OXIDATIVE RING OPENING REACTIONS OF A-HYDROXY KETONES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

AYŞE AYBEY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
DEPARTMENT OF CHEMISTRY

JANUARY 2008

Approval of the thesis:

OXIDATIVE RING OPENING REACTIONS OF α-HYDROXY KETONES

submitted by **AYŞE AYBEY** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. Ahmet M. Önal
Head of Department, **Chemistry** _____

Prof. Dr. Ayhan S. Demir
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Metin Zora
Chemistry Dept., METU _____

Prof. Dr. Ayhan S. Demir
Chemistry Dept., METU _____

Assoc. Prof. Dr. Özdemir Doğan
Chemistry Dept., METU _____

Assoc. Prof. Dr. Nursen Çoruh
Chemistry Dept., METU _____

Assist. Prof. Dr. Zuhal Gerçek
Chemistry Dept., ZKU _____

Date: January 21, 2008

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name : Ayşe, Aybey

Signature :

ABSTRACT

OXIDATIVE RING OPENING REACTIONS OF CYCLIC α-HYDROXY KETONES

Aybey, Ayşe
M. S., Department of Chemistry
Supervisor: Prof. Dr. Ayhan S. Demir

January 2008, 75 pages

Chiral polyfunctionalized 1,5-dicarbonyl compounds are important synthetic intermediates and starting materials for many biologically active compounds so their synthesis has a great importance in the literature.

In the first step, 1,3-cyclohexandione and other β-diketone derivatives are protected under acid catalyzation and their corresponding β-keto enol ether derivatives are obtained. These β-keto enol ethers are then converted to α-acetoxy enones in racemic form by $Mn(OAc)_3$ mediated oxidation. Enzymatic kinetic resolution is applied to the racemic acetoxy enones by using different lipases and enantiomerically pure α-acetoxy and hydroxy enones are obtained. Then, dicarbonyl derivatives are obtained by hydrolizing racemic α-acetoxy enones. Oxidative cleavage of racemic α-acetoxy diketones in the presence of oxone gives corresponding racemic 1,5-dimethyl ester derivatives.

By using this reaction as a reference, same reactions are applied to the chiral α-acetoxy and hydroxy diketones in order to synthesize chiral α-acetoxy and hydroxy 1,5-diester derivatives.

Keywords: $Mn(OAc)_3$ Mediated Oxidation, Enzymatic Hydrolysis, Polyfunctionalized Carboxylic acids.

ÖZ

SİKLİK α-HİDROKSİ KETONLARIN OKSİTLENEREK HALKA AÇILMA TEPKİMELERİ

Aybey, Ayşe
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Ocak 2008, 75 sayfa

Kiral çok fonksiyonel 1,5-dikarbonil bileşikleri biyolojik aktiviteye sahip birçok maddenin sentezlenmesinde önemli yapıtaşlarıdır. Bu nedenle sentezleri literatürde büyük öneme sahiptir.

Bu çalışmada kimyasal ve biyoteknolojik yöntemler kullanılarak çok fonksiyonlu kiral karboksilli asit veya onların 1,5 diester türevlerinin siklik 1,3-diketonlardan başlanarak sentezlenmesi için yeni bir yöntem geliştirilmiştir. 1,3-siklohekzandion ve diğer β-diketonlardan çıkılarak önce karbonil gruplarından biri asit katalizörlüğünde korunmuş ve β-keto enol eterler elde edilmiştir. Daha sonra $Mn(OAc)_3$ ile α'-asetoksilleme yapılmıştır. Oluşan rasemik asetoksi enonlar enzimatik kinetik ayırma metodu ile lipaz enzimi kullanılarak hidroliz edilmiş ve kiral asetoksi ve hidroksi enonlar elde dilmiştir.

Rasemik haldeki asetoksi enon bileşikleri hidroliz edilerek dikarbonil türevlerine dönüştürülmüş ve oxone varlığında bağ kırılmasıyla yükseltgenme reaksiyonu sonucu rasemik α-asetoksi 1,5-dimetil ester türevleri elde edilmiştir.

Bu reaksiyon referans olarak kullanılmış ve aynı reaksiyonlar enzimatik hidroliz sonucu elde edilen asetoksi ve hidroksi enon bileşikleri ile de gerçekleştirilmiş ve kiral yapıda 1,5-diester türevleri elde edilmiştir.

Anahtar kelimeler: $Mn(OAc)_3$ Oksidasyonu, Enzimatik Hidroliz, Polifonksiyonel Karboksilik asitler,

To My Family,

ACKNOWLEDGEMENTS

I would like to express my feelings of gratitude and appreciation to my supervisor Prof. Dr. Ayhan S. Demir for his support and guidance throughout the study.

I am indepted to my mother and my sister Asuman Aybey, for their nonstop encouragement and patience.

I wish to thank to Fatos Doganel Polat and Seda Karayılan for their friendship.

I want to thank to my lovely labmates Tuna Subaşı, Elif Köse, Hamide Fındık, Hatice Yalçınkaya and Batuhan Günay for their support, help and friendship.

I also express my sincere appreciation to all of the people in METU Organic Research Group.

TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

CHAPTER 1

INTRODUCTION

1.1. 1,3-Dicarbonyl compounds in organic chemistry

1,3-Diketones are important intermediates not only as a key building block for the synthesis of core heterocycles such as pyrazole, isoxazole, triazole and benzopyran-4-ones in medicinal chemistry, but also as an invaluable chelating ligand for various lanthanide and transition metals in material chemistry, and have also been investigated for use as potential antiviral agents[1]. For example, 1,3-diketone scaffold has been constructed in amide resin **1**, providing a starting material for pyrazole **2a** and isoxazole **2b** based heterocycle libraries (Figure 1.1). In the drug discovery context, the ability to synthesize small organic molecules with high yield on a solid support has a definite strategic relevance[2]. It facilitates the preparation of compound arrays in multiple parallel synthesis. Small organics (e.g. heterocycles) rather than chain-like biooligomers are more attractive leads for subsequent medicinal chemistry efforts.

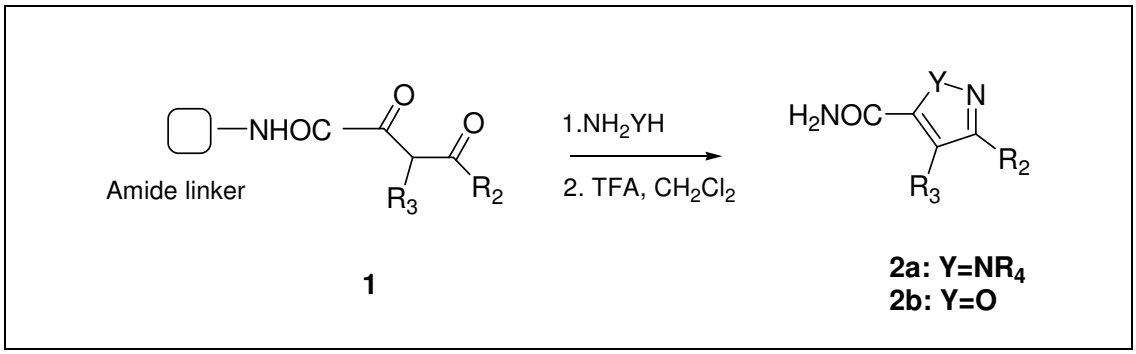


Figure 1.1. Synthesis of pyrazole

β-diketones are also encountered in nature as both metabolic intermediates in the microbial metabolism of aromatics and terpenes and also as anthropogenic environmental contaminants. The use of cyclic 1,3 diketones as key intermediates appears an attractive approach to the synthesis of monocyclic terpenes of the type represented by carvone and carvotanacetone[3] **3** (Figure 1.2).

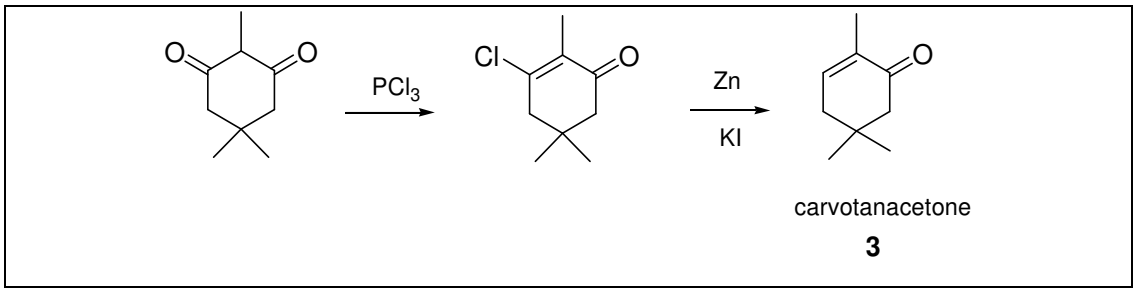


Figure 1.2. Synthesis of carvonacetone

Cyclic β- diketones are used in the synthesis of β-keto enol ethers which are versatile intermediates in the synthetic organic chemistry[4]. They have been widely used as precursors for the synthesis of different optically active compounds. For example, an asymmetric synthesis of the highly oxygenated cyclopentanoid antibiotic (+)-kjellmanianone **5** has been achieved starting from 1,3-cyclopentandione[5] **4** (Figure 1.3).

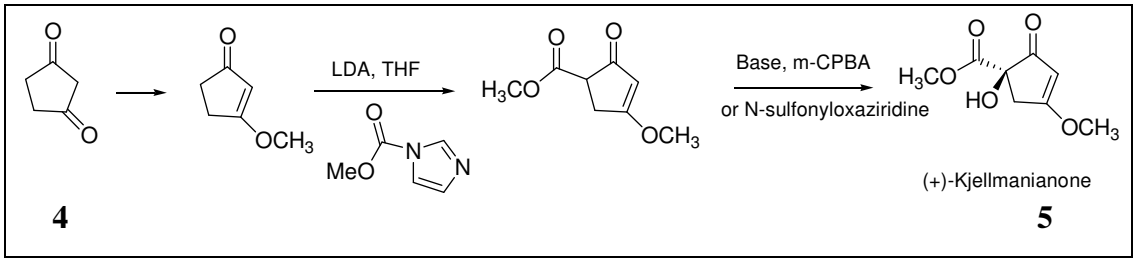


Figure 1.3. Synthesis of cyclopentanoid antibiotic (+)-kjellmanianone

Moreover, cyclic 1,3-diones are used in the synthesis of pyrroles by forming 1,4-dicarbonyl compounds as intermediates[6] (Figuren 1.4). The cyclization condensation of 1,4-dicarbonyl systems with ammonia or primary amines has been well investigated and synthetically exploited in the field of pyrroles.

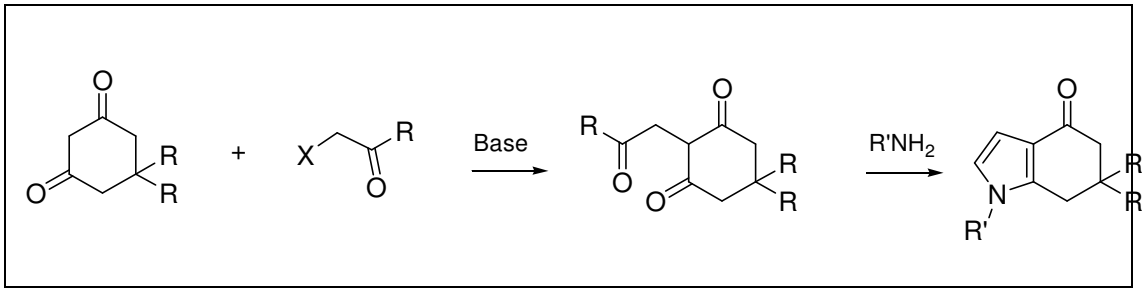
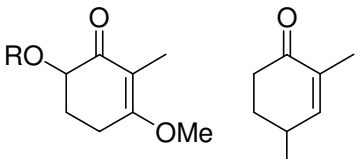


Figure 1.4. Synthesis of pyrroles

As a result of their ubiquity, the biological transformation of cyclic 1,3-dicarbonyl compounds has recently aroused interest as well in the synthesis of enantiomerically pure 4-methoxy-3-methyl-2-oxocyclohex-3-enyl acetate cyclohexenone **6** and 4-hydroxy-2-methylcyclohex-2-enone **7** which are important structural units in many biologically active compounds and important synthons for the asymmetric synthesis of natural products (Figure 1.5).



6a: R=COCH$_3$
6b: R=H

Figure 1.5. Polyoxo cyclohexenones and γ-hydroxy cyclohexenone

Some examples of the important biologically active compounds that can be synthesized from polyoxo cyclohexenones and γ-hydroxy cyclohexenone are; ML 236-A[7], a good cholesterol lowering agent, compactin[8] is another representative of a new class of cholesterol-lowering agents which is a HMG-CoA reductase inhibitor. It's an important source for producing pravastatin which is a commercial cholesterol-lowering agent.

Demir et. al. have already developed a method for the enantioselective synthesis of several cyclohexenone derivatives and γ-hydroxy enones starting from 2-methyl-1,3-cyclohexanedione[9] **8** (Figure 1.6).

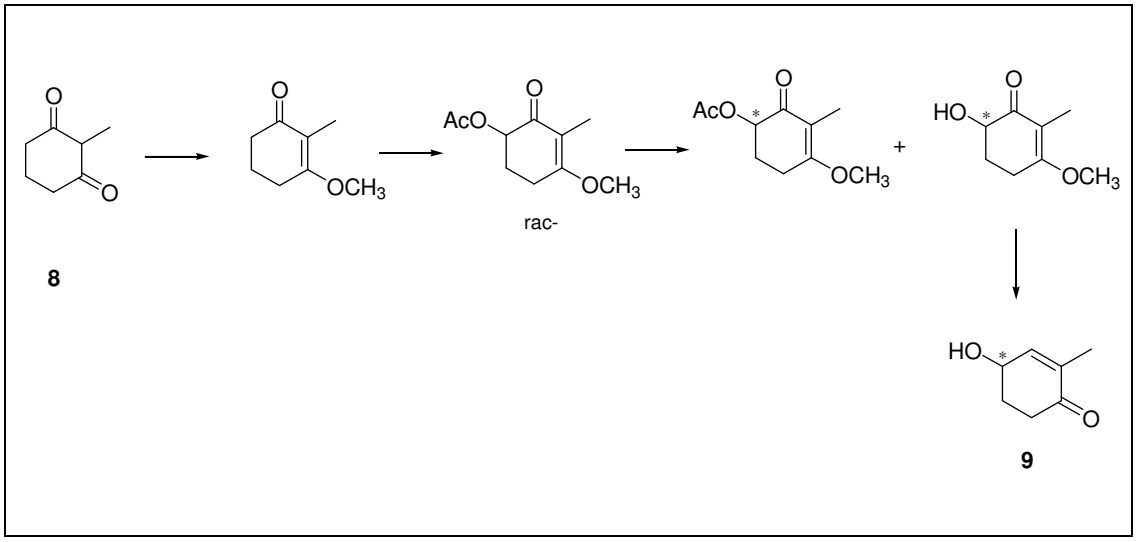


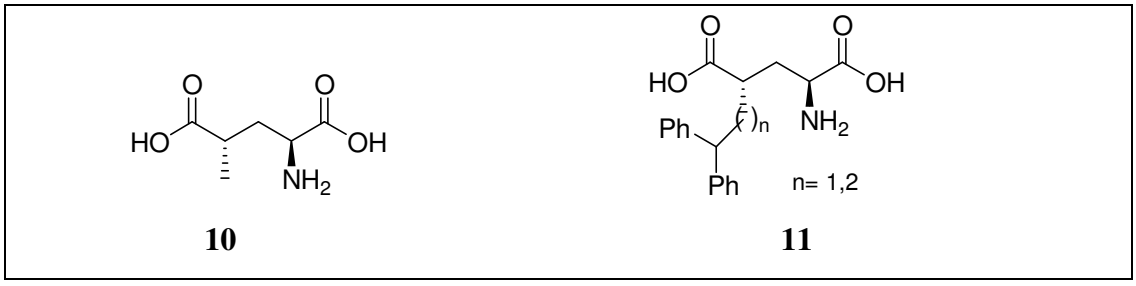
Figure 1.6. Enantioselective synthesis of γ-hydroxy enones

The first approach to enantiomerically pure products is to protect one of the carbonyl groups. Then, the synthesis of the racemic form of the corresponding acetates by using manganese (III) acetate, followed by enzymatic bioconversion by lipases and lastly reduction by $LiBH_4$ gives the corresponding 4-hydroxy-2-methylcyclohex-2-enone **9**.

1.2 α-Hydroxy-dicarboxylic acids in organic chemistry

Homochiral α-hydroxy acids, and simple derivatives have proven to be a versatile class of molecules which have been extensively exploited in asymmetric synthesis. For example, malic, mandelic, and tartaric acids are routinely employed as chiral synthons as well as precursors to both chiral ligands and auxiliaries.

1,5-dicarbonyl compounds are important class of building blocks for many natural substances[10]. Glutamic acid, an example to 1,5-dicarboxylic acids, plays a crucial role in the central nervous system. As one of the excitatory amino acids, it is a neurotransmitter for the majority of synapses. Excitatory amino acid receptors appear not only to mediate normal synaptic transmission, but also to participate in the modification of synaptic connections associated with brain development and learning or memory process. Moreower, excessive release of glutamic acid can result in some disorders such as Huntington's, Alzheimer's and Parkinson's diseases. For this reason, glutamic acid analogues appear as important tools for the investigation of glutamate receptors of the central nervous system and possible therapeutic efects due to their specificities for a particular receptor. For this purpose, a large number of analogues of glutamic acid have been synthesized in recent years and some have been shown to exhibit such specificity (Figure 1.7). Thus, (2S,4S)-4-methylglutamic acid **10** is an agonist of the mGluR1, while (2S,4S)-4-(o,o-diphenylalkyl)glutamic acid **11** is a specific mGluR2 antagonists.



10 **11**

Figure 1.7. Analogues of glutamic acid

Because this type of 1,5-dihydroxycarboxylic acid compounds and their derivatives have very often been shown to be biologically active and therapeutically useful and potentially selective glutamate receptor ligands, their synthesis gained much importance in recent years.

Homocitric acid **12**, a key intermediate in the biosynthetic pathway to the essential amino acid lysine **13** in fungi and euglenids, is another example to the α-hydroxydicarboxylic acids[11] (Figure 1.8).

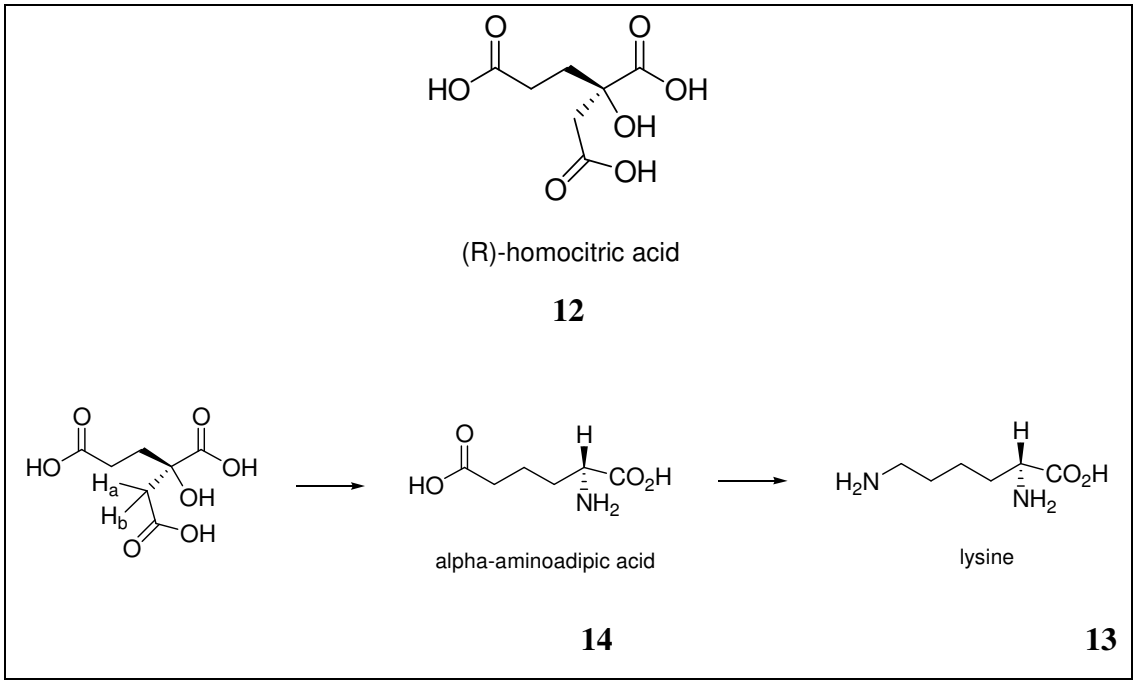


Figure 1.8. Biosynthetic pathway to the essential amino acid lysine

This pathway involves the intermediate α-aminoadipic acid **14**, required in the biosynthesis of penicillins and cephalosporins and catalysed by the protein derived from the nifV gene.

1,5-dicarbonyl compounds are the intermediates for a number of natural products and key intermediates and can also be used in the cyclisation reactions using the pinacol methodologies[12] (Figure 1.9).

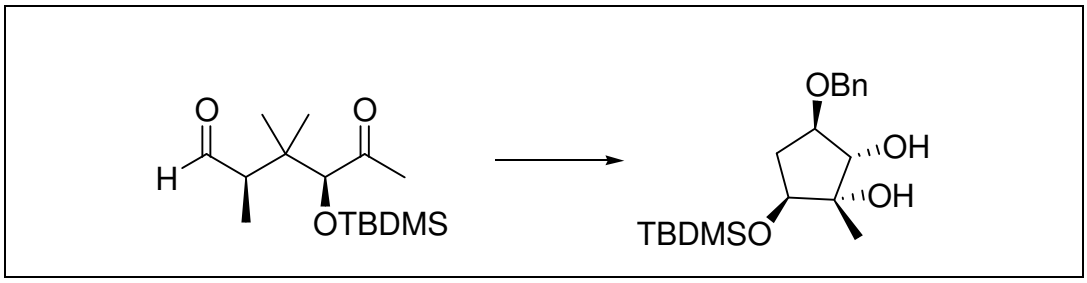


Figure 1.9. Cyclisation reactions using the pinacol methodologies

Literature reports and the writers' own work on the synthesis of saturated six-membered oxygen and nitrogen heterocycles by catalytic reduction of 1,5-diketones or diesters are also reviewed. The 1,5-pentanediones constitute interesting intermediates for the synthesis of several important hetorocyclic compounds. These heterocycles contain oxygen as pyrilium salts and pyrans, nitrogen as pyridines, and also sulfur, selenium and phosporus.

Several 1,5-diester compounds are used as a key step in the synthesis of pyrazino pyridazines **15** which are found to be high affinity ligands for the GABA receptor benzodiazepine binding site[13] (Figure 1.10).

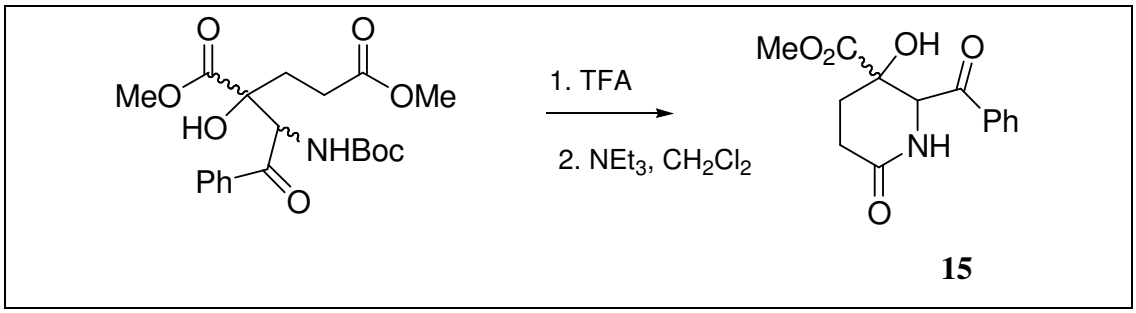


Figure 1.10. Synthesis of pyrazino-pyridazines

1.3 Manganese(III) Acetate Mediated α-Acetoxylation of protected 1,3-dicarbonyl compounds

$Mn(OAc)_3$ mediated α-oxidation of enones was applied to several enones with a variety of functional groups[14-17]. These interesting and useful intermediates were used for several transformations in synthetic organic chemistry (Figure 1.11).

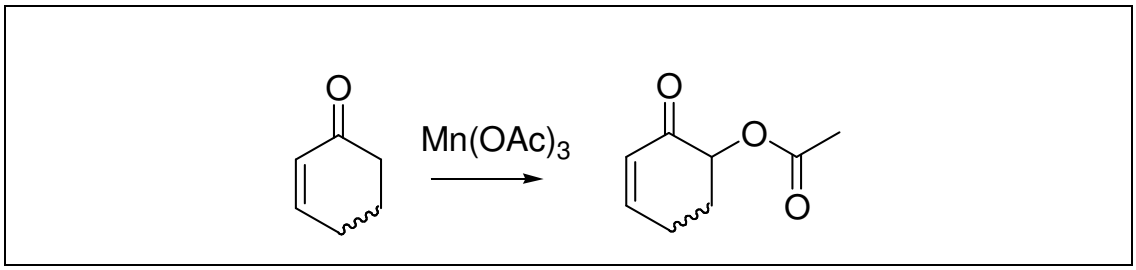


Figure 1.11. $Mn(OAc)_3$ mediated acetoxylation of enones

Oxidations with manganese(III) acetate can be broadly divided into two classes;

1. Direct Oxidation: Direct inner or outer-sphere one electron oxidation of the substrate; often determines the product is followed by the formation of manganese (III) complex where the subsequent oxidation of the intermediate radical. Numerous examples can be found such as oxidations of alcohols, amino and thio compounds, carboxylic acids and certain aromatics.

