SYNTHESIS OF CHIRAL DIENE SYSTEMS *VIA* RING CLOSING ENYNE METATHESIS AND THEIR APPLICATIONS IN DIELS-ALDER REACTIONS

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SYNTHESIS OF CHIRAL DIENE SYSTEMS VIA RING CLOSING ENYNE METATHESIS AND THEIR APPLICATIONS IN DIELS-ALDER REACTION

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ABSTRACT

SYNTHESIS OF CHIRAL DIENE SYSTEMS *VIA* RING CLOSING ENYNE METATHESIS AND THEIR APPLICATIONS IN DIELS-ALDER REACTIONS

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The main subject of this thesis is synthesis of chiral diene systems *via* Ring Closing Enyne Metathesis (RCEM). Furan and thiophene carbaldehydes were chosen as starting compounds. As a result of allylation and propargylation reaction of these aldehydes targeting racemic heteroaryl substituted homoallylic and homopropargylic alcohols were synthesized. Enantiomerically enriched alcohols were obtained by enzymatic resolution method with different enzymes (PS-II, Lipozyme) with the high enantiomeric excess values. Absolute configurations of all alcohols are known. *O*-allylation and *O*-propargylation reactions of enantiomerically pure alcohols, afforded feasible enyne units for RCEM were synthesized successfully. All RCEM reactions were performed by using Grubbs' 1st generation catalyst. The absolute configuration of all chiral diene systems were known since during the course of the all reactions, configurations were preserved. As a last step, Diels-Alder reactions were applied to some of these chiral diene systems to get bicyclic compounds and comment on the stereoselectivity. Only one diastereomeric cycloadduct was observed as a result of Diels-Alder applications.

Key words: Enzymatic resolution, ring closing enyne metathesis, Diels-Alder reaction

ÖZ

KİRAL DİEN SİSTEMLERİNİN HALKA KAPAMALI ENİN METATEZ YOLUYLA SENTEZLERİ VE DİELS-ALDER TEPKİMELERİNDEKİ UYGULAMALARI

Çayir, Merve

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Temmuz 2010, 81 sayfa

Tezin ana konusu kiral dien sistemlerinin halka kapamalı metatez yoluyla sentezlenmesidir. Furan ve tiyofen karbaldehitleri başlangıç maddeleri olarak seçilmiştir. Bu aldehitlerin alilasyon ve proparjilasyon tepkimeleri sonucunda hedeflenen rasemik heteroaryl substitute homoallilik ve homoproparjilik alkoller elde edilmiştir. Daha sonra, enzimatik rezolüsyon yoluyla değişik enzimler kullanılarak (PS-II, Lipozyme) enantiyomerce zenginleştirilmiş alkoller yüksek e.e değerleriyle elde edilmiştir. Bütün alkollerin mutlak konfigürasyonu bilinmektedir. Enantiyomerce zenginleştirilmiş alkollerin yaygın olarak kullanılan *O*-alilasyon ve *O*-proparjilasyon tepkimeleri sonucunda halka kapamalı enin metatez tepkimesi için uygun olan enin sistemleri başarıyla sentezlenmiştir. Tüm halka kapamalı enin metatez tepkimelerinde birinci jenerasyon Grubbs katalizörü kullanılmıştır. Bütün tepkimeler süresince konfigurasyonun korunmasından dolayı kiral dien sistemlerinin mutlak konfigürasyonları bilinmektedir. Bisiklik ürünler elde edip stereoseçicilik hakkında yorum yapabilmek için son basamak olarak bazı kiral dien sistemlerine Diels-Alder tepkimesi uygulanmıştır ve sadece tek diastereomerik siklokatılma ürünü gözlenmiştir.

Anahtar Kelimeler: Enzimatik rezolüsyon, halka kapamalı enin metatezi, Diels-Alder tepkimeleri

To my dear parents and lovely sister Gizem...

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LIST OF ABBREVIATIONS

CRL: *Candida frugosa* lipase

DCM: Dichloromethane

DPE: Diisopropylether

HLE: Horse liver esterase

LDA: Lithium diisopropylamide

NMP: *N*-Methyl pyrolidine

PLE: Pig liver esterase

PPL: Porcine pancreatic lipase

PSC-II: *Psedomonas cepacia* lipase on ceramics

THF: Tetrohydrofuran

CHAPTER 1

INTRODUCTION

1.1. Chirality and Its Importance

The word chiral is derived from ‘cheir’ meaning hand in Greek. If a molecule cannot be super imposable with its mirror image, it is said to be chiral. Chiral molecules are lack of plane symmetry and inversion center. Chiral substances rotate under plane-polarized monochromatic light when it is passed through. This is called as optical activity.

“The world is chiral”[1]. In living material, all the enzymes and proteins, DNA, RNA, nucleic acids are only one chiral form. The two mirror images of a chiral unit may interact differently with the receptor and can display various activities [2]. Therefore, different effects of enantiomers like different taste, smell, pharmacological effect, etc. have been observed upon their interactions with a human body [3].

