SYNTHESIS OF FUSED TRICYCLIC COMPOUNDS VIA PAUSON-KHAND CYCLOADDITION REACTIONS

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FEBRUARY 2009

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by
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Approval of the Graduate School of Natural Sciences.

Prof. Dr. Nihat Çelebi

Director

I certify that this thesis satisfies all the requirements for the degree of Master of Science.

Prof. Dr.Çetin BOZKURT

Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

SYNTHESIS OF FUSED TRICYCLIC COMPOUNDS VIA PAUSON-KHAND CYCLOADDITION REACTIONS

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February 2009, 83 pages

The Pauson-Khand cycloaddition reaction is one of the important methods for the construction of cyclopentenone. Two fused tricyclic compounds that are 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52** were synthesized by using the intramolecular Pauson Khand cycloaddition reaction. Fused tricyclic compounds including cyclopentenone ring that is building blocks in the synthesis of biologically active molecules. The resultant fused tricyclic compounds are **48** and **52** were oxidized to give 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a, 9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49** and 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53** by using $Mn(OAc)_3$ in good chemical yield. For this purpose, 1-cyclohexenylpyrrolidine

was chosen as starting compound was synthesized according to the literature procedure.

Keywords: Pauson-Khand reaction, fused tricyclic compound, cobalt carbonyl, $Mn(OAc)_3$ oxidation reaction.

ÖZET

BİTİŞİK TRİSİKLİK YAPILARIN PAUSON-KHAND SİKLOKATILMA REAKSİYONU İLE SENTEZİ

Sarıçelik, Özlem
Yüksek Lisans Tezi , Kimya Bölümü
Danışman: Assist. Prof. Dr.F.Devrim Özdemirhan

Şubat 2009, 83 sayfa

Pauson-Khand siklokatılma reaksiyonu siklopentenon oluşturmak için önemli metotlardan biridir. İntramoleküler Pauson-Khand siklokatılma reaksiyonu kullanılarak 4a-hidroksi-4a,5,6,7,8,8a,9,9a-oktahidro-1H-siklopenta[b]naftalin-2 (4H)-on **48** ve 8a-hidroksi-4a,5,6,7,8,8a,9,9a-oktahidro-1H-siklopenta[b]naftalin-2 (4H)-on **52** sentezlendi. Siklopentenon halkası içeren bitişik trisiklik bileşikler biyolojik aktif maddelerin sentezinde önemli yapı taşıdır. Bitişik trisiklik bileşikler **48** ve **52** $Mn(OAc)_3$ kullanılarak oksitlendi sonuçta 4a-hidroksi-2-okso-2,4,4a,5,6,7, 8,8a,9,9a-dekahidro-1H-siklopenta[b]naftalin-1-il asetat **49** ve 8a-hidroksi-2-okso-2, 4,4a,5,6,7,8,8a,9,9a-dekahidro-1H-siklopenta[b]naftalin-1-il asetat **53** yüksek verimle elde edildi. Bu sentezler için 1-sikloheksenilpirolidin başlangıç bileşiği olarak seçildi.

Anahtar Kelimeler: Pauson-Khand reaksiyonu, bitişik trisiklik bileşikler, kobalt karbonil, $Mn(OAc)_3$ dayalı yükseltgenme.

To my parents

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I wish to express my thanks to my parents Turgut and Atife SARIÇELİK, my sister Emel SAMANCI, my brother Özgür SARIÇELİK, my cousin Asuman DAĞ and my aunt Sevgi GÜVEN for their endless patience, support and love and I devote this thesis to them.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ac: acetyl

atm: atmosphere

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

^{13}C-NMR: Carbon-13 Neclear Magnetic Resonance

$CDCl_3$: chloroform-d

COD: 1,5-cyclooctandienyl

Cp: cyclopentadienyl

$Co_2(CO)_8$: Dicobalt octacarbonyl

$C_6H_9MnO_6.2(H_2O)$: Manganese triacetate dihydrate

$Co(acac)_2$: Cobalt(II) acetylacetonate

DME: Dimethoxyethane

DMSO: Dimethy sulfoxide

DCM: Dichloromethane

DMF: N,N-Dimethylformamide

dppe: 1,2-bis(diphenylphosphino)ethane

dppp: 1,3-bis(diphenylphosphino)propane

EtOAc: Ethyl acetate

Et_2O: diethyl ether

FT-IR: Fourier Transform Infrared

^{1}H-NMR: Proton Nuclear Magnetic Resonance

Hz: hertz

HCl: hydrochloric acid

IR: Infra Red

In: indium

KBr: Potassium bromide

$Mn(OAc)_3$: Manganese(III)acetate

$MgSO_4$: Magnesium sulfate

Me: methyl

mL: milliliter

mmol: millimole

Me_2CuLi: Lithium dimethylcopper

n-BuLi : n-Butyllithium

NMO: 4-methylmorpholine-N-oxide

NaCl: Sodium chloride

$NaBH_4$: sodium tetrahydroborate

NH_4Cl: Ammonium chloride

$NaHCO_3$: Sodium bicarbonate

OAc: Acetoxy group

PTSA: para-toluenesulfonic acid

ppm: parts per million

$P(OPh)_3$: triphenylphosphite

PPh_3: Triphenylphosphine

Ph: phenyl

rt : room temperature

Rf: Retention Factor

THF: tetrahydrofuran

TMANO: trimethylamine-N-oxide

CHAPTER I

1.INTRODUCTION

1.1 PAUSON-KHAND CYCLOAADITION REACTION

1.1.1 The Stoichiometric Pauson-Khand Reaction

In 1973 [1], Pauson and Khand discovered a cobalt-catalyzed [2+2+1] cycloaddition to construct five-membered rings. The Pauson-Khand reaction is a [2+2+1] cycloaddition between an alkyne, an alkene and carbon monoxide in the presence stoichiometric amount of $Co_2(CO)_8$, dicobalt octacarbonyl, to synthesize cyclopentenone [2] as shown in Figure 1.1.

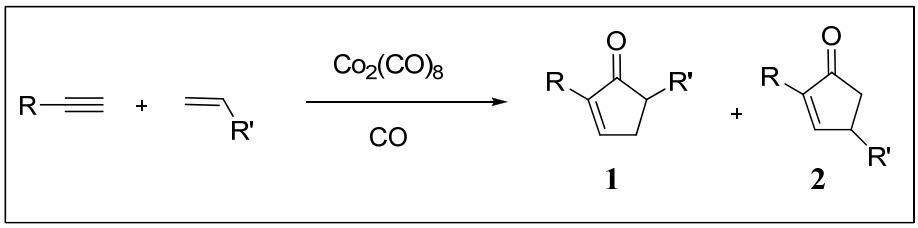


Figure 1.1.The Stoichiometric Pauson-Khand Reaction

In the intermolecular Pauson-Khand reaction, four isomeric cyclopentenones were obtained by a terminal alkyne with a terminal alkene as shown in Figure 1.2. Isomers **1** and **2,** in which the substituted end of alkyne is found adjacent to the carbonyl group, were formed in the intermolecular reaction. Isomer **3** was not observed. In the case of internal alkynes there is slight preference for the more bulky substituent to be located next to the carbonyl group. Internal alkynes were less effective than terminal alkynes. Isomer **4** is formed in the intramolecular reaction where R and R' are linked.

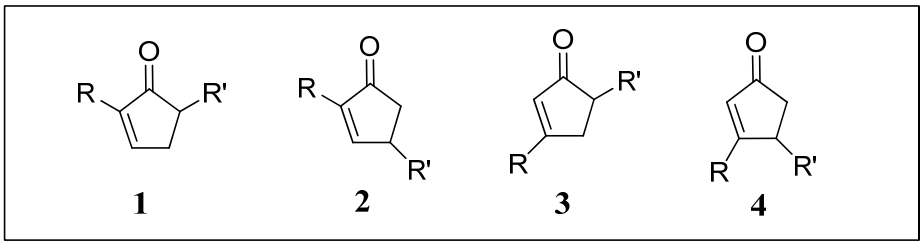


Figure 1.2.Four isomeric cyclopentenones

The applicability of the intermolecular Pauson-Khand reaction was limited by the poor reactivity and selectivity of alkenes, and also strain olefins were necessary for the efficiency of the intermolecular Pauson-Khand cycloadditon reaction. Moreover, unsymmetrical olefins lead to mixtures of regioisomeric cyclopentenones. And, long reaction times and high temperatures led to decomposition of starting materials and/or product.

The mechanism for the stoichiometric Pauson-Khand intermolecular reaction is proposed by Magnus in 1985 [3] as shown in Figure 1.3. The first step was the dicobalt octacarbonyl, $Co_2(CO)_8$, reacted with the alkyne to form dicobalt hexacarbonyl, $Co_2(CO)_6$,-alkyne complex **5**, which is only intermediate that was

observed in the mechanism. Then, loss of one of the CO ligands, and addition of the alkene bond into a carbon-cobalt bond to form complex **6**. Next, CO addition to complex **7**, and then addition of another CO and reductive elimination of Co(CO) unit give to complex **8**. Finally, the dissociation of the dicobalt unit gives the resulting cyclopentenone product **1**.

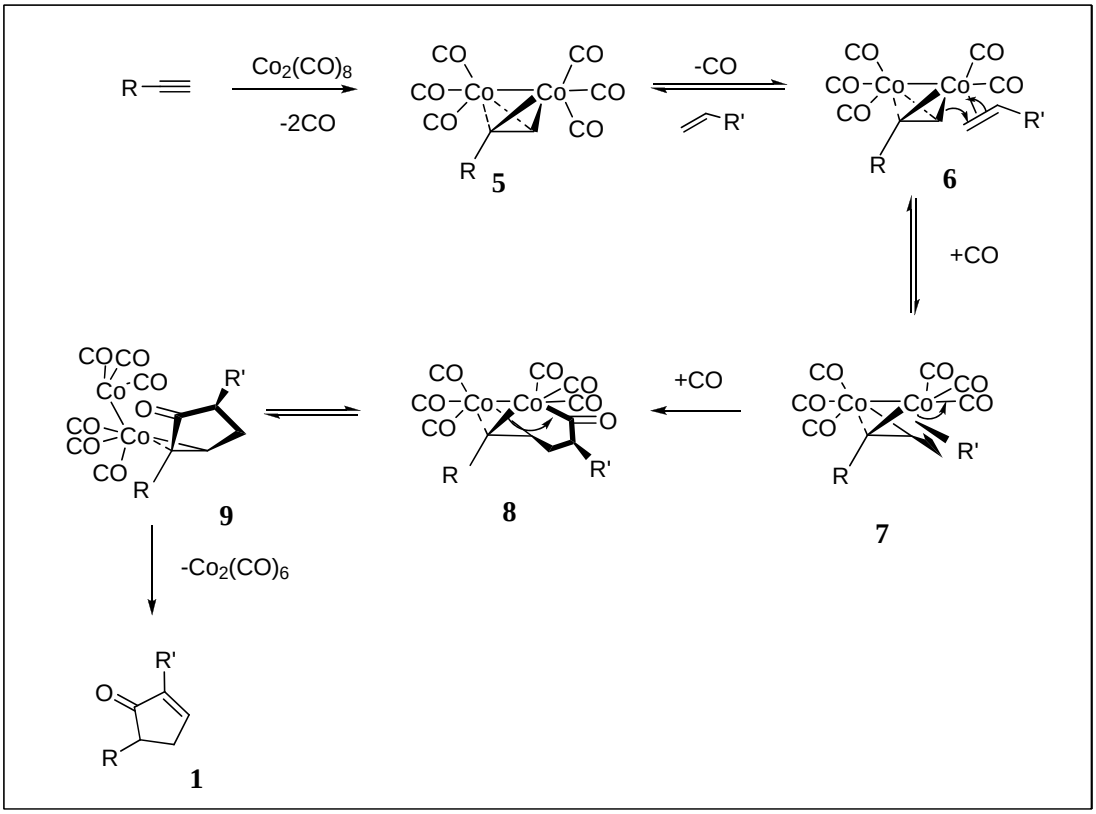


Figure 1.3.Proposed mechanism of the intermolecular Pauson–Khand reaction

In 1981, Schore [4] introduced the first examples of the intramolecular Pauson- Khand reaction as given in Figure 1.4. The intramolecular reaction leads to the formation of bicyclic product **11**. To use a strained alkene is not necessary for the intramolecular cycloaddition. The mechanism of intramolecular Pauson-

Khand reaction is similar to the mechanism of intermolecular Pauson-Khand reaction as shown in Figure 1.5.

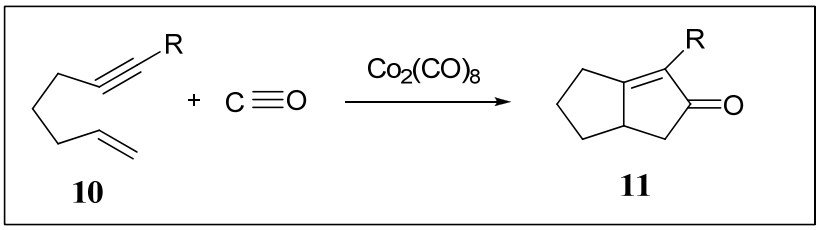


Figure 1.4.The intramolecular Pauson- Khand reaction

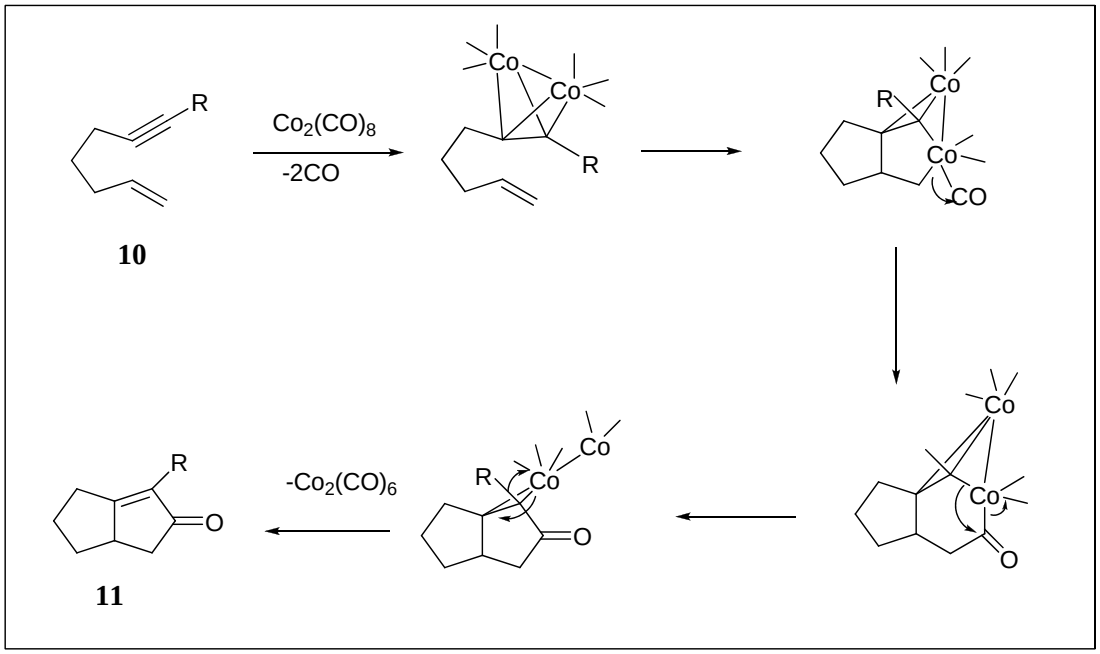


Figure 1.5.The mechanism of the intramolecular Pauson–Khand reaction

In the literature, the high temperatures, long reaction times and the stoichiometric amounts of $Co_2(CO)_8$ was necessary to effect the conditions of the Pauson-Khand reaction. The condition of the Pauson-Khand reaction was improved by the use of additives or promote which can facilitate ligand exchange at room temperature. In the Pauson-Khand reaction, tertiary amine N-oxides,

independently introduced by Schreiber [5] and Jeong [6], are widely employed as promoters or additives in both inter- and intramolecular Pauson-Khand reaction at room temperature under Ar, N_2 or O_2 atmosphere. Schreiber *et. al*. found that N-methylmorpholine N-oxide (NMO) was effective in promoting the Pauson-Khand reaction at room temperature as shown in Figure 1.6, and Jeong *et. al.* investigated both NMO and trimethylamine N-oxide(TMANO).

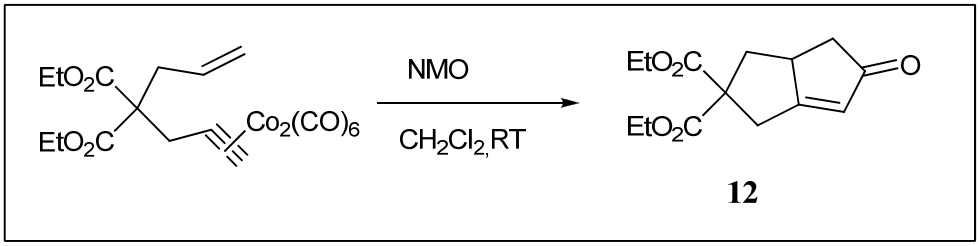


Figure 1.6.N-oxide promote intramolecular Pauson-Khand reaction

The N-oxides promoted reaction involves oxidation of a cobalt CO ligand to CO_2 as shown in Figure 1.7. Other promoters such as silica [7], amines [8], sulfides [9], and molecular sieves [10] have been also reported.

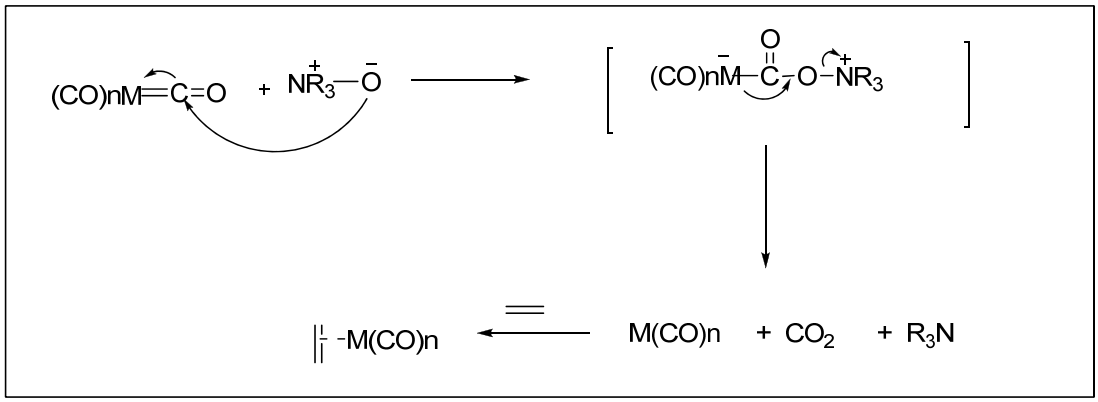


Figure 1.7.The mechanism of formation of N-oxides

The use of stoichiometric amount of $Co_2(CO)_8$ was not acceptable commercially. Therefore, cobalt and several transition metals were developed for catalytic Pauson-Khand Reaction.

1.1.2 Catalytic Pauson-Khand Reaction

In the literature, octacarbonyldicobalt has been frequently used to catalyse in the Pauson-Khand reaction. Alternatively, [2+2+1] reactions can also be catalyzed by cobalt or other transition metals such as titanium, ruthenium, rhodium and iridium.

1.1.2.1 The cobalt-catalyzed Pauson-Khand Reaction

In the literature, cobalt catalysts containing $Co_2(CO)_8$, [$Co_2(CO)_8$/ $P(OPh)_3$], [(indenyl)Co(cod)] and [$Co(acac)_2/NaBH_4$] under CO pressure, have been encountered widely.

Rautenstrauch *et. al.* [11] reported the first examples of the catalytic cycloaddition reaction that used non-strained alkenes, and was obtained employing 0.22 mol% of the catalyst [$Co_2(CO)_8$], under high pressures of carbon monoxide and ethylene in 48% chemical yield as shown in Figure 1.8.

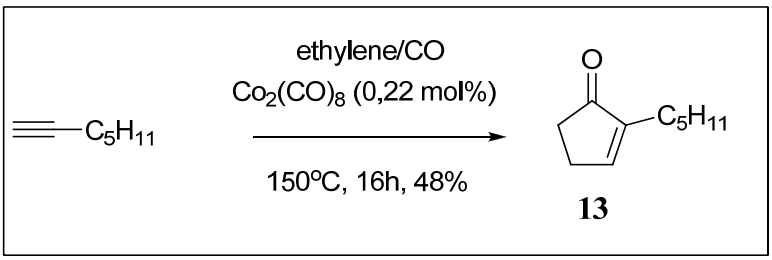


Figure 1.8.Cobalt-catalyzed under high pressures of CO and ethylene

Jeong *et. al.*[12] reported the first effective intramolecular Pauson-Khand reaction by using triphenylphosphite as an additives with $Co_2(CO)_8$ in which compound **12** is obtained in 82% chemical yield under high CO pressure at high temperature as shown in Figure 1.9. Then, they also improved the study by using a 1,5-cyclooctadiene(indenyl)cobalt(I) complexe [13] as catalyst that obtained high chamical yields under high CO pressure at 100 ^oC as shown in Figure 1.10.

