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Contraction-Expansion Protocols

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A thesis

presented to

the faculty of the Department of Chemistry

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Master of Science in Chemistry

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by

Nadine Katia Njoya

August 2008

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Dr. Ismail Kady, Ph.D

Dr. Yu Lin Jiang, Ph.D

Keywords: Contraction, Expansion, Favorskii, *Cis*-divinylcyclopropanone, Rearrangement

## ABSTRACT

### Contraction-Expansion Protocols

by

Nadine Katia Njoya

An approach to a new class of compounds known as bridgehead dienone is described. The route is based on a tandem contraction-expansion event in which the contraction triggers the expansion. The two steps involved are a palladium-catalyzed Favorskii contraction and a *cis*-divinyl cyclopropanone rearrangement. Progress towards these goals is reported.

## DEDICATION

This thesis is dedicated to my parents: my late father, Isidore Njoya and my mother, Emilienne Njoya. My sisters: Suzie, Hortense, Myriam, Louise, Annie, Michele. My brothers: Eric, Thierry, Jean-Luc.

## ACKNOWLEDGMENTS

God Almighty, thank you for all your blessings. Without You, I don't think I would have made it this far.

I would also like to express my profound gratitude to Dr. David Young for his supervision and teaching. I definitely learned a lot from him and am extremely grateful for his mentorship. Special thanks to Dr. Ismail Kady and Dr. Yu-Lin Jiang for kindly accepting to be members of my committee and revising my thesis.

The chemistry department and his entire staff have been magisterial in paving the path for and providing me with the equipment and resources needed for the successful completion of my degree. My sincere appreciation goes to Tom Webster, Dr. Ray Mosheni, Dr. Chu-Ngi Ho, and Mrs. Susan Campbell for all the help and encouragement.

“No man is an island”. I have had the privilege to meet a lot of edifying persons before and all through my program here at ETSU. Each of them has contributed in some way to the individual I am now. I am deeply indebted to Costyl Njiojob, Christian Rikong, Beatrice Simo, Patrice and Adeline Yuh. Thank you all for being part of my life, you are greatly appreciated.

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## LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
AIBN	2,2'-azobisisobutyronitrile
BiOClO <sub>4</sub> .xH <sub>2</sub> O	bismuth (III) perchlorate oxide hydrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EWG	electron withdrawing group
Et	ethyl
<i>i</i> -Pr	<i>iso</i> -propyl
LTA	lead tetraacetate
LDA	lithium diisopropylamide
Ms	mesyl
Me	methyl
NMR	nuclear magnetic resonance
Ph	phenyl
<i>t</i> -Bu or <sup>t</sup> Bu	<i>tert</i> -butyl
Bu <sub>3</sub> SnH	tributyltin hydride
TMOF	trimethylorthoformate
TMS	trimethylsilyl

## CHAPTER 1

### INTRODUCTION

A large number of synthetic routes to molecules exhibiting some biological activity incorporate a ring contraction, a ring expansion, or both in their synthetic pathways. The synthetic usefulness of such operations has been established through numerous reviews recently published and their applications have been found in domains such as organic synthesis, biochemistry, natural-product synthesis, chemical biology, and medicinal chemistry. Thus, the application of ring contraction and expansion is widespread.

To provide a backdrop for our studies, a review of the current methods for contraction and expansion is presented first; followed by our results, their discussion and an experimental section that will describe the various procedures used.

#### Main Ring Contraction Reactions

A ring contraction reaction is a type of organic reaction in which usually a hydrocarbon ring is reduced in size. Ring contraction reactions are an important method to increase molecular complexity in a single step, because, in many cases, the reorganization of the bonds occurs with a high level of selectivity, affording products not easily accessible by other approaches [1].

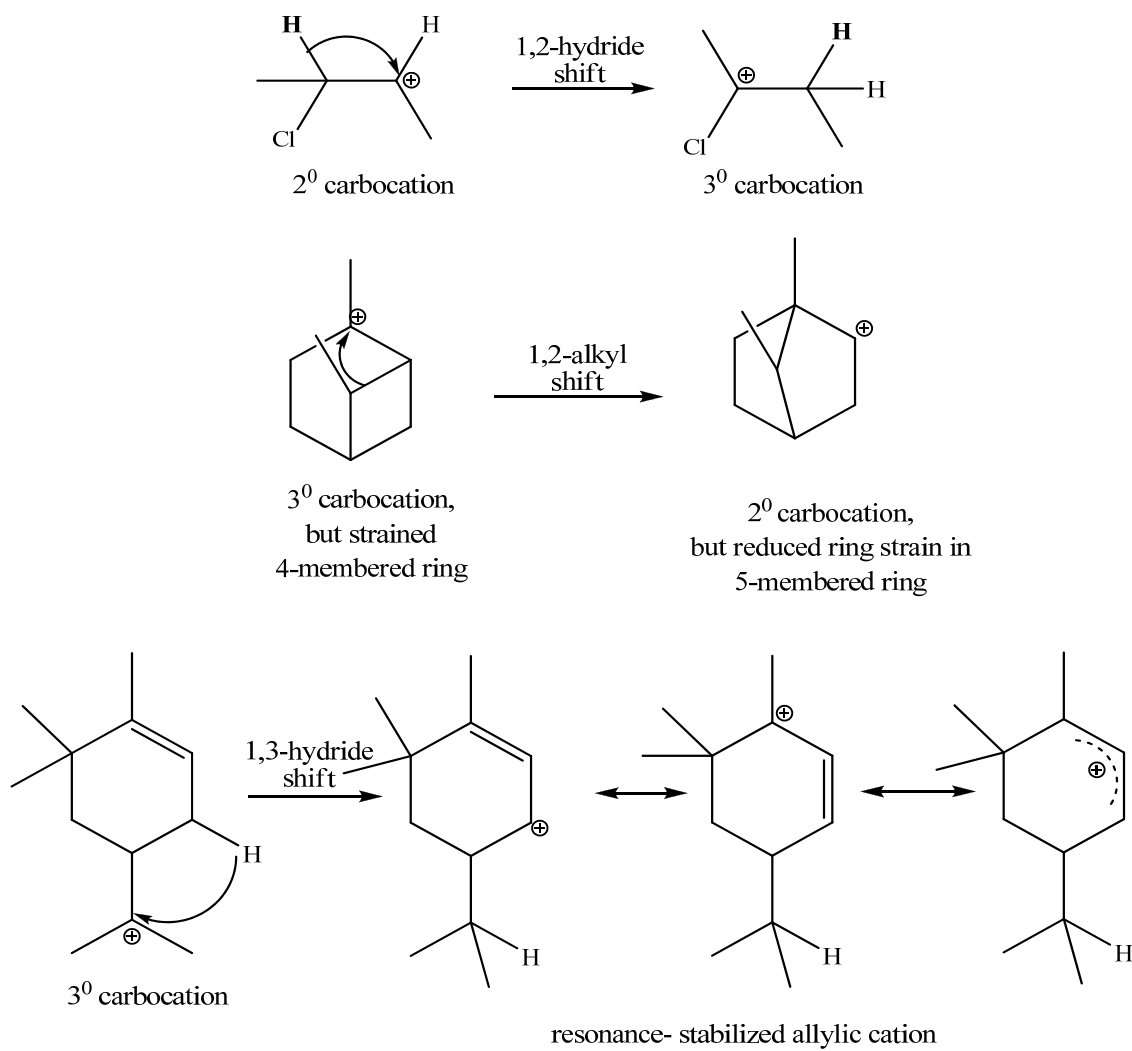
There are five principal ring contraction reactions:

- a) acid-induced ring contractions
- b) base-induced ring contractions
- c) oxidative rearrangements
- d) photochemical rearrangements
- e) Wolff rearrangements [2].

### Acid-Induced Ring Contractions

Wagner-Meerwein Rearrangements. Rearrangement in chemical reactions involving carbocation intermediates, e.g.  $S_N1$  and E1 reactions are not uncommon and typically consist of 1,2-shifts of hydride, alkyl or aryl groups. Occasionally, 1,3- or longer shifts are encountered. These shifts, known as Wagner- Meerwein rearrangements, are mainly used, depending on the most desirable outcome, to generate more stable carbocations, or relieving the ring strain. In the case of a cyclic compound, the pathway can lead to a ring contraction [2].

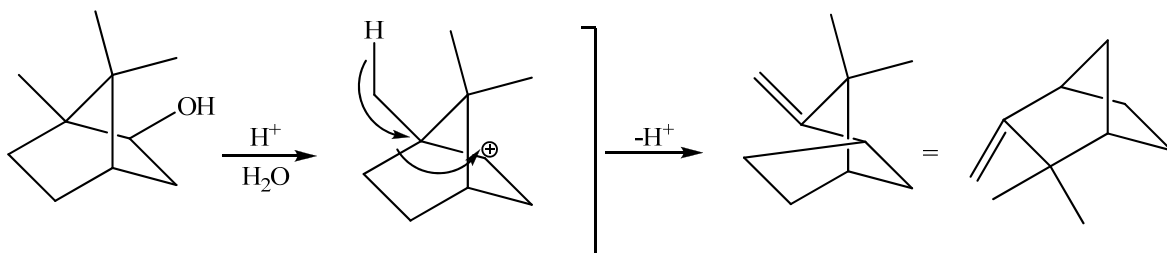




Scheme 1. Wagner-Meerwein Rearrangements<sup>3</sup>

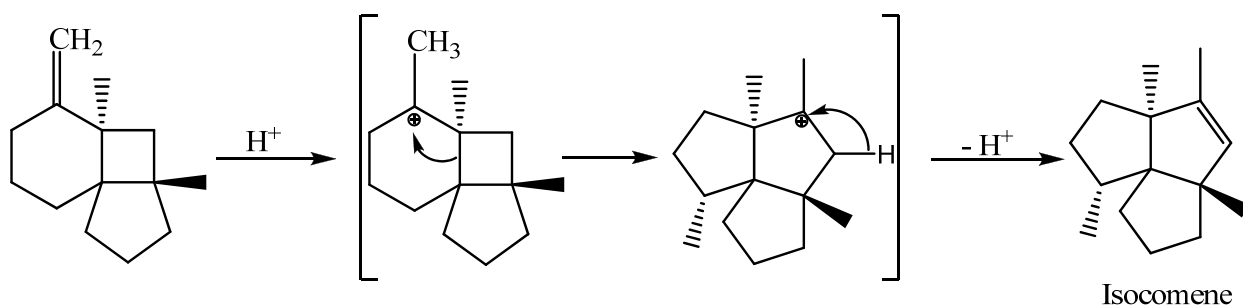
(Adapted from Medicinal Natural Products: A Biosynthetic Approach by Paul M. Dewick [3])

The rearrangement was first discovered in bicyclic terpenes [4].

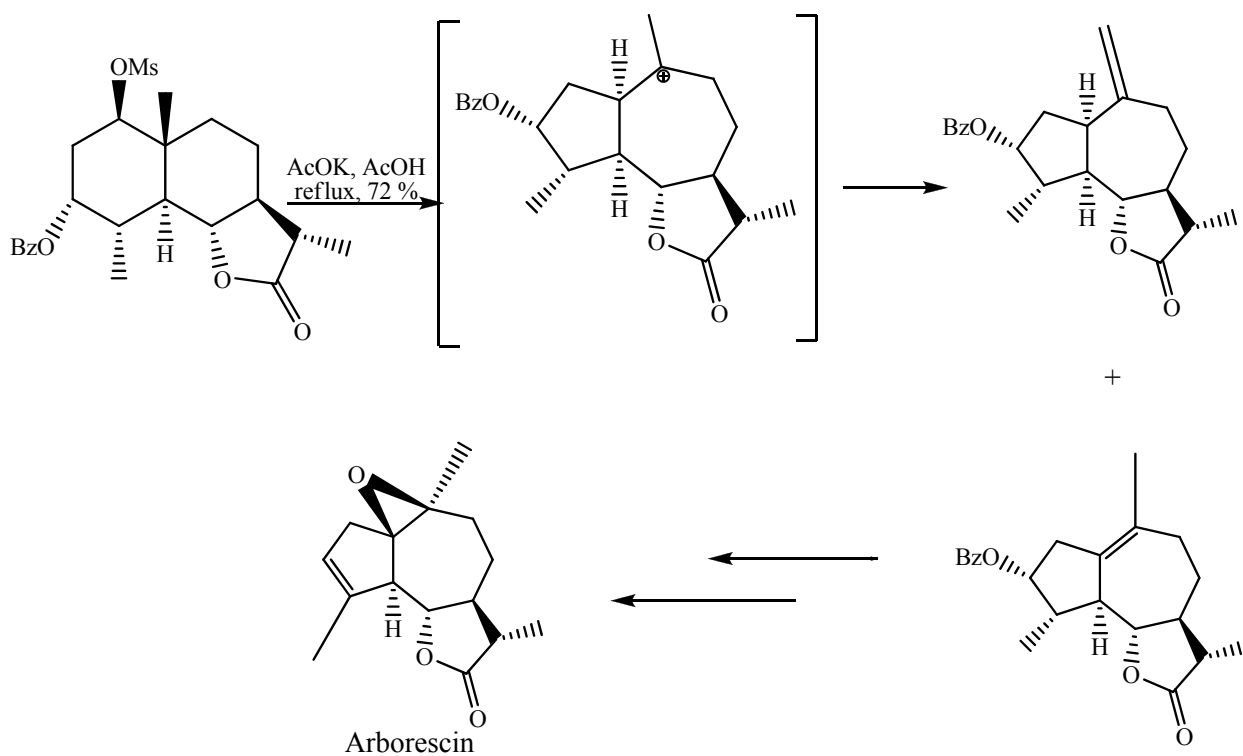


Scheme 2. Conversion of Isoborneol to Camphene<sup>4</sup>

Other examples include the synthesis of molecules such as isocomene [5], arborescin [6].



Scheme 3. Synthesis of Isocomene<sup>5</sup>

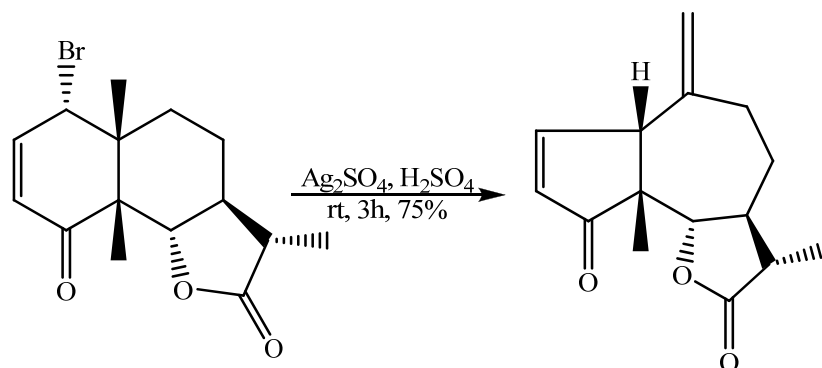


Scheme 4. Synthesis of Arborescin<sup>6</sup>

Two approaches make use of the Wagner-Meerwein rearrangement and involve the formation of 5-7 fused ring systems:

- The treatment of halides with silver salts leading to ring contraction products in good yield [2].

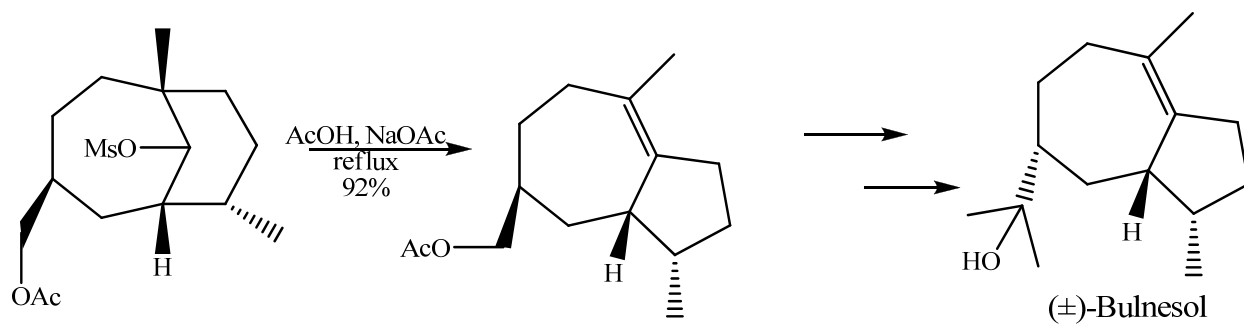
Example: A santonin derivative



Scheme 5. Treatment of Halides with Silver Salts, a Santonin Derivative<sup>2</sup>

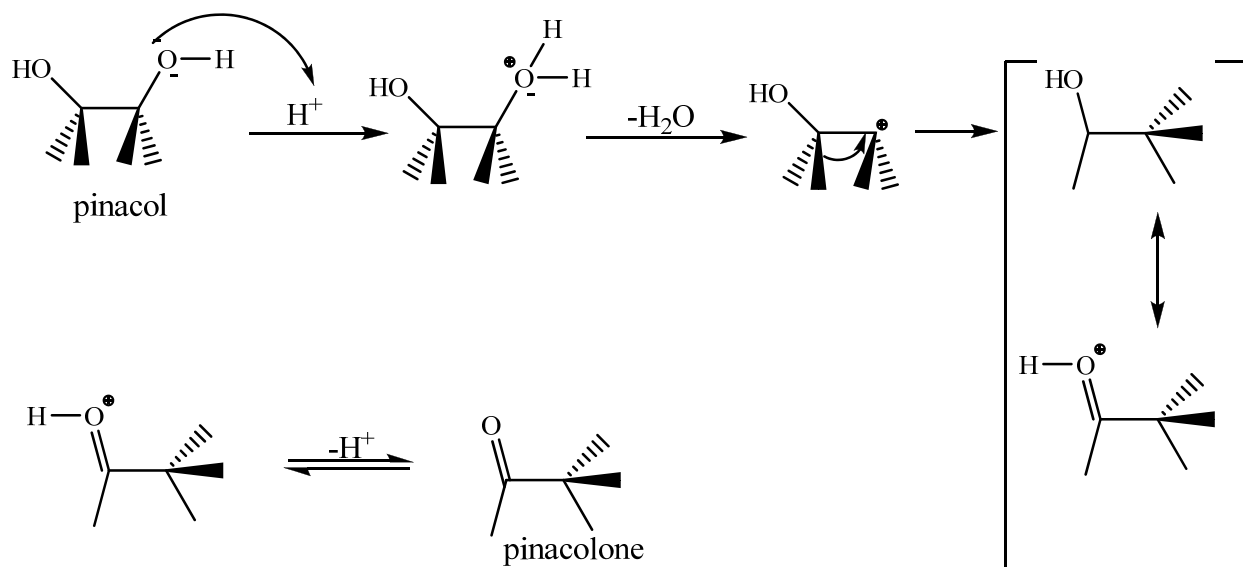
- Treatment with acetic acid and sodium acetate.

Example: synthesis of (±)-Bulnesol



Scheme 6. Synthesis of (±)-Bulnesol<sup>2</sup>

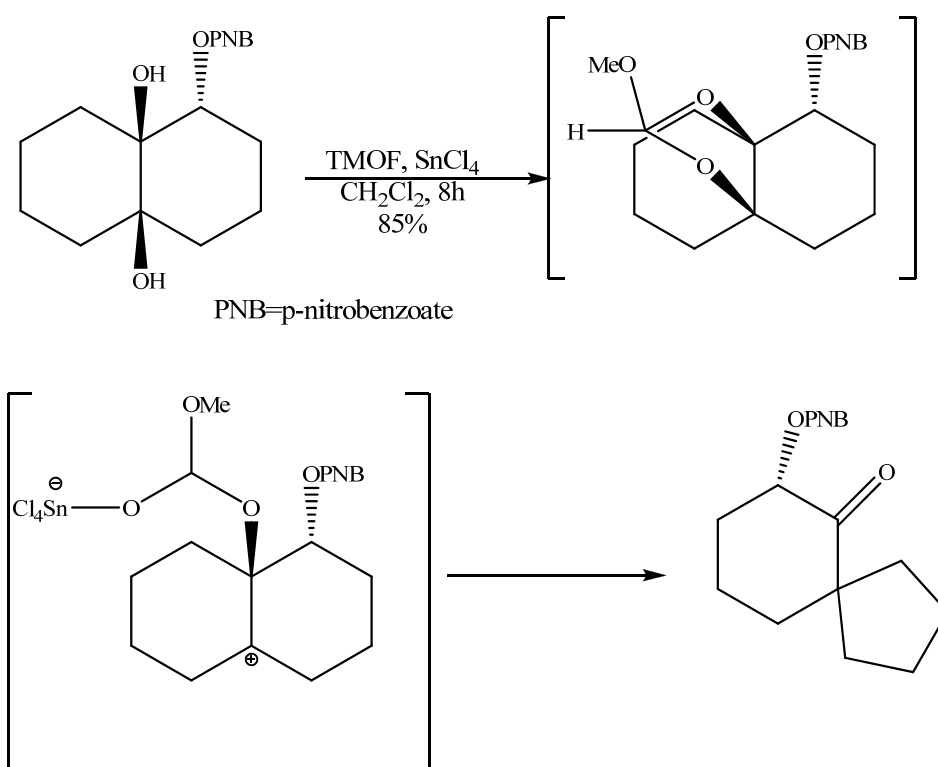
Pinacol Rearrangements. Vicinal diols can be converted to aldehydes or ketones when treated with an acid. The reaction goes through a carbenium ion intermediate with a concomitant shift of an alkyl group and owes its names to the conversion of pinacol to pinacolone [7].