2. Indirect Oxidation: Indirect oxidation of the substrate; takes place after the formation of an intermediate adduct free radical which is formed by the interaction of Mn(III) acetate. The result is an enolizable compound or subsequent oxidation/substitution and oxidative addition of enolizable compounds to unsaturated systems. Mn(III) acetate deals with addition reaction of compounds which have α-hydrogen atom to a carbonyl group with olefinic and aromatic unsaturated systems (Figure 1.12)

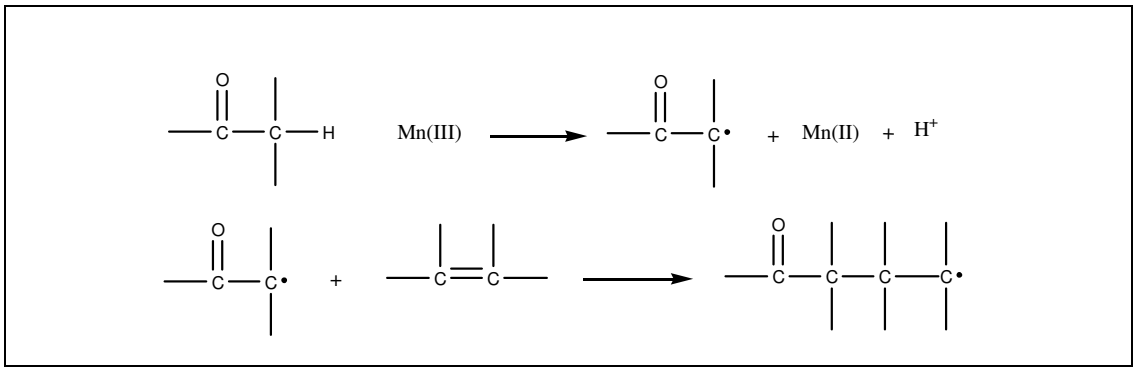


Figure 1.12. $Mn(OAc)_3$ mediated oxidation radicalic mechanism

Many target specific compounds were synthesized using this oxidation. Especially protected 1,2 and 1,3-diketones with and without functional groups were acetoxylated in good to excellent yield without affected the protecting groups. Demir and Sesenoglu already studied the synthesis of 4-hydroxy-2-cyclopenten-1-one and 4-hydroxy-2-cyclohexen-1-one. During this study 1,3-cyclopentandione and 1,3-cyclohexandione were converted to the 3-methoxy-2-cyclopenten-1-one **16** and 3-methoxy-2-cyclohexen-1-one **17**. These products were then converted to the α'-acetoxy ketones by using $Mn(OAc)_3$ oxidation (Figure 1.13).

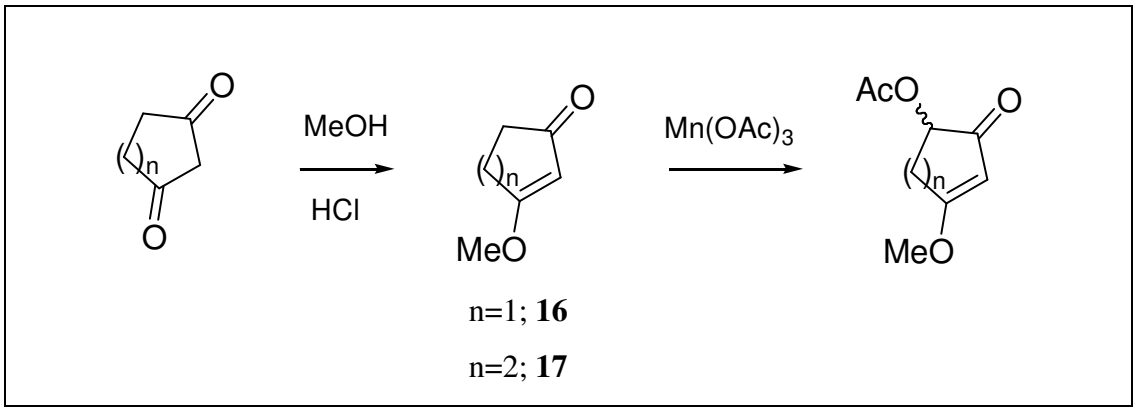


Figure 1.13. Synthesis of α'-acetoxy ketones by using $Mn(OAc)_3$ oxidation

By the investigation of the synthetic and mechanistic aspects of $Mn(OAc)_3$ mediated oxidation of enones, the successful α'-acetoxylation of a great variety of substrates was reported, in which there were some problems associated with the use of $Mn(OAc)_3$[18]. A brief list of them is as follows:(1) excess $Mn(OAc)_3$ is generally used for acceptable yields and reaction times; (2) many contradictory results can be seen when the literature reports are closely inspected.

These inconsistencies along with the use of an undesirable amount of $Mn(OAc)_3$ reduced the value of the method. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$ mediated α'-acetoxylation of enones and reaching its maximum potential has great importance from a synthetic and economic point of view. Demir and co-workers reported their investigation of their understanding of the nature of this reaction, along with increasing its efficiency and reproducibility. They presented an improved procedure that was based on the use of acetic acid as a co-solvent. According to this procedure, AcOH shortened the reaction time and increased the yields. The role of acetic acid could be related to an increased solubility of $Mn(OAc)_3$ in the reaction (Figure 1.14).

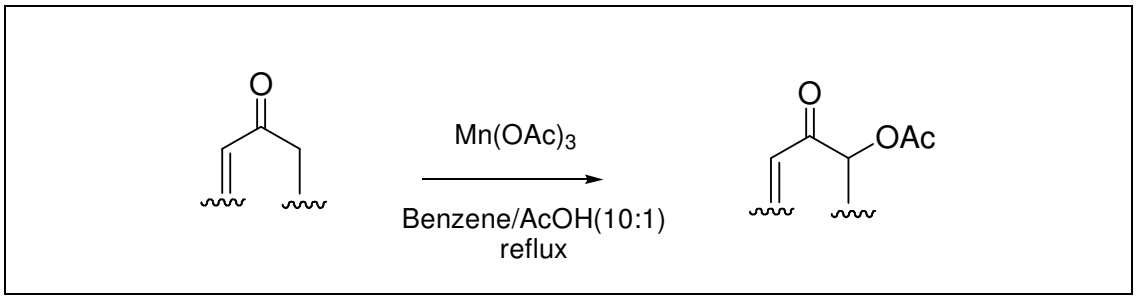


Figure 1.14. Simple methods for the direct acetoxylation of enones

1.4 Enzymatic Kinetic Resolution

The synthesis of α-hydroxy carbonyl derivatives has been of continuous interest to organic chemists since the beginning of the century[19]. Because chiral α-hydroxy ketones are important reagents for the synthesis of complex optically active natural products and are useful stereodirecting groups[20]. There are both chemical and biotechnological methods for the synthesis of α-hydroxy ketones.

An increasing interest in understanding biological processes and the general recognition that chirality plays a crucial role in nature fostered a tremendous effort in enantioselective synthesis. In the course of synthesizing natural products and designing new target compounds, chemists had to acknowledge the fact that enantiopurity is related to biological properties. Opposite enantiomers interact differently within an organism and can display various activities. This has resulted in an increasing need for efficient methods for the industrial synthesis of optically pure products.

To obtain enantiomericaly pure materials, there are several methods including classical optical resolution via diastereomers, chromatographic separation of enantiomers, asymmetric synthesis, chemical kinetic resolution, and enzymatic kinetic resolution[21]. In these methods there are two most popular strategies. The first one is asymmetric synthesis involving stereocontrolled formation of the new stereogenic center. For example; as the new chiral element is formed it is done so in a non-racemic fashion. This demands that the reactive centers experience some stereo discriminating environment in the transition state. This can originate from an existing stereogenic center in the substrate or in via a chiral reagent catalyst[22]. The second approach involves resolution: this utilizes a stereoisomeric mixture and does not demand asymmetric induction in the formation of any new chiral element. Thus preparation of a single stereoisomer by resolution of a stereisomeric mixture may be achieved via a conventional separation procedure or by exploiting the difference in reactivity (kinetic resolution).

Like asymmetric synthesis, kinetic resolution is most efficient when chiral catalysts are used. Kinetic resolution can be performed both using chemical catalysts and biocatalysis which encompass catalysis by bacteria, yeast, fungus, or their true components: enzymes. Enzymes, biological catalyst, are proteins that are capable of accelerating reactions under mild reaction condition by lowering the activation energy (Figure 1.15). Other advantages are the high degrees of substrate-, chemo-, regio- and stereoselectivity and high efficiency.

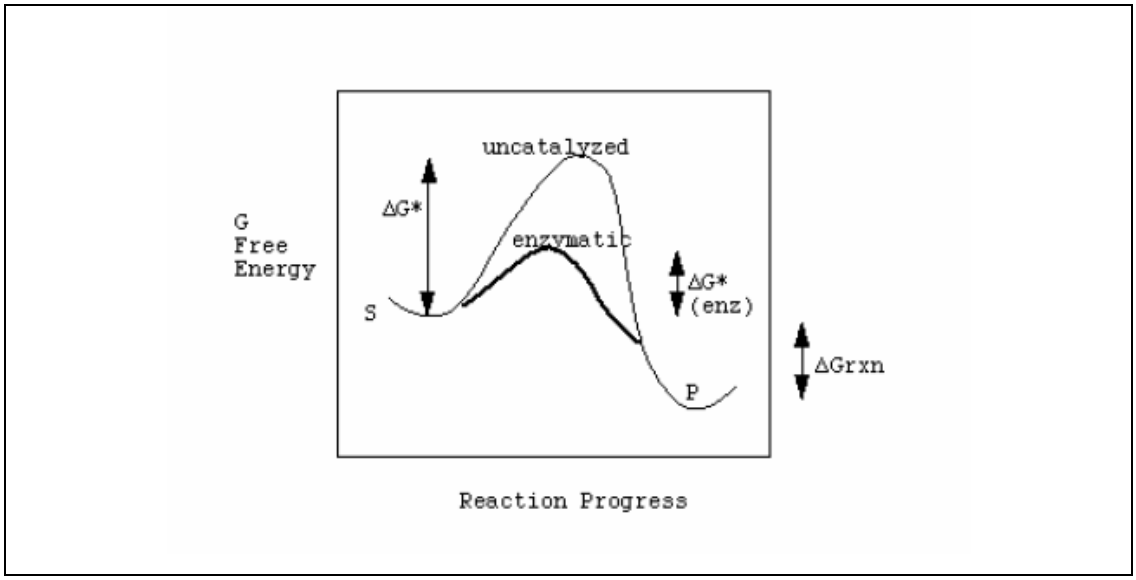


Figure 1.15.. Free energy reaction progress graphs for uncatalyzed and enzymatic reactions

Lipases have been frequently used as convenient and efficient biocatalysts for the asymmetric synthesis of a wide range of organic compounds. They have been widely used for the synthesis of optically active alcohols, carboxylic acids and esters via enantioselective esterification and transesterification in organic solvents. Although numerous α-hydroxy acids and esters have been resolved by lipases, reports on the kinetic resolution of structurally simple α-hydroxy ketones by these readily accessible enzymes are scarce.

Recently, Gala et al. have described the resolution of α-hydroxy aryl ketones (precursors of chiral azole antifungal reagents) by lipase catalyzed hydrolysis of the corresponding acetates in phosphate buffer; nevertheless, the irreversible transesterification route of this enzymatic reaction appears not to be known[23]. Also, Demir et. al. has described that the lipase Amano PS, PPL, PLE and CCL-catalyzed asymmetric ester hydrolysis and transesterification afforded the enantiomers of 3-hydroxy-2,3-dihydro-4*H*-chromen-4-one and 4-oxo-3,4-dihydro-2-chromen-3-yl acetate with high enantiomeric excess (up to 97% ee) and in good yields[24]. In another report by Demir et. al. it was described that, $Mn(OAc)_3$ oxidation of aromatic ketones afforded the α-acetoxy ketones in good yield and selective hydrolysis of the acetoxy ketones by the fungus *Rhizopus oryzae* yields (*R*)-hydroxy ketones in high enantiomeric excess[25]. Another report has been presented by Adam et al. that is the kinetic resolution of racemic α-hydroxy ketones by lipase-catalyzed irreversible transesterification with isopropenyl acetate in organic media (Figure 1.16).[26]

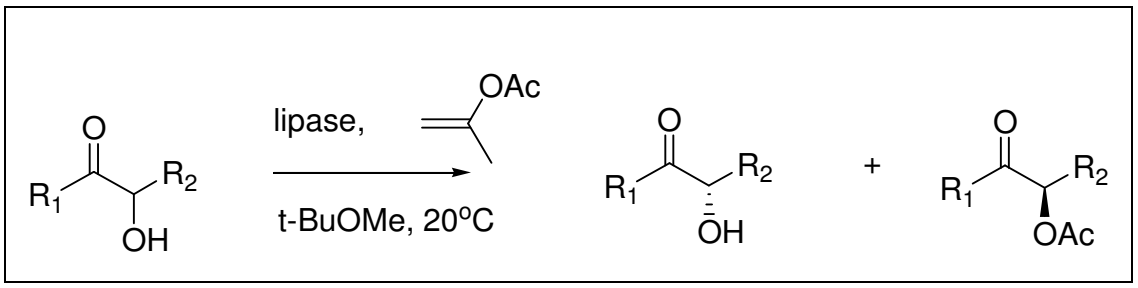


Figure 1.16. Kinetic resolution of racemic α-hydroxy ketones

1.5 Cleavege methods for cyclic 1,3-diketones

The interest in the oxidations of β-diketones comes from their use in the synthesis of natural products, such as naturally-occuring antibiotics.[27]

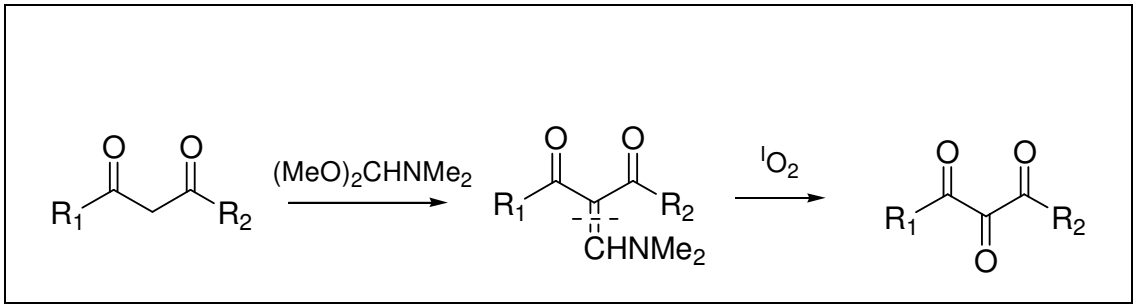


Figure 1.17. Generation of vicinal tricarbonyl systems from the corresponding β-dicarbonyl

It has been reported in the literature that the generation of vicinal tricarbonyl systems from the corresponding β-dicarbonyl precursors is achieved by forming the enamines and then photooxidation or by ozonolysis (Figure 1.17). This method for the in situ generation of vicinal tricarbonyl systems has useful application in synthesis of carbecepham derivatives, in particular for the synthesis of antibiotic PS-5 **18** (Figure 1.18).

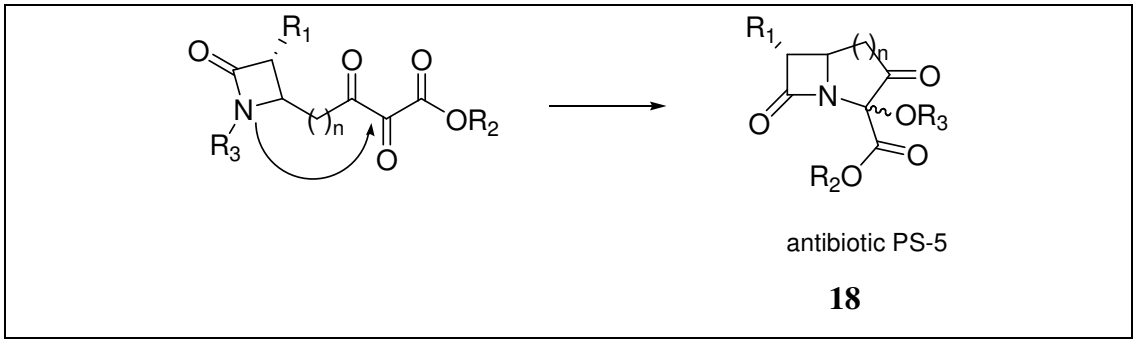


Figure 1.18. Synthesis of antibiotic PS-5

Oxidative cleavage of α-hydroxyketones, α-diones, and β-diones to their corresponding dicarboxylic acids is well precedented with reagents such as calcium hypochloride, sodium percarbonate, copper perchloride, basic peroxide, bismuth, and rhenium[28]. The oxidative cleavage of ketones by various oxidizing agents has been established mainly according to stoichiometric procedures. Catalytic oxidation of ketones have also been realized. In the case of cyclic ketones, the catalytic oxidative cleavage furnished an efficient method of preparing dicarboxylic acids or oxoacids.

1.5.1 Oxidative cleavage of cyclic 1,3-diketones by copper perchlorate-oxygen system

With the invention of obtaining (ω-1), ω-dioxocarboxylic acids, 2-alkyl cyclohexan-1,3-diones were treated by copper salts such as $CuCl_2.2H_2O$, $CuSO_4.5H_2O$, $Cu(OAc)_2.H_2O$ or $Cu(ClO_4)_2.6H_2O$ in the presence of oxygen in acetonitrile[29]. The best yields were obtained when $Cu(ClO_4)_2.6H_2O$ was used. The reaction could be extended to 1,3-dicarbonyl compounds such as β-ketoesters. The treatment of cyclic β-keto esters by using system $Cu(ClO_4)$ $6H_2O/O_2$ led to the formation of corresponding oxoalkanedioic acids monoesters in good yields (Figure 1.19)

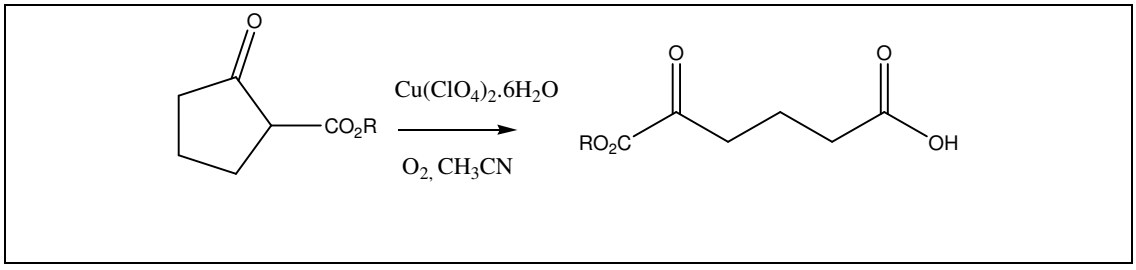


Figure 1.19. Synthesis of oxoalkanedioic acids monoesters by copper perchlorate-oxygen system

A possible mechanism or the oxidative cleavage of the 2-substituted cycloalkane 1,3-diones is shown in the scheme which is inspired from that proposed by Brackman and Volger for the oxidation of aldehydes with O_2 (Figure 1.20). The first step involves a Levis coordination of the enol with Cu(II). The reaction with oxygen generates a peroxide which undergoes cyclization to a dioxetane. This intermediate undergoes a [2+2] cycloreversion with formation of the corresponding w-dioxocarboxylic acids. This mechanism can also be applied to enolized β-ketoesters.

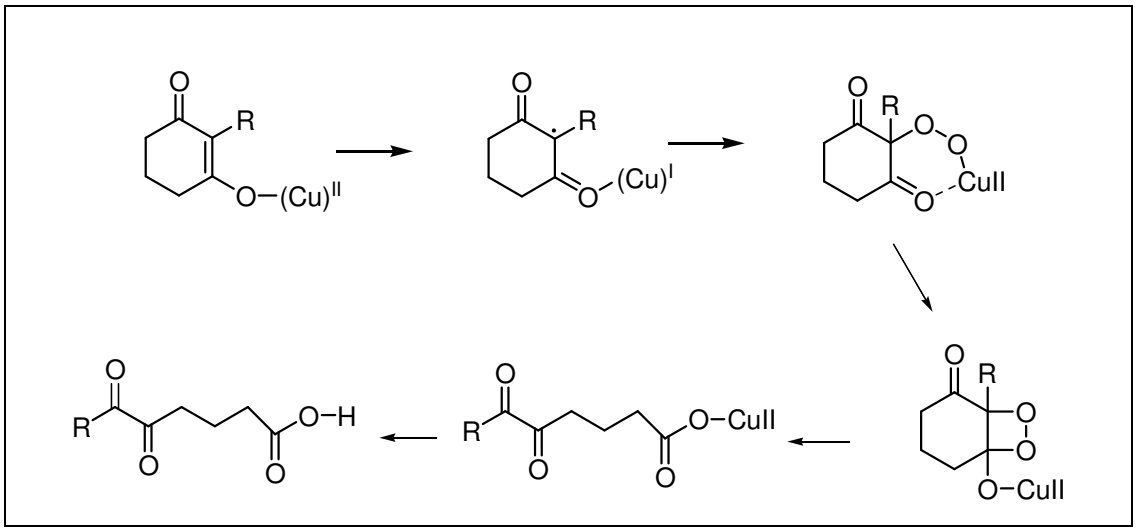


Figure 1.20. The mechanism of the oxidative cleavage of the 2-substituted cycloalkane 1,3-diones

1.5.2 Oxidations of cyclic β-diketones catalyzed by methylrhenium trioxide

Methylrhenium trioxide (CH_3ReO_3 or MTO) catalyzes the oxidation of β-diketones by hydrogen peroxide (Figure 1.21).[30] MTO has been reported as an effective catalyst for the Baeyer-Villiger oxidations of cyclic ketone to give the corresponding lactones.

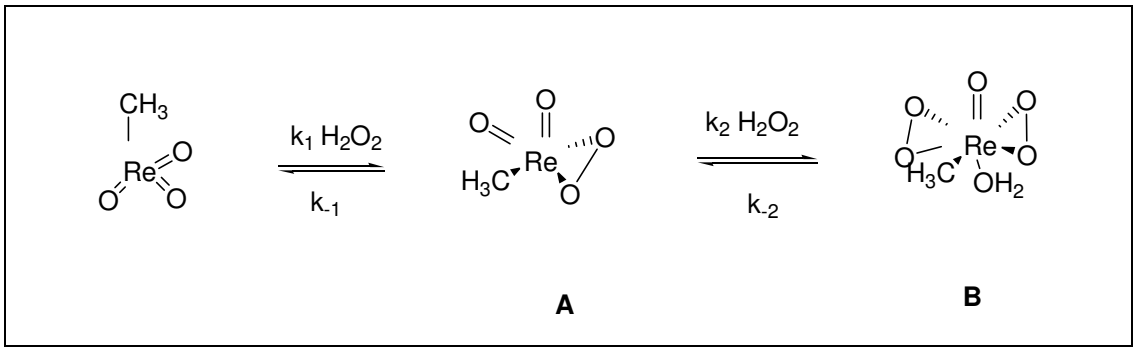


Figure 1.21. Oxidation of methylrhenium trioxide

β- diketones are present mainly in the enolic form, which is electron deficient owing to the conjugation of the double bond with the electron-withdrawing carbonyl group.

According to reported mechanism, the enol initially gives rise to an epoxide intermediate that is susceptible to cleavage via a Baeyer-Villiger oxidation in which the peroxorhenium complexes A and B may act as nucleophiles. Therefore the reaction follows the sequence of epoxidation of the enolic tautomer initially, then oxygen insertion into C-C bond, and finally rupture of the α-diketone intermediate to give organic acids (Figure 1.22)

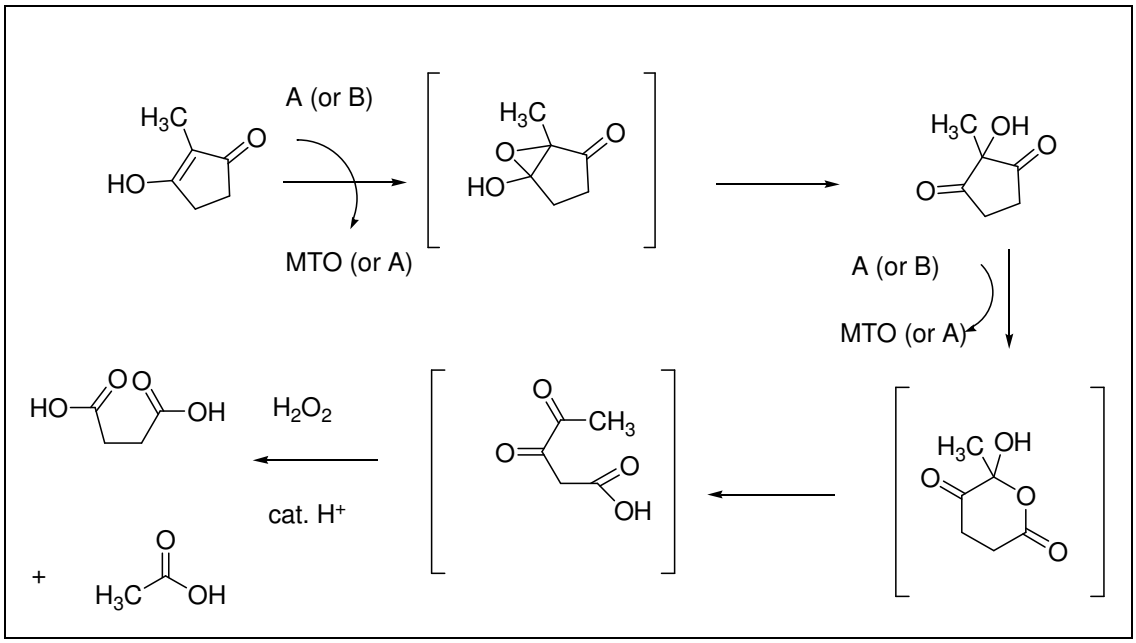


Figure 1.22. Oxidations of cyclic β-diketones catalyzed by methylrhenium trioxide

However, hydrogen peroxide suffers from its kinetic inertness and from the involvement of radical pathways that lead to mixtures of products.

