generate an aryl radical from bromides **39-43** was  $\text{SmI}_2/\text{HMPA}$  in THF. At the time this work was being done only a few examples of  $\text{SmI}_2$ 's ability to reduce a halide to the corresponding radical had been reported.<sup>42,43</sup> The

relative rates of 5-*exo* cyclization of aryl radical **49** ( $k \sim 10^7 \text{ s}^{-1}$ ), further reduction of the initially formed radical to the anion via a second electron transfer from  $\text{SmI}_2$ , and elimination of  $\text{R}^\bullet$  from intermediate **51** were not known. It was hoped that the results of our experiments with the various model systems would provide us with some indication of the relative rates of these processes for each of the three reaction conditions used.

### 1.3 Results of Model Studies

The results obtained in our model studies are listed in Table 2. All of the model compounds were reduced to aryl radical **49** with each of the different reaction conditions.



Entry	R	$n\text{Bu}_3\text{SnH}^1$ AIBN, benzene	TTMSS <sup>2</sup> AIBN, benzene	$\text{SmI}_2/\text{THF}^3$ HMPA (4 eq)
1	OCOCH <sub>3</sub>	<b>54a</b> 74%	<b>54a</b> 70%	<b>52</b> 75%
2	OCOPh	<b>54b</b> 76%	—	<b>52</b> 71%
3	SOCH <sub>3</sub>	<b>52</b> 93%	<b>52</b> 82%	<b>52</b> 91%
4	SPh	<b>52</b> 92%	—	<b>52</b> 88%
5	SOPh	<b>52</b> 91%	—	<b>52</b> 92%

1.  $n\text{-Bu}_3\text{SnH}$ , 2 eq; AIBN, cat.; benzene (distilled, degassed);  $\Delta$ , 1–4 h

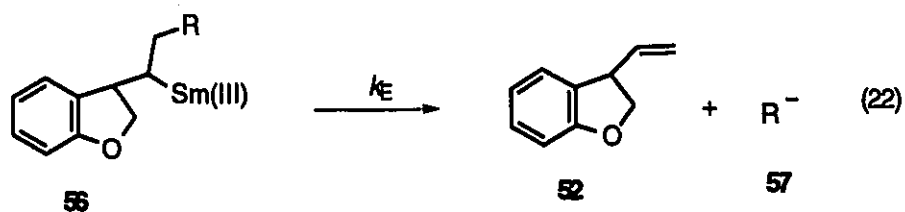
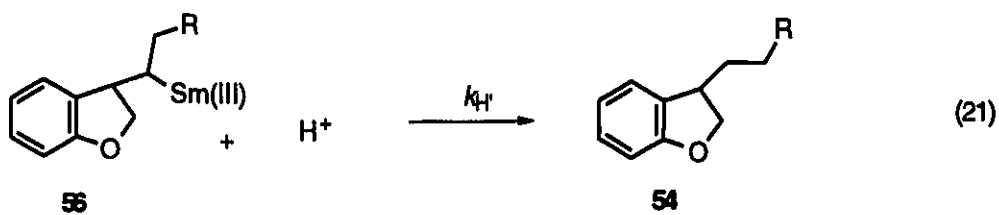
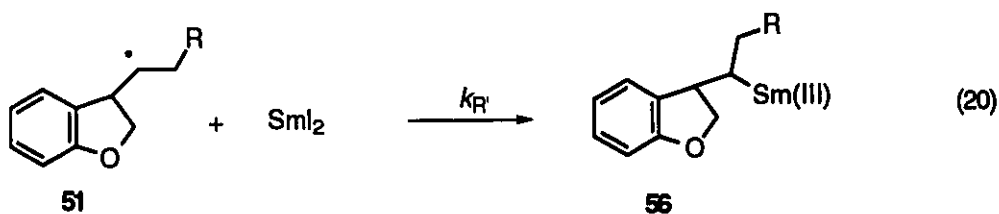
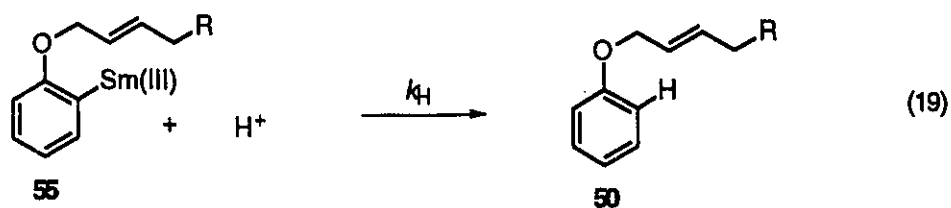
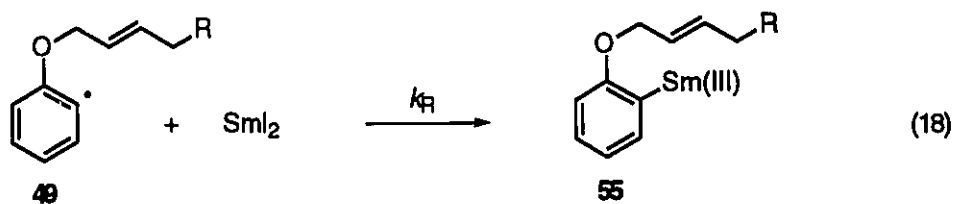
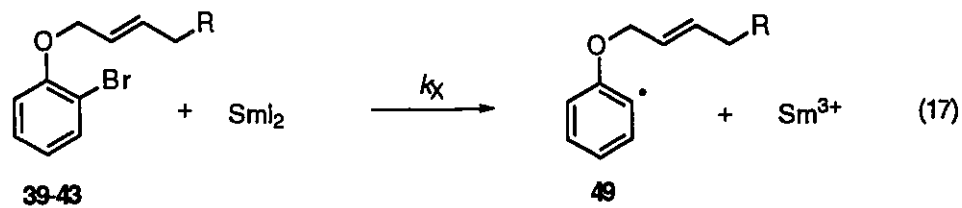
2. Tris(trimethylsilyl)silane, 1.5 eq; AIBN, cat.; benzene (distilled, degassed);  $\Delta$ , 6 h

3.  $\text{SmI}_2$ , 2.2 eq; HMPA, 4 eq; THF (distilled, degassed); 21 °C

Table 2 Cyclization/Elimination of *o*-Bromoaryl Allyl Ethers

Intermediate **49** undergoes 5-*exo* cyclization to produce a secondary alkyl radical **51** which may undergo  $\beta$ -elimination to generate vinyl dihydrofuranbenzofuran **52**, or abstract a hydrogen atom producing compound **54** (Scheme 8). Intermediate radicals **49** and **51** (Scheme 9) generated in the reactions that were carried out with SmI<sub>2</sub>/THF/HMPA have the additional possibilities of being further reduced by a second equivalent of SmI<sub>2</sub> to generate an organosamarium species **55** and **56**, that may either pick up a proton to give **50** and **54**, respectively, or undergo further anionic transformations such as the elimination of R- (**57**) to produce olefin **52** or proton abstraction to give the cyclized, reduced product **54**.

It was found that in each of the systems containing a sulfur substituent at the allylic position, cyclization of the aryl radical was followed by elimination of the sulfur group under all of the reaction conditions that were used. This result is not surprising since fragmentation to sulfur radicals, such as the phenylthio radical, by  $\beta$ -scission is known to be a facile process.<sup>25,44-46</sup> To the best of our knowledge the elimination of an alkoxy radical has not been reported previously. It was therefore somewhat of a surprise to find that both the allylic phenol and allylic acetate groups underwent elimination under SmI<sub>2</sub>/HMPA/THF conditions (Table 2, entries 1 and 2). The same substituents were not eliminated using tin hydride or TTMSS methods and it is therefore reasonable to speculate that either the cyclized secondary radical **51** is further reduced to the organosamarium species **56**, which then undergoes the more familiar elimination of an allylic alkoxide or carboxylate, or that the SmI<sub>2</sub> conditions allow a sufficiently long lifetime of the cyclized radical **51** for elimination of the oxygen based substituents to take place. A third explanation involving the possible assistance of the Sm<sup>3+</sup> species, a powerful oxophile and Lewis acid, in the elimination of the oxygen-based groups can also be considered.

Scheme 9  $\text{SmI}_2$ -Mediated Method

These results provided further evidence that our original intention to modify the heteroatom in the lactone in order to enhance the ability of the initially generated radical alpha to the

heteroatom to undergo  $\beta$ -scission was reasonable. Another exciting discovery was the finding that changing the reaction conditions to  $\text{SmI}_2/\text{HMPA}/\text{THF}$  facilitated  $\beta$ -bond cleavage. Knowledge of this fact encouraged us to exploit this methodology in an attempt to promote ring opening, and hopefully decarboxylation followed by 5-*exo* radical cyclizations in other systems.

#### 1.4 Preparation of Halolactones

A variety of iodo- and bromolactones and iodothialactones were prepared in order to investigate the possibility of effecting ring opening and decarboxylation of these systems under free radical conditions. Iodolactones **59**, **62**, and **66** (Table 3) were prepared using standard iodolactonization procedures<sup>47-49</sup> which involve dissolving the unsaturated acid in aqueous sodium bicarbonate to form the carboxylate salt, followed by treatment of this solution with a solution of iodine in aqueous potassium iodide. The substituted unsaturated acid precursors **60** and **64** were prepared by alkylating the corresponding dianion with the appropriate alkylating agent (benzyl and 5-bromo-1-pentenyl, respectively). For example, **60** was prepared from the reaction of benzyl bromide with the dianion of 2-(3-cyclopentenyl)acetic acid. The 4-pentenyl substituted acid **64** was prepared in low yield using this method, and an alternative procedure which involved the alkylation of the corresponding methyl ester **73**, followed by hydrolysis afforded **64** in 78% yield.

Five-membered ring lactones are formed preferentially over six-membered ring lactones<sup>50</sup> and the addition is strictly *anti* stereospecific when the reaction is carried out under basic conditions. The kinetically controlled *anti* addition results from initial electrophilic attack of the iodine on the olefin to form an iodonium ion, followed by an irreversible back-side opening of the iodonium ion by the carboxylate nucleophile. Iodolactonizations that are carried out under non-basic conditions, such as iodine in

chloroform, are reversible reactions that usually result in the formation of the most thermodynamically stable product.

The bicyclic iodolactones **59**, **62**, and **64** were all thick oils that decomposed readily. Substitution of either a benzyl or an alkyl group at the 3-position provided compounds that ring-opened to give less volatile products, and in the case of **66**, **67** and **68**, providing the additional benefit of possibly cyclizing to give bi- or polycyclic systems. This benefit, however, was offset by the fact that these compounds decomposed more readily than the unsubstituted parent system. The reaction times that were required to prepare the substituted systems **62** and **66** (approximately 3-4 days) were substantially longer than those required for the parent compound **59** (~12 h).

Iodothialactones **63** and **68** were prepared in low yields from the corresponding unsaturated thiolacids **61** and **65** using the standard procedure described above. Thiolacids **61** and **65** were generated from the reaction of the acid chloride derivatives of **60** and **64** (RCOCl: **74** and **75**, respectively) with potassium hydroxide and hydrogen sulfide. The crude thiolacid **61** was used immediately and no attempt was made to purify this material as it oxidizes readily.

Bromolactones **67**, **70**, and **72** were prepared from unsaturated acids **64**, **69**, and **71**, respectively. The acids were dissolved in an aqueous solution of sodium bicarbonate, and the resulting solution was cooled to 0 °C followed by dropwise addition of bromine until a slight excess remained. Although the bromolactone **67** was more stable than the corresponding iodolactone **66**, it did decompose fairly readily and could only be kept for periods of 2-3 weeks at -10 °C. By contrast, the [2.2.1]bromolactones **70** and **72** were both easily prepared in excellent yield, and appear to be stable indefinitely at -10 °C.

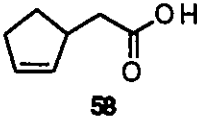
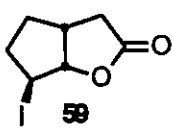
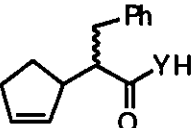
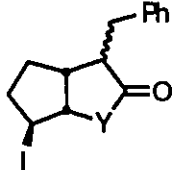
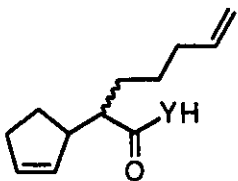
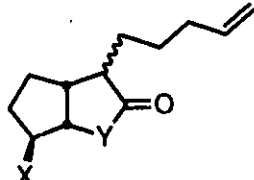
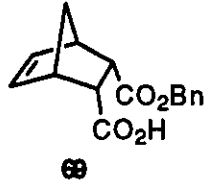
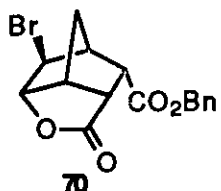
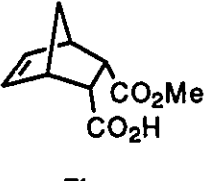
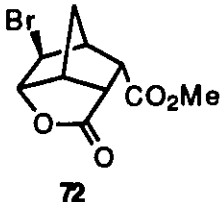
Entry	Substrate	Conditions	Product	Yield
1	 58	$\text{NaHCO}_3$ , $\text{I}_2 / \text{KI} / \text{H}_2\text{O}$	 59	86%
2	 $\text{Y} = \text{O}$ 60 $\text{Y} = \text{S}$ 61	$\text{NaHCO}_3$ , $\text{I}_2 / \text{KI} / \text{H}_2\text{O}$	 $\text{Y} = \text{O}$ 62 $\text{Y} = \text{S}$ 63	82% 73%
3	 $\text{Y} = \text{O}$ 64 $\text{Y} = \text{S}$ 65	$\text{NaHCO}_3 / \text{I}_2 / \text{KI}$ or $\text{NaHCO}_3 / \text{Br}_2$	 $\text{Y} = \text{O}$ 66 $\text{X} = \text{I}$ 67 $\text{X} = \text{Br}$ $\text{Y} = \text{S}$ 68 $\text{X} = \text{I}$	70% 74% 34%
4	 69	$\text{KI} / \text{I}_2 / \text{NaHCO}_3$ or $\text{NaHCO}_3 / \text{Br}_2$	 70	88%
5	 71	$\text{KI} / \text{I}_2 / \text{NaHCO}_3$ or $\text{NaHCO}_3 / \text{Br}_2$	 72	87%

Table 3 Preparation of Halolactones

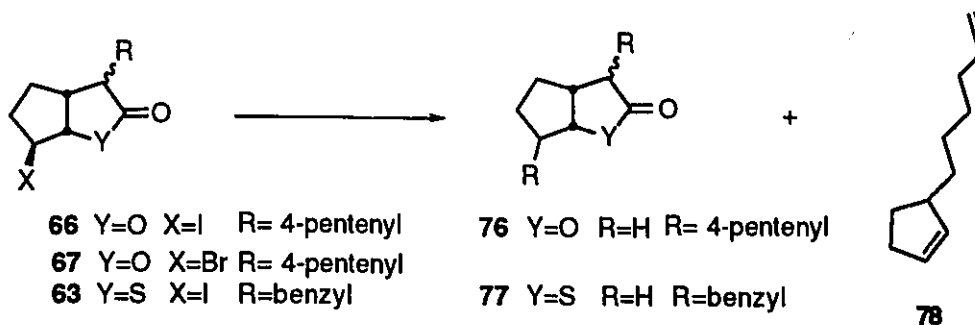
### 1.5 Attempted Ring Openings of Halolactones

Preliminary reactions of unsubstituted iodolactone **59** were problematic due to the volatility of the ring opened decarboxylated product, and the absence of chromophores in the starting materials and product which would facilitate the identification of products and allow one to monitor the reaction by thin layer chromatography (GC-MS was not available and GC was virtually unavailable). With these considerations in mind, benzyl-substituted iodolactone **62** was prepared.

Reactions were now easier to follow and it was clear from this system that radicals were being formed from the iodolactone but initial work with a variety of radical carriers indicated that the lactone was not opening since the only product isolated was the dehalogenated lactone.

Preparation of the 4-pentenyl substituted halolactones **66** and **67** and iodothialactones **63** and **68** allowed us to examine whether the various systems would open under a variety of radical conditions. The radical carrier, temperature and solvent used were all varied. The data presented in Table 4, entries 1-9, are representative of the results obtained with any of the general methods for generating free radicals. Simple halogen reduction products were obtained with both lactones and thialactones. Unlike the model system results presented above (see Table 2), reducing the carbon-heteroatom bond strength of the halolactone by changing from a C-O bond in the lactone to a C-S bond in the thialactone had no effect on the outcome under the conditions used.

Fortunately, the successful results that were obtained in the model system using  $\text{SmI}_2/\text{HMPA}/\text{THF}$  as the method for generating radicals were reproduced in this system as well. As entries 10 and 11 in Table 4 indicate, successful ring opening and subsequent decarboxylation of bromo- and iodolactones as well as iodothialactone occurred upon treatment with four equivalents of  $\text{SmI}_2/\text{HMPA}$  in THF. Substituted cyclopentene **78** was characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and IR spectroscopy. All of the signals were consistent



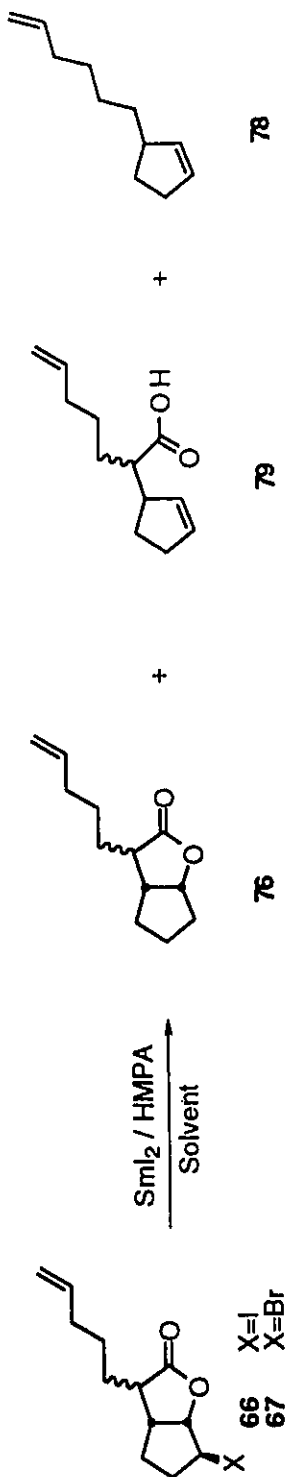
Entry	Substrate	Conditions	X	Y	Product	Yield
1	63	<i>n</i> Bu <sub>3</sub> SnH / AIBN / Δ / benzene	I	S	77	52%
2	63	<i>n</i> Bu <sub>3</sub> SnH / AIBN / Δ / benzene	I	S	77	71%
3	63	<i>n</i> Bu <sub>3</sub> SnH / AIBN / Δ / toluene	I	S	77	76%
4	63	<i>n</i> Bu <sub>3</sub> SnH / AIBN / Δ / <i>o</i> -xylene	I	S	77	54%
5	66	TMSS / AIBN / Δ / benzene	I	O	76	61%
6	63	TMSS / AIBN / Δ / benzene	I	S	77	69%
7	66	Benzoyl peroxide / Δ / benzene	I	O	76	63%
8	63	Ph <sub>3</sub> SiH / benzene / Δ	I	S	77	71%
9	63	Ph <sub>2</sub> C=CPh <sub>2</sub> Me <sub>3</sub> SnO OSnMe <sub>3</sub>	I	S	77	63%
10	66	SmI <sub>2</sub> / HMPA (4eq) / THF / Δ	I	O	78	12% <sup>a</sup>
11	67	SmI <sub>2</sub> / HMPA (4eq) / THF / Δ	Br	O	78	44% <sup>a</sup>

<sup>a</sup> Isolated yields after multiple chromatographic separations (GC yields were substantially higher 40-71 %)

Table 4 Attempted Halolactone Ring Openings

with those expected for **78**. The molecular formula of C<sub>11</sub>H<sub>18</sub> was confirmed by high resolution mass spectroscopy and is also consistent with structure **78**.

The success of the SmI<sub>2</sub>-induced ring opening and decarboxylation reactions of the halolactones led us to further investigate what effect variations in reaction conditions would



Entry	Substrate	Temperature	eq HMPA <sup>a</sup>	Solvent	Concentration	Addition <sup>b</sup>	Product	Yield <sup>c</sup>
1	<b>66</b>	21 °C	4	THF	0.03 M	normal	<b>76</b>	73%
2	<b>66</b>	21 °C	10	THF	0.01M	normal	<b>76</b>	68%
3	<b>66</b>	40 °C	4	THF	0.1 M	normal	<b>76</b> <b>78</b>	26% <sup>d,e</sup> 54% <sup>d</sup>
4	<b>66</b>	67 °C	4	THF/benzene	0.01 M	normal	<b>78</b>	71%
5	<b>66</b>	67 °C	10	THF/benzene	0.01 M	normal	<b>78</b>	74%
6	<b>66</b>	82 °C	4	CH <sub>3</sub> CN	0.01M	normal	<b>76</b>	??%
7	<b>66</b>	40 °C	4	THF	0.01	reverse	<b>79</b>	87%
8	<b>67</b>	40 °C	4	THF	0.01	reverse	<b>79</b>	81%
9	<b>67</b>	67 °C	4	THF/benzene	0.01	normal	<b>76</b> <b>78</b>	33% <sup>d</sup> 51% <sup>d</sup>

<sup>a</sup> Number of equivalents of HMPA per equivalent of SmI<sub>2</sub>

<sup>b</sup> Normal addition refers to addition of SmI<sub>2</sub> / THF to substrate / HMPA ; Reverse addition refers to addition of substrate in THF to SmI<sub>2</sub>/HMPA

<sup>c</sup> GC Yields by comparison to authentic material

<sup>d</sup> Isolated yields

<sup>e</sup> Separate experiment cf. Table 4, Entry10

Table 5 SmI<sub>2</sub>-Induced Ring Opening-Decarboxylation Reaction

have on the product distribution. The best results obtained for each of the different conditions are listed in Table 4. Elevated temperatures are required in order to obtain the decarboxylated product **78**. When reactions were carried out at room temperature (Table 5, entries 1 and 2), the simple reduction product **76** was obtained in good yield (75-85%).  $\beta$ -Cleavage and loss of CO<sub>2</sub> occurred when the reactions were carried out above 40 °C. As the reaction temperature was raised, the yield of decarboxylated material increased (cf. entries 3 and 4).

One of the restrictions inherent in the use of SmI<sub>2</sub> as a radical initiator is the fact that it is insoluble in most solvents that are commonly used in radical reactions, such as benzene which is devoid of readily abstractable hydrogen atoms. SmI<sub>2</sub> is soluble in THF, however concentrations of 0.1 M represent the upper limit of solubility.<sup>20,42,51</sup> A report of the preparation and use of SmI<sub>2</sub> in acetonitrile<sup>52</sup> prompted us to attempt the elimination-decarboxylation reaction under these conditions (note that the boiling point of CH<sub>3</sub>CN (82 °C) is 15 °C above that of THF).

Numerous attempts to obtain the reported "green blue"<sup>52</sup> SmI<sub>2</sub> solution failed to produce anything other than a yellowish solution which may have been optimistically described as yellow green. An experiment using this "SmI<sub>2</sub>/CH<sub>3</sub>CN" reagent was performed, however tlc and GC-MS analysis of the reaction mixture indicated the presence of a small amount of reduced lactone **76**, a number of intractable side-products, and a large amount of unreacted starting material.

Several possible mechanistic pathways for the generation of **78** are shown in Scheme 10. Single electron transfer from SmI<sub>2</sub> to halolactone **66** or **67** generates alkyl radical **80** which may abstract hydrogen to form the reduced lactone **76** or undergo  $\beta$ -scission to form acyloxy radical **81** which should rapidly lose CO<sub>2</sub> to give alkyl radical **82**. A second electron transfer from SmI<sub>2</sub> to **80** may occur, generating the organosamarium intermediate **83**. Anionic  $\beta$ -elimination from the organosamarium species **83** would generate samarium carboxylate **84** which, by analogy to certain metal

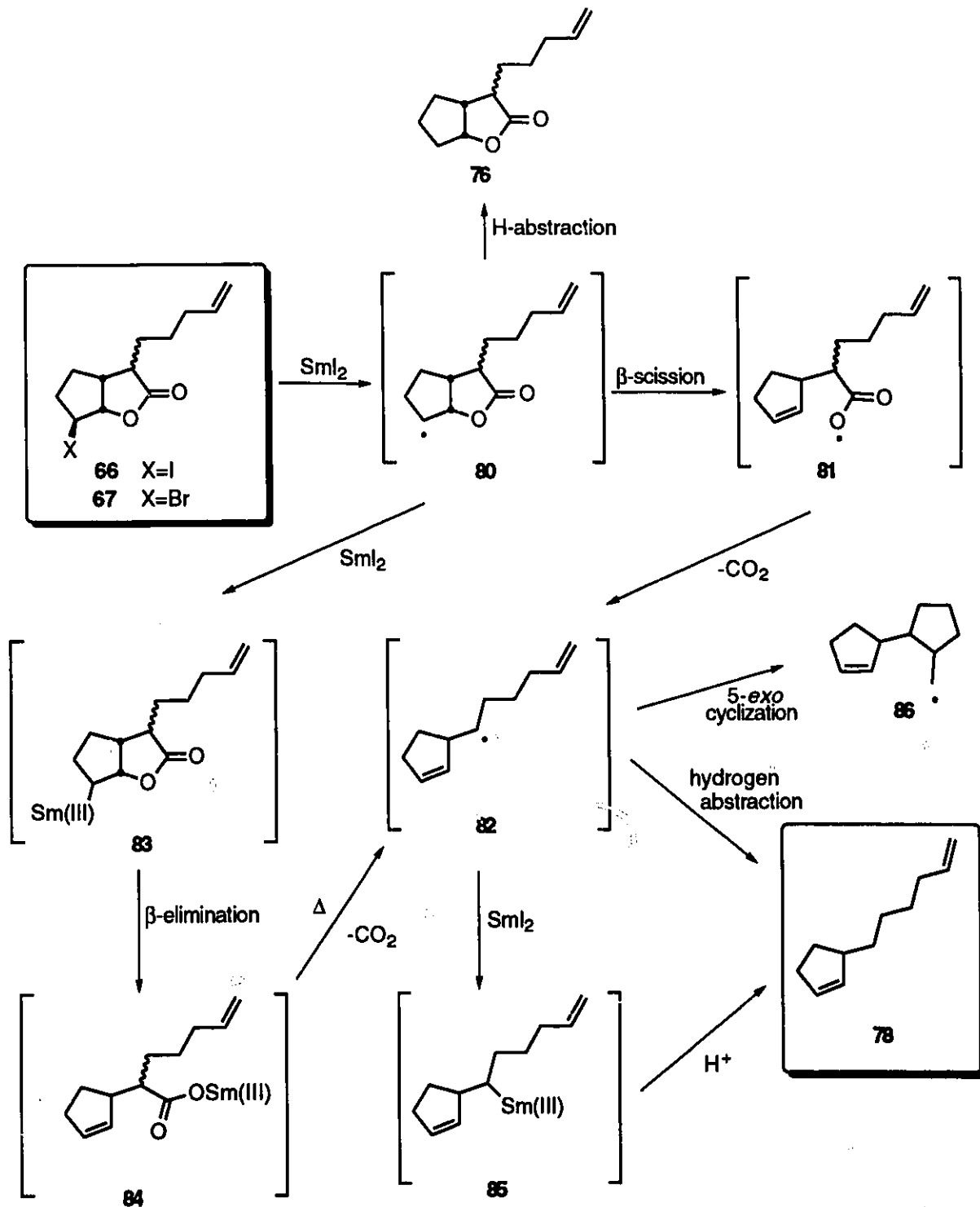
carboxylates<sup>53</sup> (e.g. copper carboxylates), may undergo rapid decarboxylation at elevated temperatures to form the secondary alkyl radical **82**.

Hydrogen abstraction by **82**, or further reduction to alkylsamarium **85** followed by proton abstraction would result in the formation of substituted cyclopentene **78**. Cyclization to the bicyclic **86** is also possible from **82** depending on the relative rates of all of these processes.

Reaction conditions play an important role in determining the product distribution as many of the rates can be altered by the appropriate choice of conditions. Recently, Hasegawa and Curran<sup>54</sup> reported that the yield of radical products(s) in SmI<sub>2</sub> reactions varied with HMPA concentration. Prior to this report we had also discovered that in order to favour a radical reaction pathway the standard method ("normal addition", Table 5) used in the attempted ring-opening decarboxylation reactions should involve dropwise addition of the SmI<sub>2</sub>•THF solution to a degassed mixture of the halolactone, HMPA, and THF. This sequence of addition enhances radical-type reactions over further reduction to the alkylsamarium as the SmI<sub>2</sub>-HMPA concentration is low relative to the substrate. The immediate discharge of the characteristic deep purple colour of the SmI<sub>2</sub>/HMPA/THF solution upon addition of SmI<sub>2</sub> to the substrate, indicated that the samarium diiodide was consumed extremely rapidly.

"Reverse addition" (Table 5) refers to the addition of substrate to a mixture of SmI<sub>2</sub>, HMPA, and THF. This method favours generation of the organosamarium species and accordingly we found that the ring-opened unsaturated acid **79** was regenerated in good yield. Transmetallation experiments on the iodolactone using *t*-BuLi at -100 °C in THF support this, as the product from this direct generation of the anion and exposure to similar reaction conditions is also the unsaturated acid **79**.

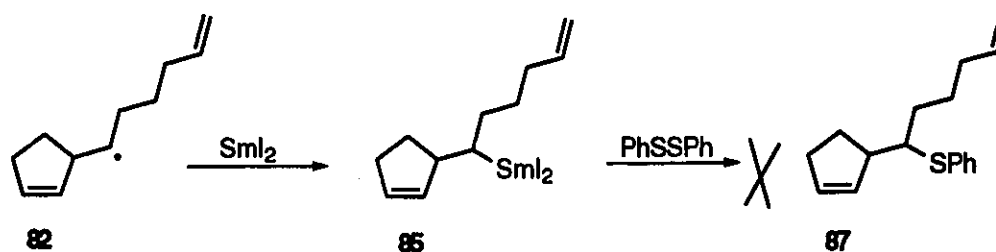
The rate of quenching of the secondary radical that is generated upon decarboxylation of either an acyloxy radical or a samarium(II) carboxylate appears to be the limiting factor in this reaction sequence. Quenching either by hydrogen abstraction or



Scheme 10 Possible Mechanistic Pathways for the Generation of 78

possibly single electron donation from the  $\text{SmI}_2$  to form the anion is apparently faster than 5-*exo* cyclization to form the bicyclic system **86**. The rate constant for the reduction of a primary carbon radical to an organosamarium species with  $\text{SmI}_2/\text{HMPA}/\text{THF}$  has recently been determined by Curran and is reported to be  $\sim 1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ .<sup>54</sup> The rate constant for secondary carbon radicals has not been reported, however one would expect the rate constant to be somewhat lower. Some evidence ( $^1\text{H}$  NMR of a partially purified sample) for the formation of the cyclized product derived from the reduction of radical **86** was obtained, however the compound was formed in low yield and was not rigorously characterized.

Trapping of organosamarium species with electrophiles is a well-documented procedure that has proven to be extremely useful in the construction of synthetic intermediates.<sup>55-59</sup> Attempts to trap the secondary organosamarium species **85**, if it indeed forms, with diphenyldisulfide were unsuccessful (Scheme 11). All of the examples given in references 57-62 describe the addition of an electrophile to a primary organosamarium species. Wipf and Venkatraman<sup>60</sup> have recently published a procedure which involves the transmetalation of organosamarium reagents. The authors point out that the use of secondary halides for the generation of organosamarium species is problematic and low



Scheme 11 Attempted Trapping of Organosamarium Species

yields (31%) were obtained in their particular example. They suggested that "the stability of secondary alkylsamarium species in  $\text{THF}/\text{HMPA}$  solutions is probably too low to result

in a high-yielding stepwise reaction protocol". This conclusion is consistent with our failure to trap the ring-opened intermediate **85** under anionic conditions.

Efforts to encourage further cyclization in the radical cascade reaction could involve the preparation of a precursor that contained an electron withdrawing substituent on the olefin side chain. It is well-known that electron withdrawing substituents that lower the LUMO energy of the alkene acceptor dramatically increase the rate of cyclization of nucleophilic alkyl radicals.<sup>37</sup> Substitution at the olefin with the appropriate substituent might therefore allow cyclization to proceed at such a rate that it can successfully compete with quenching.

### 1.6 Preliminary Investigations into the Preparation of a Hydrocarbon-Soluble Sm(II) Complex

One solution to the complications described above would be to use a different samarium(II) species which would allow reactions to be carried out in high-boiling hydrocarbon solvents that do not contain readily abstractable hydrogen atoms. X-ray structures of complexes such as bis(pentamethylcyclopentadienyl) samarium<sup>61-63</sup> all contain two molecules of THF coordinated to the Sm<sup>2+</sup> metal centre. In principle, if the required coordination were provided intramolecularly by a pendant ether, the resulting complex should be stabilized and potentially soluble in hydrocarbon solvents such as benzene and toluene. Preliminary work into the preparation of a suitable internally-coordinated Sm(II) species such as **88** (Figure 1) thus appeared promising. We had envisaged the use of a biscyclopentadienyl polyether ligand which would be capable of

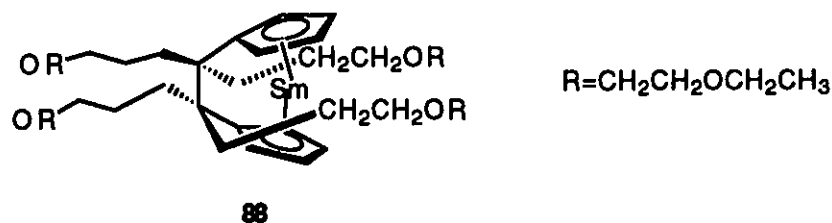
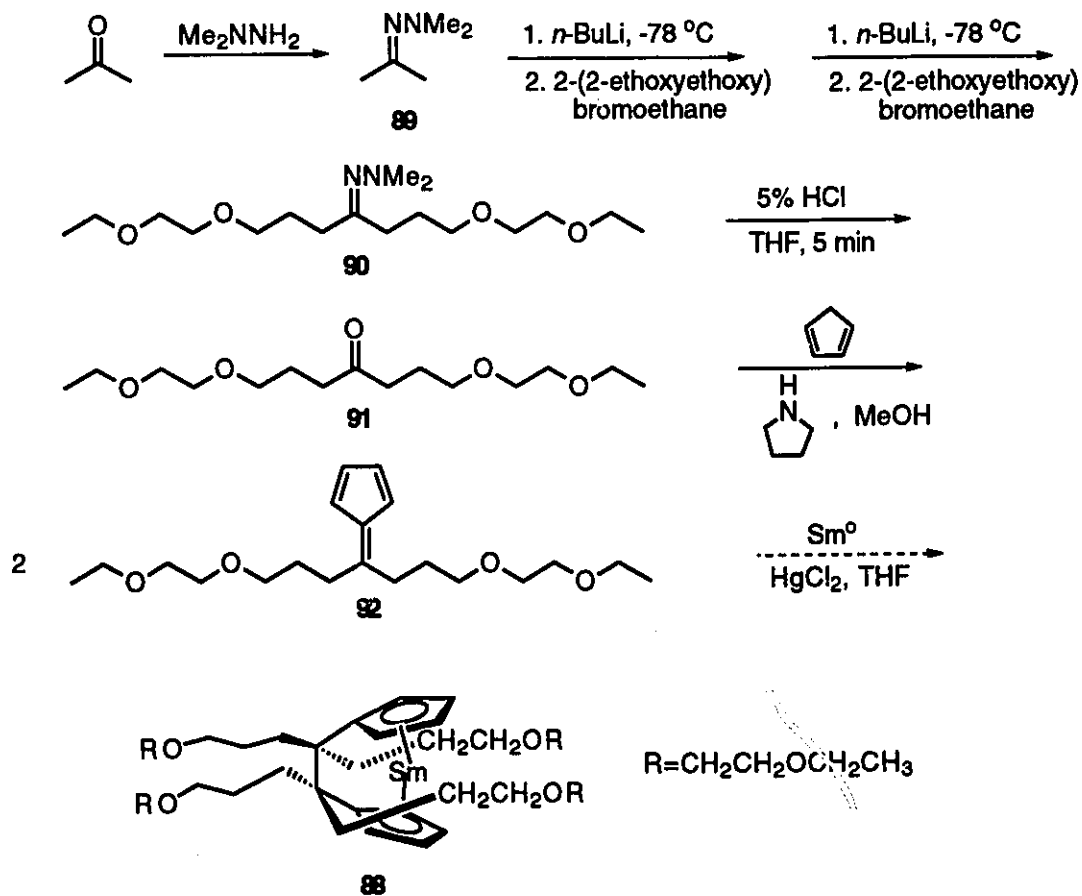


Figure 1 Internally Coordinated Benzene Soluble Sm(II) Compound

internally coordinating the biscyclopentyl  $\text{Sm}^{2+}$  species. The proposed polyether fulvene ligand **92** can be prepared from acetone in four steps (Scheme 12).

The dimethylhydrazone of acetone (**89**) was sequentially alkylated in a one-pot procedure<sup>64</sup> to give, after hydrolysis, polyether ketone **91**. Reaction of **91** with cyclopentadiene afforded the polyether fulvene **92**.<sup>65</sup> Unfortunately, characterization of the ligand **92** and preparation of the organosamarium(II) complex **88** have not been completed. Investigations into the preparation of this and other related hydrocarbon-soluble samarium(II) complexes will continue in our laboratory in the future.



Scheme 12 Preparation of Samarium(II) Complex **88**

### 1.5 Attempted Ring Opening of Other Halolactone Systems

Bromolactone **70** was prepared in order to provide us with a model system that could be used to investigate the relative rates of quenching of the radical formed after loss of CO<sub>2</sub> and further reduction of this radical to an alkylsamarium species (Figure 2).

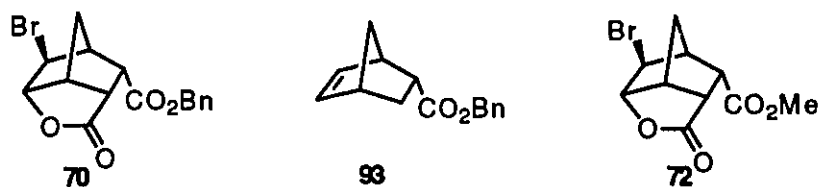


Figure 2 Bromolactones **70** and **72**

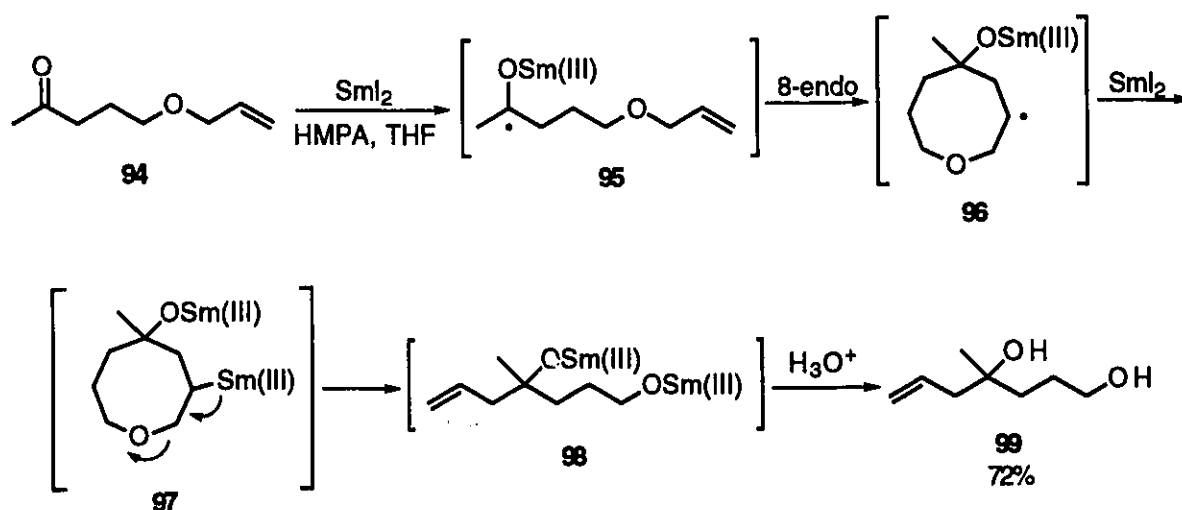
Unfortunately, reaction of **70** with SmI<sub>2</sub>/HMPA/THF at reflux did not produce the expected benzyl ester **93**, but rather a mixture of products that could not be identified. The methyl ester bromolactone **72** also produced unexpected products. The major product appears to be a hydrocarbon which does not contain any prominent distinguishing characteristics and has not been identified. A second minor product was isolated which, according to data obtained from <sup>1</sup>H, <sup>13</sup>C, and two-dimensional NMR studies, appears to be a rearranged, highly symmetric, decarboxylated dimeric compound of molecular mass of 220.1840 amu giving a molecular formula of C<sub>15</sub>H<sub>24</sub>O.

The capricious nature of the SmI<sub>2</sub>-induced ring opening and decarboxylation reaction should not be underestimated. With each of the systems used, apparently identical reactions often produced erratic and inconsistent results. The preparative use of this method thus requires more study. Nevertheless, the unprecedented nature of the discoveries that we have made (e.g. β-cleavage and decarboxylation of halolactones, and clean regeneration of unsaturated acids under mild conditions) offer a number of interesting and potentially valuable avenues of research.

A large body of information concerning many aspects of SmI<sub>2</sub> chemistry has accumulated since this work was completed.<sup>54,66-78</sup> Molander's recent report<sup>79</sup> of a

relevant cyclization/ $\beta$ -elimination sequence (Scheme 13) appears to support our earlier suspicion that  $\beta$ -elimination might be occurring via an anionic mechanism. In his example, the rapid  $\beta$ -elimination from the intermediate organosamarium avoids the persistence of the highly reactive alkylsamarium species **97** and eliminated the need for a proton source in the reaction mixture.

It is difficult to determine whether the ring-opening in our system is occurring via a radical or anionic-type mechanism, or whether both pathways are possible. The preference of one over the other may depend on the reaction conditions used. Results from "reverse addition" (Table 5) experiments point towards the conclusion that the formation of an organosamarium species is possible when reaction conditions that favour a second electron



Scheme 13<sup>79</sup>

transfer are used. Although the alkylsamarium does undergo  $\beta$ -elimination, it does not appear to be capable of decarboxylation under the reaction conditions used as only the ring opened unsaturated acid was obtained. The fact that the organosamarium does not decarboxylate but protonates, presumably on workup, suggests that a requirement for the formation of the ring-opened, decarboxylated product **78** is that the  $\beta$ -elimination occur via a radical mechanism. A large number of variables change when the method of addition,

and the resulting reagent concentrations are altered. Therefore, the conclusions proposed above remain somewhat speculative.

## CHAPTER 2

### $\alpha$ -KETO SPIROCYCLOBUTANE RING OPENINGS

#### 2.1 Introduction

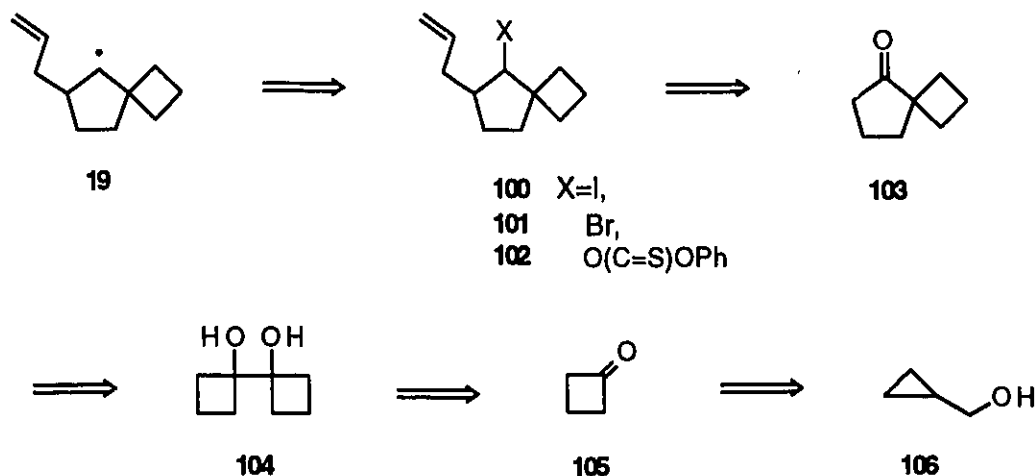
Free radical promoted ring-opening reactions of cyclobutylcarbiny systems have received relatively little attention compared to that given to the analogous cyclopropylcarbiny systems.<sup>36,80,81</sup> Beckwith<sup>82</sup> has studied the stereoelectronic requirements for the fragmentation of cyclobutylcarbiny radicals and Ingold<sup>83</sup> has reported the rate constants for the ring-opening reactions of a variety of cyclobutylcarbiny radicals.

The addition of an alkyl radical to an olefin is generally an exothermic process that is essentially irreversible, due to the fact that strong  $\sigma$  bonds are formed at the expense of weaker  $\pi$  bonds.<sup>81</sup> When ring-opening is accompanied by relief of ring strain, as is the case with cyclopropylcarbiny and cyclobutylcarbiny radicals, the ring opened form is more stable thermodynamically. The opening of cyclobutylcarbiny radicals ( $k \sim 10^3 \text{ M}^{-1}\text{s}^{-1}$ ) is much slower than that of cyclopropylcarbiny radicals ( $k \sim 10^8 \text{ M}^{-1}\text{s}^{-1}$ ) and is considered to be irreversible.<sup>28</sup>

Very little attention has been given to the use of cyclobutyl ring-opening reactions in organic synthesis. We were therefore interested in developing methods that could be used to exploit this relatively unexplored area of synthetic free radical chemistry. Our initial goal was to investigate the possibility of generating a ring-opened alkyl radical **21** (Scheme 3 in the Introduction) from a substituted spirocyclobutane **18-20**, which might be capable of undergoing further cyclizations to generate bicyclic (**22**) or polycyclic (**23**) system.

In order to generate a radical at the  $\alpha$ -carbon of a spirocyclobutane, a suitable radical precursor such as  $\alpha$ -halide or a thiocarbonate was required (Scheme 14). A

substituted thiocarbonate or halide could be prepared from the alkylation, reduction, and halogenation of a spiroketone. Pinacol coupling and rearrangement of cyclobutanone would provide the required spiroketone. Cyclobutanone can be prepared in two steps from cyclopropyl carbinol and its preparation would therefore serve as the starting point of this project.

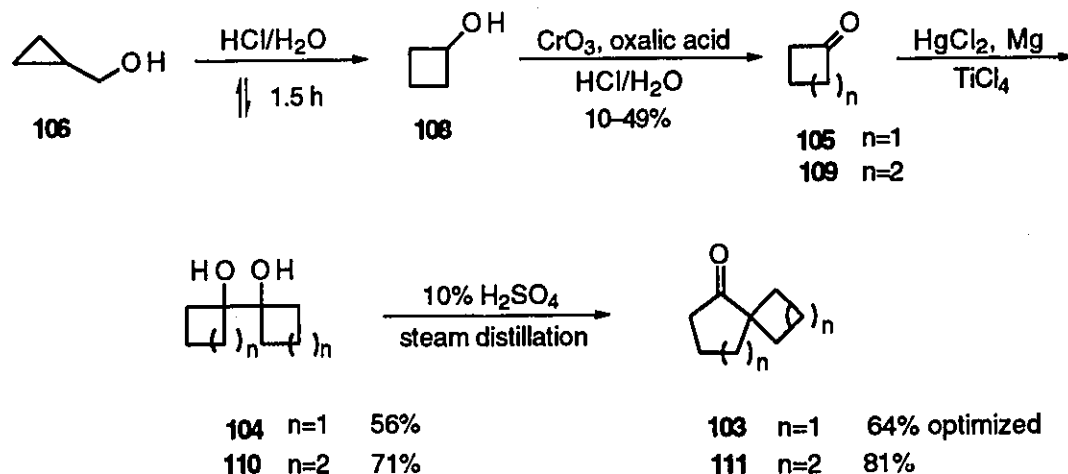


Scheme 14 Retrosynthetic Analysis

## 2.2 Preparation of $\alpha$ -Keto Spirocyclobutanone (103)

Various syntheses of cyclobutanone **105** were attempted, including the alkylation of methyl methylthiomethylsulfoxide with 1,3-dibromopropane to give 1-thiomethyl-1-methylsulfinylcyclobutane **107** followed by oxidative desulfurization with mercuric chloride or ceric ammonium nitrate (low yield; 34%),<sup>182</sup> as well as preparation and hydrolysis of the dithiane-protected cyclobutanone (low, erratic yields; ~ 40%). The procedure which provided cyclobutanone on a large scale with relative ease turned out to be the rearrangement and oxidation of cyclopropylcarbinol **106** (Scheme 15). Acid-catalyzed rearrangement of cyclopropylcarbinol **106** provided cyclobutanol **108** in

excellent yield. The crude cyclobutanol was oxidized with chromium(VI) trioxide, and purified by steam distillation to give cyclobutanone **105** in extremely poor (16%) to fair (50%) yields that



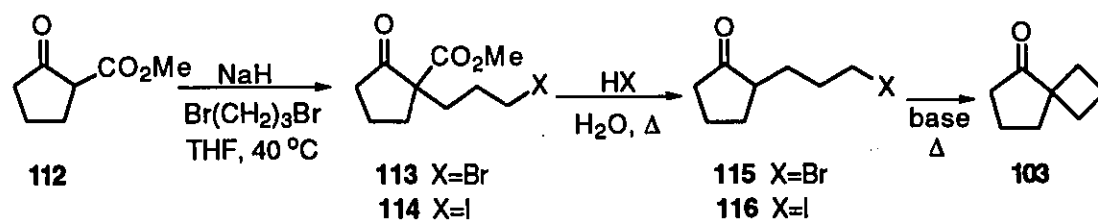
Scheme 15 The preparation of  $\alpha$ -Ketospirocycloalkanes **103** and **111**

were quite erratic. Cyclobutanone **105** exhibited a carbonyl stretch at  $1780\text{ cm}^{-1}$  in the infrared spectrum, characteristic of a strained four-membered ring ketone. Pinacol coupling<sup>84</sup> of cyclobutanone **105** and cyclopentanone **109** provided the corresponding diols **104** and **110** in moderate (56%) and good yields (71%), respectively.

Acid-catalyzed rearrangement of diol **104** afforded 5-keto[3,4]octane **103** in 64% yield. Literature descriptions<sup>84b</sup> of the rearrangement and, in particular the isolation procedures, appeared to be fairly straightforward. This was somewhat misleading, however, as the steam distillation turned out to be quite difficult. The yields obtained in the first attempts at isolating **103** were very erratic. After many trials it was discovered that as the rearrangement proceeded and the corresponding colour changes occurred, it was critically important that the steam distillation begin when the solution becomes olive-green. If the distillation was started either at an earlier or later stage, significantly lower yields were obtained (on the order of 5-10%). Low yields were also obtained with other acids or

other conditions. Rearrangement of cyclopentyl pinacol **110** to spiroketone **111** was straightforward and provided 6-ketospiro[4.5]decane **111** in good yield (81%).

The preparation of **103** from alkylation of oxocyclopentanecarboxylate **112**<sup>84c</sup> with 1,3-dibromopropane to form **113** or 1,3-diiodopropane to form **114**, followed by hydrolysis and decarboxylation to **115** or **116**, and finally cyclization to **103** (Scheme 16) proved to be less useful than the pinacol rearrangement described above.



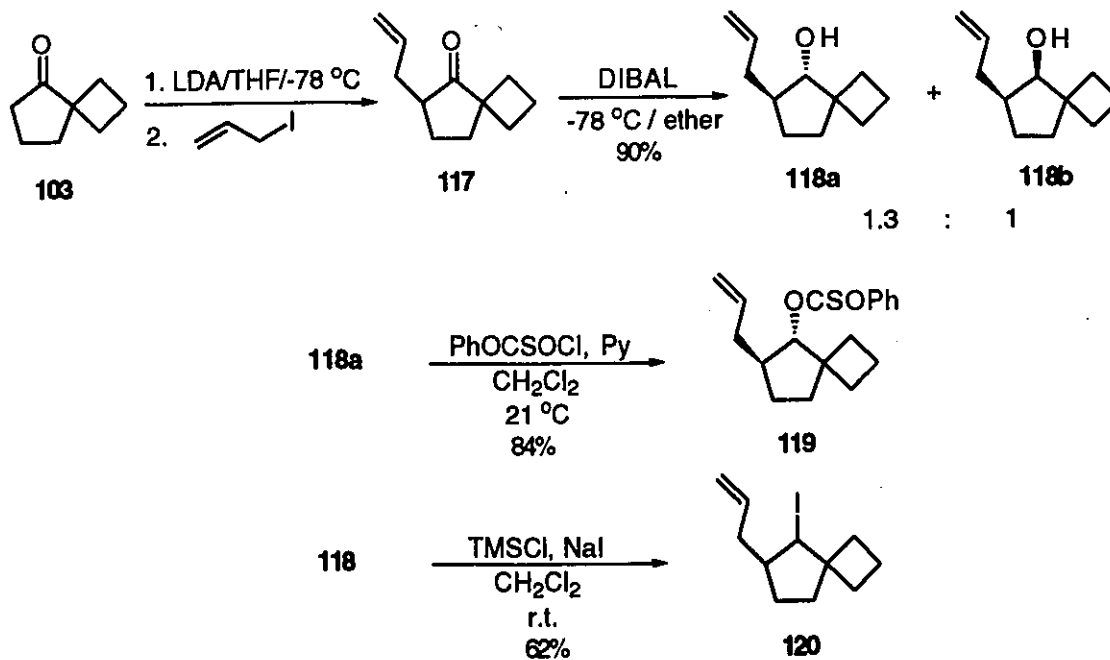
Scheme 16 Alkylation of **112** to Form Spiroketone **103**

### 2.3 Preparation of Radical Precursors (**119**) and (**120**)

Deprotonation of spiroketone **103** with LDA in THF at  $-78$  °C and alkylation with one equivalent of allyl iodide afforded the monoallylated spiroketone **117** in 62% yield (Scheme 17). Allylspiroketone **117** exhibited a strong carbonyl stretch at  $1730\text{ cm}^{-1}$  in the IR spectrum and two multiplet signals in the  $^1\text{H}$  NMR spectrum centered at  $\delta$  5.66 and 5.00 ppm that are consistent with the presence of a terminal olefin. Reduction of the ketone with DIBAL at  $-78$  °C provided a 1.3:1 mixture of diastereomeric alcohols **118a** and **118b** that were tentatively assigned as shown (Scheme 17).

The assignment of alcohols **118a** and **118b** was established as follows. Theoretical calculations (Hyperchem<sup>®</sup> MM+) provided energy-minimized conformations, from which the dihedral angles subtended by the C-H<sub>1</sub> and C-H<sub>2</sub> bonds (Figure 3) could be determined (Table 6). Coupling constants ( $J$ ) for the methine protons H<sub>1</sub> were calculated from the vicinal Karplus correlation curve<sup>85</sup> based on the minimum energy

dihedral angles ( $\phi$ ). A comparison of the observed and calculated  $J$  values suggested that the *cis* isomer was associated with the  $W_{1/2} = 9.6$  Hz coupling constant observed, and



Scheme 17 Preparation of Monoallylated Radical Precursors

that the 3.0 Hz coupling constant could be assigned to the *trans* isomer. Additional evidence for this assignment was found in the chemical shifts of the C<sub>1</sub> carbon in the <sup>13</sup>C NMR spectrum. It has been established that the higher field <sup>13</sup>C NMR resonance of methine carbons in substituted cyclopentanes and cyclobutanes is associated with the

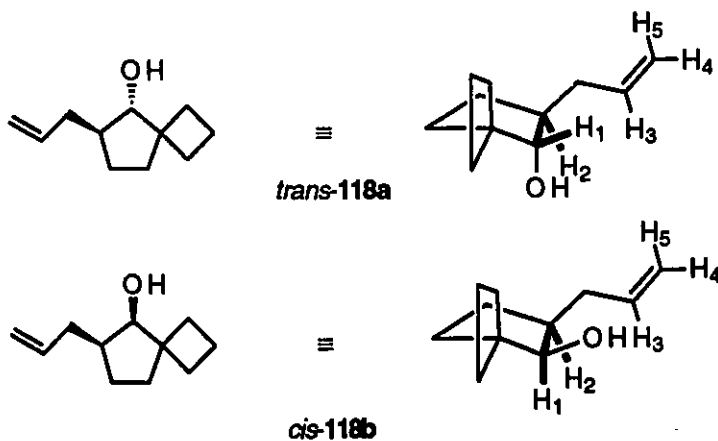


Figure 3 Diastereomeric Alcohols **118a** and **118b**

*cis* isomer.<sup>86,87</sup> The C<sub>1</sub> signal in the <sup>13</sup>C NMR spectrum of the *cis* isomer at δ 79.5 ppm is upfield of the C<sub>1</sub> signal at δ 80.5 ppm, providing additional support for the earlier assignments based on <sup>1</sup>H coupling constants.

Compound	Dihedral Angle $\phi^a$	<i>J</i> value <sup>b</sup> (calc., Hz)	<i>J</i> value (obs., Hz)	<sup>13</sup> C NMR <sup>c</sup> δ (ppm)
<b>118a</b> ( <i>trans</i> -isomer)	111.9°	1.5	3.0	80.5
<b>118b</b> ( <i>cis</i> -isomer)	16.27°	7.5	$W_{1/2} = 9.6$	79.5

<sup>a</sup> Calculated for energy-minimized conformer with Hyperchem<sup>®</sup> molecular modeling programme using the MM+ basis set.

<sup>b</sup> Calculated from theoretical dihedral angle and Karplus curve

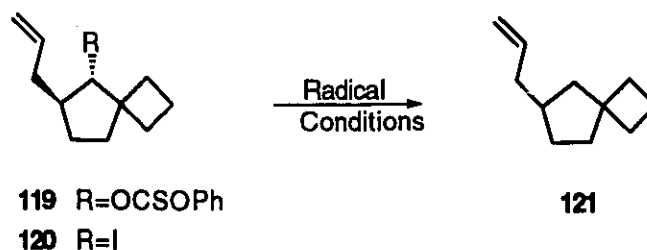
<sup>c</sup> <sup>13</sup>C methine resonance

Table 6 Configuration Correlation Data for Alcohols **118a** and **118b**

Treatment of alcohol **118a** with phenylthiochloroformate provided the phenyl thiocarbonate radical precursor **119** in 84% yield. The characteristic carbon-sulfur double bond stretch of a thiocarbonate was observed as a strong absorbance at 1200 cm<sup>-1</sup> in the IR spectrum. All other spectroscopic data were consistent with the expected product. Treatment of a mixture of alcohols **118a** and **118b** with trimethylsilyliodide that was generated *in situ* from the reaction of trimethylsilylchloride and sodium iodide<sup>88</sup> gave an epimeric mixture of iodides (~1:1 ratio) **120** in 78% yield.

