SYNTHESIS OF SPIRO CYCLOPENTENONE-PYRAN

AND

SPIRO DIHYDROPYRAN

COMPOUNDS

By

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Approval of the Graduate School of Natural Sciences.

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ABSTRACT

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Spiro cyclic compounds found in the structure of natural product that has biological activities. The structures contain cyclopentenone pyran ring composed of cylopentenone ring known as cyclopentenone prostaglandins which are used in the treatment of psychological diseases. Dihydropyran ring contain compounds found in the structure of molecules used in the anti-cancer treatment drugs. Pauson-Khand reaction and Ring Closing Metathesis are frequently used methods in the literature for synthesize of spirocyclic units.

In this study, 6-oxaspiro[4.5]deca-1,8-diene **66** and 1-oxaspiro[5.5]undeca-3,7-diene **72** was obtained by Ring Closing Metathesis using Grubbs First

Generation Catalyst with 80% and 82% overall chemical yield respectively. Then, 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** was synthesized via Pauson-Khand Reaction in the presence of NMO as a promoter and $Co(CO)_8$ with 82% overall chemical yield. In the same manner 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **74** was obtained with 84% overall chemical yield.

Keywords: Ring Closing Metathesis, Spirocyclic compounds, Pauson-Khand reaction, Grubbs' catalyst.

ÖZET

SPİRO SİKLOPENTENON-PİRAN
VE
SPİRO DİHİDROPİRAN
BİLEŞİKLERİNİN SENTEZİ

Güzel, Ayça
Yüksek Lisans Tezi, Kimya Bölümü
Tez Danışmanı: Doç. Dr. F. Devrim ÖZDEMİRHAN

Nisan 2013, 103 sayfa

Spirosiklik bileşikler birçok biyolojik aktiviteye sahip doğal ürünlerin yapısında bulunmaktadır. Siklopentenon yapısında mevcut olan siklopentenon piran halkasını içeren yapılar siklopentenon prostaglandinler olarak geçen ve birçok psikolojik hastalığın tedavisinde kullanılan yapılardır. Dihidropiran halkasını içeren yapılar doğada birçok molekülün yapısında bulunup, kanser tedavisinde kullanılan ilaçların yapısında mevcuttur. Pauson-Khand reaksiyonu ve Halka Kapama Metatezi spirosiklik yapıların elde edilmesi için literatürde yaygın olarak kullanılan metotlardır.

Bu çalışmada 6-oxaspiro[4.5]deca-1,8-dien **66** ve 1-oxaspiro[5.5]undeca-3,7-dien **72** yapıları Grubbs' birinci jenerasyon katalizörü kullanılarak, halka kapama metatezi ile %80 ve %82 kimyasal verimle elde edilmişlerdir. Daha sonrasında, 4a',5'-dihidro-1'H-spiro[siklopent[2]en-1,3'-siklopenta[c]piran]-6'(4'H)-on **68** yapısı NMO ve $Co(CO)_8$ varlığında Pauson-Khand reaksiyonu ile %82 kimyasal verimle elde edilmiştir. Aynı şekilde, 4a',5'-dihidro-1'H-spiro[siklohex[2]en-1,3'-siklopenta[c] piran]-6'(4'H)-on **74** yapısı %82 kimyasal verimle elde edilmiştir.

Anahtar Kelimeler: Halka Kapama Metatezi, Spirosiklik Bileşikler, Pauson-Khand reaksiyonu, Grubbs' katalizörü.

To the Unforgettable Memories of

My Grandfathers, Necmi SEZGİN and Ahmet Orhan GÜZEL,

My grandmother, Fatma GÜZEL,

My uncles, Zeki SEZGİN and Nejat GÜZEL.

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I wish to express my thanks to my parents Tülay GÜZEL and Tekin GÜZEL, my sister Tuğçe GÜZEL, Gülbe GÜZEL and Sıdıka GÜZEL, Doğan GÜRER, Uğur ŞENOL, Pınar ŞENOL my grandmother Müberra SEZGİN, my aunt Gülay ŞENOL and Can ŞENOL, my aunt Şerefnur GÖKÇEK and Güldem GÖKÇEK, İfakat GÜRER, Merve GÜRER, Niyazi GÜRER, Ahmet Orhan GÜRER for their endless patience, support and love.

I devote this thesis to my grandfathers Necmi SEZGİN and Ahmet Orhan GÜZEL, my grandmother Fatma GÜZEL, my uncles Zeki SEZGİN and Nejat GÜZEL to their unforgettable memories.

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LIST OF SYMBOLS AND ABBREVIATIONS

acac : Acetylacetone

atm : Atmosphere

BuSMe : Butyl methyl sulphide

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

$CDCl_3$: Chloroform-d

CH_2Cl_2 : Dichloromethane

CH_3CN : Acetonitrile

cod : 1,5-cyclooctandienyl

$Co_2(CO)_8$: Dicobalt octacarbonyl

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

DME : Dimethylethane

DCM : Dichloromethane

EtOAc : Ethyl acetate

FT-IR : Fourier Transform Infrared

Hz : Hertz

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

HPLC : High Performance Liquid Chromatography

IR : Infra Red

Ind : Indenyl

mL : Millilitre

mmol : Millimole

NMO : 4-methylmorpholine-N-oxide

$NaBH_4$: Sodium tetrahydroborate

NH_4Cl : Ammonium chloride

Ph : Phenyl

SiO_2 : Silicon dioxide

TBAI : Tetrabutyl ammonium iodide

THF : Tetrahydrofuran

TMO : Trimethyl-N-oxide

TMANO : Trimethylamine-N-oxide

TMS : 3-Bromo-1-(trimethylsilyl)-1-propyne

ppm : Parts per million

s : Singlet

ss : Strong singlet

bs : Broad singlet

d : Doublet

dd : Doublet of doublet

dt : Doublet of triplet

t : Triplet

td : Triplet of doublet

m : Multiplet

CHAPTER I

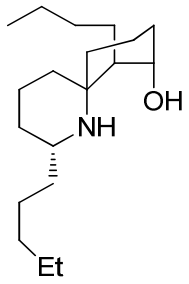
1. INTRODUCTION

1.1. SPIROCYCLIC COMPOUNDS

1.1.1. Introduction

First ‘spiran’ was introduced by Baeyer in 1990 related as a bicyclic hydrocarbon which is connected by just one single atom. The word ‘spirocyclanes’ is used to explain the family of such bicyclic hydrocarbon due to the fact that nature of the spiro-linked carbon has a tetrahedral character or environment and the ring planes are almost perpendicular to each other [1].

Spiroketals widespread occurrence are as sub-units of many sources; insects, microbes, plants, fungi and marine organisms because of their chemical reactivity and synthesis, increasing of pharmacological importance of compounds containing spiroketals assemblies have trigged [2]. Other example including the biological usage and activities of spiro carbon atom is ‘Perhydrohistrionicotoxin’ **(1)** having the retention of neurotoxic properties shown in figure 1.1 [3].



1

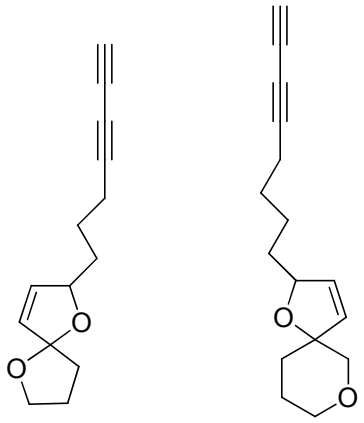
Figure 1.1. Perhydrohistrionicotoxin

The interest in the study and search of spiro compounds has become more significant due to the fact that the presence of sterically constrained spiro structure in various natural products [4]. Because of their highly pronounced biological properties, spiro compounds correspond on important unit and class of naturally occurring substances [5].

1.1.2. Biological Activities

Spirocyclic compounds found in wide range of natural products or compounds which are isolated from various sources [6]. Especially, spiroketals are related to be the sub-unit of many naturally appearing substances of biological interests and researches such as anti freed ants, insect pheromones and polyether antibiotics [2]. A series of spiroketals **(2-3)**, shown in figure 1.2 have been obtained and separated from *'Chrysanthemum Coronanium'* a vegetable in South Africa.

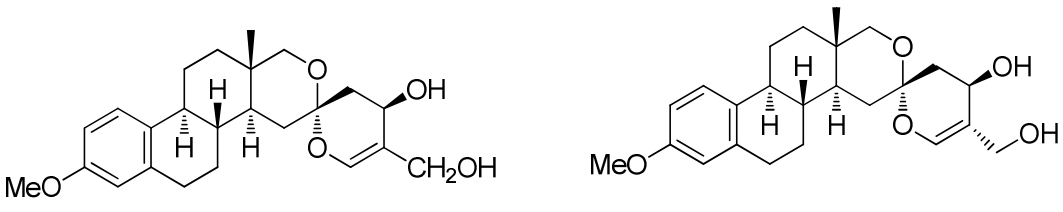
Many of these compounds are found to have spasmolytic and antiphlogistic activity [7] and antifeeding activity towards silkworm [8].



2 **3**

Figure 1.2**.** A series of spiroketals

Spiro-oxindole derivatives are found very widespread biological application like as antimicrobial, antitumor, antibiotic agents and inhibitors of human NK-1 receptor etc. [9]. Some of spiroacetals **4-5** show powerful cytotoxic activity against human cancer cells [10].



4 **5**

Figure 1.3. Some of spiroacetals show powerful cytotoxic activity against human cancer cells

1.1.3. Synthesis

A spiro compound contains mostly a carbon atom which contains two rings fused at a common point. The antithetic analysis of a spiro unit may lead to a large number of possible prestructs, which can be used for synthesis of target spiro molecules [1]. The spiro compounds can be obtained by using intramolecular cyclization, intra/inter molecular condensation. They can be also obtained by regrouping another polycyclics. Heterocyclic spiro compounds are produced by the methods used in synthesis of simple heterocyclic compounds [1].

1.2. PAUSON-KHAND CYCLOADDITION REACTION

1.2.1. The Stoichiometric Pauson-Khand Reaction

Metal-mediated reactions have played an important role for complex molecules in recently. Dicobalt hexacarbonyl complexes of alkynes are considerable stable to a wide variety of electrophilic and nucleophilic reagents. Five-membered carbocyles are very useful and powerful building blocks for the construction of complex biologically active molecules. Furthermore, many cyclopentenones (e.g. cyclopentenone prostaglandins) present a characteristic biological activity [11]. For that reason, the synthesis of five-membered rings has gained no match for the Pauson-Khand reaction which is very useful because of the potential flexibility for the atom economy [12].

I.U. Khand and P.L. Pauson, first reported in 1973, the cobalt-mediated carbonlylative [2+2+1] cycloaddition of an alkyne**,** an alkene and carbon monoxide to yield a cyclopentenone **6**, is allude to named the Pauson-Khand Reaction (PKR) [13]. A formal three-component, [2+2+1] cycloaddition, is the overall process,

incorporating the alkene π-bond, an alkyne π-bond, and the carbon atom of CO into a new five-membered ring [14].

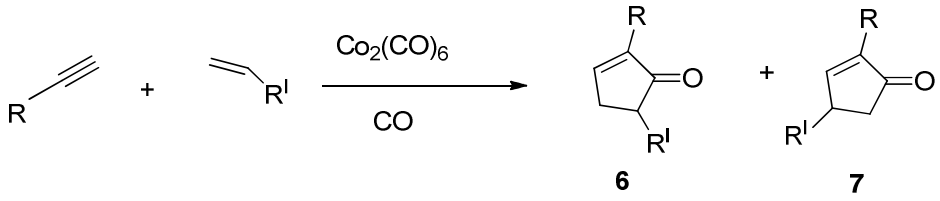


Figure 1.4. Pauson-Khand reaction

In the first successful Pauson-Khand reaction in which corresponding cyclopentenone 45% yields was obtained, is the conversion of norbornene with the phenlyacetylene-hexacarbonyldicobalt complex.

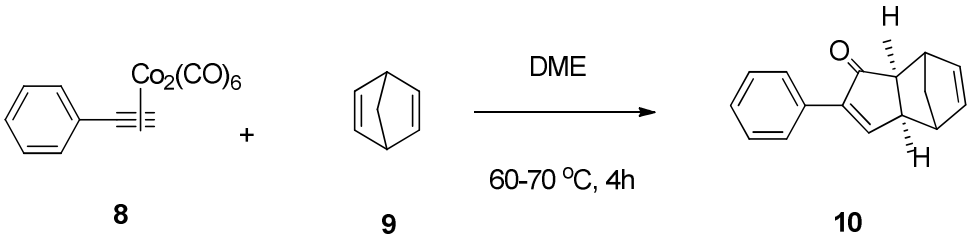


Figure 1.5. First example of Pauson-Khand reaction

Moderate cyclopentenone yields can be obtained by heating the premade alkyne-$Co_2(CO)_6$ with the alkene using Pauson-Khand reaction. Pauson-Khand reaction is resistant of extensive variety of functionality, such that; ethers, esters, tertiary amines, amides, nitriles and alcohols that makes it an important reaction for organic synthesis.

Although the Pauson-Khand reaction is able to tolerate many different functional groups, it also has many limitations. First of all, the reaction requires stoichiometric amount of $Co_2(CO)_8$ [15]. In addition of this stoichiometric amount, $Co_2(CO)_8$ is generally unstable and impure samples of commercial. $Co_2(CO)_8$ must be rigorously purified by recrystalization from degassed HPLC grade hexanes.

The other limitation of Pauson-Khand reaction is poor regioselectivity in the intermolecular reactions in which four constitutional isomers are observed and obtained the unsymmetrical alkynes and alkene. Isomers **6** and **7** are formed in intermolecular reaction. On the other hand, isomer **11** is not observed due to the bulky groups close to the carbonyl group. Besides, isomer **12** is observed in the intramolecular reaction. The stereochemistry of the complexation of an alkene at cobalt is guided by steric repulsions between the R and R groups, so that isomer **6** is favoured that was shown in figure 1.6 respectively.

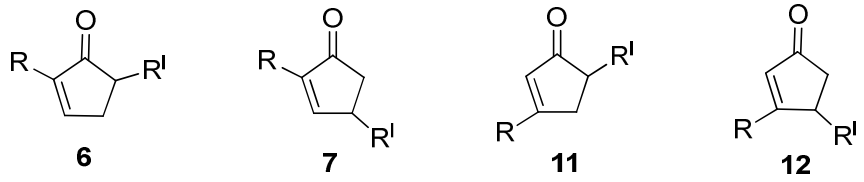
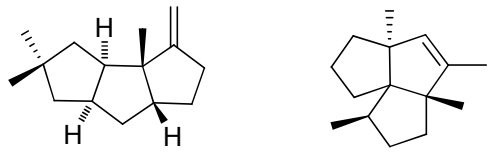


Figure 1.6. Four isomeric cyclopentenones

A natural product is a chemical substance or compound produced by a living organism that is found in nature usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. Natural products may be extracted from tissues, marine organisms or microorganism fermentation. Pauson-Khand reaction is the most useful and powerful tool to obtain cyclopentenone compounds.

Cyclopentenones are the compounds which present in a wide variety of natural products and interesting for the drug design and drug targets. Moreover, the cyclopentenone ring is very useful building block for the synthesis of biologically active compounds composed of cyclopentenone units the reason that functionality α-β-unsaturated carbonyl functionality. In addition to that they are also important mediates in Michael-type additions, conjugated 1,4-additions, or cycloadditions [16].

Cyclopentenone units are found in many important and huge number of product as a building block such as; prostanoids, jasmonoids, retrolones, and methylenomycins [17]. Some other important compounds are also triquinanes which are the subgroup of the polyquinanes; (-)-α-isocomene [18], hirsutene [19], ceratopicanol [20], epoxidictimene [21] and the most important one is prostaglandins [22].



Hirsutene

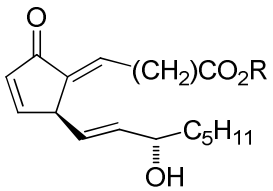
13

(-)-isocomene

14

Figure 1.7. Some important products including cyclopentenone units

Prostaglandins are hormone-like compounds found in widely all tissues and organs [23]. Prostaglandins play an important role in the human body functions and control a wide variety of physiological responses [24]. In recent years, working on biological activities of the 'cyclopentenone PGs' have increased because of these compounds have become very important role in therapeutic context.

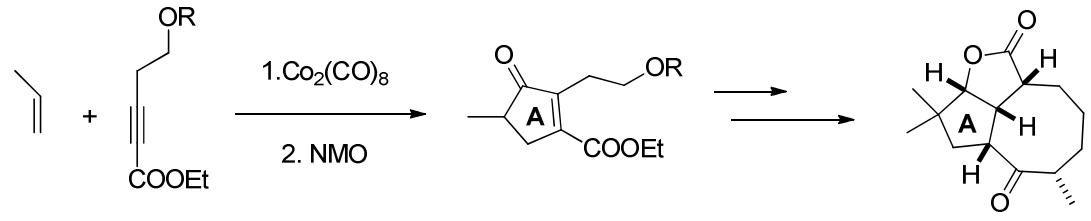


R=H
R=Me

15

Figure 1.8. Prostaglandin's hormone-like structure

One of the important groups of the cyclopentenone is 'Asteriscanolide' whose total synthesis was reported by Krafft related to 'epoxidictimene'. Main thing that based on the synthesis is regioselective intermolecular Pauson-Khand reaction with propene. Ring Closing Metathesis is the final step of the reaction shown in the figure below in which the formation of the cyclooctane ring is accomplished [25].



16 **17** **18** **19**

Asteriscanolide

Figure 1.9. Synthesis of Asteriscanolide

For 'Cedrene' skeleton an intermolecular Pauson-Khand reaction has been used as a key step. A monocyclic enyne was used as a starting material with an olefin fragment for the reaction. Consequently, a bridged material as a product was

obtained with a high yield that provides a total synthesis of α- cedrene **22** and β-cedrene **23** [26].

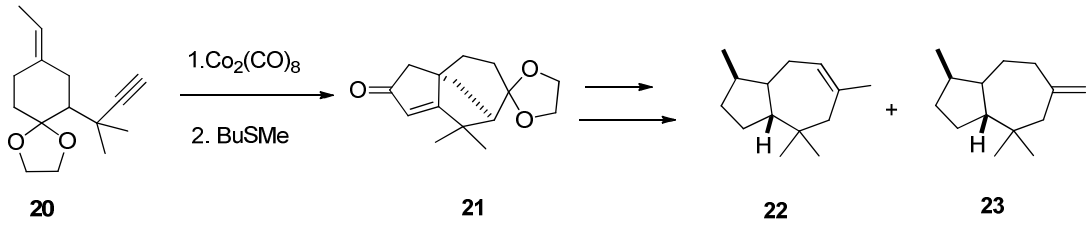


Figure 1.10. Synthesis of α- and β- cedrene

Mukai has influenced synthesis of the 8α-hydroxyatreptazolone in that the key step is an intermolecular Pauson-Khand reaction which was carried out on a 2-oxazolone derivative. Using of an enamine as the olefinic part in the reaction was implied by that. The Pauson-Khand reaction is highly stereoselective reaction because of that this compound is a natural product used in the antifungal and antibiotic activities [27].

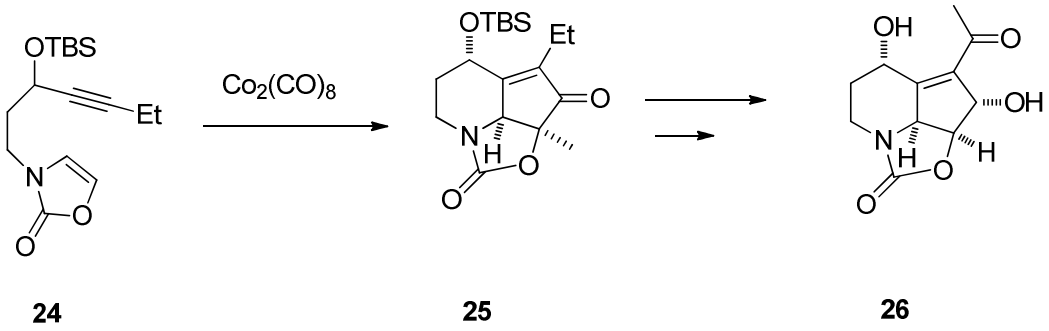


Figure 1.11. Synthesis of the 8α-hydroxyatreptazolone

Many rough conditions may affect the reaction transformation such as, high temperatures regularly cause to decomposition of substrates and/or products. While

the trisubstituted alkynes are often unreactive, terminal alkynes are more reactive then internal alkynes. Intermolecular Pauson-Khand reaction has limited selectivity and reactivity of the alkene components for that reason intramolecular Pauson-Khand reaction can be used to obtain good yields and develop the reaction. Together with the intramolecular Pauson-Khand reaction has gained much popularity, chiral cyclopentenone-pyran ring skeletons using carbohydrate templates has been reported [28].

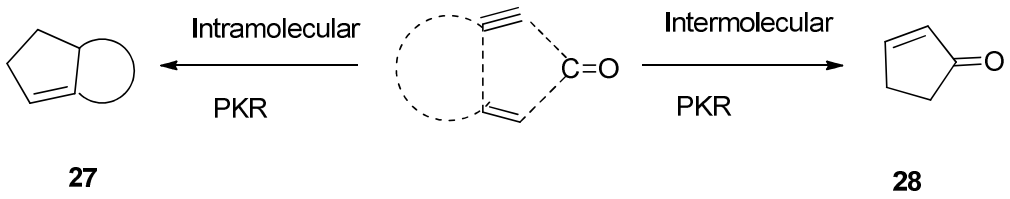


Figure 1.12. Intramolecular and intermolecular Pauson-Khand reaction

Pauson-Khand reaction first reported at the beginning of seventies, even though it was carried out thermally under relatively severe conditions, and led to transformations of mostly low efficiency. Till the mid-nineties, dicobalt octacarbonyl was the only cluster used to mediate the Pauson-Khand reaction. First examples of intramolecular Pauson-Khand reaction were introduced by Schore in 1981 [29]. Linked the alkene and alkyne moieties added to a carbon tether, resulted in a bicyclic product from an acyclic substrate. Many methods have been developed to overcome this situation. Schrider [30] and Jeong [31] first reported the improvement in the Pauson-Khand reaction. They found tertiary amine *N*-oxides that were useful promoters of the reaction. First step was loosing of CO ligand to lead coordination of alkene. This step of the reaction is needed to harsh conditions to reach thermally

promoted Pauson-Khand reaction. *N*-methlymorpholine *N*-oxide (NMO) is effective to reach harsh conditions in promoting Pauson-Khand reaction at room temperature, was found by Schreiber.

Jeong found both *N*-methlymorpholine *N*-oxide NMO and trimethlyamine *N*-oxide (TMANO). *N*-oxides have a function that could remove a CO ligand from the metal oxidatively as carbon dioxide and also using *N*-oxides in promoting of the Pauson-Khand cycloaddition provides much milder conditions in the transformation. The Pauson-Khand reaction can now be effected as asymmetrically, catalytically and on a solid support. Consequently, there has been a re-generation and re-emergence of the application of this reaction to the synthesis of natural products.

There are more promoters other than *N*-oxides such as, silica [32-33], amines [34-36], sulfides [37-38], and molecular sieves [39-41]. Even though these promoters exist and have being used, *N*-oxides are widely used.

1.2.2. Catalytic Pauson-Khand Reaction

In Pauson-Khand reaction other transition metals can be used other than cobalt metal complexes. In general Pauson-Khand reaction octacarbonlydicobalt is widely used and it is a starting point of catalytic PKR. On the other hand, the other transition metals, which are titanium, ruthenium, rhodium and iridium, can be used as metal complexes mentioned in the beginning on the catalytic Pauson-Khand reaction.

1.2.3. The cobalt-catalyzed Pauson-Khand Reaction

According to the literature cobalt is widely used as metal catalyst in Pauson-Khand reactions containing as $Co_2(CO)_8$, $[Co_2(CO)_8/P(OPh)_3]$, [(indenly)Co(cod)]

and [$Co(acac)_2/NaBH_4$] under CO pressure [42]. First examples of catalytic cycloaddition reaction were reported by Rautenstraunch *et. al.* [43] as used non-strained alkenes, and was obtained 0.22 mol % of catalyst [$Co_2(CO)_8$] under high carbon monoxide pressure and ethylene in 48% chemical yield **18**. It was an example of intermolecular Pauson-Khand reaction.

