T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
Department of Chemistry

SYNTHESIS OF CYCLOPENTENE BASED SPIROCYCLIC COMPOUNDS VIA RING CLOSING METATHESIS AND PAUSON KHAND CYCLOADDITION REACTION

DOCTOR OF PHILOSOPHY

DURUKAN KOÇ

ACADEMIC SUPERVISOR
Prof. Dr. F. Devrim ÖZDEMİRHAN

BOLU, OCAK - 2024

APPROVAL OF THE THESIS

SYNTHESIS OF CYCLOPENTENE BASED SPIROCYCLIC COMPOUNDS VIA RING CLOSING METATHESIS AND PAUSON-KHAND CYCLOADDITION REACTION submitted by **Durukan KOÇ** and defended before the Examining Committe Members listed below in partial fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University in 3.01.2024** by

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ABSTRACT

SYNTHESIS OF CYCLOPENTENE BASED SPIROCYCLIC COMPOUNDS VIA RING CLOSING METATHESIS AND PAUSON-KHAND CYCLOADDITION REACTION
PHD THESIS
DURUKAN KOÇ
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF. DR. F. DEVRİM ÖZDEMİRHAN)

BOLU, JANUARY 2024
xiii + 77

N-containing heterospirocyclic compounds.is extremely important to synthesize due to its active role in biological, chemical, and pharmaceutical chemistry.
The conformational properties of spirocyclic compounds from the quaternary carbon atom are important for organic asymmetric synthesis chemistry and therefore for the synthesis of new pharmaceutical active substances. In addition, it is known that *N*-containing heterocyclic compounds are found in many useful natural products and are highly effective and widely applied.
Due to these features, Ring Closing Metathesis (RCM), one of the important and effective methods of olefin metathesis, was chosen to synthesize azo spiro compounds.
Grubbs's second generation catalyst was preferred among Ru-based catalysts for these methods due to their thermal stability and high catalytic activity. On the other hand, the Pauson-Khand reaction, the most effective method for the cyclopentene ring, was preferred and it was used in the presence of NMO for reaction enhancement.
According to this information, synthesis of 2-methyl-6-azaspiro [4.5] deca-1,8-diene and benzyl 7-methyl-1-azaspiro[4.4]nona-3,6-diene-1-carboxylate by Ring Closing Metathesis and synthesis of 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[*c*]pyridin]-2-en-6'(4'*H*)-one and benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[*c*]pyrrol]-2-ene-2'-carboxylate via Pauson-Khand reaction.
Continuing research on chirally spiro structures, which we have successfully synthesized, is aimed to help with new drug discoveries from drug chemistry, synthesis chemistry, and *N*-containing hetero spiro compounds.

KEYWORDS: Asymmetric Synthesis, *N*-Heterospirocyclic Compound, Ring Closing Metathesis, Pauson-Khand Reaction.

ÖZET

SİKLOPENTENE HALKASI İÇEREN SPİROSİKLİK BİLEŞİKLERİN HALKA KAPAMA METATEZİ VE PAUSON KHAND SİKLOKATILMA REAKSİYONU ÜZERİNDEN SENTEZİ

DOKTORA TEZİ
DURUKAN KOÇ
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF. DR. F. DEVRİM ÖZDEMİRHAN)

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N - heterospirosiklik bileşiklerin biyolojik, kimyasal ve farmasötik kimyadaki aktif rolü nedeniyle sentezlenmesi son derece önemlidir.
Spirosiklik bileşiklerin kuaterner karbon atomundan gelen konformasyonel özellikleri organik asimetrik sentez kimyası ve bundan dolayı yeni ilaç etken maddelerin sentezi için önemlidir. Ek olarak, *N* - hetero bileşiklerin birçok yararlı doğal üründe bulunduğu ve oldukça etkili yaygın olarak uygulandığı bilinmektedir Bu özelliklerinden dolayı azo spiro bileşiklerinin sentezlenmesinde olefin metatezinin önemli ve etkili yöntemlerinden biri olan Halka Kapama Metatezi (HKM) seçilmiştir. Bu yöntemler için, termal kararlılıkları ve yüksek katalitik aktiviteleri nedeniyle Ru bazlı katalizörler arasında Grubbs'un 2. nesil katalizörü tercih edildi. Öte yandan, siklopenten halka sentezi için en etkili yöntem olan Pauson-Khand reaksiyonu tercih edilmiş ve reaksiyon güçlendirme için NMO varlığında kullanılmıştır.
Bu bilgiler ışığında, Halka Kapama Metatezi tarafından 2-methyl-6-azaspiro [4.5] deca-1,8-diene ve benzyl 7-methyl-1-azaspiro[4.4]nona-3,6-diene-1-carboxylate sentezi ve 3-methyl-1',2',4'a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[*c*]pyridin]-2-en-6'(4'*H*)-one ve benzyl 3-methyl-5'-oxo-3',5',6',6'a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[*c*]pyrrol]-2-ene-2'-carboxylate sentezi Pauson-Khand reaksiyonu ile gerçekleştirilmiştir.
Başarılı bir şekilde sentezlediğimiz kiral spiro yapıları üzerinde devam eden araştırmalar, ilaç kimyası, sentez kimyası ve *N*-hetero spiro bileşiklerinden yeni ilaç keşiflerine yardımcı olmayı amaçlamaktadır.

ANAHTAR KELİMELER: Asimetrik Sentez, *N*-Heterospirosiklik Bileşikler, Halka Kapama Metatezi, Pauson-Khand Reaksiyonu

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LIST OF ABBREVIATIONS AND SYMBOLS

Acac: Acetylacetone

Atm: Atmosphere

Cbz: Carboxybenzyl

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

$CDCl_3$: Chloroform-d

CH_2Cl_2 : Dichloromethane

$Co_2(CO)_6$: Dicobalt hexacarbonyl

$Co_2(CO)_8$: Cobalt Carbonyl

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

CO: Carbon monoxide

3D: Three dimensional

^oC: Centigrade

NHC: N-Heterocyclic carbene

Ru: Ruthenium

Mo: Molibdium

DNA: Deoxyribonucleic Acid

RNA: Ribonucleic Acid

DCM: Dichloromethane

EtOAc: Ethyl acetate

Glu: Glutamic acid

Hz: Heartz

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

IR: Infra Red

ml: Milliliter

mmol: Millimole

RCM: Ring Closing Metathesis

NMO: 4-methyl-morpholine N-oxide

RCEYM: Ring Closing Eneyne Metathesis

ROM: Ring Opening Metathesis

IUPAC: The International Union of Pure and Applied Chemistry

AChE: Acetylcholinesterase

ROMP: Ring Opening Metathesis polymerization

CM: Cross Metathesis

HMTs: Histone methyltransferase

UV: Ultra-violet

TLC: Thin Layer Chromatography

RRM: Ring Rearrangement Metathesis

$NaBH_4$: Sodium tetrahydroborate

NH_4Cl: Ammonium Chloride

PD: Parkinson's Disease

Ph: Phenyl

$P(OPh)_3$: Triphenyl phosphite

PKR: Pauson-Khand Reaction

SiO_2: Silicon dioxide

TMANO: Trimethylamine-N-oxide

Ts: Tosyl

ppm: Parts per million

s: Singlet

bs: Broad singlet

d: Doublet

dd: Doublet of doublet

ddd: Doublet of doublet of doublet

t: Triplet

tdd : Triplet of doublet of doublet

qd : Quartet of doublet

dt: Doublet of triplet

td: Triplet of doublet

m: Multiplet

ddt: Doublet of doublet of triplet

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1. INTRODUCTION

1.1 Cyclic Chemistry

Cyclic compound is defined well where some of its atoms form a ring structure. They can be carbocycles (only carbon atoms), inorganic cyclic compounds (no carbon atoms), or heterocyclic compounds (both carbon and non-carbon atoms) (1).

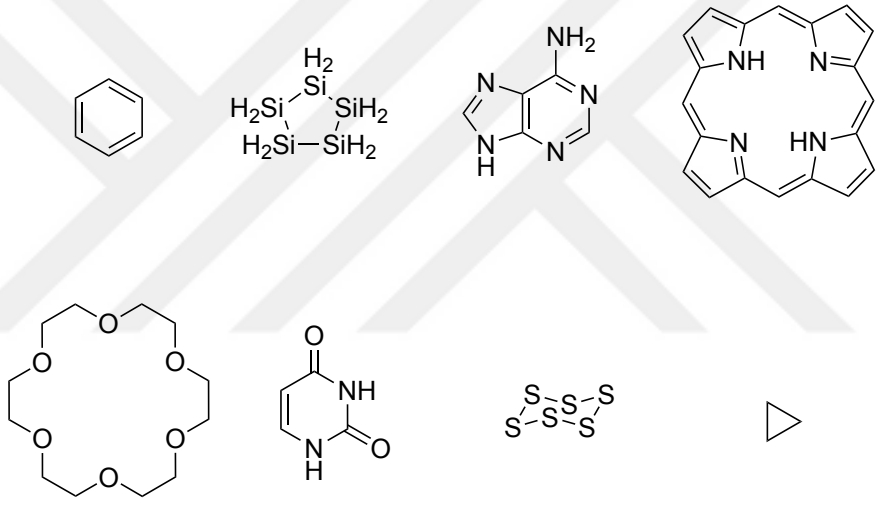


Figure 1.1 Examples of Cyclic Compounds

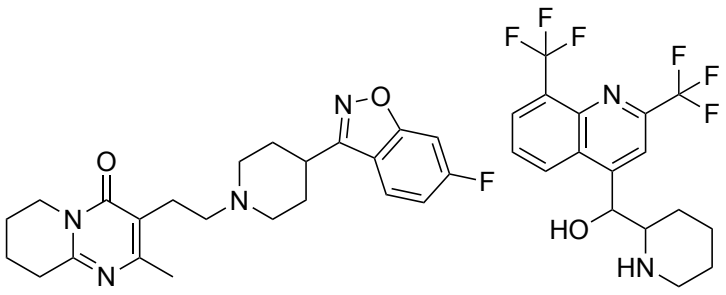
The complex structures of natural compounds, both acyclic and macrocyclic, have fascinated organic chemists since their elucidation in the 1950s due to their intricate stereochemical relationships (2).

1.2 Bicyclic Chemistry

Bicyclic compounds are organic compounds consisting of two rings that are connected in one of three ways: fused, bridged, or spiro-linked. The way in which these rings are connected plays a significant role in determining the compound's physical and chemical properties.

Studying bicyclic compounds is an essential aspect of organic chemistry, it can cause the discovery of new materials, drugs, and other compounds that could prove valuable in multiple industries.

Piperidine is one of the most popular rings used in drugs and bioactive agents (3). Recently, researchers have shown a preference for using small cyclic molecules that are rich in sp3. Therefore, the intrinsically conformationally restricted bicyclic piperidines have gained interest in drug discovery programs. For instance, the antipsychotic drug Risperidone and the antimalarial drug mefloquine contain the saturated bicyclic piperidine fragment, as shown in Figure 1.2 (4).



risperidone
antipsychotic drug

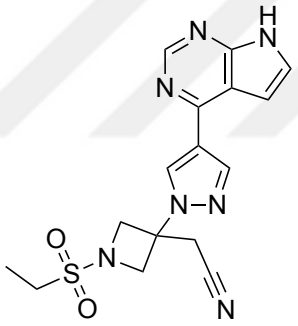
mefloquine
antimalarial drug

Figure 1.2 Bicyclic Compounds Examples

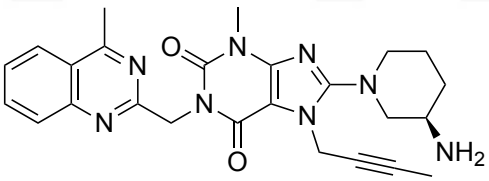
1.2.1 Fused Bicycle Compound

Fused compounds in chemistry occur when two separate molecular rings share one or more bonds, leading to the formation of an interconnected structure (5). Fused compounds, such as steroids, vitamins, and alkaloids, are frequently found in natural products and possess diverse biological activities.

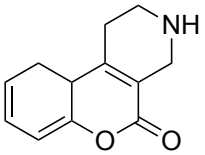
N-heterocycles, such as pyrimidines and purines, are essential components of RNA and DNA (6). Bicyclic heterocyclic fused with pyrimidine has been used in many treatments and has also led to the development of various drugs due to its powerful biological properties. For instance, Baricitinib, an anti-inflammatory drug, and Linagliptin, an antidiabetic drug, can be given as examples of pyrimidine-fused bicyclic heterocyclic drugs used in clinical practice (7). Additionally, tetrahydropyrido[3,4-c] coumarins have shown potential as anticancer, antifungal, antipsychotic, and anticholinergic bronchodilators (8) .



Baricitinib



Linagliptin



tetrahydropyrido[3,4-c]coumarins

Figure 1.3 Examples of Fused Bicyclic Compounds

1.2.2 Bridged Bicyclic Compound

Atoms tethering across a ring can create compounds. This structure is uneven, and where reactions occur on one side of the atom bridge.

Core structures found in natural and nature-inspired molecules, such as alkaloids play a crucial role in synthesizing bridged azabicyclic systems. These systems have potential medical submissions, including the improvement of anticancer and antiparasitic drugs. Selective transformations, such as transannular ring contraction and cycloaddition, are used to achieve the desired outcome (9).

The lycopodium alkaloids, such as lycopodine, lycodine, fawcettimine, and miscellaneous, are classified as quinolizine, pyridine, and alpha-pyridone alkaloids (10). These alkaloids are known to be potent inhibitors of acetylcholinesterase (AChE) (11). Huperzine A has been studied as a potential treatment for diseases characterized by neurodegeneration, including Alzheimer's disease (12).

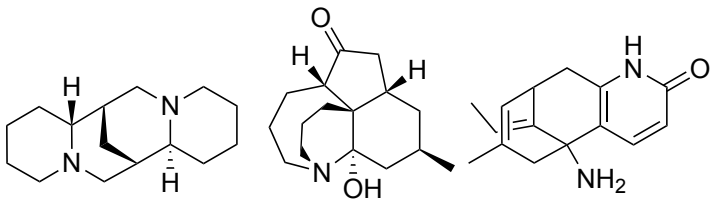


Figure 1.4 Examples of Bridged Bicyclic Compounds

1.3 Spirocyclic Chemistry

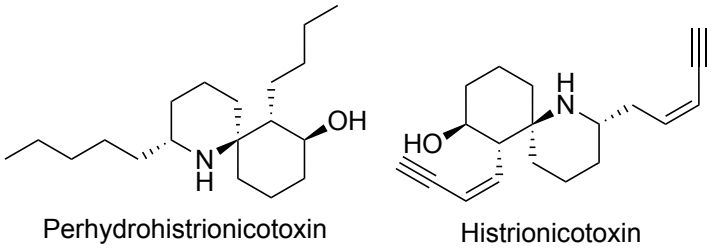
1.3.1 General Information

The study of spirocycles dates back to the late 1890s when Von Baeyer conducted initial research on this class of bicyclic hydrocarbons. Spiro rings are defined as systems are two or more rings connected by a single shared atom by IUPAC (10).

Organic compounds known as spiro compounds are composed of rings linked together by a single atom, resulting in distinctive properties like three-dimensional structural attributes that stem from their innate rigidity (11). The chirality of the spiro carbon is particularly noteworthy since it gives the molecule asymmetry, which is crucial for biological function (12). Recently, spiro compounds have gained attention because of their intriguing conformational traits and structural effects on the system of biological (13).

The neurotoxic properties of perhydrohistrionicotoxin are related to the spiro carbon atom (14).

The Dendrobats histrionius, dart frog a species of poisonous frog in Columbia, produces a strong substance that works against nicotinic receptors. This substance is known as (K)-histrionicotoxin and is classified as a spirocyclic alkaloid (15).



Perhydrohistrionicotoxin Histrionicotoxin

Figure 1.5 Perhydrohistrionicotoxin and Histrionicotoxin

1.3.2 Classification of Spirocylic Compounds

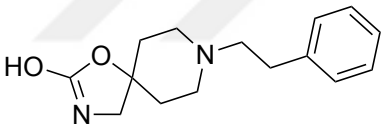
Spiro compounds can be categorized into three different varieties subject to the type of spirocycles present in the molecule.

Firstly, also known as 'isolated' spiro compounds, are those in which the two rings are not fused to any other rings.

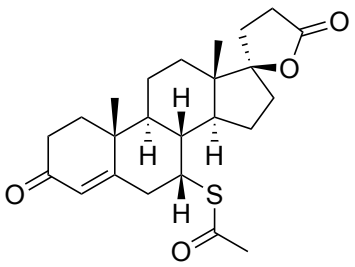
The second one, also known as 'condensed' spiro compounds, are those in which the two rings are fused to each other.

Finally, also known as 'bridged' spiro compounds, are those in which the two rings are fused to each other by a bridge (16).

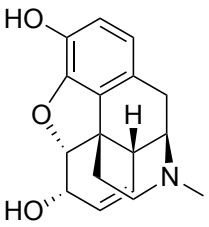
Fenspiride, spironolactone (17), and morphine (18) can be given as examples of these classes, respectively.



fenspiride



spironolactone



morphine

Figure 1.6 Example of Fused, Bridged, and Spiro Compounds

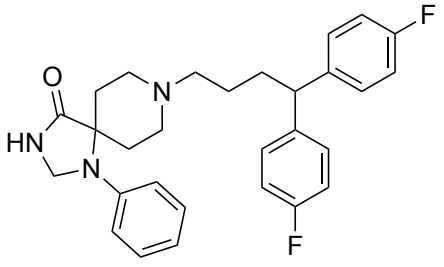
1.3.3 Importance of Spirocyclic Compounds

Spirocyclic compounds offer a varied range of biological activities. Their intricate and inflexible scaffold structures provide numerous advantages for drug discovery initiatives (19). Designing the 3D orientation of pharmacophores by using the rigid structure of these compounds can efficiently enhance H-bonding, hydrophobic, and p-stacking interactions (20). This results in improved recognition between the drug and its target, as well as better physicochemical properties, including solubility and lipophilicity (21).

The unique three-dimensional characteristics of spirocyclic compounds, owing to their ring systems, allow drug leads to break free from the constraints of flat aromatic molecules (22). With the limitations of medicinal chemistry efforts in this area being explored extensively in recent years, researchers are hopeful that chemical saturation, distinct three-dimensionality (23), and stereochemical richness might produce novel chemical entities that can be effectively developed into drug leads (24). The spiro functionality is a well-known feature of phytochemicals such as alkaloids, lactones, and terpenoids (25).

The aza-spiro compounds are tachykinin antagonists used to treat various conditions such as depression, anxiety, painful, inflammation, migraine, emesis, and postherpetic neuralgia (19).

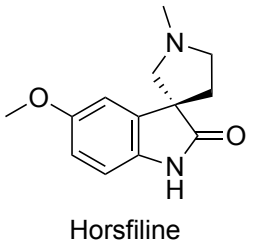
Fluspirilene, a spirocyclic antipsychotic drug, was discovered by Janssen Pharmaceutica in 1963. It was approved for treating schizophrenia by 1970 (26).



Fluspirilene

Figure 1.7 Structure of Fluspirilene

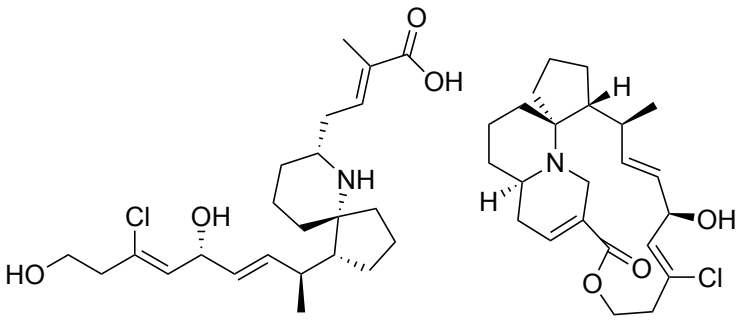
1991 by Bodo et al. an oxindole alkaloid with a spiro[indole-pyrrolidone] nucleus Horsfiline, was discovered in Horsfieldia Superba, a Malaysian tree commonly used in local medicine (27,28).



Horsfiline

Figure 1.8 Structure of Horsfiline

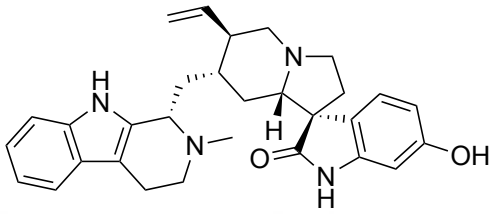
In 1996, Uemura and et.al. published a report on the discovery and analysis of two unprecedented alkaloids. Known as Pinnaic acid, these compounds were extracted from Pinna muricata and have been observed to possess inhibitory properties against cytosolic. Additionally, Halichlorine was secluded from the marine sponge Halichondria Okadai and has demonstrated its ability to inhibit the vascular cell adhesion molecule. Halilchlorine, an inhibitory variant of the vascular cell adhesion molecule, has been inaccessible from the marine sponge Halichondria Okadai. (29).



Pinanpinnaic acid Halichlorine

Figure 1.9 Pinanpinnaic acid and Halichlorine

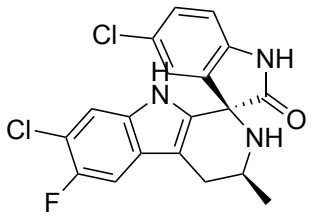
Additionally, Antitumor alkaloids known as Strychnofoline are found in the leaves of Strychnos usambarensis. melanoma and Ehrlich tumor cell cultures have a potent antimitotic effect on mice (30).



Strychnofoline

Figure 1.10 Strychnofoline

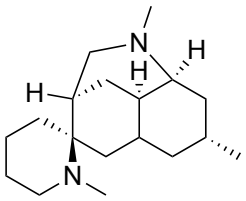
The Novartis Institute of Tropical Diseases discovered a new spiroindolone compound, formerly known as cipargamin, through high-throughput screening. This compound exhibits potent and novel antimalarial activity (31).



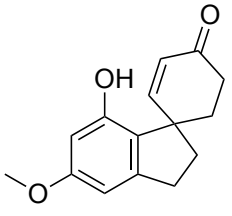
Cipergamin

Figure 1.11 Structure of Cipargamin

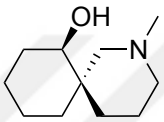
1.3.4 Examples of Spirocylic Compounds in Natural Products



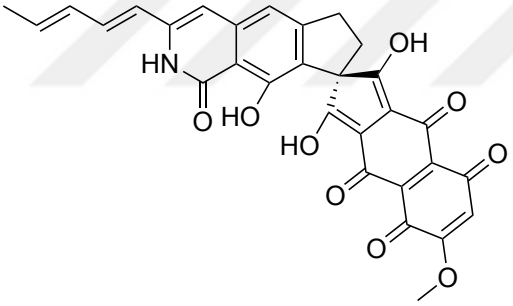
Nankakurine B



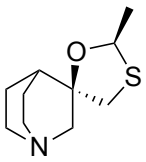
Cannabispirenone A



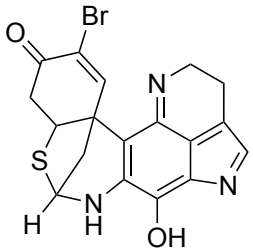
(+)-Sibirine



Fredericamycin



Cevimeline



Discorhabdin A

Figure 1.12 Examples of Spirocylic Compounds in Natural Products

1.3.5 Synthesis of Spirocyclic Compounds

Synthesizing spiro compounds is a challenging task due to a variety of factors. One of the major challenges involved is group compatibility. One of the biggest challenges in this context is dealing with a quaternary and chiral spiro atom in a way that is stereoselective (26). It's important to note that the spiro atom in these compounds can have both central and axial chirality. Despite the lack of an asymmetric center, the rigidity of the spirocycle makes it possible to form two enantiomers (32).

To analyze a spiro unit, there are several methods, but antithetic analysis can information on a large number of potential structures that can be used to synthesize target spiro molecules. To conduct the analysis, bond disconnection can be performed either at the branch appendages (bonds other than exocyclic), at the ring appendages that exocyclic bond, or at both locations (32).