In the drug industry, chiral compounds are playing very important role. Most of useful drugs exist in enantiomeric forms and generally, one of these enantiomers is much more effective than its mirror image enantiomer, exhibiting a better fit to its receptor and also in some cases the other enantiomer may even be harmful. For example, one enantiomer of Thaliomide is sedative and the other form is teratogenic (Figure 1). In 1960s, a drug with thalidomide was sold to pregnant women. One form helped against nausea, the other one caused fetal damage [4,5]. Penicillamine [6], ketamine [7], timolol [8] are other important examples of chiral drugs whose enantiomers show different pharmacological activity.

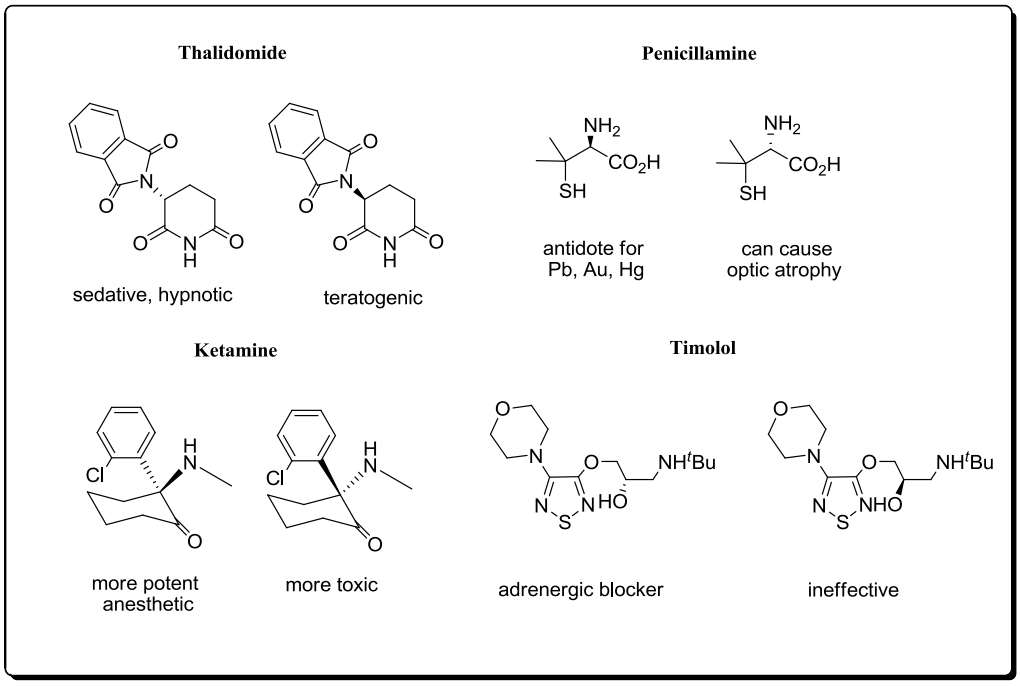


Figure 1. The structure and pharmacological effect of the enantiomers of some chiral compounds

1.2. Asymmetric Synthesis

Asymmetric synthesis was described firstly by Marckwald in 1904. According to Marckwald, asymmetric synthesis is "a process for the formation of an optically active compound through reaction of an achiral substrate with a chiral reagent" [9]. In 1971, this definition was expanded by Morrison and Mosher. Their definition describes asymmetric synthesis as "a reaction where an achiral unit in an ensemble of substrate molecules is converted by a reactant into chiral unit in such manner that the stereoisomeric products are formed in unequal amounts" [2].

Today, asymmetric synthesis is more important to obtain enantiomerically rich compounds in terms of research, industry especially in drug industry.

There are three major methods to produce optically active compounds. These compounds can be achieved by chiral pool, separations of racemates and from prochiral compounds (Figure 2) [10].