## 2.4 Attempted Radical Ring-Opening Reactions of (119) and (120)

Radical initiated ring-opening reactions of thiocarbonate **119** and iodide **120** were attempted under a number of "tin hydride" conditions and typical results are given in Table 7. In each case the only identified product was the reduced spiroalkane **121**. The quenching rate of the secondary alkyl radical with tin hydride is apparently faster than the



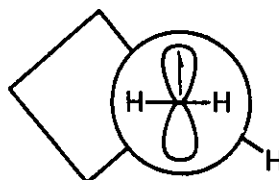
Entry	Substrate	Conditions	Yield
1	<b>119</b>	<i>n</i> Bu <sub>3</sub> SnH/AIBN/benzene/ $\Delta$ (syringe pump)	51%
2	<b>119</b>	<i>n</i> Bu <sub>3</sub> SnCl/NaCNBH <sub>3</sub> <sup>t</sup> BuOH	61%
3	<b>119</b>	<i>n</i> Bu <sub>3</sub> SnH/AIBN/toluene/ $\Delta$	57%
4	<b>120</b>	<i>n</i> Bu <sub>3</sub> SnH/AIBN/toluene/ $\Delta$	46%

Table 7 Attempted Radical Ring-Opening of **119** and **120**

rate of ring-opening of the spirocyclobutane radical. Rate constants for the ring-opening of some cyclobutylcarbinyl systems are known.<sup>82,83,89</sup> To the best of our knowledge no examples involving spirocyclobutylcarbinyl systems have been reported.

Ingold<sup>83</sup> has determined that the cyclobutylmethyl radical adopts form **122** as its preferred conformation. Beckwith has been proposed that cyclobutylcarbinyl ring-opening

is under stereoelectronic control and proceeds only when conformations that favour efficient overlap of the semi-occupied orbital and the bond to be cleaved.<sup>82</sup> He goes on to conclude that his results are "consistent with the hypothesis that the transition state is reactant-like, ...and unsymmetrical in that it involves little formation of the new  $\pi$  bond, but some weakening of the  $\beta\gamma$ -bond and partial rehybridization of the  $\gamma$ -carbon".



122<sup>83</sup>

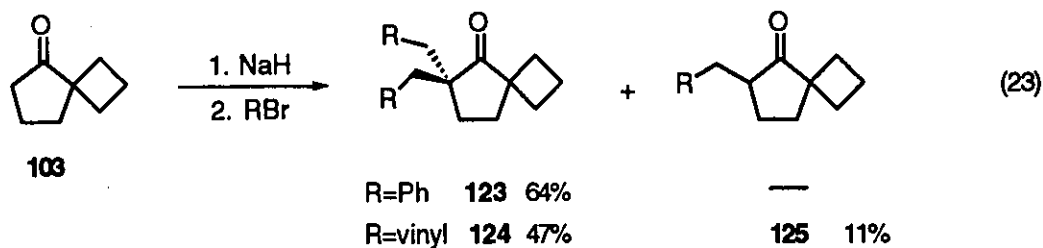
At the outset we considered that this stereoelectronic requirement for ring-opening would be met in our case, given that our system is in a relatively fixed conformation that closely resembles the optimum orientation. Other important factors must be influencing the fate of the radical that is generated initially in our experiments, as only the reduced precursor was obtained under our initial conditions, and no evidence for any ring-opened product was found.

## 2.5 Samarium Ketyl-Induced Ring Openings

The successful use of  $\text{SmI}_2$  in the halolactone ring-openings described in the previous chapter prompted us to investigate the possibility of generating a samarium ketyl which might undergo ring-opening and perhaps allow cyclization to the desired bi- or polycyclic ring systems (Scheme 3 in the Introduction).

Up to this point, the work on this project had been completed prior to our studies of the  $\text{SmI}_2$ -induced halolactone ring-opening. In order to examine the potential of carrying out the desired ring-opening with  $\text{SmI}_2$  more starting material needed to be prepared. We therefore took this opportunity to improve our experimental system in order to circumvent some of the difficulties that had been encountered in handling both the starting materials

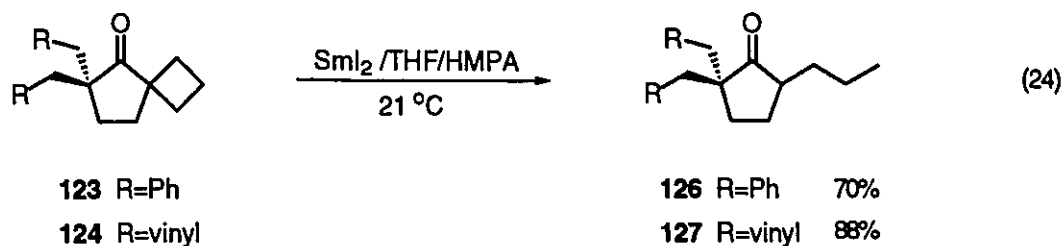
and products in the previous work. For example, the volatility of the spiroketone was a significant problem that made the starting material difficult to handle, and the product virtually impossible to isolate and purify without losing material.



Dibenzyl- and diallyl-ketospirocyclobutanes **123** and **124** were prepared from the parent spiroketone **103** by exhaustive alkylation with sodium hydride and an excess of benzyl bromide or allyl bromide, respectively (eq. 23). In both cases the major product was the expected dialkylated material. Other unidentified side products were formed in low yields and were presumably the result of O-alkylation of the unsubstituted and the monosubstituted ketones.

The benzylic signals in the  $^1\text{H}$  NMR for **123** appear as two equivalent overlapping AB systems with an integration corresponding to four protons. All other spectral data were consistent with the assigned structure. The diallylated material **124** exhibited characteristic multiplets centered at  $\delta$  5.58 and 4.94 ppm in the  $^1\text{H}$  NMR spectrum due to the presence of the two terminal olefins.

Under standard  $\text{SmI}_2$  conditions ( $\text{SmI}_2$  (3.6 eq.), HMPA (5 eq.) in THF), both of the disubstituted spiro systems underwent efficient ring-opening to the corresponding ketones (eq. 24). Both **126** and **127** displayed  $^1\text{H}$  and  $^{13}\text{C}$  NMR, infrared and high



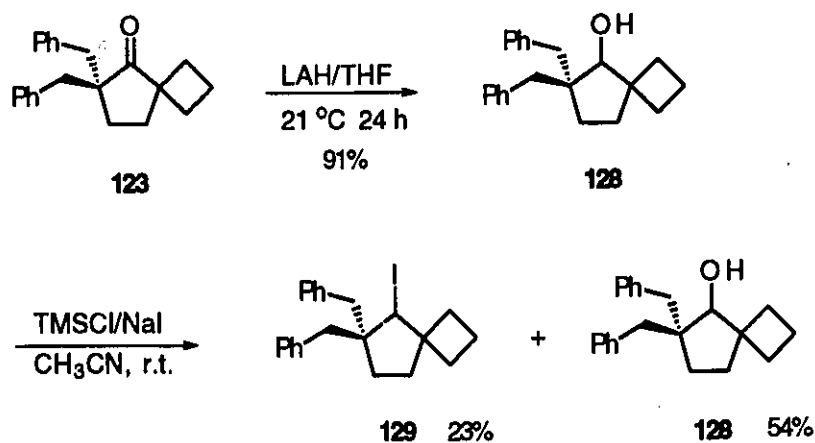
resolution mass spectral data which were consistent with that expected for the ring-opened ketones. Strong bands at 1728 and 1732  $\text{cm}^{-1}$  in the IR spectra of **126** and **127**, respectively, and carbonyl carbon signals at  $\delta$  224.6 and 223.8 ppm in the  $^{13}\text{C}$  NMR spectra indicated the presence of a five-membered ring ketone in each compound. A diagnostic terminal methyl triplet was clearly visible in both of the  $^1\text{H}$  NMR spectra ( $\delta$  0.77 ppm for **126** and 0.86 ppm for **127**). The benzylic protons that had previously appeared as two equivalent AB systems in the symmetrical cyclobutyl ketone **123**, now appeared as four doublets corresponding to two non-equivalent AB spin systems for compound **126**.

In reactions carried out with the allylated ketone **124**, none of the cyclized bicyclic material was found, which indicates that the primary radical generated upon  $\beta$ -scission of the samarium(III) ketyl radical is either quenched by hydrogen abstraction from the solvent, or undergoes a second electron transfer to generate an alkylsamarium species that is protonated upon aqueous work-up (see discussion of quenching versus further reduction of an alkyl radical in Chapter 1).

To investigate whether the use of  $\text{SmI}_2/\text{HMPA}/\text{THF}$  conditions were responsible for the difference in rates of the various radical processes, such as the rate of quenching, we decided to repeat the alkyl ring-opening reactions using  $\text{SmI}_2$  as the radical initiator. It was important for us to determine whether the  $\text{SmI}_2$  reaction conditions were allowing a sufficiently long lifetime for the cyclobutyl ketyl to open, or whether the ketyl nature of the radical itself was a factor.

## 2.6 Preparation and Attempted $\text{SmI}_2$ -Induced Ring-Opening of Iodospirocyclobutane (**129**)

Reduction of dibenzyl ketone **123** with lithium aluminium hydride in THF at  $0\text{ }^\circ\text{C}$  afforded alcohol **128** in excellent yield (Scheme 18). The characteristic broad band centered at  $3436\text{ cm}^{-1}$  in the IR due to the alcohol O-H stretch, and the one-proton singlet at  $\delta\ 3.42$  ppm in the  $^1\text{H}$  NMR due to the methine proton geminal to the hydroxyl group both confirmed the presence of the hydroxyl group in the product. In addition, deuterium oxide exchange resulted in the reduction in the integration of the 9-proton multiplet centered at  $\delta\ 1.80$  ppm by one proton, and the appearance of a new signal at  $\delta\ 4.77$  ppm due to the presence of HOD. The previously equivalent benzylic protons which appeared as two overlapping identical AB systems in the ketone, were now coupled to the methine bearing the hydroxyl group and appeared as two multiplets centered at  $\delta\ 2.74$  and  $2.40$  ppm.

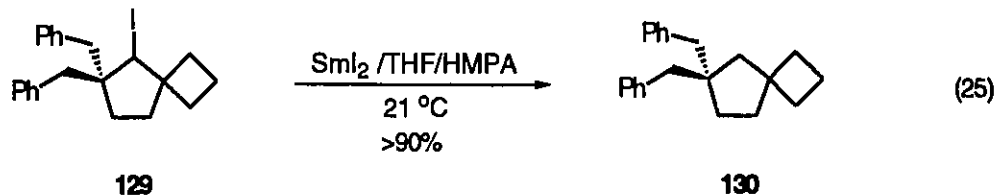


Scheme 18 Preparation of Iodospirocyclobutane **129**

Conversion of alcohol **128** to iodide **129** proved to be difficult. This was not unexpected as the alcohol is adjacent to two quaternary centres and is therefore extremely sterically hindered. Trimethylsilyl iodide has been shown to be effective for the iodination of sterically encumbered alcohols,<sup>90</sup> and after two days at room temperature we were able to isolate the desired iodide in 23% yield. The remainder of the material isolated from the

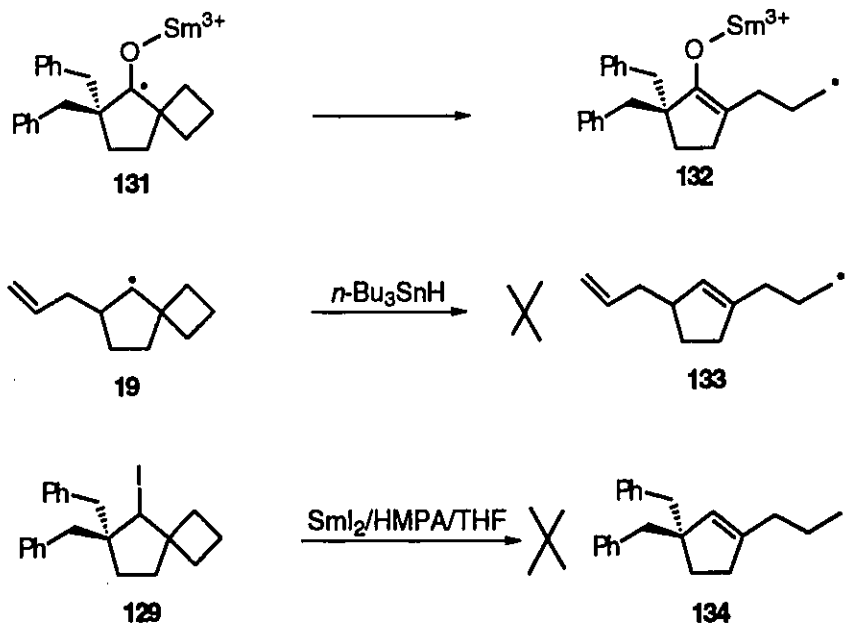
reaction was the starting alcohol **128**.  $^1\text{H}$  and  $^{13}\text{C}$  NMR, infrared and mass spectral data were all consistent with that expected for iodide **129**. The methine proton signal at  $\delta$  3.42 ppm in the  $^1\text{H}$  NMR spectrum of **128** due to the proton on the carbon bearing the hydroxyl group was no longer present as the methine on the corresponding iodide now appeared in a 9H multiplet centered at  $\delta$  2.08 ppm.

A sufficient quantity of the iodide was obtained to attempt the  $\text{SmI}_2$ -initiated radical ring-opening of iodide **129**. Exposure of iodospirocyclobutane **129** to the standard  $\text{SmI}_2/\text{HMPA}/\text{THF}$  conditions did not produce the ring-opened alkene, but rather an excellent yield of the reduced starting material **130** (eq. 25).



## 2.7 Conclusion

As a result of our investigation into the radical-promoted ring-opening of these spirocyclobutanes, we have found that an initially generated samarium(III) ketyl radical is sufficiently long-lived under the reaction conditions used, that the ring-opening of the spirocyclobutanes via  $\beta$ -scission can occur (Scheme 19). Two independent publications



Scheme 19 Samarium(III) Ketyl Ring-Opening

have appeared recently which report a photochemically generated ketyl radical anion adjacent to a fused cyclobutane inducing the opening of the cyclobutane ring.<sup>91,92</sup> Our results on the spirocyclobutyl systems are consistent with these reports and will hopefully provide a starting point for the exploration of the potential for the application of this new reaction in the synthesis of natural products.

Thus, the ability to open  $\alpha$ -keto spirocyclobutanes in excellent yield with  $\text{SmI}_2$  to give a new radical species affords the opportunity to use this intermediate in subsequent radical transformations. Alternatively, further reduction to the reactive primary alkylsamarium species will allow access to anionic reactions with a wide variety of electrophiles to produce highly functionalized synthetic intermediates.

## CHAPTER 3

# REARRANGEMENT OF DONOR-ACCEPTOR CYCLOPROPANES

### 3.1 Introduction

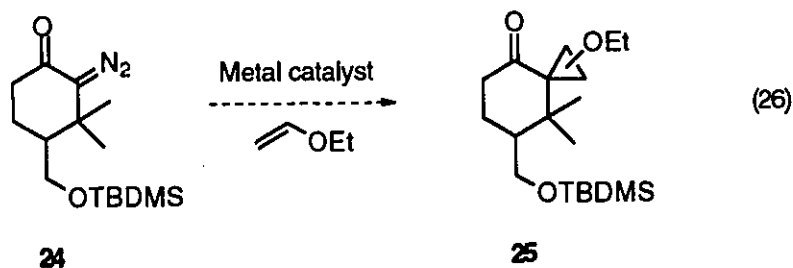
Within most realms of human endeavour hindsight is often an unforgiving teacher by which our future actions are modified. Chemistry is by no means spared of this trait. On the contrary, it is exactly this feature of the science that allows an individual to grow as a scientist as one advantageously exploits past experiences in the development of one's process of doing future chemistry. The end result is not only a growth in the direct knowledge obtained in the first instance, but also a refinement of the method that one uses to tackle future projects.

This chapter can be viewed as a sequence of these types of experiences. Although chemistry Ph.D. theses are not generally an arena for storytelling, the nature of the questions and answers, as well as the puzzles and solutions contained within this project lend themselves very well to a chronological "story" of their emergence and resolution.

### 3.2 The Initial Question

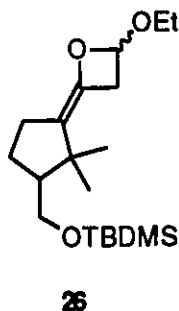
As part of the research efforts in our group directed towards the total synthesis of the potent anti-tumor agent Taxol<sup>®</sup>, one synthetic approach required, as a key intermediate, cyclopropane **25**. A number of different routes to **25** were attempted in vain, and as work progressed it became evident that this type of substituted  $\alpha$ -keto-spirocyclopropane system was much more challenging to prepare than had been initially envisaged.<sup>93</sup>

One route to compound **25** involved the metal-catalyzed cyclopropanation of  $\alpha$ -diazoketone **24** (eq.26). The catalytic decomposition of  $\alpha$ -diazoketones in the presence of olefins is generally considered to be an efficient method of generating highly functionalized cyclopropanes.<sup>53,94-96</sup> Unfortunately, in this particular case the reaction



failed to yield cyclopropane **25**. A variety of reaction conditions were attempted, using a number of different catalysts that are commonly used in preparative cyclopropanation reactions of  $\alpha$ -diazoketones. A single major product was consistently isolated from all of the trials involving cyclopropanation with ethyl vinyl ether. The yields varied considerably (10-75%), and were dependent on the type of catalyst used. Reactions with  $\text{Rh}_2(\text{OAc})_4$  consistently gave the highest yields (~75%) followed by those of  $\text{Pd}(\text{OAc})_2$  (~70%) and  $\text{CuCl}$  (~25%).

The unexpected product formed on treatment of **24** with, for example,  $\text{Rh}_2(\text{OAc})_4$  (2 mol %, 21 °C) in the presence of excess ethyl vinyl ether, was tentatively assigned structure **26**.<sup>93</sup> The mechanistic origin, as well as the spectroscopic assignments of **26** had not been determined unequivocally (see below), therefore, the first question that



needed to be addressed in this project was whether the structure assigned to the major product in the metal catalysed cyclopropanation of **24** with ethyl vinyl ether was correct.

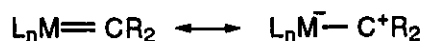
Before discussing the reasoning behind the original assignment of structure **26** as the product of the intended cyclopropanation reaction, a brief overview of transition-metal catalyzed cyclopropanation reactions of diazocarbonyl compounds will be presented.

### 3.3 Catalytic Metal Carbene Transformations

#### 3.3.1 Catalysts

The cyclopropanation of olefins with  $\alpha$ -diazocarbonyl compounds in the presence of various metal catalysts is a commonly used reaction that has been thoroughly studied. Although the details of the reaction mechanism are not completely understood, a good working model has been developed which allows the researcher to make some educated guesses as to the expected success or failure of their intended project.

It is now generally accepted, as originally suggested by Yates,<sup>97</sup> that transition metal catalysts react with diazo compounds to generate transient electrophilic carbenes **135**.



**135**

Loss of dinitrogen is believed to occur when the diazo compound adds to the transition metal.<sup>98</sup> The resulting metal carbene intermediate is termed a "carbenoid"<sup>99</sup> to indicate that the reacting species is neither a free carbene nor an activated diazo compound. Free carbenes undergo reactions with low selectivity and competing carbene rearrangements. The coordination of a carbene to a metal centre reduces the reactivity of the divalent carbon species and enhances the selectivity of the reaction. Metal-stabilized carbenoids are therefore of much greater synthetic utility than free carbenes.

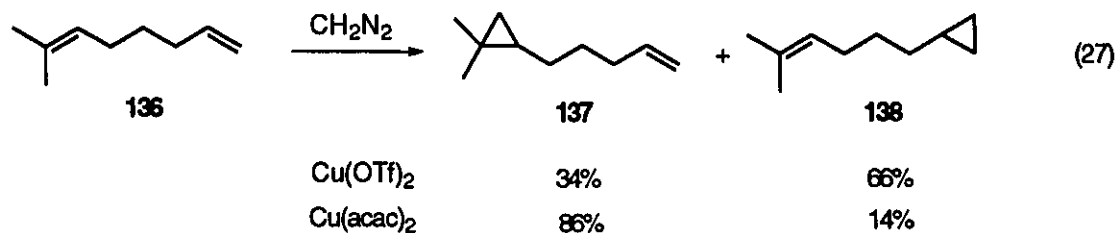
Transition metal-catalyzed decomposition of diazo compounds originated in 1912 with the discovery by Wolff<sup>100</sup> that the decomposition temperature of diazoketones was significantly lowered in the presence of either copper powder, cupric sulfate, or silver salts. All of the early work was done using insoluble copper catalysts such as copper bronze, CuO, Cu<sub>2</sub>O, CuBr, Cu<sub>2</sub>Cl<sub>2</sub>, and CuCl<sub>2</sub>. These catalysts are still in use today although the use of efficient homogeneous copper catalysts has become far more common.

In the late seventies Teyessié and coworkers found that rhodium carboxylates were extremely effective catalysts for a wide variety of catalytic transformations involving diazo compounds.<sup>101-104</sup> This discovery renewed interest in the field of diazo carbenoid chemistry, and is widely held as being of "singular importance in the history of this developing methodology".<sup>98,105</sup> Other rhodium complexes, as well as a variety of Pd and Co complexes have been introduced as catalysts for carbenoid reactions, but none have been found to have the general utility of the rhodium(II) carboxylates.

Rhodium carboxylates are both thermally stable and air stable, and are not susceptible to redox transformations with diazo compounds. Under normal catalytic conditions the carboxylate ligands are resistant to exchange, thus providing an efficient catalyst that has been used in concentrations as low as 0.05 mole percent without any significant reduction in product yields.<sup>105</sup> An important feature of rhodium(II) carboxylates is their inability to form  $\pi$  complexes with olefins in solution.<sup>102,107</sup> There are, however, reports of measurements which indicate the existence of such complexes in the gas and solid phase.<sup>108</sup> The ability to coordinate an olefin is important from a mechanistic viewpoint as it places these complexes within the second half of the two-fold division of carbenoid metal catalysts. The separation of catalysts into 1) multiple coordination site catalysts and 2) single coordination site catalysts has been created in an attempt to classify, according to mechanism, the huge amount of information that has accumulated pertaining to catalysts and their ability to effect the decomposition of diazo compounds.

### 3.3.1.1 Multiple Coordination Site Catalysts

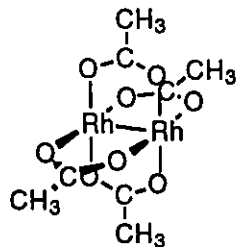
As mentioned above, the ability to coordinate with an olefin is what distinguishes a multi-coordination site catalyst from the others. Of the copper catalysts commonly used, copper(II) triflate is unique in its ability to coordinate with alkenes. In cyclopropanation reactions competition experiments have shown that catalysts that are capable of forming olefin complexes favour addition to the less substituted double bond, whereas those that do not form olefin complexes (e.g.  $\text{Cu}(\text{acac})_2$ ) preferentially add to the more substituted double bond (eq 27).<sup>109</sup>



Palladium catalysts such as palladium(II) acetate and palladium(II) chloride are also effective in carbenoid reactions and are well-known to form complexes with olefins.<sup>110</sup> In reactions with multi-coordination site catalysts, dissociation of the olefin is necessary for activation of the catalyst towards the diazo compound, and the rate of diazo decomposition is inversely proportional to the concentration of the olefin.

### 3.3.1.2 Single Coordination Site Catalysts

$\text{Rh}_2(\text{OAc})_4$  (**139**) is a commercially available binuclear compound with four bridging acetate ligands and one available coordination site per metal centre. Of all the single coordination site catalysts, rhodium(II) acetate has proven to be the most versatile and efficient, consistently producing the highest yields of cyclopropanation products under mild conditions.



135

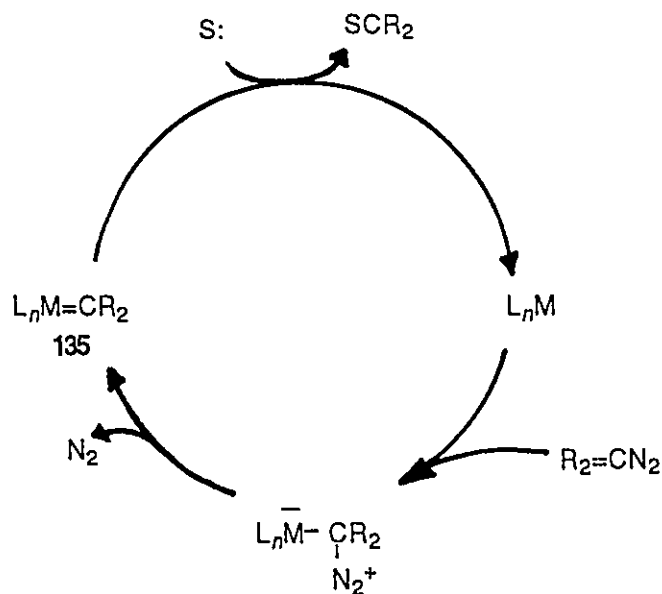
Rhodium(II) carboxylates have played a central role in the evolution of a basic understanding of the mechanisms associated with various carbenoid transformations. Rhodium(II) compounds are now the catalysts of choice for carrying out diverse carbenoid transformations ranging from cyclopropanation<sup>94</sup> and insertion reactions<sup>98,111,112</sup> to dipolar additions<sup>113,114</sup> and ylide generation-rearrangement reactions.<sup>115</sup> Many excellent reviews have been published which cover a wide range of topics throughout the field of transition metal-catalysed decomposition of diazo compounds, including the transformations mentioned above.<sup>98,111,112,116-120</sup> Most of the detailed studies that have shed some light on possible reaction intermediates in the diazo compound-catalyst systems have been published recently by either Doyle, or Noe's and Hubert.<sup>98,102-104,111</sup>

### 3.3.2 Mechanism of Metal-Catalyzed Cyclopropanation Reactions

The most widely used reaction of  $\alpha$ -diazocarbonyl compounds involves the formation of cyclopropyl derivatives from olefins. It is not surprising therefore that the vast majority of information on rhodium carboxylate catalysts has been obtained from studies related to the addition of carbenoid species to olefins.

The catalytic activity of the transition metal is dependent on the coordinative unsaturation at the metal centre, as it is this coordinative unsaturation that allows them to add to diazo compounds as electrophiles. Diazocarbonyl compounds such as ethyl diazoacetate undergo this rate-limiting electrophilic addition at approximately  $-20\text{ }^{\circ}\text{C}$ .<sup>117</sup> This addition is believed to cause the loss of dinitrogen, generating an electrophilic metal-

stabilized carbene **135** which is the active intermediate in carbenoid reactions (Scheme 20). Although these intermediates have never been isolated or observed directly, there is strong

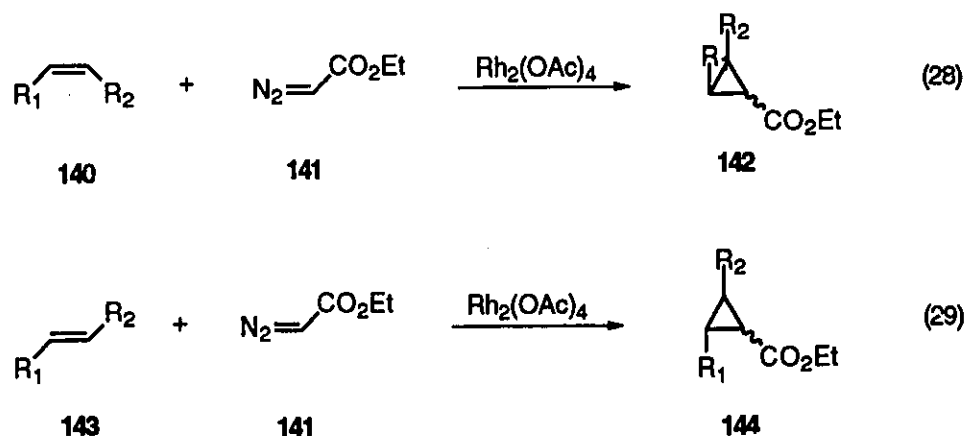


Scheme 20 Metal Carbenoid Catalytic Cycle

indirect evidence to suggest their participation in cyclopropanation reactions.<sup>121,122</sup> These carbenoids rapidly transfer the carbene moiety to electron-rich substrates such as alkenes and alkynes, regenerating the catalyst in the process, thus completing the catalytic cycle.

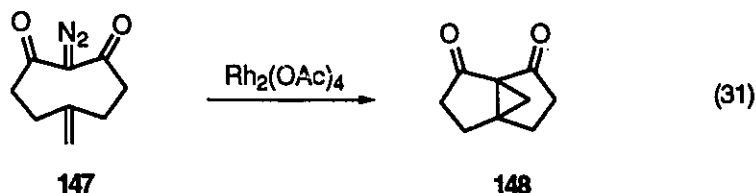
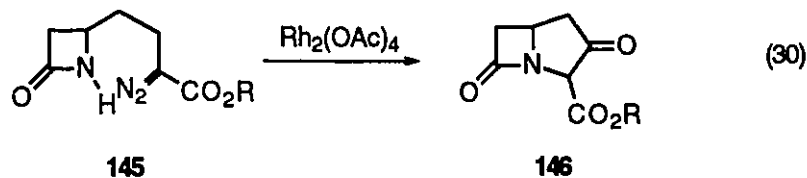
Cyclopropanation reactions of diazocarbonyl compounds with  $\text{Rh}_2(\text{OAc})_4$  have extremely rapid reaction rates and are generally carried out with 1–3% catalyst (by weight) at room temperature in non-reactive solvents such as methylene chloride or other halogenated hydrocarbons. Studies involving competitive cyclopropanations (with Rh(II) carboxylates) of two olefins have shown that electron-rich alkenes react preferentially. Electron-poor alkenes do not undergo cyclopropanation under these reaction conditions. For example the formation of pyrazolines, rather than cyclopropanes is the dominant pathway in the reaction of  $\alpha,\beta$ -unsaturated nitriles (e.g. methacrylonitrile, acrylonitrile) with diazocarbonyl compounds under  $\text{Rh}_2(\text{OAc})_4$  catalysis.<sup>123</sup>

Cyclopropanation of alkenes generally proceeds stereospecifically from the point of view of the alkene (Scheme 21). *Cis* and *trans* olefins react to produce cyclopropanes where the substituents derived from the olefin maintain the same relationship (*cis* or *trans*, respectively) in the cyclopropane product.



Scheme 21 Stereospecificity of  $\text{Rh}_2(\text{OAc})_4$  Catalyzed Cyclopropanation of Olefins

Two notable problems are inherent in intermolecular cyclopropanation reactions. The first is that due to the highly reactive nature of the carbenoid intermediates and accompanying side-reactions.<sup>124</sup> To avoid this problem, reactions are generally run with an excess of olefin (often as the solvent), and the rate of addition of the diazo carbonyl compound is controlled (syringe pump) to maintain a low effective concentration of the carbene in solution. The second problem is that unless particular attention is given to "matching" the olefin, catalyst, and substrate accordingly, intermolecular cyclopropanation reactions are relatively non-selective (by today's standards).<sup>118</sup> Intramolecular cyclopropanations, on the other hand, provide greater selectivities due to the geometric constraints present during ring formation. This method has become increasingly popular as a means of constructing natural and non-natural products (Scheme 22) and is evidenced by an extensive review of this area that was published recently.<sup>125</sup>



Scheme 22 Preparation of Carbapenem **146**<sup>126</sup> and Tricyclo[3.3.1]propellane-2,8-dione **148**<sup>127</sup>

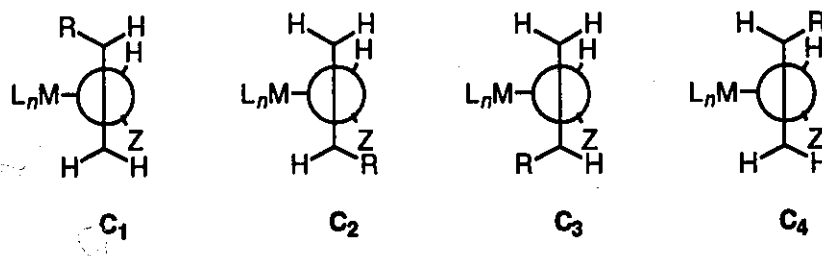
Doyle and coworkers<sup>128</sup> undertook a systematic investigation of the stereoselectivity of cyclopropanation reactions with ethyl diazoacetate. Four variables were found to be potential sources of regio- and stereochemical control in catalytic cyclopropanation reactions. These are the transition metal, its associated ligands, the diazo compound, and the olefin. The influence of the olefin was found to be the weakest, while the electronic influences derived from the transition metal were found to provide the majority of the regio- and stereochemical control.

Studies involving the correlation of various metal catalysts with regioselectivities<sup>102,129</sup> and results from investigations of asymmetric induction with chiral catalysts<sup>130,131</sup> have confirmed that the transition metal is directly involved in the product-forming step, and also imply that the factors that govern the product-determining step in each case are identical.

Stereoselectivities in catalytic cyclopropanations vary according to the catalyst used, with most systems providing the more stable *trans* cyclopropanes. The stereoselectivities are invariant to changes in the catalyst concentration, the rate of addition of the diazo compound, and to the molar ratio of olefin to diazo compound. Doyle<sup>98</sup> has developed a

mechanistic model for cyclopropanation reactions in order to explain the observed carbenoid-dependent differences in selectivity.

The cyclopropanation process is proposed to occur through an initial interaction between the olefin  $\pi$  bond and the electrophilic centre of the metal carbenoid, followed by  $\sigma$  bond formation with backside displacement of the catalyst (see Schemes 23 and 24).<sup>121</sup>



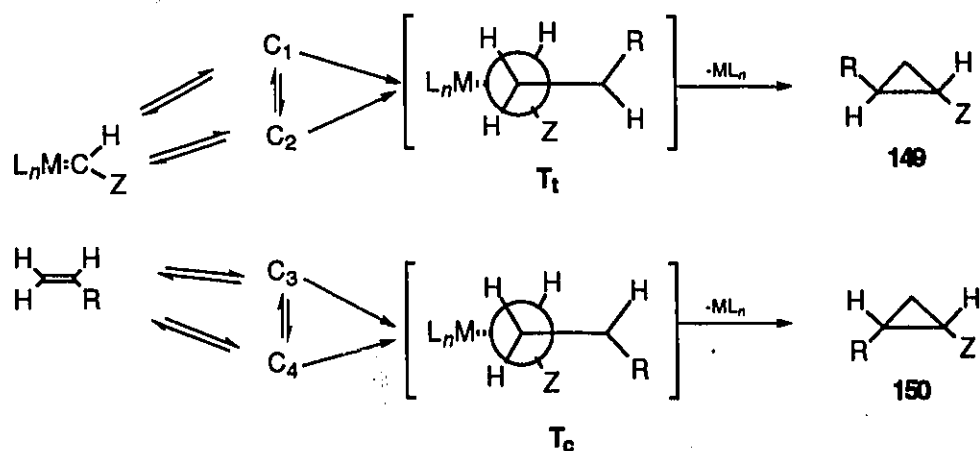
Scheme 23 Stable  $\pi$  Complex Orientations<sup>121</sup>

If the initially formed  $\pi$  complex has an independent existence, four stable conformations ( $C_1$ – $C_4$ ) may be proposed as a basis set (Scheme 23). For monosubstituted olefins (as shown in Scheme 24),  $C_1$  and  $C_3$  are higher in energy than  $C_2$  and  $C_4$  due to unfavourable interactions between the olefin substituent and the ligands on the metal. Using this same reasoning it can be anticipated that  $C_4$  should be favoured over  $C_2$ .

As the reaction proceeds the  $\pi$  complexed olefin now rotates around the electrophilic centre into an orientation that places the C-C bond of the olefin parallel to the metal-carbon bond, resulting in the more substituted carbon of the olefin being oriented *anti* to the metal (Scheme 24). This produces two possible transition states as  $C_1$  and  $C_2$  are transformed into  $T_t$ , and  $C_3$  and  $C_4$  are transformed into  $T_c$  (Scheme 24). The crossover between  $C_1$ – $C_2$  and  $C_3$ – $C_4$  can only occur if the olefin dissociates from the  $\pi$  complex.

The orientation of the olefin with respect to the carbenoid substituents at the  $\pi$  complex (if transition state energies  $T_t$  and  $T_c$  are nearly equal), or in the transition state,

where the energies differ as a result of interactions between R and Z, determines the predominance of one isomer over the other. Other mechanisms have been proposed for

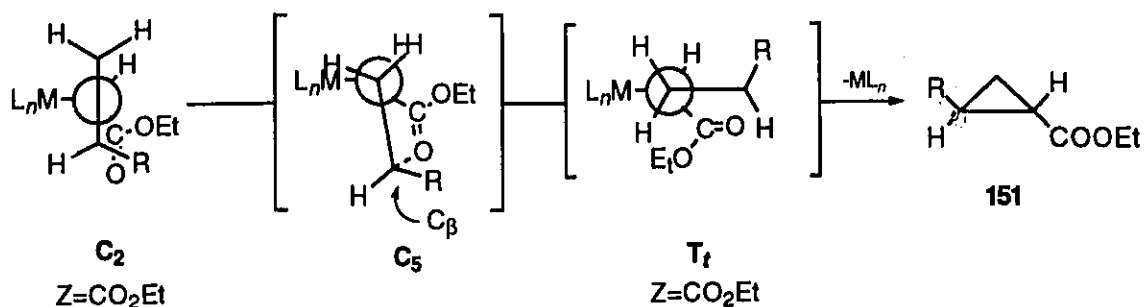


Scheme 24 Doyle's Cyclopropanation Mechanism<sup>121</sup>

catalytic cyclopropanation by alkyl- and arylcarbenes.<sup>132,133</sup> The major differences between those proposed mechanisms and the one suggested by Doyle are the existence of an equilibrium between the separated metal carbene and alkene, and the absence of a metallocyclobutane intermediate. A recent study by Noels and Hubert supports the existence of a free carbene-carbenoid equilibrium.<sup>134</sup>

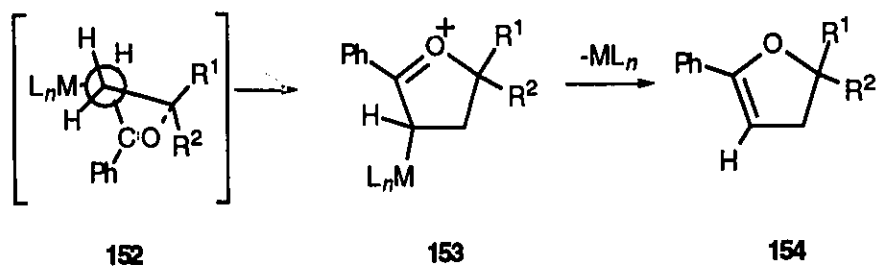
The model given in Scheme 24 suggests that in reactions such as the decomposition of ethyl diazoacetate and related diazocarbonyl compounds, stereochemical preference should not be for the *trans* isomer as is observed experimentally, but rather for the *cis* isomer. An examination of the influence of the carbonyl group on the conversion of the intermediate  $\pi$  complex to the cyclopropane explains this apparent discrepancy (Scheme 25). As the reaction proceeds and  $C_2$  passes to  $T_t$ , the developing electrophilic  $C_\beta$  of the original olefin passes over the nucleophilic carbonyl oxygen in  $C_5$  resulting in the stabilization of the transition state leading to the *trans*-cyclopropane. This type of stabilization is not possible in the transition state leading to the *cis*-isomer ( $T_c$ ), which would account for the predominant *trans* stereoselectivity in these reactions.

A key point which is relevant to the results discussed later in this chapter is the suggested effect of increasing the nucleophilicity of the carbonyl oxygen and/or the



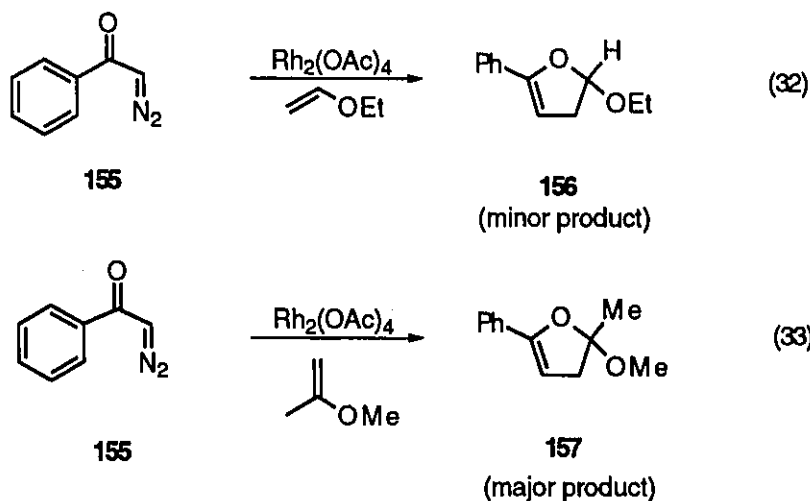
Scheme 25 Transition State Leading to the *trans*-Cyclopropane

electrophilicity of the  $\beta$ -carbon in  $C_5$ . These changes have been proposed to alter the course of the reaction in favour of forming dihydrofuran products (Scheme 26). Dihydrofurans have been obtained from copper catalyzed reactions of diazomalonates, 2-diazo-3-oxybutyrates, and 3-diazo-2,4-pentanedione with various vinyl ethers.<sup>135-139</sup>



Scheme 26 Transition State Leading to the Dihydrofuran 154

For example, dihydrofuran **156** was obtained as a minor product in the  $Rh_2(OAc)_4$  catalyzed reaction of  $\alpha$ -diazoacetophenone and ethyl vinyl ether (eq. 32), and **157** was formed as the major product in the same reactions carried out with of 2-methoxypropene (eq.33) (Scheme 27).<sup>121</sup> These findings will be discussed in relation to our results at the end of this chapter. Having presented the above brief overview, the problem related to the assignment of structure **26** described in section 3.1 can now be discussed in detail.



Scheme 27 Examples of Dihydrofuran Formation

### 3.4 Why Structure (26) ?

The key points that lead to the assignment of **26** as the structure of the major product of the cyclopropanation reaction between **24** and ethyl vinyl ether are given below (Kennedy Thesis<sup>93</sup>).

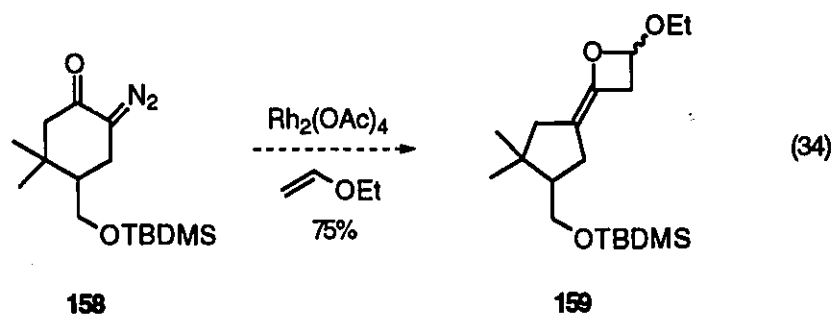
- 3.4.1 • The product isolated from the reaction of **24** with excess ethyl vinyl ether and  $\text{Rh}_2(\text{OAc})_4$  (2 mol %, 21 °C) did not exhibit a C=O stretch in the infrared spectrum, as would be expected for the cyclopropane, but did show a very strong absorption at  $1100\text{ cm}^{-1}$  that was thought to arise from a C-O-C stretch.
- A one proton multiplet appeared at  $\delta$  5.4 ppm in the  $^1\text{H}$  NMR and was consistent with the chemical shift that would be expected for the acetal methine proton in the oxetane ring.

- The  $^{13}\text{C}$  NMR spectrum showed two olefinic signals at  $\delta$  148.0 and 104.6 ppm. These values were reasonable for their assignment to the oxetane and cyclopentane olefin carbons respectively.

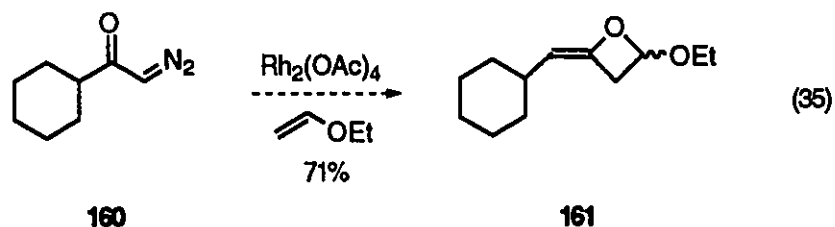
- The high resolution mass spectrum confirmed a molecular formula of  $\text{C}_{19}\text{H}_{36}\text{O}_2\text{Si}$  which is consistent with the structure assigned to **26**.

3.4.2 • Initially it was proposed that **26** arose via ketene addition to ethyl vinyl ether. It was thought that the steric hindrance imposed by the *gem*-dimethyl substituent permitted Wolff rearrangement by retarding the formation of the desired cyclopropane.

- This assumption proved to be incorrect as the corresponding  $\alpha$ -diazoketone which lacked the *gem*-dimethyl substituent  $\alpha$  to the diazo functionality (**158**) was prepared and also appeared to provide the analogous product **159** in high yield (75%) (eq. 34).



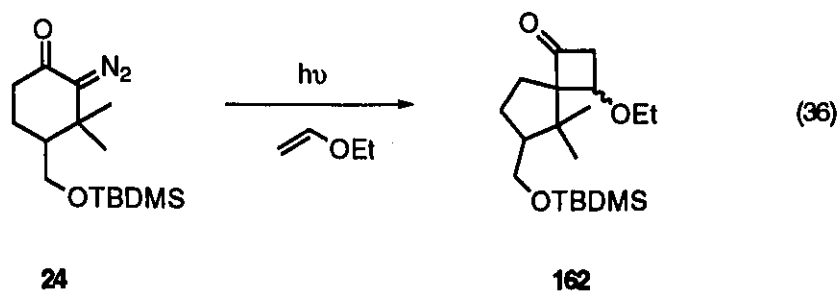
In fact, even acyclic systems such as **160** gave a similar result (**161**, eq.35).



- In view of these these results, it was felt that the reaction pathway was not strongly influenced by the structure of any particular  $\alpha$ -diazoketone, but was a general feature of their reaction with ethyl vinyl ether in  $\text{Rh}_2(\text{OAc})_4$ .

3.4.3 • If the reaction product was the result of Wolff rearrangement to the ketene followed by subsequent cycloaddition to ethyl vinyl ether, direct photochemical generation of the ketene derived from **24** in the presence of the vinyl ether may result in the formation of oxetane **26**.

- The irradiation of  $\alpha$ -diazoketone **24** in the presence of ethyl vinyl ether did not lead to oxetane **26**, but rather to the characteristic [2+2] cycloaddition product cyclobutanone **162** (eq. 36). Although this suggests that the mechanism does not involve a discrete ketene intermediate, this type of pathway cannot be ruled

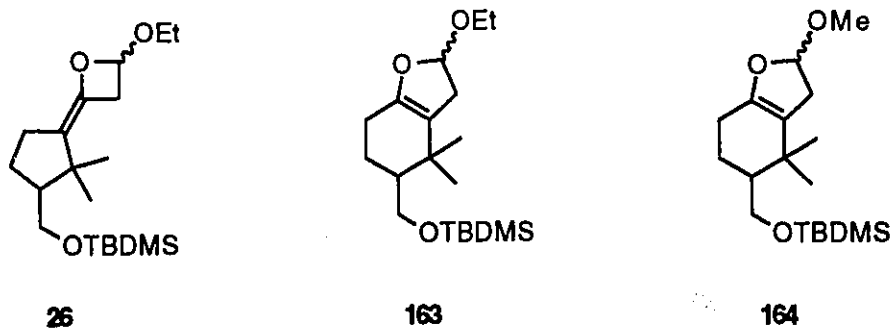


out and may still be responsible for the formation of oxetane **26** if the ground and excited state reactions differ.

3.4.4 • To investigate the effect of the  $\text{Rh}_2(\text{OAc})_4$  catalyst on the reaction, several other cyclopropanation catalysts were examined. Palladium(II) acetate and copper(I) chloride both gave similar results to those obtained with  $\text{Rh}_2(\text{OAc})_4$ , although the yields were considerably lower in both cases.

3.4.5 • A second possible structure, dihydrofuran **163**, was also considered for the product of the  $\alpha$ -diazoketone/ $\text{Rh}_2(\text{OAc})_4$ /ethyl vinyl ether reaction. As there is

more literature precedent for this type of structure, it was ruled out only after a similar compound (**164**) was prepared by another route. When the spectra of these two nearly identical compounds were compared, it became obvious that the olefinic  $^{13}\text{C}$  NMR signals ( $\delta$  148 and 113 ppm) of **164** differed significantly from those found with **163** ( $\delta$  148 and 104 ppm). The replacement of the ethyl

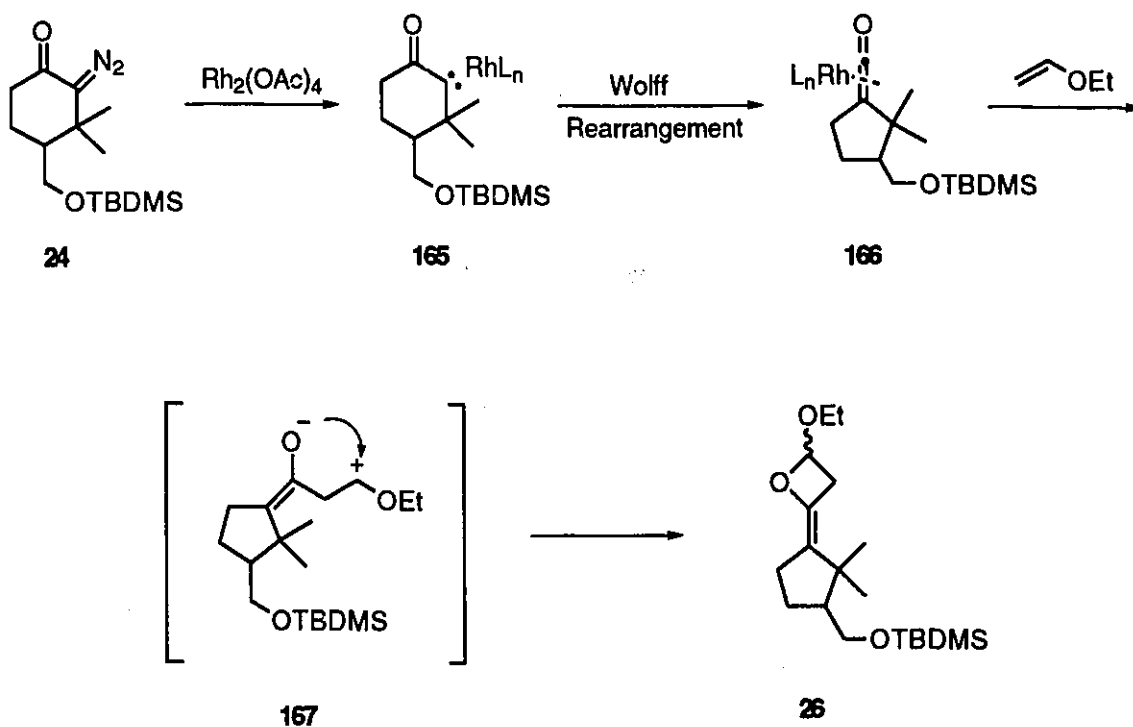


group in **163** with a methyl group in **164** would not be expected to alter the chemical shift of one of the olefinic signals by 9 ppm. This became the most convincing piece of data by which structure **163** was ruled out and the product assigned structure **26**.

At this point the synthetic route to Taxol<sup>®</sup> which required the preparation of cyclopropane **25** was abandoned and work on a modified approach began. At a later date, re-examination of the literature surrounding the cyclopropanation of metal carbenoids with ethyl vinyl ethers, as well as some serious reservations about the proposed mechanistic interpretation of the formation of **26** (see below) led us to re-investigate the problem in order to determine the real identity of the major product of the metal catalyzed reaction of  $\alpha$ -diazoketones and ethyl vinyl ether.

### 3.5 Mechanism Proposed to Explain the Formation of (26)

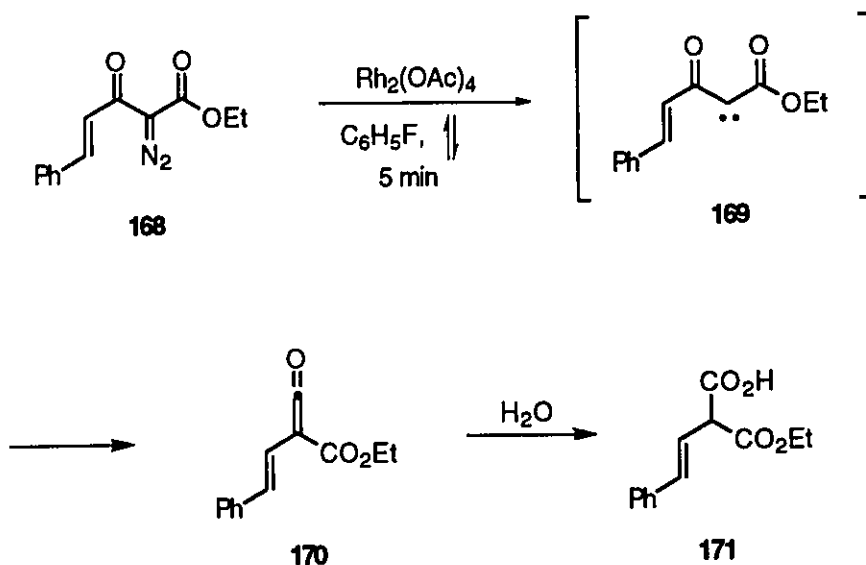
The mechanism that had been proposed to explain the formation of **26** is shown in Scheme 28.<sup>93</sup> This mechanism requires that the initially formed metal-carbenoid undergo a Wolff rearrangement followed by a [2+2] cycloaddition between the enol ether and the ketene carbonyl via zwitterionic intermediate **167**. Catalytic conditions usually suppress Wolff rearrangement as a result of the stabilization offered to the carbene by complexation



Scheme 28 Proposed Mechanism for the Formation of **26**<sup>93</sup>

with a transition metal.<sup>94,112</sup> Metal-catalyzed Wolff rearrangements are commonly observed with silver salts and have been documented in reactions catalyzed by some copper species.<sup>140</sup> Rhodium(II) catalysis is known to be very specific for cyclopropanation.<sup>118</sup> Precedent for the proposed mechanism shown in Scheme 28 was given<sup>93</sup> in an example of

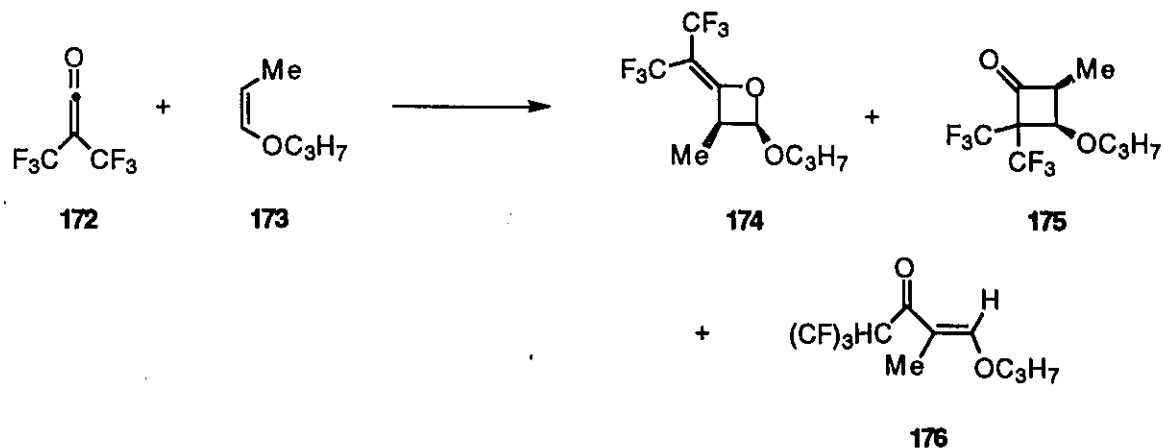
a  $\text{Rh}_2(\text{OAc})_4$  catalyzed decomposition of an  $\alpha$ -diazoketone which was proposed to occur via a Wolff rearrangement (Scheme 29).<sup>141</sup>



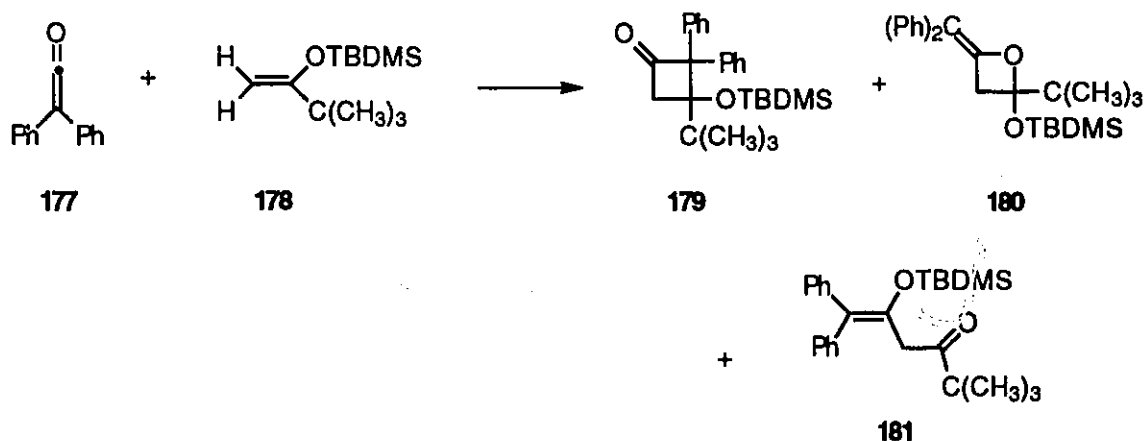
Scheme 29  $\text{Rh}_2(\text{OAc})_4$  Catalyzed Wolff Rearrangement Reported by Davies and Taylor<sup>141</sup>

Ketenes normally form cyclobutanones in reactions with both activated and unactivated alkenes. In order to support the mechanism proposed in Scheme 28, examples of ketene dimerizations to form  $\beta$ -lactones were given.<sup>93</sup> A dipolar intermediate such as that shown in the proposed [2+2] cycloaddition (Scheme 28) is known to occur in other systems.<sup>142</sup> Support for this type of transformation was also found in reactions reported between bis(trifluoromethyl)ketene **172** and an enol ether **173** (Scheme 30), and diphenylketene **177** and a variety of silyl enol ethers (e.g. **178**) (Scheme 31).<sup>143</sup>

In all of the examples given the products were thought to result from an intermediate zwitterionic species which undergoes either ring closure (1 of 2 modes) or rearrangement to give the products shown. Thus, it was thought that precedent for the proposed mechanism for the formation of the oxetane **26** in the metal-catalyzed reaction of **24** and ethyl vinyl ether was firmly established.