Scheme 7. Conversion of Pinacol to Pinacolone<sup>7</sup>

Ring contraction products, with a good level of selectivity, have been obtained using this approach [2]; this can be exemplified as follows:

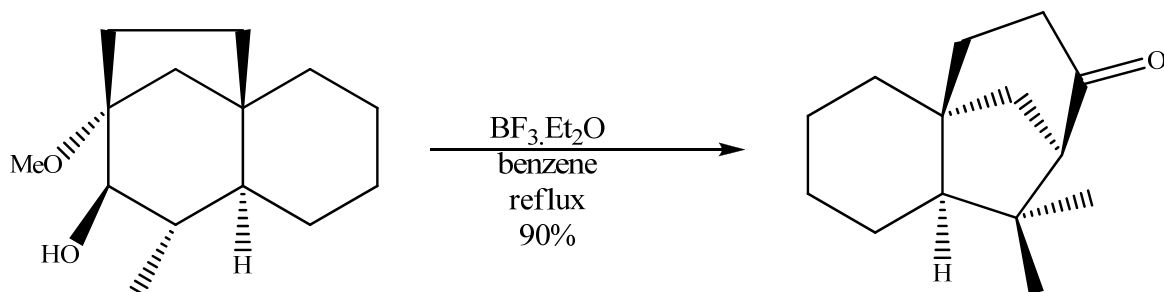
- Enhancement of the rearrangement of some vicinal diols by combining a Lewis acid with a trialkyl orthoester. Spirocyclic molecules are obtained in appreciable yields via a cyclic ortho ester intermediate.



Scheme 8. Enhancement of Vicinal Diols Rearrangement<sup>2</sup>

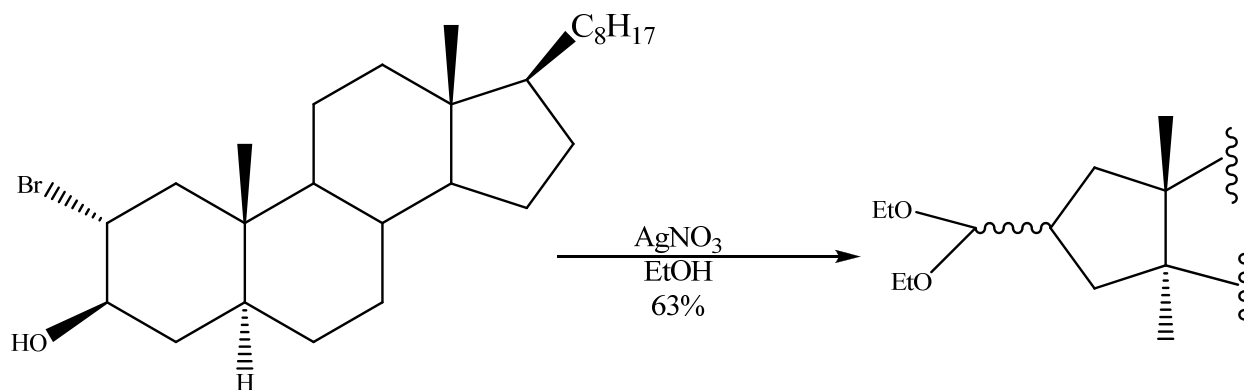
Also examples of ring contraction products have been obtained by semi-pinacol rearrangement:

- Rearrangement of mono-protected 1,2-diol substrate:



Scheme 9. Rearrangement of a Mono Protected 1,2-diol Substrate<sup>2</sup>

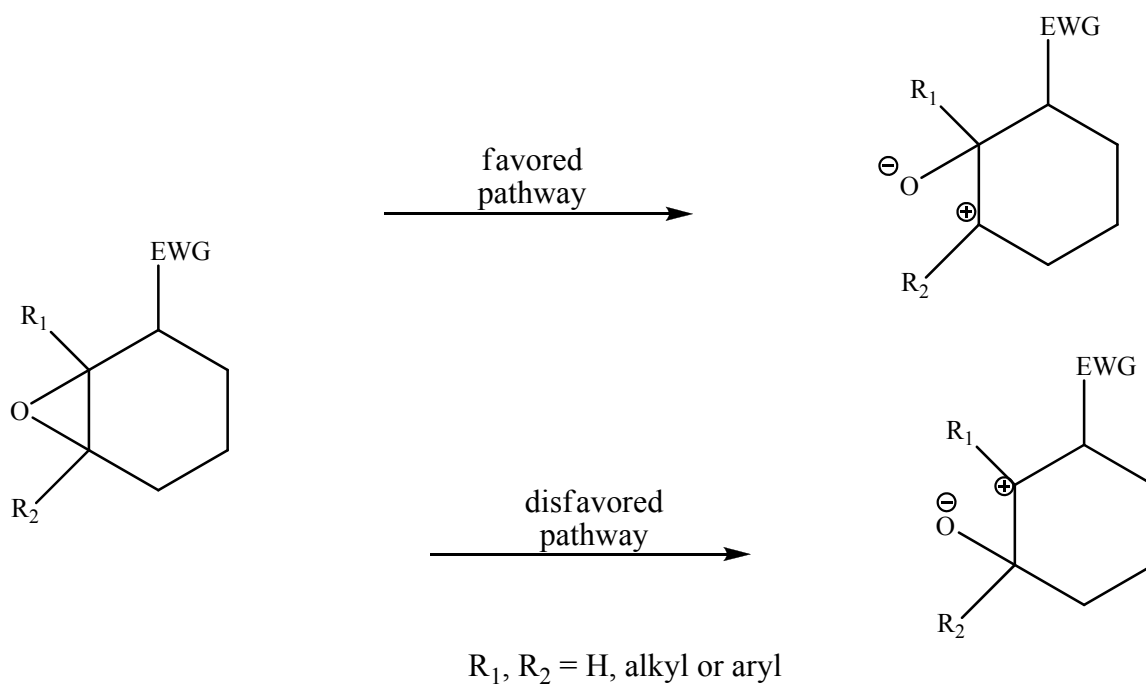
- Rearrangement of  $\alpha$ -halohydrins:



Scheme 10. Rearrangement of  $\alpha$ -Halohydrins<sup>2</sup>

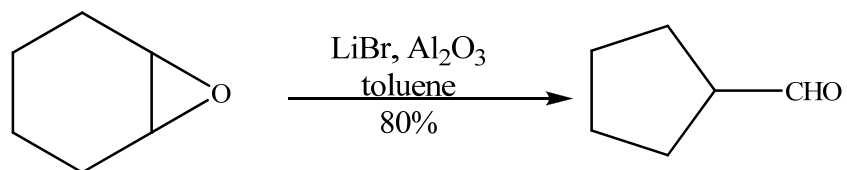
Rearrangement of Epoxides. Epoxides are one of the most versatile functional groups in organic chemistry due to their ready availability and ease of transformation into a wide variety of functional groups. The rearrangement of epoxides to carbonyl compounds is a useful synthetic transformation and several reagents have been utilized for this purpose. The constitution of the rearrangement product is determined by the identity of the Lewis acid, the migratory aptitude of the epoxide substituents, and the solvent [8].

Often, the presence of an electron withdrawing group in the substrate directs the oxirane opening, allowing a good level of regioselectivity in the reaction as outlined in below.



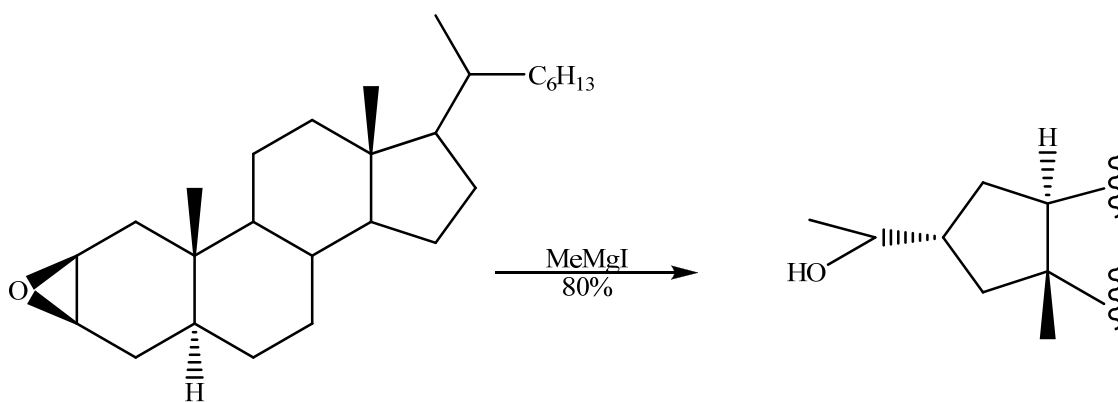
Scheme 11. Regioselectivity of Epoxides Rearrangement<sup>2</sup>

The ring contraction of cyclohexene oxide leads to cyclopentanecarboxaldehyde in good yield as illustrated below.



Scheme 12. Ring Contraction of Cyclohexene Oxide<sup>2</sup>

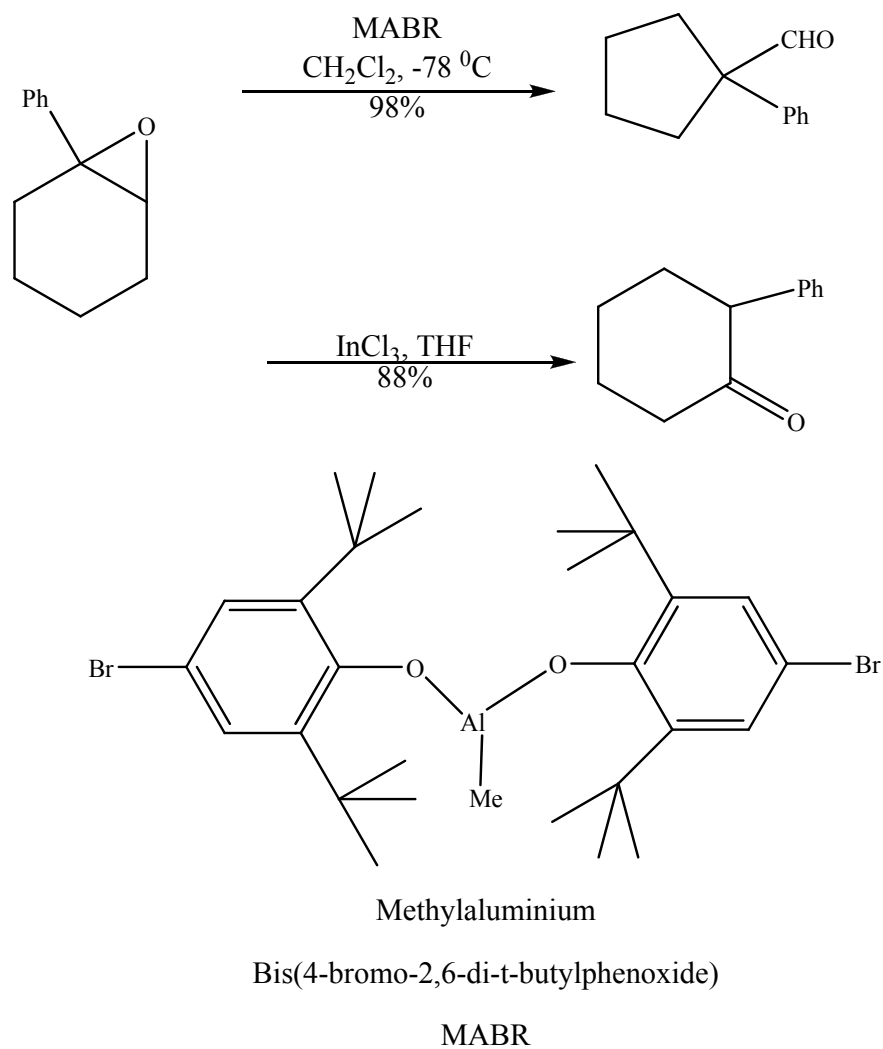
An unusual way to obtain ring contraction products from epoxides has been observed by treating an epoxy-cholestane with a Grignard reagent as shown below:



Scheme 13. Epoxides Ring Contraction by Treatment with Grignard Reagent<sup>2</sup>

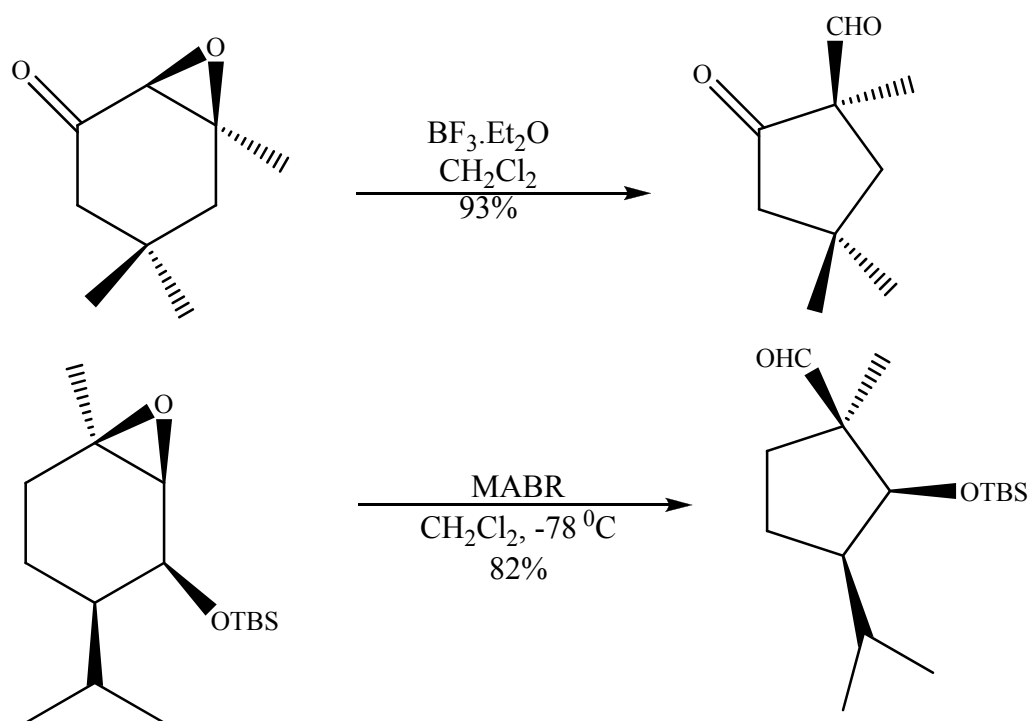
Upon treatment with acids, trisubstituted epoxides undergo ring opening following the Markovnikov rule, yielding ring contraction products bearing a quaternary carbon stereocenter. However, cyclohexanones are formed exclusively depending on the reaction conditions because hydride migration occurs preferentially to the alkyl group [2]. An example is illustrated below:





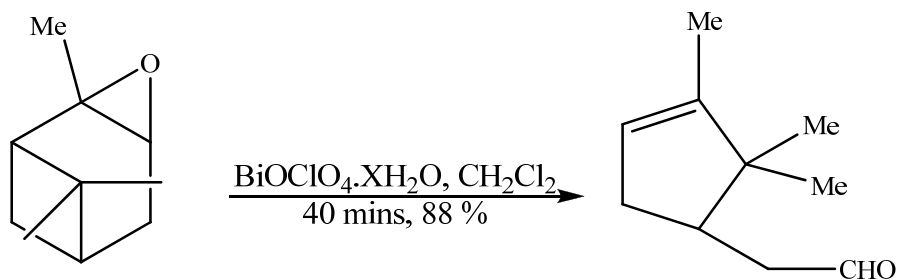
Scheme 14. Differences in Substituted Epoxides Reactivity with varying Reaction Conditions<sup>2</sup>

A useful application of the rearrangement of trisubstituted epoxides is the construction of functionalized enantiomerically pure cyclopentanes as exemplified below [2]:



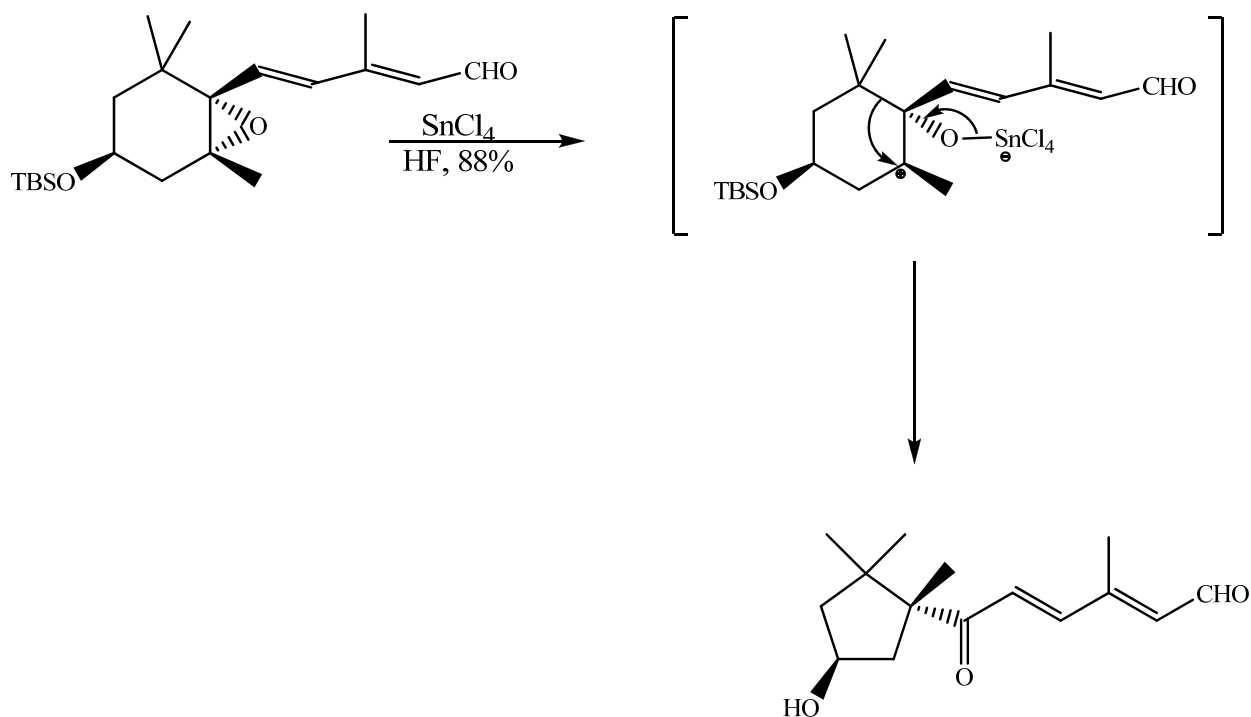
Scheme 15. Formation of Cyclopentanes from Substituted Epoxides<sup>2</sup>

Recently, the acidity of bismuth has also been exploited to promote the rearrangement of epoxides to carbonyl compounds. For example, the rearrangement of  $\alpha$ -pinene oxide occurs quite readily at room temperature to give the expected aldehyde in good yield [8]:



Scheme 16. Rearrangement of  $\alpha$ -Pinene Oxide<sup>8</sup>

Tetrasubstituted epoxides within a carbocyclic structure can also undergo rearrangements to yield ring contraction products. As expected, the ring opening process can occur in two different ways giving rise to a mixture of isomers. However, a control of the reaction conditions may result in a favored stereochemistry of the product. Yamano and Ito reported the following reaction:



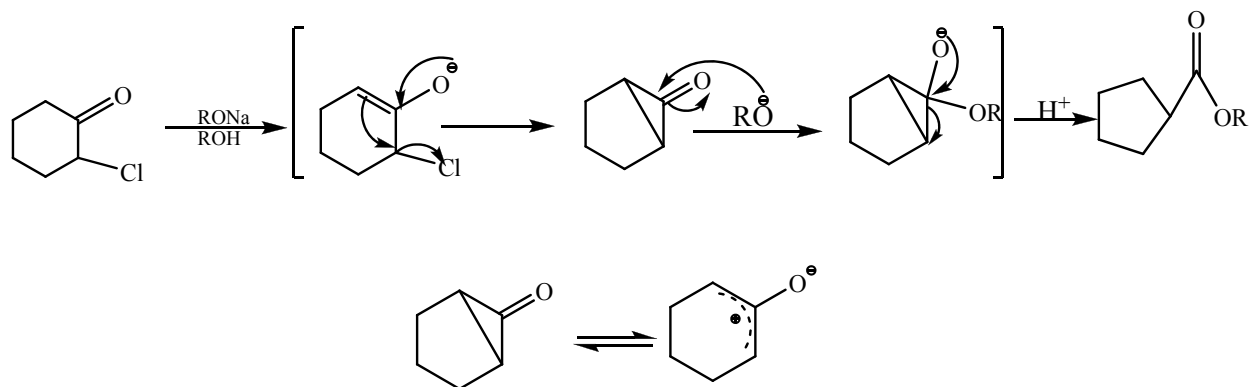
Scheme 17. Ring Contraction of Tetrasubstituted Epoxides<sup>9</sup>

In this instance, the most stable carbon atom bears the positive charge at the transition state making the reaction stereospecific.