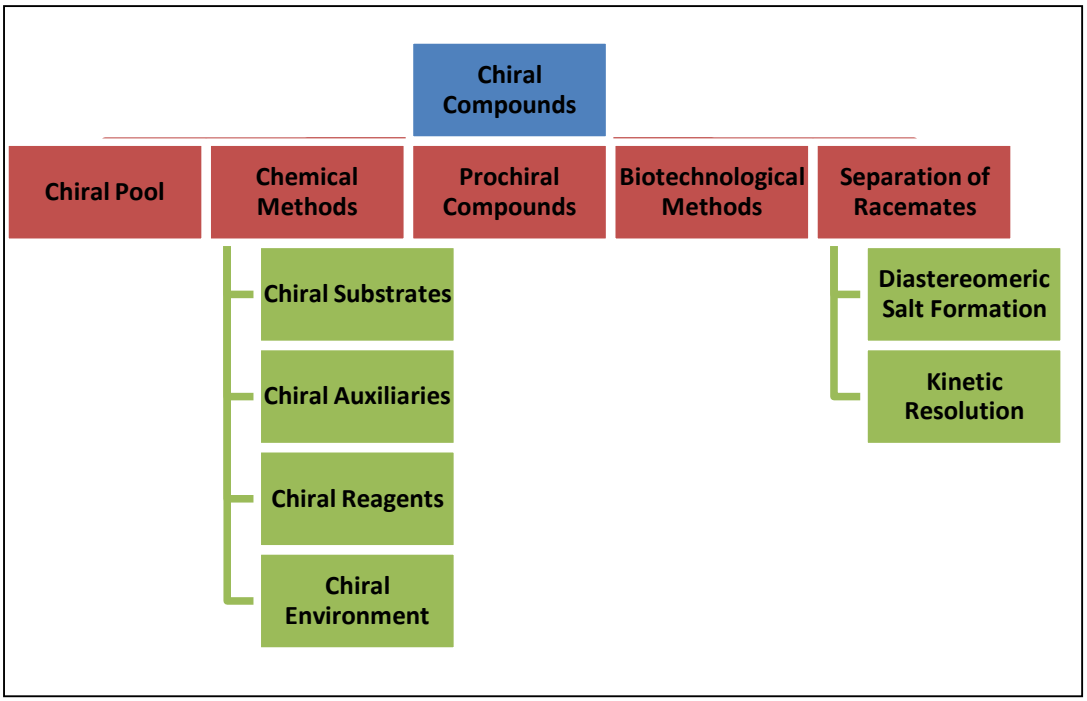


Figure 2. Methods to obtain chiral compounds

1.3. Chiral Pool

In chiral pool method, an enantiomerically pure natural compound is used as chiral starting material to synthesize the target product [11]. Chiral pool method is an economical technique but has some limitations in terms of natural sources and their isolation cost. These compounds, which are used as a chiral pool, are incorporated into target pattern with any necessary modification to achieve the desired chiral properties [10]. Aminoacids and carbohydrates are the specific examples of chiral pool substances (Figure 3).

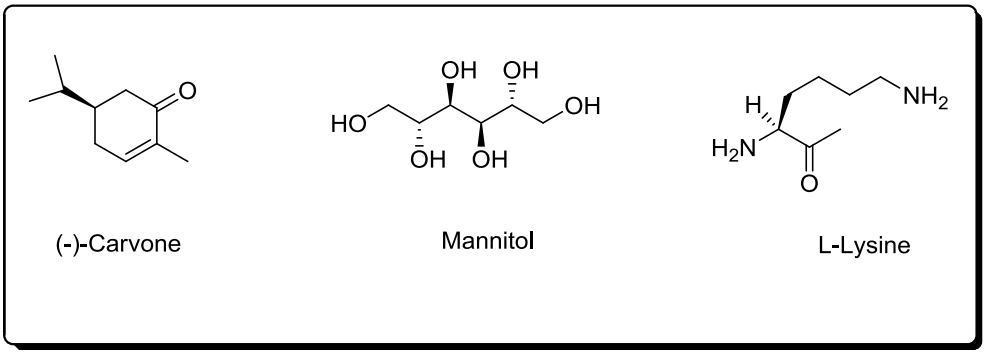


Figure 3. Some examples of chiral pool substances

1.4. Chiral Substances from Prochiral Compounds

In stereochemistry, prochiral means that a molecule can become a chiral compound from achiral form in a single step reaction. If a tetrahedral carbon has two identical substituents, it is prochiral and after replacement of one of these substituents it converts to a chiral form. This operation is also known as asymmetric synthesis. Asymmetric synthesis has two major methods; chemical and biotechnological.

1.5. Chemical Methods

In these types of methods, enantiomerically pure compounds can be achieved either by controlling reagents e.g. chiral catalyst or controlling substrate e.g. chiral auxiliaries [12].

1.5.1. Chiral Substrates

In this method, a chiral starting material is chosen that can control stereoselectivity of reaction. Chiral pool substances composed of these types of chiral starting materials. This approach has often some limitations in terms of availability of natural products and the price of their isolation [13].

1.5.2. Chiral Auxiliaries

As indicated in previous part, the number of convenient natural products is not large or in order to convert useful intermediate may need many steps; sometimes these steps may include expensive reagents. Thus, some chiral groups have been developed which are attached to an achiral compound. These chiral groups cause selectivity through a following reaction to afford diastereoselectivity.

After removing of this chiral auxiliary, there is a product that is enriched in one enantiomer. Chiral auxiliary approach involves two additional steps; the insertion and removal of auxiliary. If chiral auxiliaries recover at the end of the process, they can be reusable [13].

1.5.3. Chiral Reagents

In this method, a prochiral substrate reacts with a chiral reagent for obtaining enantiomerically enriched compounds. Chiral reagents should be used in stoichiometric amount which is main drawbacks of methods because of their high cost. These reagents should be selective in terms of the addition and functional group specifity [14].

1.5.4. Chiral Environment

The environment of a reaction can be made chiral. Chiral solvents and additives are major examples of this class [13].