The synthesis of spirocycles: (a) alkylation strategies, (b) metal-catalyzed cyclization, (c) ring-closing metathesis, (d) cycloaddition reaction, (e) radical methods, and (f) rearrangement (22). Advantages our group focused on the RCM and the Pauson-Khand cycloaddition reaction in this study.

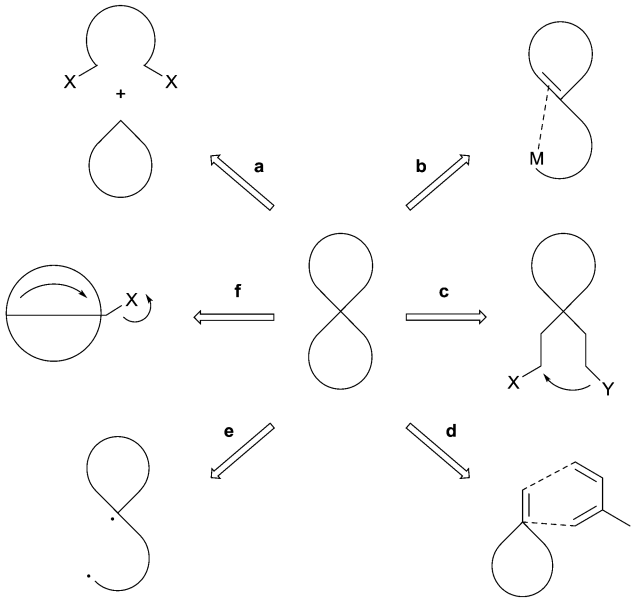


Figure 1.13 Synthesis of Spirocyclic

1.4 Heterocyclic Chemistry

1.4.1 General information

Heterocyclic compounds are a diverse class of cyclic organic compounds that include at least one hetero atom, which is an atom other than carbon, in their ring system. These compounds are widely explored due to their versatile biological and pharmaceutical activities. The heteroatoms that are commonly found in heterocyclic compounds are nitrogen (N), oxygen (O), and sulfur (S), but other heteroatoms such as phosphorus, selenium, and boron can also be present (33).

Heterocyclic compounds are widely used in drug design and development due to their excellent pharmacological properties. Additionally, these compounds find applications in various fields including agrochemicals, materials science, and electronics (34).

1.4.2 Classification Of Heterocyclic Compounds

Heterocyclic compounds are categorized as aliphatic or aromatic based on their structure and electronic arrangement.

- Aliphatic heterocyclic compounds that do not have double bonds in saturated heterocycles include cyclic amines, amides, ethers, and thioethers (35).

- Aromatic heterocyclic compounds are similar in structure to benzene, which is a six-membered ring of carbon atoms with alternating double bonds. Aromatic heterocyclic compounds also follow Huckel's rule, which is a set of guidelines that determines the aromaticity of organic compounds. It must be cyclic in nature, have a planar geometry, and have a system of conjugated double bonds (36).
  Aromatic heterocyclic compounds work a vital role in a variety of natural and synthetic processes. They are commonly found in many organic molecules, including DNA, amino acids, and vitamins. Understanding the properties and behavior of these compounds is essential for the development of new drugs and materials.

1.5 Olefin Metathesis

1.5.1 General Information and History

Olefin metathesis is one of the frequently used excited as a synthetic method for forming carbon-carbon double bonds (37). This metathesis is a metal-catalyzed transformation that rearranges carbon-carbon double bonds through cleavage and recombination (38).

The Ziegler-Natta reaction was first observed in the 1950s during polymerization processes (39). An industrial chemist named DuPont discovered Alumina-supported molybdenum species were used as a catalyst to transform propene into 2-butenes and ethylene ultimately leading to the polymerization of cyclopentene and norbornene, which were formerly unknown polymers (40). These findings were followed by the development of enriched catalytic systems depending on molybdenum and tungsten, which could also catalyze the polymerization of cyclo olefins and the dismutation or conversion of lined olefins (41).

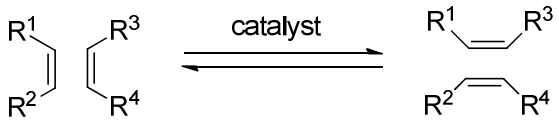


Figure 1.14 Metathesis of Two Olefinic Bond

1.5.2 General Mechanism of Olefin Metathesis

The olefin reaction mechanism was discovered in the 1950s, but it was not until 1971 that a generally accepted mechanism was found. Consistent with this mechanism, introduced by Chauvin, the coordination of an olefin to a metal carbene catalytic kind results in the reversible formation of a metal cyclobutane (42).

There are two possible directions for the cyclization of this intermediate. The first of these ways results in the regeneration of non-productive starting materials. Other pathways yield an olefin that replaces carbon with the alkylidene of the catalyst (41).

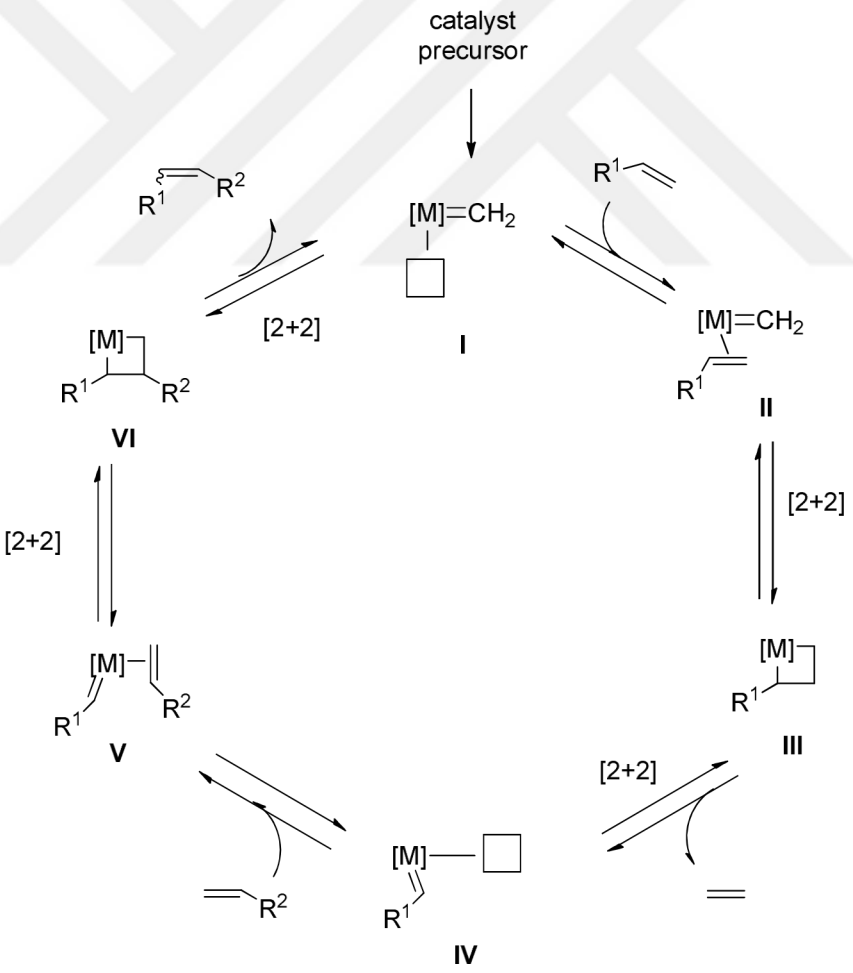


Figure 1.15 Olefin Mechanism

1.5.3 Catalyst in Olefin Metathesis

Olefin metathesis has significant advancements in the development of catalysts that have been a major focus of research. Through the application of organometallic principles and an understanding of fundamental reaction mechanisms, exceptional catalysts have been developed. These catalysts allow for previously impossible reactions or deliver unparalleled efficiency and selectivity.

Molybdenum and tungsten-essential alkylidines are catalysts with a good degree of oxidation and allow for complementary modes of reactivity and functional group tolerance.

After the improvement of a tantalum-based alkylidene complex in the 1970s (43), many catalysts have been developed for olefin metathesis reactions. One of them, the Schrock catalyst, is a four-coordinate 14-electron alkylidene complicated. Mo-1 is highly reactive and has been found to have great open-mindedness to functional groups (44).

In 1992 the Grubbs group determined the first precise, metathesis-active ruthenium-based catalyst. They reacted $RuCl_2(PPh_3)_4$ with 3,3-diphenyl cyclopropene, due to its low reactivity, the complex was active only in the ring-opening metathesis polymerization (ROMP) of norbornene (45).

The utilization of PCy_3 as a substitution for PPh_3 eventuated a notable rise in metathesis efficiency and led to the discovery of Ru-0,(46), which has proven to be highly effective in catalyzing RCM. However, the catalyst has restricted synthetic utility due to the low beginning rate of the resultant diphenylvinyl carbene and the prolonged synthesis of the cyclopropane (47).

In 1996, the Grubbs group developed the benzylidene complex (48), that is namely the first-generation Grubbs catalyst (49). It was designed to address certain issues related to olefin metathesis reactions(50). The first-generation catalyst pathway operates through dissociation via a 14-electron complex (51). Based on mechanistic studies, it has been determined that the dissociation of phosphine is the step that determines the rate (52). While Ru-1 is effective, electron-poor olefin may not work well in reactions (53).

Grubb's second-generation catalyst exhibited a much higher catalytic activity compared to the first-generation catalyst in the Ring Closing Metathesis reaction of diethyl diallylmalonate, much more times faster(54). Surprisingly, second-generation catalyst is efficient in catalyzing metathesis reactions with replaced olefins and electron-deficient olefins (55), whereas first-generation catalyst absent effectiveness in these reactions (56).

Catalyst stability in solution limits turnover numbers, especially for challenging substrates. In this case, it is necessary to add a catalyst continuously or in large amounts to the mixture (37)

The first-generation catalysts decompose in solution swiftly when submitted to oxygen, notwithstanding their superb steadiness in the solid state (57).

Compared to the first-generation catalyst, second-generation catalysts exhibit enhanced thermal stability, both in the solid state and in solution (54). This is because the second-generation catalysts have lower rates of phosphine dissociation, which contributes to their improved thermal stability (58) (59)

The steric and electronic effects exhibited by NHC ligands (60) are properties that prolong the life of the catalyst and mainly affect the activity of the catalyst. (61)

The Chauvin (62) mechanism for olefin metathesis involves a 16-electron alkylidene complex that serves as a precatalyst, coordinated with a phosphine or NHC (63). The complex dissociates to form a 14-electron active catalyst, which binds with an olefin to form a metallacyclobutane intermediate (64). Finally, the intermediate undergoes cycloreversion to produce the alkene and alkylidene, completing the metathesis (65).

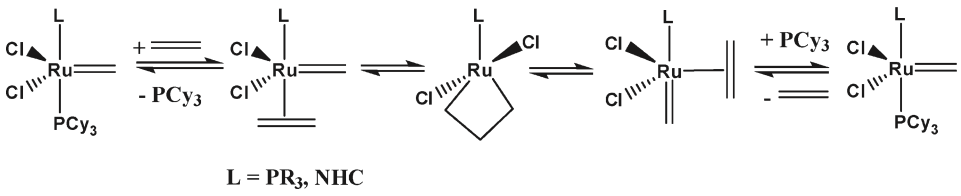


Figure 1.16 Mechanism of Ru Catalyst in Olefin Metathesis

The Hoveyda group achieved a further improvement in catalyst stability in 1999 (66). Ru-3 is beginning RCM 30 times slower at the reaction indicated but propagates x4 faster in the catalytic cycle than Ru-1. The handling of 2-isopropoxystyrene with Grubbs first generation catalyst resulted in the creation of Ru-3, which displays unparalleled stability when exposed to air and moisture. Furthermore, this complex is also recyclable due to its remarkable stability during silica gel column chromatography (67).

The Hoveyda group defined the catalyst Ru-4 in 2000. This catalyst combines the improved stability of Ru-3 due to the chelated styrenyl ether ligand, with the enhanced catalytic reactivity of the NHC ligand of Grubbs second generation catalyst (68).

The "Hoveyda" or "Hoveyda-Grubbs" recyclable catalyst is not only highly reactive but also incredibly resistant to air and moisture. The Ru-4 catalyst has a broad substrate scope and reactivity (69), including electron-poor olefin substrates like acrylonitriles (70), fluorinated alkenes (71), sulfones (72), and vinyl chlorides (73).

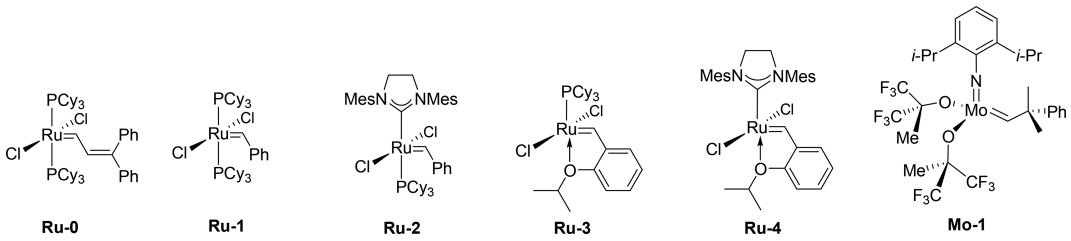


Figure 1.17 Some of the Catalysts in Olefin Metathesis

1.5.4 Type of Olefin Metathesis

Functionalized polymers were made using Ring Opening Metathesis Polymerization, while small to large heterocyclic systems were synthesized through Ring Closing Enyne Metathesis and Ring Closing Metathesis, and olefins with functional groups were Cross Metathesis (74).

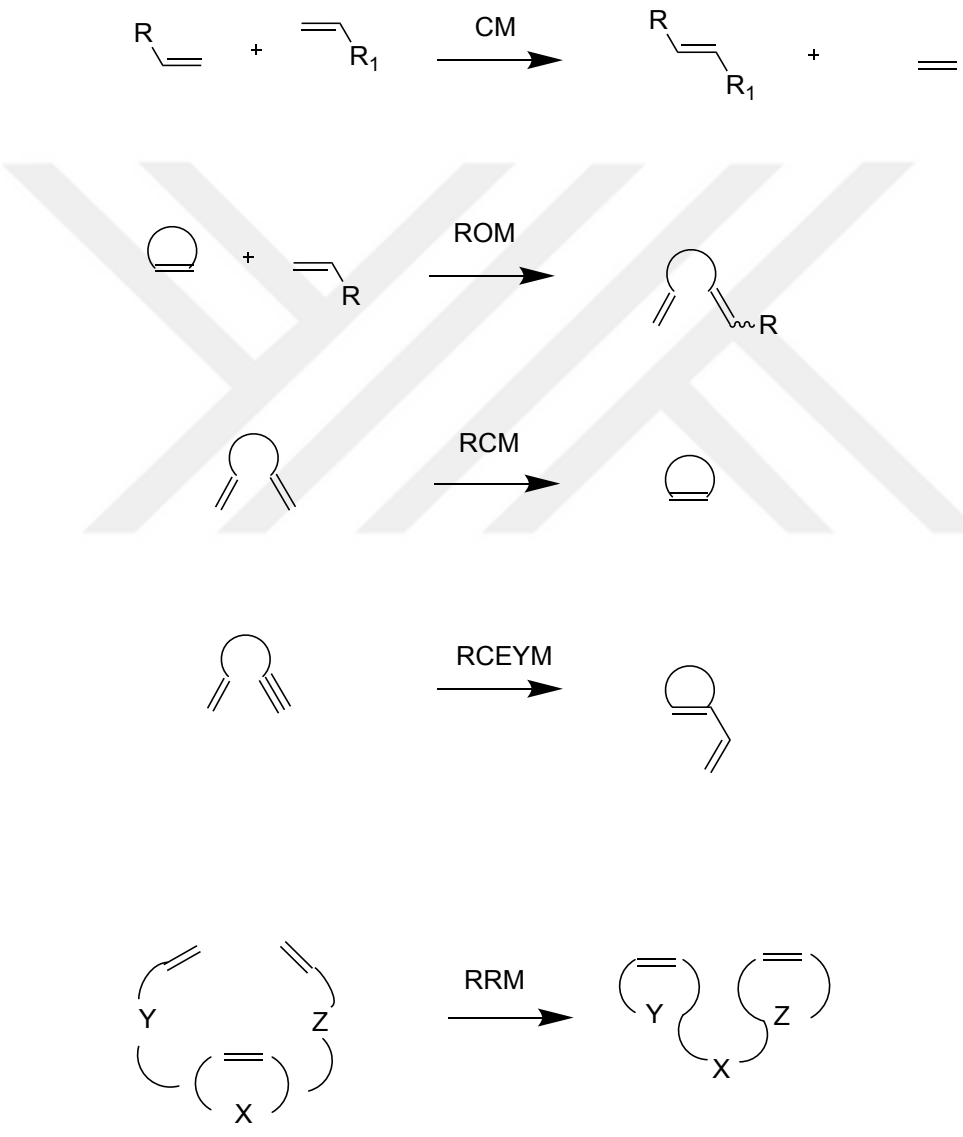


Figure 1.18 Type of Olefin Metathesis

1.5.5 Ring Closing Metathesis Detail

Ring-closing metathesis (RCM) is a major tool for constructing spirocyclic scaffolds via synthetic methodologies applied to obtain heterocyclic, carbocyclic, and spirocyclic compounds (75).

Multiple or cascade RCM reactions can efficiently generate diverse bicyclic systems from 2 to 5 from acyclic precursors in a single step (76).

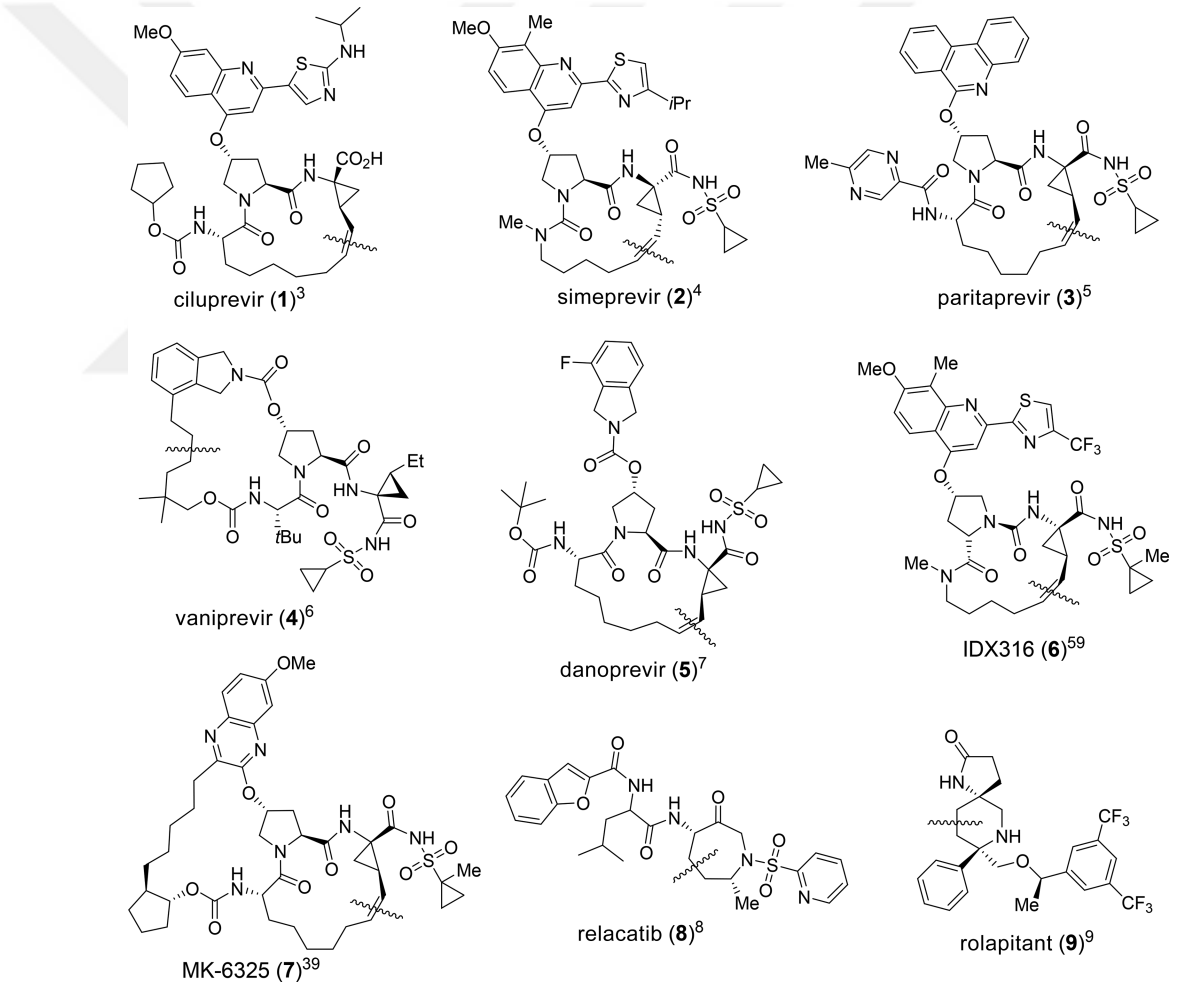


Figure 1.19 Some examples of natural products via RCM

In the synthesis of the NK1 receptor antagonist, the ring-closure metathesis is one of the reaction mechanisms (77) (78).

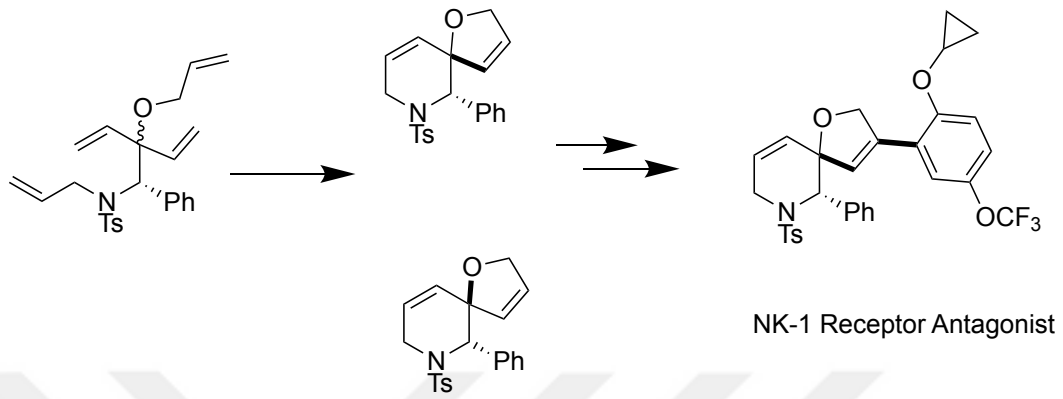


Figure 1.20 Synthesis of NK-1 Receptor Antagonist

Another example for Ring closing Metathesis synthesis of rolapitantthat has been approved for the treatment of chemotherapy-induced nausea and vomiting. The core structure is a diazaspirocyclic ring that contains two quaternary stereogenic centers (79).

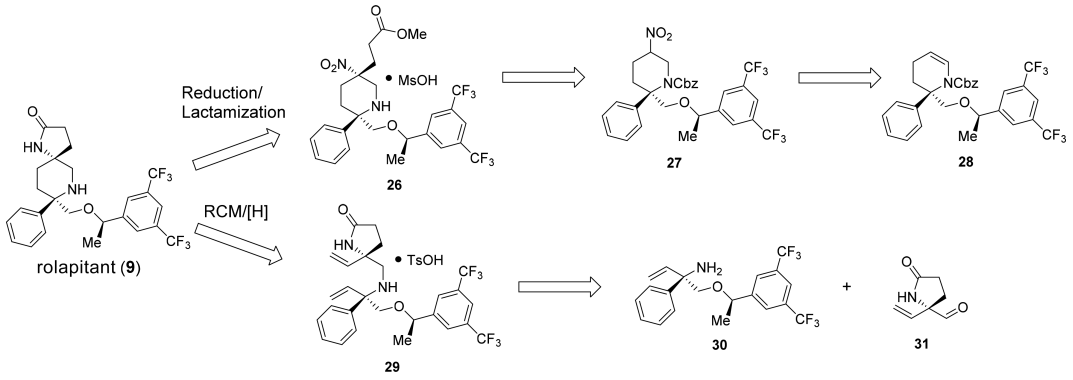


Figure 1.21 Synthesis of Rolapitant

1.6 Pauson-Khand Cycloaddition Reaction

Metal complex catalysts have been used since the 1950s in organic chemistry to speed up the creation of new organic compounds. One approach is the Pauson-Khand reaction, a [2+2+1] cycloaddition reaction. It involves alkyne, alkene, and one molecule of carbon monoxide that comes from a cobalt complex. This reaction was briefly mentioned in a 1971 article (80). In 1973, the Pauson research group accidentally discovered a reaction that produced a cyclopentenone compound instead of cobalt-containing molecules. The process involved a hexacarbonylalkynedicobalt complex reacting with norbornadiene, resulting in the formation of a derivative of cyclopentenone (81).