### Base-Induced Ring Contractions

Farvoskii Rearrangement. Named after its discoverer, Alexei Yevgrafovich Favorskii, this method is widely used in the ring contraction of six-membered carbocyclic compounds. It

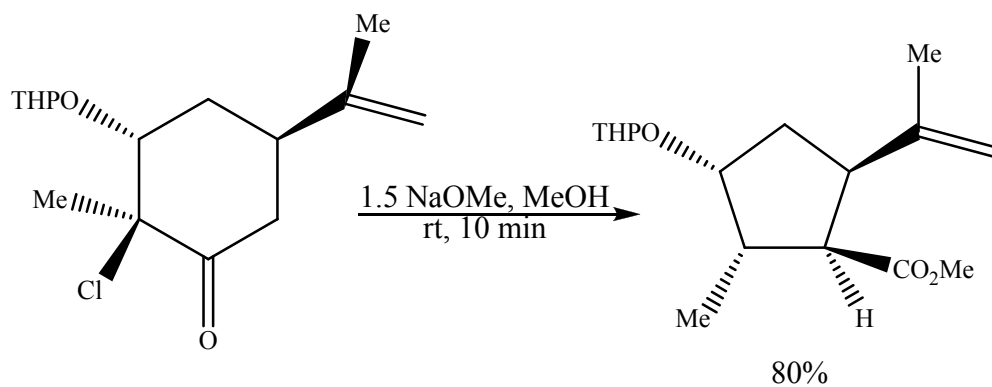
involves the treatment of  $\alpha$ -halogenated ketones (having acidic  $\alpha'$ -hydrogens) with nucleophilic bases. The reaction usually proceeds via a cyclopropanone intermediate which undergoes ring opening and yields the contracted product. This can be shown below [10]:



Scheme 18. Favorskii Rearrangement<sup>10</sup>

Favorskii rearrangements can be promoted either by:

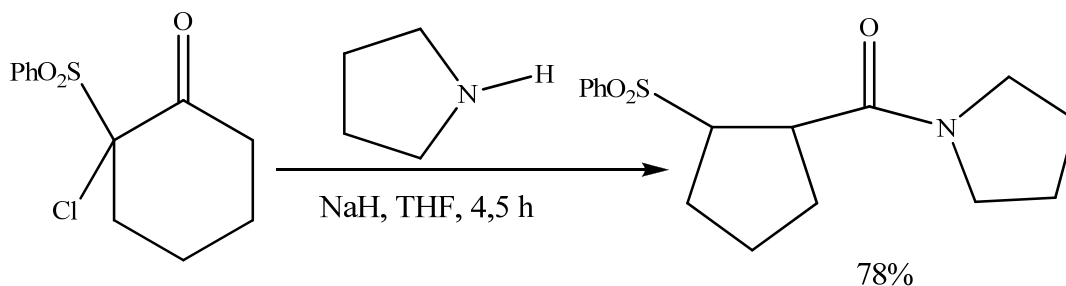
- Alkoxides:



Scheme 19. Alkoxides-Promoted Favorskii Rearrangement<sup>11</sup>

Or by

- Amines:



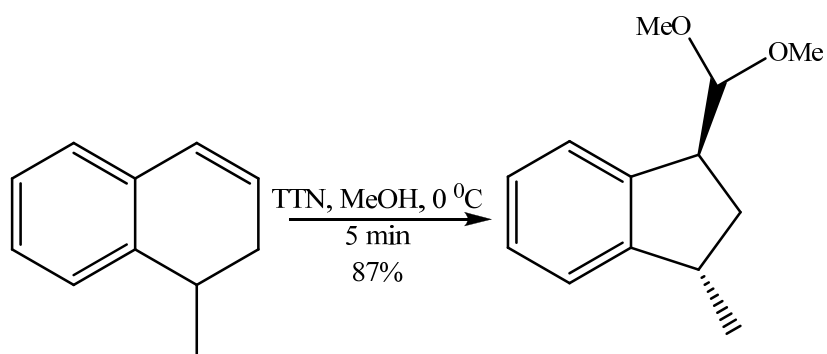
Scheme 20. Amines-Promoted Favorskii Rearrangement<sup>11</sup>

This rearrangement will be discussed more thoroughly later on.

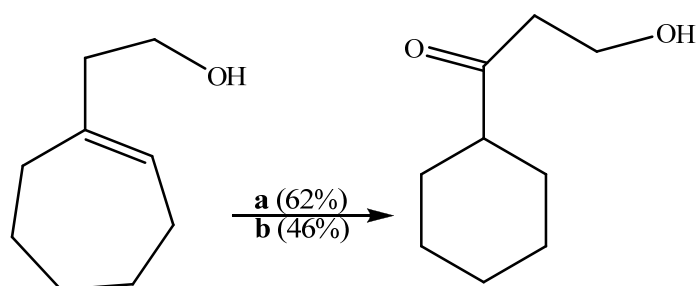
### Oxidative Rearrangements

A relatively low number of oxidizers can actually lead to ring contraction product although they are widespread in organic chemistry. Those are outlined in the following paragraphs:

Thallium (III)-Promoted Ring Contraction. The three most common salts of thallium are thallium tri-acetate (TTA), thallium *tris*-trifluoroacetate (TTFA), and thallium trinitrate (TTN), the latter being the most widespread [12]. Among the most useful synthetic applications of these salts are the ring contraction of simple cyclic olefins such as cyclobutene, cyclohexenes, cycloheptene, and cyclooctene [13] and the cyclofunctionalization of unsaturated alcohols [14]. The following reactions illustrating successively the formation of indans and the oxidation of 3-alkenols have been reported:



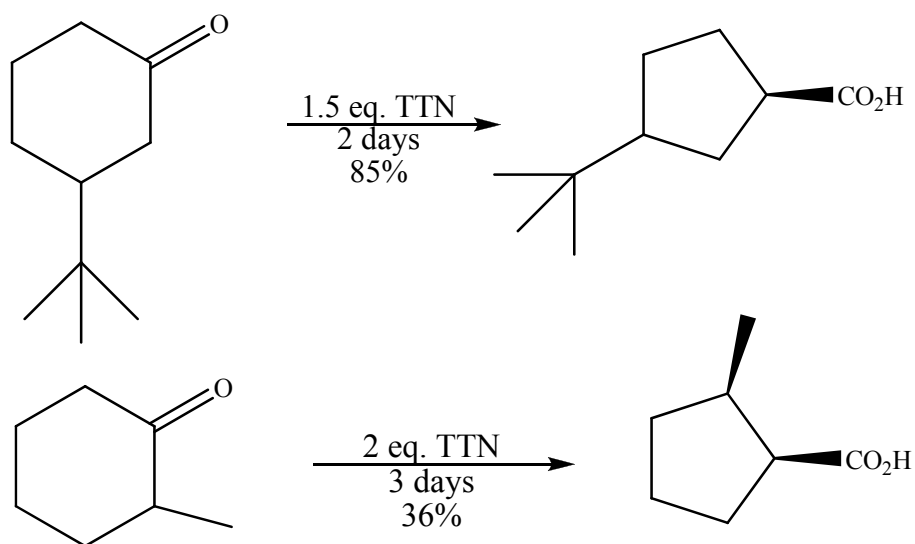
Scheme 21. Formation of Indans<sup>13</sup>



- (a) 1.2 TTN, 50% aqueous AcOH, rt, 8 min  
 (b) 1.0 TTN, MeOH, 0 °C, 2 min

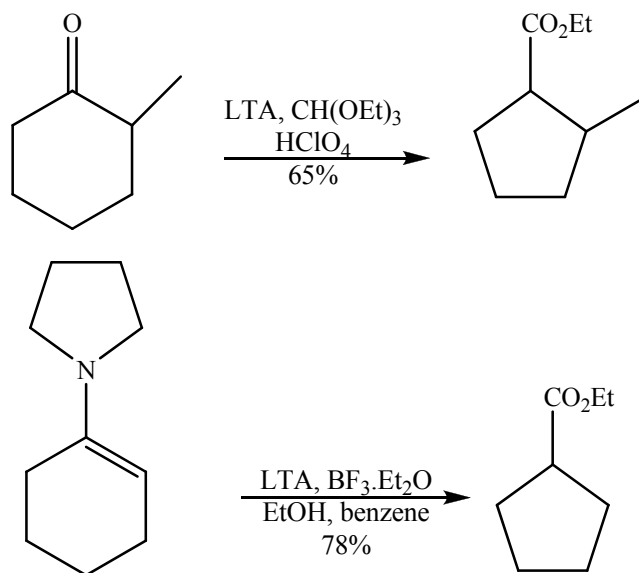
Scheme 22. Oxidation of 3-Alkenols<sup>14</sup>

Another important use of TTN is that it promotes the ring contraction of alkylcyclohexanones to cyclopentanecarboxylic acids by oxidative rearrangement [2]. This can be exemplified as follows:



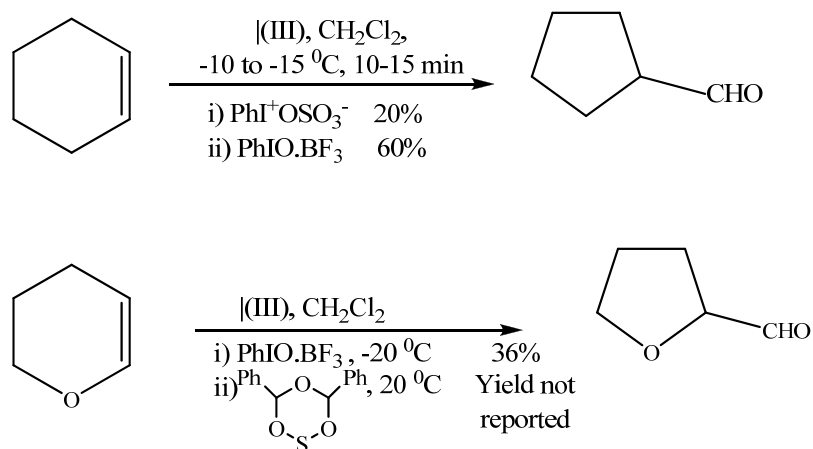
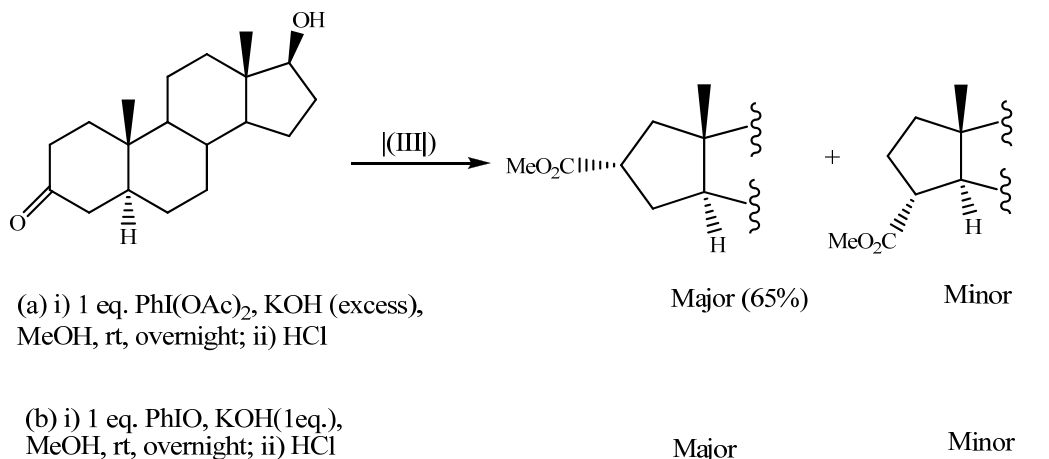
Scheme 23. TTN- Promotion Ring Contraction of Alkylcyclohexanones<sup>15</sup>

Lead (IV)-Promoted Ring Contraction. The most common oxidant is lead tetraacetate (LTA). Examples have been found in which cyclohexanones or their corresponding enamines are contracted to cyclopentyl units.



Scheme 24. Lead (IV)-Promoted Ring Contraction<sup>2</sup>

Hypervalent Iodine-Promoted Ring Contraction. Hypervalent iodine reagents are useful in the oxidative rearrangement of cycloalkenes and cycloalkanones which lead to a ring contraction [16]. This is outlined successively in the equations below:



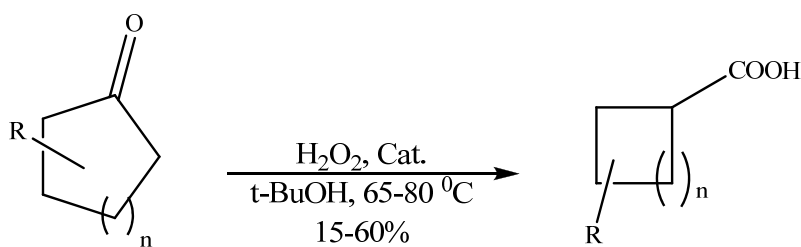
Scheme 25. Hypervalent Iodine-Promoted Ring Contraction<sup>16</sup>

Selenium (IV) -Promoted Ring Contraction. It is known that cycloalkanones oxidized with hydrogen peroxide in the presence of selenium dioxide undergo Favorski-type rearrangement involving ring contraction and formation of cycloalkanecarboxylic acids.

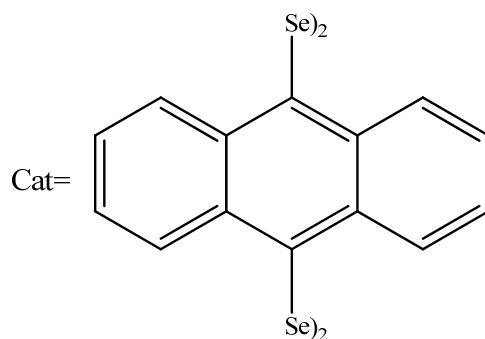


Recently, the action of poly(bis-9,10-anthracenylene) diselenide, named PADS has been investigated and good yields of cycloalkanecarboxylic acids have been obtained [17].

This is shown in the equation below:



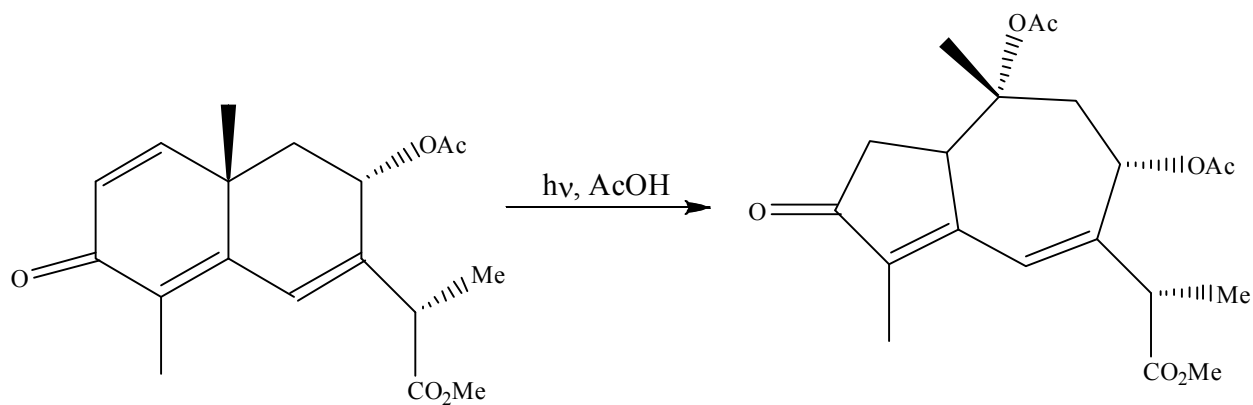
$n = 1-4$ ;  $8 R = H, Me, t-Bu, Ph$



Scheme 26. Selenium (IV)-Promoted Ring Contraction<sup>17</sup>

### Photochemical Rearrangements

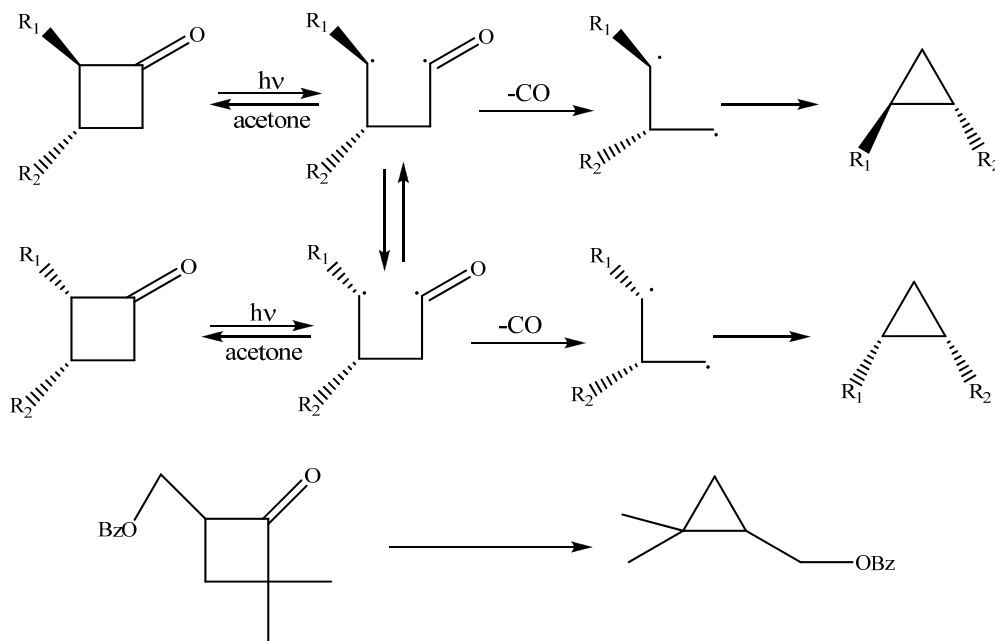
The most common photochemical rearrangements lead to the ring contraction of cross-conjugated dienones as displayed by the following equation in which a santonin derivative undergoes photochemical conversion on radiation in acetic acid to yield an enone. This is also an efficient way of making fused 5 and 7 ring systems.



Scheme 27. Santonin Derivative Ring Contraction on Radiation<sup>18</sup>

(Adapted from Photochemistry by A. Gilbert [18])

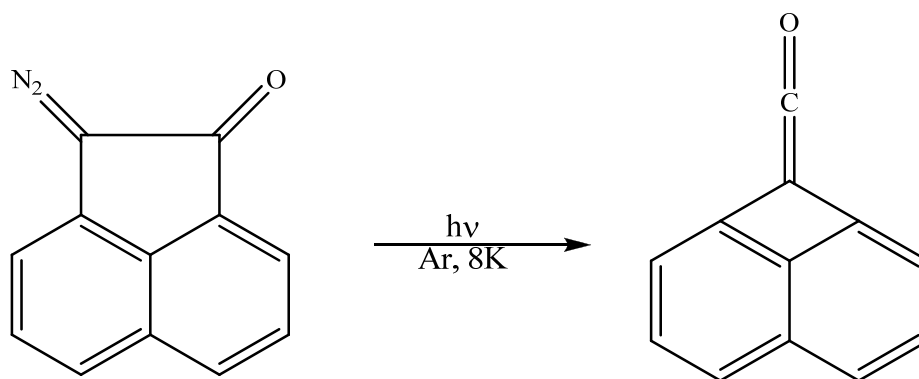
Another example of photochemical rearrangement involves the preparation of cyclopropanes from cyclobutanones that is done through photodecarbonylation [19].



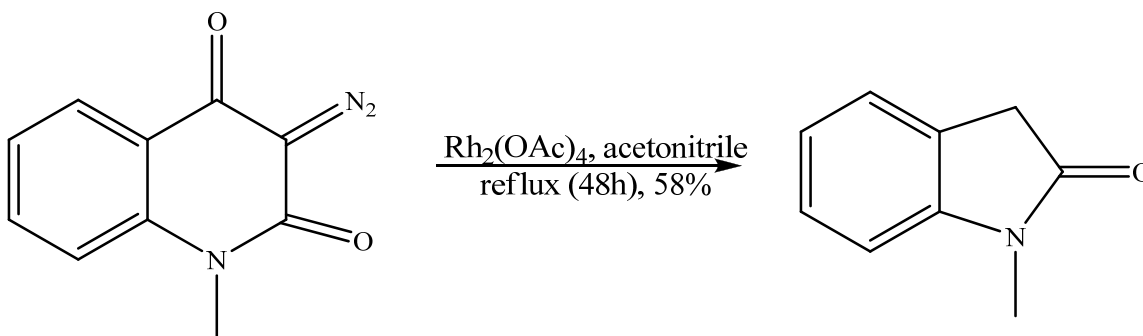
Scheme 28. Formation of Cyclopropanes from Cyclobutanones through Photodecarbonylation<sup>19</sup>

## Wolff Rearrangements

This type of rearrangement converts  $\alpha$ -diazo-ketones into ketenes. It is catalyzed by light, heat, or transition metals such as silver [20]. Ketenes are usually intermediate compounds and can be further reacted to amides, carboxylic acids, or esters. An illustration of the light and rhodium-catalyzed Wolff rearrangements is shown below:



Scheme 29. Light-Catalyzed Wolff Rearrangement<sup>21</sup>



Scheme 30. Rhodium-Catalyzed Wolff Rearrangement<sup>22</sup>

Now, we will proceed with an investigation of the most common ring expansion reactions.