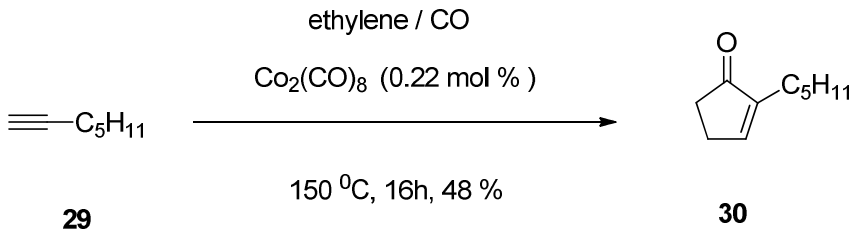


Figure 1.13. Cobalt-catalyzed under high pressure of CO and ethylene

1.2.4. The Intermolecular Pauson-Khand Reaction

First intermolecular Pauson-Khand reaction was discovered in 1971 [15a]. Although the Pauson-Khand reaction was first discovered in its intermolecular form, the capacity of intermolecular reaction in synthetic projects and works has been limited by the poor selectivity and reactivity of simple alkenes at all times [44]. Maximizing of the synthetic attractiveness of Pauson-Khand reaction has elevated this powerful reaction to a method of choice in the synthetic planning of complex biologically active molecules, by using catalytic intermolecular Pauson-Khand reaction would use in which to develop of an efficient, versatile, environmentally friendly reaction [45]. Studies have been limited to use of strained alkenes such as norbornene, norbornadiene and bicyclo[3.2.0.]hept-6-ene, while the thermodynamically more favoured, using intermolecular type has gained most interested [46]. Even though substituted ethylenes and some cyclic olefins for

example; cyclopentenes or dihydrofuranes can respond the reaction, in many occasions the yields using unstained olefins are low. In the early studies of the intermolecular Pauson-Khand reactions, the reason of obtaining the low yields and poor selectivity was due to being used of unsymmetrical alkynes and alkenes [12].

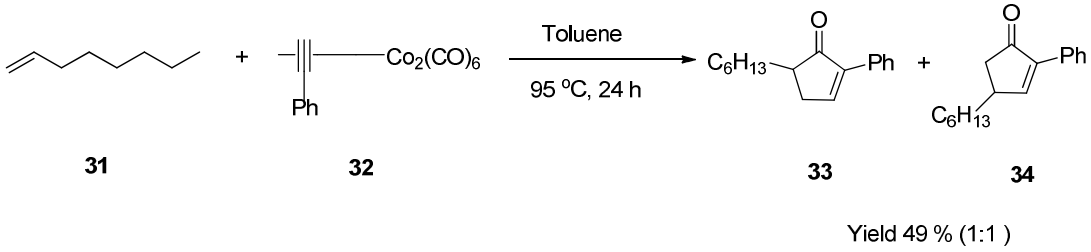


Figure 1.14. An intermolecular Pauson-Khand reaction of a terminal alkene

In order to synthesize synthetically powerful, useful and also selective cyclopentenone compounds, symmetrical and active alkenes have been used in recent years. The bulkier substituents of the alkyne are placed to the carbonyl in the cyclopentenone products as to the regioselectivity [47].

Furthermore, the important and fundamental improvement of intermolecular form of Pauson-Khand reaction was begun by Krafft in 1988 [48]. The way of Krafft *et. al.* followed is the secondary interactions which occurred between the molecules were generally used to optimize and increase the rate or /and the selectivity of that reaction [49]. Examples of that issue, hydrogen bonding or Lewis acid-base interactions protected in the chemical transformation time and let it to be a highly ordered transition state which often yielded important changes in the rate and selectivity of the reaction [44].

Krafft and his co- works, who considered the recommended mechanism,

found that a heteroatom tethered to the alkene by a carbon chain that coordinate to cobalt, and also controlled the regioselectivity of the suggested reaction.

It is known that bidentate olefinic ligands could afford the mechanism to obtain high yields from products. According to that; sulphur, oxygen and nitrogen substituted alkenes have better activity on Pauson-Khand reaction also, they give better yields and regioselectivity than alcohols and methoxymethyl ethers substituted alkenes [47]. It must be mentioned that the oxygen containing olefins, give poor regioselectivities. Furthermore, it is known that the chain length extension between the heteroatom and the alkene declines regioselectivity [48].

The initial step was the dicobalt octacarbonyl, $Co_2(CO)_8$, reacted with the alkyne to obtain dicobalt hexacarbonyl, $Co_2(CO)_6$-alkyne complex, **35**, that was just intermediate in the mechanism. After that, loosing of one of the CO ligands, and then joining of the alkene bond into a carbon-cobalt bond to form complex **36**. After that step, CO addition to complex **37**, and so joining of another of CO and Co(CO) unit **38** was reduced and eliminated to obtain complex **39**. Consequently, cyclopentenone unit **6** was obtained to the dissociation of the dicobalt unit [42].

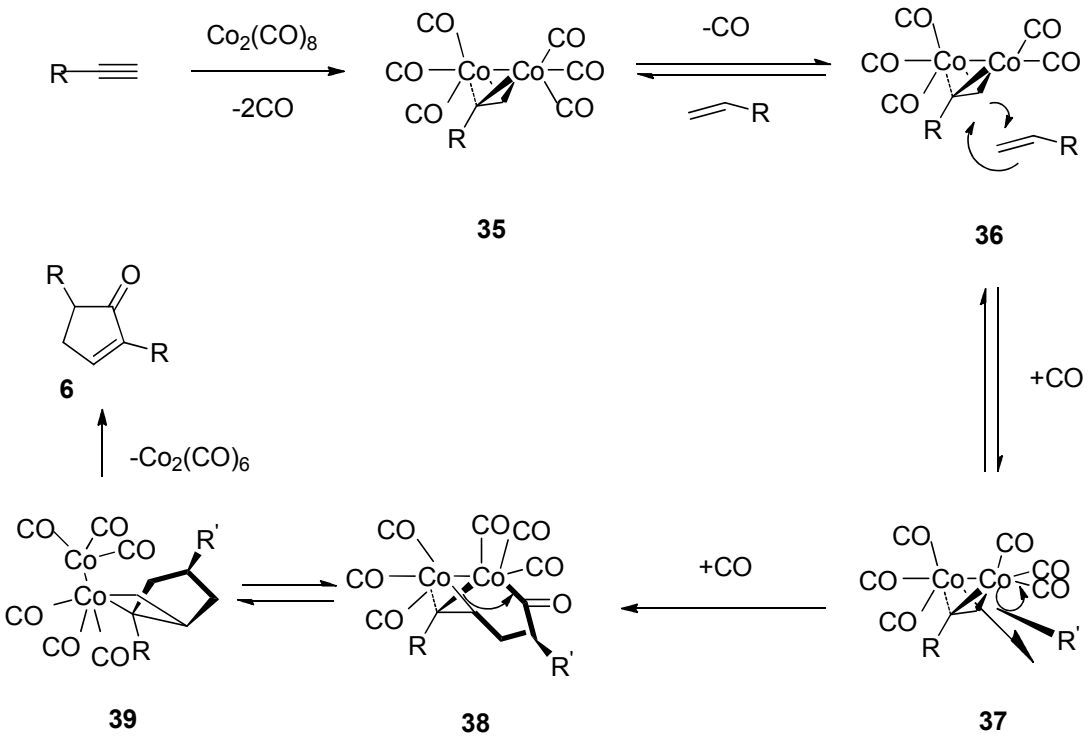


Figure 1.15. Proposed mechanism of the intermolecular Pauson-Khand reaction

Another studied that had been obtained in this field was reported by Carretero and his workers in 2003. The importance of this study was that the first study worked on the asymmetric synthesis of the Pauson-Khand reaction through chiral sulfoxides [50]. Using of chiral 2-(*N,N*-dimethylamino) phenyl vinyl sulfoxide **41** as an alkene gives high stereo selective and regioselective products [47]. Besides to this using *ortho*-amino-substituted sulfoxide ***(R)*-30** (-)-pentenomycin **43** was enhance and developed [50].

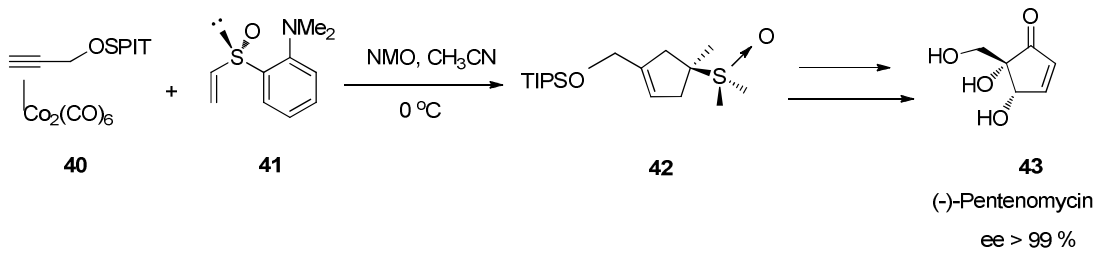


Figure 1.16. Synthesis of (-)-pentenomycinI

Consequently, scientist has been making lots of works on the Pauson-Khand reaction especially in intermolecular Pauson-Khand reaction which is environmentally friendly, asymmetric and catalytic types of Pauson-Khand reaction [44].

1.2.5. The Intramolecular Pauson-Khand Reaction

In the first part of general Pauson-Khand reaction, it was mentioned that the Pauson-Khand reaction is able to tolerate many different functional groups, it also has many limitations. Many rough conditions may affect the reaction transformation such as; high temperatures regularly cause to decomposition of substrates and/or products. Another problem is regioselectivity. On the other hand, one of the most important advantages of this methodology is that the regiochemistry which is predetermined by the position of the substituent in the enyne as a starting material, while the carbonyl group is introduced to the one of the terminal carbon atoms of the alkene and also to the alkyne where the cobalt atoms are placed to close in the transition state [51].

Schore and Croudace was reported an important development in intramolecular Pauson-Khand reaction in 1981 which was known that first example of intramolecular form of Pauson-Khand type reaction. In this process, the natural

products which showed biological activity and were the derivatives of bicyclo[3.3.0]octane ring system **45**, was synthesized straight from acyclic starting materials with complete regioselectivity [52]. The mechanism of intramolecular Pauson-Khand reaction is also so familiar to the mechanism of intermolecular Pauson-Khand reaction.

The only intermediate that has been isolated is the initial, stable alkyne-$Co_2(CO)_6$ complex. It is assumed that the next step involves dissociation of a CO ligand and coordination of the alkene. The alkene then irreversibly inserts into one of the cobalt-carbon bonds. This step is thought to be rate-determining as well as product-determining. Migratory insertion of a CO ligand bound to cobalt to form the carbonyl moiety and reductive elimination of the $Co(CO)_3$ fragment follows. Loss of the $Co_2(CO)_6$ fragment liberates the cyclopentenone product.

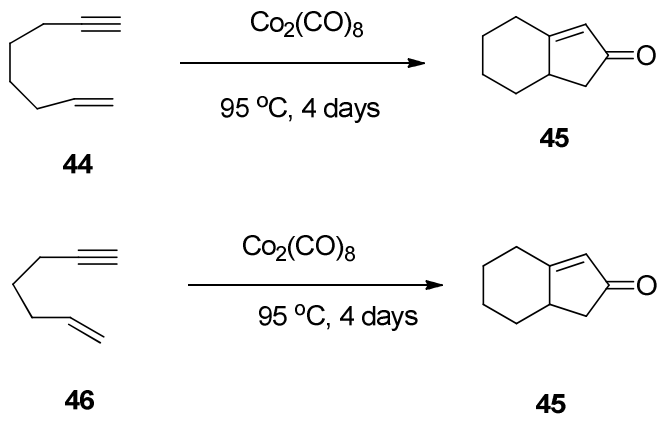


Figure 1.17. The intramolecular Pauson-Khand reaction.

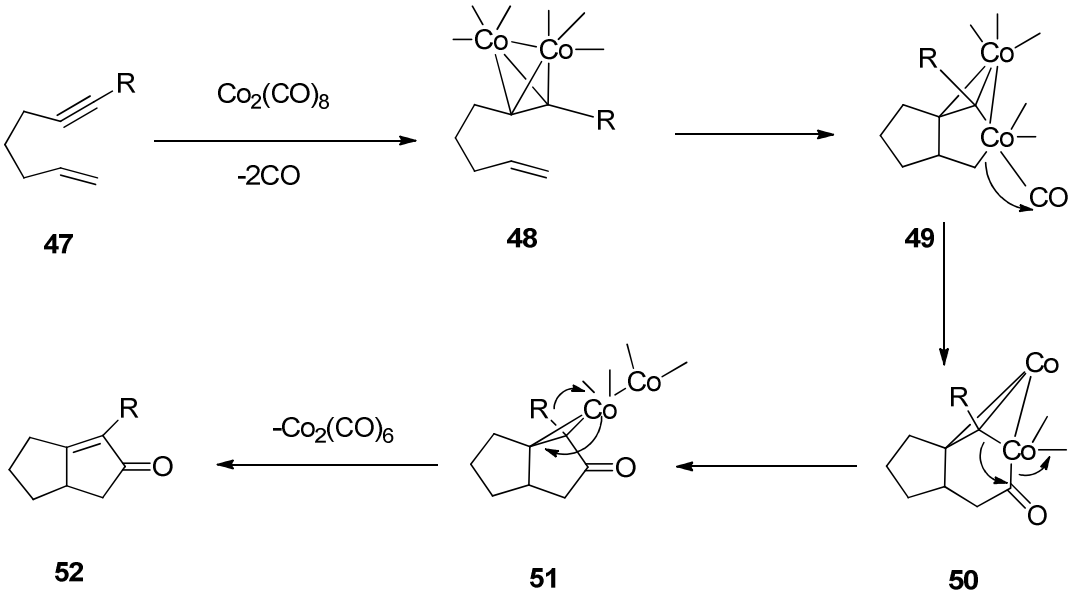


Figure 1.18. The mechanism of intramolecular Pauson-Khand reaction

Jeong. *et. al.* [53] first reported effective intramolecular Pauson-Khand reaction by using triphenylphosphite as an additive with $Co_2(CO)_8$ in which the compound **54** is obtained in 82% yield under high pressure carbon monoxide and also at high temperature.

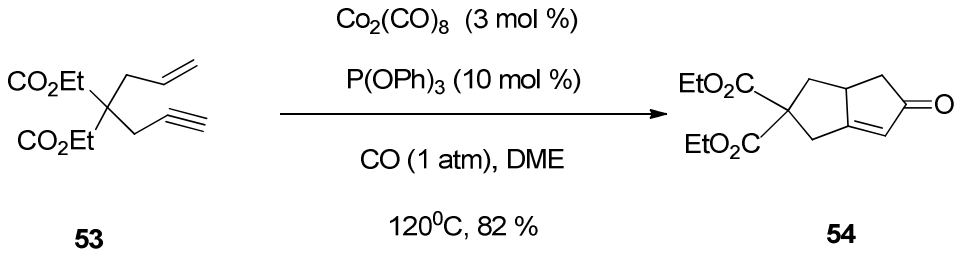


Figure 1.19. Cobalt-catalyzed with triphenylphosphite as an additive

After this claim they also improved another way to obtain compound **54** by using a 1,5-cyclooctadiene(indenyl)cobalt(I) complex [54] as a catalyst again in a

high carbon monoxide pressure and 100 ^{0}C.

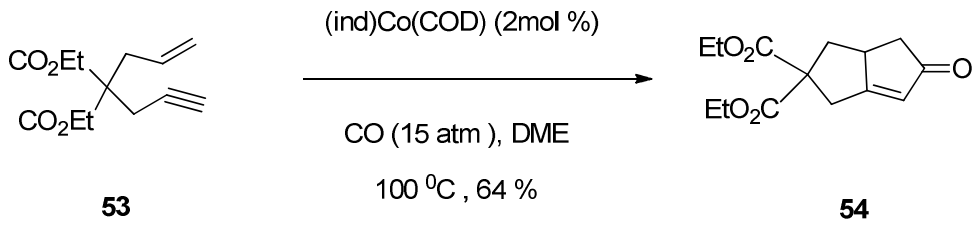


Figure 1.20. 1,5-cyclooctadiene (indenyl)cobalt(I) complex-catalyzed under CO

Livinghouse *et. al.* reported photochemical [55] and thermal [56] version of a catalytic system of Pauson-Khand reaction [55-56]. He applied the technique to promote an efficient Pauson-Khand reaction using $Co_2(CO)_8$ under CO pressure, both exposing to high intensity irradiation and heating at the same time [42]. Consequently, the photo chemically promoted Pauson-Khand reaction was found more efficient than the thermal variation [42].

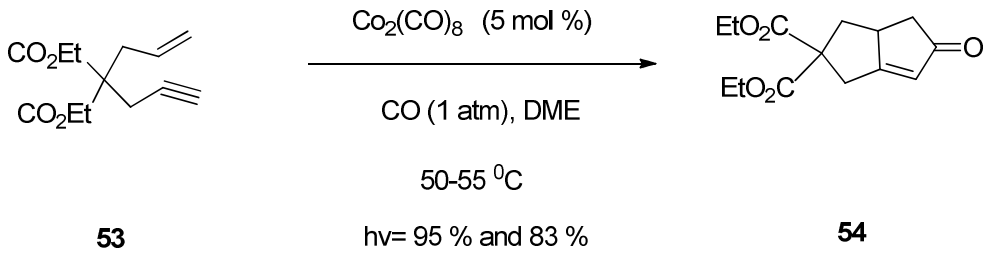


Figure 1.21. Photochemical and thermal version of catalytic system

The other study as mentioned in the beginning of the catalytic Pauson-Khand reaction using [$Co(acac)_2$/$NaBH_4$] under CO pressure, was reported by Chung [57]. This combination is consist of $Co(acac)_2$ and $NaBH_4$ and highly efficient to promote

intramolecular and intermolecular Pauson-Khand reaction cycloaddition under high carbon monoxide pressure.

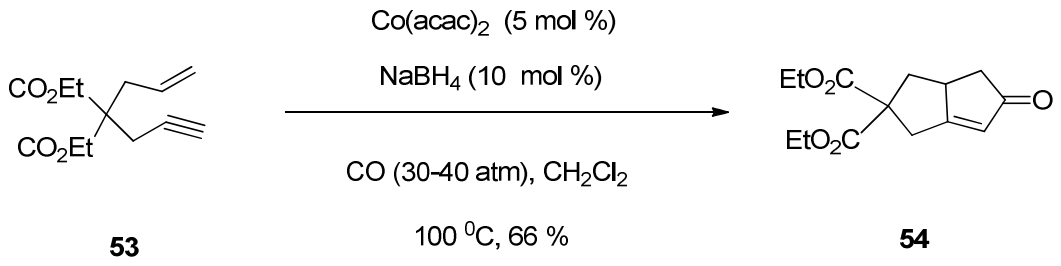


Figure 1.22. Alternative cobalt catalyst, $Co(acac)_2$

Jeong [31a] and Schreiber [30a] found two independent groups which accelerated the Pauson-Khand reaction. Addition of *N*-oxide derivatives, for example, *N*-methylmorphine *N*-oxide (NMO) and trimethylamine *N*-oxide (TMO) is also known accelerating agents of Pauson-Khand reactions, gives the high yields of cyclopentenone **54** syntheses at room temperature. CO is removed with the help of the *N*-methylmorphine *N*-oxide (NMO) and trimethylamine *N*-oxide (TMO) from the transitions metals oxidatively as Co_2 [14,29,58].

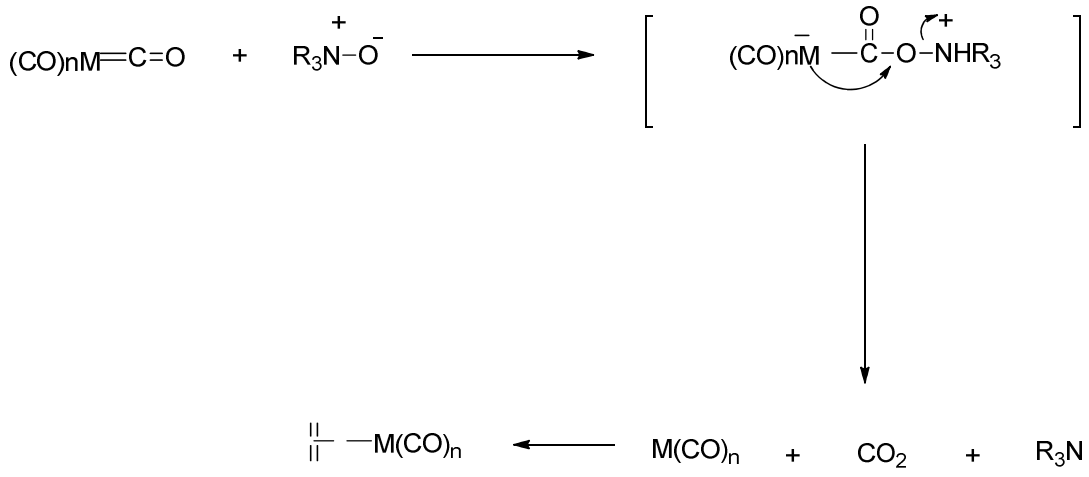
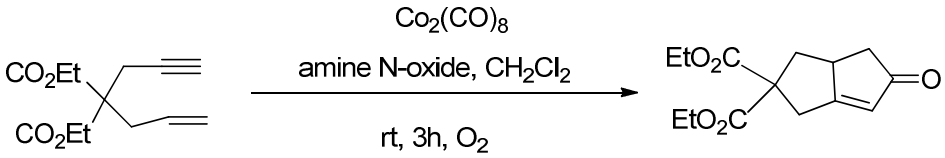


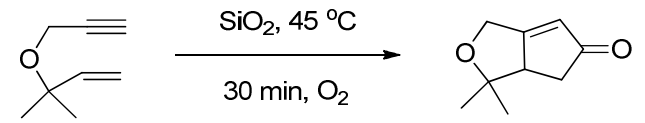
Figure 1.23. The mechanism of formation of N-oxides

These promoting agents were very helpful and useful for Pauson-Khand reaction because there had been still problems which the reaction required high temperature about 60-120 ^{o}C and very long reaction times about 6h-4 days [14]. These problems were solved as we told by Jeong [31a] and Shreiber [30a]. Other accelerating agents other than *N*-oxides are such as, silica [32-33], amines [34-36], sulfides [37-38], and molecular sieves [39-41], to yield cyclopentenones 56 and **58.**

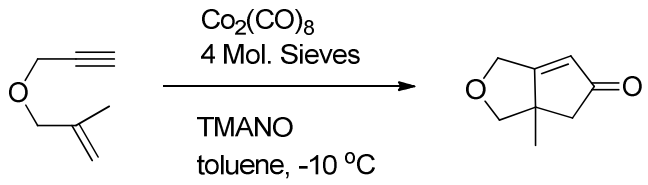


53 **54**

Figure 1.24. Effect of additives to the Pauson-Khand reaction



55 **56**



57 **58**

Figure 1.25. The intramolecular Pauson-Khand cycloaddition reactions

The only example of Pauson-Khand reaction which was performed on a solid support in the intramolecular types was reported by Bolton [59]. The examples that

were reported by Bolton, azabicyclo[4.3.0]nonen-8-one systems were quickly synthesized via a polymeric bead. Bolton also added a propargyl or an allyl α-amino acid into the polymeric support through an ester linkage. Using either *N*-methylmorphine *N*-oxide (NMO) or and trimethylamine *N*-oxide (TMO) as promoters, the eyne was formed and the cycloaddition was occurred through the cobalt complex. The reaction was followed by the esterification of the obtaining acid that afforded Pauson-Khand cycloadducts **60** and **62** in high and good yield 38-88% from the eyne. By this method it was shown by the Bolton the eyne could be diversified at the time attached to the resin leading the way to development of combinational derivatives [46d].