Scheme 30 Oxetane Formation in [2+2] Cycloaddition Reactions

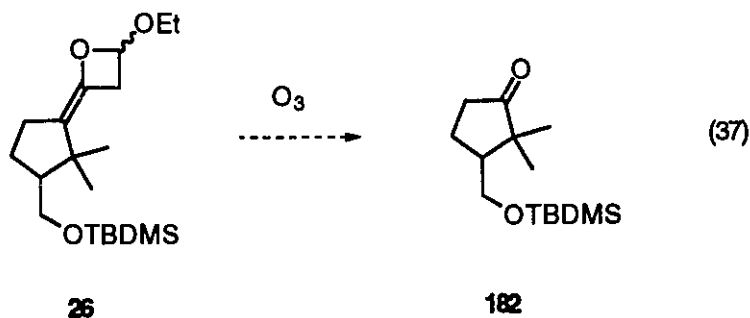


Scheme 31 Examples of Oxetane Formation in [2+2] Cycloaddition Reactions

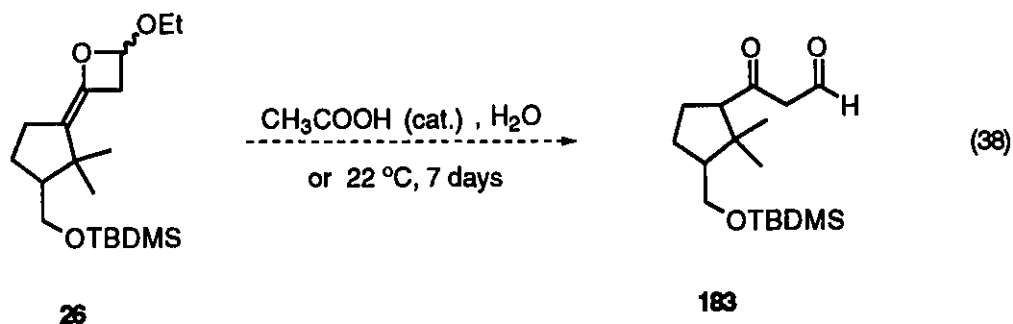
Successful ozonolysis of **26** should provide unambiguous proof of the structure (eq. 37), however, with this particular substrate no identifiable products were isolated.<sup>93</sup> Thermolysis of **26** in dry toluene at 100 °C (sealed tube) for 2 days had also not resulted in any new products being formed.<sup>93</sup>

When **26** was stirred in aqueous acetone containing a catalytic amount of acetic acid a keto-aldehyde was obtained which was assigned structure **183**.<sup>93</sup> The identical

compound was also obtained if **26** was allowed to stand in wet ether or benzene at room temperature (21 °C) for 7 days.



A minor product was also described that had been found in some of the rhodium(II) acetate catalyzed decomposition reactions. Crude <sup>1</sup>H NMR spectra and TLC analysis had suggested that the compound was identical to that assigned the structure **183**, but this was found to be incorrect (eq.38).<sup>93</sup>



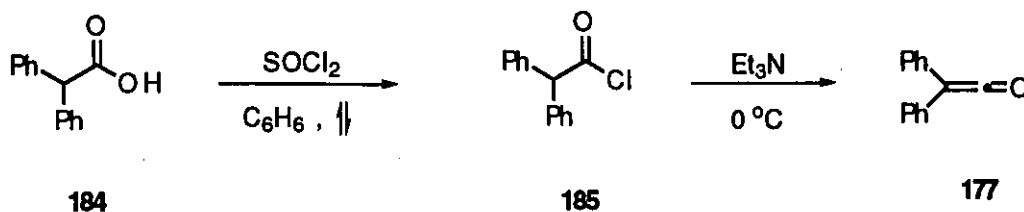
### 3.6 Investigation of the Possibility that (26) is Formed via a Discrete Ketene Intermediate

The mechanism that was proposed for the formation of **26** (Scheme 28) is shown as proceeding through a ketene-type intermediate **166**. As was described in section 3.3.3, irradiation of diazocompound **24** in the presence of excess vinyl ether did not lead to the oxetane **26**.<sup>93</sup> The reaction was carried out with a large excess of benzophenone as a triplet sensitizer in the presence of ethyl vinyl ether. The fact that the oxetane **26** was not

formed does not rule out the possibility that the ground state reaction of an initially formed metal-carbenoid may proceed through a Wolff rearrangement to a ketene-type intermediate. In order to investigate this possibility, a simple ketene was prepared as a model compound and exposed to reaction conditions identical to those used in the preparation of **26**.

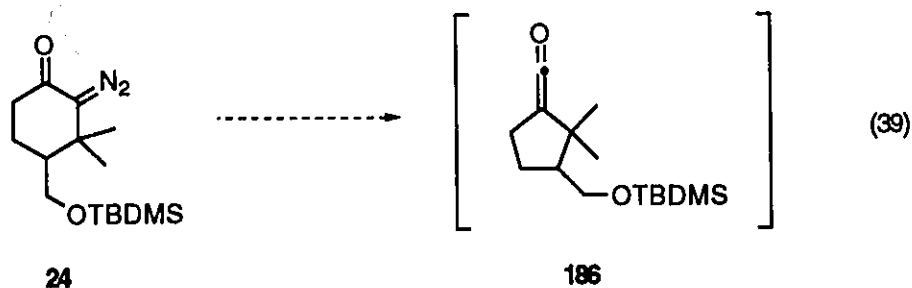
### 3.6.1 Preparation and Reactions of Diphenylketene **177**

Diphenylketene was prepared using a modified literature procedure that involves the preparation of diphenylacetic acid chloride **185** from diphenylacetic acid **184** followed by a base-promoted elimination reaction (Scheme 32).<sup>144,145</sup> Compound **177** was obtained as a bright yellow oil which exhibited a characteristic ketene infrared (IR) absorption at 2097  $\text{cm}^{-1}$ . The ketene dimerizes readily, and must therefore be used immediately.



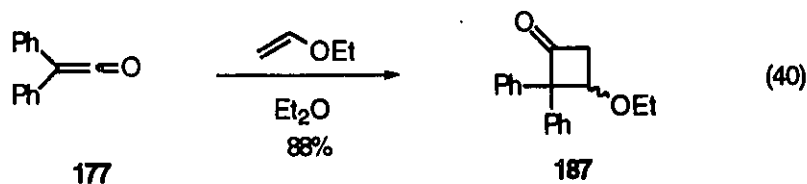
Scheme 32 Preparation of Diphenylketene **177**<sup>144,145</sup>

If the proposed mechanism for the formation of oxetane **26** is correct, one would expect that if any particular intermediate could be prepared independently and subsequently exposed to the standard reaction conditions, the product of the reaction should be **26**. It was not possible to prepare and isolate the ketene corresponding to  $\alpha$ -diazoketone **186** (eq. 39), therefore diphenylketene **177** was chosen as a model compound as it could be prepared in two steps and was stable enough to allow for its isolation and use in further reactions.



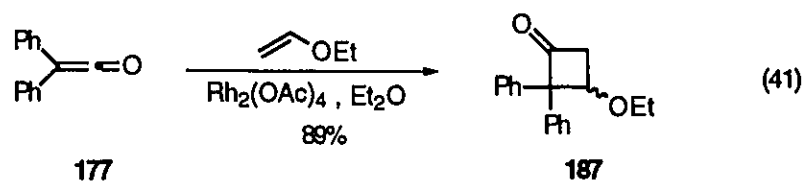
There are at least two possible intermediates in the proposed mechanism which could add to the ethyl vinyl ether to give oxetane **26**. The first is a discrete ketene intermediate which adds to the alkene in a straightforward fashion. This is unlikely to be operative as ketenes are known to react with all types of olefins to form cyclobutanones as a result of addition of the alkene in a [2+2] fashion across the carbon-carbon double bond of the ketene. The second possibility is a metal-ketene type species that could add to ethyl vinyl ether, resulting in the formation of oxetane **26**.

To test the first possibility a solution of diphenyl ketene and ethyl vinyl ether in freshly distilled ether was stirred overnight under argon. Cyclobutanone **187** was obtained in 88% yield after chromatography (eq. 40), and was readily identified by the characteristic C=O stretch at  $1779\text{ cm}^{-1}$  in the IR spectrum. The absence of any oxetane formation suggests, once again, that a discrete ketene intermediate is not involved in this transformation (cf. section 3.4.3).



To determine whether a metal-ketene intermediate was adding to the olefin, a solution of diphenylketene in freshly distilled ether was added to a mixture of the  $\text{Rh}_2(\text{OAc})_4$  and excess ethyl vinyl ether over a period of 7 hours (syringe pump). Once

again, an excellent yield (89%) of cyclobutanone **187** was obtained after chromatography of the crude material (eq. 41).



This result forces one to strongly question the validity of the mechanism presented in Scheme 29. In this particular case, one could imagine that the proposed metal-ketene species **166** shown in Scheme 29 is an intermediate in the reaction that is *only* accessible through a metal-carbenoid to metal-ketene type transition, and this local minimum (of intermediate **166**) is not accessible to the ketene (even in the presence of the metal) if another lower energy trajectory on the free energy surface is available (such as the pathway producing cyclobutanone **187**). As is often the case with mechanistic studies, a negative result becomes a non-result. The fact that oxetane formation did not occur when ketene **173** was subjected to the standard reaction conditions cannot rule out the possibility that when one uses an  $\alpha$ -diazoketone to form a metal-carbenoid, Wolff rearrangement of this species might produce a ketene-type intermediate similar to **166** that is capable of adding to ethyl vinyl ether in such a fashion so as to produce oxetane **26**.

### 3.6.2 Mechanism of the Wolff Rearrangement

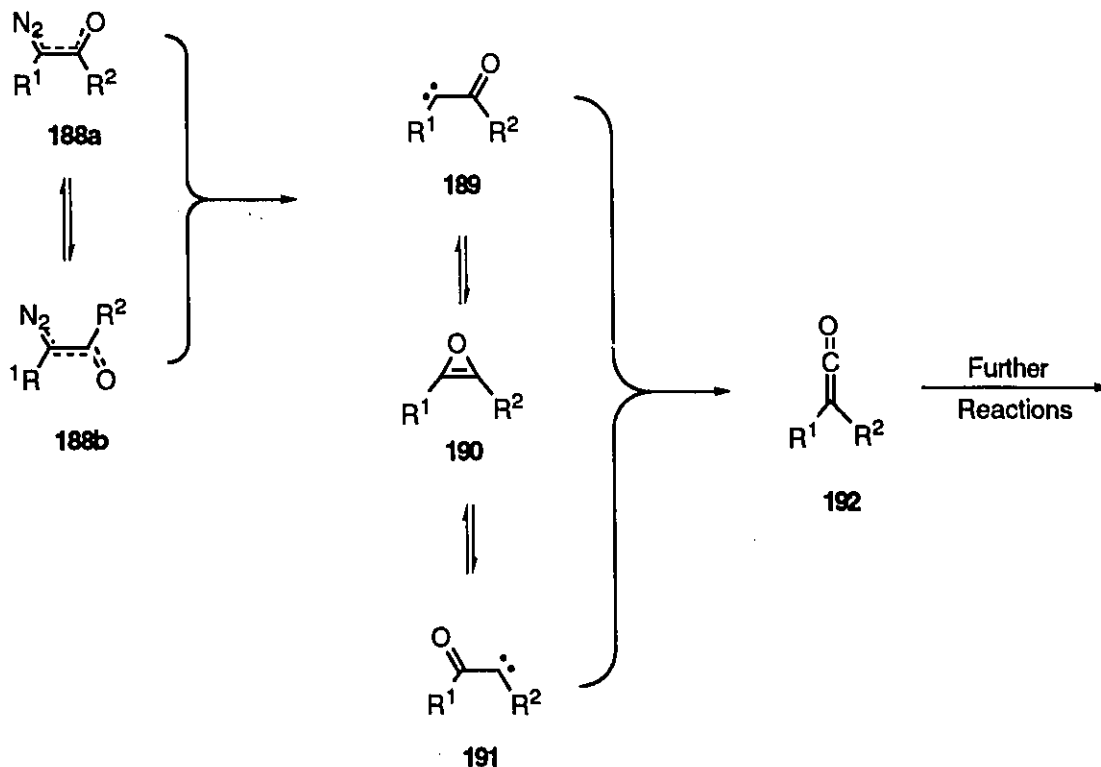
A brief examination of the vast amount of literature that has been published within the past decade alone on the subject of carbenes presents a wide variety of mechanistic information which can appear to be contradictory and difficult to integrate. Padwa points out in his 1992 review of intramolecular carbenoid reactions that "A survey of the literature dealing with the topic of catalytic diazo decomposition can be both enlightening and frustrating". I would agree wholeheartedly with this appraisal.

If one restricts the search to only that information which is directly concerned with the Wolff rearrangement some relief can be found, although as Gill points out in the 1991 Comprehensive Organic Synthesis chapter on the Wolff rearrangement, "There is as yet no general agreement on all of the mechanistic detail connecting reactant to product...".<sup>140</sup> Fortunately, there are some features of the mechanism which are now regarded as secure. The disagreements mainly concern the exact interconnection and participation of particular reactive intermediates such as  $\alpha$ -ketocarbenes and oxirenes. A general mechanism for the Wolff rearrangement is given in Scheme 33.<sup>140</sup>

The first accepted fact with respect to the mechanism of the rearrangement is that acyclic  $\alpha$ -diazoketones exist as an equilibrium mixture of the *s*-(Z) **188a** and *s*-(E) **188b** forms with a rotational barrier of approximately 38–75 kJ mol<sup>-1</sup> (9–18 kcal mol<sup>-1</sup>). The second undisputed fact is that the rearrangement leads to a ketene intermediate **192** which is generally trapped by acids or other agents (Scheme 33).

In the *s*-(Z) form of the diazocarbonyl compound **188a** the migrating group (R<sup>2</sup>) and the leaving group (N<sub>2</sub>) are located relative to one another in an antiperiplanar geometry which is ideal for a concerted N<sub>2</sub> extrusion/rearrangement. This type of concerted mechanism has been proposed to account for the stereocontrol that is observed in the photolysis and thermolysis of some  $\alpha$ -diazo carbonyl compounds.<sup>140</sup> In photolysis experiments involving both direct and triplet-sensitized irradiation, product ratios have led to the proposal of a concerted component from *s*-(Z) **188a** and a nonconcerted carbenic component from *s*-(E) **188b**.<sup>146</sup>

These types of studies are not regarded as proof for a concerted mechanism as there is compelling evidence for the intermediacy of both  $\alpha$ -ketocarbenes **189** and **191** and oxirenes **190**.<sup>140</sup> A wide variety of groups R<sup>1</sup> or R<sup>2</sup> in carbenes **189** and **191** have been found to migrate in the rearrangement to the ketene **192**. For thermal reactions the migratory aptitude of various groups follows the sequence H > Ph > Me > NR<sub>2</sub> > OR. Under photochemical conditions the methyl and phenyl positions in the sequence are



Scheme 33 Mechanism of the Wolff Rearrangement<sup>140</sup>

exchanged.<sup>147</sup> It is probable that the mechanism of a metal-catalyzed Wolff rearrangement shows appreciable differences to the one presented here.<sup>140,147</sup>

The photolysis of  $\alpha$ -diazoketones to form ketenes via the Wolff rearrangement has become an important reaction in preparative organic chemistry<sup>140,147</sup> and is a valuable method for various transformations including the one-carbon homologation of a carboxylic acids (Arndt-Eistert reaction; Scheme 34),<sup>140,147</sup> the preparation of strained cyclic systems through ring contractions of cyclic  $\alpha$ -diazoketones (Scheme 35<sup>148</sup>), and the construction of diverse ring systems through intramolecular cycloaddition reactions (Scheme 36).<sup>149</sup>

General transformation:

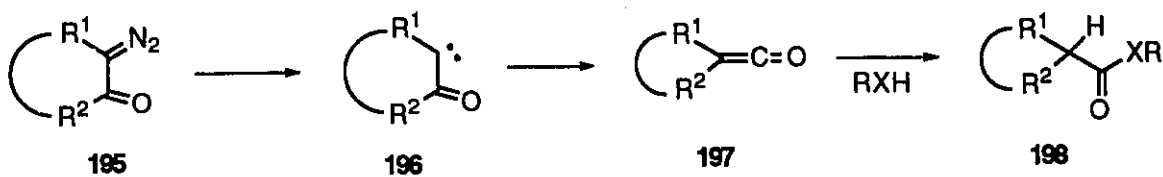


*e.g.*

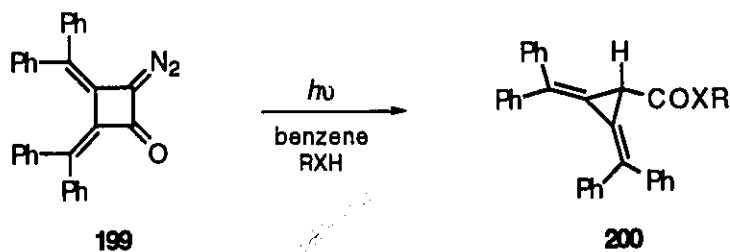


Scheme 34 The Arndt-Eistert Reaction

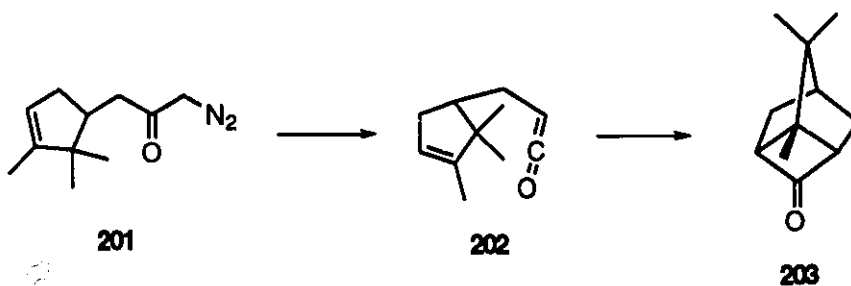
General transformation:



*e.g.*

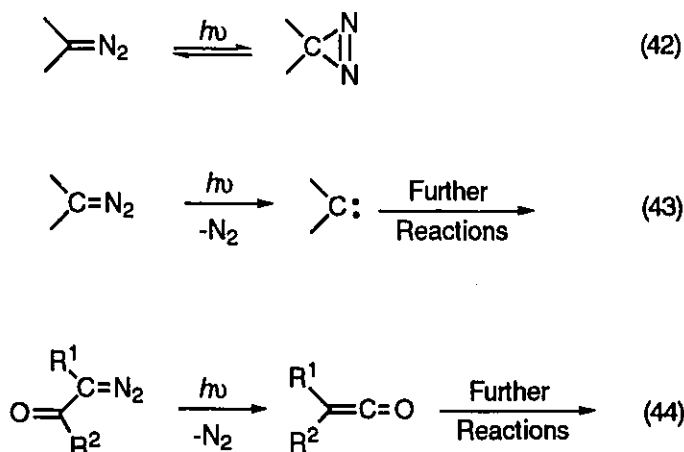


Scheme 35 Ring Contraction<sup>148</sup>



Scheme 36 [2+2] Cycloaddition<sup>149</sup>

Depending on the structure and substitution of a particular  $\alpha$ -diazocarbonyl compound, irradiation with 200–500 nm light results in three possible reaction pathways (Scheme 37)<sup>119</sup>: (1) Reversible rearrangement to a diazirine (eq. 42). (2) Nitrogen elimination to form a carbene (eq. 43). (3) Rearrangement of an  $\alpha$ -diazocarbonyl and loss of nitrogen (Wolff rearrangement) to form a ketene (eq.44). As was described above, this type of transformation need not occur through a ketocarbene intermediate.

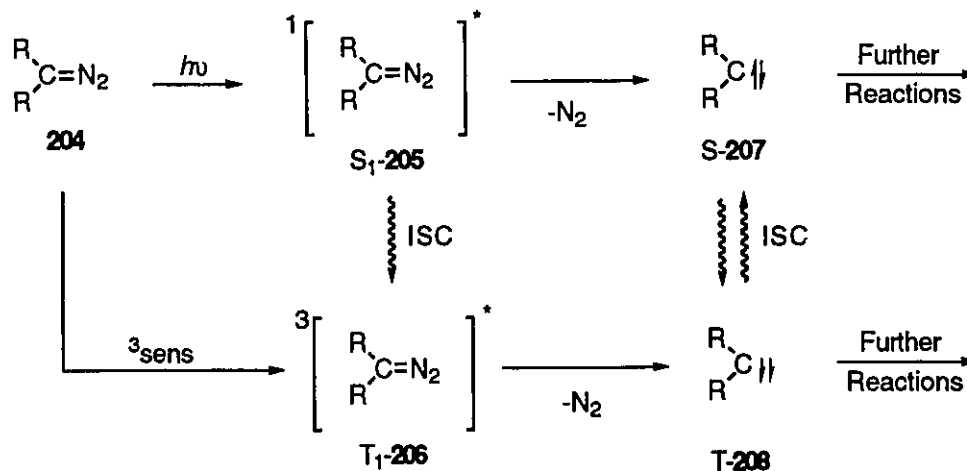


Scheme 37

Photoexcitation of the diazo group of **204** gives rise to the first excited singlet state of the diazocompound **205** which may react according to two different pathways (Scheme 38)<sup>119,150</sup>: (1) Intersystem crossing to the diazo compound T<sub>1</sub>-**206**.\* (2) Reversion to the ground state **204** by internal conversion in a radiationless decay process. (3) Decomposition to the singlet carbene S-**207** through the elimination of nitrogen.

Loss of nitrogen from **206** forms the triplet carbene **208**. Typical triplet reactions occur if the reactions are faster than spin reversion to the triplet carbene, which is often more stable. Intersystem crossing (ISC) from the singlet state S<sub>1</sub>-**205** to the triplet T<sub>1</sub>-**206** is possible followed by N<sub>2</sub> loss. The triplet carbene T-**208** can be formed in this way. The triplet state T<sub>1</sub>-**206** can be selectively populated through the use of a triplet

\* The existence of triplet diazo species T<sub>1</sub>-**206** has not been established (J.C. Scaiano personal communication).



Scheme 38 Possible Reaction Pathways in the Photodecomposition of Diazocompound 204

sensitizer, although competing reactions can occur depending on the particular compound, the temperature, and the solvent used. Intersystem crossing (ISC) is shown in both directions between the singlet and triplet carbenes (S-207 and T-208 respectively). An interesting feature of carbene photochemistry is the presence of these two energetically proximate states; S-202 and T-204. The energy level of the triplet carbene for any given system can be higher/lower or almost degenerate to the singlet carbene.<sup>119</sup>

Singlet and triplet carbenes do not react similarly in terms of both selectivity and stereospecificity. Typical reactions of a singlet carbene are 1,2-sigmatropic shifts, stereospecific insertion into  $\sigma$  bonds, and addition of a nucleophile.<sup>150</sup> If the compound contains an  $\alpha$ -carbonyl group Wolff rearrangement to the ketene is generally the preferred mode of reactivity.

Typical reactions of triplet carbenes are atom abstractions to produce radicals, nonstereospecific additions to  $\pi$  bonds, and the addition of radicals or radical-like substrates.<sup>150</sup> Wolff rearrangements are linked to the singlet state and are not thought to occur with triplet ketocarbenes.<sup>119</sup> Correspondingly, Wolff rearrangement is either

eliminated or suppressed when a triplet sensitizer is used in reactions with diazocarbonyl compounds.

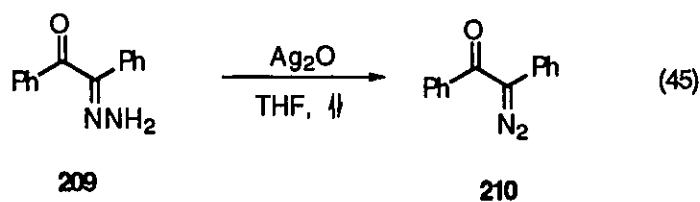
Wolff products are often not totally suppressed and considerable amounts have been formed in reactions when >98% of the light is absorbed by the sensitizer.<sup>146</sup> In these cases, it is assumed that the singlet ketocarbene is populated through ISC and undergoes the Wolff rearrangement.

With these considerations in mind, photochemical experiments were performed using azibenzil **210** (the  $\alpha$ -diazoketone which corresponds to the the previous model studies carried out with diphenylketene).

### 3.7 Photochemical and Transition Metal-Catalyzed Reactions of Azibenzil (210)

#### 3.7.1 Preparation of Azibenzil (2-Diazo-1,2-diphenyl-1-ethanone) 210

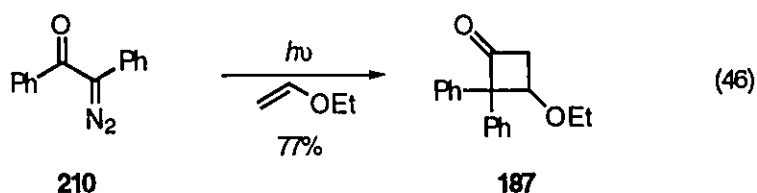
Azibenzil (2-diazo-1,2-diphenyl-1-ethanone) **210** was prepared by the oxidation of benzil monohydrazone with silver(I) oxide (eq.45).<sup>151</sup> Refluxing the hydrazone **209** with 1.1 equiv. of  $\text{Ag}_2\text{O}$  in THF gave, after recrystallization, the bright-orange diazoketone **210** in 84% yield.



### 3.7.2 Irradiation of Azibenzil **210** in the Presence of Ethyl Vinyl Ether

An attempt to effect the cyclopropanation of diazoketone **210** under photochemical conditions in the presence of ethyl vinyl ether should provide the ketene and possibly the oxetane product similar to compound **26** that was observed in the previous study carried out by Kennedy.

Direct irradiation of a solution of azibenzil **210** in ethyl vinyl ether did not result in the formation of any oxetane product, but rather in the formation of cyclobutanone **187** via



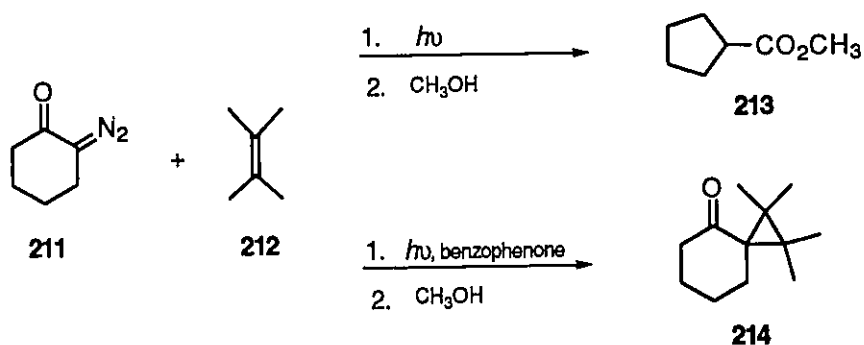
the Wolff rearrangement of **210** (eq. 46). Cyclobutanone **187** displayed the characteristic IR stretch at  $1779\text{ cm}^{-1}$  identical to that found for the compound isolated from previous experiments with diphenylketene (section 3.6.1). All other spectral data were identical to that found for **187**.

As with the previous experiments using diphenyl ketene directly, these results suggest that a ketene-type intermediate is not the species responsible for the formation of oxetane-type products.

A final photochemical experiment was performed which entailed the triplet sensitized irradiation of azibenzil in the presence of ethyl vinyl ether. As was mentioned previously, Wolff rearrangements are thought to occur only from the singlet carbene, with the triplet carbene preferring to react through the pathways mentioned above such as hydrogen abstraction or cyclopropanation (section 3.6.2).

Jones and Ando<sup>152</sup> have shown that Wolff rearrangement is suppressed or eliminated completely if the triplet carbene is generated through energy transfer from a triplet sensitizer. In the previous example excellent suppression of rearranged and insertion

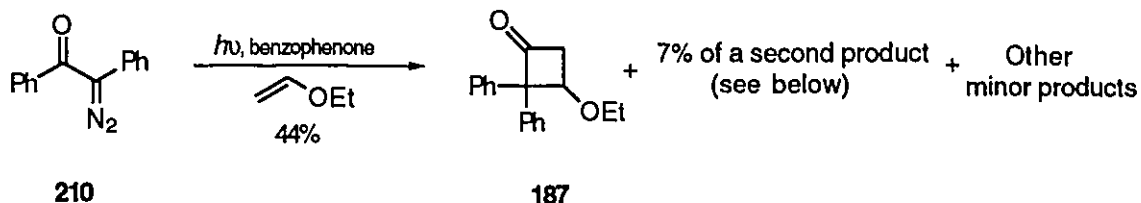
products compared to cyclopropanation was found when the reaction was carried out in the presence of a triplet sensitizer (Scheme 39).



Scheme 39<sup>152</sup>

To examine what effect the specific generation of the triplet carbene would have on our system, especially the possibility of isolating the cyclopropanation product, a benzophenone sensitized decomposition of **210** was carried out. Yamamoto found that a large excess of benzophenone was required in order to populate the triplet state effectively if, instead of specifically exciting the sensitizer with a specific wavelength light (not possible in our case), a high pressure Hg lamp was used.

In accordance with this, a degassed solution of azibenzil **210** in ethyl vinyl ether containing 10 equivalents of benzophenone was irradiated for 4.5 h (Scheme 40). A complex mixture of at least four different products was obtained. Repeated chromatography resulted in the isolation of cyclobutanone **187** (44%) as well as a small amount (7%) of another product whose structure was identified at a later date (see section below). Product isolation was complicated by the large amount of benzophenone present, which has a polarity virtually identical to that of the products of the reaction.

Scheme 40 Sensitized Irradiation of **210**

The formation of a large percentage of the cyclobutanone product associated with the singlet carbene most likely occurred as a result of initial population of the triplet carbene, followed by ISC to the nearby singlet state. Singlet/triplet equilibria have been inferred from the behaviour of a number of carbenes.<sup>153-156</sup> Wolff rearrangement of the singlet carbene and subsequent addition to the olefin, would produce cyclobutanone **187** in the manner discussed previously.

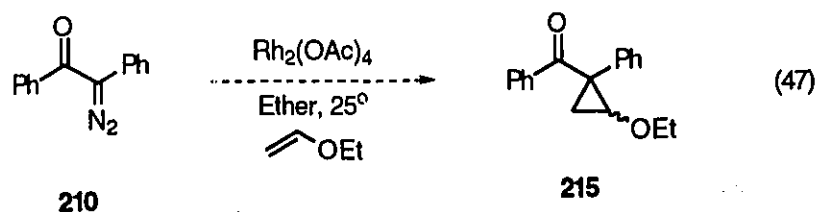
The results obtained in these experiments did not support the proposed mechanism for the formation of the oxetane **26** in the rhodium(II) acetate catalyzed reaction of **24** and ethyl vinyl ether. A new approach was therefore taken. Using this same model system (azibenzil **210**), it was decided that repetition of the original experiments could be beneficial in establishing the assignment and mechanistic origin of the major product of the cyclopropanation of **24**. It was hoped that experiments with a simplified model compound would allow easier interpretations of the spectral assignments, and allow a better understanding of what was actually occurring in the reaction.

### 3.8 Rh<sub>2</sub>(OAc)<sub>4</sub> Catalyzed Addition of Azibenzil to Ethyl Vinyl Ether

#### 3.8.1 General Reaction

Attempted cyclopropanation reactions of diazoketone **210** were carried out in the same manner as those used in the attempted cyclopropanation of **24**. The addition of a

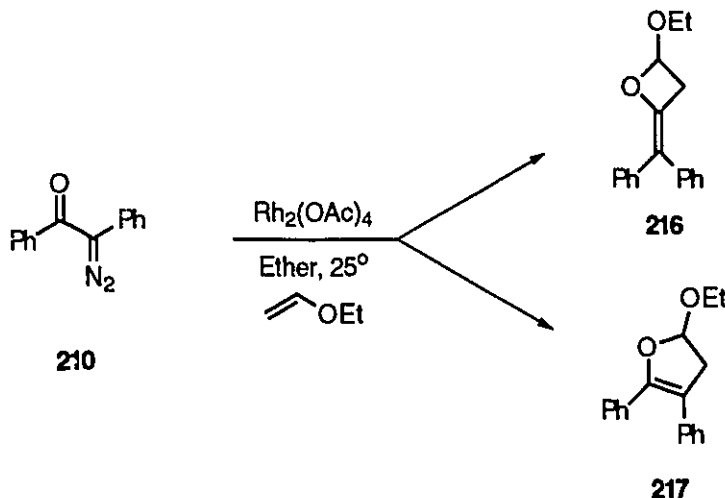
solution of diazoketone **210** in ether to a stirred suspension of rhodium(II) acetate and ethyl vinyl ether in freshly distilled ether over five hours with a syringe pump afforded what appeared to be a single compound by GC-MS. TLC analysis indicated that the material decomposed readily on silica gel, however a small sample was isolated by flash chromatography which was suitable for spectroscopy. All of the spectral data were recorded immediately after purification.



### 3.8.2 Spectral Information

The  $^1\text{H}$  NMR spectrum of the material clearly indicated that the cyclopropanation product **215** (eq. 47) had not been formed as no signals were found in the  $\delta$  0.0–1.0 ppm range. The  $^{13}\text{C}$  NMR spectrum confirmed this as the signal that was the farthest upfield was at 15.3 ppm. The IR spectrum of the compound lacked the carbonyl stretch expected for **215** but did show a number of medium and strong absorption bands in the area of 1200–1000  $\text{cm}^{-1}$ .

Having eliminated the expected cyclopropane as the compound that was isolated, consideration was given to the two products that were analogous to the possible reaction products that had been discussed in the initial work.<sup>93</sup> The oxetane-type product **216**, which was thought to have been the product in the previous work, and the dihydrofuran-type product **217** which was ruled out as a possibility in the initial system (see section 3.4.5) were both examined as possible structures (Scheme 41).



Scheme 41 Possible Structures for the Isolated Product From the  $\text{Rh}_2(\text{OAc})_4$  Catalyzed Cyclopropanation of Ethyl Vinyl Ether with **210**

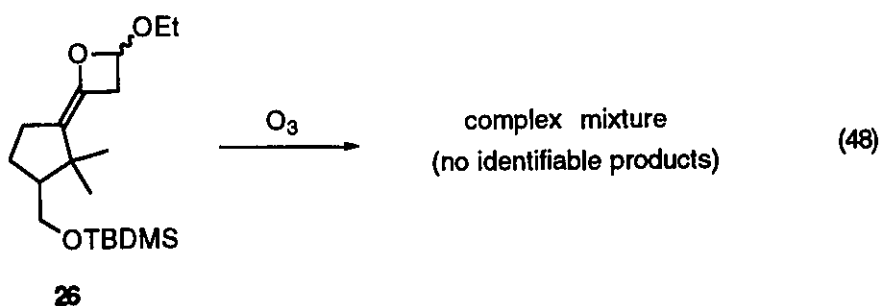
Structures **216** and **217** appear to be quite distinct at first glance, however this is somewhat deceptive. Closer examination reveals their similarity with respect to  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, and MS spectra. High resolution mass spectroscopy confirmed the molecular formula as  $\text{C}_{18}\text{H}_{18}\text{O}_2$ , although both compounds **216** and **217** would have this molecular formula. Disregarding the phenyl substituents, both structures contain one methine attached directly to two ether oxygen's, two methylene groups, the methyl group of an ethoxy substituent, and two quaternary carbons of an enol ether.

Each structure contains the same number of CH,  $\text{CH}_2$ ,  $\text{CH}_3$ , and quaternary carbons and the  $^{13}\text{C}$  NMR DEPT experiments were therefore of no avail. Similarly, two-dimensional  $^1\text{H}$ - $^1\text{H}$  COSY,  $^1\text{H}$ - $^1\text{H}$  ROESY, and  $^1\text{H}$ - $^{13}\text{C}$  HETCOR experiments were also inconclusive. A  $^{13}\text{C}$ - $^{13}\text{C}$  coupling INADEQUATE experiment was attempted which should have allowed us to differentiate between the two different olefin substitution patterns in structures **216** and **217** by making use of known  $^{13}\text{C}$  coupling constants. Unfortunately, the olefin carbon atoms had long relaxation times (approximately 10 s), making it impossible to collect a sufficient amount of information to give an acceptable signal to noise ratio in a reasonable length of time (~60 hours).

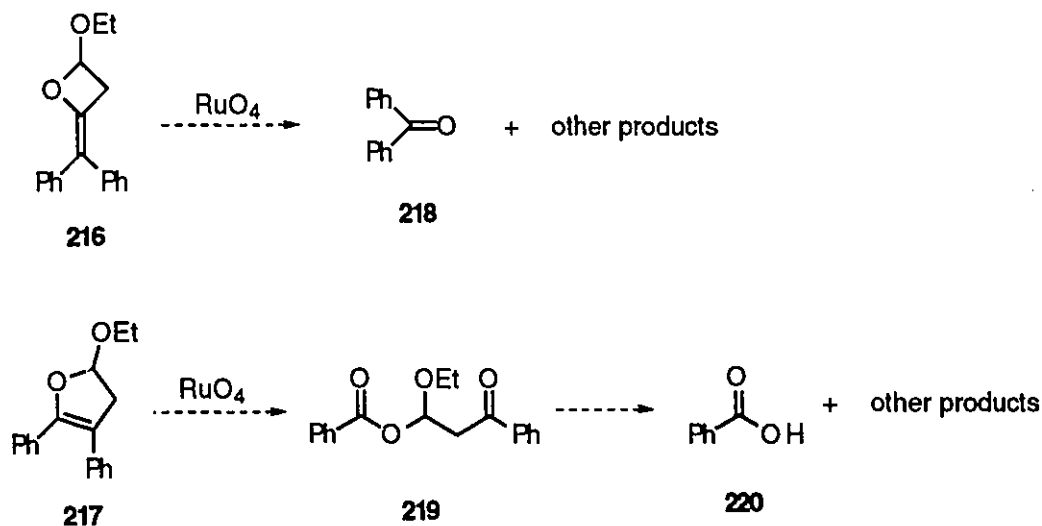
### 3.8.3 Degradation experiments

After encountering difficulty in assigning the structure unambiguously based on spectral data, it was decided that degradative experiments should allow one to distinguish between the two possible constitutional isomers **216** and **217**. Standard hydrolysis (*p*-toluenesulfonic acid) was attempted initially, but was not successful as complex mixtures were obtained.

Oxidative cleavage of the olefin would also identify which of the two possible products had been formed. Ozonolysis had proven to be problematic in the previous study<sup>93</sup> (eq. 48), therefore, for the present system RuO<sub>2</sub> was used (Scheme 42). A catalytic amount of RuO<sub>4</sub> with an excess of sodium periodate, which oxidizes the reduced



RuO<sub>2</sub> back to the active RuO<sub>4</sub> catalyst was used.<sup>157,158</sup> If either benzophenone **218** or benzoic acid **220** could be isolated and identified, it would provide excellent evidence for either structure **216** or **217**, respectively. Unfortunately, the reactions consistently produced a complex mixture of products from which neither **218** or **220** could be identified conclusively. Even with access to an authentic sample of each of the expected products nothing could be isolated which compared favourably with the actual material. This somewhat disappointing result led us to attempt an acid-catalyzed transketalization with 2,2-dimethyl-1,3-propanediol.

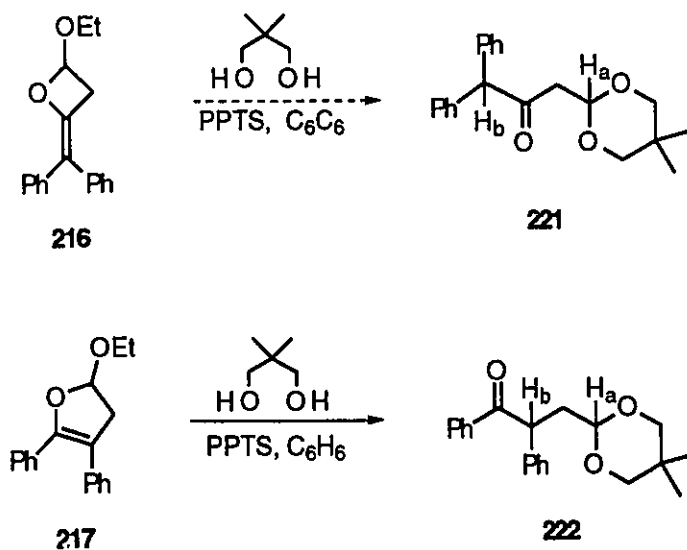


Scheme 42 Expected Results From the Oxidative Degradation of **216** and **217**

#### 3.8.4 Preparation and Identification of 2,2-Dimethyl-1,3-propanediol Trapped Product of Azibenzil Cyclopropanation Reaction

The unidentified material that had been isolated from the attempted cyclopropanation reaction of azibenzil and 2,2-dimethyl-1,3-propanediol was dissolved in benzene and a single crystal of 3-[5-(sulfophenyl)-2-pyridyl]-1,2,4-triazin-5-ylbenzenesulfonic acid, disodium salt (PPTS) was added. The reaction mixture was stirred overnight at 21 °C. Concentration and chromatography of the crude product afforded a single compound in 68% yield that was determined to be **222** (Scheme 43).

The  $^1\text{H}$  NMR spectrum of the protected keto-aldehyde **222** exhibited a characteristic one-proton doublet of doublets (dd) at  $\delta$  4.91 ppm ( $J = 7.8, 7.0$  Hz) that was assigned to the acetal proton  $\text{H}_a$  (Figure 4). The coupling of  $\text{H}_a$  with each of the diastereotopic methylene protons gives rise to the dd pattern observed. A second one-proton doublet of doublets at  $\delta$  4.31 ppm ( $J = 4.9, 5.6$  Hz) was assigned to the methine proton  $\text{H}_b$  adjacent to the carbonyl group. The splitting pattern seen with this signal also



Scheme 43 Transketalization of **216** and **217**

arises from independent couplings with each of the diastereotopic methylene protons  $H_e$  and  $H_f$ . Scheme 43 clearly shows that this type of coupling is only possible in structure **222**. Proton  $H_b$  in structure **221** has no adjacent carbons bearing protons and would therefore be expected to appear as a singlet in the  $^1\text{H}$  NMR spectrum.

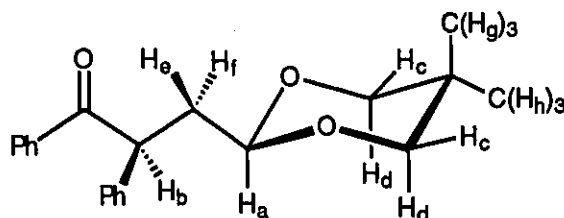


Figure 4 Compound **222**

This information, together with all of the other spectral data which were consistent with the assigned structure, provided unambiguous proof that the dihydrofuran **217** was obtained as the product of the attempted cyclopropanation reaction and not the oxetane as had been suggested previously.<sup>93</sup>

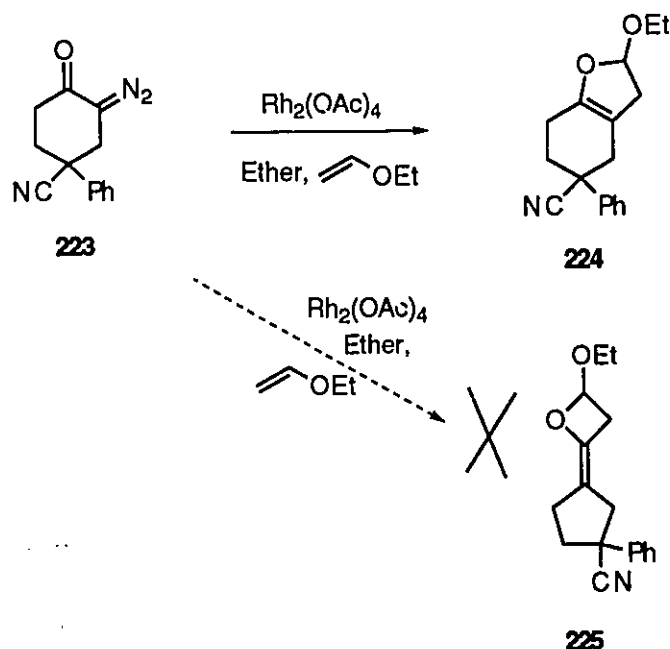
Now that it was firmly established that dihydrofuran **217** was formed in the  $\text{Rh}_2(\text{OAc})_4$ -catalyzed addition of azibenzil and ethyl vinyl ether a new question had to be

posed: Did the fact that dihydrofuran **217** was formed with the model substrate necessarily mean that when **24** was the substrate, that the oxetane **26** was not being formed? As is always the case with models, whether the result is positive or negative one invariably ends up trying it again with "the real thing". This was precisely the path we chose.

### 3.8.5 *Preparation and Identification of 2,2-Dimethyl-1,3-propanediol Transketalization Product of 2-Diazo-4-oxo-1-phenylcyclohexane- carbonitrile 224*

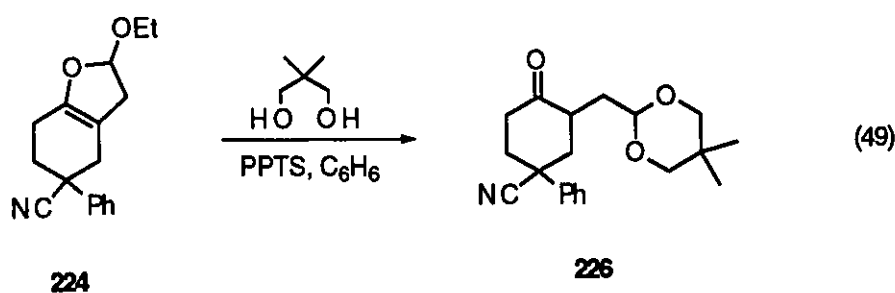
A number of samples had been stored from the previous work that had been done on this project.<sup>93</sup> Fortunately, out of seven samples tested, one compound, **224**, had not completely decomposed. Small amounts of impurities were detected by TLC and GC-MS analyses, however, these were easily removed by passing the sample through a 'Pasteur pipette' column of silica gel.

The sample that was purified was originally prepared from the  $\text{Rh}_2(\text{OAc})_4$  catalyzed reaction of  $\alpha$ -diazoketone **223** and ethyl vinyl ether (Scheme 44). From the results described above, there was good evidence that the oxetane structure **225** that had been assigned to the product was not correct, and that the product was actually dihydrofuran **224**. In order to verify this, transketalization of dihydrofuran **224** was carried out in the same manner as was described above for the model compound (eq. 49).



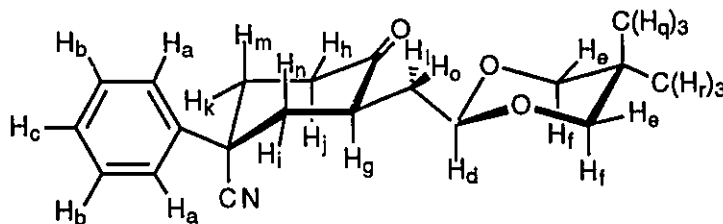
Scheme 44 Preparation of 224

Chromatography of the crude product afforded the protected keto-aldehyde **226** in 56% yield. All of the spectra for compound **226** were recorded immediately. The aromatic, acetal methine, and *gem*-dimethyl protons of compound **226** were readily assigned from the  $^1\text{H}$  NMR spectrum. A single carbonyl signal in the  $^{13}\text{C}$  NMR spectrum at  $\delta$  208.4 as well as the acetal methine carbon signal at 100.1 ppm, clearly indicate that the transketalization had been successful.



$^1\text{H}$ ,  $^{13}\text{C}$ , DEPT,  $^1\text{H}$ - $^1\text{H}$  COSY, and  $^1\text{H}$ - $^1\text{H}$  homonuclear decoupling NMR experiments (500 MHz, see spectra in Appendix II) allowed the complete assignment of all of the carbon and proton signals (Figure 5) of **226**. For example, two separate  $^1\text{H}$ - $^1\text{H}$

homonuclear decoupling experiments established the assignment of the cyclohexanone ring protons together with H<sub>i</sub>, H<sub>o</sub>, and H<sub>d</sub>. Thus, irradiation of the methine proton at  $\delta$  3.24 ppm due to H<sub>g</sub> caused the collapse of the signal at  $\delta$  2.67 Hz due to H<sub>i</sub> to a dd ( $J = 13.6, 3.7$  Hz), and also the signal at  $\delta$  2.32 Hz due to H<sub>i</sub> to a doublet of doublets



226

Figure 5

( $J = 14.3, 3.9$  Hz). Both of the signals at  $\delta$  1.98 (H<sub>n</sub>) and  $\delta$  1.45 ppm (H<sub>o</sub>) also collapsed to a dd with coupling constants of  $J = 13.6, 13.6$  Hz and  $J = 14.3, 5.9$  Hz, respectively. A second irradiation experiment of the acetal methine (H<sub>d</sub>) signal at  $\delta$  4.58 ppm caused the collapse of the signals at  $\delta$  2.32 due to H<sub>i</sub> to a dd ( $J = 14.3, 6.1$  Hz), and at  $\delta$  1.45 due to H<sub>o</sub> to a dd ( $J = 14.3, 5.9$  Hz).

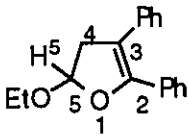
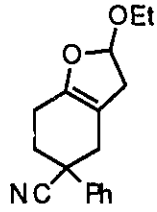
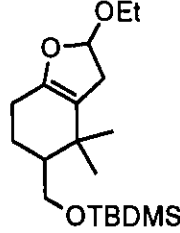
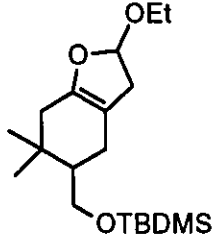
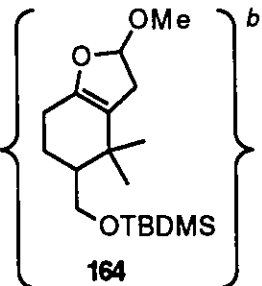
The unambiguous assignment of keto-acetal **226** lead directly to the conclusion that, as with the azibenzil model system, the product isolated from the attempted Rh<sub>2</sub>(OAc)<sub>4</sub> catalyzed cyclopropanation of **223** is dihydrofuran **224** and not oxetane **225**, as was assigned previously. With this unambiguous proof of the structure of **224**, it should now be possible to re-examine the spectral data of all of the suspected oxetanes and establish clearly that they also belong to the family of compounds with the dihydrofuran-type structure.

Table 8 lists all of the available spectral data for the dihydrofuran products that were isolated from attempted cyclopropanation reactions. The characteristic acetal methine signal

at approximately  $\delta$  5.5 ppm in the  $^1\text{H}$  NMR spectrum is apparent for each of the compounds. The olefinic  $^{13}\text{C}$  signals around  $\delta$  148 and 102 ppm are consistent with each compound with the exception of entry 5. All of the other spectral data given for entries 2–4 are also consistent with the assigned dihydrofuran structure. The structures for compounds **163** and **227** (entries 3 and 4) can now be assigned with certainty as those of the dihydrofuran type shown in Table 8, thus answering the original question that was posed at the outset of this project.

Compound **164**, however, shown in entry 5, displays spectral data which are conspicuously different from that given for all of the other dihydrofurans in Table 8. The discrepancy is readily evident when the data are presented in a table such as that given below. It must be kept in mind however, that at the time the original work was being done, the dihydrofuran structure given here was not considered as the most likely structure for compounds **224**, **163**, and **227**. As was described in section 3.4.5, compound **164** was prepared by a separate route in order to provide a direct comparison against the spectral data that had been obtained for the suspected oxetane **26**. The most obvious difference is seen in the  $^{13}\text{C}$  NMR chemical shifts for the olefinic carbons. Replacement of an ethyl ether with a methyl ether that is quite removed from the alkene would not be expected to cause a 9 ppm shift in the signal due to the most upfield olefinic carbon. It was this information that led to the initial assignment of the oxetane-type structures for the products isolated from the attempted  $\text{Rh}_2(\text{OAc})_4$  catalyzed cyclopropanation reactions.

To explain the apparent discrepancies in the NMR chemical shift data, the preparation and assignment of compound **164** was re-investigated.

Entry	Compound <sup>a</sup>	$\delta$ H <sup>5</sup> (ppm)	$\delta$ C <sup>2</sup> (ppm)	$\delta$ C <sup>3</sup> (ppm)
1	 <p style="text-align: center;"><b>217</b></p>	5.62 (dd, $J = 7.2, 2.6$ Hz)	148.2	102.6
2	 <p style="text-align: center;"><b>224</b></p>	5.55 (m)	149.3	102.0
3	 <p style="text-align: center;"><b>163</b></p>	5.45 (m)	148.3	102.4
4	 <p style="text-align: center;"><b>227</b></p>	5.45 (m)	148.3	102.4
5	 <p style="text-align: center;"><b>164</b></p>	5.55	148.2	113.2

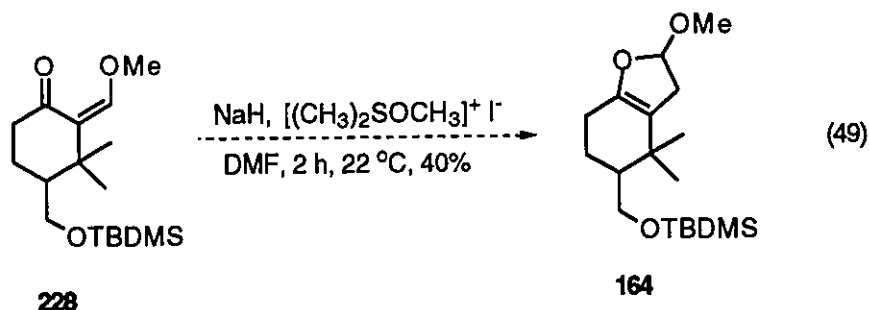
<sup>a</sup> Data from entries 2–4 were taken from reference 93

<sup>b</sup> Tentatively assigned structure taken from reference 93

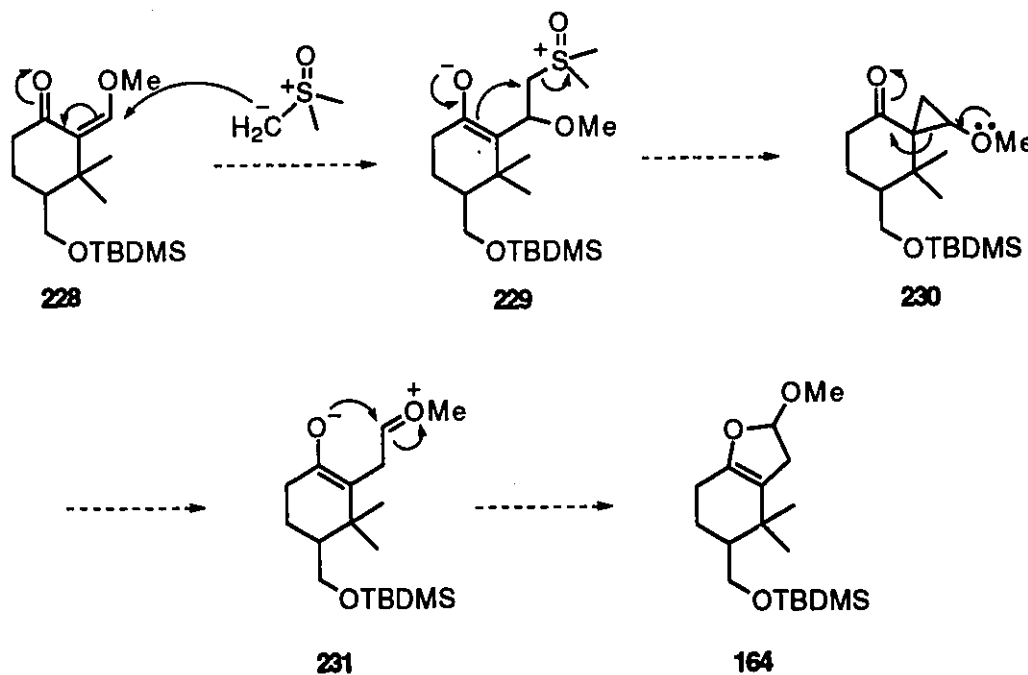
Table 8 Dihydrofuran Spectral Data

### 3.8.6 Re-investigation of the preparation and identification of **164**

Dihydrofuran **164** was reported by Kennedy<sup>93</sup> to have been prepared from keto-enol ether **228** (eq. 49) using a procedure that was developed by Corey and Chaykovsky<sup>159</sup> which entailed the addition of trimethylsulfoxonium iodide to a suspension of sodium hydride and



**228** in THF. It was proposed that **164** was formed as a result of addition of dimethylsulfoxonium methyllide in a Michael fashion to **228** to generate a dipolar intermediate **229** which cyclized to spirocyclopropane **230** before undergoing further rearrangement to dipolar intermediate **231**, and finally to hexahydrobenzofuran **164**.

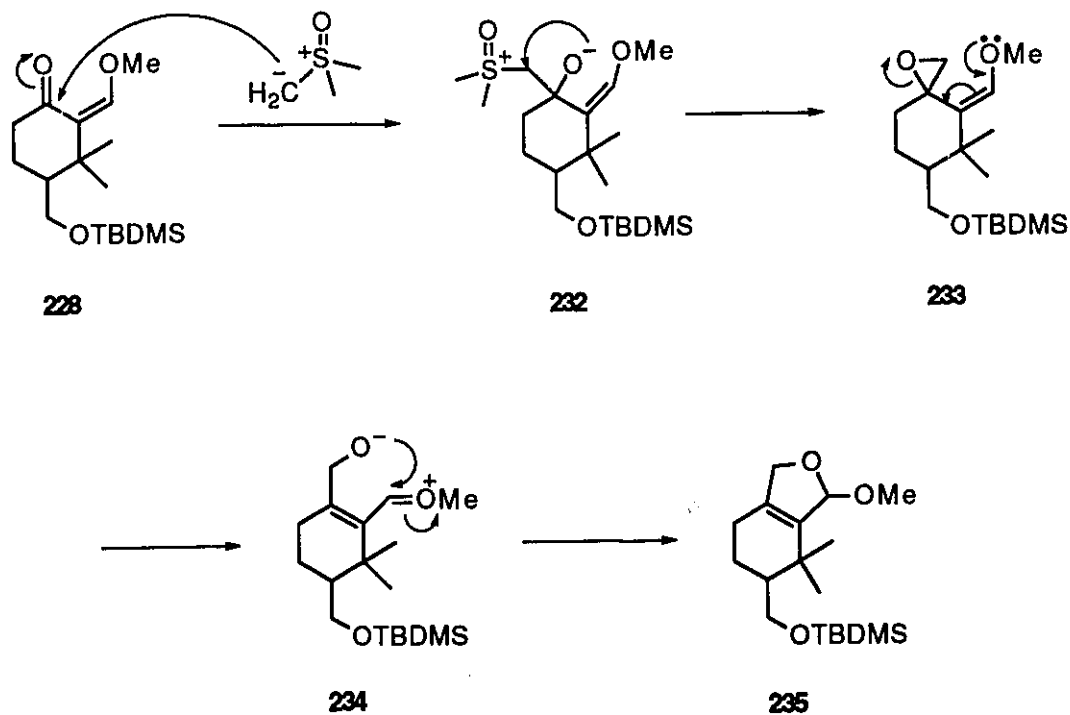


Scheme 45 Proposed Mechanism for the Formation of Dihydrofuran **164**<sup>93</sup>

Comparison of the spectral data for the proposed methyl ester **164** and what was thought to be oxetane **26**, as well as the fact that the hydrolysis of **164** required more drastic conditions than did oxetane **26**, led to the conclusion that the oxetane structure was correct. With the new information gained from this work it is now obvious that the hexahydrobenzofuran was formed and not the oxetane as previously thought, therefore, the explanation for the above transformation was re-examined.