## Main Ring Expansion Reactions

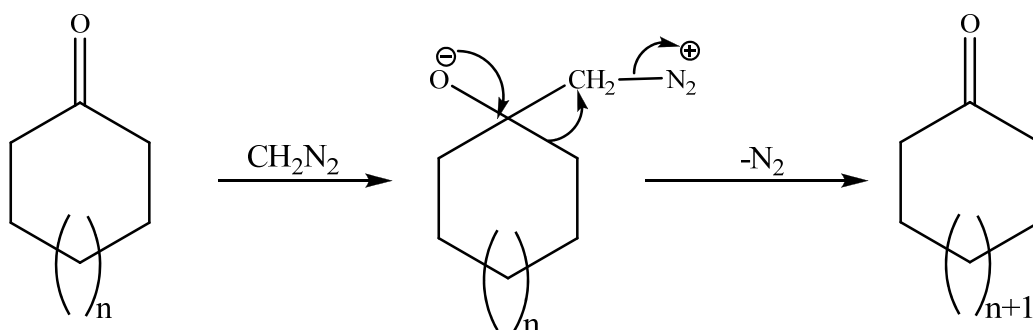
When a carbocycle or heterocycle gains one or more atoms and is consequently enlarged, it has undergone a ring expansion.

Ring expansion reactions are of great interest in synthetic organic chemistry because they provide efficient tactics for the preparation of biologically active natural products and drugs [23]. Over the past decades, the research in this area has increased exponentially. This point is supported by the numerous papers published on the subject; papers exhibiting great advances or refinements in the techniques of ring enlargement. In the following paragraphs, the most common ring expansion reactions are described and illustrated and some innovative approaches are also be mentioned.

The following classification presents reactions according to the number of atoms being incorporated in the ring enlarging step [24]:

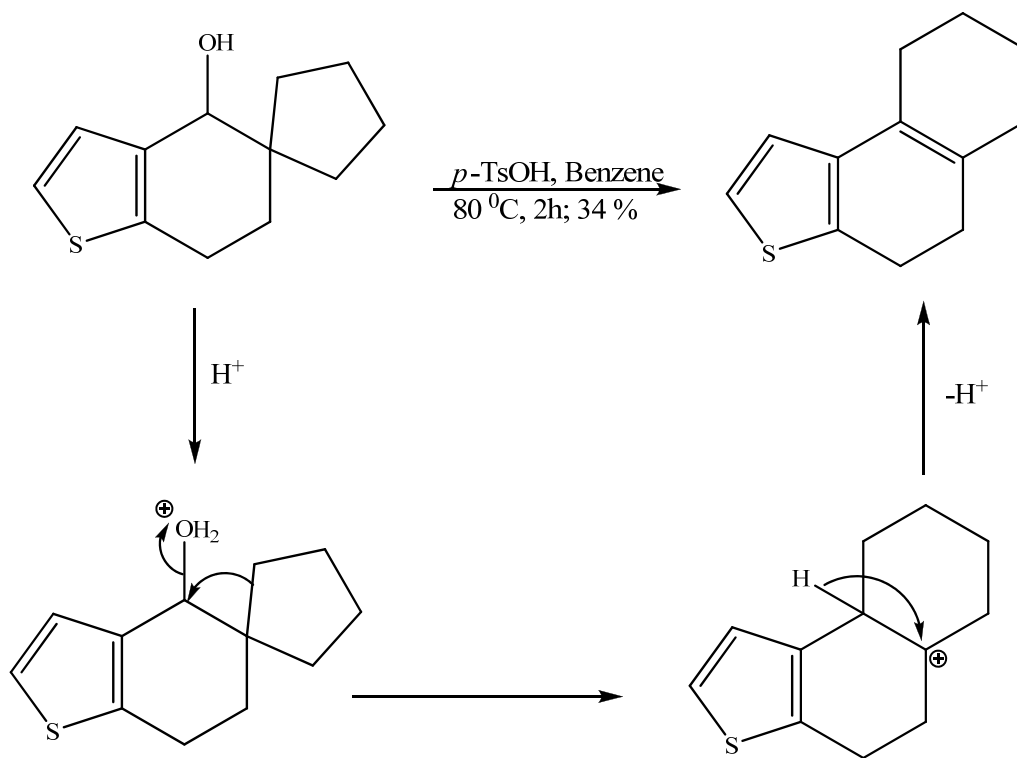
### Ring Enlargement by One Carbon Atom

- Wolff rearrangement:



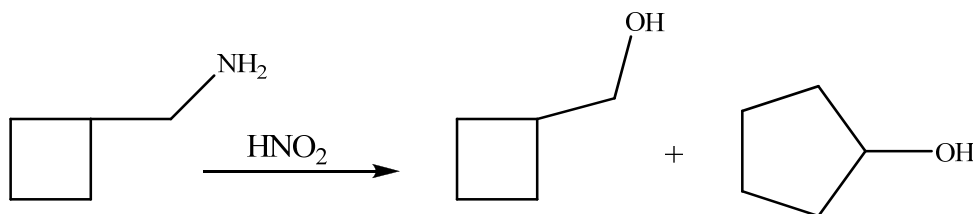
Scheme 31. Wolff Rearrangement

- Wagner- Meerwein rearrangement:



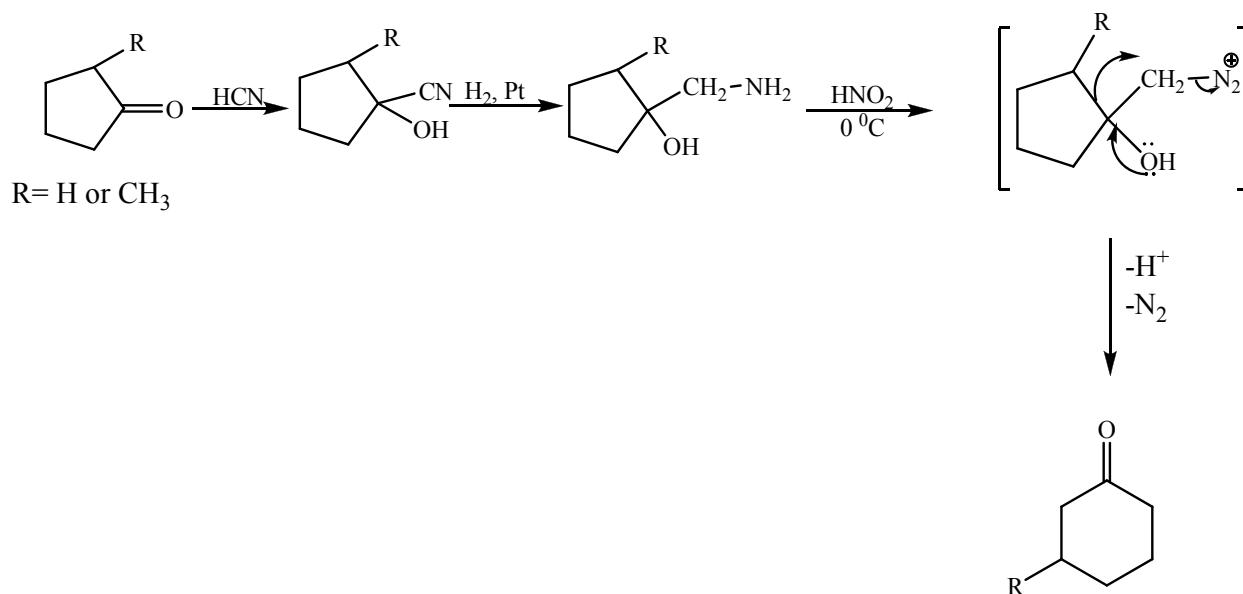
Scheme 32. Wagner-Meerwein Rearrangement<sup>25</sup>

- Demjanov rearrangement: Chemical reaction of primary amines with nitrous acid to give rearranged alcohols [26].



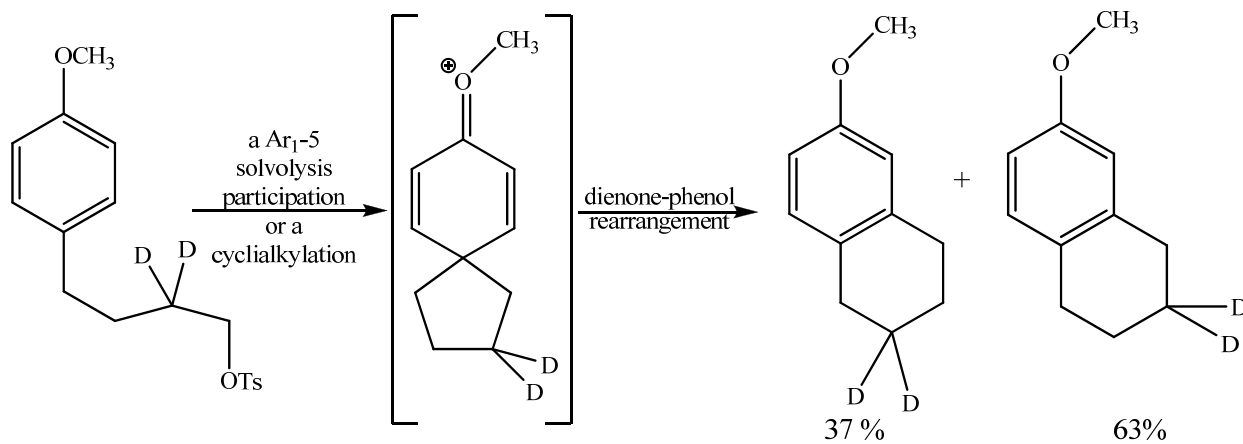
Scheme 33. Demjanov Rearrangement<sup>26</sup>

- Tiffeneau-Demjanov rearrangement: Often used to transform a cyclic ketone into a homologue that is one ring size larger [27].



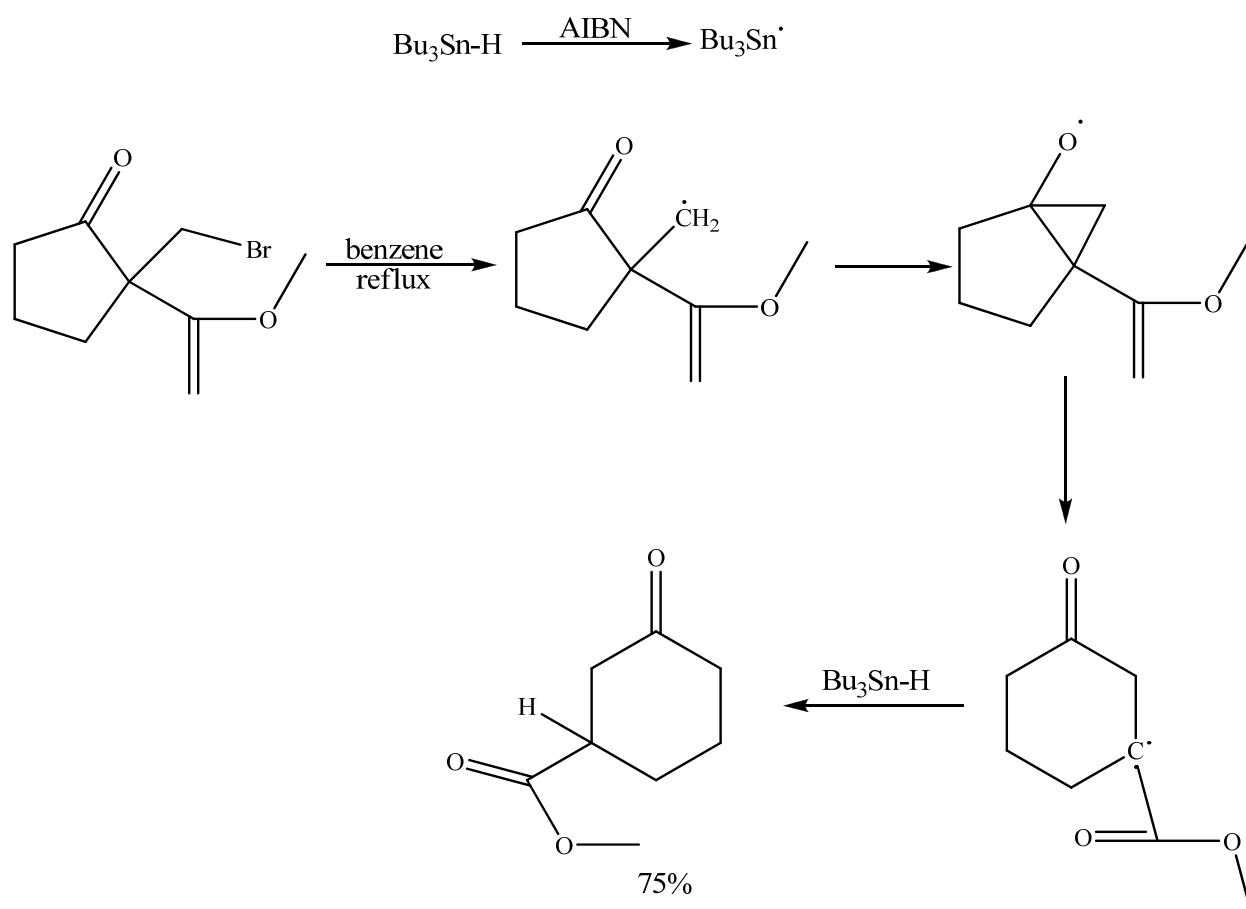
Scheme 34. Tiffeneau-Demjanov Rearrangement<sup>27</sup>

- Dienone-phenol rearrangement:



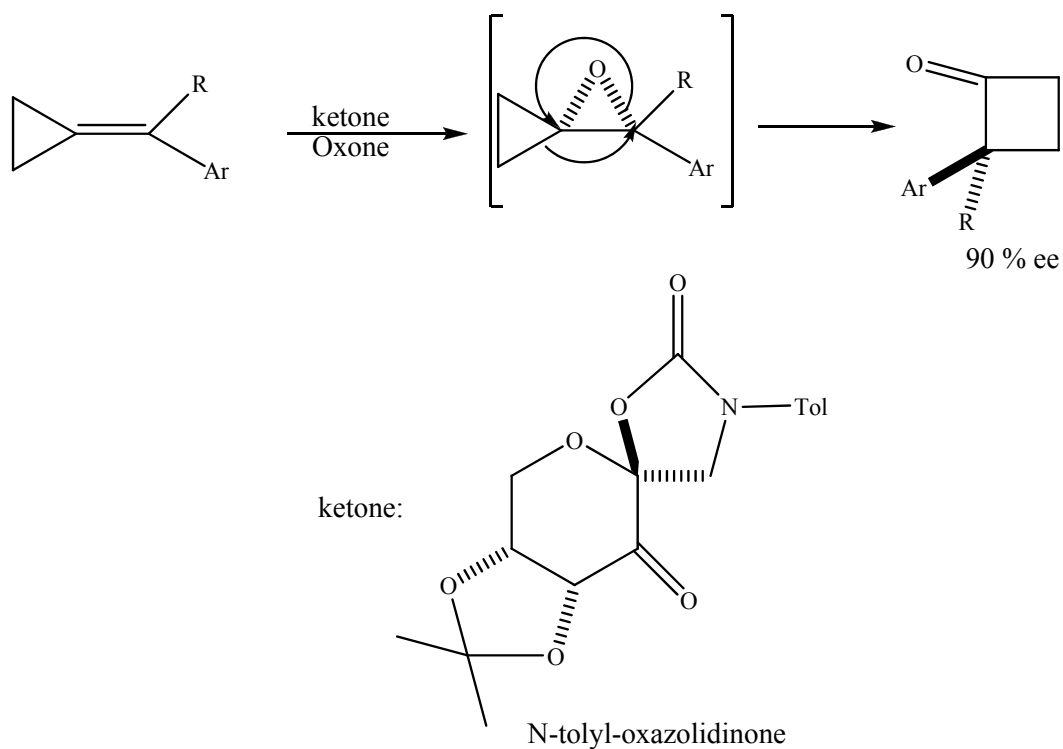
Scheme 35. Dienone-Phenol Rearrangement<sup>28</sup>

- Dowd-Beckwith ring expansion reaction: This reaction is initiated by thermal decomposition of AIBN and involves a bicyclic intermediate [29].



Scheme 36. Dowd-Beckwith Ring Expansion<sup>29</sup>

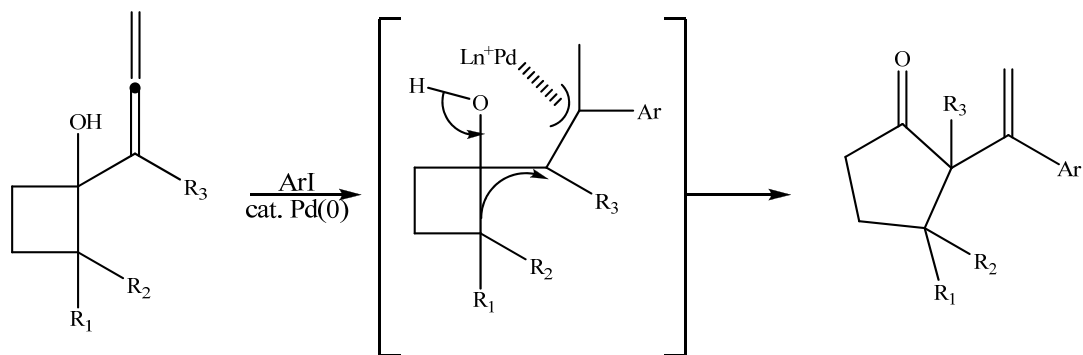
- Asymmetric epoxidation:



Scheme 37. Asymmetric Epoxidation<sup>30</sup>

A good number of metal-catalyzed one-carbon ring expansion reactions have been reported.

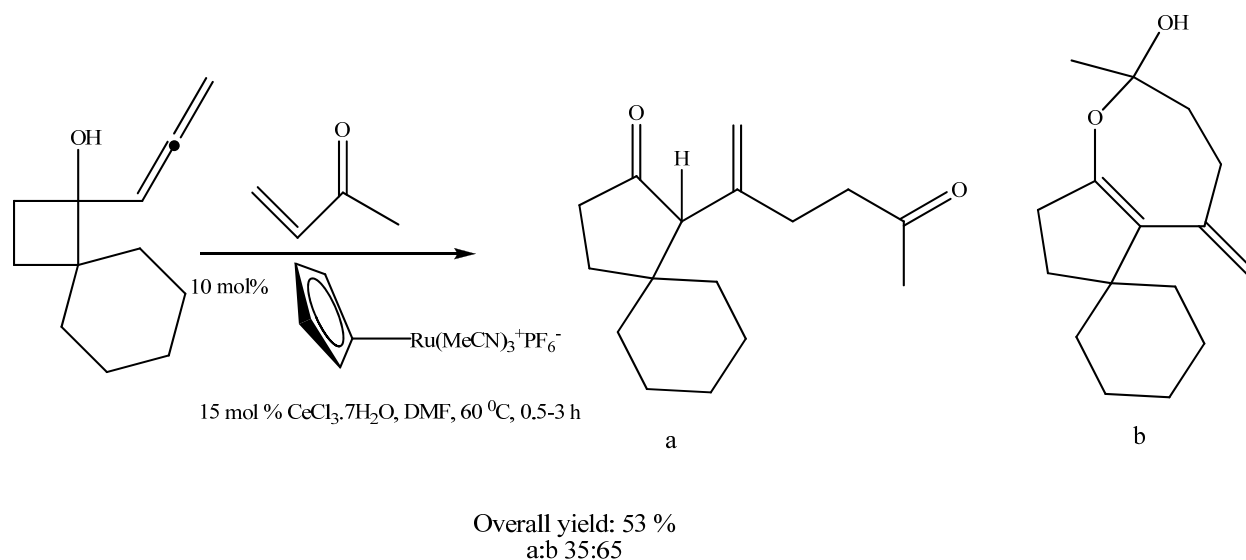
❖ Pd-catalyzed ring expansion:



Scheme 38. Pd-Catalyzed Ring Expansion<sup>31</sup>



❖ Ru-catalyzed ring expansion:

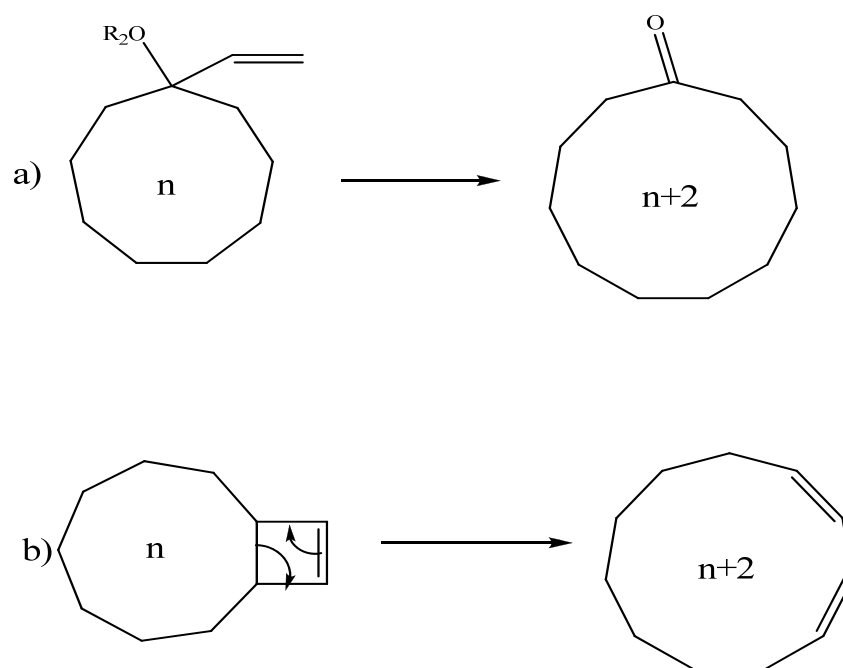


Scheme 39. Ru-Catalyzed Ring Expansion<sup>32</sup>

In addition, examples of gold [33], zinc [34], samarium [35], lithium, and magnesium [36] one-carbon ring expansion reactions have also been reported.