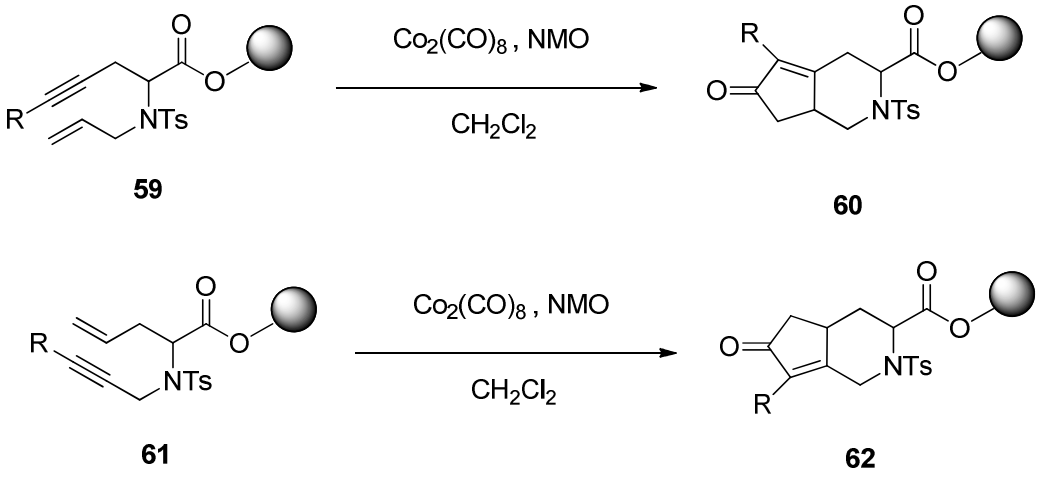


Figure 1.26. Esterification of acid afforded Pauson-Khand cycloadducts

1.2.6. Spiro cyclopentenone-pyran via Pauson-Khand Reaction

'Pyran' or 'Oxide' word is referred to a six-membered hetereocyclic, non-aromatic ring, consisting of five carbon atoms and one oxygen atom and containing two double bonds. Even though the pyrans themselves have little significance in chemistry area or in their single usage, many of their derivatives have important biological activity and importance using as building blocks such as pyranflavanoids.

Consequently, Prostaglandins have importance because of containing cyclopentenone rings and containing cyclopentenone ring derivatives. In this time cyclopentenone ring's importance and the spiro type compounds importance make influenced us to obtain spiro-cyclopentenone derivatives which is used in psychological diseases treatment and some of the derivatives used as anti-cancer drug treatment.

1.3. OLEFIN METATHESIS

1.3.1. Introduction

The term of 'metathesis' or 'olefin metathesis' was first introduced by Calderon in 1967 to define the double bonds which was subjected to the catalytic disproportionation shown in figure below [60].

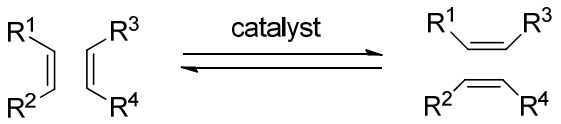


Figure 1.27. Metathesis of two olefinic bonds.

The reaction was firstly observed by the Ziegler-Natta in 1950s while the polymerization processes [61]. DuPont, who was an industrial chemist, found alumina-supported molybdenum species, catalyzed the transformation of propene turn to 2-butenes and ethylene and finally the polymerization of cyclopentene and norbornene which were polymers not found so far [62]. These founds were followed by the using improved catalytic systems which were based on molybdenum and

tungsten, either catalyzed the polymerization of cycloolefins or the dismutation or changing of linear olefins [63].

1.3.2. Mechanism of Olefin Metathesis

In 1971, supporting by the other scientists [64], Chauvin using the early studies, proposed a mechanism that was supported by the experimental evidence [65]. In general reaction, this mechanism is made up of a sequence of [2+2]-cycloadditions and cycloreversions shown in figure 1.28. Accordance of an olefin to a metal alkylidene species (**I** ⟶ **II**), forming a metallacyclobutane complexes (**III**) and then subsequent releasing of a dissimilar olefin, concludes in the formation of new metal alkylidene (**IV**).

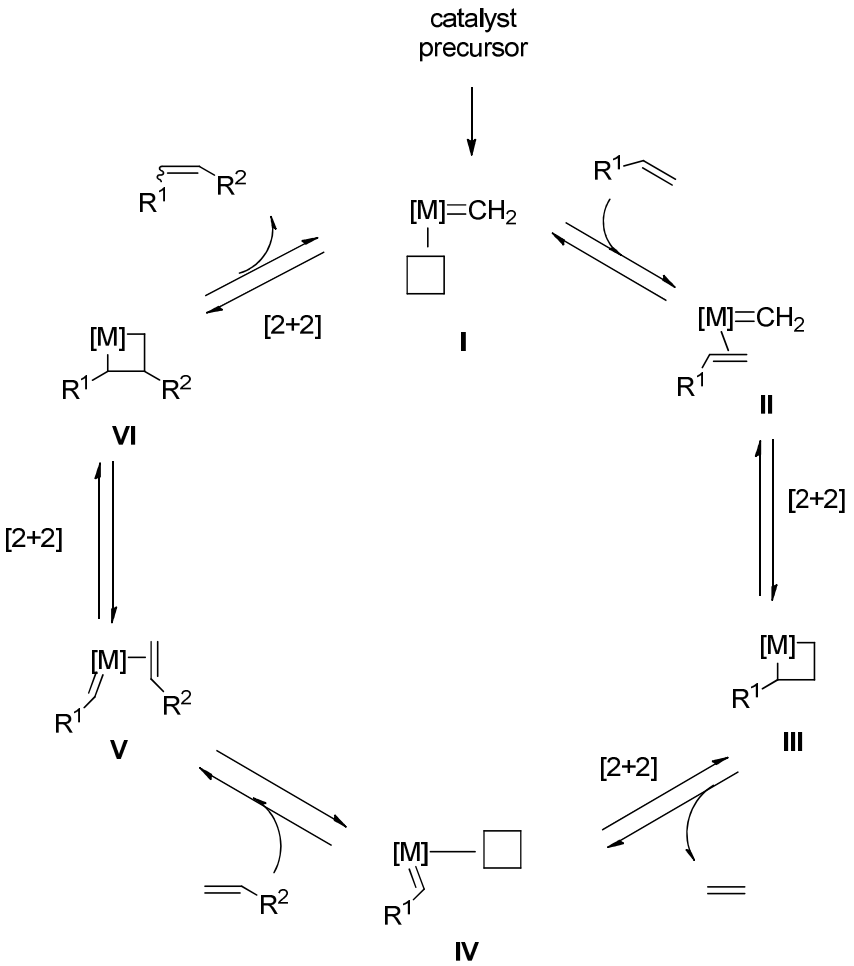


Figure 1.28. Mechanism of transition metal-catalyzed olefin metathesis

1.3.3. Well-Defined Catalytic Systems in Olefin Metathesis Reaction

In well-defined homogeneous or heterogeneous catalyst systems till the mid-1970s was used in olefin metathesis. Katz published the first well-defined metal carbine in 1976. The $[W(CO)_5(=CPh_2)]$ (shown in the figure as Katz 1975) complex shown below in the figure 1.29, introduced metathesis which was varied di- and trisubstituted cycloalkenes and *E*- and *Z*-2-pentenes [66-67]. At that time, Schrock and his co-workers had started their work on high-oxidation state metal alkylidene complexes that were examined in the presence of olefins [68]. The development of Nb/Ta-complexes catalyzed the metathesis of *cis*-2-pentene in 1980.

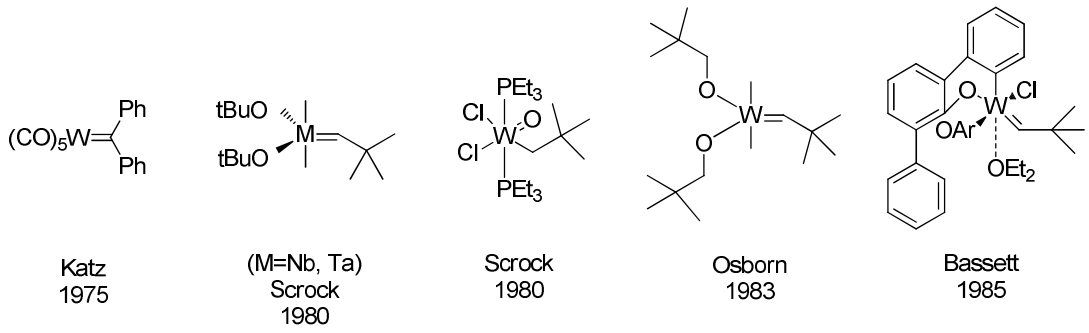


Figure 1.29. Early olefin metathesis catalysts.

In early results that poorly showed the high-oxidation state W-based systems offered that alkylidene complexes of group 6 transition metals (i.e. W and Mo) can be used as active catalyst for olefin metathesis [69]. The very first stable W-alkylidene complexes were reported in 1980s by Schrock [60], Osborn [61], and Basset [62]. Consequently, it was reported by Schrock in 1990 a range of imido alkylidene species where two bulky alkoxide ligands provided to the proportional stability of the complexes. These compounds have been still using actively in this

day time in numerous organic synthesis and they are the most commercially active catalysts as well.

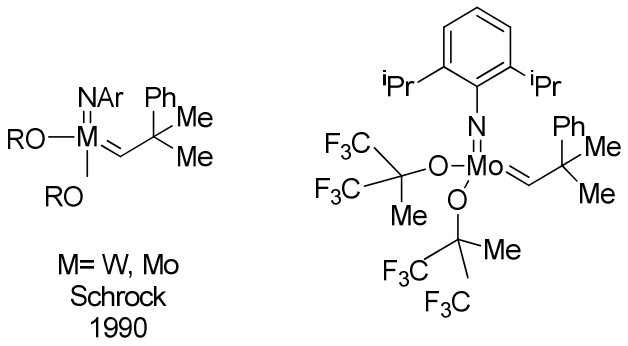


Figure 1.30. General structures of Schrock catalyst and the currently commercially available version.

The disadvantages of Schrock catalyst are unsuited with the number of polar functional groups and also they show high sensitivity to air in inert atmosphere. After that, it was investigated more effective and important catalyst by Grubbs in 1992 [69]. Instead of Tungsten and Molybdenum, Ruthenium metal complex was used by Grubbs [70]. In 1992 the first catalyst investigated by Grubbs is not as active as molybdenum catalyst; however, it is air-stable like a solid and also moderately resistant to water, alcohols and acids [70b]. The best result obtained in 1995 by Grubbs after investigation of 1992. The catalyst was not only the available to synthetic method but also higher than the dipenylvinylcarbene that is investigated in 1992 [71].

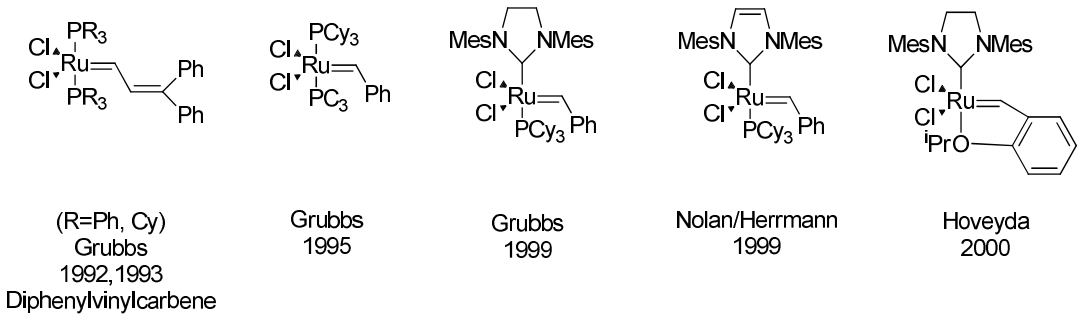


Figure 1.31. Different Ruthenium-based olefin metathesis catalysts

1.3.4. Grubbs Catalysts

Grubbs catalysts are a series of transition metal carbine complexes which are used as catalyst in olefin metathesis. Robert H. Grubbs first synthesized them that the reason it was named as Grubbs catalyst. In the industry and research laboratories two kind of Grubbs catalyst are used, named as first generation Grubbs catalyst and second generation Grubbs catalyst shown in the figure 1.32 as below [72]. Grubbs' catalysts have become more popular because of the fact that they tolerate the other functional groups in the alkene, and they are air-tolerant and also compatible with an extensive range of solvents [73].

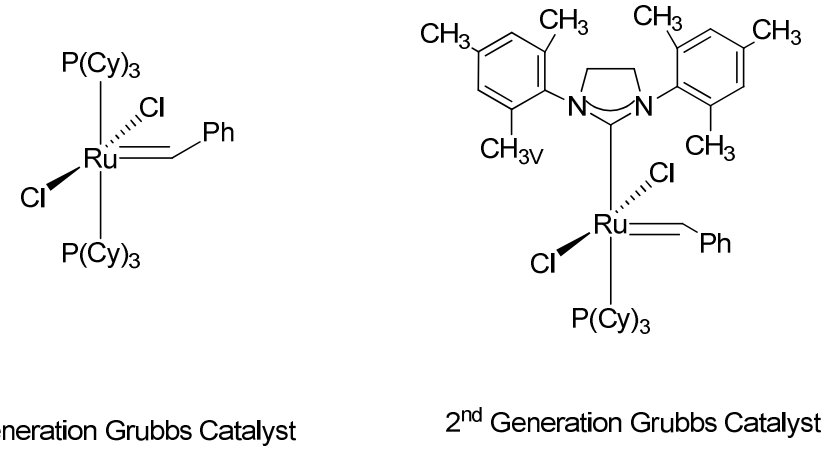


Figure 1.32. First generation and Second generation Grubbs Catalyst

1.3.5. First Generation Grubbs Catalyst

In organic synthesis the First Generation Grubbs catalyst is generally used in olefin-cross-metathesis, ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization (ADMET) and ring-closing metathesis (RCM). The First Generation Grubbs catalyst is obtained synthesising from $RuCl_2(PPh_3)_3$ [74], phenyldiazomethane and tricyclohexylphosphine in one step synthesis [75]. The IUPAC name of first generation grubbs catalyst is 'benzylidene-bis(tricyclohexylphosphine)dichlororuthenium'. It has a good activity in synthesize processes and also is relatively stable in air that makes handling very easily.

Although it has a good activity as we mentioned before the first generation grubbs catalysts made in 1992-1993 and the other one 1995 (shown in the above figure 1.31) they are less active then molybdenum-based Schrock catalysts.

1.3.6. Second Generation Grubbs Catalyst

In 1999, Grubbs and the other scientist had developed a new generation catalyst which made by substituting one phosphine by a more strongly electron-donating group *N*-heterocyclic carbene (NHC) ligand, resulted a new catalyst named 'Second Generation Grubbs Catalysts'. The Second Generation Grubbs Catalyst is more active than the first generation catalyst that is caused by the NHC ligands which is helped to increased metathesis activity of PC_{y3}-substituted catalysts [70]. This catalyst has sensitivity to air and water so that it must be handled under a nitrogen or argon atmosphere. The IUPAC name of second generation Grubbs catalyst is 'benzylidene[1,3-bis-(2,4,6-trimethylphenyl)imidazolidine)'. The one of the second generation catalysts was made in 1999 (shown the figure 1.31) thus far is the most reactive and active early transition-metal catalyst [76, 77, 78]. One of the

first and significant adaptations of Grubbs second generation catalyst [79] was reported by the group Hoveyda in 2000 [79]. After that modification, many of modifications was reported and worth examples of that phosphine-free complex by Grubbs [80] and the 14 electron complex by Piers [81].

In recent years The First and Second Generation grubbs catalyst have been used in commercially available in industry and research laboratories used in olefin metathesis reactions. In 2005, the revolutions in this area resulted by using of metathesis catalyst were recognized by the Royal Swedish Academy Of Sciences, awarding the Nobel Prize in chemistry to Chauvin, Schrock and Grubbs [82].

1.3.7. Types of Olefin Metathesis Process

Last attention has been documented for olefin metathesis, particularly in the past 20 years. Extensive research in this area has resulted in fruitful discoveries in more efficient catalysts and new applications. Several classes of olefin metathesis including;

- Cross Metathesis (CM)
- Ring-Opening Metathesis (ROM)
- Ring-Closing Metathesis (RCM)
- Ring Opening Metathesis Polymerisation (ROMP)
- Acyclic Diene Metathesis (ADMET)

1.3.8. Cross Metathesis (CM)

Cross Metathesis (CM) is in that two different olefins react to obtain a new product olefin and also a by-product as a volatile olefin (generally ethylene) [83]. Using simple alkene precursors, it can be obtained and routed to functionalize and

higher olefins with olefin cross metathesis (CM). Olefin cross metathesis (CM), on the other hand, represents an understudied area. Low yields and unpredictable reaction scope make many chemists reluctant to incorporate CM into a complex, target-oriented synthesis plan, especially as a late stage strategy. Indeed, issues such as alkenes' stereo selectivity and cross product selectivity associated with CM are inevitable challenges dictated by the unique mechanism of olefin metathesis [84].

Two major issues are important in cross metathesis which must control homodimerization due to obtain useful yields and the other one *E/Z* ratios are hard to control and predict [85].Olefin metathesis is a thermodynamically controlled process. Although the thermodynamically favoured trans olefins are usually the major products, a mixture of *E*, *Z* isomers can be obtained when the energy difference between them is small.

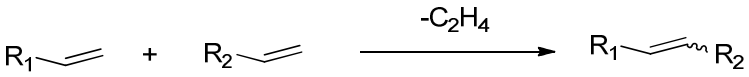


Figure 1.33. General Cross Metathesis Reaction

1.3.9. Ring-Opening Metathesis (ROM)

Ring-opening metathesis (ROM) in which a cyclic olefin and an acyclic olefin produce a new cyclic olefin [86]. Ring-opening of strained cyclic olefin to give open chain metal carbine provides driving force in the ring-opening metathesis. Using terminal olefin is resulted in exclusive formation of monosubstitued diene; yet *E/Z* ratios are low. Functionality in the substrate is decided by selection of catalyst.

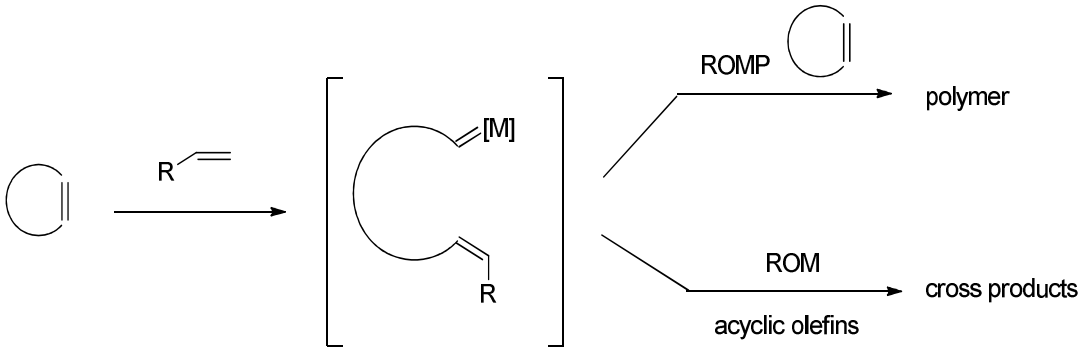


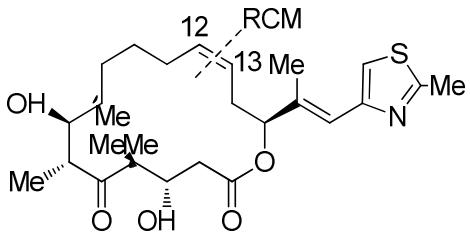
Figure 1.34. General Ring-Opening Metathesis reaction

1.3.10. Ring-Closing Metathesis (RCM)

In olefin metathesis, there are number of metathesis that help to obtain many organic compounds substances from nature or synthetically. Using transition-metal catalyzed olefin metathesis [87] has been increased and reached the high degree of attention in recent years. A number of synthetic transformations are visualized, based on the metathesis of two olefinic bonds consistent with the Chauvin mechanism. Metathesis process is a reversible process, the starting materials and products are in equilibrium. Most ruthenium-based catalyst catalyze both intermolecular and intramolecular reactions between one double and one triple bond (enyne metathesis) for instance the catalysts that are found by Grubbs in 1995-1999 and by Hoveyda 2000 shown in the figure 1.31 above [88]. Ring closing metathesis is the most powerful method for ring formation recently.

The intramolecular ring-formation version (the ring-closing metathesis) [89] is the most widely used and variant that is allowed the synthesis of both carbocyclic and hetereocyclic ring systems [90]. Moreover, in all functional groups even in sensitive molecules, the reaction conditions are smooth [91].

Early examples of ring closing metathesis, which represent a class of potent anticancer agents, are the synthetic investigations in macrocyclization [92]. Given an example of that, the complete synthesis of epothilone C has been a favourite subject of research area, with many approaches depending on the formation of the C12-C13 connection by the Ring closing metathesis in figure 1.35 [93].



epothilone C

Figure 1.35. Structure of epothilone C[38,39]

Consequently, Hirama and his co-works had given an exciting illustrations of the powerless of ring closing metathesis that is the total synthesis of the marine polyether ciguatoxin CTX3C (figure 1.36). That complex, neurotoxin, was synthesize by ring closing metathesis , containing thirteen fused hetereocyclic rings together with the nine-membered ring F being closed at the last stage of the synthesis [94].

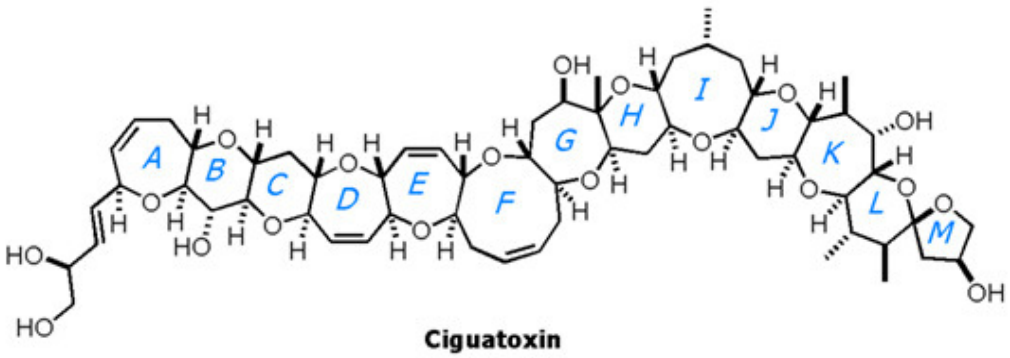


Figure 1.36. Ciguatoxin CTX3C[40]

Ring closing metathesis is the one that we use in our experiments to achieve dihydrofuran and dihydropyran compounds' derivatives. Moreover, it has been used in many organic syntheses by the researcher so many years.

1.3.11. Ring-Opening Metathesis Polymerization (ROMP)

Ring-opening metathesis polymerization (ROMP), in which a cyclic olefin is the substrate and a polymer is the product [95]. In this metathesis, industrially important products can be obtained. ROMP is thermodynamically favoured for strained ring systems, such as 3-, 4-, 8- and larger-membered compounds. Ring strain is the driving force in this metathesis because of the ROMP catalytic cycle requires a strained cyclic structure. There are many metal catalysts that are used in ring-opening metathesis polymerization process such as Grubbs catalyst is used based on the ruthenium. The ring then opens giving the beginning of the polymer: a linear chain double bonded to the metal with a terminal double bond as well. The new carbene reacts with the double bond on the next monomer, thus propagating the reaction [96].

Figure 1.37. General Ring-Opening Metathesis Polymerization Mechanism

Consequently, the main idea in the Ring-opening metathesis polymerization (ROMP) uses metathesis catalysts to generate polymers from cyclic olefins. ROMP is most effective on strained cyclic olefins, because the relief of ring strain is a major driving force for the reaction and Ring-opening metathesis polymerization has achieved some commercial success, with a variety of ROMP polymers available on the market place and the industry.

1.3.12. Acyclic Diene Metathesis (ADMET)

Acyclic diene metathesis is another special type of olefin metathesis that is used to polymerize from terminal dienes to polyenes. This process is reversible because of it is actually a variation of on cross-metathesis which is ethylene must be removed to drive the polymerization to completion. In this process, so high purity monomers are usually necessary to obtain high molecular weight polymer. New double bonds can be formed in cis- or trans- configuration besides; exact ratio depends on the monomer and catalyst structures which are used. However, ring-opening metathesis polymerization is chain growth addition polymerization; acyclic diene metathesis is step growth polymerization process [97].

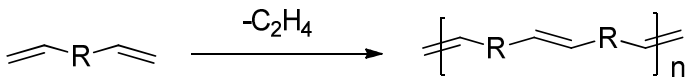


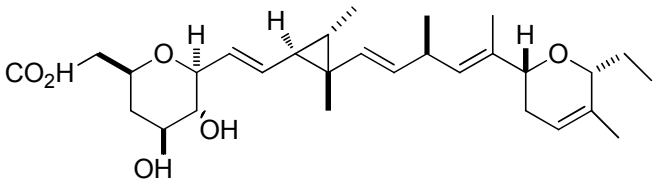
Figure 1.38. General Acyclic Diene Metathesis Mechanism

ADMET has been used in the synthesis of very attractive polymers because of the fact that it requires higher degree of control other than in usual radical polymerization. It has been used to synthesize model polymers which could be difficult to prepare. Some of the examples that are obtain whit this process are purely linear polyethylene and block copolymers of ethylene with a number of other vinyl polymers [98]. New supramolecular structures are synthesized with ADMET due to tolerance of ruthenium-catalyzed process which has high functional group tolerance [99].