The most common uses of sulfur ylids are the formation of epoxides from ketones and aldehydes, and the cyclopropanation of  $\alpha,\beta$ -unsaturated compounds.<sup>160</sup> Dimethylsulfoxonium methylide is known to attack cyclohexanone derivatives reversibly to give a mixture of stereoisomers that usually contains more of the isomer derived from equatorial attack. This indicates the greater thermodynamic stability of the intermediate in which the  $\text{Me}_2\text{SOCH}_2$  group is in the equatorial position. If one face of the carbonyl is sterically hindered, attack will occur exclusively from the less-hindered side.

When a Michael acceptor is available, such as the olefin of an  $\alpha,\beta$ -unsaturated ketone, attack of the carbanion will usually occur at this site. This was the mode of reaction that was proposed in the previous study (Scheme 45). It appears that little is known on the relative ease of 1,2- versus 1,4- attack if the 4-position is sterically hindered. Presumably it is likely that in this type of situation, such as with compound **228**, 1,2-addition takes precedence if attack at the 4-position is hindered. This type of mechanism (Scheme 46) is proposed as an alternate pathway to the Michael-type addition shown in Scheme 45, and leads to a different, although similar, product **235**. This accounts for the discrepancies that were apparent in the spectral data of the compound assigned structure **164** and leads to a revised structure **235**.



Scheme 46 Alternate Pathway for the Reaction of **228** to Produce **235**

Initial addition of dimethylsulfoxonium methylide to the carbonyl of **228** generates a dipolar intermediate **232**, which undergoes an intramolecular displacement of the positively charged sulfur leaving group with the oxyanion to give oxirane **233**. Ring-opening of **233** to dipolar structure **234**, followed by intramolecular closure of the oxyanion onto the oxonium ion provides ether **235** as the final product.

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals that differed significantly from similar positions on other dihydrofuran-type structures (see Table 8, entry 5), and were therefore not consistent with structure **164**, can now be readily interpreted as belonging to the isomeric structure **235**. The acetal methine proton signal at  $\delta$  5.55 ppm is consistent with an acetal proton that is further deshielded by an olefin in the  $\alpha$  position. The olefinic carbon signals at  $\delta$  104.6 and 148.0 ppm are also consistent with the compound **235**.

The observation that entry 5 in Table 8, which can now be assigned as acetal **235**, was more difficult to hydrolyze than the other dihydrofuran-type structures (entries 1–4,

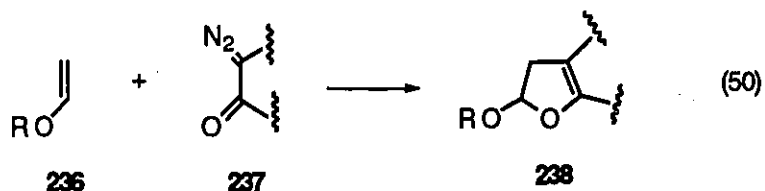
Table 8) is now easily understood as the enol ether acetals **217**, **224**, **163**, and **227** would be expected to hydrolyze more readily than the  $\alpha,\beta$ -unsaturated acetal **235**.

The preparation and identification of what is now identified as acetal **228** had been the key experiment that provided the most convincing piece of data that suggested that the product of the intended cyclopropanation was not the dihydrofuran **163**, but rather the oxetane **26**.<sup>93</sup> Retrospectively it is relatively straightforward to see that the mechanistic interpretation of the dimethylsulfoxonium reaction was incorrect, however, this conclusion was reached with the knowledge that the product of the rhodium-catalyzed reaction is definitely the dihydrofuran. Without this information, it is obvious that any other conclusion must be made only tentatively, thus the earlier conclusion that the sulfoxonium methylene route produced the dihydrofuran and therefore the  $\text{Rh}_2(\text{OAc})_4$  catalyzed reaction did not, was exactly the opposite of the actual outcome.

### 3.8.7 Mechanism of dihydrofuran formation

As was described in section 3.3.2, there is literature precedent and a proposed mechanistic interpretation for the formation of dihydrofuran products in rhodium(II) acetate-catalyzed reactions of  $\alpha$ -diazoketones with vinyl ethers.

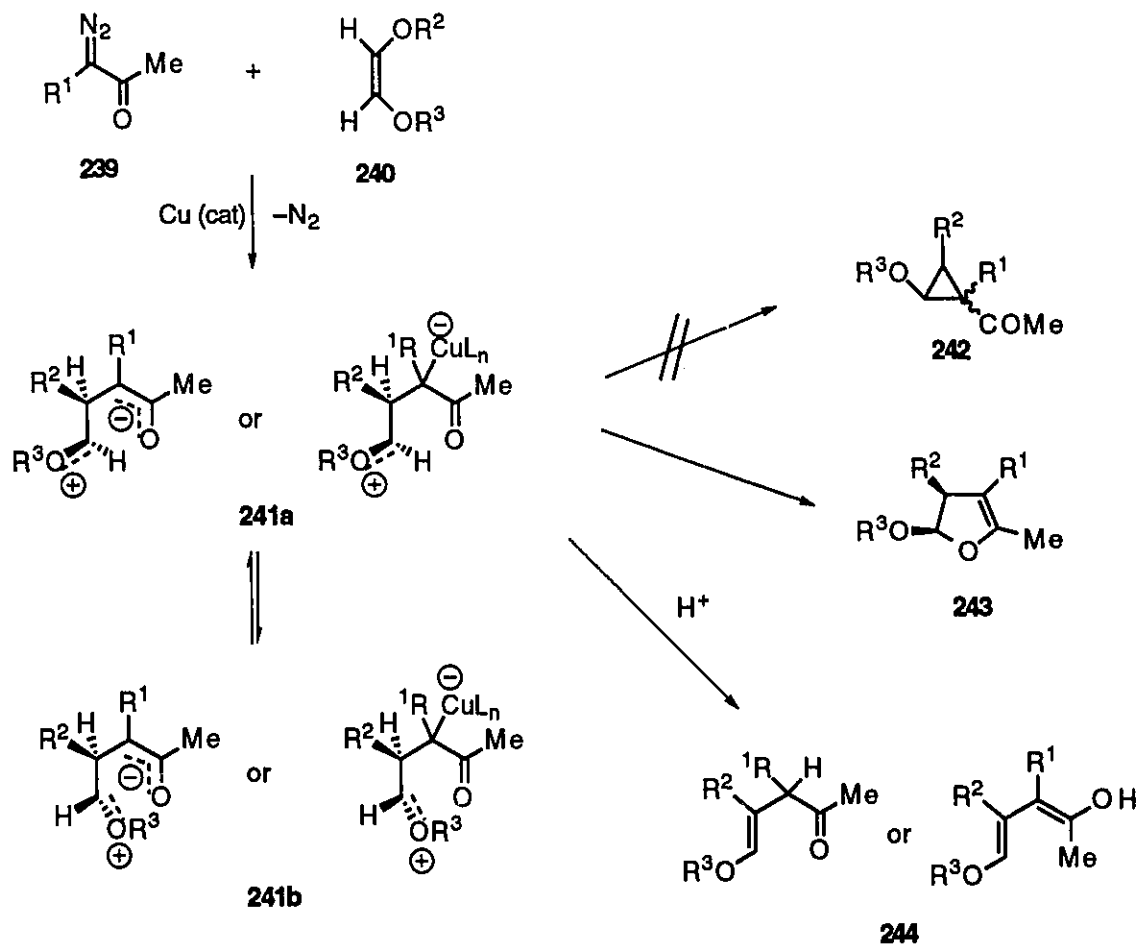
A number of natural products that contain a furan ring have been synthesized using the copper-catalyzed reaction of diazocarbonyl compounds and vinyl ethers.<sup>135-139,161</sup> The formation of dihydrofurans from alkyl vinyl ethers and certain  $\alpha$ -diazocarbonyl compounds is formally a 1,3-dipolar addition reaction (eq. 50).



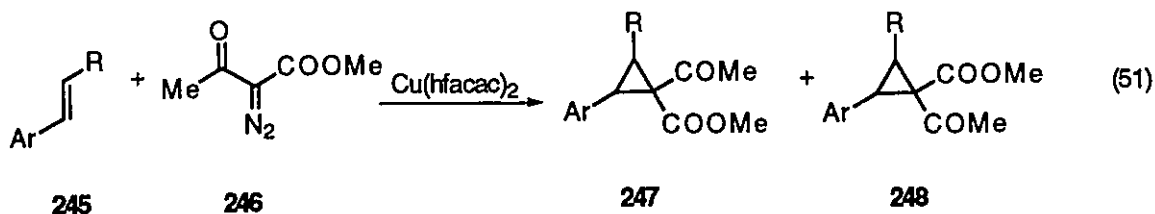
Diazoesters such as diazoacetate do not undergo this transformation, but react to give cyclopropanes exclusively. Other  $\alpha$ -keto diazoesters, however, as well as a number of diazoketones do undergo the dipolar addition reaction preferentially. The only olefins that have been found to add to metal-carbenoids in this fashion are vinyl ethers, including furans.

The formal dipolar cycloaddition has been explained mechanistically in terms of an extension of Doyle's cyclopropanation mechanism (Scheme 26). The increased stabilization that is provided by the carbonyl group to the developing electrophilic centre on the olefin is proposed to alter the reaction course allowing the formation of dihydrofuran products. Vinyl ethers are especially suited to this type of transformation as they allow for greater charge development in the transition state than is possible with other olefins. The preference for ketone carbonyls undergoing this transformation over ester type carbonyls is explained as being due to the increased nucleophilicity of the former.

Alonso and co-workers have also suggested a mechanism to explain the formation of the dihydrofuran and acyclic products that they observed in several attempted cyclopropanation reactions (Scheme 47). They proposed that a dipolar intermediate **234** is the precursor to both the acyclic and dihydrofuran products. In order to obtain dihydrofuran products, 1,3 ring closure must be disfavoured with respect to the 1,5 cyclization. Based on previous work by Alonso<sup>162</sup> which demonstrated that dihydrofurans were formed stereospecifically, it was assumed that the dihydrofuran obtained above (Scheme 47) was also formed stereospecifically. This statement rests on weak ground however, as the isolated yield of **243** was only 21%. If this assumption is correct, stereospecific formation of the dihydrofuran implies that the 1,5 ring closure of dipolar intermediate **241** is distinctly faster than carbon-carbon bond rotation about the former enol ether double bond.

Scheme 47 Alonso's Mechanism for Dihydrofuran Formation<sup>163</sup>

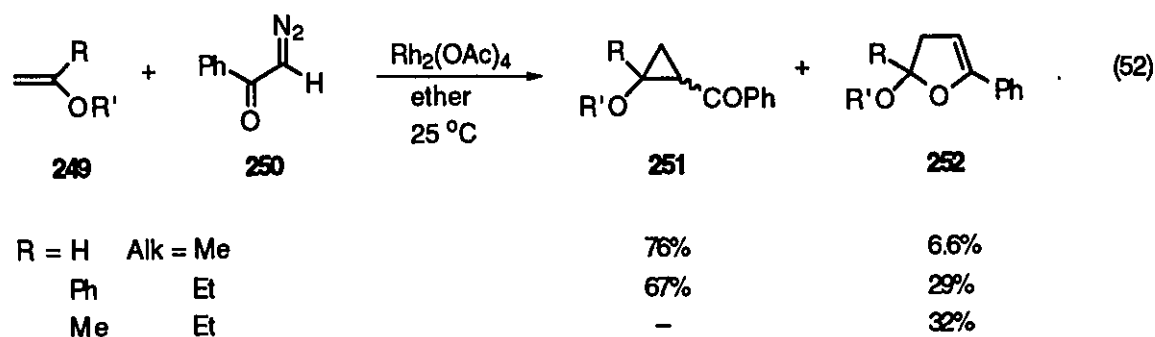
A number of other mechanistic possibilities have been ruled out, although not with complete certainty. In an attempt to determine whether the dihydrofuran is a primary product or whether it arises from rearrangement of a primarily formed, but not isolated cyclopropane, **247** and **248** (eq. 51) were isolated and re-subjected to reaction conditions (refluxing fluorobenzene with or without the copper catalyst).<sup>163</sup> The cyclopropanes did not undergo ring expansion to dihydrofurans and were isolated unchanged.



Pyrolysis of the same cyclopropanes does lead to dihydrofuran products, although the stereochemical information originally contained in the olefin had been lost. The open chain compounds **244** that were obtained in the experiments shown in Scheme 47 were also re-exposed to the reaction conditions and were found not to isomerize to dihydrofurans.

As with Doyle's proposed mechanism, the dipolar intermediate that is suggested by Alonso can be stabilized to a greater or lesser extent depending on the substituents that are present. The extent of stabilization is suggested to be the controlling factor which determines the pathway that any particular substrate will follow.

In both of the mechanisms given, an increase in the nucleophilicity of the enolate oxygen increases the ease of 1,5-cyclization over 1,3-cyclization. An excellent example of this is shown in equation 52.<sup>121</sup> Increasing the nucleophilicity of the olefin oxygen by changing from methyl vinyl ether to 2-ethoxypropene or  $\alpha$ -ethoxystyrene increased the yield of the dihydrofuran product relative to the cyclopropane.

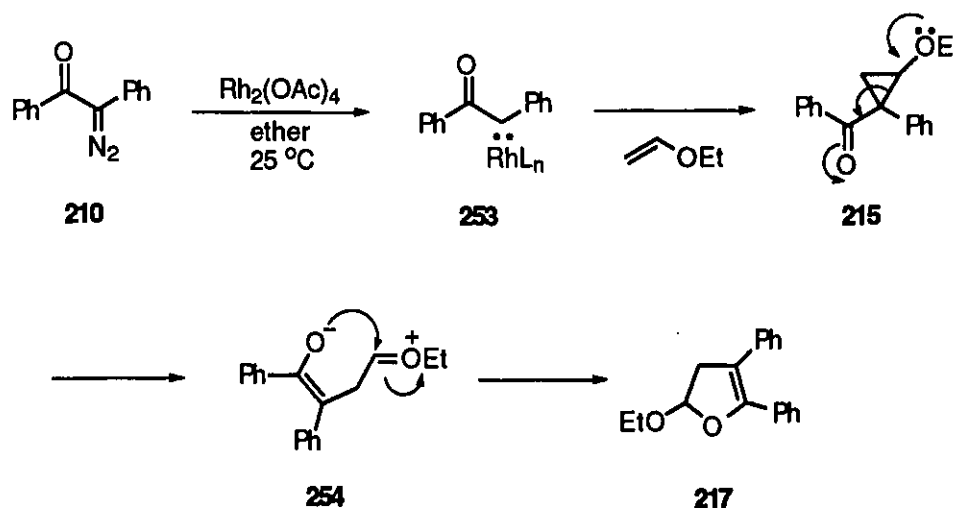


The products obtained were not interconvertible under the reaction conditions and the product ratio was not affected by changes in catalyst concentration or reaction times

(up to 10 h). Although the transformations presented here can be adequately explained using a dipolar intermediate-type mechanism, the hypothesis that dipolar intermediates are in fact involved in the reaction needs to be confirmed.<sup>112</sup>

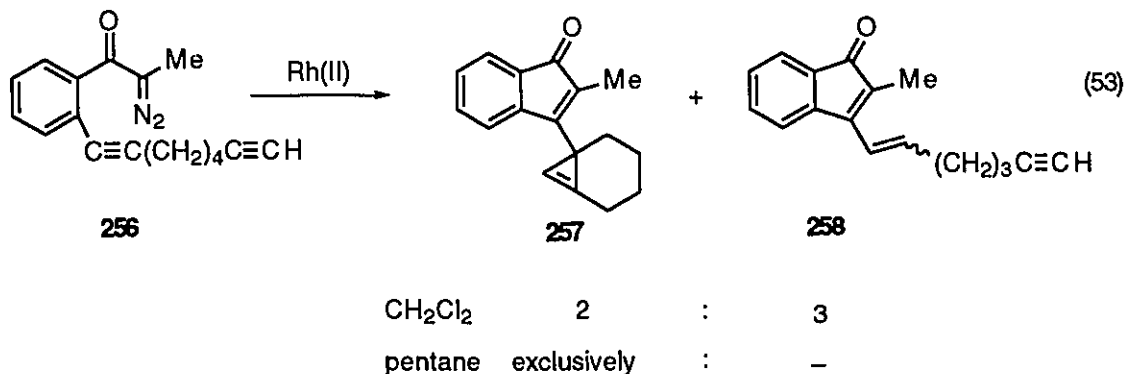
Compound **217** may arise via one of at least two possible mechanistic routes (Schemes 48 and 49). The first possibility is rearrangement of a cyclopropane intermediate **215** to give a dipolar type structure **254** that further cyclizes to dihydrofuran **217** (Scheme 48). The results described above appear to rule out this possibility, as cyclopropanes that were isolated from a reaction did not undergo rearrangement when they were re-exposed to the reaction conditions.

The second possible mechanism for the formation of **217** is shown in Scheme 49. Addition of the vinyl ether with loss of nitrogen produces a dipolar intermediate **248**. It is not known whether a metal-containing species such as **255b** is closer to reality than intermediate **255a**. 1,5-Ring closure of **255a** or **255b** would lead directly to dihydrofuran **217**. The literature data available at this time favours the use of the mechanism shown in Scheme 49 as a working hypothesis for understanding the outcome of the formal cycloaddition reaction leading to dihydrofuran products.



Scheme 48 Mechanism of Dihydrofuran **217** Formation via a Cyclopropane Intermediate

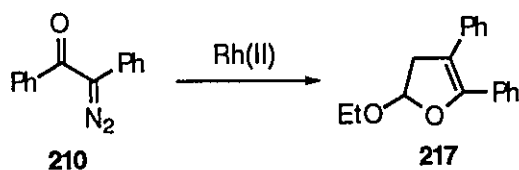




For example, competition experiments<sup>164</sup> between cyclopropanation and insertion into a tertiary C–H bond indicated that with  $\text{Rh}_2(\text{OAc})_4$  as the catalyst, a 44:56 ratio of cyclopropanation to insertion products was obtained. Exchanging the acetate ligands for others that produce a metal carbenoid that is more electrophilic than  $\text{Rh}_2(\text{OAc})_4$  (e.g. perfluoroborate), resulted in formation of hydrogen abstraction products exclusively. In contrast to this, only cyclopropanation products were obtained when rhodium(II) caprolactamate [ $\text{Rh}_2(\text{cap})_4$ ] was used as the catalyst.  $\text{Rh}_2(\text{cap})_4$  produces a metal carbenoid species that is less electrophilic than  $\text{Rh}_2(\text{OAc})_4$ , and it is thought that the insertion into the C–H bond is therefore suppressed by this, whereas addition to the C=C bond has been shown to be relatively unaffected by changes in carbenoid electrophilicity.<sup>164</sup>

The catalyst that has been used most commonly for the enhancement of cyclopropanation products relative to dihydrofuran products is rhodium(II) pivalate [ $\text{Rh}_2(\text{OPiv})_4$ ].<sup>118,165</sup>  $\text{Rh}_2(\text{OPiv})_4$  was prepared in 66% yield according to a related literature procedure for the preparation of  $\text{Rh}_2(\text{OAc})_4$ .<sup>166</sup>

In an attempt to change the selectivity in favour of the cyclopropanation product we carried out a number of experiments under a variety of reaction conditions (Table 9). In each case the dihydrofuran **217** was the major product isolated along with some dihydrofuran decomposition products.



entry	catalyst	solvent	yield <sup>a</sup>
1	Rh <sub>2</sub> (OAc) <sub>4</sub>	ether	97%
2	Rh <sub>2</sub> (OAc) <sub>4</sub>	pentane	91%
3	Rh <sub>2</sub> (OPiv) <sub>4</sub>	ether	94%
4	Rh <sub>2</sub> (OPiv) <sub>4</sub>	pentane	94%

<sup>a</sup> Yields were determined by GC-MS

Table 9 Effect of Catalyst and Solvent on Dihydrofuran **217** Formation

To ensure that the transformation being investigated in this project remains in perspective, it could be pointed out that within the scope of transition metal catalyzed additions of alkenes to diazocarbonyl compounds, the formation of dihydrofuran products is extremely rare. The vast majority of possible alkene/diazocarbonyl combinations produce cyclopropanes in good yields. It is only in the special cases when the "electronics" of both the reacting partners are "tuned" to stabilize a dipolar intermediate that any appreciable amount of dihydrofuran is formed. In fact, of all of the reported examples of dihydrofuran formation, most report the heterocycle as being formed as a minor byproduct.<sup>2,121,139,167,168</sup>

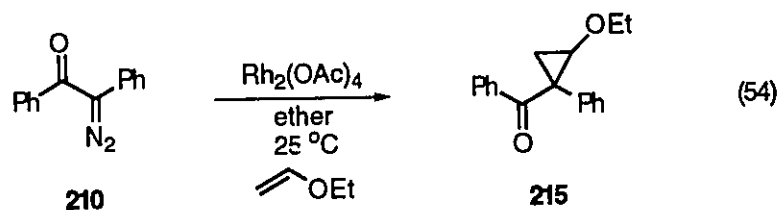
### 3.10 Isolation and Trapping of Cyclopropane (215)

A careful examination of the experimental data surrounding the entire issue of initial cyclopropanation and rearrangement versus direct formation of dihydrofuran reveals a

common theme. All of the dihydrofurans isolated decomposed readily, and if cyclopropanes were also isolated they tended to be extremely labile. Particularly striking are the similar problems that have been encountered by workers such as Dowd<sup>167</sup> who found that  $\text{Rh}_2(\text{OAc})_4$  catalyzed reactions of ketene acetals with methyl diazoacetate yielded cyclopropyl esters that were extremely unstable and could be trapped *in situ* with lithium aluminium hydride in poor yield. When an analogous reaction was performed with diazoacetone, the expected cyclopropyl ketone could not be detected spectroscopically and attempts to trap it failed to yield the alcohol. Dowd concluded that the ketone was too reactive to be isolated and probably rearranged through a dipolar intermediate and in fact a small amount of dihydrofuran was isolated from one reaction.

A second feature common to all of the experimental procedures appeared to be some form of filtration and purification of the reaction products prior to spectroscopy. All of the initial work that we had done on the model azibenzil system also included filtration and purification of the crude reaction mixture. It was felt that if a cyclopropane was indeed being formed, and this was undergoing further rearrangement to the dihydrofuran upon work-up, it might be possible to obtain spectroscopic evidence of its presence in the crude reaction mixture.

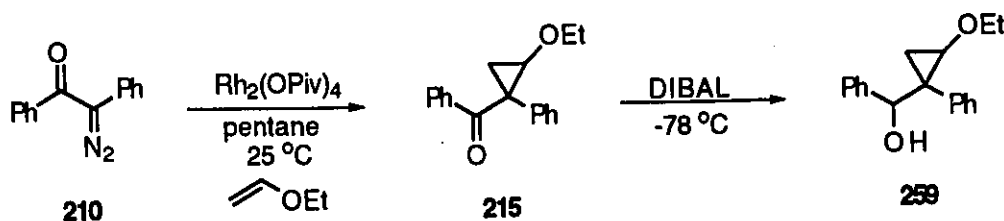
In an attempt to investigate the possibility that the cyclopropanation/rearrangement mechanism shown in Scheme 48 may be operative in the model system studied, attempts were made to isolate or trap the initially formed cyclopropane. The reaction was carried out as usual (both  $\text{Rh}_2(\text{OAc})_4$ /ether and  $\text{Rh}_2(\text{OPiv})_4$ /pentane conditions were used) however, the excess ethyl vinyl ether and diethyl ether were removed under a stream of argon and the crude material was taken up in  $\text{CDCl}_3$  that had been passed through basic alumina immediately prior to use and transferred directly to an NMR tube. The spectra of the crude material did indeed show characteristic cyclopropane signals at  $\delta$  0.6–0.9 ppm in the  $^1\text{H}$  NMR spectrum and at higher field than  $\delta$  16 ppm in the  $^{13}\text{C}$  NMR spectrum. A strong



absorption at  $1675\text{ cm}^{-1}$  in the IR and a signal at  $\delta\ 194.5\text{ ppm}$  in the  $^{13}\text{C}$  NMR spectrum both indicate the presence of a carbonyl group consistent with the expected cyclopropyl ketone **215**. Conjugation with cyclopropane is known to lower the C=O stretching frequency by approximately  $20\text{ cm}^{-1}$ .<sup>169</sup> Additional conjugation with a phenyl ring would be expected to lower the frequency further. All of the other spectral data were consistent with cyclopropyl ketone **215**.

All attempts to purify **215**, other than filtration under an inert atmosphere, resulted in either partial or complete conversion to dihydrofuran **217**. Samples of **215** that were stored at  $-15\text{ }^\circ\text{C}$  were slowly converted into mixtures of dihydrofuran **217** and other decomposition products.

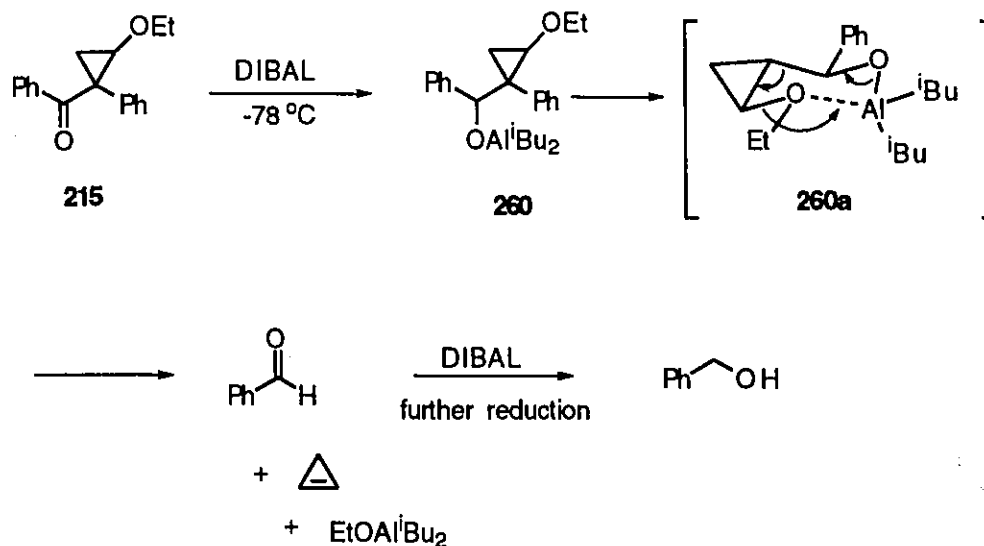
The extremely labile nature of **215** led us to attempt to trap the cyclopropane *in situ* with DIBAL (Scheme 50). The general reaction procedure was followed with the conditions that are considered most likely for the generation of the desired cyclopropane



Scheme 50 Trapping of Cyclopropane **215** with DIBAL

( $\text{Rh}_2(\text{OPiv})_4$  in pentane). The crude reaction was cooled to  $-78\text{ }^\circ\text{C}$  and 2 equivalents of DIBAL were added. TLC analysis of the bright red solution indicated the presence of a new polar spot. GC-MS analysis also indicated a new compound (23%) had been formed

with a mass corresponding to that of cyclopropanol **259** ( $m/z$  268). Aqueous work-up followed by chromatography led only to the isolation of a small amount of dihydrofuran **217** and a small amount of benzyl alcohol which presumably results from a Grob-type fragmentation<sup>170-172</sup> of the intermediate aluminate (Scheme 51).



Scheme 51 Formation of Benzyl Alcohol in DIBAL Reduction of **215**

The results of the trapping experiments together with the previous spectroscopic evidence of the formation of cyclopropane **215** provide excellent evidence that dihydrofuran **217** is not formed by a distinct mechanistic pathway involving a dipolar intermediate, but rather as a result of facile rearrangement of the initially formed cyclopropane.

### 3.11 Conclusion

With the discovery that cyclopropane **215** is formed as the primary product of the rhodium(II) catalyzed addition of ethyl vinyl ether to azibenzil, followed by rearrangement to the now unambiguously assigned dihydrofuran **217**, the initial questions that were raised concerning the identity of the isolated products have been answered. In the process many new questions have arisen, some of which can be understood in terms of the mechanism proposed.

The lack of any significant effect that changing the catalyst and solvent had on the reaction can now be understood in terms of the mechanism shown in Scheme 48. Under all of the reaction conditions used cyclopropane **215** was formed in good yield. Samples of cyclopropane **215** rearranged cleanly to dihydrofuran **217** in the GC-MS. This provides an indication of the efficiency of the cyclopropanation.

With this particular substrate it appears that dihydrofuran **217** is not formed via a mechanistic pathway involving a dipolar intermediate (Scheme 48), but rather as a result of exposure to virtually any type of work-up conditions (including simply being passed through a plug of Celite<sup>®</sup>, or standing at -10 °C). Variation in the polarity of the reaction conditions had no significant effect on the outcome of the reaction, and it is therefore unlikely that a dipolar intermediate is involved in the formation of cyclopropane **215** (as was suggested by Alonso, see Scheme 49). The best mechanistic interpretation for this process is the cyclopropanation mechanism suggested by Doyle that includes the *possibility* of forming a dihydrofuran as a competing primary reaction product, but doesn't go so far as to suggest that the reaction necessarily proceeds through a discrete dipolar intermediate (see section 3.3.2).

Many authors in this area have pointed out the difficulties that arise when a single mechanism is applied to all transition metal-catalyzed decomposition reactions for diazocarbonyl compounds. It is obviously a difficult task to develop a mechanism that will

include all of the various possibilities if one is restricted to just the rhodium(II) acetate-catalyzed cyclopropanation reactions of  $\alpha$ -diazoketones with a variety of olefins.

The fact that much of the literature experimental data reported was not from work done on crude reaction products before the dihydrofuran products were isolated suggests that, as is the case with our model compound, cyclopropanes are frequently formed as the primary reaction products which rearrange to the isolated dihydrofurans upon work-up. This implies that much of the mechanistic work and corresponding conclusions compiled to date should be re-investigated under more controlled neutral conditions.

## EXPERIMENTAL

### General Experimental

Infrared spectra (IR) were obtained either as thin films on sodium chloride or potassium bromide discs, chloroform solutions in potassium bromide solution cells, or as potassium bromide pellets. All IR spectra were recorded on either a Perkin-Elmer 710B scanning spectrophotometer (calibrated with the  $1610\text{ cm}^{-1}$  band of a polystyrene film), a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR)(internal calibration), or a Nicolet 5DX FTIR (internal calibration).

All nuclear magnetic resonance (NMR) spectra were obtained from deuteriochloroform solutions unless otherwise noted. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded at 200 MHz on a Varian Gemini spectrometer, or at 300 MHz on either a Varian XL-300 or Bruker AC300 spectrometer, or at 400 MHz on a Bruker WM 400 spectrometer relative to an internal deuterium lock on the  $\text{CDCl}_3$  signal ( $\delta$  7.25 ppm) of deuteriochloroform. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane ( $\delta$  scale).<sup>85</sup> The multiplicity, number of protons, coupling constants, and assignments (where possible) are indicated in parentheses.

Carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded at 50 MHz on a Varian Gemini spectrometer, or at 75 MHz on either a Varian XL-300 or Bruker AC300 spectrometer, or at 125 MHz on a Bruker WM500 spectrometer relative to an internal deuterium lock on deuteriochloroform ( $\delta$  77.0 ppm). Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane ( $\delta$  scale).

Gas chromatography was performed on a Varian 6000 Gas chromatograph equipped with a 25 m x 0.25 mm i.d. silicone gum capillary column. Gas

chromatography-mass spectroscopy (GC-MS) determinations were performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 25 m polysiloxane coated glass capillary column connected to a Hewlett Packard 5971A mass selective detector. Low resolution mass spectroscopy (MS) using either electron impact (EI), or chemical ionization (CI) mode was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV. High resolution mass spectroscopy (HRMS) (used whenever Exact Mass is quoted) was performed on a Kratos Concept-IIA mass spectrometer with an electron beam energy of 70 eV. All compounds which were characterized by high resolution mass measurements were homogeneous by GC-MS and TLC.

Microanalyses were performed at M-H-W Laboratories, Phoenix, Arizona.

Analytical thin layer chromatography (TLC) was performed on commercial aluminium-backed silica gel plates (E. Merck, type 5554). Visualization was accomplished with ultraviolet light, iodine vapour, and/or heating the plate after immersion in either a 5% solution of ammonium molybdate in 10% aqueous  $\text{H}_2\text{SO}_4$  (w/v) or a 2.5% solution of *p*-anisaldehyde in ethanol containing 3%  $\text{H}_2\text{SO}_4$ . Conventional (drip) and flash column chromatography<sup>173</sup> were performed with E. Merck Silica Gel 60 (70-230 or 230-400 mesh respectively). Radial chromatography was performed on a Harrison Research Chromatotron<sup>®</sup> model 7924T using silica gel (Merck Silica Gel 60, PF<sub>254</sub> containing gypsum) plates of 1, 2, or 4 mm thickness and 10-11 cm radius.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Distillation temperatures are uncorrected and unless otherwise indicated are from Kugelrohr bulb-to-bulb distillations.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry, deoxygenated argon in flame- or oven-dried glassware equipped with a magnetic stirring bar and rubber septa. Standard inert atmosphere techniques were used in handling all air- and/or moisture-sensitive compounds.

## Solvents and Reagents

Petroleum ether refers to a hydrocarbon mixture with a boiling range of 30-60°C. Ether refers to diethyl ether (Et<sub>2</sub>O). Tetrahydrofuran (THF) and diethyl ether were freshly distilled from potassium- and sodium-benzophenone ketyls, respectively. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), benzene, and toluene were freshly distilled from CaH<sub>2</sub>.

Methanol (MeOH), hexamethylphosphoramide (HMPA), triethylamine (Et<sub>3</sub>N), acetonitrile (CH<sub>3</sub>CN) and diisopropylamine (*i*-Pr<sub>2</sub>NH) were distilled from CaH<sub>2</sub> and stored over activated 4Å molecular sieves.

Dimethylformamide (DMF) was dried with activated 4Å molecular sieves. Diiodomethane was passed through a short column (Pasteur pipette) of basic alumina (activity I) immediately prior to use.

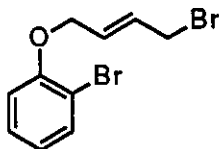
Diiodoethane was purified by dissolving the solid in ether and washing the organic solution with aqueous sodium thiosulfate (saturated). After drying over magnesium sulfate, and concentrating under reduced pressure the white crystals were protected from light (aluminium foil) and placed under vacuum overnight.<sup>174</sup>

Triphenylphosphine was purified by recrystallization from methanol-ethyl acetate.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of *n*-butyllithium in hexanes (1.05 eq) to a cooled (-78 °C) solution of dry diisopropylamine (1.05 eq) in freshly distilled THF. The resulting colourless or slightly yellow solution was stirred at 0 °C for 15 min before use.

All other reagents were commercially available and were used without further purification.

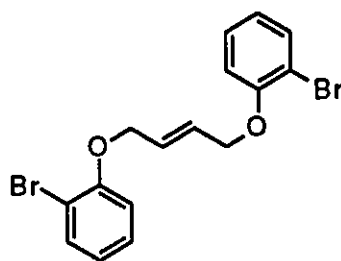
## Chapter 1 Experimental

(E)-1-Bromo-4-(2-bromophenoxy)-2-butene (38)<sup>175</sup>**38**

A solution of *o*-bromophenol (10.0 mL, 86.2 mmol) and *trans*-1,4-dibromo-2-butene (5 mL, 3.42 g, 16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added to a vigorously stirred solution of sodium hydroxide (5.17 g, 129 mmol, 1.5 equiv) and benzyltriethylammonium chloride (8.04 g, 35 mmol, 0.41 equiv) in distilled water (200 mL). After 5 days of stirring at room temperature (21 °C) (TLC analysis indicated that most of the starting material had been consumed; 1 major, 1 minor, and 3 trace products), the aqueous layer had gradually changed from being colourless to light yellow in colour. The aqueous layer was made basic (~ pH 12.0) with NaOH (10% v/v) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic layers were washed with distilled water, brine, dried, filtered, and concentrated to give a thick brownish-yellow oil. Addition of petroleum ether produced a fine beige precipitate which was removed by filtration (Büchner flask), washed with petroleum ether, and dried under vacuum to give 5.14 g (30%) of the bisether **47** as the minor product. Radial chromatography\* (4 mm silica gel plate, eluted with a gradient of 0–5% ethyl acetate in petroleum ether) of the concentrated filtrate successfully separated the remaining compounds. The appropriate middle fractions were combined and concentrated to give 17.90 g (69%) of the alkylated dibromide **38** as a colourless oil that crystallized upon standing.

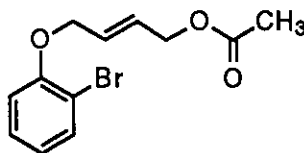
\* In an earlier attempt to prepare compound **38** using standard anion chemistry, (NaH, THF etc.), it was noted that the desired compound has an R<sub>f</sub> value that lies between that of the other reaction products, no matter what solvent system is used. It was, therefore, very difficult to separate **38** from the side-products in the crude reaction mixture using either conventional drip, or flash column chromatography.

**Compound 38:** mp 28–29 °C; IR (KBr): 3063 (w), 2965 (w), 2896(w), 2856 (w), 1586 (s), 1572 (m, sh), 1480 (vs), 1443 (s), 1378 (m), 11300 (s), 1278 (s), 1248 (s), 1028 (s), 968 (s), 749 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.52 (dm, 1H,  $J = 9$  Hz, phenyl  $\underline{\text{C}}\text{H}$ ), 7.23 (tm, 1H,  $J = 8$  Hz, phenyl  $\underline{\text{C}}\text{H}$ ), 6.90–6.68 (m, 2H, 2 x phenyl  $\underline{\text{C}}\text{H}$ ), 6.21–5.84 (m, 2H, 2 x olefin  $\underline{\text{C}}\text{H}$ ), 4.62–4.53 (d, 2H,  $J = 6$  Hz,  $\text{O}\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ) 4.02–3.92 (d, 2H,  $J = 8$  Hz,  $\text{Br}\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  154.6 (phenyl  $=\underline{\text{C}}\text{O}(\text{C})$ ), 133.6, 129.4, 129.2, 128.5, 122.3, 113.5, 112.3, 68.1 ( $\text{O}\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ), 31.8 ( $=\underline{\text{C}}\text{H}\underline{\text{C}}\text{H}_2\text{Br}$ ) ppm; **MS:**  $m/z$  303.9 ( $\text{M}^+$ , 7.7%), 253.9 (1.9%), 251.9 (3.9%), 249.9 (1.9%), 227.0 (4.7%), 225.0 (5.0%), 174.0 (base peak), 172.0 (98.6%), 145.0 (12.4%), 143.0 (13.0%), 135.0 (33.7%), 133.0 (35.2%), 119.0 (4.5%), 117.0 (4.3%); **Exact Mass** calcd for  $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}$  303.9098, found 303.9074.



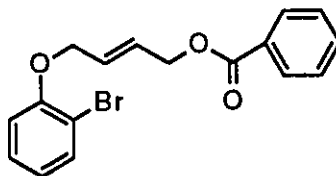
47

**Compound 47:** mp 107–108 °C;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.46 (dm, 2H,  $J = 8$  Hz, phenyl  $\underline{\text{C}}\text{H}$ ), 7.21 (tm, 2H,  $J = 7$  Hz, phenyl  $\underline{\text{C}}\text{H}$ ), 6.90–6.77 (m, 4H, 4 x phenyl  $\underline{\text{C}}\text{H}$ ), 6.17–6.11 (m, 2H, 2 x olefin  $\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ), 4.69–4.55 (m, 4H, 2 x  $\text{O}\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz, DEPT):  $\delta$  154.8 (s, phenyl  $=\underline{\text{C}}\text{O}(\text{C})$ ), 133.4 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 128.4 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 127.6 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 122.1 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 113.6 (d, vinyl  $=\underline{\text{C}}\text{H}$ ), 112.3 (s, phenyl  $\underline{\text{C}}-\text{Br}$ ), 68.6 (t,  $\text{O}\underline{\text{C}}\text{H}_2\text{CH}=\text{}$ ) ppm; **MS:(EI)**  $m/z$  395.9 ( $\text{M}^+$ , 5.3%), 227.0 (46.6%), 226.0 (43.4%), 225.0 (48.4%), 224.0 (42.5%), 174.0 (26.3%), 173.0 (18.8%), 172.0 (26.1%), 171.0 (18.7%), 146.1 (base peak), 145.1 (46.4%), 144.9 (31.6%), 142.9 (32.6%), 131.0 (47.6%), 117.1 (14.5%), 100.2 (14.4%). **Exact Mass** calcd for  $\text{C}_{16}\text{H}_{14}\text{Br}_2\text{O}_2$  395.9360, found 395.9355.

**(E)-1-Acetoxy-4-(2-bromophenoxy)-2-butene (39)****39**

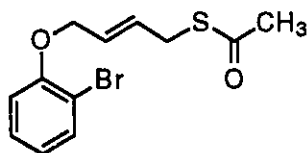
Dibromide **38** (2.00 g, 6.54 mmol) was added to a vigorously stirred slurry of AgOAc (1.64 g, 9.81 mmol) and AcOH (7 mL, glacial) and distilled water (5 mL). The resulting thick white mixture was heated to reflux, and after 30 min a purple-grey precipitate had formed. The reaction was allowed to cool to 21 °C, ice-cold distilled water was added, and the entire mixture was poured into a large flask containing ice-cold NaHCO<sub>3</sub> (10% aqueous solution, 200 mL). The aqueous layer was separated, extracted with ether, and the combined organic extracts were washed with brine, dried, filtered, and concentrated. The crude acetate was subjected to radial chromatography (4 mm silica gel plate, eluted with a gradient of 0-30% ethyl acetate in petroleum ether) and the appropriate fractions were combined, concentrated, and evacuated to give 1.62 g (87%) of **39** as white needles.

Compound **39**: mp 40–41 °C; IR (KBr pellet): 2863 (w), 2921 (m), 1738 (s), 1583 (m), 1479 (s), 1442 (m), 1375 (m), 1250 (s, br), 1084 (m), 1049 (m, sh), 1027 (s), 970 (m, sh), 838 (w), 750 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 7.48 (dm, 1H, *J* = 9 Hz, phenyl CH), 7.17 (tm, 1H, *J* = 7Hz, phenyl CH), 6.86-6.71 (m, 2 x phenyl CH), 5.95-5.89 (m, 2H, 2 x CH<sub>2</sub>CH=), 4.58-4.46 (m, 4H, 2 x CH<sub>2</sub>CH=), 2.02 (s, 3H, CH<sub>3</sub>C=O) ppm; <sup>13</sup>C NMR (50 MHz): 170.6 (C=O), 154.7 (phenyl C-O), 133.3, 128.4, 128.4, 127.1, 122.1, 112.2, 68.4 (OCH<sub>2</sub>CH=), 64.0 (=CHCH<sub>2</sub>O(C=O)), 20.9 (CH<sub>3</sub>(C=O)) ppm; MS: (EI) *m/z* 285.8 (3.0%), 283.8 (M<sup>+</sup>, 3.2%), 197.0 (19.5%), 179.0 (18.8%), 173.9 (81.0%), 171.9 (84.1%), 152.0 (12.3%), 150.9 (17.0%), 144.9 (18.7%), 142.9 (17.8%), 131.0 (11.7%), 123.0 (26.9%), 114.0 (26.9%), 113.0 (base peak), 108.9 (13.8%), 92.0 (10.3%), 88.0 (12.4%), 80.9 (10.8%), 71.0 (88.2%), 38.9 (45.3%); **Exact Mass** calcd for C<sub>12</sub>H<sub>13</sub>BrO<sub>3</sub> 284.0048, found 284.0030.

**(E)-1-Benzoyloxy-4-(2-bromophenoxy)-2-butene (40)****40**

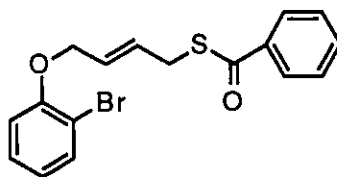
Dibromide **38** (1.00 g, 3.27 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) and added to a vigorously stirred solution of NaOH (0.118 g, 4.91 mmol, 1.5 equiv) and benzyl tri-*n*-butyl ammonium bromide (0.478 g, 1.34 mmol, 0.41 equiv), and benzoic acid (0.400 g, 3.27 mmol) in distilled water (30 mL). After stirring the mixture at 21 °C for 4.75 days, the layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). The organic extracts were combined, dried, filtered, and concentrated. Radial chromatography (4 mm silica gel plate, eluted with 5% ethyl acetate in petroleum ether containing 0.4% MeOH) of the crude bromobenzoate provided 0.620 g of **40** as a white solid.

**Compound 40:** mp 59-61 °C; IR (KBr pellet): 3050 (w), 2941 (w), 2863 (w), 1721 (s), 1586 (m), 1486 (s), 1452 (m), 1273 (s), 763 (s), 719 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  8.06 (dm, 2H,  $J = 8$  Hz, 2 x phenyl CH), 7.65-7.30 (m, 4H, 4 x phenyl CH), 7.29-7.06 (m, 1H phenyl CH), 6.96-6.67 (m, 2H, 2 x phenyl CH), 6.24-5.87 (m, 2H, 2 x  $\text{CH}_2\text{CH}=\text{}$ ), 4.87 (d, 2H,  $J = 6$  Hz,  $\text{Ph}(\text{C}=\text{O})\text{OCH}_2\text{CH}=\text{}$ ), 4.61 (d, 2H,  $J = 4$  Hz,  $\text{PhOCH}_2\text{CH}=\text{}$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz, DEPT): 166.2 (s,  $\text{C}=\text{O}$ ), 154.8 (s, phenyl  $\text{C}-\text{O}$ ), 133.4 (d), 133.1 (d), 130.0 (s, phenyl  $\text{C}(\text{C}=\text{O})$ ), 129.7 (d), 128.5 (d), 128.4 (d), 127.3 (d), 122.2 (d), 113.6 (d), 112.3 (s, phenyl  $\text{CBr}$ ), 68.5 ( $\text{OCH}_2\text{CH}=\text{}$ ) 64.5 ( $=\text{CHCH}_2\text{O}(\text{C}=\text{O})$ ) ppm; MS: (EI)  $m/z$  345.8 ( $\text{M}^+$ , 0.9%), 254.9 (3.8%), 252.9 (3.1%), 176.0 (41.6%), 175.0 (base peak), 145.0 (17.0%), 142.9 (15.9%), 131.0 (10.8%), 106.0 (74.2%), 105.0 (98.5%), 78.0 (15.9%), 77.1 (100%), 76.1 (15.3%), 64.1 (14.6%), 63.0 (16.6%), 54.1 (56.1%), 53.1 (29.4%), 50.9 (42.4%), 40.9 (13.6%), 38.9 (37.5%); Exact Mass calcd for  $\text{C}_{17}\text{H}_{15}\text{BrO}_3$  346.0205, found 346.0210.

**(E)-2-Oxo-3-thio-7-(2-bromophenoxy)-5-heptene (41)****41**

Sodium hydride (0.107 g, 3.59 mmol, 1.1equiv, 80% dispersion in mineral oil, Aldrich) was added to a flask (250 mL, round bottom) equipped with a dropping funnel and a cooling bath. The NaH was washed with *n*-pentane (3 x 2 mL), dried under a stream of nitrogen, THF (50 mL) was added, and the mixture cooled to 0 °C. A solution of thiolacetic acid (0.257mL, 0.273 g, 3.59 mmol) in dry THF (50 mL) was added dropwise so that a smooth, continuous evolution of H<sub>2</sub> was maintained. The mixture was allowed to stir for an additional 15 min after the evolution of H<sub>2</sub> had ceased. Dibromide **38** (1.00 g, 3.27 mmol) was added to the pale yellow reaction mixture in one portion. After stirring for 30 min, saturated aqueous NH<sub>4</sub>Cl (50 mL) was added carefully. The aqueous layer was separated, extracted with ether, and the combined ethereal extracts were washed with brine, dried, filtered, and concentrated. Radial chromatography (4 mm silica gel plate, eluted with petroleum ether) of the crude thiolester afforded, after concentration, 0.87 g (89%) of **41** as a light yellow oil.

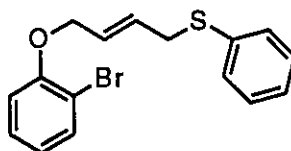
Compound **41**: <sup>1</sup>H NMR (200 MHz): δ 7.51 (dm, 1H, *J* = 7 Hz, phenyl CH), 7.22 (tm, 1H, *J* = 8 Hz, phenyl CH), 6.88-6.75 (m, 2H, 2 x phenyl CH), 4.51(d, 2H, *J* = 3 Hz, SCH<sub>2</sub>CH=), 3.53 (d, 2H, *J* = 7 Hz, OCH<sub>2</sub>CH=) 2.29 (s, 3H, CH<sub>3</sub>C=O) ppm; <sup>13</sup>C NMR (50 MHz): 194.9 (C=O), 154.8 (phenyl C-O), 133.4, 128.6, 128.4, 127.9, 122.1, 113.6, 112.3 (phenyl C-Br), 68.7 (OCH<sub>2</sub>CH=), 30.8 (=CHCH<sub>2</sub>S(C=O)), 30.6 (CH<sub>3</sub>C=O) ppm; MS: (EI) *m/z* 216.0 (27.6%), 214.0 (27.3%), 174.0 (99.1%), 171.8 (99.0%), 156.9 (13.5%), 154.9 (13.6%), 145.0 (55.3%), 142.9 (52.3%), 129.0 (97.1%), 118.9 (13.5%), 117.0 (13.4%), 87.1 (97.9%), 85.1 (99.3%), 63.1 (56.3%), 54.1 (69.5%), 53.1 (base peak), 45.1 (99.9%), 43.0 (90.0%), 38.9 (93.1%), 27.2 (49.6%).

**(E)-1-Phenyl-1-oxo-2-thio-6-(2-bromophenoxy)-4-hexene (42)****42**

Thiobenzoate **42** was prepared using the same conditions as described above in the preparation of thiolester **41**. The scale was the same with respect to dibromide **38** (1.00 g, 3.27 mmol) but in this case thiobenzoic acid (0.423 mL, 0.496 g, 3.59 mmol) was deprotonated at 0 °C with NaH, resulting in the formation of a bright yellow solution. The work-up and separation were performed as described above for **41**. After purification by radial chromatography, 0.62 g (52%) of **42** was obtained as white needles.\*

Compound **42**: mp 32-34 °C; IR (KBr): 3062 (w), 2916 (w), 1662 (s,  $\nu(\text{C}=\text{O})$ ), 1584 (m), 1478 (s), 1445 (m), 1277 (m), 1206 (s), 1030 (m), 913 (s), 749 (m), 689 (s), 648 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.95 (dm, 2H,  $J = 8$  Hz, 2 x phenyl CH), 7.61-7.13 (m, 5H, 5 x phenyl CH), 6.88-6.73 (m, 2H, 2 x phenyl CH), 6.02-5.93 (m, 2H, 2 x  $\text{CH}_2\text{CH}=\text{}$ ), 4.55 (d, 2H,  $J=3$  Hz,  $\text{OCH}_2\text{CH}=\text{}$ ), 3.75 (d, 2H,  $J = 6$  Hz,  $=\text{CHCH}_2\text{S}(\text{C}=\text{O})$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz): 191.5 ( $\text{C}=\text{O}$ ), 154.8 (phenyl  $\text{C}-\text{O}$ ), 136.7 (phenyl  $\text{C}(\text{C}=\text{O})$ ), 133.5, 133.4, 128.7, 128.5, 128.4, 128.3, 127.3, 122.1, 113.6, 112.3 (phenyl  $\text{CBr}$ ), 68.7 ( $\text{OCH}_2\text{CH}=\text{}$ ), 30.7 ( $=\text{CHCH}_2\text{S}(\text{C}=\text{O})$ ) ppm; MS: (EI)  $m/z$  191.0 (7.4%), 174.0 (36.1%), 171.9 (37.4%), 145.0 (4.4%), 142.9 (4.5%), 105.1 (base peak) 77.0 (72.4%), 63.1 (10.5%), 53.1 (35.2%), 50.9 (33.0%), 39.0 (16.4%), 27.2 (12.0%).

\* Unlike the methyl thioester **41**, thiobenzoate **42** was not stable to chromatography and slowly decomposed on the silica gel plates. Four compounds were obtained after chromatography although the initial TLC of the crude product showed one major spot and one very small second spot. The isolated yield obtained also reflects this fact as the crude yield for the reaction before chromatography was 0.86 g (72%).

**(E)-1-Thiophenoxy-4-(2-bromophenoxy)-2-butene (43)****43**

Thiophenol **43** was prepared using the same conditions as described above in the preparation of thioester **41**. The scale was the same with respect to dibromide **38** (1.00 g, 3.27 mmol) but in this case thiophenol (0.336 mL, 0.360 g, 3.27 mmol) was deprotonated at 0 °C with NaH, resulting in the formation of a white precipitate. The work-up and separation were performed as described for **41**. Radial chromatography provided 0.88 g (80%) of **43** as a colourless oil.

**Compound 43:** IR (film, NaCl): 3061 (m), 2920 (w), 1582 (s), 1478 (vs), 1440 (s), 1279 (s), 1240 (s), 1126 (m), 1030 (s), 966 (m), 744 (vs), 691 (m), 663 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.53 (dm, 2H,  $J = 8$  Hz, 2 x phenyl CH), 7.38-7.14 (m, 5H, 5 x phenyl CH), 6.87-6.72 (m, 2H, 2 x phenyl CH), 6.04-5.65 (m, 2H, 2 x  $\text{CH}_2\text{CH}=\text{O}$ ), 4.48 (d, 2H,  $J = 5$  Hz,  $\text{OCH}_2\text{CH}=\text{O}$ ), 3.56 (d, 2H,  $J = 8$  Hz,  $=\text{CHCH}_2\text{SPh}$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz): 154.8 (phenyl C-O), 135.6 (phenyl C-S), 133.4, 130.1, 129.2, 128.9, 128.4, 127.6, 126.4, 122.0, 113.6, 112.3 (phenyl C-Br), 68.7 ( $\text{OCH}_2\text{CH}=\text{O}$ ), 36.0 ( $=\text{CHCH}_2\text{SPh}$ ) ppm; MS: (EI)  $m/z$  335.9 (1.8%), 333.9 (1.9%), 163.0 (base peak), 135.0 (47.2%), 130.0 (32.0%), 129.0 (11%), 108.9 (43%), 86.0 (56.1%), 84.0 (84.1%), 65.1 (23.1%), 53.1 (11.8%), 48.9 (15.5%), 47.0 (24.8%), 39.0 (15.4%), 28.1 (16.1%); Exact Mass calcd for  $\text{C}_{16}\text{H}_{15}\text{BrOS}$  334.0027, found 334.0035.

## **Radical Cyclizations of Substituted Bromoalkenes**

### *Procedure A: Tin hydride*

A solution of the substituted bromide in freshly distilled benzene containing a catalytic amount of AIBN (~3 mg) was degassed either by bubbling argon through the solution for 15 min or performing three freeze-pump-thaw cycles. The solution was heated to reflux, *n*-Bu<sub>3</sub>SnH (2 equiv) was added and heating was continued for a further 4 hours. The mixture was allowed to cool and concentrated under reduced pressure. The crude product was taken up in ether and the tin residue removed by extraction with an aqueous solution of KF (10%). The ethereal solution was washed with brine, dried, filtered, and concentrated, the resulting crude product was purified as described below.

### *Procedure B: Tris(trimethylsilyl)silane*

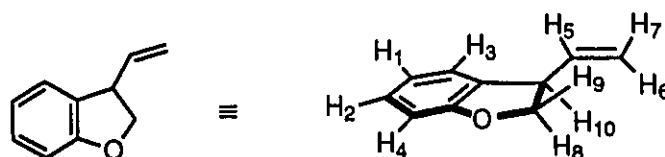
A solution of the substituted bromoalkene in freshly distilled benzene was degassed either by bubbling argon through it for 15-20 min, or performing three freeze-pump-thaw cycles. A catalytic amount of AIBN (~4 mg) and TTMSS were added and the solution was heated at reflux for 4 h. The reaction was cooled to room temperature, the solvent removed under reduced pressure, and ether (50 mL) was added. The ether was washed with water and brine, and dried. After filtration and concentration, the crude products were purified by column chromatography.

### *Procedure c: Samarium diiodide*

The substituted bromoalkene, freshly distilled THF (50 mL), and HMPA (500  $\mu$ L, 2.9 mmol) were added to a Schlenk flask (150 mL) and the mixture was degassed using

three freeze-pump-thaw cycles. Samarium diiodide (6 mL, 0.600 mmol, 3.6 equiv, 0.1 M in THF) was added in one portion and the resulting deep-purple solution was allowed to stir at 21 °C until GC-MS analysis indicated that no starting material remained. After quenching the reaction with saturated aqueous NaHCO<sub>3</sub> (10 mL), the aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub>, distilled water, and brine, dried, concentrated, and purified by chromatography.

**3-Vinyl-2,3-dihydrobenzofuran (52)**



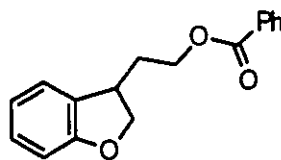
**52**

Following the general procedures outlined above, compounds **39** to **43** produced **52** in varying yields (see discussion) as a colourless oil.

**Compound 52:** IR (film, NaCl): 3061 (w), 2925 (m), 2852 (w), 1738 (s), 1586 (w), 1479 (s), 1442 (w), 1374 (m), 1242 (s), 1083 (w), 1030 (m), 969 (w, sh), 969 (w), 751 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 7.12 (dm, 2H,  $J_{1,2} = J_{2,1} = 7$  Hz, H<sub>1</sub> and H<sub>2</sub>), 6.95-6.75 (m, 2H, H<sub>3</sub> and H<sub>4</sub>), 5.94 (ddd, 1H,  $J_{5,6} = 17.1$  Hz,  $J_{5,7} = 9.4$  Hz,  $J_{5,10} = 8.4$  Hz, H<sub>5</sub>), 5.22 (dm, 1H,  $J_{6,5} = 17.1$ , H<sub>6</sub>), 5.16 (dm, 1H,  $J_{7,5} = 9.4$  Hz, H<sub>7</sub>), 4.71 (dd, 1H,  $J_{8,9} = 8.4$  Hz,  $J_{8,10} = 8.4$  Hz, H<sub>8</sub>), 4.24 (dd, 1H,  $J_{9,8} = 8.4$  Hz,  $J_{9,10} = 8.4$  Hz, H<sub>9</sub>), 4.11 (ddd, 1H,  $J_{10,5} = 8.4$  Hz,  $J_{10,8} = 8.4$  Hz,  $J_{10,9} = 8.4$  Hz) ppm; <sup>13</sup>C NMR (50 MHz): 159.5 (phenyl C-O), 137.9, 134.7, 128.5, 128.3, 125.6, 124.9, 120.6, 116.6, 109.6, 76.2, 47.0 ppm; MS: (EI) *m/z* 146.0 (2.0%), 145.1 (2.3%), 141.0 (3.3%), 129.0 (6.8%), 123.1

(7.0%), 113.1 (9.5%), 111.0 (12%), 109.0 (10%), 105.1 (13%), 97.1 (20%), 95.1 (15%), 85.1 (26%), 83.1 (24%), 81.0 (17%), 71.0 (43.9%), 69.9 (17%), 69.0 (35%), 67.1 (13%), 57.1 (75%), 56.2 (17%), 55.2 (45%), 43.1 (base peak), 41.0 (41%), 29.0 (20%); Exact Mass calcd for C<sub>10</sub>H<sub>10</sub>O 146.0732, found 146.0735.