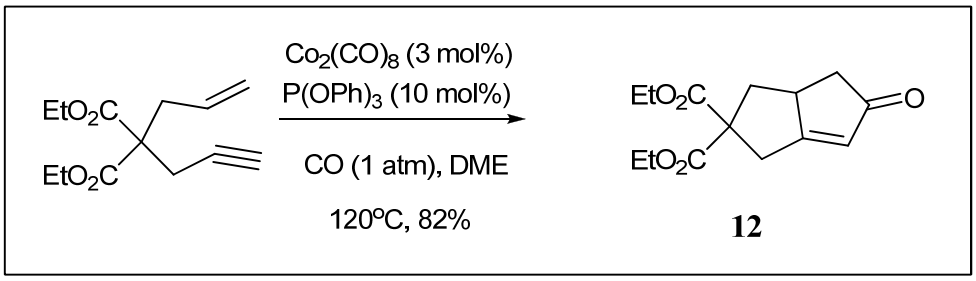


Figure 1.9.Cobalt-catalyzed with triphenylphosphite as an additives

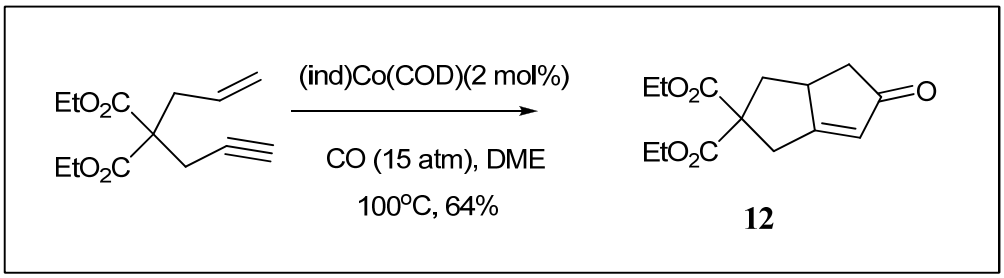


Figure 1.10.1,5-cyclooctadiene (indenyl)cobalt(I) complexe-catalyzed under CO

Photochemical [14] and thermal [15] version of a catalytic system which were reported by Livinghouse [14-15]. He used both high intensity irradition and heat to promote an efficient Pauson-Khand reaction using $Co_2(CO)_8$ under CO pressure as shown in Figure 1.11. Under these conditions, the photochemically promoted catalytic Pauson-Khand reaction was found slightly more efficient than the thermal variation.

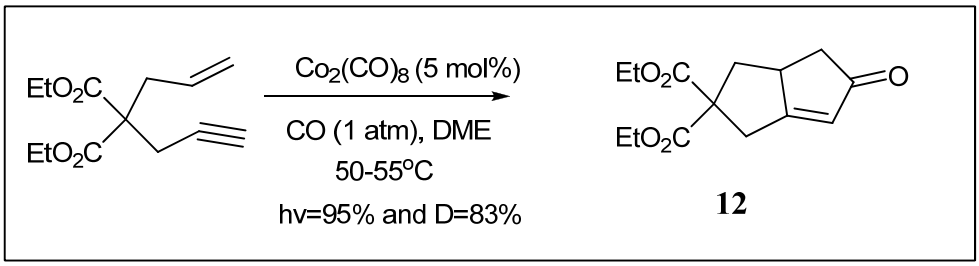


Figure 1.11.Photochemical and thermal version of a catalytic system

In another study which was reported by Chung [16] about alternative cobalt catalyst such as $Co(acac)_2$ as shown in Figure 1.12. The combination of $Co(acac)_2$ and $NaBH_4$ can effictively promote both the inter- or intramolecular Pauson-Khand reaction cycloaddition under high presure of CO.

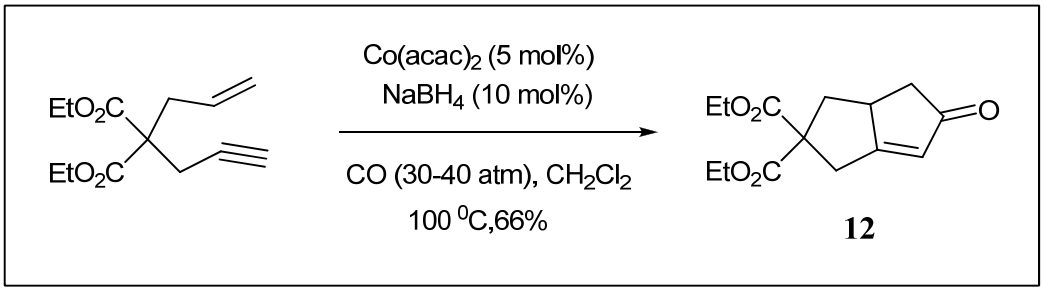


Figure 1.12.Alternative cobalt catalyst, $Co(acac)_2$

1.1.2.2 The titanium-catalyzed Pauson-Khand Reaction

Besides cobalt complexes, several other transition metal complexes such as titanium are known to catalyze the Pauson-Khand reaction.

Buchwald *et. al.* [17] reported titanocenes catalyst in the Pauson-Khand reaction. In the literature, $Cp_2Ti(PMe_3)_2$, Cp_2TiCl_2 and nickel(0) were used to as the titanocene reagents which catalyze the intramolecular [2+2+1] cycloaddition reaction of enynes with CO. In this study, bicyclic iminocyclopentene intermediates **15** from an enyne **14** with an isocyanide in the presence of

titanocenes were hydrolyzed to the cyclopentenones **16** as given in Figure 1.13 [17-18]. Under these conditions the intramolecular cycloaddition provided bicyclic enones in 42 to 80% chemical yields .

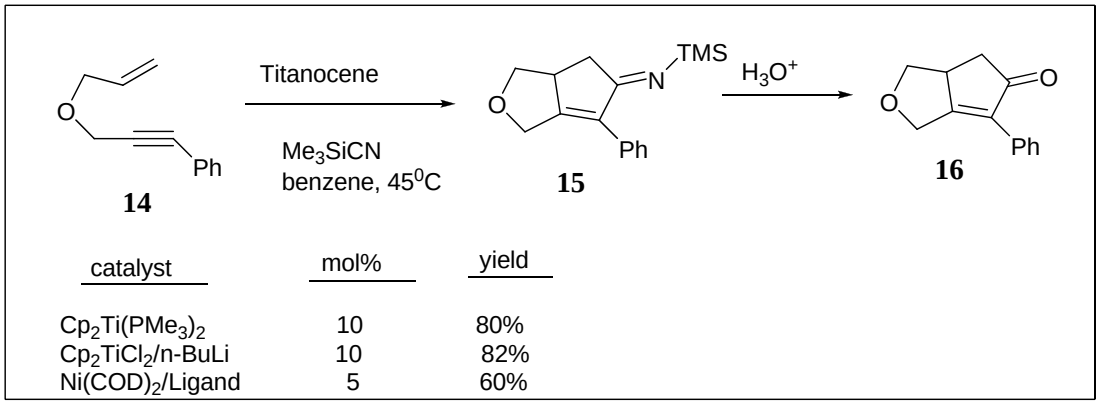


Figure 1.13.The titanocenes catalyzed Pauson-Khand Reaction

1.1.2.3 The rhodium-catalyzed Pauson-Khand Reaction

Rhodium has been also used to catalyze the intramolecular Pauson-Khand cycloaddition reaction. Narasaka *et. al*. [19] reported that $[RhCl(CO)_2]_2$ serves as a catalyst of the intramolecular Pauson– Khand reaction.Cyclopentenone derivatives are prepared from various 1,6-and 1,7-enynes with catalytic amounts of $[RhCl(CO)_2]_2$ in dibutyl ether under a CO atmosphere (1 atm) at 130-160^oC to afford 41-94% in chemical yields of bicyclic cyclopentenones **17** as shown in Figure 1.14.

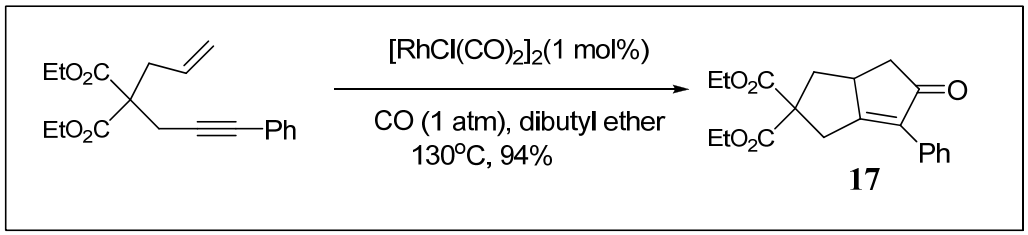


Figure 1.14.The rhodium carbonyl complex catalyzed Pauson-Khand Reaction

Jeong *et.al.* [20] reported that other rhodium(I) complexes such as RhCl $(PPh_3)_3$, *trans*-RhCl(CO)$(PPh_3)_2$, RhCl(CO)(dppe) and *trans*-[RhCl(CO)(dppp)]$_2$ are also catalyze in the intramolecular Pauson-Khand reactions. When RhCl $(PPh_3)_3$ or *trans*-RhCl(CO)$(PPh_3)_2$ was used as a catalyst, the reaction in the absence of silver(I) as an additive as given in Figure 1.15.

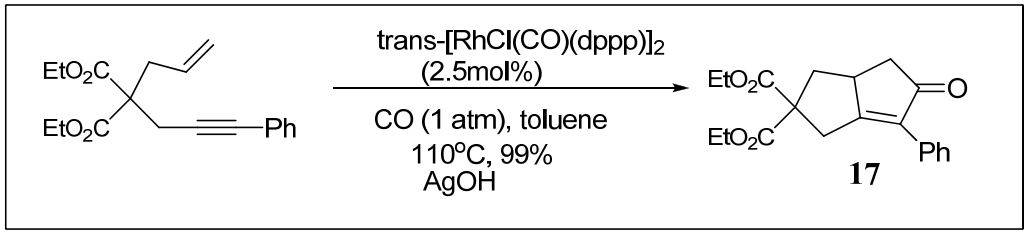


Figure 1.15.trans-[RhCl(CO)(dppp)]$_2$-catalyzed Pauson-Khand Reaction

1.1.2.4 The ruthenium and iridium-catalyzed Pauson-Khand Reaction

The ruthenium catalyzed Pauson Khand reaction, independently reported for the first time in 1997 by Kondo *et. al.* [21] and Morimoto et al. [22] which require high temperatures and high pressures under CO. $Ru_3(CO)_{12}$ effectively catalyzed the intramolecular Pauson-Khand Reaction of enynes to form cyclopentenones as shown in Figure 1.16.

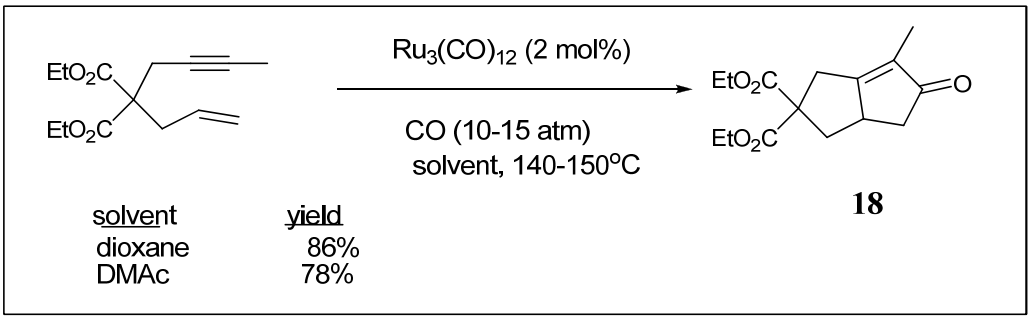


Figure 1.16.The ruthenium catalyzed Pauson Khand reaction

The iridium complex has been used to obtain highly enantioselective intra- and intermolecular Pauson-Khand reactions which yields compound **19** and **20** with 93% and 32% enantiomeric excess respectively as shown in Figure 1.17 [23]. The chiral Ir catalyst was prepared in situ $[IrCl(COD)]_2$ and (S)-tolBINAP.

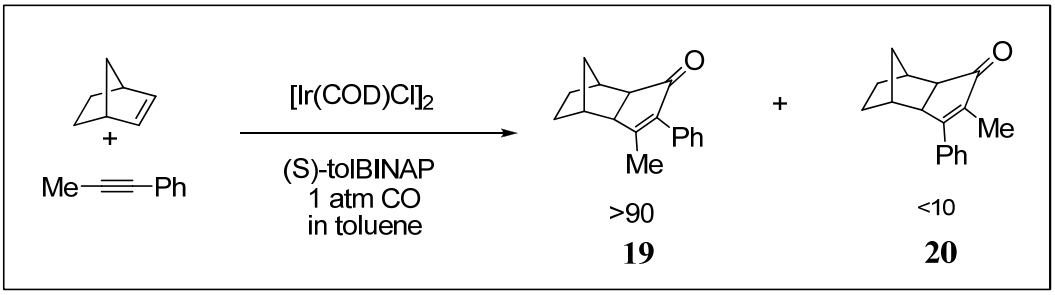
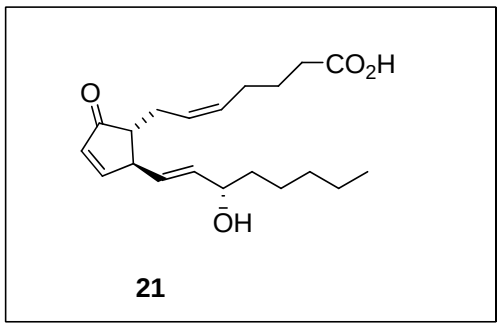


Figure 1.17.The iridium complex catalyzed Pauson Khand reaction

1.1.3 The Pauson-Khand reaction used in the synthesis of natural product

A natural product is a chemical compound or substance produced by a living organism-found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. The Pauson-Khand reaction is one of the most powerful reactions for the generation of cyclopentenones compounds and the synthesis of natural product. The

intramolecular Pauson-Khand reaction has been often used as the key step of total synthesis of natural products in many applications [24]. Cyclopentenones are very important building blocks for natural products, pharmaceuticals, fine chemicals such as prostaglandins [25], different triquinanes and polyquinanes like ceratopicanol [26], hirsutene [27], epoxidictimene [28], and isocarbacyclins [29].One of the examples of the important biologically active compounds that can be synthesized from cyclopentenones is prostaglandins **21** as shown in Figure 1.18. Several natural prostaglandins and analogues are used as drugs and exhibit characteristic biological activity.



21

Figure 1.18.Prostaglandins

The synthesis of the natural product (+)-epoxydictymene **22** was reported by Schreiber *et. al.*[28]. They used N-oxide as promote to prepare the fused ring skeletons. This synthesis was prepared fused enones via intramolecular Pauson-Khand reaction, and cobalt cluster **24** was a logical precursor to **23**. The Nicholas reaction [30] (the Lewis acid-promoted conversion of **25**) was used for the preparation of the Pauson-Khand substrate **24**. Then, the precursor **23** was converted into the epoxydictymene **22** as shown in Figure 1.19.

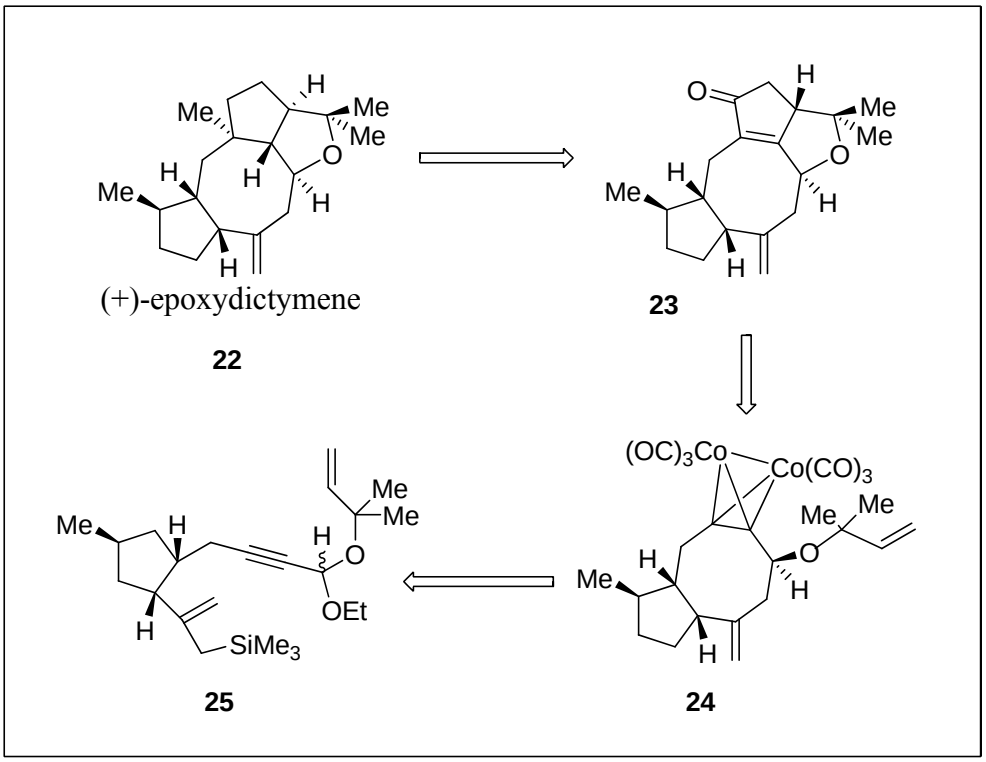


Figure 1.19.Retrosynthetic strategy of the synthesis of (+)-epoxydictymene.

The other example of the synthesis of the angularly fused triquanine system using the Pauson-Khand reaction was reported by Schore [31]. The tricyclic enone was formed in 35% chemical yield containing a quaternary carbon. The resulting tricyclic enone is easily converted to the bisnorisocomene as given in Figure 1.20.

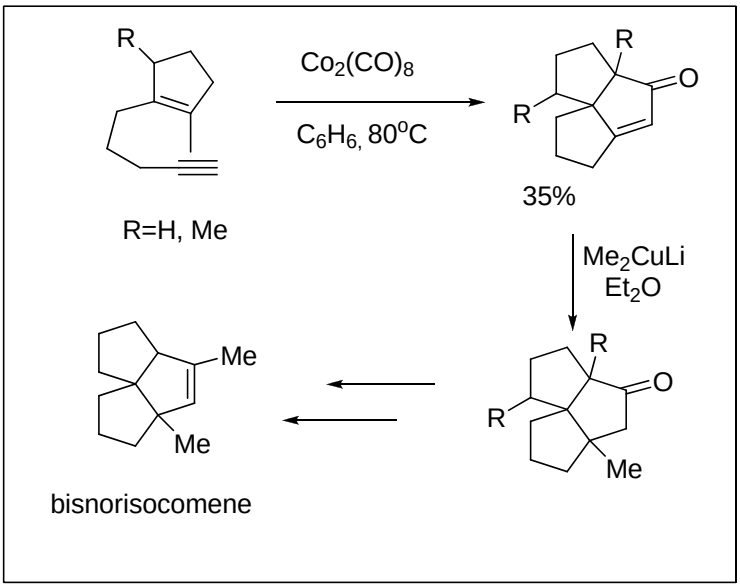


Figure 1.20.The Pauson-Khand reaction in synthesis of a triquinane system

In another study, Mukai *et. al.*[26] reported alternative the total synthesis of (±)-cepartopicanol based on the intramolecular Pauson-Khand reaction.The natural product **26** was derived from **27** and tricyclic fused compund **27** obtained from intramolecular Pauson-Khand reaction of the enyne compound **28**, which would be obtained from 2-allyl-2-methylcyclopenta-1,3-dione **31** as shown in Figure 1.21.

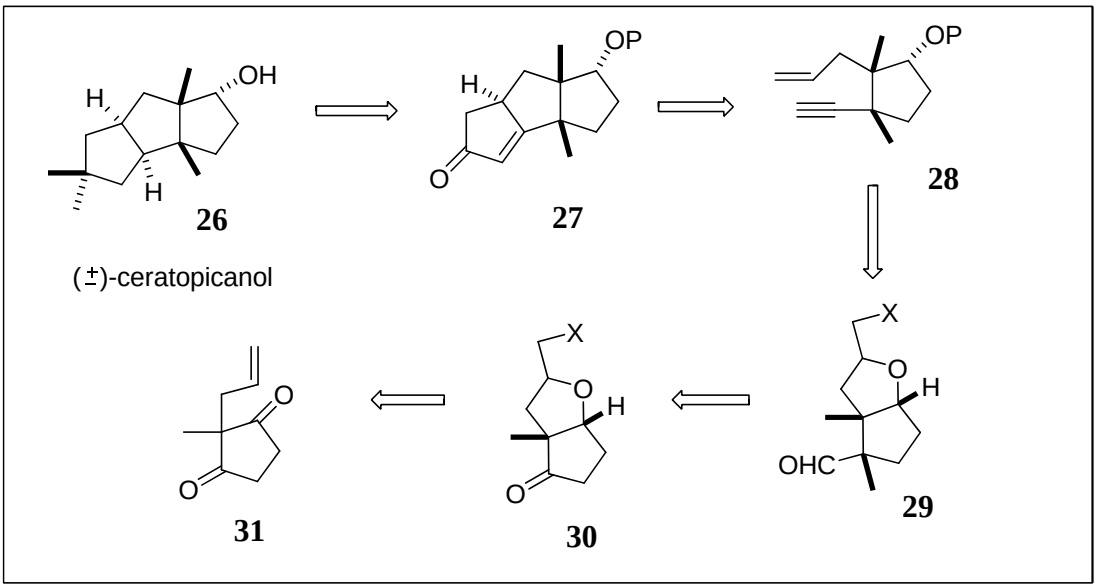


Figure 1.21.Retrosynthetic strategy of total synthesis of (±)-cepartopicanol

1.2 METAL-CATALYZED OXIDATION OF ENONES

Oxidation in organic chemistry refers to either the elimination of hydrogen or the replacement of the hydrogen atom bonded to carbon with more electronegative element such as oxygen. Metal salts are used as oxidants in the oxidative process involving the generation of radicals by an electron transfer from either a (electron rich) double bond or an organometallic reagent.

In the literature, selective α'-acetoxylation of α,β-unsaturated ketones occupy a central position in the syntheses of various complex natural products. Enones can be regioselectively oxidized to α'-acetoxy enones by using lead(IV) tetraacetate [32], mercuric acetate [33], and manganese triacetate [34-35]. Manganese(III) acetate mediated acetoxylation is the most commonly used procedure for the synthesis of α'-acetoxy α,β-unsaturated ketones.

1.2.1 Manganese(III) Acetate Oxidations

Manganese triacetate has been used as oxidizing agents of the oxidative reaction. Manganese(III) acetate or Manganese triacetate is an inorganic chemical that is usually found as the dihydrate. Its structural formula is represented as $C_6H_9MnO_6{\cdot}2(H_2O)$. Manganese triacetate is usually prepared from potassium permanganate and manganeous acetate in acetic acid [36]. Anhydrous $Mn(OAc)_3$ is slightly more reactive than the dihydrate. Reaction times with the anhydrous reagent are usually somewhat shorter but the yield of products are usually comparable. Both trifluoroacetic acid and potassium or sodium acetate have been used with $Mn(OAc)_3$. Use of trifluoroacetic acid as a cosolvent usually increases the rate of the reaction, but often decreases the yield of products. Acetate anion may accelerate enolization and act as a buffer. Acetic acid, DMSO, ethanol, methanol, dioxane, and acetonitrile are used as solvent for $Mn(OAc)_3.2H_2O$ reactions.