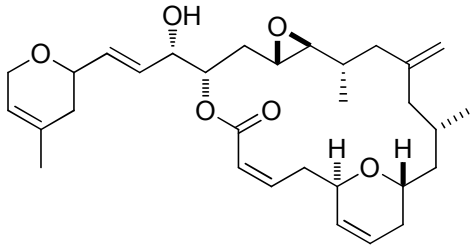
1.3.13. Using Grubbs Catalyst Obtaining Pyran Derivatives via Ring Closing Metathesis

'Pyran' or 'Oxide' word is referred to a six-membered hetereocyclic, non-aromatic ring, consisting of five carbon atoms and one oxygen atom and containing two double bonds.

'Furan' is a heterocyclic organic compound consisting of a five-membered aromatic ring with four carbon atoms and one oxygen atom. The class of those compounds is also named as furans. Dihydropyrans are found in a variety of biologically active natural products. The dihydropyrans are usually di- or tri-substituted, such as Laulimalidel [100] and Ambruticin S [101].



(+)-Ambruticin S



Laulimalidel

Figure 1.39. Dihydropyrans which are di- tri- substituted; Laulimalidel and (+)-Ambruticin S

The early invention affiliated to dihydropyran derivatives, for processing and preparing these derivatives and for preparing vitamin intermediates, in particular vitamins A and E intermediates, using the dihydropyran derivatives. Furthermore; the present invitation of vitamin intermediates by the hydrolysis of dihydropyrans.

On the other hand dihydrofurans are the common units that are used in treatment of many cancer diseases.

Consequently, they are used in psychological diseases treatment and some of the derivatives of them used as anti-cancer drug treatment and obtained from vitamins.

1.4. AIM OF THE WORK

The aim of this work is to synthesize spiro dihydropyran compounds; 6-oxaspiro[4.5]deca-1,8-diene **66** and 1-oxaspiro[5.5]undeca-3,7-diene **72** compounds were obtained via Ring Closing Metathesis by using Grubbs First Generation catalyst also to obtain 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** and 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta [c]pyran]-6'(4'H)-one **74** compounds via Pauson-Khand cycloaddition reaction in the presence of NMO and $Co(CO)_8$, spiro cyclopentenone-pyran compounds which are found in the structure of natural product that has biological activities.

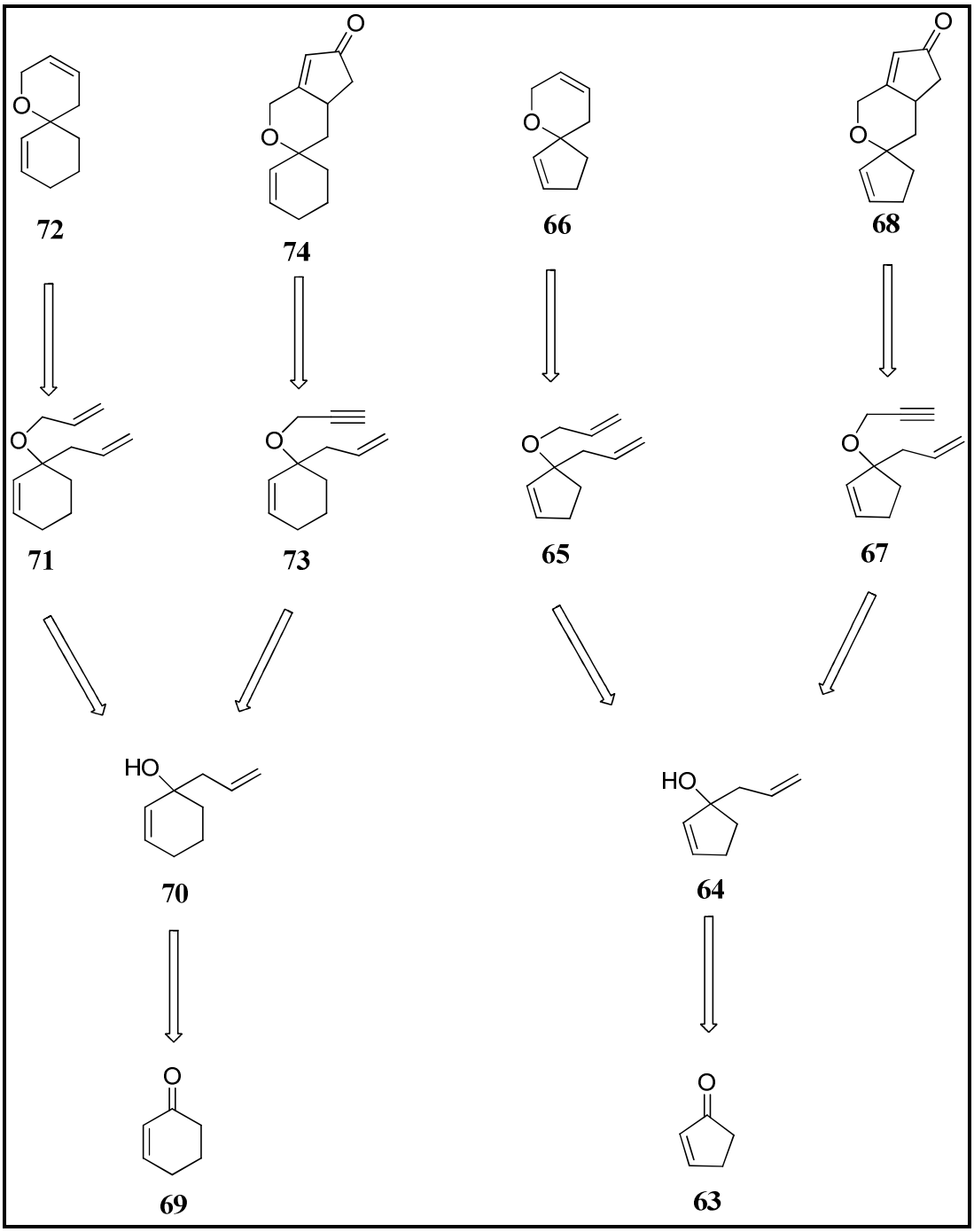


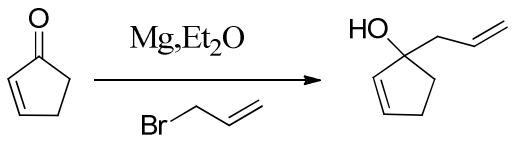
Figure 1.40. Retrosynthesis of the work

CHAPTER II

2. RESULT AND DISCUSSION

2.1. Synthesis of 1-allylcyclopent-2-enol 64

1-allylcyclopent-2-enol **64** was prepared from cyclopent-2-enone **63** and allyl bromide in the presence of di ethyl ether by a Grignard reaction shown in Figure 2.1. After work up, 1-allylcyclopent-2-enol **64** was obtained as colourless oil with 78% chemical yield.



63 **64**

Figure 2.1. Synthesis of the 1-allylcyclopent-2-enol **64**

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

^{1}H-NMR spectrum of 1-allylcyclopent-2-enol **64** shows a singlet at 1.71 ppm is due to the –O-*H* protons of 1-allylcyclopent-2-enol. The diastereotopic methylene protons at fifth position of the ring show doublet of doublet of quartet at 1.86 ppm with J_1=4.4, J_2=8.6 and J_3=13.5 Hz values. The multiplet between 2.12-2.33 ppm

belongs to the one of the diastereotopic methylene protons at fourth position of the ring. The doublet at 2.34 ppm with *J*=3.8 Hz belongs to the allylic methylene protons. The other diastereotopic methylene proton at fourth position of the ring shows multiplet between 2.38-2.47 ppm. Terminal vinylic protons; Ha and Hb exhibit singlet at 5.04 ppm and doublet at 5.10 ppm with *J*=5.2 Hz respectively. One of the methine protons at third position of the ring shows multiplet between 5.60-5.63 ppm. Finally, the multiplet between 5.76-5.83 ppm is due to the other methine proton at second position of the ring and internal vinylic proton;Hc of the allyl group.

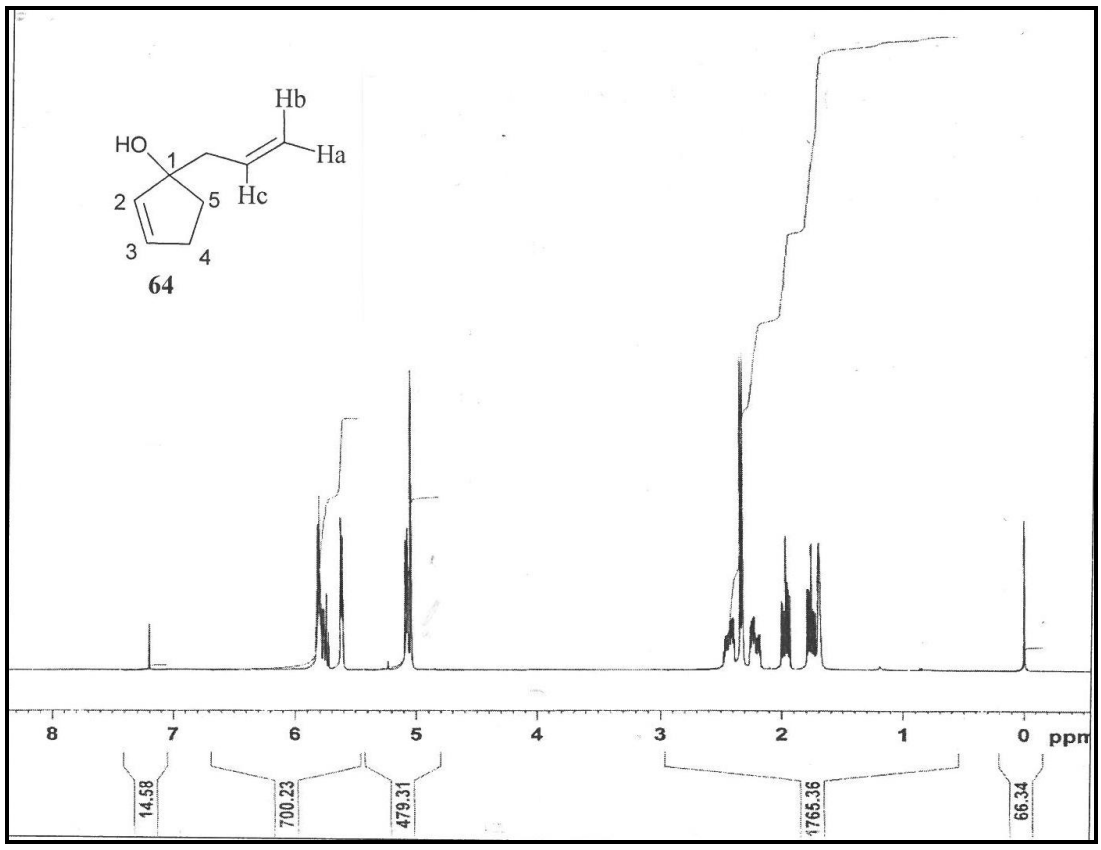


Figure 2.2. ^{1}H-NMR spectrum of 1-allylcyclopent-2-enol **64**

^{13}C-NMR spectrum of 1-allylcyclopent-2-enol **64** shows signals at 30.0 and 36.3 ppm for the methylene carbons at fifth and fourth position of the ring. The

allylic methylene carbon exhibits a signal at 44.3 ppm. The signal at 84.0 ppm belongs to the quaternary carbon. The signals at 117.3 ppm and 132.5 ppm are due to the vinylic carbons. Finally, the methine carbons of the ring at third and second position of the ring exhibit signals at 133.0 and 135.1 ppm.

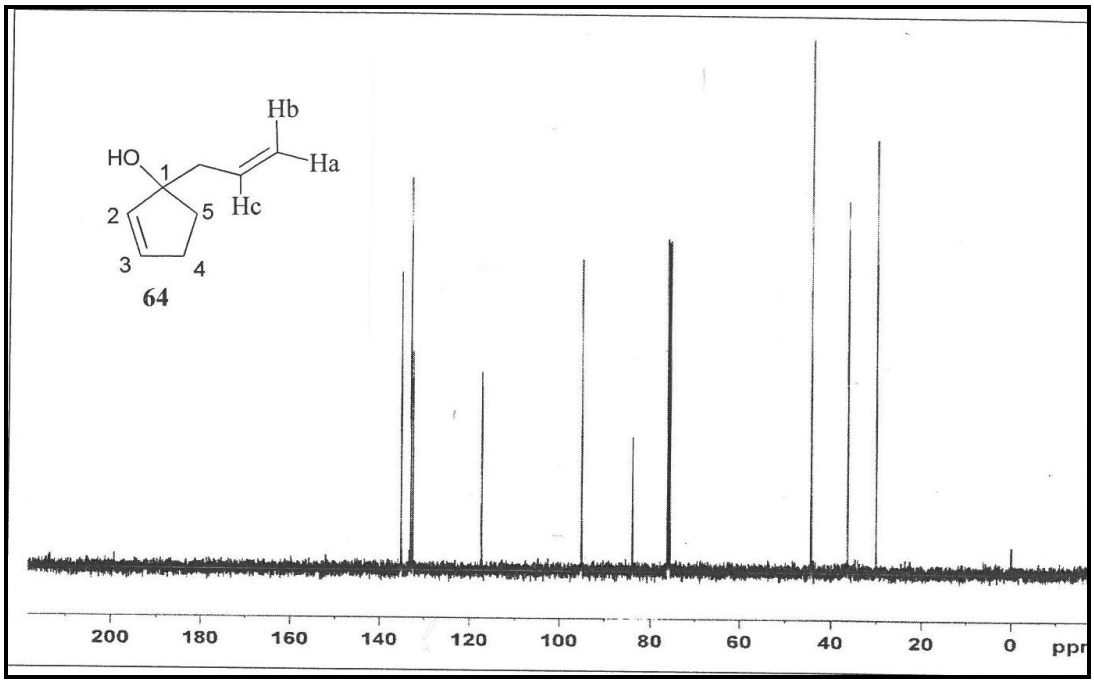


Figure 2.3. ^{13}C-NMR spectrum of 1-allylcyclopent-2-enol **64**

2.2. Synthesis of 3-allyl-3-(allyloxy)cyclopent-1-ene 65

1-allylcyclopent-2-enol **64** was allowed to react with allyl bromide in the presence of THF, KH and TBAI to give 3-allyl-3-(allyloxy)cyclopent-1-ene **65** as shown in Figure 2.4. After work up, 3-allyl-3-(allyloxy)cyclopent-1-ene **65** was obtained as yellow oil with 85% chemical yield.

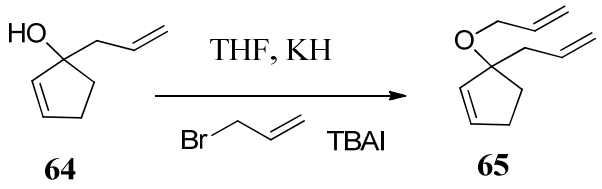


Figure 2.4. Synthesis of 3-allyl-3-(allyloxy)cyclopent-1-ene **65**

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

^{1}H-NMR spectrum of 3-allyl-3-(allyloxy)cyclopent-1-ene **65** shows multiplet 1.77-1.89 ppm is due to the diastereotopic methylene protons at fifth position of the ring. One of the diastereotopic methylene protons at fourth position of the ring exhibits multiplet between 2.18-2.25 ppm. The other diastereotopic proton shows doublet at 2.36 ppm with J=7.2 Hz. Allylic methylene protons show multiplet 2.30-2.39 ppm of the allyl group. The multiplet between 3.70-3.79 ppm is due to the allylic methylene protons of the *o*-allyl group. The terminal vinylic protons of the allyl group show multiplet between 4.95-5.03 ppm overlaps with one of the terminal vinylic proton of *o*-ally group. The other terminal vinylic proton of the *o*-allyl group exhibits quartet of doublet at 5.17 ppm with J_1=3.6 and J_2=17.2 Hz. The doublet of doublet of doublet at 5.54 ppm with J_1=2.4 and J_2=4.8 and J_3=5.6 Hz is due to the methine proton at third position of the ring. The multiplet between 5.72-5.88 ppm is due to the internal vinylic protons. Finally, a doublet of doublet at 5.89 ppm with J_1=2.4 and J_2=5.6 Hz belongs to the other methine proton at second position of the ring.

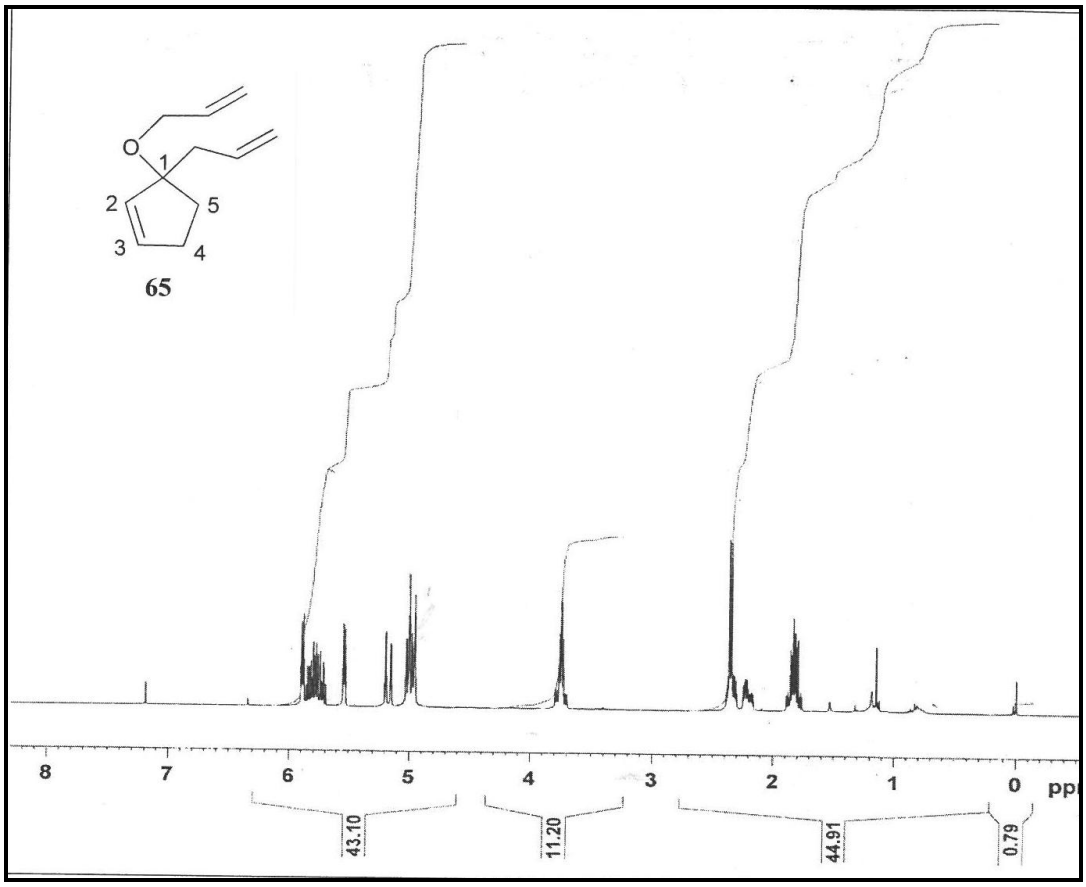


Figure 2.5. ^{1}H-NMR spectrum of 3-allyl-3-(allyloxy)cyclopent-1-ene **65**

^{13}C-NMR spectrum of 3-allyl-3-(allyloxy)cyclopent-1-ene **65** shows signal at 31.8 and 44.4 ppm for fourth and fifth methylene carbons of the ring. The allylic methylene carbon of the allyl group shows a signal at 63.7 ppm. The signal at 77.0 ppm belongs to the allylic methylene carbon of the *o*-allyl group. The quaternary carbon shows a signal at 90.7 ppm. The signals at 115.3 and 117.1 ppm are due to the vinylic carbons. The other vinylic carbon atoms show signals at 133.8 and 134.5 ppm. Finally, the methine carbon at the third position of the ring exhibits a signal at 134.9 ppm and the signal at 136.1 ppm is due to the other methine carbon at second position of the ring.

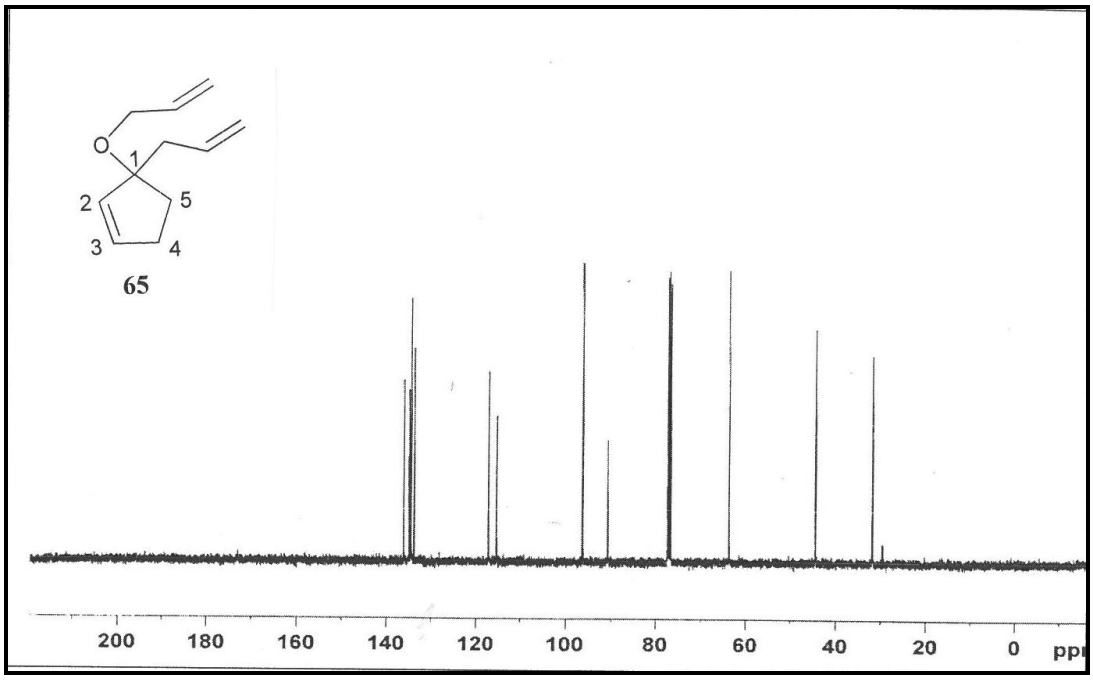


Figure 2.6. ^{13}C-NMR spectrum of 3-allyl-3-(allyloxy)cyclopent-1-ene **65**

2.3. Synthesis of 6-oxaspiro[4.5]deca-1,8-diene 66 via Ring Closing Metathesis (Diastereomeric Mixture)

6-oxaspiro[4.5]deca-1,8-diene **66** was synthesized from 3-allyl-3-(allyloxy)cyclopent-1-ene **65** in the presence of DCM by using Grubbs First Generation catalyst with Ring Closing Metathesis shown in Figure 2.7. After work up, 6-oxaspiro[4.5]deca-1,8-diene **66** was obtained as colourless oil with 84% chemical yield.

