SYNTHESIS AND ENZYMATIC RESOLUTION OF VARIOUS CYCLOPENTENOID AND CYCLOHEXENOID TYPE COMPOUNDS

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

BY

ÇİĞDEM İYİGÜN

IN PARTIAL FULFILLMENT OF THE REQUIREMENT
FOR
THE DEGREE OFDOCTOR OF PHILOSOPHY
IN
CHEMISTRY

JUNE 2005

Approval of the Graduate School of Natural And Applied Sciences

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ABSTRACT

SYNTHESIS AND ENZYMATIC RESOLUTION OF VARIOUS CYCLOPENTENOID AND CYCLOHEXENOID TYPE COMPOUNDS

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The aim of this thesis is to synthesize enantiomerically enriched cyclopentenoid and cyclohexenoid type of compounds with quaternary carbon stereocenters that are the simplest precursors of the complex natural products. The first part of the study involves the preparation of α'-acetoxy α'-substituted α,β-unsaturated cyclic ketones. Methylation, ethylation, benzylation and allylation of cyclohexenone and cyclopentenone derivatives are performed. Then, these compounds are regioselectively oxidized at the α'-position by $Mn(OAc)_3$. This is the first successful example in the literature that α'-*tert*-position is oxidized by $Mn(OAc)_3$. The oxidations were also performed by $Pb(OAc)_4$ and both methods were compared. Related to this study, in the second part, the enantiomeric resolution of the acetoxy derivatives were performed by various hydrolases. This study is the first example where the hydrolases are used to resolve tertiary positions. Among the enzymes used, Candida *cylindracea* lipase (CCL) showed the best enantioselectivity.

Key words: $Mn(OAc)_3$ oxidation, $Pb(OAc)_4$ oxidation, enzymatic resolution.

ÖZ

ÇEŞİTLİ SİKLOPENTENOİD VE SİKLOHEKZENOİD TİPİ BİLEŞİKLERİN SENTEZİ VE ENZİMATİK REZOLÜSYONU

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Haziran 2005, 174 sayfa

Bu tezin amacı, komplike doğal ürünlerin basit başlangıç maddeleri olan enantiyomerce zenginleştirilmiş kuaterner stereomerkezli siklopentenoid ve siklohekzenoid tipi bileşiklerin sentezlenmesidir. Çalışmanın ilk bölümü α'-asetoksi α'-sübstitüe α,β-doymamış siklik ketonların sentezini içerir. Siklopentenon ve siklohekzenonların metilleme, etilleme, benzilleme ve alillemesi gerçekteştirilmiştir. Bu bileşikler daha sonra α'-konumlarında rejioseçici olarak yükseltgenmiştir. Bu çalışma, kimya yazınında ilk defa α'-tersiyer pozisyonun $Mn(OAc)_3$ ile yükseltgenmesini içerir. $Pb(OAc)_4$ ile de yükseltgemeler yapılmış ve bu iki metod karşılaştırılmıştır. Bu çalışma ile bağlantılı olarak, ikinci kısımda, bu asetoksi türevlerinin enantiyomerlerine ayrıştırılması çeşitli hidrolaz tipi enzimlerle gerçekleştirilmiştir. Hidrolaz tipi enzimler ilk defa tersiyer pozisyonların hidrolizi için kullanılmıştır. Kullanılan enzimler arasında en iyi enantiyoseçiciliği Candida *cylindracea* lipaz (CCL) göstermiştir.

Anahtar kelimeler: $Mn(OAc)_3$ yükseltgemesi, $Pb(OAc)_4$ yükseltgemesi, enzimatik rezolüsyon.

To My Family

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my supervisor Prof. Dr. Cihangir Tanyeli for his guidance, suggestions and encouragement throughout the research with great patience.

I would also like to thank Prof. Dr. İdris M. Akhmedov for his helpful suggestions.

In addition, I would like to express my thanks to METU Organic Chemistry Research group, my lab mates and my friends for their help, friendship and cooperation. I thank to Bengü Sezen for acquiring Mass Spectra.

Finally, I would like to thank to my grandmother, my father and my fiance Timur for their endless love, encouragement, patience during the research and in all times of my life.

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LIST OF ABBREVIATIONS

DMSO: Dimethyl Sulfoxide

PLE: Pig Liver Esterase

PPL: Porcine Pancreatic Lipase

CCL: Lipase from *Candida Rugosa*

HLE: Horse Liver Esterase

HMPA: Hexamethylphosphoric triamide

THF: Tetrahydrofuran

CHAPTER 1

INTRODUCTION

1.1 Chirality and Its Consequences

The origin of the discovery of the role of stereochemistry in biochemical environments goes back to the late 1850's, when Pasteur reported about the different destruction rates of *dextro* and *levo* ammonium tartrate by the mold *Penicillium glaucum*. In the conclusion of his observations, Pasteur wrote: "*Most natural organic products, the essential products of life, are asymmetric and possess such asymmetry that they are not superimposable on their images.,,* [1]

The term Chiral is derived from the Greek name "cheir" meaning "hand" and apparently was first used by Lord Kelvin in 1904, in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light in which he stated: *"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself,,* [2]

Chiral molecules hold a central position in stereochemistry not only because they are more widespread than achiral molecules, but also enantiomerically pure compounds play an important role in the chemistry of living organisms.

"Chiral stereochemistry" deals with chiral molecules in nonracemic form, *i.e*., with molecules whose enantiomeric purity differs from zero, in other words, with

optically active molecules. However, the term “optical activity” is more restricted of only one method, *e.g*., measurements of rotation of the polarization plane, whereas other methods for evaluating the enantiomeric purity are also available. The chirality has a clear mathematical basis and is not associated with a particular method of investigation. The term “chirality” alone ensures only that the object (molecule) is non-superimposable with its mirror image. A slight deviation from the exact meaning of this term is acceptable with reverse of nonracemic molecules. One must strictly distinguish between the cases when the term “chiral” means actually “optically active” (“enantiomeric”) and when it is used in its own original sense.

The first half of the 20^{th} century was marked by discoveries and investigations of new reactions applicable, in principle, to optically active compounds as well as by isolation of new natural compounds. The stereoselective synthesis of natural compounds was an important problem organic chemists had to face. Since many compounds are optically active and their molecules often bear more than one asymmetric center, chemists considered it the matter of honor to synthesize natural enantiomers with as high optical purity as possible. In the case of compounds exhibiting pronounced biological activities, one of the goals was to prepare non-natural stereoisomers as well. These studies played an important role in the development of the organic synthesis [3].

Among the bioactive synthetic compounds, most of the chiral drugs are administered as racemates, despite the fact that the optical isomers of a racemic drug can exhibit different pharmacological profiles in living systems. These differences can be expressed in *e.g*. the affinity of the enantiomers for certain receptor subtypes or enzymes distribution rates, their metabolism and excretion, in antagonistic actions relative to each other, or their toxicological properties. Obviously, the more chiral centers present in a (drug) molecule, the more complex the situation becomes. To ensure the desired optimum therapeutic effect it appears convenient to administer the enantiomer. However, applying a single enantiomer to humans does not necessarily prevent side-effects or tissue/organ damage, since, among others, the formation of harmful metabolites, as well as chiral inversion or racemization, can occur *in vivo* [4].An example of a chiral inversion without negative side effects is ibuprofen,

where the inactive (*R*)-(–)-isomer is converted by an enzymatic mechanism into the active (*S*)-(+)-form. The (*R*)-isomer can be considered a prodrug of its (*S*)-enantiomer. A negative example is thalidomide, which was introduced to the market in the late 1960's as a sedative, in the racemic form. Even when applied in the therapeutic and harmless (+)-form, the *in vivo* interconvertion into the harmful (–)-isomer was shown to be responsible for the disastrous malformations of embryos when thalidomide was applied to women during pregnancy. However, there was also one drug reported, the diuretic indacrinon, where the presence of the distomer was useful, since it promoted the efficacy of the therapeutic eutomer by antagonizing one of its side-effects. In addition to creating a general awareness, the thalidomide drama called out for stricter controls and the reconsideration of the approval guidelines for newly developed drugs. To protect patients from unwanted "isomeric ballast" and side effects, the possibility of a different action of the individual enantiomers with regard to pharmacology and toxicology had to be taken into account [5].

Drug synthesis has an important place in the worldwide market. As a consequence, issues related to chirality have gradually pervaded chemical research. This background is to be kept in mind when appreciating the importance of chirality, whether in science or in everyday life. However, this is not the only field where processes of this kind are being developed. Tastes and smells may also depend on enantiomers which raises the importance of chirality in the food flavoring and perfumery industries. Degradation of the agrochemicals may be easier or harder dependent upon which enantiomer of the chemical substance is used. Due to the growing concern about environmental aspects in modern society, this branch of industry has an increasing need for enantioselective processes in the preparation of their products [6].

1.2 Asymmetric Synthesis

This method involves the introduction of chirality by the action of a chiral reagent, auxiliary, or catalyst that is not incorporated in the final product. During the last few decades a variety of asymmetric transformations have been developed [7,8].

The cascade of asymmetric synthesis started with the study of diastereoselectivity in reactions of chiral compounds, continued with the synthesis of enantiomerically pure compounds through auxiliary-based methods and with asymmetric catalysis. In the former case, diastereomeric mixtures ensue, and an analytical technique such as chromatography is used for isomer purification. In the latter instance, enantiomers are the products and chiral stationary phases can be used for chromatographic purification. Furthermore, many methods that generate numerous stereocenters in a single step have been developed. Highly selective reactions that produce one or more stereocenter with a high degree of selectivity via modern purification techniques, allow the preparation – in a single step – of chiral substances with an enantiomeric excess greater than 98% for many type of reactions [9].

1.3 Methods to Achieve Asymmetric Synthesis

To do an enantioselective synthesis, at least one of the agents in the system must be chiral. There are two major methods to achieve this goal: resolution and asymmetric synthesis, which makes use of a chiral starting material, a chiral auxiliary or a chiral reagent.

1.3.1 Chiral Entities

Before embarking on a synthesis, the question how a chiral center can be created should be taken into consideration. The three major methods are the use of a chemically or biologically based chiral reagent [10], the use of chiral environment [11] or chiral auxiliary [12], and the use of a chiral starting material [13].

1.3.2 Chiral Substrates

The best scenario is to have a chiral starting material which can control the stereoselection of the reaction itself. Nature produces chiral materials and a number of these are available in excess [14,15]. These compounds make up the "chiral pool". If all of the parameters are favorable, this approach is the method of choice as it has the potential to eliminate resolutions or the necessity for an enantiospecific transformation in the synthetic design.

The chiral pool is not a stagnant pond. As enzymes and reagents are discovered and developed, they can be applied to provide large quantities of useful chiral starting materials.

1.3.3 Chiral Auxiliries

This class of compound modifies the substrate molecule by the creation of a stereogenic center and has an asymmetric type of influence on the outcome of a reaction. The auxiliary which will initially attach to the substrate should be finally detached. Although this method involves two steps, if required concurrent protection of sensitive functionality can also take place. This protection and deprotection steps make the overall sequence inefficient.

1.3.4 Self Regeneration of Stereocenters

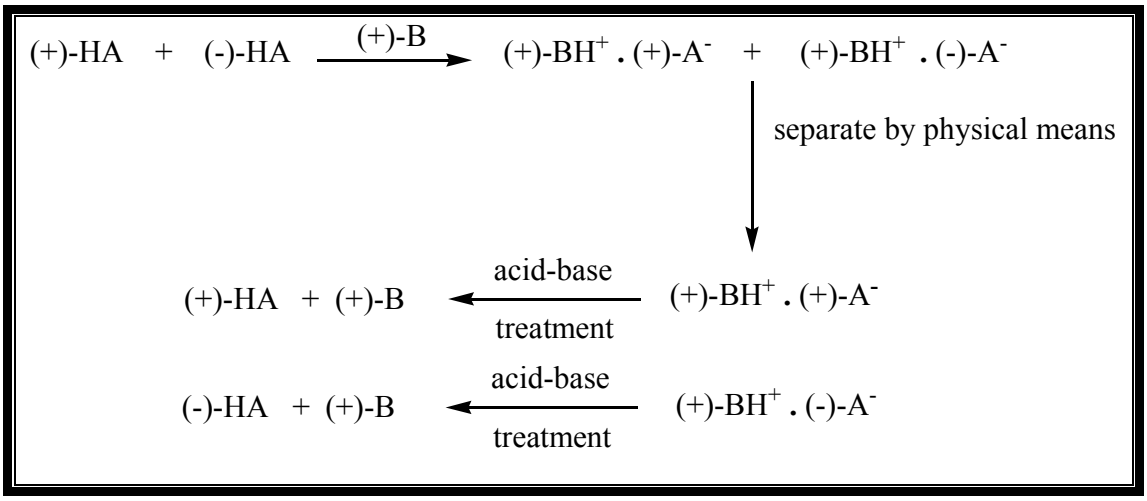
One particular chiral center can be transferred to another part of the molecule. This new chiral center then provides control for a stereoselective reaction, where a new center of asymmetry can be established, or the chirality at the center of the original starting material can be reestablished [16].

1.3.5 Chiral Reagents

Chiral reagents allow for the transfer of chirality from the reagent to the prochiral substrate. Almost all of these reactions involve the conversion of an sp^2 carbon to an sp^3 center. For example, reductions of carbonyl compounds, asymmetric hydrogenations, and asymmetric oxidations of alkenes are all of this type.

1.4 Resolution

Resolution and chirality are twins born when Louis Pasteur separated crystals of D- and L-tartaric acid salts on microscopic scale. Since then, the separation of each enantiomer from the racemic mixture has been the primary way to synthesize optically active organic compounds. Only recently, the fast and explosive new developments in asymmetric synthesis involving the use of organometallic catalysts, enzymes, and chiral auxiliaries have begun to challenge the resolution approach. Through many years of evolution, the art of resolution has become a multidisciplinary science that includes diastereomeric, kinetic, dynamic, chromatographic, enzymatic components. To effect a resolution, the compound must contain a functional group that can interact or react with another chiral agent to produce diastereomers. These diastereomers can then be separated by physical means. The resolution agent then needs to be removed from the subject material. Thus, two extra chemical steps may be necessary to use the resolution agent. In addition, as only 50% of a racemic mixture can be desired isomer, recovery is, at the very best, 50%. This destracts from the method. However, if the compound under investigation is an acid or a base, then it may be possible to form a salt that can be separated, although many factors can still affect the success of the approach (Scheme 1) [17-21].



Scheme 1. The Resolution

1.4.1 Kinetic Resolution

In this approach a substrate is acted on by a chiral agent to produce one enantiomer or diastereomer of the product at a much faster rate than the other isomer [22]. Kinetic resolution may be realized by chemical or enzymic methods; in the former case the reaction may be either catalytic or stoichiometric with respect to the optically active auxiliary; from an economic standpoint catalysis is obviously preferred. Kinetic resolutions and high e.e values are more commonly found with enzymic processes than chemical ones.

1.5 Enzymes

Enzymes are proteins that catalyze most biological reactions *in vivo*, and catalyze reactions involving both natural and unnatural substrates *in vitro*. As catalysts, enzymes accelerate the rate of reactions, and operate under mild conditions. They can be highly selective for substrates and stereoselective in reactions they catalyze, selectivity can range from very narrow to very broad. Their catalytic activity may be strongly influenced by the concentrations of substrates,

products or other species present in solution. They normally catalyze reactions under the same or similar conditions. Since enzymes are chiral, they can show high enantiodifferentiation. However, they are generally unstable (relative to man-made catalysts) [23].

The use of biocatalysis for industrial synthetic chemistry is on the verge of significant growth. Biocatalytic processes can now be carried out both in organic solvents and in aqueous environments, so that nonpolar organic compounds as well as water-soluble compounds can be modified selectively and efficiently with enzymes and biocatalytically active cells. As the use of biocatalysis for industrial chemical synthesis becomes easier, several chemical companies have begun to increase significantly the number and sophistication of the biocatalytic processes used in their synthesis operations [24].

Since the catalytic activities of enzymes are sensitive to reaction conditions, it is very often necessary to determine the kinetic parameters under the synthetic conditions being used (or as close to these conditions as possible) to obtain the best performance. There are many ways to determine kinetic parameters, and most begin by measuring initial velocities at various concentrations of substrates while maintaining pH, enzyme concentration, volume of cosolvent, etc. constant.

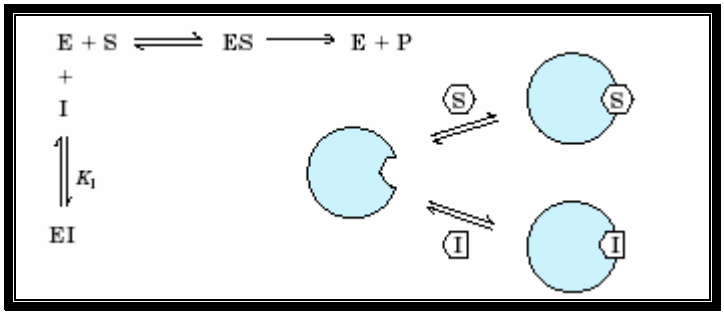
1.5.1 Enzyme Inhibition

Enzyme inhibition is decrease in catalytic activity of an enzyme as a result of a change in reaction conditions (i.e., pH, temperature, concentration of substrate or product, etc.).These conditions can cause conformational changes, blocking of active sites, or unfolding of the enzyme. Inhibition can also be reversible or irreversible.

1.5.1.1 Reversible Inhibition

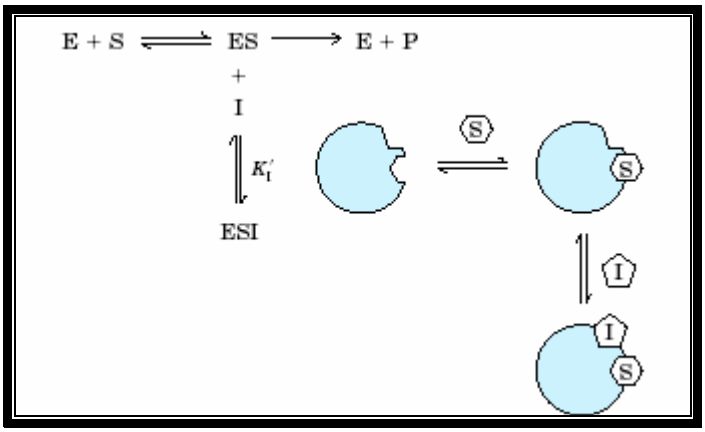
Reversible inhibition is divided into three types:

-Competitive Inhibition: competes with the substrate for the active site of an enzyme. (Scheme 2) While the inhibitor (I) occupies the active site it prevents binding of the substrate to the enzyme. Many competitive inhibitors are compounds that resemble the substrate and combine with the enzyme to form an EI complex, but without leading to catalysis. Even fleeting combinations of this type will reduce the efficiency of the enzyme. By taking into account the molecular geometry of inhibitors that resemble the substrate, we can reach conclusions about which parts of the normal substrate bind to the enzyme.



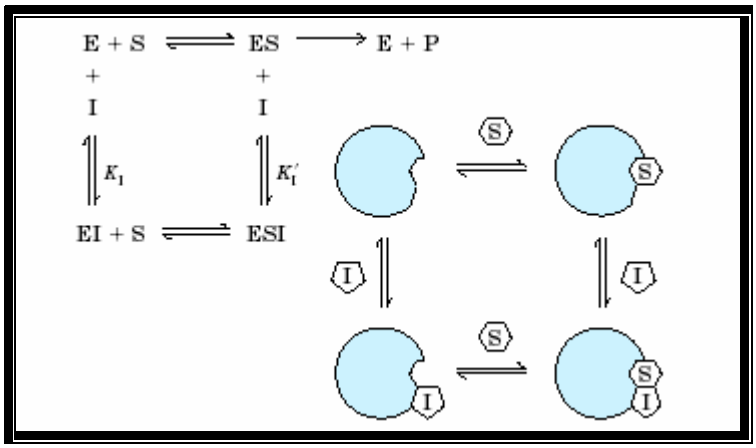
Scheme 2. Competitive Inhibition

-Uncompetitive Inhibition: Inhibitor binds at a site distinct from the substrate active site and, unlike a competitive inhibitor, binds only to the ES complex. (Scheme 3)



Scheme 3. Uncompetitive inhibition

-Mixed Inhibition: Inhibitor binds at a site distinct from the substrate active site, but it binds to either E or ES. (Scheme 4)



Scheme 4. Mixed inhibition

1.5.1.2 Irreversible Inhibition

The **irreversible inhibitors** are those that bind covalently with or destroy a functional group on an enzyme that is essential for the enzyme's activity, or those that form a particularly stable noncovalent association. Formation of a covalent link between an irreversible inhibitor and an enzyme is common. Irreversible inhibitors are another useful tool for studying reaction mechanisms. Amino acids with key catalytic functions in the active site can sometimes be identified by determining which residue is covalently linked to an inhibitor after the enzyme is inactivated.

1.6 Specificity

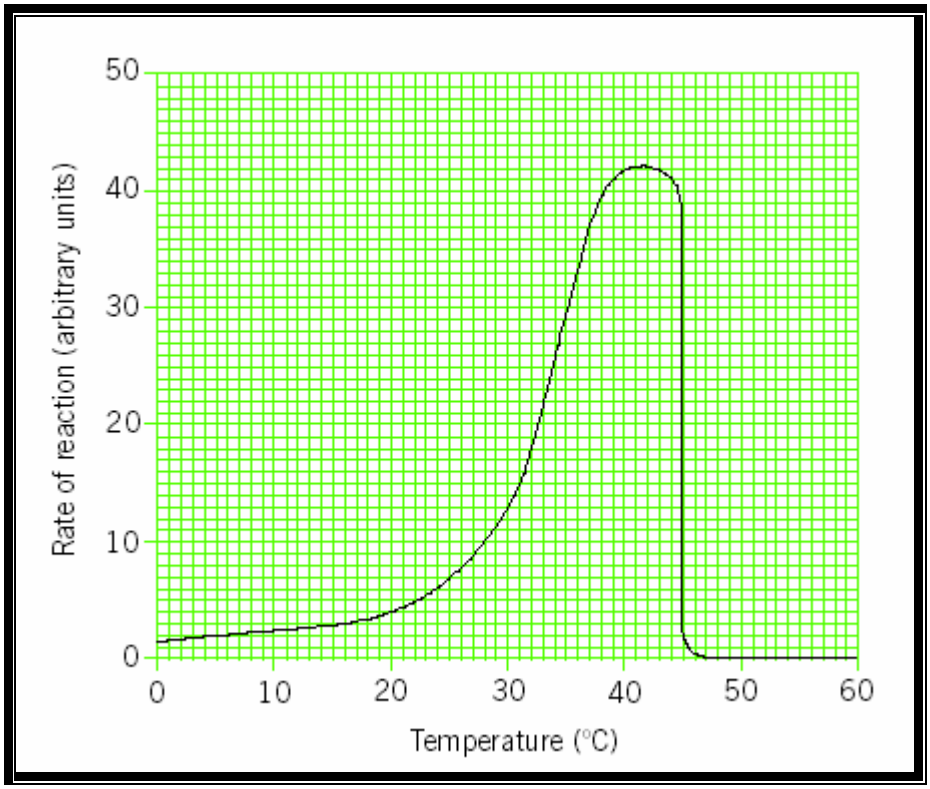
The major synthetic value of enzymes as catalysts is their selectivity. Because enzymes are large chiral molecules with unique stereo-structures in the active site; they can be highly selective for certain types of substrates and reactions. Useful type of enzyme-catalyzed reactions include the *chemoselectivity* [25] (reaction of one of several different functional groups in a molecule); *regioselectivity* [26,27] (reaction of one of the same or similar groups in a molecule); *enantioselectivity* [28] (reaction of one enantiomer of a racemic pair or one of the enantiotopic faces or groups); and *diastereoselectivity* (reaction of one or a mixture of diastereomers or one of the diastereomeric faces or groups). All such selective reactions occur because during a reaction, the prochiral or chiral reactants form diastereomeric enzyme-transition-state complexes that differ in transition state energy ($\Delta G^{\ddagger}$).

1.7 Factors that affect the rate of an enzyme-catalyzed reaction

The key factors that effect the rate of an enzyme-catalyzed reaction are; temperature, pH, concentration of substrate, and concentration of enzyme.

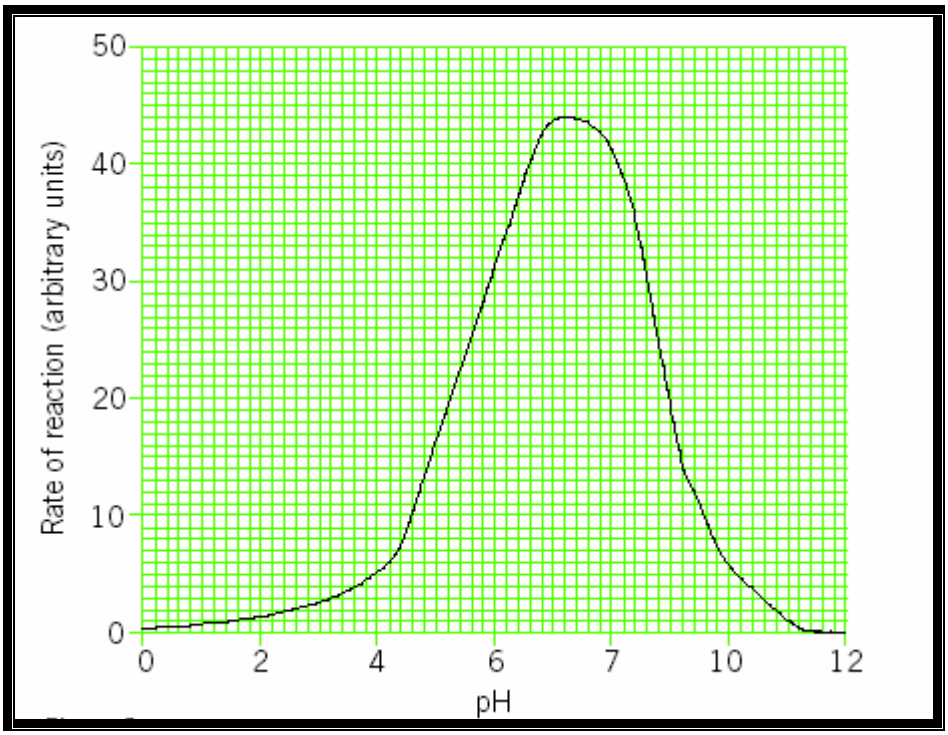
If the temperature at which an enzyme catalyzed reaction takes place is increased from 0°C to 100°C, the following changes to the rate of reaction will

occur. As the temperature increases from 0°C to the **optimum temperature**, the rate of reaction increases. This happens because the reacting particles have more and more energy and there are more and more energetic collisions per second. At the optimum temperature (this is normally near to 40°C) the rate of reaction reaches a maximum. Above the optimum temperature, the rate of reaction rapidly decreases until the reaction stops. At this point the enzyme no longer functions as a catalyst. Scheme 5 is an illustration to show the effect of temperature on an enzyme catalyzed reaction.



Scheme 5. A typical graph to show the effect of temperature on enzyme activity

As the pH increases from 0 to 14, the following changes happen to the rate of reaction. As the pH increases, the rate of reaction increases from zero until it reaches a maximum. The pH value that gives the maximum rate of reaction is called the **optimum pH**. Above the optimum pH the rate of reaction falls rapidly back to zero. (Scheme 6)

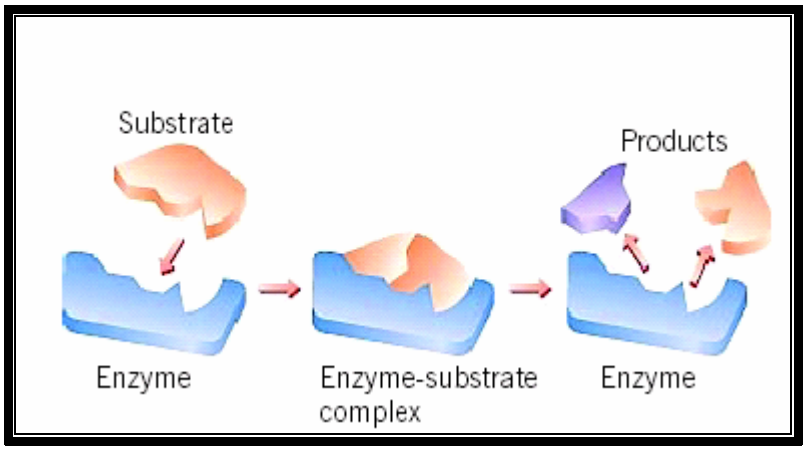


Scheme 6. A typical graph to show the effect of pH on the rate of an enzyme-catalyzed reaction

In simple terms, as the concentration of either the enzyme or the substrate increases so does the rate of reaction. This is because there are more collisions per second between the enzyme and substrate.

1.8 Mechanistic Aspects

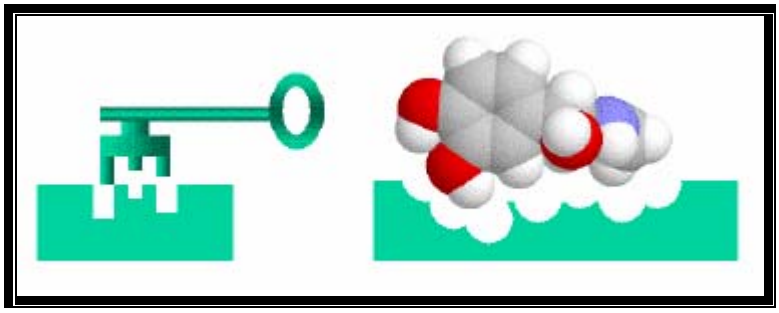
The distinguishing feature of an enzyme-catalyzed reaction is that it takes place within the confines of a pocket on the enzyme called the **active site** (Scheme 7). The molecule that is bound in the active site and acted upon by the enzyme is called the **substrate.** The surface of the active site is lined with amino acid residues with substituent groups that bind the substrate and catalyze its chemical transformation. Often, the active site encloses a substrate, sequestering it completely from solution. The enzyme substrate complex, whose existence was first proposed by Charles-Adolphe Wurtz in 1880, is central to the action of enzymes. It is also the starting point for mathematical treatments that define the kinetic behavior of enzyme-catalyzed reactions and for theoretical descriptions of enzyme mechanisms.

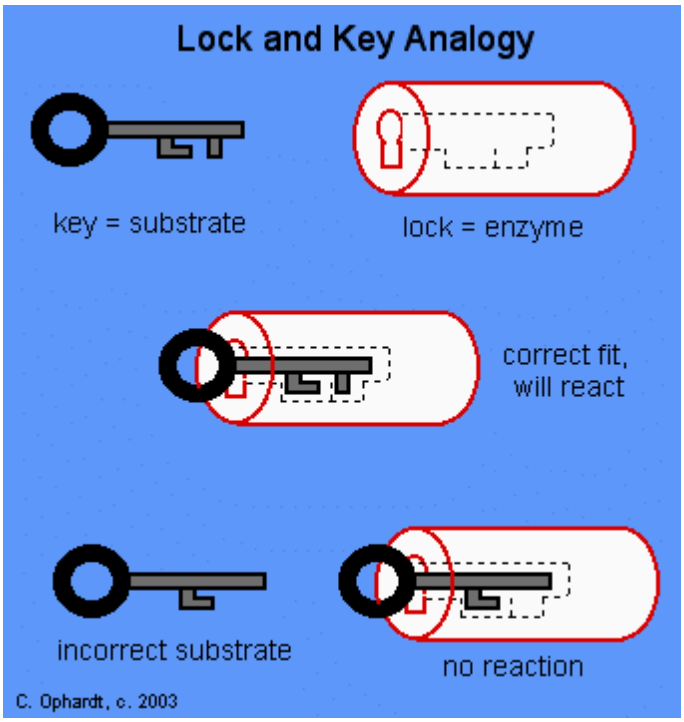


Scheme 7. The formation of an enzyme-substrate complex

Around the turn of the twentieth century, Emil Fischer proposed the 'lock and key' mechanism for protein binding [29]. This mechanism can be best illustrated by the enzyme substrate-binding process. The enzyme active site was believed to be a rigid and sturdy lock, with an exact .fit to only one substrate (key). The specificity of enzymatic catalysis was believed to be the outcome of matching. This simplistic

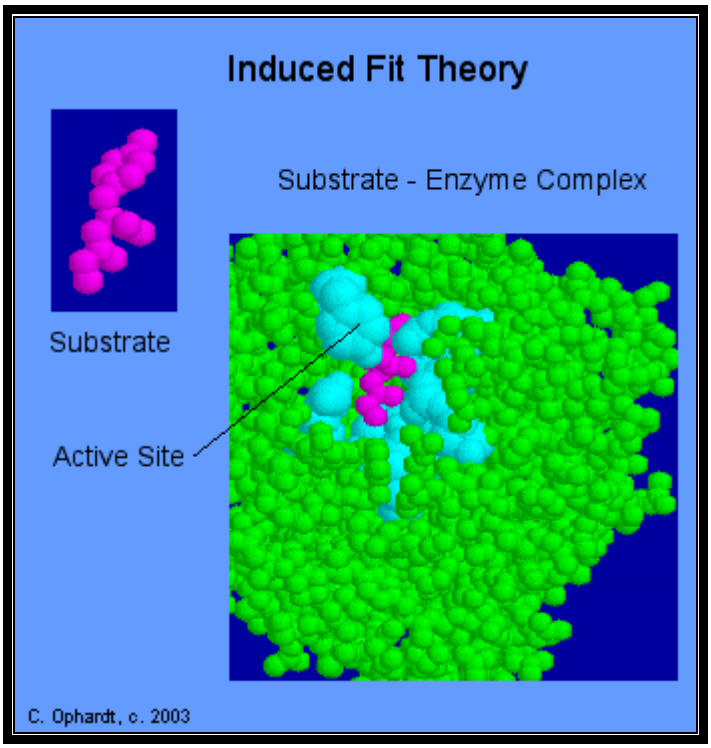
process had been accepted as the universal mechanism for enzyme ligand/substrate binding for more than half a century, until challenged by an alternative mechanism of 'induced fit' of Koshland in 1958 [30].





Scheme 8. Lock and Key Model

According to the induced fit theory, proteins need not be rigid locks. (Scheme 9). They can accommodate the substrate by flexibly adapting their substrate-binding site. The rigid and flexible binding modes have subsequently been distinguished by comparing the structures of the free, unbound, protein molecule with the structure when complexed with its ligand. If the structures are similar, the binding mode has been classified as belonging to the rigid, 'lock and key' type mechanism; if the structural comparison illustrates a relatively large conformational change, the binding mode has been considered to belong to the 'induced fit' category. These views of molecular associations have since been widely accepted.



Scheme 9. Induced-fit mechanism

1.9 Nomenclature of Enzymes

The International Union of Biochemistry has classified enzymes into six main classes according to type of reactions they catalyze.

Oxidoreductases: They catalyze oxidation/reduction reactions transferring hydrogen, oxygen, and/or electrons, between molecules. This important class includes dehydrogenases (hydride transfer), oxidases (electron transfer to molecular oxygen), oxigenases (oxygen transfer from molecular oxygen), and peroxidases (electron transfer to peroxide).

Tranferases: They catalyze the transfer of groups of atoms e.g. amino-, acetyl-, phosphoryl-, glycosyl-, etc. from a donor to a suitable acceptor.

Hydrolases: They catalyze the hydrolytic cleavage of bonds. Many commercially important enzymes belong to this class, e.g. proteases, amylases, acylases, lipases and esterases.

Lyases: They catalyze the non-hydrolytic cleavage of e.g. C-C, C-O, C-N bonds by elimination reactions leaving double bonds or in reverse adding groups to a double bond. Examples are fumarases, aspartases, decarboxylases, dehydratates, and aldolases.

Isomerases: They catalyze isomerization and transfer reaction within one molecule. The most prominent member of this group is D-xylose ketolisomerase, commonly known as glucose isomerase.

Ligases: They catalyze the covalent joining of two molecules coupled with the hydrolysis of an energy rich bond in ATP or similar triphosphates. An example is γ-L-glutamyl-Lcysteine:cglycine ligase (ADP forming) also found under the same glutathione synthetase.

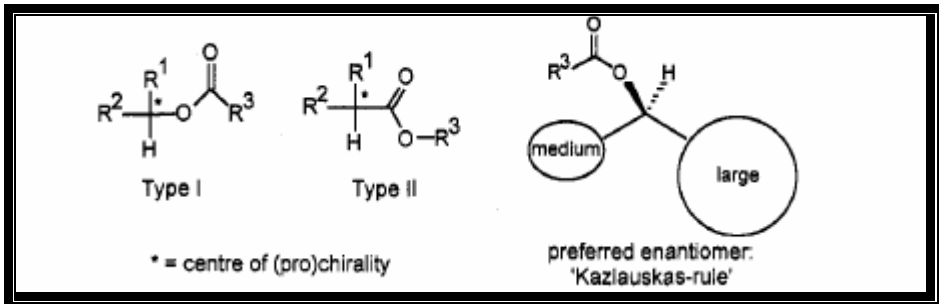
1.10 Hydrolases

Throughout the thesis various hydrolase type of enzymes were used. Therefore, the importance and characteristics of the hydrolases will be mentioned in this section. Reactions catalyzed by various types of hydrolases are predominant among biotransformations. The lack of sensitive cofactors, which have to be recycled, makes them particularly attractive for organic synthesis. Consequently, they account for about two thirds of all reactions reported. In particular, reactions involving the cleavage (or formation) of an amide- or ester bond are most easy to perform by using lipases, esterases and proteases, respectively. Other types of hydrolysis reactions involving phosphate esters, epoxides, organo-halogens and nitriles are still hampered by a restricted availability of enzymes, but they hold great synthetic potential [31].

1.11 Lipases

A large number of fat-cleaving enzyrnes-lipases-are produced on an industrial scale for applications in the food and detergent industry [32]. This is facilitated by the fact that many of them are formed extracellularly by fungi and bacteria. This ready availability has created an enormous spin-off with respect to the enantioselective hydrolysis and formation of carboxyl esters [33]. Bearing in mind that the natural substrates for lipases-glycerides-possess a chiral alcohol moiety, it is understandable, that lipases are particularly useful for the resolution or asymmetrization of esters bearing a chiral alcohol moiety (Scheme 10)**.** From the data available, the following general guidelines for the design of lipase-substrates can be given: (i) The center of chirality should be located as close as possible to the site of the reaction *(i. e* . the ester carbonyl group) to ensure an optimal chiral recognition. Thus, esters of secondary alcohols are usually more selectively transformed than those of primary alcohols. (ii) There is a wide tolerance for the nature of both substituents R^1 and R^2, but they should differ in size and or polarity to aid the chiral recognition process. They may be also linked together to form cyclic structures. Polar groups, such as carboxylate, amide or amine-which would be

heavily hydrated in an aqueous environment are not tolerated and, if they are required, they should be protected with a lipophilic unit. (iii) The alkyl chain of the acid moiety (R^3) should be preferably of straight-chain nature possessing at least three to four carbon atoms. Insufficient reaction rates may be improved by using 'activated' esters bearing haloalkyl groups, *e.g.* Cl-CH_2- and Cl-$(CH_2)_2$- for Type I and II, respectively. (iv) The remaining hydrogen atom in both substrate types must not be replaced by a substituent, since esters of tertiary alcohols and α, α, α-trisubstituted carboxylates are usually not accepted by lipases. (v) The stereochemical preference of the most commonly used lipases *(e.g.* from *Pseudomonas* and *Candida* spp.) for esters of secondary alcohols follows an empirical model generally referred to as 'Kazlauskas-rule' [34]. A related rationale for primary alcohols has been developed more recently [35].



Enzyme type	Preferred substrate type	R^1, R^2	R^3
Lipases	Type I > Type II	wide tolerance of (functionalized) alkyl and aryle;	long-chain (≥ n-C_3H_7)
Esterases and proteases	Type II > Type I	different in size, not too polar	short-chain (CH_3 > C_2H_5)

Scheme 10. Substrate types for lipases, esterases or proteases.

The strength of lipases is the ample availability of bulk-enzymes from various microbial sources. It can be anticipated that almost every secondary alcohol can be

resolved by employing lipase-technology by following the general guidelines described above. Whereas the stereochemical preference for one enantiomer of a given substrate (a 'digital' decision) can be predicted with fair accuracy, the stereoselectivity (i.e. an 'analog' value) has to be determined in practice. Despite an impressive effort in molecular modelling, attempts to develop reliable methods for the prediction of lipase- stereoselectivity have failed so far. One of the reasons for this obvious weakness of lipase-technology is the fact that these studies have (almost invariably) been based on the X-ray structure of lipases which provides only static information. Bearing in mind that the enzyme-substrate interaction consists of a considerable dynamic nature, it can be assumed that the application of other techniques may help to provide solutions.

The high stability of lipases towards organic solvents makes them extremely useful for the reverse reaction, i.e**.** ester formation by condensation or (more advantageous) transesterification reactions [36,37]. The use of non-natural nucleophiles in acyl-transfer reactions such as amines, ammonia, hydrazine, oximes, and hydrogen peroxide allows the lipase-catalyzed aminolysis, ammonolysis [38], hydrazinolysis [39], oximolysis and perhydrolysis [40] of esters giving rise to carboxamides, hydrazides, hydroxamic acids and peracids, respectively. Whereas hydrazine and oxime derivatives have been used more scarcely, lipase-catalyzed aminolysis and perhydrolysis is particularly advantageous for those cases where traditional chemical catalysis fails and where side reactions dominate.

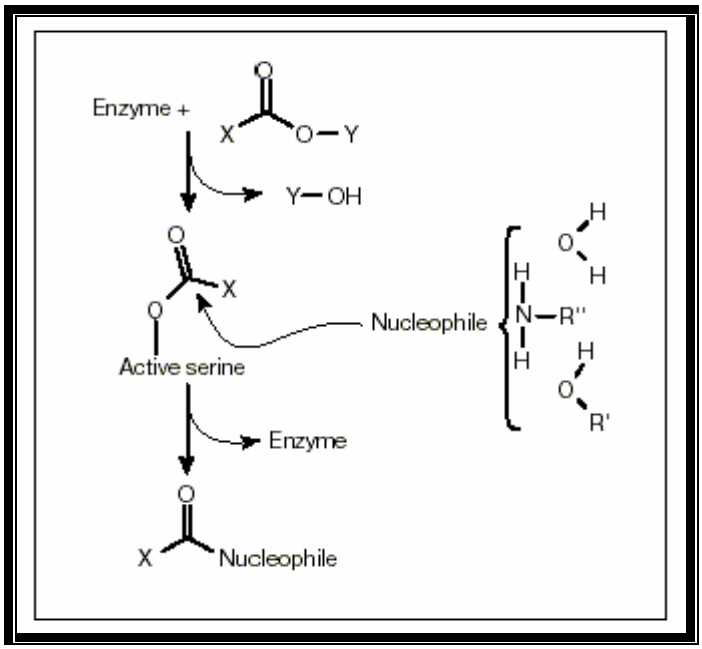
The use of organic media at low water activity offers a unique possibility to tune stereoselectivity through variation of the solvent. Bearing in mind that enzymes possess delicate and soft structures, it may be anticipated that any solvent exerts a significant influence on the catalytic properties of an enzyme, such as reaction rate, and its various types of selectivities. Thus, it can be expected that an enzyme's specificity can be controlled by varying the solvent's properties [41]. For reactions performed in water, however, this is hardly possible, because its physicochemical properties are determined by Nature and can be altered only within a very narrow margin. On the other hand, an organic solvent can be chosen within certain limits from a wide arsenal having different properties such as dipole moment, water-

solubility, straight-chain or cyclic structure, flexibility and the ability to form hydrogen bonds [42]. As a consequence, the stereoselectivity of an enzyme-catalyzed reaction-this is particularly true for lipases can be controlled by choosing the appropriate organic solvent. Any attempts to predict these effects, however, have failed so far and the selectivity-enhancement of lipase catalyzed reactions by medium engineering is still a largely empirical task, despite the tremendous amount of data published to date. However, the empirically obtained selectivity-improvement rates are often impressive and even a complete reversal of stereochemical preference is possible [43]. At present, lipases are continuously used for the generation of enantiomerically enriched primary and secondary alcohols and-to a somewhat lesser extent-of chiral carboxylic acids and secondary amines.

Several useful techniques for the **selectivity-enhancement** are available to turn lipase-technology into a reliable tool for the creation of chiral synthons [44]. However, limitations with respect to the predictability of stereoselectivity will persist for some time.

Lipids are compounds that can be extracted in chloroform–methanol mixtures. They consist primarily of fatty-acid chains, which are linked by ester bonds to an alcohol or polyol backbone. Lipases belong to a large class of enzymes that hydrolyse the ester bond between the fatty-acyl side chains and the lipid backbone. Understanding the catalytic cycle of lipases has been of significant importance to their widespread use in different biotechnological applications. The lipase active site is composed of three different residues: serine, histidine and aspartate or glutamate.

The hydrolysis of an ester involves an acyl enzyme complex. The catalytic cycle starts by nucleophilic attack of the hydroxyl group of the serine side chain on the carbonyl carbon atom of the ester bond. The complex is resolved by the nucleophilic attack of water, the fatty acid is liberated and the enzyme is regenerated (Scheme 11).



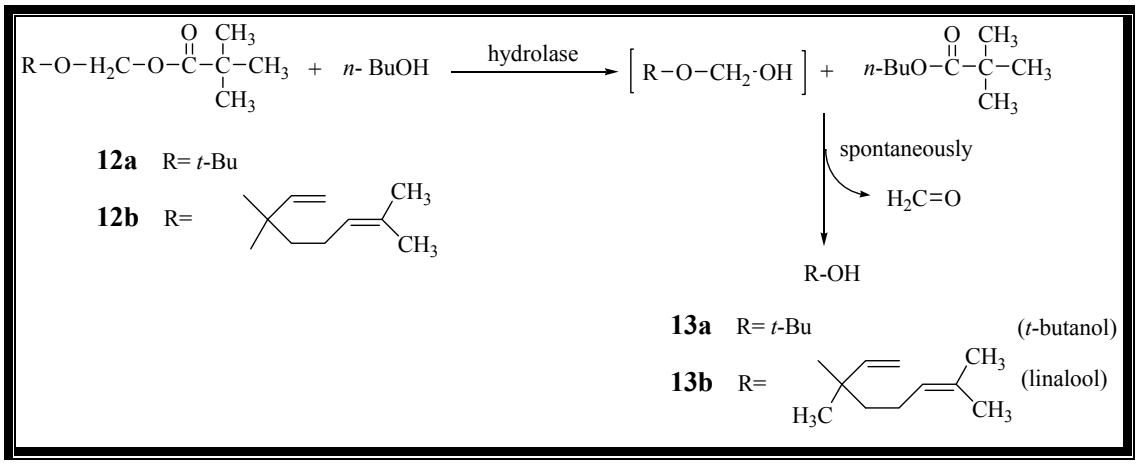
Scheme 11. Reaction mechanism of lipase biocatalysis

1.11.1 Candida sp. Lipase (CCL or CRL)

Several crude lipases are available from the yeasts Candida lipolytica, C. Antarctica and C. rugosa (CRL, formerly denoted as C. cylindracea). The latter enzyme has been frequently used for the resolution of esters of secondary alcohols [45,46] and –to a lesser extent- for the resolution of α-substituted carboxylates [47]. As CCL is able to accommodate relatively bulky esters in its active site, it is the lipase of choice for the selective hydrolysis of esters of cyclic secondary alcohols [48].