Figure 1.22 Synthesis of Norborndiene

1.6.1 Cobalt Carbonyl ($Co_2(CO)_8$)

This compound has a red-orange crystal with a melting point of 51°C. If this compound is exposed to air, it changes its color to dark violet. Soluble in ether and alcohols. Prepared by the combination of cobalt metal with carbon monoxide at 200°C, 100 atm. (82). The structure of this compound is presented by two isomers. In the solid state and in the solution at low temperatures, the bridge state is predominant. However, in solution at room temperature, the non-bridge state is predominant. In the non-bridge state, the cobalt has hybridizing of dsp^3 each cobalt has 5 hybrid orbitals, one half-filled orbital overlapped with other Co half-filled orbitals, and four orbitals gain lone pair electrons from carbon monoxide (CO). Thus, four coordinate bonds Co ← CO. However, the hybridization of the bridge state is d^2sp^3. First, the two half-filled hybridized orbital overlapped each other on the cobalt atoms to make a Co-Co bond.

1.6.2 Mechanism of Pauson-Khand Reaction

Philip Magnus suggested the mechanism of the Pauson-Khand reaction in 1985, this method was accepted by other researchers. He suggested (as shown in 1.23) that the alkyne-hexacarbonyldicobalt with 18-electron (I) suffered one carbon monoxide ligand to be alkyne-bentacarbonyldicobalt complex with 16-electron. The last complex coordinates with the olefin to be an 18-electron complex (II). That allows the insertion of olefin to form a cyclo-cobalt complex (III). The cobalt atom that lost (IV) is coordinating with new carbon monoxide (CO) to insert with cyclo-cobalt complex. After that, the reduction would occur to form (VII) and finally elimination process to form cyclopentenone (VIII) and Hexacarbonyldicobalt (83).

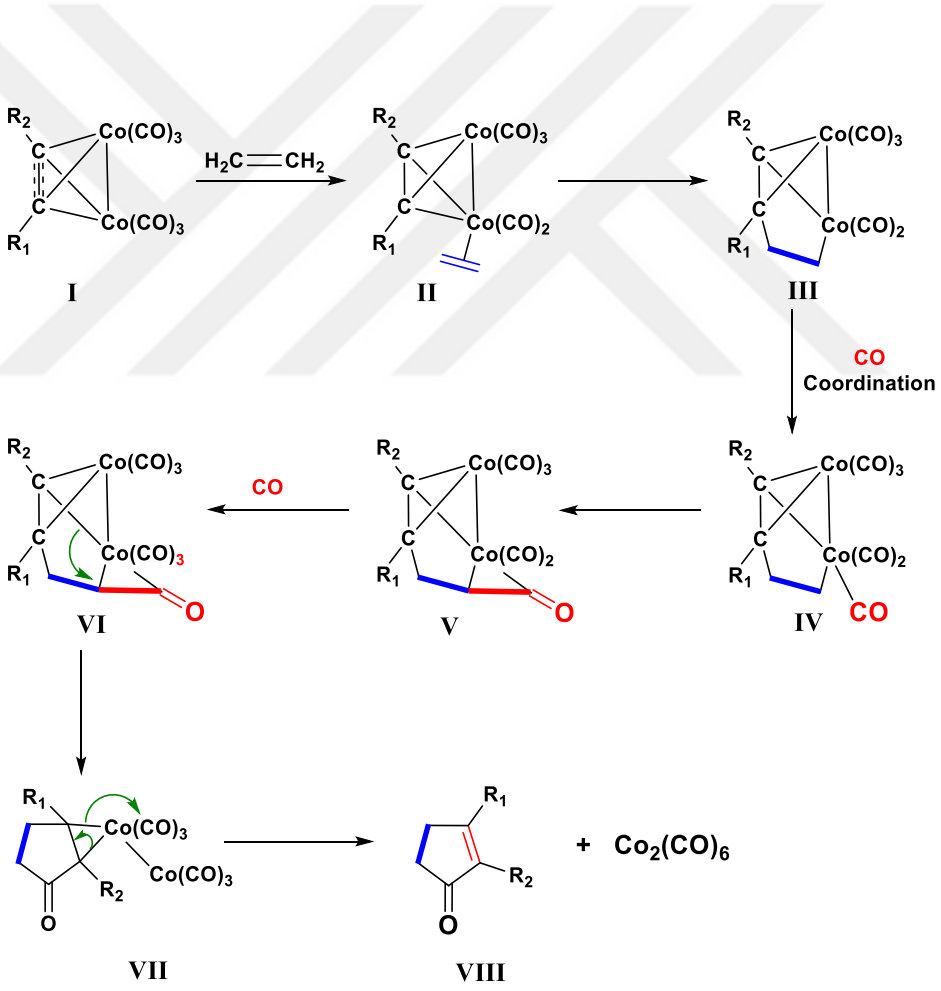


Figure 1.23 Mechanism of Pauson-Khand Reaction

1.6.3 Intermolecular Pauson-Khand Reaction

All the examples shown above are "Intermolecular Pauson-Khand reactions". N. E. Schore performed the first intramolecular Pauson Khand reaction in 1981. This approach allowed the metal-complex-mediate synthesis to prepare many important natural or unnatural products. The first acyclic compound (hept-6-en-1-ynes and oct-7-en-1-ynes) that converted to a bicyclic compound (84).

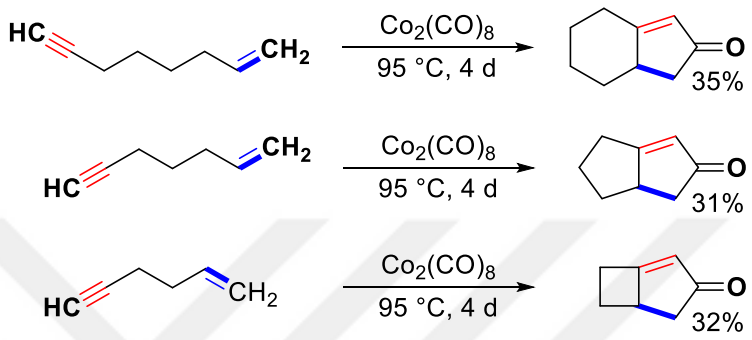


Figure 1.24. Intramolecular Pauson-Khand Reaction

Magnus conducted research on stereoselectivity, which is important for synthesizing natural products. He focused on intramolecular reactions using two natural products called Hirsutic acid and Coriolin. The results showed that when a bulky substituent is present on the (C-3) position of propargyl or on the (C-5) position of allylic, the selectivity can be improved. Moreover, if there is another bulky group on the (C-1) position of propargyl (on the terminal alkyl carbon atom), the selectivity can be further enhanced(83)(84).

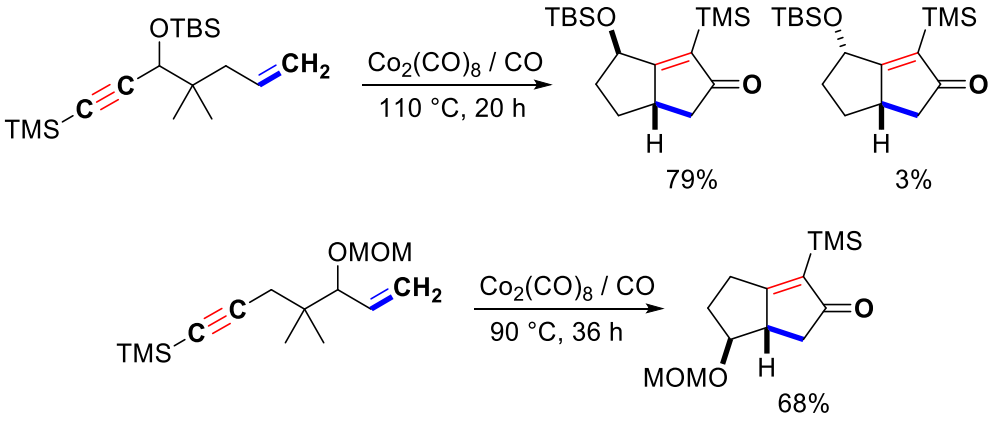


Figure 1.25. Effect of the bulky group on stereoselectivity

1.6.4 Pauson-Khand Cycloaddition Reaction Promoting

Microwave for Pauson-Khand Enhancing

In 2002, Evans and his research group were the first to use a microwave approach in the Pauson-Khand reaction. Intra and intermolecular reactions were observed in the microwave, which resulted in faster reaction times, improved yields, and enhanced acceleration (85).

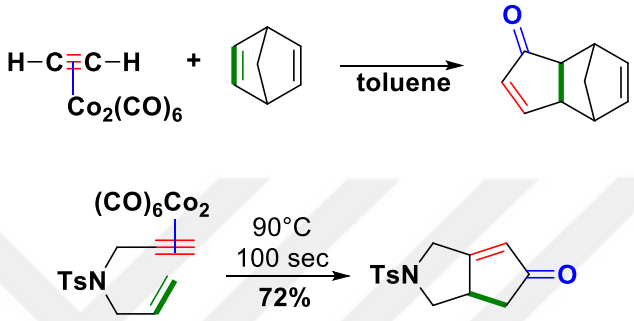


Figure 1.26. Effect of microwave on PKR

N-Oxide as Pauson-Khand Reaction Promoter

Schreiber and his colleagues were the first researchers to use *N*-oxides in the Pauson-Khand reaction. They discovered that these tertiary (3rd) amine-oxides enhance the reaction by reacting with one of the carbon monoxide (CO) ligands and oxidizing it to CO_2, which is a weak ligand that coordinates with the Cobalt. Thus, the *N*-oxide is utilized as a free site that helps the olefin to coordinate with the cobalt atom (86).

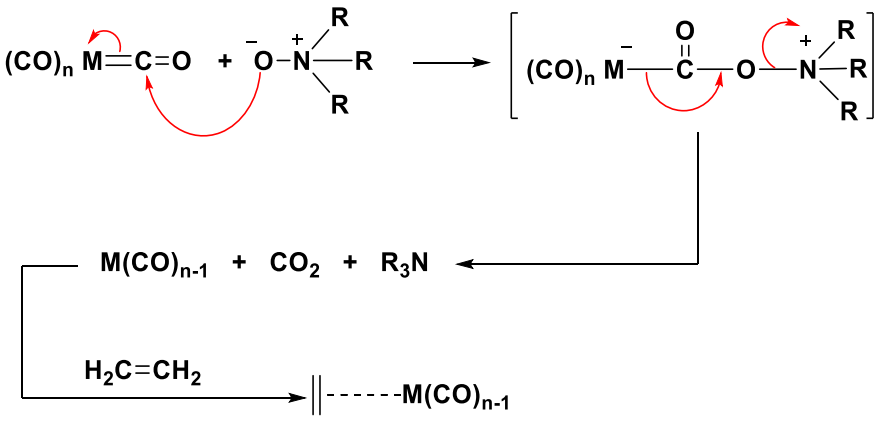


Figure 1.27. Effect of N-oxide on the Pauson-Khand Reaction.

The yield clearly increases, for example, the first equation in (Figure 1.28), when comparing the ultrasonic Pauson-Khand reaction (45% yield at 45°C) with the addition of NMO to Pauson-Khand reaction (68% yield at r.t) (87).

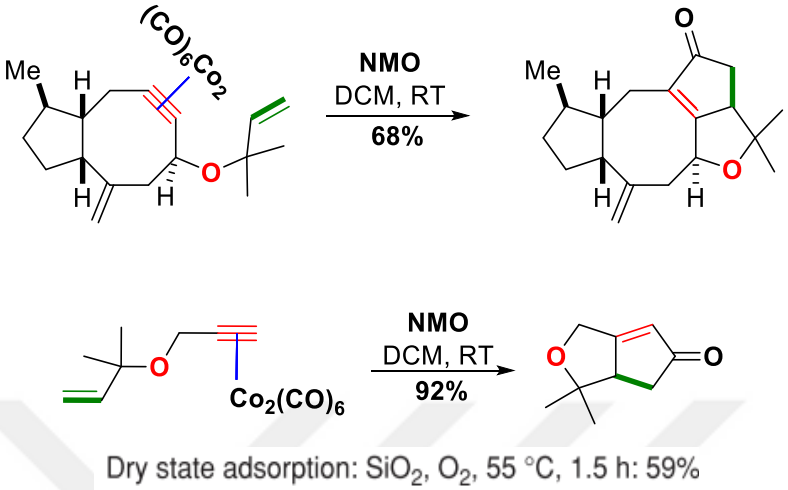


Figure 1.28. Effect of NMO on Pauson-Khand Reaction

Here we will count some amine-oxide compounds that are used as promoters for PKR. N-Methylmorpholine-*N*-oxide (NMO)(87), Trimethylamine-N-oxide (TMANO)(88). Quinine-*N*-oxide especially for enantioselective reactions(89), Sparteine *N*-oxides(90), 2,2,6,6-tetramethylpiperidine *N*-oxide-free radical particularly in reaction that have stearic alkyne (91), and Burcine *N*-oxide(92).

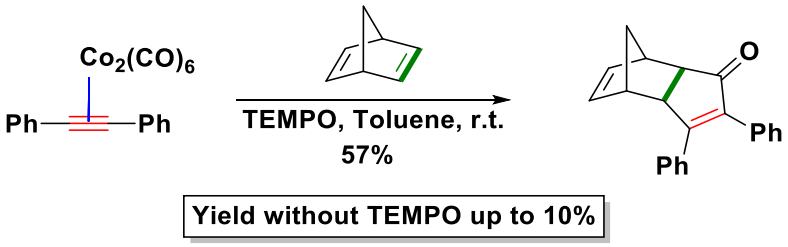


Figure 1.29 Effect of N-oxide free radical

Examples of Amine Oxide Compounds

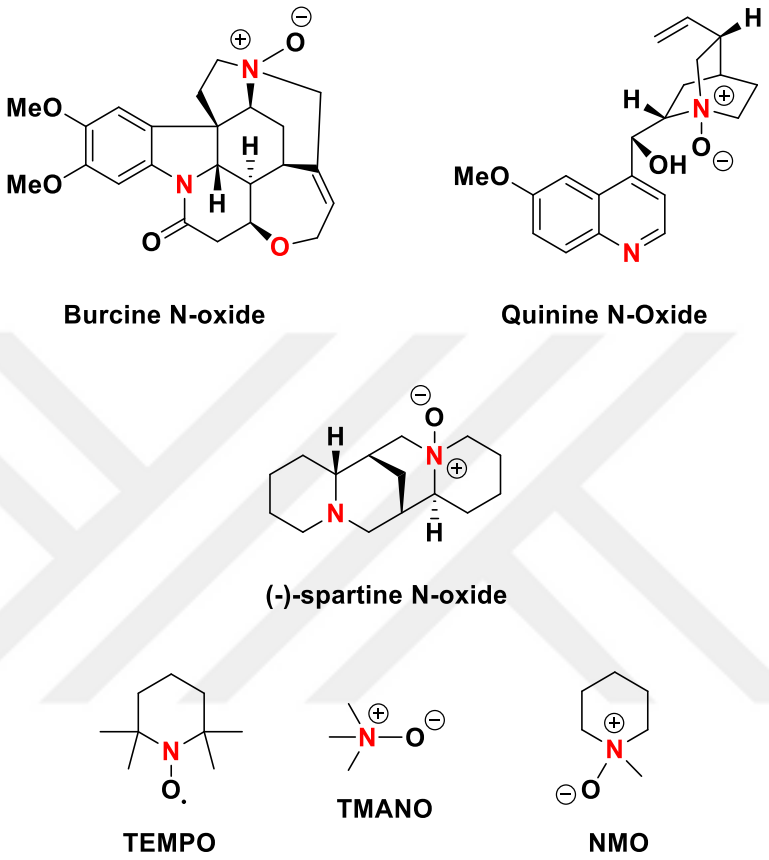


Figure 1.30. Examples of amine-oxide compound

These amine-oxides allowed the reaction to occur in mild conditions (at room temperature with a decrease in reaction time). In contrast, the disadvantage of these compounds require an excess of N-oxide that needs more filtration and purification.

1.7 Aza-Spiro-Compounds

Spirocyclic compounds that contain nitrogen atoms in at least one cycle of their structure are known as Azaspiro compounds. These skeletons are found in numerous natural products, such as alkaloids. Chemists and pharmacists are interested in these types of compounds due to their potential properties in drug discovery, and they can be used as building blocks and scaffolds in medicinal compounds (93).

An examination of pK_a values usually shows that the amines of these compounds are more basic, and polar than the corresponding monocyclic system. However, less oxidative degradation in the liver of both mice and humans (94). Hereafter some azaspiro compounds have interesting biological activities or pharmaceutical utilities.

(±)-pandamarine isolated from Pandanus. That is used for the treatment of rheumatism and epilepsy(95). Azaspiro [4,5]decane structure (NK-1 receptor antagonist) has three chiral centers that are used in the treatment of inflammation, anxiety, and emesis(16). Azaspiro [3.3] heptane derivatives are also important scaffolds for drug manufacturing due to low metabolic clearance averages like an anti-bacterial agent or anti-vasopressin agent that treatment for hyponatremia in patients with heart failure congestive (96)(97).

Pyrrolidine (A-366) is another spiro compound that has biological activity as a strong, special selective inhibitor of Histone Methyltransferase (HMTs) especially (G9a). There is a connection between (HMTs) and leukemia, lung cancer, and cancer cells of the prostate)(98). Pteropodine is a compound that is isolated from Cat's claw plant and exhibits anti-inflammatory, protective impact of DNA damage and anti-proliferative action to ovarian carcinoma and lymphoblastic leukemia cells (99). In azaspirone species, there is a compound that is commercial called Buspirone. This drug has an anti-anxiety purpose by doing a physiological agonist reaction toward the serotonin receptor (100). In conclusion, we can see that spirocyclic skeletons with five and six-member rings are predominantly used in drug utility, while three and four-membered rings are used less frequently.

1.7.1 Examples of Aza-Spiro Compounds

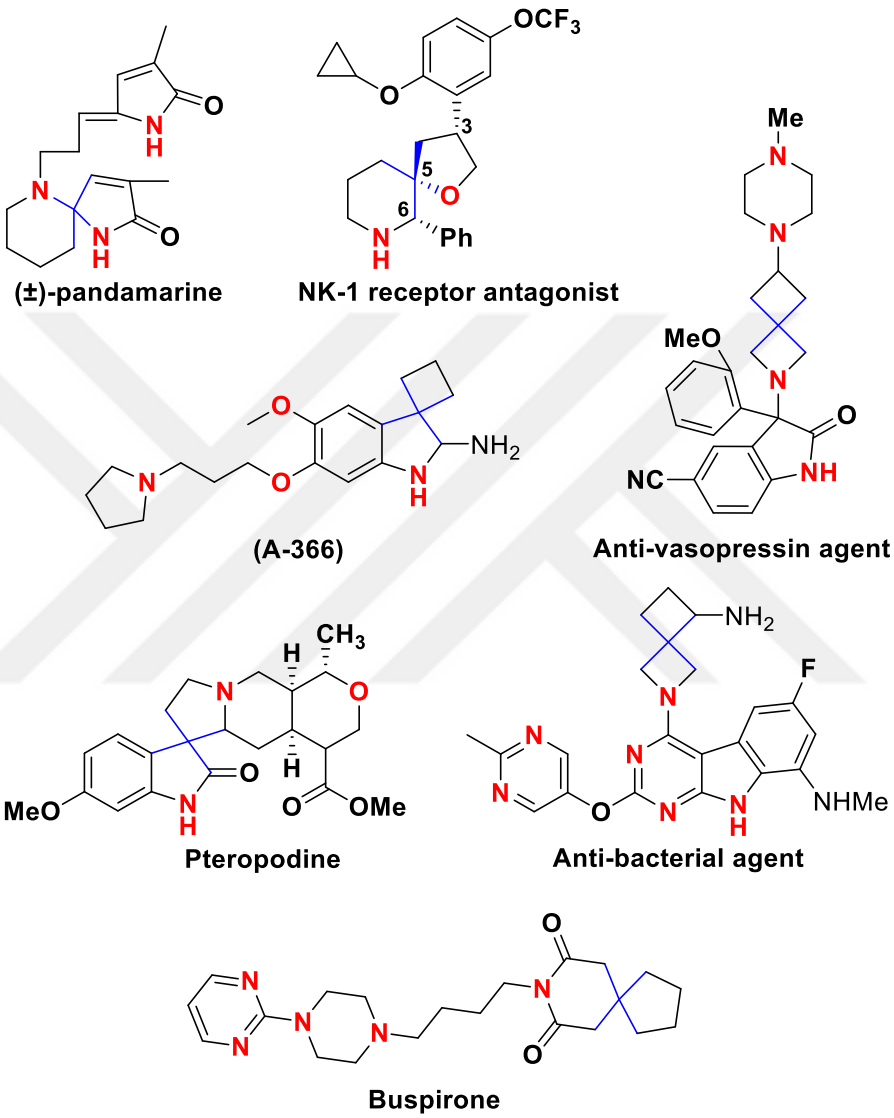


Figure 1.31 Examples of Aza-Spiro Compounds

2. AIM AND SCOPE OF THE STUDY

Our project aims to develop a novel set of spirocyclic substrates that can be utilized to make incremental modifications in the molecular design of various compound collections. The synthesis of *N*-containing hetero spiro compounds is of utmost importance in the pharmaceutical industry due to their diverse biological and pharmaceutical applications, and the potential for further development.

To achieve our objectives, we have selected Ring Closing Metathesis and Pauson-Khand Cycloaddition reaction methods, which have proven to be effective in synthesizing five and six-ring spirocyclic compounds. The plan is to synthesize dihydropyrrole using the RCM methods in the presence of Grubbs second generation catalyst to produce tetrahydropyridine. Additionally, we will employ PKR, which is the most well-organized pathway for the cyclopentenone ring system.

The importance and efficacy of new aza spiro compounds have made their synthesis important. For this purpose, we have successfully synthesized the compounds shown below, following the retrosynthesis scheme.

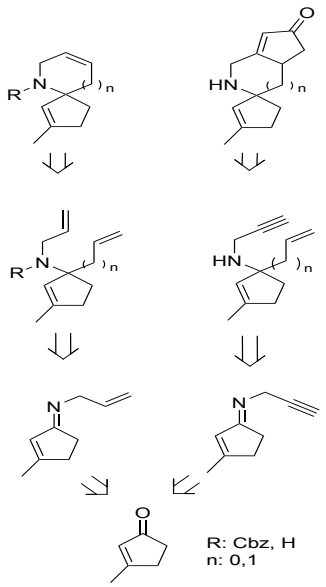


Figure 2.1 Retro Synthesis Mechanism of Thesis

3. MATERIALS AND METHODS

Solvents (Dichloromethane, Tetrahydrofuran, Benzene, Hexane, Ethyl acetate, Triethylamine, Diethyl ether, Ethanol...), Molecular sieves, Dicopaltoctamonoxide catalyst and other reagents (Allyl Amine, vinyl amine, propargylamine, p-toluene sulfonic acid monohydrate, N-methyl morpholine N-oxide, Grignard reagents...) are commercially purchased from either Aldrich, Merck, or Acros. Cyclopentanone and its derivatives were selected due to the presence of these compounds in highly functionalized, important chiral-bioactive components.