1.5.3 Cleavage of cyclic 1,3-diketones with dithio tosylate

A mild method for cleaving 1,3-diketones has been described by propane-1,3-dithio tosylate[31]. Treatment of cyclohexane-1,3-dione with propane-1,3-dithio tosylate gives corresponding keto-ester product by forming the 2-acyldithiane as the intermediate (Figure 1.23).

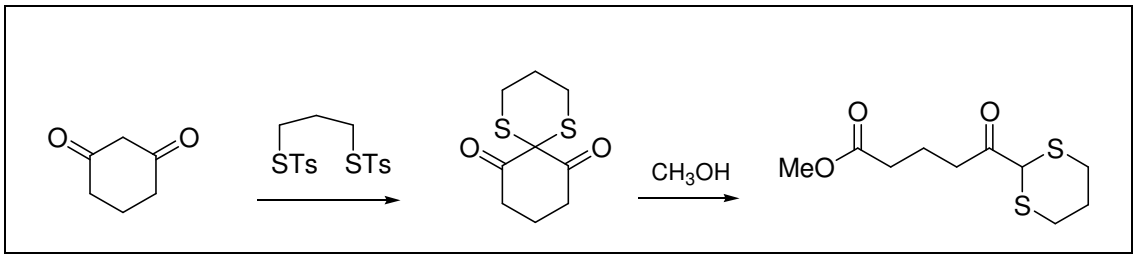


Figure 1.23. Cleavage of cyclic 1,3-diketones with dithio tosylate

Subsequent studies indicated that the above cleavage reaction most likely proceeds in two stages with initial attack by methoxide on the carbonyl followed by subsequent proton abstraction of the presumed adduct. The products of the reactions are 2-acyldithianes and these $RCOCO^-$ synthons can be alkylated under mildly basic conditions.

1.5.4 Periodate oxidation of cyclic 1,3-diketones

Oxidations of carbon compounds with aqueous periodate ion at room temperature or below can conveniently be divided into two types; those producing carbon-carbon bond cleavage and those where no such cleavage takes place[32]. The second reaction type occurs when a hydrogen attached to a carbon flanked by carbonyl groups is transformed into an hydroxyl function. This gives rise to an hydroxyl ketone, thus making the compound susceptible to the first type of oxidation. The second type periodate oxidation was noted to take place in malic, malonic, acetoacetic acids and their derivatives. Other examples of this type of oxidation have appeared in cyclic 1,3-diketones. From known periodate oxidations, the oxidation of cyclohexan-1,3-dione has been suggested according to following scheme (Figure 1.24).

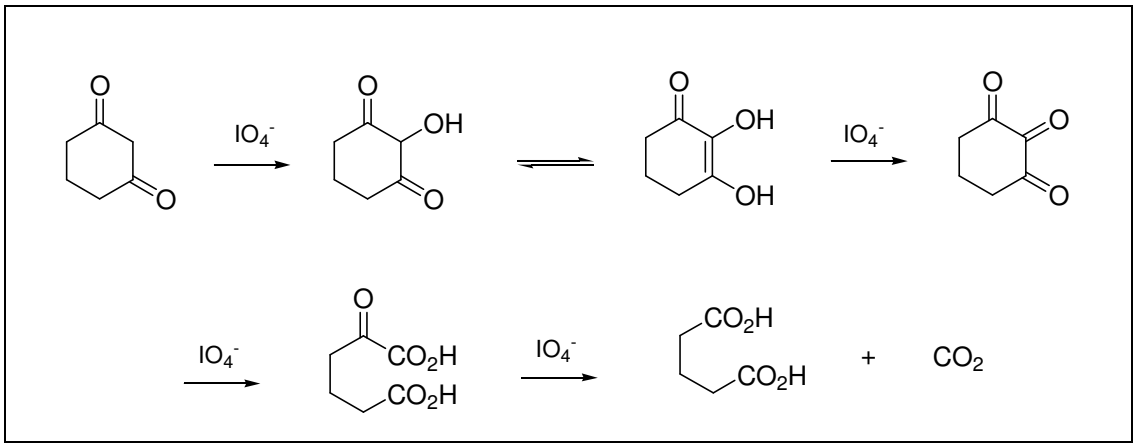


Figure 1.24. Periodate oxidation of cyclic 1,3-diketones

1.5.5 Direct oxidative cleavage of β-dicarbonyls to diesters with oxone ($KHSO_5$)

The use of oxone as an efficient and mild oxidant has grown rapidly. Oxone is a triple salt containing two parts $KHSO_5$, one part $KHSO_4$, and one part K_2SO_4. It is an effective oxidant for numerous transformations. For instance, oxone is well-known for its oxidations of boron-, nitrogen-, phosphorus-, and sulphur- containing compounds and it is also widely used to prepare dimethyl-dioxirane (DMDO) in buffered acetone, which subsequently epoxidizes olefins. It has become an increasingly popular reagent for oxidative transformations such as the oxidation of aldehydes to acids or esters, deprotection of functional groups, functional-group transformations, and cleavage of linker molecules from solid support[33] (Figure 1.25).

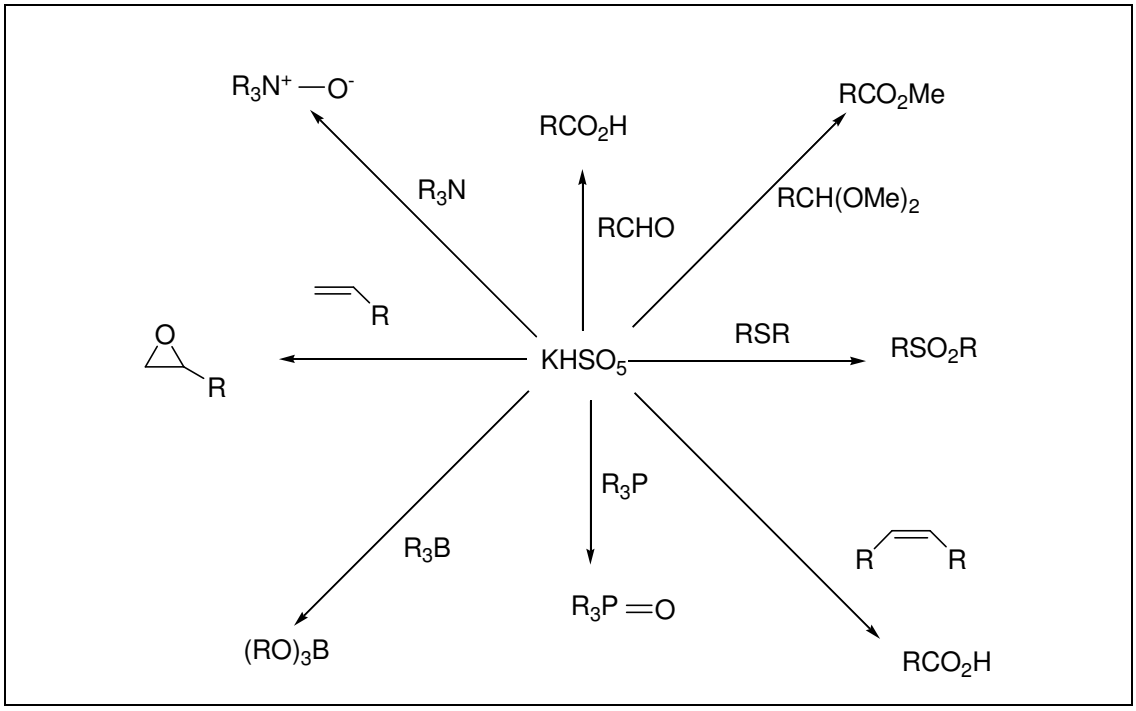


Figure 1.25. Oxidative transformations of oxone ($KHSO_5$)

Continuing studies showed that β-diones could be oxidatively cleaved to the corresponding one-carbon-deleted carboxylic acids by using oxone (Figure 1.26)

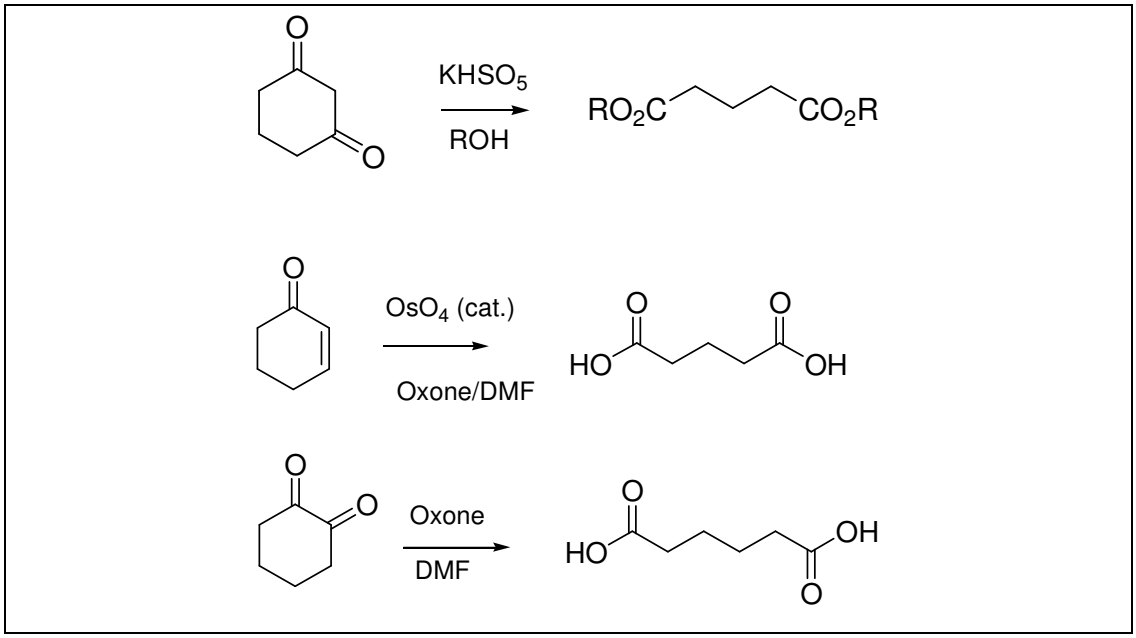


Figure 1.26. Synthesis of one-carbon-deleted carboxylic acids by using oxone

Figure 1.27 depicts possible routes to both monoesters and diesters from β-diones. The route to monoesters would most probably involve the intermediacy of a peroxyhemiacetal, which upon Baeyer-Villiger-like rearrangement would lead to the carboxylic acid functionality of the monoesters. This is shown for β-diones , which upon oxidative rearrengement lead to the monoester or the aldehyde, respectively. Further oxidation of aldehyde with oxone in the alcoholic solvent would lead to the monoesyter. Conversely, the intermediacy of peroxyacetal could lead to the isolation of the diesters without the need for esterification of monoesters to the diesters.

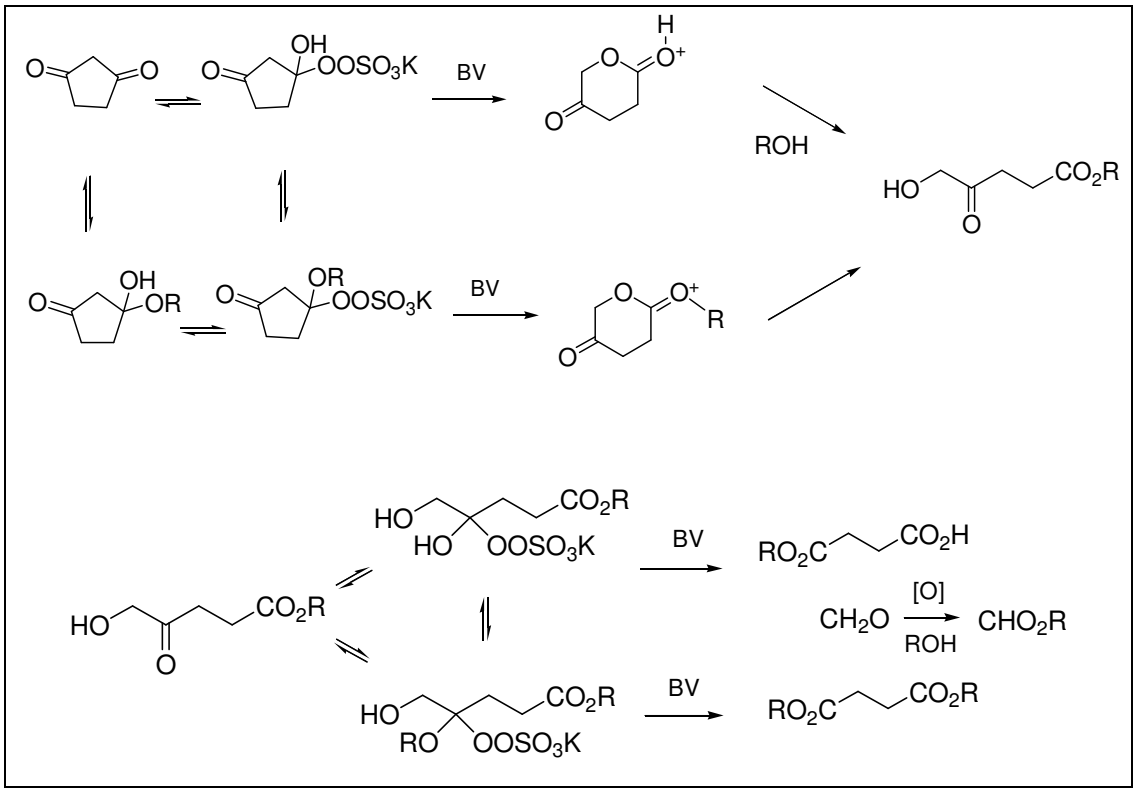


Figure 1.27. A possible routes to both monoesters and diesters from β-diones

This method compliments existing methodologies and is in general a milder alternative to the other oxidation methods.

1.5.6 Enzyme-catalyzed β-diketone cleavage

It has recently been observed that enzymes can also catalyze the cleavage of the C-C bond between the carbonyl groups of β-diketones[34]. One of the earliest inferences of a neutral β-diketone-cleaving enzyme was made in 1966 by Chapman. Cyclohexane 1,3 –dione was reported to be hydrolysed to 5-oxohexanoic by cell extracts of a Pseudomonas strin grown under anaerobic conditions on cyclohexanol as sole carbon source. The enzyme, named cyclohexan-1,3-dione hydrolase was not isolated and the enzyme shown not to accept cyclohexan-1,2-dione or cyclohexan-1,4-dione as substrates (Figure 1.28).

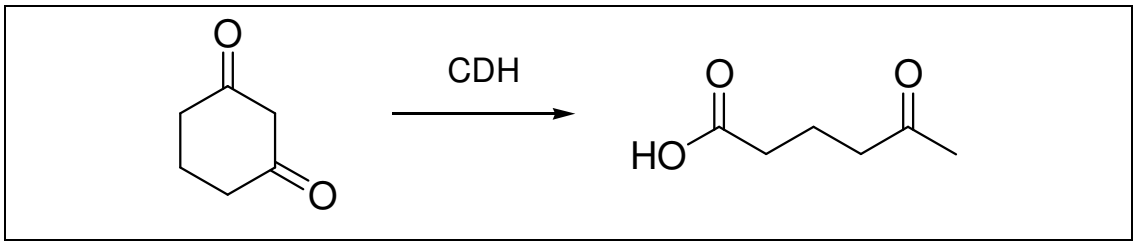


Figure 1.28. Enzyme-catalyzed β-diketone cleavage

Two β-diketone–cleavege enzymes were reported to be active in the metabolism of atropine by pseudomonas. An induced hydrolase was found to act regiospecifically on cycloheptane-1,3,5-trione cleaving one β-diketone regioselectively to yield a product , but not the alternative product. The product **19** itself a β-diketoacid, was cleaved by a β-diketone hydrolase to yield succinate **20** and acetone (Figure 1.29).

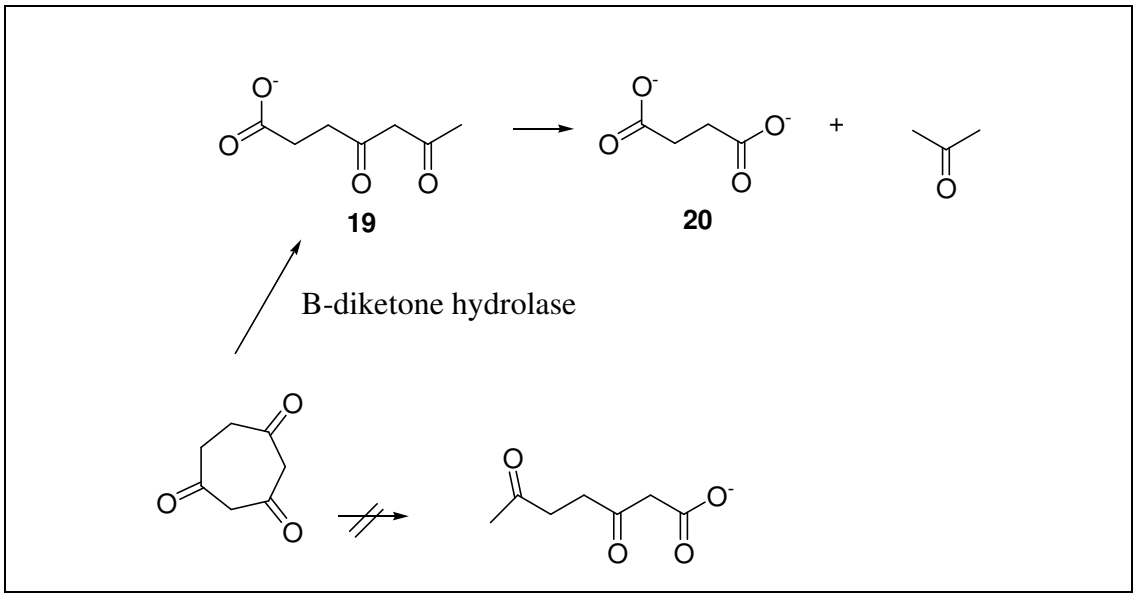


Figure 1.29. Synthesis of succinate and acetone by a β-diketone hydrolase

1.6 Aim of the work

The major aim this research is to develop simple and selective method for the synthesis of chiral α-hydroxydicarboxylic acids or their diester derivatives which are very important class of building blocks for many natural substances. The aim of this work is shown retrosynthetically in Figure 1.30.

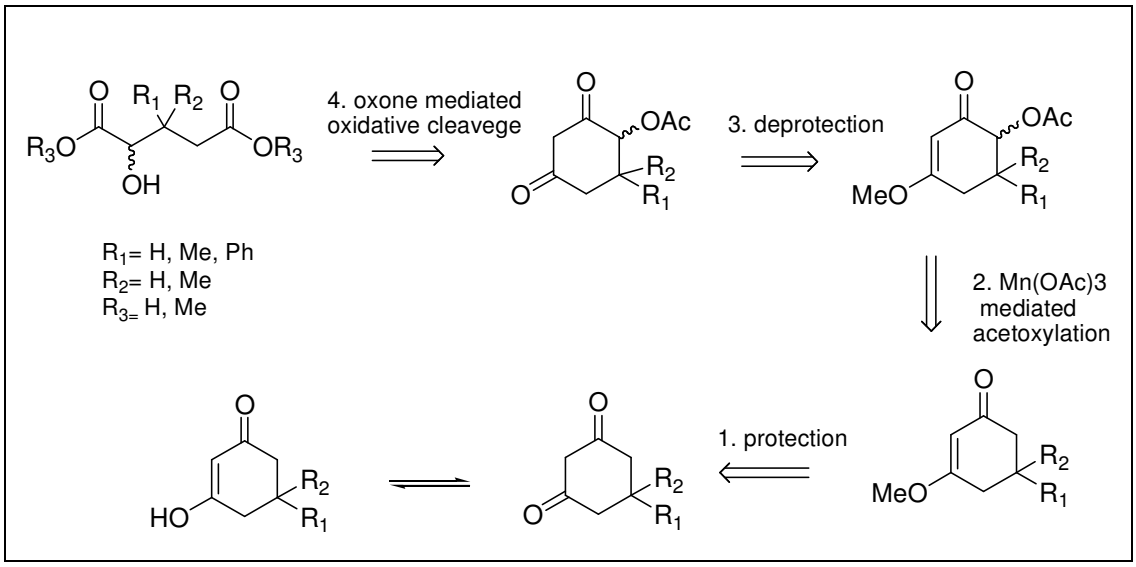


Figure 1.30. Retrosynthetic scheme of α-hydroxy 1,5-diester product

Our first approach to enantiopure α-hydroxydicarboxylic acids was to synthesize the racemic form of the corresponding diester derivatives starting from some cyclic 1,3-diketone compounds. Synthesis of racemic α-hydroxydicarboxylic acid diester derivatives was aimed by using protection of 1,3-diketone compounds, followed by manganese(III) acetate mediated acetoxylation of protected 1,3-diketones, deprotection of those acetoxylated products, and finally oxone mediated oxidative cleavage of corresponding cyclic ketones.

It was also aimed to find the optimum conditions for enzymatic bioconversions of cyclic α-acetoxy ketones in order to synthesize enantiopure α-hydroxydicarboxylic acid diesters in good optical yield. After synthesizing the corresponding chiral α-acetoxy ketones, the effect of oxidative cleavage reaction on enantiopurity will be examined.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Perspective of the work

1,5-dicarbonyl compounds are important class of building blocks for many natural substances. The biological importance of α-hydroxy-1,5-diester compounds (Figure 2.1) has been clearly demonstrated over the last few years. 1,5 dicarbonyl compounds are versatile substrates for the general synthesis of γ-lactams and γ-amino acids which have found wide pharmaceutical applications. Several 1,5-diester compounds are used as a key step in the synthesis of pyrazino pyridazines which are found to be high affinity ligands for the GABA receptor benzodiazepine binding site[13].

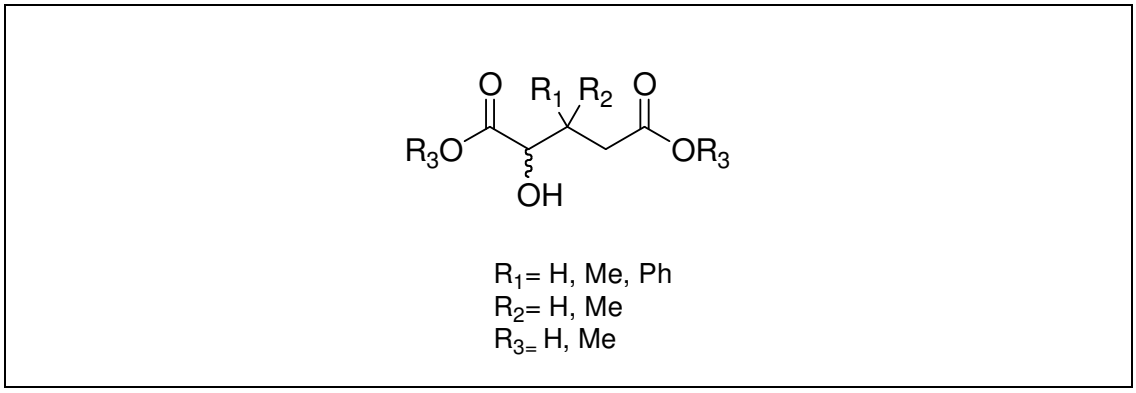


Figure 2.1. α-hydroxy-1,5-diester compounds

Synthesis of chiral polyfunctional dicarboxylic acids and their ester derivatives has a great importance in the literature since they are the key intermediates for many biologically active compounds.

However, up to today there is no general way for the enantioselective synthesis of these chiral α-hydroxydicarboxylic acids and their diester derivatives. The synthesis of polyoxo cyclohexenones has already been accomplished by Demir's group and their synthesis gave us an approach for the enantioselective synthesis of chiral diesters[35]

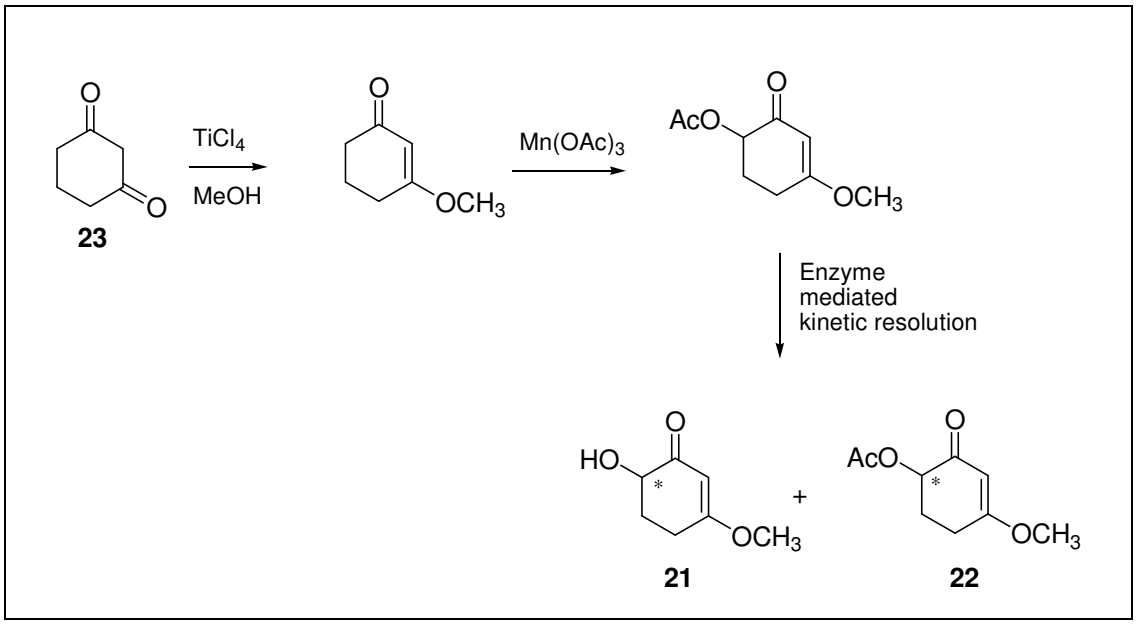


Figure 2.2. Chemoenzymatic route for the enantioselective synthesis of α-functionalized enol ethers

Here, chemoenzymatic route for the enantioselective synthesis of 6-hydroxy-3-methoxycyclohex-2-enone **21** and 6-acetoxy-3-methoxycyclohex-2-enone **22** from 1,3-cyclohexandione **23** via protection, $Mn(OAc)_3$ mediated acetoxylation followed by enantioselective ester hydrolysis by using lipases is presented (Figure 2.2).