Commercially available hydrolases are not reactive towards tertiary alcohols or esters thereof because either the substrate is too bulky to penetrate into the enzyme active site, or because correct positioning of the substrate inside the active site is impossible due to steric restrictions of the binding pocket. To solve this problem Groot group placed a spacer between the tertiary carbon atom and the reaction centre (Scheme 12). They prepared pivaloyloxymethyl derivatives of *t*-butanol and linalool.

From commercially available 20 lipases, only CCL is well suited for the kinetic resolution of linalool with only 9.7-9.9 % enantiomeric excess [49].



Scheme 12. Alcoholysis of pivaloyloxymethyl derivatives of *t*-butanol and linalool.

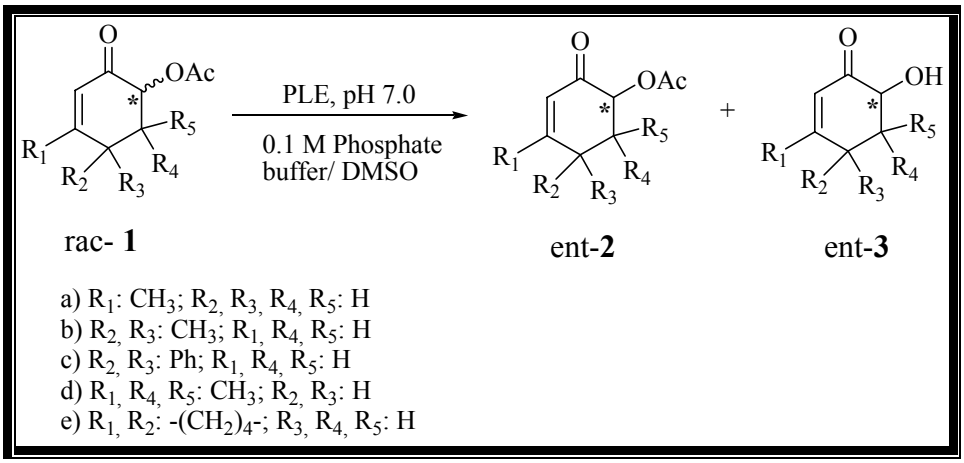
CCL also shows high enantioselectivities in enzymatic desymmetrization reactions [50].

1.12 Esterases

In contrast to the large number of commercially available microbial lipases, less than a handful of true esterases are available [51]. The large majority of esterase-catalyzed reactions have been performed by using porcine liver esterase (PLE) [52]. This enzyme has been widely used for the hydrolysis of Type II esters (Scheme 10) with R^3 being preferably methyl or ethyl, whilst Type I substrates (employed as the acetate esters) have been used to a lesser extent. In comparison to lipases, the applicability of PLE is significantly restricted to reactions performed in an aqueous medium, as PLE has been shown to exhibit low activity and erratic results with

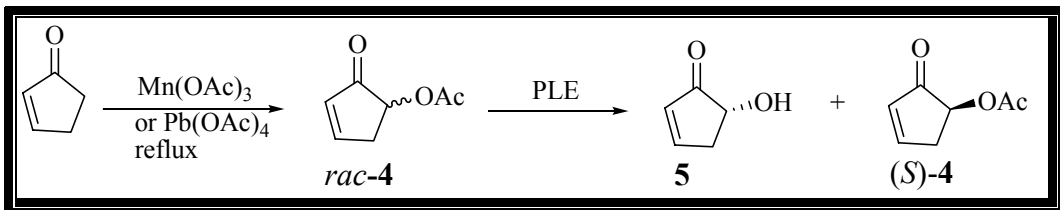
respect to stereoselectivity when placed in (nearly) anhydrous organic solvents. Thus, in contrast to lipases, selectivity-tuning is limited to the addition of water-miscible organic co-solvents, which only can be used in fractions of about up to 20% of volume [53]. Other esterases, such as the enzyme from horse or rabbit liver have been shown to possess a related and often slightly altered substrate specificity as compared to PLE [54]. In general terms, they are of limited use. Likewise, the applications of acetylcholine esterase are also few in number due to the fact that this enzyme is predominantly isolated from the electric eel which makes it prohibitively expensive, particularly for the production scale. The enantioselectivities achieved, however, are often excellent [55]. Cholesterol esterase is also of limited use, since it seems to work only on relatively bulky substrates, which show some similarities to its natural substrates, *i.e.* steroid esters [56].

PLE catalyzed enantiomeric separation of 6-acetoxy-α,β-unsaturated cyclic ketones is shown in Scheme 13. In the study performed by Tanyeli et al. the 6-hydroxy derivatives were resolved with 85-98 % e.e [57].



Scheme 13. PLE catalyzed resolution

In another study of Tanyeli et al., chemoenzymatic synthesis of α′- and α-acetoxylated ketones were reported with 96-98 % enantiomeric excess via PLE hydrolysis (Scheme 14) [58]. Various lipases were tested with racemic substrates. Among the hydrolases, PLE gave the best results whereas the other enzymes afforded poor chemical yields and enantiomeric excess values.

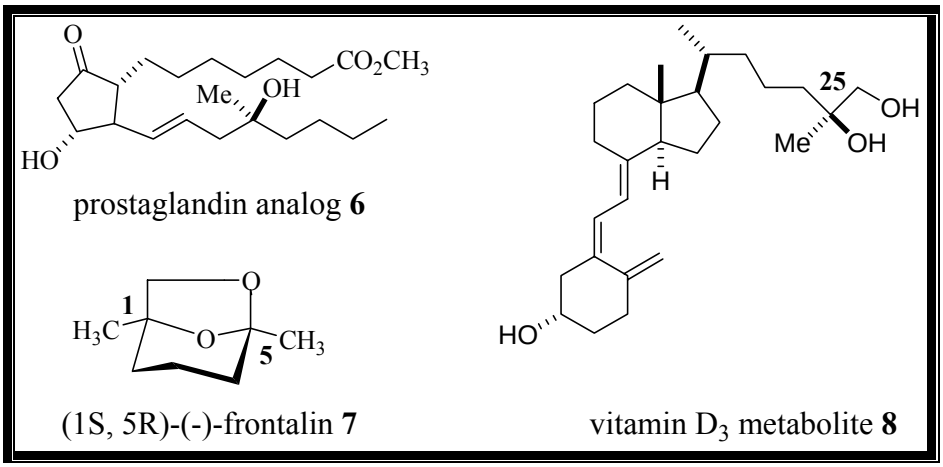


Scheme 14. Chemoenzymatic synthesis of α′- and α-acetoxylated ketones

1.13 The Importance of Optically Active Tertiary Alcohols

A broad repertoire of chiral auxiliaries, reagents, and catalysts can be utilized for the reliable generation of tertiary stereocenters [59]. In contrast, the asymmetric construction of molecules with quaternary carbon stereocenters, that is, carbon stereocenters with four different nonhydrogen substituents, represents, a very challenging and dynamic area in organic synthesis. The preparation of compounds with these centers with catalytic enantioselective reactions is particularly demanding [60].

Tertiary alcohols and their derivatives containing tertiary C-O bonds are useful building blocks for many drugs and natural products (Scheme 15), such as prostaglandin analog **6** [61], frontalin **7** [62], and vitamin D_3 metabolite **8** [63]. In comparison with the great process in preparing optically active secondary alcohols, synthesis of enantiomerically pure tertiary alcohols is still a challenging problem.

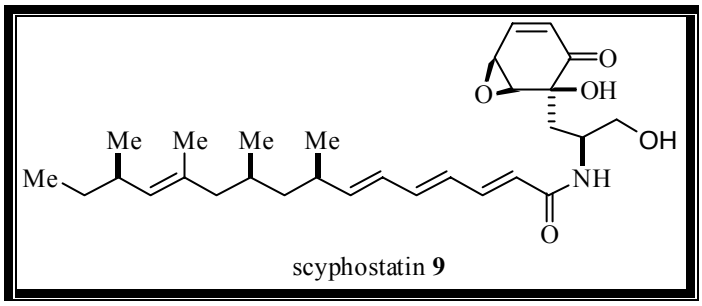


Scheme 15. Exemplified natural products and drugs containing tertiary C-O bonds

The α-hydroxy carbonyl array is a common feature of many biologically important molecules and key intermediates in the synthesis of natural products [64]. Some of the biologically important compounds containing α-hydroxy carbonyl moieties are given below.

1.13.1 Scyphostatin

Scyphostatin **9** (Scheme 16), isolated from the culture broth of *Dasyscyphus mollissimus* SANK-13892 by the Sankyo research group in 1997, has been shown to be a powerful and specific inhibitor of neutral sphingomyelinase (N-SMase) [65-67]. The use of N-SMase inhibitors can regulate the level of ceramide, the product of sphingomyelin hydrolysis by N-SMase, in a wide variety of cells [68]. Therefore, Scyphostatin is anticipated to be a promising agent for the treatment of ceramide-mediated pathogenic states such as inflammation and immunological and neurological disorders [69].

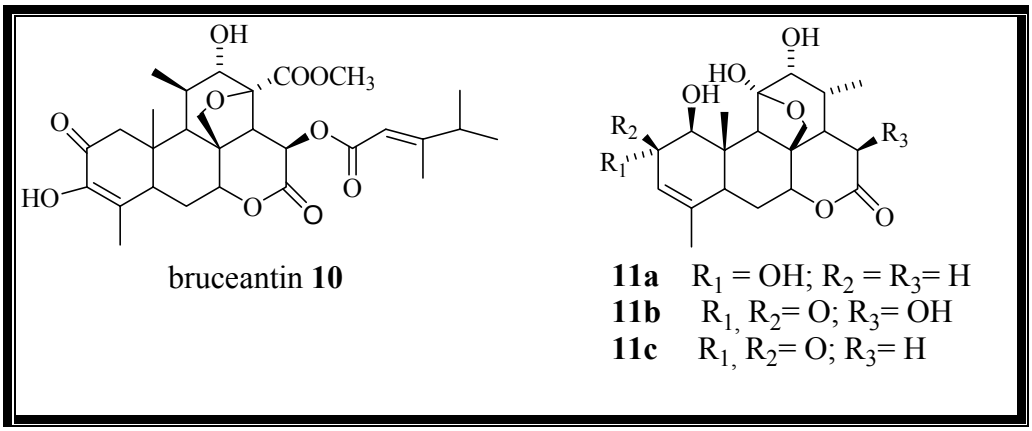


scyphostatin **9**

Scheme 16. Scyphostatin **9**

1.13.2 Quassinoids

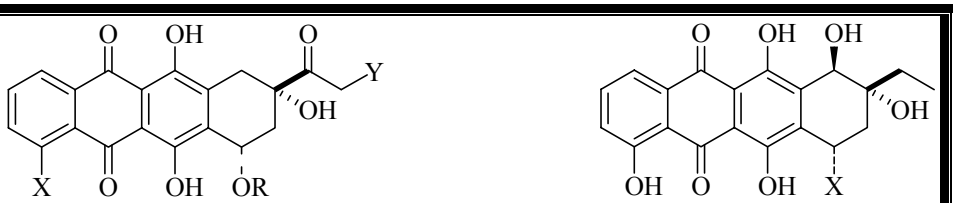
The quassinoids [70,71], are a group of degraded triterpenes and constitute the bitter principles isolated exclusively from the plants of the Simaroubaceae family. Interest in the quassinoids has accelerated rapidly with the finding by the National Cancer Institute, U.S.A., in 1975 that some of them possess strong antileukemic activity in the murine lymphocytic leukemia P-388 test system. Bruceantin **10** (Scheme 17) isolated from *Brucea antidyssenterica* [72], was selected for clinical trials in the U.S.A. Since then the quassinoids have been shown to exhibit a wide spectrum of useful biological activities such as anti-malarial, antiviral, amoebicidal, insecticidal, anti-feedent and leishmanicidal properties. Quassinoids have also attracted much attention as synthetic target molecules and numerous synthetic approaches have been developed which include the total synthesis of the parent compound quassin [73] and also that of castelanolide [74]. Structural requirements for the antineoplastic activity exhibited by numerous quassinoids are well established [75]. Chapparin **11a** which can be obtained in relatively large amounts from the Mexican Castela species lacks these structural features and does not possess antineoplastic activity [76].



Scheme 17. Examples of quassinoids

1.13.3 Anthracycline Antitumor Antibiotics

The clinical utility of the anthracycline antitumor antibiotics (Scheme 18) such as adriamycin **12**, and daunomycin **13** is well established. Their therapeutic efficacy is, however, limited due to a number of toxic side effects. 4-Demethoxyadriamycin **14**, and 4-demethoxydaunomycin **15** are totally synthetic analogues that exhibit an improved pharmacological profile. Since the biological activity of the anthracyclinones is critically dependent on the chirality of the α-hydroxy ketone moiety at C-9 extensive efforts have been devoted to their asymmetric synthesis [77]. Moreover, the rhodomycinones **16 a, b** are the principal aglycones of rhodomycins and recently isolated potent anthracyline antibiotics such as betaclamycin A and distrisarubicin B. Although many asymmetric synthesis of anthracyclinones have been accomplished, there are a few studies on the asymmetric synthesis of rhodomycinones [78].



12, X=OMe, Y=OH R= Daunosaminyl
13, X=OMe, Y=H
14, X=H, Y=OH
15, X=Y=H

16 a, X=H
16 b, X=OH

Scheme 18. Anthracycline antitumor antibiotics

The classical method for preparation of optically active tertiary alcohols is via separation of their properly derivatized diastereomers [79]. Another common method involves multistep transformations from chiral pools [80] of natural products such as terpenes, amino acids, and carbohydrates. The asymmetric synthesis by addition of chiral organometallic reagents to unsymmetric ketones [81] is a promising approach to obtain optically active tertiary alcohols. The catalytic asymmetric synthesis by dihydroxylation of 1,1-disubstituted olefins [82] is so far the most effective method. The catalytic asymmetric epoxidation 1,1-disubstituted olefins [83], followed by treatment with a base or nucleophile, leads to various tertiary alcohols. However, microbial or enzymatic methods including lipases are unsuccessful, since tertiary alcohols are usually too bulky to have access to the active sites of lipases [84].

1.14 Synthesis of Chiral Tertiary α-Hydroxy Carbonyl Compounds

Several methods for the synthesis of chiral tertiary α-hydroxy carbonyl compounds are mentioned below.

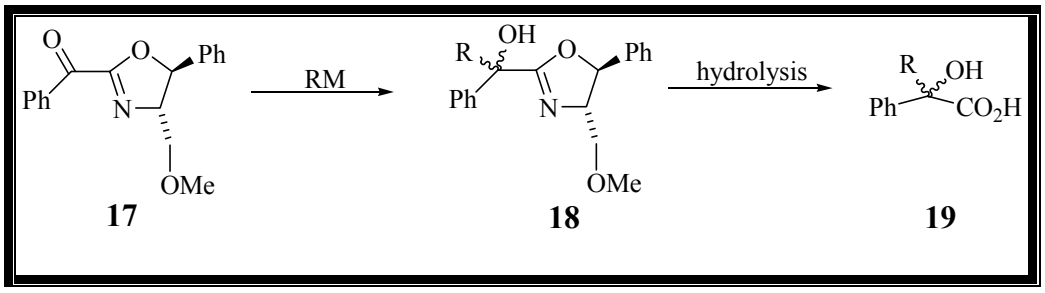
1.14.1 Asymmetric Reduction of Ketones with $NaBH_4$

Asymmetric induction in the borohydride reduction of carbonyl compounds has been carried out in the presence of optically active catalysts under phase-transfer conditions [85]. Almost all prochiral ketones undergo borohydride reduction in the presence of various optically active "onium" salts as catalysts to afford chiral carbinols. The highest optical yield in the studies was 32 % for phenyl *tert*-butyl ketone [86].

Yamazaki et al. reported asymmetric reduction of ketones with sodium borohydride in nonaqueous solution in the presence of various monosaccharide derivatives [87].

1.14.2 Addition of Grignard reagents to chiral α-keto oxazolines

Addition of Grignard and organolithium reagents to α-keto oxazolines results in α-substituted α-hydroxy oxazoline derivatives which on hydrolytic removal of the chiral auxiliary groups give rise to α-hydroxy acids in 30-87 % enantiomeric excess.(Scheme 19) [88].



17 **18** **19**

Scheme 19. Addition of Organometallics to Benzoyloxazoline

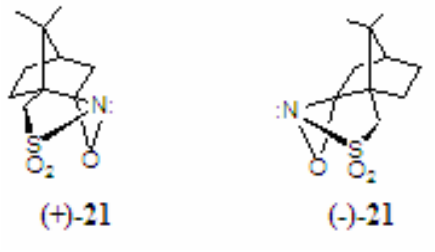
1.14.3 Asymmetric Oxidation of Ketone Enolates

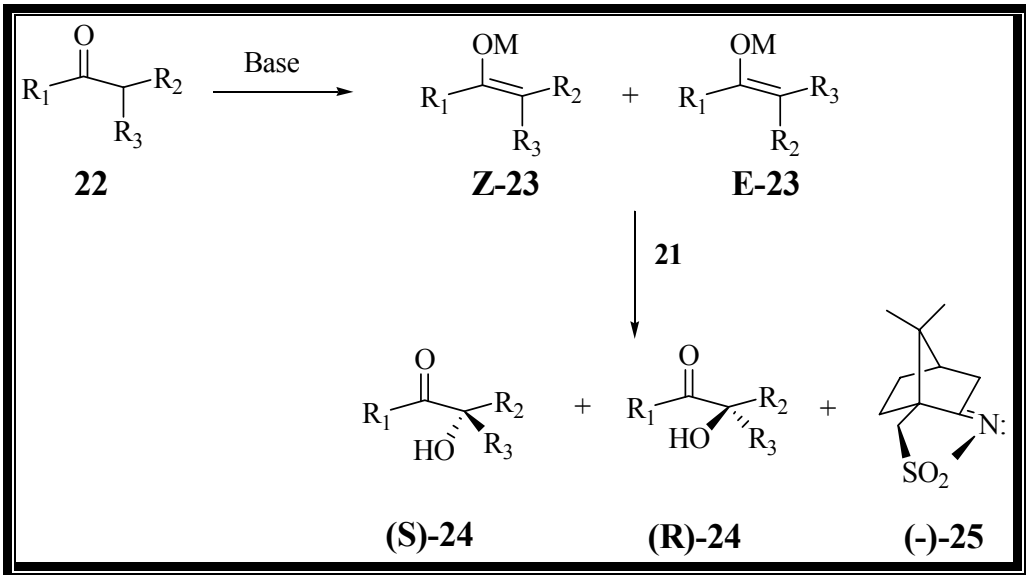
The oxidation of prochiral enolates to optically active α-hydroxy carbonyl compounds requires an aprotic, asymmetric oxidizing agent. Enantiomerically pure N-sulfonyl oxaziridines (**20** and **21**) have been introduced for asymmetric oxidation of enolates. To date the (+) and (-)-(camphorsulfonyl)-oxaziridines are the most useful of these reagents because they are stable, easily prepared, and commercially available [89,90].

Davis et al. reported the reagent-controlled enantioselective oxidation of prochiral ketone enolates to optically active α-hydroxy ketones and enamines (Scheme 20) [91-93].

(S,S)-**20a**, Z*= (+)-camphor

20b; Z*= (-)-(S)-N-(α-methylbenzyl)-N benzylamine

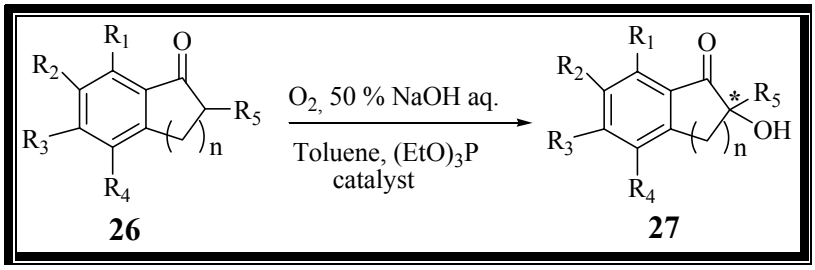




Scheme 20. Asymmetric oxidation of enolates

1.14.4 Enantioselective Oxidation of Aromatic Ketones by Molecular Oxygen

One of the most attractive methods to synthesize optically active α-hydroxy ketones is the oxidation of ketone enolates in a two phase system by molecular oxygen, because only catalytic amounts of phase transfer catalysts are needed and cheap chemicals are used [94]. The study of Shioiri group is shown in Scheme 21.



Scheme 21. Synthesis of α-Hydroxy Ketones Using Phase Transfer Catalysts

In another study, enantioselective oxidation of aromatic ketones by molecular oxgen, catalyzed by monoaza-crown ethers were reported by Brussee et al [95].

1.15 Direct Preparation of α-Acetoxy Ketones

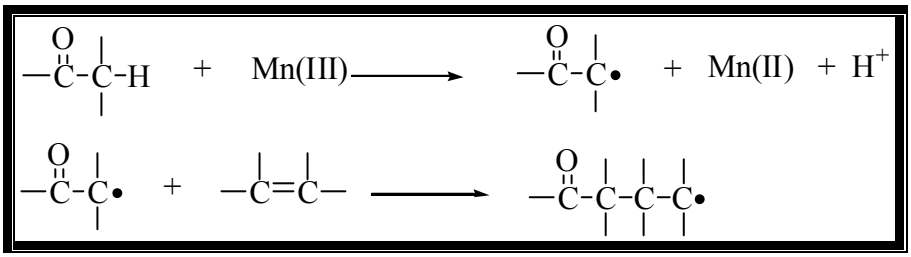
Currently there are only a few methods that deal with the direct preparation of α-acetoxy ketones. These involve the oxidation of ketones with lead tetraacetate [96-98], the oxidation of ketones with manganese triacetate in acetic acid [99], the oxidations with mercuric acetate [100,101], and the oxidation of aromatic ketones with a hypervalent iodine reagent followed by solvolysis in acetic acid in the presence of silver carbonate [102].

1.15.1 Manganese(III) Acetate Oxidations

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

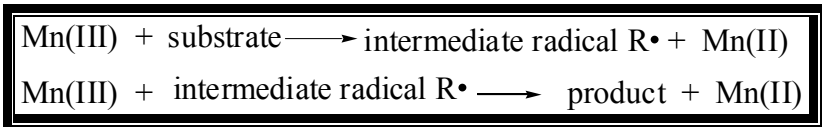
1. Direct inner- or outer-sphere one-electron oxidation of the substrate- after formation of an inner- or outer-sphere substrate-Mn(III) complexes. Often subsequent oxidation of an intermediate radical is product determining. Numerous examples can be found in oxidations of alcohols, amino and thio-compounds, carboxylic acids and certain aromatics. Direct inner or outer-sphere one electron oxidants with $Mn(OAc)_3$ in many cases proceed through the primary formation of an intermediate radical. The fate of this primary radical depends on the nature of the substrate and reaction conditions. Thus, with excess Mn(III) in many cases it is rapidly oxidized in a ligand transfer reaction to an acetate. However, the primary radical may dimerize, disproportionate, lose a proton, or enter in a sequence of transfer or addition reactions with other compounds, in a one-step procedure from substrates to products which otherwise require a multistep sequence.

2. Indirect oxidation of the substrate after formation of an intermediate adduct free radical from interaction of manganese(III) acetate and an enolizable compound and subsequent addition or substitution of this radical to the substrate. Manganese(III) acetate deals with addition reaction of compounds having α-hydrogen atom to a carbonyl group with olefinic and aromatic unsaturated systems (Scheme 22).



Scheme 22. Indirect Oxidation with Manganese(III) Acetate

Manganese(III) acetate, bear many similarities with respect to a given substrate class with other one-electron oxidants like Co(III), Ce(IV) and some two electron oxidants like Tl(III) and Pb(IV). However, lower reactivity and higher selectivities is observed with manganese(III) acetate compared with the other oxidizing agents. Many of these reactions proceed according to the simplified scheme shown below.

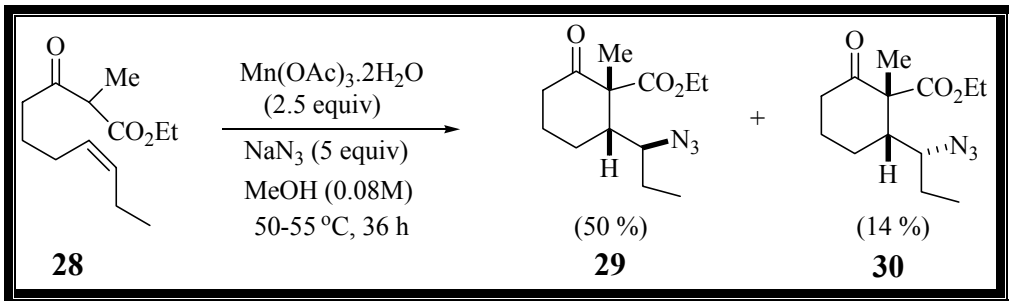


Scheme 23: The Simplified Reaction of Manganse(III) Acetate

Complications may arise in the presence of water, since water causes disproportionation of trivalent manganese into Mn(IV) and Mn(II) and alternative two electron oxidants may take place by Mn(IV) [103].

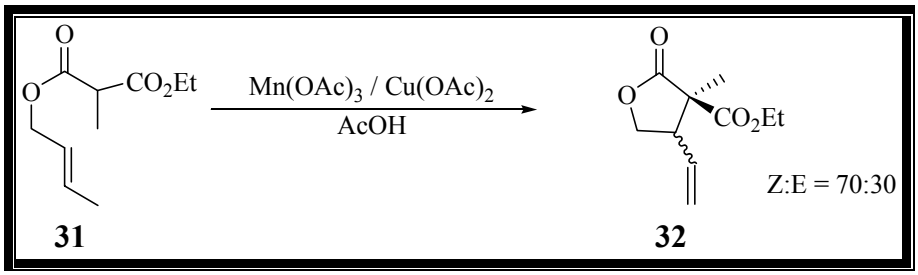
1.15.2 Examples of Manganese(III) Acetate Oxidations

Snider's group has recently reported that the radicals formed in Mn(III)-based oxidative free-radical cyclizations of β-keto esters and malonate esters can be trapped with sodium azide and Mn(III) to give cyclic and bicyclic azides in 30-80% yield. (Scheme 24). Reduction of the azide gives bi- and tricyclic lactams [104].



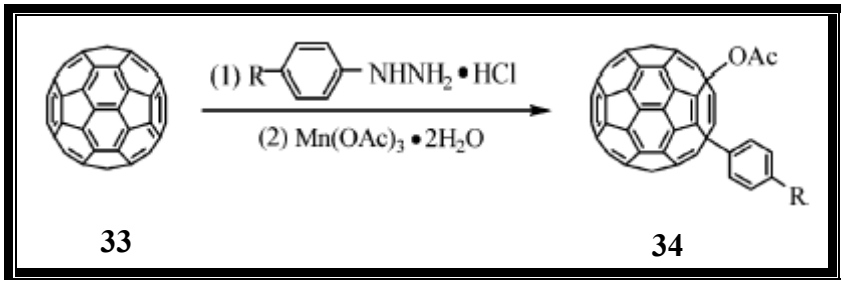
Scheme 24. Oxidative free radical cyclization with $Mn(OAc)_3$

In another study, Sung et al. reported the cyclizations of the substituted allyl α-methyl-β-ketoester radicals (Scheme 25) [105].



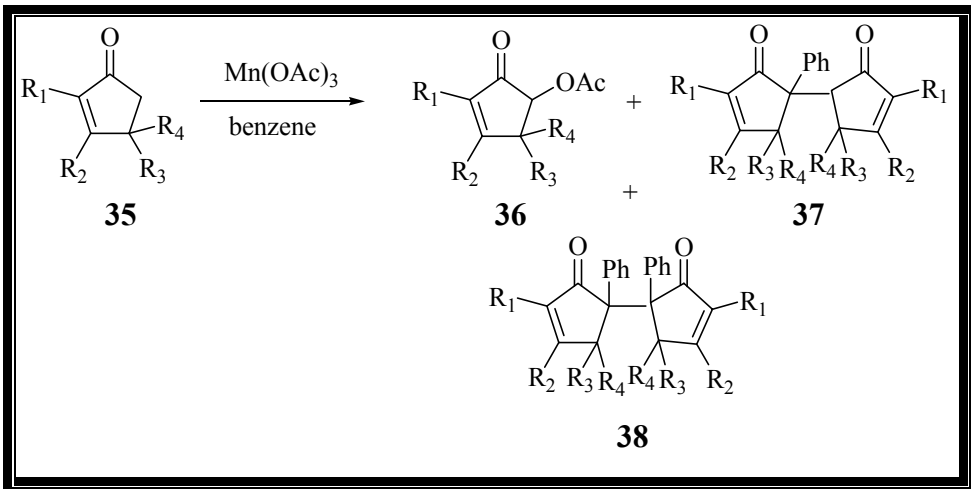
Scheme 25. Cyclization of substituted allyl α-methyl-β-ketoester radical

The reaction of [60]fullerene with 4-substituted phenylhydrazine hydrochlorides in refluxing chlorobenzene under aerobic conditions afforded 1-(4-substituted phenyl)-1,2-dihydro[60]fullerenes, which could be subsequently oxidized to 1-acetoxyl-4-aryl-1,4-dihydro[60]fullerenes by manganese(III) acetate dihydrate in one pot. The transformation of ArC_{60}-H to ArC_{60}-OAc has been realized with $Mn(OAc)_3\ 2H_2O$ for the first time (Scheme 26) [106].



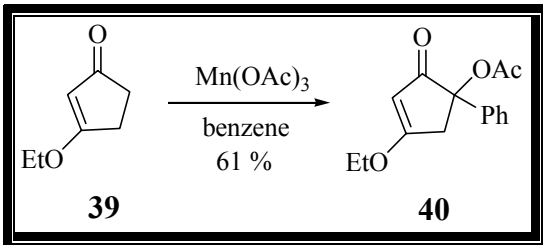
Scheme 26. Reaction of fullerene with $Mn(OAc)_3$

Manganese(III) acetate based regioselective oxidation of α,β-unsaturated cyclopentenones were reported to afford α′-acetoxy α,β-unsaturated cyclopenteones in good yields by Tanyeli et al (Scheme 27) [107].



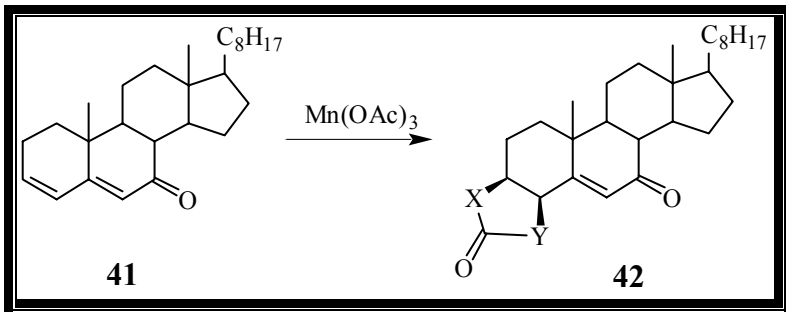
Scheme 27. Manganese(III) acetate promoted acetoxylation

Tanyeli et al. has recently reported the unusual results of manganese(III) acetate based tandem oxidation of various α and β-alkoxy α,β-unsaturated ketones to afford the corresponding α′-acetoxy-α′-phenyl substituted oxidation products in good yields. The tandem oxidation to monoacetoxylation ratio can be tuned by the amount of manganese(III) acetate (Scheme 28) [108].



Scheme 28. $Mn(OAc)_3$ based tandem oxidation

Ahmad et al. reported reaction of some α,β-unsaturated ketones from the cholestane series with manganese(III) acetate to afford a γ-lactone in low yields [109]. This was the first example of the oxidation with manganese(III) acetate on a compound containing substituted α′-position.



Scheme 29. Synthesis of a γ-lactone

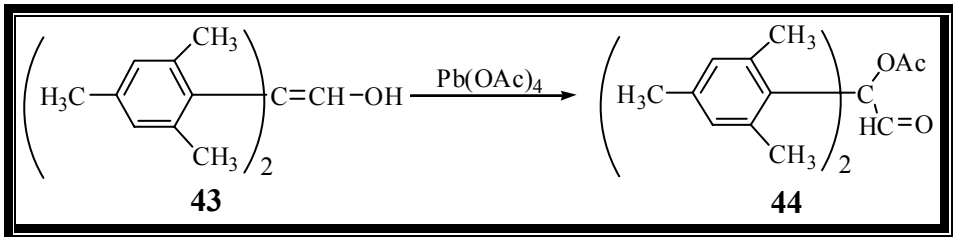
1.15.3 Oxidations with Lead(IV) Acetate

The lead tetraacetate oxidation is a general method for the preparation of α-acetoxy-ketones. In addition to mono-acetoxylation, some di-acetoxylation may occur at α and α' where such positions are available. Correspondingly, α-acetoxy ketones react to yield α,α'-diacetoxy compounds. The reactions are faster in acetic acid but give better yields in benzene.

Reactions of lead tetraacetate with C-H bonds usually result in substitution by an acetoxy group, but dehydrogenation and other reactions are also known. Generally, only activated C-H bonds are attacked. C-H bonds are activated toward lead tetraacetate by adjacent carbonyl groups, aromatic rings, or C=C double bonds.

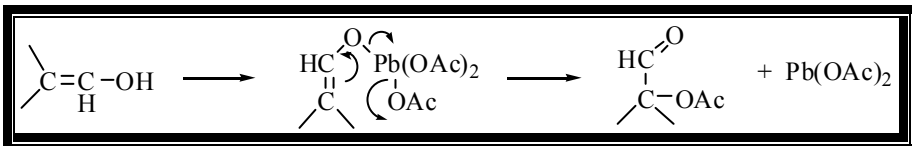
Lead tetraacetate converts carbonyl compounds to α-acetoxy derivatives. The reactivity increases in the sequence: acid anhydride < ester < ketone. It is

especially high when two activating groups are adjacent to the C-H bond. The tendency to enolize increases in the same sequence, so that one is tempted to assume that the enols are the species that are actually attacked. This assumption is supported by a number of observations. The first comes from Fuson's [110] studies of compounds which can exist only as phenols. In acetic acid at 40ºC they are oxidized almost quantitatively to α-acetoxy aldehydes (Scheme 30).



Scheme 30. The Oxidation of the Enol to α-Acetoxy Aldehydes with $Pb(OAc)_4$

The mechanism should be as below:



Scheme 31. The Mechanism of the Oxidation with $Pb(OAc)_4$

Ichikawa and Yanaguchi [111] found that the rate of oxidation of ketones depends only on the concentration of ketones, not on that of lead tetraacetate. As with the bromination of ketones, the rate determining step is the enolization.

Henbest et al. [112] observed that the oxidation of ketones is strongly accelerated by boron trifluoride, so much that it can be accomplished in benzene at room temperature. They explain the catalysis as an acceleration of enol formation due to the boron trifluoride. In addition, however, boron trifluoride could increase the dissociation of lead tetraacetate and thus the formation of the cation $Pb(OAc)_3^+$.

1.18 Aim of the Work

Many biologically active natural products contain quaternary carbon stereocenters, that is carbon stereocenters with four different nonhydrogen substituents. The synthesis of complex molecules with quaternary stereocenters is one of the most demanding tasks in multistep organic synhthesis. The challenge of this thesis is to synthesize enantiomerically enriched quaternary carbon stereocenters on cyclopentenoid and cyclohexenoid type of compounds, that are the simplest precursors of the complex natural products.

The unusual results of the manganese(III) acetate based tandem oxidation of various α- and β-alkoxy α,β-unsaturated ketones to afford the corresponding α'-acetoxy α'-phenyl substituted oxidation products reported by Tanyeli et al. in 2000 and 2002, was the starting point of this work. [108, 113]. It was aimed to synthesize cyclopentenoid and cyclohexenoid type of compounds that are substituted at the α'-position, then regioselectively oxidize these enones to yield α'-acetoxy enones. So far, studies on the selective oxidation of cyclic enones by $Mn(OAc)_3$ in the literature have been concerned with substrates that are unsubstituted at the α'-position, except for one example of a steroidal substrate involving a tertiary α'-position reported by Ahmad et al [109]. However, in this exceptional study, Ahmad et al. failed to synthesize the α'-acetoxy enones. The lack of a selective oxidation method for the α'-tertiary position of α,β-unsaturated cyclic ketones prompted us toward the

development of a new method. It was attempted to synthesize the α'-acetoxy, α'-alkyl α,β-unsaturated cyclic ketones by $Mn(OAc)_3$ and as well as by $Pb(OAc)_4$ oxidation.

Enantiomerically pure α-hydroxy carbonyl compounds are important synthons for the asymmetric synthesis of natural products and are useful stereodirecting groups. Some of these compounds have interesting biological properties and are used in a number of medical preparations (e.g. monosaccharide carba-analogues as components for anti-viral medicines, hydroxycyclopentenones as anti-cancer drugs, etc.) [114]. From this point of view, it was aimed to resolve the prepared α'-acetoxy, α'-alkyl α,β-unsaturated ketones to yield the enanatiomerically enriched α'-acetoxy ketones and α'-tertiary hydroxy ketones. The other challenge of this thesis is to resolve these α'-substituted acetoxy compounds by hydrolase type enzymes. This will be the first time in the literature that hydrolase type enzymes are used in the resolution of α'-tertiary positions.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 General Perspective of the Work

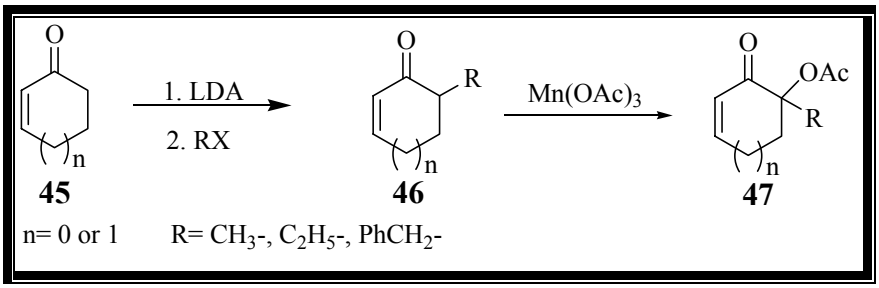
Several new methods and strategies for the synthesis of quaternary carbon stereocenters have been developed in recent years. However, the enantioselective synthesis of organic compounds with quaternary stereocenters is still a demanding and challenging task. The aim of this thesis is to synthesize enantiomerically enriched quaternary carbon stereocenters on cyclopentenoid and cyclohexenoid type of compounds, since these are the simplest precursors of more complex natural products.

Tanyeli et al. reported the unusual results of manganese(III) acetate tandem oxidation of β-alkoxy α,β-unsaturated ketones to afford the corresponding α'-acetoxy α'-phenyl substituted oxidation products in 2000 [113]. It was found that trapping the α'-keto radicals obtained from β-alkoxy α,β-unsaturated ketones by benzene used as a solvent is much faster than acetoxylation. This work was an example of the formation of a quaternary carbon stereocenter. From this point of view, it was aimed to synthesize α'-alkyl α,β-unsaturated ketones, then regioselectively oxidize them to α'-acetoxy ketones. In the literature, there are a few methods for the selective oxidation of enones. Two of them are $Mn(OAc)_3$ and $Pb(OAc)_4$ oxidations. It was decided firstly to monitor the oxidation reactions of α'-alkyl ketones by $Mn(OAc)_3$, since there is only one unsuccesful example reported on the oxidation of the substituted α'-position. The oxidation of the α'-substituted ketones were also

performed by lead(IV) acetate oxidation. The details of the work will be explained in the later sections below.

In 1976, Williams and Hunter reported that $Mn(OAc)_3.2H_2O$ oxidation of enones in acetic acid at reflux afforded α'-acetoxy enones in low yields [99]. Watt et al. reinvestigated this procedure and obtained acceptable yields of the desired α'-acetoxy enones [115-118]. So far, studies on the selective oxidation of cyclic enones in the literature have been concerned with the substrates that are unsubstituted at the α'-position, except for the study of Ahmad and co-workers [109]. Ahmad et al. reported the $Mn(OAc)_3$ oxidation of a steroidal compound that was substituted at the α'-position affording a γ-lactone in low yields. The lack of a selective oxidation method for the α'-*tert*-position of α,β-unsaturated ketones prompted us toward the development of a new method. First of all α'-alkyl substituted cyclopentenones and cyclohexenones were prepared , then these α'-alkyl substituted cyclopentenones and cyclohexenones were oxidized by $Mn(OAc)_3$ to yield α'-acetoxy-α'-alkyl α,β-unsaturated cyclic ketones.

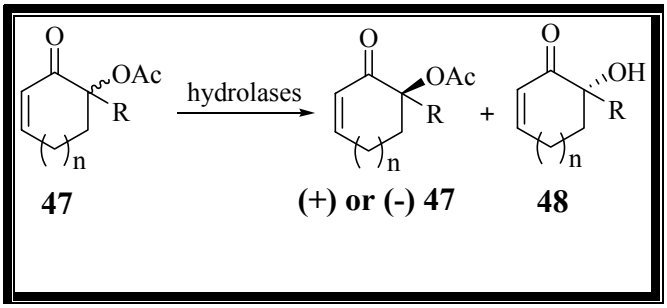
The reaction sequence is shown in Scheme 32.



Scheme 32. The reaction sequence

The second part of the study involves the resolution of α'-acetoxy-α'-alkyl α,β-unsaturated cyclohexenones and cyclopentenones by various hydrolase type

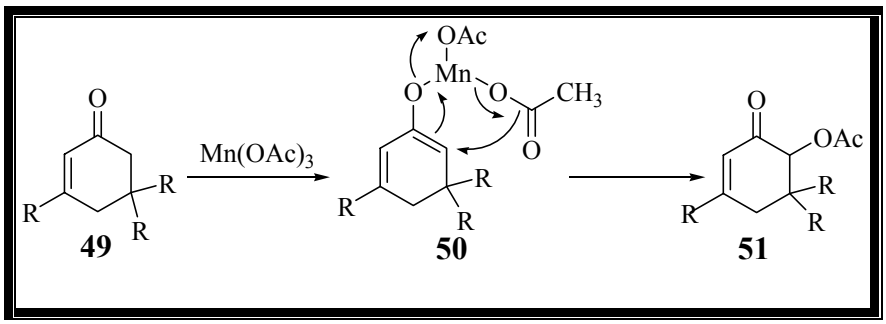
enzymes which is illustrated in Scheme 33. This work is the first example in the literature that hydrolase type enzymes are used in the resolution of tertiary α'-positions. The stereochemistry of the compounds are shown arbitrarily.



Scheme 33. Resolution with hydrolase type enzymes

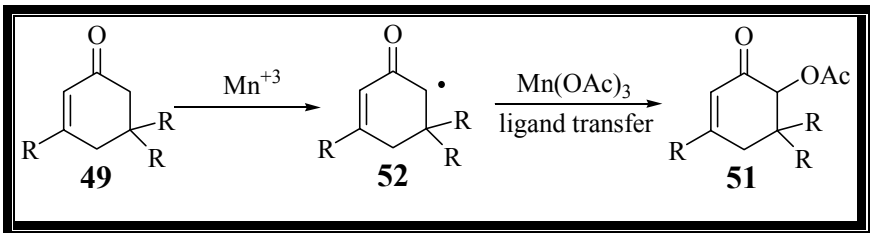
2.2 Mechanistic Considerations

There are two proposed mechanisms for the oxidation of enones by $Mn(OAc)_3$ [119]. The first mechanism is thought to proceed through the formation of a metal enolate with acetate transfer that is illustrated in Scheme 34.



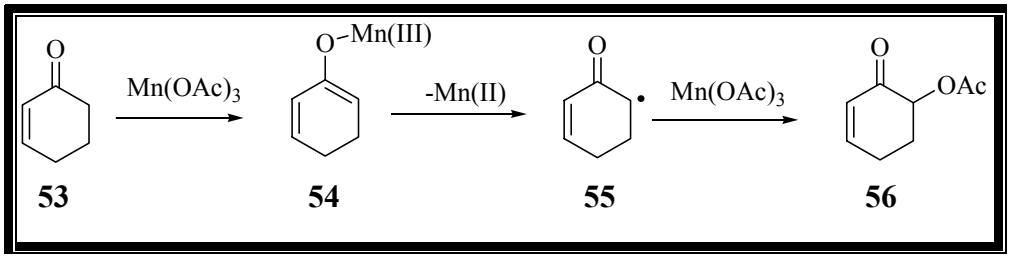
Scheme 34. The proposed mechanism for oxidation of enones involving metal enolate complex

The second mechanism involves the keto radical formation followed by ligand transfer to the product (Scheme 35).



Scheme 35. The oxidation mechanism involving keto radical formation

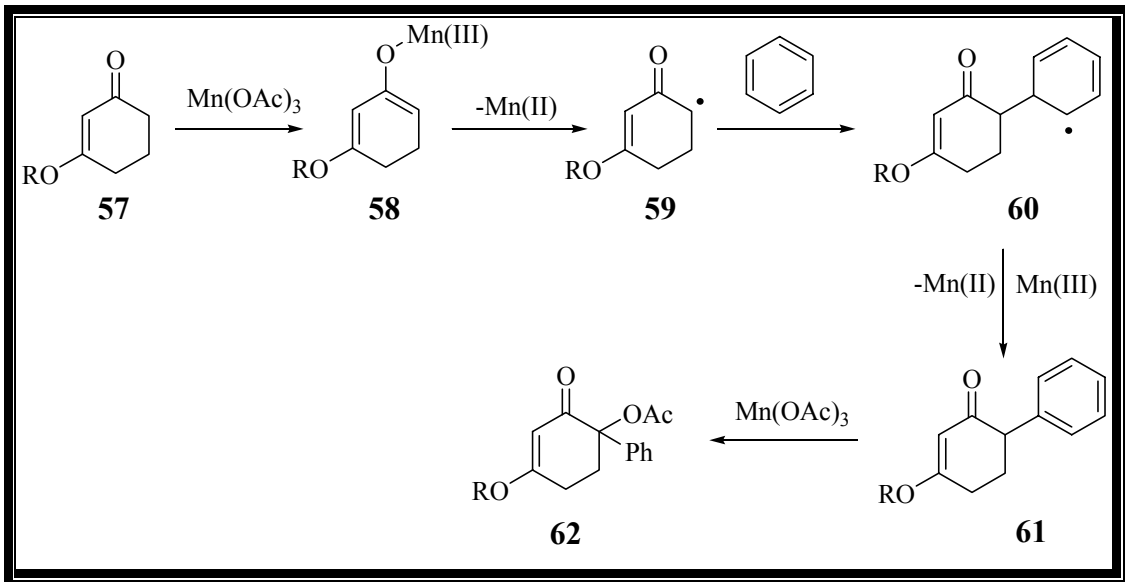
In 1996, Snider et al. reported that the reaction is thought to proceed via the formation of Mn(III) enolate, which loses Mn(II) upon one-electron oxidation to give the α'-keto radical. Oxidation of radical by a second equivalent of $Mn(OAc)_3$ provided the acetate [120].