All reactions were fulfilled under a nitrogen atmosphere unless mentioned and all chemicals, that were air or water sensitive, were stored under (N_2) "inert atmosphere". Flash column chromatography was accomplished using "Silica gel" from J.T. Baker (70-230 mesh ASTM). Thin layer chromatography (TLC) was used to monitor reactions using (Silica gel 60 F_{254}) from Merck. In addition, TLC was monitored by UV light (UV-Leuchte 254 nm) (or/and) molybdatophosphoric acid hydrate (Merck) dye solved in ethanol heating with hot gun. Infrared (IR) Spectra were recorded on "FTIR 8400-S SHIMADZU". Nuclear Magnetic Resonance (NMR) spectra were measured by using 'JEOL ECS-400 spectrometer'. The chemical shift was expressed in parts per million (ppm) and correlated to the residual proton and carbon resonance of the solvent $CDCl_3$ at 295 K (δ 7.26 for ^{1}H-NMR and 77.0 for ^{13}C-NMR). Chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, br = broadened, *J* = coupling constant (Hz). Anhydrous magnesium sulphate ($MgSO_4$) (Merck) was used to dried all the desired extractions before concentrating them in be rotary evaporator (under vacuum). All reactions were made in a '**Reaction System'** consisting of a round-bottomed flask (two-necked) equipped with a water-cooled condenser (Graham condenser), rubber septum fitted with nitrogen inlet gas (as an inert gas) and (2,5 cm) magnetic stir bar.

3.1 Research Plan for Ring Closing Metathesis

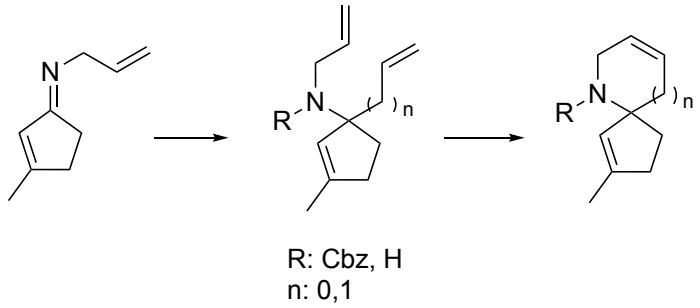


Figure 3.1 Research Plan for Ring Closing Metathesis

3.1.1 Synthesis of Imine for RCM

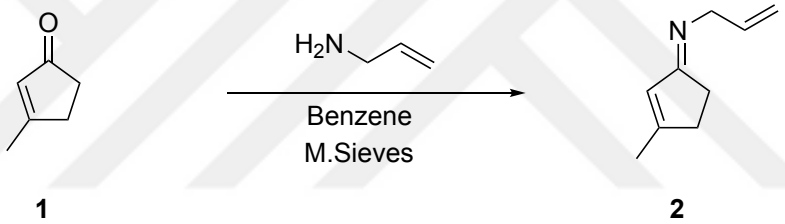


Figure 3.2 Synthesis of Imine for Ring Closing Metathesis

Synthesis of (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine, In this experiment, a 100-ml flask is used which is equipped with a water-cooled condenser, rubber septum, and magnetic stir bar. The rubber septum is filled with nitrogen as an inert gas. The flask is charged with 3-methyl cyclopentenone derivatives **1** (1.5 g, 1 equiv.), allylamine (2 equiv.), and molecular sieves (2.5 g.). The solvent used is benzene (30 mL). The reaction mixture is heated and allowed to stir in an oil bath at 55 °C for 3 days. The resulting brown slurry is filtered and washed with diethyl ether. The solvent is then removed by vacuum. After that, the solution is treated with nitrogen gas to remove benzene and obtain crude imine product **2**, which is used directly without any purification.

3.1.2 Synthesis of Dienes with Grignard Reaction

General Procedure for Allyl Addition

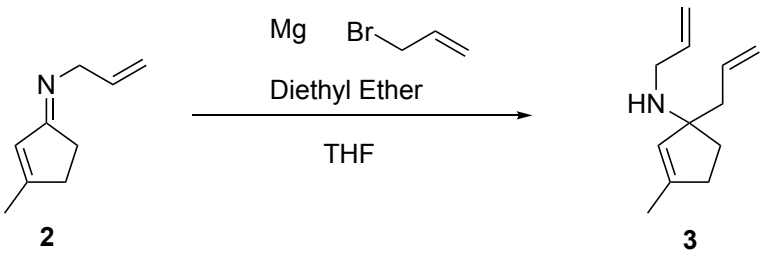


Figure 3.3 Synthesis of Allyl Addition by Grignard Reaction

To synthesis of *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **3**, magnesium turnings (2.5 equiv.) were added to 25 ml of anhydrous diethyl ether in a 100-ml flask. Allyl bromide (2 equiv.) was added, and the mixture was stirred for 1.5 hours at room temperature before cooling to 0°C. Imine **2** (1 equiv.) was added dropwise and the mixture was stirred overnight. The reaction mixture was hydrolyzed with NH_4Cl, and the organic phase was extracted with diethyl ether. The resulting organic mixture was dried with $MgSO_4$, filtered, and the solvent was removed under vacuum. Column chromatography was used to purify the crude product using a system solvent of ethyl acetate, hexane, and triethylamine (EtOAc: Hexane: Et_3N).

General Procedure for Vinyl Addition

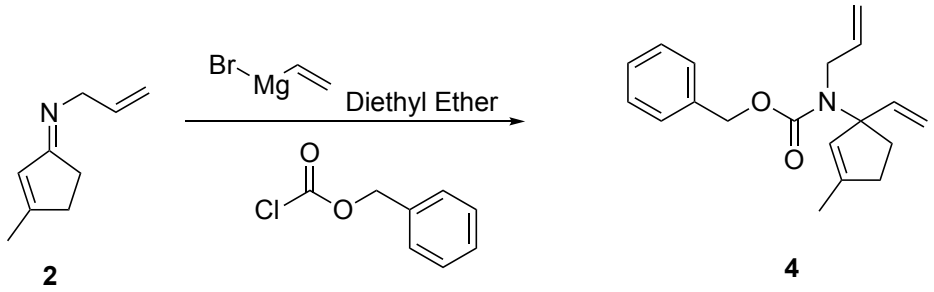


Figure 3.4 Synthesis of Vinyl Addition by Grignard Reaction

The crude imine **2** was placed in a 100-mL flask along with 30 mL of THF. The flask was sealed with a 'Graham condenser' and rubber septum equipped with a nitrogen inlet gas. Next, benzyl chloroformate (1.5 equivalents) was added to the mixture. The reaction mixture was heated to 60°C for 2.5 hours, as verified by TLC. The crude product was then cooled down to -78°C, and 1 M vinyl magnesium bromide in THF was added to the mixture. After stirring overnight at room temperature, the reaction mixture was hydrolyzed using a saturated solution of ammonium chloride (NH_4Cl). The organic phase was extracted with ethyl acetate (EtOAc) and then washed with a solution of sodium bicarbonate (NaHCO3) and brine (20 ml each). The final organic mixture was dried using magnesium sulfate and then filtered. The solvent was evaporated under vacuum, and the crude product was purified using flash chromatography with a suitable ratio of EtOAc: Hexane: Et_3N.

3.1.3 Ring Closing Metathesis Procedure

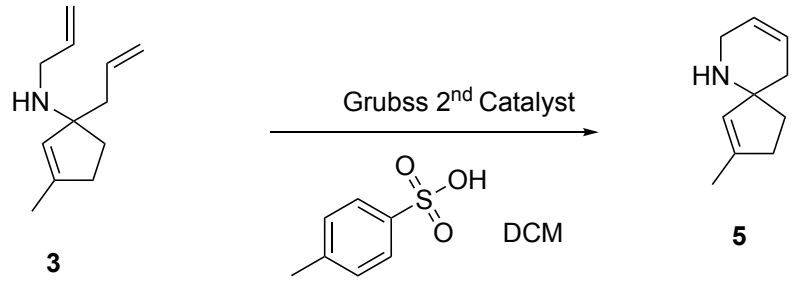


Figure 3.5 Synthesis of Ring Closing Product for Allyl

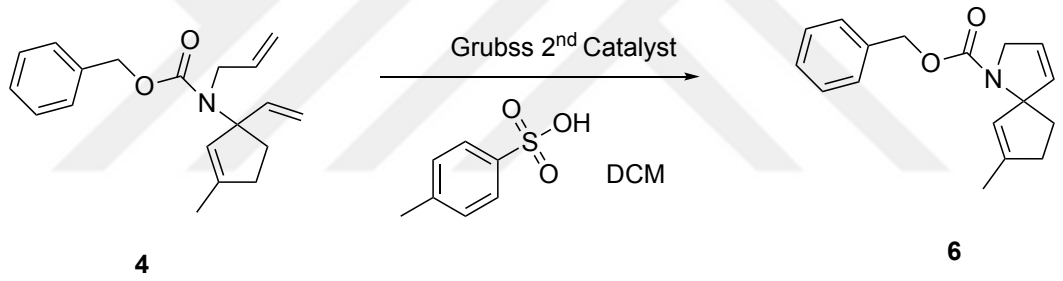


Figure 3.6 Synthesis of Ring Closing Product for Vinyl

The diene product **3** or **4** were mixed with p-toluene sulfonic acid monohydrate and 30 mL DCM in a 50-ml flask. The mixture was stirred at 50°C for 2 hours and cooled to room temperature. Grubbs's 2nd generation catalyst was added, and the mixture was stirred for 48 hours. Sodium bicarbonate and solid potassium carbonate were added until the pH reached 11. The organic phase was extracted using DCM and dried using $MgSO_4$. The desired product was isolated by column chromatography using (EtOAc: Hexane: Et_3N) in suitable ratios.

3.2 Research Plan for Pauson-Khand Reaction

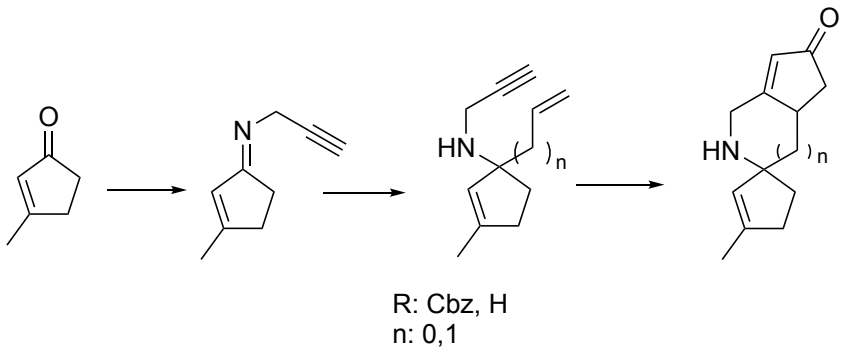


Figure 3.7 Research Plan of Pauson-Khand Reaction

3.2.1 Synthesis of Imine for Pauson-Khand Reaction

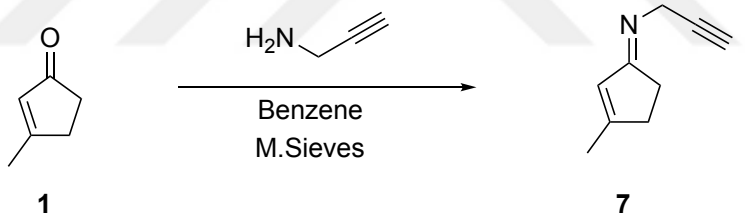


Figure 3.8 Synthesis of Imine for Pauson-Khand Reaction

In this experiment, 1.5 g of 3-methyl cyclopentenone derivatives **1**, 2 equivalents of propargylamine, and 2.5 g of molecular sieves are mixed in a 100 ml flask with 30 mL of benzene. The mixture is heated to 45°C and stirred for 3 days. The resulting slurry is filtered and washed with diethyl ether. The crude imine product **7** is obtained by removing the solvent and blowing nitrogen gas onto the residue.

3.2.2 Synthesis of Enyne with Grignard Reaction

General Procedure for Allyl Addition

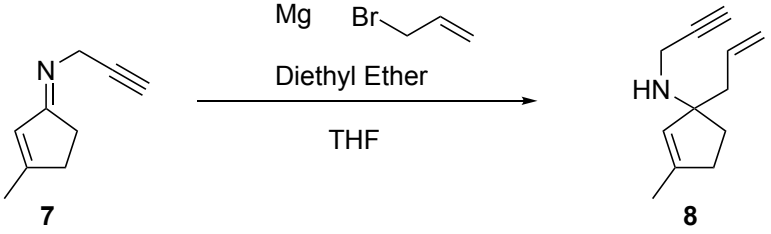


Figure 3.9 General Procedure for Allyl Addition

Grignard reagent was made by adding allyl bromide (2 equiv.) to magnesium turnings (2.5 equiv.) in 25 ml of anhydrous diethyl ether. After that, the system was cooled down to 0 °C. Imine **7** (1 equiv.) was added drop-wise to it. The mixture was allowed to stir overnight at room temperature. Then the reaction mixture was hydrolyzed by saturated solution of ammonium chloride followed by extraction the organic phase by diethyl ether (3x). The resulting organic mixture was dried by anhydrous magnesium sulfate ($MgSO_4$) and filtered it. The solvent was removed under vacuum. Column chromatography was used to purify the crude product using system solvent of (ethyl acetate, hexane and triethylamine) (EtOAc: Hexane: Et_3N) in suitable ratios.

General Procedure for Vinyl Addition

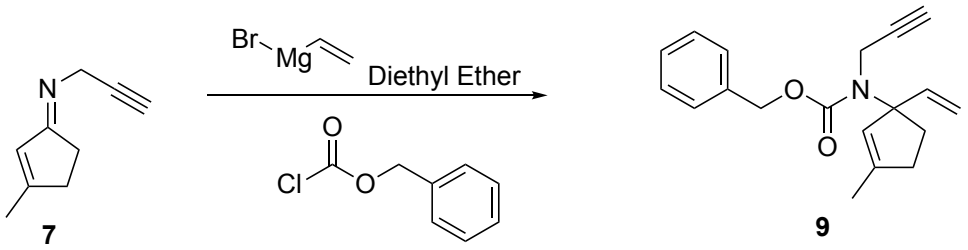
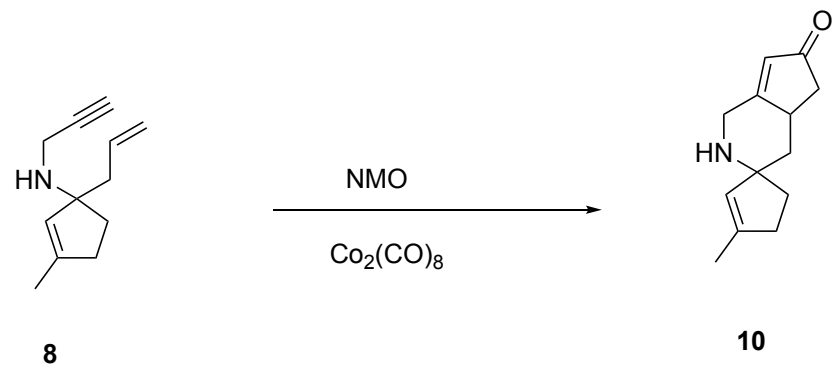


Figure 3.10 General Procedure for Vinyl Addition

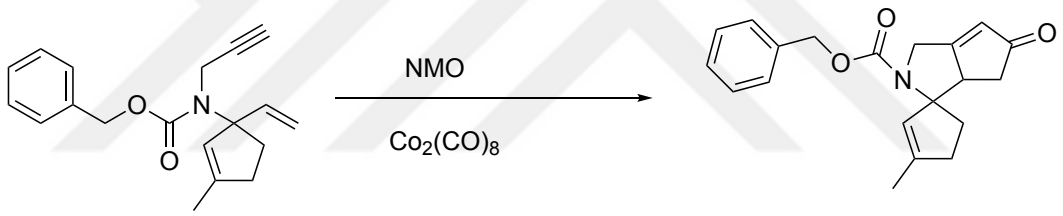
The experiment involved adding crude imine to a 100-mL flask containing 30 mL of THF, which was then sealed with a Graham condenser and rubber septum fitted with a nitrogen inlet gas. Benzyl chloroformate (1.5 equivalents) was added to the mixture and heated to 60°C for 2.5 hours (monitored by TLC). The crude product was then cooled to -78°C and vinyl magnesium bromide (1M in THF) was added. The mixture was warmed to room temperature and allowed to stir overnight. Then, the reaction mixture was hydrolyzed using a saturated solution of ammonium chloride (NH_4Cl). The organic phase was extracted using EtOAc and washed with a solution of 20 ml of sodium bicarbonate ($NaHCO_3$) and 20 ml of brine. The final organic mixture was dried using magnesium sulfate and filtered. The solvent was evaporated under vacuum and the crude product was purified using column chromatography with a suitable solvent system of EtOAc: Hexane: Et_3N in appropriate ratios.

3.2.3 General Procedure for Pauson-Khand Reaction



8 **10**

Figure 3.11 General Procedure for Pauson-Khand Reaction of Allyl



9 **11**

Figure 3.12 General Procedure for Pauson-Khand Reaction of Vinyl

In 50 mL flask, **8** o**r 9** (1 equiv.) was put in presence of CH_2Cl_2, cobalt carbonyl $Co_2(CO)_8$ (1.8 equiv.) with 5 ml DCM was added to it. The reaction mixture allowed stirring for 2.5 h. (controlled by TLC). After that, NMO (10 equiv.) was added to it and the reaction mixture allowed to stir overnight. The final product was purified by flash column chromatography used (EtOAc: Hexane: Et_3N) as eluent in suitable ratios.

4. RESULTS

4.1 Result and discussion for RCM product

4.1.1 Synthesis of Imine for RCM

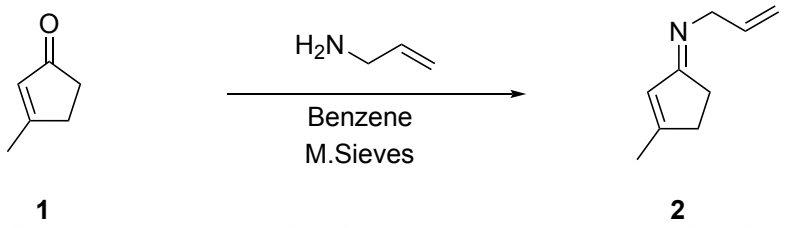
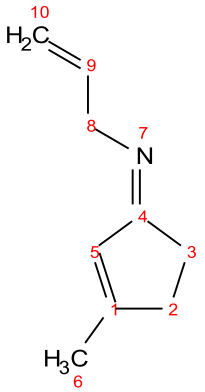


Figure 4.1 Synthesis of (Z)-N-allyl-3-methylcyclopent-2-en-1-imine

Compound **2**, which is (Z)-N-allyl-3-methylcyclopent-2-en-1-imine, was synthesized using 3-methylcyclopent-2-en-1-one and allylamine in the presence of benzene and molecular sieves as depicted in Figure 4.1. The reaction mixture was filtered, benzene was removed by nitrogen gas, and the product was obtained as a yellowish oil with 92% chemical yield after evaporation.



^{1}H-NMR In the spectrum of (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine shows multiplet between 6.41-6.28 ppm from internal vinylic proton at 9. position. Olefinic methine proton 5 presents singlet at 6.26 ppm. The next peak multiplet is between 5.54-5.43 and the other one is 5.44-5.35 for terminal vinylic proton at 10 positions. Allyl methylene proton at 8 position shows doublet of triplet at 4.27 ppm with J = 25.5, 5.5 Hz value. In the ring one of the methylene protons at 3 positions gives doublet of doublet of a doublet at 2.89 ppm with J = 2.9, 2.3, 1.4 Hz, and another methylene proton at 2 positions gives a triplet at 2.79 ppm with J = 5.3 Hz. In the ring, other methylene protons at 3' positions give multiplet 2.75-2.70 ppm. Finally, methyl protons at the 6 position show singlet at 2.45 ppm.

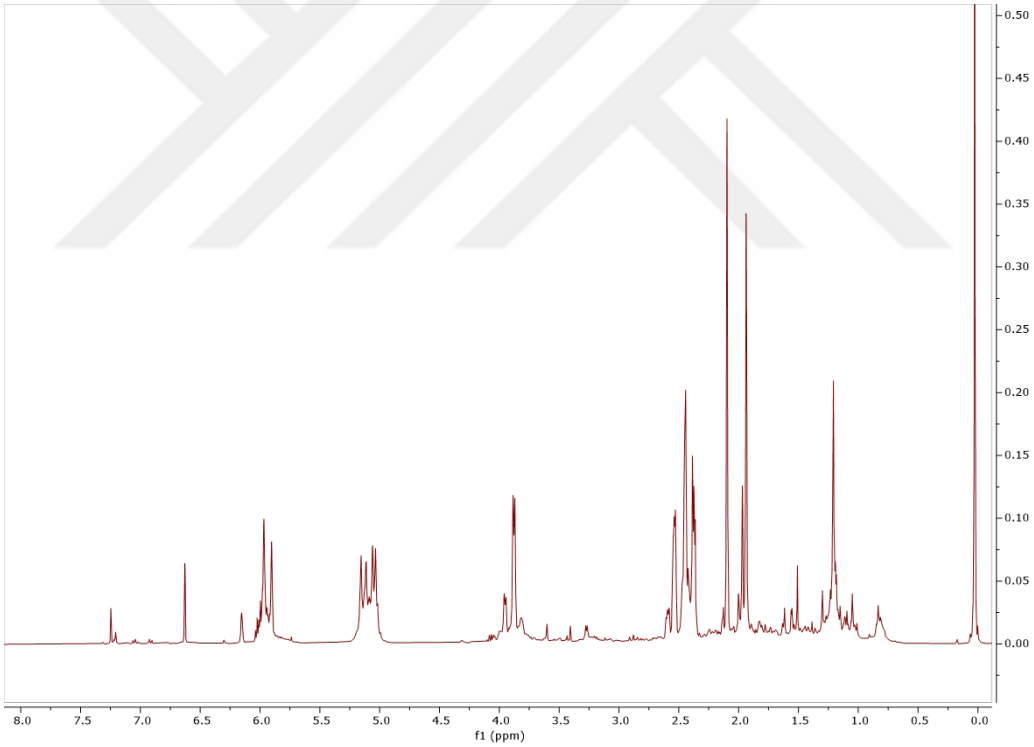


Figure 4.2 The ^{1}H-NMR spectrum of (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine

^{13}C-NMR spectrum of (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine shows a signal at 179.0 ppm for imine carbon at 4 positions. The quaternary carbon 1 shows a signal at 162.9 ppm. Moreover, the internal at 9 and terminal at 10 vinylic carbons show signals at 136.4, and 116.2 ppm respectively. The olefinic methine carbon at 5 gives a signal at 130.7 ppm. In addition, allylic methylene carbon in position 8 shows a signal at 55.7 ppm. Furthermore, the methylene carbons in positions 2 and 3 show signals at 29.8 ppm and 27.6 ppm respectively. Finally, methyl carbon 6 shows a signal at 19.5 ppm.