Manganese(III)-mediated radical reactions have become a valuable method for the formation of carbon-carbon bonds during the past thirty years. The studies on $Mn(OAc)_3$ based oxidations help us to know the mechanism of the reaction. The mechanism of oxidation of monocarbonyl substrates with $Mn(OAc)_3.2H_2O$ has been extensively studied. Fristad and Peterson shown that the rate determining step in the oxidation of acetic acid by $Mn(OAc)_3.2H_2O$ which is actually an oxo-centered triangle of Mn(III) with bridging acetates [37], is the loss of a proton from the complexed acetate such as **32** to give **33** as shown in Figure 1.22 [37-38]. Rapid electron transfer to the oxo-centered metal system gives radical **34** which adds to the alkene to give **35**. The reaction rate is

independent of alkene concentration, since the alkene is not involved in the rate determining step.

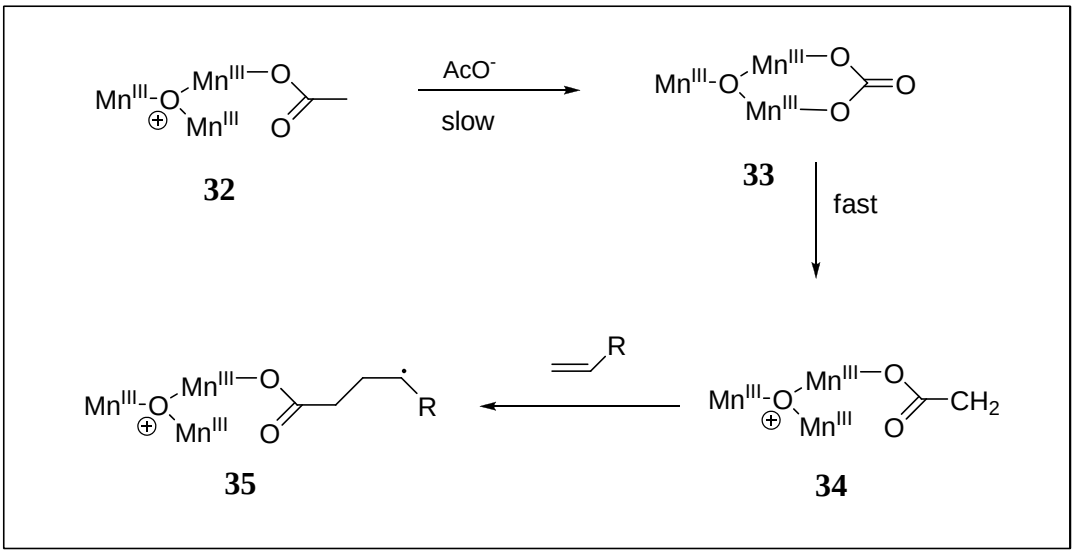


Figure 1.22.Mechanism for oxidation of monocarbonyl substrate

On the other hand, Snider [39] has suggested a similar mechanism which is operative in the oxidation of α -alkyl β-keto esters that is shown in Figure 1.23.

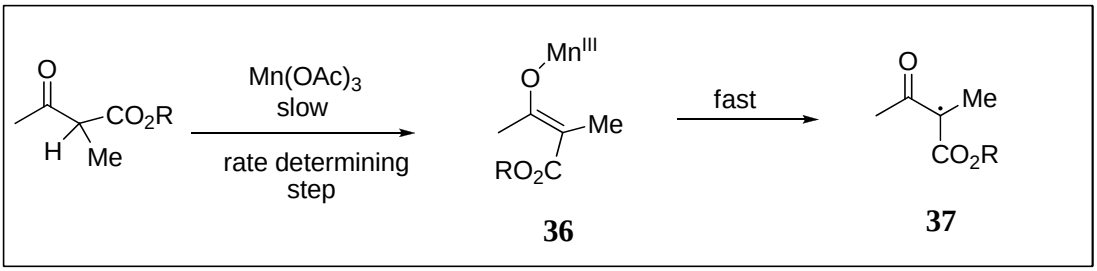


Figure 1.23.Proposed mechanism for the oxidation of α-alkyl β-keto Esters.

Enolization to give **36** is slow; electron transfer with loss of Mn(II) to give **37** is rapid. Therefore, the rate of reaction is independent of alkene concentration. Radical **37** reacts from the geometry shown as determined by analysis of the stereochemistry of the products as examined below. Comparable regio- and stereochemical results are obtained from a series of Mn(III)-based oxidative cyclizations and iodine or bromine atom transfer cyclization [40].

This result indicates that free radical **37** is involved in the Mn(III)-mediated oxidative cyclizations. Some differences in regiochemistry or stereochemistry between oxidative cyclizations and atom-transfer cyclizations would be expected if a Mn(III)-complexed radical was involved.

In 1976, Williams and Hunter reported that the oxidation of enones to α'-acetoxyenones using manganese (III) acetate in acetic acid in 6% to 36 % chemical yield [41]. The mechanisms for oxidation of the enones of α'-acetoxyenones is shown in Figure 1.24. The interaction of the enol or enolate of aromatic ketone with manganese (III) acetate would result in acetate transfer **38**.

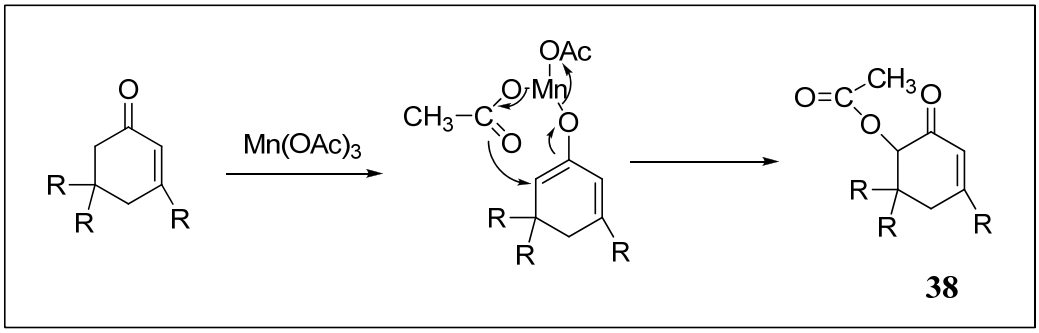


Figure 1.24.The mechanisms for oxidation of the enones of α'-acetoxyenones

Another suggested mechanism the formation of an α-keto radical resulting from the oxidation of an enol or enolate anion by Mn(III). It is possible that α'-acetoxylation reaction also proceeds via α-keto radical formation followed by ligand transfer oxidation to the product [42] as shown in Figure 1.25.

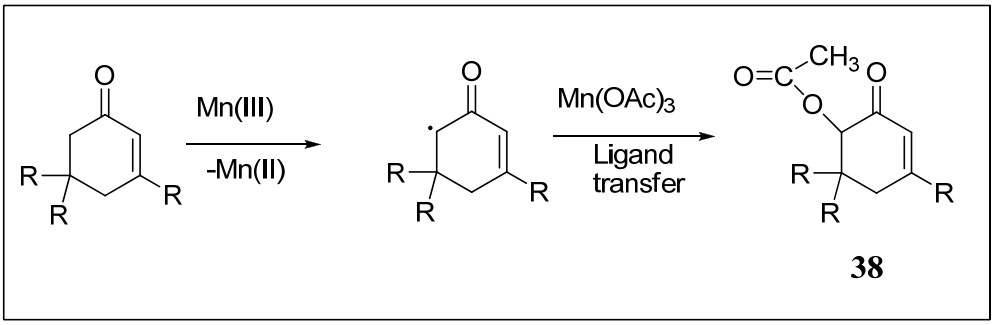


Figure 1.25.The oxidation of an enol or enolate anion by Mn(III).

In another work, Tanyeli *et. al.* [43] described the results of $Mn(OAc)_3$ 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 as shown in Figure 1.26.

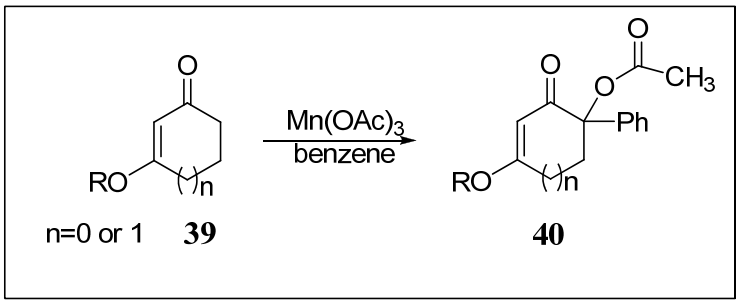


Figure 1.26.The $Mn(OAc)_3$ based tandem oxidation of β-alkoxy α,β-unsaturated ketone

The reaction of α,β-unsaturated ketone with $Mn(OAc)_3$ proceeds via the formation of the Mn(III) enolate **41**, which loses Mn(II) upon one-electron oxidation to give α'-keto radical **42**. Addition of this radical to benzene yields another radical **43**.One-electron oxidation of the resultant radical **43** gives α'-phenyl β-alkoxy α,β-unsaturated ketones **44**. Oxidation of phenyl substituted intermediate **44** by another equivalent of $Mn(OAc)_3$ provides α'-acetoxy α'-phenyl β-alkoxy α,β-unsaturated ketones **40**. This proposed mechanism is given in Figure 1.27.

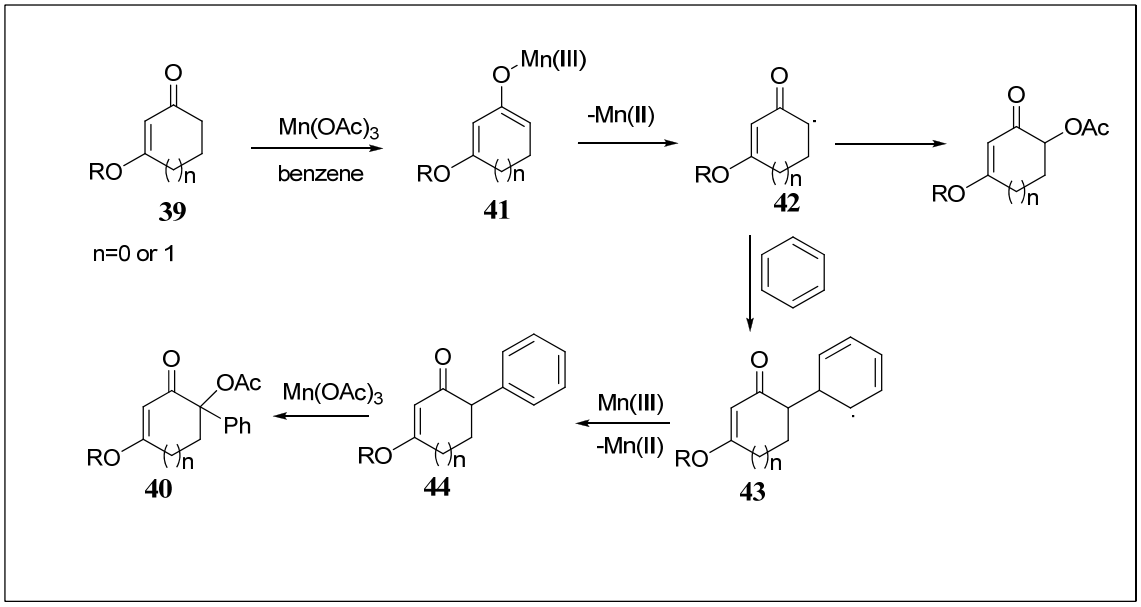


Figure 1.27.Proposed mechanism for the $Mn(OAc)_3$ based tandem oxidation of β-alkoxy α,β-unsaturated ketones

1.3. THE AIM OF THE WORK

The aim of this work is to synthesize 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8, 8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52** via the intramolecular Pauson-Khand cycloaddition reaction. The Pauson-Khand reaction is one of the most powerful reactions for the preparation of cyclopentenones compound which are very important building blocks used in the synthesis of natural products skeleton.

In our synthesis strategy, 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8, 8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52** are oxidized to give 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49** and 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53** by using $Mn(OAc)_3$ as shown in Figure 1.28.

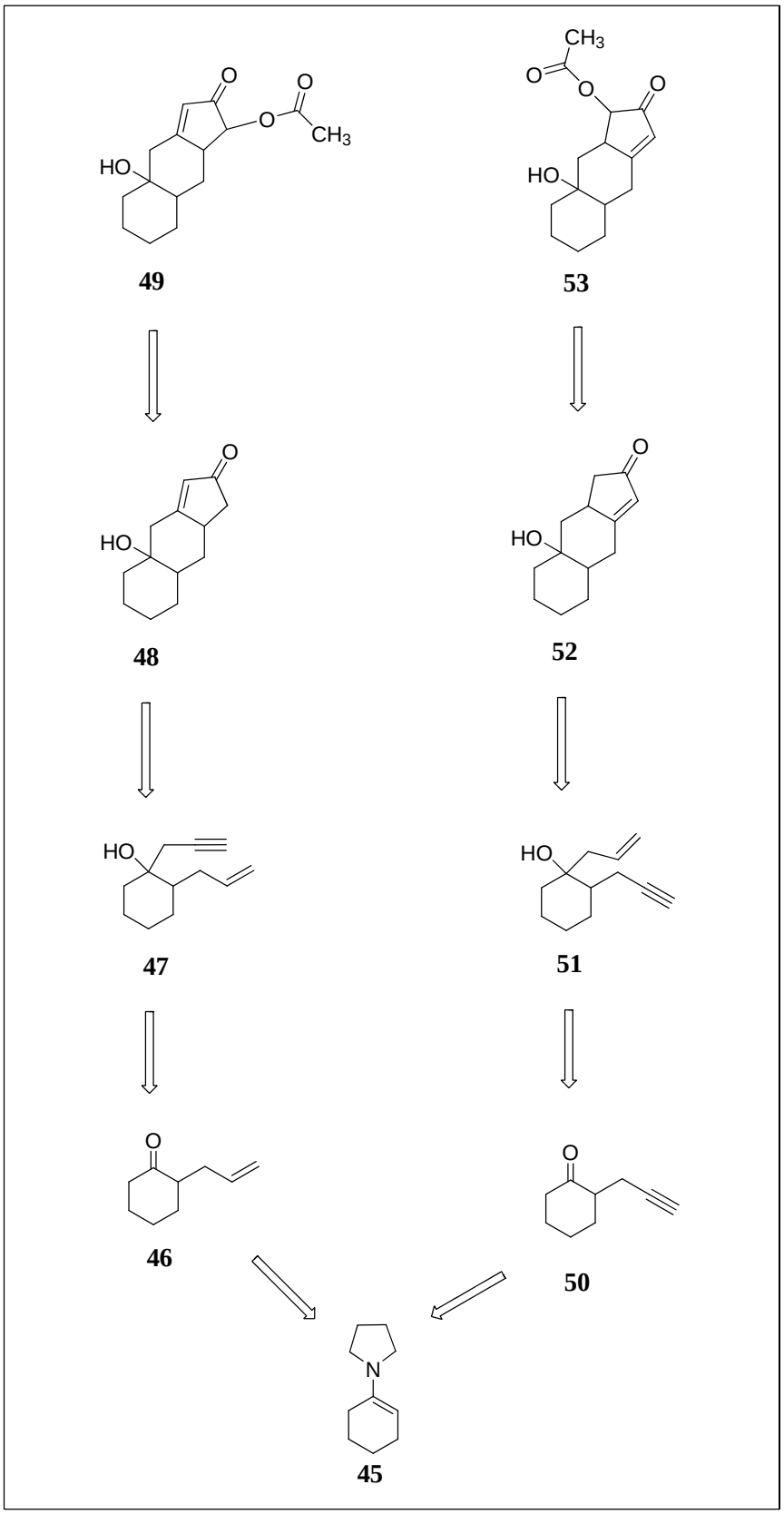


Figure 1.28.Retrosynthesis of this work

CHAPTER II

2. RESULTS AND DISCUSSION

The cyclopentenone ring is a very useful building block in the synthesis of biologically active molecules [42]. The Pauson-Khand reaction is one of the most important methods for the construction of cyclopentenones.

In our present work, the intramolecular Pauson-Khand cycloaddition reaction was applied to the synthesis of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52**. After that, $Mn(OAc)_3$ based oxidation of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b] naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52** afforded 4a-hydroxy-2-oxo-2,4,4a,5,6,7, 8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalene-1-yl acetate **49** and 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b] naphthalene-1-yl acetate **53**, respectively.

In our synthesis strategy, 1-cyclohexenylpyrrolidine **45** was chosen as the starting compound for the preparation of 2-allycyclohexanone **46** and 2-(prop-2.ynyl) cyclohexanone **50**.

2.1 Synthesis of 1-cyclohexenylpyrrolidine 45

1-cyclohexenylpyrrolidine **45** was prepared from cyclohexanone and pyrrolidine in the presence of the PTSA by an acid catalyzed addition-elimination reaction as shown in Figure 2.1.The product was obtained as orange oil with 65% chemical yield.

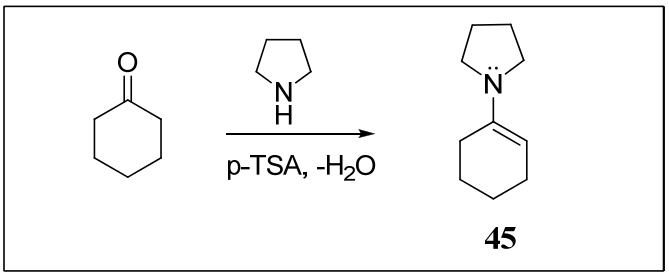


Figure 2.1.Synthesis of the 1-cyclohexenylpyrrolidine **45**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the 1-cyclohexenylpyrrolidine **45** shows two multiplet between 1.45-1.52 ppm and 1.58-1.68 ppm due to methylene protons at the fourth and the fifth position of cyclohexene ring, respectively. The two methylene protons of pyrrolidine ring show the multiplet between 1.71-1.86 ppm. One of the methylene protons at the third position of cyclohexene ring shows the singlet at 2.03 ppm and the other one shows the singlet at 2.12 ppm. The triplet at 2.27 ppm with J= 7 Hz is for the methylene protons at the sixth position of cyclohexene ring. One of the methylene protons attached to the nitrogen atom of the pyrrolidine ring shows the triplet at 2.85 ppm with J= 6 Hz and the other one shows the singlet at 2.93 ppm. Finally the olefinic proton shows the singlet at 4.22 ppm.

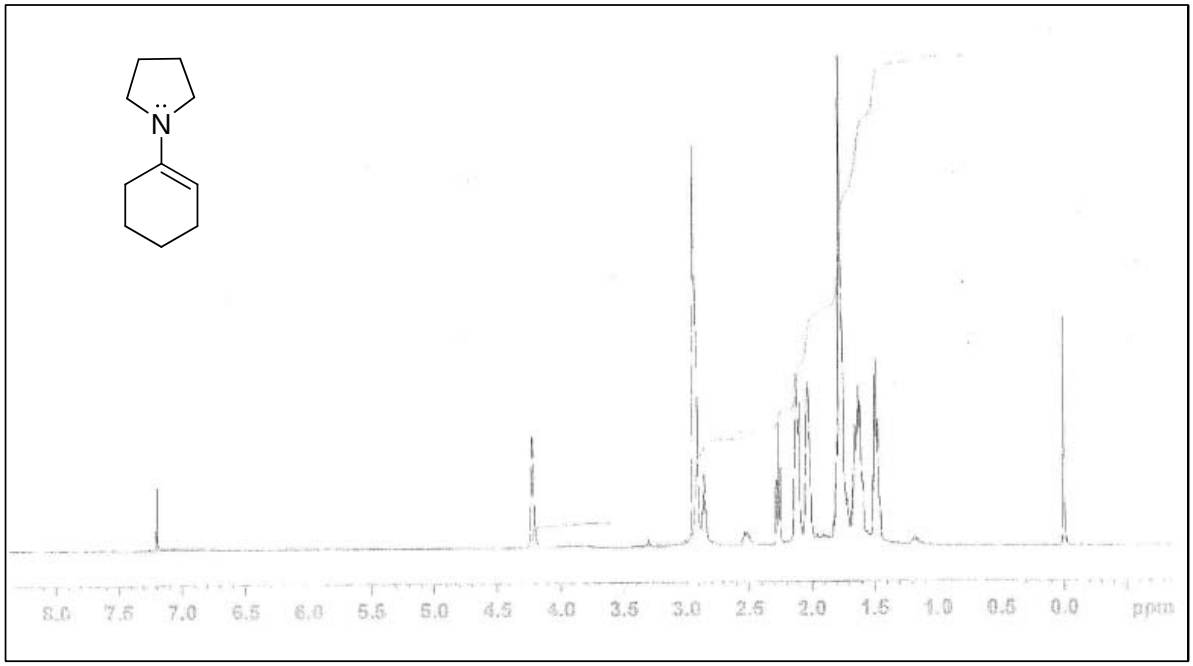


Figure 2.2.^{1}H-NMR spectrum of the 1-cyclohexenylpyrrolidine **45**

^{13}C-NMR spectrum of the 1-cyclohexenylpyrrolidine **45** exhibits the signal at 23.0 and 23.2 ppm for the methylene carbons at the fourth and the fifth position of the cyclohexene ring, respectively. The methylene carbon at the third position of the cyclohexene ring exhibits the signal at 25.0 ppm. The methylene carbons of the pyrrolidine ring exhibit the signal at 25.2 ppm and 27.5 ppm. The signal at 32.1 ppm is due to the methylene carbon at the sixth position of the cyclohexene ring. The methylene carbons attached to the nitrogen atom of the pyrrolidine ring shows the signal at 42.0 ppm and 51.5 ppm. The olefinic carbon exhibits the signal at 93.5 ppm. Finally the quaternary carbon of the compound exhibits the signal at 143.3 ppm.