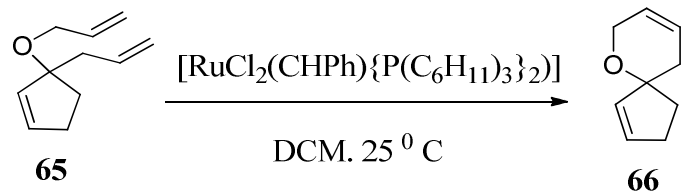


Figure 2.7. Synthesis of 6-oxaspiro[4.5]deca-1,8-diene **66**

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

^{1}H-NMR spectrum of 6-oxaspiro[4.5]deca-1,8-diene **66** shows multiplet between 1.64-1.69 ppm for the one of the diastereotopic methylene protons of the fifth position of 2-cyclopentene. The multiplet between 1.69-1.77 ppm is due to the other diastereotopic methylene proton. The multiplet between 1.92-1.98 ppm is due to the diastereotopic methylene protons of the 2-cyclopentene of the other diastereomer. The allylic methylene protons at tenth position of dihydropyran ring exhibit multiplet between 2.00-2.18 ppm. The multiplet between 2.15-2.89 ppm is due to the other allylic methylene protons of tenth position of dihydropyran ring of the other diastereomer. The allylic methylene protons of 2-cyclopentene show multiplet between 2.41-2.50 ppm at fourth position for two diastereomers. One of the diastereomer of methylene protons at seventh position of dihydropyran ring exhibit multiplet between 4.08-4.11 ppm. The other diastereomer shows singlet at 4.57 ppm for the methylene protons at seventh position of dihydropyran of the other diastereomer. The multiplet between 5.52-5.57 ppm is due to the methine protons at third position of 2-cyclopentene for two diastereomers. The other methine protons of 2-cyclopentene ring of two diastereomers show multiplet between 5.61-5.67 ppm. The methine proton at eighth position of dihydropyran of one of the diastereomer shows multiplet between 5.71-5.73 ppm. The signal of the other methine proton of the other diastereomer overlaps with the signal of the methine proton of the ninth position of dihydropyran of one of the diastereomer show multiplet between 5.76-5.79 ppm. Finally, the methine proton of the other diastereomer exhibits multiplet between 5.86-5.89 ppm.

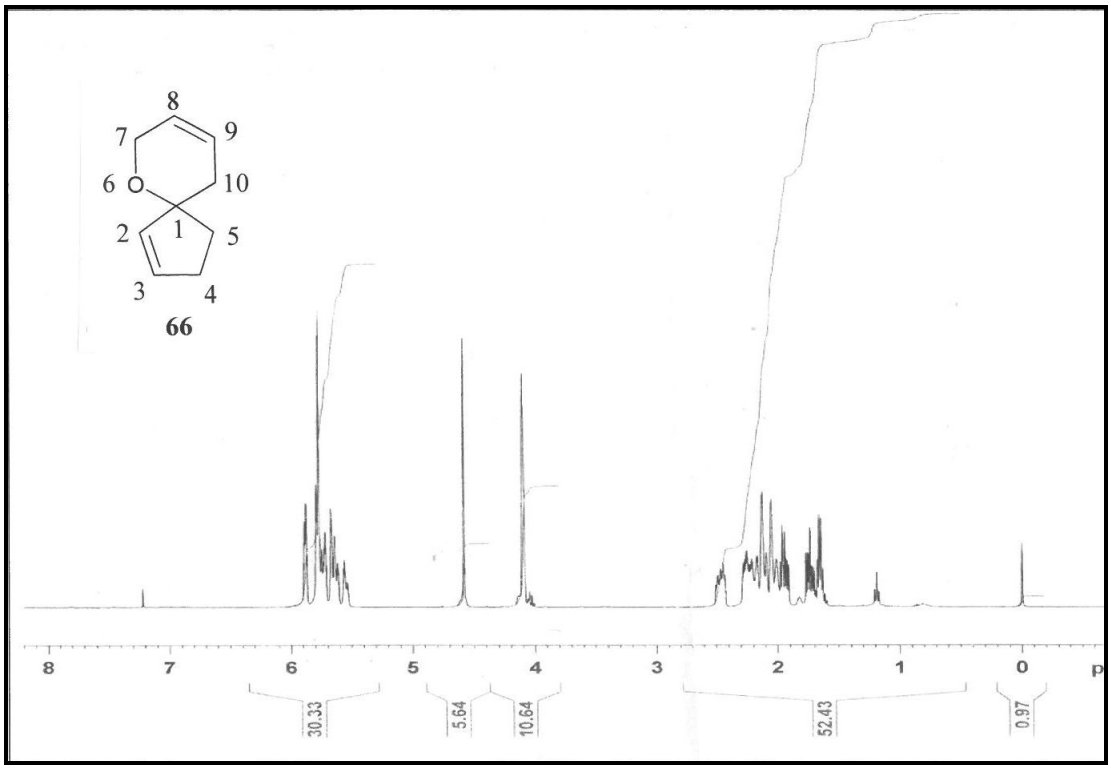


Figure 2.8. ^{1}H-NMR spectrum of 6-oxaspiro[4.5]deca-1,8-diene **66**

In ^{13}C-NMR spectrum of 6-oxaspiro[4.5]deca-1,8-diene **66**; the methylene carbon at fifth position of 2-cyclopentene shows signal at 34.3 ppm for the two diastereomers. The signal at 35.7 ppm is due to the allylic methylene carbon at tenth position of dihydropyran of two diastereomers. The other allylic methylene carbon atoms of two diastereomers at fourth position of 2-cyclopentene exhibits signal at 36.8 ppm. The signals at 62.1 and 73.8 ppm are due to the seventh position of two diastereomers. The quaternary carbons of dihydropyran of two diastereomers exhibit signal at 84.7 and 87.7 ppm. The signals at 123.7 and 124.8 ppm are due to the methine carbons at eighth position of dihydropyran of two diastereomers. The other methine carbons of two diastereomers of dihydropyran show signals at 125.6 and 126.0 ppm. The signals at 126.5 and 133.2 ppm are due to the methine carbons at

third position of 2-cyclopentene of two diastereomers. Finally, the other methine carbons of two diastereomers of 2-cyclopentene exhibit signals at 133.9 and 134.4 ppm.

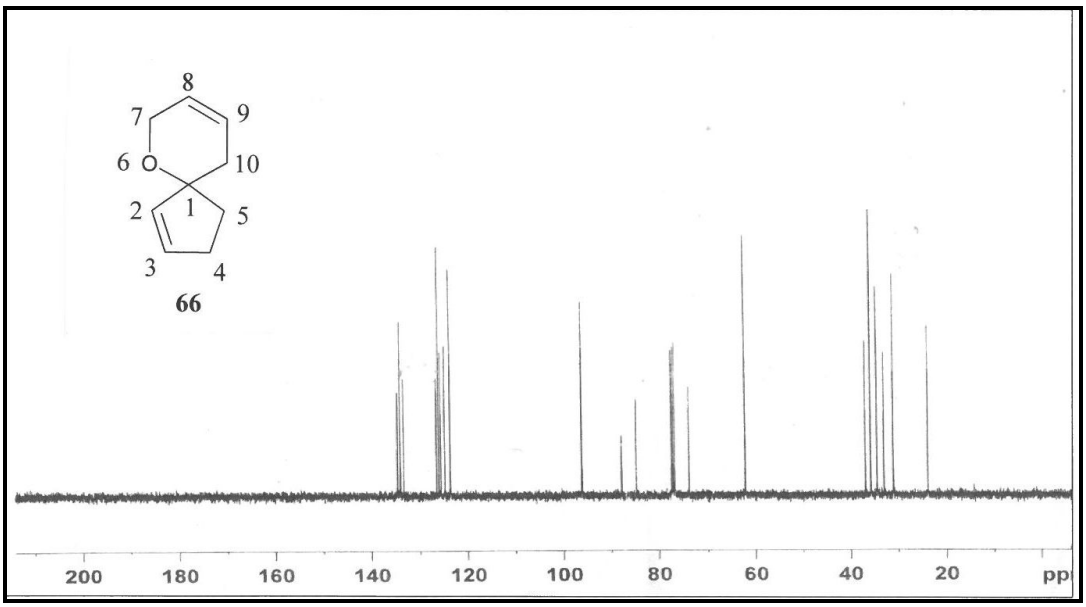


Figure 2.9. ^{13}C-NMR spectrum of 6-oxaspiro[4.5]deca-1,8-diene **66**

2.4. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene 67

1-allylcyclopent-2-enol **64** was allowed to react with 3-Bromo-1-(trimethylsilyl)-1-propyne (TMS) in the presence of THF, KH and TBAI to give 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** as shown in Figure 2.10. After work up, 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** obtained as dark yellow oil with 85% chemical yield.

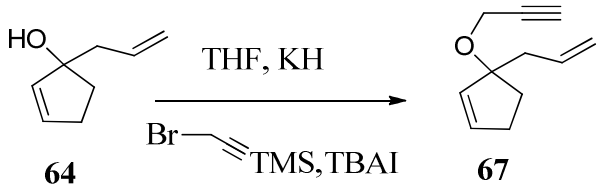


Figure 2.10. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67**

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

^{1}H-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** shows multiplet between 1.67-1.75 ppm and 1.78-1.85 ppm for two diastereotopic methylene protons at fifth position of the ring. The triplet at 2.13 ppm with J=2.4 Hz is due to the acetylenic proton. One of the diastereotopic metylene protons at fourth position shows multiplet between 2.06-2.15 ppm. The other diastereotopic methylene proton exhibits doublet at 2.25 ppm with J=7.2 Hz. The multiplet between 2.21-2.29 ppm is due to the allylic methylene protons of the allyl group. Methylene protons of the propargyl group exhibit multiplet between 3.73-3.82 ppm. Terminal vinylic protons show a multiplet between 4.85-4.89 ppm. The multiplet between 5.42-5.45 ppm is due to the methine proton at third position of the ring. Internal vinylic proton exhibits multiplet between 5.57-5.67 ppm. Finally, the multiplet between 5.82-5.85 ppm belongs to the other methine proton of the ring.

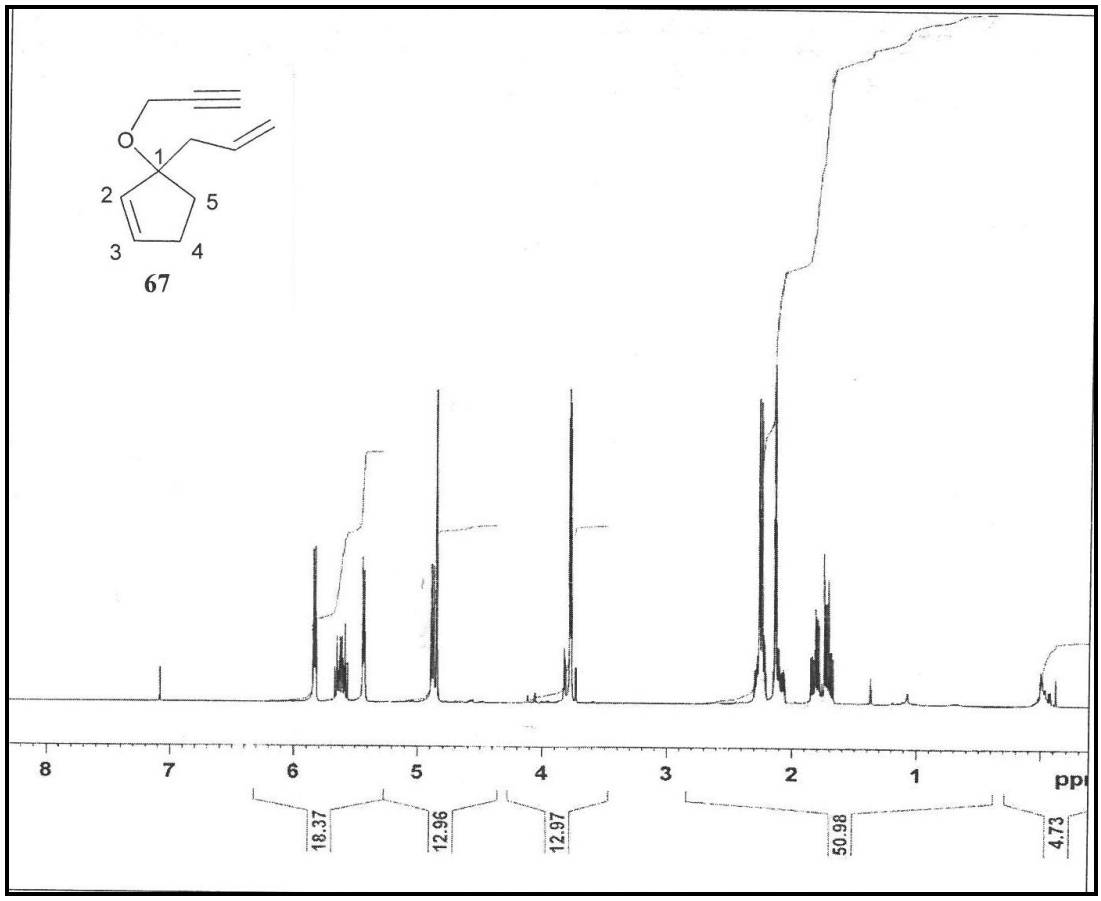


Figure 2.11. ^{1}H-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67**

^{13}C-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** shows signal at 31.8 ppm and 44.4 ppm are due to the fifth and fourth methylene carbons of the ring. The signal at 51.0 ppm belongs to the allylic carbon of the allyl group. The other allylic carbon found in the propargyl group exhibits a signal at 72.9 ppm. The signals at 77.0 ppm and 81.7 ppm are due to the methine and quaternary carbons of the propargyl group. The quaternary carbon of the ring exhibits a signal 91.8 ppm. The signals at 117.4 and 133.1 ppm are due to the vinylic carbon atoms. Finally, the methine carbon atoms at third and second position of the ring show signals at 134.1 and 136.1 ppm.

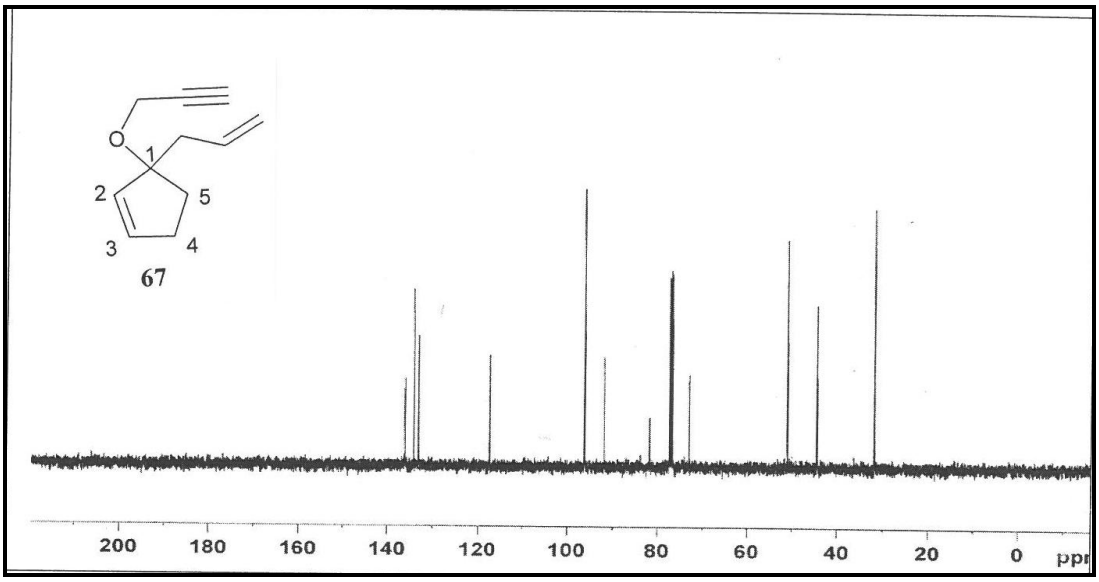
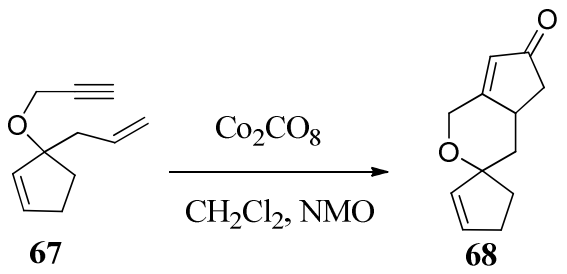


Figure 2.12. ^{13}C-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67**

2.5. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c] pyran] -6'(4'H)-one 68 via Pauson-Khand cycloaddition reaction (Diastereomeric Mixture)

4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** was synthesized by using the Pauson-Khand cycloaddition reaction. 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** was reacted with dicobalt octacarbonyl in the presence of NMO as a promoter to obtain 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran] -6'(4'H)-one **68** in CH_2Cl_2 via Pauson-Khand cycloaddition reaction as shown in figure 2.13. After work up, 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** was obtained as yellow oil with 84% chemical yield.



67 **68**

Figure 2.13. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran] -6'(4'H)-one **68**

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

^{1}H-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta [c]pyran] -6'(4'H)-one **68**; the methylene protons of fourth prime position of dihydropyran of one diastereomer overlaps with one of the diastereotopic methylene protons at fourth prime position of dihydropyran of other diastereomer between 1.56-1.74 ppm as multiplet. Furthermore, the other diastereotopic methylene protons of fourth prime position of the other diastereomer and one of the diastereotopic methylene protons of fifth position of cyclopentene of one diastereomer overlaps between 1.75-1.84 ppm as multiplet. Moreover, the multiplet between 1.92-2.00 ppm is due to the other distereotopic methylene protons at fifth position of cyclopentene of the other diastereomer. One of the diastereotopic methylene protons of fifth position of cyclopentene ring of the other diastereomer and the allylic methylene protons of fourth position of cyclopentene of one diastereomer overlaps between 2.11-2.18 ppm shown as multiplet. The multiplet between 2.31-2.40 ppm belongs to the allylic methylene protons at fourth position of cyclopentene of the other diastereomer. The methine protons at the 4a□ position exhibits multiplet between 2.43-2.50 ppm. The doublet of doublet with J_1=6.4 Hz

and J_2=18.4 Hz at 2.54 ppm is due to the methylene protons at the fifth prime position of one of the diastereomer. The methine proton of the other diastereomer of 4a□ position is shown as a quartet with J=8 Hz at 2.77 ppm. Moreover, doublet at 2.95 ppm with J=6.8 Hz is due to the one of the methylene protons at fifth prime position of the other diastereomer. The other one of the methylene protons of the diastereomer exhibits as multiplet between 2.99-3.02 ppm. The doublet of doublet with J_1=14.0 Hz and J_2=65.6 Hz at 4.40 ppm is due to the methylene protons bonded to the oxygen atom. The methine protons at the second position of diastereomers show multiplet between 5.12-5.19 ppm. Furthermore, the multiplet between 5.49-5.52 ppm is due to the methine proton at third position of one of the diastereomers. The methine proton of the other diastereomer shows multiplet between 5.82-5.84 ppm of the other diastereomer. Finally, the singlet at 5.85 ppm is due to the olefinic proton at seventh prime position of one of diastereomer. The olefinic proton of the other diastereomer shows multiplet between 5.82-5.92 ppm.

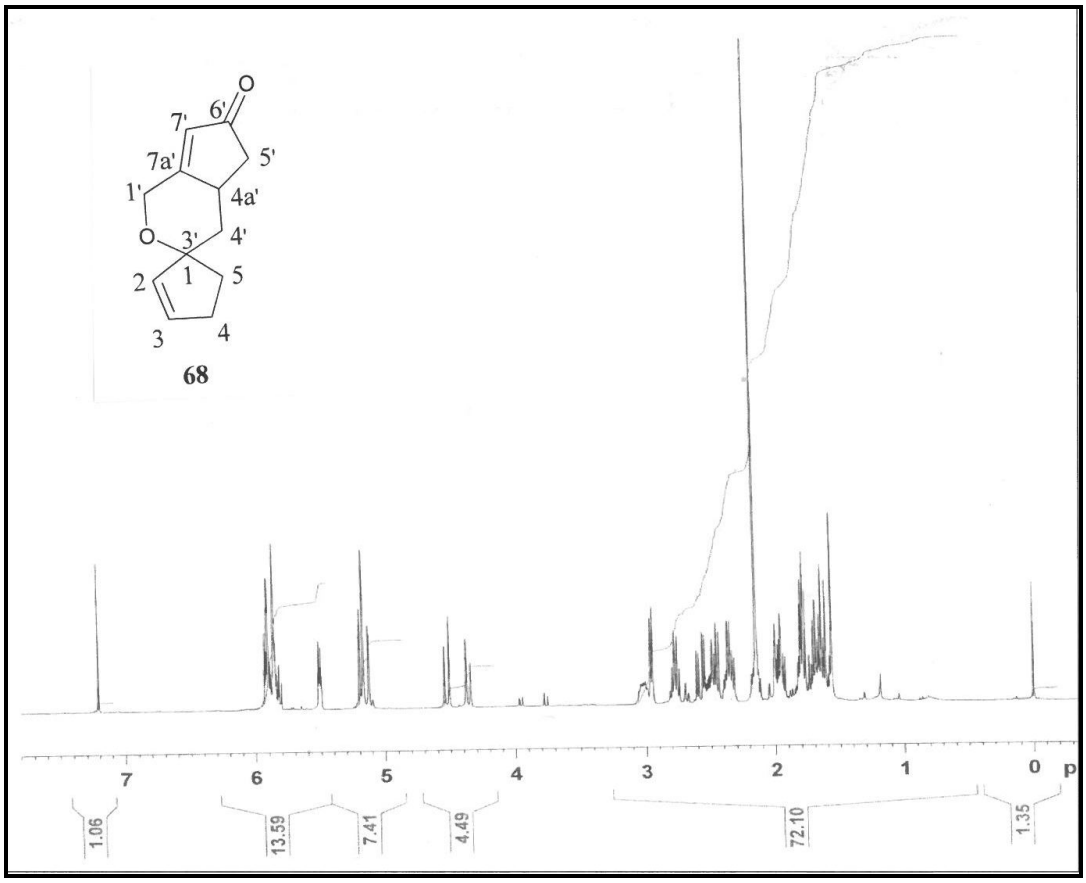


Figure 2.14. ^{1}H-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran] -6'(4'H)-one **68**

^{13}C-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** shows signal at 19.9 and 24.3 ppm for the methylene carbons of the two diastereomers at fifth position. The signals at 30.7 and 31.4 ppm are due to the methylene carbons of the two diastereomers at fourth prime position. The signals at 36.4 and 39.6 ppm are for the allylic methylene carbon atoms of two diastereomers at fourth position of cyclopentene. Furthermore, the methylene carbons of two diastereomers at fifth prime position exhibit signals at 41.9 and 42.8 ppm. The methine carbons of the two diastereomers at the 4a' position show signals at 45.4 and 51.7 ppm. The signals at 57.8 and 62.4 ppm are for the methylene

carbons of two diastereomers bonded to the oxygen atom. The quaternary carbons of two diastereomers exhibit signal at 80.2 and 88.0 ppm. Moreover, the signals at 119.9 and 127.0 ppm are due to the methine carbons of the two diastereomers at third position. The other methine carbons of the two diastereomers at second position show signals at 131.7 and 133.1 ppm. The signals at 134.4 and 135.0 ppm are for the quaternary carbons of the two diastereomer. The other quaternary carbons of the two diastereomers at 7a' position give signals at 176.1 and 177.9 ppm. Finally, the signals at 207.7 and 211.6 ppm are due to the carbonyl carbons of the two diastereomers.

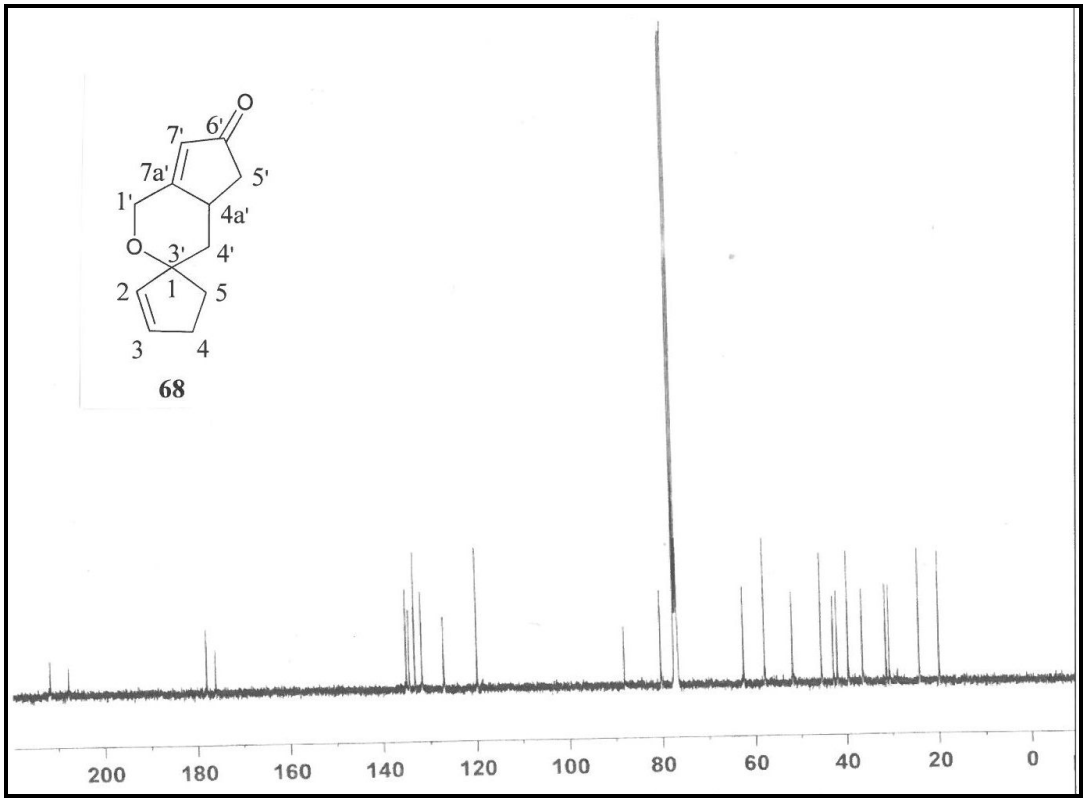


Figure 2.15. ^{13}C-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran] -6'(4'H)-one **68**

2.6. Synthesis of 1-allylcyclohex-2-enol 70

1-allylcyclohex-2-enol **70** was prepared from cyclohex-2-enone **69** and allyl bromide in the presence of diethyl ether by a Grignard reaction shown in Figure 2.16. After work up, 1-allylcyclohex-2-enol **70** was obtained as colourless oil with 80% chemical yield.