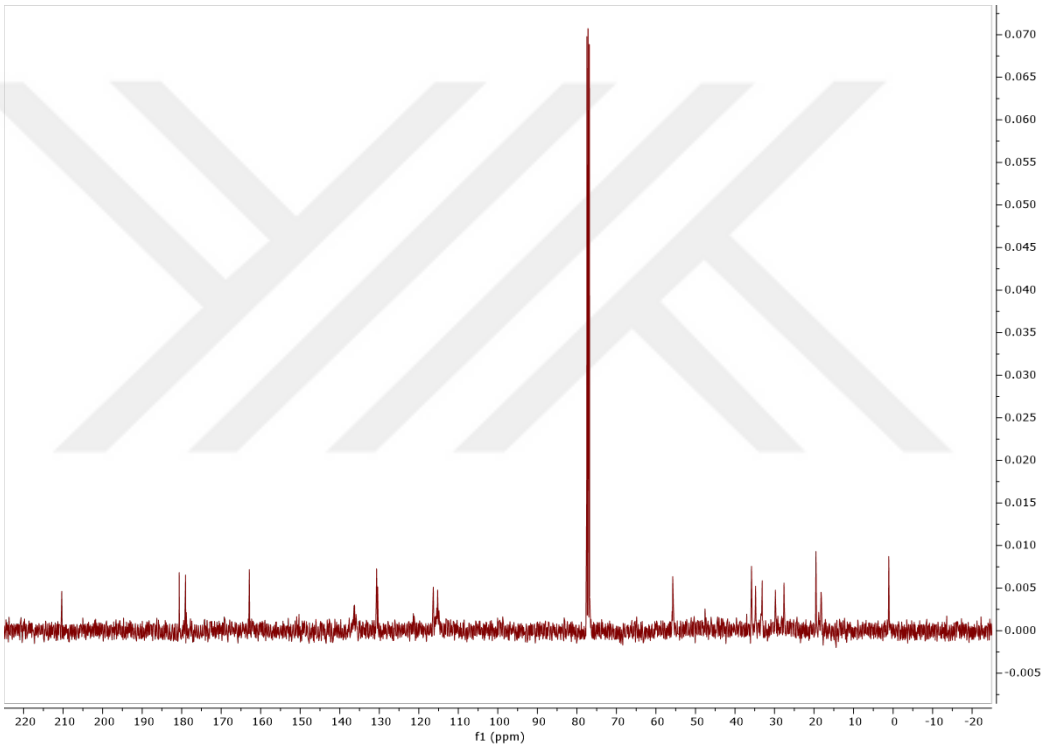


Figure 4.3 The ^{13}C-NMR spectrum of (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine

4.1.2 Synthesis of Grignard Reaction

General procedure for Allyl Addition

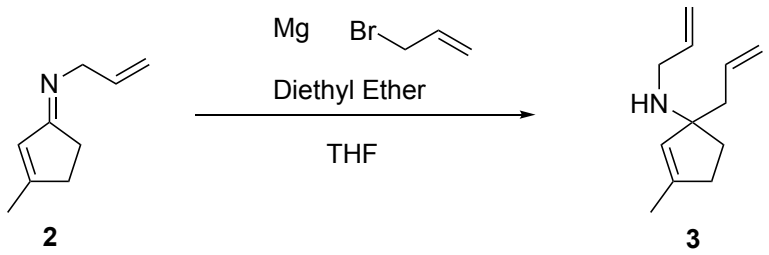
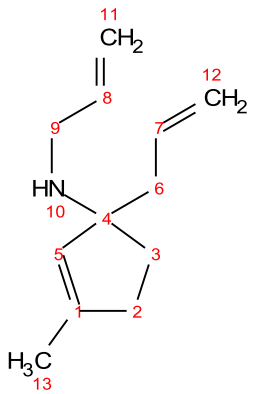


Figure 4.4 General Procedure for Allyl Addition

Using (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine **2** and allyl bromide, a Grignard reaction depicted in Figure 4.4 was employed to create *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **3** in the presence of diethyl ether. The mixture was left to stir at room temperature overnight before undergoing workup. Flash chromatography was used to purify the crude product, resulting in a yellowish oil with a chemical yield of 84% after evaporation.



The ^{1}H-NMR spectrum of (*N*,1-diallyl-3-methylcyclopent-2-en-1-amine **3** shows multiplet 6.01-5.79 ppm for internal vinylic proton 8. Other internal vinylic protons at the 7 give multiplet between 5.79-5.55 ppm. Singlet at 5.23 ppm for the olefinic methine proton 5. The terminal vinylic protons 11 and 12 give multiplet at 5.21-4.84 ppm. One of the *N*-methylene allylic protons at position 9 shows a triplet of a doublet at 3.12 ppm with J = 18.2, 5.1 Hz, and others show a triplet of a doublet at 2.97 ppm with J = 13.3, 5.3 Hz respectively. Methylene protons at position 2 show a multiplet between 2.40-2.15 ppm. Other methylene allylic methylene at 6 protons give multiplet between 2.11-1.96 ppm and 1.88-1.76 ppm respectively. 3 position in the ring methylene proton show doublet of triplet at 1.67 ppm with J = 15.0, 4.7 Hz. Finally singlet at 1.52 ppm for methyl protons 13.

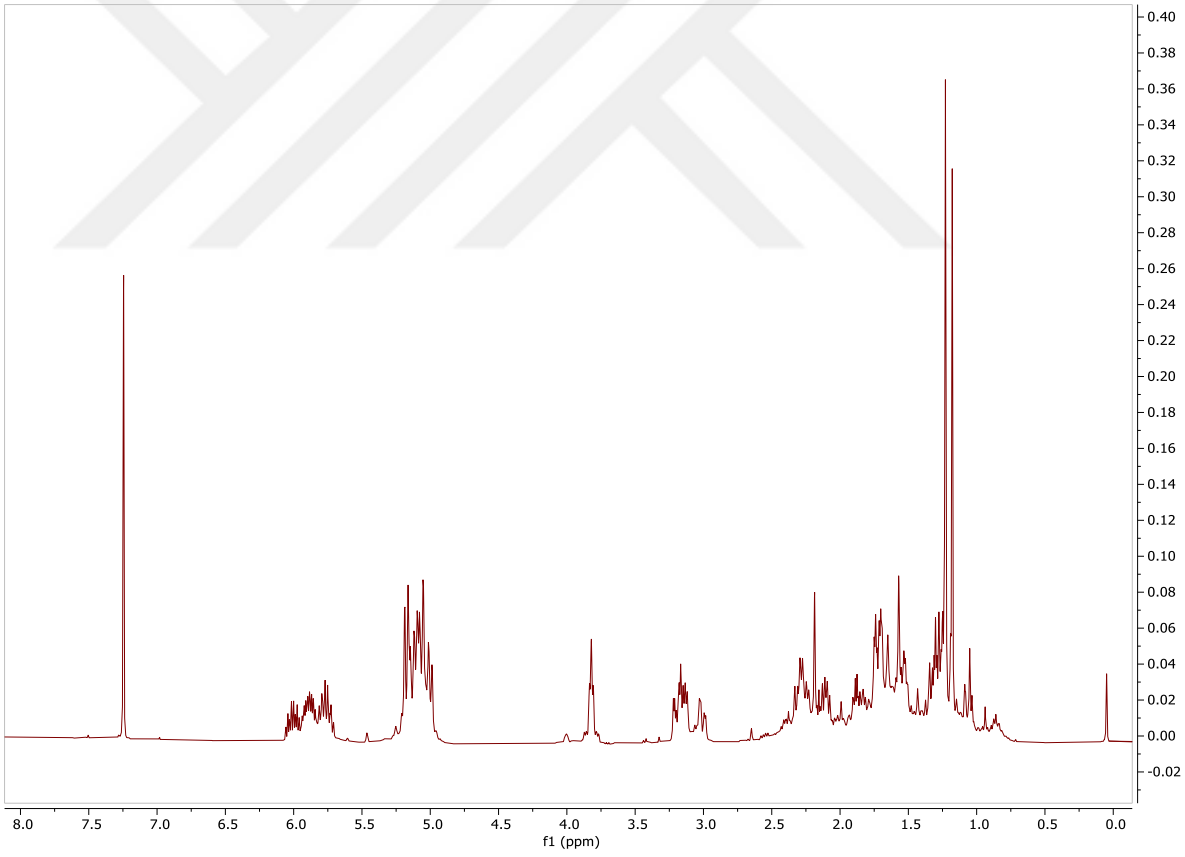


Figure 4.5 The ^{1}H-NMR spectrum (*N*,1-diallyl-3-methylcyclopent-2-en-1-amine

The ^{13}C-NMR spectrum of (*N*,1-diallyl-3-methylcyclopent-2-en-1-amine) **3** displays various signals at different positions. The quarternary carbon at the first position shows a signal at 138.2 ppm The vinylic carbons at positions 8 and 7 give signals at 136.4 ppm and 134.2 ppm respectively, while the olefinic methine carbons at position 5 exhibit a signal at 119.1 ppm. The terminal vinylic carbon at positions 11 and 12 give signals at 115.4 ppm and 114.5 ppm respectively. Additionally, the chiral carbon at position 4 shows a signal at 62.3 ppm. The allylic methylene carbons at positions 9 and 6 exhibit signals at 47.7 ppm and 38.2 ppm respectively. Finally, the methylene carbons at positions 2 and 3 display signals at 33.4 ppm and 30.7 ppm respectively, while the methyl carbon at 13 shows a signal at 22.6 ppm.

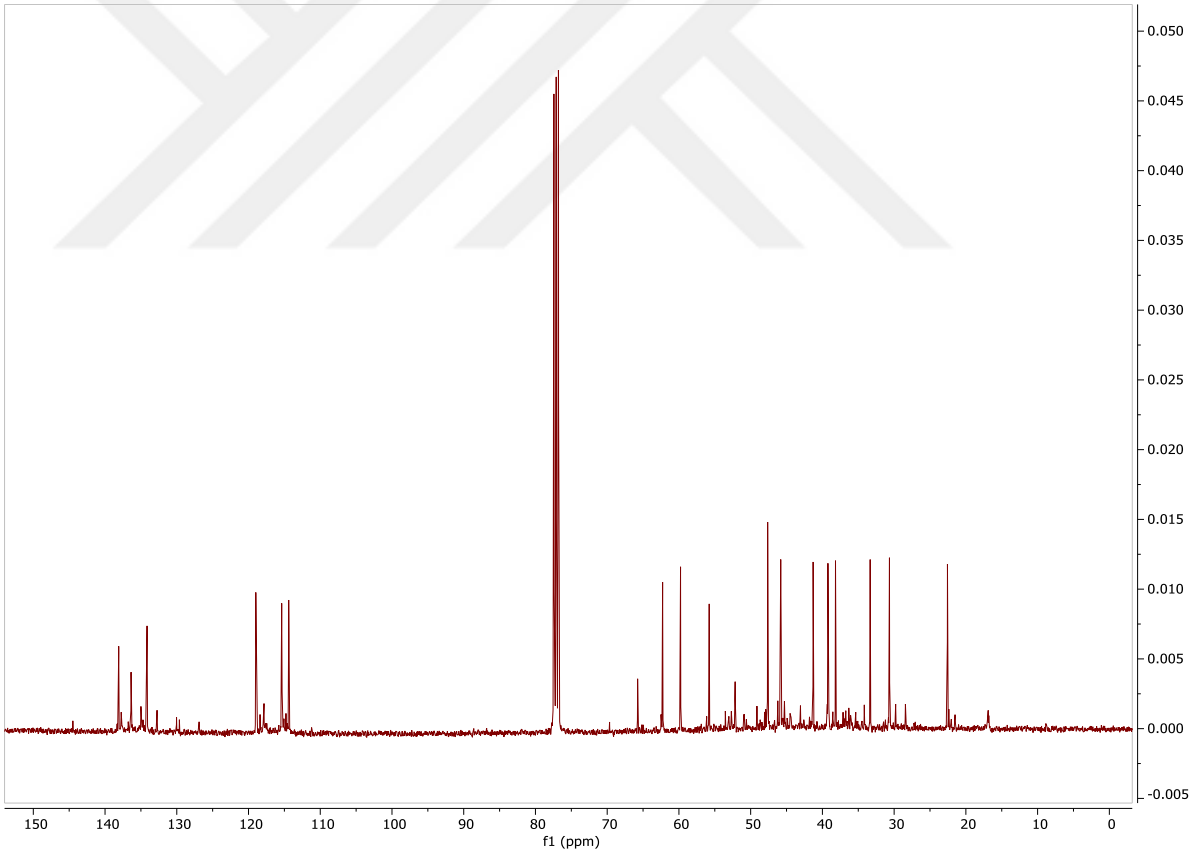


Figure 4.6 ^{13}C-NMR spectrum of (*N*,1-diallyl-3-methylcyclopent-2-en-1-amine

General Procedure of Vinyl Addition Reaction

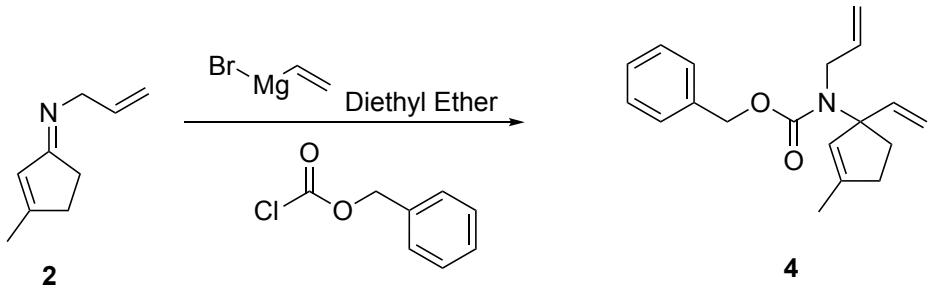
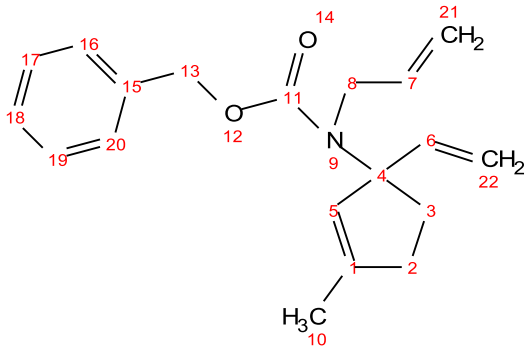


Figure 4.7 General Procedure for Vinyl Addition

Using (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine **2** and vinyl magnesium bromide, a Grignard reaction depicted in Figure 4.7 was employed to create benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl) (prop-2-yn-1-yl) carbamate **4** in the presence of diethyl ether. The mixture was left to stir at room temperature overnight before undergoing workup. Flash chromatography was used to purify the crude product, resulting in a yellowish oil with a chemical yield of 84% after evaporation.



The ^{1}H-NMR spectrum of benzyl allyl(3-methyl-1-vinylcyclopent-2-en-1-yl) carbamate **4** shows phenyl ring protons multiplet between 7.44- 7.29 ppm. Each of internal vinylic protons 6 and 7 show multiplet between 5.95 – 5.82 ppm. And then, doublet at 5.89 ppm with J = 4.2 Hz. is due to olefinic methine protons 5. Moreover the terminal vinylic protons 21 and 21` are given doublet of doublet J =. 7.2 and 2.0 Hz. at 5.22 and 5.18 ppm respectively. One terminal vinylic proton 22 exhibits doublet of doublet at 5.11 ppm with J = 9.8 and 4.4 Hz., and the other one exhibit doublet of doublet at 5.01 ppm with J = 21.4 and 8.0 Hz. Benzylic methylene protons 13 show singlet at 5.19 ppm. In addition, one of allylic methylene proton 8 shows doublet at 4.31 ppm with J = 5.2 Hz, and the other allylic methylene proton shows doublet at 4.29 ppm with J = 5.2 Hz. Methylene proton 2 shows doublet at 2.05 ppm with J = 1.2Hz. The methyl protons show doublet at 1.97 ppm with J = 0.6 Hz. Moreover, methylene protons 3 show doublet of doublet at 2.62 ppm with J = 20.2 and 6.0 Hz. The same with methylene protons 3’ show doublet of doublet at 1.66 ppm with J = 13.6 and 1.6 Hz.

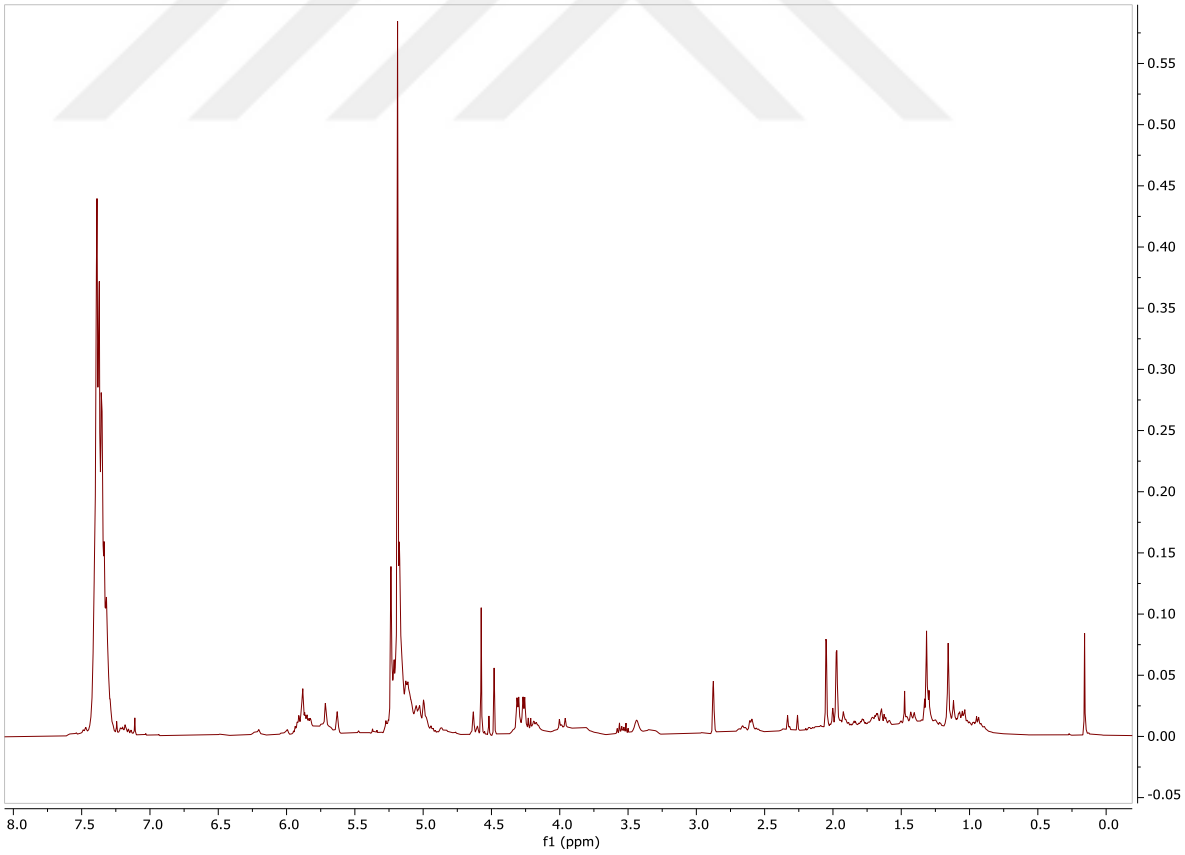


Figure 4.8 ^{1}H-NMR spectrum of benzyl allyl(3-methyl-1-vinylcyclopent-2-en-1-yl) carbamate

The ^{13}C-NMR spectrum of benzyl allyl(3-methyl-1-vinylcyclopent-2-en-1-yl) carbamate **4** shows the signal at 155.2 ppm is due to ester carbon 11. The quaternary carbons 1 and 15 exhibit signals at 140.9 and 136.9 ppm. Internal vinylic carbons 5 and 4 show signals at 136.5 and 136.1 ppm respectively. Phenyl ring carbon shows at 135.4, 133.9, 133.7, 133.3 and 128.7 ppm. Moreover, the signal at 128.5 ppm is due to the olefinic methine carbon 5. Terminal vinylic carbons 7 and 6 exhibit signals at 128.2 and 116.6 ppm respectively. In addition, the signal at 69.8 ppm is due to benzylic methylene carbon 13. The quaternary carbons 4 shows a signal at 67.7 ppm. The signal at 53.0 ppm for allylic carbon 8. Signals at 42.6 and 29.7 ppm are due to the methylene carbons 2 and 3 in the ring respectively. Finally, the methyl carbon 10 shows a signal at 19.2 ppm

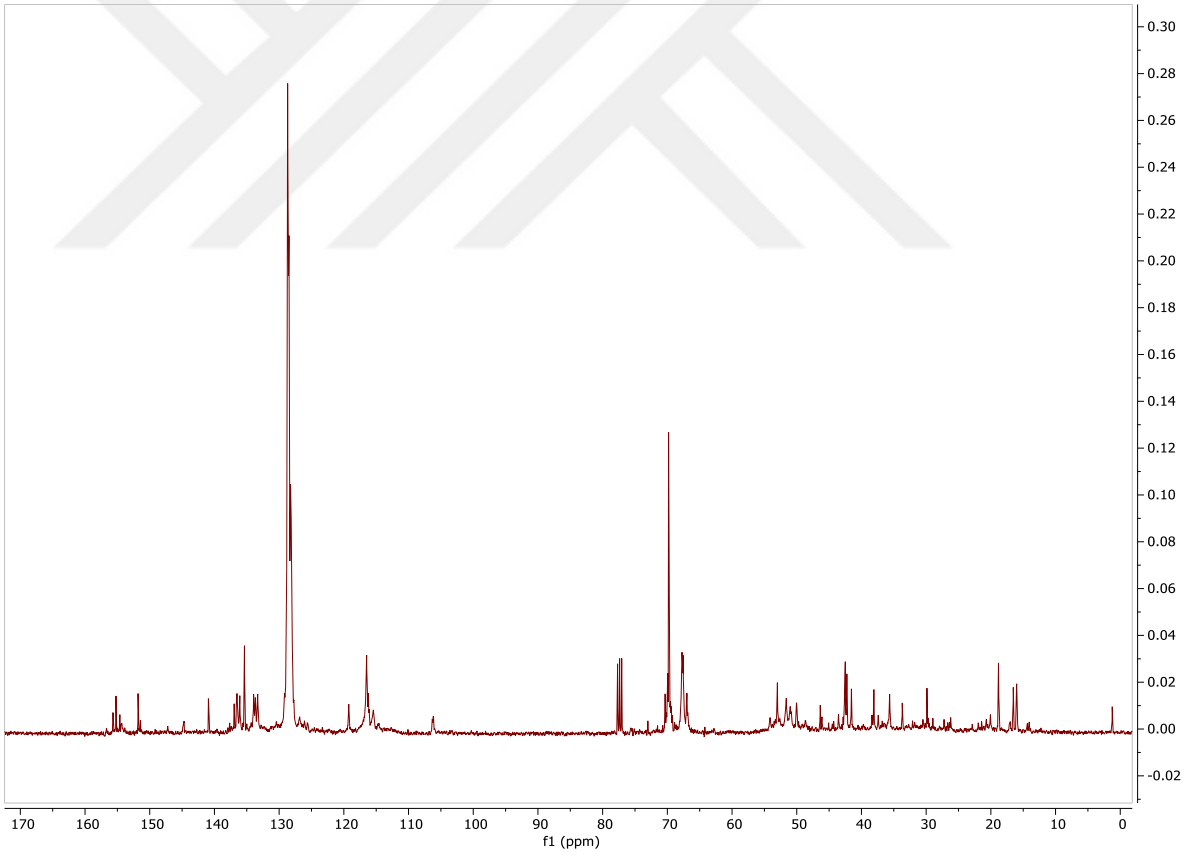


Figure 4.9 ^{13}C-NMR spectrum of benzyl allyl(3-methyl-1-vinylcyclopent-2-en-1-yl) carbamate

4.1.3 General Procedure for Ring Closing Reaction

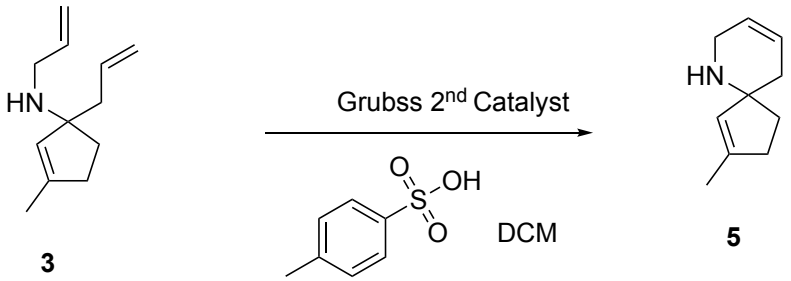
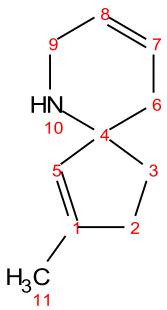


Figure 4.10 General Procedure for Ring Closing Reaction

A chemical compound named 2-methyl-6-azaspiro [4.5] deca-1,8-diene **5** was created by using *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **3** and p-toluenesulfonic acid monohydrate in DCM. This was achieved by applying Grubbs Second Generation catalyst with Ring Closing Metathesis as shown in Figure 4.10. The product was obtained as a dark brown oil with 79% chemical yield after carrying out the necessary workup procedures.