Consequently, on the basis of this preliminary information from the previous work with biocatalyst-mediated reactions and the chemical methods in the literature about oxidative cleavage reaction, gave us an idea to develop an approach for the synthesis of chiral α-hydroxy 1,5-dicarboxylic acids or their ester derivatives (Figure 2.3).

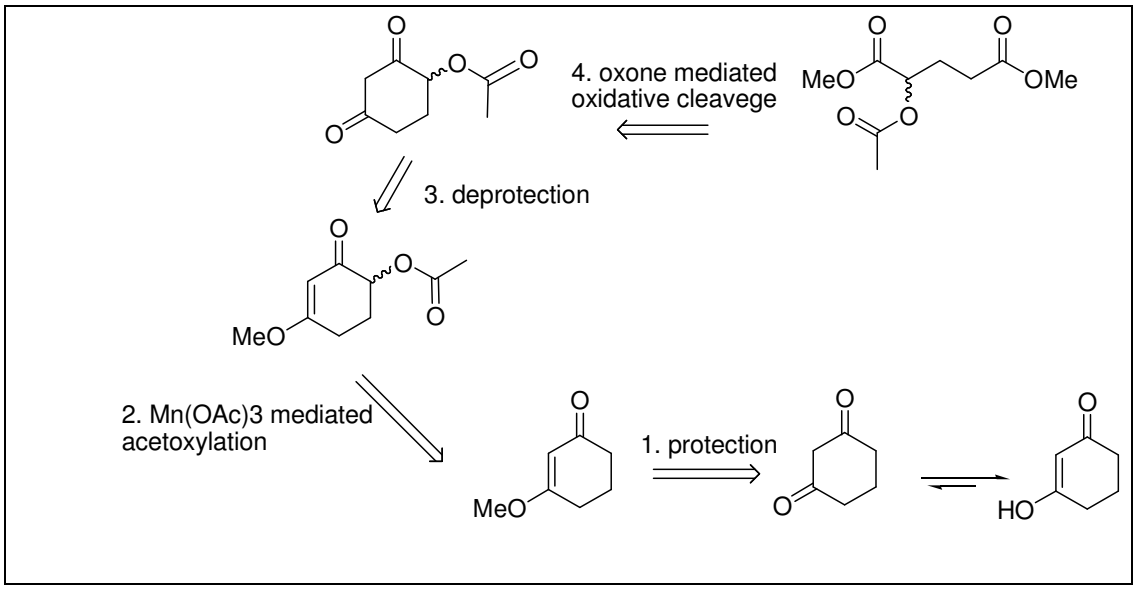


Figure 2.3. Retrosynthetic scheme of chiral α-hydroxy 1,5-diester compounds

2.2 Synthesis of α-acetoxy enones

2.2.1 Protection of cyclic 1,3-diketones

Several methods have been demonstrated for the synthesis of β-keto enol ethers from cyclic β-diketones; such as p-toluene sulfonic acid catalyzed etherification, methylation using diazomethane, catalytic etherification by iodine and $TiCl_4$ and the use of lanthanide complexes as catalyst.

Due to low yields and hazard of the the other techniques, efficient synthesis of β-keto enol ethers from cyclic β-diketones were performed in good to excellent yields using a catalytic amount of $TiCl_4$ as described in the literature[36]. 1,3-cyclohexandione **23** was chosen as the starting material and it was allowed to react with methanol in the catalysis of $TiCl_4$ solution, under argon. The reaction was monitored by TLC (Silica gel, EtOAc/Hex 2:1). After concentration of the reaction mixture, product was purified with column chromatography (EtOAc/Hex 1:1). Desired product, 3-methoxy 2-cyclohexen-1-one **24** was obtained as yellow oily compound in 89% yield (Figure 2.4).

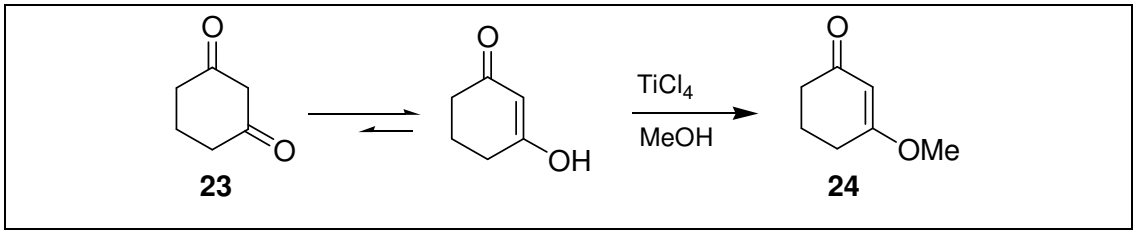
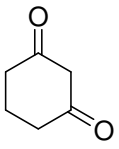
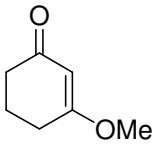
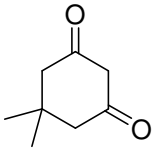
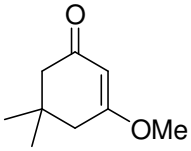
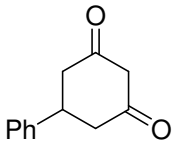
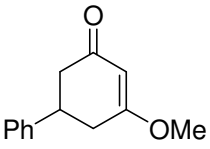


Figure 2.4. Synthesis of β-keto enol ethers from cyclic β-diketones

This reaction was used as reference and then 5,5-dimethylcyclohexan-1,3-dione (dimedone) **25** and 5-phenylcyclohexan-1,3-dione **27** were subjected to etherification reaction at room temperature in the presence of $TiCl_4$ catalyst to give corresponding β-keto enol ethers **26** and **28** in good yields. The results are summarized in Table 1.

Table 1. $TiCl_4$ catalyzed etherification of cyclic β-diketones

Substrate	Product	% Yield of enol
 **23**	 **24**	89%
 **25**	 **26**	85%
 **27**	 **28**	86%

The products of the reactions were identified by NMR spectroscopy. We observed a singlet at 3.67 ppm for $–OCH_3$ protons and a singlet at 5.25 ppm for the –CH proton for the compound **26**. Likely, appearance of a singlet at 3.63 ppm for OCH_3 protons and a singlet protons at 5.35 ppm for –CH proton in the ^{1}H-NMR spectroscopy were the evidences of the compound **27.**

2.2.2 $Mn(OAc)_3$ mediated acetoxylation of β-alkoxy enone

For the acetoxylation reaction, synthesized β-keto enol ethers were allowed to react with 3 equivalent of $Mn(OAc)_3$ in benzene and refluxed under a Dean-Stark trap to give the desired acetoxy derivatives in racemic form.

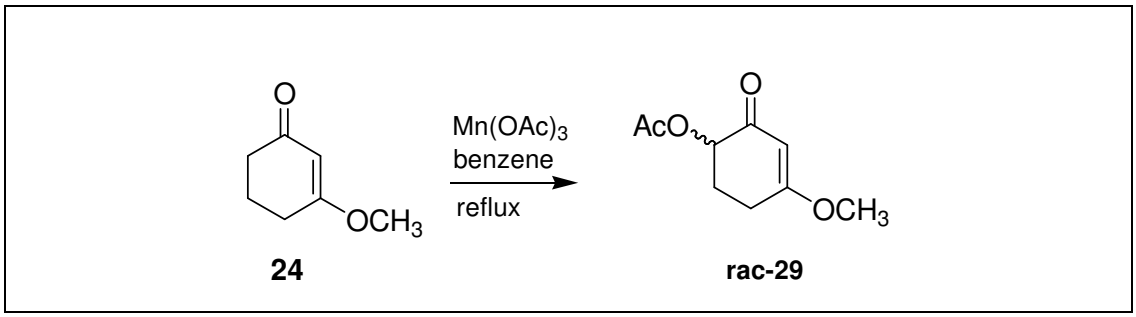
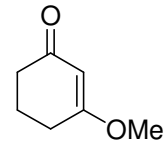
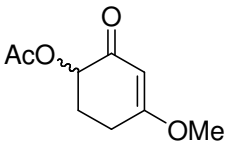
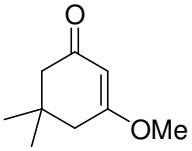
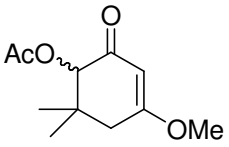
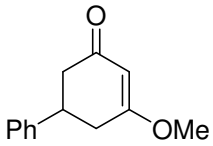
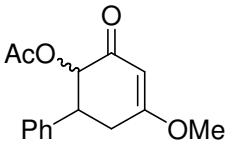


Figure 2.5. $Mn(OAc)_3$ mediated acetoxylation of β-alkoxy enone

3-Methoxy-2-cyclohexen-1-one **24** was allowed to react with 3 equivalent of $Mn(OAc)_3$ in benzene's reflux temperature to give the corresponding acetoxy derivative **29** in racemic form (Figure 2.5). The reaction was monitored by TLC (Silica gel, EtOAc/Hex 1:3). After the work-up and purification of the crude product by column chromatography (EtOAc/Hex 1:3), the desired product, racemic 6-acetoxy-3-methoxy-2-cyclohexen-1-one **29** was obtained as a yellow solid in 83% yield. The same reaction conditions were applied to the other β-keto enol ethers to obtain the corresponding racemic acetoxy derivatives. The results are given in Table 2.

Table 2. $Mn(OAc)_3$ mediated acetoxylation of cyclic β-keto enol ethers

Substrate	Product	% Yield of acetoxy
 **24**	 **29**	83%
 **26**	 **30**	70%
 **28**	 **31**	87%

The products were identified by NMR spectroscopy. From the ^{1}H-NMR spectrum of compound **30** we observed a singlet at 2.11 ppm from the $-CH_3$ group protons and singlet at 5.07 ppm for the α-proton. From the ^{13}C-NMR spectrum we observed a singlet at 20.6 ppm for the CH_3 carbon and a singlet at 169.0 ppm for the $-OCOCH_3$ ester carbon.

The ^{1}H-NMR spectrum of **31** showed the formation of the product by appearing as a singlet at 1.84 ppm ($-CH_3$), d at 5.52 ppm (J= 12.6) for the proton at α-position. The ^{13}C-NMR spectrum also showed the formation of product by appearing as a singlet at 21.2 ppm for the $-CH_3$ carbon and at 170.4 ppm for the $-OCOCH_3$ ester carbon.

As mentioned before, there are several mechanisms about α-acetoxylation with manganese (III) acetate but two of them have general acceptability. First one is based on the formation of a metal enolate followed by acetate transfer. Figure 2.6 shows us the mechanism which is applied on the synthesis of 3-methoxy-2-cyclohexene-1-one **24** to obtain the desired product **29.**

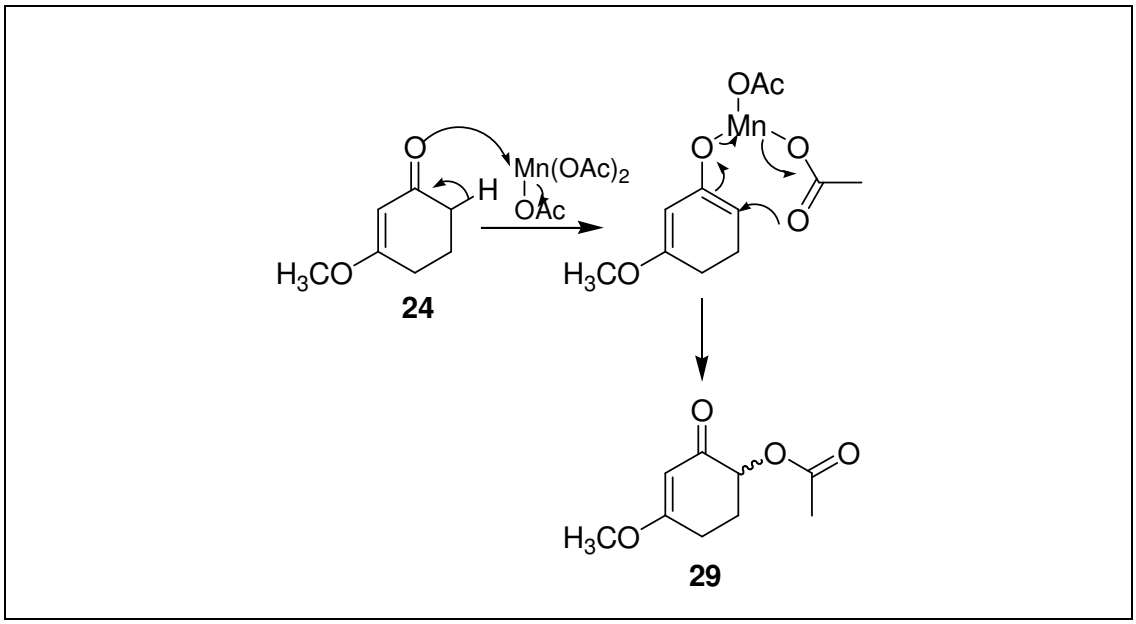


Figure 2.6. First suggested mechanisms about α-acetoxylation with manganese (III) acetate

Another suggested mechanism includes the formation of an α-keto radical resulting from the oxidation of an enol or enolate anion by Mn(III) (Figure 2.7).

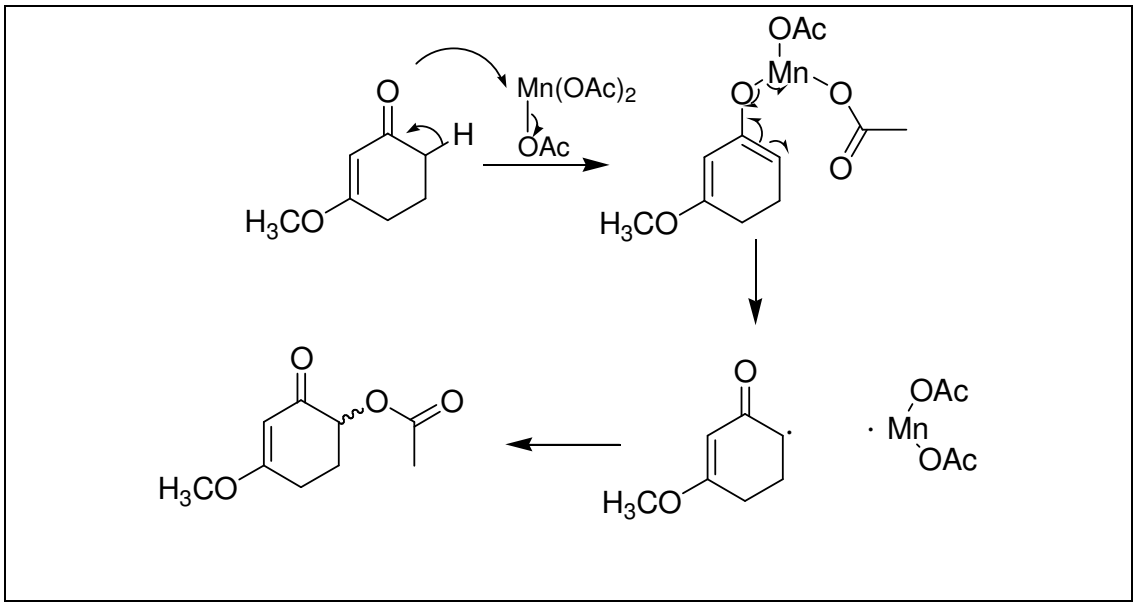


Figure 2.7. Second suggested mechanisms about α-acetoxylation with manganese (III) acetate

2.3 Enzyme mediated hydrolysis of acetoxy ketones

Hydrolytic enzymes are the biocatalysts most commonly used in organic synthesis. Of particular interest among the classes of hydrolytic enzymes are;amidases, proteases, esterases and lipases. These enzymes catalyze the hydrolysis and formation of ester and amide bonds. Among them, lipases (triacylglycerolhydrolases, EC 3.1.1.3) are the most widely employed enzymes not only because they are cheap and readily available from many different sources but because they possess high enantioselectivity for a broad range of substrates and high stability in organic solvents. The enantioselectivity of lipase-catalyzed reactions in aqueous solutions, water-organic solvent mixtures, and in anhydrous organic solvents follows the classical homocompetitive equation.

Demir et al. have published several papers about the $Mn(OAc)_3$-mediated direct acetoxylation of enones and aromatic ketones followed by the enzyme mediated resolution of acetoxy enones to obtain optically pure hydroxy ketones[35]. (Figure 2.8).

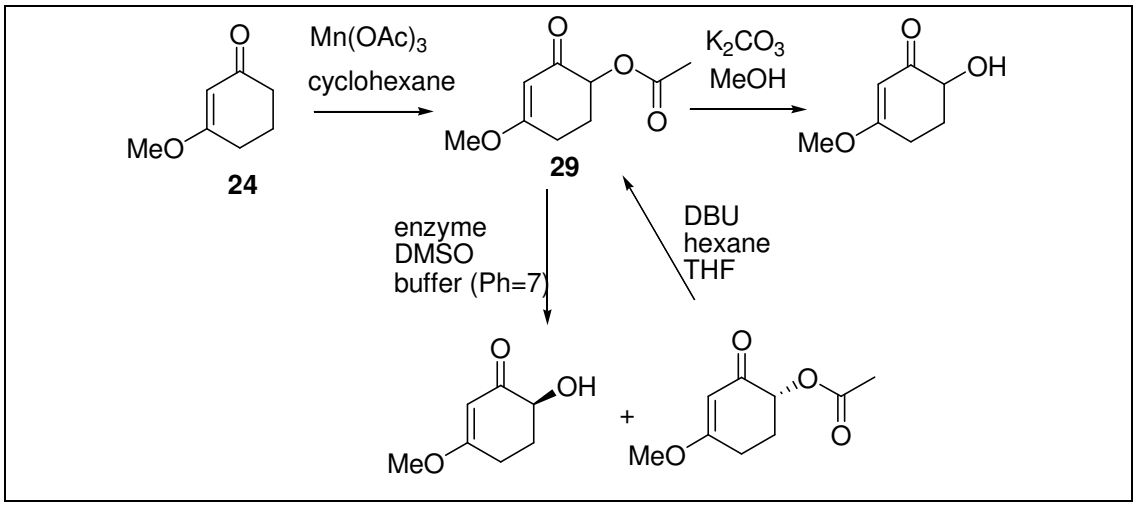


Figure 2.8. Enzyme mediated hydrolysis of acetoxy ketones

On the basis of this preliminary information, enzymatic hydrolysis reaction of **29** was tried with Amano PS enzyme since it is the best enzyme giving highest optical yield (Figure 2.9).

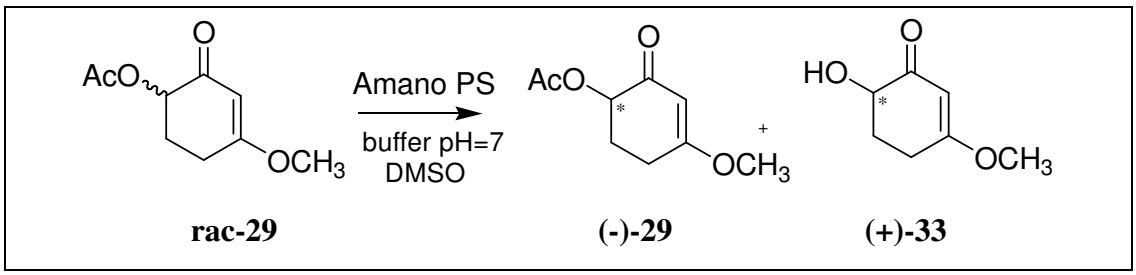


Figure 2.9. Enzymatic hydrolysis of acetoxy enone **29**

The products were identified by using NMR spectroscopy. From the ^{1}H-NMR spectrum **(-)-29**, we observed a singlet at 2.02 ppm from the $-CH_3$ group and dd at 5.24 ppm (J= 12.5 and 5.2 Hz) for the α-proton. From the ^{1}H-NMR spectrum (+)-33, we observed a dd at 4.04 ppm (J= 13 and 5.5 Hz) for the α-proton and a singlet at 5.42 ppm for the –CH enolic proton.

Careful monitoring of the reactions with HPLC furnished the (-)-29 with 90%ee and (+)-33 with 92%ee. Enantiomeric excess values were determined with HPLC (Chiralpak AD column, UV detection at 254 nm, eluent hexane/2-propanol 90:10, flow 0.80 mL min^{-1} 20 °C) using literature conditions as reference.

Then we tried a series of enzymes for screening the enantioselective hydrolysis of other acetoxy enone **30.** Ester hydrolysis of racemic 6-acetoxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one **30** was investigated using ten readily available enzymes; PLE, CCL, WGL, HPL, Amano PS, MJL, PRL, RAL, TL, QLM (Figure 2.10). Only three of them affected the hydrolysis of acetoxy enone including WGL, HPL, TL with WGL exhibiting the highest enantioselectivity. Careful monitoring of the reaction with TLC and HPLC furnished the acetoxy enone with 81 % enantiomeric excess (Table 3).

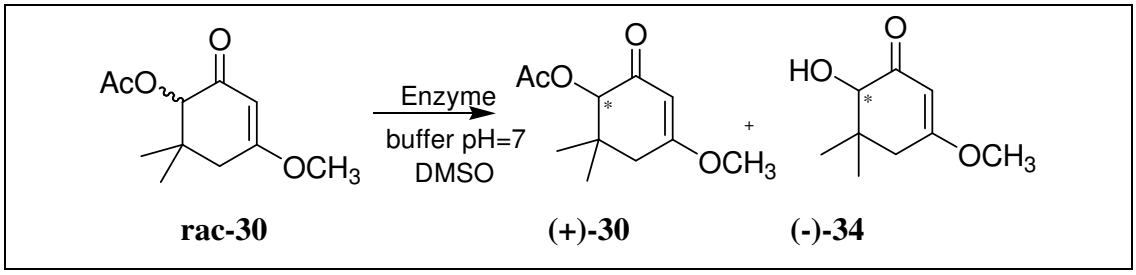


Figure 2.10. enantioselective hydrolysis of acetoxy enone **30**

All reactions were carried out in phosphate buffer (pH=7) at room temperature. Because of the poor solubility of the substrate in aqueous medium, a few mililiter's of DMSO was used as an organic solvent. The mixture was stirred at room temperature in the presence of enzyme. The reaction was monitored by TLC and when approximately 50% conversion was attained, the crude product was separated by column chromatography to afford chiral 6-acetoxy-5,5-dimethyl-3-methoxy-2-cyclohexen-1-one **(+)-30** and 6-hydroxy-5,5-dimethyl-3-methoxy-2-cyclohexen-1-one **(-)-34**. The products were identified by using NMR spectroscopy.

From the ^{1}H-NMR spectrum of **(+)-30,** we observed a singlet at 2.11 ppm from the $-CH_3$ group and a singlet at 5.07 ppm for the α-proton. From the NMR spectrum of **(-)-34,** we observed a singlet at 3.72 for the α-proton.

Table 3. Enzyme mediated hydrolysis of **30** using several enzymes

Enzyme	Reaction time (h)	Conversion%	Acetate		Alcohol	
			ee%	yield%	ee%	yield%
WGL	72	55	81	40	75	47
TL	120	40	17	55	15	35
HPL	96	38	37	51	30	30

Enantiomeric excess values were determined with HPLC (Chiralcel AD column, eluent: hexane/2-propanal=90/10, flow rate: 0.8 ml/min) by using peak area %'s of the enantiomers.

2.4 Deprotection of racemic and chiral acetoxy enones

In order to convert racemic and chiral acetoxy enones to the dicarbonyl compounds, hydrolysis reaction was achieved by HCl acetone system (Figure 2.11).