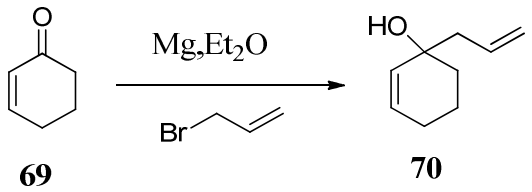


Figure 2.16. Synthesis of 1-allylcyclohex-2-enol **70**

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

^{1}H-NMR spectrum of 1-allylcyclohex-2-enol **70** shows multiplet between 1.23-1.27 ppm for one of the diastereotopic methylene protons at fifth position of the ring. The other methylene proton at fifth position and the methylene protons bonded to the sixth carbon atom show multiplet between 1.55-1.77 ppm. The broad singlet at 1.86 ppm is due to the –O-*H* proton of the 1-allylcyclohex-2-enol **70**. The multiplet between 1.89-1.96 ppm belongs to the one of the diastereotopic methylene protons at fourth position of the ring. The other one shows multiplet between 2.01-2.08 ppm. The doublet at 2.35 ppm with *J*=7 Hz is due to the allylic methylene protons. The multiplet between 5.09-5.14 ppm is due to the terminal vinylic protons; Ha and Hb. The methine proton at second position of the ring exhibits a doublet at 5.62 ppm with *J=10* Hz. The multiplet between 5.87-5.97 ppm is due to the other methine proton at

third position of the ring. Finally, internal vinylic proton; Hc shows multiplet between 5.88-5.93 ppm.

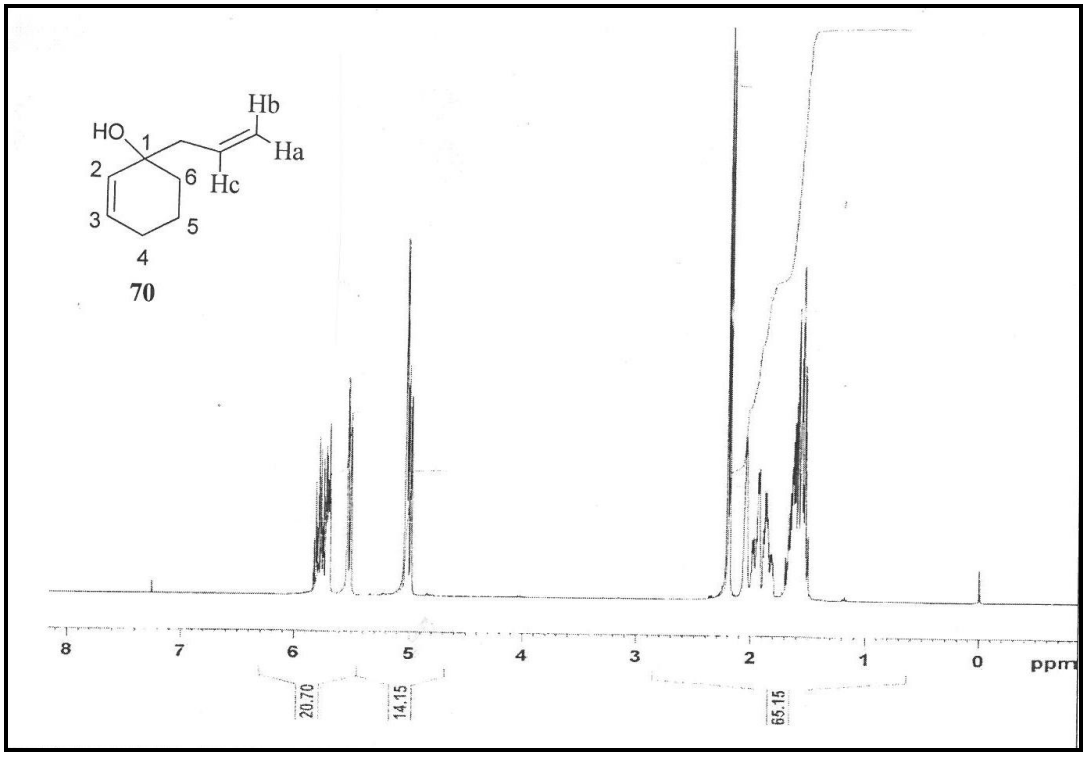


Figure 2.17. ^{1}H-NMR spectrum of 1-allylcyclohex-2-enol **70**

^{13}C-NMR spectrum of 1-allylcyclohex-2-enol **70** shows signals at 18.9 ppm and 25.1 ppm for the methylene carbons of fifth and sixth position of the ring. The methylene carbon at fourth position exhibits a signal at 35.4 ppm. The signal at 46.7 ppm is due to the allylic methylene carbon. The quaternary carbon shows a signal at 69.1 ppm. The signals at 118.0 ppm and 133.9 ppm are due to the vinylic carbons. Finally, methine carbons at third and second position of the ring show signals at 129.6 ppm and 132.4 ppm.

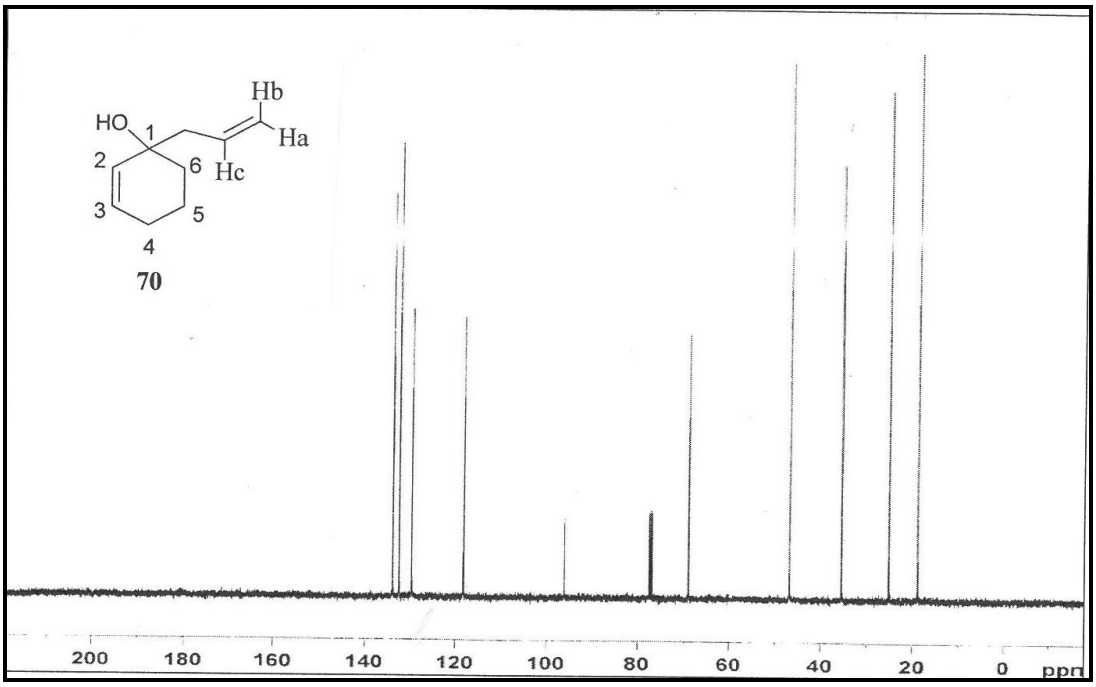


Figure 2.18. ^{13}C-NMR spectrum of 1-allylcyclohex-2-enol **70**

2.7. Synthesis of 3-allyl-3-(allyloxy)cyclohex-1-ene 71

1-allylcyclohex-2-enol **70** was allowed to react with allyl bromide in the presence of THF, KH and TBAI to give 3-allyl-3-(allyloxy)cyclohex-1-ene **71** as shown in Figure 2.19. After work up, 3-allyl-3-(allyloxy)cyclohex-1-ene **71** was obtained as yellow oil with 80% chemical yield.

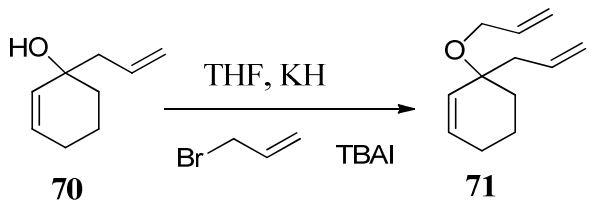


Figure 2.19. Synthesis of 3-allyl-3-(allyloxy)cyclohex-1-ene **71**

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

^{1}H-NMR spectrum of 3-allyl-3-(allyloxy)cyclohex-1-ene **71** shows multiplet between 1.45-1.56 ppm for the diastereotopic methylene protons at fifth position of the ring which overlaps one of the diastereotopic methylene protons at sixth position of the ring. The other diastereotopic methylene proton at fifth position of the ring and one of the diastereotopic methylene protons at fourth position show multiplet between 1.64-2.79 ppm. The multiplet between 1.82-2.00 ppm is due to the other diastereotopic methylene proton at fourth position of the ring. The allylic methylene protons exhibit multiplet 2.22-2.33 ppm of the allyl group. The triplet of doublet at 3.87 ppm with J_1=*1* Hz and J_2=5 Hz belongs to the allylic methylene protons of the *o*-allyl group. One of the terminal vinylic protons shows multiplet between 4.96-4.98 ppm and the other one shows multiplet between 5.00-5.02 ppm. The other terminal protons show multiplet between 5.03-5.04 ppm and quartet of doublet at 5.19 ppm with J_1=2 Hz and J_2=17 Hz. The triplet of doublet at 5.21 ppm with J_1=2 Hz and J_2= 10 Hz is due to the methine proton at the third position of the ring. Finally, the signals of internal vinylic protons and methine proton at second position of the ring overlap between 5.51-5.87 ppm as multiplet.

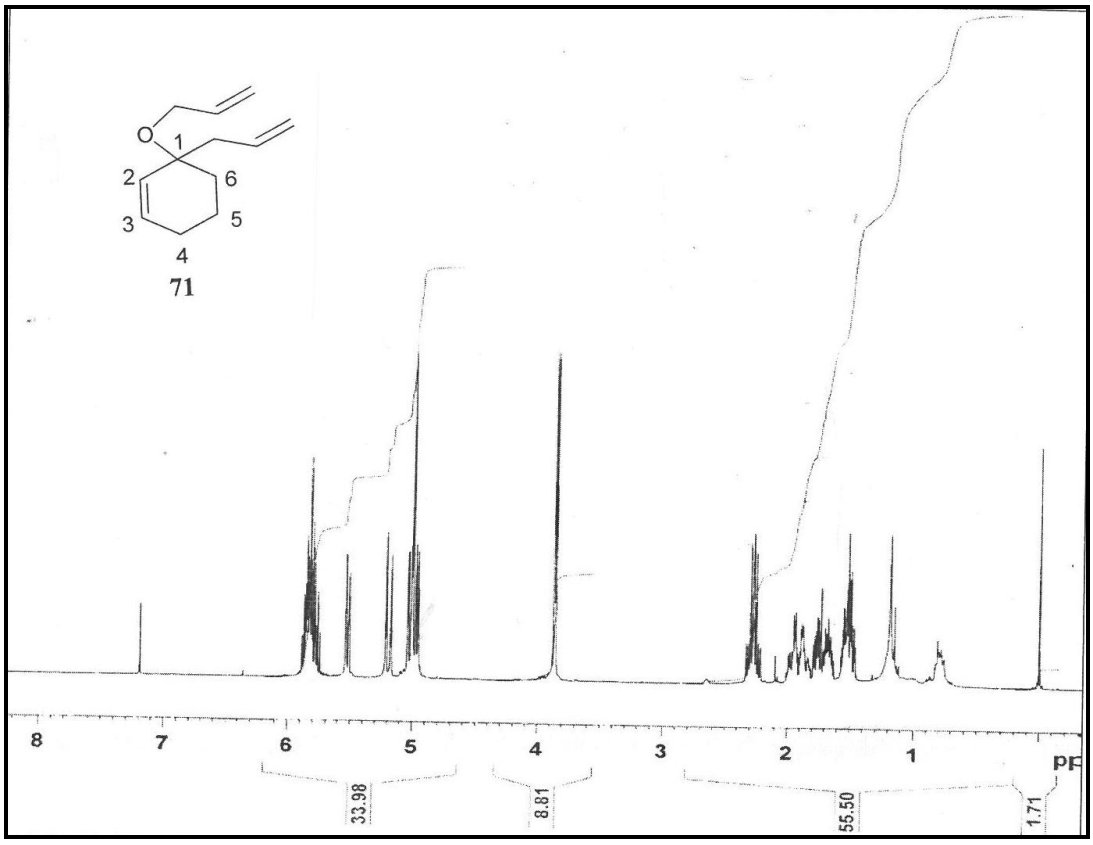


Figure 2.20. ^{1}H-NMR spectrum of 3-allyl-3-(allyloxy)cyclohex-1-ene **71**

^{13}C-NMR spectrum of 3-allyl-3-(allyloxy)cyclohex-1-ene **71** shows signals at 18.3 and 24.0 ppm for the fifth and the sixth methylene carbons of the ring. The methylene carbon at the fourth position exhibits a signal at 30.8 ppm. The signal at 43.0 ppm belongs to the allylic carbon atom of the allyl group. The other allylic carbon atom of the allyl group shows a signal at 62.3 ppm. The signal at 73.4 belongs to the quaternary carbon atom of the ring. Vinylic carbons exhibit signals at 114.3 ppm and 116.1 ppm. The signal at 129.6 ppm is due to the methine carbon at third position of the ring. The other vinylic carbons show signals at 130.5 and 133.2 ppm. Finally, the other methine carbon of the ring exhibits a signal at 135.2 ppm.

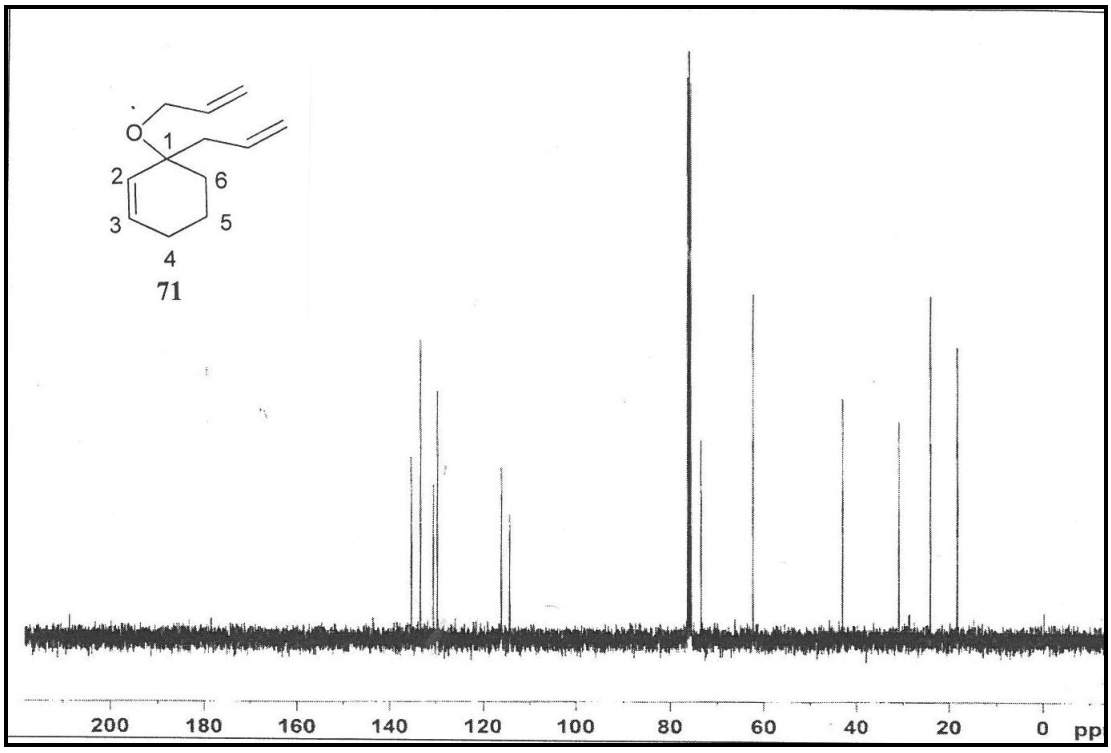


Figure 2.21. ^{13}C-NMR spectrum of 3-allyl-3-(allyloxy)cyclohex-1-ene **71**

2.8. Synthesis of 1-oxaspiro[5.5]undeca-3,7-diene 72 via Ring Closing Metathesis

1-oxaspiro[5.5]undeca-3,7-diene **72** was synthesized from 3-allyl-3-(allyloxy)cyclohex-1-ene **71** in the presence of DCM by using Grubbs First Generation catalyst with Ring Closing Metathesis shown in Figure 2.22. After work up, 1-oxaspiro[5.5]undeca-3,7-diene **72** was obtained as dark coloured oil with 83% chemical yield.

Figure 2.22. Synthesis of 1-oxaspiro[5.5]undeca-3,7-diene **72**

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

^{1}H-NMR spectrum of 1-oxaspiro[5.5]undeca-3,7-diene **72** shows multiplet between 1.48-1.56 ppm for diastereotopic methylene protons at tenth position of cyclohexene. The multiplet between 1.70-1.77 ppm is due to the other diastereotopic methylene at eleventh position of cyclohexene. The allylic methylene protons at ninth position of cyclohexene exhibit multiplet between 1.87-1.95 ppm. The multiplet between 1.97-2.07 ppm is due to the allylic methylene protons of dihydropyran. The methylene protons at second position of dihydropyran show multiplet between 4.05-4.18 ppm. The signals belong to the methine protons at seventh and eighth position of cyclohexene and one of the methine protons at third position of dihydropyran overlaps between 5.65-5.70 ppm as multiplet. Finally, the other methine proton of dihydropyran shows multiplet between 5.78-5.82 ppm respectively.

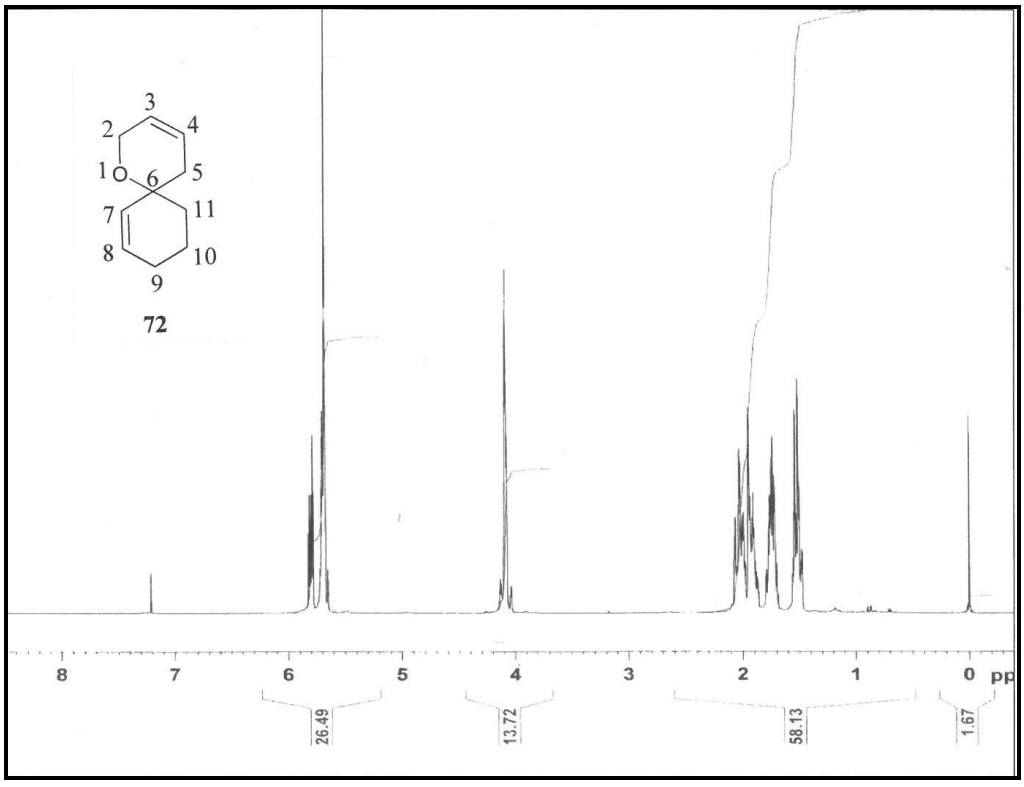


Figure 2.23. ^{1}H-NMR spectrum of 1-oxaspiro[5.5]undeca-3,7-diene **72**

The signal at 17.6 ppm in the ^{13}C-NMR spectrum of 1-oxaspiro[5.5]undeca-3,7-diene **72** is due to the methylene carbon at tenth position of cyclohexene. The methylene carbon at eleventh position of cyclohexene shows a signal at 32.6 ppm. Furthermore, the signals at 34.3 and 34.6 ppm are due to the methylene carbon of ninth position of cyclohexene and fifth position of dihydropyran, respectively. The methylene carbon of dihydropyran bonded to the oxygen atom shows as signal at 60.1 ppm. Moreover, the signal at 67.6 ppm is due to the quaternary carbon atom. The olefinic carbon atoms found in third position and eighth position of cyclohexene exhibit a signal at 121.7 and 124.9 ppm, respectively. Finally, the signals at 128.9 and 129.9 ppm are due to the other olefinic carbon at fourth position of dihydropyran and seventh position of cyclohexene.

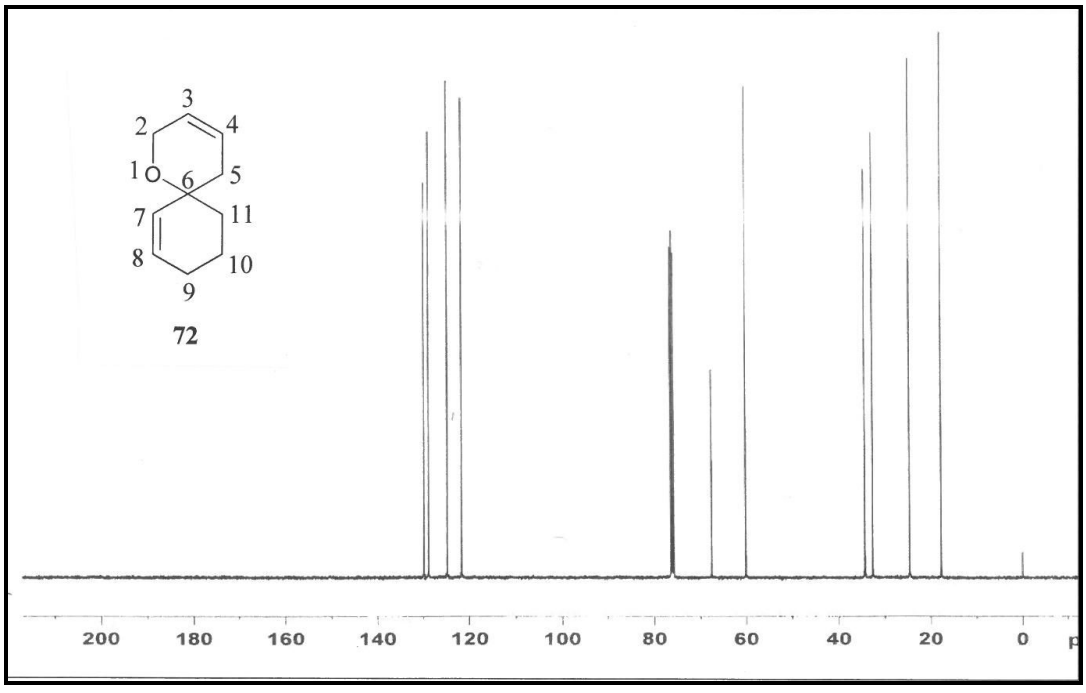


Figure 2.24. ^{13}C-NMR spectrum of 1-oxaspiro[5.5]undeca-3,7-diene **72**

2.9. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene 73

1-allylcyclohex-2-enol **70** was allowed to react with 3-Bromo-1-(trimethylsilyl)-1-propyne (TMS) in the presence of THF ,KH and TBAI to give 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** as shown in Figure 2.25. After work up, 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** obtained as yellow oil with 90% chemical yield.