Scheme 36. Mechanism proposed by Snider et al.

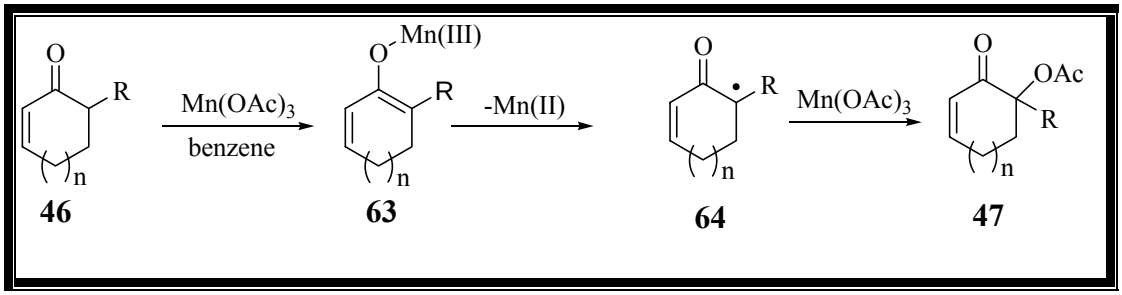
The radicalic mechanism is proven by the tandem oxidation reported by Tanyeli et al. Addition of the radical to benzene yielded another radical. One electron

oxidation of the resultant radical gave α'-phenyl β-alkoxy α,β-unsaturated ketones (Scheme 37) [113]. The introduction of aryl groups adjacent to ketones was reported to be confined to acetone, by Vinagradov et al. [121] since α'-keto radicals which would dimerize, or tertiary radicals that were prone to further oxidation.



Scheme 37. The reaction mechanism of tandem oxidation

The proposed reaction mechanism of this work is illustrated in Scheme 38.



Scheme 38. The reaction mechanism of this work

The presence of α-alkyl group has the following effects. An alkyl group should slow down the formation of Mn(III) enolate **63**, since it is electron donating and decreases the acidity of the α-proton. On the other hand, the alkyl group should facilitate the oxidation of **63** to **64**, since it can stabilize the radical. Electrochemical data for the oxidation of enolates of β-dicarbonyl compounds to the radical in DMSO support this hypothesis. The presence of an α-methyl group facilitates the oxidation by 0.25-0,4 V [122, 123]. The nature of the reaction depends on two variables: the rate of formation of the Mn(III) enolate, which corresponds to the pK_a, and the ease of oxidation of the enolate to give free radical. For most compounds enolization is the rate determining step. For very acidic compounds such as α-unsubstituted β-keto esters and β-diketones, enolization occurs readily and oxidation is slow [124].

2.3 α'-Alkylation of Six Membered Rings

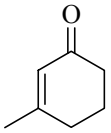
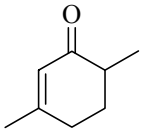
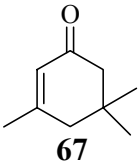
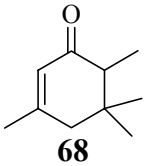
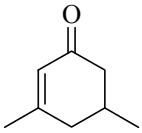
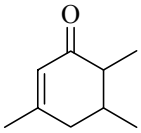
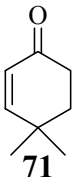
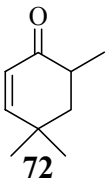
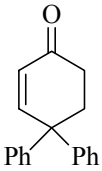
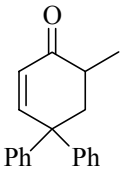
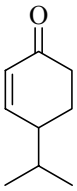
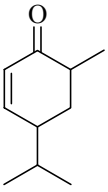
Methods for the preparation of substituted cyclohexenones have been the subject of much attention because of the important nature of these structural units in both natural and unnatural products [125].

There are several methods for the preparation of α'-alkyl compounds. One of the methods is the enamine alkylation of carbonyl compounds reported by Stork et al. [126]. Stork and co-workers found that enamines derived from an ordinary aldehyde or ketone led to predominant carbon alkylation. Since no base or other catalyst was needed, monoalkylation was easily carried out. From this point of view, the preparation of the morpholine enamine of 3-methyl-2-cyclohexen-1-one was targeted. One equivalent of 3-methyl-2-cyclohexen-1-one was refluxed with two equivalents of morpholine. To see clear water separation *p*-toluene sulfonyl chloride was added. However, after 27 hours reflux no enamine formation was observed. Since the rate of the reaction is affected by the basicity and steric environment of the secondary amino group; we changed the amine and used pyrrolidine which gives a higher reaction rate than the more weakly basic morpholine.After the synthesis of pyrrolidine enamine, by the addition of water ,the product 3,6-dimethyl-2-

cyclohexen-1-one was formed, but the yield was very low, so we decided to find a new procedure for alkylation.

The α-substitution of ketones and other carbonyl compounds is most directly accomplished by the alkylation of enolates with electrophiles [127]. After the preparation of lithium enolates by LDA at -78 ºC, the cyclohexenone derivatives were methylated by the addition of iodomethane. The results of α'-methylation of the cyclohexenones are summarized in Table 1.

Table 1. α'-Methylation of Cyclohexenones

Reactant	Product	Yield (%)
 **65**	 **66**	60
 **67**	 **68**	62
 **69**	 **70**	74
 **71**	 **72**	69
 **73**	 **74**	63
 **75**	 **76**	52

The compound **66**, 3,6-dimethyl-2-cyclohexen-1-one was synthesized in 60% chemical yield. The ^{1}H and ^{13}C-NMR spectra of the compound **66**, are in accordance with the literature data [128].

In the ^{1}H-NMR spectrum of compound **68**, 3,5,5,6-tetramethyl-2-cyclohexen-1-one, a singlet is observed at 5.75 ppm corresponding to the olefinic proton. A multiplet is observed between 2.17-2.03 ppm for the methine proton attached to C-6. A triplet (*J*= 7 Hz) is observed at 2.11 ppm corresponding to the methylene protons. A singlet is observed between 1.99 ppm corresponding to the methyl group protons substituted at the third carbon. The diastereotopic methyl group protons attached to the fifth carbon are observed as singlets at 0.97 and 0.80 ppm, respectively. A doublet is observed at 0.96 ppm (*J*= 6 Hz) corresponding to the methyl group protons attached to sixth carbon.

Compound **70**, 3,5,6-trimethyl-2-cyclohexen-1-one, was synthesized in 70% chemical yield. The ^{1}H and ^{13}C-NMR spectra are in accordance with the literature data [129].

In the ^{1}H-NMR spectrum of compound **72**, 4,4,6-trimethyl-2-cyclohexen-1-one, a doublet of doublets is observed at 6.52 ppm (*J*= 2, 10 Hz) corresponding to the olefinic proton attached to β-carbon. A doublet is observed at 5.72 ppm (*J*= 10 Hz) corresponding to double bond proton of the α-carbon. A multiplet is observed between 2.52-2.42 ppm corresponding to the CH proton. The AB system of the methylene protons is observed as a doublet of doublet between 1.77-1.72 ppm (*J*= 2, 13 Hz) and as a triplet (*J*= 13 Hz) at 1.59 ppm. A singlet is observed at 1.13 ppm corresponding to one of the methyl group protons attached to the fourth carbon. The other methyl group protons attached to the fourth carbon is observed as a singlet at 1.06 ppm. A doublet at 1.04 ppm is observed (*J*= 7 Hz) corresponding to the methyl group protons attached to the sixth carbon. In the ^{13}C-NMR spectrum of compound **72**, peak at 202.3 corresponds to the carbonyl group carbon. The β and α carbons are observed at 159.1 and 126.8 ppm respectively. The methine carbon is observed at 45.4 ppm, the methylene carbon is observed at 38.0 ppm. The fourth carbon is observed at 34.0 ppm. The carbons of the methyl groups attached the fourth carbon

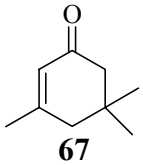
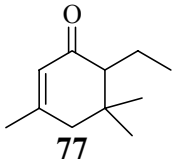
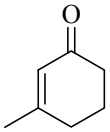
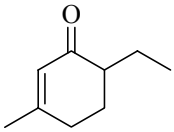
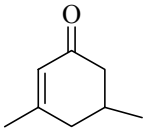
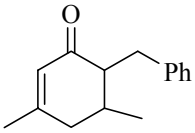
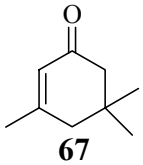
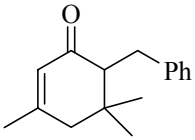
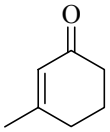
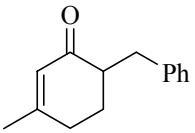
are observed at 28.7 and 25.8 ppm, respectively. The signal at 15.4 ppm is observed for the methyl group carbon attached to the sixth carbon.

In the ^{1}H-NMR spectrum of 6-methyl-4,4-diphenyl-2-cyclohexen-1-one, compound **74**, a multiplet between 7.37-7.06 ppm is observed for the phenyl group protons. A doublet (*J*= 10 Hz) is observed at 7.12 ppm for the double bond proton of the β-carbon. A doublet at 6.04 ppm (*J*= 10 Hz) is observed for the proton attached to the α-carbon. A multiplet between 2.55-2.52 ppm is observed corresponding to the methine proton. A multiplet is observed between 2.39-2.26 ppm corresponding to the methylene protons. A doublet at 1.00 ppm (*J*= 6 Hz) is observed for the methyl group protons. In the ^{13}C-NMR spectrum of compound **74**, in addition to other signals, a peak at 15.1 ppm is observed for the carbon of the methyl substituent.

In the ^{1}H-NMR spectrum of compound **76**, 6-methyl-4-isopropyl-2-cyclohexen-1-one, a doublet of doublet between 6.83-6.80 ppm (*J*= 3, 10 Hz) is observed for the double bond proton attached to the β-carbon. The other double bond proton attached to the α-carbon arises between 5.89-5.86 ppm as a doublet of doublets (*J*=2, 10 Hz). A multiplet between 2.50-2.45 ppm is observed for the methine proton attached to the sixth carbon and the methine proton attached to the fourth carbon. A multiplet is observed between 2.23-2.21 ppm corresponding to the CH proton of the isopropyl group. AB system of the methylene protons are observed as a multiplet between 1.94-1.87 ppm and 1.81-1.69 ppm. A doublet is observed at 1.09 ppm (*J*= 7 Hz) for the methyl group protons attached to the sixth carbon. A doublet at 0.95 ppm (*J*= 7 Hz) is observed for the methyl group protons of the isopropyl substituent.

Moreover, ethyl and benzyl substituted derivatives of cyclohexenones were prepared to see the effect of different groups in the oxidation step. The lithium enolates of cyclohexenones were reacted at -78 ºC with ethyl iodide and benzyl bromide, respectively. The results are illustrated in Table 2.

Table 2. α'-Ethylation and Benzylation of Cyclohexenones

Reactant	Product	Yield (%)
 **67**	 **77**	49
 **65**	 **78**	43
 **69**	 **79**	58
 **67**	 **80**	57
 **65**	 **81**	54

In the ^{1}H-NMR spectrum of compound **77**, 6-ethyl-3,5,5-trimethyl-2-cyclohexen-1-one, a singlet at 5.71 ppm is observed for the double bond proton. The AB system of the methylene protons of the fourth carbon is observed as a doublet (J= 8 Hz) at 2.19 ppm and a doublet (J= 10 Hz) at 2.12 ppm. A singlet is seen at 1.82 ppm corresponding to the protons of the methyl group attached to the third carbon. A multiplet is observed between 1.75-1.78 ppm for the methine proton. A multiplet is seen between 1.48-1.56 ppm for one of the methylene protons of the ethyl substituent. Another multiplet is seen between 1.33-1.41 ppm for the other methylene proton of the ethyl substituent. The diastereotopic methyl group protons corresponding to the methyl protons attached to the fifth carbon are observed as a singlet at 0.94 ppm and another singlet at 0.89 ppm. A triplet (J= 7 Hz) is observed for the methyl group protons of the ethyl substituent at 0.85 ppm. In the ^{13}C-NMR spectrum of the same compound, in addition to the other signals peaks at 13.5 and 19.4 indicate the ethyl substitution.

The ^{1}H and ^{13}C-NMR spectra of the compound **78**, are in accordance with the literature data [130].

In the ^{1}H-NMR spectrum of 6-benzyl-3,5-dimethyl-2-cyclohexen-1-one, compound **79**, a 1:9 diastereomeric mixture of *cis* and *trans* isomers are observed from the integration of the methyl protons attached to the fifth carbon. Multiplets between 7.23-7.28 ppm and 7.15-7.20 ppm are observed for the aromatic protons. A singlet at 5.87 ppm is observed for the double bond proton. AB system of the methylene protons of the benzyl substituent is observed between 3.58-3.31 ppm as a multiplet and another doublet of doublet (J= 7, 14 Hz) between 3.01-2.91 ppm. The methine proton attached to the sixth carbon arises between 2.55-2.43 ppm as a multiplet. The methine proton attached to the fifth carbon is observed between 2.08-1.92 ppm as a doublet of doublet (J= 7, 14 Hz). A singlet is observed corresponding to the methyl protons substituted to the third carbon at 1.91 ppm. A doublet (J= 7 Hz) is observed for the methyl group protons attached to the fifth carbon of the major isomer at 1.01 ppm, a doublet with (J= 7 Hz) is observed at 0.91 ppm for the methyl group protons attached to the fifth carbon of the minor isomer.

In the ^{1}H-NMR spectrum of compound **80**, multiplets between 7.39-7.24 and 7.22-7.07 ppm are observed for the phenyl group protons. A singlet is observed for the olefinic proton at 5.83 ppm. The methlyene protons of the benzyl substituent are observed as a doublet of doublets between 2.96-2.92 ppm (*J*= 7, 14 Hz) and another doublet of doublet (*J*= 4, 14 Hz) between 2.75-2.71 ppm. The methine proton is observed as a doublet of doublet between 2.39-2.30 ppm (*J*= 4, 8 Hz). The methylene protons attached to the fourth carbon of the ring are observed as a doublet at 2.21 ppm (*J*= 12 Hz), and another doublet at 1.06 ppm (*J*= 12 Hz). A singlet is observed for the methyl group protons attached to the third carbon at 1.84 ppm. The methyl group protons attached to the fifth carbon are observed as singlets at 1.09 and 1.03 ppm, respectively. In addition to the other signals, the peaks between 129.4-125.5 indicate the benzyl group substitution in the ^{13}C-NMR spectrum of the compound.

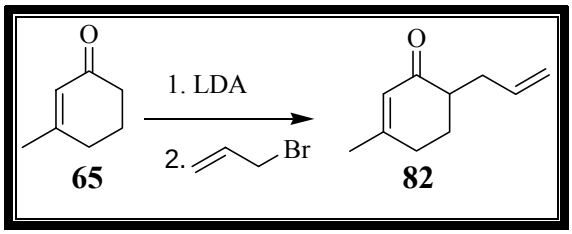
When the ^{1}H-NMR spectrum of compound **81**, 6-benzyl-3-methyl-2-cyclohexen-1-one, is analyzed, multiplets between 7.26-7.19 ppm and 7.15-7.01 ppm are observed for the phenyl group protons. A singlet at 5.83 ppm is observed for the double bond proton. The methylene protons of the benzyl substituent is observed as a doublet of doublet beteen 3.29-3.27 ppm (*J*= 2, 10 Hz) and 2.45-2.40 ppm (*J*= 2, 10 Hz). A multiplet is observed between 2.40-2.30 ppm corresponding to the methine proton attached to the sixth carbon. The methylene protons of the fourth carbon are observed as a triplet at 2.17 (*J*= 6 Hz) and a doublet of doublet between 1.92-1.83 ppm (*J*= 2, 6 Hz). A singlet is observed at 1.86 ppm corresponding to the methyl group protons attached to the third carbon. A multiplet is observed between 1.57-1.49 ppm corresponding to the methylene protons of the fifth carbon. In the ^{13}C-NMR spectrum of the same compound, peaks around 129.2 and 126.1 ppm indicate the benzyl substitution.

2.4 α'-Allylation of 3-methyl-2-cyclohexen-1-one

Metal-mediated allylation has a central position in the synthesis of various complex natural products. A wide variety of allylation reactions are well known in the literature as useful methods for carbon-carbon bond formation [131]. One of the

methods is the $Mn(OAc)_3$ mediated allylation of α,β-unsaturated ketones, reported by Tanyeli et al. in 2002 [132]. In this study, regioselective allylation of α,β-unsaturated ketones were performed in one pot with two equivalents of $Mn(OAc)_3$ and one equivalent of allyl bromide at reflux temperature of benzene.

The allylation of 3-methyl-2-cyclohexen-1-one was performed with LDA and allyl bromide at -78 ºC in this thesis. The 6-allyl-3-methyl-2-cyclohexen-1-one was synthesized in 65 % yield. The ^{1}H and ^{13}C-NMR spectra are in accordance with the literature data [132]. The reaction sequence is shown in Scheme 39.



Scheme 39. α'-Allylation of 3-methyl-2-cyclohexen-1-one

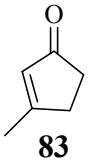
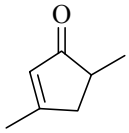
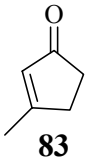
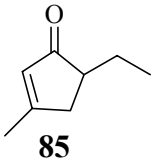
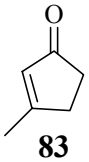
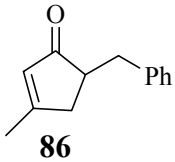
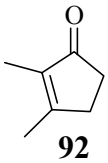
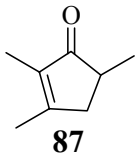
2.5 α'-Alkylation of Five Membered Rings

Cyclopentenones are the major structural features of numerous natural products. The biological importance and the high diversity of cyclopentenoid molecules justify the intensity of research efforts devoted to their synthesis within the last decades [133]. Because of this reason, the synthesis of 5-substituted cyclopentenones were attempted. However, cyclopentenones are very sensitive and easily polymerize. So, their purification by distillation or chromatography on silica gel or alumina led to partial decomposition and their alkylation yields were lower than that of cyclohexenones. Furthermore, in the alkylation of cyclopentenones, HMPA was added as a solvent, after the formation of LDA at -78 ºC, before the addition of alkyl halide. This increased the chemical yield interestingly. HMPA

(hexamethylphosphoric triamide) is known to coordinate to the metal cations, and is a useful reagent to enhance the rate of alkylation reaction of lithium enolates [134].

The chemical yields of the alkylations were decreased, because the alkylation can not be stopped at monoalkylation stage, under basic conditions polyalkylations can occur. The results of the alkylations are summarized in Table 3.

Table 3. The results of the α'-alkylations.

Reactant	Product	Yield (%)
 **83**	 **84**	72
 **83**	 **85**	67
 **83**	 **86**	61
 **92**	 **87**	53

In the ^{1}H-NMR spectrum of compound **84**, 3,5-dimethyl-2-cyclopenten-1-one, a singlet arises at 5.80 ppm corresponding to the double bond proton. The methylene protons of the ring are seen as a doulet of doublet between 2.65-2.58 (*J*= 2, 6 Hz) and a triplet at 2.15 ppm (*J*= 6 Hz). A multiplet is observed between 2.28-2.18 ppm corresponding to the methine proton of the fifth carbon. A singlet at 2.10 ppm is observed for the methyl group protons attached to the third carbon. A doublet (*J*= 7 Hz) arises at 1.09 ppm corresponding to methyl protons attached to the fifth carbon.

In the ^{1}H-NMR spectrum of 5-ethyl-3-methyl-2-cyclopenten-1-one,compound **85**, a singlet at 5.84 ppm is observed for the double bond proton. A doublet of doublet with (*J*= 6, 18 Hz) is observed between 2.63-2.69 ppm for one of

the methylene protons substituted at the ring. The other methylene proton is observed at 2.19 ppm (*J*= 18 Hz) as a doublet. The methine proton is observed as a multiplet between 2.25-2.30 ppm. A singlet is observed at 2.06 ppm corresponding to the methyl group protons attacehd to the third carbon. The diastereotopic methylene protonsa re observed as multiplets between 1.72-1.78 and 1.30-1.38 ppm. A triplet (*J*= 7 Hz) is seen at 0.87 ppm for the methyl group protons of the ethyl substituent. In the ^{13}C-NMR spectrum of this compound, the peaks at 24.6 and 12.0, in addition to the other peaks indicate the substitution of the ethyl group.

The ^{1}H and ^{13}C-NMR spectra of the compounds **86** and **87** are in accordance with the literature data [135, 136].

2.6 Manganese(III) Acetate Based Oxidations

Manganese(III) acetate oxidation is one of the valuable regioselective oxidation methods for the synthesis of α'-acetoxy α,β-unsaturated ketones. However, all the examples in the literature are concerned with the substrates that are unsubstituted at the α'-position. To the best of our knowledge, the only example reported on the attempt to α'-acetoxylation of an enone with a tertiary α'-carbon was that of a steroidal compound. As mentioned before, Ahmad et al reported that they obtained unexpected products with low yields and not the α'-acetoxy enone. This was the only exception reported to the high regioselectivity of the manganese(III) acetate oxidations. From this point of view, it was aimed to study the manganese(III) acetate oxidation of substituted α'-positions on various cyclopentenones and cyclohexenones. This thesis is the first example in the literature that a one-pot synthesis of a quaternary carbon stereocenter is generated by the formation of α'-*ter*t-acetoxy group on cyclic enones.

The screening reactions were examined at first to obtain an effective procedure for the α'-acetoxylation of enones. Cyclopentenones and cyclohexenones were tested with $Mn(OAc)_3$ by varying the molar ratio of the substrate/oxidizing agent from 1:1 to 1:6. A 1:2 molar ratio proved to be suitable for the regioselective

acetoxylation of α'-substituted enones. In the past, 1:6 molar ratio was used, however, this high amount of manganese(III) acetate does not affect the yield of the formation of the α'-acetoxy ketones. So, in all of our reactions a 1:2 substrate/oxidizing agent ratio was used.

A mixture of $Mn(OAc)_3$ in benzene was refluxed for 45 min under a Dean-Stark trap, then cooled to room temperature. The α'-substituted cyclic ketone was gradually added and the mixture was allowed to reflux with TLC monitoring until the dark brown color disappeared. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in *vacuo*. The crude product was separated by flash column chromatography.

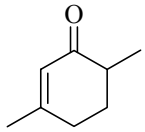
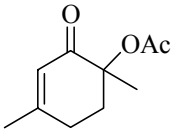
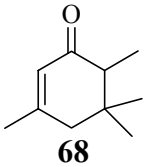
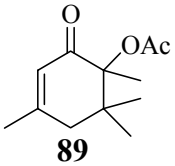
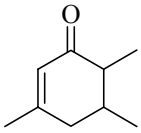
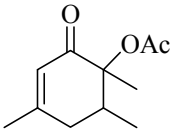
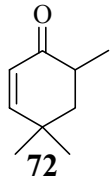
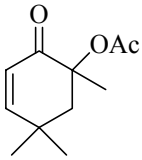
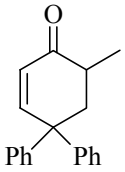
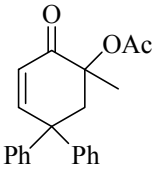
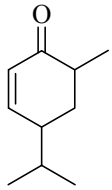
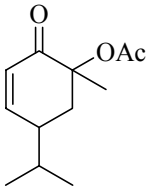
Manganese(III) acetate is obtained commercially from Sigma or Aldrich. Since all the manganese(III) acetate used is not in the same purity, different yields can be obtained under the similar conditions for the same compounds. The yield of manganese(III) acetate oxidations increased when $Mn(OAc)_3$ was dried effectively. Molecular Sieve 4A was decided to be used in the course of reflux, to get higher yields. However, this procedure was not effective on the increase in the chemical yield.

The use of $Cu(OAc)_2$ with $Mn(OAc)_3$ was reported to enhance the yield of the oxidations [137, 138]. Hence, 2 equivalents of $Mn(OAc)_3$ was used with one equivalent of $Cu(OAc)_2$ in the course of the oxidations. But, there was no change in the product formation and the chemical yield.

The reaction presumably proceeds via the formation of the Mn(III) enolate, which loses Mn(II) upon one-electron oxidation to give α'-radical. Oxidation of the intermediate by another $Mn(OAc)_3$ provides α'-acetoxy enones. Vinagradov and co-workers reported that α'-keto radicals generated from higher ketones result in the formation of secondary radicals which dimerize or tertiary radicals which are prone to further oxidation. In contrast to this conclusion, no dimerization was observed.

The cyclohexenones that are methyl substituted at the α'-position are subjected to the oxidation with manganese(III) acetate at first. The results of $Mn(OAc)_3$ oxidations of α'-methyl α,β-unsaturated cyclohexanones are summarized in Table 4. Characterization of the products revealed the introduction of an acetoxy moiety at the α'-position.

Table 4. The results of $Mn(OAc)_3$ oxidations of α'-methyl substituted cyclohexenones

Reactant	Product	Yield (%)	Time (h)
 **66**	 **88**	64	10
 **68**	 **89**	76	10
 **70**	 **90**	81	12
 **72**	 **91**	78	10
 **74**	 **92**	47	28
 **76**	 **93**	82	12

Among methyl substituted 2-cyclohexenone derivatives, the best yield was observed in the synthesis of 6-acetoxy-6-methyl-4-isopropyl-2-cyclohexen-1-one. The other substrates gave similar, acceptable yields (64-81 %). However, there was a drastic decrease in yield for the diphenyl substituted derivative (47 % yield). Although the reaction time was increased after 10 h to 28 h, there was no change in the yield of product formed.

In the ^{1}H-NMR spectrum of 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one **88**, a singlet arises at 5.83 ppm corresponding to double bond proton. The methylene protons attached to the fourth carbon are observed as a doublet of doublet of doublet (*J*= 7, 12, 18 Hz) between 2.77-2.85 ppm and a doublet of quartet (*J*= 2, 12 Hz) between 1.81-1.86 ppm. A multiplet is seen between 2.26-2.41 ppm corresponding to the methylene protons attached to the fourth carbon. The methyl protons of the acetoxy group is observed at 1.99 as a singlet. The methyl group protons attached to the third and sixth carbons are observed as singlets at 1.89 and 1.36 ppm, respectively. In the ^{13}C-NMR spectrum, the presence of the acetoxy group's carbonyl carbon is indicated at 170.0 ppm.

In the ^{1}H-NMR spectrum of 6-acetoxy-3,5,5,6-tetramethyl-2-cyclohexen-1-one **89**, the double bond proton is observed as a singlet at 5.70 ppm. The diastereotopic methylene protons are observed as a doublet (*J*= 18 Hz) at 2.45 ppm, and another doublet at 1.79 ppm (*J*= 18 Hz). The acetoxy group methyl protons are observed as a singlet at 1.90 ppm. The methyl protons attached to the third carbon are observed as a singlet at 1.77 ppm. The diastereotopic methyl group protons attached to the fifth carbon are observed as singlets at 1.36 and 1.08 ppm respectively. The methyl group protons attached to the sixth carbon are observed as a singlet at 1.02 ppm. In the ^{13}C-NMR spectrum the presence of the acetoxy group's carbonyl carbon is indicated a 172.0 ppm.

When the ^{1}H-NMR spectrum of 6-acetoxy-3,5,6-trimethyl-2-cyclohexen-1-one **90** is analyzed, a non-separable 1:1 diastreomeric mixture of syn/anti isomers is observed from the integration of methyl protons attached to the fifth carbon.The olefinic proton is observed at 5.83 ppm for one isomer. The olefinic proton of the

other isomer is observed at 5.76 ppm. The methine proton of both isomers are observed between 3.18-3.09 ppm as a multiplet.The methylene protons attached to the fourth carbon are observed between 2.62-2.21 ppm as multiplets.The methyl group protons of the acetoxy moiety is observed as a singlet at 2.01 ppm for one isomer, and as another singlet at 1.97 ppm for the other isomer. The methyl group protons attached to the third carbon are observed as a singlet at 1.88 and 1.84 ppm for the diastereomers respectively. The methyl group protons attached to the sixth carbon are observed as singlets at 1.49 and 1.19 ppm for the isomers, respectively. The methyl group protons attached to the fifth carbon are observed as doublets (J= 7 Hz) for the isomers at 0.99 and 0.93 ppm, respectively. The presence of the acetoxy group is indicated in the ^{13}C-NMR, at 169.8 and 169.5 ppm for the acetoxy group carbonyl carbons of the diastereomers.

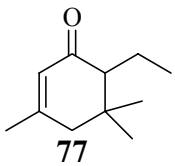
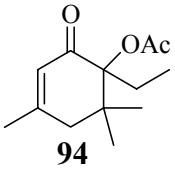
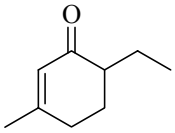
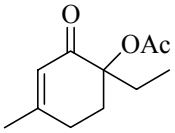
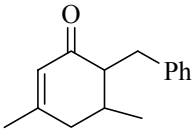
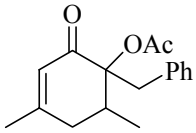
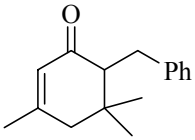
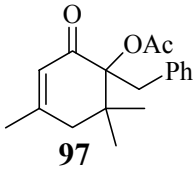
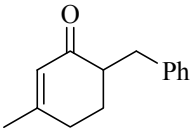
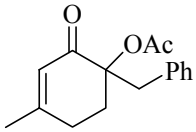
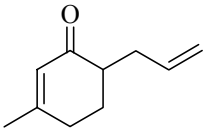
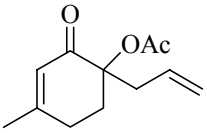
In the ^{1}H-NMR spectrum of 6-acetoxy-4,4,6-trimethyl-2-cyclohexen-1-one **91**, the double bond proton attached to the β-carbon is observed as a doublet at 6.52 ppm (J=10 Hz), the double bond proton attached to the α-carbon appears at 5.81 ppm as a doublet (J=10 Hz). The diasereotopic methylene protons are observed at 2.62 ppm as a doublet (J=14 Hz) and at 1.79 ppm as a doublet (J= 14 Hz). The acetoxy group methyl protons are seen at 1.90 ppm as a singlet. The methyl protons attached to the sixth carbon are seen as a singlet at 1.46 ppm. The methyl group protons that are attached to the fourth carbon are seen as singlets at 1.16 and 1.14 ppm, respectively. The ^{13}C-NMR spectrum indicates the presence of the acetoxy group carbonyl carbon at 170.5 ppm.

In the ^{1}H-NMR spectrum of 6-acetoxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one **92**, a multiplet is seen between 7.32-7.11 ppm correponding to aromatic protons and one proton attached to the β-carbon. A doublet (J= 6 Hz) is observed at 6.21 ppm corresponding to the proton attached to α-carbon. An AB system corresponding to the methylene protons are observed as a doublet at 3.66 ppm (J= 14 Hz) and another doublet at 2.75 ppm (J= 14 Hz). At 1.88 ppm a singlet is observed for the methyl protons of the acetoxy group. Another singlet is observed at 0.97 ppm for methyl protons. In the ^{13}C-NMR spectrum, the carbonyl carbon of the acetoxy group is observed 170.2 ppm.

In the ^{1}H-NMR spectrum of 6-acetoxy-6-methyl-4-isopropyl-2-cyclohexen-1-one **93**, 8:2 diastereomeric mixture is observed from the integration of acetoxy group methyl protons. For the major isomer, a doublet of doublet is seen at 6.69 ppm corresponding to the double bond proton attached to β-carbon (*J*= 10, 4 Hz). A doublet is seen at 5.96 ppm corresponding to the α-proton of the double bond carbon (*J*= 10 Hz). A multiplet arises between 2.49-2.53 ppm correponding to the methine proton of the ring. Another multiplet is seen between 2.42-2.44 ppm corresponding to the methine proton of the isopropyl group. A multiplet is seen between 1.99-2.07 ppm for the methylene protons, a singlet is seen at 1.93 ppm for methyl protons of acetoxy group and another singlet arises at 1.47 ppm correponding to the methyl protons attached to the sixth carbon. A doublet is observed with (*J*= 7 Hz) for the methyl protons of the isopropyl group. For the minor isomer, a doublet of doublet is observed at 6.69 ppm for the β-proton (*J*= 10, 4 Hz). A doublet is seen at 5.96 ppm (*J*= 10 Hz) for α-proton. A multiplet arises between 2.44-2.48 ppm for the methine proton of the fourth carbon. A multiplet is seen between 2.42-2.44 ppm for the methine proton of isopropyl group and another multiplet is seen between 1.99-2.07 ppm for the methylene protons. A singlet arises at 1.95 ppm for acetoxy group mehyl protons, a singlet is observed at 1.49 ppm for methyl protons and a doublet is seen with (*J*= 7 Hz) for the methyl protons of the isopropyl group. In the ^{13}C-NMR spectrum, the ester carbon is observed at 170.2 ppm for the major isomer and at 169.2 ppm for the minor isomer.

$Mn(OAc)_3$ oxidations were applied to ethyl, benzyl and allyl substituted cyclohexenones as well. The results of the oxidations are shown in Table 5, illustrated below.

Table 5. $Mn(OAc)_3$ Oxidations of Ethyl, Benzyl and Allyl Substituted Cyclohexenones

Reactant	Product	Yield (%)	Time (h)
 **77**	 **94**	48	14
 **78**	 **95**	72	12
 **79**	 **96**	77	5
 **80**	 **97**	57	18
 **81**	 **98**	57	9
 **87**	 **99**	40	18

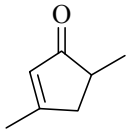
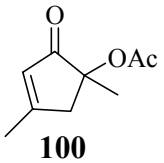
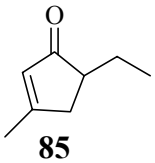
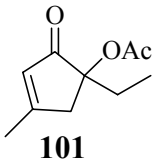
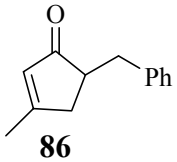
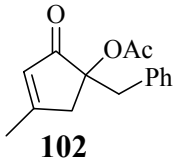
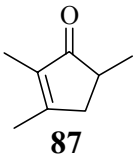
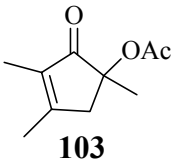
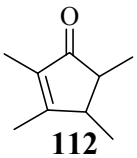
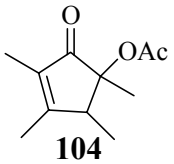
The acetoxylation yields of ethyl substituted derivatives were lower than their methyl substituted derivatives. Presumably, this can be due to the sterical effect of the ethyl group. Among the ethyl substituted derivatives, the best yield was observed in the oxidation of 6-ethyl-3-methyl-2-cyclohexen-1-one. The time needed to perform the acetoxylation of the ethyl substituted derivatives is around 12 h. This is more or less the same as the methyl substituted derivatives.

The best yield in the acetoxylation of the benzyl substituted derivatives was observed in the oxidation of 6-benzyl-3,5-dimethyl-2-cyclohexen-1-one. The oxidation was completed in 5 h in 77% yield. The time of the acetoxylation is lower than the acetoxylation of the methyl substituted derivative of the same compound, since the oxidation of the 3,5,6-trimethyl-2-cyclohexen-1-one was completed in 12 h in 81% yield. The acetoxylation of 6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one was completed in 57% yield. Increasing the reaction time beyond 18 h failed to improve the yield of the product formed.

The oxidation of the allyl substituted derivative was performed in 40% yield. The increase in the reaction time beyond 13 h till 18 h did not affect the yield of the product formed. This can be due to the sterical effect of the allyl group. The compound 6-acetoxy-6-allyl-3-methyl-2-cyclohexen-1-one is not stable. It can decompose easily. It should be kept in the refrigerator, under Ar atmosphere. Since it is light sensitive, it is advised to store in a dark bottle.

The $Mn(OAc)_3$ oxidation of cyclopentenone derivatives were performed in similar conditions to the cyclohexenones. The results are summarized in Table 6.

Table 6. The Oxidation of α'-Substituted Cyclopentenones

Reactant	Product	Yield (%)	Time (h)
 **84**	 **100**	72	8
 **85**	 **101**	42	24
 **86**	 **102**	51	18
 **87**	 **103**	48	9
 **112**	 **104**	68	8

Among the oxidation of the 2-cyclopentenone derivatives, 3,5-dimethyl-2-cyclopenten-1-one gave the best yield. The oxidation yields of α'-ethyl and benzyl substituted 3-methyl cyclopentenones were lower than α'-methyl substituted derivative. Increasing the reaction time beyond 16 h failed to improve the yield of the product formed. All the cyclopentenone derivatives are air sensitive. They should be stored under Ar atmosphere.

In the ^{1}H-NMR spectrum of 5-acetoxy-3,5-dimethyl-2-cyclopenten-1-one **100**, a singlet is seen at 5.71 ppm for the double bond proton. The methylene protons are observed as a doublet (*J*= 18 Hz) at 2.80 ppm and another doublet (*J*= 18 Hz) at 2.32 ppm. A singlet is seen at 1.88 ppm for methyl protons of the acetoxy group, another singlet arises at 1.82 ppm for methyl protons attached to the third carbon. The methyl protons attached to the fifth carbon are observed as a singlet at 1.16 ppm. The presence of the acetoxy group carbonyl carbon can be seen from the ^{13}C-NMR spectrum at 173.1 ppm.

In the ^{1}H-NMR spectrum of 5-acetoxy-5-ethyl-3-methyl-2-cyclopenten-1-one **101**, a singlet is observed at 5.88 ppm for the double bond proton. An AB system is observed at 2.87 ppm as a doublet (*J*= 18 Hz) and at 2.51 ppm as another doublet (*J*= 18 Hz). The acetoxy group methyl protons are seen at 2.07 ppm as a singlet, the methyl protons attached to the third carbon are observed at 1.99 ppm as a singlet. The methylene protons of the ethyl substituent are seen as a multiplet between 1.55-1.75 ppm. A triplet (*J*= 7 Hz) is observed at 0.84 ppm for methyl group protons. The presence of the acetoxy group carbonyl carbon is indicated in the ^{13}C-NMR spectrum at 173.2 ppm.

In the ^{1}H-NMR spectrum of compound **102** , a multiplet between 7.02-7.24 ppm is observed for the phenyl group protons. A singlet is seen at 5.80 ppm corresponding to the olefinic proton. The methylene protons of the benzyl substituent are observed as a doublet at 3.43 ppm (*J*= 18 Hz) and another doublet at 2.45 ppm (*J*= 18 Hz). The methylene protons of the ring are observed as a doublet at 2.42 ppm (*J*= 14 Hz) and another doublet at 1.93 ppm (*J*= 14 Hz). The methyl group protons of the acetoxy group is observed at 2.03 ppm as a singlet. The methyl group protons attached to the third carbon are seen as a singlet at 1.97 ppm. In the ^{13}C-NMR spectrum of the same compound, the presence of the acetoxy group carbonyl carbon is observed at 178.5 ppm.

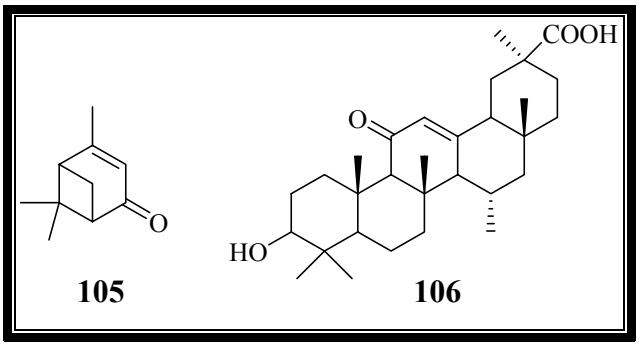
In the ^{1}H-NMR spectrum of compound **103**, 5-acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one, the methylene protons of the ring are observed as a doublet at 3.03 ppm (*J*= 14 Hz) and another doublet at 2.78 ppm (*J*= 14 Hz). The acetoxy group

methyl protonsa re seen as a singlet at 2.03 ppm, the methyl group protons attached to the third and second carbon are observed as singlets at 1.88 and 1.73 pm, respectively. The protons of the methyl group attached to the fifth carbon are seen as a singlet at 1.21 ppm.

The ^{1}H-NMR spectrum of 5-acetoxy-2,3,4,5-tetramethyl-2-cyclopenten-1-one **104** is observed as 9:1 diastereomeric mixture from the integration of methyl protons attached to the fourth carbon. In the major isomer is a multiplet is observed between 2.73-2.75 ppm for the methine proton. The acetoxy group methyl protons are seen at 1.68 ppm as a singlet. The methyl group protons attached to the α and β-carbons are seen as singlets at 1.63 and 1.48 ppm, respectively. The methyl group attached to the fifth carbon is observed at 0.88 ppm as a singlet. The methyl grou attached to fourth carbon is observed as a doublet at 0.82 ppm (J= 8 Hz). In the minor isomer, a multiplet is seen between 2.34-2.36 ppm for methine proton. The acetoxy group methyl protons arise at 1.70 ppm as a singlet. The methyl protons attached to the α and β-carbons of the double bond are observed as singlets at 1.65 ppm and 1.48 ppm, respectively. The methyl group attached to fifth carbon is seen at 1.04 ppm as a singlet and the methyl group attached to the fourth carbon is observed as a doublet at 0.74 ppm (J= 8 Hz). In the ^{13}C-NMR spectrum, the ester carbon is seen at 169.8 ppm for the major isomer and at 170.1 ppm for the minor isomer.

The manganese(III) acetate oxidation results of the cylohexenones and cyclopentenones are different from each other. So, they can not be compared in the reaciton time or the yield of the product formed.

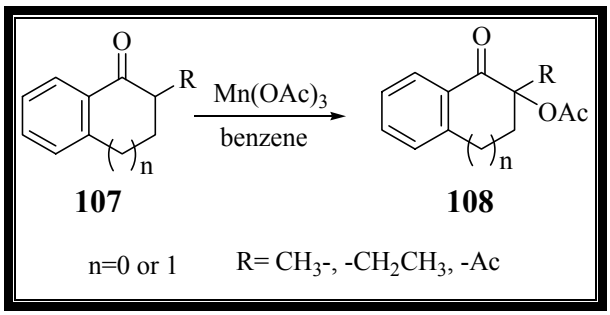
Apart from cyclopentenones and cyclohexenones, the manganese(III) acetate oxidations were applied on natural products like (1*S*)-(-)-Verbenone **105** and 18-*β*-Glycyrrhetinic acid **106** (Scheme 40). In the (*1S*)-(-)-Verbenone case, after 10 h reflux a new product was formed. However, this was not the desired acetoxy product. According to the ^{1}H-NMR data it was thought to dimerize. In 18- *β*-Glycyrrhetinic acid case, two new products were formed after 12 h reflux,;however, these could not be identified.



Scheme 40. (1*S*)-(-)-Verbenone **105** and 18-*β*-Glycyrrhetinic acid **106**

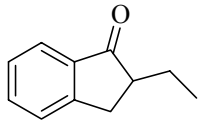
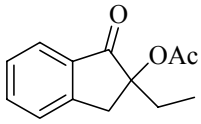
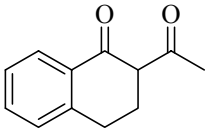
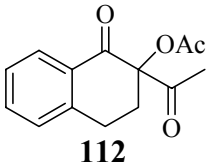
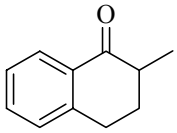
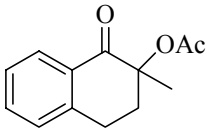
2.7 Manganese(III) Acetate Oxidations of α'-Substituted Aromatic Ketones

It is well known in the literature that $Mn(OAc)_3$ regioselectively oxidizes the aromatic ketones as well as enones [139]. In this study,the regioselective oxidation of α'-substituted aromatic ketones was investigated. (Scheme 41). It can be seen from Table 3 that oxidation of aromatic ketones were completed in 18 h with 30-56 % yields (Table 7).



Scheme 41. Oxidations of the α'-substituted aromatic ketones

Table 7. Selective oxidation of α'-substituted aromatic ketones

Reactant	Product	Yield (%)	Time (h)
 **109**	 **110**	30	18
 **111**	 **112**	46	18
 **113**	 **114**	56	18

Compounds 2-ethyl indanone (**109**) and 2-acetyl tetralone (**111**) were purchased from Aldrich. 2-methyl tetralone was synthesized according to known procedure with LDA and methyl iodide at -78 ºC (60 % yield).

In the ^{1}H-NMR spectrum of 2-acetoxy-2-ethyl indanone, a doublet arises at 7.71 ppm (*J*= 8 Hz), a triplet is seen at 7.53 ppm (*J*= 8 Hz), a multiplet arises between 7.30-7.33 corresponding to the aromatic protons. AB system of the methylene protons of the ring arises as a doublet at 3.35 ppm (*J*= 17 Hz), another doublet at 3.15 ppm (*J*= 17 Hz). The acetoxy group methyl protons arise at 2.02 ppm as a singlet. The methylene protons of the ethyl substituent are observed as a multiplet between 1.75-1.86 ppm and another multiplet between 1.63-1.72 ppm. A triplet (*J*= 7 Hz) is seen at 0.87 ppm corresponding to methyl group protons of the ethyl substituent.