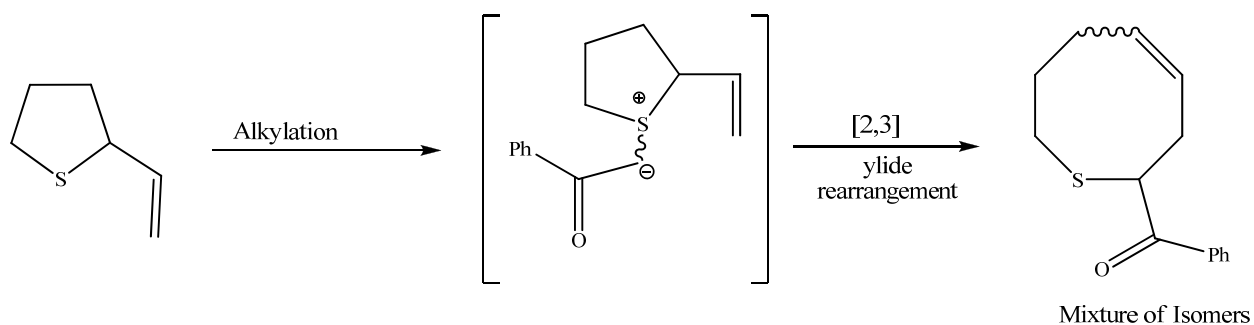
Ring Enlargement by Two or More Carbon Atoms

Common methods such as the migration of allylic alcohols [37] (scheme 40, a) or ethers or the thermal cycloconversion of [2+2]-cycloadducts [38] (scheme 40, b) usually yield carbocycles enlarged by two carbon atoms.



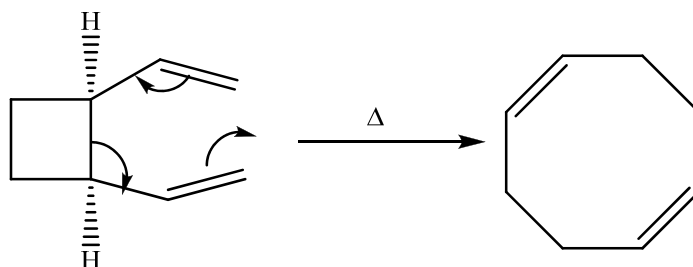
Scheme 40. Ring Enlargement by Two or More Carbon Atoms<sup>37,38</sup>

Examples of cobalt [39], nickel [40], potassium carbonate [41] catalyzed and free radical [42] two-carbon ring expansion reactions have been recently published. Three-carbon ring enlargement can be effected by ylide or Vedejs rearrangement [43] (Scheme 41), radical processes [44,45,46], and Flash Vacuum Thermolysis (FVT) [24]



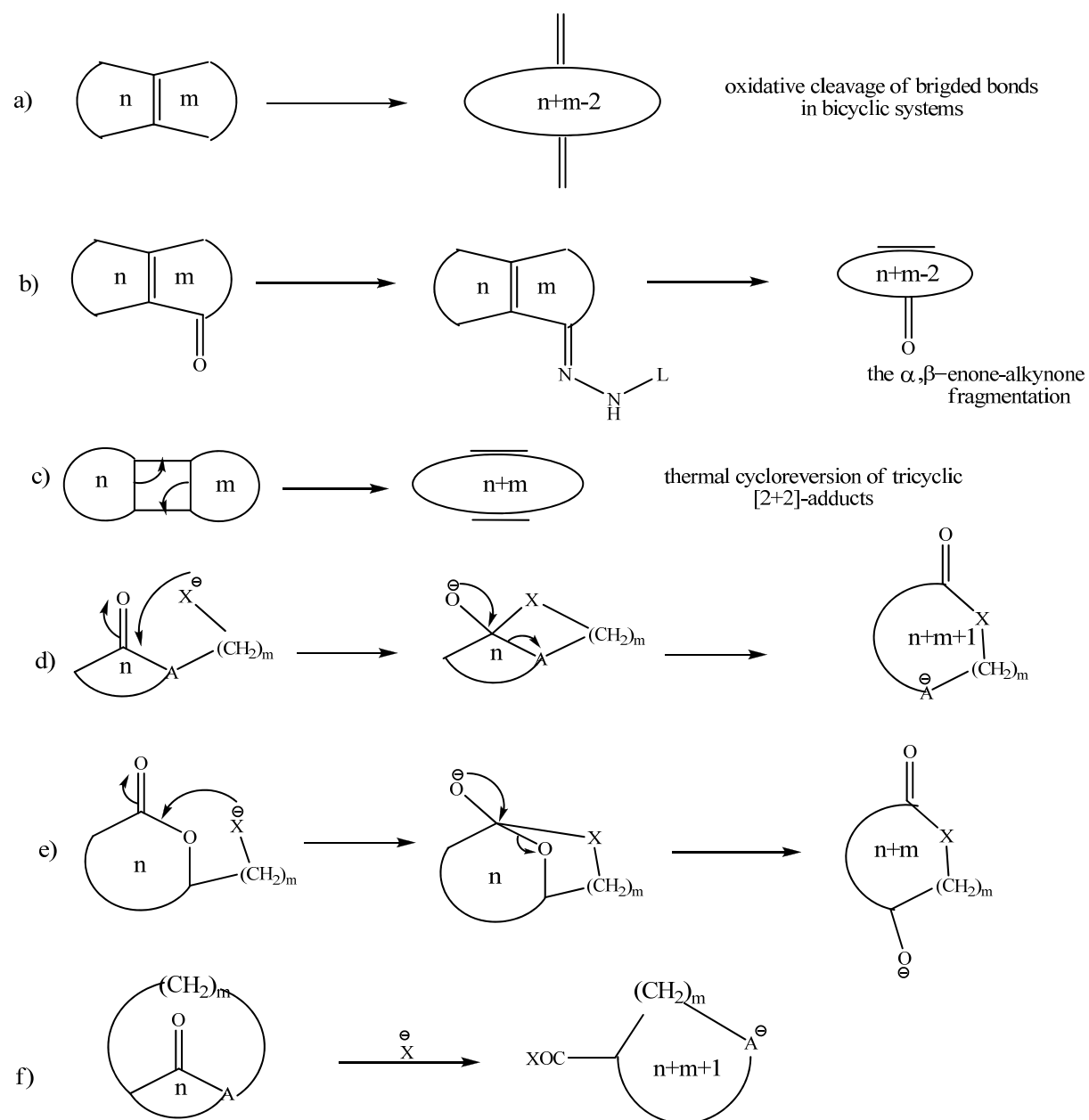
Scheme 41. Ylide Rearrangement<sup>4</sup> (Adapted from Nitrogen, Oxygen and Sulfur

The four-carbon ring enlargement is carried through the Cope rearrangement [47]:



Scheme 42. Cope Rearrangement <sup>47</sup>

Recent publications expand on the rhodium-catalyzed [48], anionic [49], and free radical [50] four-carbon ring expansion reactions.

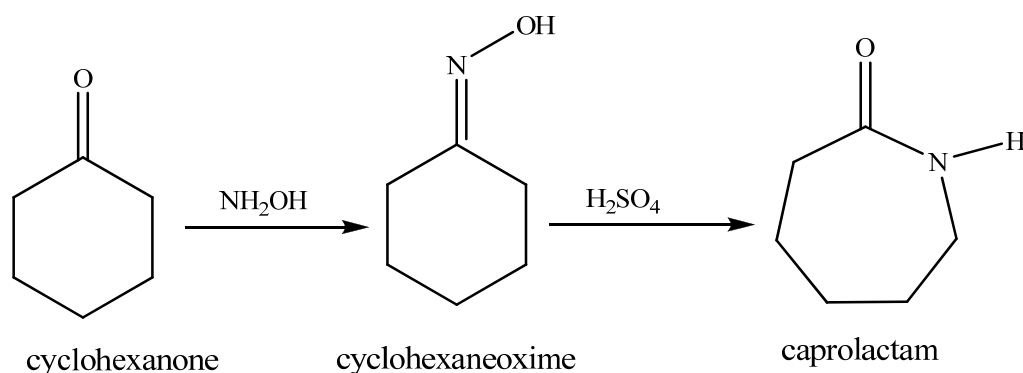


Scheme 43. Ring Enlargements by Varying Number of Carbon Atoms<sup>24</sup>

In the scheme above, the reactions a, b, and c allow the insertion of a specific number of carbon atoms while d, e, and f display ways by which starting rings can be expanded by an unspecified number of carbon atoms.

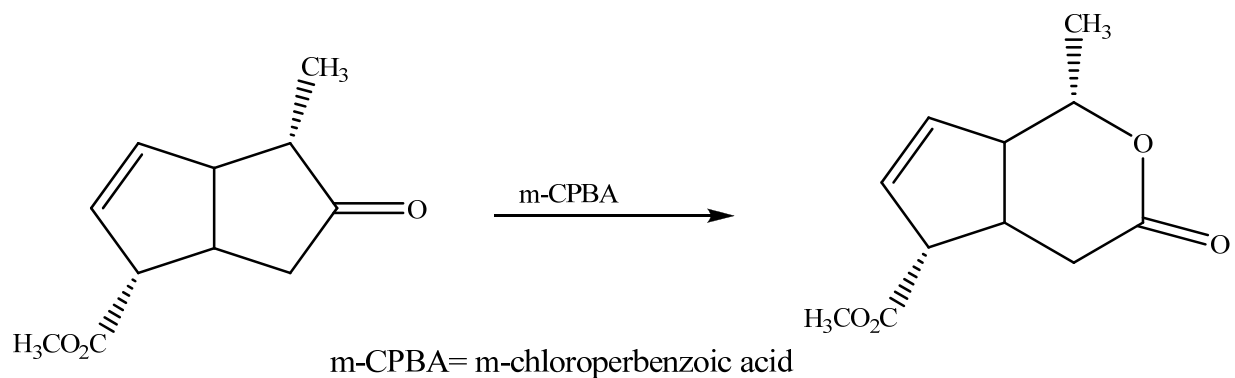
## Heterolytic Ring Enlargement

Beckmann Rearrangement. It is an acid-catalyzed rearrangement of an oxime to an amide [51].



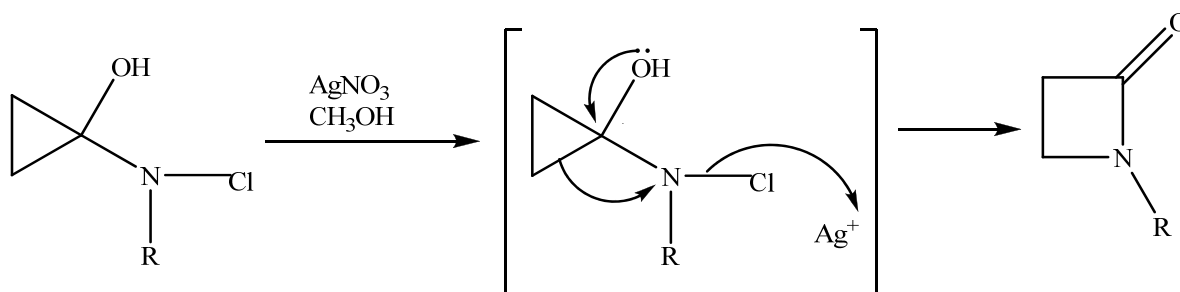
Scheme 44. Beckmann Rearrangement<sup>51</sup>

Baeyer-Villiger Rearrangement. It involves the acid-catalyzed reaction of ketones with hydroperoxide derivatives [27].



Scheme 45. Baeyer-Villiger Rearrangement<sup>27</sup>

Stieglitz Rearrangement. It consists in the rearrangement of azacations by a mechanism similar to the pinacol rearrangement.



Scheme 46: Stieglitz Rearrangement<sup>27</sup>

This summarizes some of the most common and well-known ring contraction and enlargement reactions. Many discoveries or improvements of the existing methods have already been made and more are still to come. It is therefore undeniable that the processes of ring contraction and expansion play a very important part in most of the synthetic routes. Ours is not an exception to the rule and the following section is dedicated to the objective of our research.

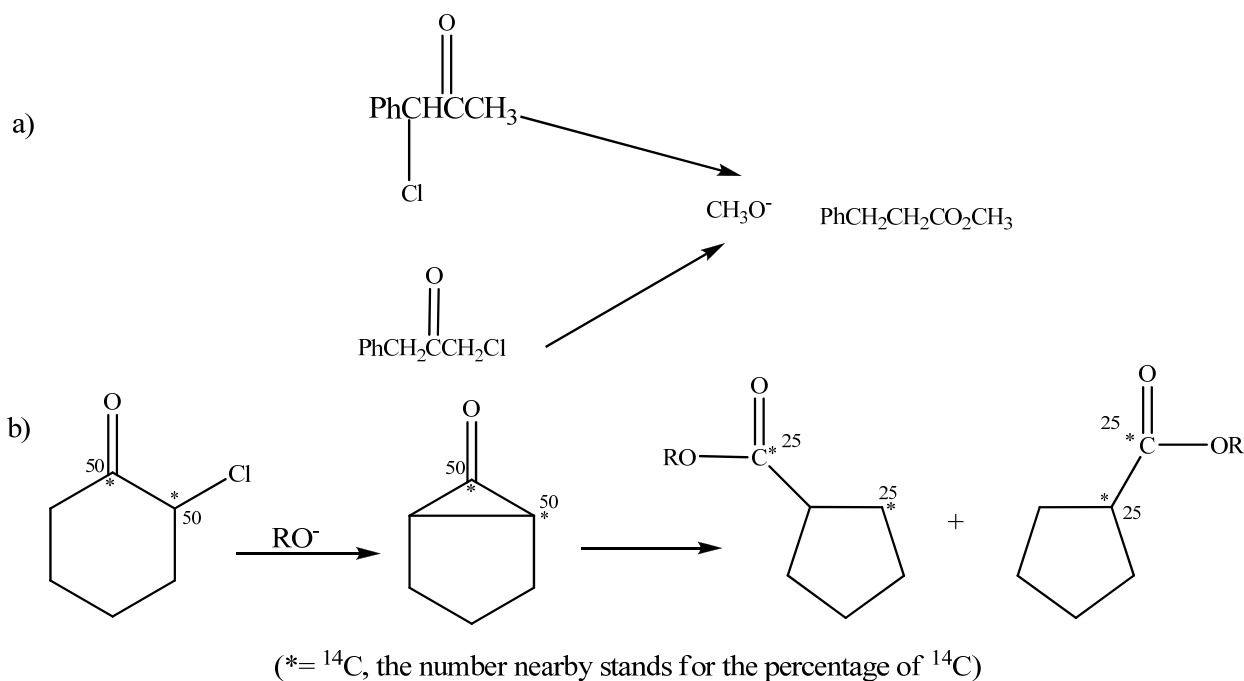
### Objective of the Research

Our project aims at the synthesis of a bridged 6-7 carbon-membered ring. In order to do so several approaches have been devised, all having in common two final key-steps:

- A new palladium-catalyzed Favorskii rearrangement: This step will yield a contracted 3-membered ring intermediate which will not be isolated but convert (because of the strain) into an expanded ring through:
- A never-before encountered *cis*-divinylcyclopropanone rearrangement that will give rise to the final compound.

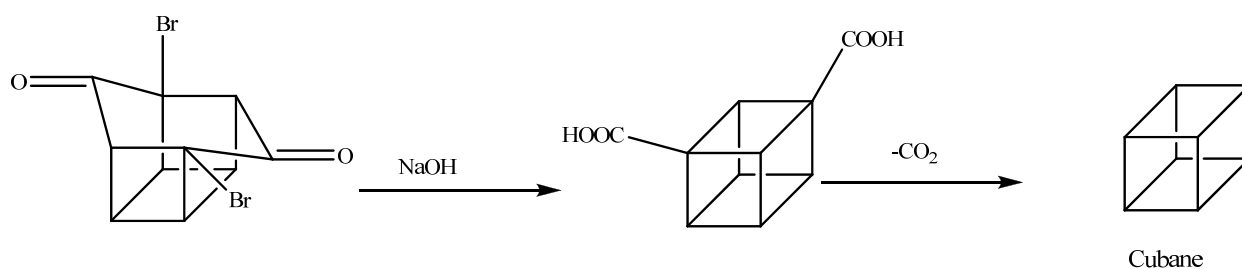
## Previous Studies

The Favorskii Rearrangement. As mentioned earlier, it is a base-catalyzed rearrangement and was discovered in 1914. Its mechanism was not really obvious to chemists for a while. Some insight came with the work of Bordewell and Lotfield, who proved the existence of a cyclopropane intermediate. The former scientist observed the formation of the same product from two different  $\alpha$ -haloketones (scheme 47, a). The latter, using  $^{14}\text{C}$  isotope labeling on 2-chlorocyclohexanone, detected an even distribution of the isotope between the two formed products (scheme 47, b) [52].



Scheme 47. Elucidation Steps for the Mechanism of the Favorskii Rearrangement<sup>52</sup>

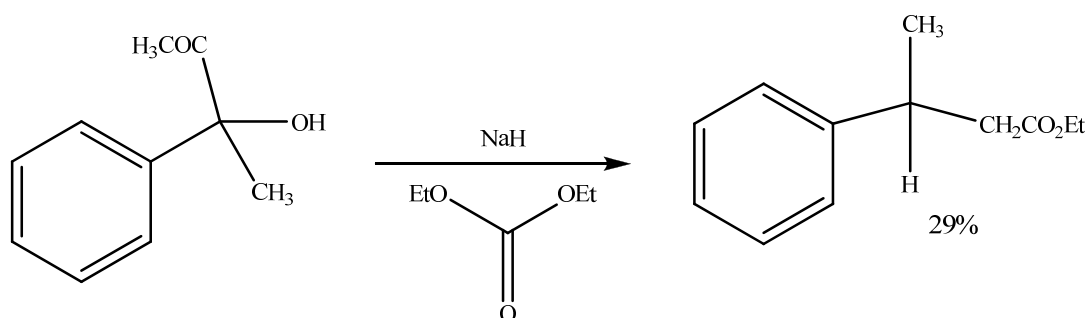
The Favorskii rearrangement is fairly well known for the synthesis of cubane in which it is used twice in a consecutive fashion [53].



Scheme 48. Synthesis of Cubane<sup>53</sup>

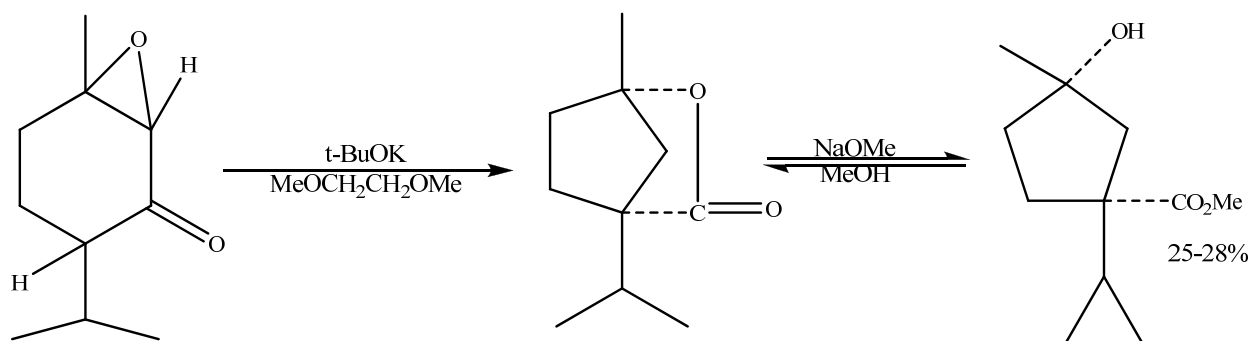
Apart from  $\alpha$ -haloketones, the Favorskii rearrangement has also been performed on:

-  $\alpha$ -hydroxyketones:



Scheme 49: Favorskii Rearrangement of  $\alpha$ -Hydroxyketones<sup>54</sup>

-  $\alpha,\beta$ -epoxyketones:

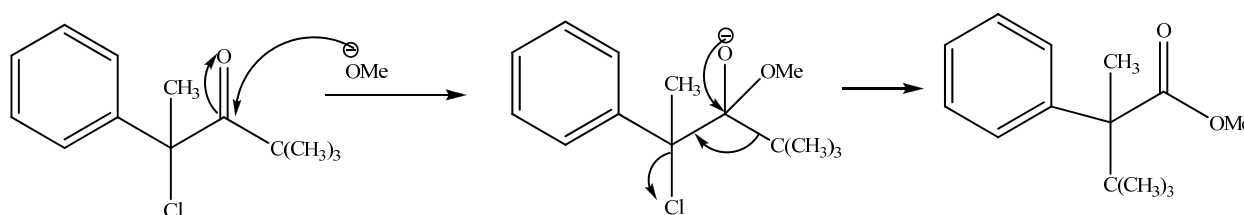


Scheme 50: Favorskii Rearrangement of  $\alpha,\beta$ -Epoxyketones<sup>55</sup>



There exist two main variants to the Favorskii rearrangement:

- The Wallach degradation: Conversion of 2,6-dibromocyclohexanone to cyclopentanone
- The Quasi-Favorskii rearrangement: It differs from the Favorskii rearrangement by the lack of acidic  $\alpha$ -hydrogens from the starting material and it proceeds through the semi-benzilic mechanism [56].