The ^{1}H-NMR spectrum of 2-methyl-6-azaspiro [4.5] deca-1,8-diene **5** displays a range of readings. Methine protons 8 and 7 exhibit a multiplet between 5.73-5.60 ppm, while olefinic methine proton 5 shows a singlet at 5.35 ppm. Methylene protons 9 show a singlet of 3.36 ppm. Methylene protons 6 has a doublet of a triplet of doublet at 2.25 ppm with J = 29.8, 15.1, 6.6 Hz. Methylene proton 2 displays a triplet at 2.03 ppm with J = 21.8 Hz, while the other one, 3, shows a multiplet between 1.92-1.69 ppm. Finally, there is a singlet at 1.67 ppm due to methyl protons.

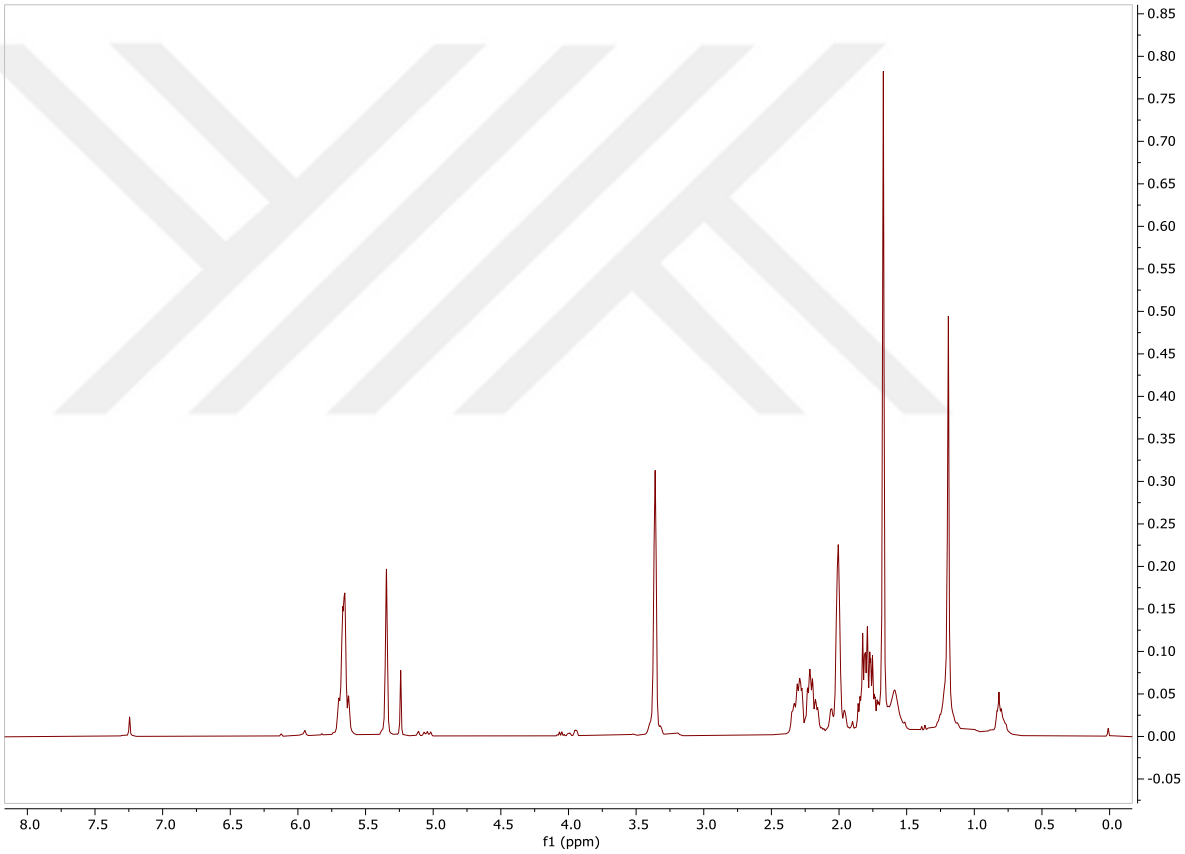


Figure 4.11 ^{1}H-NMR Spectrum of 2-methyl-6-aza spiro [4.5] deca-1,8-diene

The ^{13}C-NMR spectrum of 2-methyl-6-aza spiro [4.5] deca-1,8-diene **5** displays signals at 141,6 130.8, 125.8, and 125.0 ppm for the olefinic methine carbons at positions 1, 5, 8, and 7, respectively. The chiral carbon at position 4 exhibits a signal at 65.0 ppm. Additionally, the methylene carbons at positions 9, 6, and 2 exhibit signals at 42.6, 37.2, and 35.1 ppm, respectively. The methylene carbon at position 3 displays a signal at 29.7 ppm. Lastly, the methyl carbon at position 11 shows a signal at 16.9 ppm.

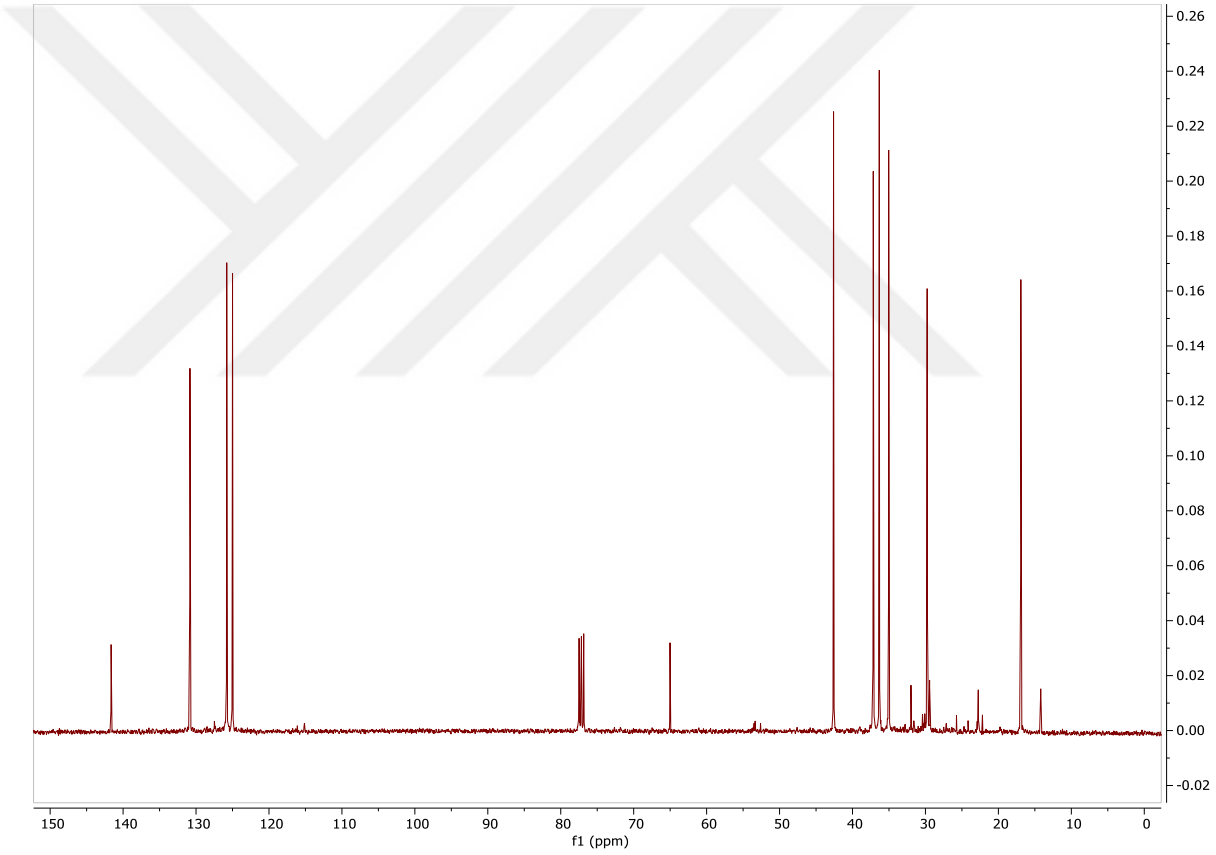


Figure 4.12 ^{13}C-NMR spectrum of 2-methyl-6-aza spiro [4.5] deca-1,8-diene

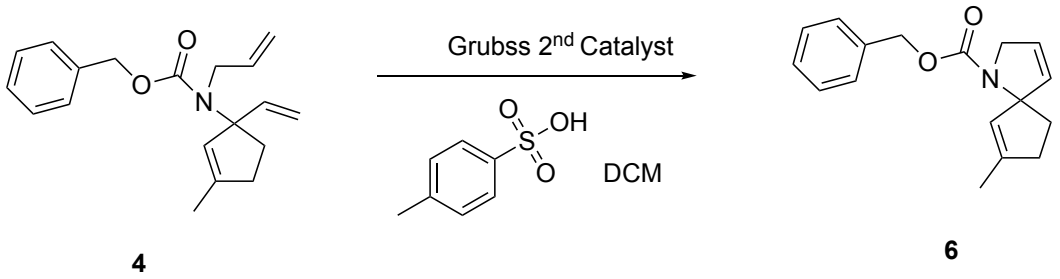
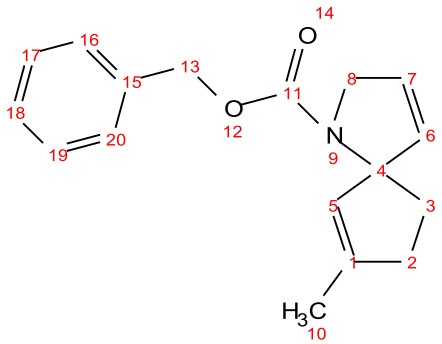


Figure 4.13 General Procedure for RCM for Vinyl

A chemical compound named benzyl allyl(3-methyl-1-vinylcyclopent-2-en-1-yl) carbamate **4** and p-toluenesulfonic acid monohydrate in DCM. This was achieved by applying Grubbs Second Generation catalyst with Ring Closing Metathesis. The product **6** was obtained as a dark brown oil with a 79% chemical yield after carrying out the necessary workup procedures.



The ^{1}H-NMR spectrum of benzyl 7-methyl-1-azaspiro [4.4] nona-3,6-diene-1-carboxylate **6** phenyl ring protons show multiplet between 7.38 – 7.11 ppm. Methine proton 7 shows singlet at 5.94 ppm. The other methine proton 6 shows doublet at 5.59 ppm with J = 5.6 Hz. On the other hand, olefinic methine proton 5 exhibits a signlet at 5.0 ppm. One of the benzylic methylene protons in position 13 shows doublet at 5.17 ppm with J = 6.8 Hz. and another at 5.15 ppm with J = 6.8 Hz. and then *N*- methylene protons 8 shows doublet of doublet at 3.87 ppm with J = 14.4 and 6.8 Hz. and other one show doublet of doublet at 3.43 ppm with J = 14.0 and 2.8 Hz. one of the methylene protons 3 exhibit doublet of doublet at 2.63ppm with J = 21.8 and 4.0 Hz and another show doublet at 1.79 ppm with J = 10.2 Hz. Methylene proton 2 shows broad signlet at 1.54 ppm and the other one gives doublet of doublet at 1.31 ppm with J = 15.6 and 4.4 Hz. Finally, methyl protons show signlet at 1.25 ppm.

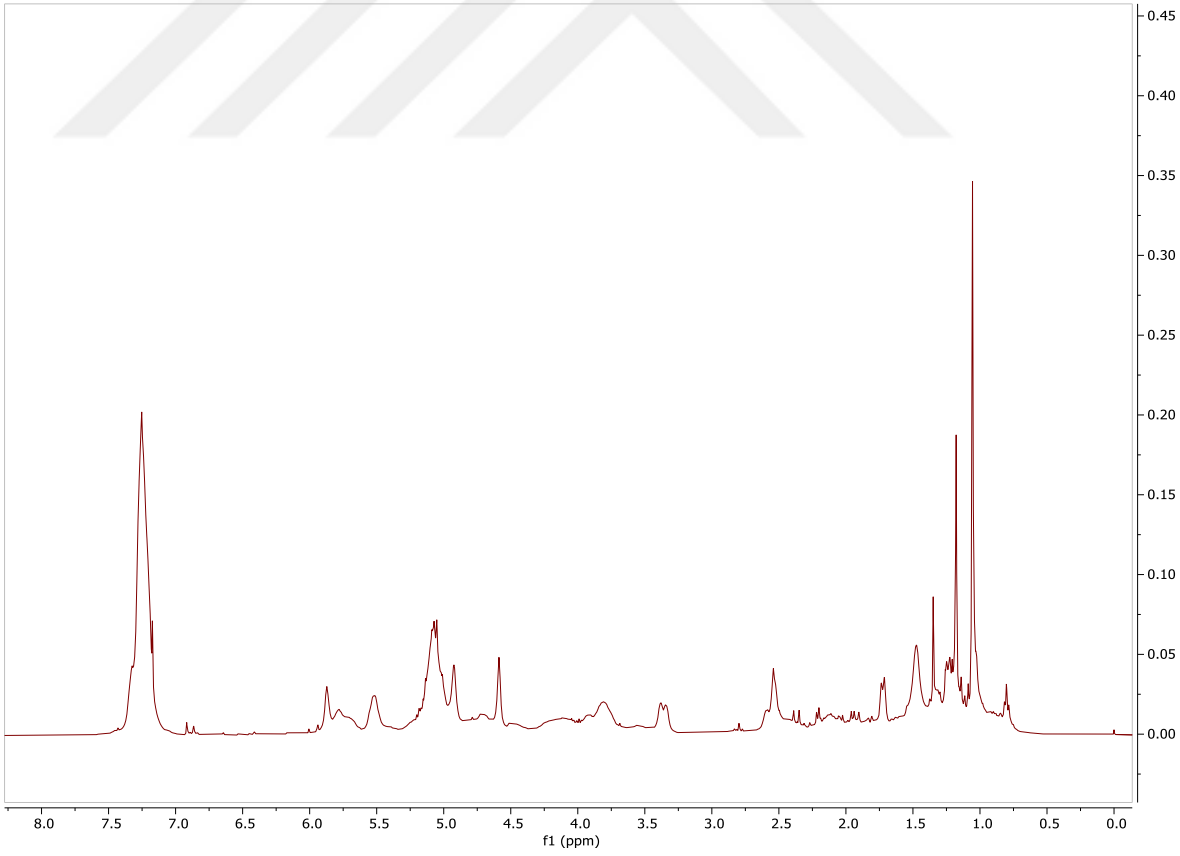


Figure 4.14 ^{1}H-NMR spectrum of benzyl 7-methyl-1-azaspiro [4.4] nona-3,6-diene-1-carboxylate

The ^{13}C-NMR spectrum of benzyl 7-methyl-1-azaspiro [4.4] nona-3,6-diene-1-carboxylate **6** shows the ester carbon 11 shows signal at 154.4 ppm. Quaternary carbons 1 and 15 show signals at 149.0 and 136.6 ppm respectively. Olefinic methine carbon 5 shows a signal at 136.0 ppm. Furthermore, methine carbons in the phenyl ring show signal at 135.1, 128.5, 128.0, and 126.6 ppm respectively. Methine carbons 7 and 6 show signals at 126.0 and 125.6 ppm. Quaternary carbon 4 exhibits a signal at 67.7 ppm. Moreover, benzylic methylene carbon 13 shows a signal at 67.4 ppm. Methylene carbon 8 shows a signal at 53.6 ppm. In addition, methylene carbon 2 and 3 signals at 42.8 and 37.3 respectively. Lastly, methyl carbon exhibits a signal at 29.8 ppm.

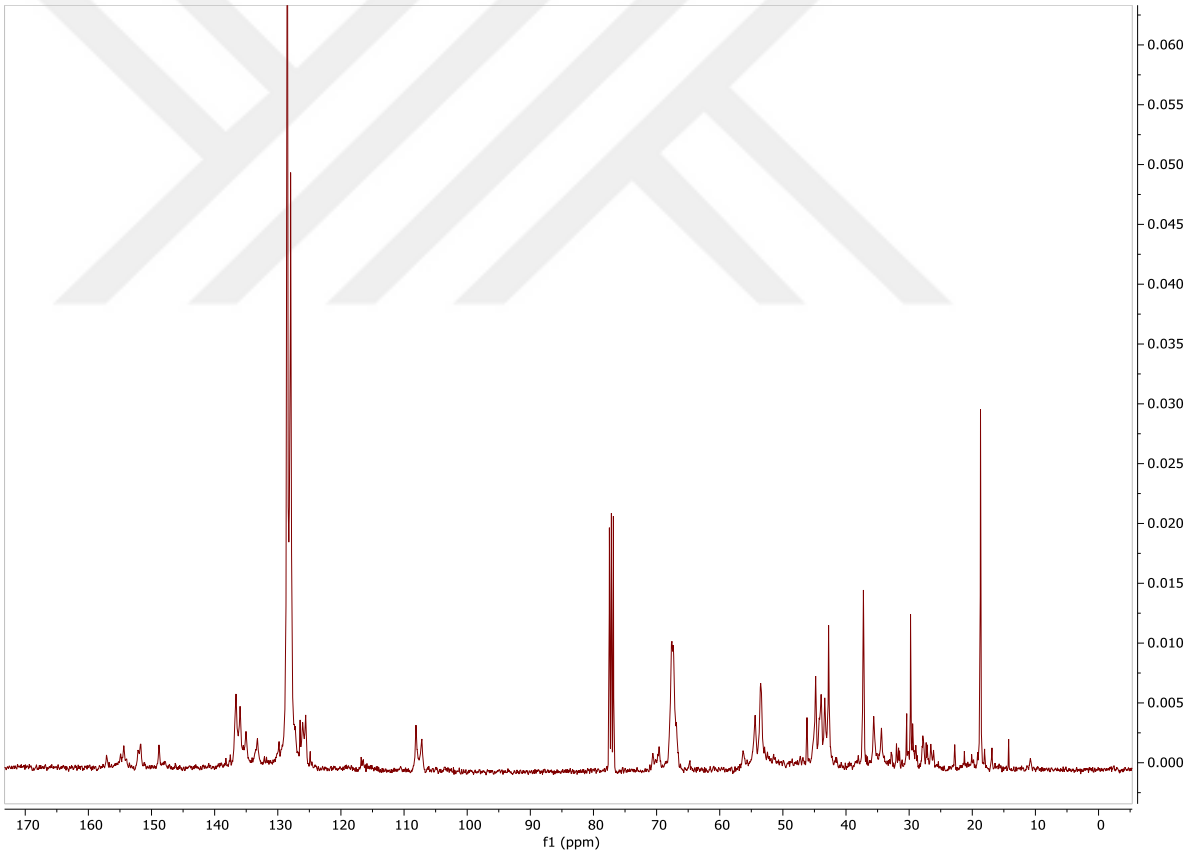


Figure 4.15 13C-NMR spectrum of benzyl 7-methyl-1-azaspiro [4.4] nona-3,6-diene-1-carboxylate

4.2 Result for Pauson-Khand Reaction Product

4.2.1 Synthesis of Imine for PKR

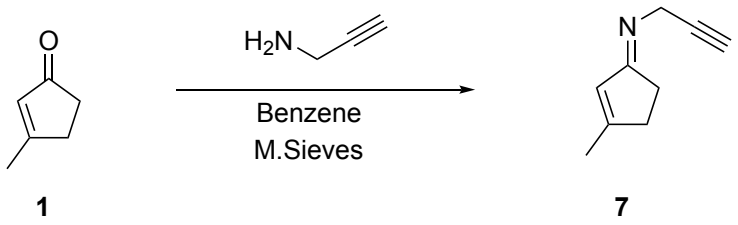
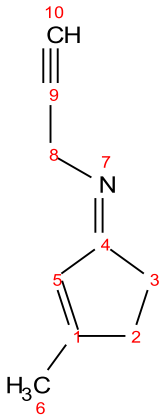


Figure 4.16 General Procedure Imine for PKR

(*E*)-3-methyl-*N*-(prop-2-yn-1-yl) cyclopent-2-en-1-imine **7** was synthesized from 3-methylcyclopent-2-en-1-one **1** and propargylamine using dry ether and anhydrous magnesium sulfate. The product was obtained as yellowish oil with a 90% yield.



In the ^{1}H-NMR spectrum of (E)-3-methyl-*N*-(prop-2-yn-1-yl) cyclopent-2-en-1-imine **7** displays methine proton at 5 positions in the ring doublet 5.91 ppm with $J = 23.7$ Hz. The methylene protons at position 8 exhibit doublet at 4.00 ppm with $J = 20.7$ Hz. The methylene protons at position 3 give rise to multiplet between 2.63-2.47 ppm. One of the methylene proton at 2 positions give a multiplet of 2.39-2.31 ppm and other methylene protons give a multiplet of 1.82-1.75. Additionally, the acetylenic proton at position 10 appears as a triplet at 2.16 ppm with $J = 2.6$ Hz. Finally, the methyl proton at position 6 displays a singlet at 1.93 ppm.

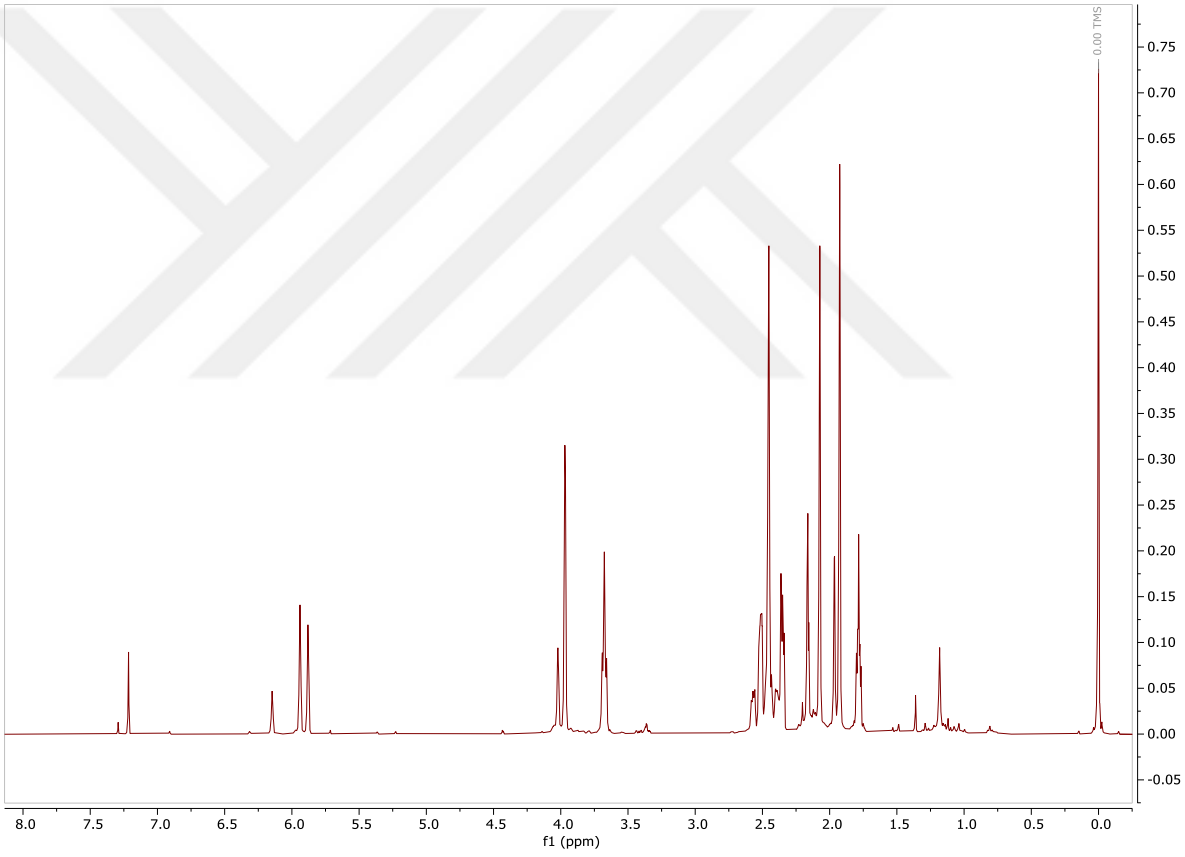


Figure 4.17 ^{1}H-NMR: The spectrum of (E)-3-methyl-N-(prop-2-yn-1-yl) cyclopent-2-en-1-imine

The ^{13}C-NMR spectrum for (E)-3-methyl-*N*-(prop-2-yn-1-yl) cyclopent-2-en-1-imine **7** displays various signals. Imine carbon 4 shows a signal at 182.7 ppm, while quaternary carbon 1 has a signal at 163.8 ppm. Methine carbon 5 has a signal at 121.2 ppm, and acetylenic carbons 9 and 10 display signals at 81.9 and 70.5 ppm, respectively. The propargylic methylene carbon at position 8 has a signal at 41.6 ppm. Additionally, the methylene carbons at positions 2 and 3 have signals at 34.9 ppm and 33.6 ppm, respectively. Lastly, the methyl carbon 6 exhibits a signal at 19.5 ppm.