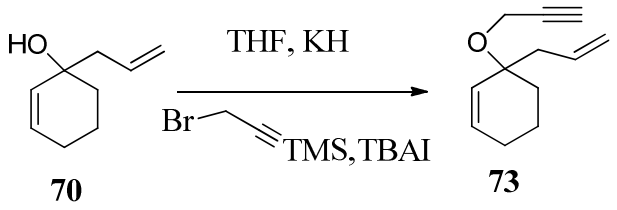


Figure 2.25. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73**

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

^{1}H-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73**, the diastereotopic methylene protons at fifth position show multiplet between 1.46-159 ppm. The multiplet between 1.66 and 1.71 ppm is due to the one of the methylene protons at sixth position of the ring. The other diastereotopic proton exhibits multiplet between 1.86-2.01 ppm. The multiplet between 1.76-1.82 ppm belongs to the diastereotopic protons at fourth position of the ring. Allylic methylene protons show multiplet between 2.27-2.34 ppm. The triplet at 2.26 ppm with *J=2.4* Hz belongs to the acetylenic proton. The doublet at 4.02 ppm with *J*=2.8 Hz is due to the diastereotopic methylene protons of propargyl unit. Terminal vinylic protons show multiplet between 4.95-5.01 ppm. The methine protons at third position of the ring exhibits triplet of doublet at 5.52 ppm with J_1*=2* Hz and J_2*= 10* Hz. The

multiplet between 5.75-5.83 ppm is due to the internal vinylic proton. Finally, the other methine proton of the ring exhibits triplet of doublet at 5.90 ppm with J_1=3.6 Hz and J_2= 10 Hz.

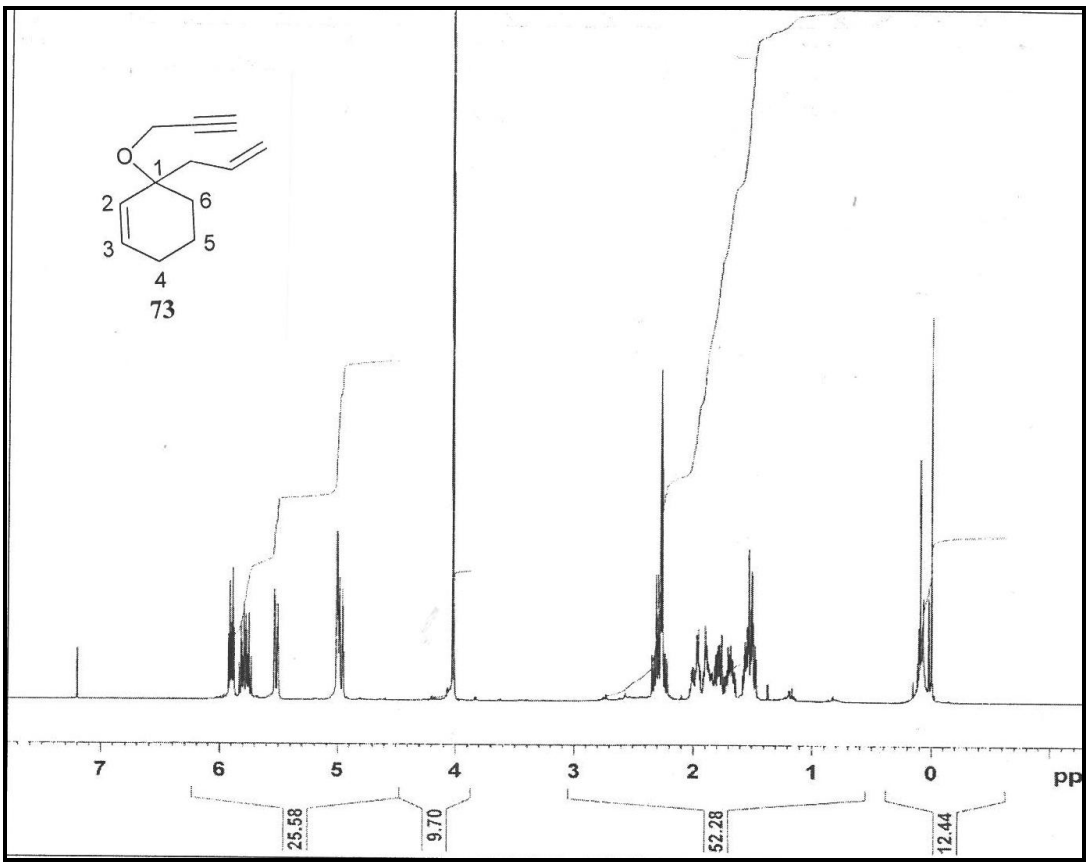


Figure 2.26. ^{1}H-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73**

^{13}C-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** shows signals at 17.7 and 23.6 ppm belong to the fifth and sixth methylene carbons of the ring. The fourth methylene carbon exhibits a signal at 30.5 ppm. The signal at 42.9 ppm belongs to the allylic methylene carbon of the allyl group. The other methylene carbon found in the propargyl group exhibits a signal at 49.4 ppm. The signal at 71.4 belongs to the quaternary carbon of the ring. The methine and quaternary carbon of the propargyl unit exhibit signal at 74.1 ppm and 80.3 ppm, respectively. The signals

at 116.0 ppm and 131.2 ppm are due to the vinylic carbons. Finally, third and second methine carbons of the ring show signals at 128.3 ppm and 133.4 ppm.

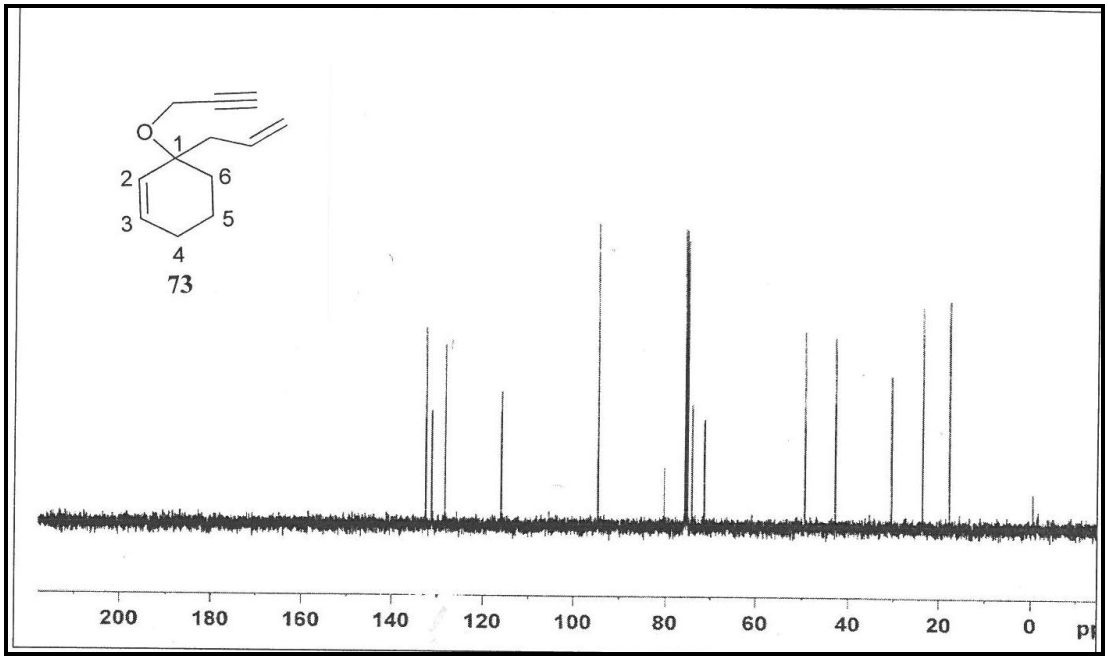
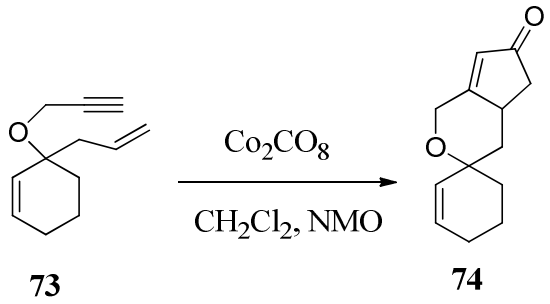


Figure 2.27. ^{13}C-NMR spectrum of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73**

2.10. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c] pyran]-6'(4'H)-one 74 via Pauson-Khand cycloaddition reaction (Diastereomeric mixture)

4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **74** was synthesized by using the Pauson-Khand cycloaddition reaction. 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** was reacted with dicobalt octacarbonyl in the presence of NMO as a promoter to obtain 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'- cyclopenta [c]pyran]-6'(4'H)-one **74** in CH_2Cl_2 via Pauson-Khand cycloaddition reaction as shown in figure 2.28. After work up, 4a',5'-dihydro-1'H-

spiro[cyclohex[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **74** was obtained as yellow oil with 84% chemical yield.



73 **74**

Figure 2.28. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'- cyclopenta [c]pyran]-6'(4'H)-one **74**

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

^{1}H-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta [c]pyran]-6'(4'H)-one **74** exhibits multiplet between 1.19-1.29 ppm for the diastereotopic methylene protons at sixth position and for the one of the diastereotopic methylene protons at fifth position of cyclohexene. The multiplet between 1.42-1.48 ppm is due to the other diastereotopic proton at fifth position of cyclohexene. One of the diastereotopic methylene protons at fourth prime position exhibits multiplet between 1.61-1.66 ppm. The multiplet at 1.80-1.87 ppm is due to the other diastereotopic methylene protons at fourth prime position. Furthermore, the allylic methylene protons at fourth position of cyclohexene shows doublet of quartet at 2.40 ppm with J_1=6.4 Hz and J_2=14.2 Hz. The quartet at 2.70 ppm with J=7.6 Hz belongs to the methine proton at 4a' position. Moreover, the diastereotopic methylene protons at fifth prime position show multiplet between 3.00-3.02 ppm. The quartet between with J=14.4 Hz at 4.56 ppm is due to the methylene protons that is bonded

to the oxygen atom. The methine proton at third position shows multiplet between 5.03-5.11 ppm. The singlet at 5.08 ppm is due to the olefinic proton that is found at the seventh prime position. Finally, the other methine at second position shows multiplet between 5.80-5.90 ppm.

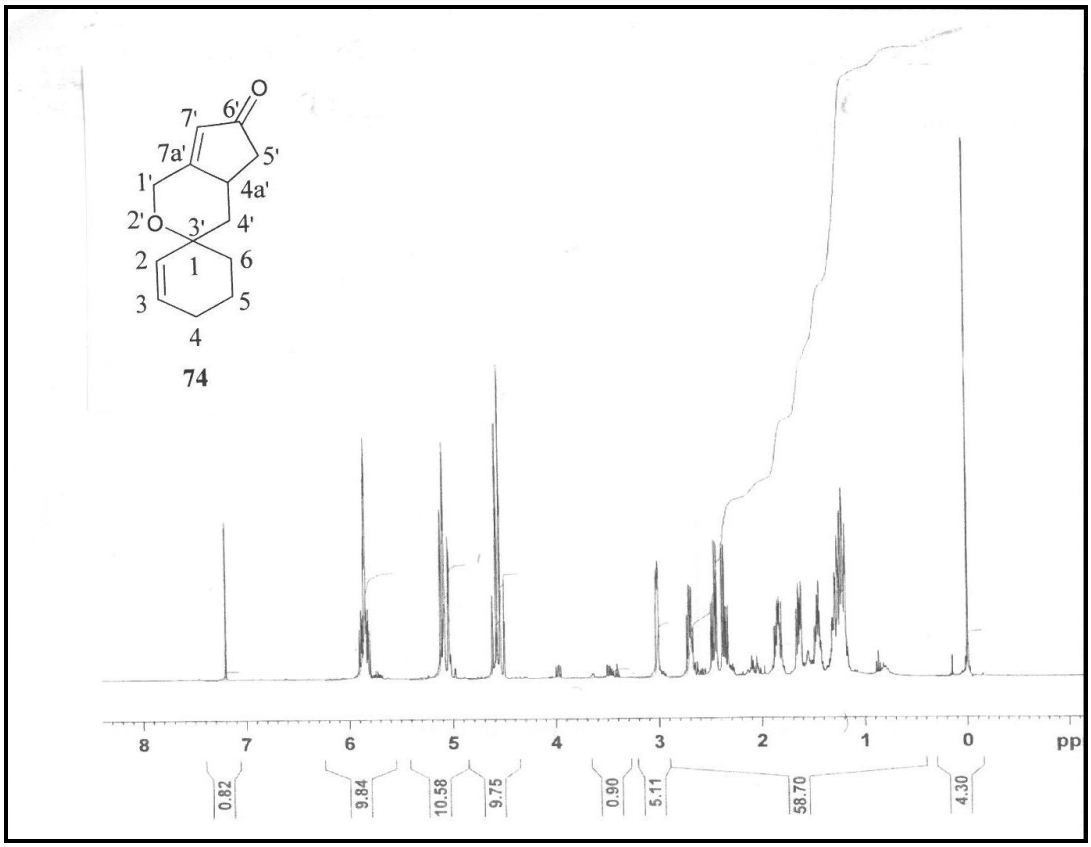


Figure 2.29. ^{1}H-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta [c]pyran]-6'(4'H)-one **74**

^{13}C-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c] pyran]-6'(4'H)-one **74** shows a signal at 20.9 ppm for the methylene carbon at fifth position of cyclohexene. The other methylene carbon at sixth position of cyclohexene exhibits a signal at 25.7 ppm. The methylene carbons at the fourth and fourth prime position show signals at 33.1 and 43.9 ppm, respectively.

Moreover, the signal at 46.8 ppm belongs to the methine carbon at 4a position. The methylene carbon at fifth prime exhibits a signal at 51.1 ppm. The signal at 65.0 ppm is for the methylene carbon that is bonded to the oxygen atom. The quaternary carbon shows a signal at 81.3 ppm. The methine carbons at third and second position of the cyclohexene show signals at 118.8 and 121.7 ppm respectively. Furthermore, the methine carbon at seventh prime position exhibits a signal at 133.7 ppm. The signal at 183.2 ppm belongs to the quaternary carbon at 7a' position. Finally, the carbonyl carbon exhibits a signal at 212.8 ppm.

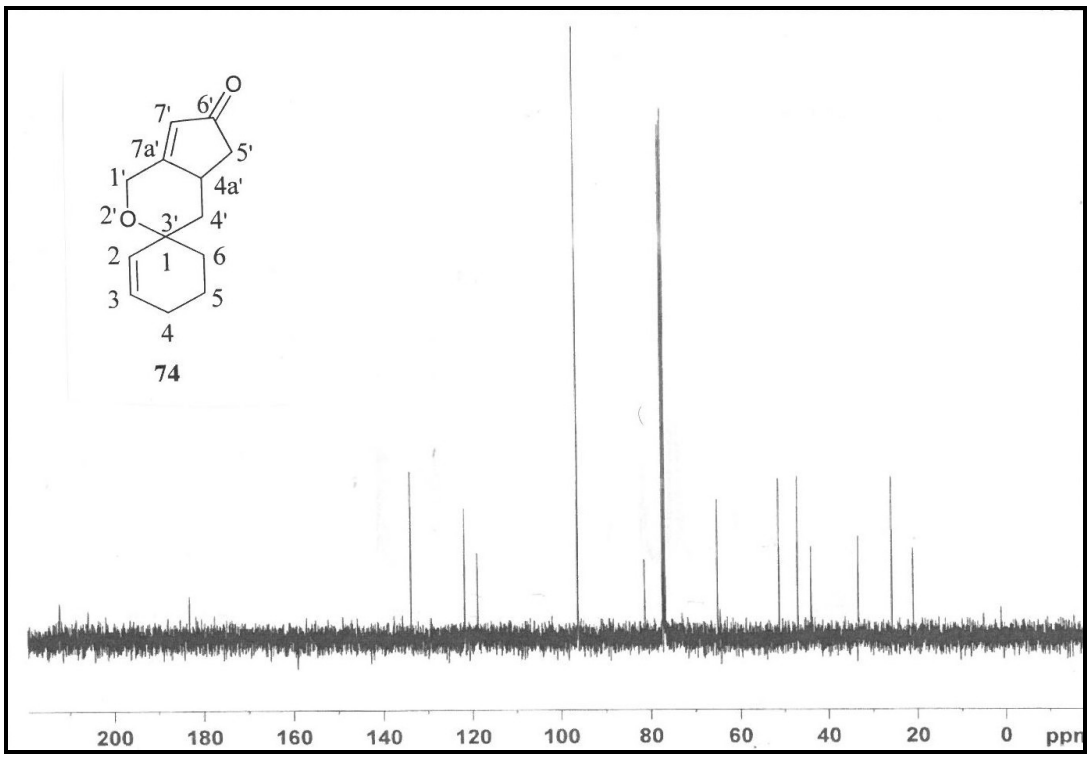


Figure 2.30. ^{13}C-NMR spectrum of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta [c]pyran]-6'(4'H)-one **74**

CHAPTER III

3. EXPERIMENTAL

In this study, the instruments which are written below for the structure characterization of the compounds were used.

^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker Spectrospin Avance DPX 400 spectrometer, 400 MHz High Performance Digital FT-NMR Spectrometer, and Bruker AC 80 MHz FT-NMR Spectrometer by using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. Chemical Shifts are given parts per million (δ) from internal standard tetramethylsilane. Spin multiplicities are mentioned as: s (singlet), ss (strong singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), td (triplet of doublet), m (multiplet).

IR spectra were recorded on SHIMADZU FTIR 8400-S instrument (KBr pellet). Bond positions were reported in reciprocal centimetres. (cm^{-1}).

Optical rotations were measured in $CHCl_3$ in a 1 dm cell using Bellingham & Stanley P20 polarimeter.

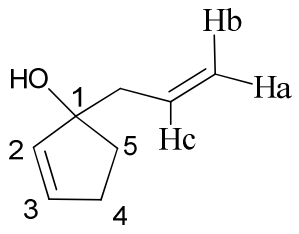
Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-

254), visualized with UV-light and polymolbyden phosphoric acid in ethanol as appropriate.

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

3.1. Synthesis of 1-allylcyclopent-2-enol 64

To a stirred solution of Mg turnings (1.27g, 53.1 mmol) and iodine turning (2 pieces) in dry ethyl ether (10 mL) at 25^{o}C equipped with a reflux condenser was added dropwise a mixture of allyl bromide (31.3 mmol) in anhydrous diethyl ether (2mL) with a injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0^{o}C and the cyclopent-2-enone **63** (41.8 mmol) in diethyl ether (2 mL) was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (3X30 mL) and dried over anhydrous $MgSO_4$ and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc / hexane at the ratio of 1:5 as the eluent to obtain 1-allylcyclopent-2-enol **64** as colourless oil 78% chemical yield.



64

R*f*=0.24 (silica gel – (EtOAc – Hexane), (1:5)

IR (neat): 3310, 1465,1342,1205,1172,915,702 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.71 (s, 1H, -O-*H* proton)

1.86 (ddq, J_1=4.4 Hz, J_2=8.6 Hz, J_3=13.5 Hz, 2H, for the diastereotopic methylene protons at fifth position of the ring)

2.12-2.33 (m, 1H, for one of the diastereotopic methylene protons at the fourth position of the ring)

2.38-2.47 (m, 1H, for the other diastereotopic methylene proton at the fourth position of the ring)

2.34 (d, 2H, for the allylic methylene protons)

5.04 (s, 1H, for one of the terminal vinylic proton Ha)

5.10 (d, *J*=5.2 Hz, 1H, for the other terminal vinylic proton Hb)

5.60-5.63 (m, 1H, for one of the methine protons at third position of the ring)

5.76-5.83 (m, 2H, for the other methine proton at third position of the ring and internal vinylic proton of allyl group Hc)

^{13}C-NMR ($CDCl_3$) δ ppm

30.0 (for the methylene carbon at fifth position)

36.3 (for the methylene carbon at fourth position of the ring)

44.3 (for the allylic methylene carbon)

84.0 (for the quaternary carbon of the ring)

117.3 (for the one of the vinylic carbon)

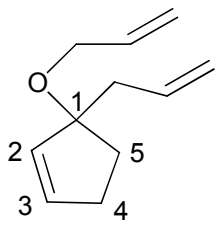
132.5 (for the other vinylic carbon)

133.0 (for the methine carbon at third position of the ring)

135.1 (for the methine carbon at second position of the ring)

3.2. Synthesis of 3-allyl-3-(allyloxy)cyclopent-1-ene 65

A 30% suspension of KH in mineral oil (1.13g, equivalent 28.2 mmol of active hydride) was washed with dry hexane under argon atmosphere. 10 mL dry tetrahydrofuran was added. 1-allylcyclopent-2-enol **64** (3.5 mmol) was added into the mixture with 3 mL THF. After 45 minutes allyl bromide (7 mmol) was added with 3 mL THF dropwise. At the same time TBAI (0.27g, 0.72 mmol) was added respectively. It was stirred until alcohol was disappeared by TLC control. The reaction stopped adding 5 mL water. The resultant mixture was extracted with diethyl ether (3x25 mL) and dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/hexane in ratio of 1:20 as the eluent to obtain 3-allyl-3-(allyloxy)cyclopent-1-ene **65** as yellow oil 85% chemical yield.



65

R*f*=0.76 (silica gel – (EtOAc – Hexane), (1:15)

IR (neat): 3042, 1647,680 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.77-1.89 (m, 2H, for the diastereotopic methylene protons at fifth position)

2.18-2.25 (m, 1H, for the one of the diastereotopic methylene protons at fourth position of the ring)

2.36 (d, J=7.2 Hz. 1H, for the other diastereotopic proton at fourth position of the ring)

2.30-2.39 (m, 2H, for the allylic methylene protons of the allyl group)

3.70-3.79 (m, 2H, for the allylic methylene protons of *o*-allyl group)

4.95-5.03 (m, 3H, for the terminal vinylic protons of allyl group and overlaps one of the terminal vinylic proton of o-allyl group)

5.17 (qd, J_1=3.6 Hz, J_2=17.2 Hz, 1H, for the other terminal vinylic proton of the *o*-allyl group)

5.54 (ddd, J_1=2.4 Hz, J_2=4.8 Hz, J_3=5.6 Hz, 1H, for the methine proton at third position of the ring)

5.72-5.88 (m, 2H, for the internal vinylic protons)

5.89 (dd, J_1=2.4 Hz, J_2=5.6 Hz, 1H, for the other methine proton at second position of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

31.8 (for the methylene carbon at fourth position of the ring)

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

63.7 (for the allylic methylene carbon of allyl group)

77.0 (for the allylic methylene carbon of *o*-allyl group)

90.7 (for the quaternary carbon of the ring)

115.3 (for the vinylic carbon atom)

117.1 (for the vinylic carbon atom)

133.8 (for the vinylic carbon atom)

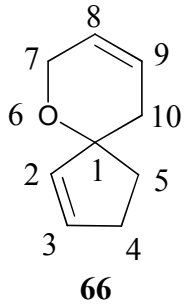
134.5 (for the vinylic carbon atom)

134.9 (for the methine carbon at third position of the ring)

136.1 (for the methine carbon at second position of the ring)

3.3. Synthesis of 6-oxaspiro[4.5]deca-1,8-diene 66 via Ring closing metathesis (Diastereomeric mixture)

3-allyl-3-(allyloxy)cyclopent-1-ene **65** (2.25 mmol) in CH_2Cl_2 (10 mL) was added Grubbs first generation catalyst (0.08g, 0.10 mmol), and stirred for 24 hour (TLC monitoring). The product 6-oxaspiro[4.5]deca-1,8-diene **66** was obtained as colourless oil purified by flash column chromatography in 84% chemical yield.