Scheme 51. Quasi-Favorskii Rearrangement<sup>56</sup>

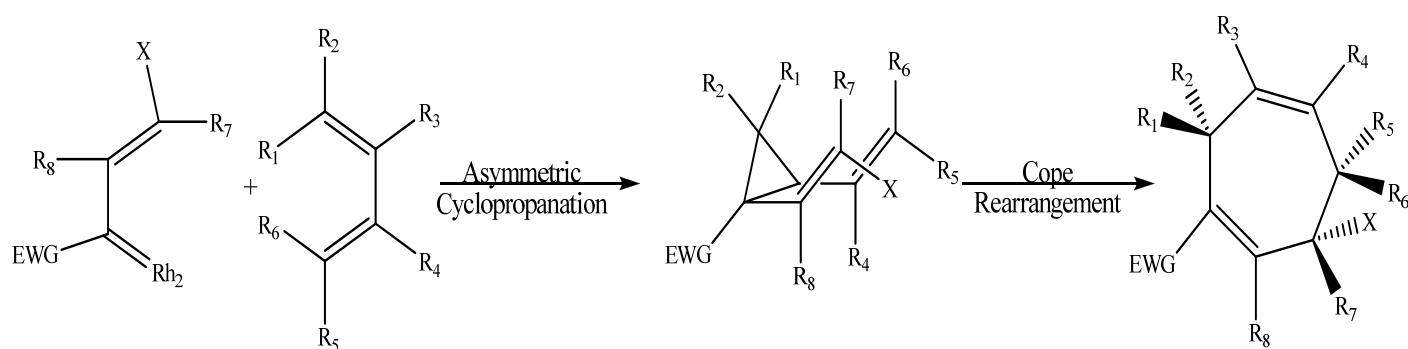
A *cis*-divinylcyclopropanone rearrangement has never been reported in the literature. The closest mechanism to it is:

#### The Cis-Divinylcyclopropane Rearrangement.

It usually occurs in the sequence:

- Asymmetric cyclopropanation
- Cope rearrangement

The product, whose main framework is made of a cycloheptadiene, exhibits controlled stereochemistry at three stereocenters. This can be explained by the stereodefined boat-like shape of the transition state [57].



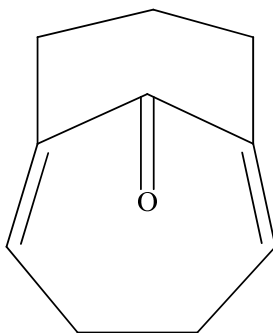
Scheme 52. Cis-Divinylcyclopropane Rearrangement<sup>57</sup> (Adapted from Modern Rhodium-Catalyzed

Organic

Reactions by A. Evans and J. Tsuji [57])

### Proposed Approach

Our goal is to synthesize (1Z,5Z)-bicyclo[4.3.1]deca-1,5-dien-10-one shown below:

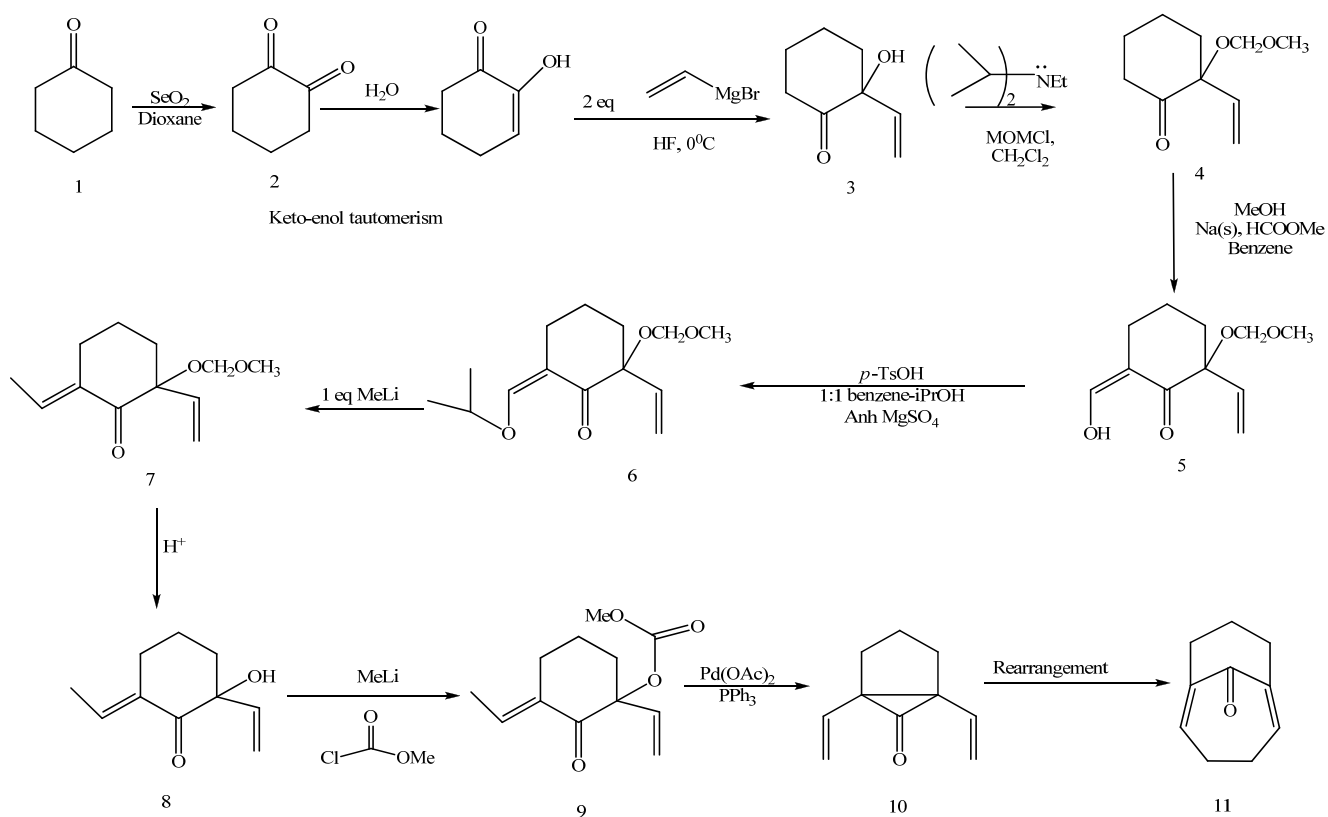


**11**

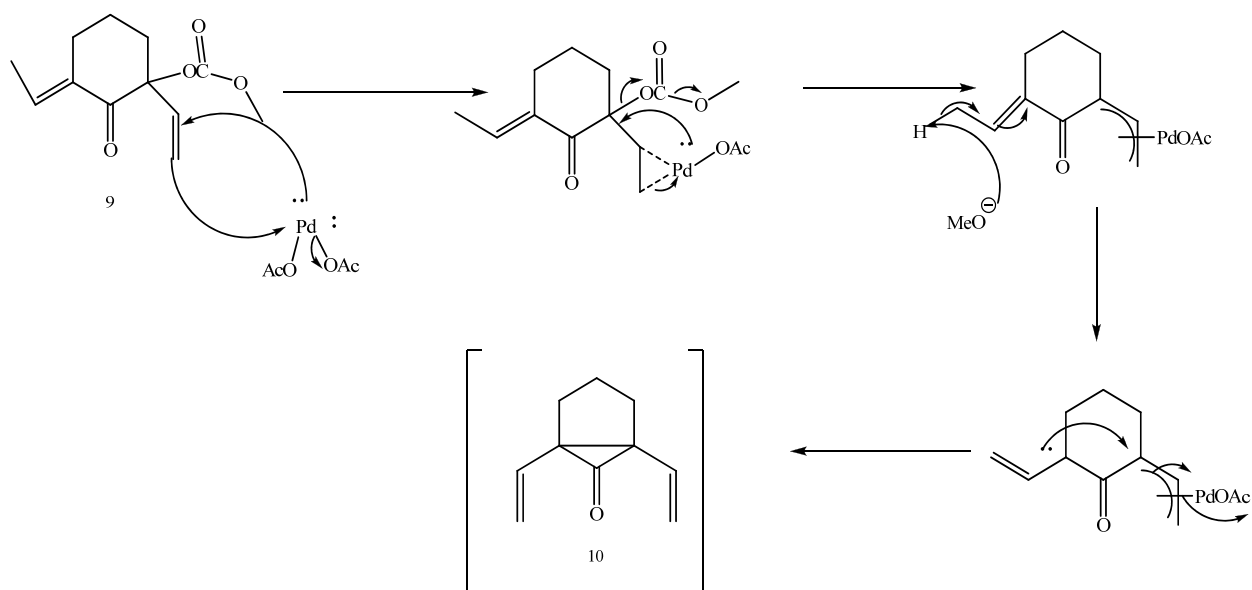
In order to do so, a number of approaches have been devised. The original consists of eight steps excluding the first two which yield known compounds (Scheme 5, 2 and 3). They are:

- An alcohol function protection

- An addition reaction to form an enol
- Isopropylation of the alcohol function of the enol
- Elimination of the isopropoxide group
- Deprotection of the alcohol function
- Acylation of the alcohol function
- Favorskii rearrangement
- Cyclopropanone rearrangement



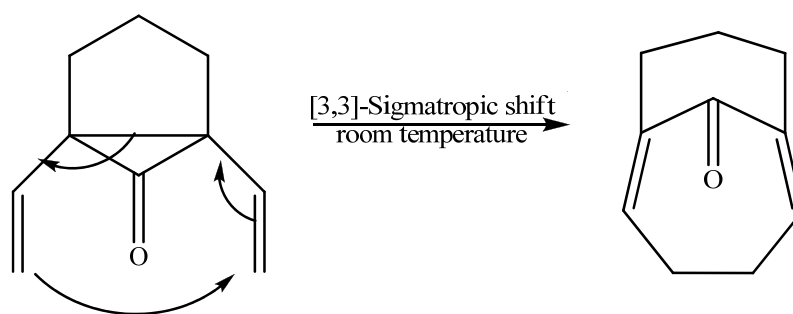
Scheme 53. Proposed Synthetic Pathway



9= (Z)-3-ethylidene-2-oxo-vinylcyclohexyl methyl carbonate

10= 1,5-cis-divinylbicyclo[3.1.0]hexan-6-one

Scheme 54. Proposed Mechanism for the Favorskii Rearrangement

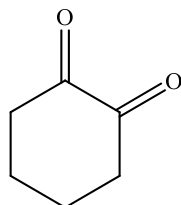


Scheme 55. *Cis*-Divinylcyclopropanone Rearrangement

## CHAPTER 2

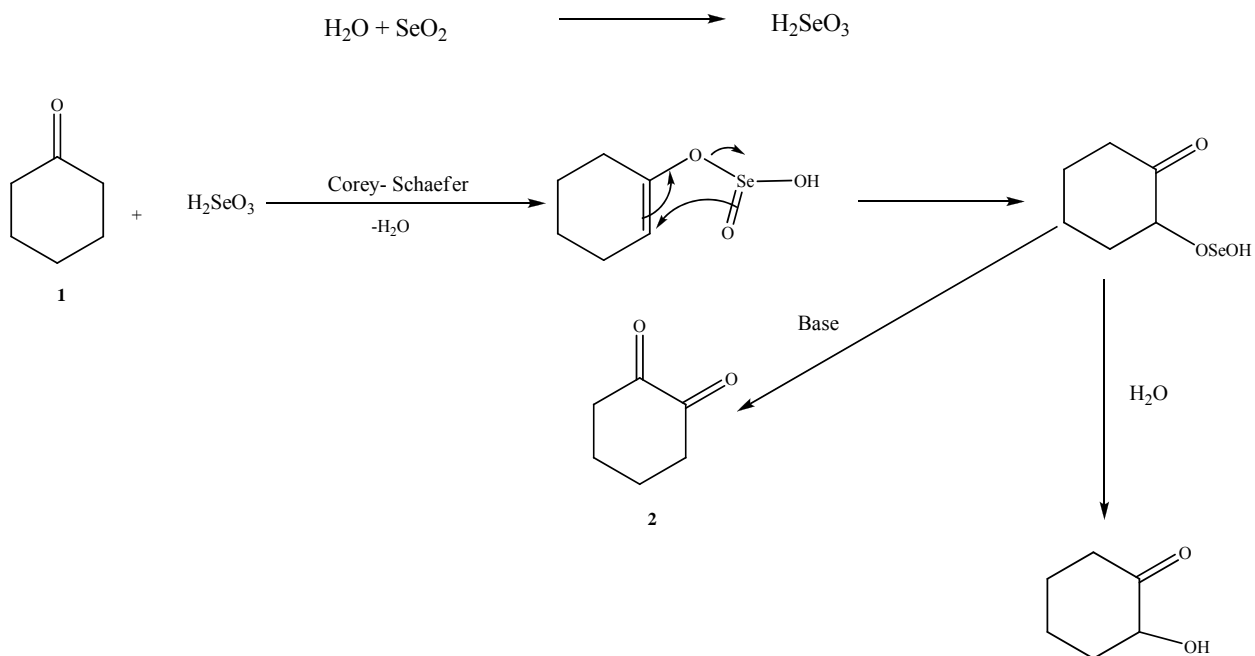
### RESULTS AND DISCUSSION

#### Synthesis of Cyclohexane-1,2-dione



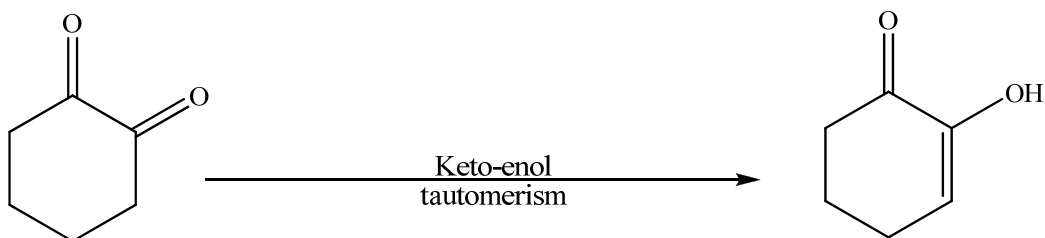
2

This compound was prepared, following a known procedure, by slow addition of a mixture of  $\text{SeO}_2$ , dioxane, and water to cyclohexanone with continuous cooling (Scheme 56) [58].



Scheme 56. Selenium Dioxide Oxidation of Cyclohexanone<sup>59</sup>

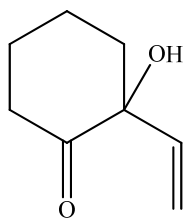
The diketone **2** in aqueous conditions undergoes keto-enol tautomerism and yields the corresponding enol (which is the predominant product according to the  $^1\text{H}$  NMR spectrum interpretation, appendix A).



Scheme 57. Keto-Enol Tautomerism

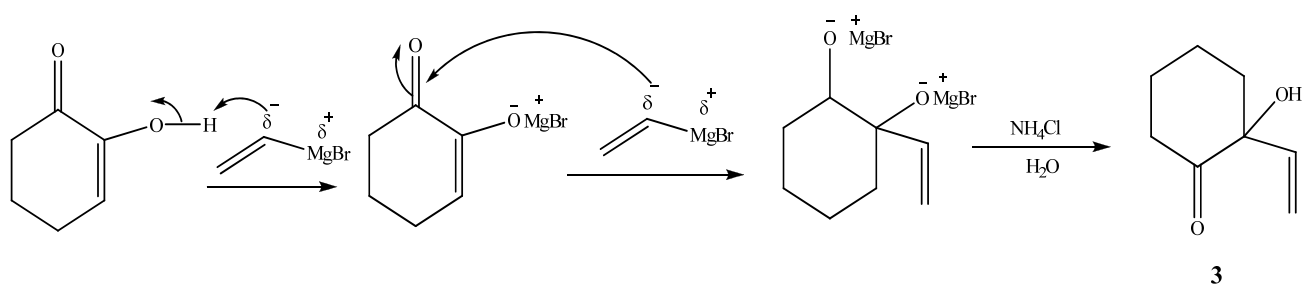
The product was initially obtained as a light yellow oil which crystallizes quite readily at room temperature. The yield was 63%. The main difficulty encountered with this reaction was the handling of toxic selenium formed in its course.

#### Synthesis of 2-Vinyl-2-hydroxycyclohexanone



**3**

This compound was obtained by adding two equivalents of vinylmagnesium bromide in 1M THF to the diketone **2** in THF. The proposed mechanism of the reaction is as follows:

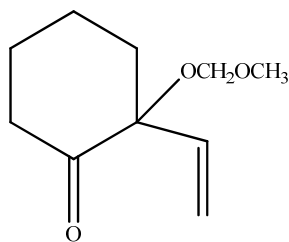


Scheme 58. Grignard Addition Step Mechanism

The Grignard addition product (compound **3**) is a brown oil. The yield was never more than 48% although a 98% yield is reported in the literature [60]. Our approach involved dropwise addition of the vinylmagnesium bromide to compound **2** in THF dropwise at 0 °C. Since the reaction is exothermic, we made sure that its temperature never rose above 5 °C. In order to improve the yield, we decided first to carry out the addition at -78 °C and then allow the temperature to rise gradually to 0 °C. Due to the fact that vinylmagnesium bromide crystallizes at temperatures below 25 °C [61], we could not add it in a dropwise fashion; also attempts to stir the reaction mixture also failed due to its solidification.

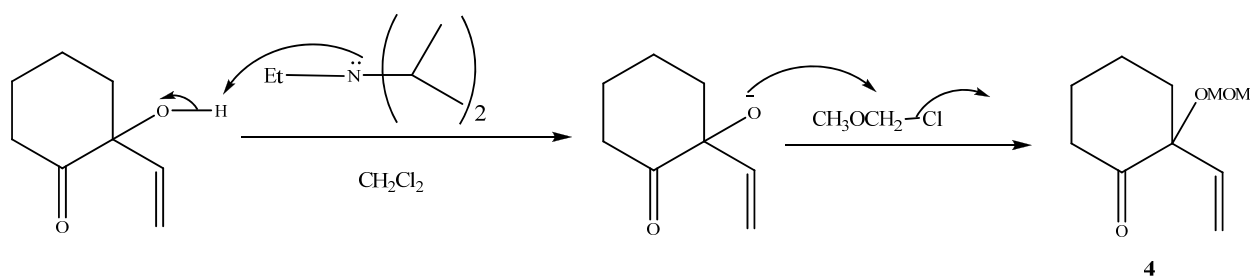
Another alternative way was to add ketone **2** in THF to the Grignard reagent at 0 °C (dropwise while monitoring the temperature). This also was not really efficient as less than 20% of the product was obtained.

## Synthesis of 2-(Methoxymethoxy)-2-vinylcyclohexanone



4

The purpose of this step was to protect the alcohol function of the Grignard addition product **3**. The reaction usually takes 3-4 days at room temperature, however when heated at reflux, the reaction went to completion upon overnight stirring. The proposed mechanism of the reaction is as follows:



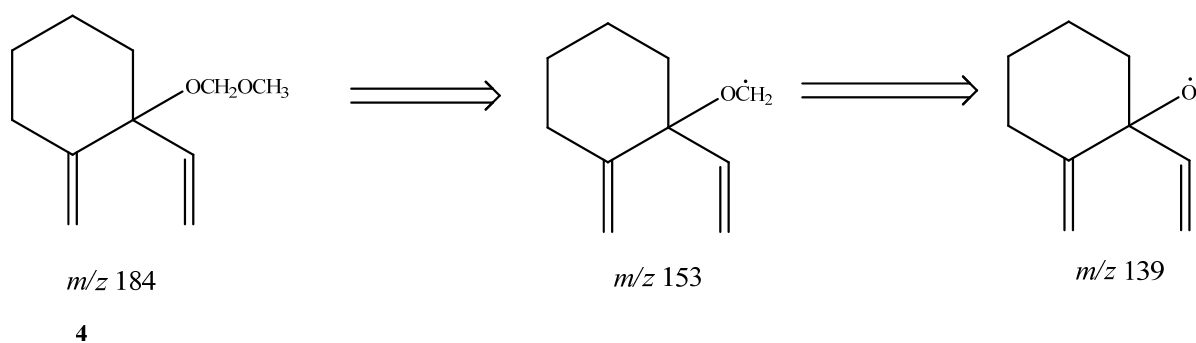
4

Scheme 59. Mechanism of the MOMCl Addition

This compound was characterized using  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR (Infrared) and GCMS (Gas Chromatography-Mass Spectrometry) spectra and the characteristic peaks are reported in the experimental section.