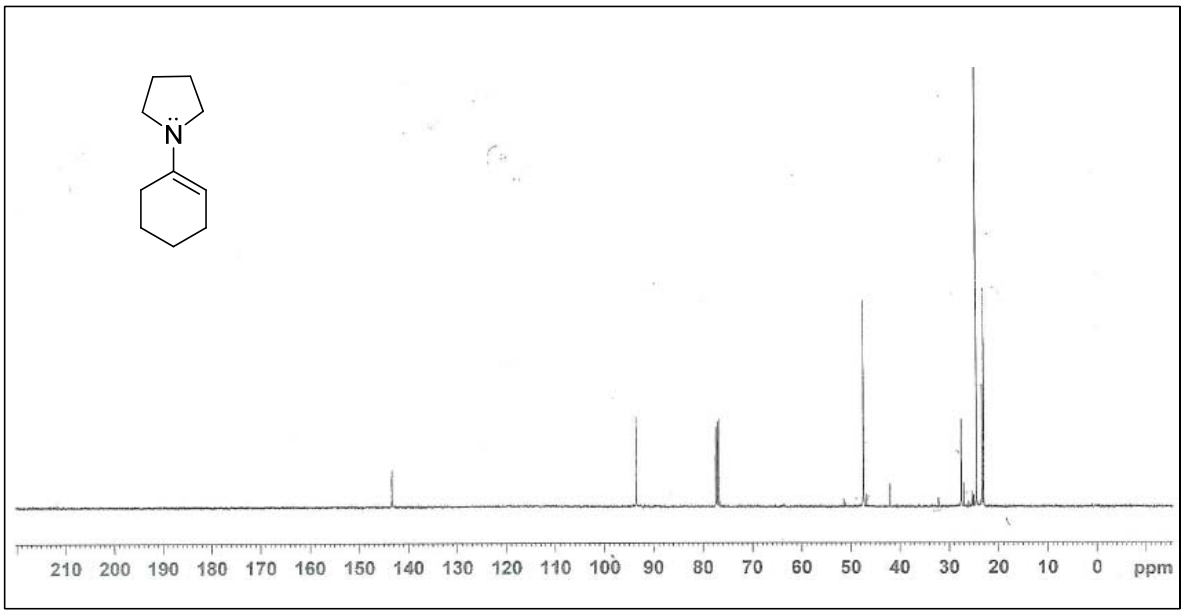


Figure 2.3. ^{13}C-NMR spectrum of the 1-cyclohexenylpyrrolidine **45**

2.1.1 Synthesis of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate 49

According to our synthesis strategy as shown in Figure 1.28. The first step was the synthesis of 2-allylcyclohexanone **46** to reach target 4a-hydroxy-2-oxo-2,4,4a,5, 6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalene-1-yl acetate **49**. The 1-cyclohexenylpyrrolidine **45** has been chosen as starting compound to obtain 2-allylcyclohexanone **46**.

2.1.1.1 Synthesis of 2-allylcyclohexanone 46

1-cyclohexenylpyrrolidine **45** was allowed to react with allyl bromide in dioxane and then hydrochloric acid was added to give the 2-allycyclohexanone **46** as shown in Figure 2.4. After work up, 2-allycyclohexanone **46** was obtained as yellow oil with 79% chemical yield.

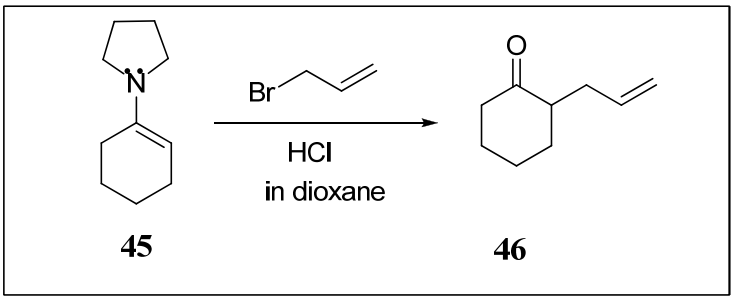


Figure 2.4.Synthesis of the 2-allylcyclohexanone **46**

The product was identified by using ^{13}C-NMR and ^{1}H-NMR spectroscopy and IR. ^{1}H-NMR spectrum of the 2-allylcyclohexanone **46** shows multiplet between 1.32-1.42 ppm for one of the diastereotopic methylene protons and the other one shows the doublet at 1.53 with J=7 Hz at the fourth position of the ring. The methylene protons at the fifth positions of ring show the multiplet between 1.60-1.73 ppm. One of the diastereotopic methylene protons at third position of the ring shows multiplet between 1.81-1.88 ppm. The other one at third position of the ring overlaps with one of the diastereotopic methylene protons at sixth position of the ring show the multiplet between 1.94-2.08 ppm and the other one shows the multiplet between 2.09-2.16. The multiplet between 2.24-2.42 ppm are for the allylic methylene protons and the multiplet between 2.50-2.57 ppm are due to methine proton of ring. The terminal vinylic protons; Ha shows the multiplet between 4.98-5.01 ppm, and the terminal vinylic protons;Hb shows the doublet at 5.04 ppm with j=1 Hz. Finally the internal vinylic proton;Hc shows multiplet between 5.72-5.83 ppm.

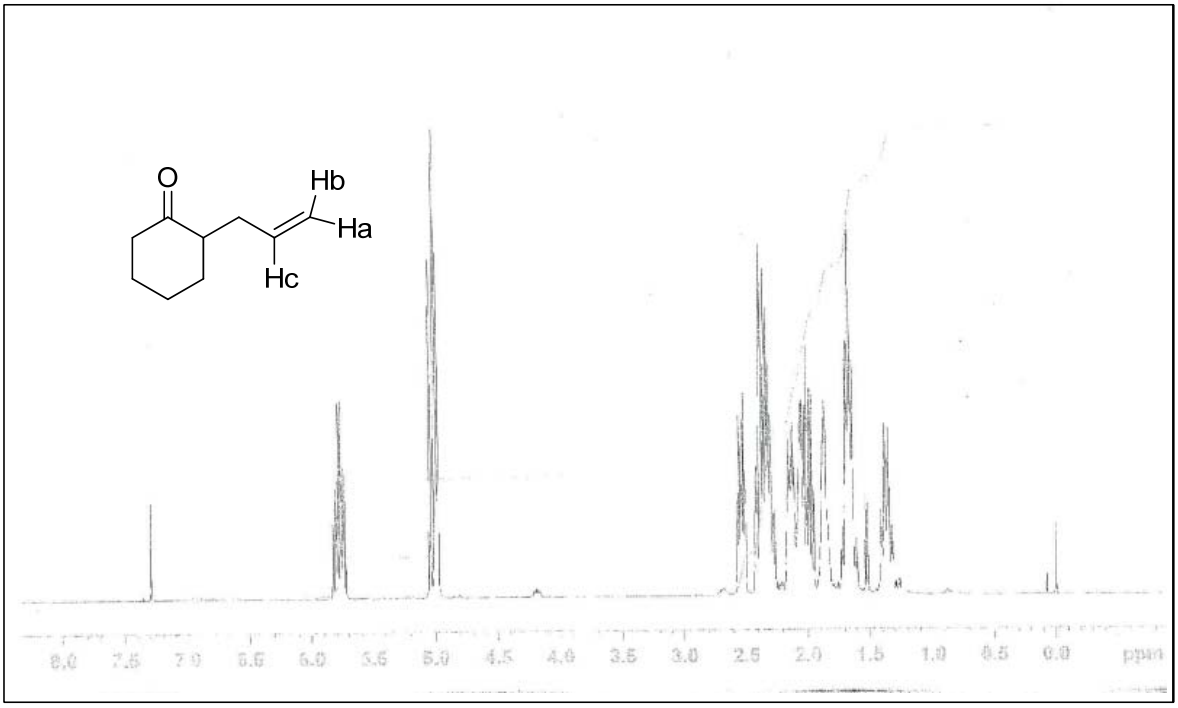


Figure 2.5.[1]H-NMR spectrum of the 2-allylcyclohexanone **46**

[13]C-NMR spectrum of the 2-allylcyclohexanone **46** shows a signal at 25.4 ppm and 27.9 ppm for methylene carbon at the fourth and the third position of the ring. The methylene carbon at the fifth positions of the ring exhibits the signal at 33.3 ppm. The signal at 33.7 ppm belongs to the methine carbon of the ring. The signal at 42.0 ppm is for the allylic methylene carbon, and the methylene carbon at the sixth positions of the ring exhibits the signal at 50.2 ppm. The signal at 116.1 and 136.5 ppm are for the vinylic carbons of the allyl group. Finally the carbonyl carbon exhibits the signal at 212.3 ppm.

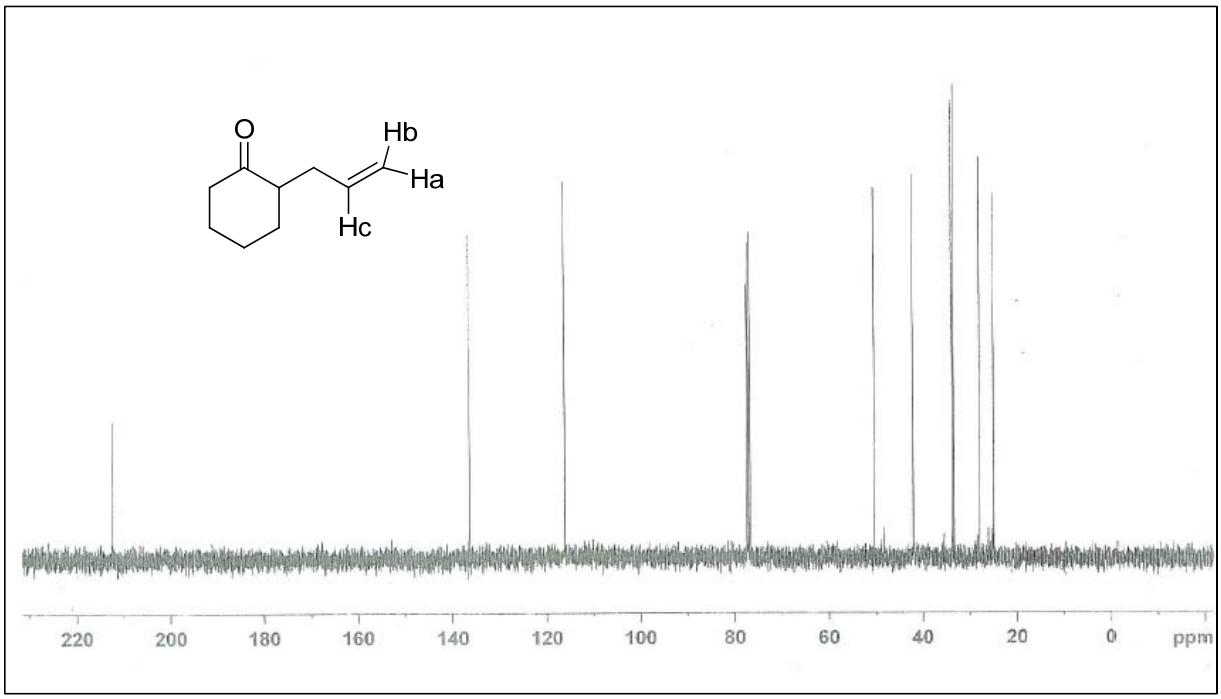


Figure 2.6. ^{13}C-NMR spectrum of the 2-allylcyclohexanone **46**

2.1.1.2 Synthesis of 2-allyl-1-(prop-2-ynyl) cyclohexanol 47

2-allyl-1-(prop-2-ynyl) cyclohexanol **47** was synthesized by using metal mediated Barbier type reaction which is an organic reaction between an alkyl halide and a carbonyl group in the presence of aluminium, zinc, indium, tin or its salts.

2-allylcyclohexanone **46** was reacted with propargyl bromide in presence of Zn-Cu couple in THF to afford 2-allyl-1-(prop-2-ynyl) cyclohexanol **47** as shown in Figure 2.7.The product was obtained as yellow oil in 75 % chemical yield.

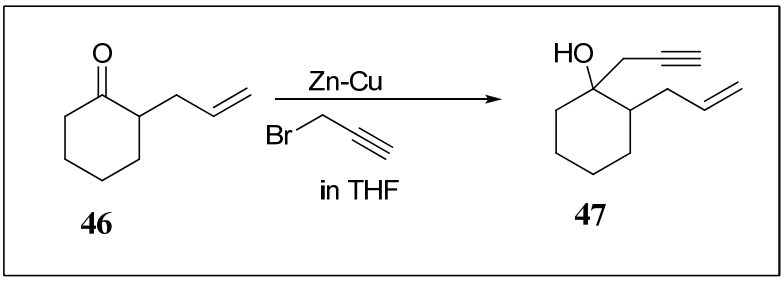


Figure 2.7.Synthesis of 2-allyl-1-(prop-2-ynyl) cyclohexanol **47**

The product was identified by using ^{1}H and ^{13}C-NMR spectroscopy and IR.

^{1}H-NMR spectrum of the 2-allyl-1-(prop-2-ynyl) cyclohexanol **47** shows a multiplet between 1.13-1.29 ppm for the diastereotopic methylene protons at the fourth position of the ring. The diastereotopic methylene protons at the fifth positions of the ring show the multiplet between 1.47-1.51 ppm. The diastereotopic methylene protons at the third and the sixth positions of the ring show the multiplet between 1.53-1.56 ppm and 1.57-1.62 ppm, respectively. The methine proton of ring shows the multiplet between 1.67-1.74 ppm. The multiplet between 1.84-1.94 ppm is for the allylic methylene protons. The acetylenic methine proton shows the triplet at 2.00 ppm with J=3 Hz, and the multiplet between at 2.28 and 2.40 ppm is due to the methylene protons of the propargly group overlaps with OH proton. The two doublets at 4.98 ppm with j=18 Hz and at 4.94 ppm with j=19 Hz are for the terminal vinylic protons Ha and Hb, respectively. Finally the internal vinylic proton; Hc shows multiplet between 5.64-5.80 ppm.

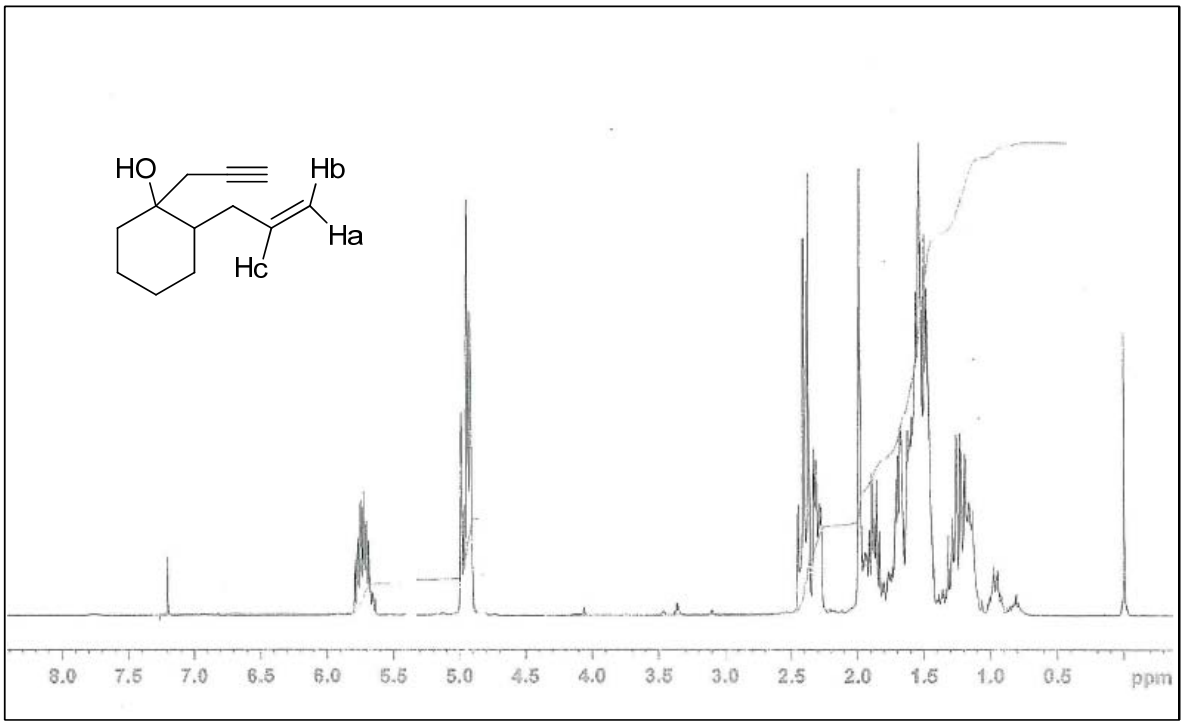


Figure 2.8.[1]H-NMR spectrum of the 2-allyl-1-(prop-2-ynyl) cyclohexanol **47**

[13]C-NMR spectrum of the 2-allyl-1-(prop-2-ynyl) cyclohexanol **47** exhibits a singal at 20.7 ppm and 24.2 ppm for the methylene carbons at the fourth and the fifth positions of the ring, respectively. The signal at 25.9 ppm belongs to the methylene carbon at the third positions of the ring and the signal at 30.2 ppm for the methylene carbon at the sixth positions of the ring. The methine carbon of the ring exhibits the signal at 32.9 ppm. The signal at 35.7 ppm is due to the allylic methylene carbon. The methylene carbon and the methine carbon of propargyl group exhibit the signal at 41.6 and 70.2 ppm, respectively. The quaternary carbon of the ring exhibits the signal at 71.8 ppm and the quaternary carbon of the propargyl group exhibits the signal at 79.8 ppm. Finally the signal at 114.9 and 136.9 ppm are for the vinylic carbons of the allyl group.

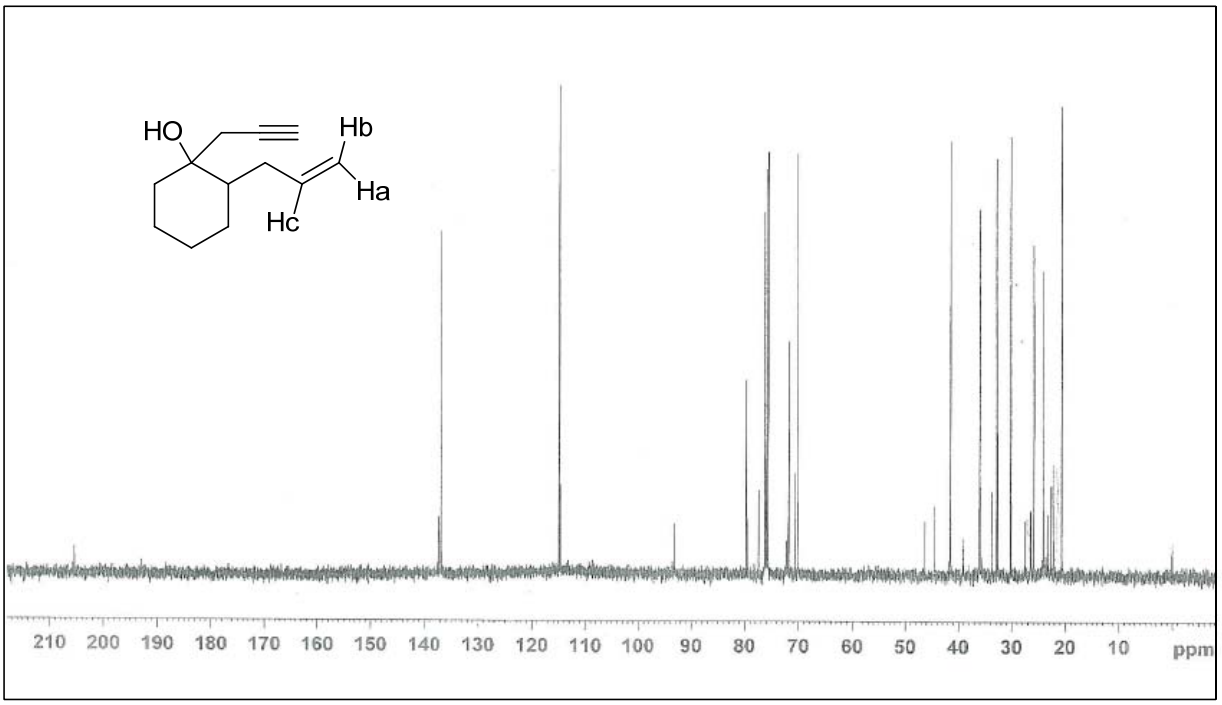


Figure 2.9. ^{13}C-NMR spectrum of the 2-allyl-1-(prop-2-ynyl) cyclohexanol **47**

2.1.1.3 Synthesis of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta [b]naphthalen-2(4H)-one 48 via the Pauson-Khand cycloaddition reactions

4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalene-2 (4H)-one **48** was synthesized by using the Pauson-Khand cycloaddition reactions. 2-allyl-1-(prop-2-ynyl) cyclohexanol **47** was allowed to react with dicobalt ocatacarbonyl in the presence of NMO as a promoter to give 4a-hydroxy-4a, 5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** in CH_2Cl_2 via the Pauson-Khand cycloaddition reactions as shown in Figure 2.10. The product was obtained as white solid in 61% chemical yield.

The first step of the Pauson-Khand cycloaddition reactions, the dicobalt ocatacarbonyl, $Co_2(CO)_{8,}$ was reacted with enyne to form cobalt-alkyne complexes in the molar ratio of 1.0:1.3.

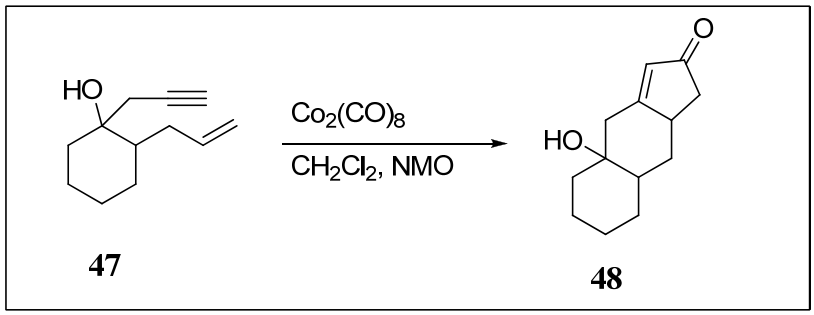


Figure 2.10.Synthesis of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta [b]naphthalen-2(4H)-one **48**

The product was identified by using ^{1}H and ^{13}C-NMR spectroscopy and IR.