1.6. Biotechnological Methods

In addition to chemical methods, biological ways using enzymes, cell cultures are also effective and practical to obtain enantiomerically enriched compounds from prochiral substances [15].

1.7. Separation of Racemates: Resolution

Resolution is a method for separation of racemic molecules into their enantiomers [16]. One important point of this method is that the molecule should contain a functional group which can react with another chiral agent to form diastereoisomers. In addition, the resolution agent must be removed from subject molecule after reaction. At the end of resolution, desired isomer can be formed as 50% of racemic mixture [13]. There are generally two techniques used for resolution; diastereomeric salt formation and kinetic resolution.

1.7.1. Diastereomeric Salt Formation

Resolution of a racemic mixture is mostly performed by generation of diastereomeric derivative, which can be separated by certain differences in physical properties. These differences can be boiling point, solubility in a crystalline derivative, chromatographic adsorption. One of well-known way is that a racemic mixture solution (methanol or water) interact with pure enantiomer, then a mixture of diastereomers forms. After crystallization of this mixture, diastereoisomers are separated [17].

1.7.2. Kinetic Resolution

In this method, two enantiomers show different reaction rate with a chiral agent. It means that, one diastereomer forms faster than the other isomer [3]. If reaction continues, the enantiomeric excess of starting compound increases but chiral product's enantiomeric excess decreases [13].

Kinetic resolution is an old concept to obtain chiral compounds. It was firstly found by Marckwald and McKenzie in 1899. Racemic mandelic acid was subjected to an esterification reaction with chiral (–)-menthol. (*R*)-enantiomer of acid shows higher reaction rate, reaction mixture was enriched in (*S*)-mandelic acid. After that, the hydrolysis of the incomplete mixture gave an excess of (*R*)-mandelic acid (Figure 4) [18].

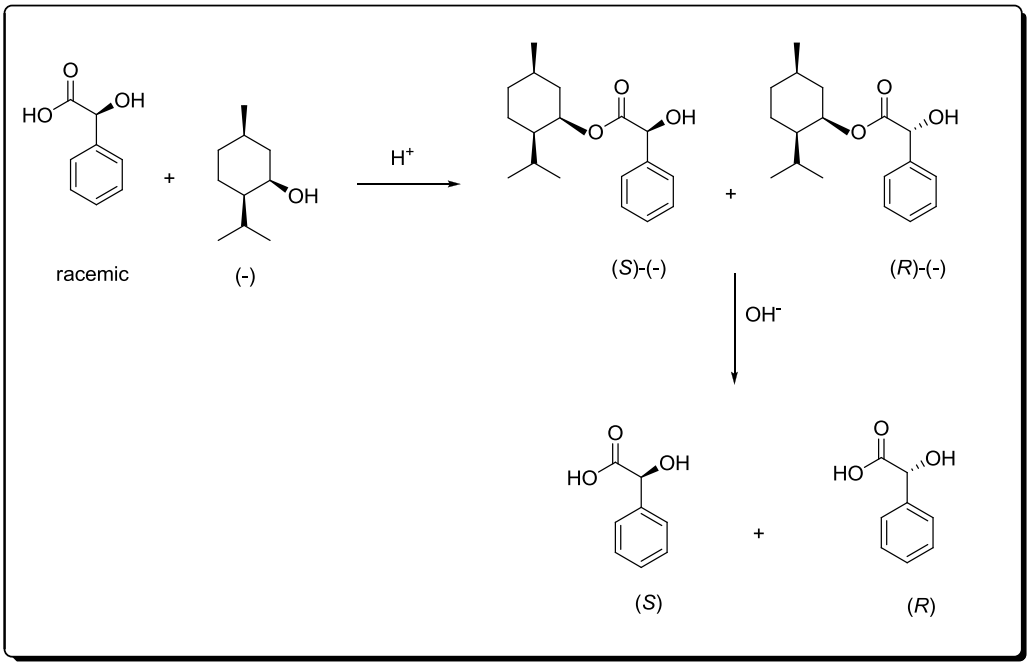


Figure 4. Kinetic resolution reaction of mandelic acid

Kinetic resolution can be achieved by chemical and enzymatic methods; enzymatic resolution is more preferable than the chemical process because of catalytic process.

1.8. Enzymes

"Enzymes are proteins; they catalyze most biological reaction" [19]. The reactions which involve natural and unnatural substances can be catalyzed by enzymes. They have the following properties [15].

- They increase the rate of reactions, perform under mild conditions.
- They are highly selective (chemo-, regio- and stereoselective), three dimensional structure of enzymes is the reason of this selectivity and their selectivity range extend from narrow to very wide.
- The activity of enzymes is strongly affected by the concentration of products, substrates or other species in the solution.
- They accelerate reactions in similar conditions.
- Enzymes are chiral and can display high enantiodifferiation.

As it was mentioned before, enzymes are chiral, their active sites also include chiral molecules. Main principle of enzymes is based on "Lock and Key" model. This mechanism was proposed firstly by Emil Fisher in 1894. In Lock and Key model, enzyme and substrate have particular complementary shapes which fit into one another (Figure 5) [20]. Therefore, an enzyme behaves as a lock and a substrate behaves as a key.