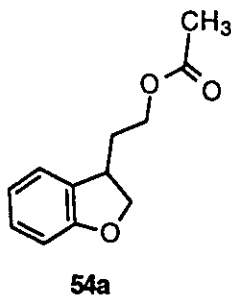
**3-(2-Benzoyloxyethyl)-2,3-dihydrofuran (54b)**



**54b**

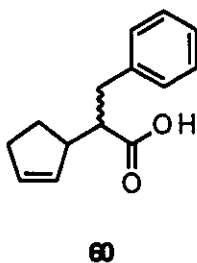
Compound **54b** was obtained as a white solid from compound **40** using procedures A and B that are described above (see discussion for details).

Compound **54b**: IR (film, NaCl): 3056 (w), 3027 (w), 2909 (s), 1722 (m), 1598 (m), 1482 (m), 1459 (s), 1416 (m), 1377 (m), 1277 (s), 1152 (w), 1075 (m), 1016 (m), 961 (m), 872 (m), 749 (m), 685 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 8.03 (dm, 2H, *J* = 7.2 Hz, 2 x phenyl CH), 7.54-7.37 (m, 3H, 3 x phenyl CH), 7.25-7.06 (m, 2H, 2 x phenyl CH), 6.89-6.75 (m, 2H, 2 x phenyl CH), 4.67 (dd, 1H, *J*" = 8 Hz, *J*' = 8 Hz, C(H')(H'')OAr), 4.53-4.20 (m, 3H, CH<sub>2</sub>OBz and C(H')(H'')OAr), 3.68-3.51 (m, 1H, OCH<sub>2</sub>CHAr), 2.32-1.90 (m 2H, CHCH<sub>2</sub>CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (50 MHz): δ 166.2 (C=O), 133.5 (phenyl C-O), 130.0 (2 x phenyl CH), 128.4, 128.9 (2 x phenyl CH), 124.8, 122.0, 110.2, 77.2 (OCH<sub>2</sub>CH), 63.4 (CH<sub>2</sub>CH<sub>2</sub>O(CO)Ph), 39.9 (OCH<sub>2</sub>CH), 34.2 (CHCH<sub>2</sub>CH<sub>2</sub>) ppm.

**3-(2-Acetoxyethyl)-2,3-dihydrofuran (54a)**

Compound **54a** was obtained as a colourless oil from compound **39** using procedure A (described above). See the discussion for details.

Compound **54a**:  $^1\text{H NMR}$  (200 MHz):  $\delta$  7.18-7.02 (m, 2H, 2 x phenyl CH), 6.89-6.71 (m, 2H, 2 x phenyl CH), 4.60 (t, 1H,  $J = 11$  Hz, OC(H')(H'')CH), 4.30-4.01 (m, 3H, OC(H')(H'')CH and CH<sub>2</sub>CH<sub>2</sub>O), 3.58-3.35 (m, 1H, OCH<sub>2</sub>CH), 2.18-1.75 (m 2H, CHCH<sub>2</sub>CH<sub>2</sub>), 2.01 (s, 3H, CH<sub>3</sub>(C=O)) ppm.

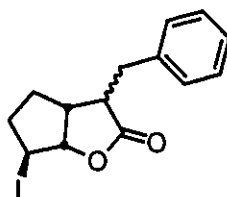
**2-Benzyl-2-(3-cyclopentyl)acetic acid (60)**

A solution of 2-(3-cyclopentenyl)acetic acid (0.603 mL, 0.630 g, 5.00 mmol) in dry THF (5 mL) was added to a stirred suspension of NaH (0.150 g, 5.00 mmol, prewashed with pentane 3 x 3 mL) in dry THF (10mL). The reaction was heated at reflux for 10 min before it was cooled to 0 °C and LDA (5.00 mmol in THF (10 mL), see general experimental for preparation) was added slowly. The resulting thick white mixture was

stirred at 40 °C for 30 min, cooled to room temperature (21 °C), and a solution of benzyl bromide (0.595 mL, 0.855 g, 5.00 mmol) in THF (5 mL) was added in one portion. The reaction was stirred at 50 °C for 4 h and room temperature (21 °C) for 1 h. Saturated aqueous NH<sub>4</sub>Cl was added and the solution was extracted with ether (10 mL). The aqueous layer was acidified (pH 5) with HCl (10% aqueous), extracted with ether (3 x 15 mL), and the combined ethereal extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated to give 1.04 g of a canary-yellow oil. Column chromatography (silica gel, 1.5 cm x 30 cm, eluted with 2:1 ethyl acetate/petroleum ether) provided 89 mg (88%) of **60** as a 2.3:1 mixture of diastereomers.

**Compound 60:** IR (film, NaCl): 3400-2450 (s, br  $\nu$ (O-H)), 3080 (m), 3039 (s), 2937 (s), 2853 (s), 1704 (vs,  $\nu$ (C=O)), 1495, 1438 (m), 1288 (m), 1247 (m), 927 (w), 700 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  11.9-11.5 (s, br, 1H, -COOH), 7.35-7.15 (m, 5H, 5 x phenyl CH), 5.92-5.84 (m, 1H, =CH), 5.83-5.74 (m) and 5.72-5.63 (m)(1H total; 1:2.3 ratio respectively, =CH), 3.14-2.78 (m, 3H, PhCH<sub>2</sub> and CH(C=O)), 2.74-2.57 (m, 1H, C=CHCH), 2.46-2.30 (m, 2H, =CHCH<sub>2</sub>), 2.23-1.99 (m, 1H, -CH<sub>2</sub>C(H<sub>a</sub>)(H<sub>a'</sub>)CH-), 1.84-1.60 (m, 1H, -CH<sub>2</sub>C(H<sub>a</sub>)(H<sub>a'</sub>)CH-) ppm; <sup>13</sup>C NMR (50 MHz):  $\delta$  (signals for each diastereomer given in brackets) (181.6, 181.5), (139.5, 139.4), (132.8, 132.6), (131.8, 131.5), 128.9, 128.5, 126.4, (52.4, 52.3), (48.0, 47.9), (35.9, 35.6), (32.0, 31.7), (27.2, 27.0) ppm; MS: (EI) *m/z* 216.1 (5.5%), 150.0 (14%), (126.0 (M-Bn, 6.3%), 107.0 (6.0%), 91.0 (53%), 79.0 (16%), 67.1 (base peak), 65.1 (19%), 53.1 (3.3%), 40.9 (25%), 39.0 (12%), 28.1 (13%); Exact Mass calcd for C<sub>14</sub>H<sub>16</sub>O<sub>2</sub> 216.1150, found 216.1152.

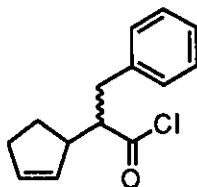
**endo- and exo-4-Benzyl-exo-8-iodo-3-oxo-2-oxabicyclo**  
**[3.3.0]octane (62)**



62

Compound **60** (0.304 g, 1.21 mmol) in dry THF (5 mL) was added to NaHCO<sub>3</sub> (15 mL, 0.5 M aqueous solution) and warmed gently until the solution became transparent. A solution of iodine (0.615 g, 2.42 mmol) and potassium iodide (1.21 g, 7.26 mmol) in distilled water (10 mL) was added to the flask which was stoppered and stirred in the dark for 4 days. Methylene chloride (20 mL) was added to the reaction and the contents of the flask were transferred to a separatory funnel. The reaction was washed with sodium thiosulfate (10 mL, 20% aqueous solution) and the organic layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give 0.39 g of crude product. Column chromatography (silica gel, 1.5 cm x 20 cm, eluted with CH<sub>2</sub>Cl<sub>2</sub>) provided 339 mg (82%) of **62** as a (1:1) mixture of epimers (pale yellow oil).

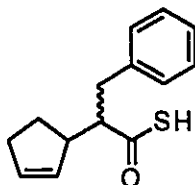
Compound **62**: IR (film, NaCl): 3026 (w), 1697 (s, ν(C=O)), 1603 (w), 1495 (m), 1027 (m), 701 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ (1:1 mixture of epimers) 7.42-7.02 (m, 5H, 5 x phenyl CH), 4.18-3.90 (m, 1H), 3.41-3.04 (m, 2H), 2.93-2.40 (m, 3H), 2.38-1.20 (m, 4H) ppm; <sup>13</sup>C NMR (50 MHz): δ (First epimer): 210.8, 138.3, 129.2, 128.6, 126.7, 60.6, 50.5, 47.3, 37.8, 33.9, 31.3, 31.2, 24.5, 24.4 ppm; (Second epimer) : 208.2, 139.9, 129.0, 128.6, 126.4, 59.8, 51.3, 46.5, 33.7, 32.2, 32.1, 25.3, 24.6, 23.7 ppm; MS: (EI) *m/z* 232.0 (M<sup>+</sup>-127, 22%), 204.0 (20%), 170.0 (5.4%), 154.0 (7.4%), 123.0 (26%), 104.1 (14%), 91.0 (base peak), 81.0 (22%), 65.1 (23%).

**2-Benzyl-2-(3-cyclopentenyl)acetyl chloride (74)**

74

A solution of **60** (1.10 g, 5.10 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was cooled to 0 °C and oxalyl chloride (0.876 mL, 1.26 g, 10.0 mmol) was added dropwise over 5 min. The solution was stirred at 0 °C for 30 min and allowed to warm to room temperature (21 °C). The reaction was concentrated and the crude acid chloride **74** (1.4 g) was used directly in the preparation of thiol acid **61**.

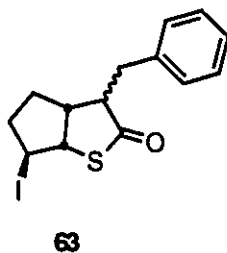
**Compound 74:** IR (film, NaCl): 3195 (m, sh), 3052 (m), 2940 (w), 1793 (s,  $\nu(\text{C}=\text{O})$ ), 1454 (m), 1438 (m), 734 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.38-7.05 (m, 5H, 5 x phenyl CH), 5.95-5.86 (m, 1H, =CH), 5.79-5.70 (m) and 5.70-5.61(m, 1H total; 1:3 ratio respectively, =CH), 3.28-2.84 (m, 3H,  $\text{PhCH}_2$  and  $\text{CH}(\text{C}=\text{O})$ ), 2.44-2.30 (m, 2H, =CHCH<sub>2</sub>), 2.55-1.98 (overlapping m, 1H,  $-\text{CH}_2\text{C}(\text{H}_a)(\text{H}_a')\text{CH}-$ ), 1.77-1.55 (m, 1H,  $-\text{CH}_2\text{C}(\text{H}_a)(\text{H}_a')\text{CH}-$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  (signals for each diastereomer given in brackets) 168.7, (138.0, 135.7), (134.0, 133.7), (130.8, 130.1), (128.9, 128.7), 126.8, (64.0, 63.9), 47.6, (36.0, 35.4), (331.9, 31.7), (26.6, 26.4) ppm.

**2-Benzyl-2-(3-cyclopentenyl)thiolacetic acid (61)****61**

Potassium hydroxide (6.60 g, 0.100 mol) and ethanol (50 mL, 90%) were placed in a flask (250 mL, 3 neck, round bottom) equipped with a dropping funnel (50 mL) and a gas inlet tube extending to the bottom of the flask, and cooled to 0 °C. Hydrogen sulfide was collected in a cold trap (immersed in liquid nitrogen) then warmed and bubbled into the solution until the mixture was no longer basic (~3 mL were required). The solution was cooled to -15 °C (NaCl/ice bath) and a solution of acid chloride **74** (11.95 g, 0.051 mol) in ethanol (20 mL) was added dropwise over 1.5 h. The resulting mixture was stirred for 1 h at 0 °C and 1 h at room temperature (21 °C). The potassium chloride which precipitated during the reaction was removed by quickly filtering the reaction through a Büchner funnel and washing the precipitate with ethanol (50 mL, 95%). The filtrate was concentrated, dissolved in distilled water (80 mL), and extracted with benzene (50 mL) to remove any neutral organic material. The aqueous layer was acidified (6N HCl) and extracted with ether (3 x 80 mL). The combined ether extracts were washed with ice-cold distilled water (2 x 30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give 11.12 g of crude thiol acid **61** as an orange oil. The crude material was used immediately in the iodolactonization as it oxidizes readily.

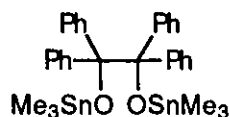
**Compound 61:** IR (film, NaCl): 3197 (m, sh), 3054 (m), 2940 (w), 2854 (w), 2560 (m,  $\nu(\text{S-H})$ ), 1707 (s,  $\nu(\text{C=O})$ ), 1450 (w), 1430 (w), 1078 (m), 1028 (m), 720 (m)  $\text{cm}^{-1}$ ; MS: (EI)  $m/z$  108.0 ( $\text{M}^+$ -(Bn and SH), 2.3%), 81.0 (13%), 79.0 (8.2%), 67.1 (22%), 60.9 (68%), 53.1 (7.3%), 45.1 (19%), 40.9 (13%), 33.0 (18%), 29.0 (base peak), 27.2 (80%).

**endo- and exo-4-Benzyl-exo-8-iodo-3-oxo-2-thiabicyclo**  
**[3.3.0]octane (63)**



Thiol acid **61** (1.16 g, 5.00 mmol) was placed in aqueous NaHCO<sub>3</sub> (40 mL, 0.5 M) and gently warmed until the solution became transparent. A solution of and I<sub>2</sub> (2.54 g, 10 mmol) and KI (5.00 g, 30 mmol) in distilled water (15 mL) was added and the mixture was protected from light (aluminium foil) and stirred at room temperature (21 °C) for 8 h. The solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 60 mL), and the combined organic extracts were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% w/v aqueous solution), dried (MgSO<sub>4</sub>), filtered, and concentrated to give a yellow oil. Radial chromatography (silica gel, 4 mm, eluted with CH<sub>2</sub>Cl<sub>2</sub>) provided 1.32 g (73%) of **63** as a 1:1 mixture of epimers.

**Compound 15:** IR (film, NaCl): 3026 (w), 2946 (m), 1697 (s, ν(C=O)), 1495 (m), 1450 (m), 1027 (m), 701 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ (approximately 1:1 mixture of epimers) 7.42-7.02 (m, 5H, 5 x phenyl CH), 4.18-3.90 (m, 1H), 3.41-3.04 (m, 2H), 2.93-2.40 (m, 3H), 2.38-1.20 (m, 4H) ppm; <sup>13</sup>C NMR (50 MHz): δ (1<sup>st</sup> epimer) 210.8 (C=O), 138.3, 129.2, 128.6, 126.7, 60.6, 50.5, 47.3, 37.8, 33.9, 31.3, 31.2, 24.5, 24.4; (2<sup>nd</sup> epimer) 208.2, 139.9, 129.0, 128.6, 126.4, 59.8, 51.3, 46.5, 33.7, 32.2, 32.1, 25.3, 24.6, 23.7 ppm; MS: (EI) *m/z* 232.0 (22%, M-127), 204.0 (20%), 170.0 (5.4%), 154.0 (7.4%), 123.0 (26%), 104.1 (14%), 91.0 (base peak), 81.0 (22%), 65.1 (23%), 40.9 (14%), 39.0 (12%).

**Bis(trimethylstannyl)benzopinacolate** <sup>176</sup>

Benzophenone (1.11 g, 6.1 mmol), hexamethylditin (1.0 g, 3.05 mmol) and benzene (50 mL, freshly distilled, degassed) were placed in a borosilicate glass tube and irradiated with light from a medium pressure Hanovia mercury lamp until the ketone carbonyl stretch at  $1670\text{ cm}^{-1}$  in the IR spectrum had disappeared and the solution became bright yellow in colour (5.5 h). The benzene was removed under reduced pressure and hexane (25 mL) was added. The resulting white precipitate was filtered, washed with hexanes and dried under vacuum to give 711 mg of bis(trimethylstannyl)benzopinacolate as a white powder. The filtrate was placed in the fridge overnight and in the morning 849 mg of colourless cubic crystals were obtained after filtration, washing (hexanes), and drying, for a combined yield of 1.56 g (74%) of bis(trimethylstannyl)benzopinacolate.

Spectra : IR (KBr disk): 3029 (w), 1659 (m), 1493 (m), 1278 (m), 1032 (m), 762 (s), 701 (s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz):  $\delta$  7.35-7.03 (m, 10H), 1.72 (s, 6H) ppm.

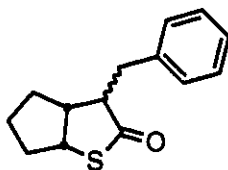
**General Experimental Procedure For Radical Ring Opening Experiments of Iodolactone (63)**

All radical reactions were carried out in freshly distilled, degassed solvent. Degassing was done either through a series of 3 freeze-pump-thaw cycles or by bubbling dry, deoxygenated argon through the solvent for 15-20 min. Each of the following reactions were performed with iodothialactone **63** (100 mg, 0.279 mmol).

### 1. Tributyltin hydride

Iodothialactone **63** and of AIBN (cat.) were added to 13 mL of benzene. (*n*-Bu<sub>3</sub>)SnH (7.5 μL, 0.028 mmol, 10 mol %) was added in one portion and the mixture was heated at 80 °C for 3 h. The solvent was removed under reduced pressure and ether (10 mL) was added. Potassium fluoride (4 mL, 20% w/v aqueous solution) was added and the solution was filtered. The organic layer was separated and washed with distilled water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give 71 mg of crude material. Column chromatography (silica gel, 1.5 x 25 cm, eluted with petroleum ether) afforded 34 mg (52%) of **77** as a 1:1 mixture of epimers.

#### *endo*- and *exo*-4-Benzyl-3-oxo-2-thiabicyclo[3.3.0]octane (**77**)



**77**

Compound **77**: IR (film, NaCl): 3061 (w), 3028 (w), 3025 (m), 1696 (s,  $\nu$ (C=O)), 1495 (m), 1451 (m), 1028 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  (approximately 1:1 mixture of epimers) 7.80-7.10 (m, 5H, 5 x phenyl CH), 4.30-3.79 (m, 1H), 3.41-3.05 (m, 1H), 2.88-2.40 (m, 3H), 2.20-1.15 (m, 6H) ppm; <sup>13</sup>C NMR (50 MHz, DEPT):  $\delta$  (First epimer) 210.9 (s), 138.3 (s), 129.2 (d), 128.6 (d), 128.5 (d), 126.6 (d), 60.6 (d), 50.5 (d), 47.2 (d), 37.9 (t), 33.9 (t), 31.2 (t), 24.4 (t) (Second epimer) 208.8 (s), 139.9 (s), 128.8 (d), 128.7 (d), 126.3 (d), 59.8 (d), 51.3 (d), 46.5 (d), 33.6 (t), 32.0 (t), 25.3 (t), 23.7 (t) ppm; MS: (EI) *m/z* 232.0 (5.4%, M<sup>+</sup>) 171.1 (12%), 151.0 (51%), 129.0 (18%), 91.0 (89%), 77.0 (54%), 68.1 (base peak), 53.0 (16%), 41.0 (19%); Exact Mass calcd for C<sub>14</sub>H<sub>16</sub>OS 232.0922, found 232.0946.

## 2. Tributyltin hydride (slow addition with syringe pump)

SnBu<sub>3</sub>H (7.5  $\mu$ L, 0.028 mmol, 10 mol%) was slowly added (syringe pump) to a solution of iodothialactone **63** and AIBN (cat.) in benzene (10 mL) over 16 h. The reaction was then worked up in the same manner as that described above in procedure 1 to give 46 mg (71%) of **77** as a 1:1 mixture of epimers.

## 3. Hexabutylditin

A mixture of hexabutylditin (8.0  $\mu$ L, 0.028 mmol, 10 mol%), iodothialactone **63**, and benzene (10 mL) was heated at reflux for 5.5 h with a General Electric sunlamp. Workup was performed in the same manner as that described above in procedure 1 to afford 41 mg (64%) of thialactone **77** as a 1:1 mixture of epimers.

## 4. Triphenylsilyl hydride

A mixture of triphenylsilylhydride (7.29 mg, 0.028 mmol, 10 mol%), iodothialactone **63**, AIBN (3 mg), and *o*-xylene were heated at either 80 °C, or reflux (140 °C) for 4 h. The solvent was removed under vacuum producing a red-brown oil that was subjected to column chromatography (silica gel, 1 cm x 30 cm, eluted with 5:1 petroleum ether/ether). Concentration of the appropriate fractions afforded either 50 mg (77%, 80 °C) or 46 mg (71 %, 140 °C) of **77** (1:1 mixture of epimers) depending on which reaction temperature was used.

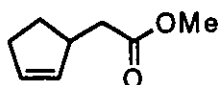
## 5. Tris(trimethylsilyl)silane<sup>177</sup>

Iodothialactone **63**, tris(trimethylsilyl)silane (86  $\mu$ L, 0.28 mmol), AIBN (5 mg) and benzene (10 mL) were heated at reflux for 3 h. Removal of the solvent and chromatography (silica gel, 20:1 petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>) afforded 40 mg (62 %) of **77**.

## 6. Bis(trimethylstannyl)benzopinolate<sup>176,178</sup>

Iodothialactone **63**, bis(trimethylstannyl)benzopinolate, and *o*-xylene (10 mL) were heated at 110-120 °C for 4.5 h. The reaction was allowed to cool to room temperature (21 °C) and the solvent was removed under vacuum. Ether (30 mL) was added to the resulting residue and washed with KF (10 % w/v aqueous solution). The organic layer was separated and washed with distilled water and brine, dried (MgSO<sub>4</sub>), filtered, and concentrated to give 52 mg of crude material. Column chromatography (silica gel, 1 cm x 25, eluted with 20:1 petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>) afforded 41 mg (63%) of **77** as a 1:1 mixture of epimers.

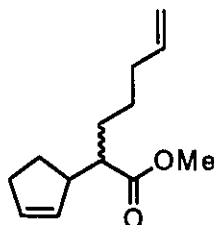
### Methyl-2-(3-cyclopentenyl)methyl acetate (73)



**73**

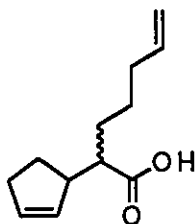
A solution of 2-(3-cyclopentenyl)acetic acid (Aldrich, 15 mL, 0.124 mol), methanol (200 mL) and H<sub>2</sub>SO<sub>4</sub> (0.30 mL) was stirred at reflux for 2 days. The reaction was allowed to cool to 21 °C, distilled water was added (50 mL) and the mixture was extracted with ether (3 x 80 mL). The aqueous layer was acidified (pH 5) with HCl (10% aqueous), extracted with ether (3 x 15 mL), and the combined ethereal extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated to give 14.57 g of the crude ester. Column chromatography (silica gel, 4 cm x 70 cm, eluted with 8:1 petroleum ether/ethyl acetate) provided 13.89 g (80%) of ester **73**.

Compound **73**: <sup>1</sup>H NMR (200 MHz): δ 5.74-5.63 (m, 1H, =CH), 5.63-5.51 (m, 1H, =CH), 3.67-3.50 (s, 3H, OCH<sub>3</sub>), 3.10-2.93 (m, 1H), 2.40-2.14 (m, 4H), 2.14-1.96 (m, 1H), 1.51-1.32 (m, 1H) ppm; <sup>13</sup>C NMR (50 MHz): δ 173.2, 133.6, 131.4, 65.7, 51.3, 41.9, 40.1, 31.7, 29.5, 15.2 ppm.

**Methyl-2-(3-cyclopentenyl)-2-(4-pentenyl)acetate (73a)****73a**

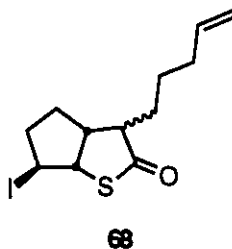
A mixture of freshly prepared LDA (17.8 mmol in THF (100 mL) (see general experimental for preparation), and HMPA (3.09 mL, 17.8 mmol) was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of **73** (2.5 g, 17.8 mmol) in THF (50 mL) was added. The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1 h and warmed to  $0\text{ }^{\circ}\text{C}$  for 10 min. The reaction was again cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of 5-bromo-1-pentene (2.11 mL, 2.65 g, 17.8 mmol) in THF (50 mL) was added in one portion. The solution was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ , 1 h at  $0\text{ }^{\circ}\text{C}$ , and warmed to room temperature. Saturated aqueous  $\text{NH}_4\text{Cl}$  was added and the solution was extracted with ether (3 x 50 mL). The combined ethereal extracts were washed with  $\text{NaHCO}_3$  (3 x 15 mL), distilled water (3 x 40 mL) and brine, dried ( $\text{MgSO}_4$ ), filtered, and concentrated to give 4.24 g of crude ester. Column chromatography (silica gel, 2.5 cm x 40 cm, eluted with 4:1 petroleum ether/ethyl acetate) afforded 288 mg (78%) of **73a** as a 2:1 mixture of diastereomers.

**Compound 73a:**  $^1\text{H}$  NMR (300 MHz):  $\delta$  (major isomer) 5.80-5.42 (m, 3H), 5.00-4.81 (m, 2H), 3.60 (s, 3H), 2.91-2.75 (m, 1H), 2.37-2.12 (m, 3H), 2.12-1.80 (m, 3H), 1.70-1.15 (m, 5H) ppm;  $^{13}\text{C}$  NMR (75 MHz):  $\delta$  (major isomer) 176.1, 138.5, 132.5, 131.9, 114.7, 50.8, 48.4, 48.1, 33.7, 32.1, 29.8, 27.7, 27.0 ppm.

**2-(3-Cyclopentyl)-2-(4-pentenyl)acetic acid (64)****64**

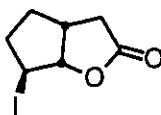
Methyl ester **63a** (1.45 g, 6.97 mmol) was added to a solution of KOH (0.586 g, 1.04 mmol) in methanol (15 mL) and water (40 mL). The mixture was heated at reflux for 26 h. After cooling to room temperature (21 °C) the reaction mixture was made basic (10% NaOH) and extracted with ether (3 x 30 mL) in order to remove any neutral material. The aqueous layer was acidified (10% HCl) and extracted with ether (3 x 50 mL). The combined ether extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, and concentrated to give 1.18 g of a crude yellow oil. The crude material was passed through a short plug of silica gel (5:1 petroleum ether/ethyl acetate) and, after removal of the solvent afforded 1.01 g (74%) of acid **64** as a 5:1 mixture of diastereomers .

**Compound 64:** IR (film, NaCl): 3068 (m), 1721 (s,  $\nu(\text{C}=\text{O})$ ), 1640 (w), 1176 (m), 994 (m)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz):  $\delta$  (major diastereomer) 11.95-11.50 (br s, 1H, COOH), 5.87-5.55 (m, 3H), 5.05-4.88 (m, 2H), 3.01-2.83 (m, 1H), 2.45-2.15 (m, 3H), 2.15-1.90 (m, 3H), 1.75-1.20 (m, 5H) ppm; <sup>13</sup>C NMR (75 MHz):  $\delta$  (major diastereomer) 182.3, 138.3, 132.2, 132.0, 114.7, 50.6, 48.1, 33.5, 32.0, 29.2, 27.4, 26.8 ppm; MS: (EI)  $m/z$  194.1 (22%, M<sup>+</sup>), 164.1 (14%), 147.1 (20%), 128.0 (17%), 124.0 (62%), 107.1 (29%), 93.1 (35%), 79.1 (base peak), 73.1 (53%); Anal. Calcd. for C<sub>12</sub>H<sub>18</sub>O<sub>2</sub>: C 74.18, H 9.34; Found: C 73.96, H 9.40; Exact Mass calcd for C<sub>12</sub>H<sub>18</sub>O<sub>2</sub> 194.1307, found 194.1309.

**exo-8-Iodo-3-oxo-4-(4-pentenyl)-2-thiabicyclo[3.3.0]octane (68)**

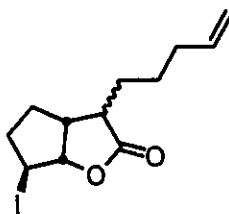
Unsaturated acid **73a** (1.00 g, 5.15 mmol) was converted to the corresponding acid chloride **75** using the same procedure as was described in the preparation of **63**. The crude acid chloride was used directly in the preparation of the thioacid **65** following the same procedure as was outlined for the preparation of benzyl substituted thioacid **61**. Iodolactonization of the crude thioacid using the same procedure as was described for the preparation of **63** afforded 350 mg of crude iodothialactone **68**. The crude material was passed through a short plug of silica gel (5:1 petroleum ether/ethyl acetate) and, after removal of the solvent afforded 230 mg of iodothialactone **68**.

**Compound 68:** IR (film, NaCl): 3072 (w), 1704 (s,  $\nu(\text{C}=\text{O})$ ), 1641 (m), 1450 (m), 1193 (m) 910 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz):  $\delta$  5.87-5.65 (m, 1H), 5.10-4.855 (m, 2H), 3.50-3.45 (m, 1H), 3.05-2.92 (m, 1H), 2.91-2.80 (m, 1H), 2.80-2.48 (m, 3H) 2.47-1.75 (m, 4H), 1.74-1.10 (m, 2H) ppm;  $^{13}\text{C}$  NMR (75 MHz):  $\delta$  209.0, 137.7, 114.8, 61.4, 60.3, 46.1, 44.1, 36.7, 33.4, 32.2, 30.2, 23.1 ppm

**exo-8-Iodo-3-oxo-2-oxabicyclo[3.3.0]octane (59)** <sup>179</sup>**59**

Iodolactonization of 2-(3-cyclopentenyl)acetic acid (1.26 g, 0.010 mmol) was carried out in the same manner as was described above in the procedure for the preparation of **62** (reaction time of approximately 12 h). Purification of the crude material by column chromatography (flash silica gel, 2 cm x 35 cm, eluted with 5:1 petroleum ether/ether/CH<sub>2</sub>Cl<sub>2</sub>) provided of 2.16 g (85%) of **59** as a colourless oil that decomposed readily upon standing over 48 h at room temperature (21 °C) and over approximately two weeks at -10 °C.

**Compound 59:** IR (film, NaCl): 2988 (s), 2962 (s), 1770 (s, ν(C=O)), 1325 (m), 1159 (s), 1000 (s), 875 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 5.10 (d, 1H, *J* = 6 Hz), 4.35 (d, 1H, *J* = 4 Hz), 3.20-2.90 (m, 1H), 2.78 (dd, 1H, *J* = 17, 10 Hz), 2.45-1.70 (m, 4H), 1.58-1.30 (m, 1H) ppm; <sup>13</sup>C NMR (50 MHz, DEPT): δ 176.6 (d), 92.2 (d), 35.9 (d), 35.7 (t), 34.6 (t), 31.8 (t), 29.6 (d), 35.7 (t) ppm; MS: (EI) *m/z* 252.0 (M<sup>+</sup>), 125.0 (base peak), 107.0 (37%), 97.0 (41%), 79.0 (90%), 67.1 (52%), 55.1 (59%), 40.9 (98%).

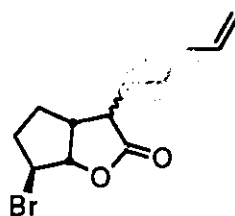
**8-Iodo-3-oxo-4-(4-pentenyl)-2-oxabicyclo[3.3.0]octane (66)****66**

Iodolactonization of **64** (1.00 g, 5.15 mmol) was carried out in the same manner as was described above in the procedure for the preparation of **62**. Purification of the crude

material by column chromatography (flash silica gel, 2 cm x 35 cm, eluted with 4:3:1 petroleum ether/ether/CH<sub>2</sub>Cl<sub>2</sub>) provided 1.16 g (70%) of **66** as a 4:1 mixture of diastereomers (colourless oil) that decomposed readily upon standing over 12-24 h at room temperature (21 °C) and over approximately one week at -10 °C.

Compound **66**: IR (film, NaCl): 3078 (w), 2931 (s), 2868 (s), 1771 (s,  $\nu(\text{C}=\text{O})$ ), 1644 (m), 1454 (m), 1440 (m), 1321 (m), 1166 (s), 997 (s), 913 (m), 744 (m)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz):  $\delta$  (approximately 4:1 mixture of diastereomers) 5.81-5.55 (m, 1H), 5.15-4.80 (m, 3H), 4.33 (br s, 1H), 3.20-3.00 (m, 0.25H), 2.80-2.55 (m, 0.75H), 2.45-2.21 (m, 2H), 2.20-1.25 (m, 9H) ppm; <sup>13</sup>C NMR (75 MHz):  $\delta$  (major epimer) 210.8, 138.3, 129.2, 128.6, 126.7, 60.6, 50.5, 47.3, 37.8, 33.9, 31.3, 31.2, 24.5, 24.4 (minor epimer) 208.2, 139.9, 129.0, 128.6, 126.4, 59.8, 51.3, 46.5, 33.7, 32.2, 32.1, 25.3, 24.6, 23.7 ppm; MS: (EI)  $m/z$  232.0 (22%,  $\text{M}^+-127$ ), 204.0 (20%), 170.0 (5.4%), 154.0 (7.4%), 123.0 (26%), 104.1 (14%), 91.0 (base peak), 81.0 (22%), 65.1 (23%), 40.9 (14%), 39.0 (12%).

**8-Bromo-3-oxo-4-(4-pentenyl)-2-oxabicyclo[3.3.0]octane (67)**



**67**

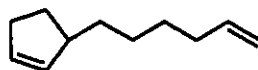
Compound **64** (1.00 g, 5.15 mmol) and NaHCO<sub>3</sub> (20 mL, 10% w/v aqueous solution) were warmed gently until the solution became transparent. The mixture was cooled to 0 °C and treated dropwise with Br<sub>2</sub> until a slight excess remained and the solution became light yellow in colour. Methylene chloride (40 mL) was added to the reaction and

the mixture was washed with sodium thiosulfate (10 mL, 20% aqueous solution) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give 1.59 g of crude **67**. Column chromatography (silica gel, 1.5 cm x 20 cm, eluted with CH<sub>2</sub>Cl<sub>2</sub>) afforded 1.04 g (74%) of bromolactone **67** as a colourless oil that decomposed within 2-3 days upon standing at room temperature, and within three weeks at -10 °C.

Compound **67**: <sup>1</sup>H NMR (300 MHz): δ 5.78-5.56 (m, 1H), 4.77-4.55 (m, 2H), 4.24-4.02 (m, 2H), 3.13-2.90 (m, 1H), 2.85-2.40 (m, 3H), 2.35-1.93 (m, 4H), 1.75-1.11 (m, 4H) ppm; <sup>13</sup>C NMR (75 MHz): δ 172.5, 134.3, 132.0, 64.9, 61.1, 56.2, 38.8, 38.4, 34.0, 27.8, 14.8 ppm.

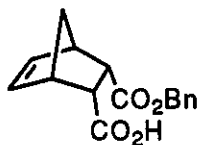
#### General Procedure for the SmI<sub>2</sub>-Catalysed Ring Opening of (**66**) and (**67**)

Halolactones **66** or **67** (0.30 mmol), freshly distilled THF, and HMPA were added to a Schlenk flask and the mixture was degassed using three freeze-pump-thaw cycles. Samarium diiodide was added dropwise and the resulting deep-purple solution was allowed to stir at 21 °C until GC-MS analysis indicated that no starting material remained. After quenching the reaction with saturated aqueous NaHCO<sub>3</sub> (10 mL), the aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub>, distilled water, and brine, dried, and concentrated. Column chromatography (flash silica gel, 1.5 x 30 cm, eluted with petroleum ether) was performed three times in order to obtain a pure sample of **78**. In subsequent experiments GC yields were calculated by comparison with this authentic material.

**3-(5-Hexenyl)cyclopentene (78)**

78

Compound 78: IR (film, NaCl): $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz):  $\delta$  5.90-5.60 (m, 3H), 5.05-4.90 (m, 2H), 3.09-2.91 (m, 1H), 2.75-2.60 (m, 1H), 2.45-2.10 (m, 1H), 2.10-1.85 (m, 2H), 1.80-0.60 (m, 8H) ;  $^{13}\text{C}$  NMR (75 MHz):  $\delta$  138.1, 131.8, 125.5, 114.9, 48.4, 33.6, 31.9, 30.3, 29.7, 27.9, 26.4 ppm; MS: (EI)  $m/z$  139.9 (3.5%,  $\text{M}^+$ ), 125.0 (1.2%), 111.0 (1.5%), 87.0 (29%), 79.0 (17%), 67.1 (base peak), 55.1 (6.9%), 40.9 (31%); Exact Mass calcd for  $\text{C}_{11}\text{H}_{18}$  150.1409, found 150.1420

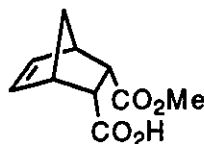
**cis-endo-5-Benzoyloxycarbonylbicyclo[2.2.1]hept-2-ene-6-carboxylic acid (69)**

69

*cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (5.53 g, 30.4 mmol, Aldrich) was added to a solution of DMAP (10 mg) in THF (150 mL). Diisopropylethylamine (5.29 mL, 30.4 mmol) and benzyl alcohol (3.15 mL, 30.4 mmol) were added to this solution and the mixture was heated at reflux for 18 h. The reaction was allowed to cool to 21 °C and the THF was removed. Methylene chloride (150 mL) was added and the mixture was washed with HCl (10% w/v aqueous solution) and extracted with  $\text{NaHCO}_3$  (3 x 50 mL, saturated aqueous solution). The aqueous layer was separated, acidified (10% v/v HCl), and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were concentrated to afford 7.2 g of a crude pale yellow solid that was recrystallized from  $\text{CH}_2\text{Cl}_2$ /petroleum ether to afford 6.62 g (80%) of compound 69 as colourless crystals.

Compound **69**: IR (film, NaCl): 3680-2400 (br s), 1746 (s,  $\nu(\text{C}=\text{O})$ , COOBn), 1702 (s,  $\nu(\text{C}=\text{O})$ , COOH), 1455 (m), 1340 (m), 1263 (s), 1228 (s), 1173 (s), 1028 (m), 749 (m), 699 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  10.00-8.80 (br s, 1H, COOH), 7.45-7.20 (m, 5H, 5 x phenyl CH), 6.35-6.14 (m, 2H), 5.10 (d, 1H  $J = 12$  Hz), 4.91 (d, 1H,  $J = 12$  Hz), 3.31 (t, 2H,  $J = 1.5$  Hz), 3.15 (br s, 2H), 1.46 (br d, 1H,  $J = 9$  Hz), 1.31 (br d, 1H,  $J = 9$  Hz) ppm;  $\text{D}_2\text{O}$  exchange: signal centered at  $\delta$  9.40 ppm disappears and a new signal (HOD) appears at  $\delta$  4.75 ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  179.0, 172.9, 136.5, 136.1, 135.0, 129.1, 128.9, 128.7, 67.1, 49.4, 49.0, 48.7, 47.2, 46.8 ppm.

**cis-endo-5-Methoxycarbonylbicyclo[2.2.1]hept-2-ene-6-carboxylic acid (71)**<sup>180</sup>



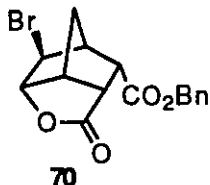
**71**

*cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (5.00 g, 27.4 mmol) was heated at reflux in MeOH for 14 h. The reaction was allowed to cool to 21 °C and the solvent was removed to give a colourless oil which solidified under vacuum. Recrystallization from  $\text{CH}_2\text{Cl}_2$ /petroleum ether afforded 5.62 g (97%) of acid **71** as colourless crystals.

Compound **71**: IR (film, NaCl): 3550-2400 (br s), 1737 (s,  $\nu(\text{C}=\text{O})$ , COOH), 1703 (s,  $\nu(\text{C}=\text{O})$ , COOMe), 1432 (m), 1347 (m), 1262 (s), 1194 (s), 926 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  10.25-9.80 (br s, 1H, COOH), 6.25-6.06 (m, 2H, =CH), 3.48 (s, 3H, COOCH<sub>3</sub>), 3.28-2.93 (m, 4H), 1.42-1.18 (m, 2H) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  178.6, 172.8, 135.5, 134.2, 51.4,

48.7, 48.1, 46.5, 46.0 ppm; MS: (EI)  $m/z$  196.1 (6.1%,  $M^+$ ), 178.0 (5.3%), 165.1 (24%), 151.1 (11%), 137.2 (20%), 131.2 (base peak), 119.2 (47%), 99.0 (56%), 92.0 (11%), 91.0 (55%), 77.1 (13%); Exact Mass calcd for  $C_{10}H_{12}O_4$  196.0736, found 196.0753..

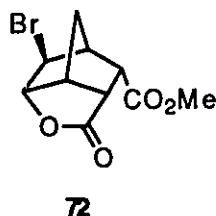
**exo-2-Bromo-endo-6-benzyloxycarbonyl[tricyclo[4.2.1.0<sup>3,7</sup>]nonan-4-oxo-5-one (70)**



A suspension of **69** (1.00 g, 3.68 mmol) in  $\text{NaHCO}_3$  (7 mL, saturated aqueous solution) was warmed until a transparent solution was obtained. The solution was cooled to 0 °C and treated dropwise with bromine until a slight excess remained. The resulting thick white-orange mixture was transferred to a separatory funnel and distilled water and  $\text{CH}_2\text{Cl}_2$  were added. The aqueous layer was separated and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). The combined organic extracts were washed with sodium thiosulfate (10% w/v aqueous solution) and brine, dried ( $\text{MgSO}_4$ ), filtered, and concentrated to give 1.43 g of crude material. Recrystallization from  $\text{CH}_2\text{Cl}_2$  afforded 1.22 g (94%) of bromolactone **70** as a white solid.

**Compound 70:** IR (film, NaCl): 3023 (m), 2931 (w), 1791 (s,  $\nu(\text{C}=\text{O})$ , lactone), 1717 (s,  $\nu(\text{C}=\text{O})$ ,  $\text{COOBn}$ ), 1454 (w), 1399 (m), 1179 (m), 1059 (m), 735 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.45-7.15 (m, 5H, 5 x phenyl CH), 5.15 (d, 1H,  $J = 12$  Hz), 5.07 (d, 1H,  $J = 12$  Hz), 4.98 (d, 1H,  $J = 5$  Hz), 4.57 (d, 1H,  $J = 2.4$  Hz), 3.40-3.24 (m, 1H), 3.15 (dd, 1H,  $J = 10.7, 3.3$  Hz), 2.94-2.72 (m, 2H), 2.40 (dt, 1H,  $J = 11.7, 1.4$  Hz), 1.73 (dm, 1H,  $J = 11.7$  Hz) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  176.8, 170.6, 135.6, 131.0, 129.3, 129.2, 88.0, 68.1, 49.9, 49.4, 48.7, 48.4, 41.2, 36.3 ppm

**exo-2-Bromo-endo-6-methoxycarbonyltricyclo[4.2.1.0<sup>3,7</sup>]nonan-4-oxo-5-one (72)** <sup>180</sup>.

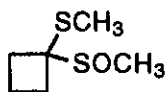


Bromolactonization of **71** (3.00 g, 15.3 mmol) was carried out in the same manner as was described above in the procedure for the preparation of **70**. Purification of the crude material by recrystallization (CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether) provided of 3.68 g (87%) of **72** as a white solid.

**Compound 72:** IR (film, NaCl): 3026 (m), 2946 (m), 2866 (w), 1697 (s,  $\nu(\text{C}=\text{O})$ ), 1495 (m), 1450 (m), 1027 (m), 701 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  4.88 (d, 1H,  $J = 5.1$  Hz), 4.48 (d, 1H,  $J = 2.4$  Hz), 3.61 (s, 3H), 3.29-3.18 (m, 1H), 3.05 (dd, 1H,  $J = 10.8, 3.4$  Hz), 2.81-2.65 (m, 2H), 2.30 (dt, 1H,  $J = 11.8, 1.4$  Hz), 1.67 (dm, 1H,  $J = 11.6$  Hz) ppm; <sup>13</sup>C NMR (50 MHz):  $\delta$  176.2, 170.4, 87.3, 52.4, 49.3, 48.6, 48.0, 47.7, 40.5, 35.7 ppm.

## Chapter 2 Experimental

### 1-Thiomethyl-1-methylsulfinylcyclobutane (107) <sup>182</sup>



**107**

Potassium hydride (26.95 g, 0.235 mol, 2.8 equiv, 35% dispersion in oil, Aldrich) was placed in a flask (500 mL, round bottom) equipped with a condenser and a dropping funnel (10 mL). The KH was washed with *n*-pentane (2 x 30 mL), dried under a stream of nitrogen, and THF (200 mL) was added. The THF/KH suspension was cooled to 0 °C and a solution of methyl methyl thiomethylsulfoxide (8.77 mL, 84.0 mmol) in THF (40 mL) was added dropwise to the stirred suspension to maintain a smooth evolution of H<sub>2</sub> (over 2 h). As the sulfoxide was added the mixture changed from a grey colour to tan. As the addition proceeded, the solution eventually became dark brown-black in colour. The mixture was stirred at 0 °C for 1 h to ensure complete deprotonation of the sulfoxide. A solution of 1,3-dibromopropane (10.41 mL, 102.5 mmol) in THF (40 mL) was added over a period of 10 min. The ice bath was replaced with a heating mantle and the solution was heated at reflux for 14 h producing a thick solution which contained a large quantity of dark brown precipitate in an opaque blue-green solution. The mixture was allowed to cool and the solution was filtered through a plug of Celite<sup>®</sup>. The collected solids were washed with CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 mL) and the organic layers were concentrated to give 25.79 g of a thick yellow-red oil. Column chromatography (silica gel, 5 cm x 80 cm, eluted with CH<sub>2</sub>Cl<sub>2</sub> → Et<sub>2</sub>O (5–100%) → MeOH (increasing from 5–60%)) provided 21.35 g (81%) of compound **107** as a colourless oil.

Compound **107**: IR (film, NaCl) : 2930 (s), 2860 (m), 1908 (m), 1714 (w), 1380 (w), 1308 (w), 1120 (m), 1065 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.88-2.60 (m, 2H), 2.30-2.10 (m, 1H), 2.35 (t, 3H,  $J =$  Hz, methyl protons), 2.10-1.95 (m, 1H), 2.01 (overlapping t, 3H,  $J =$  Hz, methyl protons), 1.95-1.60 ppm (m, 2H);  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  65.5, 31.9, 25.0, 23.3, 15.1, 12.3 ppm.

### Cyclobutanone (105) From Sulfoxide (107)



**105**

A mixture of sulfoxide **107** (2.0 g, 12.2 mmol), mercury(II) chloride (6.79 g, 25 mmol), sulfuric acid (2.0 mL, conc.), diethylene glycol (80 mL) and distilled water (10 mL) was placed in the distillation apparatus shown below (Figure 6). The contents were stirred while the temperature of the oil bath was raised to 85-95 °C. A slow, constant stream of  $\text{N}_2$  was passed through the solution, carrying the vapour through a receiving flask cooled to  $-78$  °C with a solid  $\text{CO}_2$  / acetone bath. A second receiving flask was attached so that any vapour not condensed by the first trap would do so in the second trap.

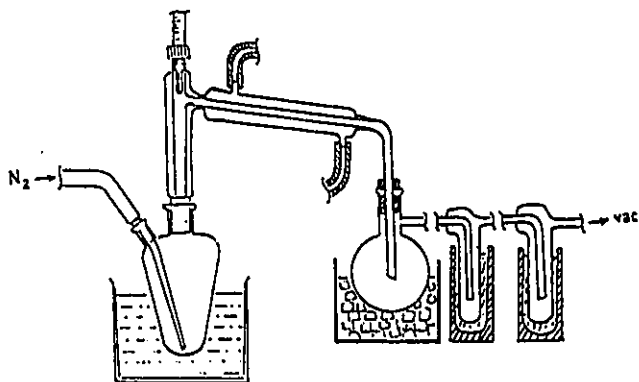
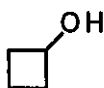


Figure 6 Apparatus for the preparation of cyclobutanone

A total of 0.32 g of crude cyclobutanone was collected which contained a small amount of water. The crude product was dried with  $\text{MgSO}_4$  and filtered to give 0.29 g (34%) of cyclobutanone **105**.

Compound **105**: IR (neat, NaCl): 2980 (s), 2925 (s), 1780 (s, C=O), 1385 (m), 1180 (s), 1308 (w), 1120 (m), 1065 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  3.04 (t, 4H,  $J = 8.2$  Hz), 1.96 (quintet, 2H);  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  209.6 (C=O), 47.4 ( $\text{CH}_2(\text{C}=\text{O})$ ), 9.35 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ) ppm.

### Cyclobutanol (108)



**108**

Cyclopropylcarbinol **106** (7.2 g, 99.8 mmol) was added to a flask (250 mL, 3 neck, round bottom) containing a solution of conc. HCl (7.0 mL) in 40 mL of distilled water. The mixture was heated at reflux for 100 min, cooled, neutralised with saturated aqueous  $\text{NaHCO}_3$  (~20 mL), saturated with  $\text{MgSO}_4$  and filtered. The solution was extracted with ether (3 x 60 mL) and fractionally distilled to remove most of the ether. The residue from the distillation (composed mainly of cyclobutanol **108**) was used in the preparation of cyclobutanone without further purification.

**Cyclobutanone (105) from cyclobutanol (108)**

105

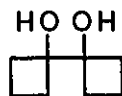
Cyclobutanol **108** (50.0 g, 0.693 mol) was placed in a flask (2 L, 3 neck, round bottom) equipped with a thermometer, dropping funnel (500 mL), and a solid CO<sub>2</sub>/acetone condenser. The reaction was cooled to -10 °C with an ice/NaCl bath, a solution of oxalic acid dihydrate (440 g, 3.52 mol) and conc. HCl (48 mL, ~0.55 mol) in distilled water (400 mL) was added. The solution was stirred at -10 °C for 15 min. A solution of CrO<sub>3</sub> (162 g, 1.62 mol) in distilled water (250 mL) was placed in the dropping funnel and added dropwise to the alcohol solution. The rate of addition was controlled to ensure that the temperature of the reaction mixture remained below -5 °C (the addition took 1.6 hr). As the addition proceeded the solution changed from its original light yellow colour to orange, then to an orange-red colour, then purple, and finally to dark purple. The ice/NaCl bath was removed and stirring was continued until the reaction had warmed to room temperature (2 hr). The crude reaction mixture was decanted into a separatory funnel and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 150 mL). The remaining solids were washed repeatedly with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts and washings were combined, dried (K<sub>2</sub>CO<sub>3</sub> + MgSO<sub>4</sub>), and filtered. Fractional distillation was carried out using a 20 cm vacuum-jacketed, silvered column (packed with glass helices) and a distillation apparatus with an adjustable stillhead that allows control of the reflux ratio. The distillation results for a typical trial are summarized below.

The yields obtained in various distillations ranged from 10–49% and were erratic. The spectral data obtained were identical to those found for cyclobutanone **105** that was obtained from sulfoxide **107**.

FRACTION	TEMPERATURE (°C)	REFLUX RATIO	VOLUME OBTAINED (mL)
1	30-80	2:1	250
2	80-90	15-20:1	300
3	90-94	18-20:1	76
4	94	20:1	12.26 *
5	94	18-20:1	4.21 *

\*The combined yield of **105** obtained from fractions 4 and 5 was 16.47 g (34%).

#### Cyclobutane pinacol (104) <sup>84a</sup>



**104**

Mercuric chloride (0.44 g, 1.60 mmol) and THF (5 mL) were placed in a flask (100 mL, 3neck, round bottom) equipped with a condenser and cooled to -78 °C with a solid CO<sub>2</sub> / acetone bath. Magnesium (1.44 g, 60 mmol, 70–80 mesh) was added to the solution and it was stirred for 40 min. The turbid supernatant was removed with a syringe and the remaining dark grey amalgam was washed with THF (3 x 5 mL). Fresh THF (15 mL) was added, cooled to -15 °C with a NaCl/ice bath and TiCl<sub>4</sub> (3.30 mL, 30 mmol)\* was added dropwise over 5 min. The solution immediately became bright yellow and smoke formed above the solution as the TiCl<sub>4</sub> was added. The resulting yellow-green solution was stirred at -15 °C before a solution of cyclobutanone **105** (1.40 g, 20.0 mmol) in THF (5 mL) was added in one portion. The reaction mixture was stirred at -10 °C for

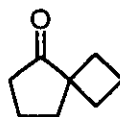
\* It was extremely helpful to use plastic disposable syringes, rather than ground-glass syringes, since the plastic syringes not as likely to "freeze-up" part-way through the addition.

1 h and 0 °C for 1 h. The dark green reaction was quenched with an aqueous solution of saturated  $K_2CO_3$  (5 mL) and stirred for another 90 min at 0 °C. The thick, dark red-burgundy mixture was diluted with ether (30 mL) and Celite® (2 g) was added. The purple water layer mixed with Celite® and the bright yellow ethereal layer were filtered through Büchner funnel containing a plug of Celite®. After washing the pad of Celite® with ether (3 x 10 mL), the filtrate was separated and the aqueous layer extracted with ether (3 x 10 mL). The combined ether extracts were washed with brine, dried, filtered, and evaporated to give 0.8 g (56%) of diol **104** as colourless crystals.\*\*

**Diol 104:** mp: 89-90 °C; IR (KBr pellet): 3600-3060 (br, s), 2990 (s), 2950 (s), 1430 (w), 1255 (s), 1155 (m), 1133 (m), 1088 (w), 1046 (w), 953 (m), 912 (m)  $cm^{-1}$ ;  $^1H$  nmr (200 MHz):  $\delta$  2.50 (broad s, 2H, OH), 2.30-2.10 (m, 4H), 2.05-1.72 (m, 6H), 1.65-1.40 (m, 2H) ppm;  $D_2O$  exchange: signal at  $\delta$  2.50 ppm disappears and a new signal appears at  $\delta$  4.78 ppm;  $^{13}C$  nmr (50 MHz):  $\delta$  30.3, 12.6 ppm; MS: (EI)  $m/z$  124.1 (1.1%,  $M^+ - 18$ ), 114.1 (14.8%), 96.0 (20%), 95.0 (11%), 87.0 (46%), 86.0 (70%), 71.0 (47%), 68.0 (32%), 58.1 (20%), 53.1 (27%), 44.1 (24%), 43.1 (base peak), 42.0 (39%), 40.9 (30%), 39.0 (25%), 27.2 (25%); (CI)  $m/z$  125.0 ( $M+1$ , 53.1%), 124.0 ( $M^+$ , 4.1%), 123.0 (4.1%), 115.0 (14%), 114.0 (20.2%), 108.0 (32%), 107.1 (base peak); (TMS derivative): 257.1 ( $(M+1)-30$ , 5.4 %), 243.1 (7.2%), 230.0 (8.3%), 167.0 (15%), 147.0 (29%), 143.1 (30%), 107.1 (19%), 75.1 (23%), 73.1 (base peak), 45.1 (16%).

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\*\* The yields obtained in 8 trials of this reaction varied between 20 and 82 % with an average yield of 53 %. The yields were highest when a new bottle of magnesium with a mesh size of 70-80 was used.

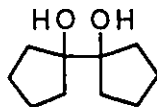
**5-Ketospiro[3.4]octane (103)** <sup>183</sup>.**103**

A solution of 10% sulfuric acid (18.4 mL) was added to a flask (250 mL, 2 neck, round bottom) assembled for a steam distillation. Before the diol was added to the sulfuric acid, the flask containing water for generating the steam was pre-boiled to ensure that a flow of steam could be started at the appropriate time. Upon addition of diol **104** (17.30 g, 0.122 mol) to the stirred acid solution, the light yellow solution began to change colour. These colour changes were characteristic of the reaction and progressed through the same stages each time the reaction was repeated. Although the original reference made no mention of any colour changes during the distillation, it was established that it was extremely important to start the flow of steam when the reaction became olive-green in colour. If the distillation was started at either an earlier or later stage in the reaction, the yield of the spiroketone was lowered by 30-50%. A rough correlation of the reaction time and colour are given below. When the reaction was carried out under optimum conditions, as described above, the isolated yield of spiroketone **103** was 9.7 g (78.2 mmol, 64%).

**Compound 103:** IR (neat, NaCl): 3032 (w), 2913 (w), 1778 (vs), 1491 (m), 1221 (m), 1000 (s), 743 (s),  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz):  $\delta$  2.21-2.06 (m, 4H), 1.95-1.81 (m, 4H), 1.77-1.68 (m, 4H) ppm;  $^{13}\text{C}$  NMR (75 MHz, DEPT):  $\delta$  220.9 (s, C=O), 50.9 (s, spiro carbon), 40.2 (t,  $\underline{\text{C}}\text{H}_2$ ), 36.9 (t,  $\underline{\text{C}}\text{H}_2$ ), 36.8 (t,  $\underline{\text{C}}\text{H}_2$ ), 29.7 (t,  $\underline{\text{C}}\text{H}_2$ ), 18.9 (t,  $\underline{\text{C}}\text{H}_2$ ), 15.6 (t,  $\underline{\text{C}}\text{H}_2$ ) ppm; MS: (EI)  $m/z$  124 ( $\text{M}^+$ , 34.4%), 109.0, 9.0%, 96.0 (46.4%), 95.0 (24.9%), 80.9 (16.2%), 79.0 (8.1%), 68.1 (90.4%), 67.1 (base)

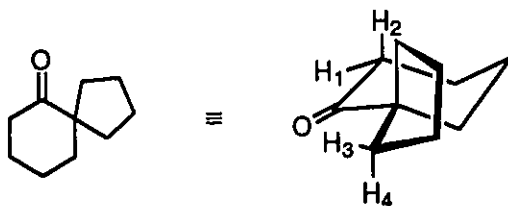
peak), 55.1 (19.8%), 54.1 (14.3%), 53.1 (23.4%), 40.9 (25.4%), 39.9 (36.3%), 39.0 (41.4%); Exact Mass calcd for  $C_8H_{12}O$  124.0888, found 124.0891.

TIME (min)	COLOUR
0 (add diol 104)	yellow
1	light blue
6	turquoise
8	light lichen-green
9	light fir-green
10 (start distillation)	olive-green
12	dark green
22	red
30	dark red

**Cyclopentane pinacol (110)**<sup>184</sup>**110**

Diol **110** was prepared from cyclopentanone (0.177 mL, 0.162 g, 2.0 mmol) using the same procedure as that reported for diol **104**. After the reaction was worked-up, the ethereal extracts were combined, dried, filtered, and concentrated to give 142 mg of crude pinacol **110** as light yellow crystals. Recrystallization from ether/petroleum ether afforded 120 mg (71%) of **110** as long white needles.