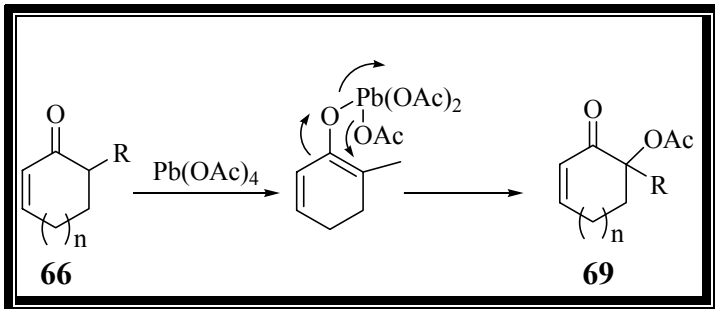
In the ^{1}H-NMR spectrum of 2-acetoxy-2-acetyl tetralone, the aromatic protons are seen between 8.58-7.35 ppm as multiplet, the methlyene protons of the ring appear as a multiplet between 2.79-3.02 ppm, the acetoxy group methyl protons are seen at 2.26 ppm as a singlet and the acetyl group methyl protons arise at 2.23 ppm as another singlet. Although the acidity is increased, there is no change in the chemical yield of the oxidation in this example.

In the ^{1}H-NMR spectrum of 2-acetoxy-2-methyl tetralone, the aromatic protons appear as multiplet between 8.00-7.15 ppm, the methylene protons of the ring are seen as a multiplet between 2.89-2.99 ppm, the acetoxy group methyl protons appear as a singlet at 2.00 ppm and the methyl group protons are seen at 1.47 ppm as a singlet.

2.8 Oxidations with Lead(IV) Acetate

Oxidation with lead(IV) acetate is another method for the synthesis of α-acetoxy ketones. Because of this reason, the oxidation reaction of α'-substituted aromatic ketones and α'-substituted enones by $Pb(OAc)_4$ was also investigated.

The reaction mechanism of the lead(IV) acetate oxidation is thought to proceed through the following reaction mechanism (Scheme 42). Lead(IV) acetate oxidation is performed in benzene in a 1:3 substrate/oxidizing agent ratio. Cyclohexane is the other solvent of choice.



Scheme 42. The reaction mechanism of $Pb(OAc)_4$ oxidation

The reaction of 2-ethyl indanone was examined first. One equivalent of 2-ethyl indanone was refluxed in dry benzene with 3 equivalents of $Pb(OAc)_4$. After 20 h reflux, 2-acetoxy-2-ethyl indanone was synthesized in 30% yield. The reaction of 2-methyl tetralone with $Pb(OAc)_4$ was also examined. One equivalent of 2-methyl tetralone was refluxed in dry benzene for 18 h and the product was obtianed in 50% yield.

The 3,5,6-trimethyl-2-cyclohexen-1-one was chosen as the model compound in the trial reaction including enones, since it gave the best result in the $Mn(OAc)_3$ oxidation. It was refluxed in dry benzene with three equivalents $Pb(OAc)_4$ for 15 h. The 6-acetoxy-3,5,6-trimethyl-2-cyclohexen-1-one was obtained in 78% yield.

If we compare the results of $Pb(OAc)_4$ oxidations with that of the $Mn(OAc)_3$ oxidations, the chemical yields are similar. In almost same reaction times, the oxidations were completed. Monitoring $Pb(OAc)_4$ oxidations were easier since a clear solution was formed in benzene. Since manganese(III) acetate is safer and more environmentally friendly than toxic $Pb(OAc)_4$, $Mn(OAc)_3$ was preferred as the oxidizing agent in the course of the studies.

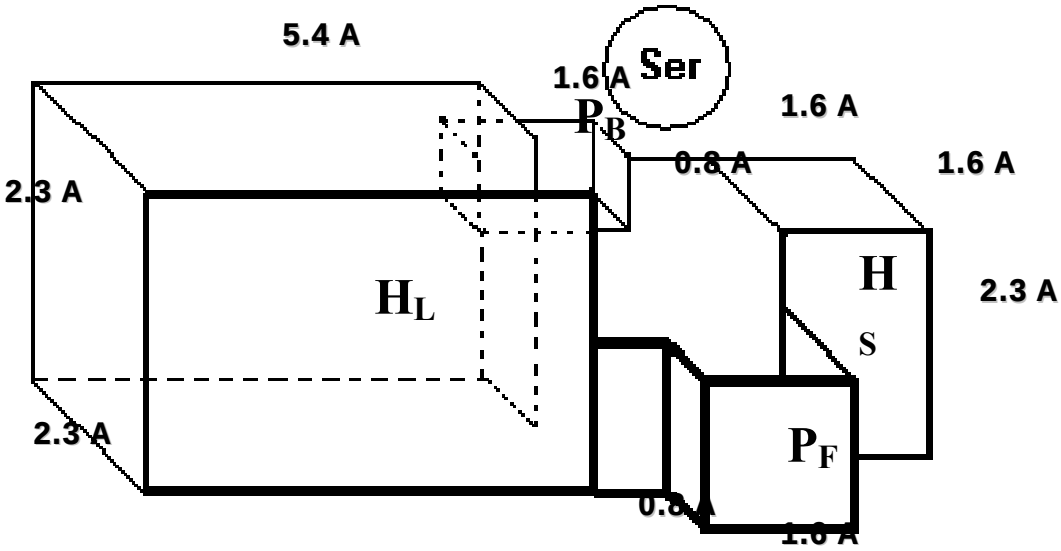
2.9 Resolutions with Hydrolase Type Enzymes

Stereoselective synthesis of enantiomerically pure α'-*tert*-hydroxy ketones has been a challenge for chemists since last decades. There are several methods reported on this subject, however, the resolution by hydrolase type enzymes has not been reported. The lack of known sysnthesis of enantiomerically enriched α'-acetoxy-α'-alkyl-α,β-unsaturated ketones prompted us towards the development of a new method involving resolution with hydrolases.

It was reported by Tanyeli et al in 1996 [140] that (±)-6-acetoxy-3-methyl-2-cyclohexen-1-one was resolved by PLE catalyzed hydrolysis to afford enantiomerically enriched 6-hydroxy derivative with 85-98% e.e. Therefore, it was decided to examine the hydrolysis reaction of α'-substituted α'-acetoxy α,β-

unsaturated cyclic ketones by PLE which is known for its broad substrate specificity and high stereoselectivity. 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one, compound **88** was chosen as a model compound and subjected to enzymatic resolution with PLE Treatment of the substrate in the absence of enzyme revealed that it does not undergo autohydrolysis. The enzymatic hydrolysis reaction was performed according to the following procedure. To a stirred solution of 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one (100 mg) in phosphate buffer (pH 7.00, 10 mL), was added PLE (100 μL) in one portion and the mixture was stirred at 20 ºC. The reaction was monitored by TLC. However, no hydrolysis was recorded after 156 h. Since the enantioselectivity of the enzymatic reactions depends on the pH, temperature and the addition of co-solvent, screening reactions were performed by changing the parameters mentioned. The effect of temperature was examined by changing it from 14-28 ºC. No change in the reaction was observed. Upon changing co-solvents (dimethylsulfoxide (DMSO), *i*-propanol, *tert*-butyl methyl ether and *n*-butanol), no new effect was recorded. It was decided to see the effect of pH on the reaction. The substrate was subjected to pH 7.5 and pH 8.0 buffers in the absence of enzyme. It is observed that the substrate does not undergo any autohydrolysis in the absence of enzyme between this pH range. Finally, the substrate was subjected to enzymatic hydrolysis by the addition of 100 μL PLE in pH 7.5 and pH 8.0 buffers, respectively. It was recorded that in pH 8.0 buffer, the enzymatic hydrolysis started in 48 h. There was no hydrolysis at pH 7.5. Around 50% conversion was completed within 96 h in pH 8.0 buffer system with PLE. The crude product was separated by flash column chromatography. (-)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one was obtained in 42% yield with 5% e.e. Although the enantioselectivity was low, the first example showed that α'-substituted α'-acetoxy α,β-unsaturated cyclic ketones can be resolved by hydrolase type enzymes, although, PLE is not suitable for these hydrolysis reactions.

The low stereoselectivity of the reaction should be considered from the active site model of PLE, which was developed by Jones et al. in 1990 (Scheme 43) [141]



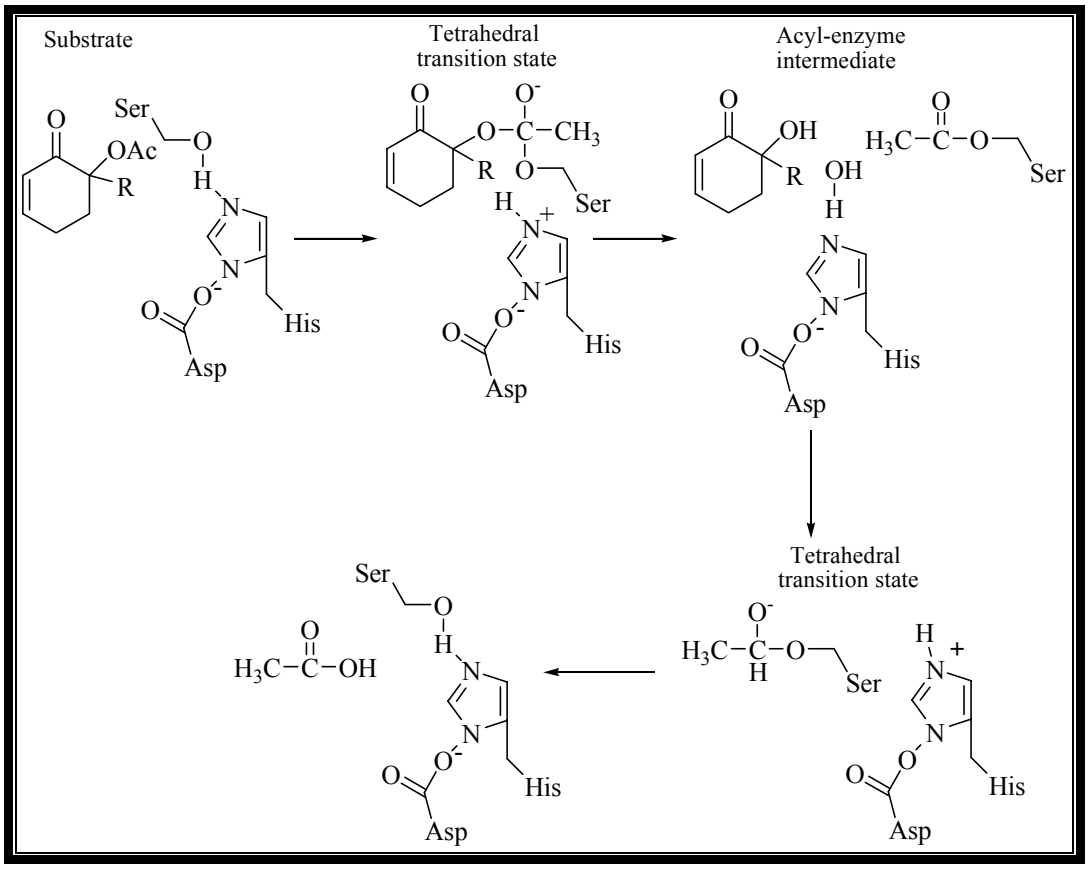
Scheme 43. Active site model of PLE

The boundaries of the model represent the physical constraints placed on the available substrate-binding volume by the amino acid residues of the enzyme. The important binding regions for specificity determinations are two hydrophobic pockets, H_L and H_S, and two pockets of more polar character, P_F and P_B. The best fit, if any, of a substrate is determined by locating the ester group to be hydrolyzed within the serine sphere and then placing, if possible, the remaining substrate moities in the H and P pockets according to the simple set of rules. In our substrate, the presence of the 6-methyl group which is very close to the ester group that should be hydrolyzed presumably, blocks the fit of the enzyme to the substrate. Because of this reason, the enantioselectivity is decreased.

From this point of view, it was decided to examine the enzymatic hydrolysis reactions of the model compound, 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one, with various hydrolases like CCL, PPL and HLE. The screening reactions were first performed to find out the optimum conditions in the hydrolysis reactions. The hydrolysis reactions were performed in 1:0.5 substrate:enzyme molar ratio at pH 7.0. At this pH, no hydrolysis was recorded. The pH was increased to pH 8.0 by the

addition of 1 N NaOH. At pH 8.0, the hydrolysis reactions of the substrate with CCL was complete in 78 h with 48 % e.e at 20 ºC. No hydrolysis was recorded with PPL and HLE. When the pH was increased to 8.5, complete racemization of the substrate was recorded. So, the optimum pH in the hydrolysis should be pH 8.0. The temperature effect was also investigated. The temperature was changed from 14-28 ºC, and the optimum temperature was found as 20 ºC, for the enzyme CCL. Unfortunately, no hydrolysis was recorded with HLE and PPL. It was totally focused on the enzymatic hydrolysis reactions with CCL and the optimum conditions were found for the reaction to be pH 8.0 buffer, at 20 ºC, with dimethylsulfoxide (DMSO) used as a co-solvent. The enzyme:substrate molar ratio was changed from 0.5:1 to 1:1, and the enantiomeric excess was increased to 99 %. That is, when the enzyme is used in stoichiometric amount, the enantioselectivity is increased. (-)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one was synthesized in 46 % isolated yield in 99% enantiomeric excess at pH 8.0 buffer, at 20 ºC. CCL, which is generally known for its stereoselectivity in the hydrolysis of secondary alcohols, appeared to be the best enzyme tested.

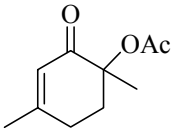
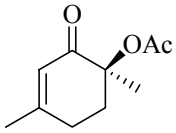
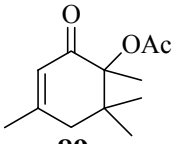
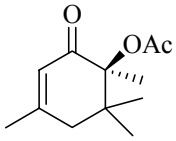
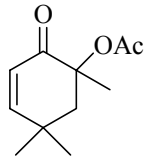
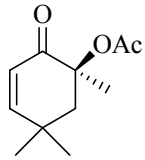
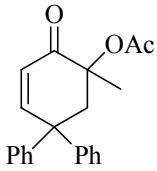
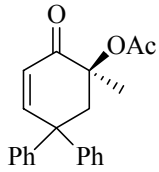
The hydrolysis with CCL can be explained through serine hydrolases. The serine hydrolase contains a catalytic triad in the active site composed of Asp, His and Ser, with Ser acting as the nucleophile. The catalytic triad is shown in Scheme 44. In the catalytic triad, after CCL has bound its substrate, the serine residue is ideally situated to attack the acyl carbon of the substrate. The serine residue is made more nucleophilic by transferring its proton to the imidazole nitrogen of the histidine residue. The imidazolium ion that is formed is stabilized by the polarizing effect of the carboxylate ion of the aspartic acid residue. Nucleophilic attack by the serine leads to an acylated serine through a tetrahedral intermediate. The new N-terminal end diffuses away and is replaced by a water molecule.



Scheme 44. Catalytic triad

Candida *cylindracea* lipase (CCL), which is a lipase type enzyme, is used for the first time in the literature for the hydrolysis of a tertiary acetoxy group in this study. In order to the see the effect of the substituents on the cyclohexenone ring system, various α'-methyl substituted α'-acetoxy cyclohexenones were subjected to hydrolysis by CCL. The results of the enzymatic resolutions on different substrates that contain α'-acetoxy α'-methyl cyclohexenones are listed in Table 8. The reaction was performed according to the following procedure. 100 mg substrate was added to pH 8.00 buffer (20 mL) in 1 mL DMSO. 100 mg CCL was added to the solution and shaken for 96-148 h by TLC monitoring at 20 ºC.

Table 8. Resolutions with CCL

Substrate	Product	Time (h)	Conversion (%)	Ee (%)	$[\alpha]^{20}_D$
 **88**	 **(-)-88**	96	46	99	-13.1
 **89**	 **(-)-89**	108	51	62	-1.80
 **91**	 **(-)-91**	122	52	94	-42.2
 **92**	 **(-)-92**	136	48	73	-29.2

It can be easily seen from the Table 8 that the presence of the substituents at the fifth carbon, nearby the carbon atom of the stereogenic center, significantly decreases the enantioselectivity of the reaction. 6-acetoxy-6-methyl-4,4-dimethyl-2-cyclohexen-1-one and 6-acetoxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one were employed to see the effect of substitution on the fourth carbon. A rapid decrease on the enantioselectivity was observed when the substituents were changed to phenyl group. However, this can be attributed to the solubility problem of the diphenyl substrate. The presence of the methyl substituent at the third carbon has no effect on the enantiomeric excess value.

The resolution of (-)-6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one, compound **(-)-88**, was completed in 96 hours in 99 % enantiomeric excess. The racemic 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one, compound **88**, was subjected to CCL hydrolysis in pH 8.00 buffer. The reaction was monitored by TLC. After 50 % conversion, the crude product was separated by flash column chromatography. However, the 6-hydroxy-3,6-dimethyl-2-cyclohexen-1-one can not be isolated. It is thougth to aromatize according to the ^{1}H-NMR spectrum. In the ^{13}C-NMR spectrum, the peaks at 126.5, 127.6 and 128.5 show the aromatization. The enantiomeric excess value was measured by HPLC, Chiralcel OD-H chiral column, 85:15 hexane:isopropanol as eluent at 1.0 mL/min flow rate. The configuration of (-)-6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one is unknown.

(-)-6-acetoxy-3,5,5,6-tetramethyl-2-cyclohexen-1-one **(-)-89**, was resolved in 108 h, in 62 % enantiomeric excess. The decrease in the stereoselectivity can be attributed to the presence of two methyl groups at the C-5, which neighbours the center of chirality. The 6-hydroxy-3,5,5,6-tetramethyl-2-cyclohexen-1-one can not be isolated. This can be due to the aromatization of the hydroxy compounds on silica gel. The enantiomeric excess value of (-)-6-acetoxy-3,5,5,6-tetramethyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 88:12 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

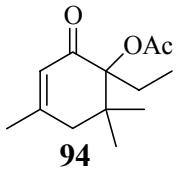
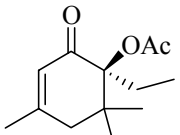
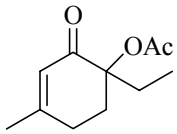
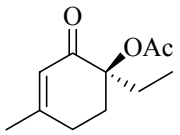
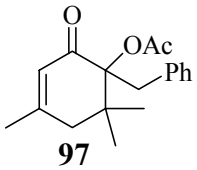
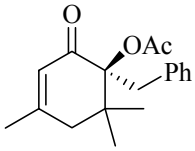
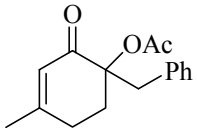
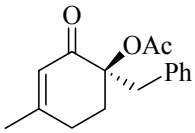
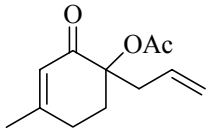
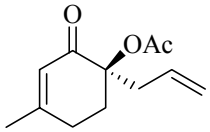
(-)-6-acetoxy-4,4,6-trimethyl-2-cyclohexen-1-one, compound **(-)-91**, was resolved in 122 h, in 94 % enantiomeric excess. The presence of the methyl groups has no effect on the stereoselectivity, since they are far away from the center of chirality. The 6-hydroxy-4,4,6-trimethyl-2-cyclohexen-1-one can not be isolated in enantiomerically enriched form due to the reason stated above. The enantiomeric excess value of (-)-6-acetoxy-4,4,6-trimethyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 90:10 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

The resolution of (-)-6-acetoxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one was completed in 136 h, in 73 % enantiomeric excess. The presence of the phenyl groups has an effect on the stereoselectivity, although they are far away from the

stereogenic center. The enantiomerically enriched form of 6-hydroxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one can not be isolated. The enantiomeric excess value of (-)-6-acetoxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one **(-)-92** was measured by HPLC, Chiralcel OD-H chiral column, 88:12 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

The effect of the bulkier substituents on the stereogenic center was examined by CCL hydrolysis of ethyl, benzyl and allyl substituted acetoxy cyclohexenones, shown in Table 9.

Table 9. Enzymatic resolution of ethyl, benzyl and allyl substituted cyclohexenones

Reactant	Product	Time (h)	Conversion (%)	e.e (%)	$[\alpha]^{20}_{D}$
 **94**	 **(-)-94**	132	49	45	-3.20
 **95**	 **(-)-95**	148	47	71	-12.5
 **97**	 **(+)-97**	138	45	36	+0.15
 **98**	 **(+)-98**	142	48	61	+0.33
 **99**	 **(-)-99**	168	49	30	-0.02

When the resolution of (-)-6-acetoxy-6-ethyl-3,5,5-trimethyl-2-cyclohexen-1-one **(-)-94** is examined, it is seen to be completed in 146 h, in 65 % enantiomeric excess. The presence of bulkier ethyl group decreases the enantioselectivity.The enantiomeric excess value of (-)-6-acetoxy-6-ethyl-3,5,5-trimethyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 85:15

hexane:isopropanol as eluent at 1.0 mL/min flow rate. The enantiomerically enriched form of 6-hydroxy-6-ethyl-3,5,5-trimethyl-2-cyclohexen-1-one could not be isolated, this can be due to the aromatization of hydroxy compounds under basic conditions.

(-)-6-acetoxy-6-ethyl-3-methyl-2-cyclohexen-1-one **(-)-95**, was resolved in 71 % enantiomeric excess in 132 h. The enantiomerically enriched 6-hydroxy-6-ethyl-3-methyl-2-cyclohexen-1-one can not be recovered. The enantiomeric excess value of (-)-6-acetoxy-6-ethyl-3-methyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 87:13 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

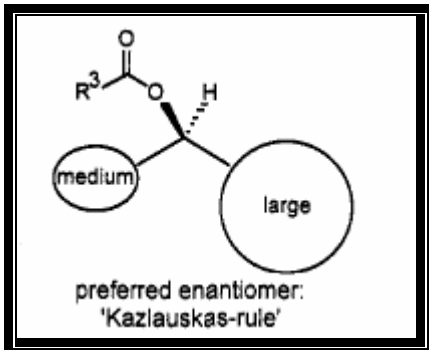
(+)-6-acetoxy-6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one **(+)-97**, was resolved in 148 h, in 36 % enantiomeric excess.The decrease in the enantioselectivity can be attributed to the presence of both benzyl and methyl substituents. The 6-hydroxy-6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one can not be isolated in enantiomerically enriched form. The enantiomeric excess value of (+)-6-acetoxy-6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 90:10 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

(+)-6-acetoxy-6-benzyl-3-methyl-2-cyclohexen-1-one, compound **(+)-98**, was resolved in 138 h, in 61 % enantiomeric excess. The 6-hydroxy-6-benzyl-3-methyl-2-cyclohexen-1-one can not be isolated in enantiomerically enriched form. When the enantioselectivity of the benzyl and methyl substituted derivatives are compared, it can be seen that the presence of the bulkier benzyl group decreases the stereoselectivity. The enantiomeric excess value of (+)-6-acetoxy-6-benzyl-3-methyl-2-cyclohexen-1-one was measured by HPLC, Chiralcel OD-H chiral column, 85:15 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

When the resolution of the α'-alkyl α,β-unsaturated cyclohexenones are examined, it is seen that the alkyl group has a great effect on the stereoselectivity. The methyl substituted derivatives can be resolved in high enantiomeric excess values. The presence of bulkier ethyl, benzyl (or allyl) substituents decrease the enantioselectivity. This can be explained according to the substrate-enzyme

interactions. In the case of bulkier substituents, the enzyme can not attach to the center of chirality easily, so the enantioselectivity is decreased. The presence of bulkier substituents of fifth carbon, the carbon near the stereogenic center also effects the enantioselectivity. When the ethyl and benzyl substituted derivatives are compared, the ethyl substituted cyclohexenones are resolved more selectively, this can be due to the steric effect of the benzyl group.

The stereoselectivity of the reaction with lipases can be explained according to the Kazlauskas-rule [34]. This active site model is used for the secondary alcohols. Since there is no example including tertiary alcohol hydrolysis, the stereoselectivity will be illustrated from this model.



Scheme 45. Kazlauskas rule

The simplest models for enzyme selectivity, predict only which enantiomer reacts faster, usually based on either the size or hydrophobicity of the substituents at the stereocenter. Kazlauskas rule states that secondary alcohols having substituents which differ significantly in size should be more effectively resolved than secondary alcohols having substituents which are similar in size. In our substrates, the presence of the methyl group at the stereogenic center has a positive effect on the

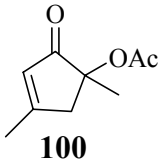
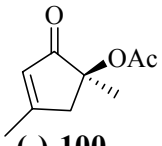
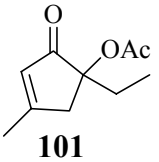
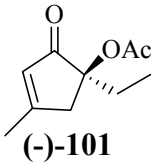
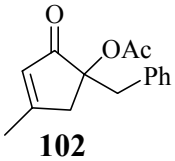
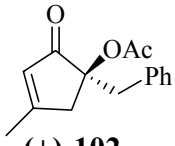
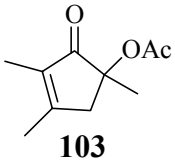
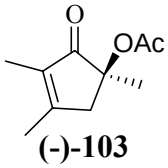
enantioselectivity of the reactions. However, when the methyl group is replaced by rather bulkier ethyl, benzyl and allyl groups the enantioselectivity is decreased.

Sequencing the gene of CCL showed several nonidentical DNA sequences which code for this enzyme, thus it is likely that the commercial enzymes are a mixture of isoenzymes. The enantioselectivities of isoenzymes of PLE were similar, but not identical, a similar situation may hold for the isoenzymes of CCL. This heterogenity frustrate attempts to precisely define the size and shape of the active site [142].

The enzymatic hydrolysis reaction with CCL was also applied to 5-acetoxy-5-substituted cyclopentenones. If we compare the stereoselectivities of cyclopentenones and cyclohexenones on similar substrates, there is not much difference in the stereoselectivity. The results are summarized in the Table 10 illustrated below.

Among cyclopentenones, the highest enantioselectivity was observed in the hydrolysis of 5-acetoxy-3,5-dimethyl-2-cyclopenten-1-one. The presence of bulkier substituents like ethyl and benzyl groups decrease the stereoselectivity. When cyclopentenones and cyclohexenones are compared among each other, closer enantiomeric excess values are obtained in similar derivatives. In both cases, when the substituent at the stereogenic center is changed from methyl to ethyl or benzyl groups, the enzyme activity is decreased because of the sterical factors.

Table 10. Enzymatic hydrolysis of cyclopentenones

Reactant	Product	Time (h)	Conv.(%)	e.e (%)	$[\alpha]^{20}_D$
 **100**	 **(-)-100**	94	48	99	-33.6
 **101**	 **(-)-101**	100	52	53	-8.40
 **102**	 **(+)-102**	136	47	43	+1.19
 **103**	 **(-)-103**	98	46	90	-23.8

(-)-5-acetoxy-3,5-dimethyl-2-cyclopenten-1-one **(-)-100**, was resolved in 94 h, in 99 % enantiomeric excess. The 5-hydroxy-3,5-dimethyl-2-cyclopenten-1-one can not be isolated in enantiomerically enriched form. According to the ^{1}H-NMR spectrum it is thought to dimerize. The enantiomeric excess value of (-)-5-acetoxy-3,5-dimethyl-2-cyclopenten-1-one was measured by HPLC, Chiralcel OD-H chiral column, 90:10 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

(-)-5-acetoxy-5-ethyl-3-methyl-2-cyclopenten-1-one, **(-)-101**, was resolved in 100 h, in 53 % enantiomeric excess. The decrease in the stereoselectivity can be due to the steric effect of the ethyl group. The 5-hydroxy-5-ethyl-3-methyl-2-cyclopenten-1-one can not be isolated in enantiomerically enriched form. The enantiomeric excess value of (-)-5-acetoxy-5-ethyl-3-methyl-2-cyclopenten-1-one

was measured by HPLC, Chiralcel OD-H chiral column, 90:10 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

(+)-5-acetoxy-5-benzyl-3-methyl-2-cyclopenten-1-one **(+)-102**, was resolved in 136 h, in 43 % enantiomeric excess. The presence of the benzyl group decreases the selectivity. The 5-hydroxy-5-benzyl-3-methyl-2-cyclopenten-1-one can not be isolated in enantiomerically enriched form. The enantiomeric excess value of (+)-5-acetoxy-5-benzyl-3-methyl-2-cyclopenten-1-one was measured by HPLC, Chiralcel OD-H chiral column, 85:15 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

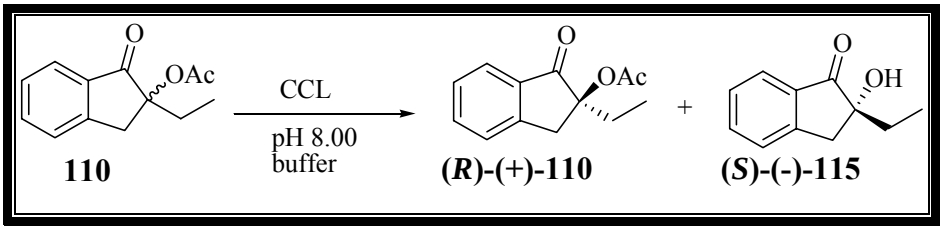
(-)-5-acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one **(-)-103**, was resolved in 98 h, in 90 % enantiomeric excess. The 5-hydroxy-2,3,5-trimethyl-2-cyclopenten-1-one can not be isolated in enantiomerically enriched form due to the decomposition of the hydroxy compounds. The enantiomeric excess value of (-)-5-acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one was measured by HPLC, Chiralcel OD-H chiral column, 90:10 hexane:isopropanol as eluent at 1.0 mL/min flow rate.

2.10 Resolution of Aromatic Ketones

Optically active tertiary α-hydroxy aromatic ketones are valuable intermediates in the enantioselective synthesis of complex natural products such as anthracycline antitumor antibiotics [143] and kinamycins [144]. Chiral tertiary α-hydroxy aromatic ketones have been prepared by several methods, however, the enzymatic resolution including hydrolase type enzymes has not been reported in the literature. Because of this reason, it was aimed to apply the enzymatic hydrolysis reactions on the α-substituted α-acetoxy aromatic ketones, and stereoselectively synthesize tertiary α-hydroxy aromatic ketones, which are valuable precursors to the synthesis of more complex natural products.

2.10.1 Enzymatic Resolution of (±)-2-Acetoxy-2-Ethyl-1-Indanone 110

The enzymatic resolution of (±)-2-acetoxy-2-ethyl-1-indanone **110**, was performed in pH 8.00 phosphate buffer with CCL, according to the known procedure stated above. The reaction was completed in 136 h, when approximately 50 % conversion was reached. The crude product was separated by flash column chromatography to afford (+)-2-acetoxy-2-ethyl-indanone **(+)-110**, and (-)-2-hydroxy-2-ethyl-1-indanone **(-)-115** (Scheme 46).

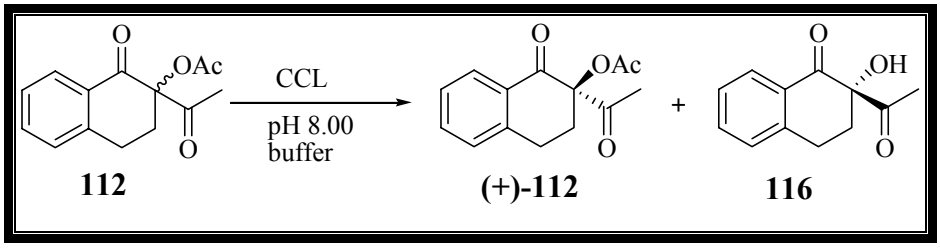


Scheme 46. The enzymatic resolution of compound **110**

(+)-2-Acetoxy-2-ethyl-indanone was resolved in 46 % chemical yield with 68 % enantiomeric excess. The enantiomeric excess was determined by HPLC, Chiralcel OD-H chiral column,with 85:15 hexane: isopropanol system with the flow rate of 1.0 mL/min. The configuration is determined as (*R*). (-)-2-hydroxy-2-ethyl-indanone was resolved in 48 % chemical yield. The enantiomeric excess value of the (-)-2-hydroxy-2-ethyl-indanone could not be obtained, because of the mismatching of the column type. $[\alpha]^{25}_{D}$ of 2-hydroxy-2-ethyl-indanone **115** was measured as -4.56 (c=1, $CHCl_3$). The configuration of the (-)-2-hydroxy-2-ethyl-indanone is determined as (*S)*. In the literature, $[\alpha]^{25}_{D}$ = + 18.1 (c=0.67, $CHCl_3$) is denoted as (*R*) [145].

2.10.2 Enzymatic Resolution of (±)-2-Acetoxy-2-Acetyl-1-Tetralone 112

The enzymatic resolution of (±)-2-acetoxy-2-acetyl-1-tetralone **112**, was carried out in pH 8.00 buffer with CCL. 100 mg of (±)-2-acetoxy-2-acetyl-1-tetralone in 1 mL DMSO was added to 25 mL pH 8.00 phosphate buffer and shaken for 136 h.,when approximately 50 % conversion was reached. The crude product was separated by flash column chromatography to afford (+)-2-acetoxy-2-acetyl-1-tetralone **(+)-112**, and 2-hydroxy-2-acetyl-1-tetralone **116** (Scheme 47).



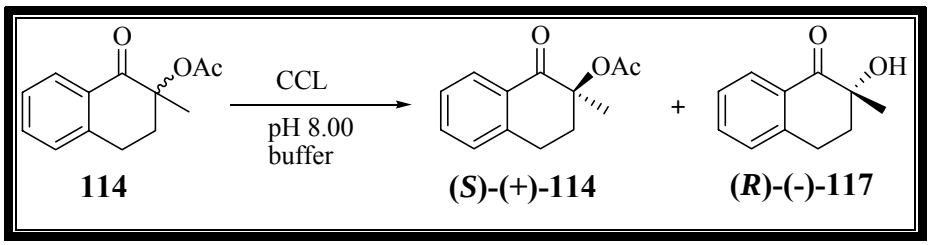
Scheme 47. The enzymatic resolution of compound **112**

(+)-2-Acetoxy-2-acetyl-tetralone was resolved in 51 % chemical yield with 62% enantiomeric excess. The enantiomeric excess was determined by HPLC, Chiralcel OD-H chiral column, with 85:15 hexane: isopropanol system with the flow rate of 1.0 mL/min. The enantiomerically enriched 2-hydroxy-2-acetyl-1-tetralone **116** could not be recovered since the hydroxy compounds can easily decompose.

2.10.3 Enzymatic Resolution of (±)-2-Acetoxy-2-Methyl-1-Tetralone 114

The enzymatic resolution of (±)-2-acetoxy-2-methyl-1-tetralone **114**, was carried out in pH 8.00 buffer with CCL. 100 mg of (±)-2-acetoxy-2-methyl-1-tetralone in 1 mL DMSO was added to 25 mL pH 8.00 phosphate buffer and shaken

for 136 h.,when approximately 50 % conversion was reached. The crude product was separated by flash column chromatography to afford (+)-2-acetoxy-2-methyl-1-tetralone **(+)-114**, and (-)-2-hydroxy-2-acetyl-1-tetralone **117** (Scheme 48).



Scheme 48. The enzymatic resolution of compound **114**

(*S*)-(+)-2-Acetoxy-2-methyl-1-tetralone was resolved in 45 % chemical yield with 69 % enantiomeric excess. The enantiomeric excess was determined by HPLC, Chiralcel OD-H chiral column, with 85:15 hexane:isopropanol system with the flow rate of 1.0 mL/min. (-)-2-hydroxy-2-acetyl-1-tetralone was resolved in 42 % chemical yield. The enantiomeric excess value of the (-)-2-hydroxy-2-acetyl-1-tetralone could **117** not be obtained, because of the mismatching of the column type. The configuration of (-)-2-hydroxy-2-acetyl-1-tetralone is determined as (*R*) through the sign of the optical rotation [146].

When the hydrolysis of 2-acetoxy-2-methyl-1-tetralone was performed with PLE in pH 8.00 buffer, the (-)-2-acetoxy-2-methyl-1-tetralone was obtained in 48 % isolated yield with 7 % enantiomeric excess. The importance of this reaction is the recovery of the other enantiomer by changing the enzyme. When CCL is used, the (*S*) enantiomer is resolved. However, when PLE is used as the enzyme, the (*R*) enantiomer is resolved. According to the preferrence of which enantiomer is desired, the enzyme can be changed. This is a very useful and cheap method of synthesizing both enantiomers of the 2-acetoxy-2-methyl-1-tetralone.

CHAPTER 3

EXPERIMENTAL

In this study, the structure elucidation of the compounds was done with the aid of the following instruments.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm from tetramethylsilane. Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet).

IR spectra were obtained from a Perkin-Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Optical rotations were measured in solvent solution in a 1 dm cell using a Bellingham & Stanley P20 polarimeter at 20 °C.

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-254), visualized with UV-light and polymolbyden phosphoric acid in ethanol as appropriate.

All extracts were dried over anhydrous magnesium sulfate ($MgSO_4$) and solutions were concentrated under vacuum by performing rotary evaporator.

3.1 General Procedure for Alkylation of Cyclohexenones

To a two necked flask was added under argon atmosphere at 0 ºC, freshly distilled diisopropyl amine (4.99 mmol, 0.7 mL) in 10 mL anhydrous THF. *n*-BuLi (1.97 mL of a 2.5 M solution in hexane) was added through a syringe and the solution was brought to -78 ºC, then stirred for 30 min at this temperature. Cyclohexenone (4.56 mmol, 0.50 mL) was added in 5 mL anhydrous THF and the solution was stirred for an additional 30 min at -78 ºC. Alkyl or benzyl halide (9.98 mmol, 0.62 mL) was added to the solution, stirred for 1 h at -78 ºC, then was allowed to warm up to room temperature slowly and stirred overnight. Ethyl acetate (50 mL) was added to the reaction mixture, and the organic layer was washed with saturated NH_4Cl (2x25 mL), brine (2x25 mL), and dried over $MgSO_4$. After filtration the solvent was evaporated and the crude product was purified by flash column chromatography using ethyl acetate/hexane as eluent.

3.1.1 3,6-Dimethyl-2-Cyclohexen-1-one 66

R_f (Ethyl acetate/Hexane 1:7) 0.28

ν_{max} (neat) 2928, 2252, 1666, 908, 706 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.75 (s, 1H, =C*H*)
2.30- 2.25 (m, 1 H, CHMe)
2.23-2.20 (m, 1H, =CMeCH_aH$_b$)
2.21-2.17 (m, 1 H, =CMeCH$_a$$H_b$)
2.01-1.98 (m, 1H, CH_aH$_b$)
1.66-1.62 (m, 1H, CH_aH$_b$)
1.88 (s, 3H, =C*Me*)
1.19 (d, 3H, *J*= 7Hz, CH_3)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 201.4 (C=O), 160.4 (=*C*Me), 126.7 (=*C*H), 40.8 (*C*H), 31.1 (=CMe*C*H_2), 30.1 (MeCH*C*H_2), 24.5 (=C*C*H_3), 15.5 (*C*H_3)

3.1.2 3,5,5,6-Tetramethyl-2-Cyclohexen-1-one 68

R_f (Ethyl acetate/Hexane 1:2) 0.80

ν_{max} (neat) 3421, 2967, 1660, 1440, 909, 649 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.75 (s, 1H, =C*H*)
2.17-2.03 (m, 1H, MeC*H*)
2.11 (t, 2H, *J*= 7 Hz, =CMeC*H*$_2$)
1.99 (s, 3H, =C*M*e)
0.88 (s, 6H, *CH*$_3$)
0.73 (d, 3H, *J*= 6 Hz, CHC*H*$_3$)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 202.7 (*C*=O), 158.7(=*C*Me), 125.3 (=*C*H), 51.5 (*C*H), 45.6(*C*H_2) , 36.4 (*C*MeMe), 29.1 (=C*Me*), 24.5 (C*Me*), 22.6 (C*Me*), 10.0 (CH*Me*)

3.1.3 3,5,6-Trimethyl-2-Cyclohexen-1-one 70

R_f (Ethyl acetate/Hexane 1:4) 0.60

ν_{max} (neat) 3427, 2964, 1678, 1455, 1379 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz) (1:1 diastereomeric mixture)

δ (ppm): 5.78 (s, 2x1H, =C*H*)

2.21-2.26 (m, 2x1H, MeC*H*CO)

1.98-2.05 (m, 2x2H, CMeCH_2)

1.87-1.92 (m, 2x1H, MeC*H*CH_2)

1.85 (s, 3H, =C*Me*)

1.60 (d, 3H, *J*= 7 Hz, *Me*CHCO)

1.06 (d, 3H, *J*= 7 Hz, *M*eCHCH_2)

1.00 (d, 3H, *J*= 7 Hz, *Me*CHCH_2)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 202.2 (*C*=O), 160.5 (=*C*Me), 128.4 (=*C*H), 126.4 (=*C*H),73.1 (*C*H), 71.6 (*C*H), 47.8(*C*H_2) , 39.6 (*C*HMe), 36.4 (*C*HMe), 24.5 (CH*Me*), 24.4 (CH*Me*), 20.3 (CH*Me*), 20.2 (CH*Me*),14.5 (*C*H*Me*),10.0 (CH*Me*)

HRMS (EI): M^+, found 138.1043, $C_9H_{14}O$ requires 138.1045

3.1.4 4,4,6-Trimethyl-2-Cyclohexen-1-one 72

R_f (Ethyl acetate/Hexane 1:4) 0.23

ν_{max} (neat) 3405, 2960, 1709, 1465, 1375 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 6.52 (dd,1H, *J*= 2, 10 Hz, =C*H*)

5.74 (d, 1H, *J*= 10 Hz , =C*H*)

2.52-2.42 (m, 1H, MeC*H*)

1.77-1.72 (dd, 2H, *J*= 7, 2 Hz, MeCH_aCH_b)

1.59 (t, 2H, *J*= 13 Hz, C$H_a$$H_b$)

1.13 (s, 3H, *Me*MeC)

1.06 (s, 3H, Me*Me*C)

1.04 (d, 3H, *J*= 7 Hz, *M*eCH)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 202.3 (*C*=O), 159.1 (=*C*H), 126.8 (=*C*H), 45.4(*C*HMe) , 38.0 (*C*H_2), 34.0 (*C*MeMe), 28.7 (CMe*Me*), 25.8(C*Me*M*e*), 15.4 (CH*Me*)

3.1.5 6-Methyl-4,4-Diphenyl-2-Cyclohexen-1-one 74

R_f (Ethyl acetate/Hexane 1:5) 0.83 (m.p=98-100 ºC)

ν_{max} (neat) 3065, 1680, 1600 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.37-7.06 (m, 11H, Ph)
7.12 (d, 1H, *J*= 10 Hz, =CH_β)
6.04 (d,1H, *J*=10 Hz, =CH_α)
2.55-2.52 (dd, 1H, *J*=2, 14 Hz, MeC*H*)
2.39-2.26 (m, 2H, MeCHCH_2)
1.00 (d, 3H, *J*= 6 Hz, *M*eCH)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 201.7 (*C*=O), 155.5 (=*C*H), 148.1 (=*C*H), 143.8 (*C*PhPh), 129.0 (Ph), 128.9, (Ph), 128.8 (Ph), 128.3 (Ph), 128.0 (Ph), 127.5 (Ph), 127.3 (Ph), 127.0 (Ph), 50.3(*C*H_2), 38.7 (*C*HMe),15.1 (CH*Me*)

3.1.6 6-Methyl-4-Isopropyl-2-Cyclohexen-1-one 76

R_f (Ethyl acetate/Hexane 1:4) 0.82

ν_{max} (neat) 3062, 1679, 1215 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 6.83-6.80 (dd, 1H, *J* = 3, 10 Hz, =C*H*)
5.89- 5.86 (dd,1H, *J*= 2, 10 Hz, =C*H*)
2.50-2.45 (m, 1H, MeC*H*)
2.23-2.21 (m, 1H, C*H*CHMe$_2$)
1.94-1.89(m, 1H, one of the mehylene protons of fifth carbon)
1.81-1.69 (m, 1H, the other methylene protons of the fifth carbon)
1.09 (d, 3H, *J* = 7 Hz, CH*M*e)
0.95 (d, 6H, *J* = 7 Hz, CH*Me$_2$*)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 203.4 (*C*=O), 153.4 (=*C*H), 128.7 (=*C*H), 143.8 (*C*PhPh), 39.6(*C*HCHMe$_2$), 39.6 (*C*HMe), 32.5 (*C*HMe$_2$), 31.7 (*C*H$_2$), 20.6 (C*Me*Me), 20.5 (CMe*Me*), 16.2 (CH*Me*)

3.1.7 6-Ethyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 77

R_f (Ethyl acetate/Hexane 1:6) 0.70

ν_{max} (neat) 3421, 2967, 1660 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.71 (s, 1H, =C*H*)

2.19 (d,1H, *J*= 10 Hz, $Me_2CC\mathit{H}_a H_b$)

2.12 (d,1H, *J*= 10 Hz, $Me_2CCH_a\mathit{H}_b$)

1.82 (s, 3H, =C*Me*)

1.75-1.78 (dd, 1H, *J*= 4,10 Hz, $MeCH_2C\mathit{H}$)

1.48-1.56(m, 1H, $MeC\mathit{H}_aCH_bCH$)

1.33-1.41 (m, 1H, $MeCH_aC\mathit{H}_bCH$)

0.94 (s, 3H, Me_aMe_bC)

0.89 (s, 3H, $Me_a\mathit{Me}_bC$)

0.85 (t, 3H, *J*= 7 Hz, *Me*CH_2)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 203.4 (*C*=O), 158.2 (=*C*HMe), 124.9 (=*C*H), 59.4 (*C*HCH_2Me), 44.3 (*C*H_2), 36.4 (*C*MeMe), 29.4 (Me), 24.4 (Me), 23.3 (Me), 19.4 (CH_2), 13.5 (CH_2*Me*)

3.1.8 6-Ethyl-3-Methyl-2-Cyclohexen-1-one 78

R_f (Ethyl acetate/Hexane 1:6) 0.56

ν_{max} (neat) 3421, 2967, 1660 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.76 (s, 1H, =C*H*)

2.31-2.16 (dd, 1H, *J*= 7, 13 Hz, C*H*)

2.07-2.01 (m, 2H, =CMeC$\mathit{H}_a\mathit{H}_b$)

2.07-1.96 (m, 2H, $CH_3C\mathit{H}_2$)

1.86 (s, 3H, =C*Me*)

1.48-1.56(m, 2H, EtCHC$\mathit{H}_a\mathit{H}_b$)

0.85 (t, 3H, *J*=7 Hz, *Me*CH_2)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 203.4 (*C*=O), 158.2 (=*C*HMe), 124.9 (=*C*H), 59.4 (*C*HCH$_2$Me), 44.3 (*C*H$_2$), 36.4 (*C*MeMe), 29.4 (Me), 24.4 (Me), 23.3 (Me), 19.4 (CH$_2$), 13.5 (CH$_2$*Me*)

3.1.9 6-Benzyl-3,5-Dimethyl-2-Cyclohexen-1-one 79

R_f (Ethyl acetate/Hexane 1:8) 0.27

ν_{max} (neat) 3012, 2961, 1680, 1493 cm^{-1}

^{1}H-NMR (CDCl$_3$, 400 MHz) (1:9 diastereomeric mixture)

δ (ppm): 7.23-7.28 (m, 2H, Ph)
7.15-7.2 (m, 3H, Ph)
5.87 (s, 1H, =C*H*)
3.58-3.31 (dd, 1H, *J*= 7, 14 Hz, PhCH_aH$_b$)
2.01-2.91 (dd, 1H, *J*= 7, 14 Hz, PhCH$_a$$H_b$)
2.55-2.43 (m, 1H, PhCH$_2$C*H*)
2.29-2.34 (m, 1H, MeC*H*)
1.92-2.08 (dd,1H, *J*= 7, 14 Hz, MeCHCH_2)
1.91 (s, 3H, =C*Me*, major isomer)
1.89 (s, 3H, =C*Me*,minor isomer)
1.01 (d, 3H, , *J*= 7 Hz, *Me*CH, major isomer)
0.91 (d, 3H, , *J*= 7 Hz, *Me*CH, minor isomer)

^{13}C-NMR (CDCl$_3$, 100.6 MHz)

δ (ppm): 201.2, 160.0, 140.2, 129.6, 129.3, 128.7, 127.3, 126.5, 126.0, 54.4, 37.4, 34.7, 31.5, 20.4, 14.4

3.1.10 6-Benzyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 80

R_f (Ethyl acetate/Hexane 1:3) 0.39

ν_{max} (neat) 3012, 2961, 1680, 1493 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.39-7.24 (m, 2H, Ph)
7.22-7.07 (m, 3H, Ph)
5.83 (s, 1H, =C*H*)
3.01-2.96 (dd, 1H, *J*= 7, 14 Hz, PhCH_aH$_b$)
2.75-2.72 (dd, 1H, *J*= 4, 14 Hz, PhCH$_a$$H_b$)
2.39-2.30 (dd, 1H, *J*= 4, 8 Hz, PhCH_2C*H*)
2.29-2.34 (m, 1H, MeC*H*)
2.21 (d,1H, *J*= 12 Hz, =CMeCH_aH$_b$)
1.91 (s, 3H, =C*Me*)
1.09 (s, 3H, CMe*Me*)
1.06 (d,1H, *J*= 12 Hz, =CMeCH$_a$$H_b$)
1.03 (s, 3H, C*Me*Me)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 201.4 (*C*=O), 158.0 (=*C*Me), 142.0 (=*C*H), 129.0 (Ph), 128.6 (Ph), 126.1 (Ph), 125.5 (Ph), 59.7 (*C*H), 45.8 (*C*H_2Ph), 37.2 (*C*H_2), 31.6 (*C*MeMe), 30.0 (C*M*eMe), 23.8 (=C*Me*)

3.1.11 6-Benzyl-3-Methyl-2-Cyclohexen-1-one 81

R_f (Ethyl acetate/Hexane 1:8) 0.27

ν_{max} (neat) 3012, 2961, 1680, 1493 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.26-7.19 (m, 2H, Ph)
7.15-7.01 (m, 3H, Ph)
5.83 (s, 1H, =C*H*)
3.29-3.27 (dd, 1H, *J*= 2, 10 Hz, PhCH_aH$_b$)
2.45-2.40 (dd, 1H, *J*= 4, 14 Hz, PhCH$_a$$H_b$)
2.40-2.30 (m, 1H, PhCH$_2$C*H*)
2.17 (t, 1H, =CMeCH_aH$_b$)
1.92-183-2.16 (dd,1H, *J*= 2, 6 Hz, =CMeCH$_a$$H_b$)
1.86 (s, 3H, =C*Me*)
1.57-1.49 (m, 2H, CH_aH_b of fifth carbon)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 200.0 (*C*=O), 161.3 (=*C*Me), 139.7 (=*C*H), 128.7 (Ph), 128.5 (Ph), 125.6.1 (Ph), 125.1 (Ph), 46.8 (*C*H), 37.3 (*C*H$_2$Ph), 35.8 (*C*H$_2$), 34.9 (*C*H$_2$), 23:7 (=C*Me*)

3.1.12 6-Allyl-3-Methyl-2-Cyclohexen-1-one 82

R_f (Ethyl acetate/Hexane 1:6) 0.28

ν_{max} (neat) 3024, 2923, 2895, 2357, 1659, 1378 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.78 (s,1H, =*CH*)
5.65-5.76 (m, 1H, for the internal vinylic proton)
5.09 (d, 1H, *J*= 18 Hz, for the trans vinylic proton)
4.96 (d, 1H, *J*= 9 Hz , for cis vinylic proton)
2.53-2.56 (m, 1H, methylene proton of fouth carbon, CH_aH$_b$)

2.15-2.23 (m, 3H, allylic methylene protons and the methylene proton of the fourth carbon, CH_aH_b)

1.98-2.09 (m, 2H, for one of the methylene protons at the fifth carbon and methine proton)

1.87 (s, 3H, =C*Me*)

1.58-1.70 (m, 1H, for one of the methylene protons of the fifth carbon)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 201.2 (*C*=O), 162.3(=*C*Me), 136.7 (=*C*H), 126.7 (=*C*H), 117.0 (=*C*H_2), 45.4 (*C*H), 34.1 (*C*H_2), 30.7 (*C*H_2), 27.5 (*C*H_2), 24.6 (*Me*)

3.2 General Procedure for the Alkylation of Cyclopentenones

To a stirred solution of freshly distilled diisopropylamine (4.0 mmol, 2.80 mL) in 5 mL dry THF was added at 0 ºC under argon atmosphere, *n*-BuLi (2.45 M in hexane) and the resultant mixture was cooled to -78 ºC. HMPA (4.0 mmol, 2.48 mL) was added and stirred for 30 min at -78 ºC. Corresponding cyclopentenone (4.0 mmol, 2.26 mL) was added and stirred for an additional 30 min at -78 ºC. Alkyl or benzyl halide (4.2 mmol, 1.31 mL) was added to the mixture, stirred for 1 h at -78 ºC, then was allowed to warm to room temperature and stirred overnight. The solution was diluted with ethyl acetate (20 mL), extracted with NH_4Cl (2 x 25 mL), brine (25 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash column chromatography using ethyl acetate:hexane as eluent.