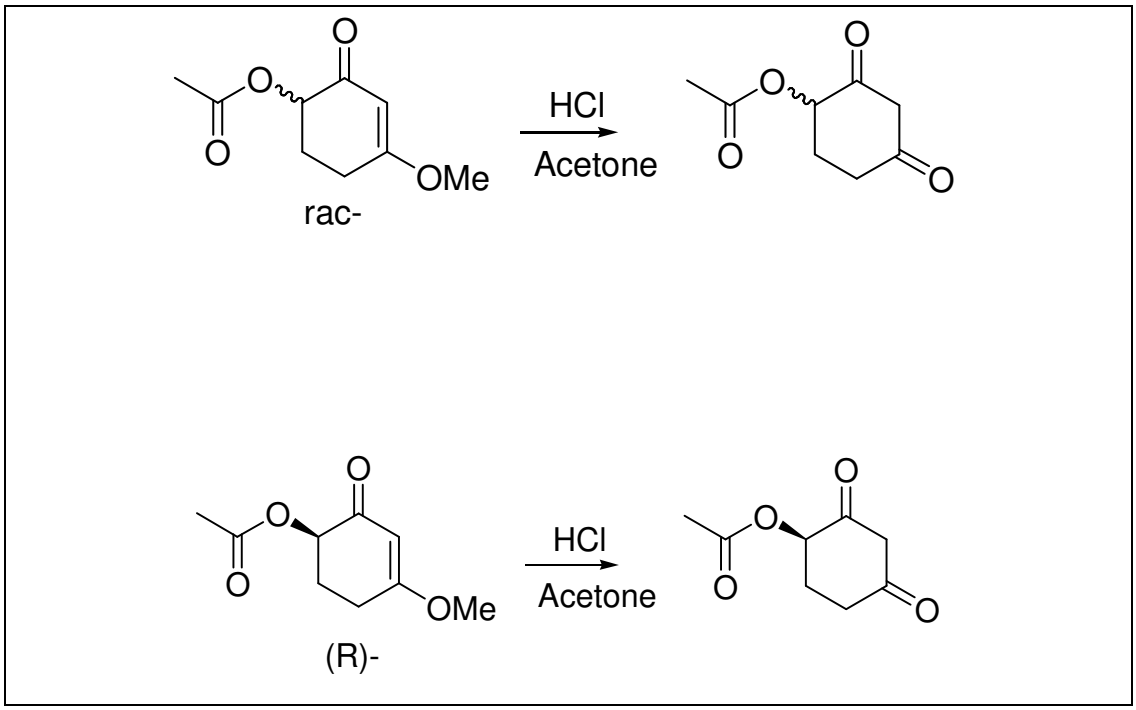
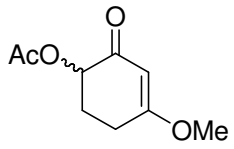
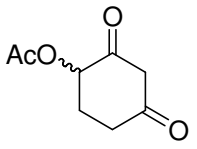
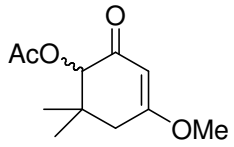
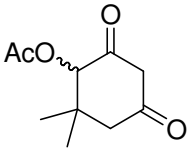
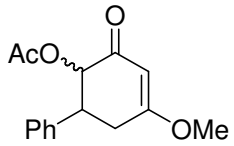
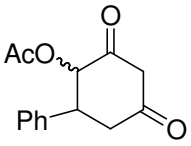


Figure 2.11. Deprotection of racemic and chiral acetoxy enones

Beside 6-acetoxy-3-methoxycyclohex-2-en-1-one; 5,5-dimethyl-6-acetoxy-3-methoxycyclohex-2-en-1-one and 5-phenyl-6-acetoxy-3-methoxycyclohex-2-en-1-one were also subjected to the hydrolysis reaction by HCl, acetone system (Table 4) and the products were identified by NMR spectroscopy. From the ^{1}H-NMR spectrum of the compounds**,** we observed the disappearance of –OCH_3 protons and appearance of -CH_2 protons instead of –CH protons of the starting compounds.

Table 4. Deprotection of racemic acetoxy ketones

Substrate	Product	% Yield of acetoxy
 **29**	 **35**	71%
 **30**	 **36**	70%
 **31**	 **37**	78%.

2.5 Oxone mediated oxidative cleavage of diketones

Oxidation of diketones were performed in methanol at room temperature for 18 hours with the oxone ($KHSO_5$) as described in the literature (Figure 2.12).

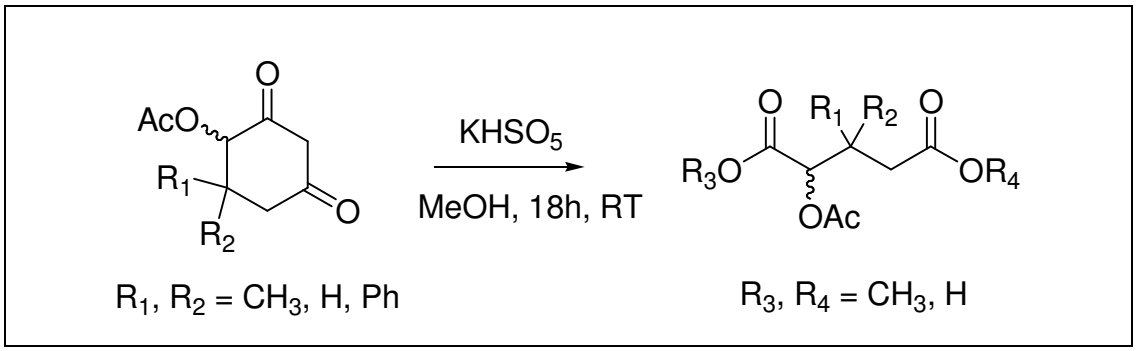
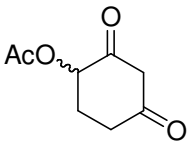
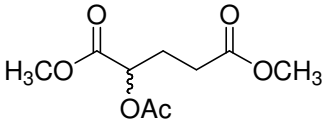
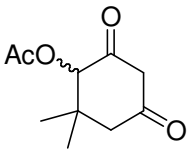
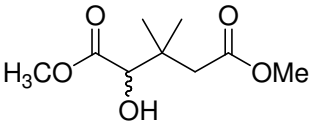
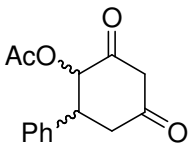
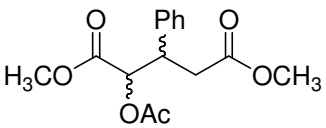


Figure 2.12. Oxone mediated oxidative cleavage of diketones

First, racemic acetoxy diketones were subjected to oxidative cleavage reaction by oxone and corresponding products were used as the reference for the later chiral diester products. As can be seen from Table 5, oxidation of the compounds; 4-acetoxy-1,3-cyclohexanedione, 4-acetoxy-5,5-dimethyl-1,3-cyclohexanedione and 4-acetoxy-5-phenyl-1,3-cyclohexanedione in methanol provided desired dimethyl esters. For instance, 4-acetoxy-1,3-cyclohexanedione **35** provided the diester product **38** in 63% yield, however; 4-acetoxy-5,5-dimethyl-1,3-cyclohexanedione **36** was converted to the dimethyl ester derivative **39** and 4-acetoxy-5-phenyl-1,3-cyclohexanedione **37** to corresponding dimethyl ester **40** but with poor yields leading to only 30% and 25% of the desired diesters with 40% and 45% of the starting material being recovered.

Table 5. Oxone mediated oxidative cleavage of diketones

Substrate	Product	Yield
 **35**	 **38**	63%
 **36**	 **39**	30%
 **37**	 **40**	25%

The products of the reactions were identified by NMR spectroscopy. For example, the evidence for the synthesis of dimethyl 2-acetoxypentandioate **38**, starting from 4-acetoxy-1,3-cyclohexanedione was the disappearance of multiplet $-CH_2$ protons of starting compound at 2.69 ppm and 2.75 ppm and appearance of $-OCH_3$ protons of the product at 3.62 ppm and 3.69 ppm. In addition ^{13}C-NMR spectrum also showed the formation of product by appearing at 169.4 ppm for the ester-carbonyl groups.

Other product dimethyl-2-hydroxy-3,3-dimethyl-pentandioate **39** was obtained as a colorless oily compound and identified by NMR spectroscopy. We observed a singlet at 3.74 ppm for $-OCH_3$ protons and also observed the disappearance of $-CH_2$ protons at 2.45 ppm (J=14.9 Hz) and 2.60 ppm (J=14.9 Hz) appearing as doublet. From the ^{13}C-NMR spectra of the product, we observed two singlet at 174.3 ppm and 168.7 ppm for the ester-carbonyl carbons.

Dimethyl-2-acetoxy-3-phenyl-pentandioate **40** was identified in the same way; by observing two singlets at 3.60 ppm and 3.61 ppm for $-OCH_3$ protons and observing the disappearance of multiplet methylene protons at 3.48 ppm.

In oxidative cleavage reactions, many diffuculties were encountered during the controll of the the reactions and purification of the products since the resulting 1,5 diesters and carboxylic acid compounds are not UV active. Thus, controlling the reactions with TLC only was not enough. Then the reactions were checked by GC-MS and they were stopped when the expected signals of the desired compounds were seen and satisfied conversions were obtained. Since the reaction contained both starting compounds and the desired diester and sometimes carboxylic acid derivatives, purification of the compounds was necessary. Flash column chromatography was applied to the compounds but some difficulties were met again during the collection of the fragments because of the unactivity of the resulting 1,5 diesters in UV region. Then all the probable fragments were collected and the expected diester derivatives were obtained as pure and defined by the NMR spectroscopy.

Thus, mainly low yields were obtained despite the good conversions. These difficulties encountered during the isolation of the products explain the reasons of poor yields.

After synthesizing the racemic 1,5-diester derivatives, chiral α-acetoxy-1,3-cyclohexandione derivatives were subjected to oxidative cleavage reaction by oxone in order to obtain chiral 1,5 diesters and see whether any racemization takes place during the reaction.

First, chiral 4-acetoxy-1,3-cyclohexanedione was used as the starting material and when treated with oxone in MeOH, corresponding chiral dimethyl 2-acetoxypentandioate was obtained and optical rotation of the compound (α_D^{20}) was measured as -28.5 (c 0.6 CH_3OH) (Figure 2.13).

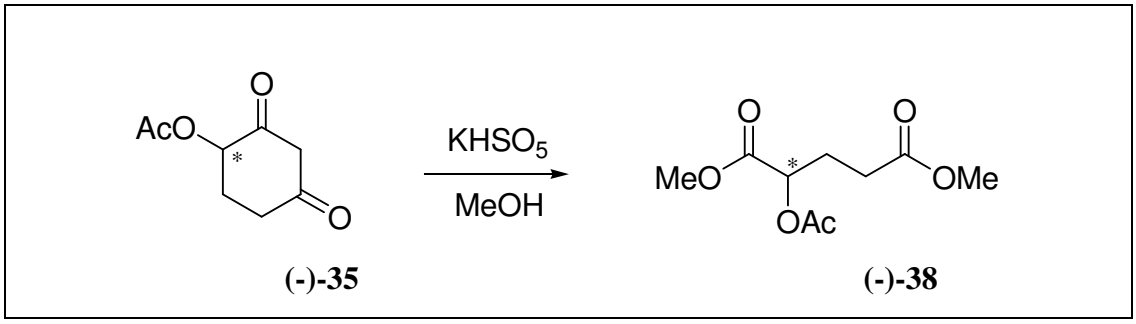


Figure 2.13. Synthesis of chiral dimethyl 2-acetoxypentandioate

Then chiral 4-hydroxy-1,3-cyclohexandione was treated with oxone and corresponding chiral dimethyl 2-hydroxypentandioate **(-)-41** was obtained and its optical rotation was measured as α_D^{20}= -71.1 (c 0.2 CH_3OH) (Figure 2.14).

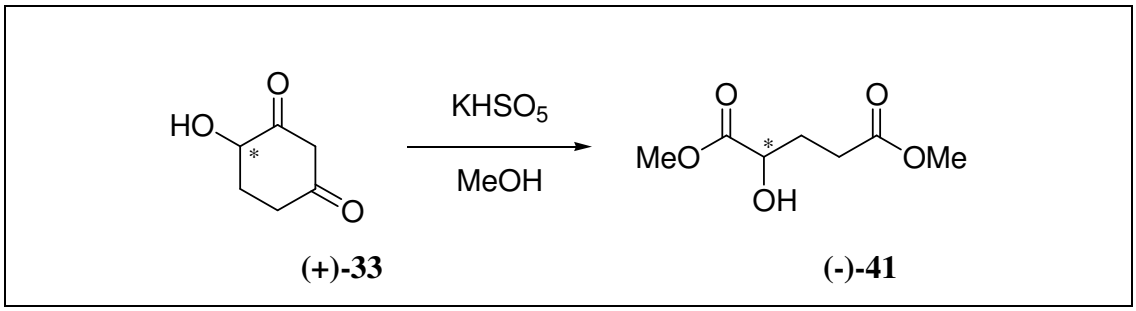


Figure 2.14. Synthesis of chiral dimethyl 2-hydroxypentandioate

Next, we performed the same reaction with chiral 4-hydroxy-5,5-dimethyl-1,3-cyclohexanedione **(+)-36** (Figure 2.15).

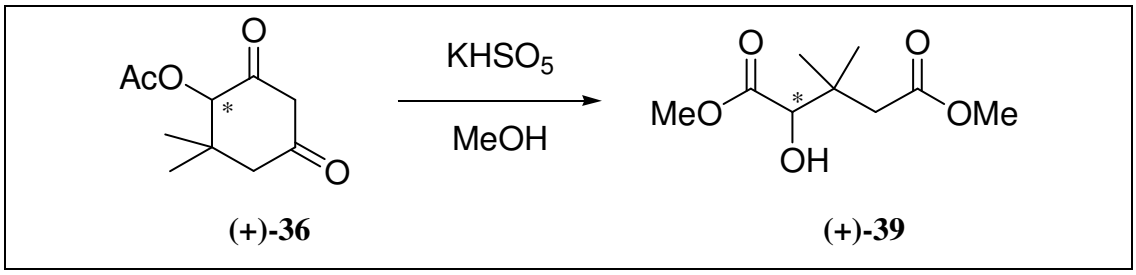


Figure 2.15. Synthesis of dimethyl-2-hydroxy-3,3-dimethyl-pentandioate

The product of the reaction was obtained with 40% enantiomeric excess. Therefore we concluded that there were no racemization during the reaction since the enantiomeric excess of the starting compound was 45% at the beginning of the reaction. Enantiomeric excess values were determined with HPLC (Chiralcel AD column, eluent: 90/10 hexane-isopropanol, flow rate: 0.8 ml/min, 220 nm)

According to literature, the mechanism of the oxidative cleavage reactions of β-diketones proposed by Yan et al., firstly one of the oxygen of $KHSO_5$ which is found in the structure of oxone, interacts with the carbonyl group and seven membered lactone ring is formed as a result of Baeyer-Villiger type oxidation (Figure 2.16). Then ring opening occurs with the MeOH and at the end mono ester derivative is obtained.

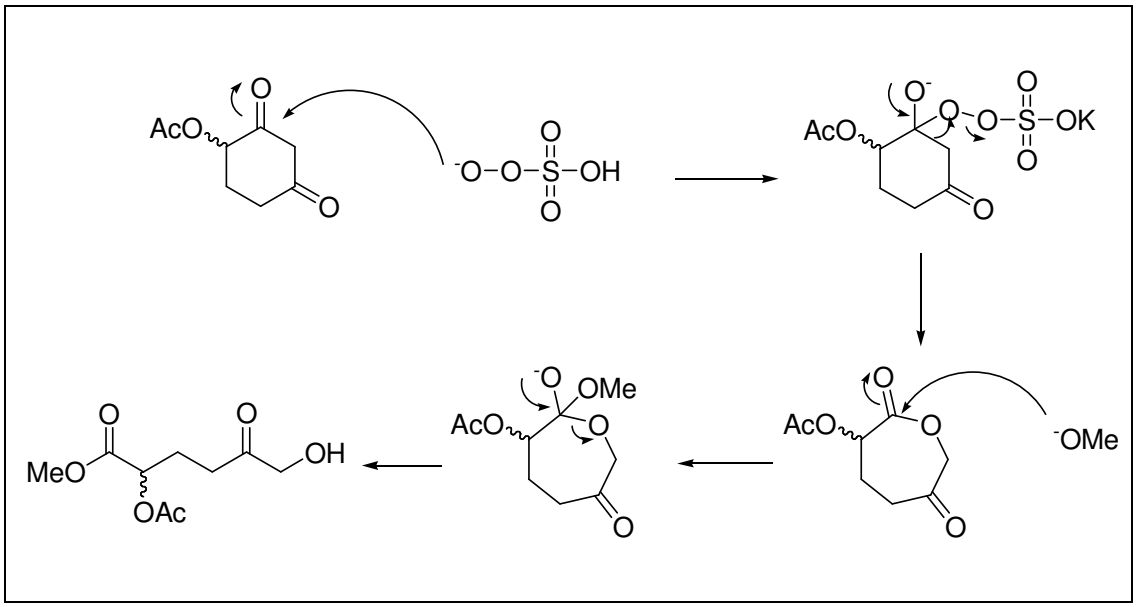


Figure 2.16. Mechanism of the oxidative cleavage reactions of β-diketones

One more Baeyer-Villiger type oxidation with oxone and reaction with MeOH forms 1,5 diester derivatives (Figure 2.17).

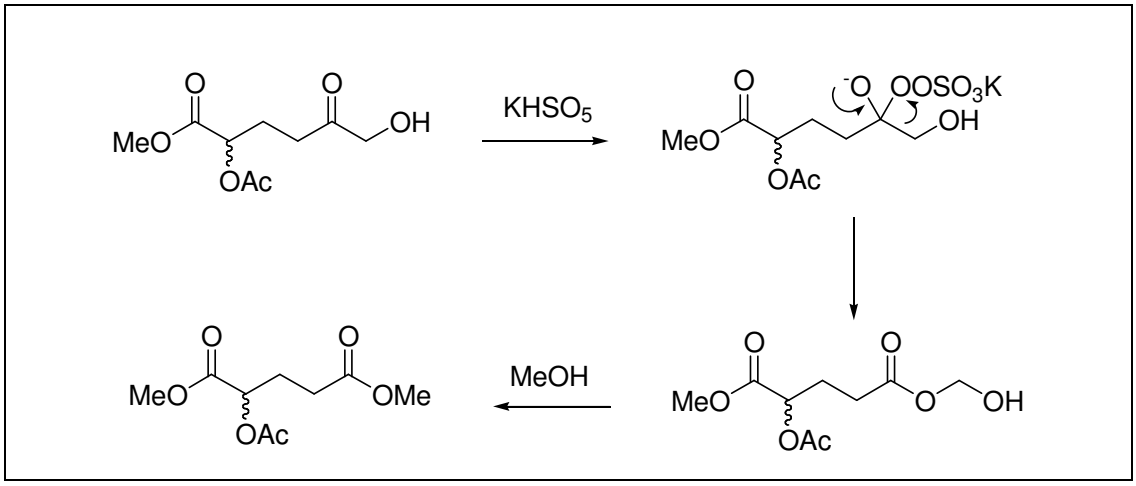


Figure 2.17. Baeyer-Villiger type oxidation with oxone

In summary, it was described here, the first efficient synthesis of chiral 1,5-diester and carboxylic acid derivatives starting from the corresponding β-diketone starting compounds via oxone mediated oxidative cleavage reactions. As a future work, we are going to try the cleavage experiments for also chiral 5-phenyl-6-acetoxy-1,3-cyclohexanedione **37** to obtain chiral corresponding diester product **40** and observe whether any racemization takes place during the reaction.

CHAPTER III

EXPERIMENTAL

3.1 Materials and Methods

In this study all compounds were identified by using Nuclear Magnetic Resonance Spectometer (NMR) (Bruker DPX 400 MHz) by using tetramethylsilane (TMS) as an internal Standard and deutereo chloroform as solvent.

Flash column chromatography was done for purifying the products by using Merck Silica Gel 60 (partical size 40-63 μm).

Optical rotations were measured with a Bellingham-Stanley P20 polarimeter. Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC-LC-MS equipped with an appropriate optically active column.

3.2 General Procedures

3.2.1 General procedure for protection of β-dicarbonyl compounds

To a solution of **23, 25** and **27** (1g) in dry methanol (70 mL), 1mL 1.0 M $TiCl_4$ solution is added dropwise under argon. Reaction is monitored by TLC. Stirring is continued for additional two hours. Reaction mixture is concentrated and purified by column chromatography to yield desired enones **24, 26** and **28.**

3.2.1.1 Synthesis of 3-metoxy-cyclohex-2-en-1-one (24)

The product was isolated as a yellow oil after column chromatography (1:1 EtOAc:Hexane) with 89% yield.

^{1}H-NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.98 (p, *J*=10.6 and 6.3 Hz, 2H)
2.32 (t, *J*= 6.3 Hz, 2H)
2.41 (t, *J*= 6.3 Hz, 2H)
3.70 (s,3H)
5.35 (s, 1H)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 198.6, 178.0, 102.2, 55.3, 36.6, 28.7, 21.4

3.2.1.2 Synthesis of 5,5 dimethyl-3-methoxycyclohex-2-en-1-one (26)

The product was isolated as a yellow oil after column chromatography (1:1 EtOAc:Hexane) with 70% yield.

^{1}H-NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.03 (s, 6H)
2.25 (s, 2H)
3.22 (s, 2H)
3.67 (s,3H)
5.25 (s, 1H)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 197.8, 176.5, 100.9, 55.8, 50.8, 46.4, 42.5, 28.3

3.2.1.3 Synthesis of 5-phenyl-3-methoxycyclohex-2-en-1-one (28)

The product was isolated as a colorless oil after column chromatography (1:1 EtOAc:Hexane) with 87% yield.

^{1}H-NMR ($CDCl_3$+CCl_4):

δ (ppm): 2.40-2.55 (m, 4H)
3.63 (s, 3H)
5.35 (s, 1H)
3.24 (m, 1H)
7.17 (m, 5H)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 197.9, 177.3, 142.6, 128.9, 128.7, 128.1, 126.9, 126.6, 102.1, , 55.7, 43.8, 39.4, 36.4

3.2.2 General Procedure For $Mn(OAc)_3$ Oxidation

A solution of **24, 26** and **28** (4.76 mmol), $Mn(OAc)_3$ (5.10 g, 19.04 mmol), acetic acid (7ml) and benzene (70ml) were heated under reflux for 2 days. The reaction was monitored by TLC. After cooling, the reaction mixture was filtered then washed with saturated $NaHCO_3$ solution. The solution was then dried over $MgSO_4$, concentrated and purified by column chromatography to yield the desired racemic α-acetoxy polyoxo enones **29, 30** and **31**.

3.2.2.1 Synthesis of 6-acetoxy 3-metoxy-cyclohex-2-en-1-one (29)

The product was isolated as an orange colored solid after flash column chromotography (1:3 EtOAc:hexane) with 83% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 2.01 (s, 3H, C*H*$_3$),
2.09 (ddd, *J*= 24.0, 12.5 and 5.7 Hz, 1H),
2.26 (m, 1H),
2.53 (m, 1H),
2.76 (m, 1H),
3.65 (s, 3H),
5.24 (dd, *J*= 12.5 and 5.2 Hz, 1H),
5.32 (s, 1H)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 193.5, 171.8, 170.5, 101.4, 96.6, 72.6, 56.7, 26.7, 20.8.

3.2.2.2 Synthesis of 6-acetoxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one (30)

The product was isolated as an orange colored solid after flash column chromotography (1:1 EtOAc:hexane) with 70% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm):0.95 (s, 3H),
1.03 (s, 3H),
2.11 (s, 3H),
2.20 (d, *J*= 17.5 Hz, 1H),
2.55 (d, *J*= 17.5 Hz, 1H),
3.63 (s, 3H),
5.07 (s, 1H),
5.27 (s, 1H);

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 191.8, 174.6, 170.0, 100.1, 79.7, 55.8, 43.1, 36.4, 27.2, 20.6, 18.7

3.2.2.3 Synthesis of 5-phenyl-6-acetoxy-3-methoxycyclohex-2-en-1-one (31)

The product was isolated as an orange colored solide after flash column chromotography (1:1 EtOAc:hexane) with 83% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.84 (s, 3H),
2.60 (dd, *J*= 4.9 and 17.6 Hz, 1H),
2.78 (m, 1H),
3.39 (m, 1H),
3.65 (s, 3H),
5.37 (s, 1H),
5.52 (d, *J*= 12.6 Hz, 1H),
7.17 (m, 5H);

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 191.6, 175.7, 169.5, 139.3, 128.7, 128.4, 128.1, 127.4, 127.2, 101.2, 73.8, 56.1, 44.6, 36.7, 20.6.

3.2.3 General Procedure for the Lipase-Catalyzed Hydrolysis of Racemic α-Acetoxy Ketones

Lipase (200-300 mg) was dissolved in potassium phosphate buffer (20mM, pH7, 30ml) and added to a solution of the pure substrate (200mg) in organic solvent (2ml) and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC and when 50% conversion is obtained, the reaction was terminated by adding excess $CHCl_3$. Reaction mixture was washed with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The unreacted acetate and the product was seperated by flash column chromatography.

3.2.3.1 Synthesis of (S)-(+)-6-hydroxy-3-methoxycyclohex-2-en-1-one (+)-33

The unreacted acetate (-)-**29** and the product (+)-**33** were seperated by column chromatography (3:1 EtOAc: Hexane). The product was isolated as a white solid with 49% yield.

^{1}H-NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.86 (ddd, *J*= 25.4, 12.7 ve 5.3 Hz, 1H)
2.35 (m, 1H)
2.52 (m, 1H)
2.65 (m, 1H)
3.76 (s, 3H)
4.04 (dd, *J*= 13.0 ve 5.5 Hz, 1H)
5.42 (s, 1H)

^{13}C-NMR ($CDCl_3$+CCl_4):

δ (ppm):) 194.6, 172.5, 102.7, 98.9, 71.2, 55.5, 26.7.

The ee's of the ester and the alcohol were determined by chiral HPLC analysis by using the literature conditions.

HPLC (Chiralpak AD column, UV detection at 254 nm, eluent hexane/2-propanol 90:10, flow 0.80 mL min)

3.2.3.2 Synthesis of (-)-6-hydroxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one (-)-34

The unreacted acetate (+)-**30** and the product (-)-**34** were seperated by column chromatography (1:1 EtOAc: Hexane). The product was isolated as a white solid with 47% yield.

^{1}H-NMR ($CDCl_3$+CCl_4):

δ (ppm): 0.80 (s, 3H)
1.14 (s, 3H)
2.16 (d, J=17.6 Hz, 1H)
2.45 (d, J=17.6 Hz, 1H)
3.66 (s, 3H)
3.72 (s, 1H)
5.32 (s, 1H)

^{13}C-NMR ($CDCl_3$+CCl_4):

δ (ppm): 198.1, 176.4, 98.4, 79.0, 55.9, 43.0, 38.2, 27.6, 18.3.

The ee's of the ester and the alcohol were determined by chiral HPLC analysis.

HPLC (Chiralcel AD column, eluent: hexane/2-propanal=95/5, flow rate: 0.8 ml/min) R_f: for (+)-**30**: 17 min; (-)-**30:** 22 min ; $[\alpha]_D^{20}$ = + 167.3 (c 0.3, $CHCl_3$); R_f: for (-)-**34** : 19 min; R_f: for (+)-**34** : 22 min;

3.2.4 General Procedure For Deprotection of racemic acetoxy enones

The solution of **29, 30** and **31** was hydrolyzed by dissolving in acetone (20 ml) containing 0.12 ml of 2N HCl. After 12 h at room temperature the solvent was evaporated and the residue was dissolved in chloroform (15 ml). The organic solution was washed with water and brine (5 ml of each), dried over MgSO4, and evaporated to give desired diketones **35, 36** and **37** as colorless crystals.