Compound **110**: IR (film, NaCl): 3545 – 2800 (s, br,  $\nu(\text{O-H})$ ), 2954 (s), 2867 (w, sh), 1182 (m), 1076 (w), 997 (s), 844 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.17 (s, 2H, O-H), 1.80-1.49 (br, m, 16H, 8 x  $-\text{CH}_2-$ ) ppm;  $\text{D}_2\text{O}$  exchange: A new signal appears at  $\delta$  4.90 ppm and the singlet at  $\delta$  2.50 ppm disappears;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  87.7, 37.0, 25.4 ppm; MS:  $m/z$  152.0 (M-18, 1.9%), 148.9 (2.9%), 123.1 (3.0%), 111.0 (6.3%), 85.1 (base peak), 84.1 (38%), 67.1 (39%), 57.1 (11%), 43.1 (15%), 40.9 (22%); Exact Mass calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_1$  (M-18) 152.1201, found 152.1201.

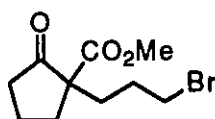
**6-Ketospiro[4.5]decane (111)**<sup>84a,b</sup>**111**

Ketone **111** was prepared by a pinacol rearrangement of diol **110**. Sulfuric acid (2 mL, 50% v/v aqueous solution) was added to a flask (10 mL, round bottom) containing

diol **110** (100 mg, 0.587 mmol). The reaction was stirred vigorously for 15 min, neutralized with an ice-cold aqueous solution of NaOH (10% w/v), and poured into a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The ethereal extracts were combined, dried, filtered, and concentrated cautiously to give a volatile, pale-yellow oil which was subjected to column chromatography (silica gel, 1 cm x 22 cm, eluted with petroleum ether). The appropriate fractions were combined and carefully concentrated to give 72 mg (81%) of ketone **111** as a volatile colourless oil.

Compound **111**: IR (film, NaCl): 2942 (m), 2870 (w, sh), 1703 (s,  $\nu(\text{C}=\text{O})$ ), 1195 (m), 1140 (w), 740 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.53-2.32 (m, 3H, H<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub>), 2.15-1.20 (br, m, 13H, 6 x  $-\text{CH}_2-$  and H<sub>4</sub>) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  216.0 ( $\underline{\text{C}}=\text{O}$ ), 56.7, 39.8, 39.3, 36.2, 35.2, 27.1, 25.0, 24.6, 22.6 ppm.

**2-(3-Bromopropyl)-2-methoxycarbonylcyclopentanone (113)** <sup>84c</sup>



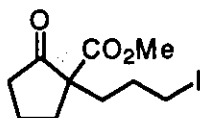
**113**

Sodium hydride (1.055 g, 35.20 mmol, 80% dispersion in oil) was placed in a flask (250 mL, 3 neck, round bottom) equipped with a dropping funnel, a condenser, and a heating mantle. The NaH was washed with *n*-pentane (3 x 6 mL), dried under a stream of nitrogen, and dry THF (100 mL) was added. A solution of methyl-2-oxocyclopentanecarboxylate (1.75 mL, 2.00 g, 14.1 mmol, Aldrich) in dry THF (10 mL) was added dropwise over 15 min. As the addition proceeded, a fine white precipitate

began to form. When all of the  $\beta$ -ketoester had been added, the solution was warmed gently and 1,3-dibromopropane (1.43 mL, 2.87 g, 14.1 mmol) was added. The mixture was heated to 40 °C causing the white precipitate to dissolve and the solution to become light yellow. After the reaction had stirred overnight at 40 °C, TLC analysis indicated that the starting material had been consumed. The reaction was allowed to cool to room temperature and a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (70 mL) was added. The aqueous layer was separated, extracted with ether (3 x 60 mL), washed with brine, dried, filtered, and concentrated to give 3.21 g of a crude red oil. Column chromatography (silica gel, 3 cm x 60 cm, eluted with  $\text{CH}_2\text{Cl}_2$ ) afforded 2.76 g (75%) of **113** as well as 0.38 g of the corresponding O-alkylated product.

**Compound 113:** IR (film, NaCl): 2980 (m), 2964 (m), 2893 (w, sh), 1760 (vs,  $\nu(\text{C}=\text{O})$  ketone), 1730 (vs,  $\nu(\text{C}=\text{O})$  ester), 1440 (s), 1348 (s), 1300 (s), 1245 (s), 1207 (s), 1109 (s), 1006 (m), 960 (m), 840 (m), 768 (m) 550 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  3.70 (s, 3H,  $\text{CH}_3\text{O}$ ), 3.43-3.24 (m, 2H,  $\text{CH}_2\text{I}$ ), 2.65-2.40 (m, 10H) ppm;  $^{13}\text{C}$  nmr (50 MHz):  $\delta$  214.6 (cyclopentanone  $\text{C}=\text{O}$ ), 171.4 (ester  $\text{C}=\text{O}$ ), 59.6 (quaternary  $\text{C}$ ), 52.5 ( $(\text{C}=\text{O})\text{OCH}_3$ ), 37.6, 33.1, 32.9, 32.3, 28.0, 19.4 ppm

**2-(3-Iodopropyl)-2-methoxycarbonylcyclopentanone (114)** <sup>84c</sup>



**114**

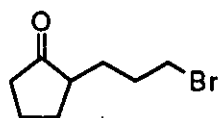
Sodium hydride (1.055 g, 35.20 mmol, 1.00 equiv, 80% dispersion in oil) was placed in a flask (500 mL, 3-neck, round bottom) equipped with a dropping funnel, a condenser, and a heating mantle. The NaH was washed with *n*-pentane (3 x 6 mL), dried under a stream of nitrogen, and dry benzene (200 mL) was added. A solution of methyl-2-

oxocyclopentanecarboxylate (4.37 mL, 5.00 g, 35.2 mmol) in 50 mL of dry benzene was added at such a rate so as to maintain a smooth evolution of H<sub>2</sub>. Once all of the β-ketoester was added, heating commenced and a solution of 1,3-diiodopropane (4.04 mL, 10.41 g, 35.2 mmol) in dry benzene (15 mL) was added in one portion. The mixture was heated at reflux for 5 h before TLC analysis indicated that the majority of the starting material had been consumed. The mixture was allowed to cool to 21 °C and the resulting light pink-orange solution was stirred for a further 10 h to ensure complete reaction.

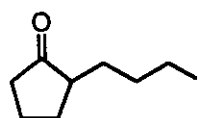
Removal of the solvent afforded 9.87 g of a crude yellow oil. Column chromatography (silica gel, 3 cm x 80 cm, eluted with a gradient of 100% petroleum ether to 3:1 methylene chloride/petroleum ether) afforded 8.79 g (81%) of **114** as well as 0.77 g of the O-alkylated product.

**Compound 114:** IR (film, NaCl): 2961 (w, sh), 2895 (w, sh), 2885 (w, sh), 1755 (vs,  $\nu(\text{C}=\text{O})$  ketone), 1726 (vs,  $\nu(\text{C}=\text{O})$  ester), 1461 (m), 1435 (m), 1322 (w, sh), 1234 (s), 1165 (s), 1005 (w), 735 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  3.64 (s, 3H, CH<sub>3</sub>O), 3.20-2.99 (m, 2H, CH<sub>2</sub>I), 2.53-2.10 (m, 4H), 2.05-1.50 (m, 6H) ppm; <sup>13</sup>C NMR (50 MHz):  $\delta$  214.5 (cyclopentanone C=O), 170.5 (ester C=O), 59.2 (quaternary C), 52.1 ((C=O)OCH<sub>3</sub>), 37.3, 34.0, 32.3, 28.2, 19.0 (CH<sub>2</sub>CH<sub>2</sub>I), 5.4 (CH<sub>2</sub>I) ppm; MS: (EI) *m/z* 183.1 (M-127, 25%), 168.9 (62%), 154.1 (25%), 151.0 (21%), 126.9 (22%), 123.1 (32%), 122.0 (14%), 114.1 (15%), 95.0 (46%), 94.0 (19%), 81.0 (26%), 79.9 (39%), 79.0 (19%), 67.1 (52%), 59.0 (20%), 55.1 (51%), 42.0 (16%), 40.9 (base peak), 39.0 (63%), 27.2 (49%).

**2-(3-Bromopropyl)-cyclopentanone (115) and 2-(3-Iodopropyl)-cyclopentanone (116)**



115

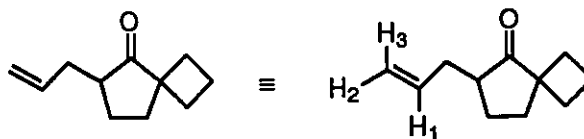


116

Haloester **113** or **114** (100 mg) was placed in a flask (10 mL, round bottom) that had been equipped with a heating mantle and a condenser. Distilled water (3 mL) and the appropriate acid, either HBr (300  $\mu$ L, 48% aqueous solution) or HI (150  $\mu$ L, 57% aqueous solution), were added and the mixture was heated at reflux for 1.5 h. The reaction mixture was allowed to cool to 21 °C and poured into a mixture of ice (20 g) and water (20 mL). The solution was made basic (pH 9.0, 10% NaOH) and extracted with ether (3 x 25 mL). The combined extracts were washed with an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% v/v), distilled water, brine, dried, filtered, and concentrated. The crude material was passed through a short plug of silica gel (2 cm x 3 cm, eluted with 5:1 petroleum ether/ether) and the appropriate fractions were combined and concentrated to give the desired halide.

**Compound 115:** Bromide **113** was obtained in 48% yield as a colourless oil. IR (film NaCl): 2985 (m), 2880 (w, sh), 1740 (vs,  $\nu$ (C=O) ketone), 1457 (w), 1270 (s), 1160 (m), 900 (w), 740 (vs) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  3.50-3.30 (m, 2H, CH<sub>2</sub>Br), 2.43-1.21 (m, 11H) ppm; <sup>13</sup>C NMR (50 MHz):  $\delta$  221.3 (C=O), 48.2, 37.8, 33.2, 30.6, 29.4, 28.2, 20.5 ppm.

**Compound 116:** Iodide **114** was obtained in 88% yield as a colourless oil that decomposed readily. IR (film, NaCl): 2960 (m), 2888 (w, sh), 1735 (vs,  $\nu$ (C=O) ketone), 1455 (w), 1233 (m), 1162 (m), 1055 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz):  $\delta$  3.61 (t, 2H, J = 7.0 Hz, CH<sub>2</sub>I), 2.45-1.15 (m, 11H) ppm; <sup>13</sup>C NMR (50 MHz, DEPT):  $\delta$  223.5 (s, C=O), 62.0 (t), 48.7 (d, (CH<sub>2</sub>)<sub>2</sub>CH(C=O)), 37.9 (t, CH<sub>2</sub>CH<sub>2</sub>(C=O)), 30.2 (t), 29.3 (t), 25.5 (t), 20.4 (t) ppm.

**4-Allyl-5-ketospiro[3.4]octane (117)**

117

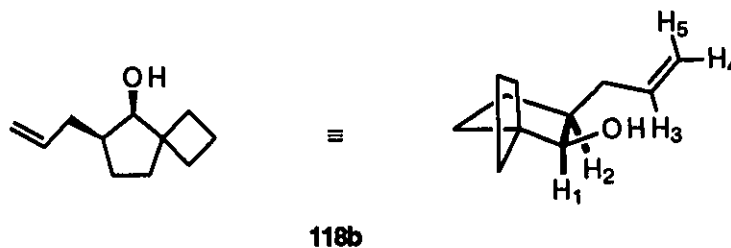
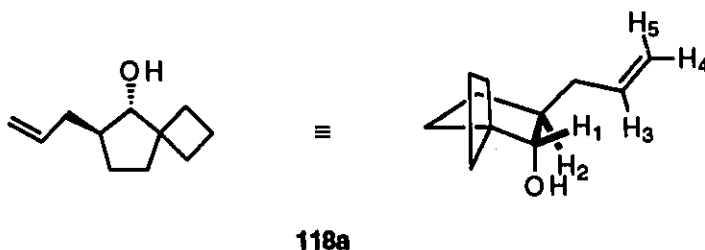
Diisopropylamine (1.24 mL, 0.898 g, 8.87 mmol) was placed in a flask (150 mL, round bottom) equipped with a dropping funnel and a cooling bath. Freshly distilled THF (60 mL) was added and the solution was cooled to  $-78\text{ }^{\circ}\text{C}$ . *n*-Butyllithium (3.42 mL, 8.87 mmol, 1.1 equiv, 2.59 M solution in hexanes, Aldrich) was added dropwise over a period of 5 min and the mixture was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ , and 15 min at  $0\text{ }^{\circ}\text{C}$ . A solution of spiroketone **103** (1.00 g, 8.06 mmol) in THF (20 mL) was added dropwise over 0.5 h. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 30 min and allyl iodide (2.21 mL, 4.06 g, 24.2 mmol, 3 equiv) was added in one portion. The reaction mixture was kept at  $-78\text{ }^{\circ}\text{C}$  for 3 h then warmed to  $0\text{ }^{\circ}\text{C}$ . The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the aqueous layer was separated and extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine, dried, filtered, and concentrated under reduced pressure\* to give a mobile orange oil as the crude product. Radial chromatography (silica gel, 4 mm plate, eluted with 20:1 petroleum ether/ethyl acetate) of the crude material resulted in the isolation of 830 mg (62%) of substituted ketone **117** as a colourless, volatile oil.

Compound **117**:  $^1\text{H}$  NMR (200 MHz):  $\delta$  5.83-5.50 (m, 1H,  $\text{H}_1$ ), 5.10-4.90 (m, 2H,  $\text{H}_2$  and  $\text{H}_3$ ), 2.61-1.30 (m, 13 H) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  223.3 ( $\text{C}=\text{O}$ ), 134.0, 118.2, 53.3, 51.8, 50.9, 40.2, 33.3, 30.1, 27.9, 15.5 ppm; MS: (EI)  $m/z$  164.4 ( $\text{M}^+$ , 7.3%), 149.0 (7.4%), 136.0 (14%),

\* The product is VERY volatile and great care must be exercised when concentrating the sample so as not to lose any material. Solvent was always left with the crude material. Chromatography was performed and the purified material was CAREFULLY evaporated.

123.0 (23%), 121.0 (10%), 107.0 (15%), 97.0 (36%), 95.1 (21%),  
 93.0 (33%), 91.0 (19%), 79.0 (48%), 67.1 (base peak), 53.1(30%),  
 40.9 (55%), 39.0 (44%), 28.1 (40%).

**trans-4-Allyl-5-hydroxyspiro[3.4]octane (118a) and cis-4-Allyl-5-hydroxyspiro[3.4]octane (118b)**

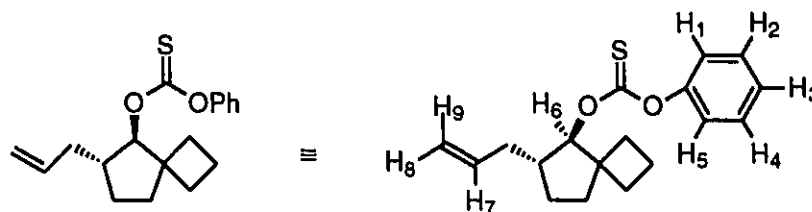


Ketone **117** (300 mg, 1.83 mmol) and freshly distilled ether (35 mL) were placed in a flask (100 mL, round bottom) equipped with a dropping funnel and a cooling bath. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and DIBAL (3.88 mL, 3.88 mmol, 2.59 M solution in hexanes) was added in one portion. The mixture was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$  and the reaction allowed to warm to room temperature ( $21\text{ }^{\circ}\text{C}$ ). Saturated aqueous sodium-potassium tartrate (3 mL) was added to the reaction and the mixture was stirred overnight. The aqueous layer was separated and extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine, dried, filtered, and concentrated to give a colourless oil. GC analysis indicated that this material consisted of two products in a 1.3:1 *cis/trans* ratio. Column chromatography (neutral alumina, 1.5 cm x 40 cm, eluted with

20 :1 petroleum ether / ethyl acetate) of the crude resulted in the isolation of 273 mg (90%) of a 1.3:1 mixture of alcohols **118a** and **118b**, respectively. Radial chromatography of this mixture (silica gel, 4 mm plate, eluted with a petroleum ether) afforded the *trans* alcohol **118a** (112 mg, homogeneous by TLC and GC).

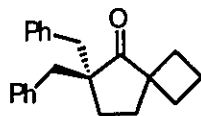
**Compound 118a:** IR (neat, NaCl): 3424 (s, br,  $\nu(\text{O-H})$ ), 3070 (m,  $\nu(\text{C-H})$ ), 1638 (m,  $\nu(\text{C=C})$ ), 1438 (m,  $\nu(\text{C=C})$ ), 1265 (s,  $\nu(\text{C-O})$ ), 1087 (m), 997 (m), 915 (s), 739 (s), 705 (m, sh)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz):  $\delta$  5.95-5.70 (m, 1H,  $\text{H}_3$ ), 5.15-4.88 (m, 2H,  $\text{H}_4$  and  $\text{H}_5$ ), 3.75 (br d, 1H,  $J = 3$  Hz,  $\text{H}_1$ ), 2.38-1.03 (m, 13H) ppm;  $^{13}\text{C NMR}$  (50 MHz):  $\delta$  138.3, 114.8, 805, 50.4, 41.5, 35.3, 34.2, 33.8, 27.1, 26.6, 15.5 ppm.

**Compound 118b:** Mainly *cis* isomer (mixture with some *trans* isomer) IR (film, NaCl): 3390 (m, br,  $\nu(\text{O-H})$ ), 3080 (m,  $\nu(\text{C-H})$ ), 1638 (m,  $\nu(\text{C=C})$ ), 1445 (m,  $\nu(\text{C=C})$ ), 1260 (w,  $\nu(\text{C-O})$ ), 1095 (m), 998 (m), 894 (m)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz):  $\delta$  5.95-5.68 (m, 1H,  $\text{H}_3$ ), 5.15-4.85 (m, 2H,  $\text{H}_4$  and  $\text{H}_5$ ), 3.85, 3.75 (br m, br d, 1H total, ratio of signals ~1.3:1,  $W_{1/2} = 9.6$  Hz,  $J = 3$  Hz,  $\text{H}_1$  (**118b**),  $\text{H}_1$  (**118a**) respectively), 2.40-1.00 (m, 14H) ppm;  $\text{D}_2\text{O}$  exchange: a broad doublet at  $\delta$  4.77 ppm appears on addition of  $\text{D}_2\text{O}$ , and integration of multiplet centered at  $\delta$  1.70 ppm decreases to 13H;  $^{13}\text{C NMR}$  (50 MHz), (less those signals assigned as belonging solely to the *trans* diastereomer):  $\delta$  137.9, 116.0, 79.5, 46.4, 38.8, 34.8, 32.0, 31.8, 26.2, 26.0, 16.0 ppm.

**trans-4-Allyl-5-(phenoxythiocarbonyloxy)spiro[3.4]octane (119)****119**

Alcohol **118a** (90.0 mg, 0.540 mmol) and  $\text{CH}_2\text{Cl}_2$  (4 mL, anhydrous) were placed in a flask (50 mL, round bottom) and stirred at 21 °C. A mixture of pyridine (87.3  $\mu\text{L}$ , 1.08 mmol, 2 equiv) and phenylthiochloroformate (96.2  $\mu\text{L}$ , 0.120 g, 0.700 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) was added in one portion, and the mixture was stirred for 3 h. The green-yellow crude reaction was concentrated and ether (10 mL) was added. The ethereal layer was washed with water (3 x 5 mL) and brine, dried, filtered, and concentrated to give 84 mg of crude material as a light yellow oil. Radial chromatography (silica gel, 1 mm plate, eluted with 20:1 petroleum ether / ethyl acetate) afforded 137 mg (84 %) of **119** as a pale yellow oil.

**Compound 119:** IR (film, NaCl): 3072 (m), 2949 (m), 2866 (m, sh), 1639 (w), 1592 (m), , 1489 (s), 1356 (w, sh), 1284 (vs), 1237 (vs), 1200 (vs,  $\nu(\text{C}=\text{S})$ ), 1014 (vs), 915 (m), 770 (s), 690 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.49-7.32 (m, 2H, H<sub>2</sub> and H<sub>5</sub>), 7.31-7.20 (m, 1H, H<sub>3</sub>), 7.09 (dm, 2H,  $J = 8$  Hz, H<sub>1</sub> and H<sub>5</sub>), 5.92-5.68 (m, 1H, H<sub>7</sub>), 5.75 (d, 1H,  $J = 3.2$  Hz, H<sub>6</sub>), 5.12-4.90 (m, 2H, H<sub>8</sub> and H<sub>9</sub>), 2.35-1.10 (m, 12H) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  195.6, 153.4, 137.2, 129.5, 126.5, 121.9, 115.7, 93.8, 50.2, 41.6, 35.9, 34.3, 33.7, 27.5, 27.1, 15.8 ppm; MS: (CI)  $m/z$  302.9 (81%), 301.9 (0.8%), 262.0 (77%), 260.8 (base peak), 234.9 (16%), 208.9 (3.4%), 189.0 (19%), 180.9 (12%), 149.9 (81%), 148.9 (100%), 147.8 (54%), 121.0 (13%), 108.0 (47%).

**4,4-Dibenzyl-5-ketospiro[3.4]octane (123)****123**

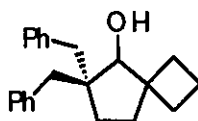
Sodium hydride (0.363 g, 12.10 mmol, 3 equiv, 80% dispersion in oil) was placed in a flask (250 mL, 2 neck, round bottom), washed with hexanes (3 x 3 mL), taken up in dry THF (200 mL) and cooled to 0 °C. Benzyl bromide (1.92 mL, 2.76 g, 16.12 mmol, 4 equiv) was then added to this stirred suspension. A solution of spiroketone **103** (500 mg, 4.03 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min. After stirring for 1 hr at 0 °C TLC analysis indicated that most of the starting material remained. The cooling bath was removed and the reaction was warmed to 21 °C and stirred for 2h. GC-MS\* analysis showed a ratio of approximately 50:50 starting material: product. The mixture was heated at reflux and monitored by GC-MS until all of the starting material had been consumed (2.5 h). Following the standard workup procedure (ether extraction etc.) column chromatography (flash silica gel, 4 cm x 60 cm, 40:1 hexanes-ether) afforded 758 mg of **123**. This sample (94% pure) was further purified by preparative HPLC (size exclusion column, 7 passes, CHCl<sub>3</sub>). The largest fraction (2nd of 3) was separated to baseline resolution and collected and concentrated to give 0.636 g (2.1 mmol, 52%) of **123** with > 99% purity.

**Compound 123:** IR (film, NaCl) : 3062 (m), 3027 (s), 2941 (vs), 2866 (m), 1952 (vw), 1885 (vw), 1812 (vw), 1723 (vs), 1601 (m), 1494 (s), 1450 (s), 1217 (m), 757 (vs), 703 (vs) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 7.24-7.16 (m, 6H), 7.09-7.04 (m, 4H), 2.98 (d, 2H, *J* = 13.1 Hz, 2 x PhCH<sub>A</sub>H<sub>B</sub>), 2.55 (d, , 2H, *J* = 13.1 Hz, 2 x PhCH<sub>A</sub>H<sub>B</sub>), 1.90-1.70 (m, 6H), 1.40-1.24 (m, 4H) ppm; <sup>13</sup>C NMR (50 MHz, DEPT): δ 224.2 (s, C=O),

\* TLC was virtually useless in this case as the R<sub>f</sub> of the product was identical to that of the starting material and they both turned green on heating after being immersed in a *p*-anisaldehyde stain.

138.3 (s, phenyl  $C=C(C)(C)$ ), 131.2 (d, phenyl *ortho*  $CH$ ), 128.7 (d, phenyl *meta*  $CH$ ), 127.1 (d, phenyl *para*  $CH$ ) 56.2 (s,  $\alpha$ -quaternary C), 52.1 (s, spiro carbon), 43.9 (t, 2 x benzylic  $CH_2$ ), 34.0 (t,  $CH_2$ ), 30.3 (t, 2 x  $CH_2$ ), 26.9 (t,  $CH_2$ ), 16.0 (t,  $CH_2$ ) ppm; MS:  $m/z$  304 ( $M^+$ , 9.0%), 214 (77%), 195 (48%), 185 (18%), 130 (31%), 117 (40%), 115 (33%), 91 (base peak), 65 (11%); Anal. Calcd. for  $C_{22}H_{24}O$ : C 86.79, H 7.94; Found: C 86.90, H 7.71; Exact Mass calcd for  $C_{22}H_{24}O$  304.1827, found 304.1810.

#### 4,4-Dibenzyl-5-hydroxyspiro[3.4]octane (128)



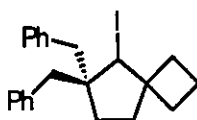
128

Spiroketone **123** (50 mg, 0.165 mmol) in dry THF (10 mL) was cooled to 0 °C and lithium aluminum hydride (165  $\mu$ L, 1 equiv, 1 M solution in THF, Aldrich) was added. The mixture was stirred for 15 min at 0 °C, warmed to 21 °C and stirred for 24 h. A saturated solution of sodium potassium tartrate (1 mL) was added and the solution was stirred for 3 h. The solution was extracted with ether (3 x 5 mL), washed with brine, dried, and concentrated. Column chromatography (flash silica gel, 1 cm x 12 cm, elution with 7:1 petroleum ether / ethyl acetate) provided 46 mg (0.150 g, 91%) of the spiroalcohol **128**.

Compound **128**: IR (film, KBr) : 3436 (m, br), 3026 (m), 2941 (vs), 2865 (s), 1950 (vw), 1884 (vw), 1812 (vw), 1601 (w), 1494 (m), 1451 (m), 1066 (s), 904 (w), 755 (m), 705 (vs)  $cm^{-1}$ ;  $^1H$  NMR (200 MHz):  $\delta$  7.40-7.02 (m, 10H, 10 x phenyl  $CH$ ), 3.42 (s, 1H,  $CH-OH$ ), 2.85-2.64 (m, 2H,  $PhCH_2$ ), 2.58-2.33 (m, 2H,  $PhCH_2$ ), 2.15-1.48 (m, 9H, 4 x  $-CH_2-$  and  $CH-OH$ ), 1.31-1.09 (m, 2H,  $-CH_2-$ ) ppm;  $D_2O$  exchange: signal at  $\delta$  4.77 ppm appears on addition of  $D_2O$ , and integration of multiplet

centered at 1.80 ppm decreases to 8H;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  139.1, 138.5, 130.8, 130.8, 127.9, 125.9, 81.8, 48.8, 47.4, 41.2, 37.9, 35.8, 33.4, 30.6, 28.2, 17.0 ppm; MS: (EI)  $m/z$  306 ( $\text{M}^+$ , 0.5%) 288 ( $\text{M}-18$ , 0.8%), 260 (1%), 214 (17%), 197 (11%), 186 (24%), 169. (3%), 141 (4.5%), 117 (20%), 91 (base peak), 77 (4.5%), 65 (12%), 55 (7%).

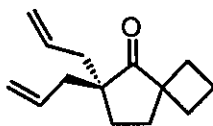
#### **4,4-Dibenzyl-5-iodospiro[3.4]octane (129)**



**129**

Spiroalcohol **128** (100 mg, 0.327 mmol) was placed in dry  $\text{CH}_3\text{CN}$  (3.0 mL) and cooled to 0 °C. Sodium iodide (50.0 mg, 0.33 mmol) and TMSCl (0.041 mL, 0.327 mmol) were added and the mixture was stirred at 0 °C for 2 h.<sup>88</sup> After warming to 21 °C the mixture was stirred for 48 h. The reaction was cooled, saturated aqueous sodium potassium tartrate (1mL) was added and the solution was stirred for 3 h. The solution was extracted with ether (3 x 5 mL), washed with brine, dried, and concentrated. Column chromatography (flash silica gel, 1 cm x 12 cm, elution with 9:1 petroleum ether/ether) provided 32 mg (24%) of spiroiodide **129**. The yield based on recovered starting material was 51%.

Compound **129**: IR (film, KBr disk) : 3060 (w), 3027 (m), 2927 (s), 2845 (s), 1601 (w), 1493 (m), 1452 (m), 1079 (w), 1030 (w), 908 (w), 738 (m), 700 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (200 MHz):  $\delta$  7.30-6.95 (m, 10H, 10 x phenyl CH), 2.80-2.55 (m, 4H, 2 x  $\text{PhCH}_2$ ), 2.34-1.81 (m, 9H, CH and 4 x  $\text{CH}_2$ ), 1.28-1.09 (m, 2H,  $\text{CH}_2$ ) ppm; MS:  $m/z$  198.1 ( $\text{M}^+ - 218.1$  (-I- Bn), 17%), 197.1 (base peak), 167.1 (3.1%), 155.0 (6.5%), 141.0 (8.9%), 129.0 (6.9%), 117. (12.6%), 105.0 (7.1%), 93.0 (8.6%), 91.0 (65%), 79.0 (7.4%), 77.1 (6.1%), 65.1 (8.3%), 55.2 (3.7%), 40.9 (8.6%).

**4,4-Diallyl-5-ketospiro[3.4]octane (124)****124**

Sodium hydride (0.363 g, 12.10 mmol, 3 equiv, 80% dispersion in oil, Aldrich) was placed in a flask (250 mL, 2 neck, round bottom) equipped with a 150 mL dropping funnel, condenser, and heating mantle. The NaH was washed with hexanes (3 x 3 mL), dried under a stream of argon before dry THF (200 mL) and allyl bromide (1.39 mL, 1.95 g, 16.12 mmol, 4 equiv) were added. Spiroketone **103** (500 mg, 4.03 mmol) and dry THF (100 mL) were placed in the dropping funnel and added dropwise to the stirred suspension over a period of 2 h. The mixture was heated at reflux overnight. GC-MS analysis showed that all of the starting material had been consumed so the mixture was allowed to cool to 21 °C. A solution of saturated aqueous NH<sub>4</sub>Cl was added carefully and the reaction mixture was extracted with ether (3 x 40 mL). The combined ethereal extracts were washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The resulting yellow oil (496 g) was purified by chromatography (preparative HPLC, size exclusion, 9 passes, CHCl<sub>3</sub>). A total of 201 mg (0.985 mmol, 47%) of the dialkylated spiroketone **124** was isolated, as well as 108 mg of monoalkylated compound.

Compound **124**: IR (film, KBr) : 3076 (m), 2978 (s), 2939 (vs), 2866 (m), 1728 (vs), 1639 (m), 1440 (m), 1332 (w), 1186 (w), 997 (s), 916 (vs) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 5.69-5.46 (m, 2H, 2 x CH=CH<sub>2</sub>), 5.01-4.88 (m, 4H, 2 x CH=CH<sub>2</sub>), 2.27-1.61 (m, 14H) ppm; <sup>13</sup>C NMR (50 MHz, APT): 223.5 (C=O), 134.5 (2 x H<sub>2</sub>C=CH(CH<sub>2</sub>)), 118.7 (2 x

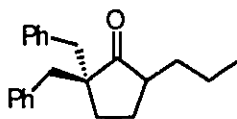
H<sub>2</sub>C=CH), 77.9 (spiro carbon)\*, 52.5, 51.6, 41.0, 34.1, 30.9, 28.7, 16.3 ppm; MS: *m/z* 204 (M<sup>+</sup>, 3.0%), 189 (1.5%), 176 (24%), 161 (8%), 149 (15%), 134 (20%), 120 (15%), 105 (23%), 93 (68%), 79 (94%), 67 (base peak), 53 (35%), 51 (12%); Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>O: C 82.30, H 9.87; Found: C 82.39, H 9.92; Exact Mass calcd for C<sub>14</sub>H<sub>20</sub>O 204.15142, found 204.14975.

### General Procedure for the SmI<sub>2</sub>-Catalysed Ring Opening of Spiroketones (123) and (124)

Spiroketone **123** or **124** (0.165 mmol), freshly distilled THF (50 mL), and HMPA (500 μL, 2.9 mmol) were added to a Schlenk flask (150 mL) and the mixture was degassed using three freeze-pump-thaw cycles. Samarium diiodide (6 mL, 0.600 mmol, 3.6 equiv, 0.1 M in THF) was added in one portion and the resulting deep-purple solution was allowed to stir at 21 °C until GC-MS analysis indicated that no starting material remained. After quenching the reaction with saturated aqueous NaHCO<sub>3</sub> (10 mL), the aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub>, distilled water, and brine, dried, and concentrated.

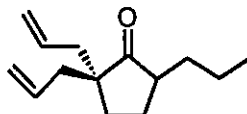
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\* This assignment was made based on the fact that this signal was not present in the ring-opened ketone **126**.

**2,2-Dibenzyl-5-propylcyclopentanone (126)****126**

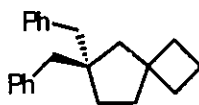
The general procedure for the  $\text{SmI}_2$ -induced ring opening of spiroketone **123** was followed exactly as described above. The crude product obtained from the reaction was passed through a plug of silica gel (eluted with ether) and concentrated. Preparative HPLC chromatography (size exclusion, 18 passes,  $\text{CHCl}_3$ ) separated the impurities from ketone **126**. The appropriate fractions gave 35 mg (0.114 mmol, 69%) of **126** which was >99% pure by GC-MS.

**Compound 126:** IR (film, KBr) : 3076 (m), 2978 (s), 2939 (vs), 2866 (m), 1728 (vs), 1639 (m), 1440 (m), 1332 (w), 1186 (w), 997 (s), 916 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.25-7.22 (m, 6H, phenyl  $\underline{\text{C}}\text{H}$ ), 7.11-7.02 (m, 4H, phenyl  $\underline{\text{C}}\text{H}$ ), 2 overlapping AB systems: {3.06 (d, 1H,  $J_{a,b} = 13.00$  Hz,  $\text{PhCH}_a\text{H}_{a'}$ ), 2.94 (d, 1H,  $J_{a',b'} = 13.09$  Hz,  $\text{PhCH}_a\text{H}_{a'}$ ), 2.56 (d, 1H,  $J_{b,a} = 13.00$ ,  $\text{PhCH}_b\text{H}_b'$ ), 2.55 (d, 1H,  $J_{b',a'} = 13.09$  Hz,  $\text{PhCH}_b\text{H}_b'$ )}, 1.96-1.44 (m, 5H), 1.26-0.98 (m, 2H), 0.94-0.71 (m, 2H, underneath methyl triplet), 0.77 (t, 3H,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR(50 MHz, DEPT): 224.7 (s,  $\underline{\text{C}}=\text{O}$ ), 138.3 (s, quaternary phenyl  $\text{HC}=\underline{\text{C}}(\text{CH})(\text{CH}_2)$ ), 138.1 (s, quaternary phenyl  $\text{HC}=\underline{\text{C}}(\text{CH})(\text{CH}_2)$ ), 131.1 (d, 2 x phenyl  $\underline{\text{C}}\text{H}$ ), 128.7 (d, 2 x phenyl  $\underline{\text{C}}\text{H}$ ), 127.2 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 127.0 (d, phenyl  $\underline{\text{C}}\text{H}$ ), 55.8 (t), 50.7 (t), 44.0 (t), 43.7 (t), 32.1 (t); 28.4 (t), 21.2 (t), 14.6 (q,  $\text{CH}_2\text{CH}_3$ ) ppm; **GC-MS:**  $m/z$  306 ( $\text{M}^+$ , 0.5%), 264 (3%), 215 (40%), 193 (3.8%), 173 (10%), 117 (24%), 91 (100%), 65 (12%), 55 (66%); **Exact Mass** calcd for  $\text{C}_{22}\text{H}_{26}\text{O}$  306.1984, found 306.1986.

**2,2-Diallyl-5-propylcyclopentanone (127)****127**

The general procedure for the  $\text{SmI}_2$ -induced ring opening of spiroketone **124** was followed exactly as described above. The crude product obtained from the reaction was passed through a plug of silica gel (eluted with ether) and concentrated. Preparative HPLC (size exclusion column, 15 passes,  $\text{CHCl}_3$ ) afforded 62 mg (0.301 mmol, 88%) of **127** which was >99% pure by GC-MS.

Compound **127**: IR (film, KBr) : 3076 (m), 2943 (vs), 2871 (m, sh), 1732 (vs), 1639 (m), 1448 (m), 1165 (w), 997 (s), 917 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  5.70-5.53 (m, 2H, 2 x  $\text{CH}=\text{CH}_2$ ), 5.04-4.94 (m, 4H, 2 x  $\text{CH}=\text{CH}_2$ ), 2.18-1.21 (m, 13H), 0.862 (t, 3H,  $J=7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR(50 MHz, DEPT):  $\delta$  223.8 ( $\text{C}=\text{O}$ ), 134.5 (d,  $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)$ ), 134.3 (d,  $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)$ ), 119.0 (t,  $\text{H}_2\text{C}=\text{CH}$ ), 118.8 (t,  $\text{H}_2\text{C}=\text{CH}$ ), 52.6 (s, quaternary di-vinyl substituted carbon), 50.0 (d,  $(\text{C}=\text{O})\text{CH}$ ), 41.2 (t), 40.7 (t), 32.6 (t), 26.3 (t), 21.3 (t), 14.6 (q, terminal methyl) ppm; GC-MS:  $m/z$  206 ( $\text{M}^+$ , 3.4%), 177 (4.4%), 163 (13%), 151 (21%), 135 (6.9%), 123 (74%), 122 (14%), 108 (21%), 93 (64%), 79 (base peak), 67 (91%), 55 (45%), 51 (9%); Exact Mass calcd for  $\text{C}_{14}\text{H}_{22}\text{O}$  206.16635, found 206.16733.

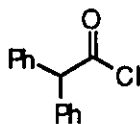
**3,3-Dibenzylspiro[3.4]octane (130)****130**

Spiroidide **129** (32 mg, 0.077 mmol), freshly distilled THF (25 mL), and HMPA (250  $\mu$ L, 1.5 mmol) were added to a Schlenk flask (150 mL) and the mixture was degassed using three freeze-pump-thaw cycles. Samarium diiodide (3 mL, 0.300 mmol, 3.6 equiv, 0.1 M in THF) was added in one portion and the resulting deep-purple solution was allowed to stir at 21  $^{\circ}$ C until GC-MS analysis indicated that no starting material remained. After quenching the reaction with saturated aqueous  $\text{NaHCO}_3$  (10 mL), the aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were washed with saturated aqueous  $\text{NaHCO}_3$ , distilled water, and brine, dried, and concentrated. The crude product was passed through a plug of silica gel (eluted with ether) and concentrated. Preparative HPLC (size exclusion column, 15 passes,  $\text{CHCl}_3$ ) afforded 21 mg (0.072 mmol, 94%) of **130**.

Compound **130**: IR (film, KBr disk) : 3024 (m), 2922 (s), 1497 (m), 1459 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (200 MHz):  $\delta$  7.28-6.98 (m, 10H, 10 x phenyl  $\text{CH}$ ), 2.73 (d, 2H,  $J = 17$  Hz,  $\text{PhCH}_2$ ) 2.60 (d, 2H,  $J = 17$  Hz,  $\text{PhCH}_2$ ), 2.30-1.83 (m, 8H, 4 x  $\text{CH}_2$ ), 1.25-1.09 (m, 4H,  $\text{CH}_2$ ), 0.87-0.70 (m, 2H,  $\text{CH}_2$ ) ppm; GC-MS:  $m/z$  288 ( $\text{M}^+ - 2$ , 95%), 207 (55%), 197.1 (98%), 169 (base peak), 155.0 (20%), 141.0 (55%), 129.0 (46%), 115. (19%), 91.0 (45%), 81 (15%).

### Chapter 3 Experimental

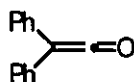
#### Diphenyl acetic acid chloride (185) <sup>174</sup>

**185**

Benzene (anhydrous, 30 mL) and diphenyl acetic acid **184** (10.6 g, 50 mmol) were added to a flask (250 mL, 3 neck, round bottom) equipped with a condenser, heating mantle, drying tube (Drierite<sup>®</sup>), and pressure equalizing dropping funnel. A solution of thionyl chloride (14.59 mL, 0.20 mole, 4 equiv) in benzene (50 mL) was placed in the addition funnel. The solution was heated to reflux, the SOCl<sub>2</sub> was added dropwise over 30 min and the solution was heated at reflux overnight. The resulting yellow solution was allowed to cool to room temperature (21 °C), and the C<sub>6</sub>H<sub>6</sub> and SOCl<sub>2</sub> were removed by vacuum distillation (0.018 mmHg). When approximately 10 mL of yellow oil remained, benzene (20 mL) was added and distilled to remove any remaining traces of SOCl<sub>2</sub>. The remaining yellow oil (~10 mL) was dissolved in hexane (30 mL) and the solution filtered by gravity. The filtrate was placed in an Erlenmeyer flask (125 mL) under an atmosphere of argon, stoppered, and placed in the refrigerator overnight. By morning pale yellow crystals had formed. These crystals were filtered, washed with cold hexane and dried in vacuo to give 1.33 g of **1** as white crystals. The filtrate was reduced in volume (15 mL) on the rotary evaporator and placed in the fridge overnight in a stoppered flask under an atmosphere of argon. A second crop of 7.82 g of white crystals was recovered in the same manner as above for a combined yield of 9.15 g of **185** (80%).

Compound **185**: IR (KBr pellet) : 3032 (w), 2913 (w), 1778 (vs), 1491 (m), 1221 (m), 1000 (s), 743 (s),  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.30-7.16 (m, 10H, aromatic protons), 5.35 (s, methine proton) ppm;  $^{13}\text{C}$  NMR (50 MHz): 137.1, 137.0, 137.0, 136.9, 136.8, 134.1, 129.6, 129.3, 128.8, 128.1 (phenyl carbons), 69.2 ( $\text{Ph}_2\text{CH}(\text{C}=\text{O})$ ) ppm; MS: (EI)  $m/z$  207 (M-15, 1.0%), 101 (3%), 85 (base peak), 69 (2%), 55 (4%).

**Diphenylketene (177)**<sup>174</sup>



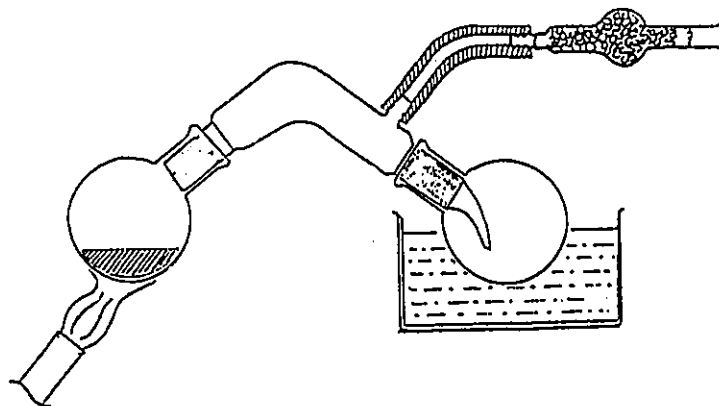
177

A Schlenk flask (100 mL) containing a solution of diphenyl acetic acid chloride **185** (4.2 g, 5.64 mmol) in  $\text{Et}_2\text{O}$  (50 mL) was cooled to  $0^\circ\text{C}$ . Triethylamine (2.36 mL, 16.9 mmol, 3 equiv) was added dropwise over 5 min to give a canary yellow solution. After stirring at  $0^\circ\text{C}$  for 90 min some  $\text{Et}_3\text{N}\cdot\text{HCl}$  had precipitated to give a bright yellow suspension. The flask was sealed under argon and placed in the fridge overnight to precipitate more  $\text{Et}_3\text{N}\cdot\text{HCl}$ . The salt was removed by filtration through a medium glass frit under an atmosphere of argon. Concentration under vacuum followed by flash vacuum distillation through the apparatus shown below gave a thick yellow oil (0.91 g, 83%).\*

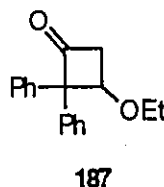
Compound **177**: bp: 120-122  $^\circ\text{C}$  at 0.15 mmHg\*\* ; IR (film, NaCl): 2097.3 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.1-7.8 (aromatic protons) ppm.

\* When conventional short-path distillation apparatus was used, with either a water- or air-filled condenser, slow distillation caused a deposition of solid material in the condenser and plugged the apparatus. These distillations initially produced a bright yellow oil (presumably the desired diphenylketene) which travelled through the distillation apparatus. Upon reaching the end of the condenser, most of the yellow oil was transformed into a pale yellow solid and began to deposit on the walls of the distillation apparatus. This solid was the dimer of diphenylketene (IR (KBr pellet):  $1762\text{ cm}^{-1}$ )

\*\* The boiling point of diphenylketene (120-122  $^\circ\text{C}$  at 0.15 mmHg) was determined during the attempted distillations described in the above footnote.



Flash vacuum distillation apparatus

**2,2-Diphenyl-3-ethoxycyclobutanone (187)***i) Without catalyst*

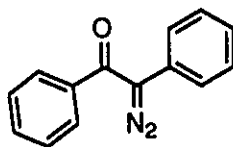
Ethyl vinyl ether (246  $\mu\text{L}$ , 2.57 mmol), diphenylketene **177** (200 mg, 1.03 mmol), and freshly distilled ether (25 mL) were placed in a 5 mL round-bottom flask and allowed to stir under argon overnight. The infrared spectrum of the resulting mobile crude yellow oil (262 mg, 95%) showed no remaining diphenylketene absorption ( $2096\text{ cm}^{-1}$ ). Excess ethyl vinyl ether was carefully removed under vacuum until the oil began to thicken. Final traces of the ether were removed under a stream of argon. The  $^1\text{H}$  NMR of the crude material appeared pure, however, the GC-MS showed a second product (~6%). The crude material was therefore chromatographed (silica gel, 5:1 petroleum ether / ethyl acetate) to give 241 mg (88%) of **187** as a bright yellow oil. The less polar minor product was found to be the dimer of diphenylketene (IR (neat):  $1814\text{ (s) cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.84-7.72 (m, 1.5H), 7.62-7.38 (m, 2H), 7.3-7.1 (m, 1.5H) 7.84-7.10 (m, aromatic protons)) ppm.

ii) *With catalyst*

A solution of diphenylketene **177** (200 mg, 1.03 mmol) and freshly distilled ether (9 mL) was placed in a disposable syringe (10 mL). A syringe pump was used to add this solution to a mixture of ethyl vinyl ether (~1 mL, vast excess) and Rh<sub>2</sub>(OAc)<sub>4</sub> (9 mg, 2 mol %) over a period of 7 h. The crude reaction mixture, after column chromatography (silica gel, 5:1 pet. ether / ethyl acetate) yielded 206 mg (89%) of cyclobutanone **187**.

Compound **187**: IR (film, NaCl): 3059, 2975, 1779, 1378, 1192, 1119, 1077, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz): δ 7.5-7.1 (m, 10H, aromatic protons), 4.82 (dd, 1H, *J* = Hz, CH), 3.6-3.11 (m, 4H, 2 x CH<sub>2</sub>), 1.06 (t, 3H, CH<sub>3</sub>) ppm; Exact Mass calcd for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub> 266.1307, found 266.1316.

**2-Diazo-1,2-diphenyl-1-ethanone** (**210**)<sup>173</sup>



**210**

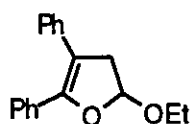
A suspension of benzil monohydrazone **209** (2.0 g, 8.92 mmol) in THF (200 mL) was heated at reflux until the mixture became homogeneous. Powdered Ag<sub>2</sub>O (2.26 g, 9.75 mmol) was added in small portions over 15 min and the resulting mixture was heated at reflux for 5 h with vigorous stirring. The silver residue was removed by hot filtration (gravity, over Celite®) and washed with two 5 mL portions of THF. The filtrate was concentrated to give ~2 g of oily orange crystals. Recrystallization from pentane yielded 1.66 g (84%) of azibenzil **210** as bright orange crystals.

Compound **210** mp 46–47 °C; IR (KBr pellet): 3051 (w), 2075 (vs), 1605 (vs), 1345 (s), 1242 (s), 1180 (m), 700 (s)  $\text{cm}^{-1}$ ;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  182.5 (C=O), 132.0, 125.9, 125.7, 123.4, 123.1, 122.6, 122.1, 121.5, 120.1, 120.0 ppm.

**General Procedure for the Metal Catalyzed Addition of  $\alpha$ -Diazoketone (210) to Ethyl Vinyl Ether**

A solution of  $\alpha$ -diazoketone **210** (500 mg, 2.25 mmol) in 5 mL of anhydrous ether, pentane, or benzene was added over 5 h (syringe pump) to a stirred solution of ethyl vinyl ether (~2 mL, excess) and  $\text{Rh}_2(\text{OAc})_4$  or  $\text{Rh}_2(\text{OPiv})_4$  (2 mol %) in freshly distilled diethyl ether, pentane, or benzene (10 mL). The crude reaction mixture was then filtered through a plug of Celite<sup>®</sup> to remove most of the catalyst, and concentrated under reduced pressure.

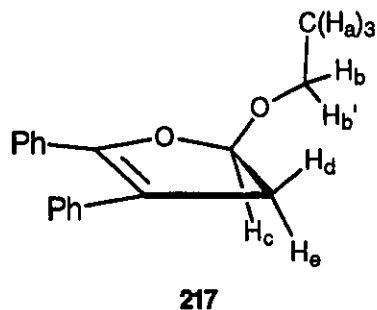
**Procedure A: 2,3-Diphenyl-5-ethoxy-4,5-dihydrofuran (217)**



**217**

The  $\text{Rh}_2(\text{OAc})_4$ -catalysed addition of ethyl vinyl ether to **210** (21 °C) using the general method described above yielded 589 mg of crude material. The  $^1\text{H}$  NMR spectrum of the crude product showed no remaining starting material. The only material present appeared to be the dihydrofuran **217**. GC-MS analysis of the crude reaction mixture showed a 97% conversion of the starting  $\alpha$ -diazoketone to the dihydrofuran **217**. Analysis by TLC (silica gel, 20:1 petroleum ether-ethyl acetate) showed at least 4 products. Suspecting that the major component was decomposing on the silica, a TLC plate was

spotted with the material and allowed to stand for ~5 min. A second spot was applied immediately before developing the plate. The "older" spot showed ~8 different compounds while the "new" spot showed only 3. A 2-dimensional TLC was also run to further check for decomposition. In the resulting chromatogram, 5 decomposition products appeared off of the diagonal, indicating the initially formed product was not stable to silica gel. A similar result was obtained when neutral alumina TLC plates were used. Dihydrofuran **217** is also destroyed on exposure to  $\text{CDCl}_3$  that has not been passed through basic alumina immediately prior to use. In order to purify a sample of **5** that would be suitable for NMR spectroscopy, crude material from a large number of experiments was combined to give a 1.6 g sample that was subjected to flash chromatography (silica gel, 40 cm x 1 cm, eluted with 20:1 hexanes / ether). The most non-polar fractions were collected to give 664 mg of **217** as a pale yellow oil. All of the spectral data was recorded immediately after purification.



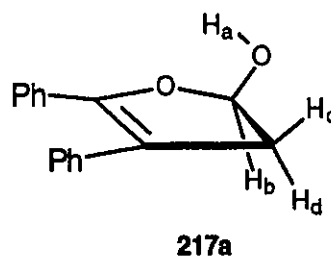
Compound **217**\* : IR (film, NaCl): 3057 (w), 2936 (m), 1650 (w), 1650 (w), 1601 (m), 1500 (m), 1444 (m), 1374 (w), 1239 (w), 1195 (m), 1091 (m), 1061 (s), 1011 (s), 760 (vs), 694 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.53-7.10 (m, 10H, aromatic protons), 5.62 (dd,  $J_{c,e} = 7.2$  Hz,  $J_{c,d} = 2.6$  Hz,  $\text{H}_c$ ), 3.97 (dq, 1H,  $J_{b,a} = 9.6$  Hz,  $J_{b,b'} = 7.1$  Hz,  $\text{H}_b$ ), 3.66 (dq, 1H,  $J_{b',a} = 9.6$  Hz,  $J_{b',b} = 7.1$  Hz,  $\text{H}_{b'}$ ), 3.41 (dd, 1H,  $J_{e,d} = 16.4$  Hz,  $J_{e,c} = 7.2$  Hz,  $\text{H}_e$ ), 2.93 (dd, 1H,  $J_{d,e} = 16.4$  Hz,  $J_{d,c} = 2.6$  Hz,  $\text{H}_d$ ), 1.06 (dd, 3H,  $J_{a,b} = J_{a,b'} = 9.6$  Hz,  $\text{C}(\text{H}_a)_3$  ppm;  $^{13}\text{C}$  NMR (50 MHz, DEPT):  $\delta$  148.2 (s,  $\text{Ph}(\text{O})\text{C}=\text{C}$ ), 135.1 and 131.7 (s, phenyl *ipso* C),

\* Reproductions of the original spectra for compound **217** are included in Appendix II.

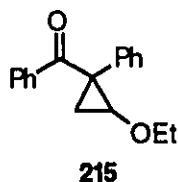
128.5, 128.2, 128.1, 127.9, 127.5, 126.1 (d, phenyl CH), 109.3 (s, C=CPh(CH<sub>2</sub>)), 102.6 (d, OCHO), 63.7 (t, CCH<sub>2</sub>CH(O)(O)), 42.3 (t, OCH<sub>2</sub>CH<sub>3</sub>), 15.3 (q, CH<sub>2</sub>CH<sub>3</sub>) ppm; Exact Mass calcd for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub> 266.1307, found 266.1331.

The final fractions from the column used to separate **217** contained the major decomposition product which was found to be lactol **217a**.

Compound **217a**: <sup>1</sup>H NMR (200 MHz): δ 9.78 (s, H<sub>a</sub>), 7.96-7.91 and 7.46-7.21 (m, 10H, aromatic protons), 5.10 (dd, H<sub>b</sub>, J<sub>b,d</sub> = 4.21 Hz, J<sub>b,c</sub> = 9.71 Hz), 3.59 (dd, H<sub>c</sub>, J<sub>c,d</sub> = 18.6 Hz, J<sub>c,b</sub> = 9.40 Hz), 2.81 (dd, H<sub>d</sub>, J<sub>d,c</sub> = 18.6 Hz, J<sub>d,b</sub> = 4.21 Hz) ppm.



**Procedure B: 1-Phenacyl-1-phenyl-2-ethoxycyclopropane (215)**



Procedure A was followed up to the point just before the crude reaction mixture was filtered through a plug of Celite®. The lime-green crude solution was concentrated under a stream of argon and dissolved in CDCl<sub>3</sub> that had been passed through basic alumina immediately prior to use. The <sup>1</sup>H and <sup>13</sup>C NMR and IR spectra of this opaque suspension were recorded immediately. The sample was stored in the freezer, without

solvent, under an atmosphere of argon. Any attempt to purify cyclopropane **215**, other than filtration under an inert atmosphere, resulted in either partial or complete conversion to dihydrofuran **217**. Slow conversion of **215** to **217** occurred on storage at low temperatures in a sealed flask under an inert atmosphere. After only a few days the sample consisted mainly of the dihydrofuran **217**, together with a number of products previously seen in the decomposition of **217**.

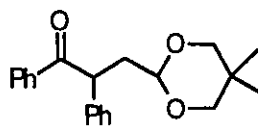
Compound **215**: IR (film, NaCl): 3062 (w), 2924 (m), 2856 (w), 1722 (w, sh), 1676 (s), 1593 (m), 1448 (m), 1211 (m), 696 (s), 641 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  7.92-7.78 (m), 7.62-6.90 (m) (10H, phenyl protons), 3.38 (q, 2H,  $\text{OCH}_2\text{CH}_3$ ), 1.41-0.90 (m, with overlapping triplet at 1.12, 5H, cyclopropane  $\text{CH}_2$  and  $\text{OCH}_2\text{CH}_3$ ), 0.90-0.62 (m, 1H, cyclopropane  $\text{CH}$ ) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  194.5, 134.8, 132.9, 129.9, 129.1, 129.0, 128.7, 128.6, 128.2, 128.1, 128.0, 65.8, 32.4, 29.7, 23.2, 15.3 ppm.

### Procedure C: Trapping Experiment with DIBAL

The general procedure was followed, except the experiment was performed in pentane (30 mL) with  $\text{Rh}_2(\text{OPiv})_4$  (2 mol %) as the catalyst. After the addition of diazo compound **210** (0.050 g, 0.223 mmol) was complete (GC-MS showed a single peak due to dihydrofuran-rearranged cyclopropane), the crude lime-green reaction mixture was cooled to  $-78\text{ }^\circ\text{C}$  and DIBAL (1.5 M in toluene, 300  $\mu\text{L}$ , 0.446 mmol) was added in one portion. Upon addition of the DIBAL, the solution immediately became bright red in colour. This mixture was allowed to stir at  $-78\text{ }^\circ\text{C}$  for 15 min. Analysis by TLC indicated that the concentration of starting material had reduced significantly, and a new polar spot had appeared. GC-MS also indicated the presence of a new peak (23% of the mixture) with a mass corresponding to the desired alcohol. The reaction was allowed to warm to room temperature before being quenched with a saturated aqueous solution of sodium

potassium tartrate (5 mL). The crude reaction mixture was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic fractions were washed with brine, filtered, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give 54 mg of crude product as a thick red-brown oil. Column chromatography (flash silica gel, 6 g, 5:1 petroleum ether/ethyl acetate) resulted in the isolation of 6 mg of benzyl alcohol, as well as 10 mg of the cyclopropyl alcohol **259**.

**3,4-Diphenylbutan-4-one propylene(2,2-dimethyl)acetal (222)**



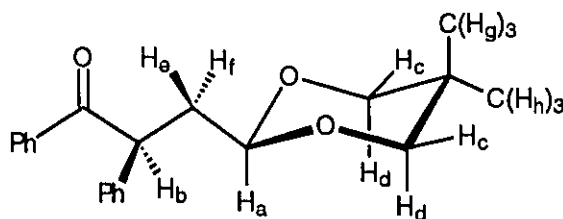
**222**

Dihydrofuran **217** (17 mg, 0.0639 mmol) and 2,2-dimethyl-1,3-propanediol (20 mg, 0.192 mmol, 3 equiv) were dissolved in dry benzene (10 mL) and a single crystal of PPTS was added. The mixture was stirred at room temperature until there was no remaining dihydrofuran by TLC analysis. The crude reaction mixture was concentrated and subjected to column chromatography (flash silica gel, 0.75 cm x 20 cm, 5:1 petroleum ether/ethyl acetate). A total of 14 mg of acetal **222** (68%) was isolated from the most non-polar fractions collected.

Compound **222**\*: <sup>1</sup>H NMR (500 MHz, COSY): δ 8.00-7.98 (m), 7.97-7.20 (m) (10H, phenyl protons), 4.91 (dd, H<sub>a</sub>, *J* = 7.8, 7.0 Hz), 4.31 (dd, H<sub>b</sub>, *J* = 5.6, 4.9 Hz), 3.38 (ddd, H<sub>c</sub>, *J* = 18.8, 10.9, 2.7 Hz), 3.29 (dd, H<sub>d</sub>, *J* = 17.2, 11.0 Hz), 2.60 (ddd, H<sub>e</sub>, *J* = 13.8, 7.9, 5.8 Hz), 2.15 (ddd, H<sub>f</sub>, *J* = 13.8, 6.8, 4.8 Hz), 1.14 (s, 3H<sub>g</sub>), 0.67 (s, 3H<sub>h</sub>) ppm;

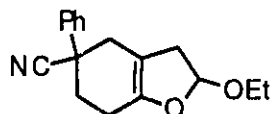
\* Reproductions of the original spectra for compound **222** are included in Appendix II.