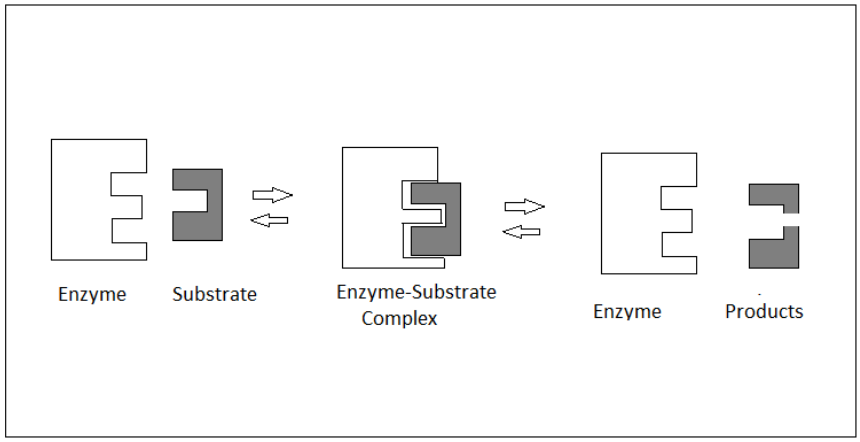


Figure 5. Key-lock model of enzyme

1.8.1. Factors Affecting the Enzyme Reaction Rate

Enzyme concentration, pH, substrate concentration, temperature, activators, inhibitors are the main factors which influence the reaction rate of enzymes.

1.8.1.1 Effect of pH

Enzymes are generally effective at a specific range of pH. The point at which enzymes are most effective is known as optimum pH. It is different for each enzyme (Table 1) [21]. Most enzymes can lost their activities at higher and lower value of pH. By altering the pH of reaction can change structure or ionization state of enzyme and reactants.

The new structure and charge distribution can or cannot fit to active enzyme and also it can or cannot change substrate selectivity.

Table 1. Optimum pH values of different enzymes

Enzyme	Optimum pH
Lipase (pancreas)	8.0
Lipase (stomach)	4.0-5.0
Pepsin	1.5-1.6
Urease	7.0
Invertase	4.5

1.8.1.2. Effect of Enzyme Concentration

If the enzyme concentration increases, the theoretical rate of reaction should also increase. Sometimes at very high enzyme concentration, there can be a falling off from linearity. This does not show a direct decrease in activity of enzyme but causes some limitations measurements techniques. If some inhibitors or activators are presence in the enzyme preparation, some deviations are observed from linearity [22].

1.8.1.3. Effect of Substrate Concentration

Substrate concentration is one of the most important factors which influence the rate of reaction. When the amount of enzyme is constant and the concentration of substrate is increased, the reaction rate increases until the maximum velocity. After that point, a rise of substrate concentration does not increase the rate of enzymatic reaction. In addition, the rate of reaction can decrease at high substrate concentration [23].

1.8.1.4. Effect of Temperature

Enzymatic reactions comprise of three steps; enzyme-substrate complex formation, changing of this enzyme-substrate complex to enzyme-product complex and dissociation to new products and starting enzyme. Temperature influences each steps of this reaction. A rise in temperature causes an increase rate of non-enzyme mediated and enzyme mediated steps (only to a point). Enzyme can be deactivated, if the temperature is increased too much.

1.8.1.5. Effect of Activators

Some substances, that the rate of reaction is greatly increased by addition of small amount of this substance, are called activator. The efficiency of an active enzyme is increased greatly by some activators. The initial rate of the enzymatic reaction is related to concentration of the activator at low concentrations that provides a method for the rate determination. The rate of reaction is independent of the amount of activator at high concentrations [24].

1.8.1.6. Effect of Inhibitors

Inhibitors are the substances, which change the action of enzyme and slow down, in some situations can stop catalyst. There are two types of enzymatic inhibitors; reversible and irreversible. For reversible inhibition, the enzymes regain its activity when the inhibitor is removed but in irreversible inhibition it is not observed. The inhibition increases regularly with the concentration of irreversible inhibitor. If enough inhibitor present in the medium to bring together all enzyme, inhibition is completed. In reversible inhibition case, inhibition is also regular but reaches to equilibrium point quickly which depends on the concentration of inhibitor. Protease inhibitors like tipranavir and ritonavir are examples of reversible inhibitors [25, 26].

1.8.2. Enzymes in Asymmetric Synthesis

Different types of enzymes are used in organic synthesis. One of the most widely used is hydrolases. They do not need any cofactors or coenzyme to perform and they have an extensive substrate range [27]. These types of enzymes catalyze the hydrolytic cleavage of bonds. Proteases, lipases, acylases, amylases and esterases belong to this class of enzyme [28].