^{1}H-NMR spectrum of the compound **48** exhibits multiplet between 1.15 and 1.36 ppm for the diastereotopic methylene protons at the ninth position of the naphthalene ring. The diastereotopic methylene protons at the eight position overlaps with the methine proton of the naphthalene ring show multiplet between 1.43 and 1.48 ppm. One of the diastereotopic methylene protons at the sixth position overlaps with the diastereotopic methylene protons at the seventh position of the naphthalene ring exhibit the multiplet between 1.49 and 1.60 ppm. The other one overlaps with the diastereotopic methylene protons at the fifth position of the naphthalene ring and the methine proton of the cyclopentenone ring exhibit the multiplet between 1.63 and 1.78 ppm. One of the diastereotopic methylene protons at the fourth position of the naphthalene ring shows the doublet of doublet at 2.05 ppm with J=2 and 19 Hz. The other one shows the doublet at 2.30 ppm with J=14 Hz. One of the diastereotopic methylene protons of the cylopentenone ring shows the doublet of doublet at 2.50 ppm with J=5 and 18Hz. The other one overlaps with the OH proton shows the multiplet between at 2.60

and 2.70 ppm. Finally the olefinic proton of the cyclopentenone ring shows a signlet at 5.85 ppm.

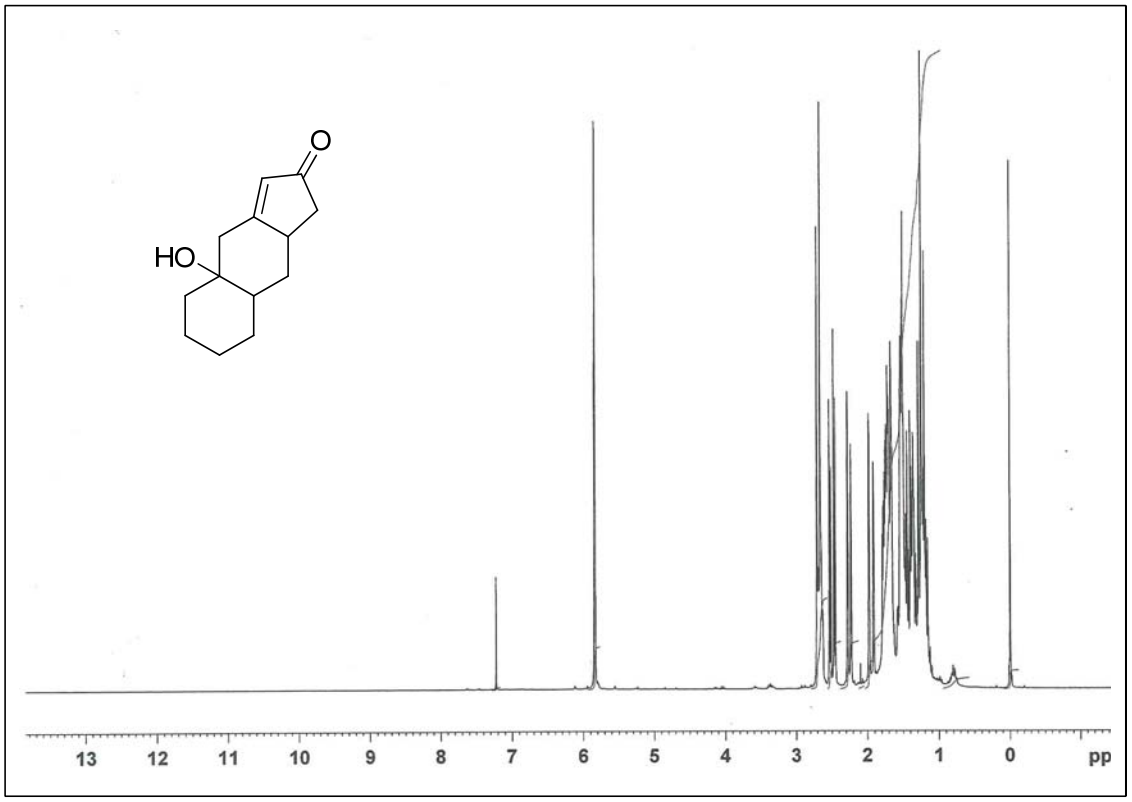


Figure 2.11.^{1}H-NMR spectrum of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b] naphthalen-2(4H)-one **48**

^{13}C-NMR spectrum of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b] naphthalen-2(4H)-one **48** exhibits a signal at 20.2 ppm and 24.8 ppm for the methylene carbon at the sixth and seventh position of the naphthalene ring. The signal at 27.0 ppm is due to the methylene carbon at ninth position of the naphthalene ring. The signal at 35.6 and 38.6 ppm are for the methylene carbon at the eight and fifth position of the naphthalene ring. The signal at 40.6 ppm belongs to the methine carbon of cyclopentenone ring. The signal at 41.3 ppm is

due to the methylene carbon of the cyclopentenone ring. The methine carbon of the naphthalene ring shows a signal 42.1 ppm. The signal at 43.9 ppm is due to the methylene carbon at the fourth position of the naphthalene ring.The quaternary carbon attached to the OH group shows a signal at the 71.3 ppm. One of the olefinic carbons shows a signal at 128.7 ppm and the other olefinic quaternary carbon shows a signal at the 181.3 ppm. Finally the carbonyl carbon shows a signal at 208.47 ppm.

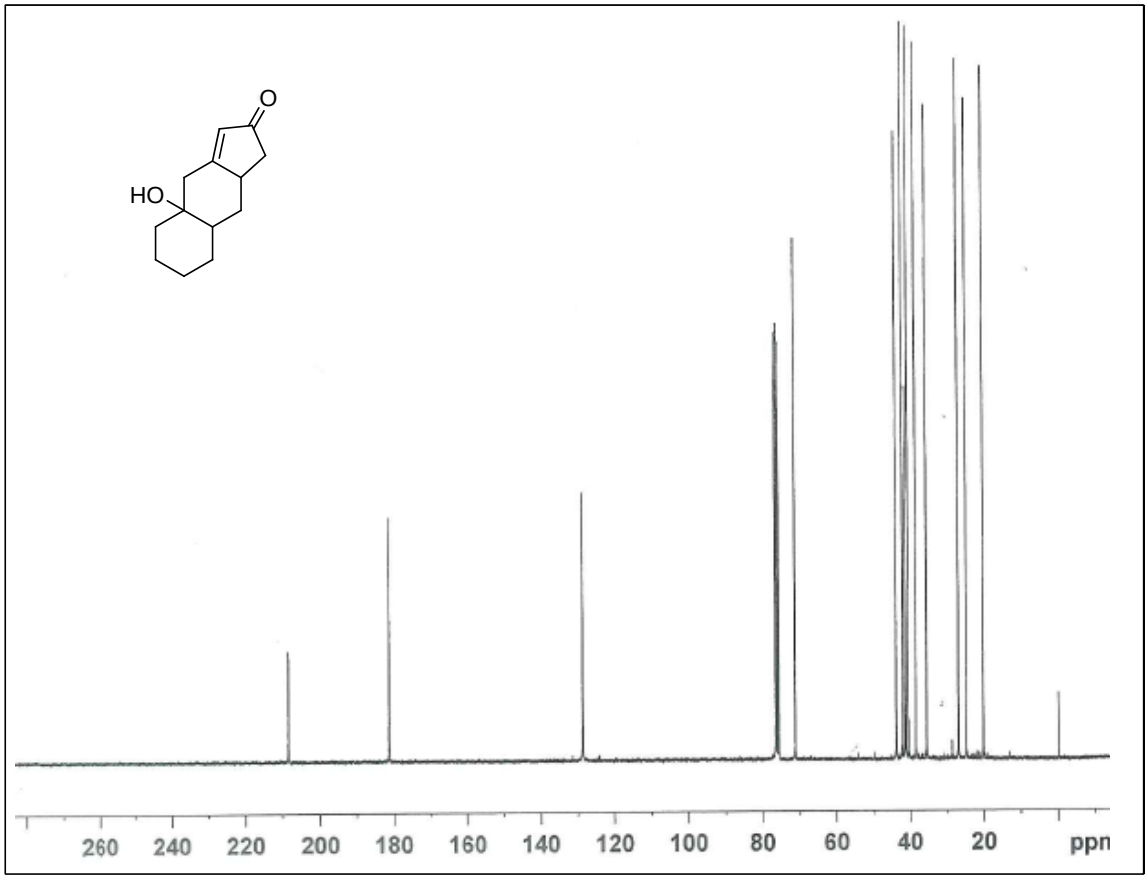


Figure 2.12. ^{13}C-NMR spectrum of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b] naphthalen-2(4H)-one **48**

2.1.1.4 $Mn(OAc)_3$ mediated oxidation reaction of 4a-hydroxy-2-oxo-2,4,4a ,5,6, 7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate 49

$Mn(OAc)_3$ based oxidation of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** afforded 4a-hydroxy-2-oxo-2,4,4a,5, 6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49** as colorless oil in 55% chemical yield as shown in Figure 2.13.

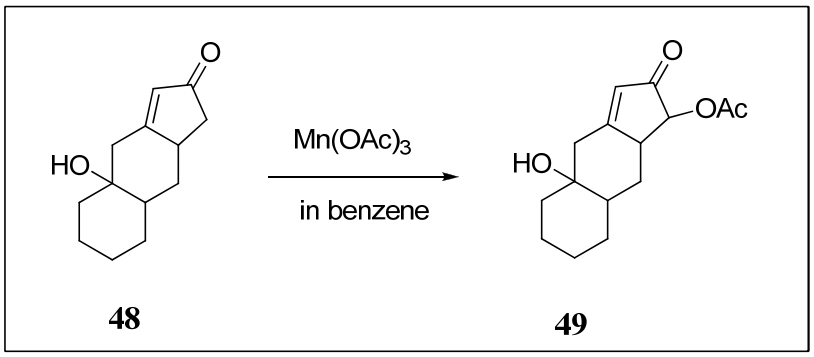


Figure 2.13.$Mn(OAc)_3$ based oxidation of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a, 9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49**

The product was identified by ^{1}H and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the compound **49** exhibits multiplet between 1.13-1.28 ppm for the diastereotopic methylene protons at the seventh position overlaps with one of the diastereotopic methylene protons at the sixth position of the naphthalene ring. The other one overlaps with the diastereotopic methylene protons at the eighth, the ninth positon and the methine proton of the naphthalene ring show the multiplet between 1.31-1.53 ppm. The multiplet between 1.60-1.70 are due to the diastereotopic methylene protons at the fifth position of the naphthalene ring .The methyl protons of the acetoxy moiety overlaps with OH proton exhibits the multiplet between 1.97-2.13 ppm. One of the diastereotopic methylene protons at

the fourth position of the naphthalene ring shows the multiplet between 2.20-2.29 ppm and the other one overlaps with the methine proton of the cyclopentenone ring exhibits the multiplet between 2.61-2.78 ppm. The methine proton of the cyclopentenone ring attached to the acetoxy group shows the doublet at 4.77 ppm with J=2 Hz. Finally the olefinic proton of the cyclopentenone ring shows a signlet at 5.93 ppm.

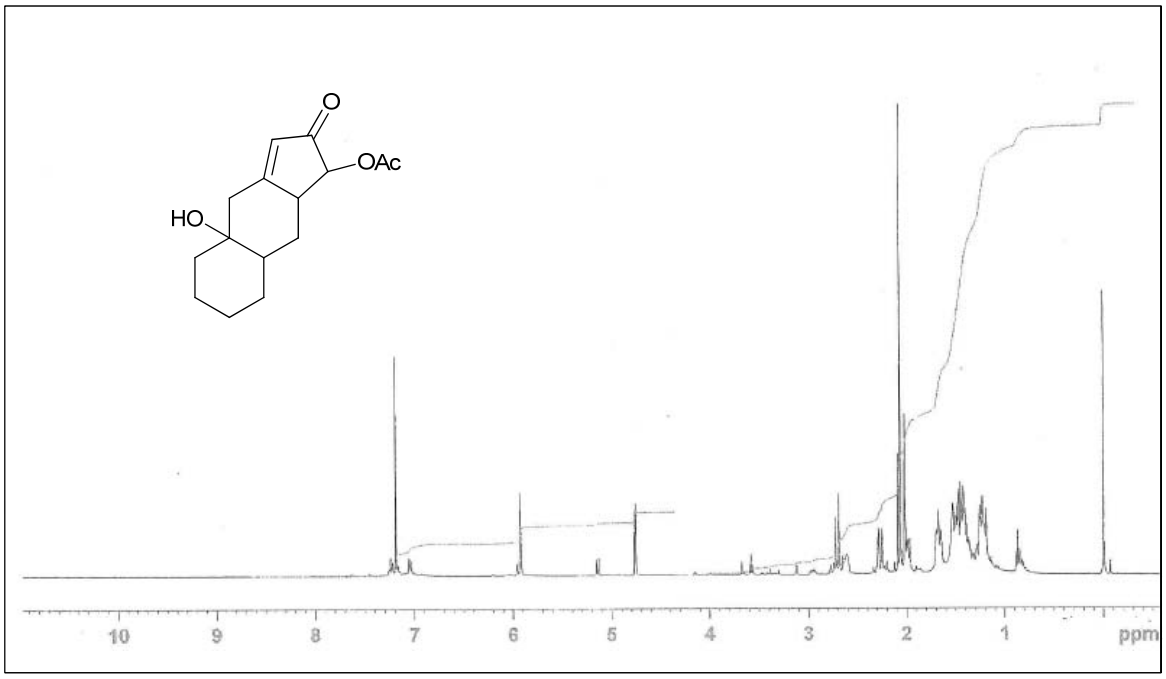


Figure 2.14.[1]H-NMR spectrum of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49**

[13]C-NMR spectrum of the compound **49** exhibits a signal at 19.6 ppm for the methyl carbon of the acetoxy group. The signals at 20.2 and 24.7 ppm are due to the methylene carbon at the sixth and the seventh position of the naphthalene ring. The signal at 27.0 and 33.0 ppm are due to the methylene carbon at the eighth and the ninth position of the naphthalene ring. The methylene carbon at the fifth

position of the naphthalene ring shows a signal at 38.5 ppm. The methine carbon of the naphthalene ring and the methine carbon of the cyclopentenone ring show signals at 41.7 and 43.9 ppm. The signal at 44.5 is for the methylene carbon at the fourth position of the naphthalene ring. The quaternary carbon attached to the OH group shows a signal at 71.0 ppm. The methine carbon of the cyclopentenone ring attached to the acetoxy group shows a signal at 77.6 ppm. The olefinic carbons of the cyclopentenone ring show signals at 127.0 and 169.6 ppm. Finally the carbonyl carbon of the acetoxy moiety and the carbonyl carbon of the cyclopentenone ring show signals at 180.0 ppm and 206.8 ppm.

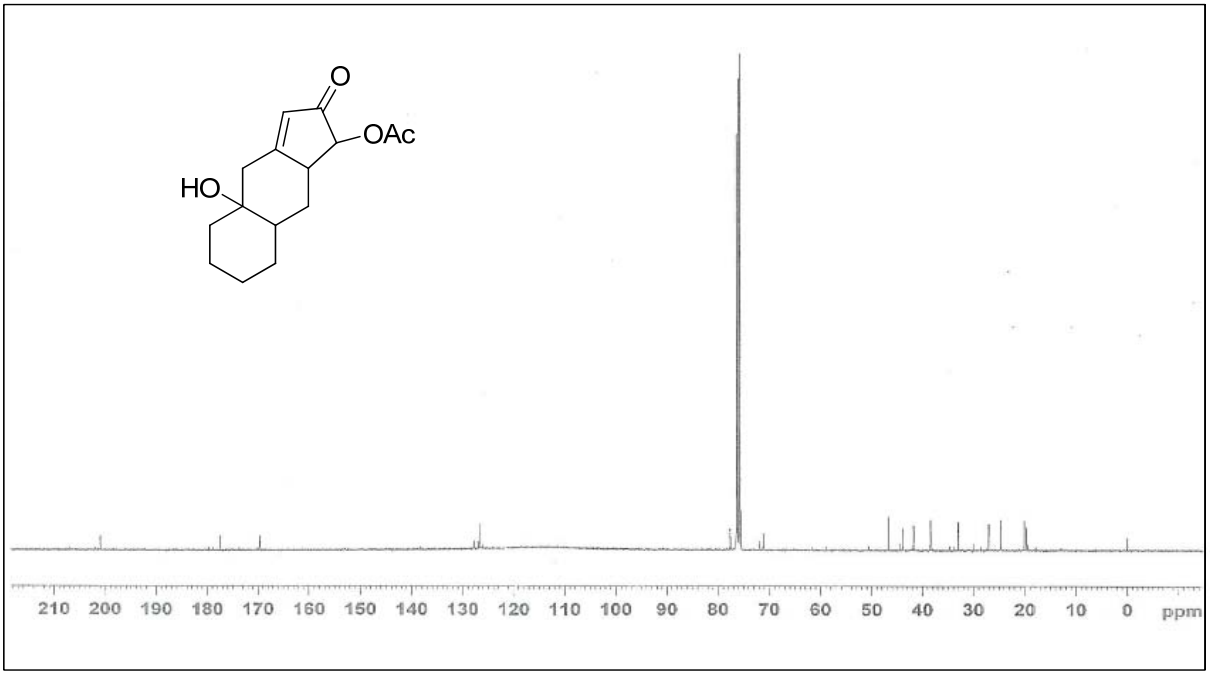


Figure 2.15. ^{13}C-NMR spectrum of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a, 9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **49**

2.1.2 Synthesis of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate 53

According to our synthesis strategy as shown in Figure 1.28. The second step was the synthesis of 2-(prop-2-ynyl) cyclohexanone **50** to reach target 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalene -1-yl acetate **53**. 2-(prop-2-ynyl) cyclohexanone **50** was obtained from the 1-cyclohexenylpyrrolidine **45** which used as starting compound.

2.1.2.1 Synthesis of 2-(prop-2-ynyl) cyclohexanone 50

1-cyclohexenylpyrrolidine **45** was allowed to react with propargyl bromide in dioxane and then hydrochloric acid was added to give the 2-(prop-2-ynyl) cyclohexanone **50** as shown in Figure 2.16. After work up, 2-(prop-2-ynyl) cyclohexanone **50** was obtained as a yellow oil with 79 % chemical yield.

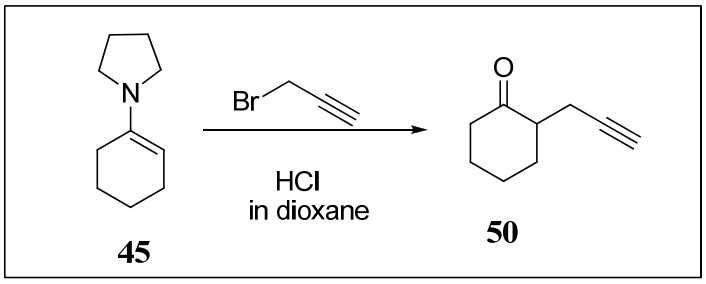


Figure 2.16.Synthesis of 2-(prop-2-ynyl) cyclohexanone **50**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the 2-(prop-2-ynyl) cyclohexanone **50** shows a doublet of quartet at 1.43 ppm with J= 4 Hz and J= 25 Hz for one of the diastereotopic methylene protons at the fourth position of the ring and the other the diastereotopic methylene protons exhibits multiplet between 1.59 and 1.65 ppm.

One of the diastereotopic methylene protons at the fifth position of the ring exhibits the multiplet between 1.66 and 1.73 ppm. The other one exhibits the multiplet between 1.91-1.93 ppm. The acetylenic proton shows triplet at 1.96 ppm with J= 3 Hz. One of the diastereotopic methylene proton at the third position of the ring exhibits multiplet between 2.04 and 2.13 ppm. The other one exhibits the doublet of quarted at 2.20 ppm with J= 3 and J= 8 Hz. The methine proton of the ring shows the multiplet between 2.27 and 2.35 ppm. The multiplet between 2.38-2.46 ppm are for the diastereotopic methylene protons at the sixth position of the ring. Finally one of the diastereotopic methylene protons of the propargyl group exhibits the multiplet between 2.48 and 2.54 ppm. The other diastereotopic methylene proton belongs to the quartet of doublets at 2.61 ppm with J= 5 and J= 17 Hz.

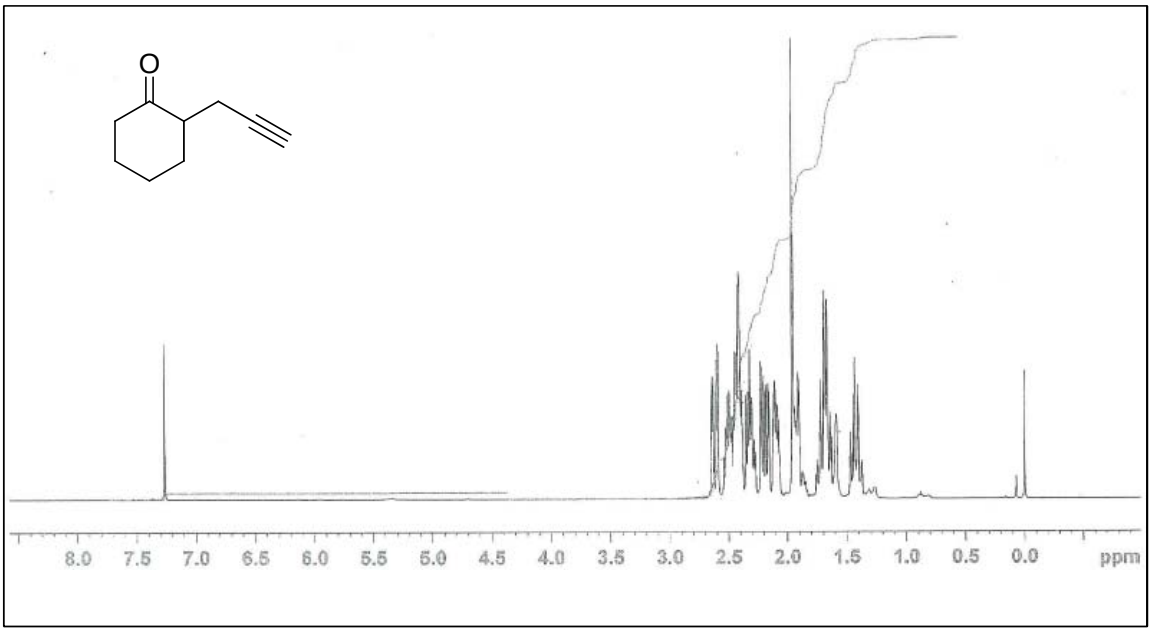


Figure 2.17.[1]H-NMR spectrum of the 2-(prop-2-ynyl) cyclohexanone **50**

^{13}C-NMR spectrum of the 2-(prop-2-ynyl) cyclohexanone **50** shows the signal at 15.1 ppm and 24.5 ppm for the methylene carbons at the fourth and the fifth position of the ring. The signal at 27.6 ppm belongs to the metylene carbon at the third position of the ring. The methylene carbon of the propargyl group exhibits the signal at 33.0 ppm. The signal at 41.7 ppm belongs to the methylene carbon at the sixth position of the ring. The methine carbon of the ring exhibits the signal at 49.3 ppm. The signal at 69.3 ppm belongs to the methine carbon of the acetylene and the quaternary carbon belongs to the signal at 82.4 ppm. Finally the signal at 210.4 ppm belongs to the carbonyl carbon.