3.2.1 3,5-Dimethyl-2-Cyclopenten-1-one 84

R_f (Ethyl acetate/Hexane 1:2) 0.53

ν_{max} (neat) 2923, 2895, 1659, 1378 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.80 (s,1H, =*CH*)

2.65-2.58 (dd, 1H, *J*= 2, 6Hz, CH_aH$_b$)

2.28-2.18 (m, 1H, C*H*)

2.15 (t, 1H, *J*= 6 Hz, CH$_a$$H_b$)

2.10 (s, 3H, =C*Me*)

1.09 (d, 3H, *J*= 7 Hz, *Me*)

δ (ppm): 212.9 (*C*=O), 177.4(=*C*Me), 129.7 (=*C*H), 42.1 (*C*H), 41.5 (*C*H$_2$), 20.1 (=C*Me*), 16.7 (*Me*)

3.2.2 5-Ethyl-3-Methyl-2-Cyclopenten-1-one 85

R_f (Ethyl acetate/Hexane 1:1) 0.63

ν_{max} (neat) 2254, 1690, 1462 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.84 (s,1H, =*CH*)

2.63-2.69 (dd, 1H, *J*= 6, 18 Hz, =CCMeCH_aH$_b$)

2.25-2.30 (m, 1H, MeCH$_2$C*H*)

2.19 (d, 1H, *J*= 18 Hz, =CMeCH$_a$$H_b$)

2.06 (s, 3H, =C*Me*)

1.72-1.78 (m, 1H, MeCH_aH$_b$)

1.30-1.38 (M, 1H, MeCH$_a$$H_b$)

0.87 (t, 3H, *J*= 7 Hz, *Me*CH$_2$)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 212.4 (*C*=O), 177.8 (=*C*Me), 130.4 (=*C*H), 53.2 (*C*H), 46.3 (*C*H_2Me), 43.4(*C*H_2), 16.5 (=*C*Me), 12.0 (*Me*).

HRMS (EI): M^+, found 124.0887, $C_8H_{12}O$ requires 124.0888.

3.2.3 5-Benzyl-3-Methyl-2-Cyclohexen-1-one 86

R_f (Ethyl acetate/Hexane 1:2) 0.32

ν_{max} (neat) 3044, 2965, 1695 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.15-7.48 (m, 5H, *Ph*)
5.92 (s, 1H, =C*H*)
3.23 (dd, 1H, *J*= 4, 14 Hz, PhC$H_a$$H_b$)
2.69-2.75 (m, 1H, C*H*CH_2Ph)
2.51-2.64 (m, 1H, PhC$H_a$$H_b$)
2.71(d, 1H, *J*= 19 Hz, =CMeC$H_a$$H_b$)
2.29 (d, 1H, *J*= 19 Hz, =CMeC$H_a$$H_b$)
2.06 (s, 3H, =C*Me*)

δ (ppm): 210.4 (*C*=O), 177.2 (=*C*Me), 139.1 (=*C*H), 129.2 (Ph), 128.5 (Ph), 128.0 (Ph), 126.2 (Ph), 48.1 (*C*H), 39.2 (*C*H_2Ph), 36.9 (*C*H_2), 19.8 (=*C*Me).

3.2.4 2,3,5-Trimethyl-2-Cyclohexen-1-one 87

R_f (Ethyl acetate/Hexane 1:1) 0.63

ν_{max} (neat) 2923, 2895, 1659, 1378 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 2.65-2.58 (dd, 1H, *J*= 2, 6 Hz,CH_aH$_b$)
2.28-2.18 (m, 1H, C*H*)
2.15 (t, 1H, *J*= 6 Hz, CH$_a$$H_b$)
2.10 (s, 3H, =C*Me*)
1.18 (s, 3H, =C*Me*)
1.09 (d, 3H, *J*= 7 Hz, *Me*)

δ (ppm): 212.9 (*C*=O), 177.4(=*C*Me), 175.7 (=*C*Me), 42.1 (*C*H), 41.5 (*C*H$_2$), 20.1 (=C*Me*), 16.7 (=*C*Me), 15.2 (*Me*).

3.3 General Procedure for $Mn(OAc)_3$ Oxidations

A mixture of $Mn(OAc)_3$ (3.25 g, 14.0 mmol) in benzene (150 mL) was refluxed for 45 min using a Dean-Stark trap. Then, the mixture was cooled to room temperature and α'-alkyl α, β-unsaturated ketone (7.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown colour disappeared (also monitored by TLC). The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1 N HCl (3 x 50 mL), followed by saturated $NaHCO_3$ (3 x 50 mL) and brine (2 x 50 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent.

3.3.1 6-Acetoxy-3,6-Dimethyl-2-Cyclohexen-1-one 88

R_f (Ethyl acetate/Hexane 1:2) 0.22

ν_{max} (neat) 3342, 2924, 1740, 1678, 1436, 1251, 1153, 1093, 1025 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.83 (s,1H, =*CH*)

2.77-2.85 (m, 1H, =CCMeC*H*$_a$H$_b$)

2.26-2.41 (m, 2H, CMeOAcC*H*$_2$)

1.99 (s, 3H, *Me*CO$_2$)

1.89 (s, 3H, =C*Me*)

1.81-1.86 (m, 1H, =CMeCH$_a$*H*$_b$)

1.36(s, 3H, COAc*Me*)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 195.9, 170.0, 160.9, 125.5, 80.4, 32.4, 30.2, 24.6, 22.2, 21.9.

HRMS (EI): M^+, found 182.0940, $C_{10}H_{14}O_3$ requires 182.0943.

3.3.2 6-Acetoxy-3,5,5,6-Tetramethyl-2-Cyclohexen-1-one 89

R_f (Ethyl acetate/Hexane 1:3) 0.25

ν_{max} (neat) 3432, 3017, 2975, 2253, 1737, 1686, 1639, 1436, 1372, 1248, 1217 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.70 (s,1H, =*CH*)

2.45 (d, 1H, *J*= 18 Hz, CMe$_2$C*H*$_a$H$_b$)

1.90 (m, 3H, *Me*CO$_2$)

1.79 (s, 3H, *J*= 18 Hz, CMe$_2$CH$_a$*H*$_b$)

1.77 (s, 3H, =C*Me*)

1.36 (s, 3H, COAc*Me*)

1.02 (s, 3H, C*Me*$_a$Me$_b$)

0.80 (s, 3H, CMe$_a$*Me*$_b$)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 199.1, 172.0, 158.4, 125.5, 87.7, 46.5, 42.8, 26.2, 24.8, 23.7, 16.0.

HRMS (EI): M^+, found 210.1255, $C_{12}H_{18}O_3$ requires 210.1256.

3.3.3 6-Acetoxy-3,5,6-Trimethyl-2-Cyclohexen-1-one 90

R_f (Ethyl acetate/Hexane 1:5) 0.22

ν_{max} (neat) 3397, 2253, 1735, 1676, 1380, 1257 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz) (1:1 diastereomeric mixture)

δ (ppm): 5.83 (s,1H, =*CH*)
5.76 (s,1H, =*CH*)
3.09-3.18 (m, 2x1H, MeC*H*)
2.21-2.62 (m, 2x2H, CMeCH_2)
2.01 (s, 3H, *Me*CO_2)
1.97 (s, 3H, *Me*CO_2)
1.88 (s, 3H, =C*Me*)
1.84 (s, 3H, =C*Me*)
1.49 (s, 3H, COAc*Me*)
1.19 (s, 3H, COAc*Me*)
0.99 (s, 3H, *J*= 7 Hz, *Me*CH)
0.93 (s, 3H, *J*= 7 Hz, *Me*CH)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 196.4, 196.0, 169.8, 169.5, 160.3, 158.1, 125.1, 123.6, 83.4, 82.6, 38.3, 37.1, 33.6, 29.7, 24.1, 23.8, 21.3, 18.8, 16.4, 14.7, 14.0.

HRMS (EI): M^+, found 196.1105, $C_{11}H_{16}O_3$ requires 196.1100.

3.3.4 6-Acetoxy-4,4,6-Trimethyl-2-Cyclohexen-1-one 91

R_f (Ethyl acetate/Hexane 1:3) 0.27

ν_{max} (neat) 3535, 3155, 2853, 1736, 1689, 1464, 1377cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 6.52 (d,1H, *J*= 10 Hz, =CH_β)
5.81 (d, 1H, *J*= 10 Hz, =CH_α)
2.62 (d, 1H, *J*= 14 Hz , CH_aH$_b$)
1.90 (s, 3H, *Me*CO_2)
1.79 (d, 1H, *J*= 14 Hz, CH$_a$$H_b$)
1.46 (s, 3H, *Me*COAc)
1.16 (s, 3H, CMe_aMe$_b$)
1.14 (s, 3H, CMe$_a$$Me_b$)

δ (ppm): 195.3, 170.5, 157.6, 126.4, 84.3, 45.6, 34.6, 29.6, 25.2, 15.3, 14.5.

HRMS (EI): M^+, found 196.1103, $C_{11}H_{16}O_3$ requires 196.1100.

3.3.5 6-Acetoxy-6-Methyl-4,4-Diphenyl-2-Cyclohexen-1-one 92

R_f (Ethyl acetate/Hexane 1:4) 0.26

ν_{max} (neat) 3717, 3155, 2926, 1709, 1462, 1363, 1095 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.32-7.11 (2x5H and 1H, m, CPhPh and =CH_β)

6.21 (d, 1H, *J*= 10 Hz, =CH_α)

3.66 (d, 1H, *J*= 14 Hz , CH_aH$_b$)

2.75 (d, 1H, *J*= 14 Hz , CH$_a$$H_b$)

1.88 (s, 3H, *Me*CO_2)

0.97 (s, 3H, *Me*COAc)

δ (ppm): 195.6, 170.2, 154.4, 147.3, 129.1, 128.9, 128.3, 127.9, 127.5, 127.2, 80.2, 50.3, 45.3, 24.2, 21.7.

HRMS (EI): M^+, found 320.1412, $C_{21}H_{20}O_3$ requires 320.1413.

3.3.6 6-Acetoxy-6-Methyl-4-Isopropyl-2-Cyclohexen-1-one 93

R_f (Ethyl acetate/Hexane 1:4) 0.17

ν_{max} (neat) 3405, 2960, 2867, 2251, 1709, 1674, 1460 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz) (8:2 diastereomeric mixture)

δ (ppm): (major isomer): 6.69 (dd, 1H, *J*= 10, 4 Hz, =CH_β)

5.96 (d, 1H, *J*= 10, 4 Hz, =CH_α)

2.49-2.53 (m, 1H, =CHC*H*)

2.42-2.44 (m, 1H, C*H*Me$_2$)

1.99-2.07 (m, 2H, CH_2)

1.93 (s, 3H, *Me*CO_2)

1.47 (s, 3H, *Me*COAc)

0.87 (d, *J*= 7 Hz, C*H*Me$_2$)

(minor isomer) 6.69 (dd, 1H, *J*= 10, 4 Hz, =CH_β)

5.96 (d, 1H, *J*= 10, 4 Hz, =CH_α)

2.44-2.48 (m, 1H, =CHC*H*)

2.42-2.44 (m, 1H, C*H*Me$_2$)

1.99-2.07 (m, 2H, C*H*$_2$)

1.95 (s, 3H, *Me*CO_2)

1.49 (s, 3H, *Me*COAc)

0.89 (d, 2x3H, *J*= 7 Hz, CH*Me*$_2$)

δ (ppm): (major isomer) 195.4, 170.2, 152.1, 128.3, 80.8, 40.2, 37.1, 31.6, 21.7, 19.6, 19.3; (minor isomer) 191.4, 169.2, 150.3, 125.6, 80.9, 41.2, 37.5, 30.6, 21.8, 21.4, 19.7, 19.1

HRMS (EI): M^+, found 210.1256, $C_{12}H_{18}O_3$ requires 210.1256.

3.3.7 6-Acetoxy-6-Ethyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 94

R_f (Ethyl acetate/Hexane 1:4) 0.22

ν_{max} (neat) 3421, 2967, 1735, 1660, 1440, 1376 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.11 (s, 1H, =*CH*)

2.47 (d, 1H, *J*=18 Hz , C*H*$_a$H$_b$)

2.31 (d, 1H, *J*=18 Hz , CH$_a$*H*$_b$)

2.13-2.19 (m, 2H, MeC*H*$_2$)

2.07 (s, 3H, *Me*CO_2)

1.88 (s, 3H, =C*Me*)

1.07 (s, 6H, *Me*$_2$C)

0.87 (t, 3H, *J*= 7 Hz, *Me*CH_2)

δ (ppm): 208.0, 171.1, 158.1, 124.9, 81.3, 59.4, 47.3, 37.4, 30.0, 27.8, 21.1, 19.2, 13.7.

HRMS (EI): M^+, found 224.1416, $C_{13}H_{20}O_3$ requires 224.1413.

3.3.8 6-Acetoxy-6-Ethyl-3-Methyl-2-Cyclohexen-1-one 95

R_f (Ethyl acetate/Hexane 1:4) 0.22

ν_{max} (neat) 3421, 2967, 1735, 1660, 1440, 1376 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.11 (s, 1H, =*CH*)
2.47 (d, 1H, *J*= 18 Hz , CH_aH$_b$)
2.31 (d, 1H, *J*= 18 Hz , CH$_a$$H_b$)
2.13-2.19 (m, 2H, MeCH_2)
2.07 (s, 3H, *Me*CO_2)
1.88 (s, 3H, =C*Me*)
1.07 (s, 6H, Me_2C)
0.87 (t, 3H, *J*=7 Hz, *Me*CH_2)

δ (ppm): 208.0 (C=O), 171.1 (MeO*C*=O), 158.1 (=*C*Me), 124.9 (=*C*H), 81.3 (*C*OAcEt), 47.3 (CH_2), 37.4 (CH_2Et), 30.0 (CH_2), 27.8 (*Me*CO_2), 21.1 (=C*Me*), 19.2 (*Me*).

HRMS (EI): M^+, found 224.1416, $C_{13}H_{20}O_3$ requires 224.1413.

3.3.9 6-Acetoxy-6-Benzyl-3,5-Dimethyl-2-Cyclohexen-1-one 96

R_f (Ethyl acetate/Hexane 1:5) 0.31

ν_{max} (neat) 3012, 2961, 1730, 1652, 1493 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.19-7.26 (m, 3H, *Ph*)

7.09 (D, 2H, *J*= 6 Hz, *Ph*)

5.93 (s, 1H, =*CH*)

3.58 (d, 1H, *J*= 14 Hz , PhCH_aH$_b$)

3.19 (d, 1H, *J*= 14 Hz , PhCH$_a$$H_b$)

2.80-2.83 (m, 2H, MeC*H*)

2.44-2.50 (dd, 1H, *J*= 18, 5 Hz, CH_aH$_b$)

2.28-2.34 (dd, 1H, *J*= 18, 5 Hz, CH$_a$$H_b$)

2.05 (s, 3H, *Me*CO_2)

1.93 (s, 3H, =C*Me*)

0.95 (d, 3H, *J*= 7 Hz, *Me*CH)

δ (ppm): 194.5, 170.2, 159.1, 135.3, 130.4, 128.2, 126.9, 125.1, 85.8, 40.3, 37.6, 35.0, 24.2, 21.5, 15.0

HRMS (EI): M^+, found 272.1401, $C_{17}H_{20}O_3$ requires 272.1413.

3.3.10 6-Acetoxy-6-Benzyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 97

R_f (Ethyl acetate/Hexane 1:5) 0.31

ν_{max} (neat) 3012, 2961, 1730, 1652, 1493 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.19-7.26 (m, 3H, *Ph*)

7.09 (d, 2H, *J*=6 Hz, *Ph*)

5.93 (s, 1H, =*CH*)

3.58 (d, 1H, *J*= 14 Hz, PhCH_aH$_b$)

3.19 (d, 1H, *J*= 14 Hz , PhCH$_a$$H_b$)

2.44-2.50 (d, 1H, *J*= 18 Hz, CH_aH$_b$)

2.28-2.34 (d, 1H, *J*= 18 Hz, CH$_a$$H_b$)

2.05 (s, 3H, *Me*CO_2)

1.93 (s, 3H, =C*Me*)

0.94 (s, 3H, CMe*Me*)

0.89 (s, 3H, C*Me*Me)

δ (ppm): 196.2 (*C*=O), 169.0 (O*C*OCH$_3$), 153.1 (=*C*Me), 137.0 (=CH), 130.4 (*Ph*), 131.6 (*Ph*), 127.7 (*Ph*), 126.3 (*Ph*), 126.2 (*Ph*), 86.8 (*C*OAcCH$_2$Ph), 44.8 (*C*MeMe), 41.2(*C*H$_2$), 33.5 (=*C*Me), 24.5 (*Me*CO$_2$), 22.5(*Me*), 14.2(*Me*)

HRMS (EI): M^+, found 272.1401, $C_{17}H_{20}O_3$ requires 272.1413.

3.3.11 6-Acetoxy-6-Benzyl-3-Methyl-2-Cyclohexen-1-one 98

R_f (Ethyl acetate/Hexane 1:5) 0.31

ν_{max} (neat) 3012, 2961, 1730, 1652, 1493 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.19-7.26 (m, 3H, *Ph*)

7.09 (d, 2H, *J*= 6 Hz, *Ph*)

5.93 (s, 1H, =*CH*)

3.58 (d, 1H, *J*= 14 Hz , PhC*H$_a$*H$_b$)

3.19 (d, 1H, *J*= 14 Hz , PhCH$_a$*H$_b$*)

2.80-2.83 (m, 2H, MeC*H*)

2.44-2.50 (dd, 1H, *J*= 18, 5 Hz, C*H$_a$*H$_b$)

2.28-2.34 (dd, 1H, *J*= 18, 5 Hz, CH$_a$*H$_b$*)

2.05 (s, 3H, *Me*CO$_2$)

1.93 (s, 3H, =C*Me*)

0.95 (d, 3H, *J*= 7 Hz, *Me*CH)

δ (ppm): 194.5, 170.2, 159.1, 135.3, 130.4, 128.2, 126.9, 125.1, 85.8, 40.3, 37.6, 35.0, 24.2, 21.5, 15.0

HRMS (EI): M^+, found 272.1401, $C_{17}H_{20}O_3$ requires 272.1413.

3.3.12 6-Acetoxy-6-Allyl-3-Methyl-2-Cyclohexen-1-one 99

R_f (Ethyl acetate/Hexane 1:5) 0.31

ν_{max} (neat) 3024, 2923, 2895, 2357, 1659, 1378 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.78 (s,1H, =*CH*)

5.65-5.76 (m, 1H, for the internal vinylic proton)

5.09 (d, 1H, *J*= 18 Hz, for the trans vinylic proton)

4.96 (d, 1H, *J*= 18 Hz , for trans vinylic proton)

2.53-2.56 (m, 1H, methylene proton of fouth carbon, CH_aH$_b$)

2.15-2.23 (m, 3H, allylic methylene protons and the methylene proton of the fourth carbon, CH$_a$*H$_b$*)

1.98-2.09 (m, 2H, for one of the methylene protons at the fifth carbon)

1.89 (s, 3H, *Me*CO_2)

1.87 (s, 3H, =C*Me*)

1.58-1.70 (m, 1H, for one of the methylene protons of the fifth carbon)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

δ (ppm): 201.2 (*C*=O), 162.3(=*C*Me), 136.7 (=*C*H), 126.7 (=*C*H), 117.0 (=*C*H$_2$), 80.1 (*C*OAc), 34.1 (*C*H$_2$), 30.7 (*C*H$_2$), 27.5 (*C*H$_2$), 24.6 (*Me*CO_2), 23.2 (Me)

3.3.13 5-Acetoxy-3,5-Dimethyl-2-Cyclopenten-1-one 100

R_f (Ethyl acetate/Hexane 1:4) 0.17

ν_{max} (neat) 3018, 2400, 1735, 1672, 1521 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.75 (s, 1H, =*CH*)
2.80 (d, 1H, *J*= 18 Hz , CH_aH$_b$)
2.32 (d, 1H, *J*= 18 Hz , CH$_a$$H_b$)
1.88 (s, 3H, *Me*CO_2)
1.82 (s, 3H, =C*Me*)
1.16 (s, 3H, *Me*COAc)

δ (ppm): 205.4, 173.1, 170.2, 127.8, 81.4, 46.3, 30.1, 23.8, 21.3, 20.0

HRMS (EI): M^+, found 168.0782, $C_9H_{12}O_3$ requires 168.0786.

3.3.14 5-Acetoxy-5-Ethyl-3-Methyl-2-Cyclopenten-1-one 101

R_f (Ethyl acetate/Hexane 1:4) 0.35

ν_{max} (neat) 2254, 1764, 1709, 1462 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.88 (s, 1H, =*CH*)
2.87 (d, 1H, *J*= 18 Hz , CH_aH$_b$)
2.51 (d, 1H, *J*= 18 Hz , CH$_a$$H_b$)
2.07 (s, 3H, *Me*CO_2)
1.99 (s, 3H, =C*Me*)

1.55-1.75 (m, 2H, MeC*H*$_2$)

0.84 (t, 3H, *J*= 7 Hz, *Me*CH$_2$)

δ (ppm): 205.4, 173.2, 170.3, 128.8, 84.2, 43.7, 30.0, 23.0, 21.3, 8.0.

HRMS (EI): M^+, found 182.0942, $C_{10}H_{14}O_3$ requires 182.0943

3.3.15 5-Acetoxy-5-Benzyl-3-Methyl-2-Cyclopenten-1-one 102

R_f (Ethyl acetate/Hexane 1:3) 0.31

ν_{max} (neat) 2254, 1732, 1704, 1469 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.02-7.24 (m, 5H, Ph)

5.80 (s, 1H, =*CH*)

3.12 (d, 1H, *J*= 18 Hz , PhC*H$_a$*H$_b$)

2.77 (d, 1H, *J*= 18 Hz , PhCH$_a$*H$_b$*)

2.25 (d, 1H, *J*= 14 Hz , C*H$_a$*H$_b$)

2.03 (s, 3H, *Me*CO$_2$)

1.97 (s, 3H, =C*Me*)

1.95 (d, 1H, *J*= 14 Hz , CH$_a$*H$_b$*)

δ (ppm): 212.3, 178.5, 174.4, 139.2, 130.3, 129.8, 129.4, 128.6, 128.3, 126.2, 84.1, 38.4, 35.7, 20.1, 19.3.

HRMS (EI): M^+, found 244.1102, $C_{15}H_{16}O_3$ requires 244.1100.

3.3.16 5-Acetoxy-2,3,5-Trimethyl-2-Cyclopenten-1-one 103

R_f (Ethyl acetate/Hexane 1:4) 0.17

ν_{max} (neat) 3018, 2400, 1735, 1672, 1521 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 5.75 (s, 1H, =*CH*)
2.80 (d, 1H, *J*= 18 Hz , CH_aH$_b$)
2.32 (d, 1H, *J*= 18 Hz , CH$_a$$H_b$)
1.88 (s, 3H, *Me*CO_2)
1.82 (s, 3H, =C*Me*)
1.16 (s, 3H, *Me*COAc)

δ (ppm): 205.4, 173.1, 170.2, 127.8, 81.4, 46.3, 30.1, 23.8, 21.3, 20.0

HRMS (EI): M^+, found 168.0782, $C_9H_{12}O_3$ requires 168.0786.

3.3.17 5-Acetoxy-2,3,4,5-Tetramethyl-2-Cyclopenten-1-one 104

R_f (Ethyl acetate/Hexane 1:4) 0.34

ν_{max} (neat) 2268, 1740, 1715, 1478 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz) (9:1 diastereomeric mixture)

δ (ppm): (major isomer) 2.73-2.75 (m, 1H, MeC*H*)
1.68 (s, 3H, *Me*CO_2)
1.63 (s, 3H, =CMe_α)
1.48 (s, 3H, =CMe_β)
0.88 (s, 3H, *Me*COAc)

0.82 (d, 3H, *J*= 8 Hz, *Me*CH)

(minor isomer) 2.34-2.36 (1H, m, MeC*H*)

1.70 (s, 3H, *Me*CO_2)

1.65 (s, 3H, =CMe_α)

1.48 (s, 3H, =CMe_β)

1.04 (s, 3H, *Me*COAc)

0.74 (d, 3H, *J*= 8 Hz, *Me*CH)

δ (ppm): (major isomer) 204.5, 169.8, 167.9, 133.0, 83.4, 45.4, 21.3, 19.4, 14.6, 11.9, 8.4; (minor isomer) 204.4, 170.1, 168.5, 132.5, 82.2, 49.6, 24.4, 21.1, 15.1, 12.8, 8.3

HRMS (EI): M^+, found 196.1099, $C_{11}H_{16}O_3$ requires 196.1100.

3.3.18 2-Acetoxy-2-ethyl-Indanone 110

R_f (Ethyl acetate/Hexane 1:4) 0.31

ν_{max} (neat) 3410, 3019, 1724, 1609, 1466, 1257 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 7.71 (d, 1H, *J*= 8 Hz, *Ar*)

7.53 (t, 1H, *J*= 8 Hz, *Ar*)

7.30-7.33 (m, 2H, *Ar*)

3.35 (d, 1H, *J*= 17 Hz , C$H_a$$H_b$)

3.15 (d, 1H, *J*= 17 Hz , C$H_a$$H_b$)

2.02 (s, 3H, *Me*CO_2)

1.75-1.86 (m, 1H, MeC$H_a$$H_b$)

1.63-1.72 (m, 1H, MeC$H_a$$H_b$)

0.87 (t, 3H, *J*= 7 Hz, *Me*CH_2)

δ (ppm): 202.8, 170.4, 149.8, 135.6, 135.3, 128.1, 126.2, 124.7, 85.1, 37.9, 30.1, 21.2, 8.0.

HRMS (EI): M^+, found 218.0937, $C_{13}H_{14}O_3$ requires 218.0943.

3.3.19 2-Acetoxy-2-Acetyl-1-Tetralone 112

R_f (Ethyl acetate/Hexane 1:4) 0.41

ν_{max} (neat) 2254, 1794, 1709, 1662, 1363, 1095, 910, 753, 715 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 8.58 (d, 1H, *J*= 8 Hz, *Ar*)
8.20 (d, 1H, *J*= 8 Hz, *Ar*)
7.35-7.65 (m, 2H, *Ar*)
2.79-3.02 (m, 4H, C*H*$_2$C*H*$_2$)
2.26 (s, 3H, *Me*CO_2)
2.23 (s, 3H, *Me*CO)

δ (ppm): 210.3, 204.2, 198.7, 162.6, 143.6, 134.4, 129.0, 127.5, 112.5, 68.4, 32.5, 30.1, 26.3, 25.1

HRMS (EI): M^+, found 246.0902, $C_{14}H_{14}O_4$ requires 246.0892.

3.3.20 2-Acetoxy-2-Methyl-1-Tetralone 114

R_f (Ethyl acetate/Hexane 1:3) 0.50

ν_{max} (neat) 2254, 1794, 1709, 1662, 1363, 1095, 910, 753, 715 cm^{-1}

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ (ppm): 8.00 (d, 1H, *J*= 8 Hz, *Ar*)
7.41 (t, 1H, *J*= 8 Hz, *Ar*)
7.26 (t, 1H, *J*= 8 Hz, *Ar*)
7.15 (d, 1H, *J*= 8 Hz, *Ar*)
2.89-2,99 (m, 3H, CH_2CH_aCH$_b$CMeOAc)
2.00 (s, 3H, *Me*CO_2)
1.97-1.99 (m, 3H, CH_2CH_aCH_bCMeOAc)

δ (ppm): 195.2, 170.1, 142.4, 134.0, 131.6, 129.0, 128.8, 127.4, 81.3, 33.4, 27.3, 22.0, 21.7.

HRMS (EI): M^+, found 218.0941, $C_{13}H_{14}O_3$ requires 218.0943.

3.4 General Procedure for $Pb(OAc)_4$ Oxidations

A mixture of $Pb(OAc)_4$ (5.00 g, 11.0 mmol) and α'-alkyl α,β-unsaturated ketone (11.0 mmol) in benzene (50 mL) was allowed to reflux for 12 h and monitoted by TLC. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with saturated $NaHCO_3$ (100 mL) water (100 mL), brine (100 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent.

3.5 General Procedure for the Enzymatic Resolution with CCL

100 mg of substrate was added to pH 8.00 buffer (20 mL) in 1 mL DMSO. 100 mg CCL was added to the solution and shaken till 50% conversion by TLC monitoring. The solution was diluted with an equal amount of ethyl acetate, the organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent.

3.5.1 (-)-6-Acetoxy-3,6-Dimethyl-2-Cyclohexen-1-one 88

(-)-88; $[\alpha]^{20}_{D}$= -13.1 (c=1, $CHCl_3$), 99% e.e

3.5.2 (-)-6-Acetoxy-3,5,5,6-Tetramethyl-2-Cyclohexen-1-one 89

(-)-89; $[\alpha]^{20}_{D}$= -1.80 (c=1, $CHCl_3$), 62% e.e

3.5.3 (-)-6-Acetoxy-4,4,6-Trimethyl-2-Cyclohexen-1-one 91

(-)-91; $[\alpha]^{20}_{D}$= -42.2 (c=1, $CHCl_3$), 94% e.e

3.5.4 (-)-6-Acetoxy-6-Methyl-4,4-Diphenyl-2-Cyclohexen-1-one 92

(-)-92; $[\alpha]^{20}_{D}$= -29.2 (c=1, $CHCl_3$), 73% e.e

3.5.5 (-)-6-Acetoxy-6-Ethyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 94

(-)-94; $[\alpha]^{20}_{D}$= -3.20 (c=1, $CHCl_3$), 45% e.e

3.5.6 (-)-6-Acetoxy-6-Ethyl-3-Methyl-2-Cyclohexen-1-one 95

(-)-95; $[\alpha]^{20}_{D}$= -12.5 (c=1, $CHCl_3$), 71% e.e

3.5.7 (+)-6-Acetoxy-6-Benzyl-3,5,5-Trimethyl-2-Cyclohexen-1-one 97

(+)-97; $[\alpha]^{20}_{D}$= +0.15 (c=1, $CHCl_3$), 36% e.e

3.5.8 (+)-6-Acetoxy-6-Benzyl-3-Methyl-2-Cyclohexen-1-one 98

(+)-98; $[\alpha]^{20}_{D}$= +0.33 (c=1, $CHCl_3$), 61% e.e

3.5.9 (-)-6-Acetoxy-6-Allyl-3-Methyl-2-Cyclohexen-1-one 99

(-)-99; $[\alpha]^{20}_{D}$= -0.02 (c=1, $CHCl_3$), 5% e.e

3.5.10 (-)-5-Acetoxy-3,5-Dimethyl-2-Cyclopenten-1-one 100

(-)-100; $[\alpha]^{20}_{D}$= -33.6 (c=1, $CHCl_3$), 99% e.e

3.5.11 (-)-5-Acetoxy-5-Ethyl-3-Methyl-2-Cyclopenten-1-one 101

(-)-101; $[\alpha]^{20}_{D}$= -8.40 (c=1, $CHCl_3$), 53% e.e

3.5.12 (+)-5-Acetoxy-5-Benzyl-3-Methyl-2-Cyclopenten-1-one 102

(+)-102; $[\alpha]^{20}_{D}$= +1.19 (c=1, $CHCl_3$), 43% e.e

3.5.13 (-)-5-Acetoxy-2,3,5-Trimethyl-2-Cyclopenten-1-one 103

(-)-103; $[\alpha]^{20}_{D}$= -23.8 (c=1, $CHCl_3$), 90% e.e

3.5.14 (+)-2-Acetoxy-2-Ethyl Indanone 110

(+)-110; $[\alpha]^{20}_{D}$= +11.2 (c=1, $CHCl_3$), 68% e.e

3.5.15 (-)-2-Hydroxy-2-Ethyl Indanone 115

(-)-115; $[\alpha]^{20}_{D}$= -4.56 (c=1, $CHCl_3$).Configuration= *S*

3.5.16 (+)-2-Acetoxy-2-Acetyl Tetralone 112

(+)-112; $[\alpha]^{20}_{D}$= +3.21 (c=1, $CHCl_3$), 62% e.e

3.5.17 (+)-2-Acetoxy-2-Methyl Tetralone 114

(+)-114; $[\alpha]^{20}_{D}$= +2.18 (c=1, $CHCl_3$), 69% e.e

(-)-114; $[\alpha]^{20}_{D}$= -0.04 (c=1, $CHCl_3$), 7% e.e (after hydrolysis with PLE)

3.5.18 (-)-2-Hydroxy-2-Methyl Tetralone 117

(-)-117; $[\alpha]^{20}_{D}$= -5.43 (c=1, $CHCl_3$). Configuration= *S*

CHAPTER 4

CONCLUSIONS

In this study, the synthesis of enantiomerically enriched quaternary carbon stereocenters on cyclopentenones and cyclohexenones were performed. The importance of cyclopentenoid and cyclohexenoid type of compounds arises from their presence in many complex natural products.

The first part of the study involves the synthesis of α'-substituted α,β-unsaturated cyclohexenones and cyclopentenones.The lithium enolates of the α,β-unsaturated ketones were alkylated by the corresponding alkyl halides in moderate yields. These compounds were then regioselectively oxidized to yield α'-acetoxy α'-substituted α,β-unsaturated ketones by $Mn(OAc)_3$. This study is the first example in the literature that $Mn(OAc)_3$ is used in the oxidation of a tertiary position of α'-substituted α,β-unsaturated ketones. This is a very convenient and one pot synthesis of compounds that are the simplest precursors of complex natural products. However, the yield of the manganese(III) acetate oxidation can vary according to the reagent used. Since, manganese(III) acetate was purchased from Aldrich or Sigma, the same quality could not be obtained in every case that can cause decreases in the chemical yields. The oxidation yields were increased when manganese(III) acetate was dried effectively. The oxidations were also performed by $Pb(OAc)_4$ in order to test which method was the best. It was observed that the chemical yields and the reaction times of the oxidations were similar. Since $Pb(OAc)_4$ is a toxic compound, the oxidations were mainly performed by $Mn(OAc)_3$, which is a more environmentally friendly reagent. In addition, the oxidations of α-substitued aromatic

ketones were performed by $Mn(OAc)_3$. The chemical yields of these oxidations were lower than the oxidations of α, β-unsaturated ketones.

In connection with this study, in the second part, the enzymatic resolution of these α'-acetoxy α'-substituted α, β-unsaturated ketones were performed by hydrolase type enzymes. There are only a few and unsuccessful attempts in the literature where hydrolases are used to resolve tertiary alcohols. This is the first example in the literature that the hydrolase type enzymes are used to resolve tertiary acetoxy groups. The first attempts were performed by PLE, which is one of the most powerful hydrolases, because of its selectivity. However, the enantiomeric excess value was lower than 10%. Although it has got some stereoselectivity, the enantiomeric excess value was not high. Therefore, it was decided to change the enzyme. Several enzymes like HLE, PPL anc CCL were tested, among the enzymes used, the best enantioselectivity was observed with Candida *cylindracea* lipase (CCL). The best activity was achieved when the hydrolysis was performed in pH 8.0 buffer, at 20 ºC, and DMSO was added as a co-solvent. The enzyme should also be used in stoichiometric amount, around 1:1 enzyme/substrate ratio.In addition, the enantiomeric excess value was changed according to the substituents near or at the stereogenic center. The highest enantioselectivities were observed with 6-acetoxy-3,6-dimethyl-2-cyclohexen-1-one and 5-acetoxy-2,5-dimethyl-2-cyclopenten-1-one. In the hydrolysis of 6-acetoxy-3,5,5-trimethyl-2-cyclohexen-1-one, the enantioselectivity was decreased because of the methyl groups present at the fifth carbon. The presence of methyl groups at fouth carbon did not affect the selectivity so much, however, when the substituents at the fourth carbon were replaced with phenyl groups, there was a drastic decrease in the enantiomeric excess value. Moreover, the methyl substituted derivatives at the stereogenic center were resolved at a faster rate and high enantiomeric excess than the ethyl, benzyl and allyl substituted ones. The presence of bulkier groups decrease the enantiomeric excess values. This can be attributed to the active site of the enzyme. When the substituents are bulkier, the enzyme can not attach to the substrate easily, so the enantioselectivity is decreased. The enantiomerically enriched forms of the hydroxy compounds could not be obtained, since these compounds are very unstable and can easily decompose on silica or alumina. The hydrolysis of α-acetoxy α-substituted aromatic ketones

were also performed by CCL. The enatiomerically enriched forms of (*R*)-(+)-2-Acetoxy-2-ethyl-indanone, (*S*)- (-)-2-hydroxy-2-ethyl-indanone, (+)-2-acetoxy-2-acetyl-tetralone, (*S*)-(-)-2-acetoxy-2-methyl-1-tetralone, and (*R*)-(-)-2-hydroxy-2-acetyl-1-tetralone were resolved successfully. In addition, when CCL is used as the enzyme, (*S)* isomer of 2-acetoxy-2-methyl-1-tetralone was resolved. When PLE is used, (*R*) enantiomer was resolved. This is a very easy method for the synthesis of both enantiomers of 2-acetoxy-2-methyl-1-tetralone, which is used as a precursor for the synthesis of anthracycline antitumor antibiotics.