3.2.4.1 Synthesis of 4-acetoxy-1,3-cyclohexanedione (35)

The product was isolated as a colorless cyristals with 71% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm):1.94 (ddd, *J*= 13.0, 13.1 and 6.2 Hz, 1H),
2.12 (s, 3H),
2.38 (m, 1H),
2.53 (m, 1H),
2.58 (m, 1H),
2.68 (m, 1H),
2.75 (m, 1H),
4.42 (dd, *J*= 12.3 ve 5.8 Hz, 1H);
5.25 (s, 1H from enol form)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 193.9, 171.6, 170.6, 102.0, 95.8, 73.0, 56.4, 23.6, 22.9, 20.8.

3.2.4.2 Synthesis of 4-hydroxy-1,3-cyclohexanedione

The product was isolated as a colorless crystals with 75% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.88 (ddd, J= 13.2, 13.0 ve 6.3 Hz, 1H),
2.24 (m, 1H),
2.48 (m, 1H),
2.58 (m, 1H),
2.64 (m, 1H),
2.77 (m, 1H),
4.12 (dd, J= 12.2 ve 5.8 Hz, 1H);

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 194.8, 171.7, 101.9, 98.8, 71.3, 55.6.

3.2.4.3 Synthesis of 4-hydroxy-5,5-dimethyl-1,3-cyclohexanedione (36)

The product was synthesized as a colorless crystals after flash column chromotograpy (1:1 EtOAc:Hexane) with 70% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 0.68 (s, 3H),
1.20 (s, 3H),
2.45 (d, J= 14.9, 1H),
2.60 (d, J= 14.9, 1H),
3.35 (d, J= 17.1, 1H),
3.43 (d, J= 17.1, 1H),
4.16 (s. 1H),
5.20 (s, 1H from enol form)

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 203.5, 200.4, 82.4, 56.7, 55.5, 26.7, 20.7, 20.6

3.2.4.4 Synthesis of 4-acetoxy-5-phenyl-1,3-cyclohexanedione (37)

The product was synthesized as a yellow cyristals after flash column chromotograpy (1:1 EtOAc:Hexane) with 78% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 1.84 (s, 3H),
2.65 (m, 1H),
2.81 (m, 1H),

3.44 (m, 1H),
5.53 (s, 1H),
5.56 (s, 1H from enol form)
5.64 (d, J= 11.9, 1H),
7.2 (m. 5H);

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm): 199.0, 191.0, 170.6, 138.9, 128.7, 128.1, 127.9, 127.4, 127.0, 103.6, 74.7, 44.9, 37.5, 20.4

3.2.5 General Procedure For Oxidative Cleavage of Diketones

$KHSO_5$ (547 mg, 3.6 mmol) was added in one portion to a solution of diketones **(35), (36), (37)** (9 mmol) in methanol (8 mL) at rt (the salt is not completely soluble). The reaction was stirred at rt for 18 h, after which it was diluted with Et_2O (8 mL) and the precipitate (presumably unreacted $KHSO_5$ and $KHSO_4$ generated during the reaction) was filtered through a pad of Celite. The filtrate was concentrated, and the crude products were purified by silica gel column chromatography (1:4 EtOAc/hexanes) to a desired furnish ester **(38), (39), (40**).

3.2.5.1 Synthesis of dimethyl 2-acetoxypentandioate (38)

The crude product was separeted by flash column chromotography (1:4 EtOAc/Hexane) in 63% yield.

^{1}H NMR ($CDCl_3$+CCl_4):

δ (ppm): 2.06 (s, 3H),
2.13 (m, 2H),
2.38 (m, 2H),

3.51 (s, 3H),
3.52 (s, 3H),
4.98 (dd. J=4.9 Hz and 7.6 Hz, 1H);

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm) 171.6, 169.3, 168.7, 69.9, 59.0, 51.0, 28.3, 19.7, 13.2

3.2.5.2 Synthesis of dimethyl-2-hydroxy-3,3-dimethyl-pentandioate (39)

The crude product was separeted by flash column chromotography (1:4 EtOAc/Hexane) in 30% yield.

^{1}H NMR (CDCl3+CCl4):

δ (ppm): 1.04 (s, 3H),
1.26 (s, 3H),
2.23 (d, J=16.9 Hz, 1H),
2.42 (d, J=16.9 Hz, 1H),
3.74 (s, 6H),
4.43 (s, 1H),

^{13}C NMR ($CDCl_3$+CCl_4):

δ (ppm) 174.3, 168.7, 84.6, 52.1, 41.9, 39.7, 27.4, 22.7.

3.2.5.3 Synthesis of dimethyl-2-acetoxy-3-phenyl-pentandioate (40)

The crude product was separeted by flash column chromotography (1:4 EtOAc/Hexane) in 25% yield.

^{1}H NMR (CDCl3+CCl4):

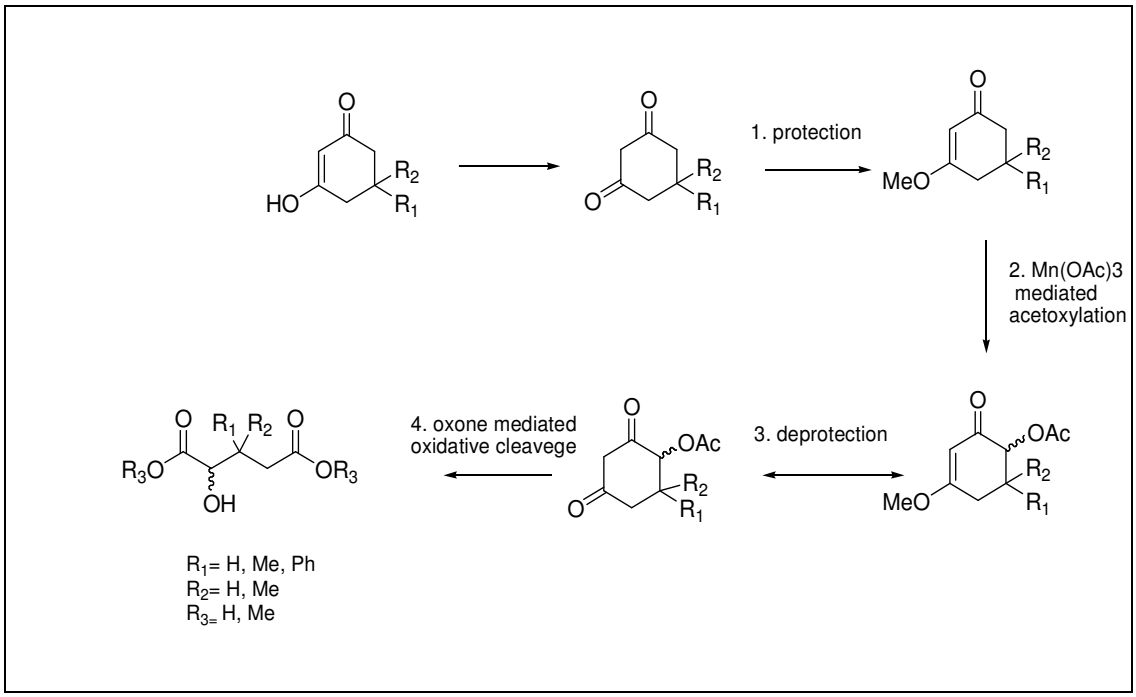
δ (ppm): 2.57 (m, 1H),
3.13 (m, 1H),
3.50 (m, 1H),
3.60 (s, 3H),
3.61 (s, 3H),
3.99 (m, 1H)
7.21 (m, 5H).

CHAPTER 4

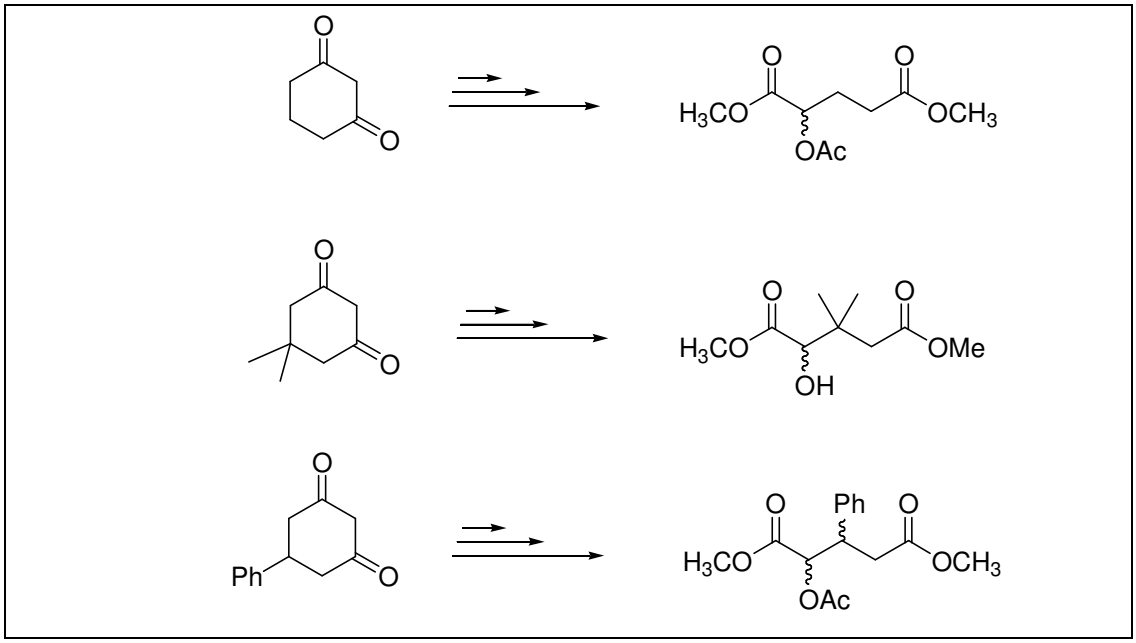
CONCLUSION

1,5-dicarbonyl compounds are important class of building blocks for many natural substances. The biological importance of α-hydroxy-1,5-diester compounds has been clearly demonstrated over the last few years. 1,5 dicarbonyl compounds are versatile substrates for the general synthesis of γ-lactams and γ-amino acids which have found wide pharmaceutical applications. Because this type of hydroxycarboxylic acid compounds and their derivatives have very often been shown to be biologically active and therapeutically useful and potentially selective glutamate receptor ligands, their synthesis gained much importance in recent years.

A new and efficient route has been developed for the synthesis of optically active α-hydroxy 1,5-dicarboxylic acids and their ester derivatives. The 1,3-diketone is protected by acid catalization. Protected enone is converted into its acetoxy derivative using $Mn(OAc)_3$ in good yield. The acetoxy enone is then converted to chiral α-hydroxy enone by using different lipases as biocatalysts. In order to convert racemic and chiral acetoxy enones to the dicarbonyl compounds, hydrolysis reaction was achieved by HCl acetone system. Finally, oxidation of diketones were performed in methanol with the oxone ($KHSO_5$) to give desired chiral α-hydroxy 1,5-dicarboxylic acid dimethyl ester derivatives.



Simple, mild, efficient and enantioselective synthesis of chiral α-hydroxydicarboxylic acids and their diester derivatives which are important starting materials for different biologically active compounds, is realized and following compounds are obtained.



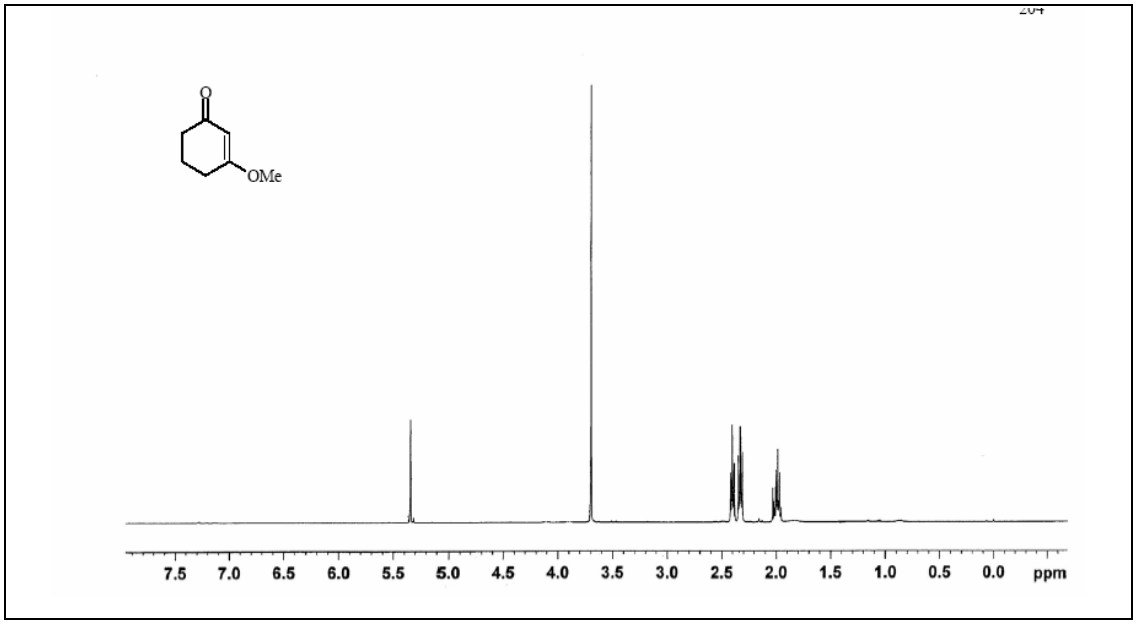


Figure 4.1. H^1 NMR spectrum of of 3-methoxy-cyclohex-2-en-1-one **(24)**

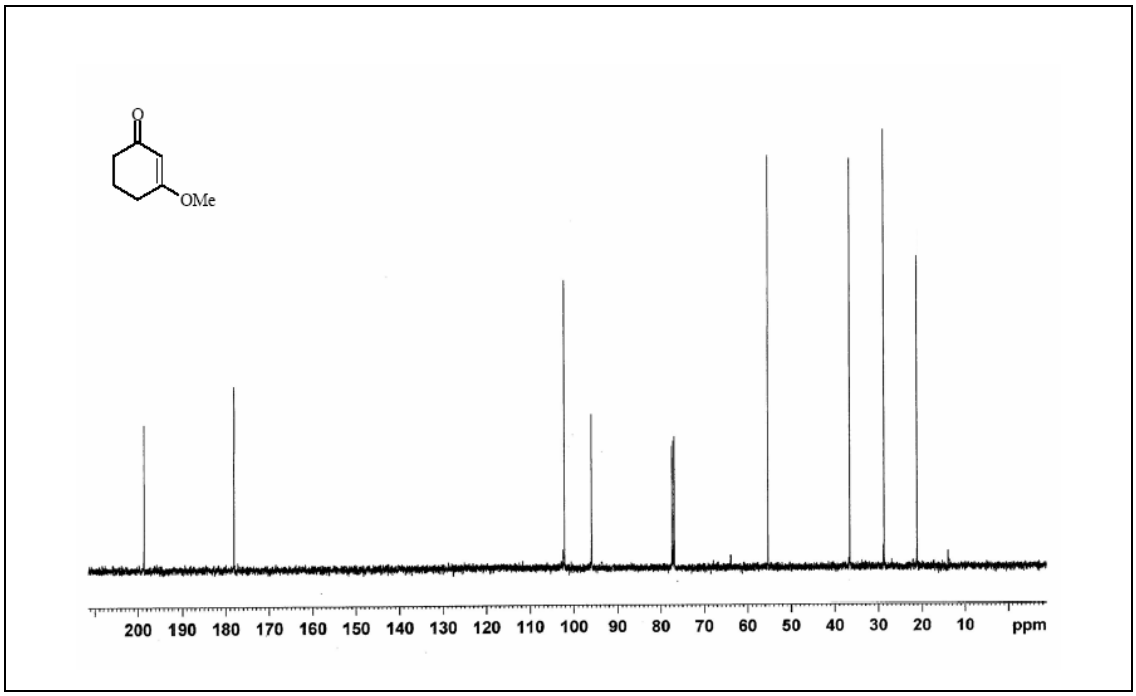


Figure 4.2. ^{13}C NMR spectrum of 3-methoxy-cyclohex-2-en-1-one **(24)**

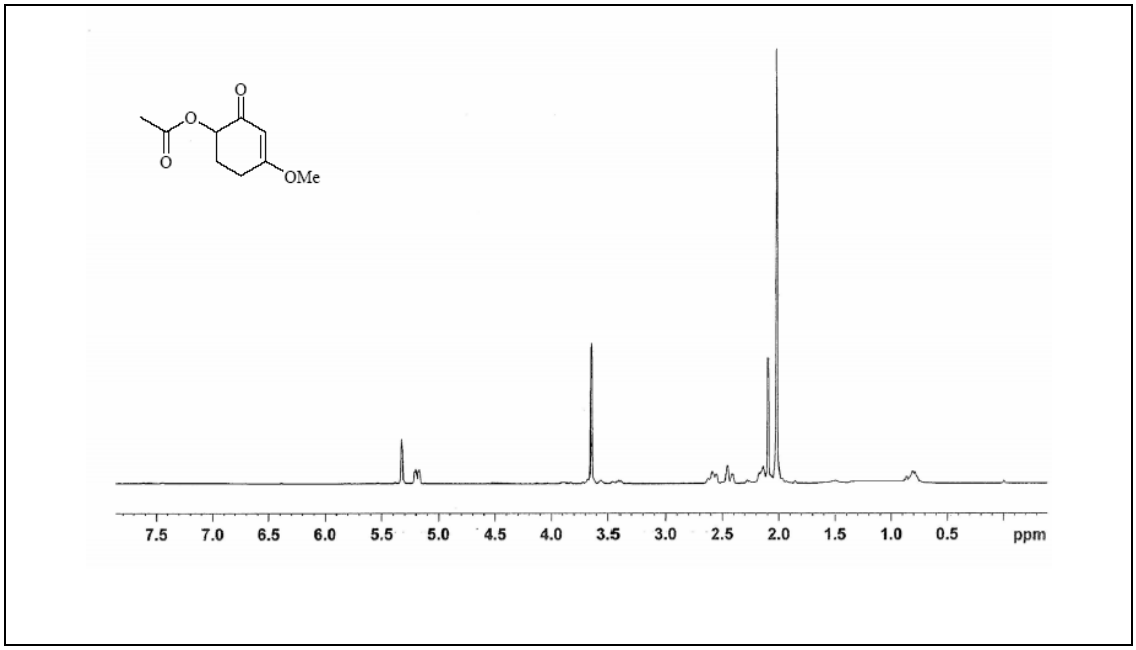


Figure 4.3. H^1 NMR spectrum of of 6-acetoxy 3-metoxy-cyclohex-2-en-1-one **(29)**

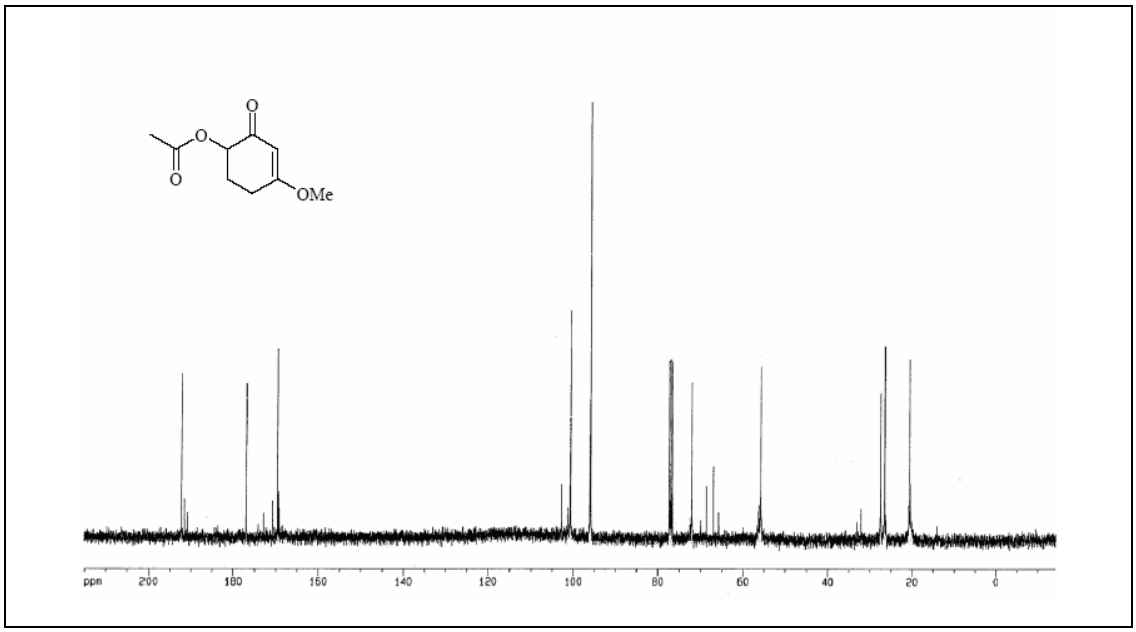


Figure 4.4. ^{13}C NMR spectrum of of 6-acetoxy 3-metoxy-cyclohex-2-en-1-one **(29)**