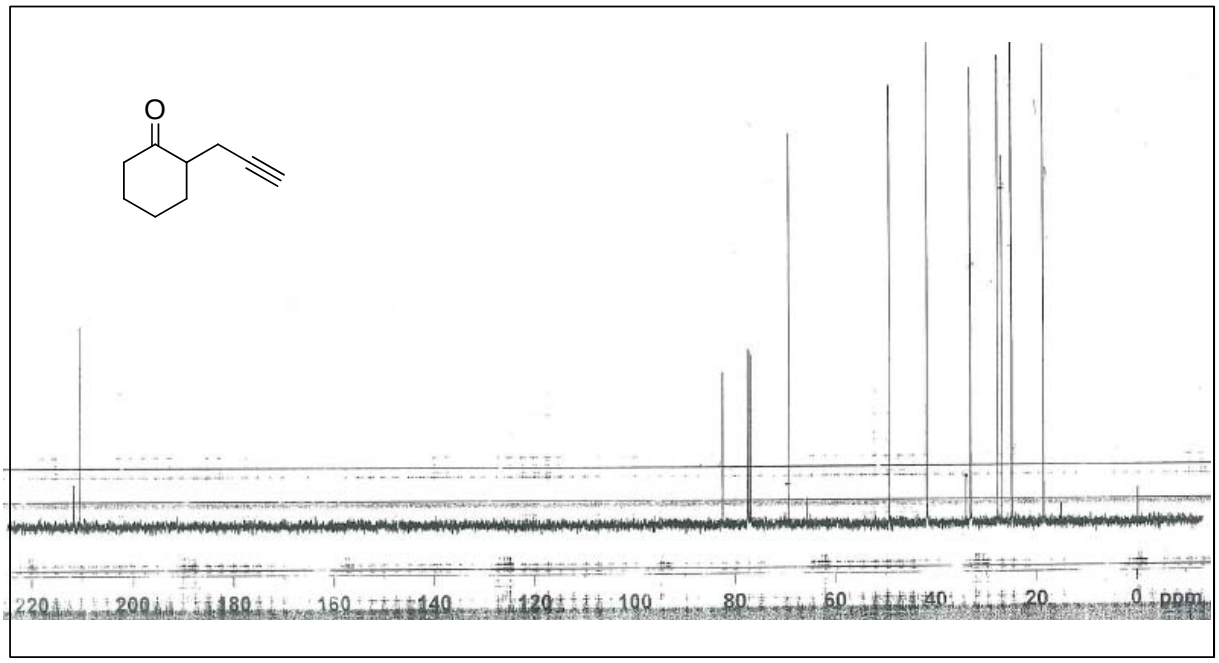


Figure 2.18. ^{13}C-NMR spectrum of the 2-(prop-2-ynyl) cyclohexanone **50**

2.1.2.2 Synthesis of 1-allyl-2-(prop-2-ynyl) cyclohexanol 51

2-(prop-2-ynyl) cyclohexanone **50** was subjected to Barbier type reaction with allyl bromide in presence of indium metal in DMF to obtain 1-allyl-2-(prop-2-ynyl) cyclohexanol **51** as yellow oil in 68 % chemical yield as shown Figure in 2.19.

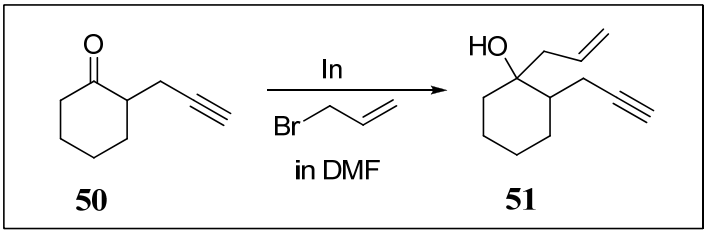


Figure 2.19.Synthesis of 1-allyl-2-(prop-2-ynyl) cyclohexanol **51**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the 1-allyl-2-(prop-2-ynyl) cyclohexanol **51** exhibits the multiplet between 1.12-1.22 ppm for one of the diastereotopic methylene protons at the fourth position of the ring.The other diastereotopic methylene proton exhibits the multiplet between 1.27-1.35 ppm.The multiplet between 1.40-1.54 ppm are due to the diastereotopic methylene protons at the third and the fifth positions of the ring. The diastereotopic methylene proton at the sixth position of the ring overlaps with OH proton exhibit multiplet between 1.63-1.66 ppm. The doublet of doublet at 1.72 ppm with J=8 and J=9 Hz belongs to the methine proton of the ring. The acetylenic methine proton exhibits triplet at 1.93 ppm with J=3 Hz. One of the methylene protons of the propargyl group exhibits the doublet of quartet at 2.15 ppm with J=3 and J= 8 Hz. The other the methylene proton overlaps with one of the methylene proton of the allyl group shows multiplet

between 2.21 and 2.25 ppm. The other the methylene proton of the allyl group shows triplet of doublet at 2.38 ppm with J=3 and J=17 Hz. The multiplet between 5.02 and 5.07 ppm are for the terminal vinylic protons Ha and Hb. Finally the internal vinylic proton shows multiplet between 5.70 and 5.80 ppm.

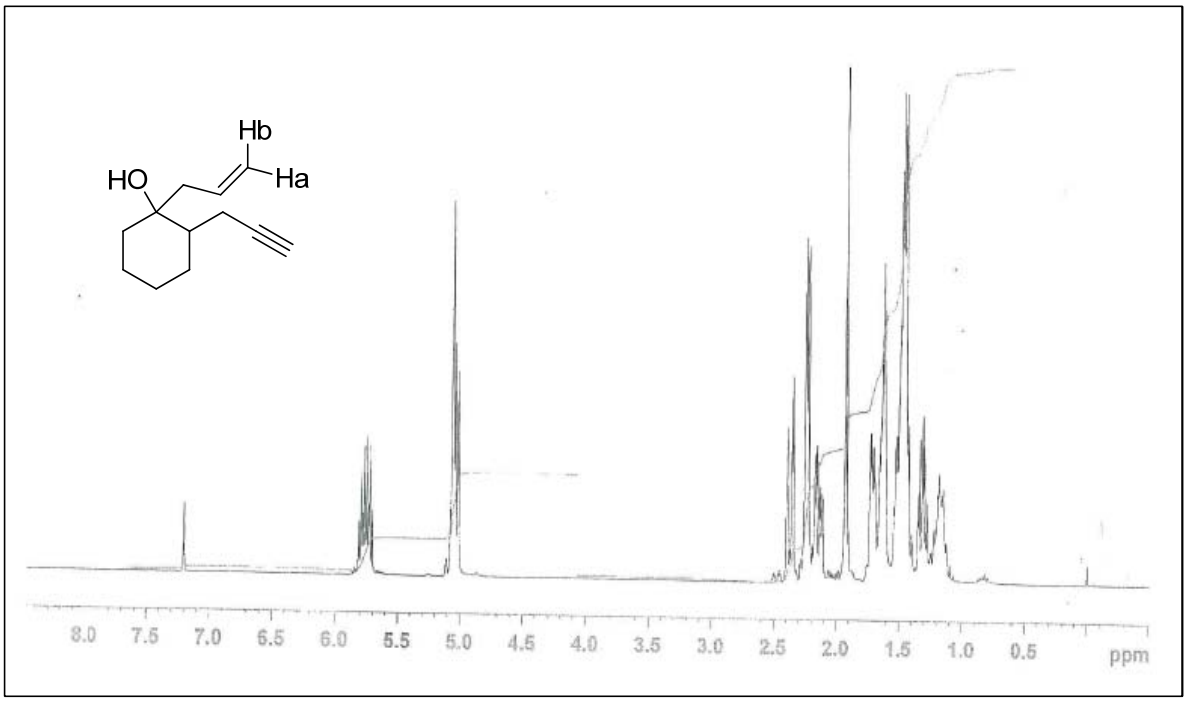


Figure 2.20.[1]H-NMR spectrum of the 1-allyl-2-(prop-2-ynyl) cyclohexanol **51**

[13]C-NMR spectrum of the 1-allyl-2-(prop-2-ynyl) cyclohexanol **51** exhibits singals at 18.9 ppm and 21.5 ppm for the methylene carbons at the fourth and the fifth position of the ring. The signal at 25.2 ppm is for the methylene carbon at the third position of the ring. The signal at 27.2 ppm belongs to the methylene carbon of the propargyl group. The methylene carbon at the sixth position of the ring shows the signal at 36.6 ppm. The signal at 42.6 ppm belongs to the allylic methylene carbon. The methine carbon of the ring shows the signal at 45.3 ppm.

The signal at 69.7 ppm is for the methine carbon of the propargyl group and the quaternary carbon of the ring shows the signal at 72.7 ppm. The quaternary carbon of the propargyl group shows the signal at 84.0 ppm. Finally the signal at 118.8 and 133.6 ppm are for the vinylic carbons of the allyl group.

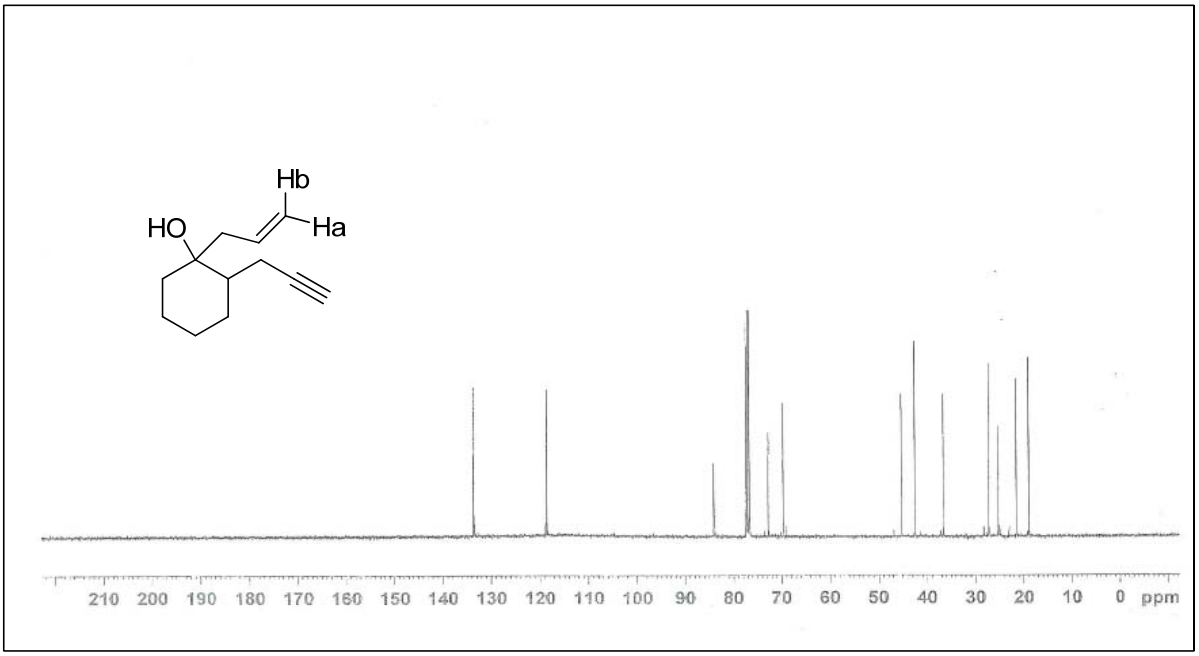


Figure 2.21. ^{13}C-NMR spectrum of the 1-allyl-2-(prop-2-ynyl) cyclohexanol **51**

2.1.2.3 Synthesis of 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta [b] naphthalen-2(4H)-one 52 via the Pauson-Khand cycloaddition reactions

8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2 (4H)-one **52** was synthesized by using the Pauson-Khand cycloaddition reactions. The 2-(prop-2-ynyl) cyclohexanone **51** was allowed to react with dicobalt ocatacarbonyl in the presence of NMO as a promoter to give 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalene-2(4H)-one **52** in dichloromethane via the Pauson-Khand cycloaddition reactions as shown in Figure 2.22.

The first step of the Pauson-Khand cycloaddition reactions, the dicobalt ocatacarbonyl, $Co_2(CO)_8$, was reacted with enyne to form cobalt-alkyne complexes in the molar ratio of 1.0:1.3.The product was obtained as 63% chemical yield.

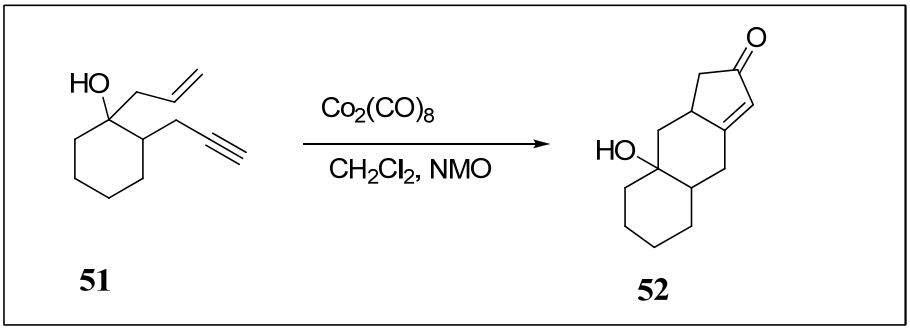


Figure 2.22.Synthesis of 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52**

The product was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the compound **52** exhibits multiplet between 1.10-1.30 ppm for the diastereotopic methylene protons at the sixth position of the naphthalene ring overlaps with the diastereotopic methylene at the seventh position of the naphthalene ring. The multiplet between 1.40 and 1.45 ppm belongs to the diastereotopic methylene protons at the fifth position of the naphthalene ring. One of the diastereotopic methylene protons at the eighth position overlaps with the methine proton of the naphthalene ring shows the mutiplet between 1.50 and 1.60 ppm. The other one shows the doublet at the 1.70 ppm with J=12 Hz. One of the diastereotopic methylene protons at the fourth position of the naphthalene ring shows the doublet at 1.90 ppm with J=18 Hz. The other one overlaps with one of the diastereotopic methylene protons at the ninth position of the naphthalene ring

belongs to the doublet of doublet at 2.00 ppm with J=6 and 13Hz. The other the diastereotopic methylene protons at the ninth position of the naphthalene ring overlaps with one of the diastereotopic methylene protons attached to the carbonyl group and the methine proton of the cyclopentenone ring exhibit the multiplet between 2.30 and 2.40 ppm. The other the diastereotopic methylene protons attached to the carbonyl group of the cyclopentenone ring belongs to the doublet of doublet at 2.50 ppm with J=5 and 19 Hz. The broad signlet at 3.10 ppm belongs to the OH proton. Finally the olefinic proton of the cyclopentenone ring shows a signlet at 5.80 ppm.

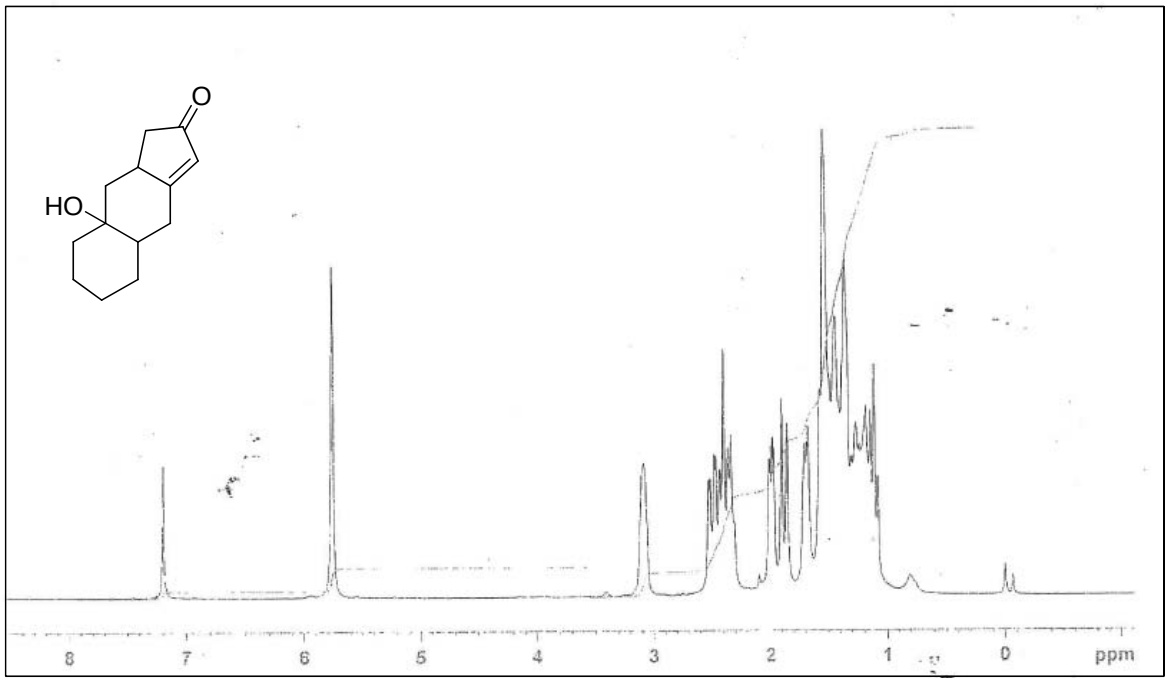


Figure 2.23.[1]H-NMR spectrum of 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52**

^{13}C-NMR spectrum of the compound **52** exhibits a signal at 21.2 ppm and 25.7 ppm for the methylene carbon at the sixth and the fifth position of the naphthalene ring. The signal at 28.7 ppm is due to the methylene carbon at the seventh position and the methine carbon of the naphthalene ring shows a signal at 33.4 ppm.The signal at 37.4 ppm is for the methylene carbon at the eighth position of the naphthalene ring. The methylene carbon at the fourth position of the naphthalene ring shows a signal at 39.1 ppm. The methine carbon of the cyclopentenone ring belongs to the signal at 42.0 ppm.The signal at 44.6 ppm is for the methylene carbon at the ninth position of the naphthalene ring. The signal at 47.6 ppm is due to the methylene carbon of the cyclopentenone ring. The quaternary carbon attached to the OH group shows a signal at the 70.1 ppm. One of the olefinic carbons shows a signal at 119.3 ppm and the other olefinic quaternary carbon a signal at 184.3 ppm. Finally the carbonyl carbon shows a signal at 210.0 ppm.

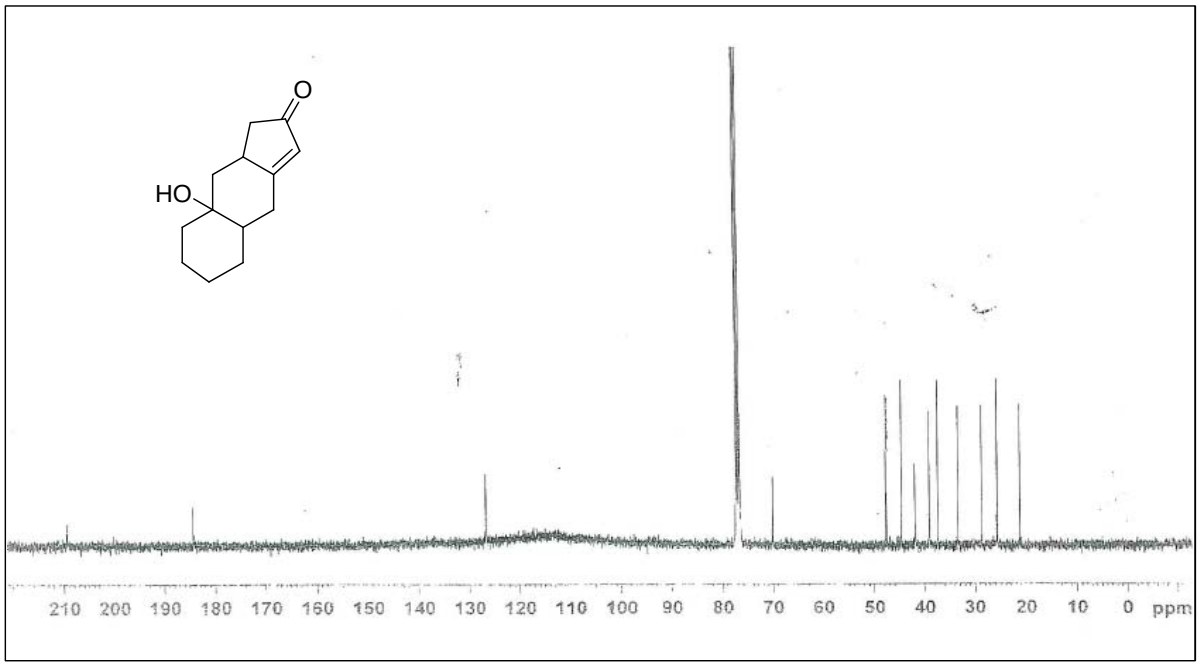


Figure 2.24. ^{13}C-NMR spectrum of 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52**

2.1.2.4 $Mn(OAc)_3$ mediated oxidation reaction of 8a-hydroxy-2-oxo-2,4,4a, 5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate 53

$Mn(OAc)_3$ based oxidation of the 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52** afforded 8a-hydroxy-2-oxo-2,4,4a,5,6,7, 8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53** and 8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **54** in 51% and 23 % chemical yield, respectively as shown in Figure 2.25.