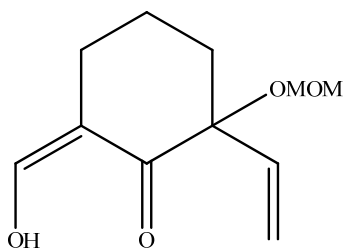
The GCMS spectrum exhibits three peaks at  $m/z$  184, 153, 139. The fragmentation can be illustrated as follows:





Scheme 60. Proposed Fragmentation for Compound **4**

Synthesis of (Z)-6-(Hydroxymethylene)-2-(methoxymethoxy)-2-vinylcyclohexanone



**6**

Literature procedure for the synthesis of compound **5** was used [62]. The protected alcohol **4** was treated with 2.8 equivalents of sodium metal in methanol and 2.5 equivalents of methyl formate in benzene. A 23% yield of brown oil was obtained. Although we never got a clean  $^1\text{H}$  NMR spectrum for compound **5**, the relevant peaks were however identified and only few peaks were assigned as impurities. Due to the small amount of product obtained (80 mg), we decided not to further purify it but instead perform the next step to test its feasibility.

Compound **6** was synthesized following reported procedure [63].

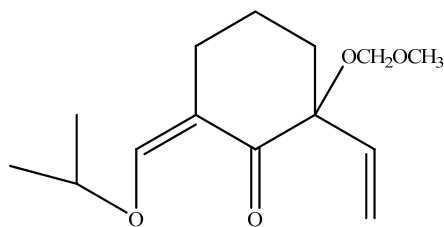
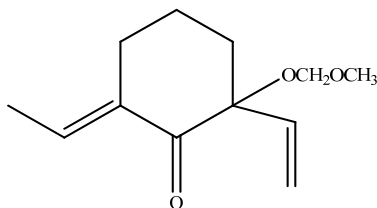


Figure 1. Structure of (E)-6-(Isopropoxymethylene)-2-(methoxymethoxy)-2-vinylcyclohexanone

The enol **5**, in a 1:1 mixture of benzene-isopropyl alcohol, was treated with 0.3 equivalents of *p*-TsOH. Upon analysis of the <sup>1</sup>H NMR of the brown sticky product, we could not account for the protons peaks of the MOM-protecting group. When setting up the reaction, we were aware of the acidic nature of the reaction mixture but did not think that 0.3 equivalents of the *p*-TsOH could take off the MOM-protection; however, that observation could only be the result of the acidic conditions under which the reaction was carried out.

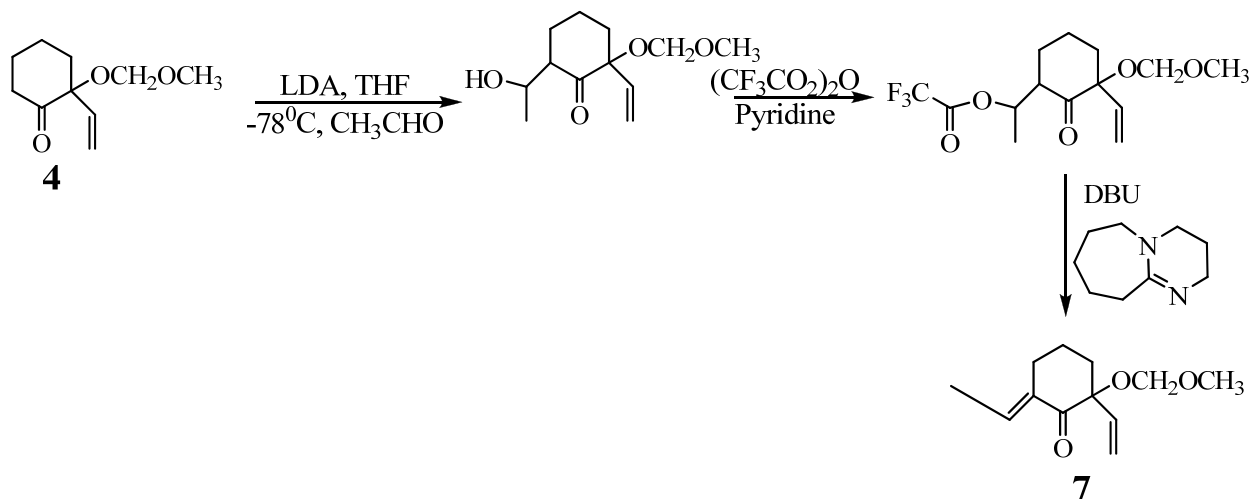
We had to find another approach to proceed with our synthetic pathway.

Alternate Routes to Compound 7: (E)-6-Ethylidene-2-(methoxymethoxy)-2-vinylcyclohexanone



**7**

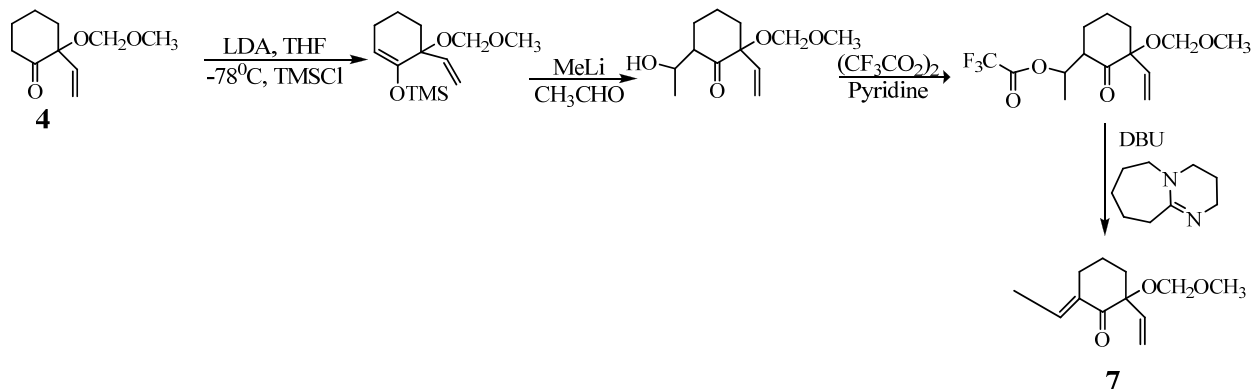
### Through Acetaldehyde Addition



Scheme 61. Proposed Synthesis of 7 via Acetaldehyde Addition

Most of the starting material was recovered upon treating 4 with acetaldehyde. We decided to slightly modify the route.

### Through Silylation of Compound 4



Scheme 62. Proposed Synthesis of 7 via Silylation of 4

The first step leading to the silylated compound has never been a success. Each time the reaction was attempted, the product turned into a white solid, insoluble in most deuterated solvents and only slightly soluble in DMSO-D<sub>6</sub>. <sup>1</sup>H NMR interpretation did not reveal any of the expected peaks.

Another concern with both routes was the predicted formation of four diastereomers of the alcohol (schemes 60 and 61), which would have lowered the yield of compound **7**.

Dr. David Gordon Joseph Young (East Tennessee State University) synthesized compound **7** (40%) from compound **4** by treating it with 1.5 equivalents of NaOH and 10 equivalents of (acetaldehyde) CH<sub>3</sub>CHO in ethanol. The reaction has been attempted several times and although the <sup>1</sup>H and <sup>13</sup>C NMR spectra exhibited the peaks of relevance, a large ratio of impurities was observed.

### Conclusions

The objective of the research has not been reached. A reason can be the low yields of the Grignard addition step. However, the yield and the purity of compound **3** have been significantly improved by reflux and column chromatography. Although all attempts to move forward were unsuccessful, we believe that more trials along with changes in conditions may lead to compound **7** in a reasonable yield. Three steps will then be left to synthesize the bridged 6-7 membered ring (including the alcohol deprotection step).

## CHAPTER 3

### EXPERIMENTAL SECTION

#### General Methods

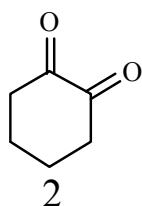
All proton ( $^1\text{H}$ ) and carbon ( $^{13}\text{C}$ ) NMR spectra were recorded on a JEOL-NMR ECLIPSE Spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. Chemical shifts were recorded as  $\delta$  values in part per million (ppm). Spectra were acquired in deuteriochloroform ( $\text{CDCl}_3$ ) at 20 °C. The internal standard was tetramethylsilane ( $(\text{CH}_3)_4\text{Si}$ ) ( $\delta$  0.00) for the  $^1\text{H}$  NMR spectra while it was the central peak of  $\text{CDCl}_3$  ( $\delta$  77.00) for the proton-decoupled  $^{13}\text{C}$  NMR spectra. The multiplicity of the signals is reported as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet. Infrared spectrum was obtained using an FTIR (Fourier Transformer Infrared Spectrophotometer) Shimadzu (IRPrestige-21). The mass spectral analysis was performed using a Shimadzu GCMS-QP2010 Plus instrument at East Tennessee State University.

Analytical thin layer chromatography (TLC) was conducted using EMD Chemicals Inc. (60 F<sub>254</sub> silica gel 20x20 cm 250  $\mu\text{m}$ ) plates. They were visualized under a 254 nm UV lamp (115 V~ 60 Hz, 0.16 AMPS) and were consequently treated with revealing dips: mainly, potassium permanganate-sodium carbonate-5% aqueous NaOH-water (3g: 20g: 5 mL: 300 mL) and phosphomolybdic acid-95% ethanol (250g: 1 gallon). Column chromatography was performed using Sorbent Technologies silica gel (230 x 450 mesh, 60 Å) as the stationary phase.

All commercial reagents were used without further purification unless otherwise noted. All reactions requiring anhydrous conditions were carried out under dry N<sub>2</sub> atmosphere, using flame dried glassware. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use.

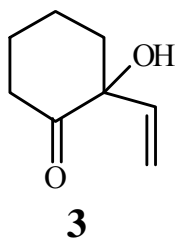
Organic solutions were concentrated under reduced pressure on a rotatory evaporator with water bath temperature generally below 200 F. Yields refer to isolated yields of material.

### Experimental Procedures

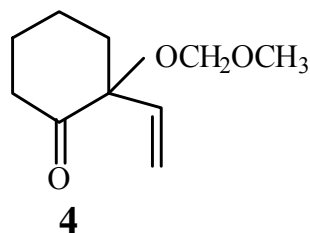


**1,2-Cyclohexanedione** [64]. To 207.1 mL (196.3 g, 2 mol) of cyclohexanone was added a solution containing 57.5 mL (59.4 g, 0.67 mol) of dioxane, 38.3 g (0.34 mol) of selenium dioxide and 11.5 mL of water over a 3-hours period. Stirring was continued for 5 additional hours at water-bath temperatures and 6 more hours at room temperature. The reaction mixture was filtered and the red solid was then returned to the flask and extracted with 34.5 mL of ethanol for 1 hour through reflux. The solution, obtained by decantation from selenium, was combined with the above filtrate and the unreacted cyclohexanone and dioxane were partially removed by concentration *in vacuo*. The concentrate was then distilled *in vacuo*. The fraction between 75-79 °C was essentially made up of the product which crystallized at room temperature (light yellow crystals, 63 % yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm) δ 1.96-2.07 (m, 2H, CH<sub>2</sub>), 2.34-2.38 (m,

2H, CH<sub>2</sub>), 2.48-2.52 (m, 2H, CH<sub>2</sub>), 5.99 (s, 1H, OH), 6.12 (t, 1H, *J* = 4.76, CH=); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm) δ 23.31 (s), 23.97(s), 36.56 (s), 118.65 (s), 147.11 (s), 195.76 (s).



**2-Hydroxy-2-vinylcyclohexanone** [60]. 2.5 g (22.32 mmol) of diketone **2** in 44.64 mL of anhydrous THF was added 44.64 mL (44.64 mmol) of vinylmagnesium bromide at 0 °C such that the temperature of the resulting solution did not exceed 5 °C. After 4 hours, the reaction was quenched with 20 mL of NH<sub>4</sub>Cl and stirred for 10 minutes. The pH of the solution was rendered neutral by gradual addition of 1 M HCl (aq). The aqueous layer was then extracted with three 30-mL portions of ether, the combined organic layers were washed with two 25-mL portions of water and with 25 mL of brine. The residue was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over 25 g of silica gel (eluted with hexanes-ethyl acetate, 6:1) to afford 1.15 g (37 %) of **3** as a brownish oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm) δ 1.71-2.53 (m, 6H, CH<sub>2</sub>), 4.11 (broad, 1H, OH), 5.45-5.24 (dd, 2H, *J* = 17.20, 10.64 MHz, H<sub>2</sub>C=), 6.14 (dd, 1H, *J* = 6.6, 10.24 MHz, CH=); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm) δ 22.54 (s), 27.89 (s), 38.54 (s), 41.34 (s), 116.81 (s), 137.42 (s), 211.41 (s).



**2-(Methoxymethoxy)-2-vinylcyclohexanone.** To a solution of 850 mg (6.07 mmol) of ketone **3** in 10 ml of CH<sub>2</sub>Cl<sub>2</sub> was added 3.01 mL (18.71 mmol) of N,N-diisopropylethylamine and 1.15 mL (15.17 mmol) of chloromethyl methyl ether (MOMCl). The reaction was refluxed overnight. The reaction was washed with 10 mL of water and the aqueous layer was extracted with three 10-mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed once 15 mL of brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed over 15 g of silica (eluted with hexanes-ethyl acetate 6:1) to afford 840 mg (71.2 %) of a light yellow oil: IR (neat) 1716 (s), 1082 (s), 1008 (w), 921 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm) δ 1.57-2.02 (m, 6H, CH<sub>2</sub>), 2.34 (m, H, HCH), 2.65 (m, H, HCH), 3.32 (s, 3H, OCH<sub>3</sub>), 4.64-4.64 (q, 2H, *J* = 6.95, OCH<sub>2</sub>), 5.20-5.37 (dd, 2H, *J* = 1.12, 17.96 MHz, CH<sub>2</sub>=), 5.97-6.19 (dd, 1H, *J* = 10.96, 4.48 MHz, CH=); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm) δ 21.85 (s), 27.84 (s), 39.42 (s), 40.18 (s), 56.31 (s), 84.23 (s), 93.04 (s), 119.09 (s), 137.12 (s), 210.00 (s); GCMS (*m/z*), 184, 153, 139.



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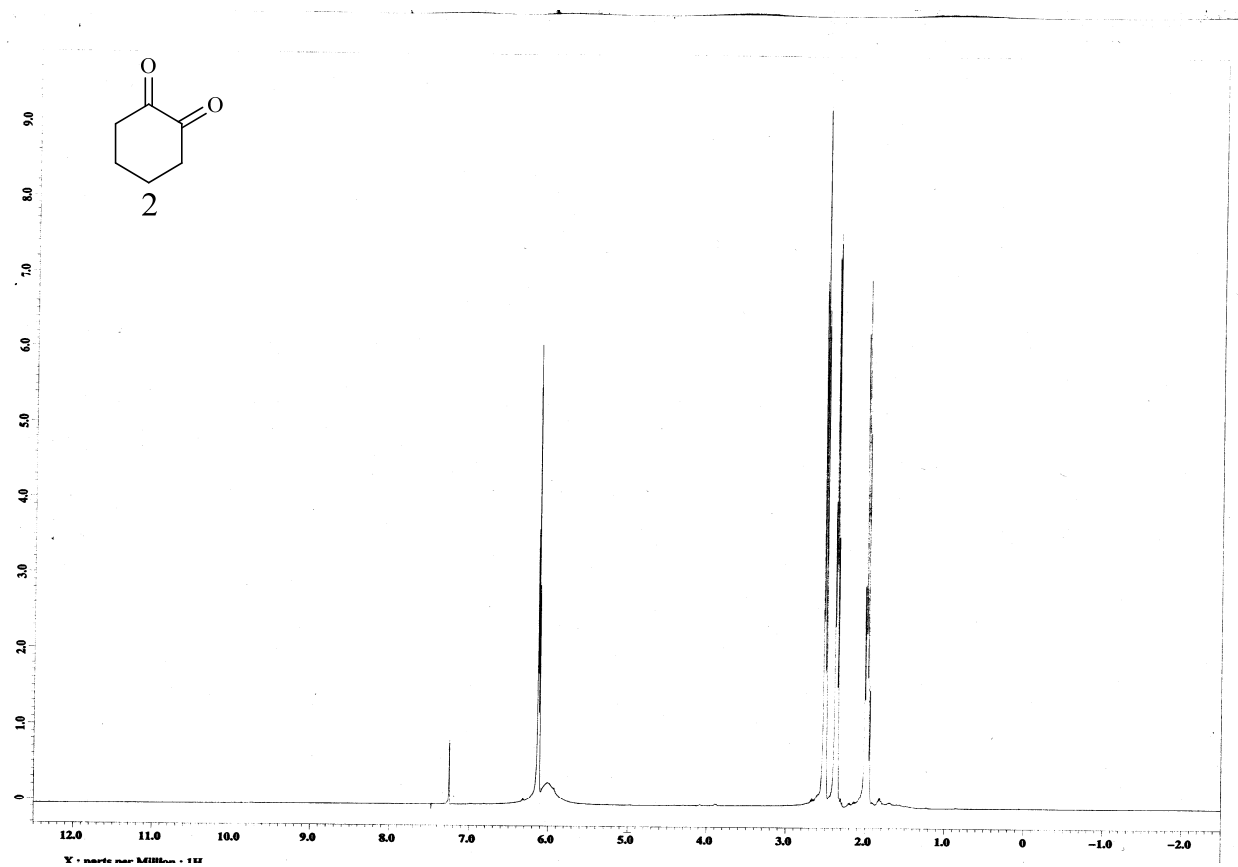
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# APPENDICES

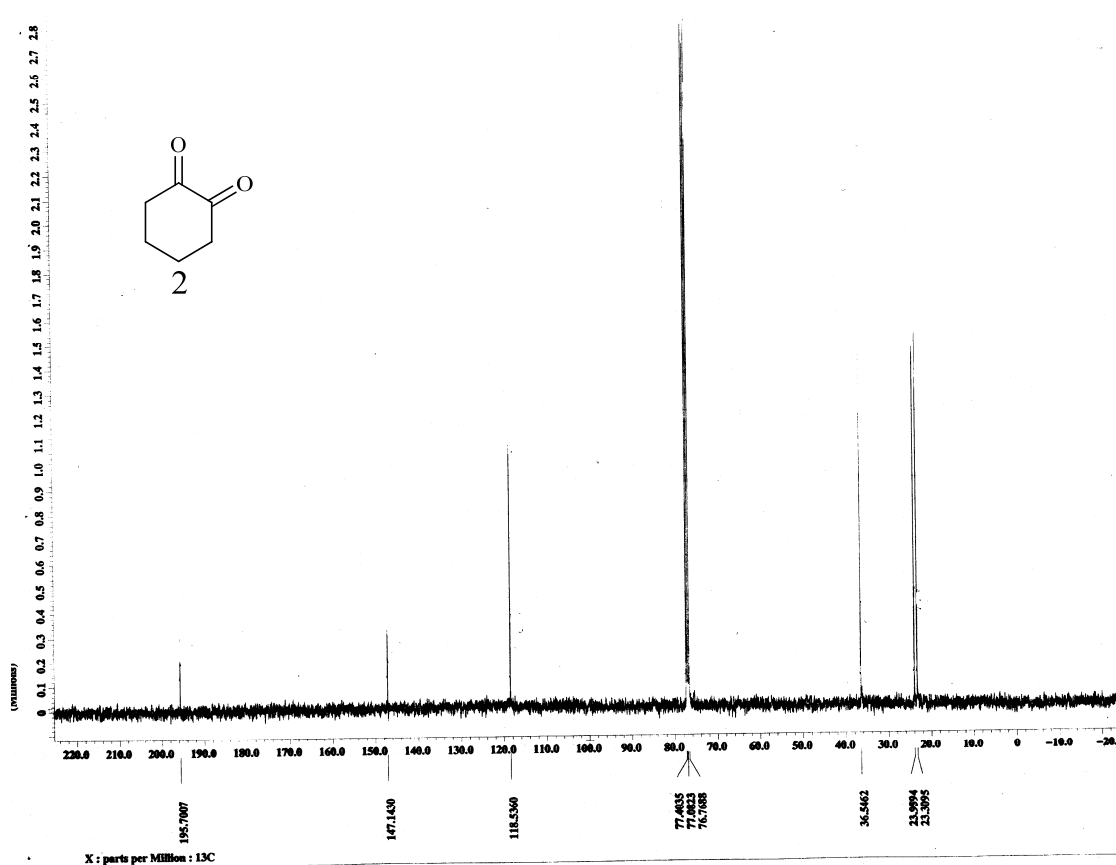
## APPENDIX A: $^1\text{H}$ NMR Spectrum of Compound **2**