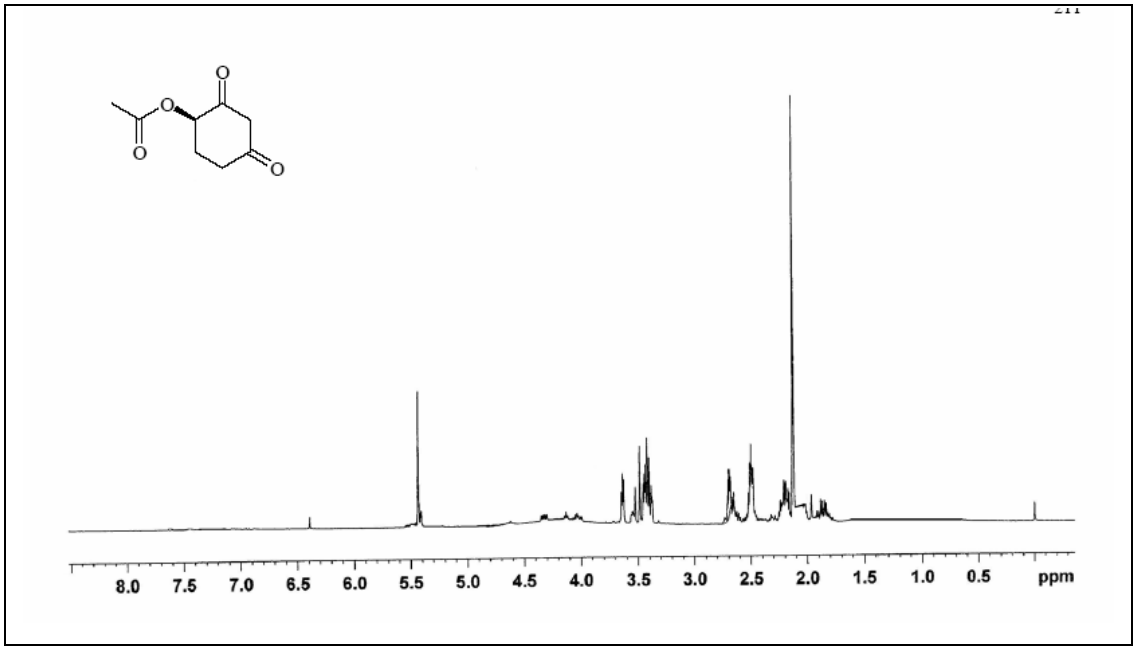


Figure 4.5. H^1 NMR spectrum of 4-acetoxy-1,3-cyclohexanedione **(35)**

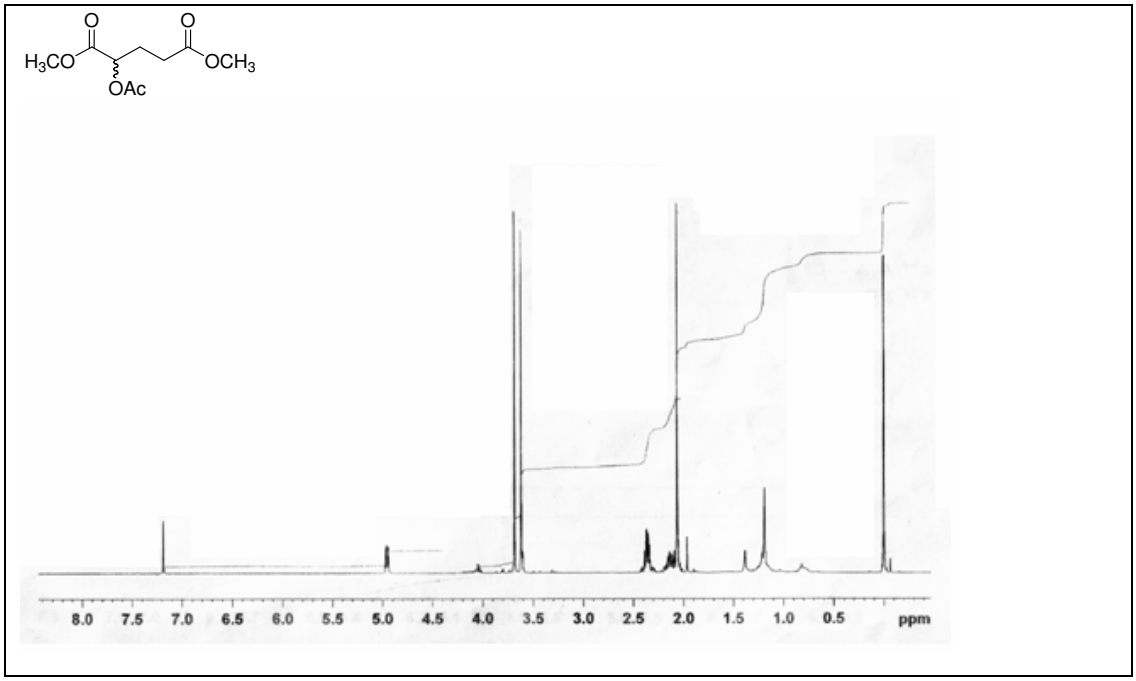


Figure 4.6. H^1 NMR spectrum of dimethyl 2-acetoxypentandioate **(38)**

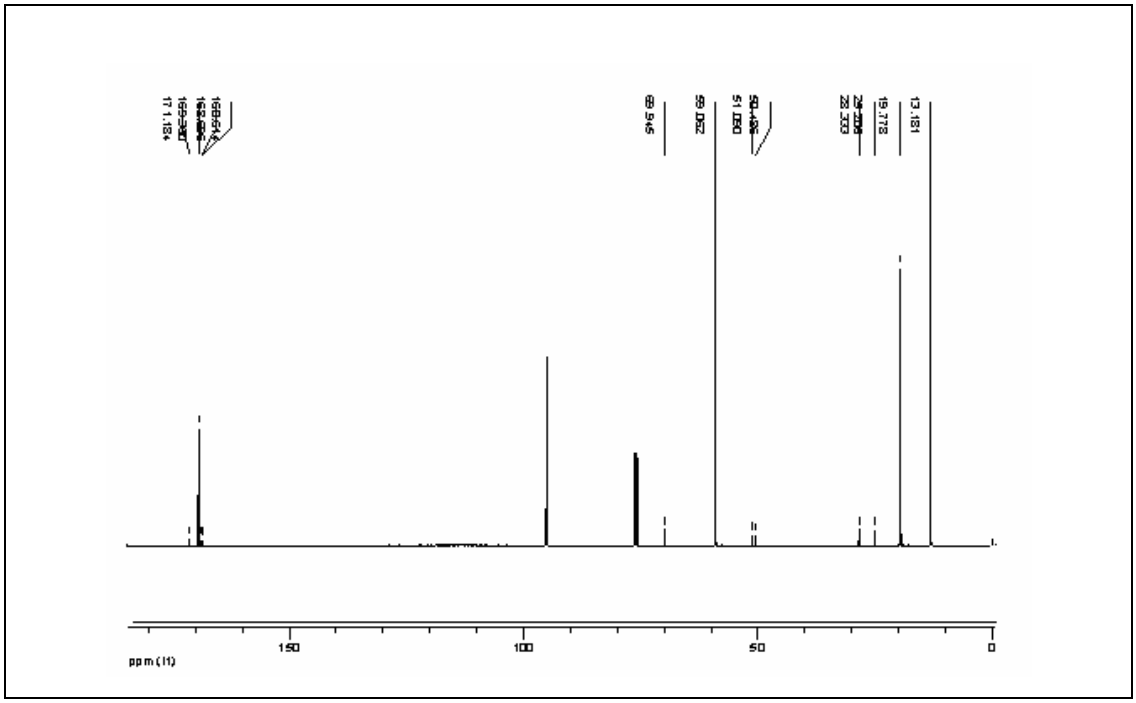


Figure 4.7. ^{13}C NMR spectrum of dimethyl 2-acetoxypentandioate **(38)**

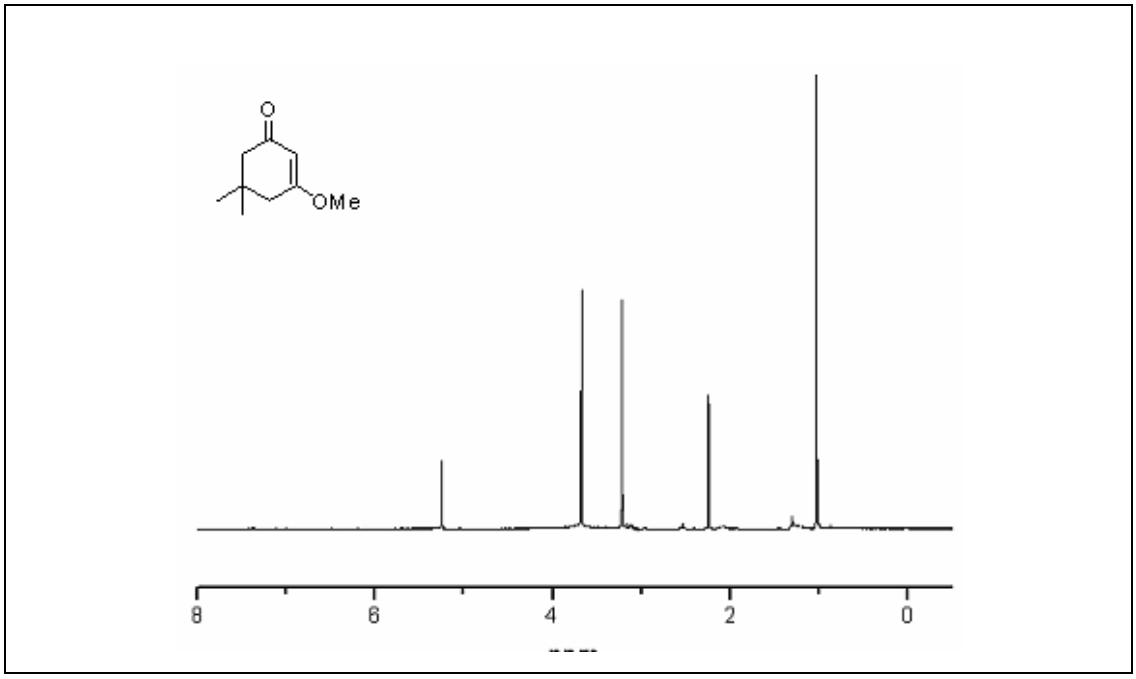


Figure 4.8. H^{1} NMR spectrum of 5,5 dimethyl-3-methoxycyclohex-2-en-1-one **(26)**

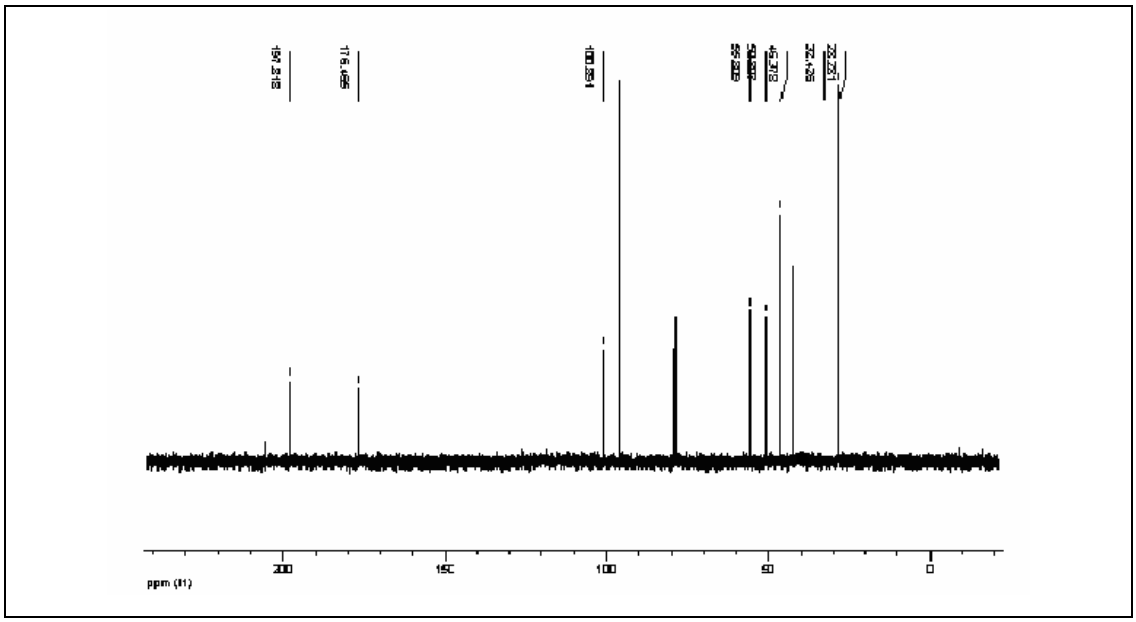


Figure 4.9. ^{13}C NMR spectrum of 5,5 dimethyl-3-methoxycyclohex-2-en-1-one **(26)**

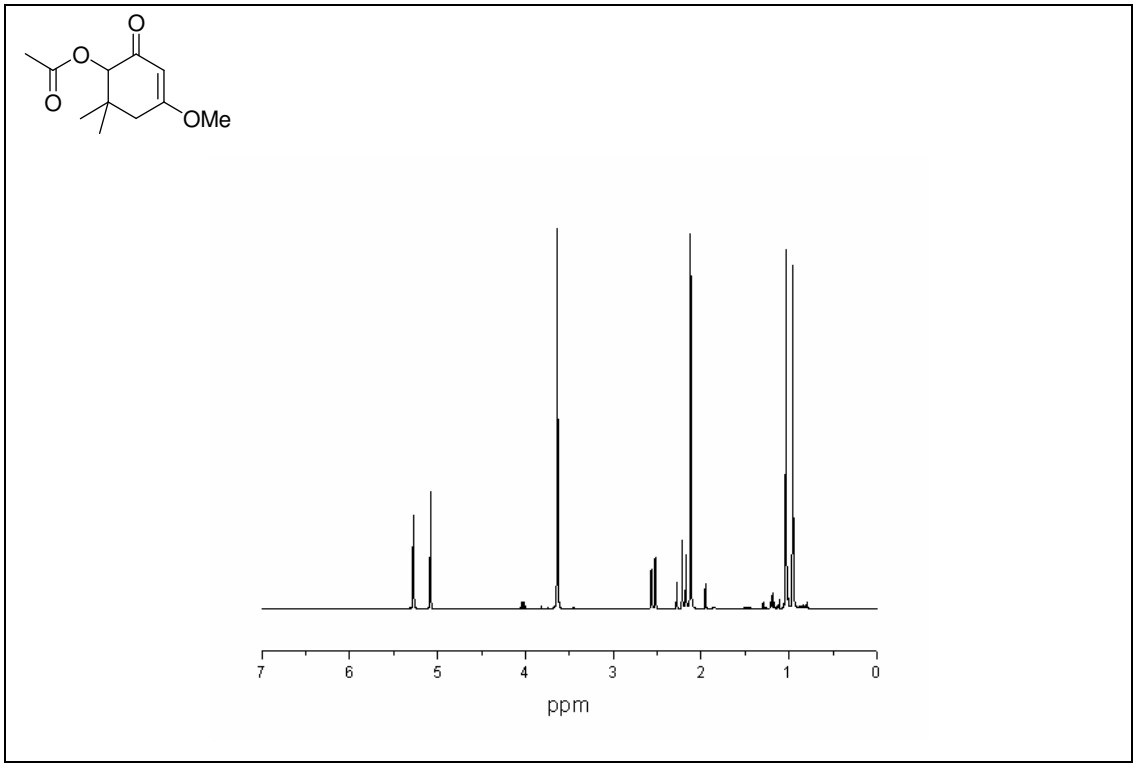


Figure 4.10. H[1] NMR spectrum of 6-acetoxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one **(30)**

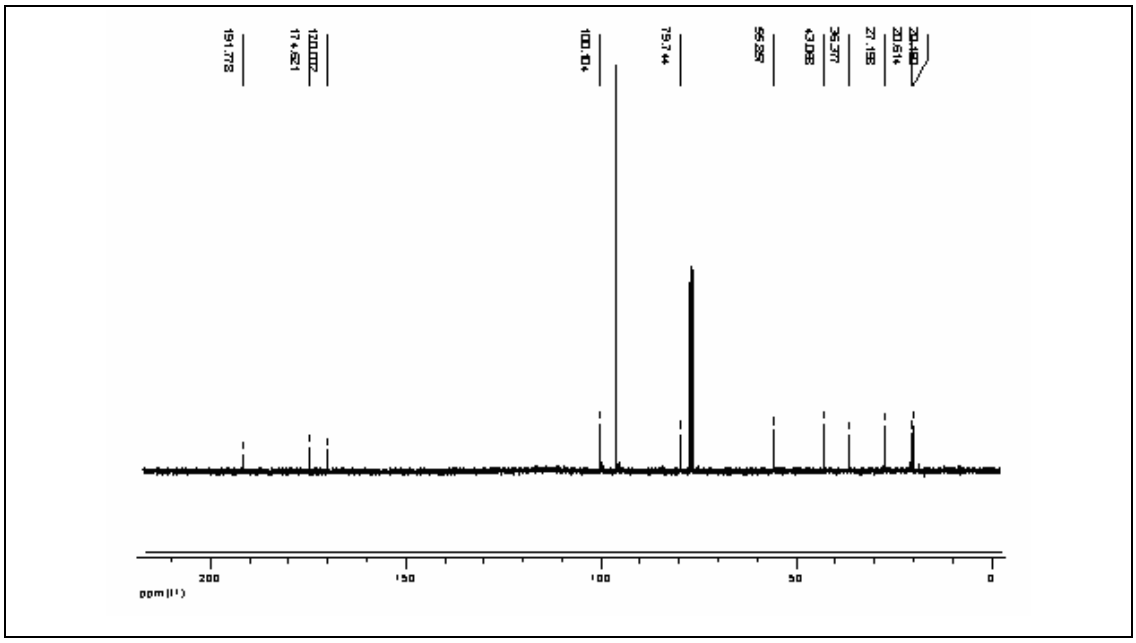


Figure 4.11. C^{13} NMR spectrum of 6-acetoxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one **(30)**

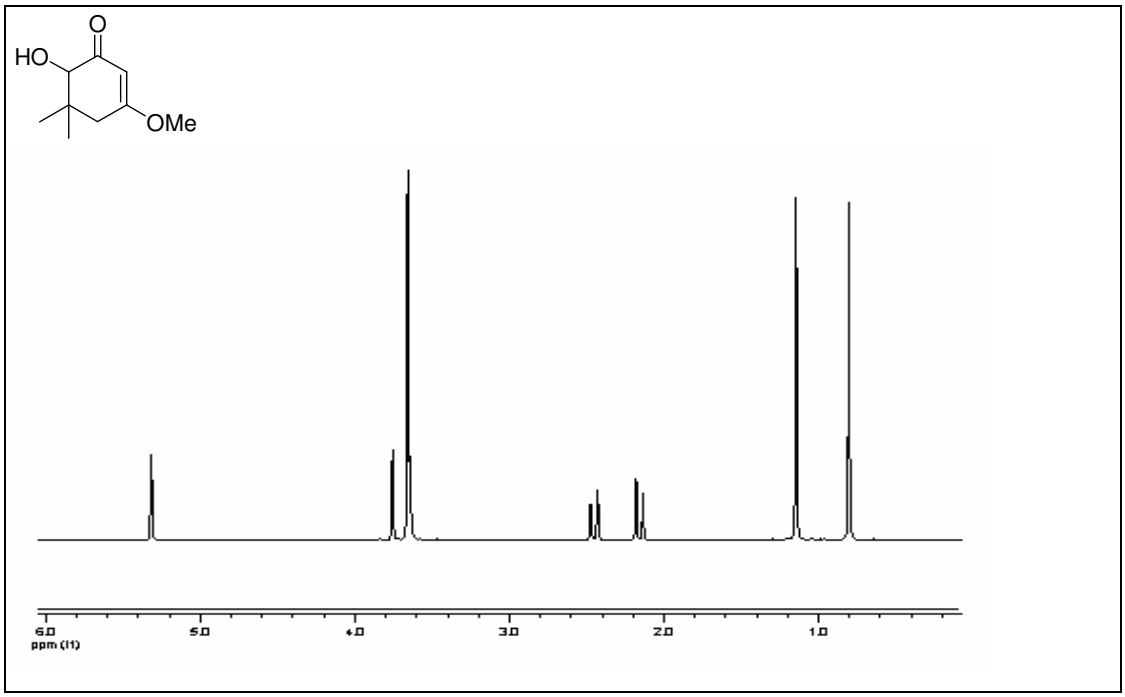


Figure 4.12. H^{13} NMR spectrum of (-)-6-hydroxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one (-)-34

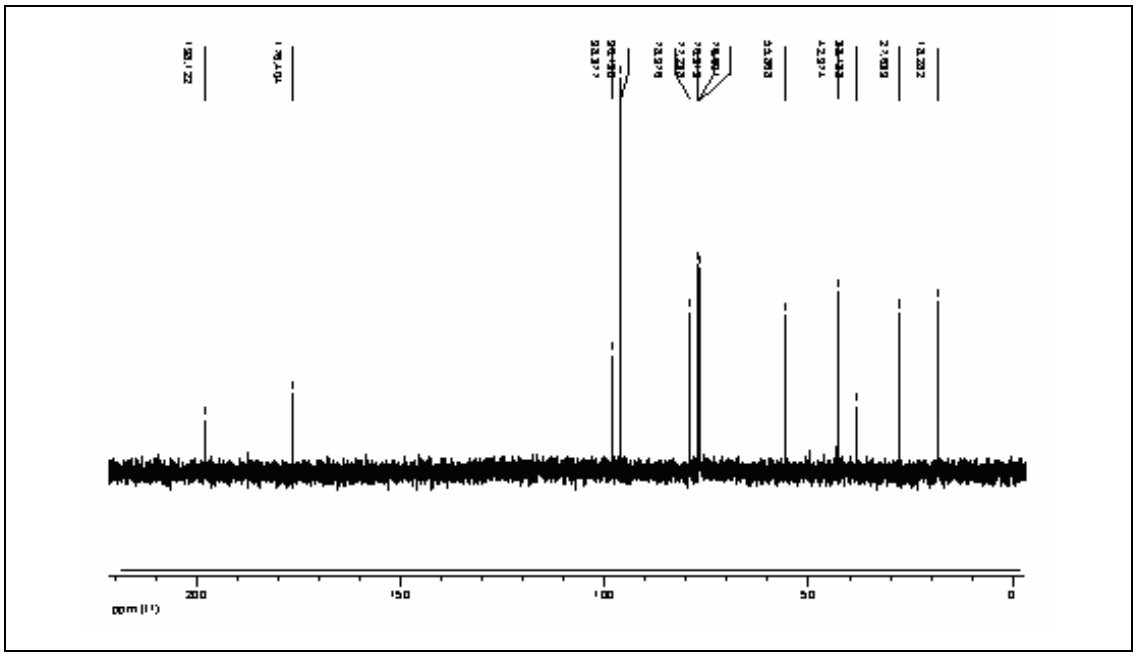


Figure 4.13. ^{13}C NMR spectrum of (-)-6-hydroxy-5,5-dimethyl-3-methoxycyclohex-2-en-1-one

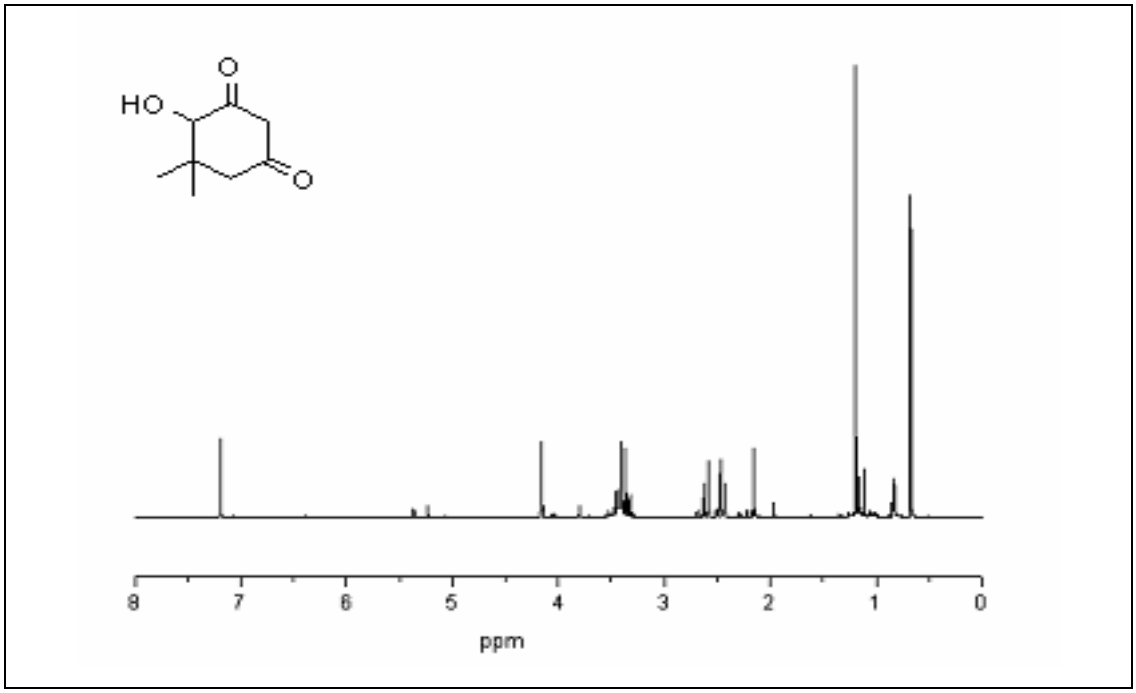


Figure 4.14. H^{13} NMR spectrum of 5,5-dimethyl 6-hydroxy-1,3-siklohekzandione **(36)**

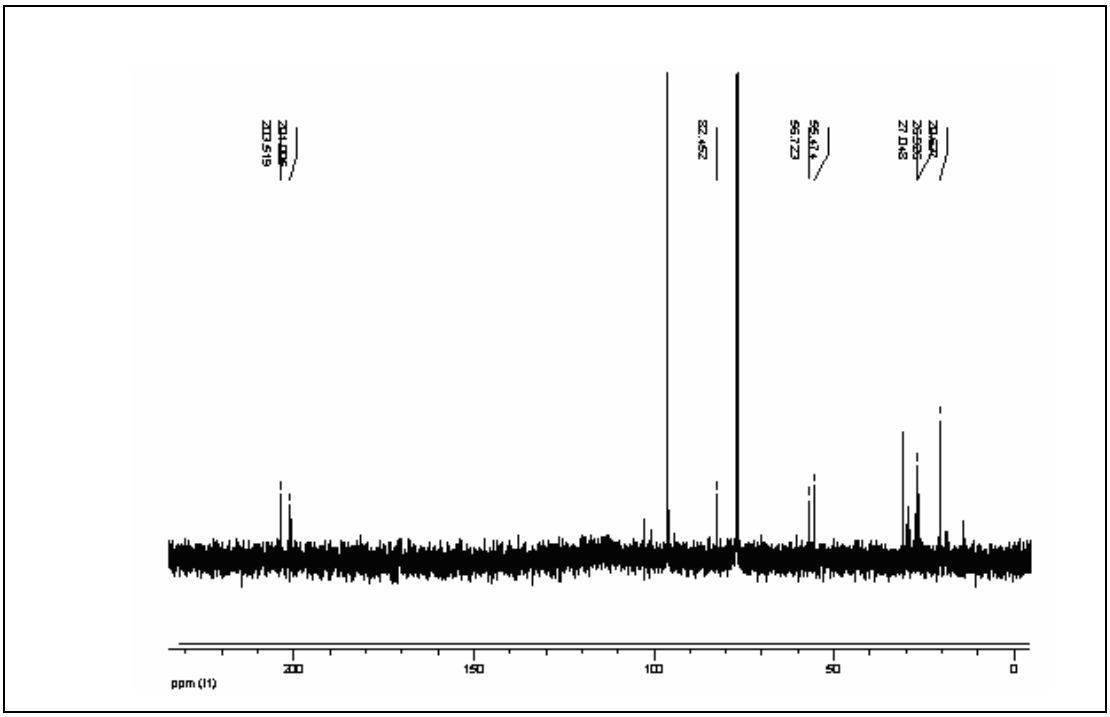


Figure 4.15. C^{13} NMR spectrum of 5,5-dimethyl 6-hydroxy-1,3-siklohekzandione **(36)**

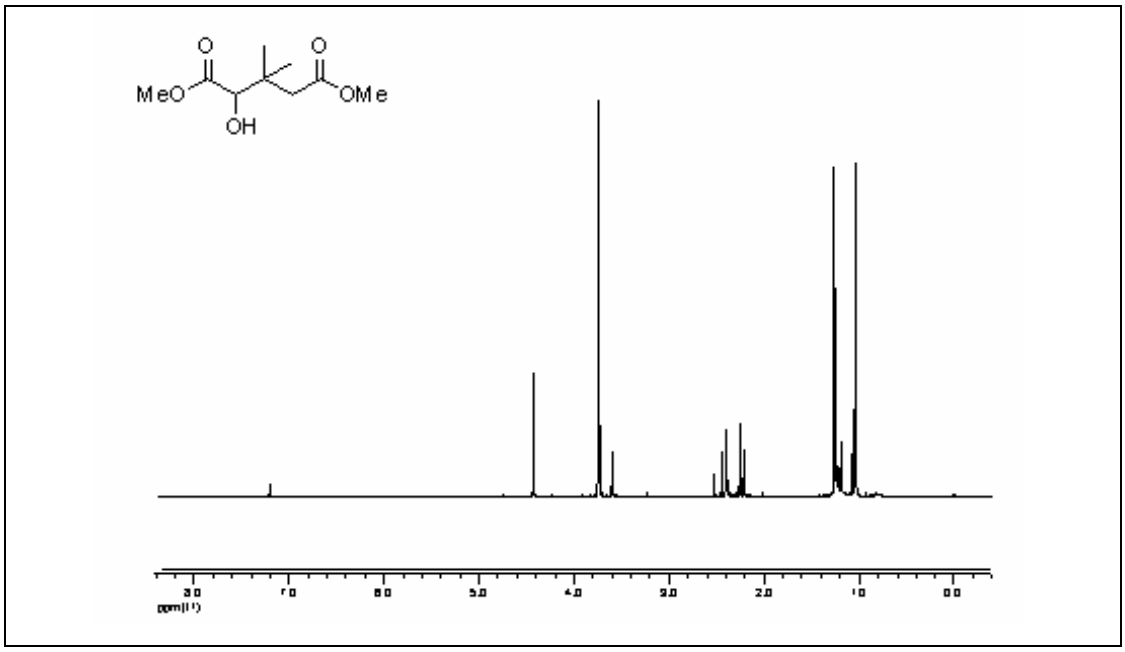


Figure 4.16. H^{1} NMR spectrum of dimethyl-2-hydroxy-3,3-dimethyl-pentandioate **(39)**