Proteases are responsible for hydrolysis of peptide bonds. They can differ in ability of hydrolyzing of various peptide bonds. Each type of peptide bonds is broken by different proteases enzyme. Pepsin, papain, trypsin, chymotrypsin are the specific examples of proteases [29].

Lipases are catalysts for hydrolysis of lipids and glycerol lipid-water interface [30]. They are soluble in water and perform important roles in digestion and transport. "Lipase-catalyzed kinetic resolution of racemates is a well-established method for the preparation of enantiomerically enriched products"[29]. Lipases are widely used in asymmetric acyl transfer reactions. These reactions are applied with a racemic substance (alcohol or amine) and achiral acyl donor (ester or acid). Kinetic resolution of enantiomers is achieved [31]. PPL, *Pseudomonas sp. Lipases* (*Pseudomonas fluorescens, Pseudomonas cepacia)* and *Candida sp. Lipases* (*Candida lipotyca,* CAL-A, CAL-B, CRL) are common examples of lipases [15].

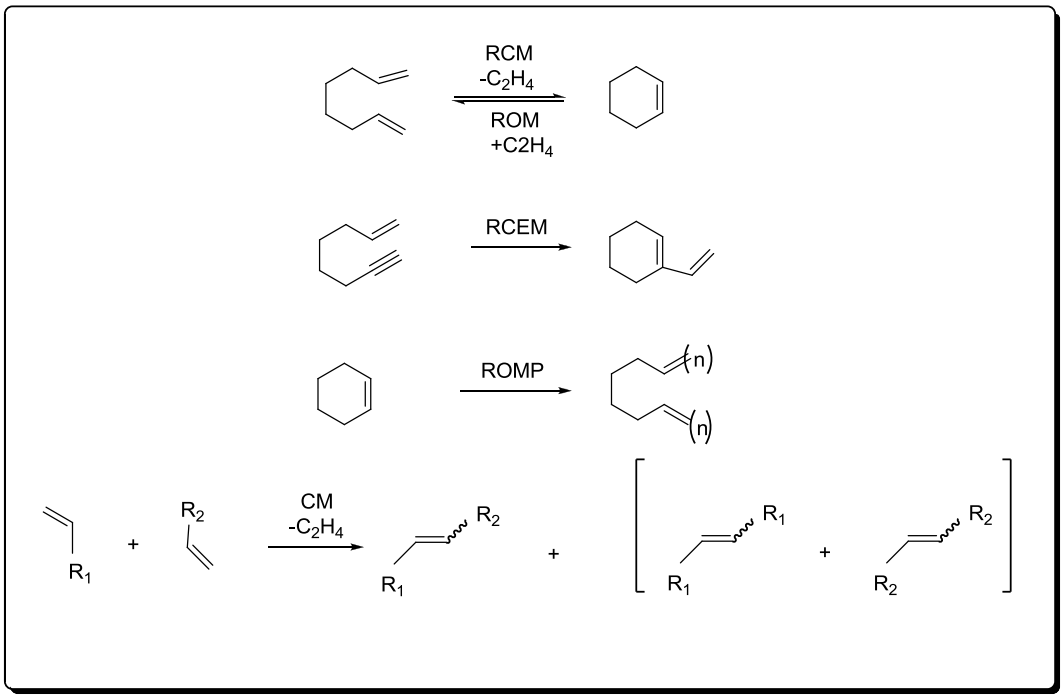
Esterases are a type of hydrolase enzyme. They cleave esters into acid and alcohol. Esterases show differences in terms of their substrate specifity, their biological function and protein structure. They are used commonly in asymmetric synthesis. PLE (Pig liver esterase) and HLE (Horse liver esterase) are specific examples of esterases [15].

1.9. General Aspects of Metathesis

Metathesis is a process which involves exchanging of bonds between two reactants, and products show similar bonding affiliations [32]. Metathesis reactions are catalyzed by alkylidene complexes that connect a wide range of functional group and arise as a powerful tool for carbon-carbon bond formation. Generally, these reactions can be divided into three major classes depending on types of unsaturated groups. These are diene, enyne and diyne metathesis. Some structural changes also occur during metathesis. According to these changes, there is another classification;

- Ring Closing Metathesis (RCM)
- Ring Opening Metathesis (ROMP)
- Cross Metathesis (CM)

Ring closing diene metathesis is the most remarkable one among these metathesis types in terms of synthesis of natural products despite the reactions in macrocyclic systems progress with low stereoselectivity. Olefin cross metathesis is not preferable for synthesis of natural products because of problems related to chemo- and stereoselectivity. Interesting natural products have been synthesized by combination of sequential ring opening and ring closing metathesis. In diene and diyne metathesis reaction, volatile alkene or alkyne is formed as by-products. In enyne metathesis reactions, alkylidene migration occurs; alkylidene part migrates from alkene unit to alkyne carbon. Enyne cross metathesis between terminal alkyne and olefin is blocked due to forming of isomers. The regiochemistry course of enyne ring closing metathesis reactions is determined by substitution model of substrate, size of new formed ring and choice of catalyst [33].