Solvent:  $\text{d-CDCl}_3$  / TMS



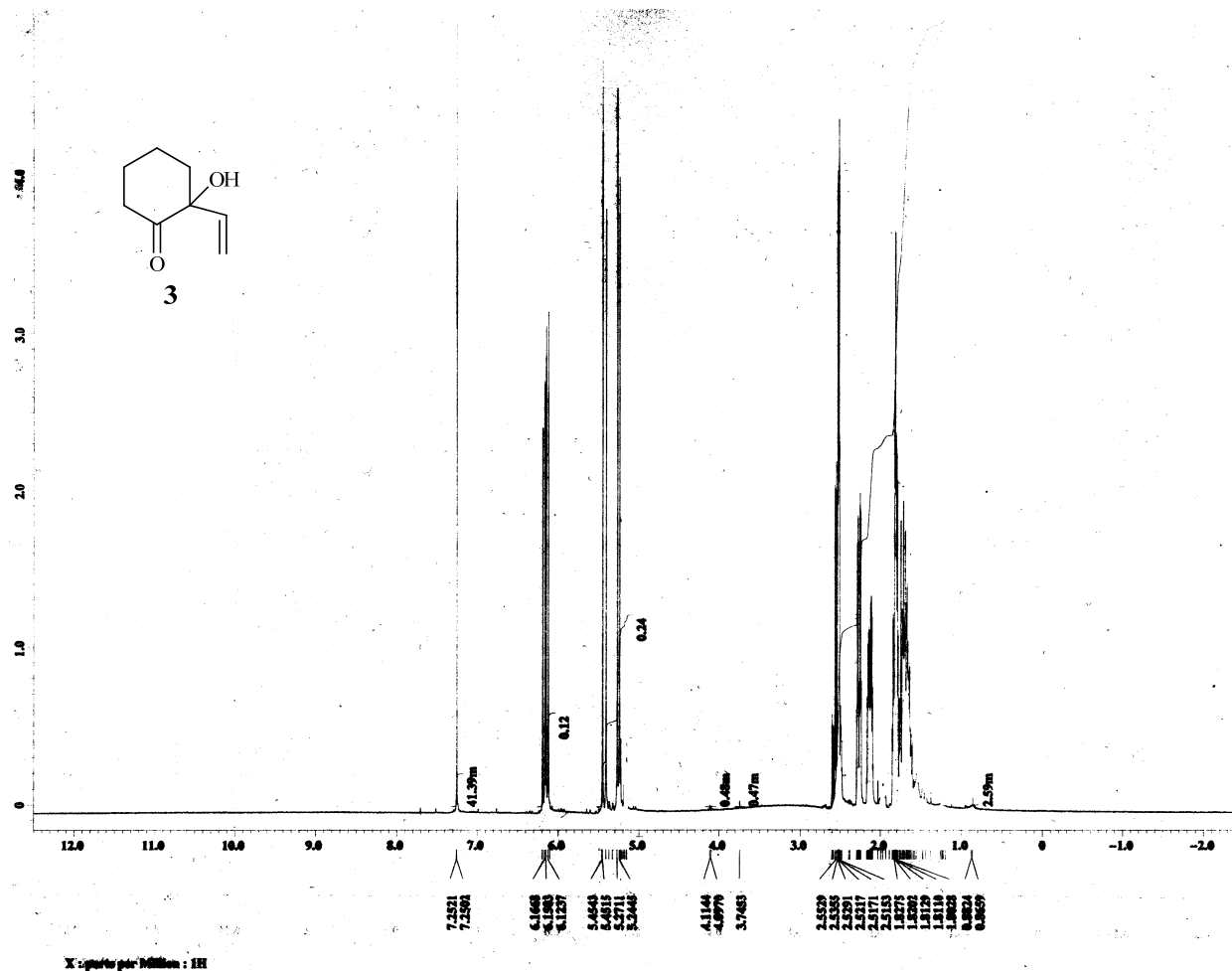
APPENDIX B:  $^{13}\text{C}$  NMR Spectrum of Compound 2

Solvent:  $\text{d-CDCl}_3$ / TMS



# APPENDIX C: $^1\text{H}$ NMR Spectrum of Compound 3

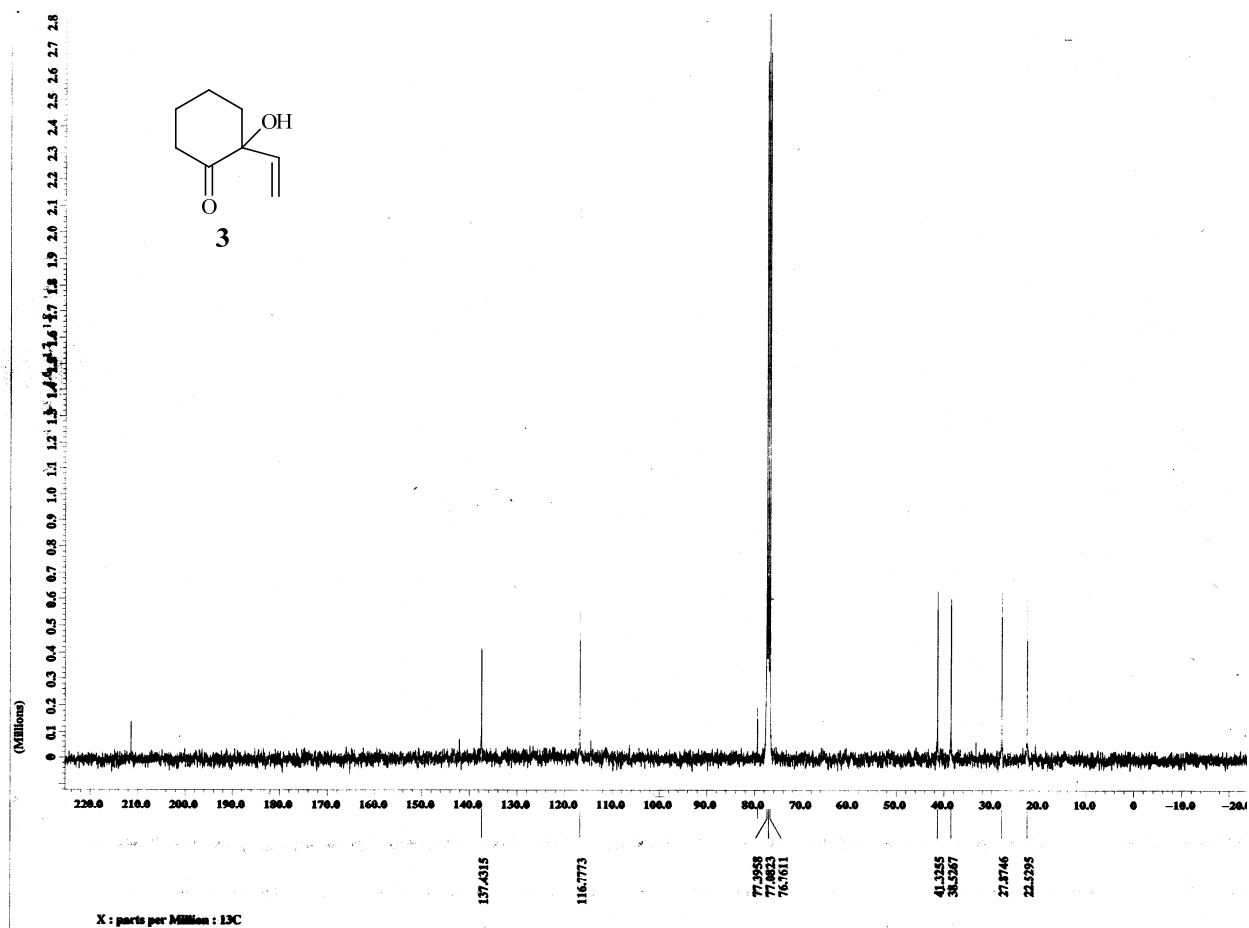
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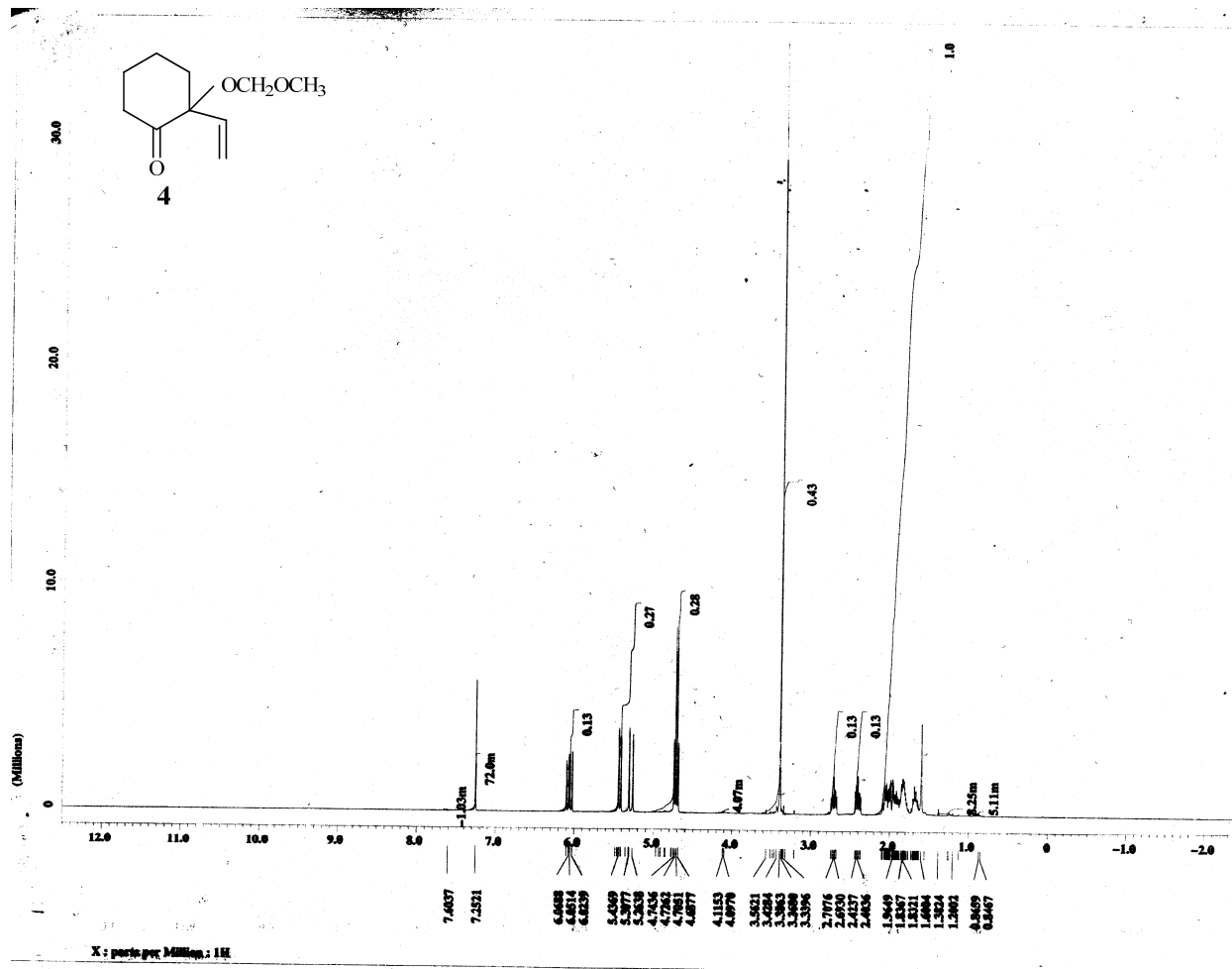
APPENDIX D:  $^{13}\text{C}$  NMR Spectrum of Compound 3

Solvent:  $\text{d-CDCl}_3/\text{TMS}$



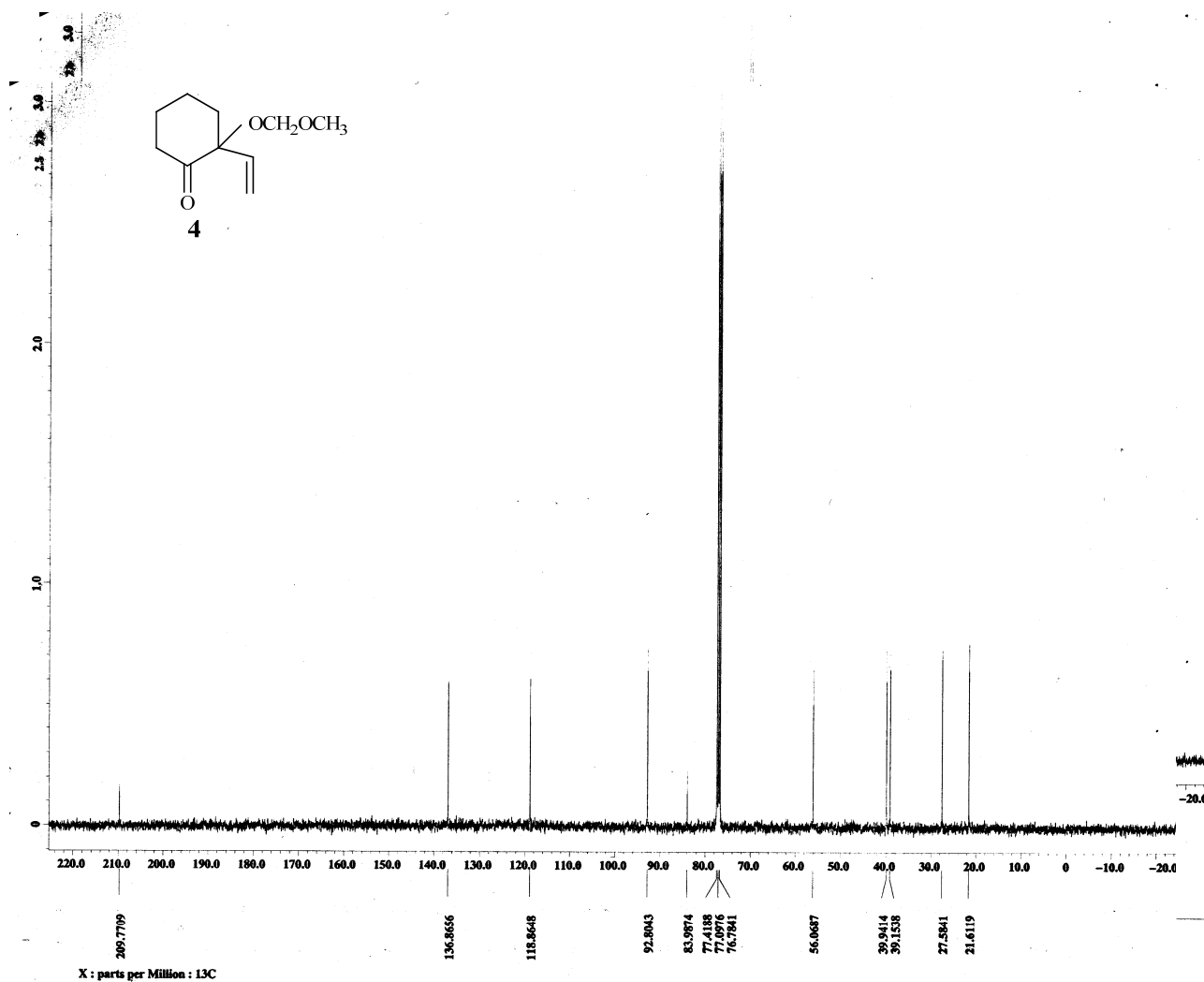
APPENDIX E:  $^1\text{H}$  NMR Spectrum of Compound 4

Solvent:  $d\text{-CDCl}_3$ / TMS



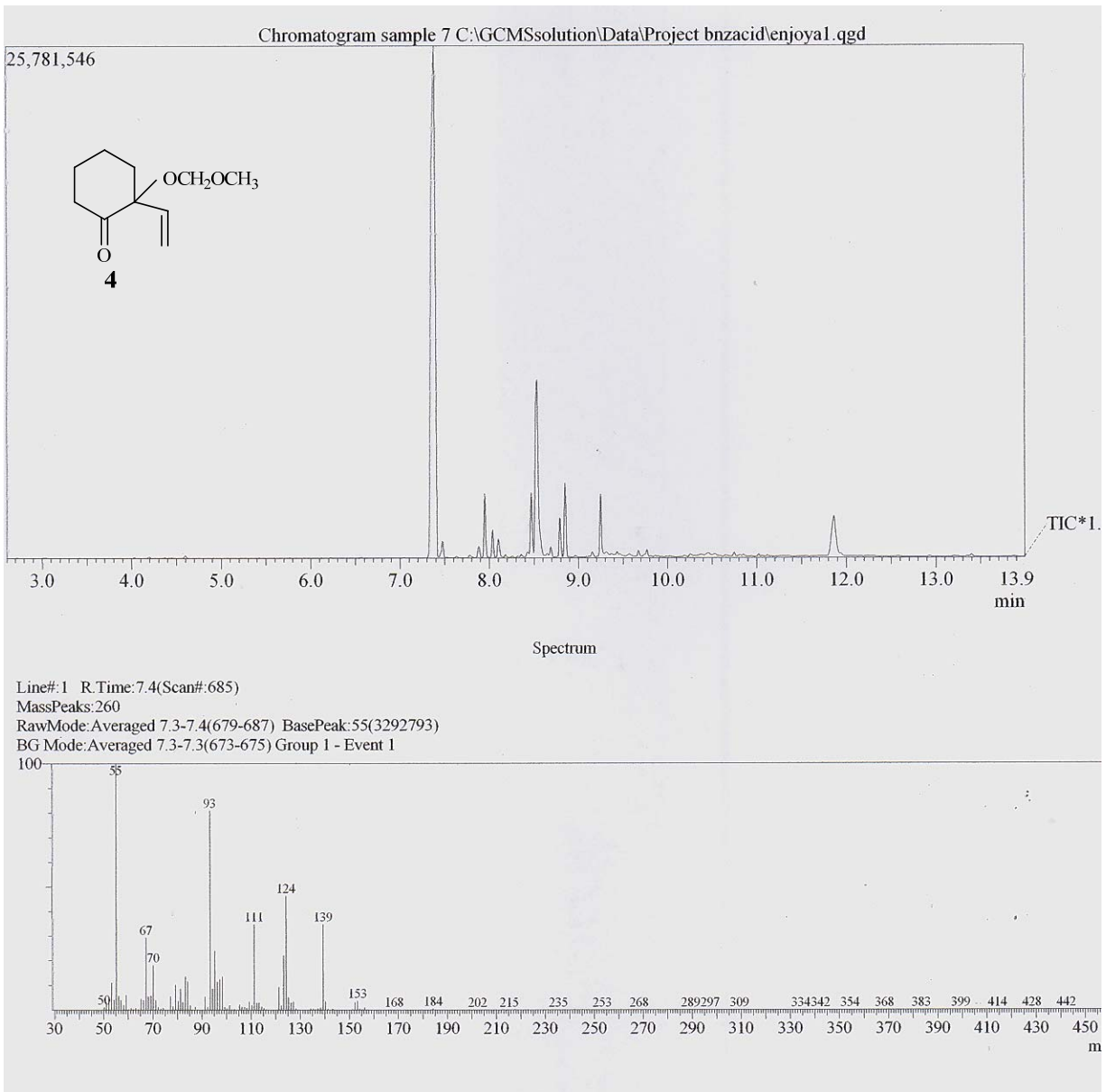
APPENDIX F:  $^{13}\text{C}$  NMR Spectrum of Compound 4

Solvent:  $\text{d-CDCl}_3/\text{TMS}$

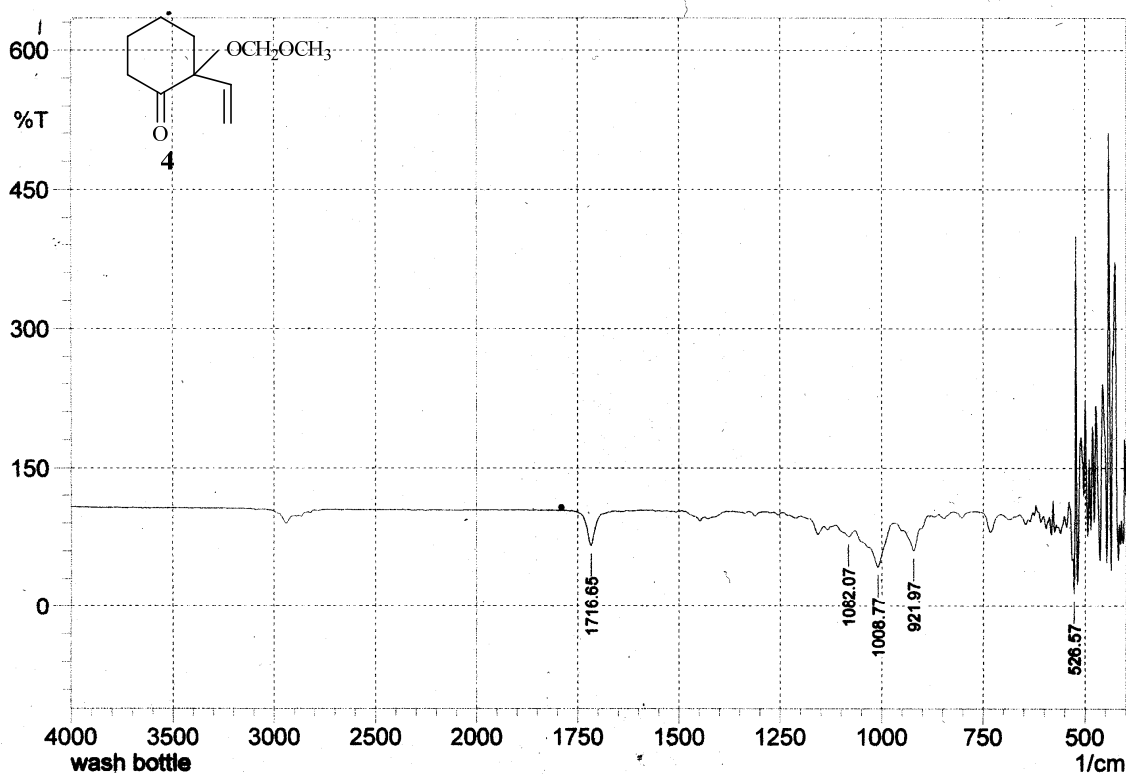


# APPENDIX G: GCMS Spectrum of Compound 4

1 mL of 100  $\mu$ L of compound 3 in 10 mL of hexanes



# APPENDIX H: IR Spectrum of Compound 4



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