$^{13}\text{C}$  NMR \* (125 MHz, DEPT):  $\delta$  199.2 (s, C=O), 139.0 (s), 136.6(s), 134.8 (d), 132.7 (d), 129.8 (d), 128.9 (d), 128.9 (d), 128.6 (d), 128.3 (d), 128.2 (d), 127.0 (d), 100.0 (d, C<sub>a</sub>), 77.71 (t, C<sub>c,d</sub>), 48.1 (d, C<sub>b</sub>), 38.5 (t, C<sub>e,f</sub>), 30.0 (s, C(CH<sub>3</sub>)<sub>2</sub>), 22.9 (q, C<sub>g</sub>), 21.7 (q, C<sub>h</sub>) ppm; MS: (EI)  $m/z$  324 (M<sup>+</sup>, 72 %), 323 (M-1, base peak), 237 (M-87, 14%), 219 (M-105, 17%), 191 (21%), 105 (C<sub>6</sub>H<sub>5</sub>C=O<sup>+</sup>, 66%), 77 (C<sub>6</sub>H<sub>5</sub><sup>+</sup>, 31%); Exact Mass calcd for C<sub>21</sub>H<sub>24</sub>O<sub>3</sub> 324.1726, found 324.1741..

**222**

**3-Cyano-3-phenyl-8-ethoxybicyclo[4.3.0]nona-7-oxa- $\Delta$ <sup>1,6</sup>-ene**

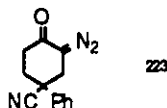
**(234)**<sup>93</sup>

**224**

Compound **224**<sup>93</sup> was obtained in 40% yield from the Rh<sub>2</sub>(OAc)<sub>4</sub>-catalyzed reaction of  $\alpha$ -diazoketone **223**\*\* and ethyl vinyl ether. The work-up given for this

\* The chemical shifts reported here differ from those given in the printout on the original spectra reproduced in Appendix II for compound **222**. The shifts given above have been corrected for  $\delta$  CHCl<sub>3</sub> = 77.0 ppm.

\*\* Compound **223** was prepared by  $\alpha$ -diazotization of the corresponding ketone.<sup>93</sup>

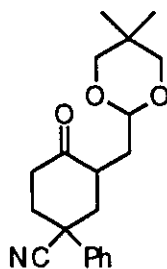


particular reaction was different from the one given in the general reaction procedure (vide supra). For this compound, the crude reaction mixture had been "concentrated, flushed through a small column of silica gel" (presumably with some eluent), "reconcentrated, and then purified by column chromatography". No other products were mentioned or identified.

The data given for compound **224**<sup>93</sup>:

"IR: 1098, 2241  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz):  $\delta$  1.23 (t, 3H,  $J=7.1$  Hz,  $\text{CH}_3\text{CH}_2$ ), 2.40 (m, 8H), 3.71 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.55 (m, 1H,  $\text{OCHO}$ ), 7.33 (m, 5H) ppm;  $^{13}\text{C}$  NMR (50 MHz):  $\delta$  149.3, 139.9, 129.0, 102.0, 64.0, 39.3, 35.9, 32.8, 21.1, 14.9 ppm; MS: (EI)  $m/z$  270, 269, 243 ( $\text{M}^+-\text{CN}$ ), 224 ( $\text{M}^+-45$ ), 196, 195, 192 ( $\text{M}^+-\text{Ph}$ ), 180, 167, 165, 152, 129, 105, 72; HRMS: calcd for  $\text{C}_{17}\text{H}_{19}\text{NO}_2$  269.1411, found 269.1382."

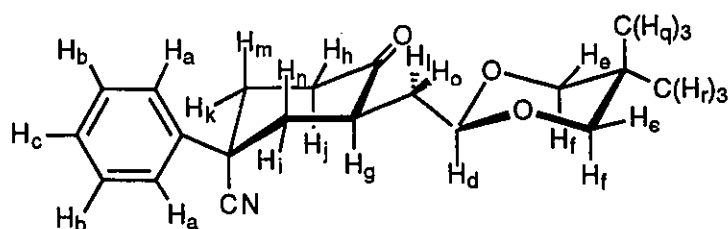
**4-Cyano-4-phenyl-2-(ethylpropylene(2,2-dimethyl)acetal)cyclohexanone**  
**(226)**



**226**

A sample of compound **224** that had been stored for ca. 8 months at 5 °C was subjected to column chromatography (neutral alumina, 1 cm x 25 cm, 5:1 petroleum ether/ethyl acetate) and yielded 18 mg of pure material (>90% by GC-MS). Compound

**224** (18 mg, 0.067 mmol) and 2,2-dimethyl-1,3-propanediol (35 mg, 0.33 mmol, 5 equiv) were dissolved in anhydrous benzene (4 mL). A single crystal of PPTS was added and the solution was stirred at room temperature for 13 h. The reaction was checked by TLC to ensure that all of the starting material had reacted before the solution was concentrated. Column chromatography (flash silica gel, 1 cm x 20 cm, 5:1 petroleum ether/ethyl acetate) provided 12.3 mg (56%) of **226** as a pale yellow oil. All of the spectra for keto-acetal **226** were recorded immediately.



226

Compound **226**\*:  $^1\text{H}$  NMR (500 MHz, COSY):  $\delta$  7.50-7.48 (m,  $\text{H}_a$ ), 7.42-7.39 (m,  $\text{H}_b$ ), 7.36-7.34 (m,  $\text{H}_c$ ), 4.58 (dd,  $\text{H}_d$ ,  $J = 5.9, 3.9$  Hz), 3.56 (dm, 2H,  $J = 11.3$  Hz,  $\text{H}_e$ ), 3.40 (d, 1H,  $J = 11.3$  Hz,  $\text{H}_f$ ), 3.37 (d, 1H,  $J = 11.3$  Hz,  $\text{H}_f'$ ), 3.24 (m,  $\text{H}_g$ ), 2.97 (m,  $\text{H}_h$ ), 2.67 (ddd,  $\text{H}_i$ ,  $J = 13.6, 5.4, 3.7$  Hz), 2.57 (ddd,  $\text{H}_j$ ,  $J = 14.3, 4.2, 2.5$  Hz), 2.450 (m,  $\text{H}_k$ ), 2.32 (ddd,  $\text{H}_l$ ,  $J = 3.91, 6.14, 14.31$  Hz), 2.25 (ddd,  $\text{H}_m$ ,  $J = 14.0, 14.0, 4.2$  Hz), 1.98 (ddd,  $\text{H}_n$ ,  $J = 13.6, 13.6, 13.6$  Hz), 1.45 (ddd,  $\text{H}_o$ ,  $J = 5.9, 5.9, 14.3$  Hz), 1.29-1.24 (m,  $\text{H}_p$ ), 1.16 (s, 3 $\text{H}_q$ ), 0.69 (s, 3 $\text{H}_r$ ). In  $^1\text{H}$ - $^1\text{H}$  decoupling experiments, irradiation of the methine proton at  $\delta$  3.24 ( $\text{H}_g$ ) caused the collapse of the following signals:  $\delta$  2.67 ( $\text{H}_i$ ) to a dd,  $J = 13.6, 3.7$  Hz;  $\delta$  2.32 ( $\text{H}_l$ ) to a dd,  $J = 14.3, 3.9$  Hz;  $\delta$  1.98 ( $\text{H}_n$ ) to a dd,  $J = 13.6, 13.6$  Hz; and  $\delta$  1.45 ( $\text{H}_o$ ) to a dd,  $J = 14.3, 5.9$  Hz. Irradiation of the acetal methine proton at  $\delta$  4.58 ( $\text{H}_d$ ) caused the collapse of the signal at  $\delta$  2.32 ( $\text{H}_l$ ) to a dd,

\* Reproductions of the original spectra for compound **226** are included in Appendix II.

$J = 14.3, 6.1$  Hz and the signal at  $\delta$  1.45 ( $H_o$ ) to a dd,  $J = 14.3, 5.9$  Hz;  $^{13}C$  NMR (125 MHz, DEPT):  $\delta$  208.4 (s,  $C=O$ ), 138.7 (s, phenyl  $=C(C)(C)$ ), 129.2 (d,  $C_b$ ), 128.5 (d,  $C_c$ ), 125.5 (d,  $C_a$ ), 121.6 (s,  $CN$ ), 100.1 (d,  $C_d$ ), 77.2 (t,  $C_{e,f}$ ), 76.7 (t,  $C_{l,o}$ ), 44.6 (s,  $C-CN$ ), 42.9 (d,  $C_g$ ), 39.0 (t,  $C_{k,m}$ ), 38.0 (t,  $C_{n,l}$ ), 33.5 (t,  $C_{h,j}$ ), 30.1 (s,  $C(CH_3)(CH_3)$ ), 23.0 (q,  $C_q$ ), 21.8 (q,  $C_r$ ); MS: (EI)  $m/z$  326 (M-1, 1.0%), 283 (M-44, 8.1%), 197 (20.3%), 149 (74%), 129 (43%), 115 (37%), 105 ( $C_6H_5C=O^+$ , 16%), 77 (22%,  $C_6H_5^+$ ), 57 (base peak), 41(81%); Exact Mass calcd for M-1( $C_{20}H_{24}NO_3$ ) 326.1834, found 326.1801.

### **Rhodium Pivalate Catalyst**<sup>166</sup>

A mixture of  $NaHCO_3$  (0.42 g, 5.0 mmol), pivalic acid (5.10 g, 50.0 mmol), and ethanol (absolute, 5 mL) was heated at reflux under argon for 1 h. Cannula addition of a solution of  $RhCl_3 \cdot 3H_2O$  (250 mg, 1.19 mmol) in ethanol (absolute, 5 mL) to the pivalic acid mixture produced a deep-red transparent solution. This solution was stirred for 3 h, then allowed to cool to room temperature. The solvent was removed and the resulting solid was dissolved in ether, and extracted with sodium bicarbonate (10% w/v aqueous solution) to remove the excess pivalic acid. The organic layer was washed with brine, dried, and concentrated. The blue-green solid that was obtained was dried under vacuum overnight to give 480 mg (66%) of a dark, fir-green, finely divided solid.

### **Photochemical Decomposition of $\alpha$ -Diazoketone (210) with Ethyl Vinyl Ether**

A solution of  $\alpha$ -diazoketone **210** (100 mg, 0.446 mmol) in ethyl vinyl ether (5 mL, 52.3 mmol) was placed in an oven-dried quartz tube (15 mm x 120 mm) that had been cooled under a stream of argon. After degassing the solution by bubbling dry

deoxygenated argon through it for 20 min, it was irradiated with a medium pressure Hanovia mercury lamp for 2.5 h until TLC analysis indicated that the starting material had been completely consumed.

Concentration of the mixture followed by column chromatography (flash silica gel, 1.5 cm x 30 cm, 11:1 petroleum ether/ethyl acetate) gave 103 mg of cyclobutanone **187** (87 %). The spectral data obtained were identical to that given for **187**.

#### **Sensitised Photochemical Decomposition of $\alpha$ -Diazoketone **210** with Ethyl Vinyl Ether**

The procedure for the non-sensitised experiment that is described above was modified by the addition of benzophenone (0.813 g, 4.46 mmol, 10 equiv) to the solution of  $\alpha$ -diazoketone **210** (100 mg, 0.446 mmol) and ethyl vinyl ether (5 mL, 52.3 mmol). After the mixture was degassed and irradiated (4.5 hr) as above. The crude reaction mixture contained at least four products by GC-MS. It appeared that some cyclopropane was present in the crude  $^1\text{H}$  NMR, although it was difficult to determine the concentration from the integration due to the tenfold excess of benzophenone. Concentration and column chromatography (flash silica gel, 1.5 cm x 30 cm, 11:1 petroleum ether/ethyl acetate) gave 63 mg of cyclobutanone **187** (contaminated with benzophenone as well as 8 mg of the rearranged cyclopropane and dihydrofuran **217** (7%)). Further radial chromatography (silica gel, 4 mm plates, 20:1 petroleum ether/ethyl acetate) of the contaminated cyclobutanone **187** afforded 52 mg of pure cyclobutanone **187** (44%). The spectral data obtained were identical to that given for **187**.

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## CLAIMS TO ORIGINAL RESEARCH

1. It was established using bromides **39-43** that those compounds containing a substituent bearing a sulfur atom at the allylic position (**41-43**) underwent elimination of the sulfur containing functional group under all of the following conditions: (a) *n*-Bu<sub>3</sub>SnH, AIBN, Benzene; (b) TTMSS, AIBN, Benzene; and (c) SmI<sub>2</sub>, THF, HMPA (4 equiv). In an unprecedented fashion, O-substituted allylic derivatives **39** and **40** underwent β-elimination to give **54** under conditions (c). A mechanistic interpretation of these findings is discussed in Chapter 1.
2. A novel SmI<sub>2</sub>-promoted ring-opening/decarboxylation reaction of halolactones was developed. Our findings indicated that the reaction proceeded via a radical mechanism. For example, iodolactone **66**, bromolactone **67**, and iodothialactone **68**, all undergo ring-opening and decarboxylation under SmI<sub>2</sub>, THF, HMPA (4 equiv) conditions to give diene **78** in good yield. These results offer a number of potentially valuable avenues of research in the field of tandem radical cyclization reactions.
3. Reaction conditions were developed that dramatically effected the results of the transformation outlined in (2). Under "reverse addition" conditions halolactones were found to undergo efficient ring-opening to the corresponding unsaturated acids. This new method represents a mild and selective alternative to traditional Zn-based methods (often incompatible with other functionality in a complex molecule) for carrying out the same transformation.

4. Studies towards the preparation of a novel hydrocarbon-soluble Sm(II) complex **88** were initiated. Successful completion of this synthesis should provide a reagent that would have the potential to significantly broaden the application of Sm(II)-mediated transformations in organic synthesis.
5. An unprecedented SmI<sub>2</sub>-induced ring-opening reaction of  $\alpha$ -keto spirocyclobutanes **123** and **124** is described in Chapter 2. Samarium ketyls of **123** and **124** ring-open to give ketones **126** and **127** in good yields. Related carbinyl species generated from thiocarbonate **119**, and iodides **120** and **129** were reduced to the corresponding hydrocarbons. The ring-opened products of spirocyclobutyl systems have the potential to participate in further intra- or intermolecular reactions with a wide variety of radical acceptors and electrophiles in radical- or anionic-type transformations.
6. Dihydrofurans **217** and **226** were prepared via an unusual rearrangement of donor-acceptor cyclopropanes that were generated from the Rh<sub>2</sub>(OAc)<sub>4</sub>-catalyzed reaction of ethyl vinyl ether with azibenzil **210** and  $\alpha$ -diazoketone **223**. The structures of compounds **217** and **226** were previously misassigned. In the work described the assignments were corrected by the unambiguous characterization of a derivative. Thus, compounds **217** and **226** were subject to transketalization with 2,2-dimethyl-1,3-propanediol and the corresponding protected keto aldehydes were characterized by spectroscopic methods.
7. In order to demonstrate that the mechanistic origin of **217** was the rearrangement of a donor acceptor cyclopropane **215** a trapping procedure was implemented. The successful isolation of **259** confirmed our hypothesis regarding the origin of **217** and poses important new questions with respect to previous work and resulting conclusions by other authors in this area.

8. Based on evidence from product-isolation studies, an unprecedented Grob-type fragmentation pathway has been postulated for the fragmentation of donor acceptor cyclopropane **215** under DIBAL reduction conditions. The isolated benzyl alcohol is thought to arise from the intermediate aluminate **260** via the 6-membered ring transition state **260a**. To the best of our knowledge the fragmentation of aluminium cyclopropylalkoxides bearing an appropriately positioned leaving group is an unknown reaction that warrants further investigation.

**APPENDIX I**  
**MISCELLANEOUS LABORATORY INFORMATION**

**TLC Stains**

*p*-Anisaldehyde:     9.2 mL *p*-anisaldehyde  
                              3.75 mL acetic acid (glacial)  
                              340 mL ethanol (95%)  
                              12.5 mL sulfuric acid (conc.)

Add *p*-anisaldehyde to ethanol and cool to 0° C. Slowly add the sulfuric acid then the acetic acid. If you don't cool the ethanol solution the mixture will turn yellow in colour upon addition of the acids.

Molybdenum:           5 g ammonium molybdate  
                              10 mL sulfuric acid (conc.)  
                              90 mL distilled water

Dissolve the ammonium molybdate in 90 mL of distilled water. Slowly add the concentrated sulfuric acid to the water.

## Cleaning baths

Acid bath:\*      400 g    potassium dichromate  
                     400 mL   water  
                     4.0 L     sulfuric acid (conc.)

The potassium dichromate is dissolved in 400 mL of water in a large thick-walled glass container. The sulfuric acid is added **CAREFULLY and SLOWLY** to the dichromate solution. The temperature of the dichromate/water mixture must not exceed 70–80 °C!!!!

Base bath:\*\*     1.0 kg    potassium hydroxide  
                     4.0 L     distilled water  
                     8.0 L     ethanol

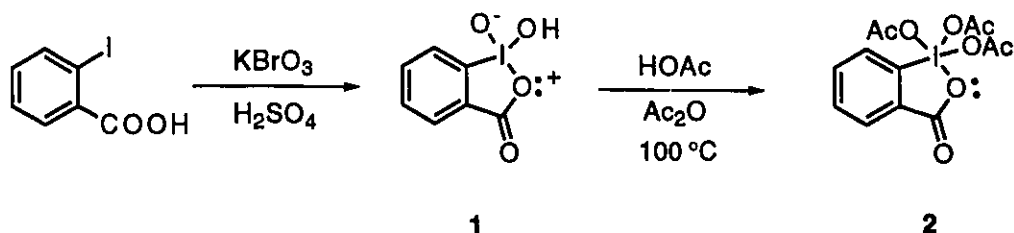
The potassium hydroxide is **SLOWLY** dissolved in the 4.0 L of water in a large plastic container. The temperature of the mixture must not exceed 70–80 °C!!!! Note that the dissolution of KOH in water is an **EXOTHERMIC** reaction. After the aqueous hydroxide solution cools to room temperature 8 L of ethanol (95%) is added carefully.

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\* Remember to LABEL the container as CORROSIVE.....Keep bases and solvents (including acetone) away.

\*\* Be sure to label the container CORROSIVE.....Keep acids away.

### Preparation of Dess-Martin periodinane <sup>185</sup>



#### Part I:

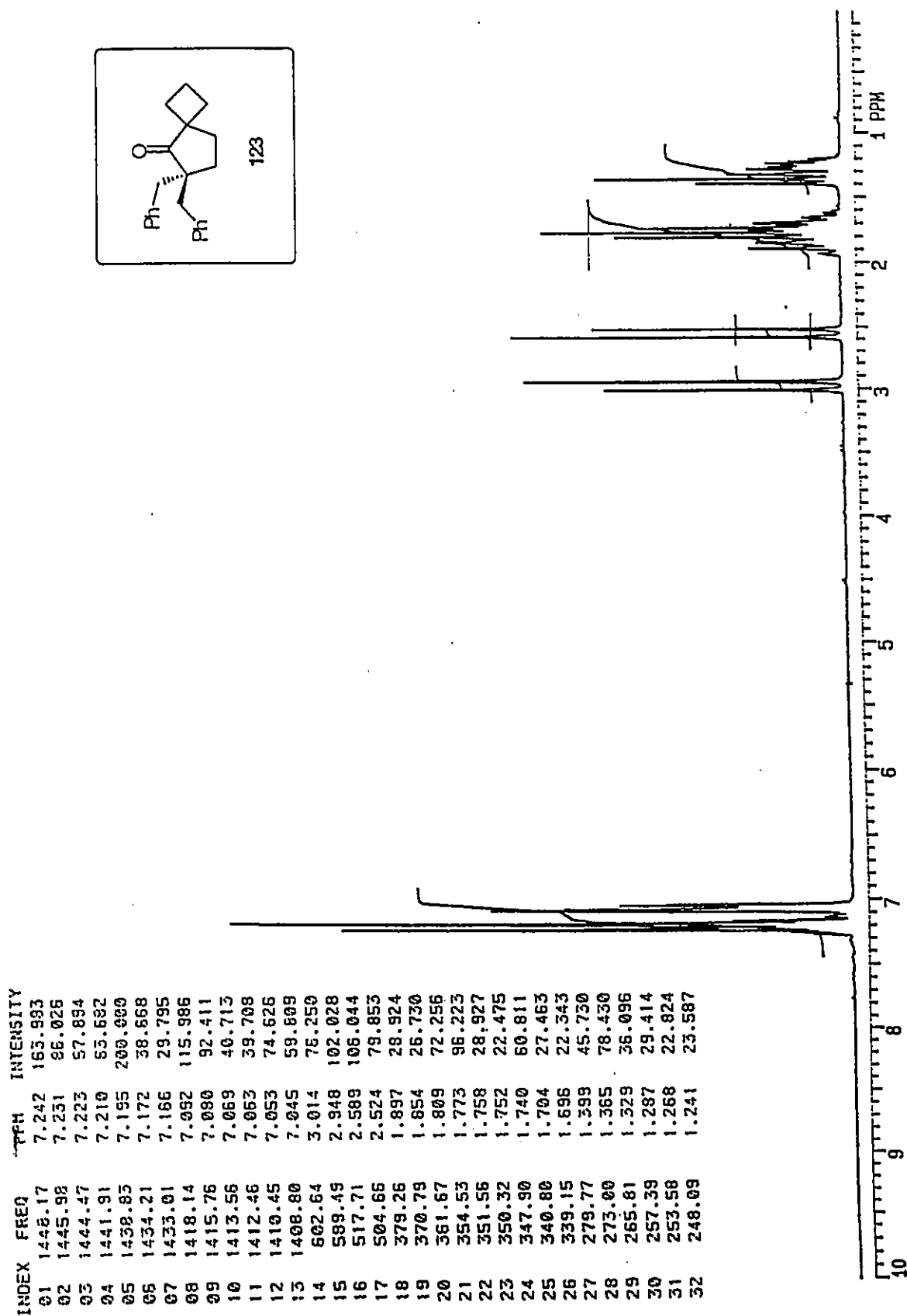
An aqueous solution of  $\text{H}_2\text{SO}_4$  (243 mL, 0.73 M)[4.38 mL of conc.  $\text{H}_2\text{SO}_4$  made up to 243 mL] and 2-iodobenzoic acid (28.4 g, 0.113 mol) were placed in a 1 L 3N r.b. flask (a **large flask is required**) equipped with a thermometer, overhead stirrer (the **mixture becomes extremely thick**), oil bath and condenser. An ice bath was kept close at hand in case the reaction over-heated. This mixture was stirred vigorously while potassium bromate (25.3 g, 0.15 mol) was added at such a rate that the temperature of the reaction did not exceed  $55\text{ }^\circ\text{C}$ . When the addition was complete, the resulting beige slurry was heated to  $65\text{ }^\circ\text{C}$  and stirred at this temperature for 6 h until the evolution of bromine was complete (**much longer than reported in the reference**).

Before filtering the reaction mixture through a medium glass fritted Büchner funnel, the entire slurry was cooled to  $0\text{ }^\circ\text{C}$  in a large ice bath. The beige solid obtained was washed with 1.5 L of ice-cold distilled water and 2 x 50 mL of cold ethanol (95%). The sticky beige solid was dried at  $60\text{ }^\circ\text{C}$  in a vacuum oven for 14 h. A total of 25.1 g (97%) of the 2-iodoxybenzoic acid was obtained as a white-beige powder.

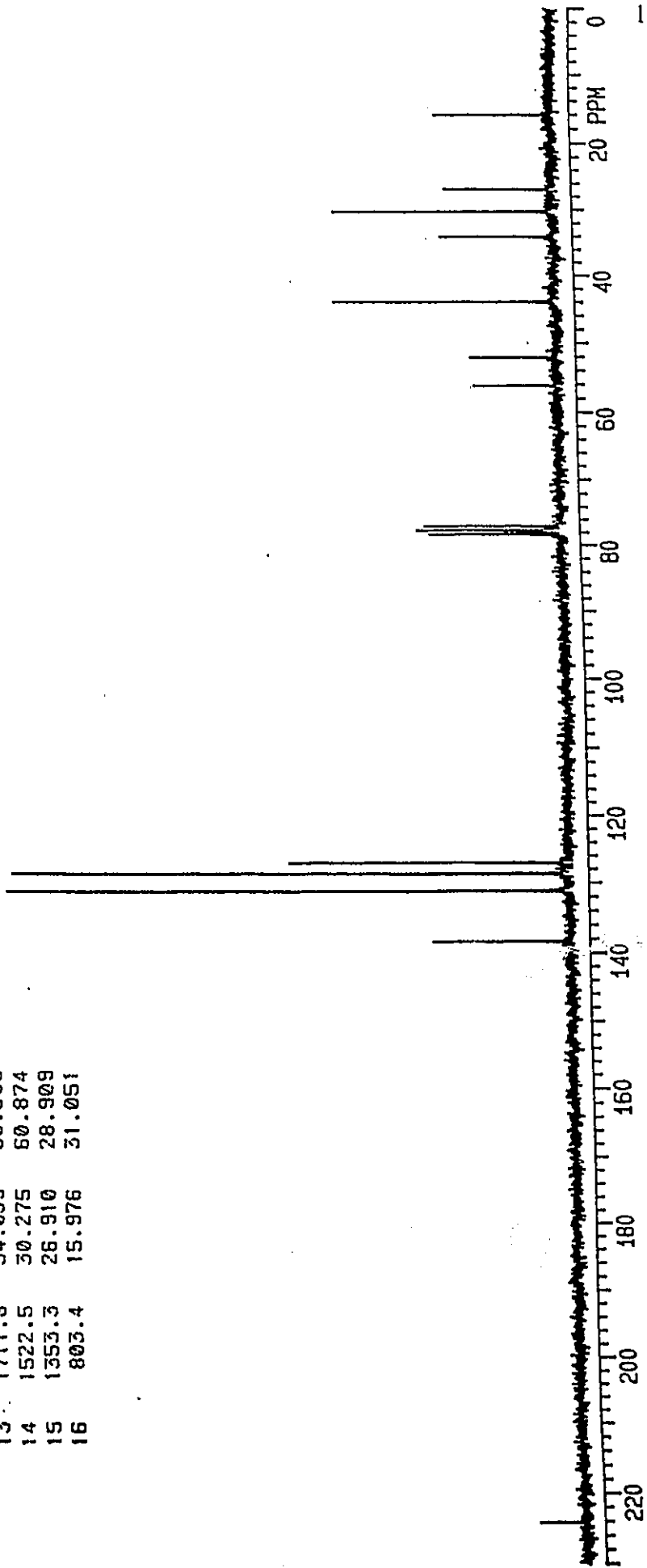
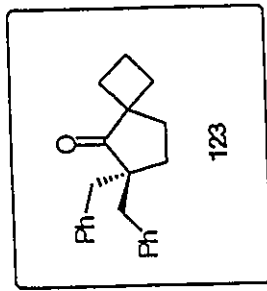
**Part II:**

A slurry of 2-iodoxybenzoic acid (25.0 g, 145 mmol), acetic acid (114 mL, glacial), and acetic anhydride (126.5 mL, 136 g, 0.164 mol) was stirred in a 500 mL 3N r.b. flask at 100 °C for 30 min. All of the solid had dissolved at this point, and the solution was allowed to cool to room temperature. The solvent was removed under vacuum until approximately 20 mL remained. As the solvent disappeared white crystals began to form. The final 20 mL of solvent was removed by filtration through a medium fritted-glass-filter under an atmosphere of argon. The solid obtained was washed with cold ether and dried under vacuum to give 42.41 g (98%) of periodinane **2**. The crystals were stored under argon in a sealed jar (screw-cap lid and parafilm) and protected from light in a cool dry place. After 19 months the reagent had not decomposed to any extent and worked well in oxidations.

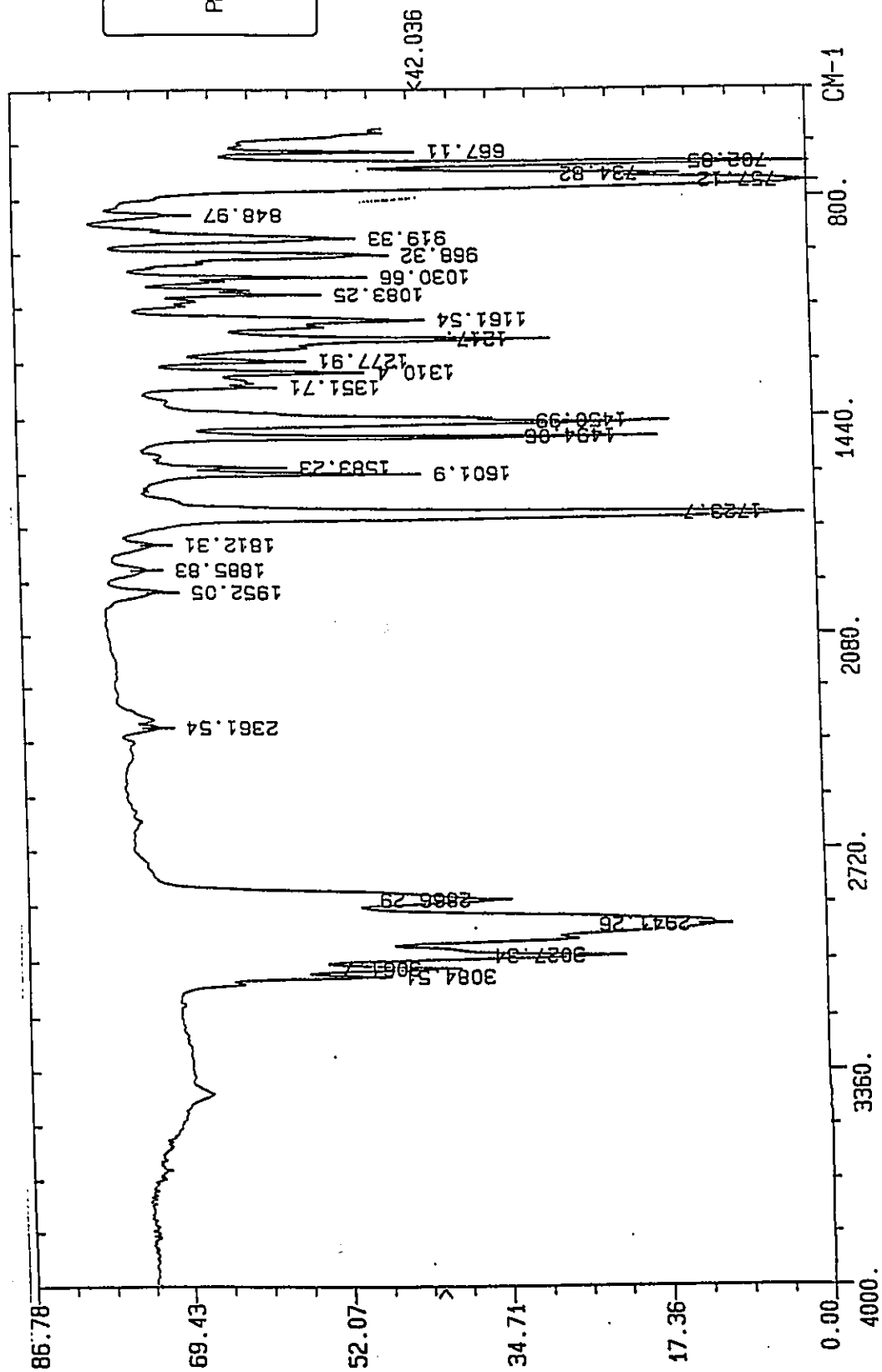
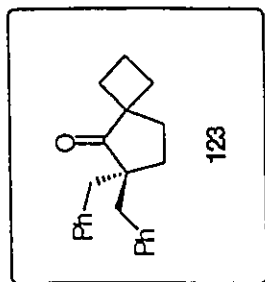
**APPENDIX II**  
**REPRODUCTIONS OF THE ORIGINAL SPECTRA OF**  
**SOME KEY COMPOUNDS DESCRIBED IN THIS THESIS**



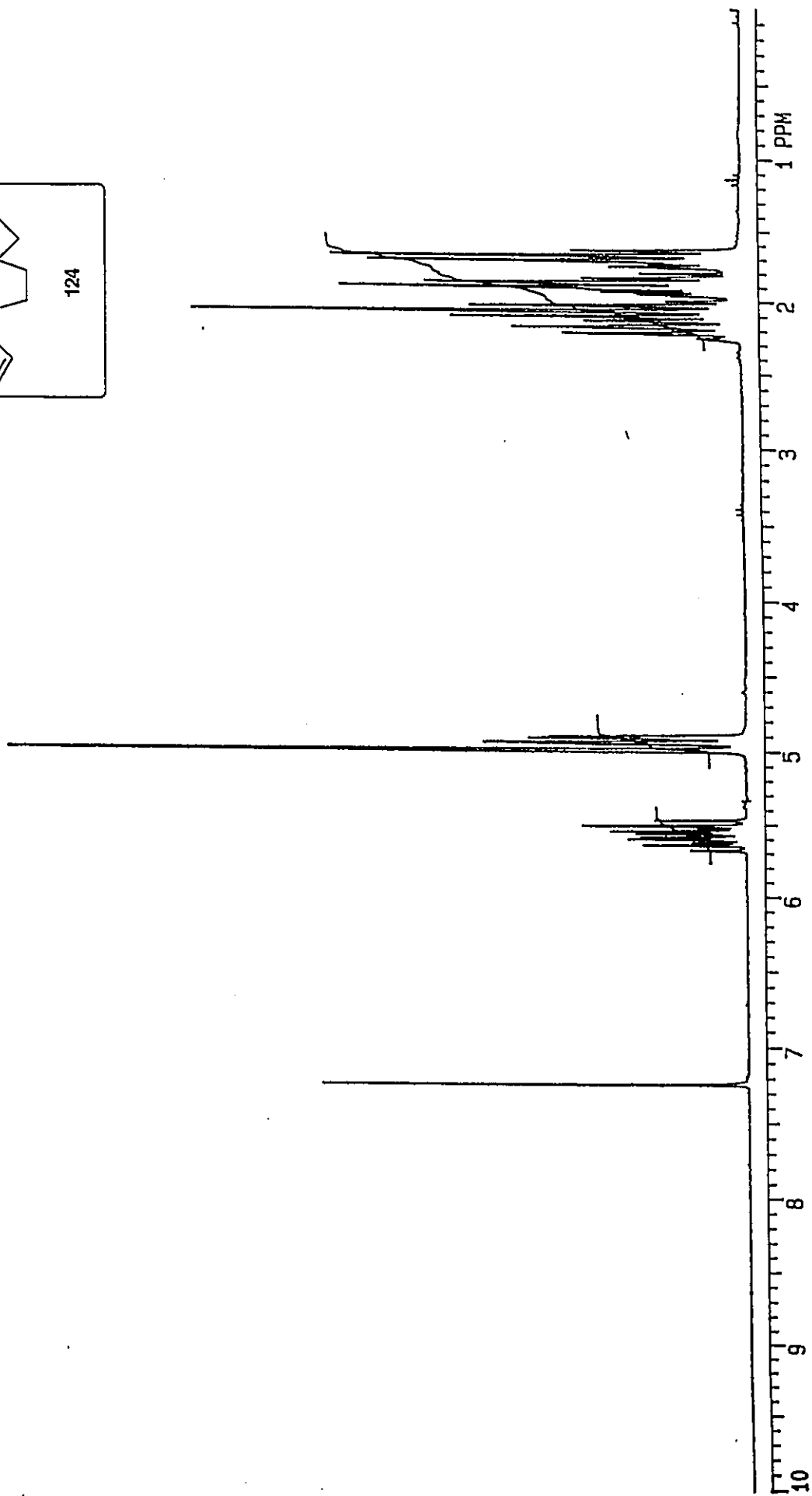
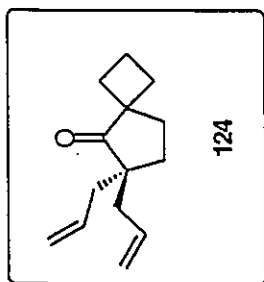
INDEX	FREQ	PPM	INTENSITY
01	11274.2	224.197	12.499
02	6956.0	138.320	39.746
03	6597.2	131.185	151.634
04	6471.1	128.676	147.271
05	6390.4	127.073	73.931
06	3937.9	78.304	35.523
07	3916.0	77.870	15.106
08	3906.0	77.670	37.876
09	3873.9	77.032	36.373
10	2824.4	56.163	23.407
11	2620.7	52.113	23.075
12	2209.9	43.943	58.979
13	1711.8	34.039	30.695
14	1522.5	30.275	60.874
15	1353.3	26.910	28.909
16	803.4	15.976	31.051



<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 50MHz) of 123

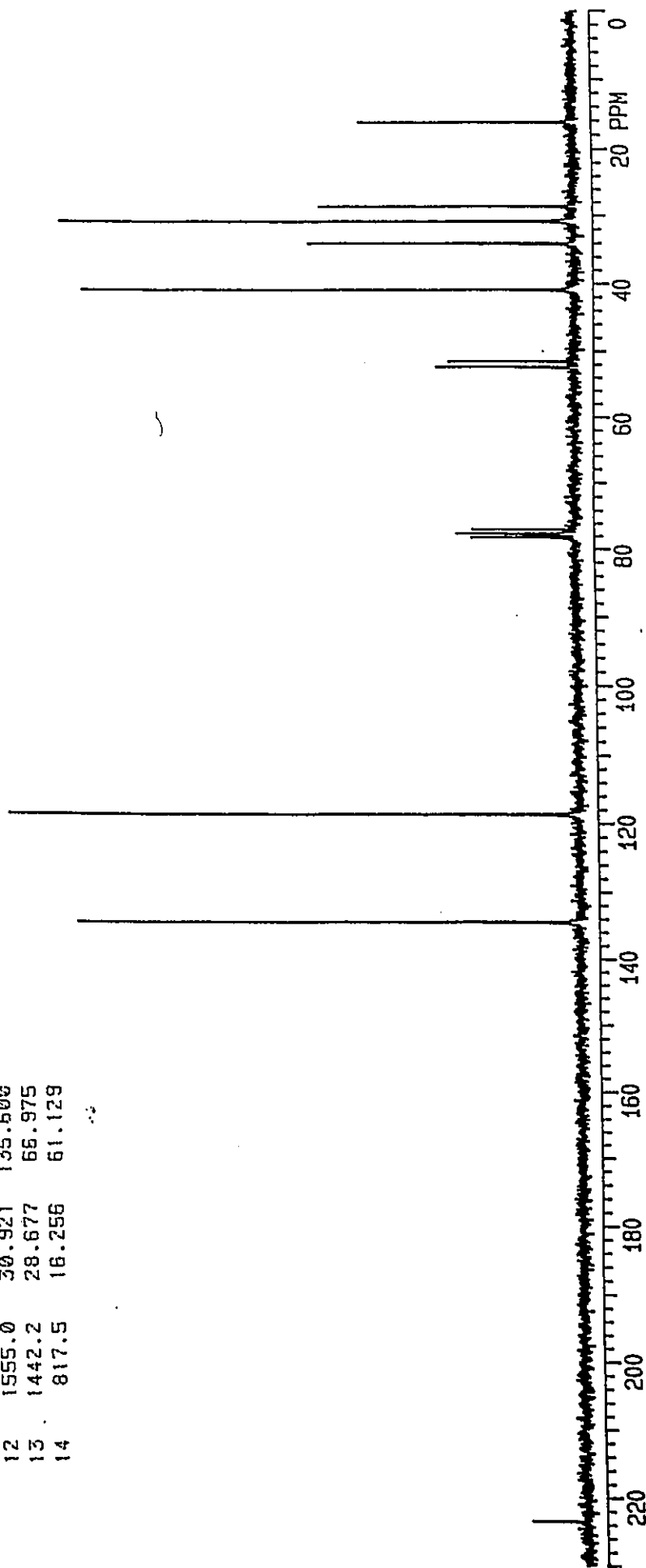
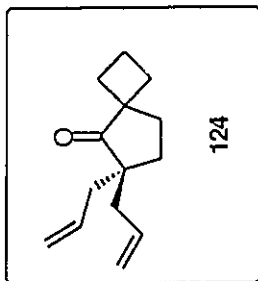


IR Spectrum of 123



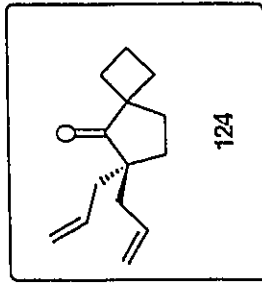
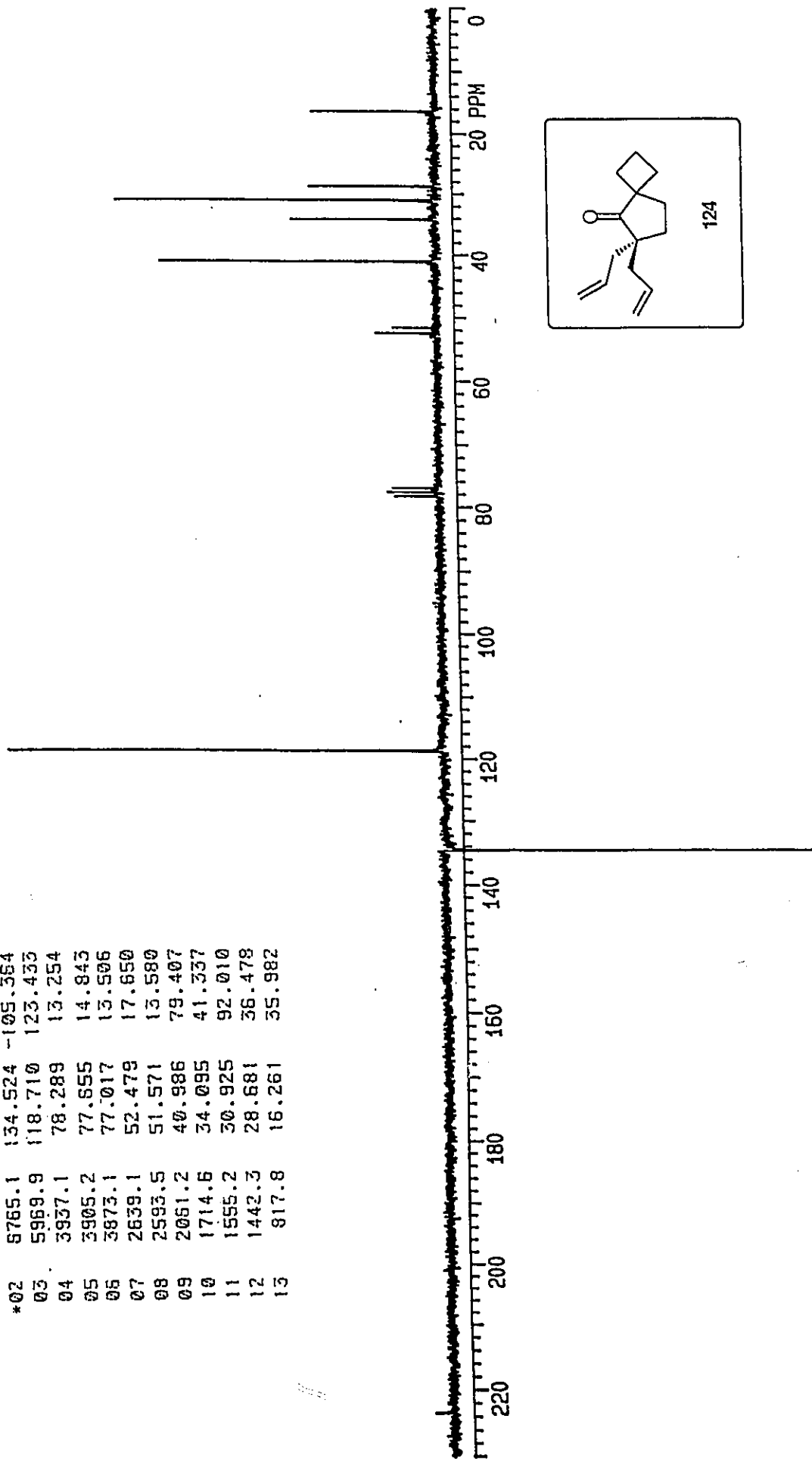
<sup>1</sup>H NMR Spectrum (CDCl<sub>3</sub>, 200MHz) of 124

INDEX	FREQ	PPM	INTENSITY
01	11241.8	223.543	15.393
02	6765.2	134.526	132.423
03	5970.0	118.712	152.154
04	3937.3	78.293	27.816
05	3915.3	77.855	18.624
06	3905.2	77.655	31.140
07	3873.1	77.017	27.530
08	2639.3	52.482	37.349
09	2593.4	51.570	38.116
10	2061.1	40.984	130.247
11	1714.6	34.095	70.282
12	1555.0	30.921	135.600
13	1442.2	28.677	66.975
14	817.5	16.256	61.129



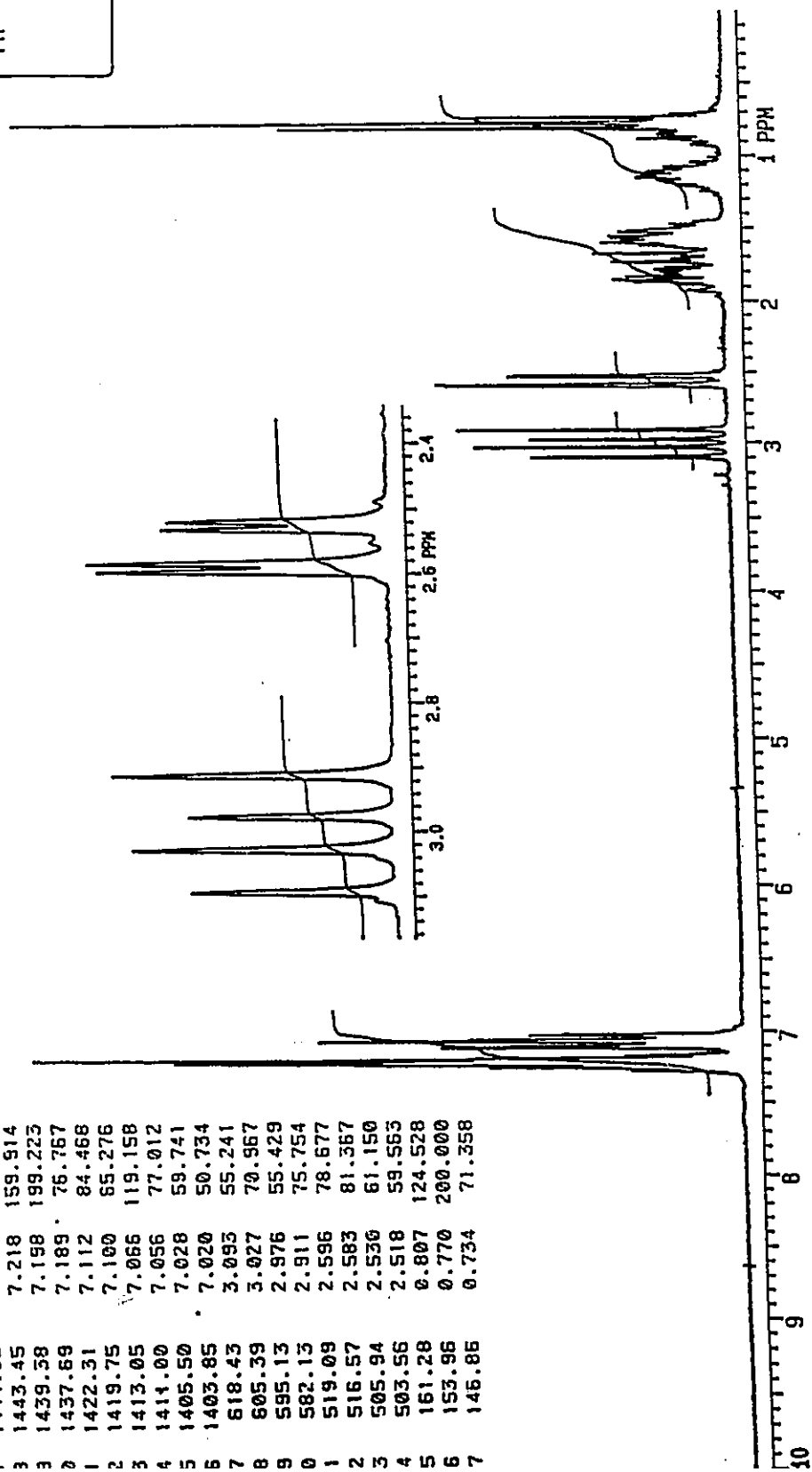
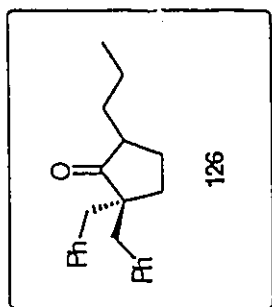
<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 50MHz) of 124

INDEX	FREQ	PPM	INTENSITY
01	11241.4	223.534	5.736
*02	8765.1	134.524	-105.364
03	5969.9	118.710	123.433
04	3937.1	78.289	13.254
05	3905.2	77.655	14.843
06	3873.1	77.017	13.506
07	2639.1	52.479	17.650
08	2593.5	51.571	13.580
09	2061.2	40.986	79.407
10	1714.6	34.095	41.337
11	1555.2	30.925	92.010
12	1442.3	28.681	36.478
13	817.8	16.261	35.982

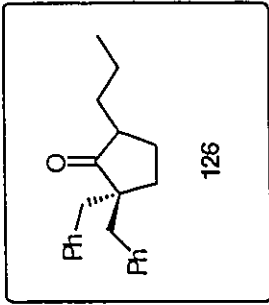


<sup>13</sup>C NMR DEPT Spectrum (CDCl<sub>3</sub>, 50MHz) of 124

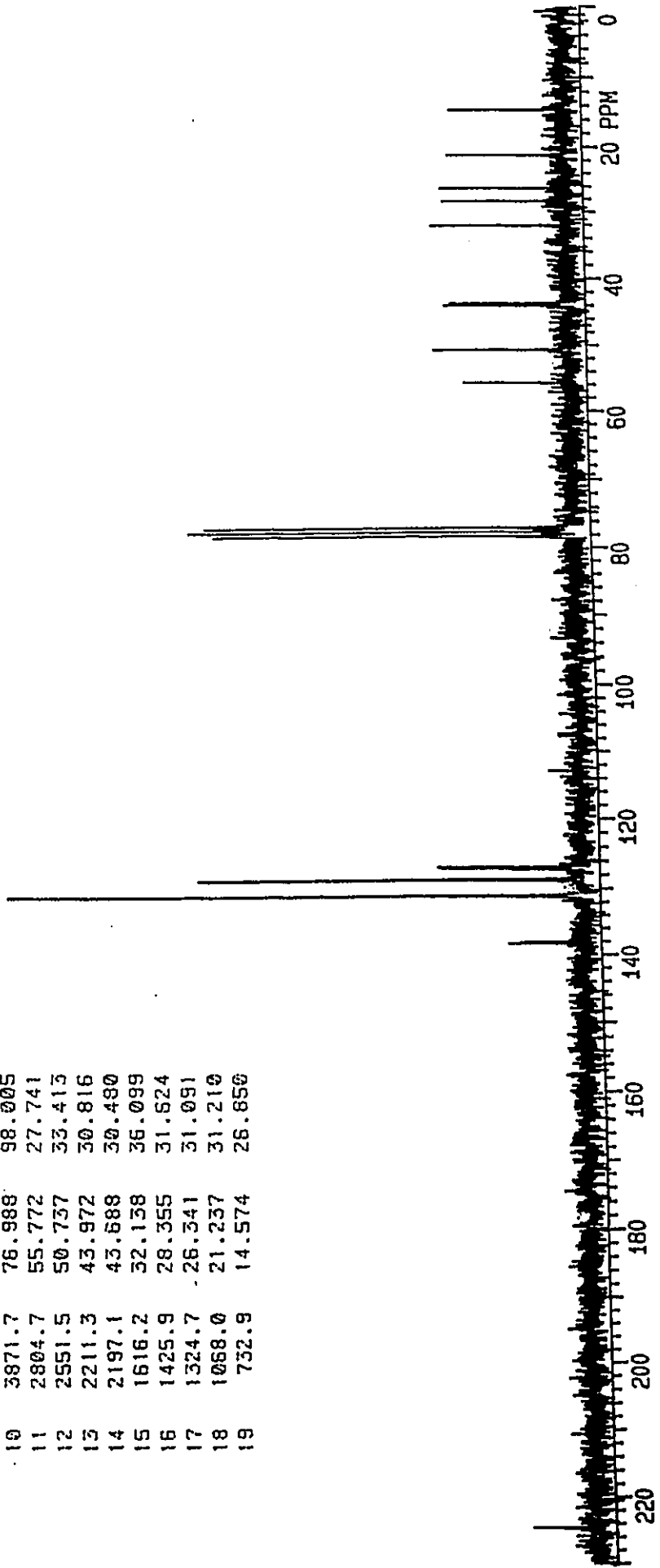
PEAK	FREQ	PPM	INTENSITY
1	1450.70	7.254	71.009
2	1449.96	7.251	63.103
3	1449.01	7.246	55.025
4	1448.32	7.242	52.711
5	1446.67	7.234	105.979
6	1446.02	7.231	106.883
7	1444.65	7.224	144.666
8	1443.45	7.218	159.914
9	1439.58	7.198	199.223
10	1437.68	7.189	76.767
11	1422.31	7.112	84.468
12	1419.75	7.100	85.276
13	1413.05	7.066	119.158
14	1411.00	7.056	77.012
15	1405.50	7.028	59.741
16	1403.85	7.020	50.734
17	618.43	3.093	55.241
18	605.39	3.027	70.967
19	595.13	2.976	55.429
20	582.13	2.911	75.754
21	519.09	2.596	78.677
22	516.57	2.583	81.367
23	505.94	2.530	61.150
24	503.56	2.518	59.563
25	161.28	0.807	124.528
26	153.86	0.770	200.000
27	146.86	0.734	71.358



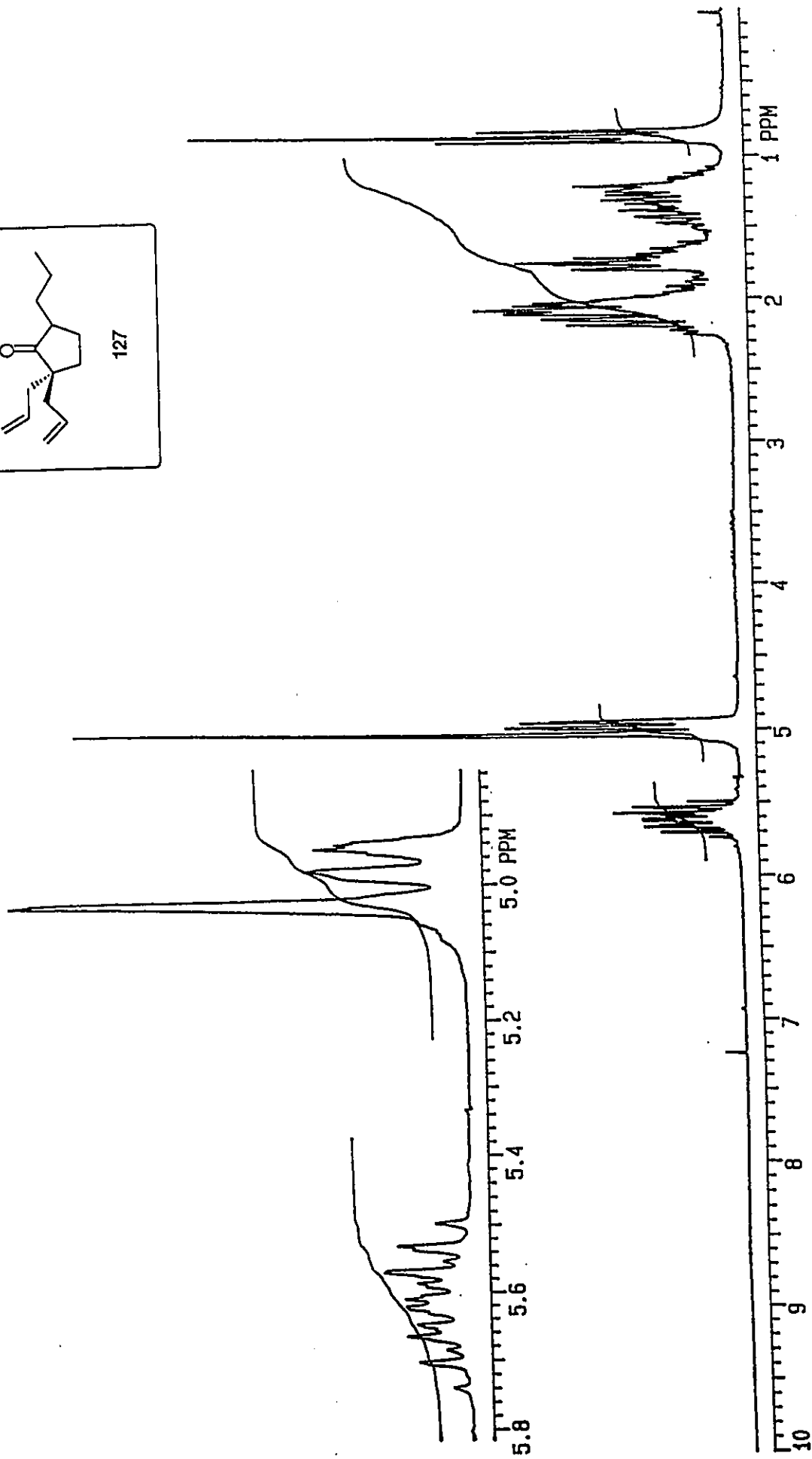
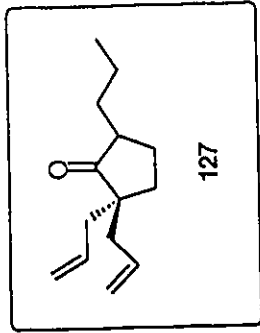
<sup>1</sup>H NMR Spectrum (CDCl<sub>3</sub>, 200MHz) of 126



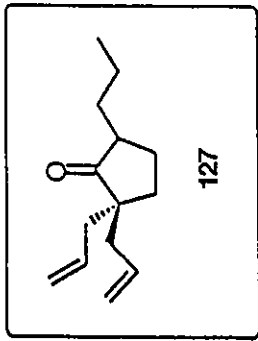
INDEX	FREQ	PPM	INTENSITY
01	11297.5	224.650	15.591
02	6957.4	138.347	19.497
03	6946.0	138.120	15.921
04	6594.2	131.124	153.420
05	6473.5	128.724	101.550
06	6396.2	127.187	36.360
07	6365.8	126.982	37.284
08	3935.7	78.260	97.303
09	3903.7	77.624	101.954
10	3871.7	76.988	98.005
11	2804.7	55.772	27.741
12	2551.5	50.737	33.413
13	2211.3	43.972	30.816
14	2197.1	43.688	30.490
15	1616.2	32.138	36.099
16	1425.9	28.355	31.524
17	1324.7	26.341	31.091
18	1068.0	21.237	31.210
19	732.9	14.574	26.650