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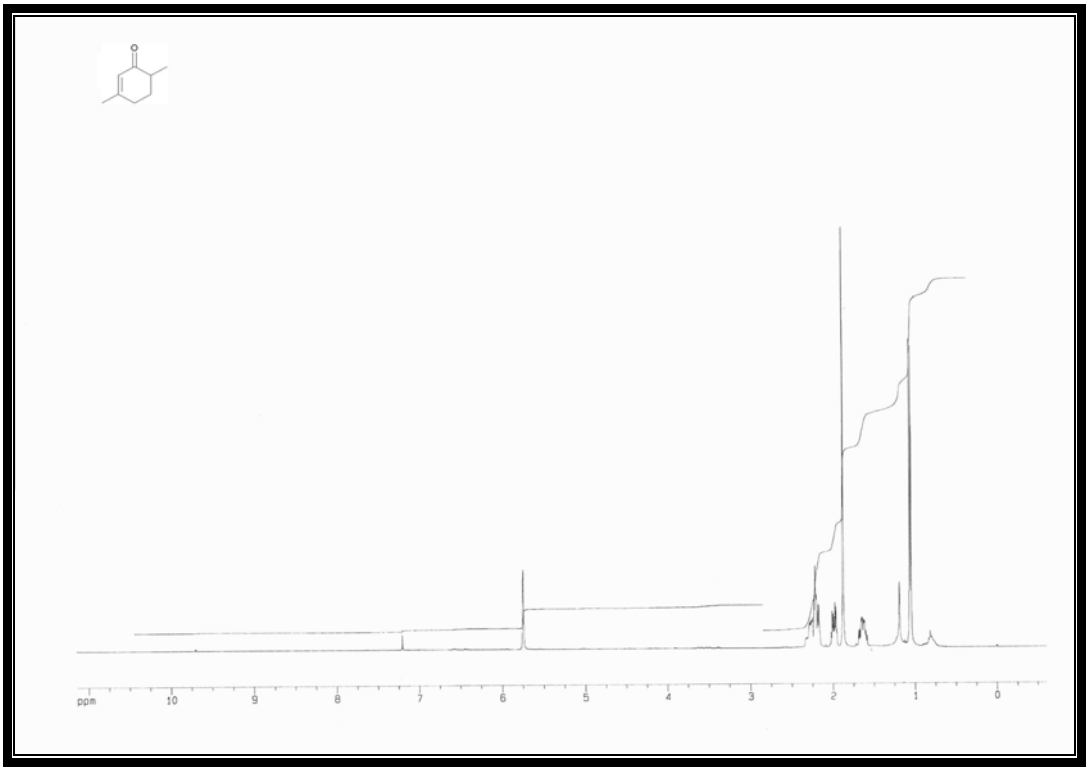
APPENDIX A