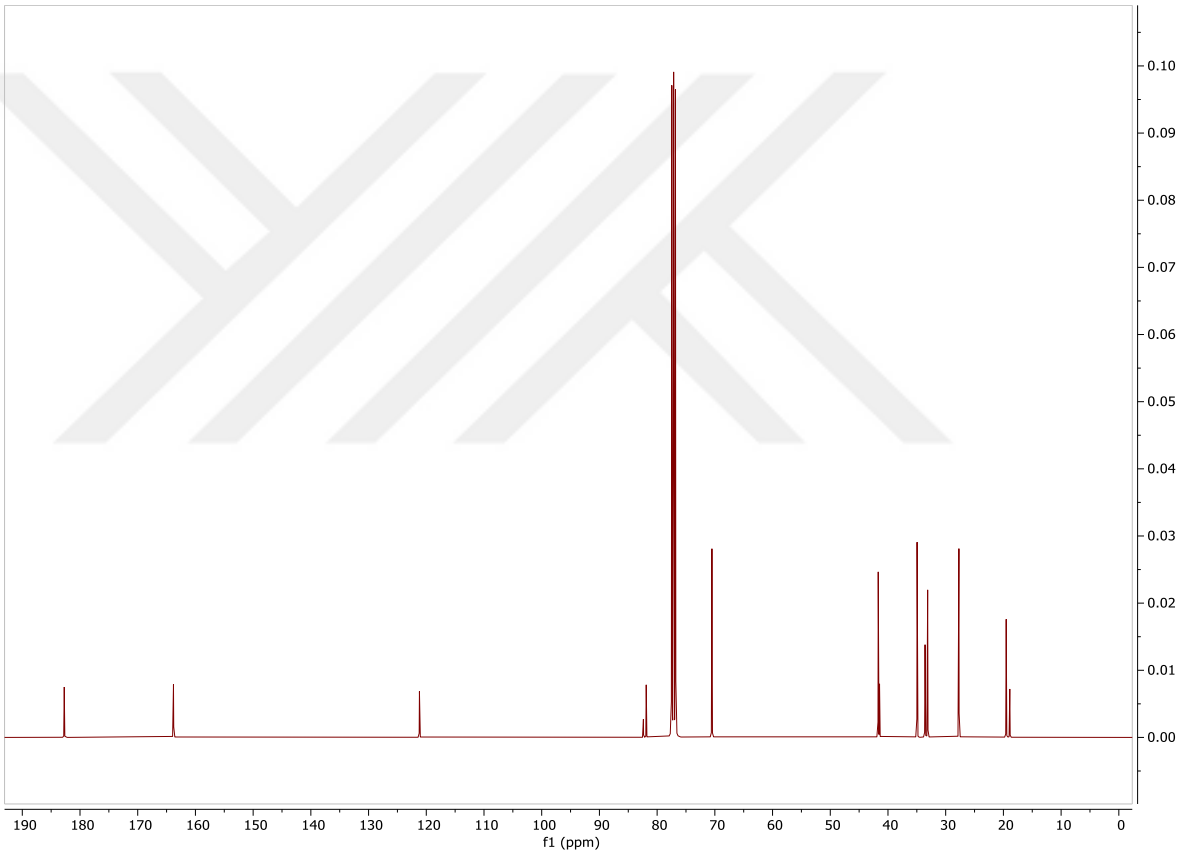


Figure 4.18 ^{13}C-NMR: The spectrum of (E)-3-methyl-N-(prop-2-yn-1-yl) cyclopent-2-en-1-imine

4.2.2 Grignard Reaction

General Procedure for Allyl Addition

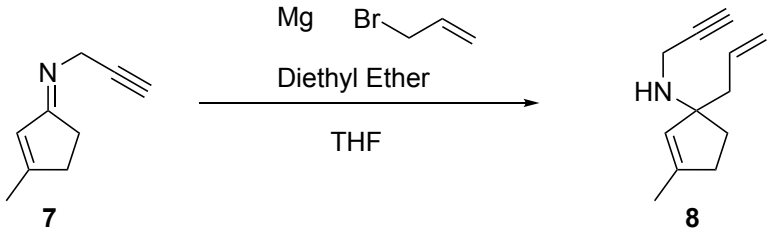
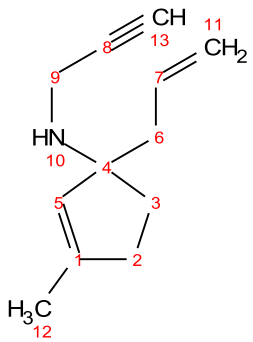


Figure 4.19 General procedure for Allyl Addition

Figure 4.19 illustrates the Grignard reaction that was used to synthesize *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **8** from (*Z*)-*N*-allyl-3-methylcyclopent-2-en-1-imine **7** and allyl bromide in the presence of diethyl ether. The mixture was left to stir at room temperature overnight and after the workup, the crude product underwent purification through flash chromatography. The final product, which was obtained as a yellowish oil, yielded 84% of the intended chemical product.



The ^{1}H-NMR of *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **8** spectrum, it appears that the internal vinylic proton 7 has a multiplet between 5.88-5.64 ppm. Additionally, the olefinic methine proton 5 shows a singlet at 5.27 ppm. Meanwhile, one of the terminal vinylic protons 11 gives doublet of a doublet at 5.08 ppm with J = 15.22, 1.9 Hz. Other terminal vinylic protons 11' show a doublet of a doublet at 5.02 ppm with J = 8.4, 3.3 Hz. respectively. The *N*-methylene protons exhibit a quartet at 4.05 ppm with *J*-values of 7.1Hz. Additionally, aliphatic methylene protons 6 show a doublet at 2.31 ppm with *J*-values of 7.3Hz and another one at the same position shows a multiplet between 1.86-1.79 ppm. The methylene protons in the ring at 2 position show multiplet between 2.26-2.19 ppm. Acetylenic proton shows triplet at 2.12 ppm with J = 2.5 Hz. The other methylene proton 3 shows a multiplet between 2.01 – 1.95 ppm and lastly, the methyl proton peak appears as a singlet at 1.68 ppm.

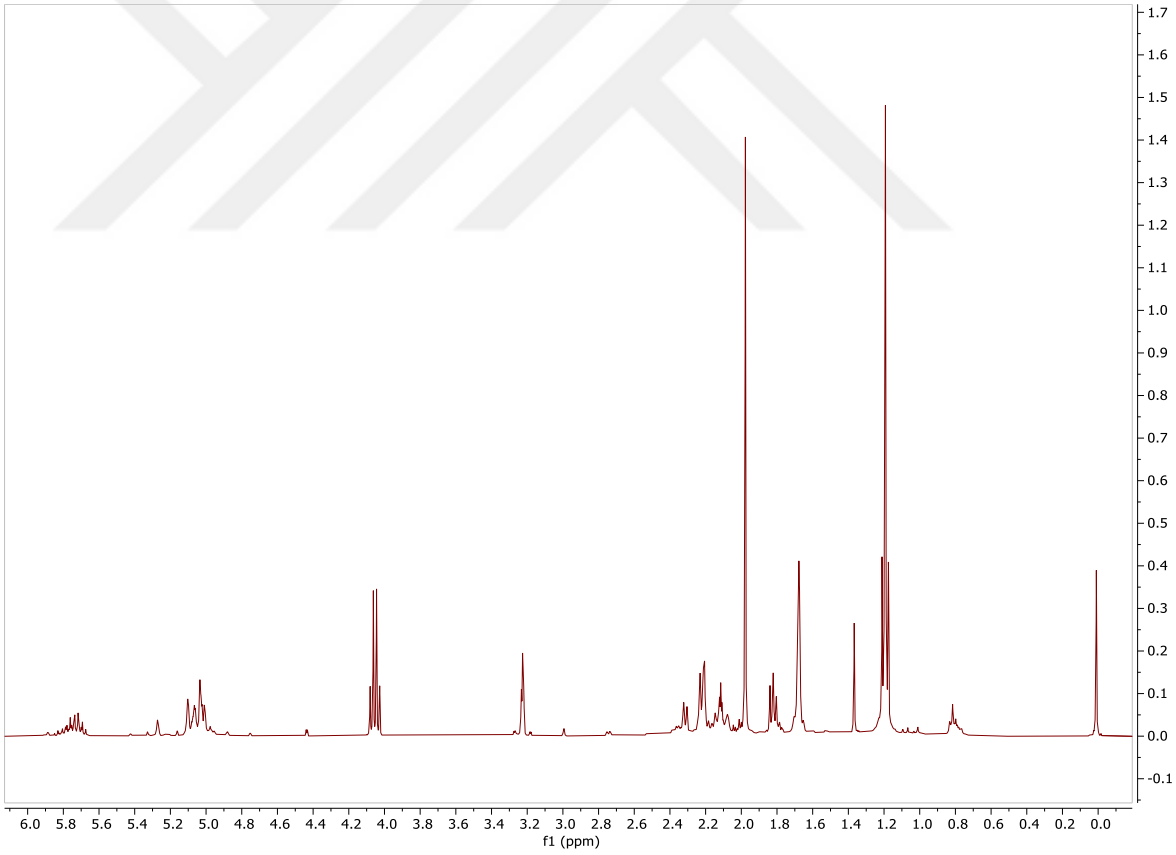


Figure 4.20 ^{1}H-NMR spectrum of N,1-diallyl-3-methylcyclopent-2-en-1-amine

The ^{13}C-NMR spectrum of *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **8** shows signals at 143.1, 134.5, and 129.2 ppm for internal vinylic carbon 1, and olefinic carbons 5 and 7 respectively. Terminal vinylic carbon 11 exhibits a signal at 118.1 ppm. Internal acetylenic carbon shows a signal at 83.5 ppm. Terminal acetylenic carbon shows a signal at 70.8 ppm. Moreover, the chiral carbon shows a signal at 60.4 ppm. The allylic methylene carbon shows a signal at 45.3 ppm. Furthermore, the signal at 35.9 ppm is due to propargylic methylene carbon 10. The methylene carbons 2 and 3 show signals at 33.9 and 29.7 ppm respectively. Finally, methyl carbon 12 shows a signal at 16.8 ppm.

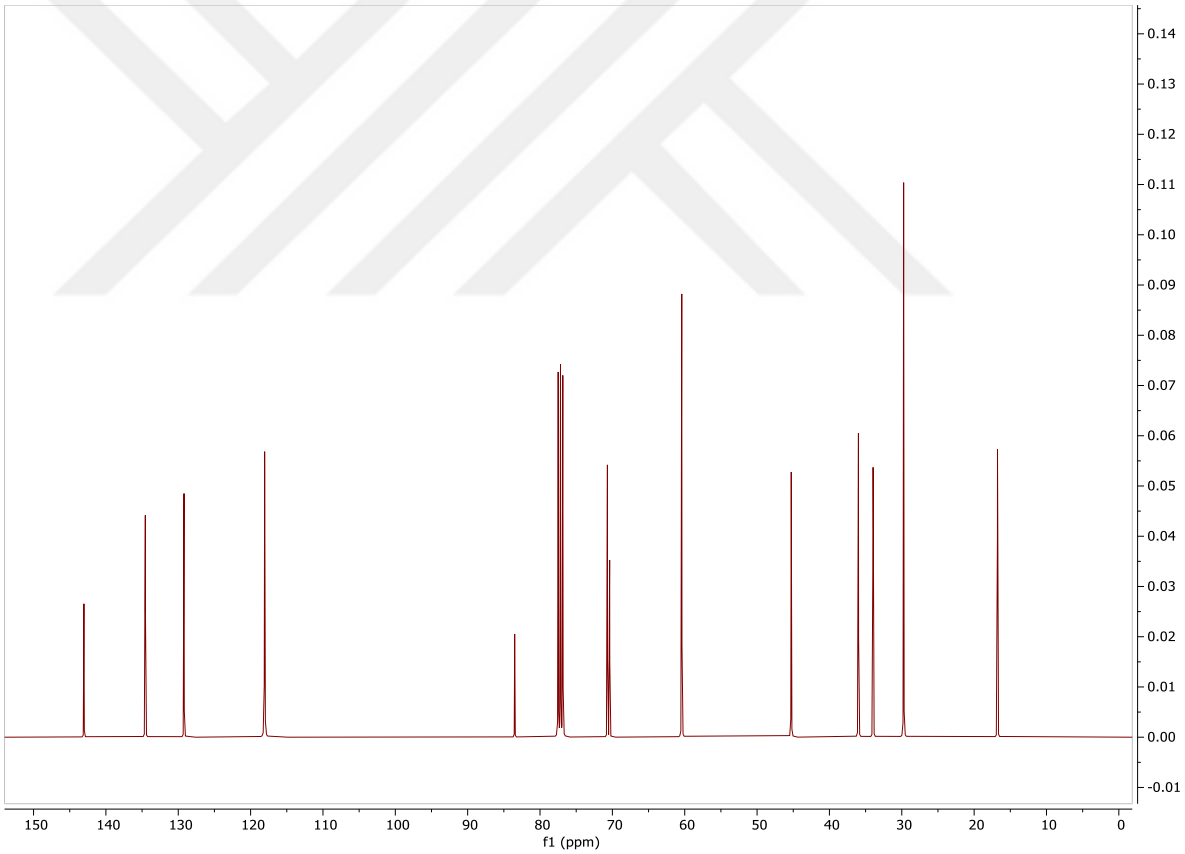


Figure 4.21 ^{13}C-NMR spectrum of *N*,1-diallyl-3-methylcyclopent-2-en-1-amine

General Procedure for Vinyl Addition

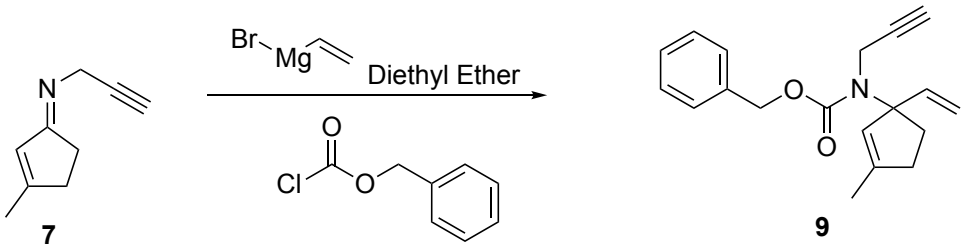
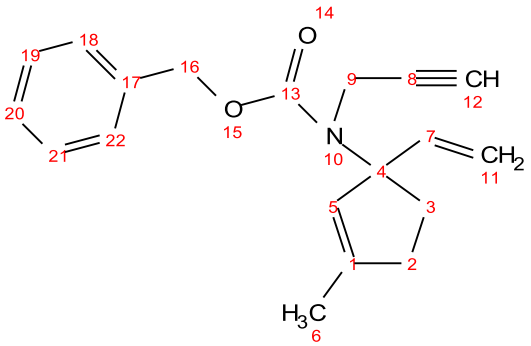


Figure 4.22 General Procedure for Vinyl Addition

Using (*Z*)-3-methyl-*N*-(prop-2-yn-1-yl)cyclopent-2-en-1-imine **7** and vinyl magnesium bromide, a Grignard reaction depicted in Figure 4.22 was employed to create benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate **9** in the presence of diethyl ether. The mixture was left to stir at room temperature overnight before undergoing workup. Flash chromatography was used to purify the crude product, resulting in a yellowish oil with a chemical yield of 84% after evaporation.



The ^{1}H-NMR spectrum of benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate **9** shows multiplet in the aromatic area due to phenyl ring protons between 7.34 – 7.31 ppm. Internal vinylic proton shows multiplet between 6.10- 5.75 ppm. Benzylic methylene protons show doublet at 5.21 ppm with J = 9.73 Hz. The terminal vinylic proton shows singlet at 5.14 ppm. Moreover, singlet at 5.09 ppm for olefinic methine proton. One of the propargylic methylene protons shows doublet of doublet at 4.39 ppm with J = 9.5 and 2.5 Hz. The other proton shows doublet of triplet at 3.94 ppm with J = 8.5 and 4.4 Hz. The multiplet for each of methylene protons shows multiplet between 2.65 - 2.46 ppm and 2.42 - 2.33 ppm respectively. The other multiplet between 2.30 - 2.25 ppm and 2.16 – 2.08 ppm is due to methylene protons. The acetylenic proton shows triplet at 2.23 ppm with J = 2.6 Hz. Finally, methyl protons show doublet at 2.06 ppm with J = 20.4 Hz.

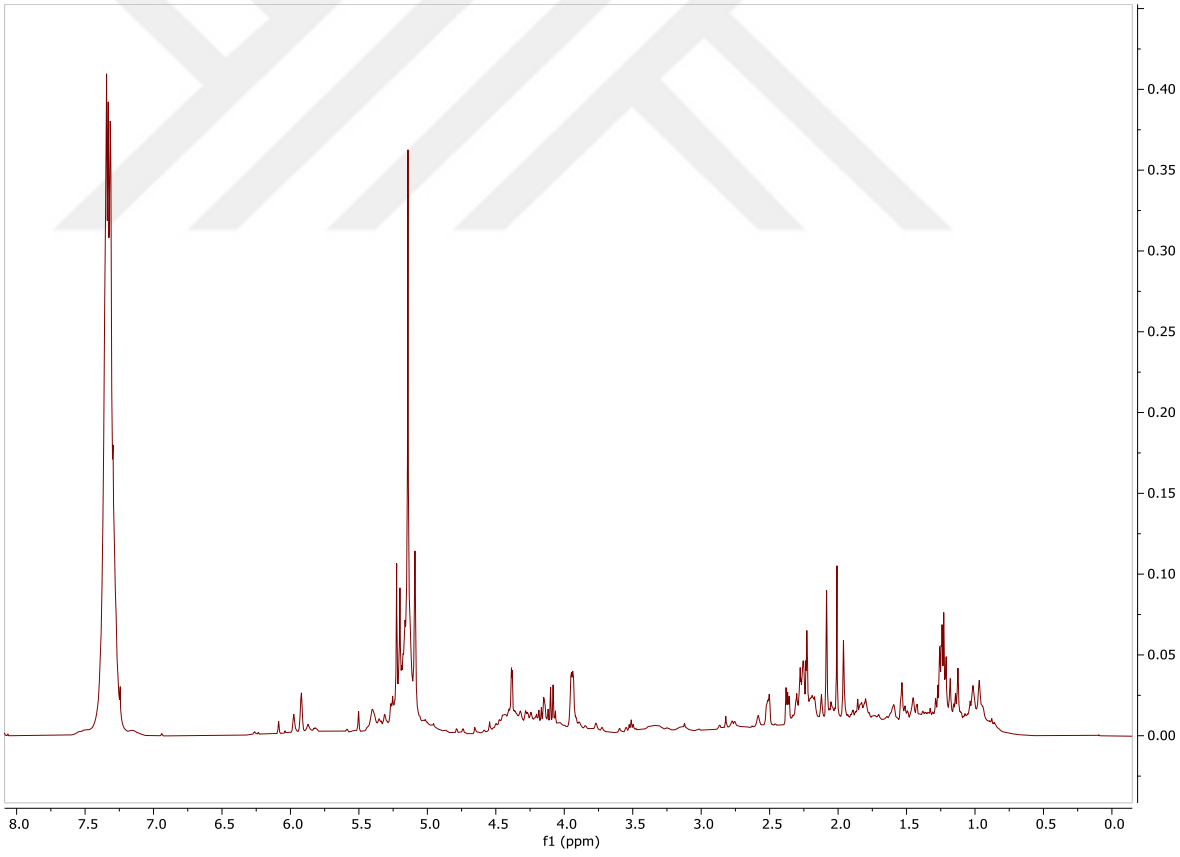


Figure 4.23 ^{1}H-NMR spectrum of benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate

The ^{13}C-NMR spectrum of benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate **9** ester carbon 13 shows signal at 155.0 ppm. The quaternary carbons 17 and 1 exhibit signals at 144.7 and 135.3 ppm. Internal vinylic carbon 7 shows signal at 130.7 ppm. Moreover, methine carbons of the phenyl ring exhibit signal at 128.7, 128.6, 128.4, 128.3 and 128.1 ppm respectively. In addition, the signal at 125.5 ppm belongs to the olefinic methine carbon 5. Terminal vinylic carbon 13 exhibits signal at 116.3 ppm. Internal and terminal acetylenic carbons 8 and 12 show signals at 80.0 and 71.7 ppm respectively. Furthermore, signal at 69.8 ppm due to benzylic methylene carbon 15. The stereogenic carbon 4 shows signal at 67.1 ppm. The signal at 35.8 ppm for propargylic methylene carbon 9. shows signals at 33.1 and 30.9 ppm due to methylene carbons 2 and 3t he ring. The methyl carbon 6 shows signal at 19.2 ppm.