66

R*f*=0.66 (silica gel – (EtOAc – Hexane), (1:15)

IR (neat): 3105, 1630, 1080, 1115 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.64-1.69 (m, 2H, for the one of the diastereotopic methylene protons of the fifth position of 2-cyclopentene)

1.69-1.77 (m, 1H, for the other diastereotopic methylene proton)

1.92-1.98 (m, 1H, for the diastereotopic methylene protons of the 2-cyclopentene of the other diastereomer)

2.00-2.18 (m, 2H, for the allylic methylene protons at tenth position of dihydropyran ring)

2.15-2.89 (m, 2H, for the other allylic methylene protons of tenth position of dihydropyran ring of the other diastereomer)

2.41-2.50 (m, 1H, for the allylic methylene protons at fourth position for two diastereomers of 2-cyclopentene)

4.08-4.11 (m, 2H, for the one of the diastereomer of methylene protons at seventh position of dihydropyran ring)

4.57 (s, 1H, for the other diastereomer of methylene protons at seventh position of dihydropyran ring)

5.52-5.57 (m, 1H, for the methine protons at third position of 2-cyclopentene for two diastereomers)

5.61-5.67 (m, 2H, for the other methine protons of 2-cyclopentene ring of two diastereomers)

5.71-5.73 (m, 1H, for the methine proton at eighth position of dihydropyran of one of the diastereomer)

5.76-5.79 (m, 2H, for the other methine proton of the other diastereomer overlaps with the signal of the methine proton of the ninth position of dihydropyran of one of the diastereomer)

5.86-5.89 (m, 1H, for the methine proton of the other diastereomer)

^{13}C-NMR ($CDCl_3$) δ ppm

34.3 (for the methylene carbon at fifth position of 2-cyclopentene for the two diastereomers)

35.7 (for the allylic methylene carbon at tenth position of dihydropyran of two diastereomers)

36.8 (for the other allylic methylene carbon atoms of two diastereomers at fourth position of 2-cyclopentene)

62.1 (for the seventh position of one of diastereomers)

73.8 (for the seventh position of the other diastereomers)

84.7 (for the quaternary carbons of dihydropyran of one of diastereomers)

87.7 (for the quaternary carbons of dihydropyran of the other diastereomers)

123.7 (for the methine carbons at eighth position of dihydropyran of one of diastereomers)

124.8 (for the methine carbons at eighth position of dihydropyran of the other diastereomers)

125.6 (for the other methine carbons of one of diastereomers of dihydropyran)

126.0 (for the other methine carbons of the other diastereomers of dihydropyran)

126.5 (for the methine carbons at third position of 2-cyclopentene of one of diastereomers)

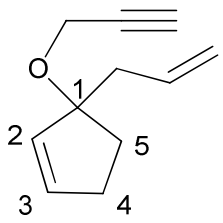
133.2 (for the methine carbons at third position of 2-cyclopentene of the other diastereomers)

133.9 (for the methine carbons of one of diastereomers of 2-cyclopentene)

134.4 (for the methine carbons of the other diastereomers of 2-cyclopentene)

3.4. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene 67

A 30% suspension of KH in mineral oil (0.86g, equivalent 6.48 mmol of active hydride) was washed with dry hexane under argon atmosphere. 10 mL dry tetrahydrofuran was added. 1-allylcyclopent-2-enol **64** (3.21 mmol) was added into the mixture with 3 mL THF. After 45 minutes 3-Bromo-1-(trimethylsilyl)-1-propyne (TMS) (6.45 mmol) was added with 3 mL THF dropwise. At the same time TBAI (0.12g, 0.32 mmol) was added respectively. It was stirred until alcohol was disappeared by TLC control. The resultant mixture was extracted with diethyl ether (3x25 mL) and dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/hexane at the ratio of 1:20 as the eluent to obtain 3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** as dark yellow oil 85% chemical yield.



67

R*f*=0.61 (silica gel – (EtOAc – Hexane), (1:20)

IR (neat): 3315, 3047, 2280, 1679, 692 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.67-175 (m, 1H, for the one of the diastereotopic methylene proton at fifth position of the ring)

1.78-185 (m, 1H, for the other diastereotopic methylene proton at fifth position of the ring)

2.13 (t, *J*=2.4 Hz, 1H, for acetylenic proton)

2.06-2.15 (m, 1H, for the one of the diastereotopic methylene proton at fourth position of the ring)

2.25 (d, *J*=7.2 Hz, 1H, for the other diastereotopic methylene proton at fourth position of the ring)

2.21-2.29 (m, 2H, for the allylic methylene protons of the allyl group)

3.73-3.82 (m, 2H, for the methylene protons of propargyl group)

4.85-4.89 (m, 2H, for the vinylic protons)

5.42-5.45 (m, 1H, for the methine proton at third position of the ring)

5.57-5.67 (m, 1H, for the internal vinylic proton)

5.82-5.85 (m, 1H, for the methine proton at second position of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

31.8 (for the methylene carbon at fifth position)

44.4 (for the methylene carbon at fourth position of the ring)

51.0 (for the allylic carbon of the allyl group)

72.9 (for the allylic carbon of the propargyl group)

77.0 (for the methine carbon of propargyl group)

81.7 (for the quaternary carbon of propargyl group)

91.8 (for the quaternary carbon of the ring)

117.4 (for the one of the vinylic carbon atom)

133.1 (for the other vinylic carbon atom)

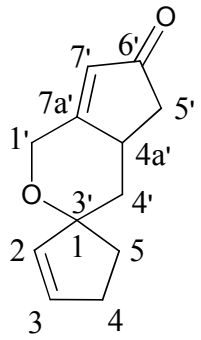
134.1 (for the methine carbon at third position of the ring)

136.1 (for the methine carbon at second position of the ring)

3.5. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c] pyran]-6'(4'H)-one 68 via the Pauson-Khand cycloaddition reaction (Diastereomeric mixture)

3-allyl-3-(prop-2-yn-1-yloxy)cyclopent-1-ene **67** (4.26 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (2.79g, 8.16 mmol), and stirred for 2h (TLC monitoring). Then, NMO (5.36g, 39.7 mmol) was added and stirred for 24h. The crude product

4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **68** was purified by flash column chromatography in 84% chemical yield.



68

R*f*=0.68 (silica gel – (EtOAc – Hexane), (1:2)

IR (neat): 1752, 1149, 715 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.56-1.74 (m, 3H, for the methylene protons of fourth prime position of dihydropyran of one diastereomer overlaps with one of the diastereotopic methylene protons at fourth prime position of dihydropyran of other diastereomer)

1.75-1.84 (m, 2H, for the other diastereotopic methylene protons of fourth prime position of the other diastereomer overlaps one of the diastereotopic methylene protons of fifth position of cyclopentene of one diastereomer)

1.92-2.00 (m, 2H, for the other distereotopic methylene protons at fifth position of cyclopentene of the other diastereomer)

2.11-2.18 (m, 3H, for the one of the diastereotopic methylene protons of fifth position of cyclopentene ring of the other diastereomer overlaps the allylic methylene protons of fourth position of cyclopentene of one diastereomer)

2.31-2.40 (m, 2H, for the allylic methylene protons at fourth position of cyclopentene of the other diastereomer)

2.43-2.50 (m, 1H, for the methine protons at the 4a' position)

2.54 (dd, J_1= 6.4 Hz and J_2= 18.4 Hz, 2H, for the methylene protons at the fifth prime position of one of the diastereomer)

2.77 (q, J=8.0 Hz, 1H, for the methine proton of the other diastereomer of 4a' position)

2.95 (d, J=6.8 Hz, 1H, for the methylene protons at fifth prime position of the other diastereomer)

2.99-3.02 (m, 1H, for the other one of the methylene protons of the diastereomer)

4.40 (dd, J_1=14.0 Hz and J_2=65.6 Hz, 2H, for the methylene protons at the second position of diastereomers)

5.12-5.19 (m, 2H, for the methine protons at the second position of diastereomers)

5.49-5.52 (m, 1H, for the methine proton at third position of one of the diastereomers)

5.82-5.84 (m, 1H, for the methine proton of the other diastereomer at third position)

5.85 (s, 1H, for the olefinic proton at seventh prime position of one of diastereomer)

5.82-5.92 (m, 1H, for the olefinic proton of the other diastereomer)

^{13}C-NMR ($CDCl_3$) δ ppm

19.9 (for the methylene carbon of the one of diastereomers at fifth position)

24.3 (for the methylene carbon of the one of the other diastereomer at fifth position)

30.7 (for the methylene carbon of the one of diastereomers at fourth prime position)

31.4 (for the methylene carbon of the one of the other diastereomer at fourth prime position)

36.4 (for the allylic methylene carbon atom of one of diastereomer at fourth position of cyclopentene)

39.6 (for the allylic methylene carbon atom of the other diastereomer at fourth position of cyclopentene)

41.9 (for the methylene carbon of one of diastereomer at fifth prime position)

42.8 (for the methylene carbon of the other diastereomer at fifth prime position)

45.4 (for the methylene carbon of the one of diastereomer at the 4a' position)

51.7 (for the methylene carbon of the other diastereomer at the 4a' position)

57.8 (for the methylene carbon of one of diastereomer bonded to the oxygen atom)

62.4 (for the methylene carbon of the other diastereomer bonded to the oxygen atom)

80.2 (for the quaternary carbon of one of diastereomer)

88.0 (for the quaternary carbon of the other diastereomer)

119.9 (for the methine carbon of the one of diastereomer at third position)

127.0 (for the methine carbon of the other diastereomer at third position)

131.7 0 (for the other methine carbon of the one of diastereomer at second position)

133.1 (for the other methine carbon of the other diastereomer at second position)

134.3 (for the quaternary carbon of one of diastereomer)

135.0 (for the quaternary carbon of the other diastereomer)

176.1 (for the other quaternary carbon of the one of diastereomer at 7a' position)

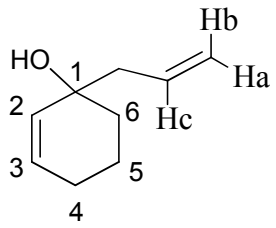
177.9 (for the other quaternary carbon of the other diastereomer at 7a' position)

207.7 (for the carbonyl carbons of the one of diastereomer)

211.6 (for the carbonyl carbons of the other diastereomer)

3.6. Synthesis of 1-allylcyclohex-2-enol 70

To a stirred solution of Mg turnings (4.54g, 37.5 mmol) and iodine turning (2 pieces) in dry ethyl ether (10 mL) at 25^{o}C equipped with a reflux condenser was added dropwise a mixture of allyl bromide (37.5 mmol) in anhydrous diethyl ether (2mL) with a injection syringe until the reaction begins. The mixture was allowed to reflux 45 minutes. The mixture was cooled down to 0^{o}C and the cyclohex-2-enone **69** (31.3 mmol) in diethyl ether (2 mL) was added dropwise. The resultant mixture was stirred 24 hours. The reaction mixture was hydrolyzed with saturated NH_4Cl solution (10 mL). The resultant mixture was extracted with diethyl ether (3X30 mL) and dried over anhydrous $MgSO_4$ and evaporated in vacuum. The crude product was purified by flash column chromatography by using EtOAc / hexane at the ratio of 1:5 as the eluent to obtain 1-allylcyclohex-2-enol **70** as colourless oil 80% chemical yield.



70

R*f*=0.26 (silica gel – (EtOAc – Hexane), (1:6)

IR (neat): 3325, 1485, 1352, 1206, 1185, 940, 710 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.23-1.27 (m, 1H, for one of the diastereotopic ethylene protons at fifth position of the ring)

1.55-1.77 (m, 3H, for the other methylene proton and the methylene protons at sixth position of the ring)

1.86 (bs, 1H, for the -O-*H* proton)

1.89-1.96 (m, 1H, for the one of the diastereotopic methylene protons at fourth position of the ring)

2.01-2.08 (m, 1H, for the other diastereotopic methylene protons at fourth position of the ring)

2.35 (d, *J*=7 Hz, 1H, for the allylic methylene protons)

5.09-5.14 (m, 2H, for the terminal vinylic protons; Ha and Hb)

5.62 (d, *J*=10 Hz, 1H, for the methine proton at second position of the ring)

5.87-5.97 (m, 1H, for the other methine proton at third position of the ring)

5.88-5.93 (m, 1H, for the internal vinylic proton; Hc)

^{13}C-NMR ($CDCl_3$) δ ppm

18.9 (for the methylene carbon at fifth position)

25.1 (for the methyl carbon at sixth position)

35.4 (for the methylene carbon at fourth position)

46.7 (for the allylic methylene carbon)

69.1 (for the quaternary carbon)

118.0 (for the vinylic carbon atom)

129.6 (for the vinylic carbon atom)

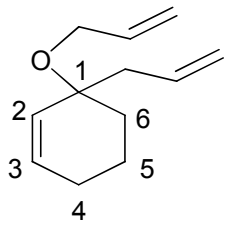
132.4 (for the third position carbon atom of the ring)

133.9 (for the second position carbon atom of the ring)

3.7. Synthesis of 3-allyl-3-(allyloxy)cyclohex-1-ene 71

A 30% suspension of KH in mineral oil (0.86g, equivalent 7.2 mmol of active hydride) was washed with dry hexane under argon atmosphere. 10 mL dry tetrahydrofuran was added. 1-allylcyclohex-2-enol **70** (3.5 mmol) was added into the mixture with 3 mL THF. After 45 minutes allyl bromide (8.51 mmol) was added with 3 mL THF dropwise. At the same time TBAI (0.27g, 0.72 mmol) was added respectively. It was stirred until alcohol was disappeared by TLC control. The reaction stopped adding 5 mL water. The resultant mixture was extracted with diethyl ether (3x25 mL) and dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash column chromatography by using

EtOAc/hexane in ratio of 1:20 as the eluent to obtain 3-allyl-3-(allyloxy)cyclohex-1-ene **71** as yellow oil 80% chemical yield.



71

R*f*=0.78 (silica gel – (EtOAc – Hexane), (1:15)

IR (neat): 1630, 1225, 980, 890 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.45-1.56 (m, 3H, for the diastereotopic methylene protons at fifth position and overlap one of the methylene protons at sixth position of the ring)

1.64-2.79 (m, 2H, for the other diastereotopic proton at fifth position and one of the diastereotopic methylene protons at fourth position)

1.82-2.00 (m, 1H, for the other diastereotopic proton at fourth position of the ring)

2.22-2.33 (m, 2H, for the allylic methylene protons of the allyl group)

3.87 (td, J_1=1 Hz and J_2=5 Hz, 2H, for the allylic methylene protons of the allyl group)

4.96-4.98 (m, 1H, for one of the terminal vinylic protons)

5.00-5.02 (m, 1H, for the other terminal vinylic proton)

5.03-5.04 (m, 1H, for one of the terminal vinylic protons)

5.19 (qd, J_1=2 Hz and J_2=17 Hz, 1H, for the other terminal vinylic proton)

5.21 (td, J_1=2 Hz and J_2=10 Hz, 1H, for the methine proton at the third position)

5.51-5.87 (m, 3H, for the internal vinylic protons and overlaps methine proton at second of the ring)

^{13}C-NMR ($CDCl_3$) δ ppm

18.3 (for the fifth position carbon atom of the ring)

24.0 (for the sixth position carbon atom of the ring)

30.8 (for the methylene carbon at fourth position)

43.0 (for the allylic carbon of the allyl group)

62.3 (for the allylic carbon of the allyl group)

73.4 (for the quaternary carbon of the ring)

114.3 (for the one of the vinylic carbon atom)

116.1 (for the other vinylic carbon atom)

129.6 (for the methine carbon at third position)

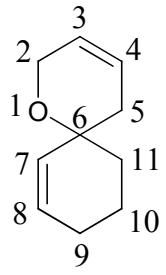
130.5 (for the vinylic carbon atom)

133.2 (for the other vinylic carbon atom)

135.2 (for the methine carbon atom at second position)

3.8. Synthesis of 1-oxaspiro[5.5]undeca-3,7-diene 72 via Ring closing metathesis using Grubbs catalyst

3-allyl-3-(allyloxy)cyclohex-1-ene **71** (2.25 mmol) in CH_2Cl_2 (10 mL) was added Grubbs first generation catalyst (0.09g, 0.11 mmol), and stirred for 24 hour (TLC monitoring). The product 1-oxaspiro[5.5]undeca-3,7-diene **72** was obtained as dark coloured oil purified by flash column chromatography in 83% chemical yield.



72

R*f*=0.68 (silica gel – (EtOAc – Hexane), (1:15)

IR (neat): 3050, 1625, 1210 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.48-1.56 (m, 2H, for the diastereotopic methylene protons at tenth position of cyclohexene)

1.70-1.77 (m, 2H, for the diastereotopic methylene at eleventh position of cyclohexene)

1.82-1.95 (m, 2H, for the allylic methylene protons at ninth position of cyclohexene)

1.97-2.07 (m, 2H, for the allylic methylene protons of dihydropyran)

4.05-4.18 (m, 2H, for the methylene protons at second position of dihydropyran)

5.65-5.70 (m, 3H, for the methine protons at seventh and eighth position of cyclohexene overlaps one of the methine protons at third position of dihydropyran)

5.78-5.82 (m, 1H, for the other methine proton of dihydropyran)

^{13}C-NMR ($CDCl_3$) δ ppm

17.6 (for the methylene carbon at tenth position of cyclohexene)

32.6 (for the methylene carbon at eleventh position of cyclohexene)

34.3 (for the methylene carbon of ninth position of cyclohexene)

34.6 (for the fifth position carbon of dihydropyran)

60.1 (for the methylene carbon of dihydropyran bonded to the oxygen atom)

67.6 (for the quaternary carbon atom)

121.7 (for the olefinic carbon atom found at third position of cyclohexene)

124.9 (for the olefinic carbon atoms found eighth position of cyclohexene)

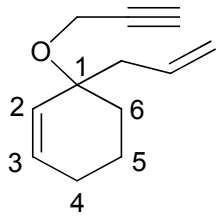
128.9 (for the other olefinic carbon at fourth position of dihydropyran)

129.9 (for the seventh position of cyclohexene)

3.9. Synthesis of 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene 73

A 30% suspension of KH in mineral oil (0.77g, equivalent 5.80 mmol of active hydride) was washed with dry hexane under argon atmosphere. 10 mL dry tetrahydrofuran was added. 1-allylcyclohex-2-enol **70** (2.90 mmol) was added into the mixture with 3 mL THF. After 45 minutes 3-Bromo-1-(trimethylsilyl)-1-propyne (TMS) (0.29 mmol) was added with 3 mL THF dropwise. At the same time TBAI

(0.12g, 0.32 mmol) was added respectively. It was stirred until alcohol was disappeared by TLC control. The resultant mixture was extracted with diethyl ether (3x25 mL) and dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash column chromatography by using EtOAc/hexane at the ratio of 1:20 as the eluent to obtain 3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** as dark coloured oil 90% chemical yield.



73

R*f*=0.63 (silica gel – (EtOAc – Hexane), (1:20)

IR (neat): 3035, 3304, 2248, 1632, 692 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.46-1.59 (m, 2H, the diastereotopic methylene protons at fifth position of the ring)

1.66-1.71 (m, 1H, for one of the methylene protons at sixth position of the ring)

1.76-1.82 (m, 2H, for the diastereotopic protons at fourth position of the ring)

1.86-2.01 (m, 1H, for the other methylene protons at sixth position of the ring)

2.27-2.34 (m, 2H, for the allylic methylene protons)

2.26 (t, *J*=2.4 Hz, 1H, for the acetylenic proton)

4.02 (d, *J*=2.8 Hz, 2H, for the diastereotopic methylene protons of propargyl unit)

4.95-5.01 (m, 2H, for the terminal vinylic protons)

5.52 (td, J_1=2 Hz and J_2=10 Hz, 1H, for the methine proton at third position of the ring)

5.75-5.83 (m, 1H, or the internal vinylic proton)

5.90 (td, J_1=3.6 Hz and J_2=10 Hz, 1H, for the methine proton at second position)

^{13}C-NMR ($CDCl_3$) δ ppm

17.7 (for the fifth position carbon atom of the ring)

23.6 (for the sixth position carbon atom of the ring)

30.5 (for the fourth position carbon atom of the ring)

42.9 (for the allylic methylene carbon of allyl group)

49.4 (for the methylene carbon in propargyl group)

71.4 (for the quaternary carbon)

74.1 (for the methine carbon in propragyl group)

80.3 (for the quaternary carbon in propargyl group)

116.0 (for the vinylic carbon)

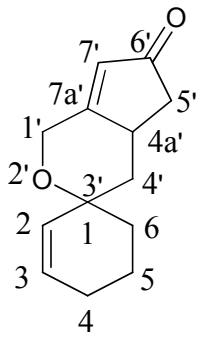
128.3 (for the third position carbon of the ring)

131.2 (for the vinylic carbon)

133.4 (for the second position carbon of the ring)

3.10. Synthesis of 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c] pyran]-6'(4'H)-one 74 via the Pauson-Khand cycloaddition reaction (Diastereomeric mixture)

3-allyl-3-(prop-2-yn-1-yloxy)cyclohex-1-ene **73** (4.26 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (2.79g, 8.16 mmol), and stirred for 2h (TLC monitoring). Then, NMO (5.36g, 39.7 mmol) was added and stirred for 24h. The crude product 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta[c]pyran]-6'(4'H)-one **74** was purified by flash column chromatography in 83% chemical yield.



74

R*f*=0.68 (silica gel – (EtOAc – Hexane), (1:2)

IR (neat): 1760, 1132, 715 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ ppm

1.19-1.29 (m, 3H, for the diastereotopic methylene protons at sixth position and for the one of the diastereotopic methylene protons at fifth position of cyclohexene)

1.42-1.48 (m, 3H, for the other diastereotopic proton at fifth position of cyclohexene)

1.61-1.66 (m, 1H, for the one of the diastereotopic methylene protons at fourth prime position)

1.80-1.87 (m, 1H, for the other diastereotopic methylene protons at fourth prime position)

2.40 (dq, J_1=6.4 Hz and J_2=14.2 Hz, 2H, for the allylic methylene protons at fourth position of cyclohexene)

2.70 (q, J=7.6 Hz, 1H, for the methine proton at 4a' position)

3.00-3.02 (m, 2H, for the diastereotopic methylene protons at fifth prime position)

4.56 (q, J=14.4 Hz, 2H, for the methylene protons that is bonded to the oxygen atom)

5.03-5.11 (m, 1H, for the methine proton at third position)

5.08 (s, 1H, for the olefinic proton that is found at the seventh prime position)

5.80-5.90 (m, 1H, for the other methine at second position)

^{13}C-NMR ($CDCl_3$) δ ppm

20.9 (for the methylene carbon at fifth position of cyclohexene)

25.7 (for the methylene carbon at sixth position of cyclohexene)

33.1 (for the methylene carbons at the fourth position)

43.9 (for the methylene carbons at the fourth prime position)

46.8 (for the methine carbon at 4a' position)

51.1 (for the methylene carbon at fifth prime position)

65.0 (for the methylene carbon that is bonded to the oxygen atom)

81.3 (for the quaternary carbon)

118.8 (for the methine carbons at third position of the cyclohexene)

121.7 (for the methine carbons at second position of the cyclohexene)

133.7 (for the methine carbon at seventh prime position)

183.2 (for the quaternary carbon at 7a' position)

212.8 (for the carbonyl carbon)

CHAPTER IV

4. CONCLUSION

In this study 6-oxaspiro[4.5]deca-1,8-diene **66** and 1-oxaspiro[5.5]undeca-3,7-diene **72** obtained by using Grubbs First Generation Catalyst with 80% and 82% overall chemical yield respectively. Then, 4a',5'-dihydro-1'H-spiro[cyclopent[2]ene-1,3'-cyclopenta[c] pyran]-6'(4'H)-one **68** was synthesized via Pauson-Khand reaction in the presence of NMO as a promoter and $Co(CO)_8$ with respect to 82% overall chemical yield. In the same manner 4a',5'-dihydro-1'H-spiro[cyclohex[2]ene-1,3'-cyclopenta [c]pyran]-6'(4'H)-one **74** obtained with 84% overall chemical yield.

Spiro dihydropyran and spirocyclopentenone-pyran compounds found in the structure of natural products that has biological activities, were synthesized by Ring Closing Metathesis and Pauson-Khand reaction which are frequently used methods in the literature for the synthesize of spirocyclic units.

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