Scheme 1. Different types of metathesis reactions

1.9.1. Olefin Metathesis

Olefin metathesis is one of the most important reactions for synthetic organic chemistry for the formation of C-C bonds [34]. In olefin metathesis reactions, alkylidene parts between alkenes are distributed again with the catalytic amount of metal carbene [35]. These metal carbenes should be compatible with several functional groups and they should be highly active for metathesis reactions. From this point of view, Schrock's type molybdenum-carbene complex and Grubbs-type ruthenium carbene complex are highly active and selective. Schrock and coworkers have developed one of the most efficient catalysts which are composed of alkoxy imido molybdenum complex, **1** (Figure 6).

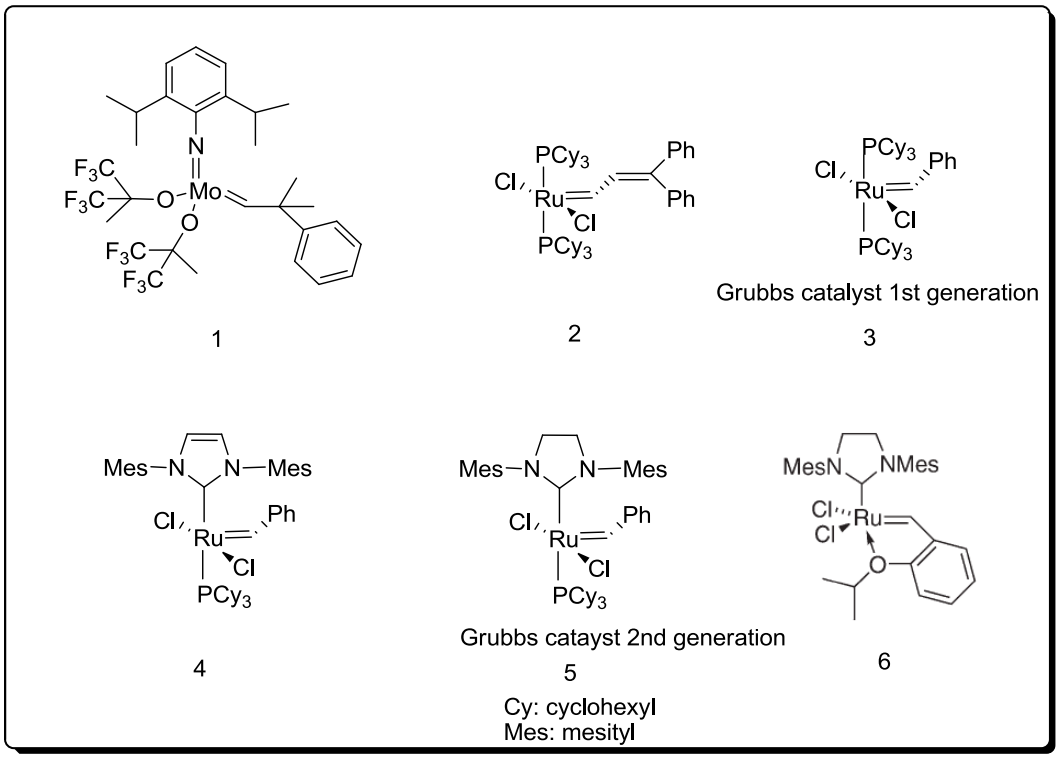


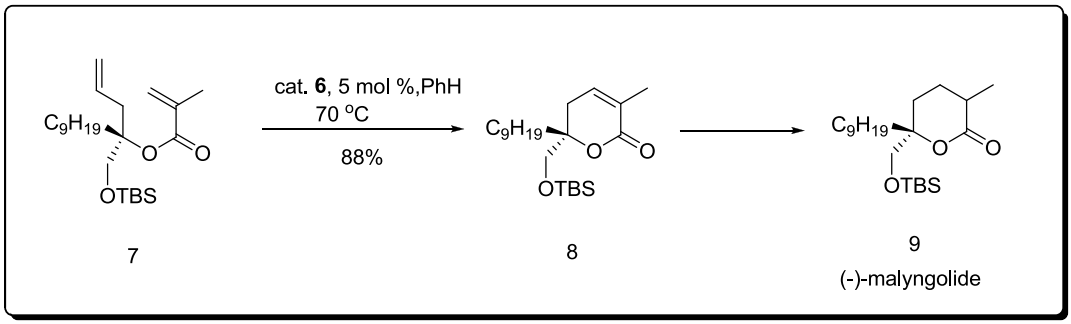
Figure 6. Schrock's molybdenum carbene catalyst and Grubbs-type ruthenium catalysts

This catalyst is highly reactive towards a wide range of substrates which have different steric and electronic properties. The alkoxides groups in this system can be easily changed to regulate their activities. However, there are some disadvantages of Mo based complex; it is high sensitive to air, moisture and impurities in solvent, thermally instable on storage and its preparation is expensive [36-39].