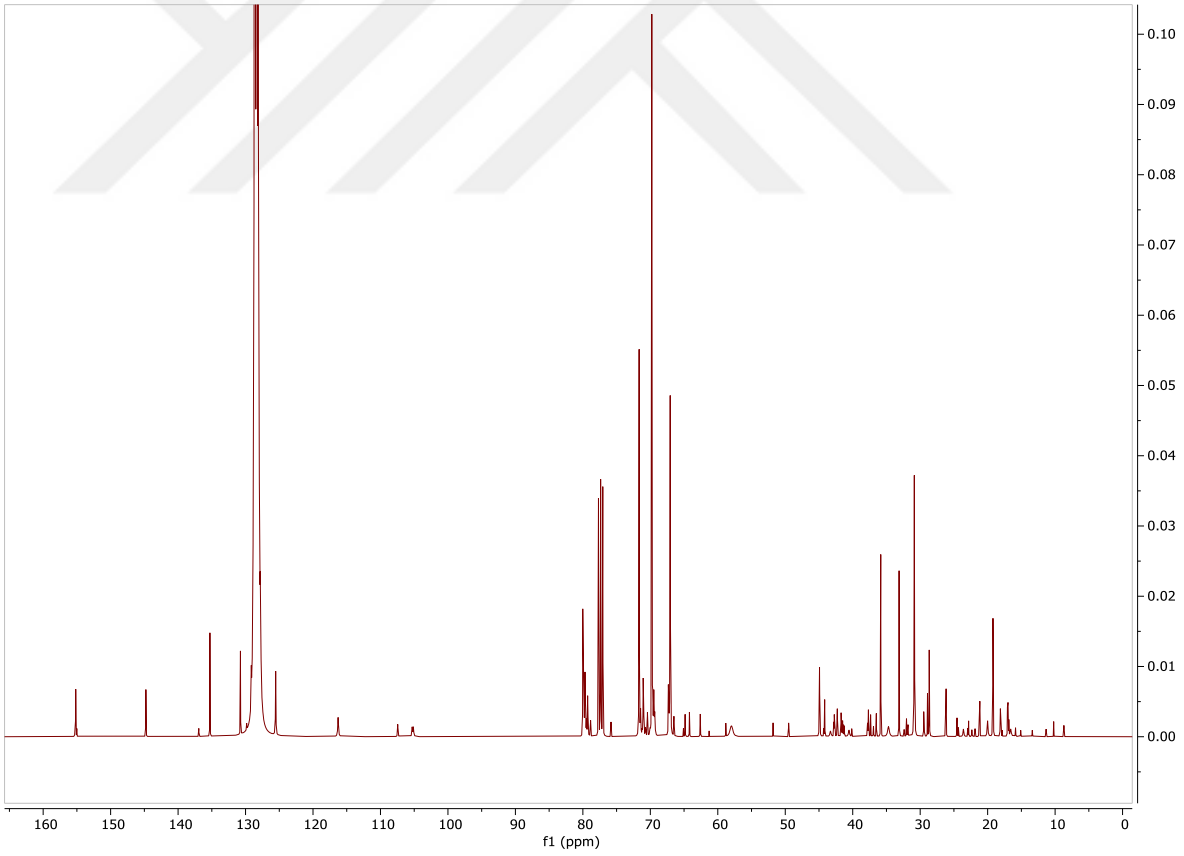
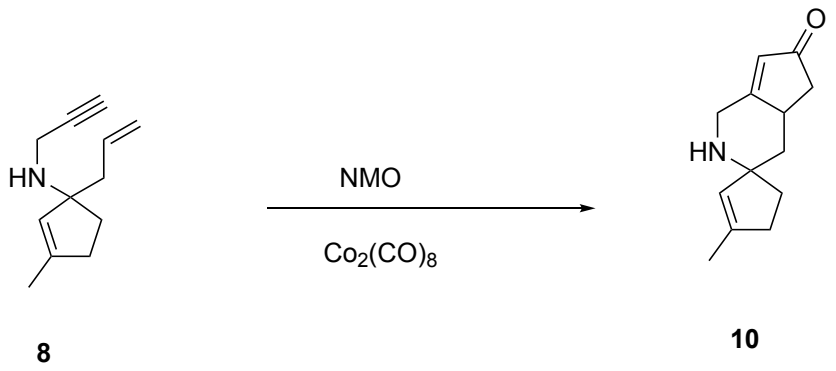


Figure 4.24 ^{13}C-NMR: the spectrum of benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate

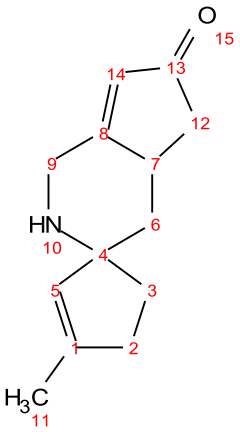
4.2.3 General Procedure for Pauson-Khand Reaction



8 **10**

Figure 4.25 General Procedure for Pauson-Khand Reaction

A chemical reaction was performed using *N*,1-diallyl-3-methylcyclopent-2-en-1-amine **8**, dicobalt octacarbonyl, and NMO as a promoter. The reaction yielded 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[c]pyridin]-2-en-6'(4'H)-one **10** in CH_2Cl_2, which was obtained as a yellow oil with a chemical yield of 78%. The reaction used Pauson-Khand cycloaddition, as shown in Figure 4.25.



The ^{1}H-NMR spectrum of 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[c]pyridin]-2-en-6'(4'H)-one **10** displays signals at various positions. The olefinic methine proton at position 14 is a singlet that appears at 5.71 ppm. The methine proton at position 5 is a doublet of a quartet that appears at 5.03 ppm and has dq with J = 12.5, 6.3 Hz value. One of the methylene protons at position 9 gives a doublet of triplet 3.56 ppm with J = 11.2, 8.5 Hz, and others show a doublet of doublet of doublet 3.24 ppm with J = 11.4, 8.6, 3.3 Hz. The methine proton at position 7 shows a doublet of doublet at 2.54 ppm with J = 12.0, 6.6 Hz. The methylene protons at position 12 show a multiplet between 2.33-2.25 ppm. One of the methylene protons at position 2 shows a doublet of a doublet at 2.20 ppm with J = 20.8, 8.5 Hz, while the other one at position 2 gives a multiplet between 2.08-1.89 ppm. The methylene protons at position 6 show a multiplet between 1.66-1.53 ppm. One of the methylene protons at position 3 gives multiplet between 1.57-1.49 ppm. The methylene proton at position 3' and methyl proton gives a multiplet between 1.46-1.29 ppm.

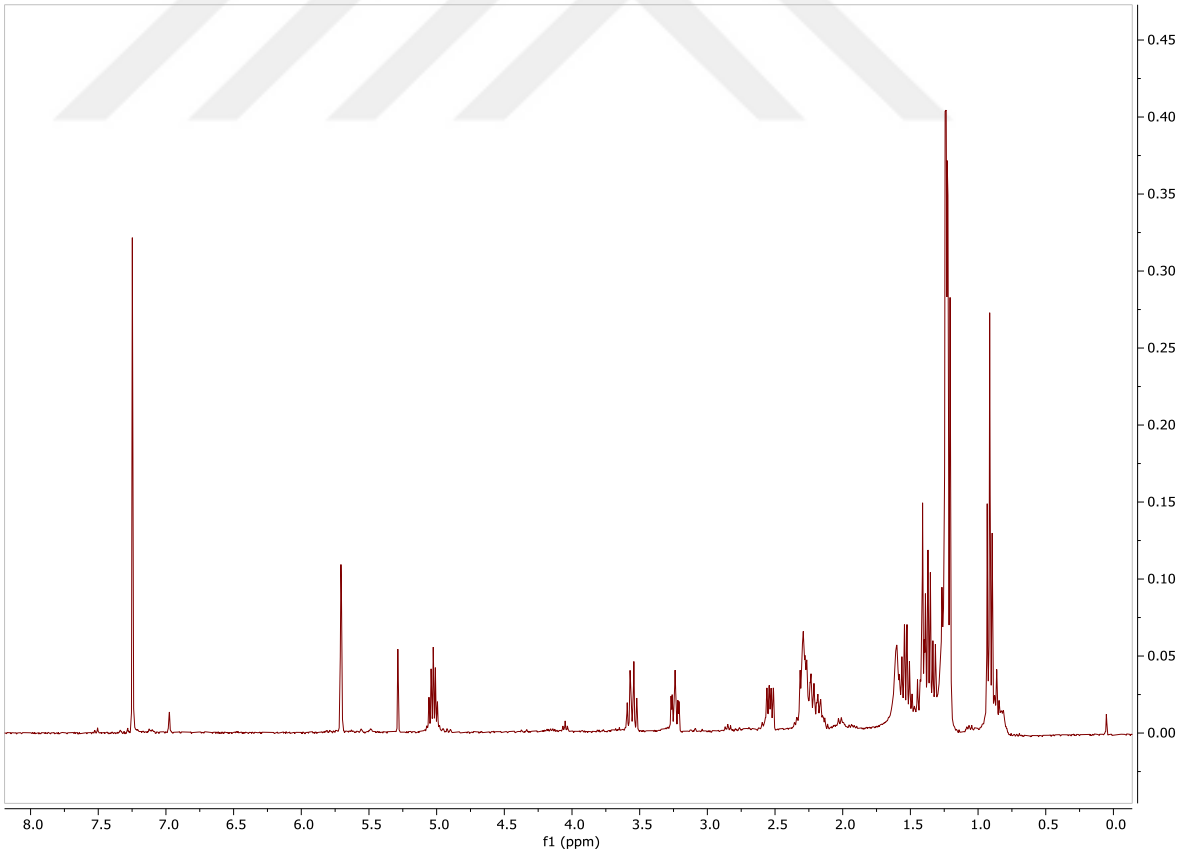


Figure 4.26 ^{1}H-NMR spectrum of 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[c]pyridin]-2-en-6'(4'H)-one

The ^{13}C-NMR spectrum of 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[c]pyridin]-2-en-6'(4'H)-one **10**, the carbonyl carbon 13 peak appears at 212.9 ppm, with vinylic carbon 8 and 1 quarternary carbon at 143.0 and 134.5 ppm, respectively. One of the olefinic carbon positions, 5, shows a peak at 130.3 ppm, while the other appears at 129.2 ppm. Additionally, the chiral carbon gives a peak at 60.4 ppm, methylene carbon 9 at 45.3 ppm, and methine carbon 7 at 38.4 ppm. Methine carbon 12, 6, 2, and 3 give 35.9, 33.9, 32.3, and 29.7 ppm, respectively, and the methyl carbon appears at 21.1 ppm.

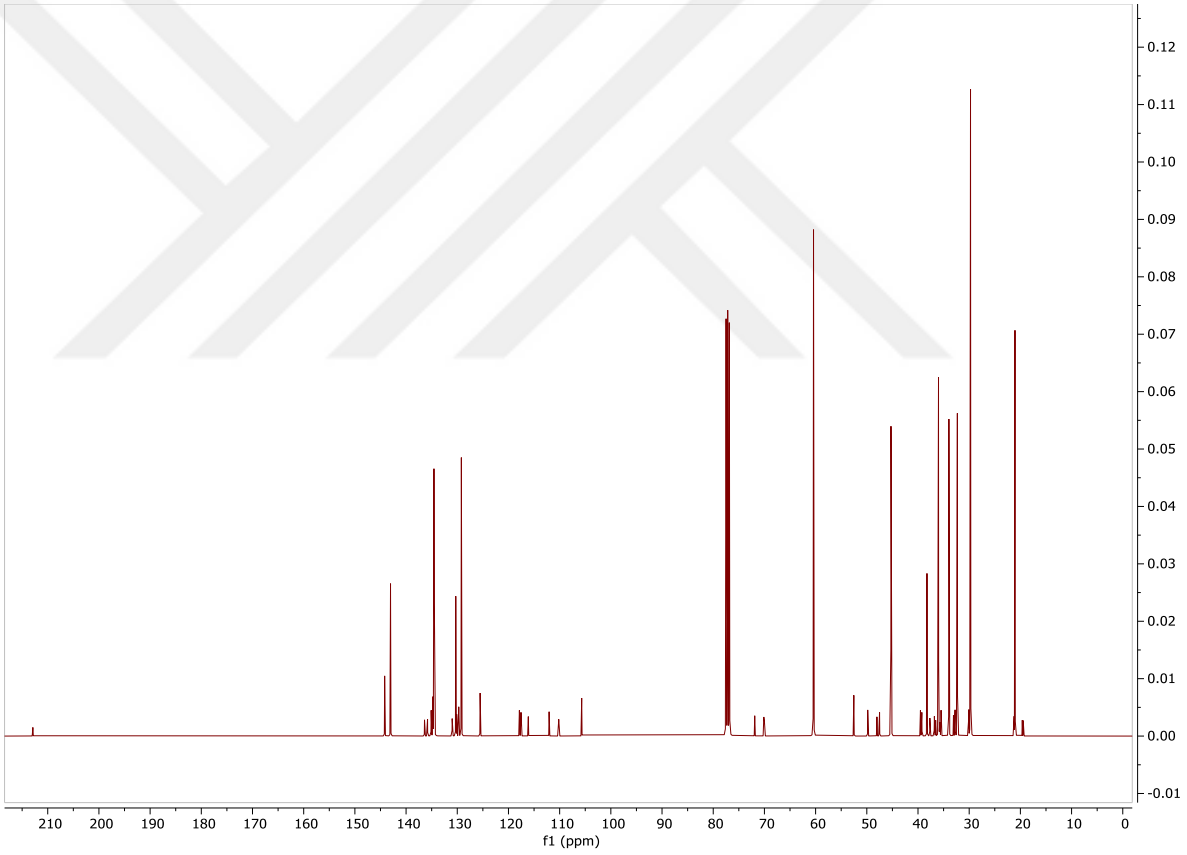
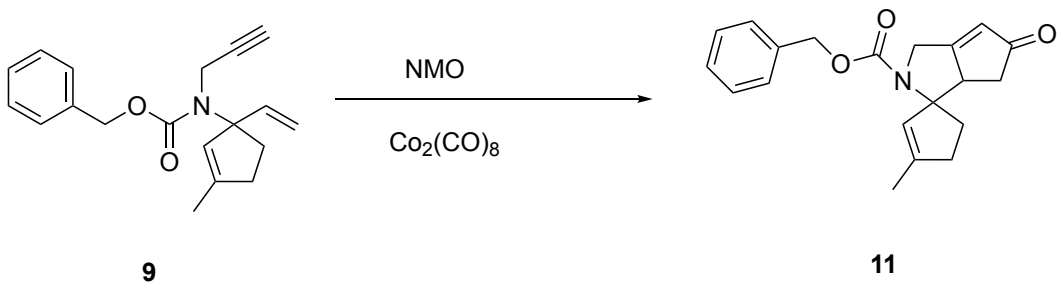


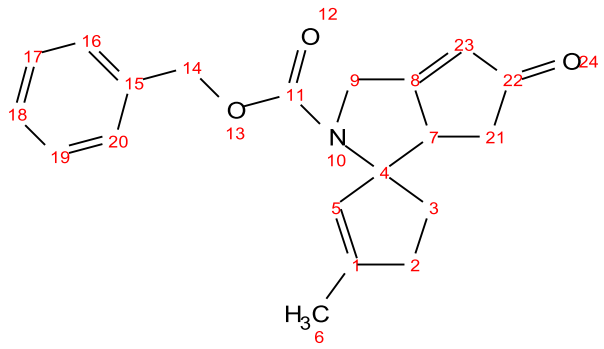
Figure 4.27 ^{13}C-NMR spectrum of 3-methyl-1',2',4a',5'-tetrahydrospiro[cyclopentane-1,3'-cyclopenta[c]pyridin]-2-en-6'(4'H)-one



9 **11**

Figure 4.28 General Procedure PKR for Vinyl

A chemical reaction was performed using benzyl (3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate **9** dicobalt octacarbonyl, and NMO as a promoter. The reaction yielded benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[*c*]pyrrol]-2-ene-2'-carboxylate 11in CH_2Cl_2, which was obtained as a yellow oil with a chemical yield of 78%. The reaction used Pauson-Khand cycloaddition, as shown in Figure 4.28.



The ^{1}H-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[*c*]pyrrol]-2-ene-2'-carboxylate **11** shows phenyl ring protons show multiplet between 7.36 – 7.33 ppm. In addition, singlet at 5.27 ppm due to olefinic methine proton 23, benzylic methylene protons 14 show doublet at 5.15 ppm with J = 6.2 Hz. And then singlet for methine proton 5 at 5.11 ppm the diastereotopic methylene proton 9 shows doublet of triplet 3.97 ppm with J = 10.5 and 5.2 Hz. The methine proton 7 shows a multiplet between 2.79 – 2.53 ppm. Moreover, one of the methylene protons 21 shows multiplet between 2.35-2.13 ppm. Another methylene proton 2 singlet at 1.75 ppm. Multiplet between 1.55 - 1.38 ppm for methylene protons 3. The methyl protons 6 show singlet at 1.23 ppm.

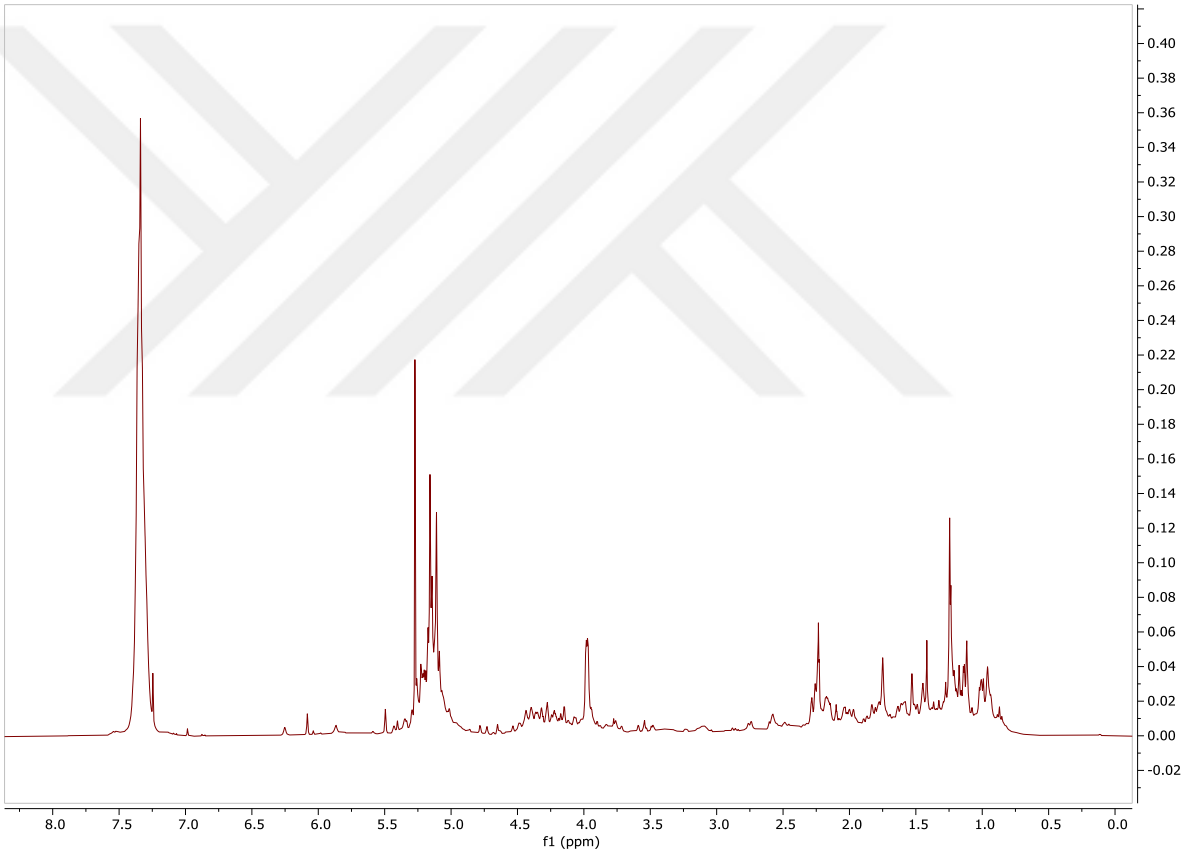


Figure 4.29 ^{1}H-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'H-spiro[cyclopentane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate

The ^{13}C-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[*c*]pyrrol]-2-ene-2'-carboxylate **11** shows signals Ester carbon and carbonyl carbon 22 and 11 exhibit signals at 210.4 and 155.2 ppm. The quaternary carbons 8, 1, and 15 show signals at 147.7, 144.7, and 135.3 ppm respectively. Moreover, methine carbons of the phenylic ring exhibit signals at 128.7, 128.6, 128.4 128.3 and 128.1 ppm respectively. Signals at 130.7 and 125.5 ppm belong to methine carbons at positions 23 and 5 respectively. In addition, signal at 67.1 ppm for benzylic methylene carbon 14. The quaternary carbon at position 4 exhibits signal at 67.1 ppm. Furthermore, the signal at 44.1 ppm for methylene carbon 9. The stereogenic carbon 7 shows signal at 35.8 ppm. The signal at 33.1 ppm due to methylene carbon 21. At 30.8 and 28.7 ppm due to methylene carbons 2 and 3 in the cyclopentene ring respectively. The methyl carbon shows signal at 19.2 ppm.

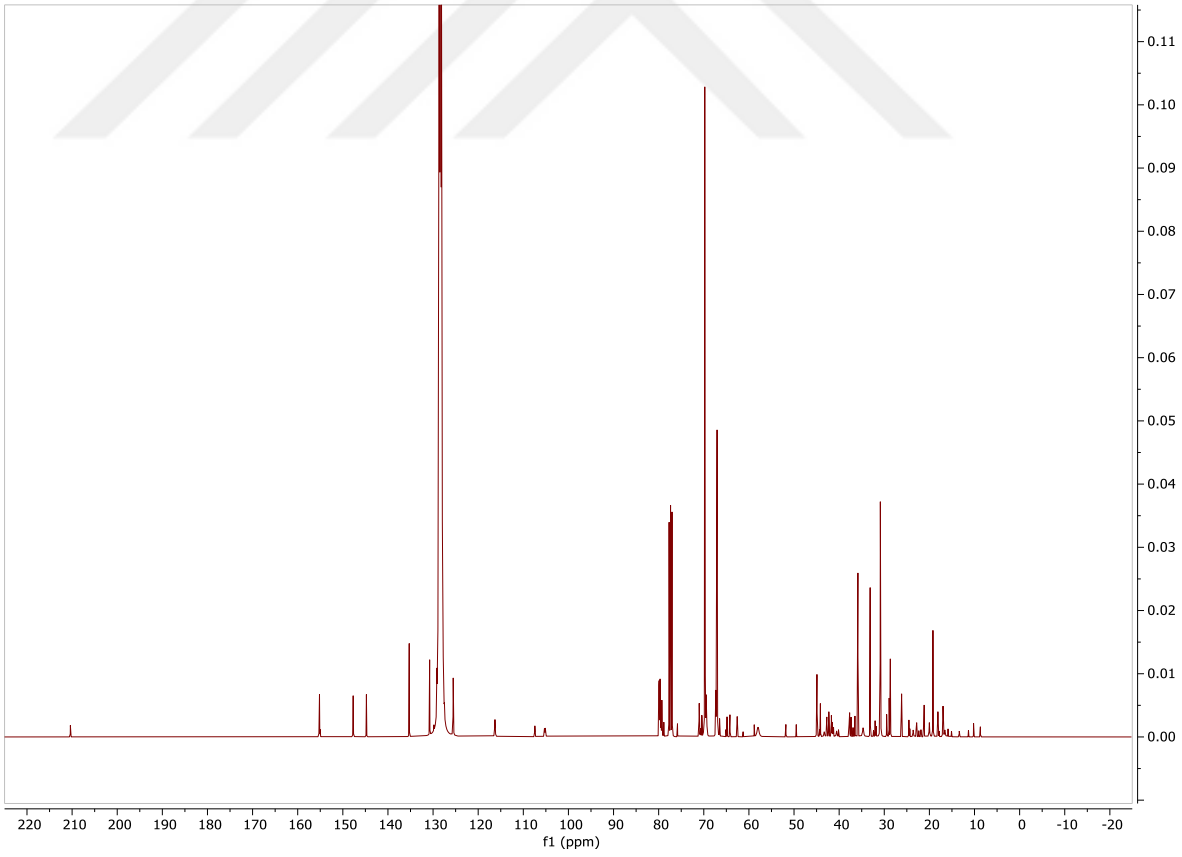


Figure 4.30 ^{13}C-NMR spectrum of benzyl 3-methyl-5'-oxo-3',5',6',6a'-tetrahydro-2'*H*-spiro[cyclopentane-1,1'-cyclopenta[c]pyrrol]-2-ene-2'-carboxylate

5. DISCUSSION

The present study outlines the development of a new synthesis pathway for aza spiro rings, which constitute a promising class of bioactive heterocycles. The successful outcomes achieved as a result of this research are expected to pave the way for novel ideas and applications in the field of chemistry and beyond. Our focus on synthesizing spiro hetero ring systems, known for their high efficacy and bioactivity, yielded notable results that point to the potential of these compounds for a variety of applications. This study aims to provide a foundation for further research into the synthesis and applications of spiro heterocycles, with the ultimate goal of advancing our understanding of the chemical properties and biological activity of these compounds.

6. CONCLUSIONS AND RECOMMENDATIONS

This study aims to synthesize new *N*-nitrogen-containing spiro compounds, to introduce innovative ideas to the emerging field of organic synthesis chemistry. We anticipate that these versatile spiro azo heteroskeletons will have practical applications in interdisciplinary fields, such as ligand exchange reactions, drug development, antibacterial research, and antiallergic studies. As we continue to develop these structures, we hope they will make a significant contribution to the scientific community and the world of synthesis chemistry. Our primary objective with this study is to create a range of novel N-nitrogen-containing spiro compounds. Through our research, we aim to bring fresh ideas and new insights to the field of organic synthesis chemistry. Our focus is on developing highly versatile spiro azo heteroskeletons, which we believe will have a wide range of practical applications across various interdisciplinary fields. These applications include, but are not limited to, ligand exchange reactions, drug development, antibacterial research, and antiallergic studies.

We believe that our ongoing work to develop these new spiro compounds will make a significant contribution to the scientific community and the world of synthesis chemistry. We are committed to pushing the boundaries of what is currently possible in the field and to discovering new ways to approach the synthesis of complex organic compounds. Our goal is to create a set of highly useful and broadly applicable compounds that can be used to advance scientific research and improve the world around us.

7. REFERENCES

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