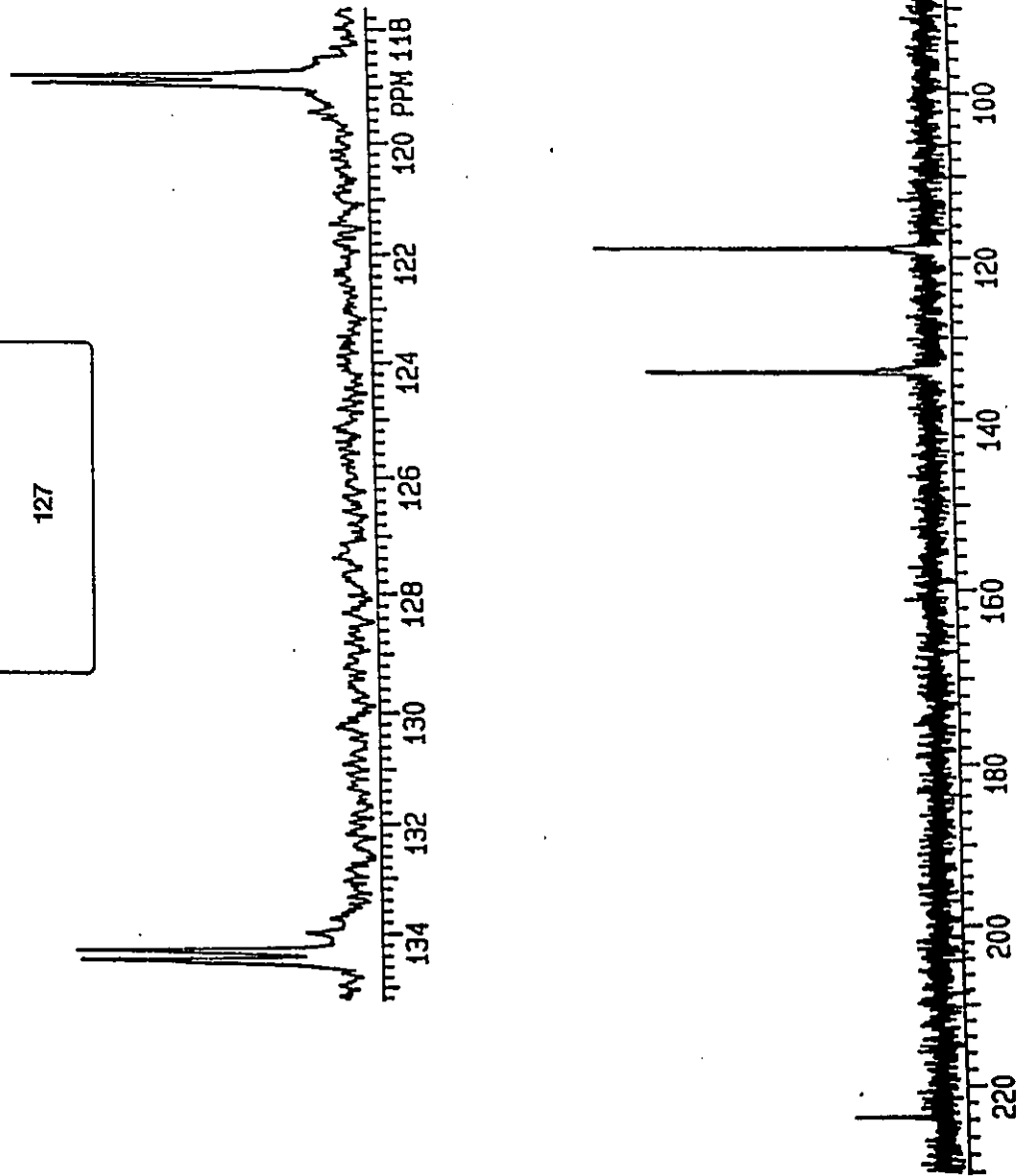
<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 50MHz) of 126



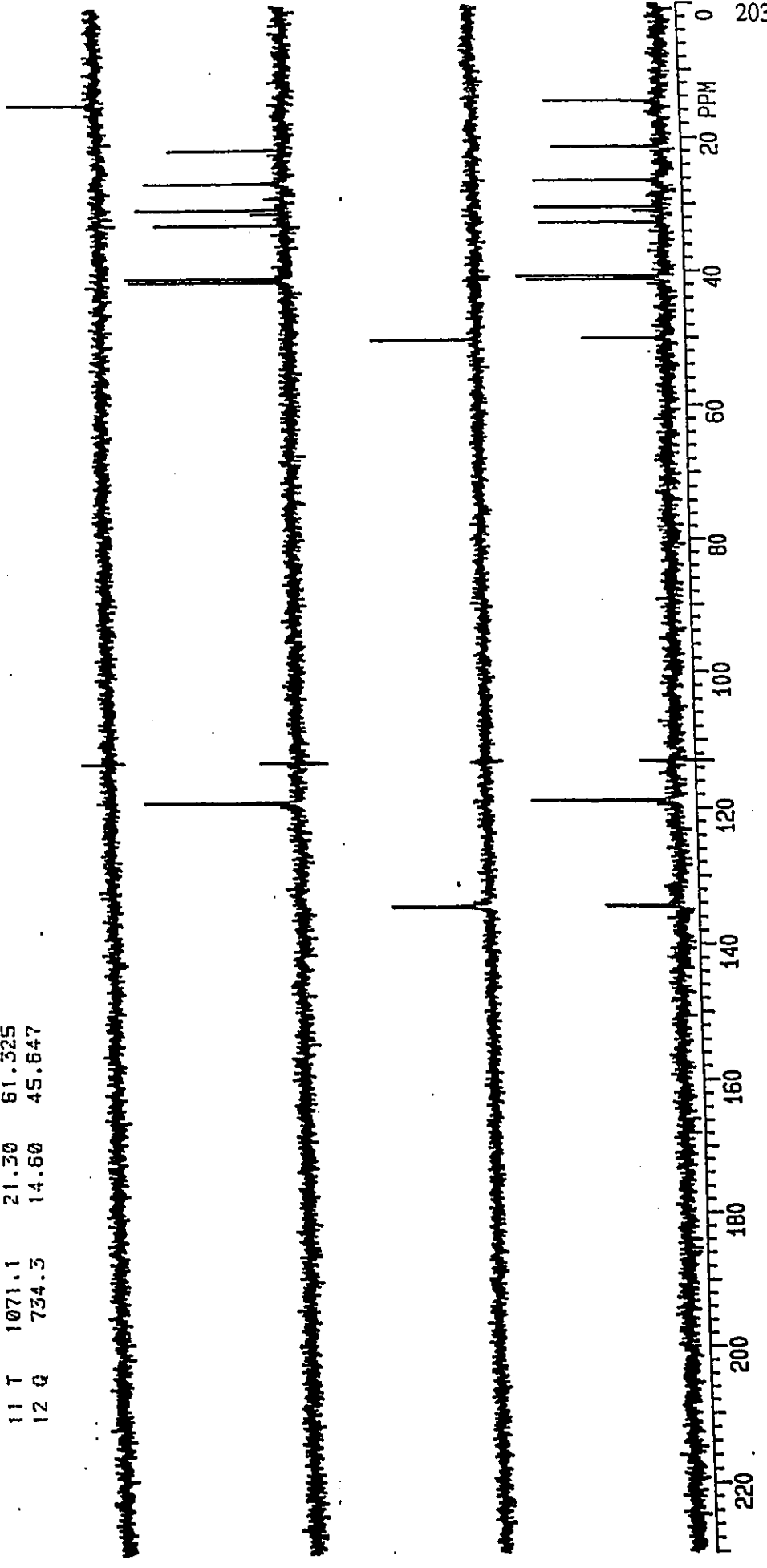
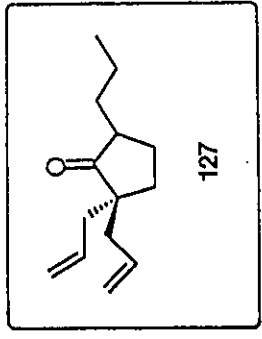
$^1\text{H}$  NMR Spectrum ( $\text{CDCl}_3$ , 200MHz) of 127



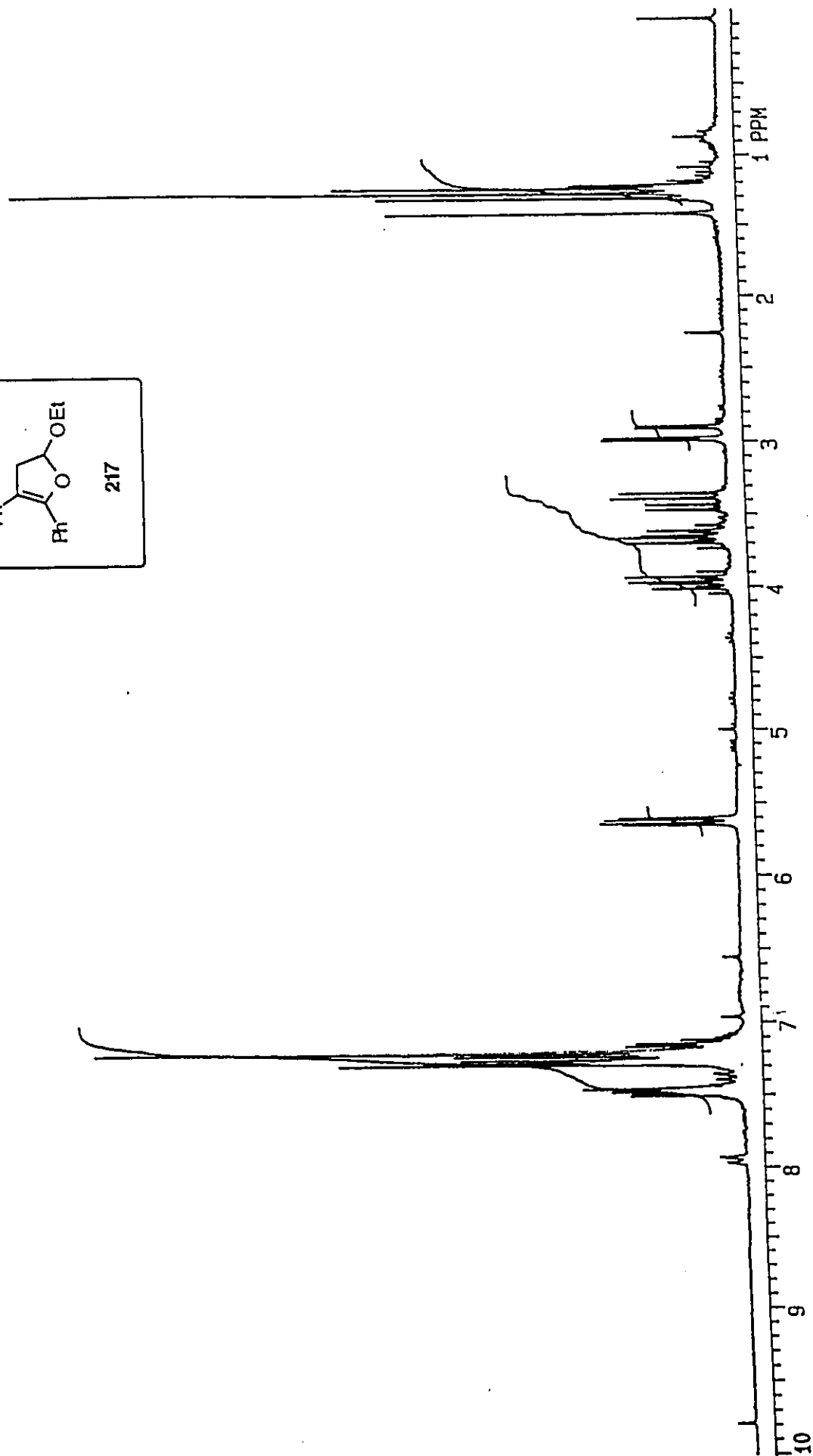
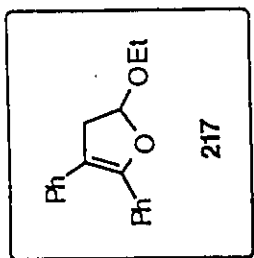
INDEX	FREQ	PPM	INTENSITY
01	11256.3	223.831	19.415
02	6763.2	134.485	60.937
03	6754.3	134.308	60.984
04	5981.6	118.944	69.139
05	5975.3	118.819	71.718
06	3936.5	78.277	47.985
07	3904.4	77.659	48.082
08	3872.5	77.005	47.579
09	2645.7	52.610	31.123
10	2516.2	50.034	57.378
11	2059.9	41.159	55.730
12	2046.1	40.686	58.335
13	1640.8	32.628	60.503
14	1528.0	30.384	59.920
15	1323.3	26.314	59.053
16	1071.1	21.300	52.925
17	734.3	14.602	50.377



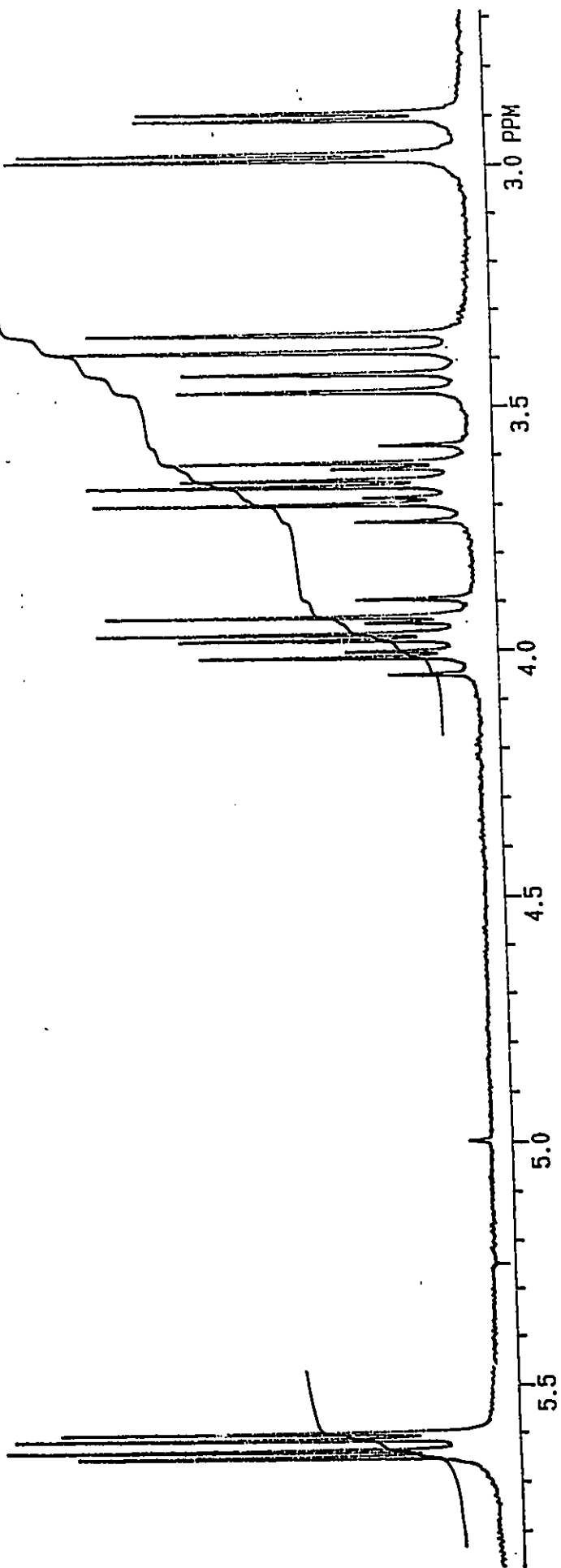
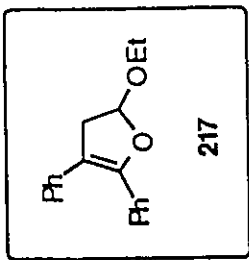
INDEX	FREQ	PPM	INTENSITY
1 D	6752.9	134.48	49.970
2 D	6753.9	134.30	52.853
3 T	5981.8	118.95	79.678
4 T	5975.6	118.82	80.424
5 D	2516.5	50.04	54.229
6 T	2089.7	41.15	84.172
7 T	2046.1	40.59	87.069
8 T	1640.8	32.63	70.924
9 T	1527.7	30.38	78.777
10 T	1323.2	26.31	72.541
11 T	1071.1	21.30	61.325
12 Q	734.3	14.60	45.647



<sup>13</sup>C NMR DEPT Spectrum (CDCl<sub>3</sub>, 50MHz) of 127

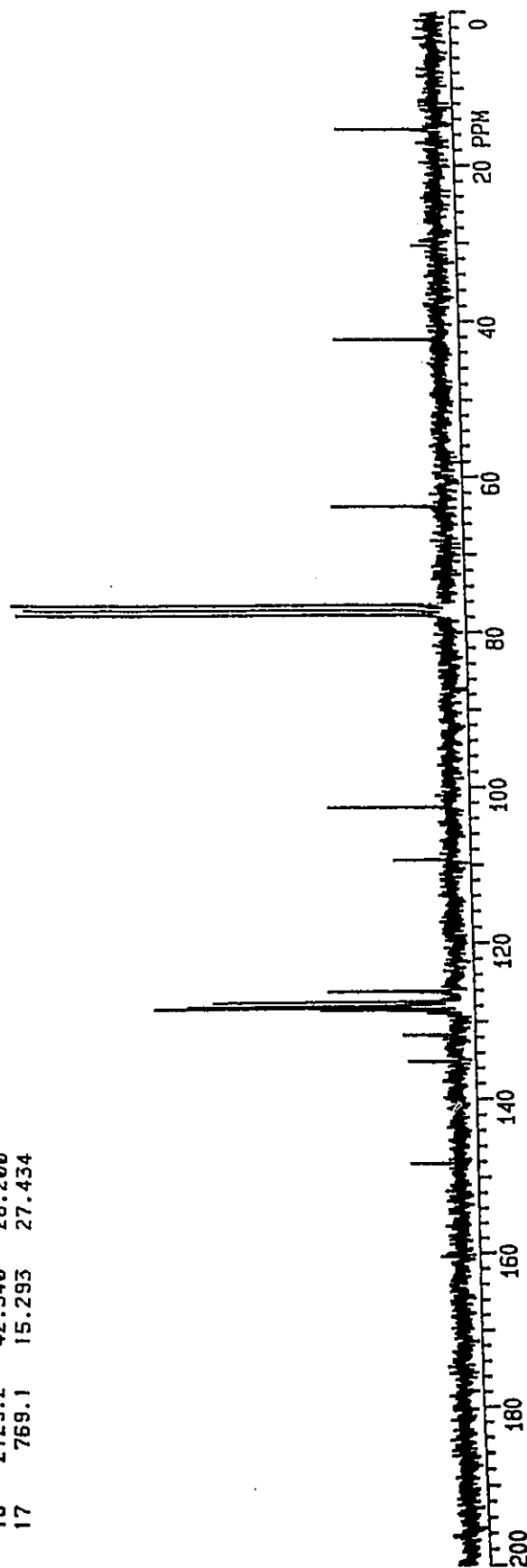
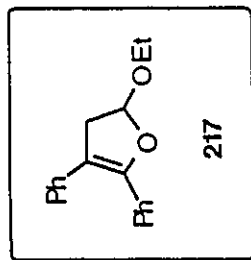


<sup>1</sup>H NMR Spectrum (CDCl<sub>3</sub>, 200MHz) of 217

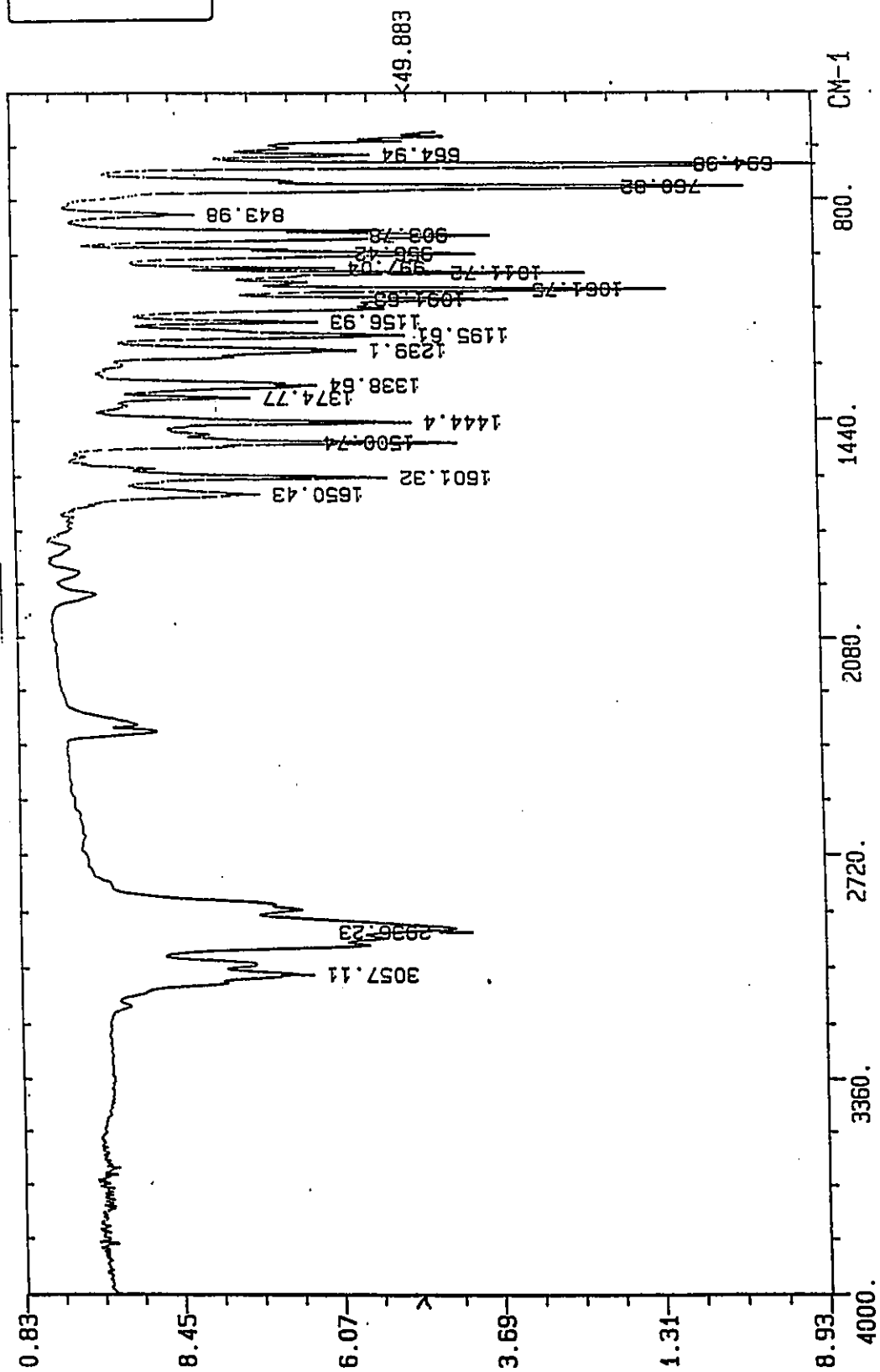
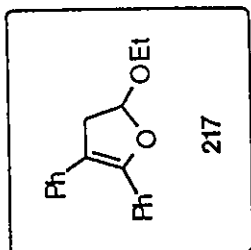


SPECTRAL LINES FOR TH= 12.65  
 RFL= 510.9 RFP= 0

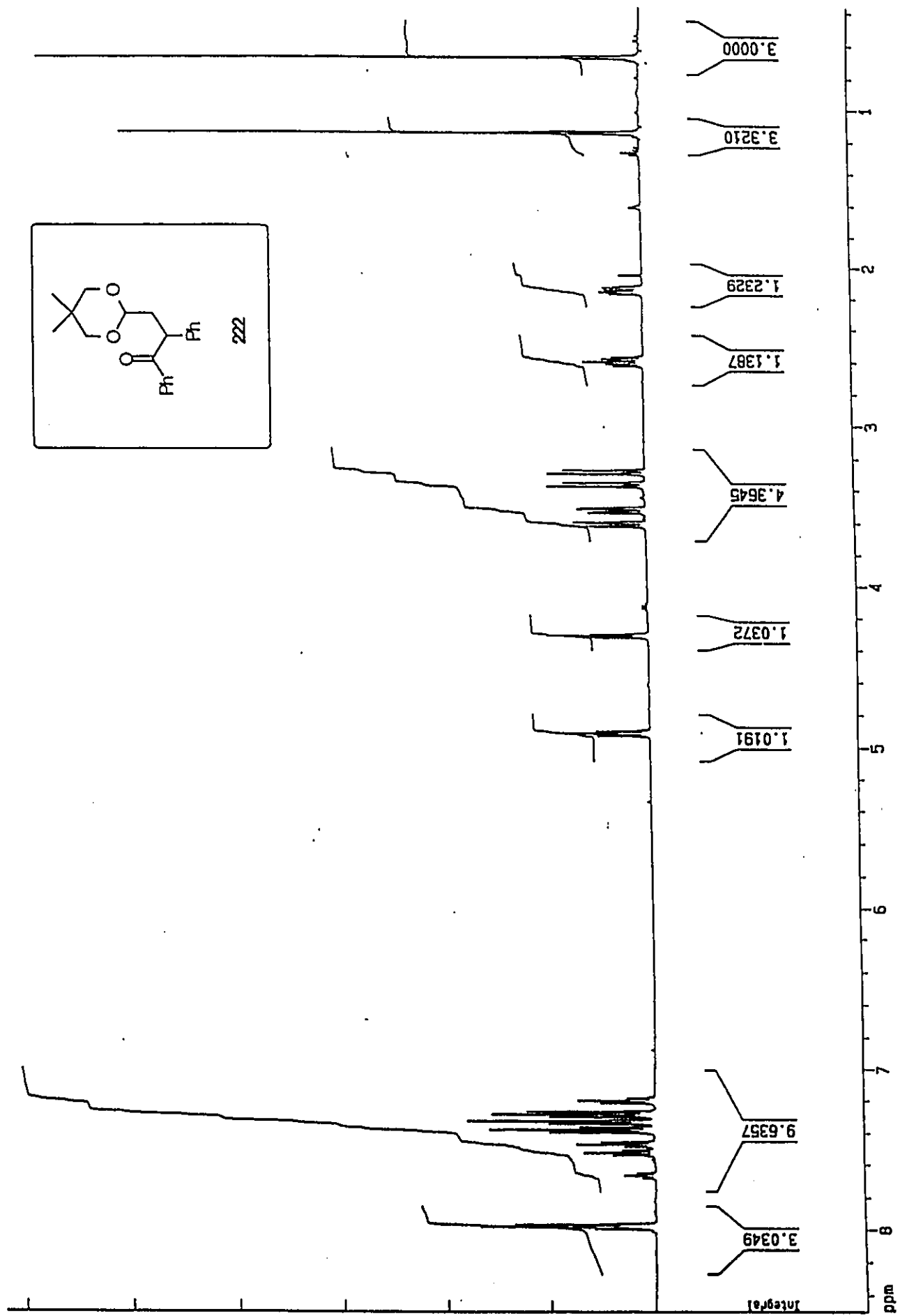
INDEX	FREQ	PPM	INTENSITY
01	7454.9	148.239	13.075
02	6796.7	135.152	12.723
03	6626.1	131.759	14.412
04	6464.2	128.541	35.811
05	6447.3	128.205	79.282
06	6443.7	128.132	75.527
07	6436.5	127.989	70.973
08	6408.7	127.457	63.789
09	6343.6	126.142	33.926
10	5498.0	109.328	16.826
11	5158.3	102.573	32.636
12	3905.3	77.656	113.919
13	3873.4	77.022	114.922
14	3841.5	76.388	114.608
15	3205.8	63.746	29.769
16	2129.2	42.340	28.200
17	769.1	15.293	27.434

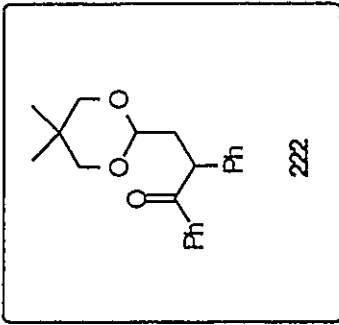


<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 50MHz) of 217

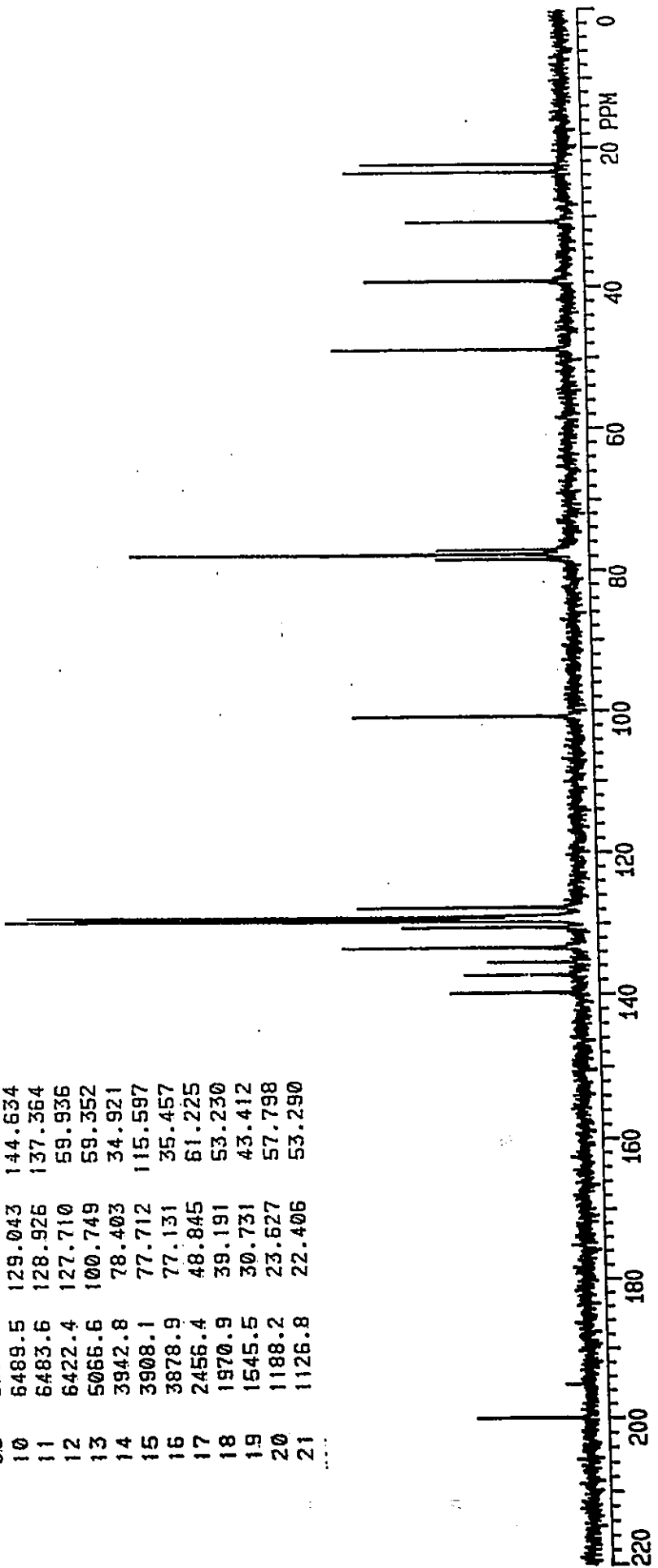


IR Spectrum of 217

$^1\text{H}$  NMR Spectrum ( $\text{CDCl}_3$ , 500MHz) of 222



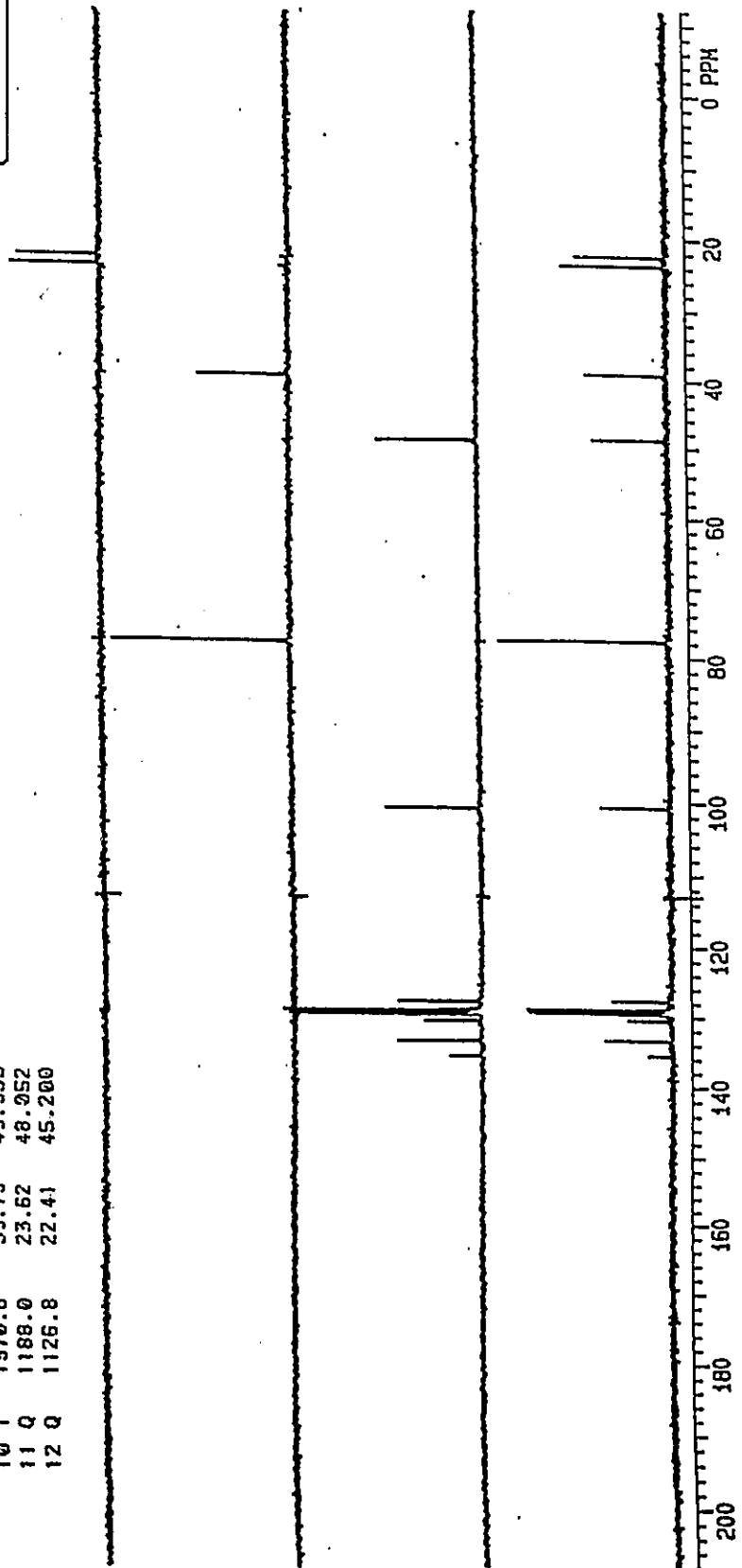
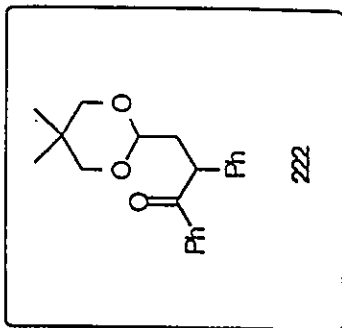
INDEX	FREQ	PPM	INTENSITY
01	10055.8	199.960	29.303
02	7028.5	139.761	34.334
03	6905.1	137.308	30.319
04	6815.1	135.518	23.825
05	6707.4	133.375	63.177
06	5562.3	130.490	47.953
07	5519.5	129.640	76.780
08	5515.7	129.564	150.000
09	5505.1	129.353	134.654
10	6489.5	129.043	144.634
11	6483.6	128.926	137.364
12	6422.4	127.710	59.936
13	5065.6	100.749	59.352
14	3942.8	78.403	34.921
15	3908.1	77.712	115.597
16	3878.9	77.131	35.457
17	2456.4	48.845	61.225
18	1970.9	39.191	53.230
19	1545.5	30.731	43.412
20	1188.2	23.627	57.798
21	1126.8	22.406	53.290



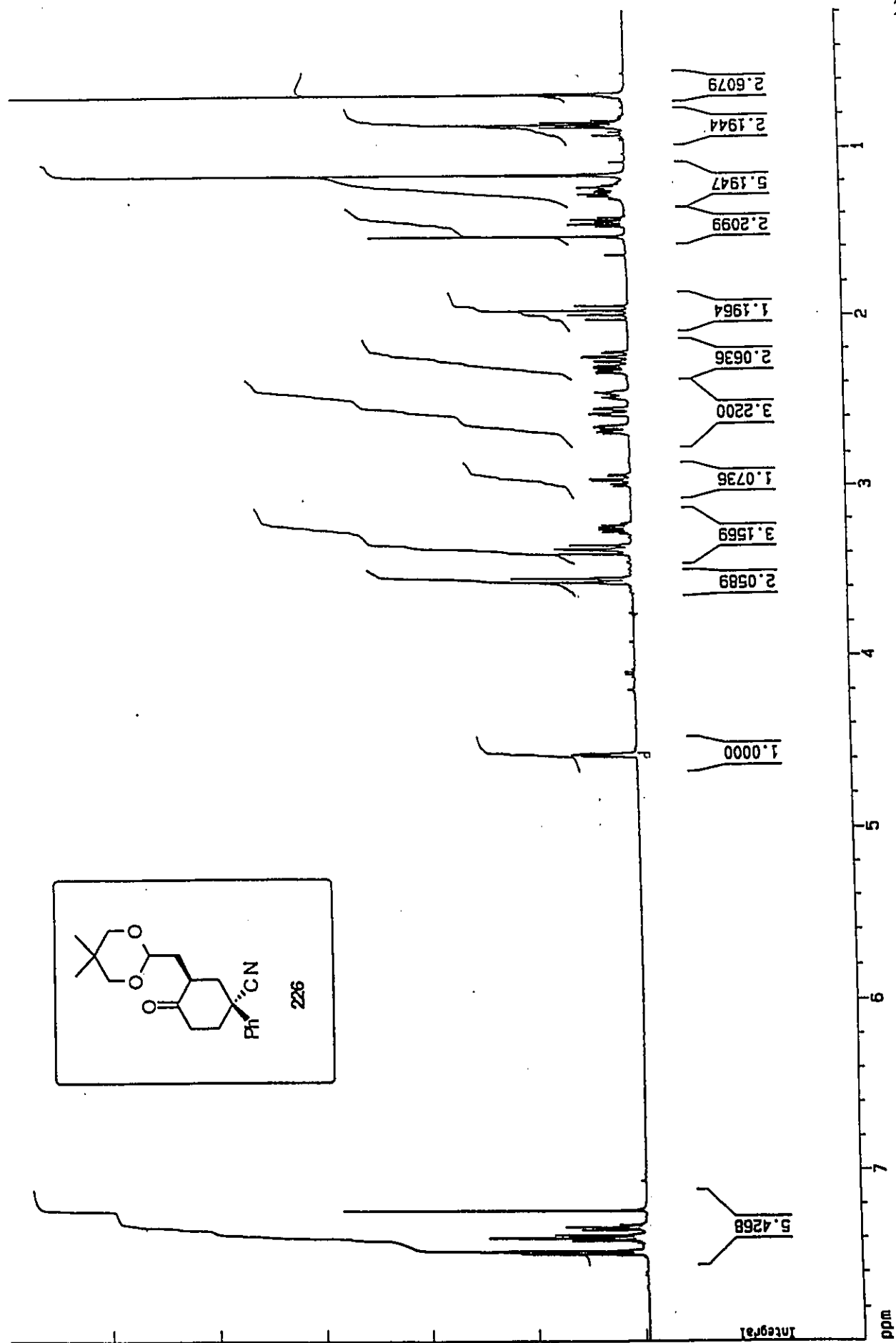
<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 50MHz) of 222

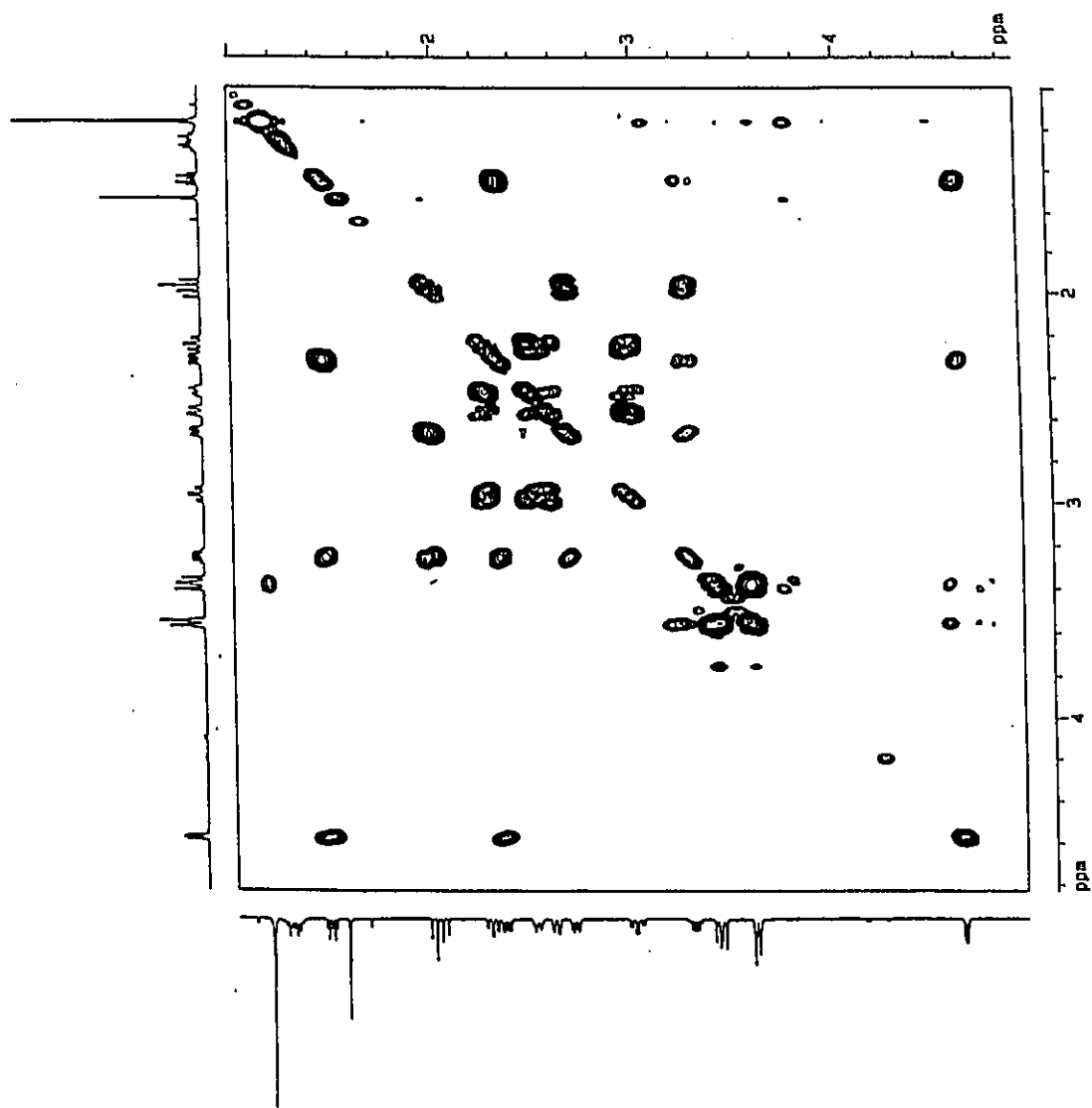
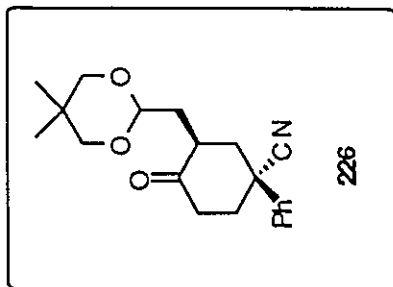
ADEPT SPECTRUM ANALYSIS:

INDEX	FREQ	PPM	INTENSITY
1 D	6707.5	133.38	46.530
2 D	6515.7	129.56	103.594
3 D	6505.1	129.35	104.245
4 D	6489.5	129.04	101.819
5 D	6483.4	128.92	107.226
6 D	6422.5	127.71	47.949
7 D	5066.6	100.75	52.723
8 T	3908.0	77.71	98.169
9 D	2456.4	48.85	54.375
10 T	1970.6	39.19	49.935
11 Q	1188.0	23.62	48.052
12 Q	1126.8	22.41	45.200

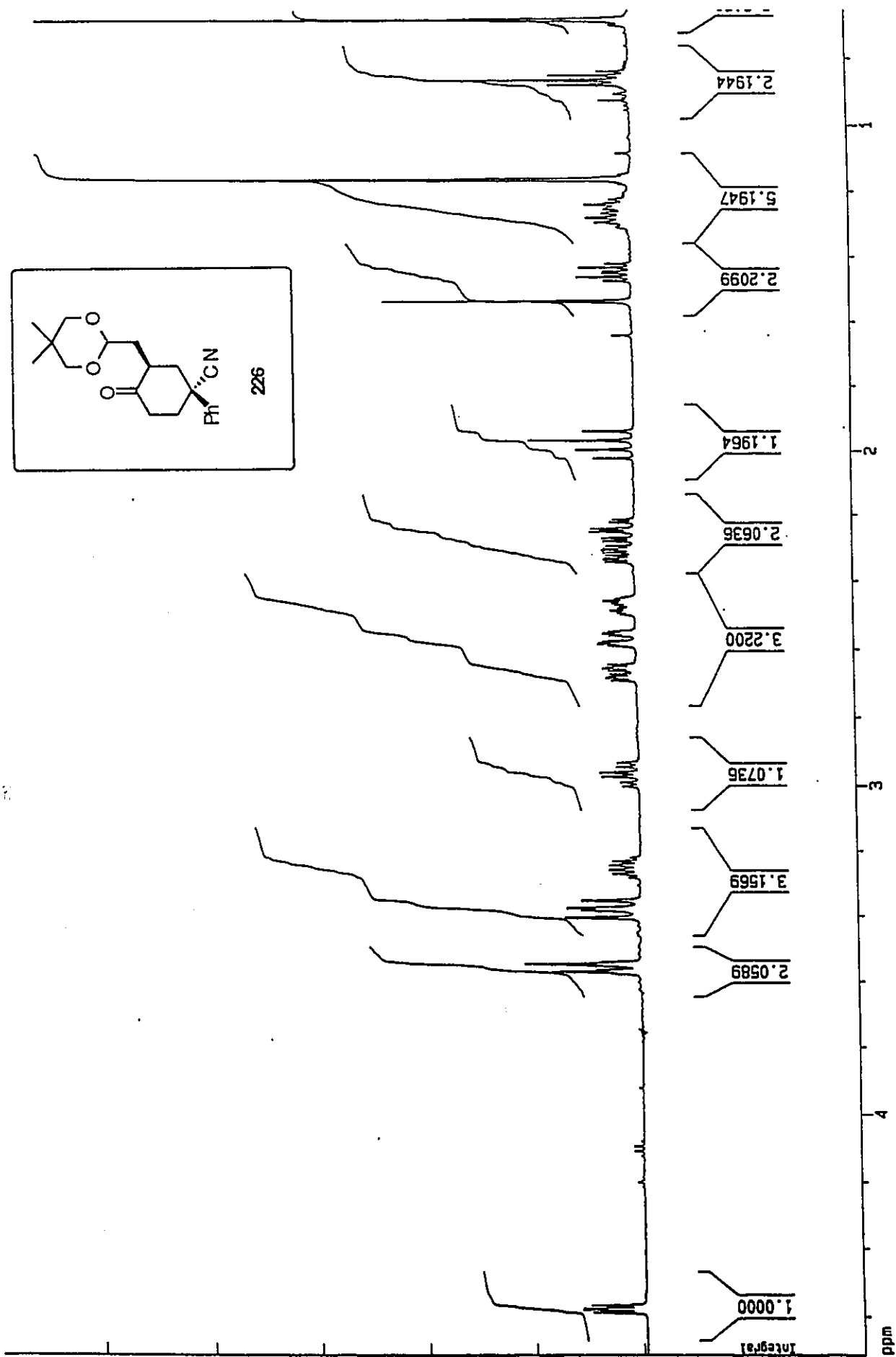


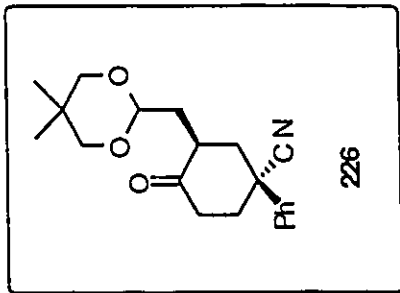
<sup>13</sup>C NMR DEPT Spectrum (CDCl<sub>3</sub>, 50MHz) of 222

$^1\text{H}$  NMR Spectrum ( $\text{CDCl}_3$ , 500MHz) of 226

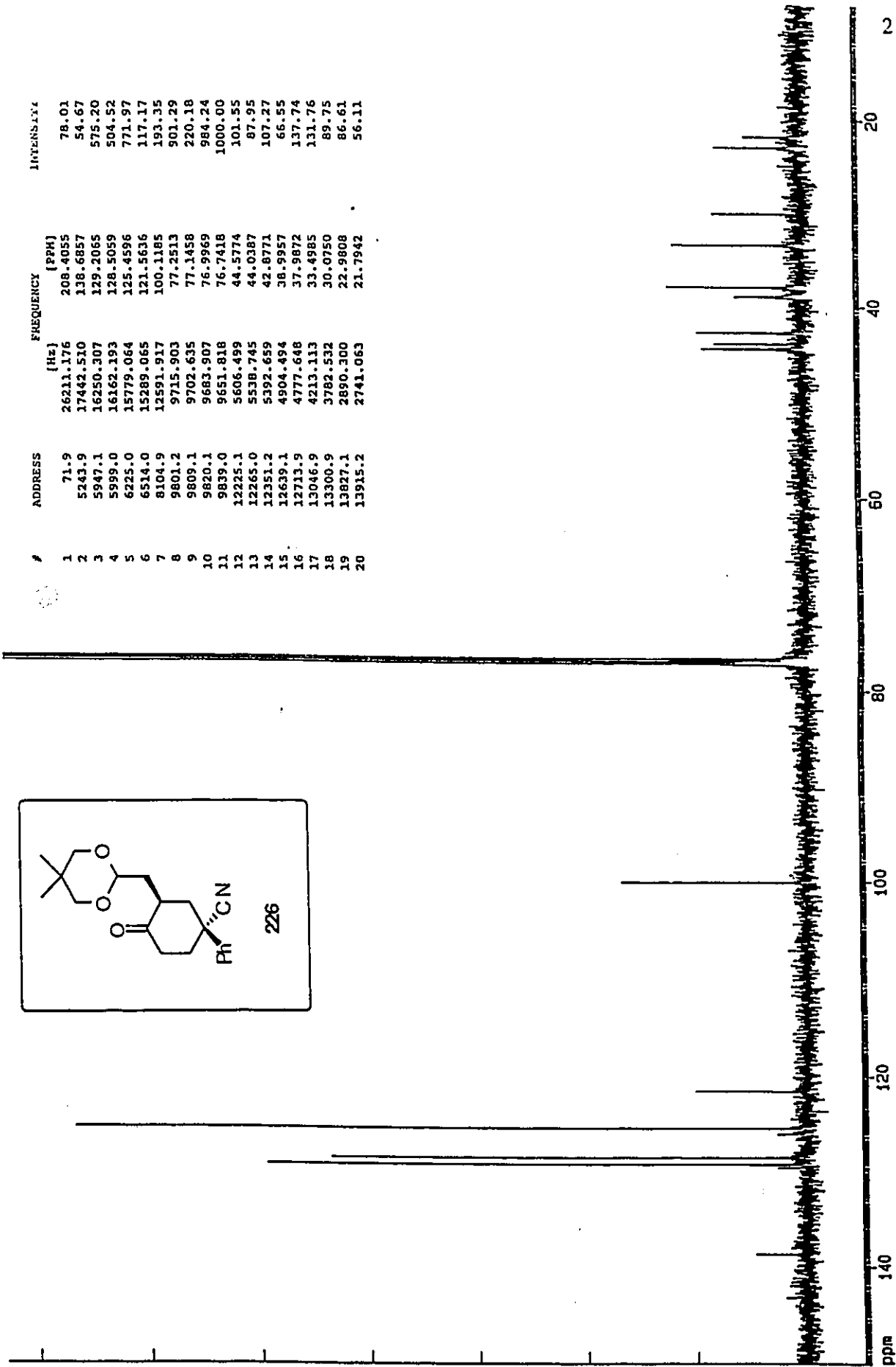


$^1\text{H}$ - $^1\text{H}$  COSY NMR Spectrum ( $\text{CDCl}_3$ , 500MHz) of 226

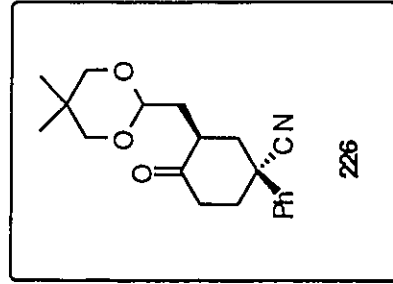
$^1\text{H}$  NMR Spectrum (Expansion)( $\text{CDCl}_3$ , 500MHz) of 226



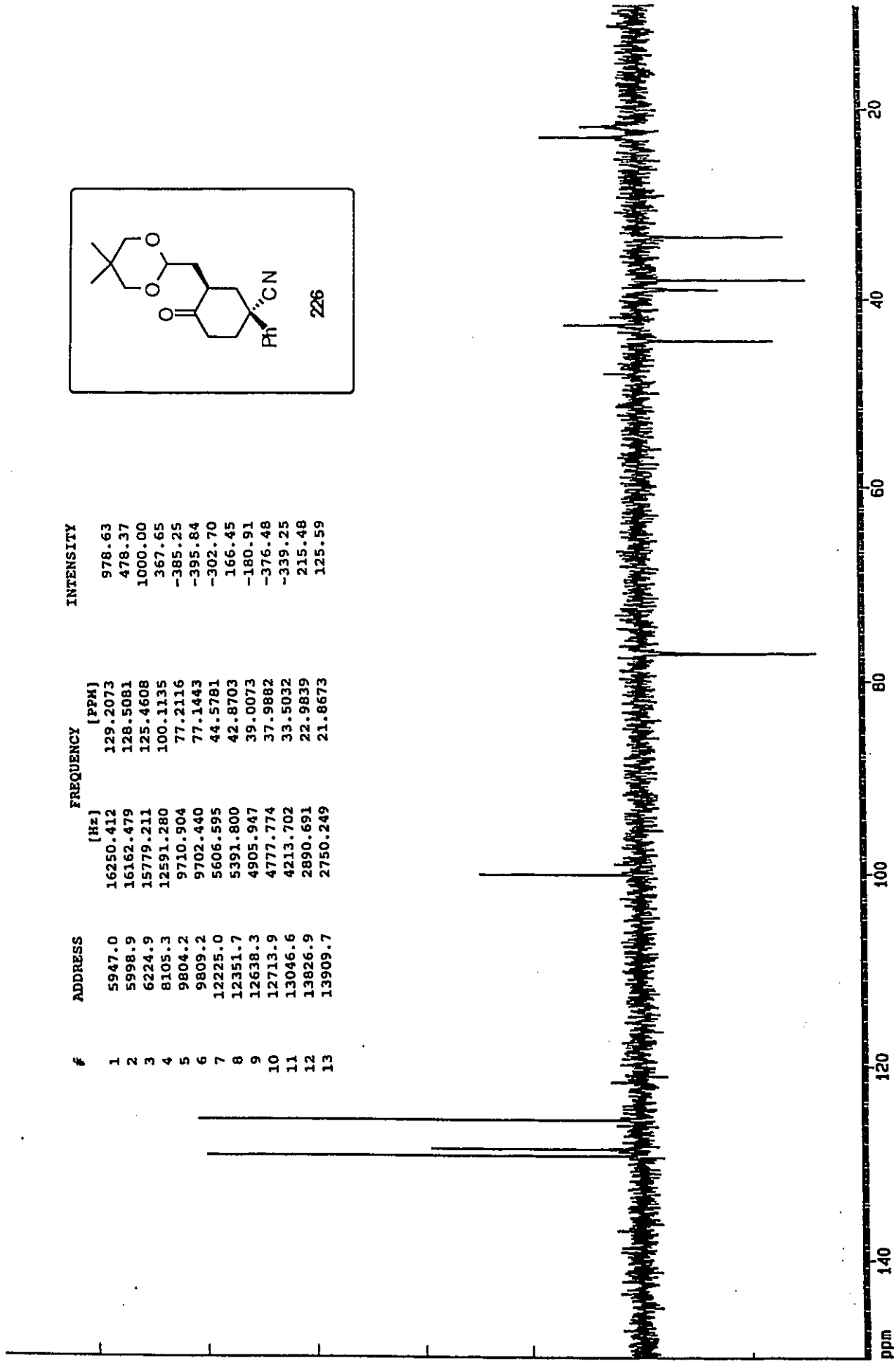
#	ADDRESS	FREQUENCY (Hz)	PPM	INTENSITY
1	71.9	26211.176	208.4055	78.01
2	5243.9	17442.510	138.6857	54.67
3	5947.1	16250.307	129.2065	575.20
4	5999.0	16162.193	128.5059	504.52
5	6225.0	15779.064	125.4596	771.97
6	6514.0	15289.065	121.5636	117.17
7	8104.9	12591.917	100.1185	193.35
8	9801.2	9715.903	77.2513	901.29
9	9809.1	9702.635	77.1458	220.18
10	9820.1	9683.907	76.9969	984.24
11	9839.0	9651.818	76.7418	1000.00
12	12225.1	5606.499	44.5774	101.55
13	12265.0	5538.745	44.0387	87.95
14	12351.2	5392.659	42.8771	107.27
15	12639.1	4904.494	38.9957	66.55
16	12711.9	4777.648	37.9872	137.74
17	13046.9	4213.113	33.4985	131.76
18	13300.9	3782.532	30.0750	89.75
19	13827.1	2890.300	22.9808	86.61
20	13915.2	2741.063	21.7942	56.11



<sup>13</sup>C NMR Spectrum (CDCl<sub>3</sub>, 75MHz) of 226



#	ADDRESS	FREQUENCY [Hz]	FREQUENCY [PPM]	INTENSITY
1	5947.0	16250.412	129.2073	978.63
2	5998.9	16162.479	128.5081	478.37
3	6224.9	15779.211	125.4608	1000.00
4	8105.3	12591.280	100.1135	367.65
5	9804.2	9710.904	77.2116	-385.25
6	9809.2	9702.440	77.1443	-395.84
7	12225.0	5606.595	44.5781	-302.70
8	12351.7	5391.800	42.8703	166.45
9	12638.3	4905.947	39.0073	-180.91
10	12713.9	4777.774	37.9882	-376.48
11	13046.6	4213.702	33.5032	-339.25
12	13826.9	2890.691	22.9839	215.48
13	13909.7	2750.249	21.8673	125.59



$^{13}\text{C}$  NMR DEPT Spectrum ( $\text{CDCl}_3$ , 75MHz) of 226