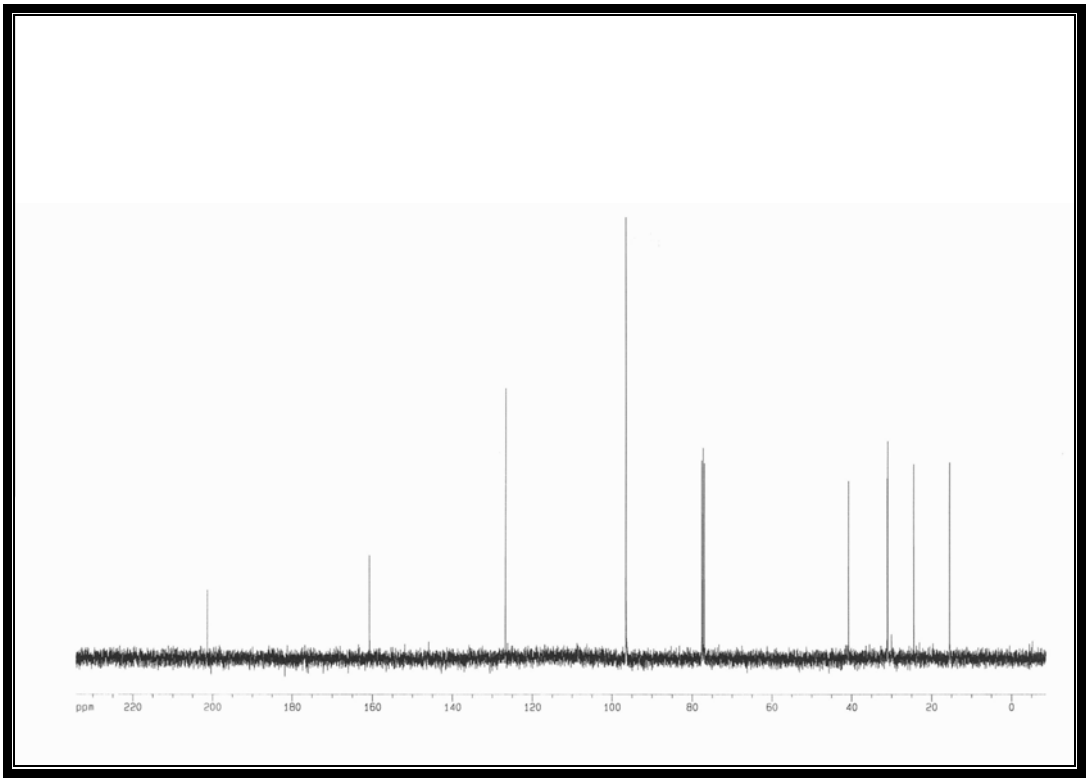


Fig A 1. ^{1}H and ^{13}C-NMR Spectra of Compound **66**

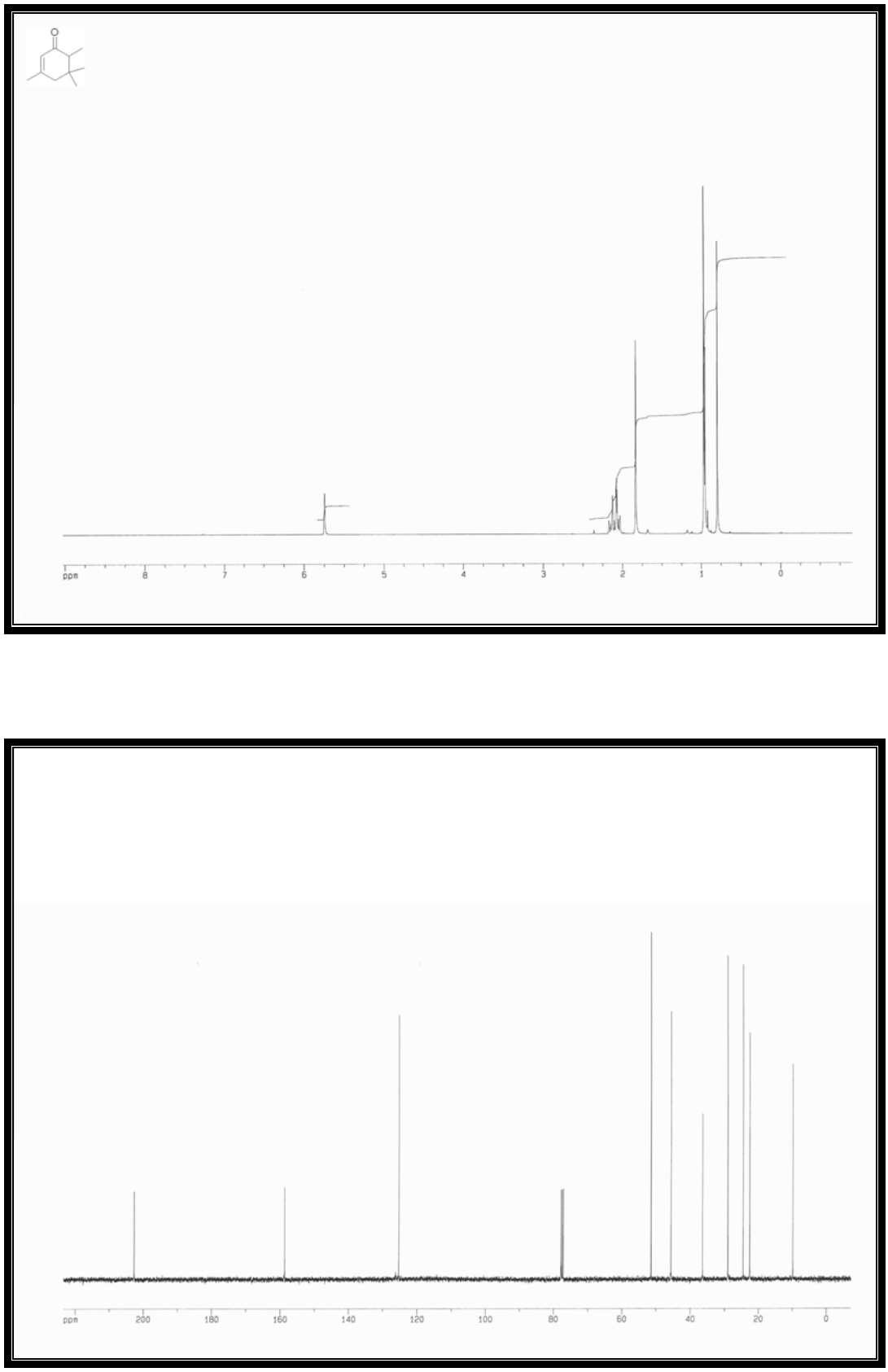


Fig A 2. ^{1}H and ^{13}C-NMR Spectra of Compound **68**

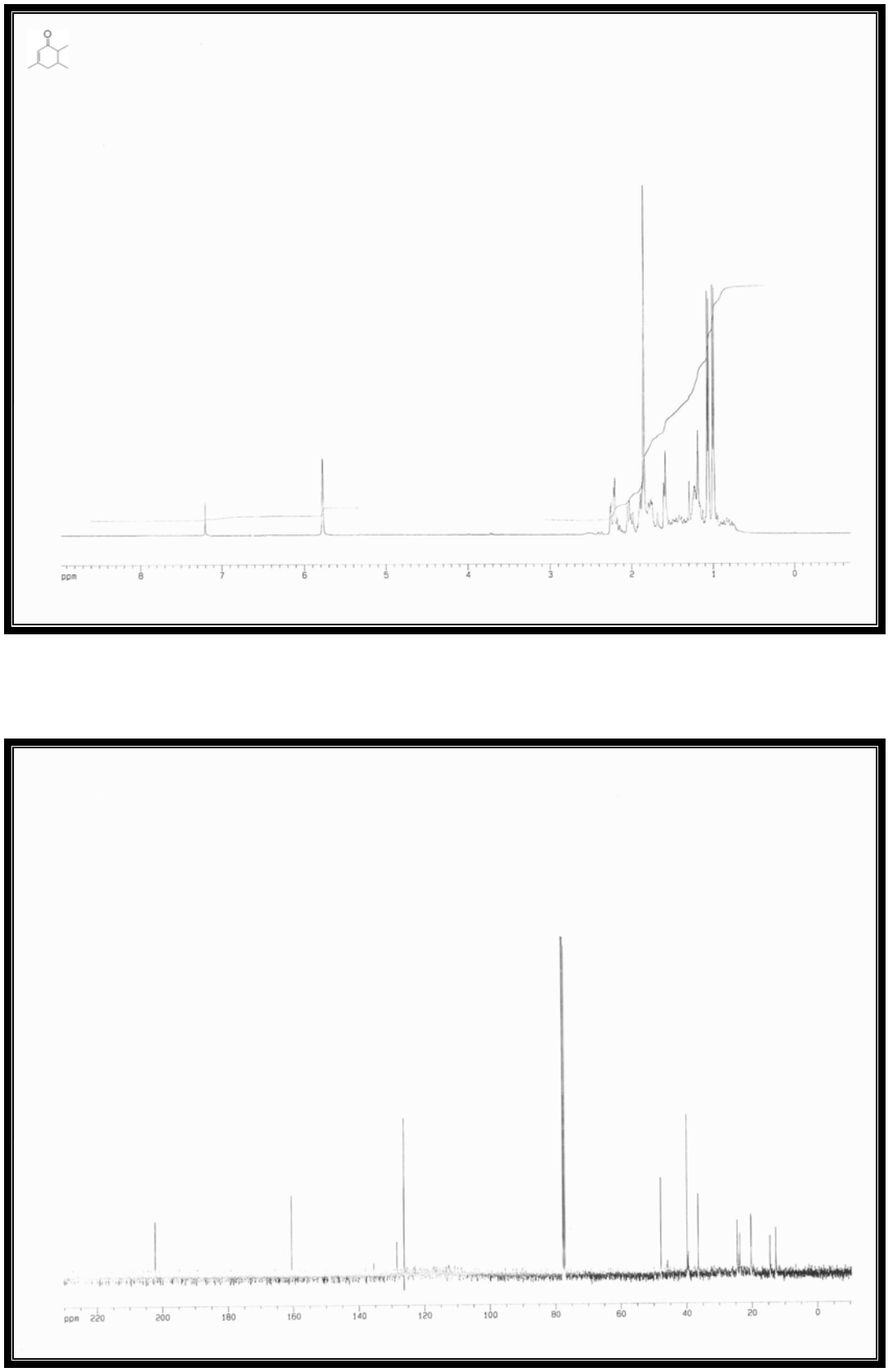


Fig A 3. ^{1}H and ^{13}C-NMR Spectra of Compound **70**

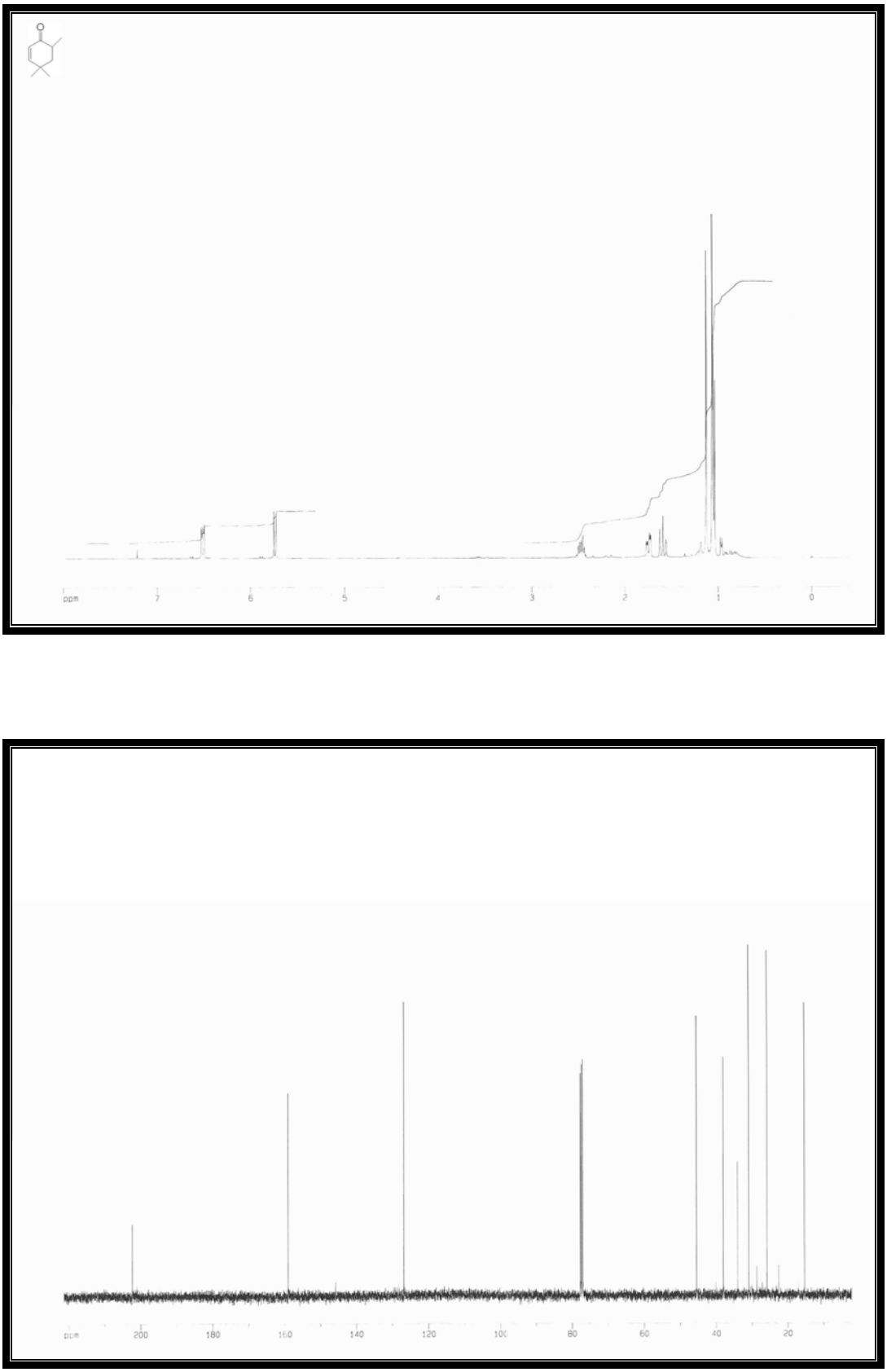


Fig A 4. ^{1}H and ^{13}C-NMR Spectra of Compound **72**

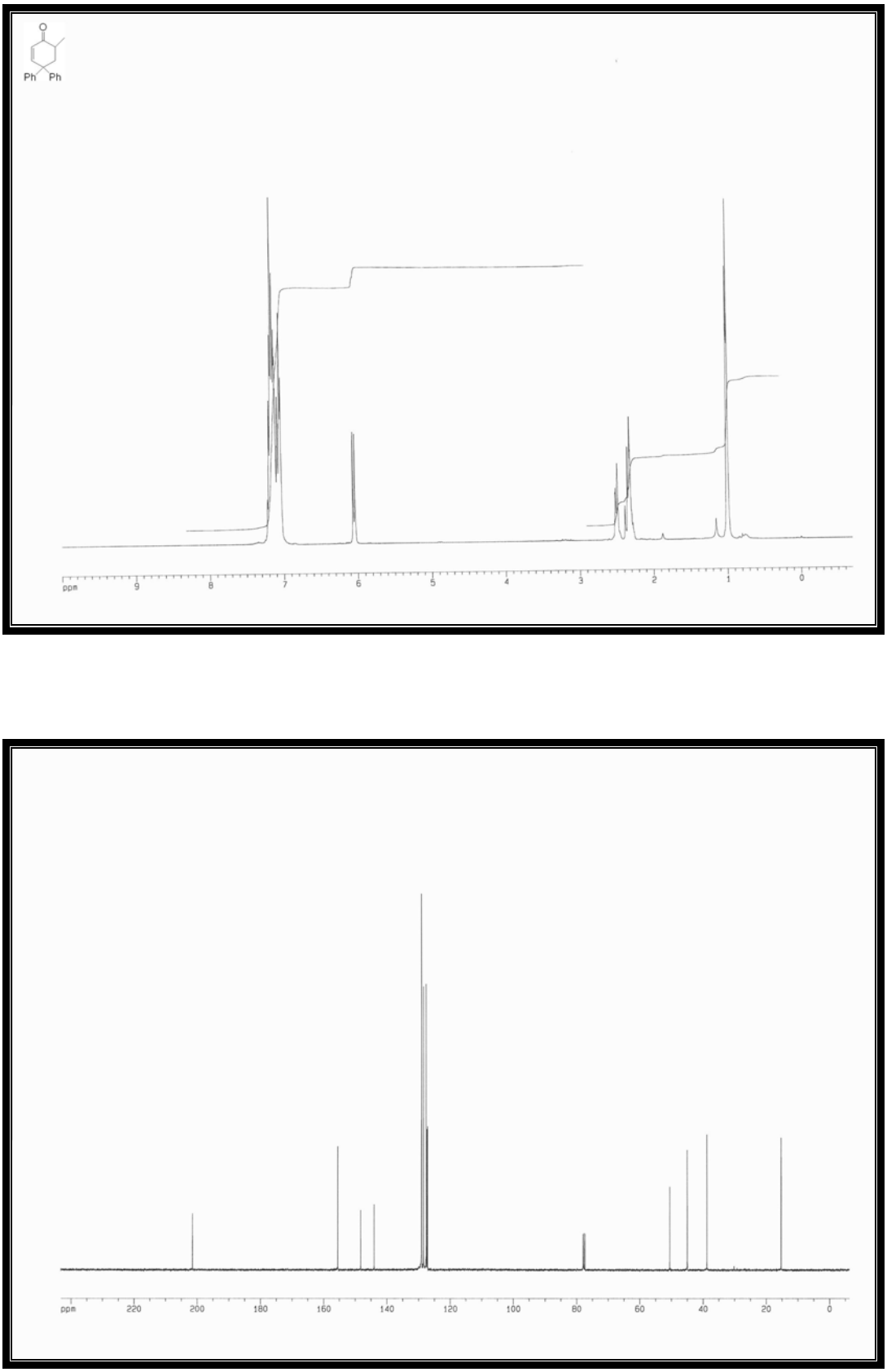


Fig A 5. ^{1}H and ^{13}C-NMR Spectra of Compound **74**

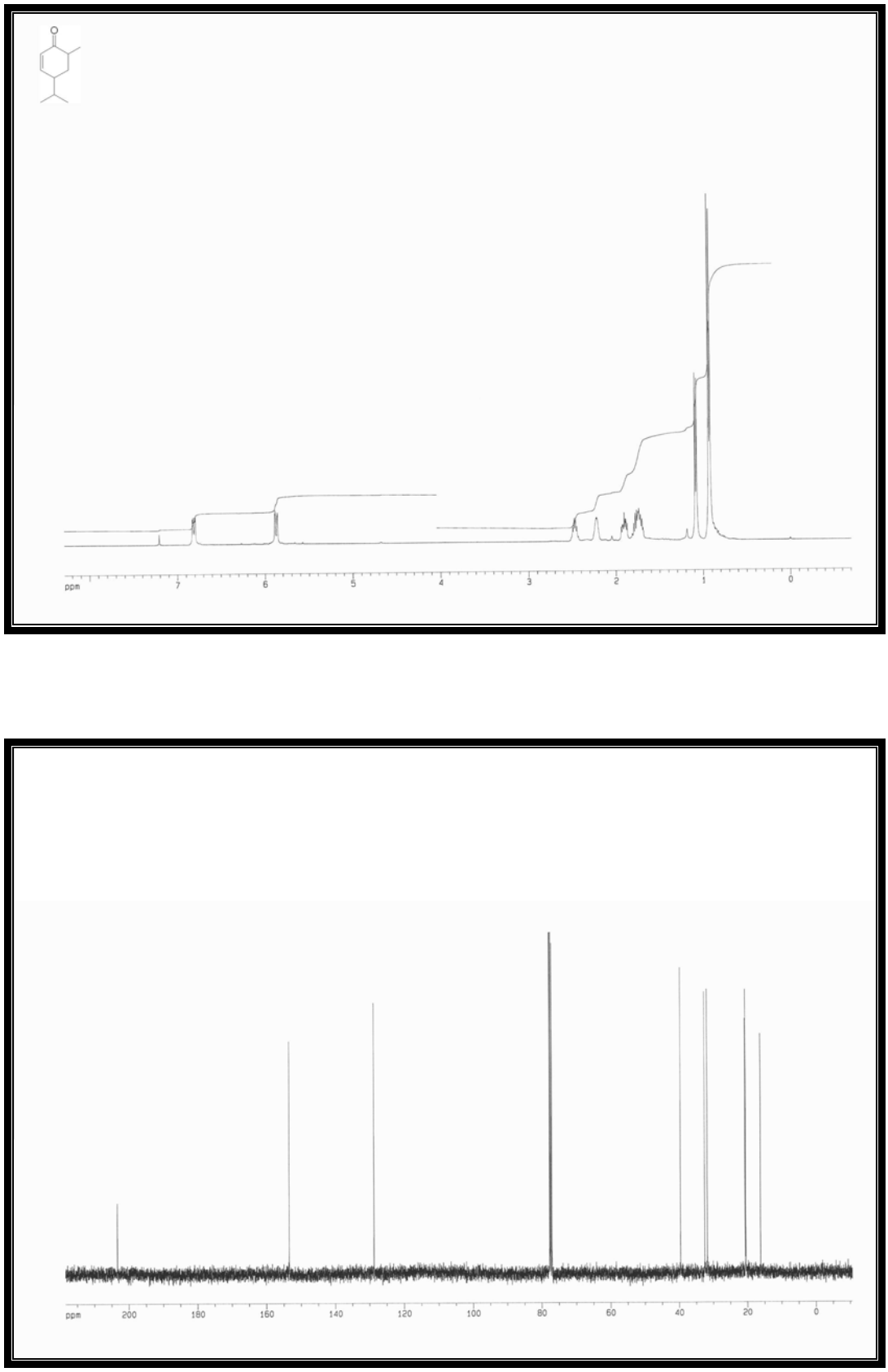


Fig A 6. ^{1}H and ^{13}C-NMR Spectra of Compound **76**

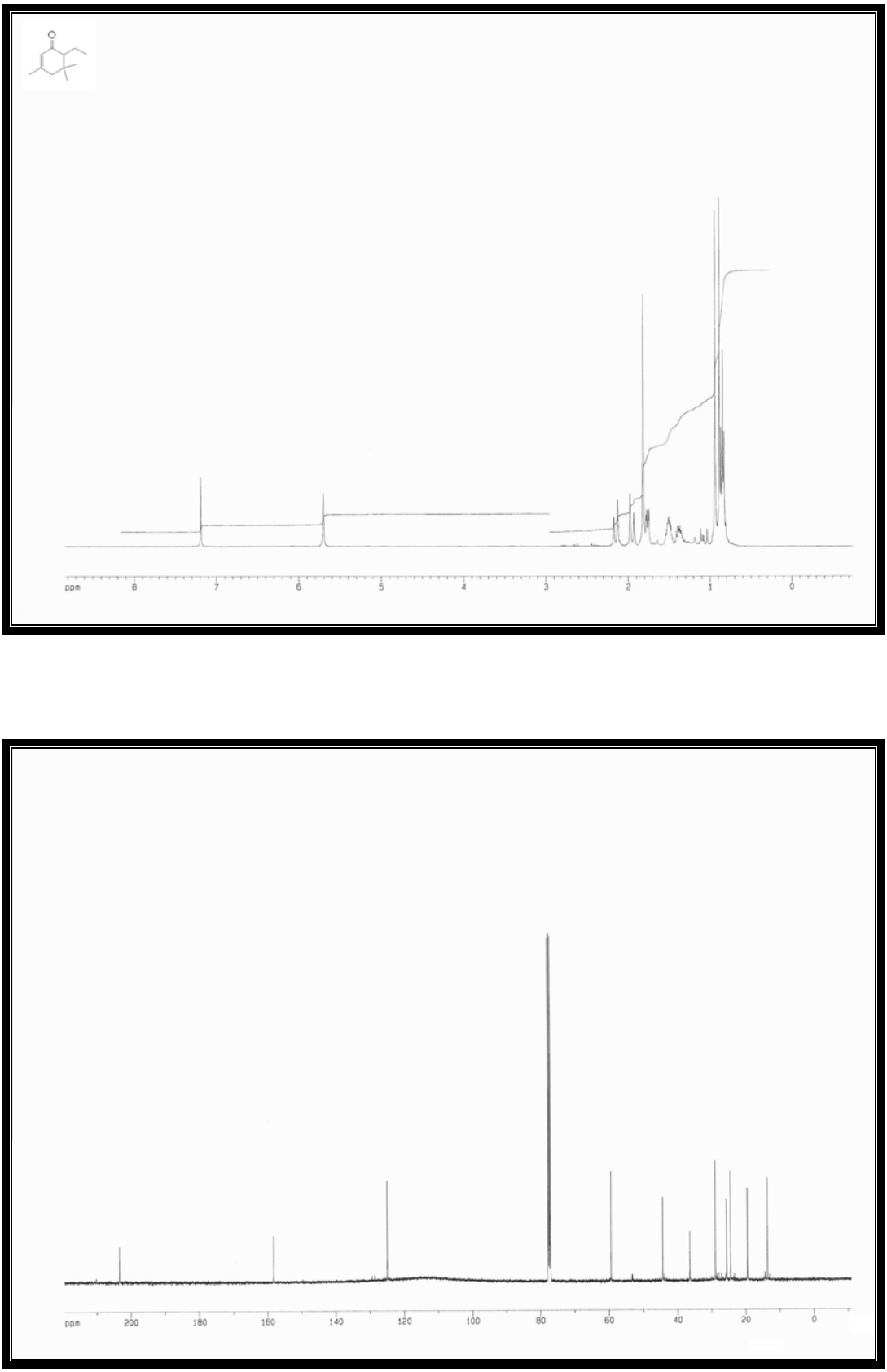


Fig A 7. ^{1}H and ^{13}C-NMR Spectra of Compound **77**

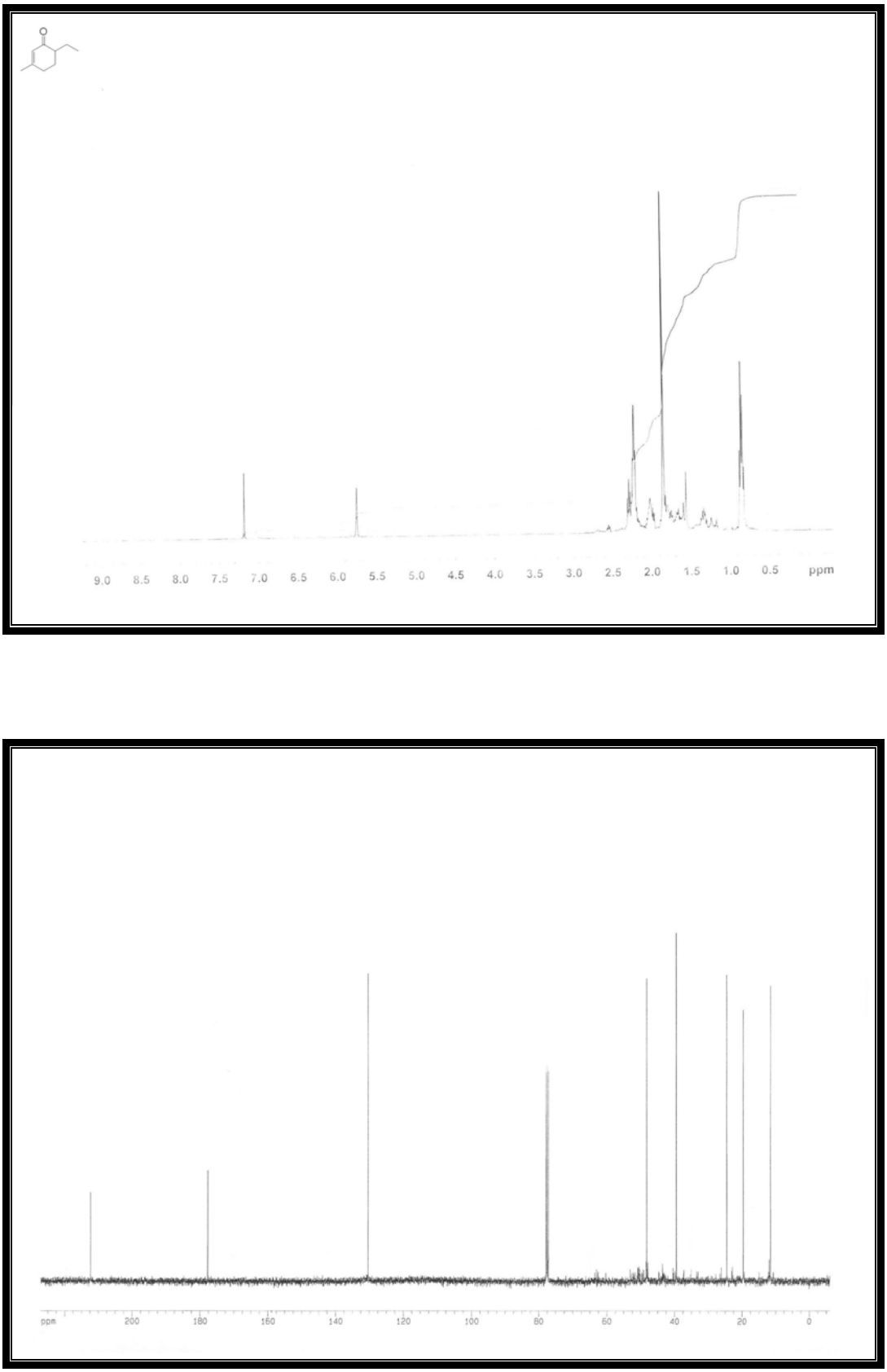


Fig A 8. ^{1}H and ^{13}C-NMR Spectra of Compound **78**

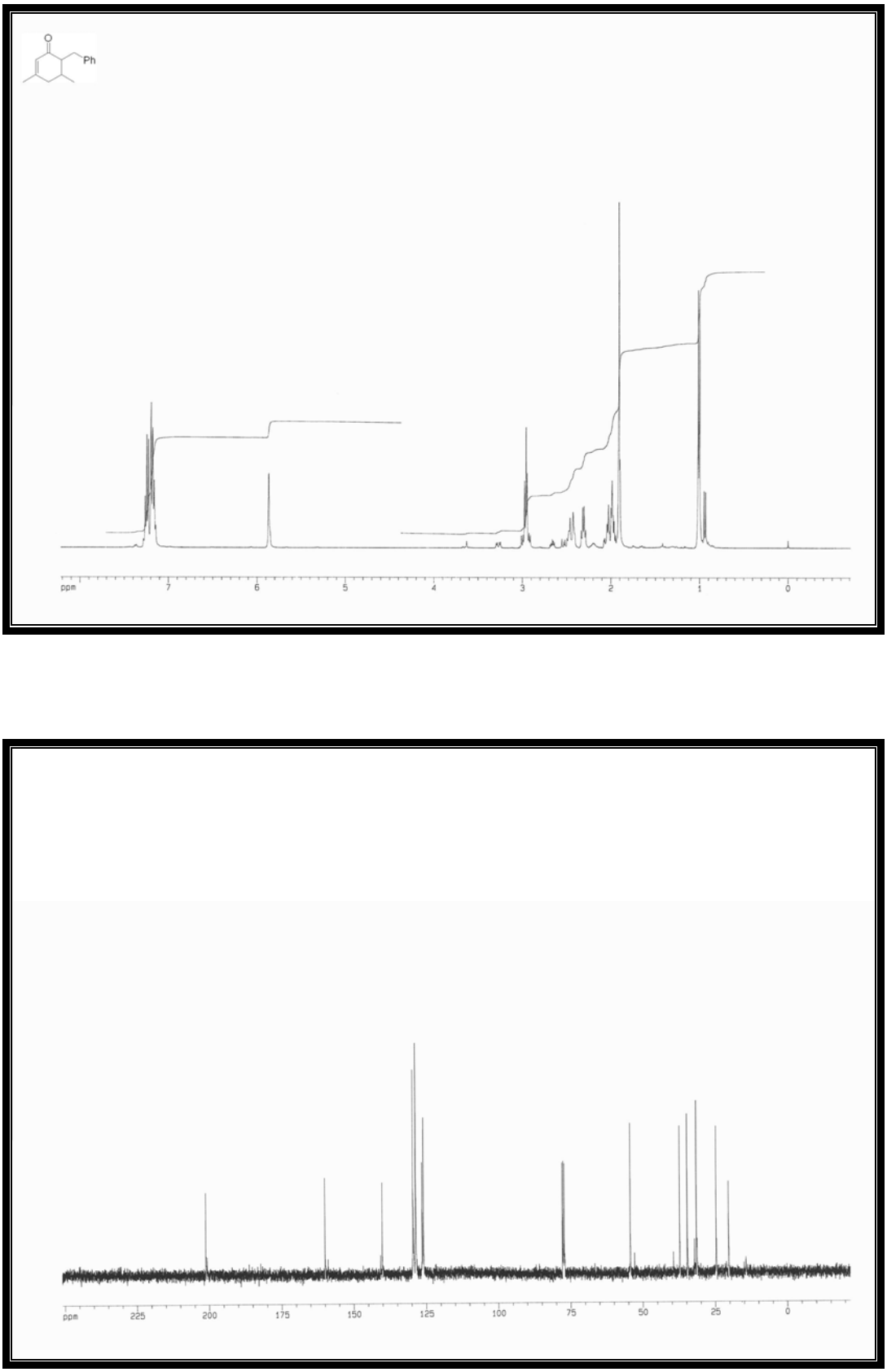


Fig A 9. ^{1}H and ^{13}C-NMR Spectra of Compound **79**

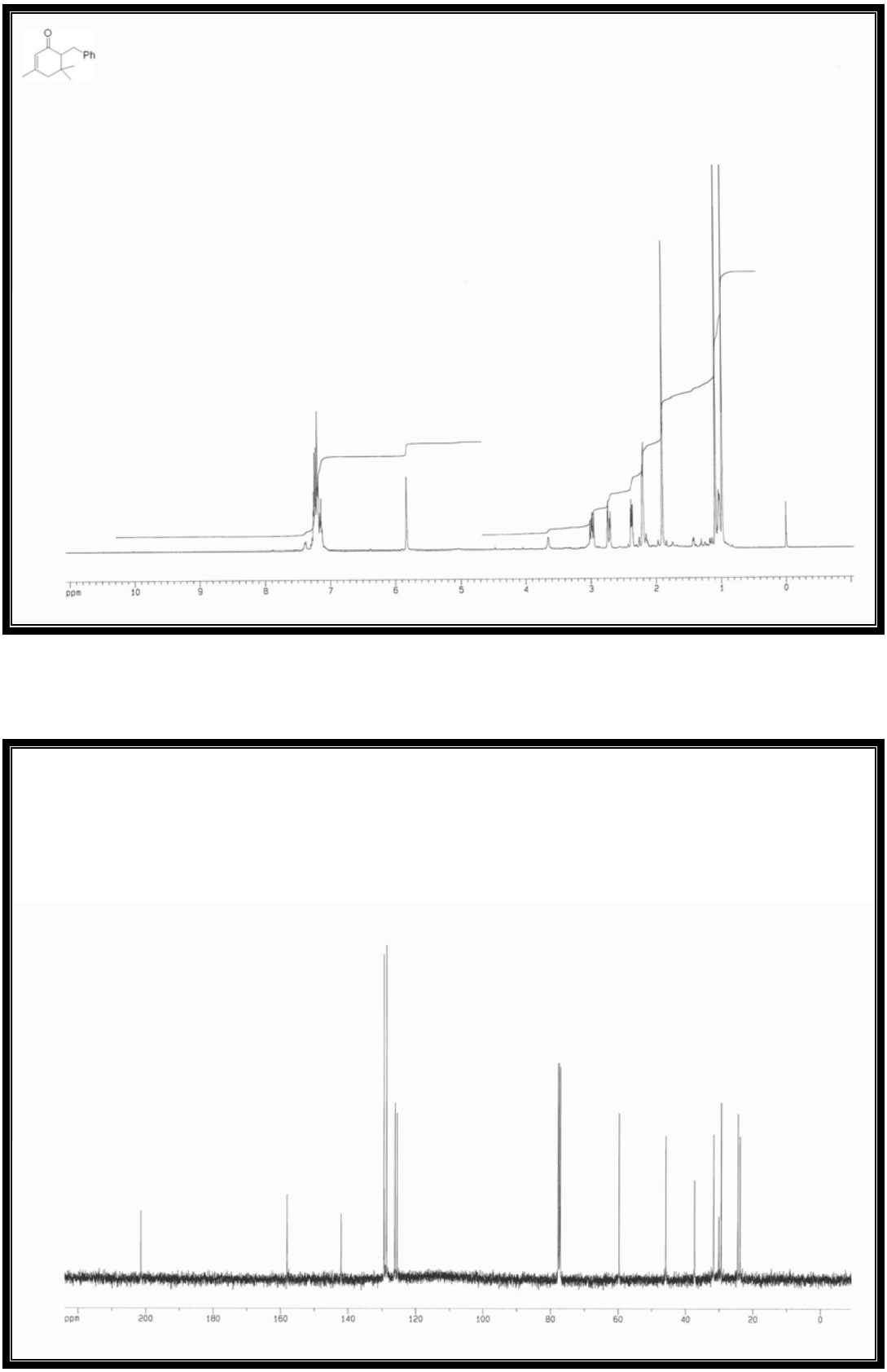


Fig A 10. ^{1}H and ^{13}C-NMR Spectra of Compound **80**

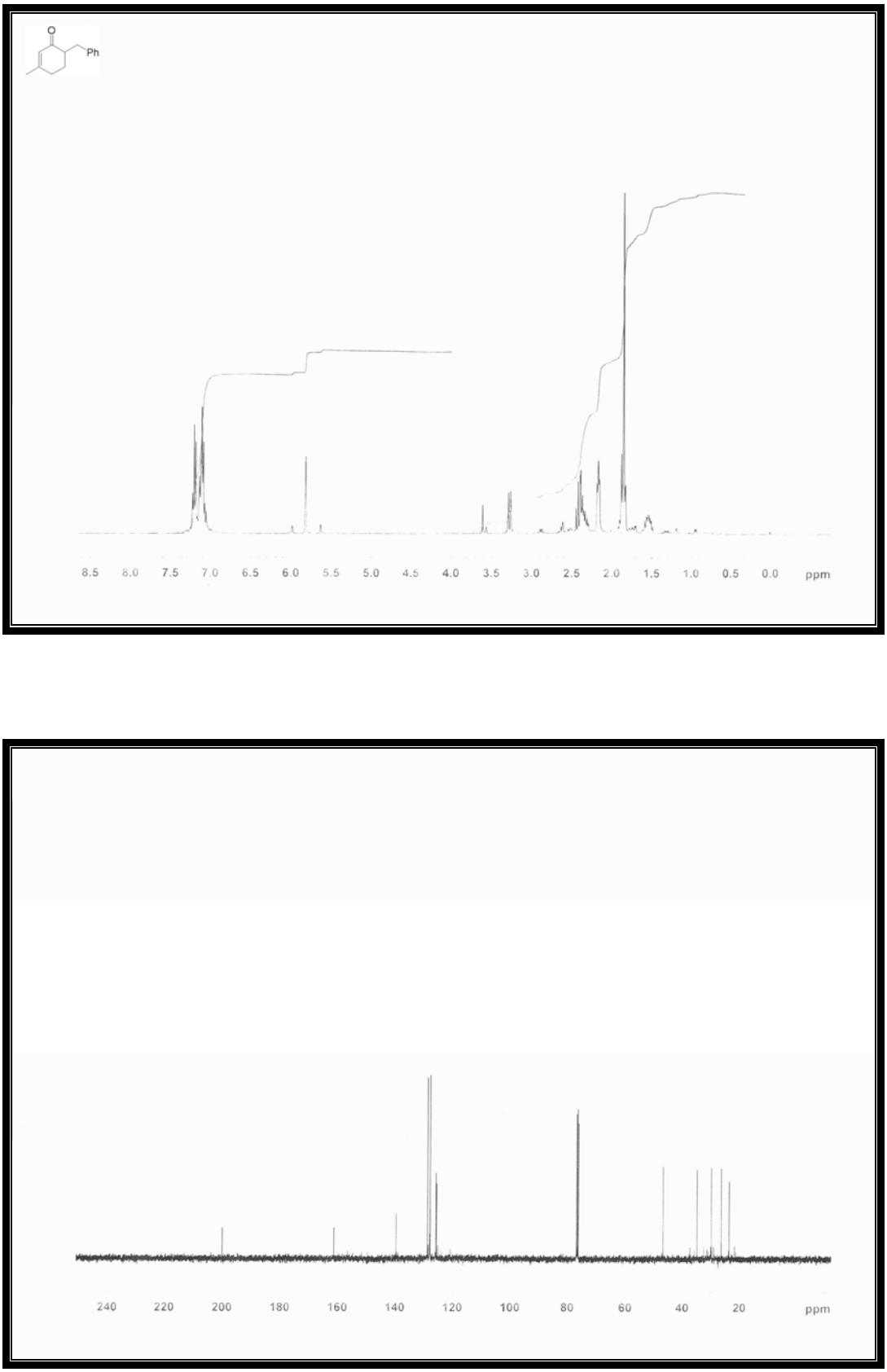


Fig A 11. ^{1}H and ^{13}C-NMR Spectra of Compound **81**

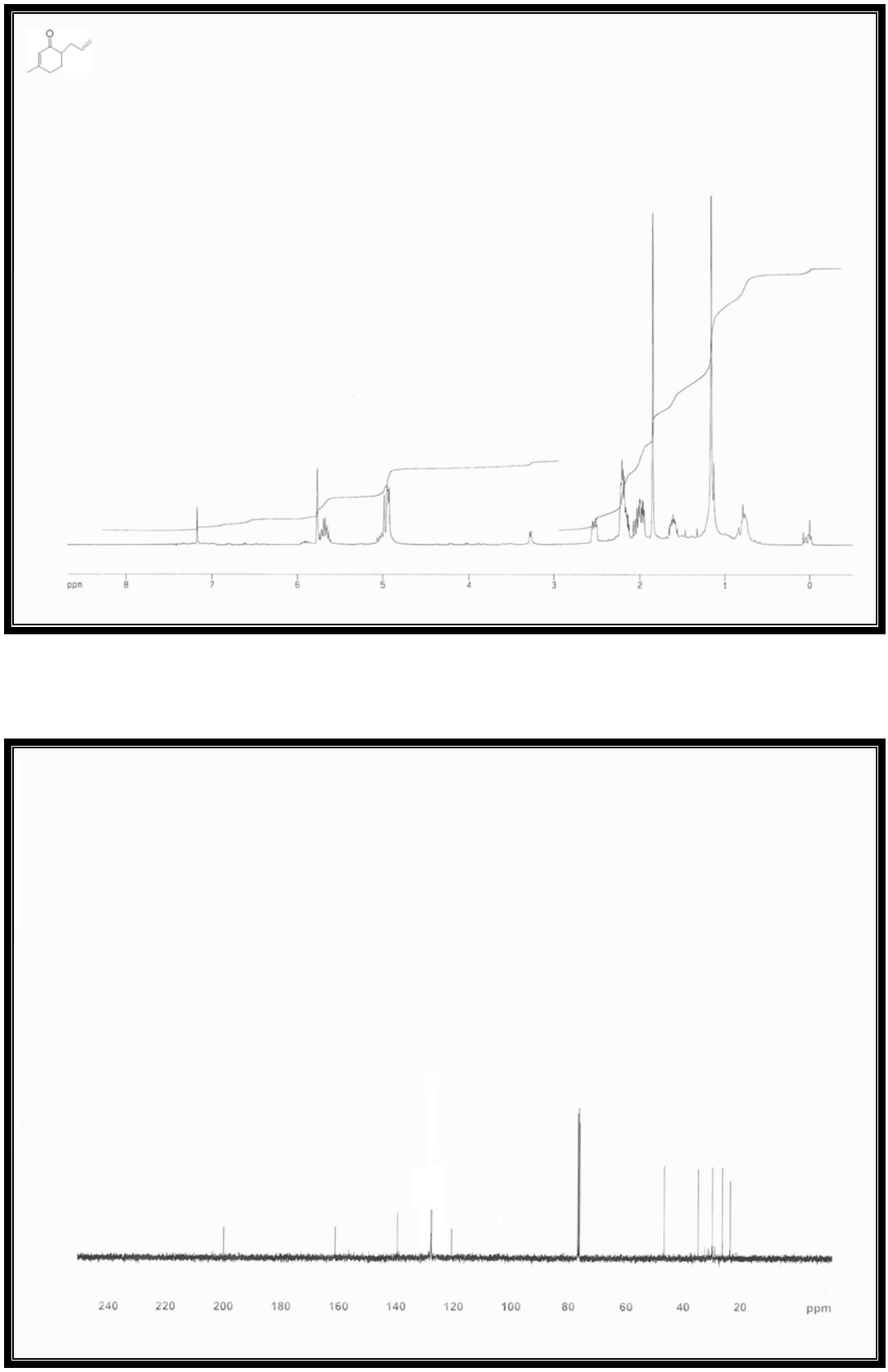


Fig A 12. ^{1}H and ^{13}C-NMR Spectra of Compound **82**

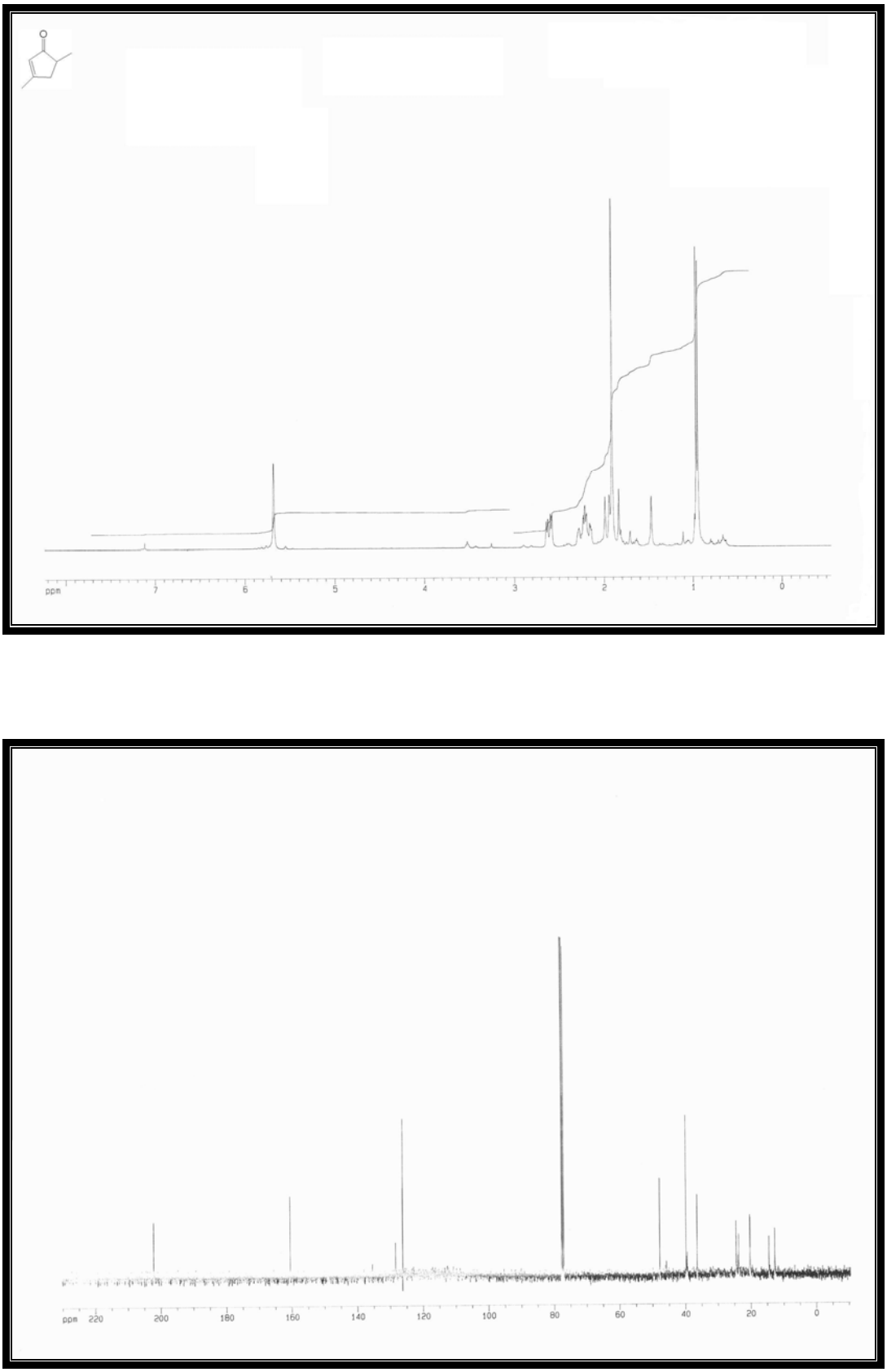


Fig A 13. ^{1}H and ^{13}C-NMR Spectra of Compound **84**

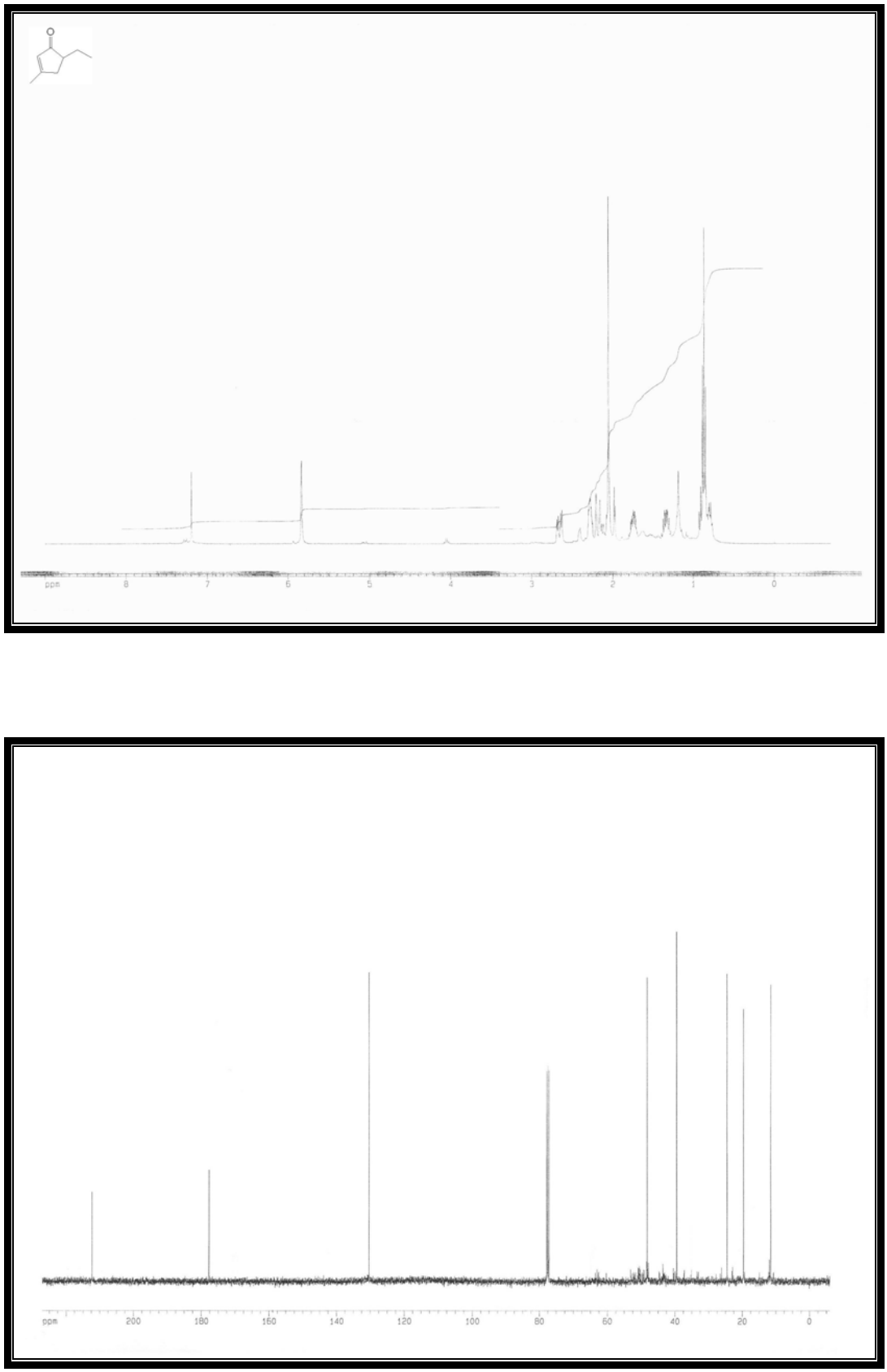


Fig A 14. ^{1}H and ^{13}C-NMR Spectra of Compound **85**

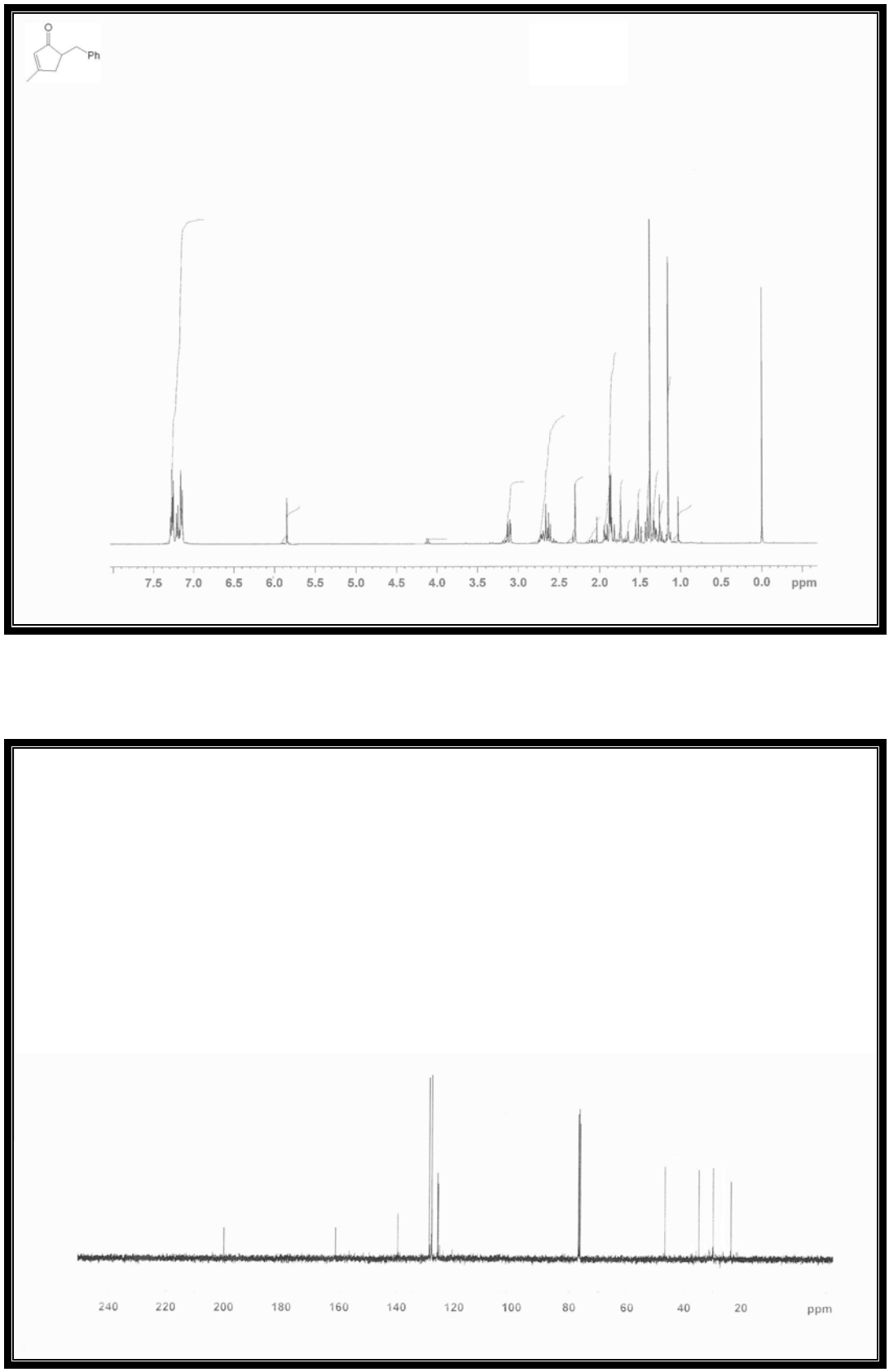


Fig A 15. ^{1}H and ^{13}C-NMR Spectra of Compound **86**

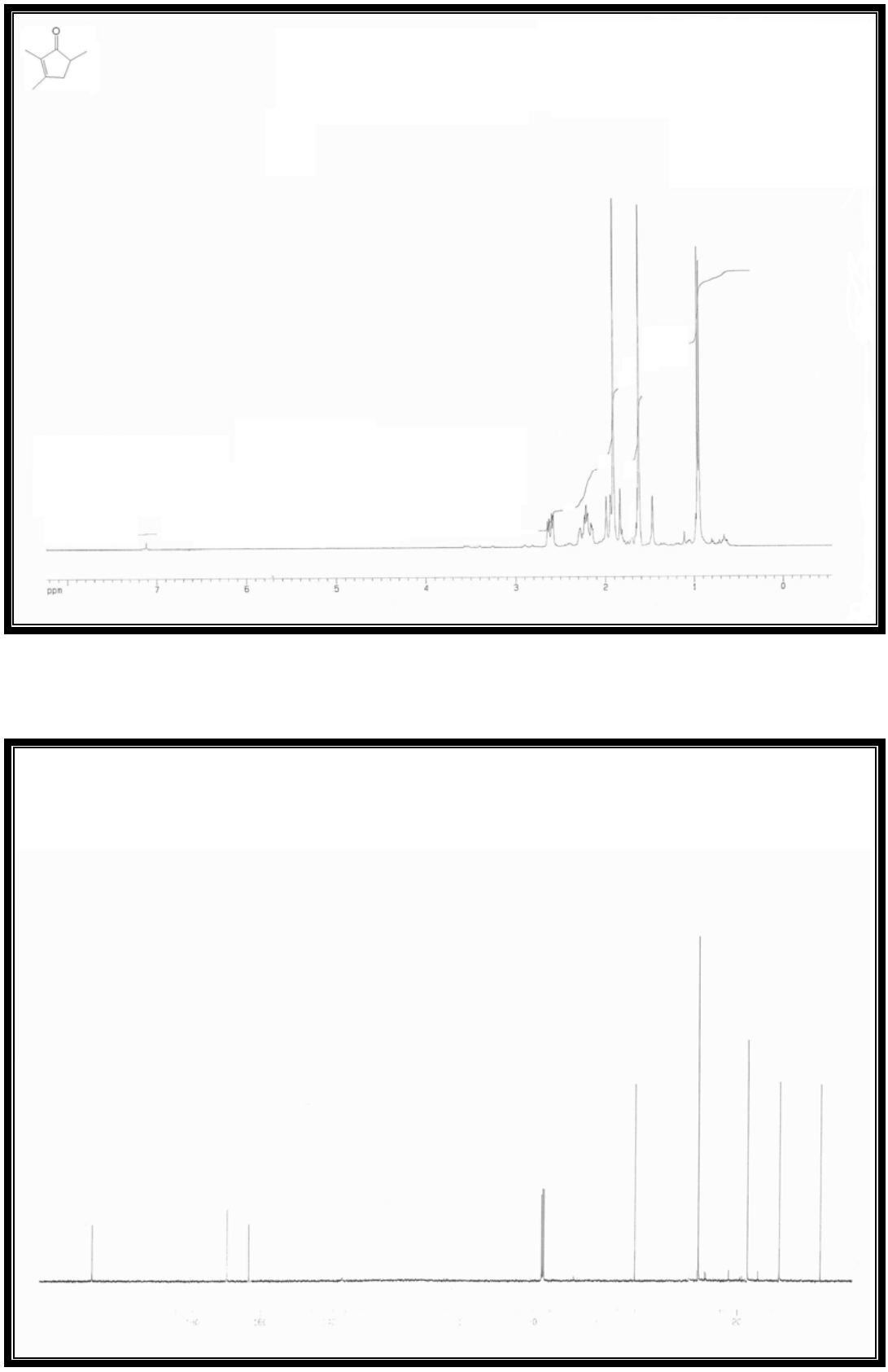
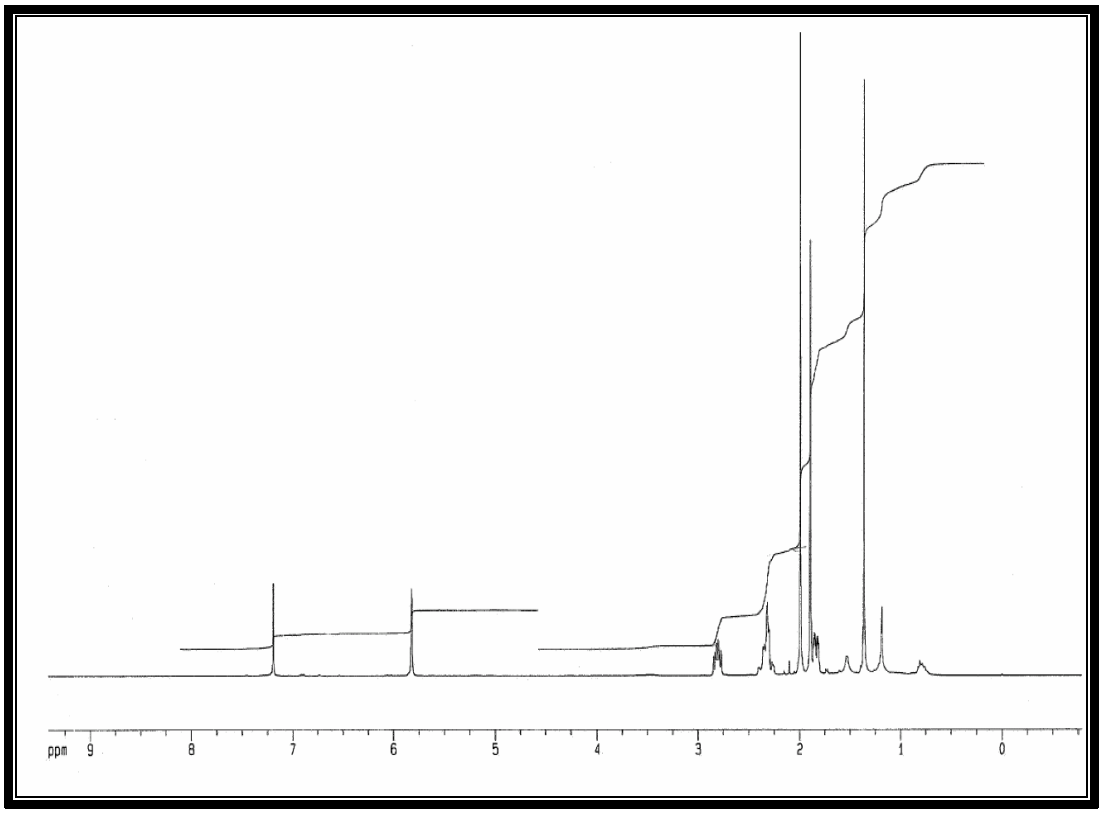