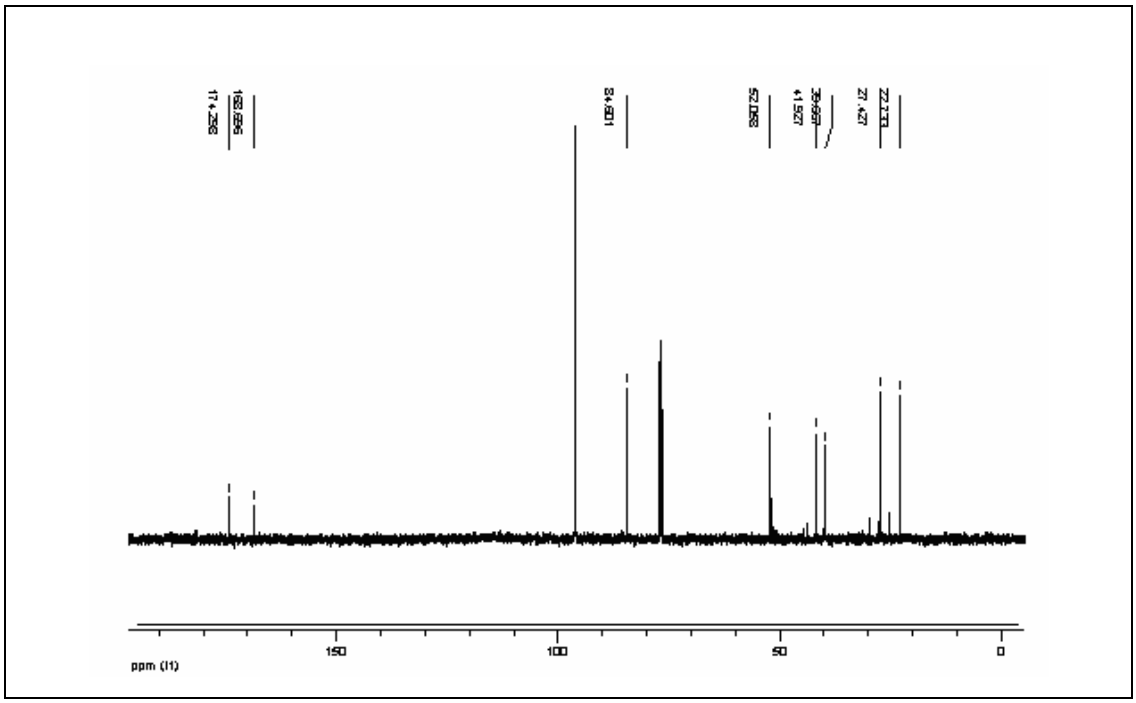


Figure 4.17. C^{13} NMR spectrum of dimethyl-2-hydroxy-3,3-dimethyl-pentandioate **(39)**

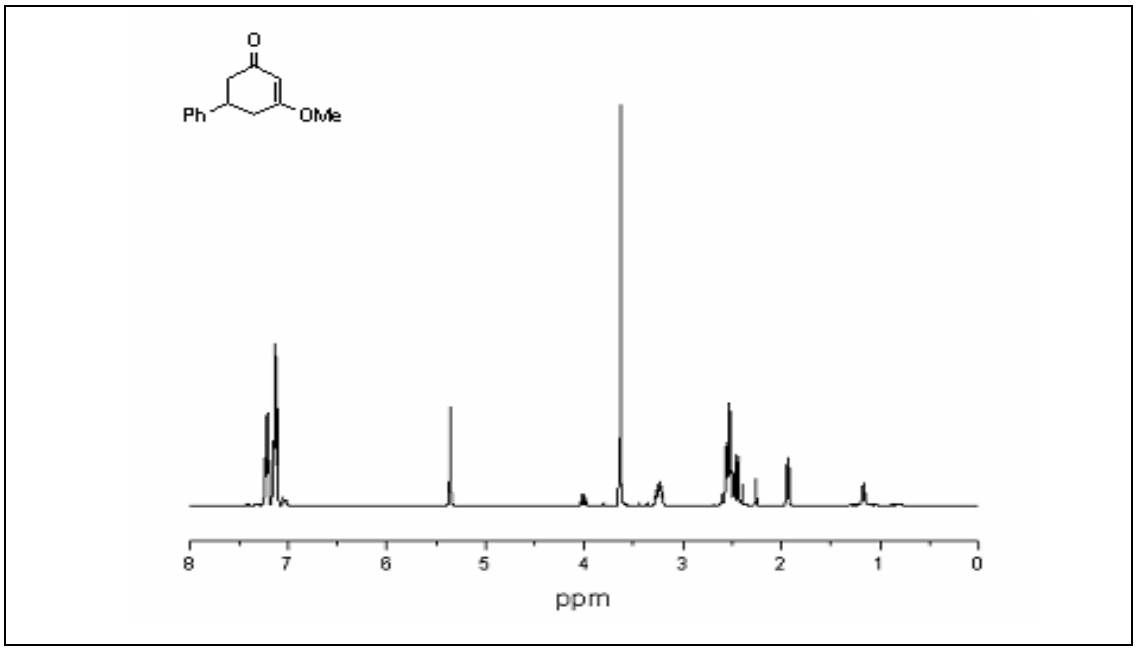


Figure 4.18. H^{1} NMR spectrum of 5-phenyl-3-methoxycyclohex-2-en-1-one **(28)**

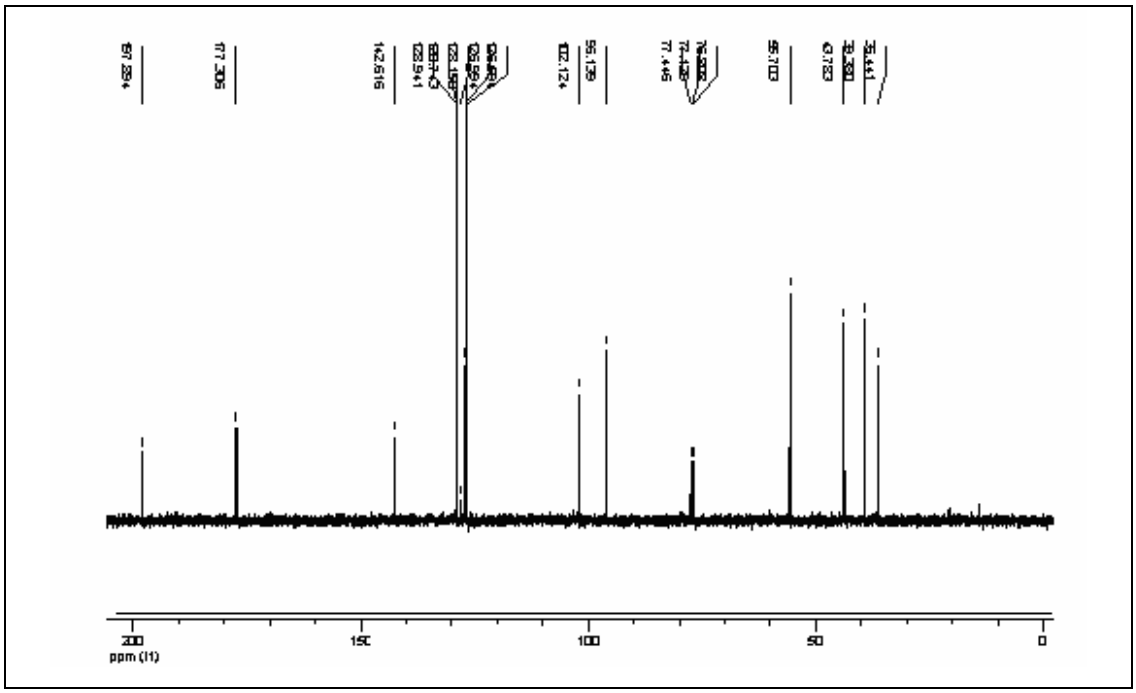


Figure 4.19. C^{13} NMR spectrum of 5-phenyl-3-methoxycyclohex-2-en-1-one **(28)**

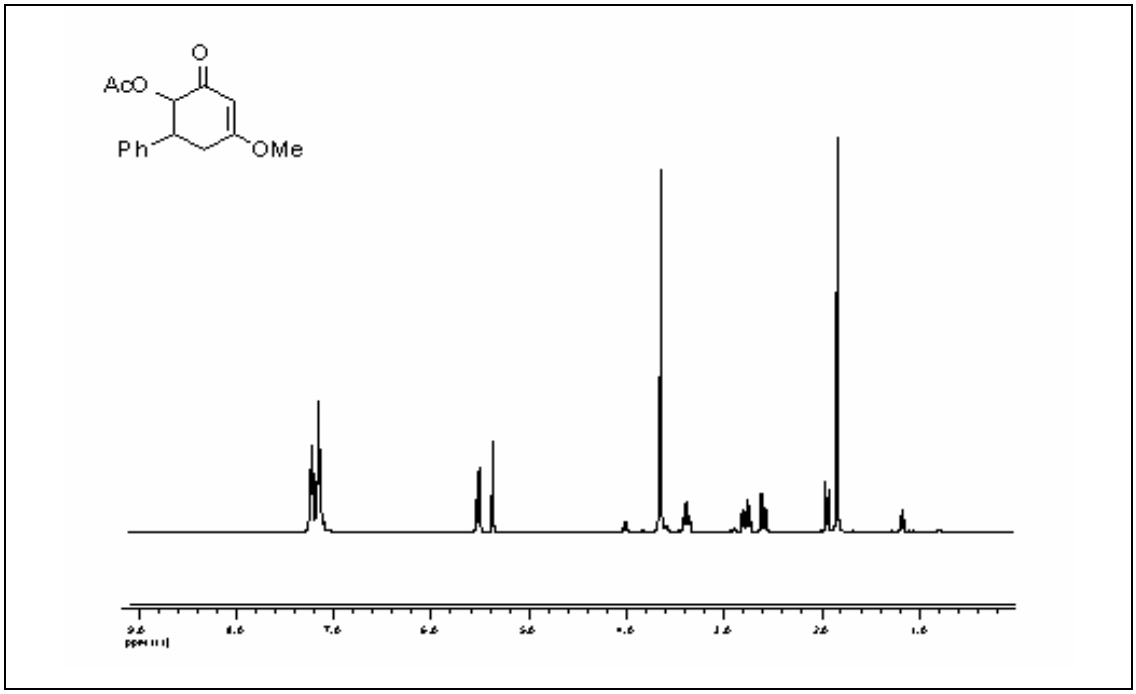


Figure 4.20. H^{1} NMR spectrum of 5-phenyl-6-acetoxy-3-methoxycyclohex-2- en-1-one **(31)**

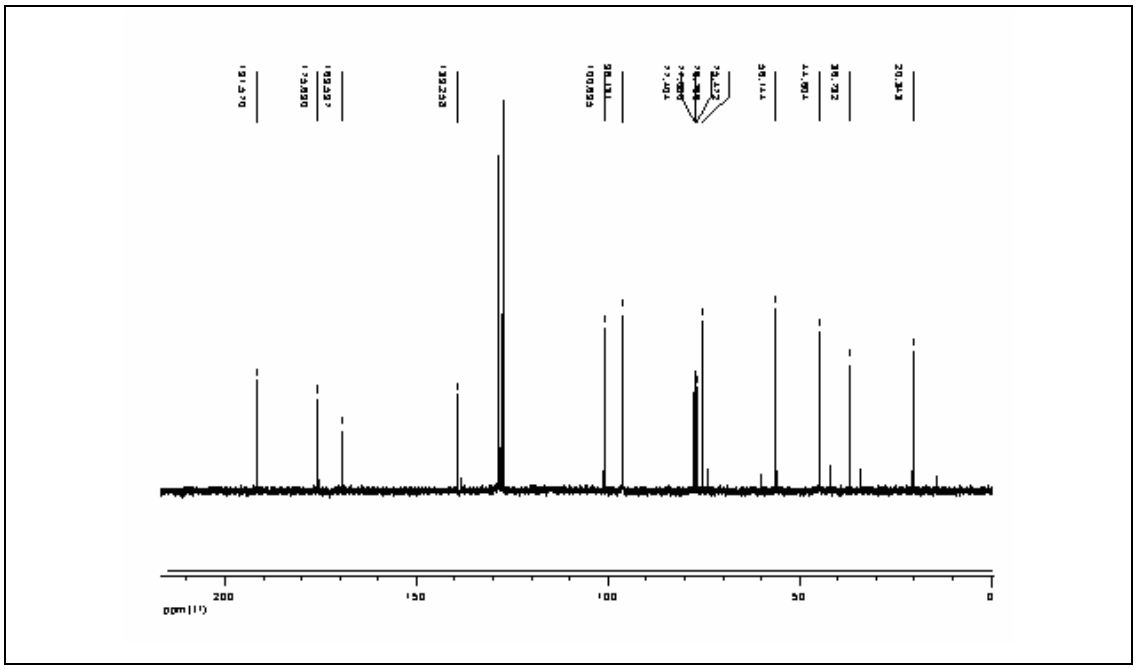


Figure 4.21. C^{13} NMR spectrum of 5-phenyl-6-acetoxy-3-methoxycyclohex- 2- en-1-one **(31)**

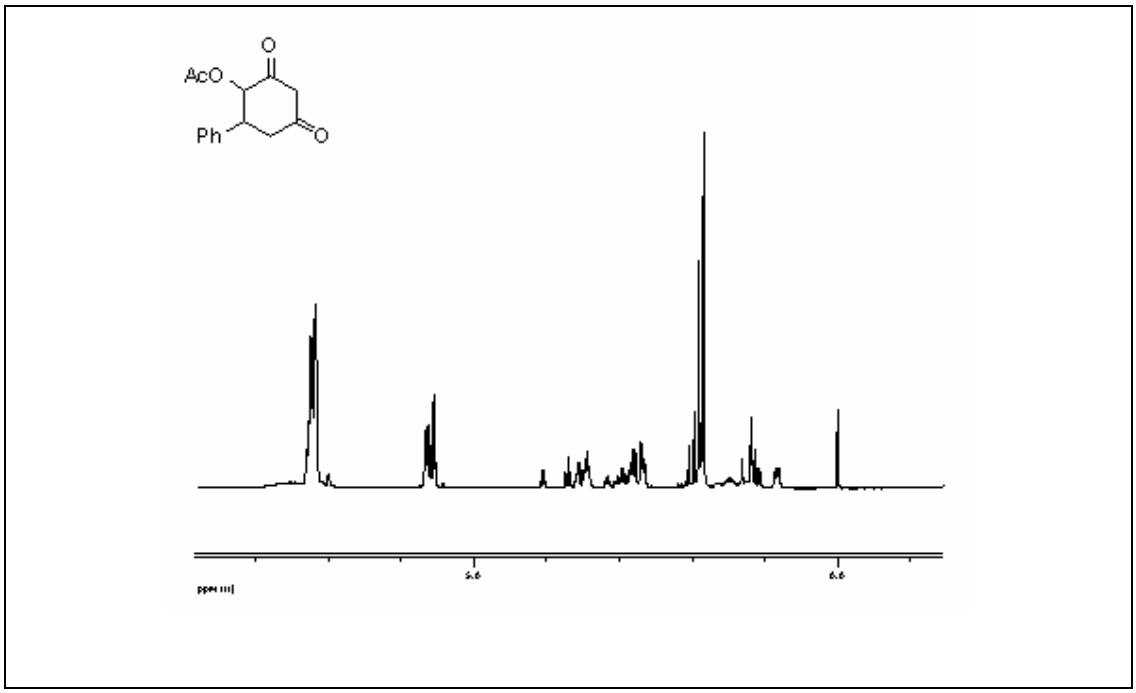


Figure 4.22. H^{1} NMR spectrum of 5-phenyl-6-acetoxy-1,3-cyclohexanedione **(37)**

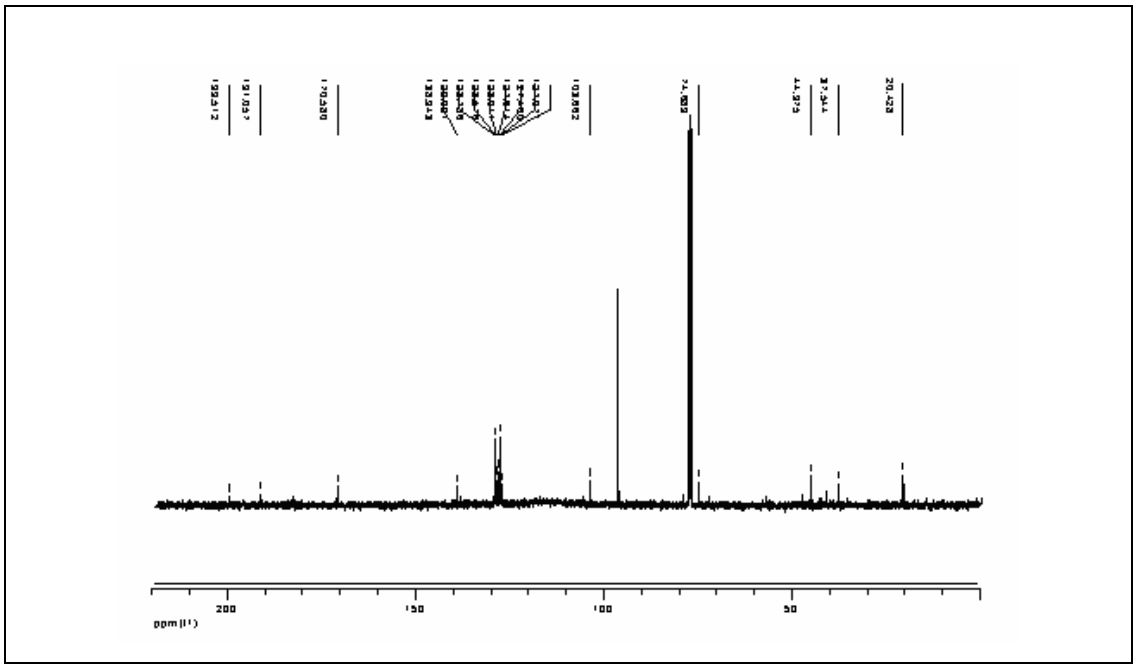


Figure 4.23. ^{13}C NMR spectrum of 5-phenyl-6-acetoxy-1,3-cyclohexanedione **(37)**

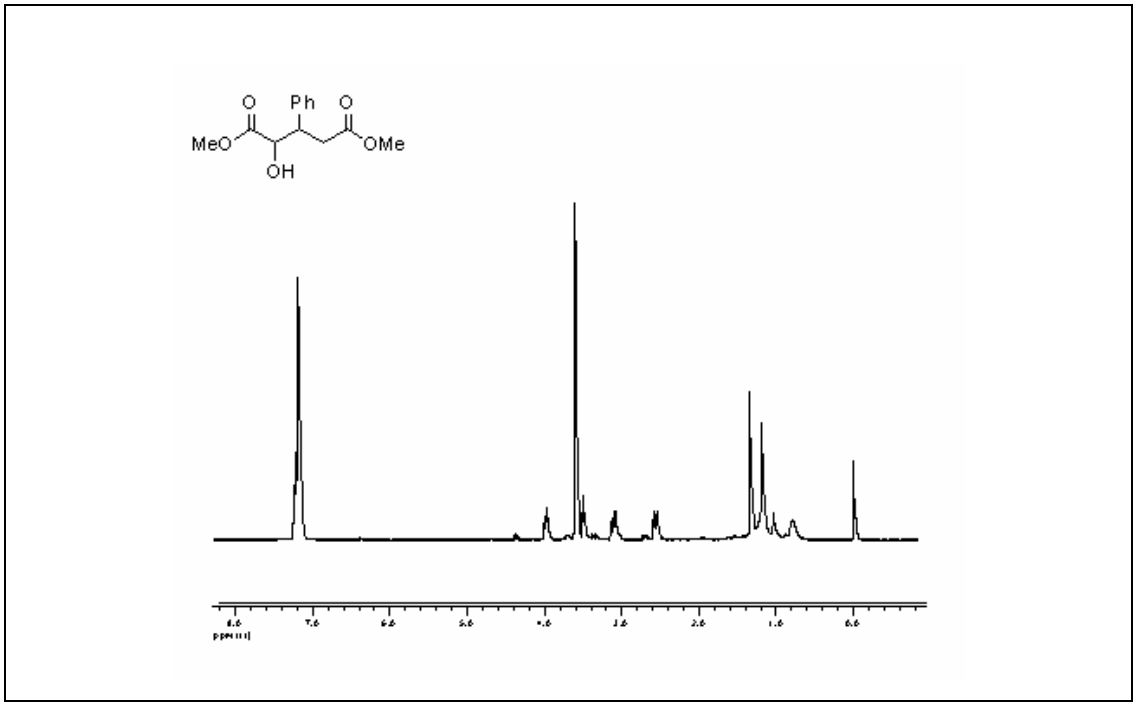


Figure 4.24. H^1 NMR spectrum of dimethyl-2-acetoxy-3-phenyl-pentandioate **(40)**

REFERENCES

[1]-Kyung-Ho, P.; Linda, J. *Tet. Lett*. **2003**, *44,*1067.

[2]- Marzinzik, A.; Felder, E. *Tet. Lett*. **1996** , *37,* 1003.

[3]- Frank, L.; Hall, K. *Monocyclic terpenes from cyclic 1,3-diketones*, **1950**.

[4]- Banerjee, B.; Mandal, S. K.; Roy, S. C. *Chemistry Letters*. **2006**, *35*, 16.

[5]- Chen, B.; Weismiller, M. C.; Davis, F. *Tetrahedron,* **1991**, *47,* 173.

[6]- Chandrasekhar, B.; Ramadas, S. R.; Ramana, D. V. *Tetrahedron,* **2000**, *56*, 5947.

[7]- Gower, T. L.; Graham, B. S., *Antimicrobial Agents and Chemotherapy* **2001**, *45*, 1231.

[8]- Endo, A.; Kuroda, M.; Tsujita, Y. *J Antibiot (Tokyo)* **1981,** *34*(5), 614.

[9]- Demir, A. S.; Şeşenoğlu, Ö. *Organic Letters* **2002**, *4*, 2021.

[10]- Dauban, P.; Saint-Fuscien, C.; Acher, F.; Preazeau, L.; Brabet, I.; Pin, J.; Dodd, R. H. *Bioorganic and medicinal chemisry letters,* **2000**, *10*, 129.

[11]- Tavassoli, A.; Duffy, J. E. S.;Young, D. W. *Tet. Lett,* **2005,** *46,* 2093.

[12]- Uenishi, Junichi; Masuda, Souichiro; Wakabayashi, Shoji. *Tet. Lett,* **1991,** *32,* 5097.

[13]- Mitchinson, A.; Blackaby, W. P.; Bourrain. S.; Carling, R. W.; Lewis, R. T., *Tet. Lett*. **2006**, *47,*2257.

[14]- Demir, A. S.; Sayrac, T.; Watt, D. S. *Synthesis* **1990,** 1119.

[15]- Demir, A. S.; Akgun, H.; Tanyeli, C.; Sayrac, T.; Watt D. S., *Synthesis* **1991,** 719.

[16]- Demir, A. S.; Jeganathan, A. *Synthesis* **1992,** 235.

[17]- Demir, A. S.; Alwarsamy, J.; Watt, D. S. *J. Org. Chem.* **1989,** *54,* 4020.

[18]- Demir, A. S.; Emrullahoğlu, M. *Current organic synthesis* **2007***, 4*, 321.

[19]- Sheehan, J.C.; O'Neill R.C.; White M.A. *J.Am.Chem.Soc*. **1950**, *72*, 3376.

[20]- Bumgardner, C. L.; Bunch, J. E.; Whangho, M. *J. Org. Chem.* **1986**, *51*, 4083.

[21]- Ojima, I. *Catalytic Asymmetric Synthesis,* VCH Publishers, **1993**.

[22]- Caddic, S.; Jenskins, K. *Chem. Soc. Reviews* **1996**, *25*, 447.

[23]- Gala, D., Dibenedetto, D. J., Clark, J. E:, Murphy, B. L., *Tetrahedron Asymmetry*, **1996**, *7*, 2207.

[24]- Demir, A. S.; Aybey, A.; Polat, F.; Şeşenoğlu, Ö., *Tetrahedron Asymmetry* **2003,** *14*, 1489.

[25]- Demir, A. S.; Hamamcı, H.; Tanyeli, C.; Doğanel, F.; Mecidoğlu, İ. A. *Tetrahedron Asymmetry* **1998**, *9*, 1673.

[26]- Waldemar, A.; Diaz, M. T.; Rainer, T.; Chantu, R. *Tetrahedron Asymmetry* **1996,** *7,* 2207.

[27]- Wassermann, H. H.; Han, W. T. *Tetrahedron Lett.* **1984***, 25,* 3743.

[28]- Yan, J.; Travis, B. R.; Borhan, B. *J .Org. Chem* **2004***, 69,* 9299.

[29]- Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tet. Lett.* **1994**, *35*, 6089.

[30]- Mahdi, M.; Espenson, A-O,; Espenson, J. H. *Organometallics* **1996**, *15*, 3543.

[31]- Bryant, R. J.; McDonald, E. *Tet. Lett.* **1975,** *44*, 3842.

[32]- Wolfrom, M. L.; Bobbitt, J. M. *Contribution from the Departmen of Chemistry of the Stete University* **1955**.

[33]- Travis, B. R.; Sivakumar, G. O.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003,** *5*, 1031.

[34]- Grogan, G. *Biochem.J Review Article* **2005,** *388*, 721.

[35]- Demir, A. S.; Şeşenoğlu, Ö. *Organic Letters* **2002**, *4*, 2021.

[36]- Clerici, A.; Pastori, N,; Porta, O. *Tetrahedron* **2001,** *57*, 217.