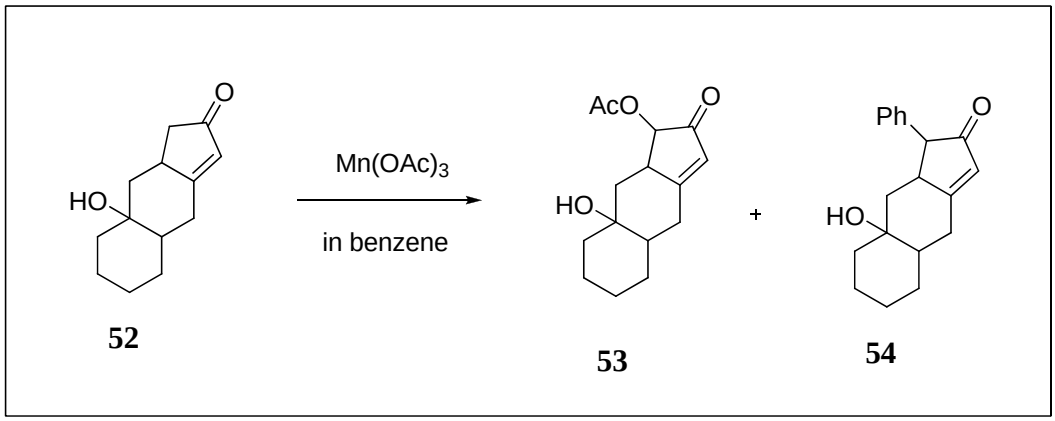


Figure 2.25.$Mn(OAc)_3$ based oxidation of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53**

The product **53** was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the compound **53** exhibits multiplet between 1.15-1.23 ppm for the diastereotopic methylene protons at the seventh position of the naphthalene ring. The multiplet between 1.27-1.37 ppm is for the diastereotopic methylene protons at the sixth position of the naphthalene ring. The multiplet between 1.38-1.45 ppm and the other multiplet between 1.49-1.60 ppm are due to the diastereotopic methylene protons at the fifth and the eighth position of the naphthalene ring. The methine proton overlaps with the diastereotopic methylene protons at the ninth position of the naphthalene ring exhibit the multiplet between 1.64-1.71 ppm. The methyl protons of the acetoxy moiety exhibit a signlet at 2.07 ppm. One of the diastereotopic methylene protons at the fourth position of the naphthalene ring shows the multiplet between 2.08-2.10 ppm and the other one belongs to the doublet of doublet at 2.24 ppm with J=6 and 13 Hz. The methine proton of the cyclopentenone ring overlaps with OH proton exhibits the multiplet between 2.34-2.47 ppm.The methine proton of the cyclopentenone ring attached

to the acetoxy group shows the doublet at 4.74 ppm with J=3 Hz. Finally the olefinic proton of the cyclopentenone ring shows a signlet at 5.83 ppm.

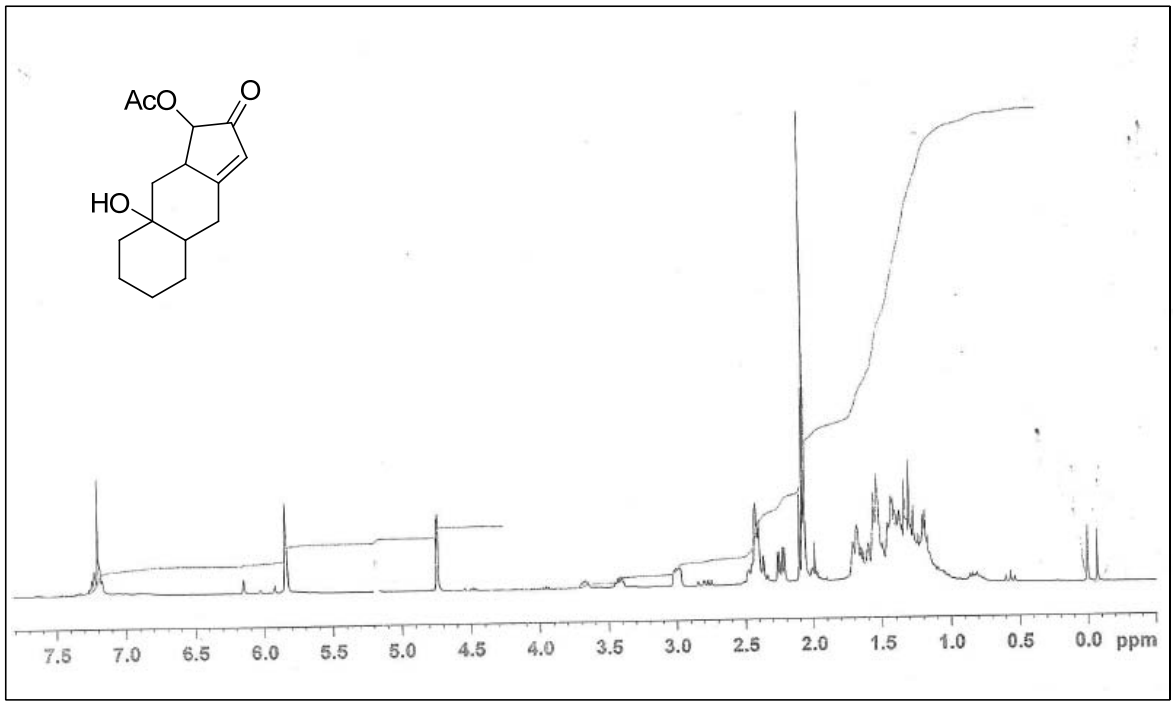


Figure 2.26.^{1}H-NMR spectrum of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53**

^{13}C-NMR spectrum of the compound **53** exhibits a signal at 19.6 ppm for the methyl carbon of the acetoxy group. The signals at 20.1 and 24.6 ppm are due to the methylene carbon at the seventh and the sixth position of the naphthalene ring. The signal at 27.6 and 32.6 ppm are due to the methylene carbon at the fifth and the eighth position of the naphthalene ring. The methylene carbon at the fourth and the ninth position of the naphthalene ring show signals at 38.0 and 41.6 ppm.The methine carbon of the naphthalene ring the and the methine carbon of the cyclopentenone ring show signals at 43.3 ppm and 44.1 ppm. The quaternary

carbon attached to the OH group shows a signal at 69.6 ppm.The methine carbon of the cyclopentenone ring attached to the acetoxy group shows a signal at 77.4 ppm. The olefinic carbons of the cyclopentenone ring show signals at 169.8 and 124.0 ppm. Finally the carbonyl carbon of the acetoxy moiety and the carbonyl carbon of the cyclopentenone ring show signals at 180.0 ppm and 203.0 ppm.

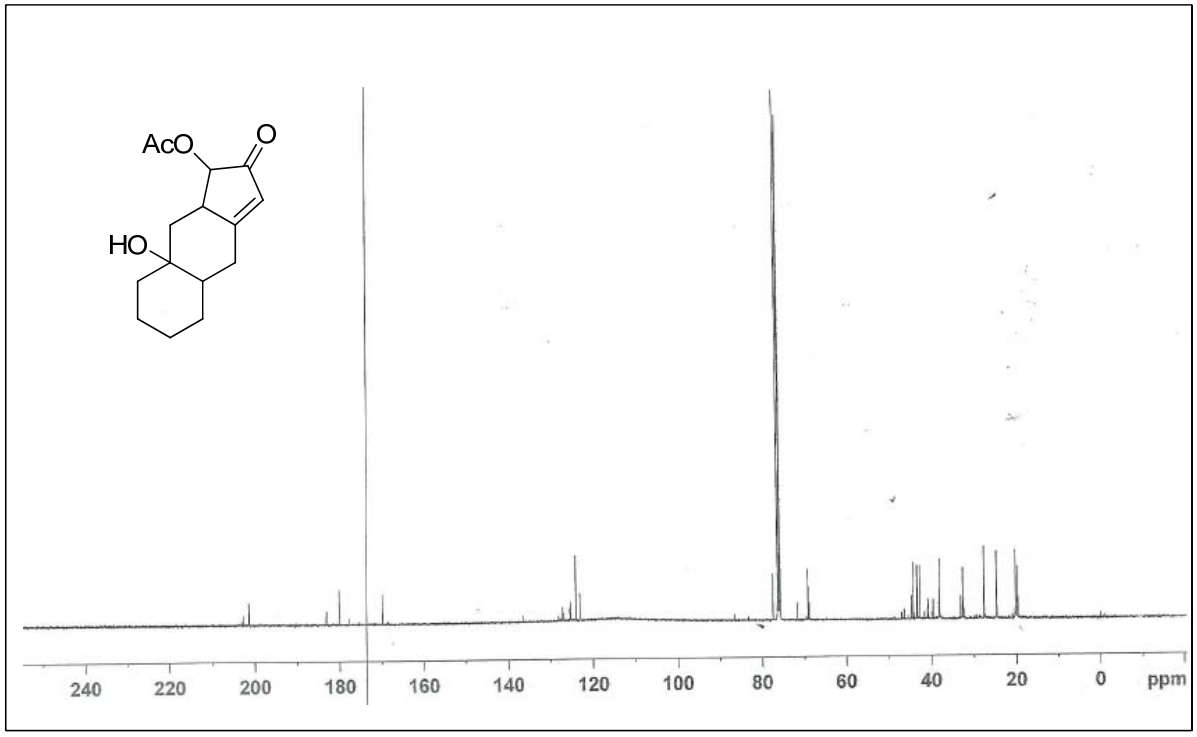


Figure 2.27. ^{13}C-NMR spectrum of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate **53**

8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2-(4H)-one **54** isolated as by product in 23 % yield, helped us to propose a reaction mechanism given in Figure 1.27. The product **54** was identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of the compound **54** exhibits a multiplet between 1.24-1.40 ppm for the diastereotopic methylene protons at the seventh position of the naphthalene ring. The diastereotopic methylene protons at the sixth and the fifth position of the naphthalene ring show the multiplet between 1.45-1.50 ppm and 1.52-1.57 ppm, respectively. The multiplet between 1.60-1.63 ppm is for the diastereotopic methylene protons at the eighth and the ninth position of the naphthalene ring. The methine proton of the naphthalene ring shows a doublet at 1.77 ppm with J=13 Hz. One of the diastereotopic methylene protons at the fourth position of the naphthalene ring shows a doublet of doublet at 2.13 ppm with J=6 and 13 Hz and the other one belongs to the multiplet between 2.43-2.49 ppm. The methine proton of the cyclopentenone ring shows multiplet between 2.52-2.62 ppm. The methine proton of the cyclopentenone ring attached to the phenyl group shows the doublet at 3.11 ppm with J=3 Hz. The broad signlet at 3.20 ppm belongs to the OH proton. The olefinic proton of the cyclopentenone ring shows a signlet at 5.93 ppm. Two methine protons of the benzene ring show the doublet at 7.12 ppm with J=7 Hz. Finally the multiplet between 7.21-7.36 ppm are for the other three methine protons of the benzene ring.

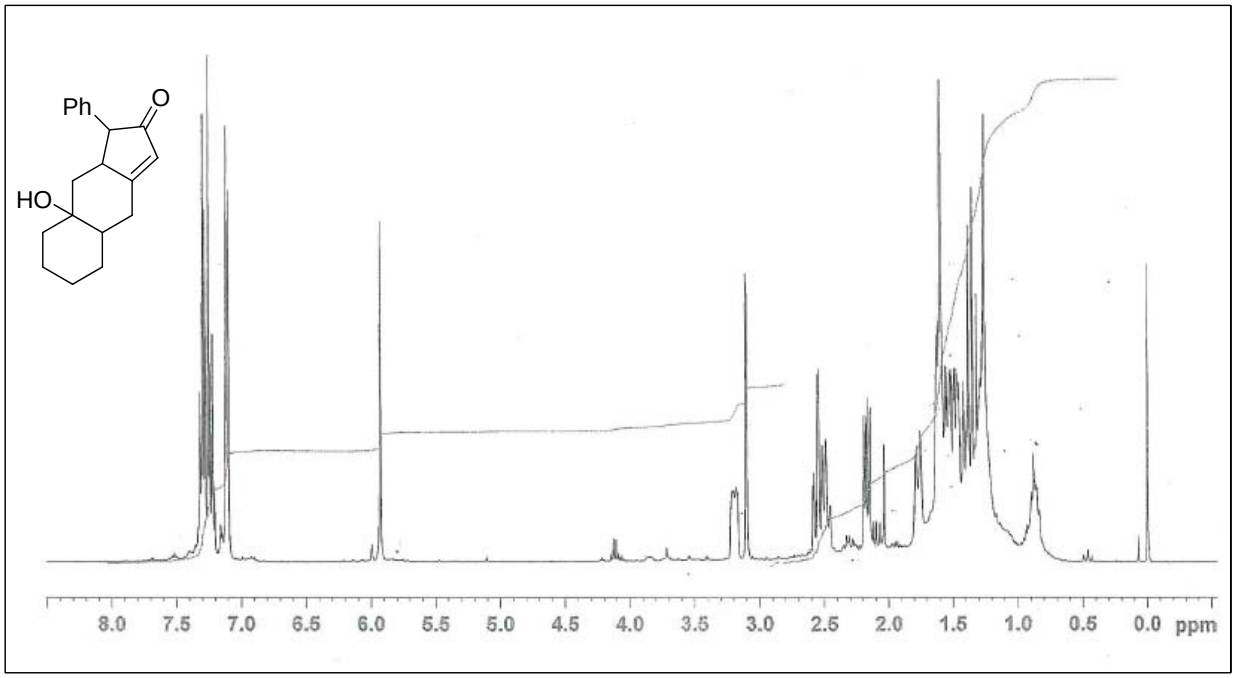


Figure 2.28.[1]H-NMR spectrum of 8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2-(4H)-one **54**

[13]C-NMR spectrum of the compound **54** exhibits a signal at 21.1 for the methylene carbon at the seventh position of the naphthalene ring and the other signal at 25.7 ppm for the methylene carbon at the sixth position of the naphthalene ring. The methylene carbon at the fifth and the eighth position of the naphthalene ring exhibit signals at 28.7 and 33.4 ppm. The methylene carbon at the fourth and the ninth position of naphthalene ring show signals at 39.2 and 44.2 ppm. The methine carbon of the naphthalene ring and the methine carbon of the cyclopentenone ring show signals at 46.8 and 47.5 ppm. The quaternary carbon attached to the OH group shows a signal at 59.8 ppm.The methine carbon of the cyclopentenone ring attached to the phenyl group shows a signal at 70.1 ppm.The signal at 125.8, 126.9 and 128.1 ppm are for the methine carbons of the benzene ring.The quaternary carbon of the benzene ring shows a signal at 128.7 ppm.The

olefinic carbons of the cyclopentenone ring show signals at 139.2 and 182.6 ppm. Finally the carbonyl carbon of the cyclopentenone ring shows a signal at 208.1 ppm.

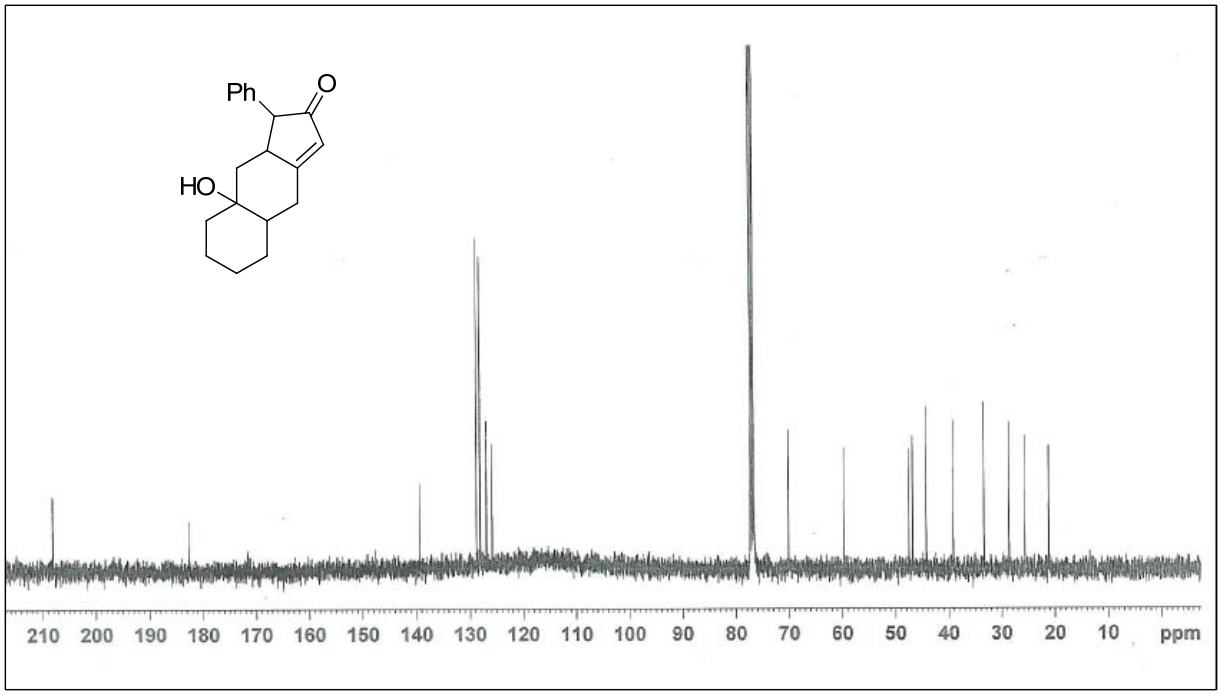


Figure 2.29. ^{13}C-NMR spectrum of 8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2- (4H)-one **54**

CHAPTER III

3. EXPERIMENTAL

In this study we used the instruments and materials which are written below for the purification and characterization of products.

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

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 by UV-light and polymolybden phosphoric acid, in ethanol as appropriate.

Infrared spectra were recorded with a SHIMADZU FTIR 8400-S instrument (KBr pellet).

3.1 Synthesis of 1-cyclohexenylpyrrolidine (45)

(14.2g, 15 mL) cyclohexanone with (17.0g, 20 mL) pyrrolidine was put into reaction and then (60 mL) benzene with a few crystals PTSA was added. The reaction mixture was refluxed for 6 hours under Dean-Stark trap. The reaction mixture was dried over $MgSO_4$ and kept for 1 day later mixture is filtered. Benzene is evaporated in vacuum. The reaction mixture is purified with vacuum distillation as orange oil with 65% chemical yield.

^{1}H-NMR ($CDCl_3$) δ ppm	1.45-1.52 (m, 2H, for the methylene protons at the fourth position of the cyclohexene ring) 1.58-1.68 (m, 2H, for the methylene protons at the fifth position of the cyclohexene ring) 1.71-1.86 (m, 4H, for two methylene protons of the pyrrolidine) 2.03 (s, 1H, One of the methylene protons at the third position of the cyclohexene ring) 2.12(s, 1H, the other one of the cyclohexene ring) 2.27 (t, J=7 Hz, 2H, for the methylene protons at the sixth position of the cyclohexene ring) 2.85 (t, J= 6Hz, 1H, for one of the methylene protons attached to the nitrogen atom of the pyrrolidine) 2.93 (s, 1H, for the other one attached to the nitrogen atom of the pyrrolidine) 4.22 (s, 1H, for olefinic proton)
^{13}C-NMR ($CDCl_3$) δ ppm	23.0 (for the methylene carbon at the fifth position of the cyclohexene ring) 23.2 (for the methylene carbon at the fifth position of the cylohexene ring) 25.0 (for methylene carbon at the third position of the cyclohexene ring) 25.2 (for methylene carbon of the pyrrolidine)

27.5 (for methylene carbon of the pyrrolidine)

32.1 (for the methylene carbon at the sixth position of the cyclohexene ring)

42.0 (for the methylene carbon attached to the nitrogen atom of the pyrrolidine)

51.5 (for the other methylene carbon attached to the nitrogen atom of the pyrrolidine)

93.5 (for the olefinic carbon)

143.3(for the quaternary carbon of the compound)

3.1.1 Synthesis of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b] naphthalen-1-yl acetate (49)

3.1.1.1 Synthesis of 2-allylcyclohexanone (46)

To a solution of the 1-cyclohexenylpyrrolidine (5g, 0.033 mol) in anhydrous dioxane (20 ml) was added a solution of allylbromide (6.7g, 0.033mol) in anhydrous dioxane (10 ml) under a atmosphere of nitrogen at 0^{o}C.After being refluxed for 3h, a 1% HCl solution (11 ml) was added to the reaction mixture and then the solution was refluxed for 3h. Solvent was removed under pressure and the aqueous layer was extracted with diethyl ether (3x30 mL). The organic layer was washed with saturated NaCl solution dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture was purified by flash column chromatography as yellow oil with 79% chemical yield.

Rf: 0.63 (silica gel EtOAc/Hexane, 1:10)

IR (neat):1723 cm^{-1}, 1672 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.32-1.42 (m, 1H, for one of the diastereotopic methylene protons at the fourth position of the ring)

1.53 (d, 1H, for the other diastereotopic methylene protons at the fourth position of the ring, J=7 Hz)

1.60-1.73 (m, 2H, for the methylene protons at the fifth positions of ring)

1.81-1.88 (m, 1H, for one of the diastereotopic methylene protons at the third position of the ring)

1.94-2.08 (m, for the other one at the third position overlaps with one of the diastereotopic methylene protons at sixth position of the ring)

2.09-2.16 (m, 1H, for the other one at the sixth position of the ring)

2.24-2.42 (m, 2H, for the allylic methylene protons)

2.50-2.57 (m, 1H, for the methine proton of the ring)

4.98-5.01 (m, 1H, for the terminal vinylic protons; Ha)

5.04 (d, 1H, for the terminal vinylic protons;Hb, j=1 Hz)

5.72-5.83 (m, 1H, for the internal vinylic proton;Hc)

^{13}C-NMR ($CDCl_3$) δ ppm 25.4 (for the methylene carbon at the fourth position of the ring)

27.9 (for the methylene carbon at the third position of the ring)

33.3 (for the methylene carbon at the fifth position of the ring)

33.7 (for the methine carbon of the ring)

42.0 (for the allylic methylene carbon)

50.2 (for the methylene carbon at the sixth position of the ring)

116.1 (for one of the vinylic carbon of the allyl group)

136.5 (for the other vinylic carbon of the allyl group)

212.3 (for the carbonyl carbon)

3.1.1.2 Synthesis of 2-allyl-1-(prop-2-ynyl) cyclohexanol (47)

A Zn–Cu couple preparation was formed in an oxygen-free environment. Zinc dust (6.5g, 100mmol) was suspended in distilled water (10mL). Acidic cupric chloride solution (0.15M in 5% hydrochloric acid, 22mL) was then added with vigorous magnetic stirring. When the evolution of gas ceased the suspension was filtered and the black solid was washed with water. The Zn–Cu was then washed twice with acetone.