Fig A 16. ^{1}H and ^{13}C-NMR Spectra of Compound **87**



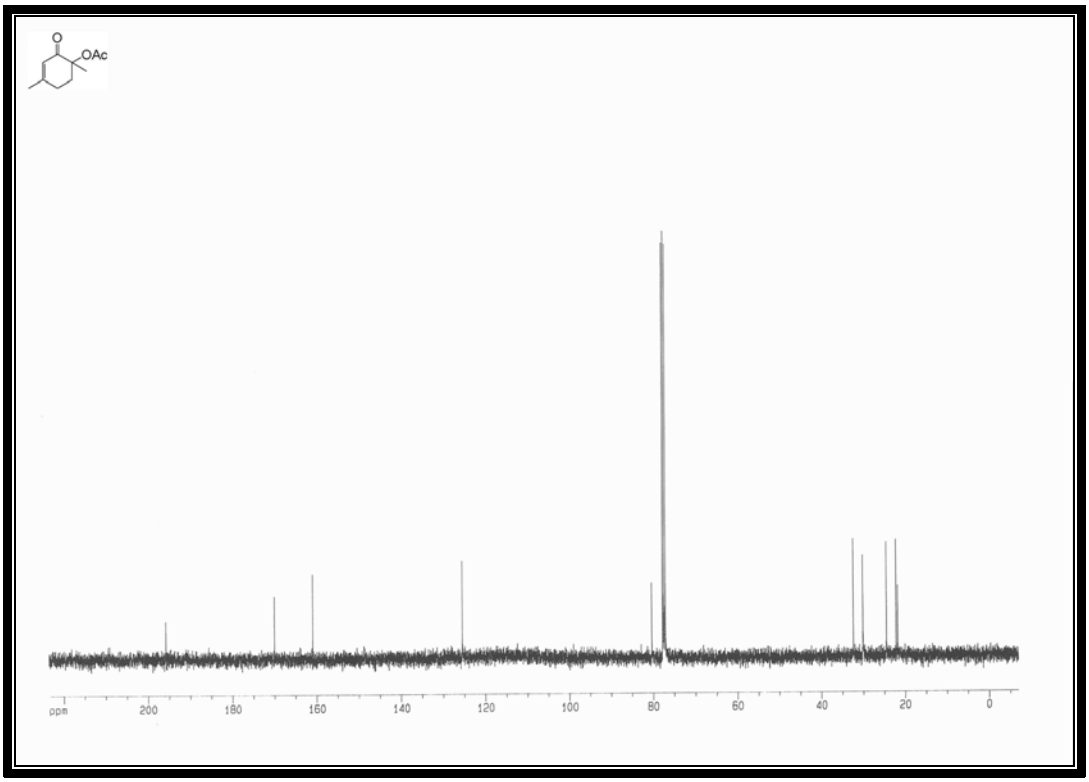


Fig A 17. ^{1}H and ^{13}C-NMR Spectra of Compound **88**

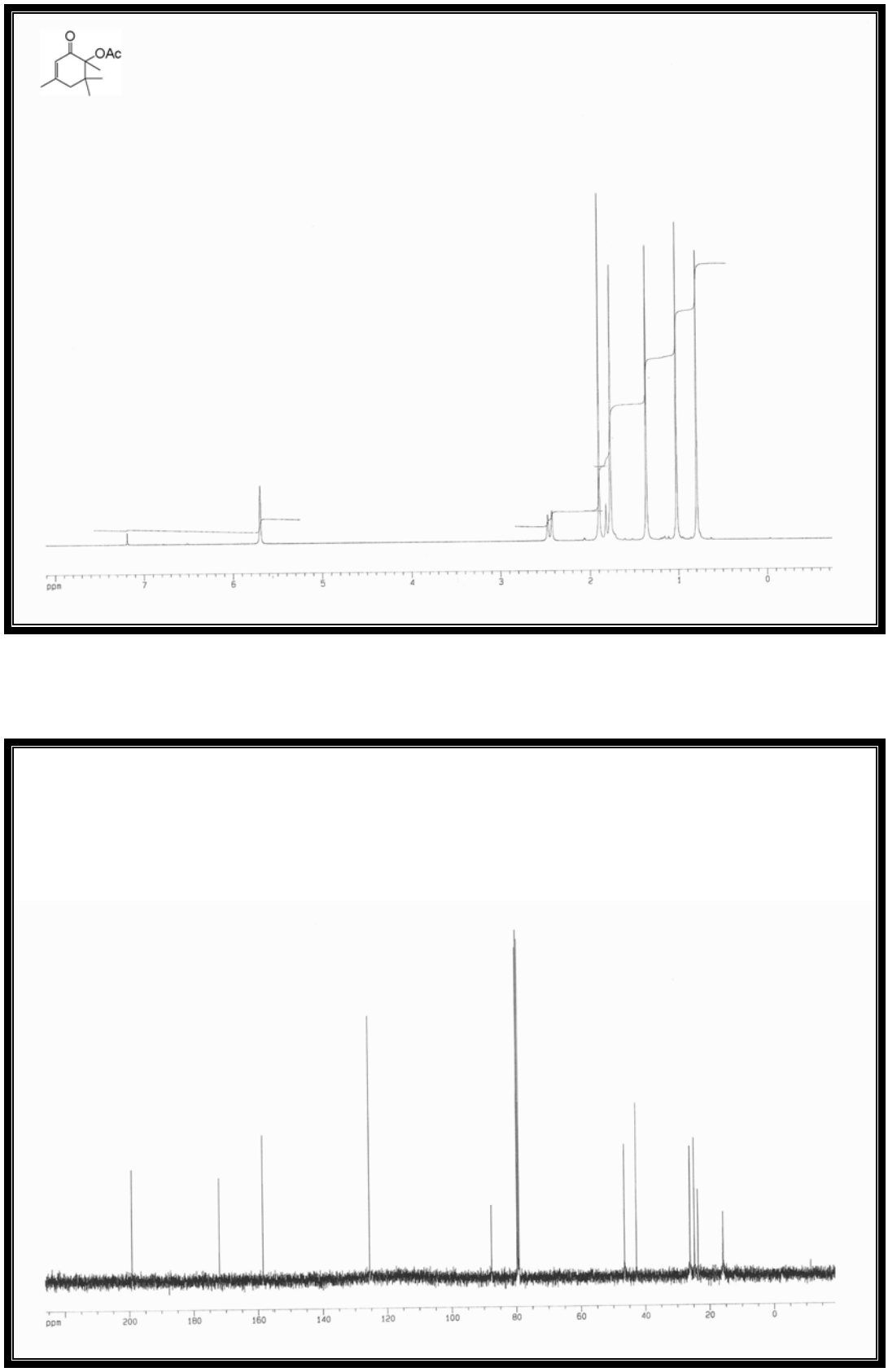


Fig A 18. ^{1}H and ^{13}C-NMR Spectra of Compound **89**

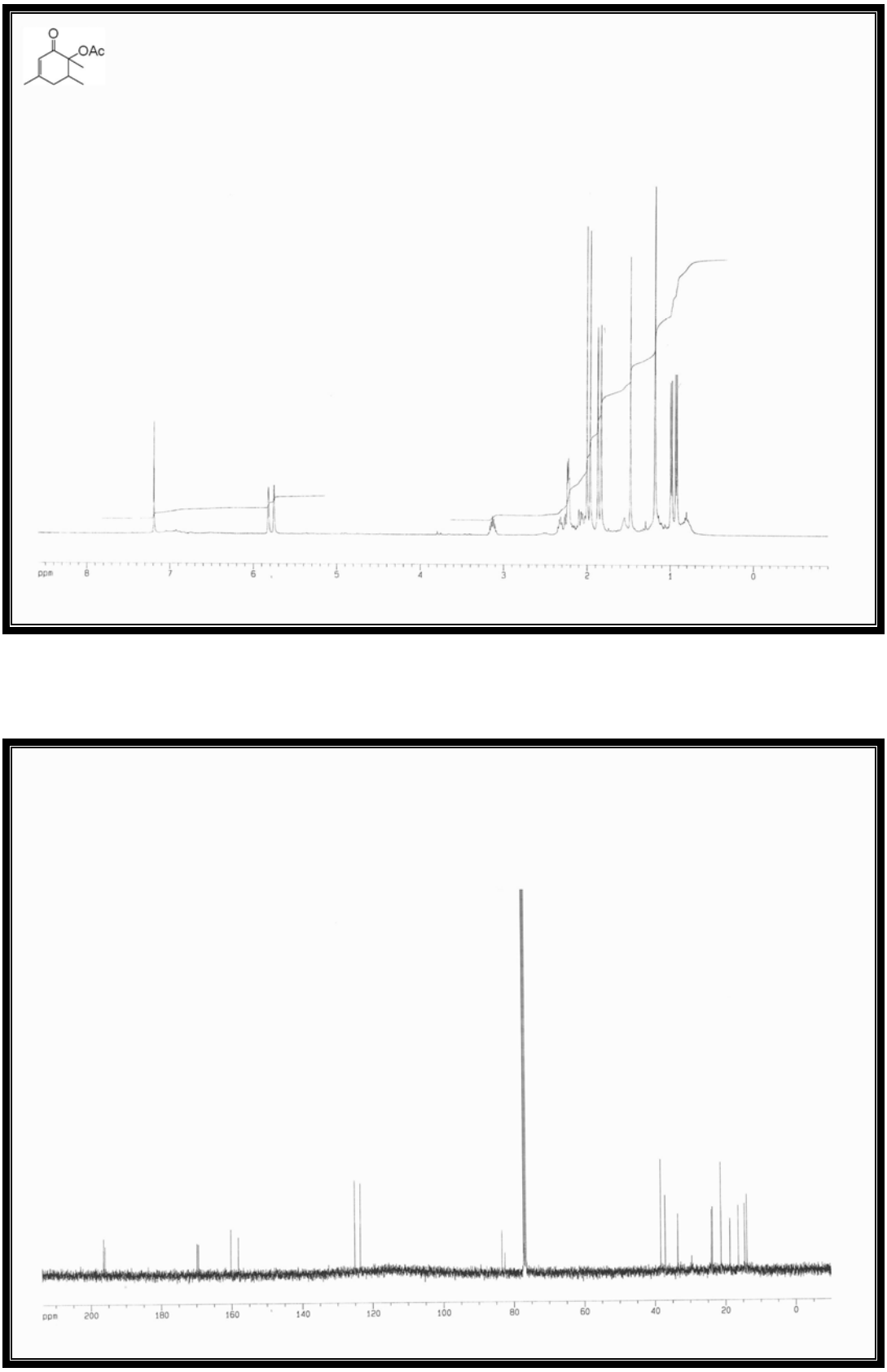


Fig A 19. ^{1}H and ^{13}C-NMR Spectra of Compound **90**

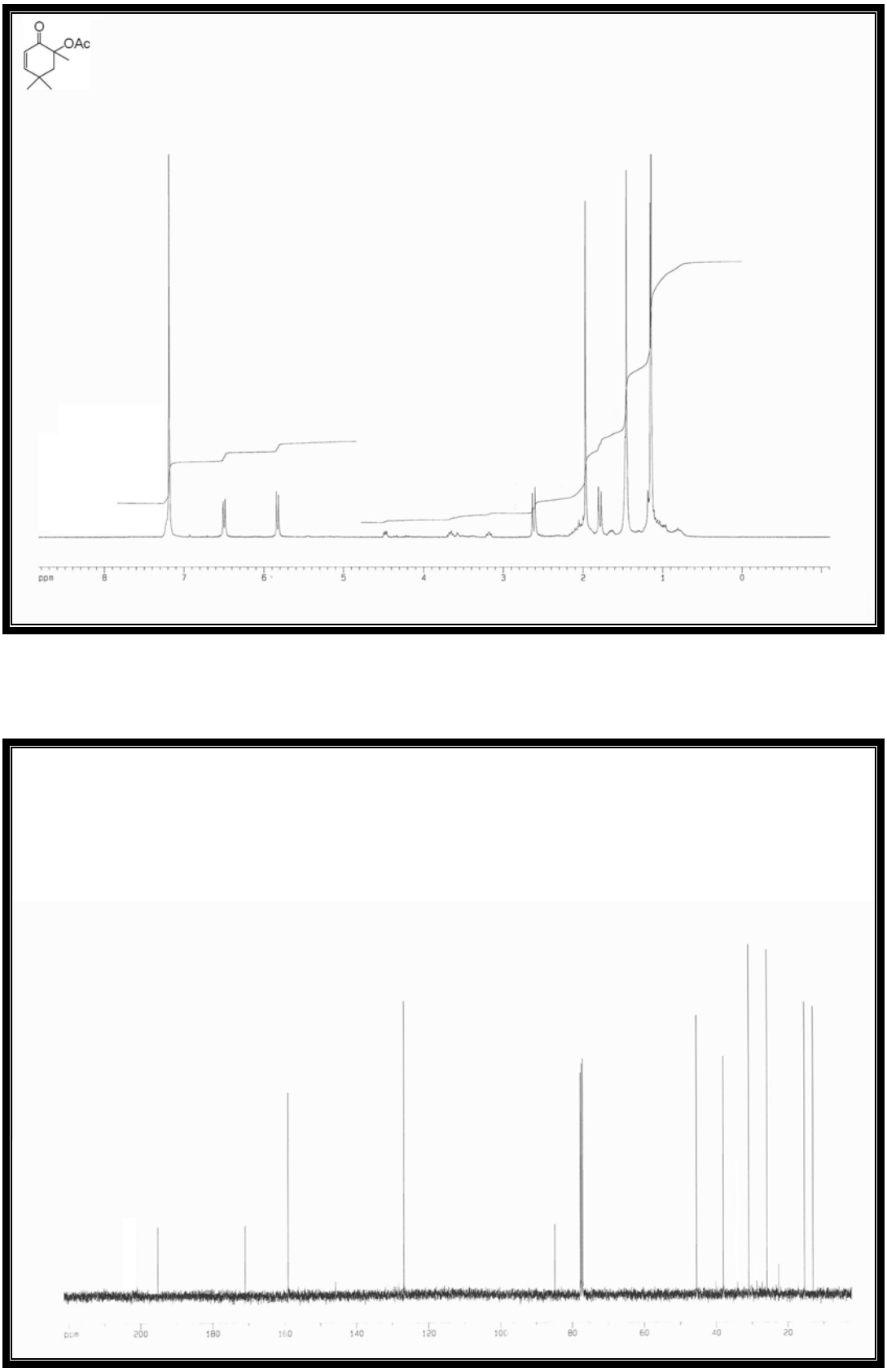


Fig A 20. ^{1}H and ^{13}C-NMR Spectra of Compound **91**

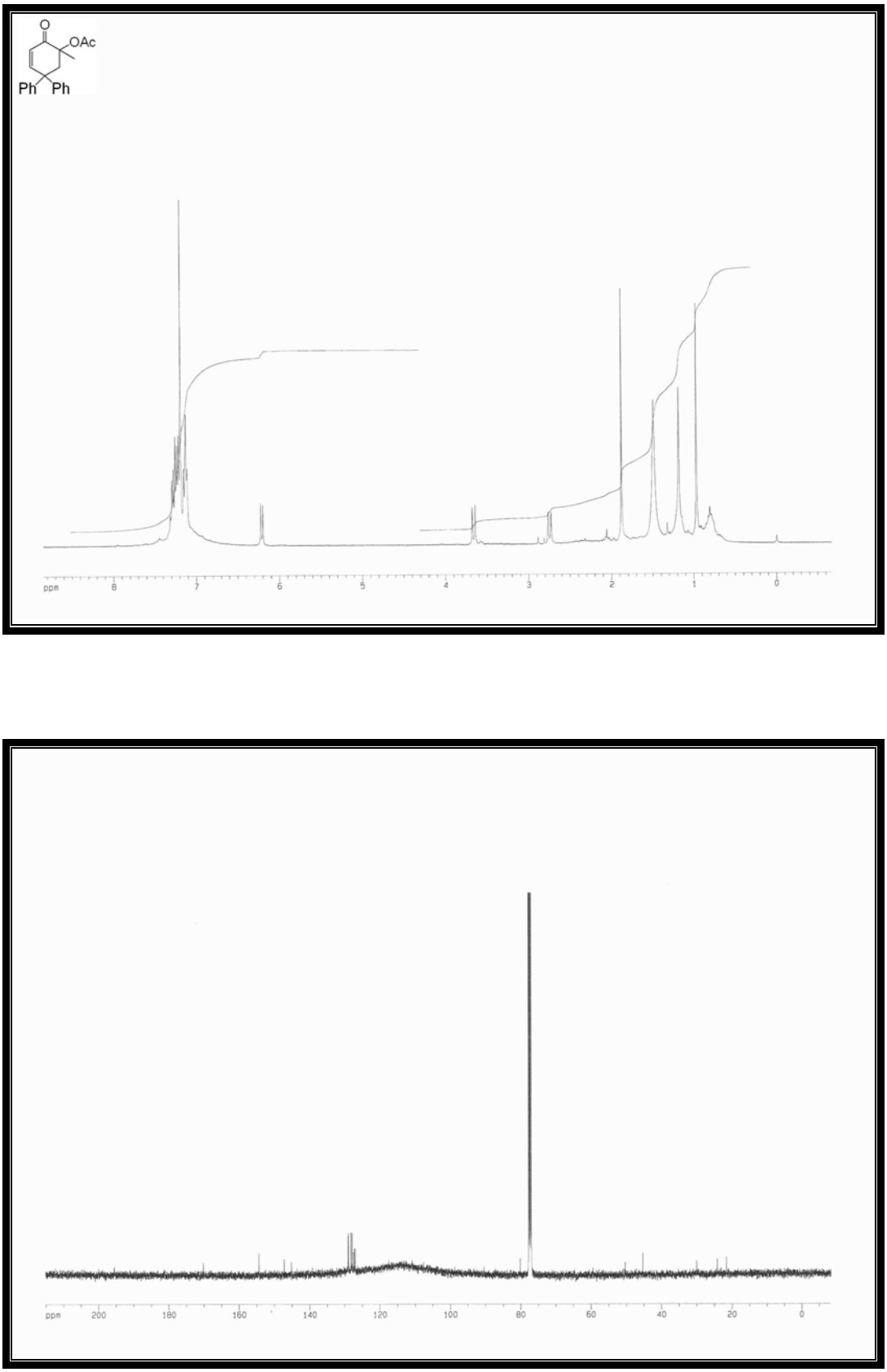


Fig A 21. ^{1}H and ^{13}C-NMR Spectra of Compound **92**

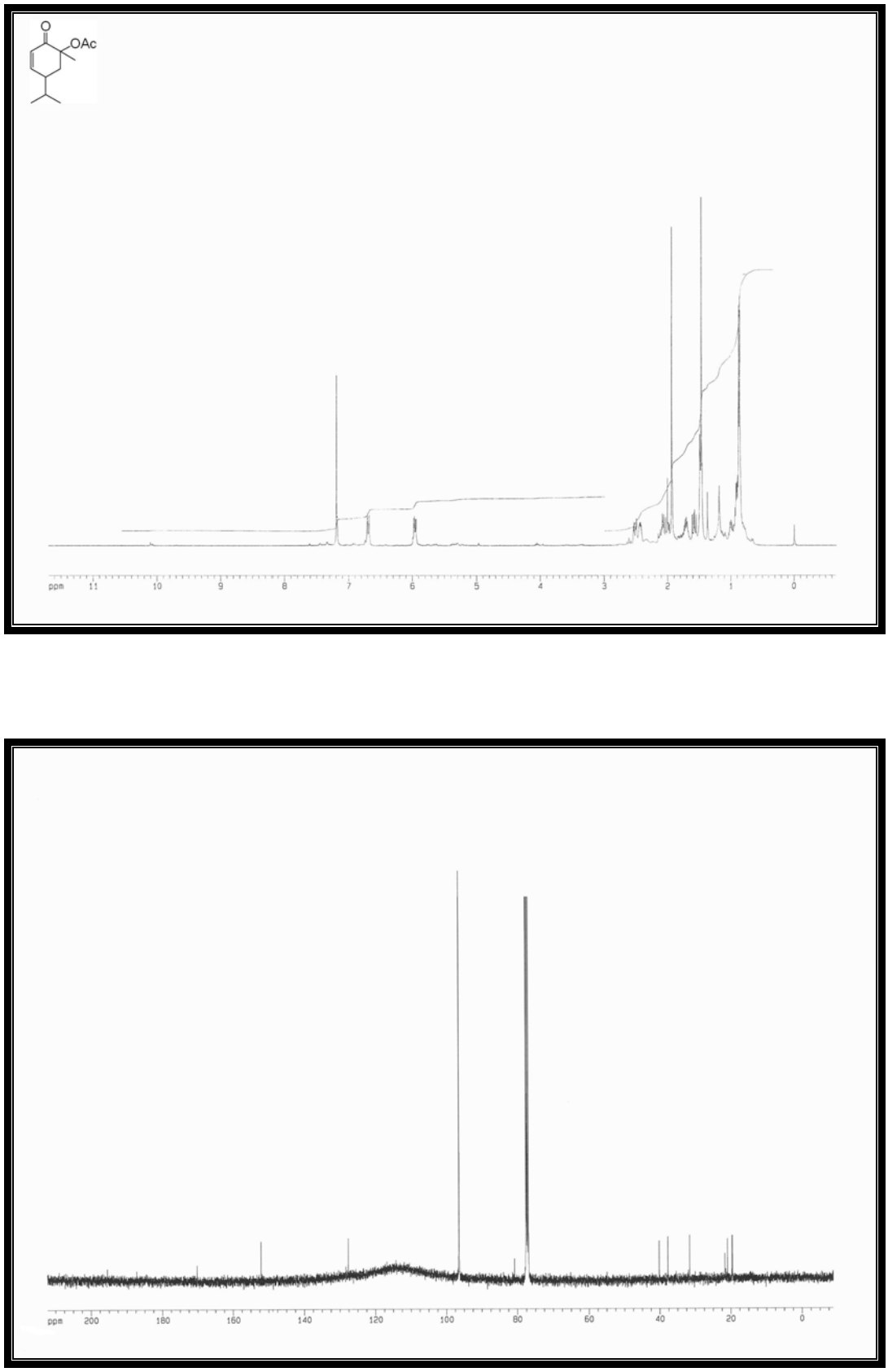


Fig A 22. ^{1}H and ^{13}C-NMR Spectra of Compound **93**

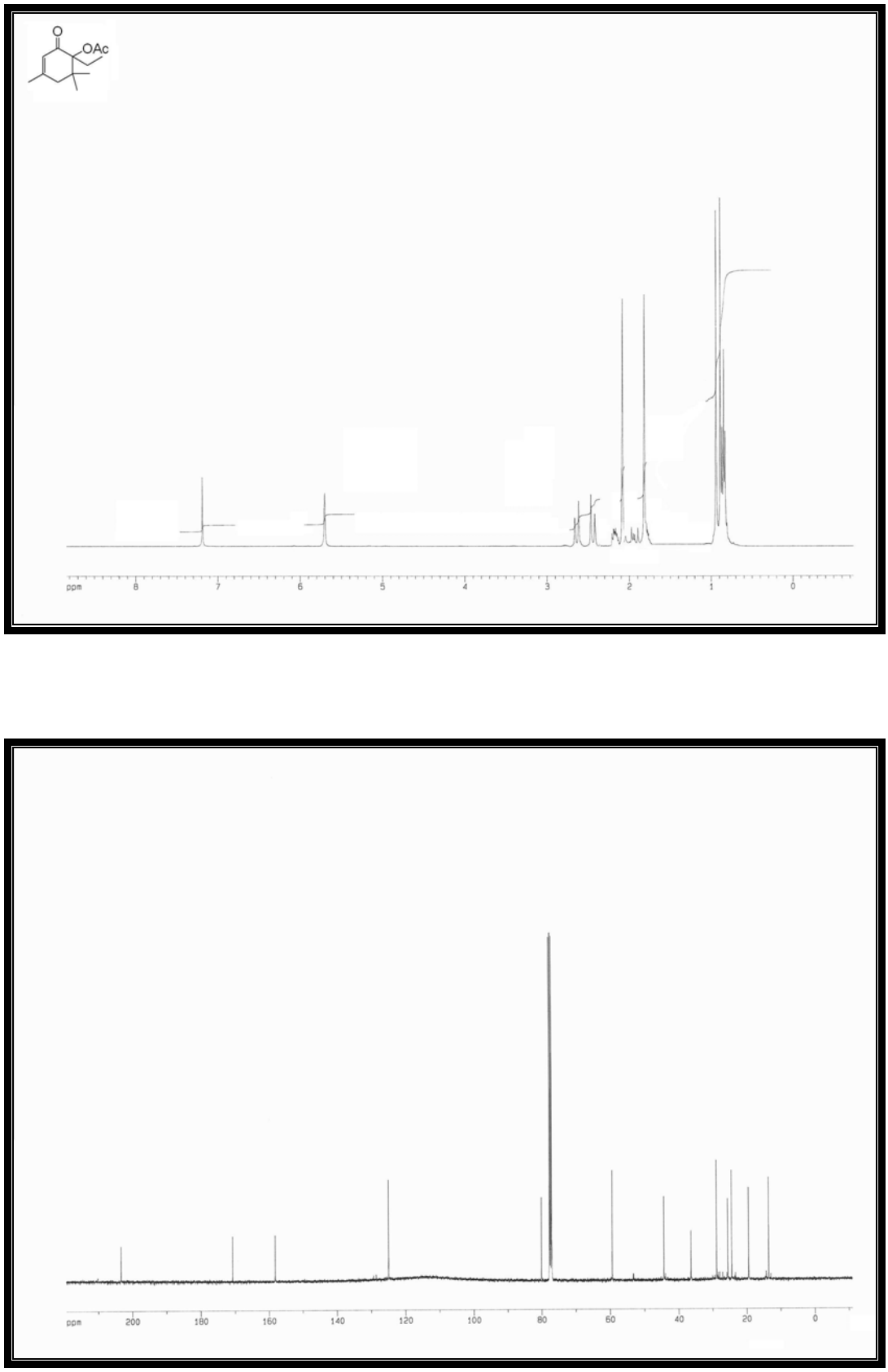


Fig A 23. ^{1}H and ^{13}C-NMR Spectra of Compound

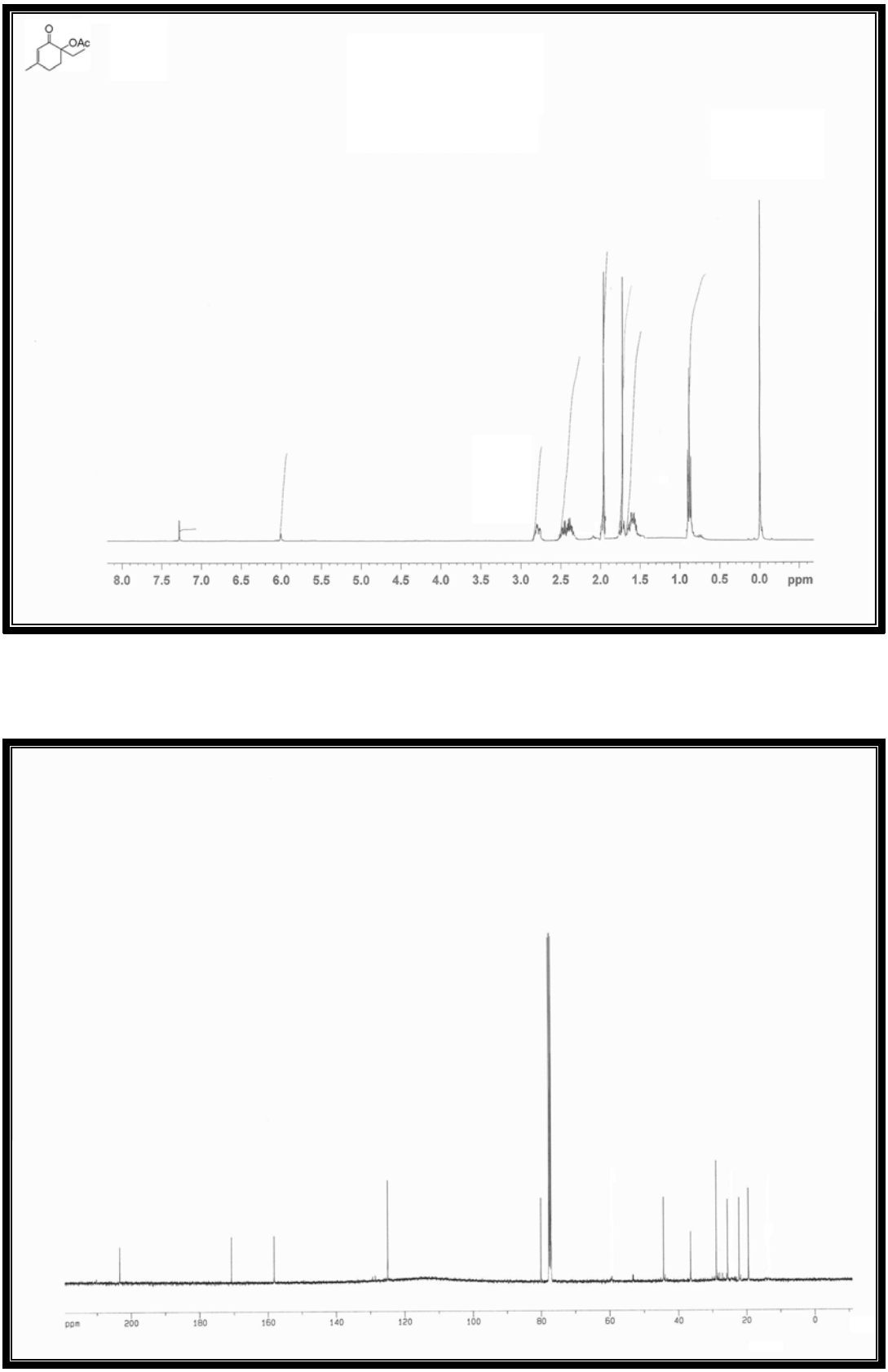


Fig A 24. ^{1}H and ^{13}C-NMR Spectra of Compound **95**

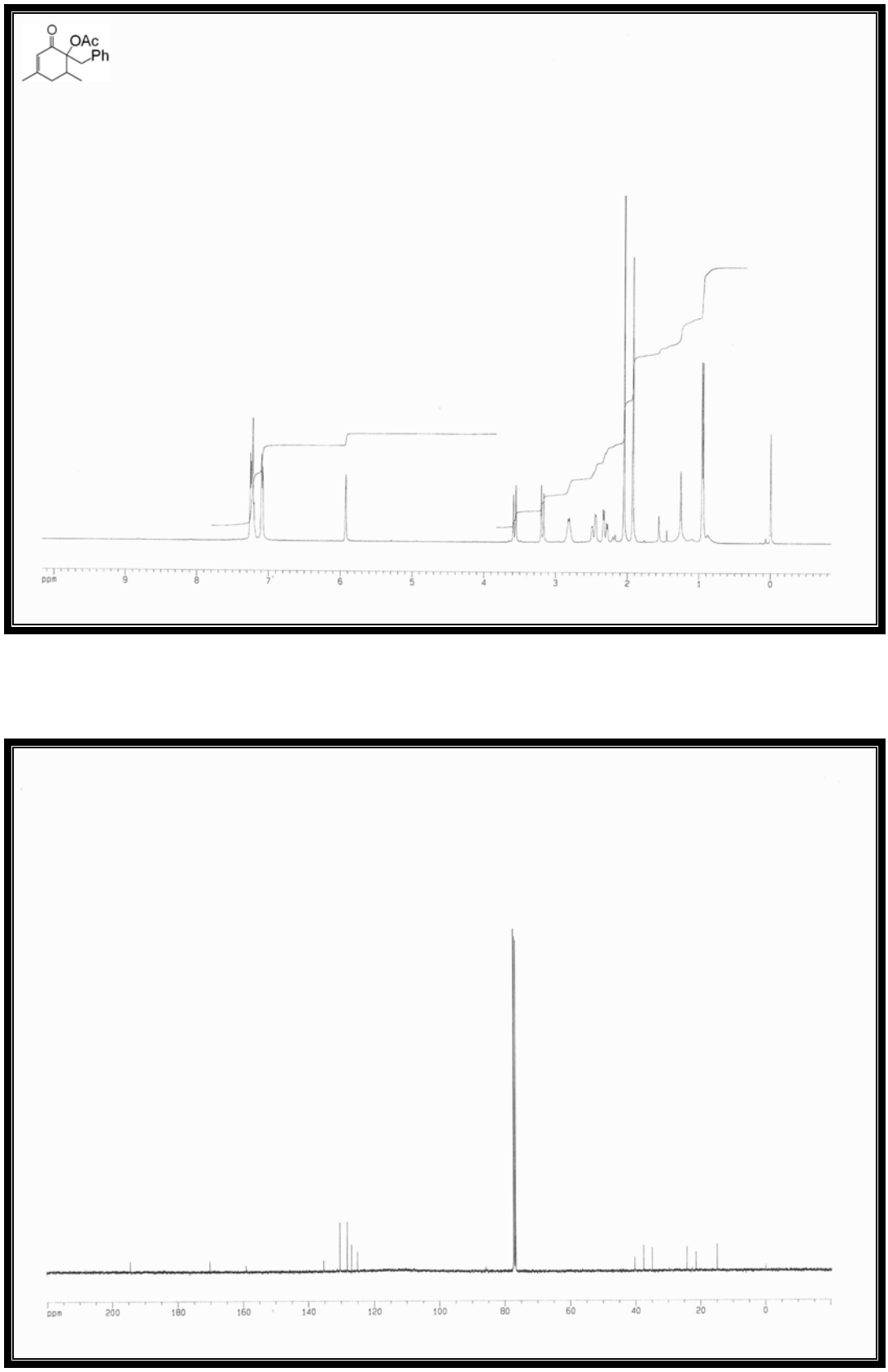


Fig A 25. ^{1}H and ^{13}C-NMR Spectra of Compound **96**

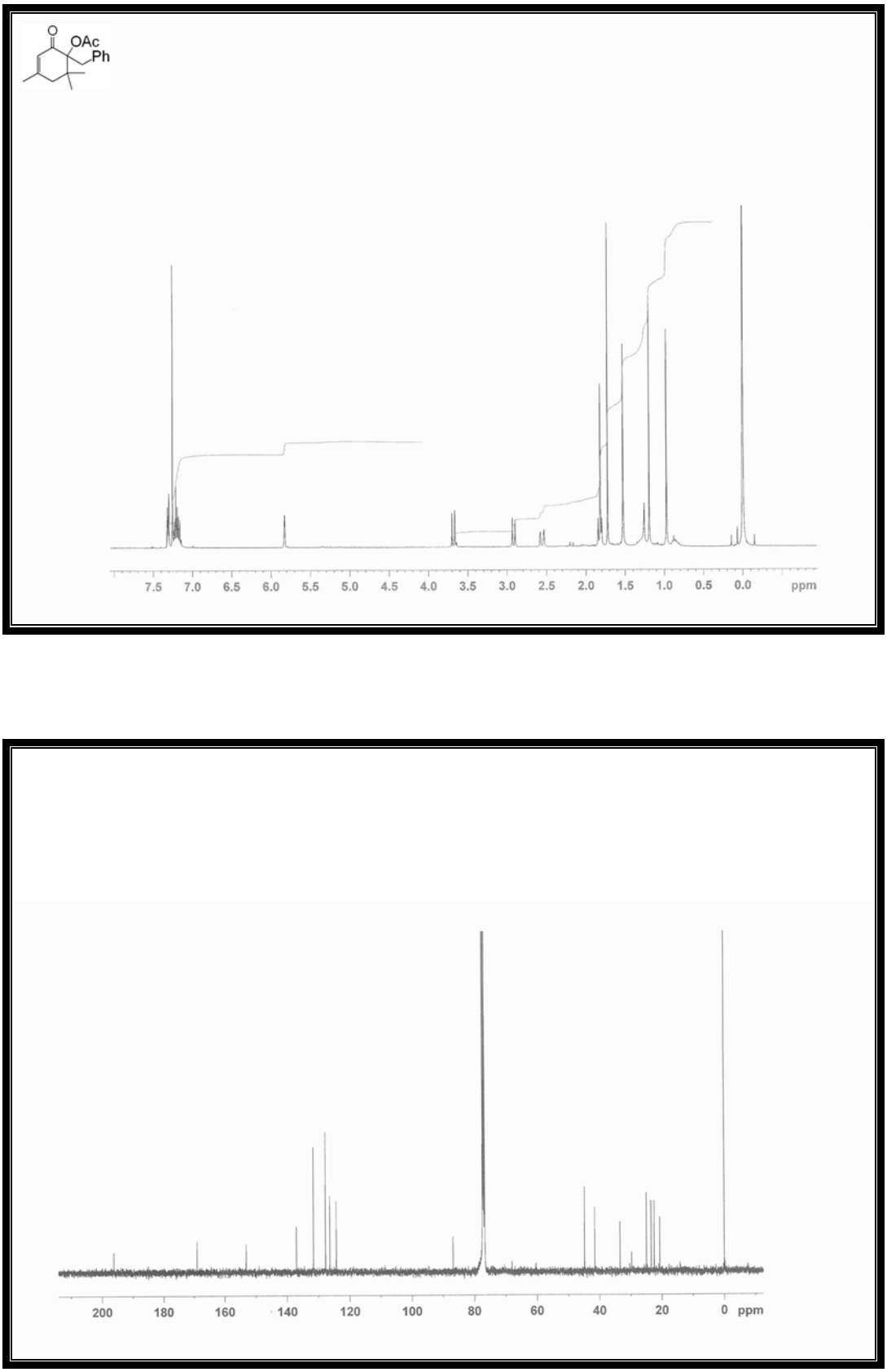


Fig A 26. ^{1}H and ^{13}C-NMR Spectra of Compound **97**

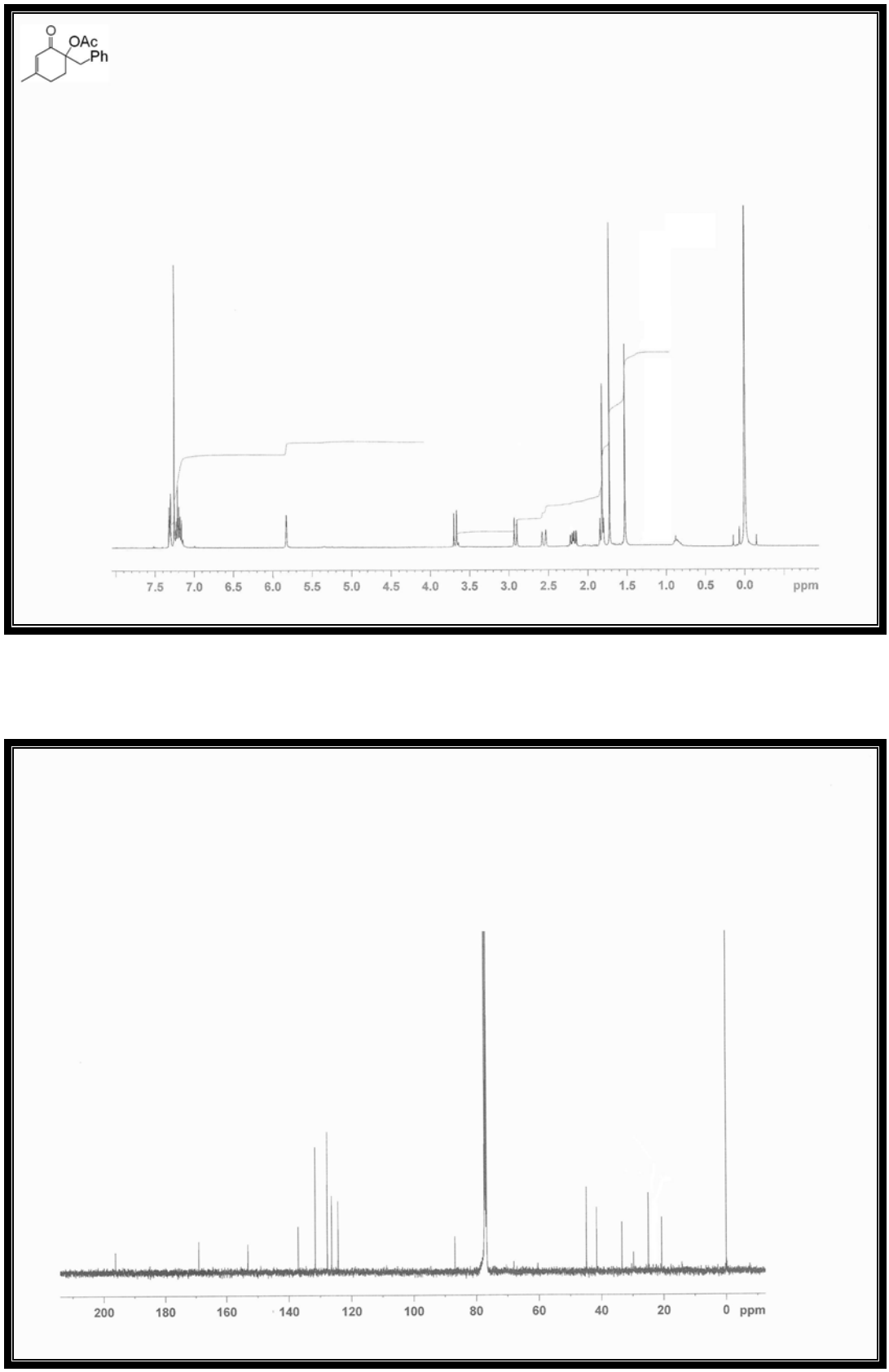


Fig A 27. ^{1}H and ^{13}C-NMR Spectra of Compound **98**

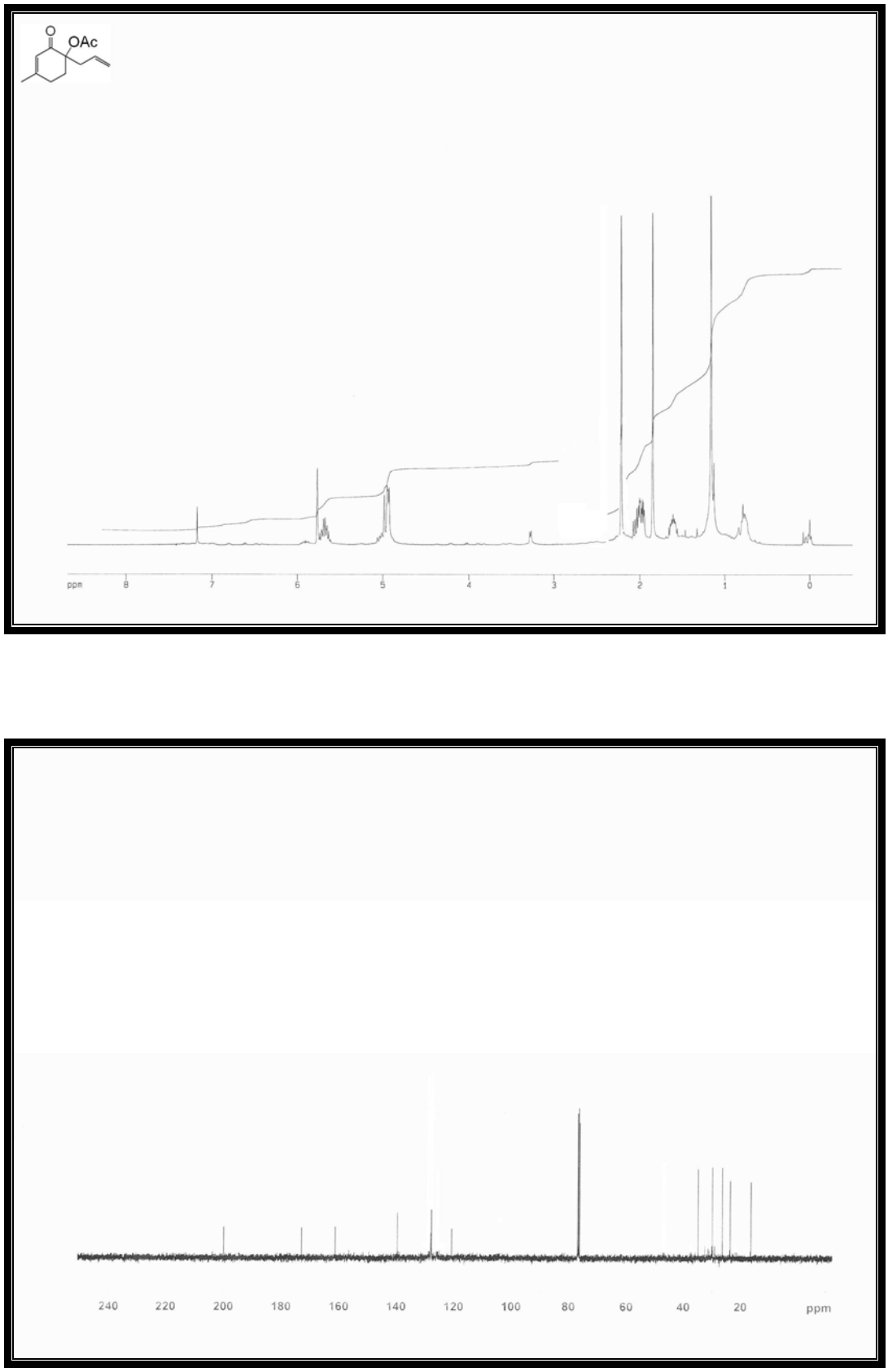


Fig A 28. ^{1}H and ^{13}C-NMR Spectra of Compound **99**

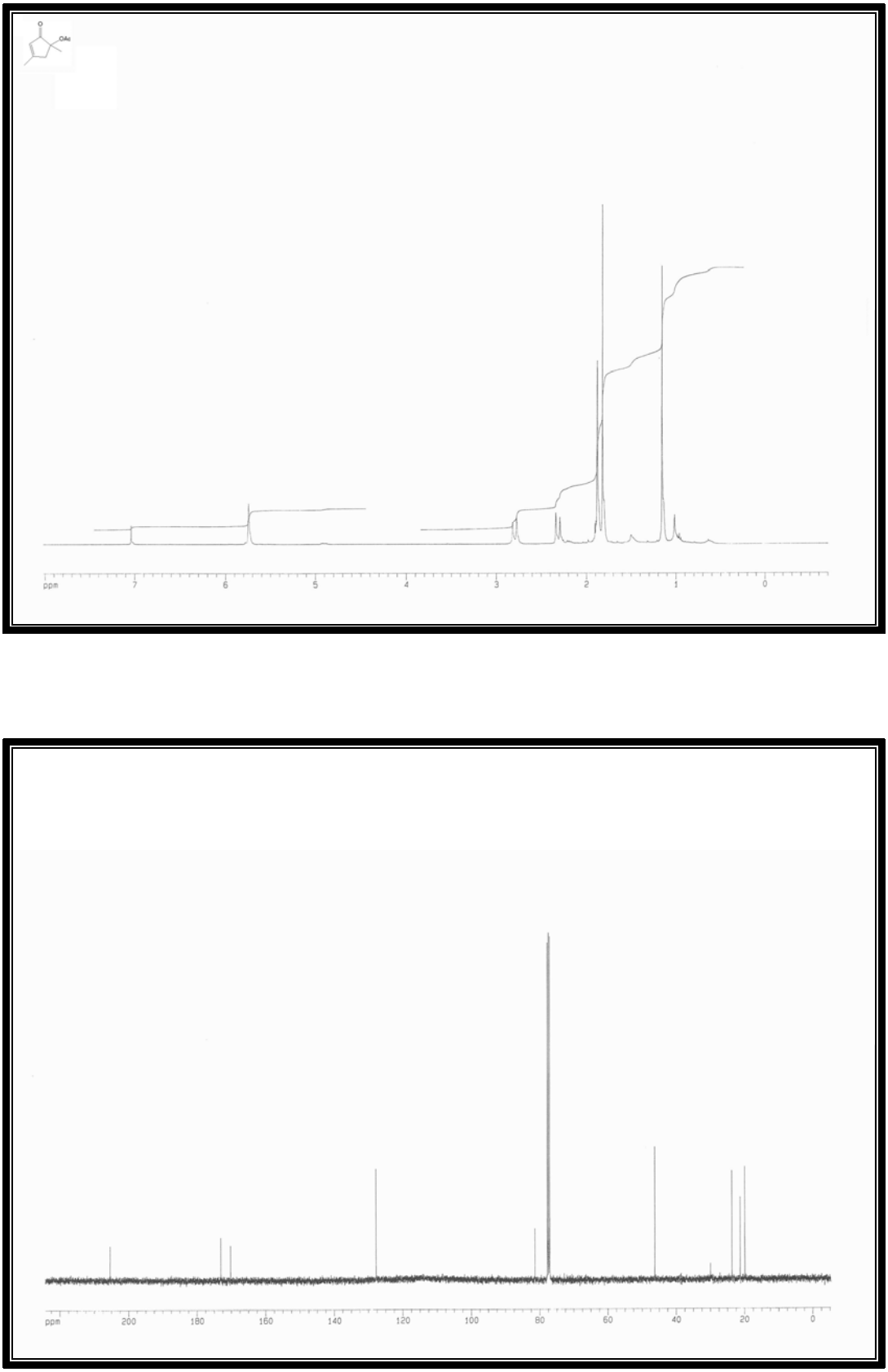


Fig A 29. ^{1}H and ^{13}C-NMR Spectra of Compound **100**

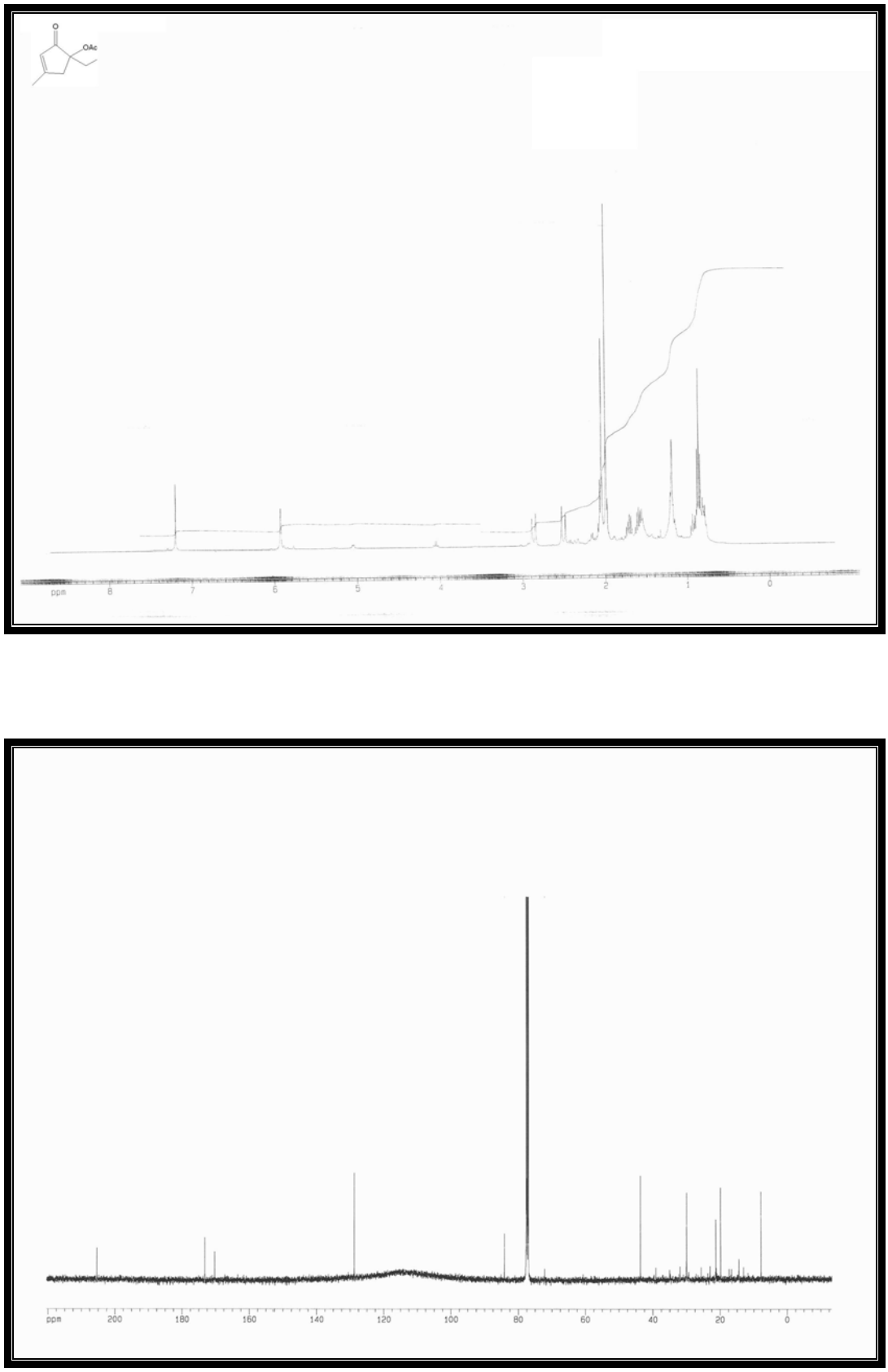


Fig A 30. ^{1}H and ^{13}C-NMR Spectra of Compound **101**

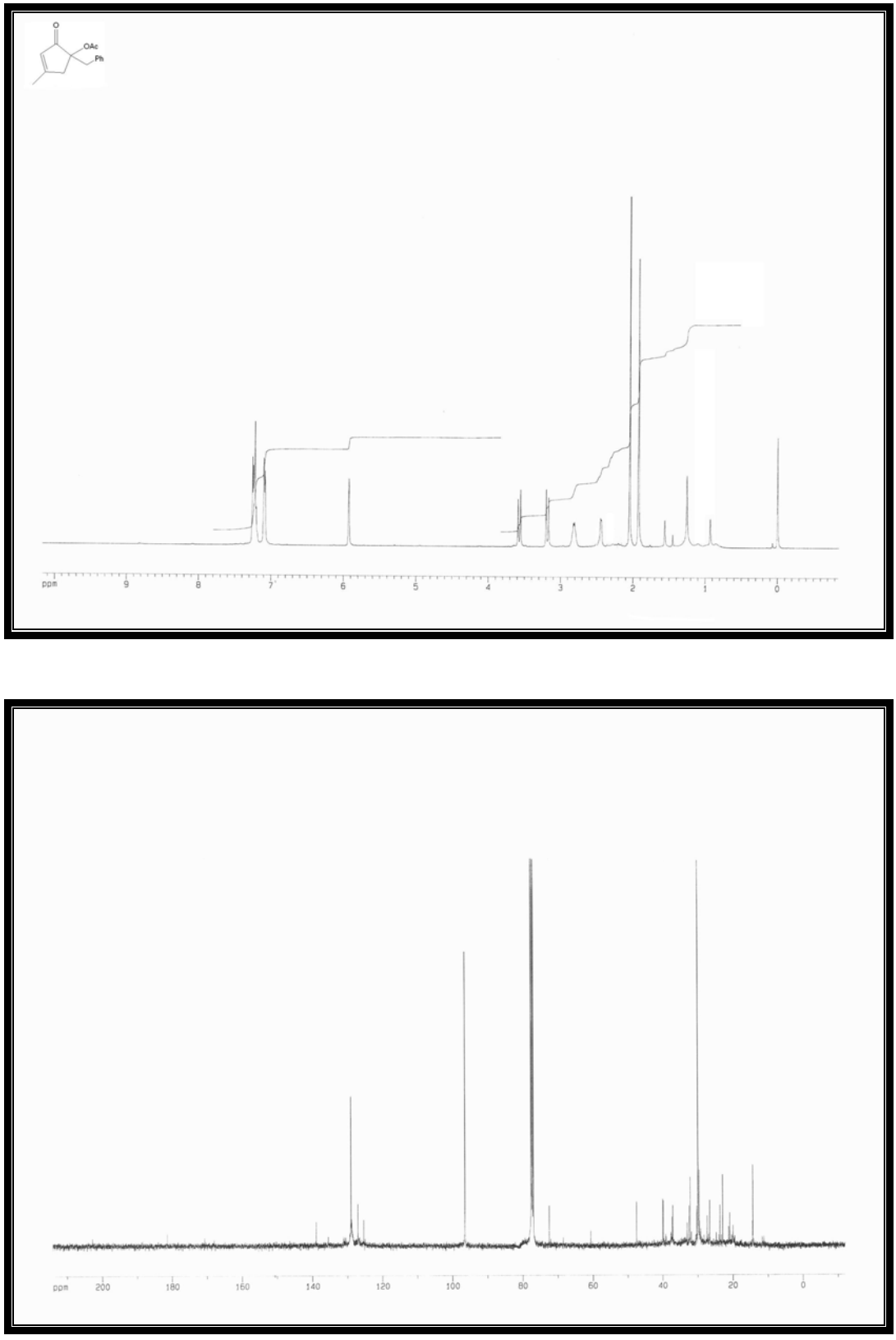


Fig A 31. ^{1}H and ^{13}C-NMR Spectra of Compound **102**

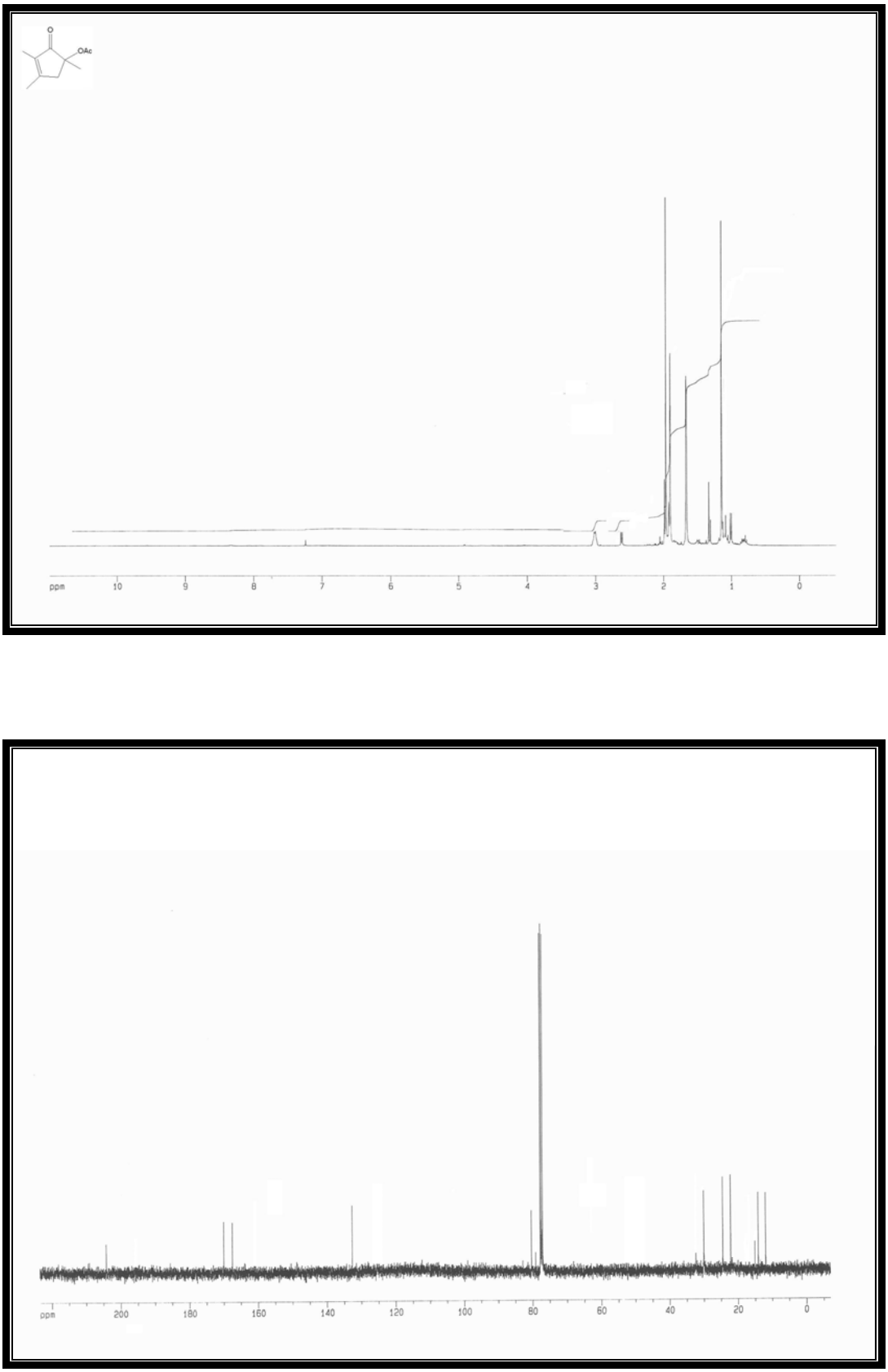


Fig A 32. ^{1}H and ^{13}C-NMR Spectra of Compound **103**

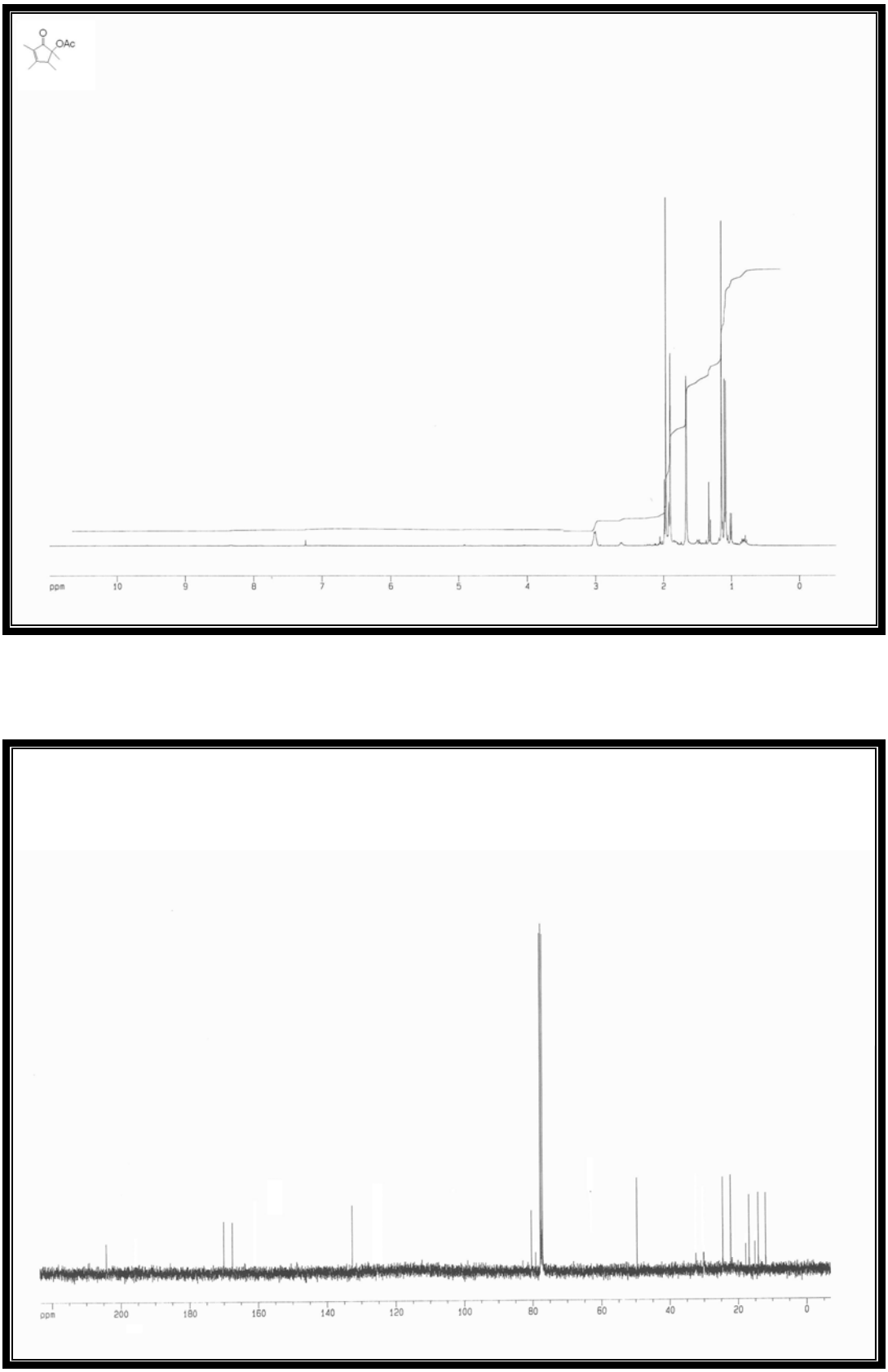


Fig A 33. ^{1}H and ^{13}C-NMR Spectra of Compound **104**

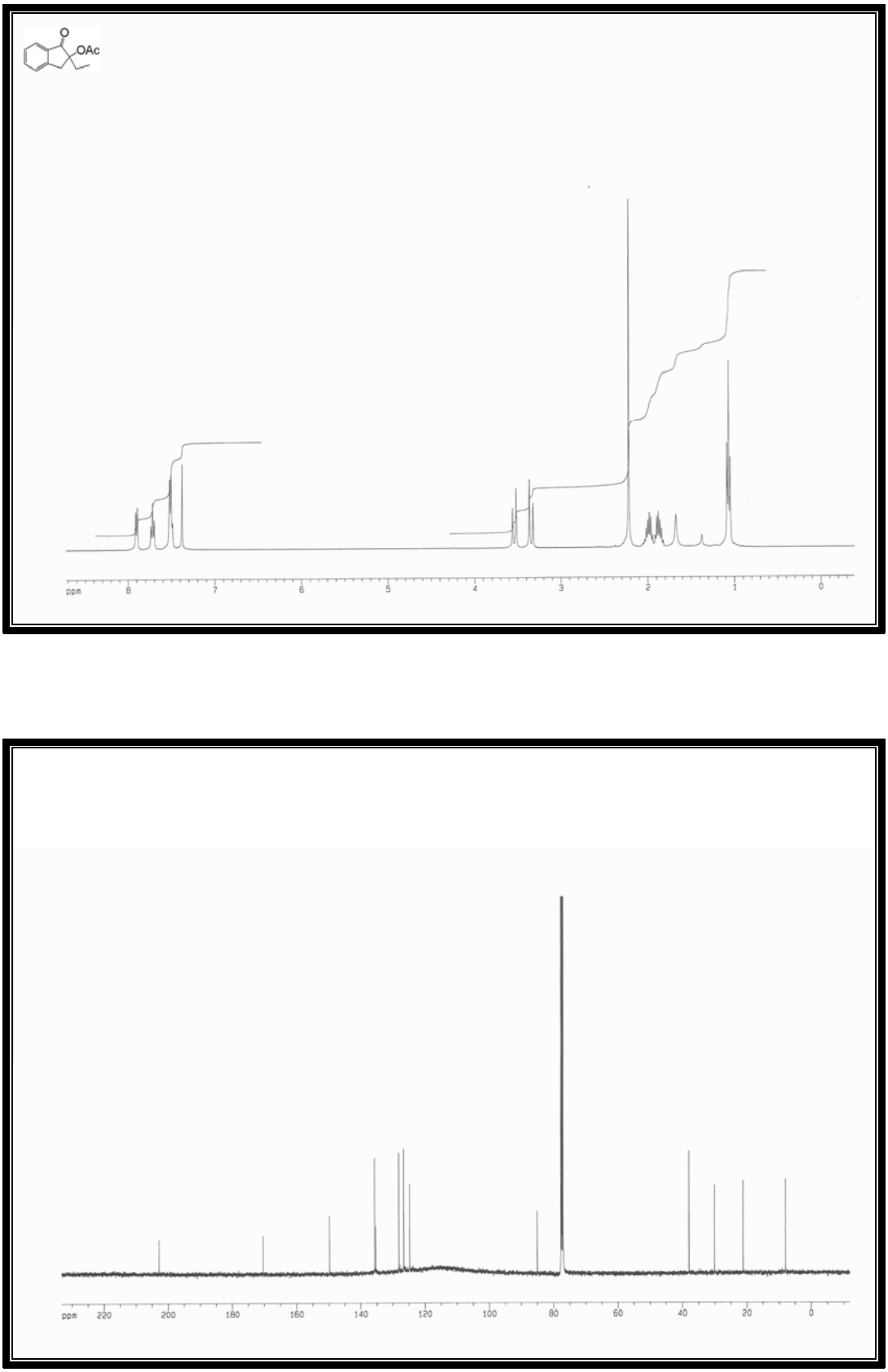


Fig A 34. ^{1}H and ^{13}C-NMR Spectra of Compound **110**

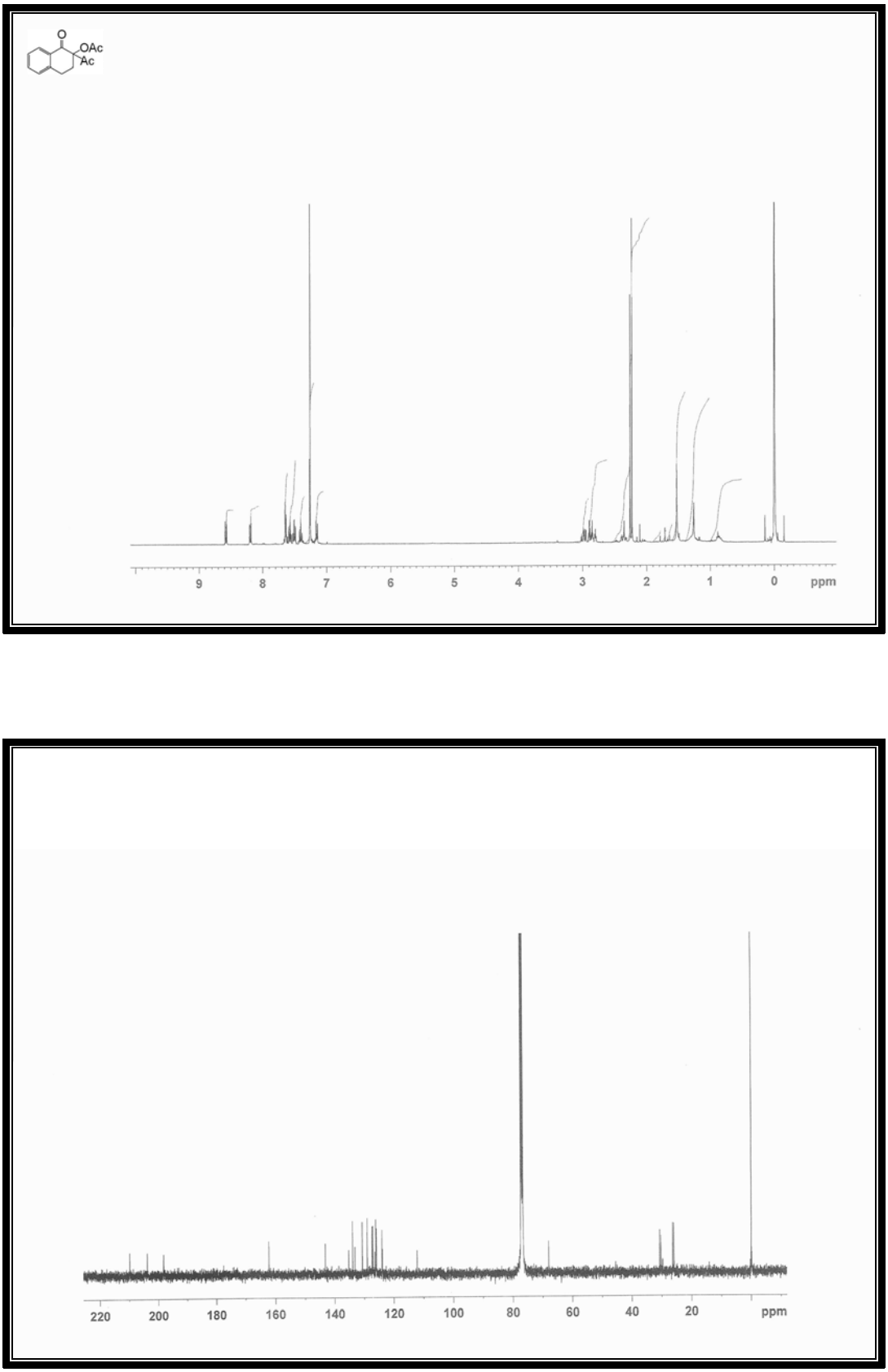


Fig A 35. ^{1}H and ^{13}C-NMR Spectra of Compound **112**

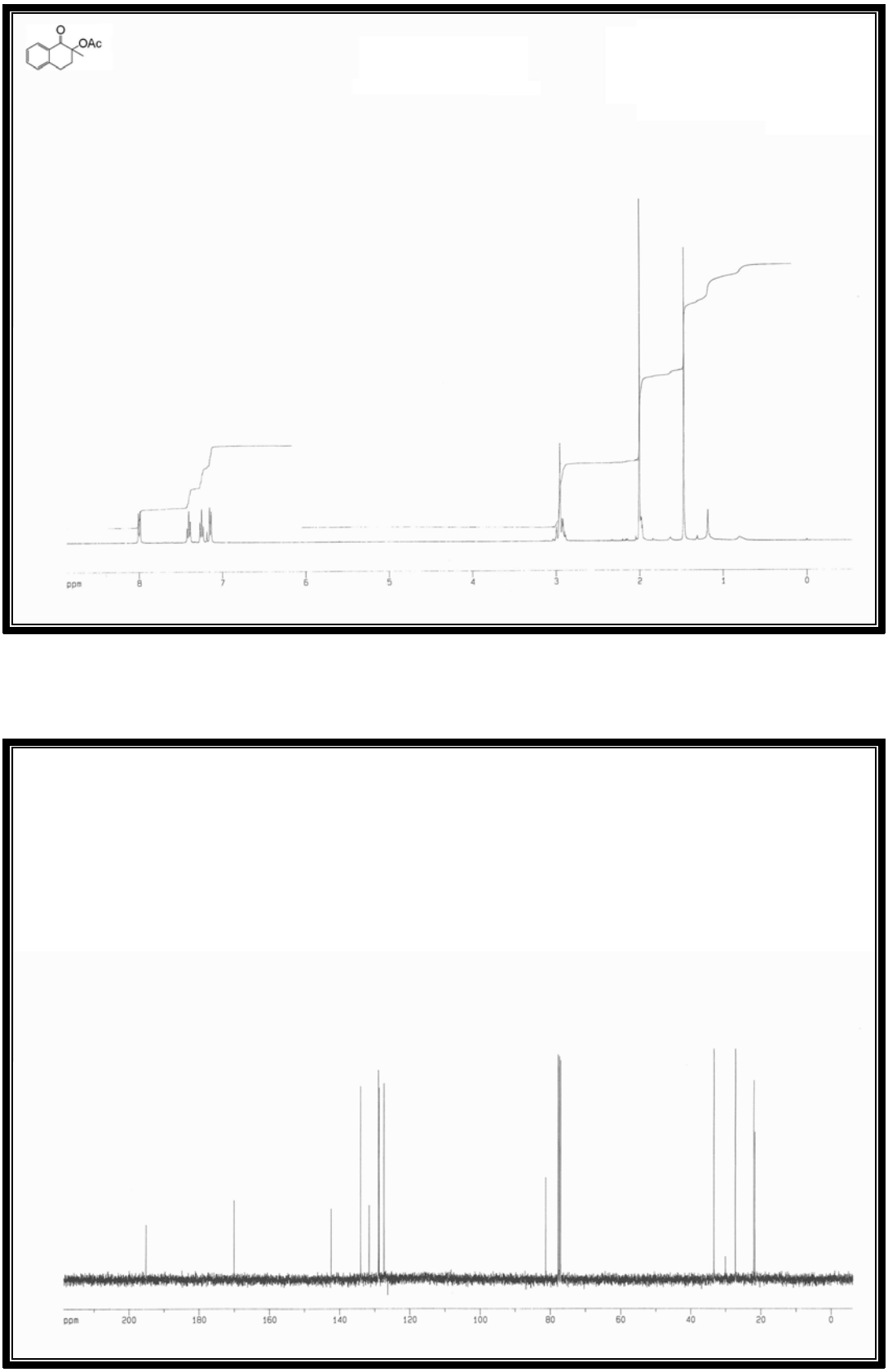


Fig A 36. ^{1}H and ^{13}C-NMR Spectra of Compound **114**

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PUBLICATIONS

1. Tanyeli, C.; Iyigün, Ç. *Tetrahedron* **2003**, *59*, 7135-7139.

2. Tanyeli, C.; Sezen, B.; İyigün, Ç.; Elmali, O. *Tetrahedron Lett*. **2001**, *42*, 6397-6399.