To a stirred mixture of 2-allylcyclohexanone (0.2g, 1.45mmol) and freshly prepared Zn-Cu couple (0.3g, 2.17mmol) in THF (10mL), propargyl bromide (0.21 ml, 1.89mmol, 0.17g, 80 % solution in toluene) was added dropwise to the mixture. The mixture was refluxed for 7h. After the reflux, the solution was filtered. The reaction mixture was diluted with THF and then diethyl ether is added to with equal to THF amount. After that, NH_4Cl solution was added to the reaction mixture. The organic phase was dried over $MgSO_4$ and evaporated in

vacuo. The crude product mixture was purified by flash column chromatography as yellow oil in 75 % chemical yield.

Rf: 0.58(Silica gel EtOAc/ Hexane, 1:10)

IR (neat):3471 cm^{-1}, 2124 cm^{-1}, 1638 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.13-1.29 (m, 2H, for the diastereotopic methylene protons at the fourth position of the ring)

1.47-1.51 (m, 2H, for the diastereotopic methylene protons at the fifth positions of the ring)

1.53-1.56 (m, 2H, for the diastereotopic methylene protons at the third positions of the ring)

1.57-1.62 (m, 2H, for the diastereotopic methylene protons at the sixth positions of the ring)

1.67-1.74 (m, 1H, for the methine proton of ring)

1.84-1.94 (m, 2H, for the allylic methylene protons)

2.00 (t, 1H, for the acetylenic methine proton, J=3 Hz)

2.28-2.40 (m, 3H, for the methylene protons of the propargly group overlaps with OH proton)

4.98 (d, 1H, for the terminal vinylic proton Ha, j=18 Hz)

4.94 (d, 1H, for the terminal vinylic proton, Hb, j=19 Hz)

5.64-5.80 (m, 1H, for the internal vinylic proton,Hc)

^{13}C-NMR ($CDCl_3$) δ ppm 20.7 (for the methylene carbon at the fourth positions of the ring)

24.2 (for the methylene carbon at the fifth positions of the ring)

25.9 (for the methylene carbon at the third positions of the ring)

30.2 (for the methylene carbon at the sixth positions of the ring)

32.9 (for the methine carbon of the ring)

35.7 (for the allylic methylene carbon)

41.6 (for the methylene carbon of propargyl group)

70.2 (for the methine carbon of the propargyl group)

71.8 (for the quaternary carbon of the ring)

79.8 (for the quaternary carbon of the propargyl group

114.9 (for one of the vinylic carbons of the allyl group)

136.9 (for the other vinylic carbons of the allyl group)

3.1.1.3 Synthesis of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta [b]naphthalen-2(4H)-one (48)

To a solution of 2-allyl-1-(prop-2-ynyl) cyclohexanol (0.204g, 1.16 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (0.683g, 2.0 mmol), and stirred for 2 h (TLC monitoring). Then, NMO (1.56g, 11.6 mmol) was added and stirred for 24 h. The crude product was purified by flash column chromatography as white solid in 71% chemical yield.

Rf: 0.56 (Silica gel EtOAc/ Hexane, 2:1)

IR (neat):3542 cm^{-1}, 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.15-1.36 (m, 2H, for the diastereotopic methylene protons at the ninth position of the naphthalene ring)

1.43-1.48 (m, 3H, for the diastereotopic methylene protons at the eight position overlaps with the methine proton of the naphthalene ring)

1.49-1.60 (m, 3H, for one of the diastereotopic methylene protons at the sixth position overlaps with the diastereotopic methylene protons at the seventh position of the naphthalene ring)

1.63-1.78 (m, 4H, for the other one overlaps with the diastereotopic methylene protons at the fifth position of the naphthalene ring and the methine proton of the cyclopentenone ring)

2.05 (d of d, 1H, for one of the diastereotopic methylene protons at the fourth position of the naphthalene ring, J=2 and 19 Hz)

2.30 (d, 1H, for the other one, J=14 Hz)

2.50 (d of d, 1H, for one of the diastereotopic methylene protons of the cylopentenone ring, J=5 and 18Hz)

2.60-2.70 (m, 2H for the other one overlaps with the OH proton)

5.85 (s, 1H, for the olefinic proton)

^{13}C-NMR ($CDCl_3$) δ ppm 20.2 (for the methylene carbon at the sixth position of the naphthalene ring)

24.8 (for the methylene carbon at the seventh position of the naphthalene ring)

27.0 (for the methylene carbon at the ninth position of the naphthalene ring)

35.6 (for the methylene carbon at the eight position of the naphthalene ring)

38.6 (for the methylene carbon at the fifth position of the naphthalene ring)

40.6 (for the methine carbon of the cyclopentenone ring)

41.3 (for the methylene carbon of the cyclopentenone ring)

42.1 (for the methine carbon of the naphthalene ring)

43.9 (for the methylene carbon at the fourth position of the naphthalene ring)

71.3 (for the quaternary carbon attached to the OH group)

128.7 (for one of the olefinic carbon)

181.3 (for the other olefinic quaternary carbon)

208.47 (for the carbonyl carbon)

3.1.1.4 Synthesis of 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate (49)

A mixture of $Mn(OAc)_3$ (3.25g, 14.0 mmol) in benzene (150 mL) was refluxed for 45 min under a Dean-Stark trap. Then the mixture was cooled down to room temperature and the cyclopentenone (7.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown color disappeared. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1 M HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over MgSO4 and evaporated in vacuo. The crude product mixture was separated by flash column chromatography using ethyl acetate/hexane as eluent to afford the product as colorless oil in 55% chemical yield.

Rf: 0.75 (Silica gel EtOAc/ Hexane, 1:3)

IR (neat):3389 cm^{-1}, 1720 cm^{-1}, 1698 cm^{-1}, 1243 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.13-1.28 (m, 3H, for the diastereotopic methylene protons at the seventh position overlaps with one of the diastereotopic methylene protons at the sixth position of the naphthalene ring)

1.31-1.53 (m, 6H, for the other one overlaps with the diastereotopic methylene protons at the eighth, the ninth position and the methine proton of the naphthalene ring)

1.60-1.70 (m, 2H, for the diastereotopic methylene protons at the fifth position of the naphthalene ring)

1.97-2.13 (m, 4H, for the methyl protons of the acetoxy moiety overlaps with OH proton)

2.20-2.29 (m, 1H, for one of the diastereotopic methylene protons at the fourth position of the naphthalene ring)

2.61 -2.78 (m, 2H, for the other one overlaps with the methine proton of the cyclopentenone ring)

4.77 (d, 1H, for the methine proton attached to the acetoxy group, J=2 Hz)

5.93 (s, 1H, for the olefinic proton)

^{13}C-NMR ($CDCl_3$) δ ppm 19.6 (for the methyl carbon of the acetoxy group)

20.2 (for the methylene carbon at the sixth position of the naphthalene ring)

24.7 (for the methylene carbon at the seventh position of the naphthalene ring)

27.0 (for the methylene carbon at the eighth position of the naphthalene ring)

33.0 (for the methylene carbon at the ninth position of the naphthalene ring)

38.5 (for the methylene carbon at the fifth position of the naphthalene ring)

41.7 (for the methine carbon of the naphthalene ring)

43.9 (for the methine carbon of the cyclopentenone ring)

44.5 (for the methylene carbon at the fourth position of the naphthalene ring)

71.0 (for the quaternary carbon)

77.6 (for the methine carbon of the cyclopentenone ring attached to the acetoxy group)

127.0 (for one of the olefinic carbons)

169.6 (for the other olefinic carbons)

180.0 (for the carbonyl carbon of the acetoxy moiety)

206.8 (for the carbonyl carbon of the cyclopentenone ring)

3.1.2 Synthesis of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta [b]naphthalen-1-yl acetate (53)

3.1.2.1 Synthesis of 2-(prop-2-ynyl) cyclohexanone (50)

To a solution of the 1-cyclohexenylpyrrolidine (5g, 0.033 mol) in anhydrous dioxane (20 ml) was added a solution of 3-bromoprop-1-yne (6.7g, 0.033mol) in anhydrous dioxane (10 ml) under a atmosphere of nitrogen at 0^{o}C.After being refluxed for 3h, a 1% HCl solution (11 ml) was added to the reaction mixture and then the solution was refluxed for 3h.Solvent was removed under pressure and the aqueous layer was extracted with diethyl ether(3x30 mL). The organic layer was washed with saturated NaCl solution dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture was purified by flash column chromatography as yellow oil with 79 % chemical yield.

Rf: 0.56 (Silica gel EtOAc/ Hexane, 1:12)

IR (neat): 2105 cm^{-1}, 1714 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.43 (d of t, 1H, for one of the diastereotopic methylene protons at the fourth position of the ring, J= 4 and J= 25 Hz)

1.59-1.65 (m, 1H, for the other one at the fourth position of the ring)

1.66-1.73 (m, 1H, for one of the diastereotopic methylene protons at the fifth position of the ring)

1.91-1.93 (m, 1H, for the other one at the fifth position of the ring)

1.96 (t, 1H, for the acetylenic proton J= 3 Hz)

2.04-2.13 (m, 1H, for one of the diastereotopic methylene proton at the third position of the ring)

2.20 (d of q, 1H, for the other one at the third position of the ring, J= 3 and J= 8 Hz)

2.27-2.35 (m, 1H, for the methine proton of the ring)

2.38-2.46 (m, 2H, for the diastereotopic methylene protons at the sixth position of the ring)

2.48-2.54 (m, 1H, for one of the diastereotopic methylene proton of the propargyl group)

2.61 (q of d, 1H, for the other proton of the propargyl group, J= 5 and J= 17)

^{13}C-NMR ($CDCl_3$) δ ppm 15.1 (for the methylene carbon at the fourth position of the ring)

24.5 (for the methylene carbon at the fifth position of the ring)

27.6 (for the methylene carbon at the third position of the ring)

33.0 (for the methylene carbon of the propargyl group)

41.7 (for the methylene carbon at the sixth position of the ring)

49.3 (for the methine carbon of the ring)

69.3 (for the methine carbon of the acetylene)

82.4 (for the quaternary carbon of propargyl group)

210.4 (for the carbonyl carbon)

3.1.2.2 Synthesis of 1-allyl-2-(prop-2-ynyl) cyclohexanol (51)

To a stirred mixture of 2-(prop-2-ynyl) cyclohexanone (0.2g, 1.47mmol) and indium powder (0.3g, 2.21mmol) in DMF (10mL), allylbromide (0.22 ml, 2.21mmol) was added dropwise under an inert atmosphere of argon. The mixture was stirred at room temperature for 8 h. After that, NH_4Cl solution was added to the reaction mixture and this mixture extracted with diethyl ether (3x30mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture wa purified by flash column chromatography using ethyl acetate/hexane as eluent to afford the product as yellow oil in 68 % chemical yield.

Rf: 0.62 (Silica gel EtOAc/ Hexane, 1:12)

IR (neat):3514 cm^{-1},2218 cm^{-1},1710 cm^{-1},1639 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.12-1.22 (m, 1H, one of the diastereotopic methylene protons at the fourth position of the ring)

1.27-1.35 (m, 1H, for the other diastereotopic methylene proton at the fourth position of the ring)

1.40-1.54 (m, 4H, for the diastereotopic methylene protons at the third and the fifth positions of the ring)

1.63-1.66 (m, 3H, for the diastereotopic methylene protons at the sixth position overlaps with OH proton)

1.72 (d of d, 1H, for the methine proton of the ring, J=8 and J=9 Hz)

1.93 (t, 1H for the acetylenic methine proton, J=3 Hz)

2.15 (d of q, 1H, for one of the methylene protons of the propargyl group, J=3 and J= 8 Hz)

2.21-2.25 (m, 2H, for the other one of the propargyl group overlaps with one of the methylene proton of the allyl group)

2.38 (t of d, 1H, for the other the methylene proton of the allyl group, J=3 and J=17 Hz)

5.02-5.07 (m, 2H, for the terminal vinylic protons Ha and Hb)

5.70-5.80 (m, 1H, for the internal vinylic proton)

^{13}C-NMR ($CDCl_3$) δ ppm 18.9 (for the methylene carbon at the fourth position of the ring)

21.5 (for the methylene carbon at the fifth position of the ring)

25.2 (for the methylene carbon at the third position of the ring)

27.2 (for the methylene carbon of the propargyl group)

36.6 (for the methylene carbon at the sixth position of the ring)

42.6 (for the allylic methylene carbon)

45.3 (for the methine carbon of the ring)

69.7 (for the methine carbon of the propargyl group)

72.7 (for the quaternary carbon of the ring)

84.0 (for the quaternary carbon of the propargyl group)

118.8 (for one of the vinylic carbons of the allyl group)

133.6 (for the other vinylic carbons of the allyl group)

3.1.2.3 Synthesis of 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta [b]naphthalene-2(4H)-one (52)

To a solution of 1-allyl-2-(prop-2-ynyl) cyclohexanol **51** (0.204g, 1.16 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (0.683g, 2.0 mmol), and stirred for 2 h (TLC monitoring). Then, NMO (1.56g, 11.6 mmol) was added and stirred for 24 h. The crude product was purified by flash column chromatography as white solid in 67% chemical yield.

Rf: 0.44 (Silica gel EtOAc/ Hexane, 2:1)

IR (neat):3458 cm^{-1}, 1712 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.10-1.30 (m, 4H, for the diastereotopic methylene protons at the sixth and the seventh position of the naphthalene ring)

1.40-1.45 (m, 2H, for the diastereotopic methylene protons at the fifth position of the naphthalene ring)

1.50-1.60 (m, 2H, for one of the diastereotopic methylene protons at the eighth position overlaps with the methine proton of the naphthalene ring)

1.70 (d, 1H, for the other diastereotopic methylene protons, J=12 Hz)

1.90 (d, 1H, for one of the diastereotopic methylene protons at the fourth position of the the naphthalene ring, J=18 Hz)

2.00 (d of d, 2H, for the other one overlaps with one of the diastereotopic methylene protons at the ninth position of the naphthalene ring, J=6 and 13Hz)

2.3-2.4 (m, 3H, for the other one overlaps with one of the diastereotopic methylene protons attached to the carbonyl group and the methine proton of the cyclopentenone ring)

2.50 (d of d, 1H, for the other the diastereotopic methylene protons attached to the carbonyl group, J=5 and 19 Hz)

3.10 (br s, 1H, for the OH proton)

5.80 (s, 1H, for the olefinic proton)

^{13}C-NMR ($CDCl_3$) δ ppm 21.2 (for the methylene carbon at the sixth position of the naphthalene ring)

25.7 (for the methylene carbon at fifth position of the naphthalene ring)

28.7 (for the methylene carbon at the seventh position the naphthalene ring)

33.4 (for the methine carbon of the naphthalene ring)

37.4 (for the methylene carbon at the eighth position of the naphthalene ring)

39.1 (for the methylene carbon at the fourth position of the naphthalene ring)

42.0 (for the methine carbon of the cyclopentenone ring)

44.6 (for the methylene carbon at the ninth position of the naphthalene ring)

47.6 (for the methylene carbon of the cyclopentenone ring)

70.1 (for the quaternary carbon)

119.3 (for one of the olefinic carbon)

184.3 (for the other olefinic quaternary carbon)

210.0 (for the carbonyl carbon)

3.1.2.4 Synthesis of 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalen-1-yl acetate (53)

A mixture of $Mn(OAc)_3$ (3.25g, 14.0 mmol) in benzene (150 mL) was refluxed for 45 min under a Dean-Stark trap.Then the mixture was cooled down to room temperature and the cyclopentenone (7.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown color disappeared. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1 M HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture was separated by flash column chromatography using ethyl acetate/hexane as eluent to afford the product as colorless oil in 51% chemical yield.

Rf: 0.77 (Silica gel EtOAc/ Hexane, 1:3)

IR (neat):3549 cm^{-1}, 1720 cm^{-1}, 1710 cm^{-1}, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.15-1.23 (m, 2H, for the diastereotopic methylene protons at the seventh position of the naphthalene ring)

1.27-1.37 (m, 2H, for the diastereotopic methylene protons at the sixth position of the naphthalene ring)

1.38-1.45 (m, 2H, for the diastereotopic methylene protons at the fifth position of the naphthalene ring)

1.49-1.60 (m, 2H, for the diastereotopic methylene protons at the eighth position of the naphthalene ring)

1.64-1.71 (m, 3H, for the methine proton overlaps with the diastereotopic methylene protons at the ninth position of the naphthalene ring)

2.07 (s, 3H, for the methyl protons of the acetoxy moiety)

2.08-2.10 (m, 1H, for one of the diastereotopic methylene protons at the fourth position of the naphthalene ring)

2.24 (d of d, 1H, for the other one J=6 and 13 Hz)

2.34-2.47 (m, 2H, for the methine proton of the cyclopentenone ring overlaps with OH proton)

4.74 (d, 1H, for the methine proton of the cyclopentenone ring, J=3 Hz)

5.83 (m, 1H, for the olefinic proton)

^{13}C-NMR ($CDCl_3$) δ ppm 19.6 (for the methyl carbon of the acetoxy group)

20.1 (for the methylene carbon at the seventh position of naphthalene ring)

24.6 (for the methylene carbon at the sixth position of naphthalene ring)

27.6 (for the methylene carbon at the fifth position of the naphthalene ring)

32.6 (for the methylene carbon at the eighth position of the naphthalene ring)

38.0 (for the methylene carbons at the fourth position of naphthalene ring)

41.6 (for the methylene carbons at the ninth position of naphthalene ring)

43.3 (for the methine carbon of naphthalene ring)

44.1 (for the methine carbon of the cyclopentenone ring)

69.6 (for the quaternary carbon)

77.4 (for the methine carbon of the cyclopentenone ring attached to the acetoxy group)

169.8 (for one of the olefinic carbons of the cyclopentenone ring)

124.0 (for thr other olefinic carbons of the cyclopentenone ring)

180.0 (for the carbonyl carbon of the acetoxy moiety)

203.0 (for the carbonyl carbon of the cyclopentenone ring)

3.1.2.5 Synthesis of 8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2 (4H)-one (54)

A mixture of $Mn(OAc)_3$ (3.25g, 14.0 mmol) in benzene (150 mL) was refluxed for 45 min under a Dean-Stark trap.Then the mixture was cooled down to room temperature and the cyclopentenone (7.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown color disappeared. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1M HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over MgSO4 and evaporated in vacuo. The crude product mixture was separated by flash column chromatography using ethyl

acetate/hexane as eluent to afford the product as colorless oil in 23 % chemical yield.

Rf: 0.77 (Silica gel EtOAc/ Hexane, 1:3)

IR (neat):3345 cm^{-1}, 3130 cm^{-1}, 1710 cm^{-1}, 1693 cm^{-1}, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm 1.24-1.40 (m, 2H, for the diastereotopic methylene protons at the seventh position of the naphthalene ring)

1.45-1.50 (m, 2H, for the diastereotopic methylene protons at the sixth position of the naphthalene ring)

1.52-1.57 (m, 2H, for the diastereotopic methylene protons at the fifth position of the naphthalene ring)

1.60-1.63 (m, 4H, for the diastereotopic methylene protons at the eighth and the ninth position of the naphthalene ring)

1.77 (d, 1H, for the methine proton of the naphthalene ring, J=13 Hz)

2.13 (d of d, 1H, for one of the diastereotopic methylene protons at the fourth position of the naphthalene ring, J=6-13 Hz)

2.43-2.49 (m, 1H, for the other one)

2.52-2.62 (m, 1H, for the methine proton of the cyclopentenone ring)

3.11 (d, 1H, for the methine proton of the cyclopentenone ring attached to the phenyl group, J=3 Hz)

3.20 (br s, 1H, for the OH proton)

5.93 (s, 1H, for the olefinic proton of the cyclopentenone ring)

7.12 (s, 2H, for the methine protons of the benzene ring, J=7 Hz)

7.21-7.36 (m, 3H, for the methine protons of the benzene ring)

^{13}C-NMR ($CDCl_3$) δ ppm 21.1 (for the methylene carbon at the seventh position of the naphthalene ring)

25.7 (for the methylene carbon at the sixth position of the naphthalene ring)

28.7 (for the methylene carbon at the fifth position of the naphthalene ring)

33.4 (for the methylene carbon at the eighth position of the naphthalene ring)

39.2 (for the methylene carbon at the fourth position of naphthalene ring)

44.2 (for the methylene carbon at the ninth position of naphthalene ring)

46.8 (for the methine carbon of the naphthalene ring)

47.5 (for the methine carbon of the cyclopentenone ring)

59.8 (for the quaternary carbon attached to the OH group)

70.1 (for the methine carbon of the cyclopentenone ring attached to the phenyl group)

125.8 (for the methine carbons of the benzene ring)

126.9 (for the methine carbon of the benzene ring)

128.1 (for the methine carbons of the benzene ring)

128.7 (for the quaternary carbon of the benzene ring)

139.2 (for the olefinic carbons of the cyclopentenone ring)

182.6 (for the olefinic carbons of the cyclopentenone ring)

208.1 (for the carbonyl carbon of the cyclopentenone ring)

CHAPTER IV

4. CONCLUSIONS

The Pauson-Khand reaction is one of the most powerful reactions for the generation of cyclopentenone compounds and the synthesis of natural products. The cyclopentenone ring is a very useful building block in the synthesis of biologically active molecules. The intramolecular Pauson-Khand reaction has gained much popularity because it can afford cyclopentenone fused ring systems, which are difficult to construct.

In this study, the intramolecular Pauson-Khand cycloaddition reaction was applied to the synthesis of 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **48** and 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b]naphthalen-2(4H)-one **52**. After the intramolecular Pauson-Khand cycloaddition reaction of fused tricyclic compounds; **48** and **52** were oxidized to 4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalene-1-yl acetate **49,** 8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1H-cyclopenta[b]naphthalene-1-yl acetate **53** and 8a-hydroxy-1-phenyl-4a,5,6,7,8,8a,9,9a-octahydro-1H-cyclopenta[b] naphthalene-2-(4H)-one **54** isolated as by product, according to the proposed reaction mechanism given in Figure 1.27 by using $Mn(OAc)_3$.

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