Grubbs and coworkers have developed different catalysts which are most remarkable Ru-based carbenes. These Ru complexes show high reactivity to ROM, ROMP and CM reactions under mild conditions. The reasons of this activity are explained by their tolerance to different organic groups [40]. Ru-carbene complexes are active in the presence of air, moisture and trace amount of impurities in the solvent. They are stable even under air atmosphere.

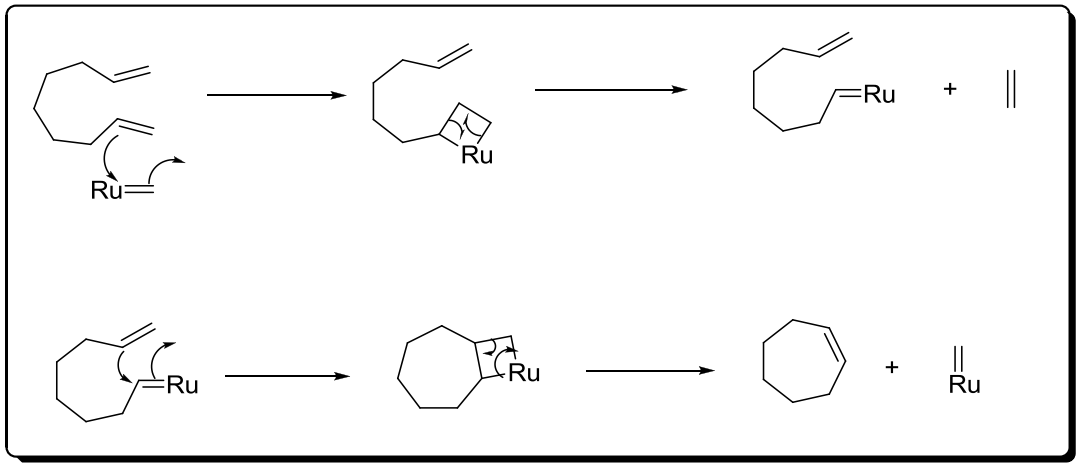
As it is shown in Scheme 1, olefin metathesis can be classified as four types of reactions; ring opening metathesis polymerization (ROMP), ring closing metathesis (RCM), cross metathesis (CM), ring opening metathesis (ROM). In ROMP, a polymer is produced at the end of the reaction and cyclic olefins are used as a substrate [41]. In RCM a cyclic olefin is produced from an acyclic diene. In CM, a new olefin is formed from the reaction of two different olefins and a volatile olefin is produced as a by-product [42]. In ROM, a cyclic olefin reacts with acyclic olefin in order to produce new acyclic olefin [43].

Olefin metathesis is very important process for synthetic organic chemistry. It can be a key step in many total syntheses of natural products. For example, synthesis of a marine lactone (-)-malyngolide was achieved by Honda and coworkers. Compound **8** was synthesized successfully *via* RCM with Hoveyda type Ru catalyst in high yield. This product is a precursor for the synthesis of (-)-malyngolide (Scheme 2) [44].



Scheme 2. Synthesis of (-) – malyngolide

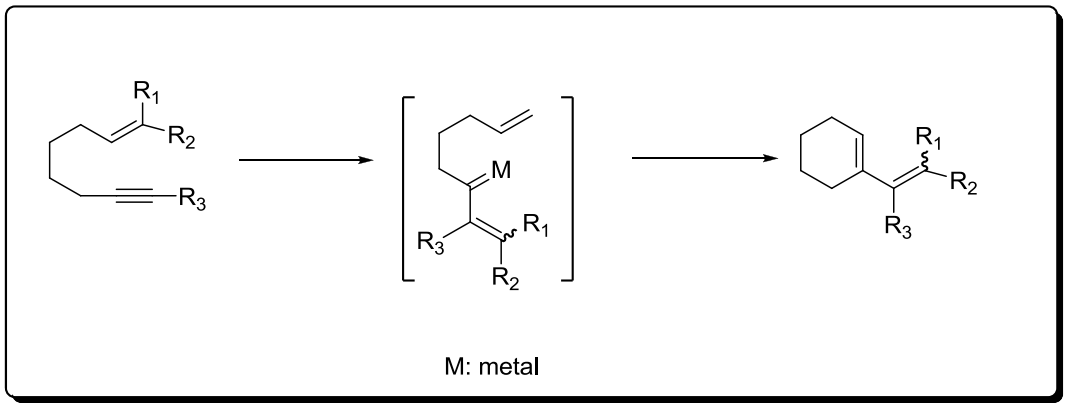
Olefin metathesis allows the formation of medium or large sized ring from acyclic diene. Formation of macrocycles depends on several factors; nature of reactants, catalyst, solvent, stability of product and concentration. One of the most important factors for synthesis of flexible ring system (min. 9-membered ring) is the conformational tendency of the starting material toward intramolecular cyclization [45]. General mechanism of ring closing olefin metathesis was suggested by Grubbs (Scheme 3).



Scheme 3. General mechanism of ring closing olefin metathesis reaction

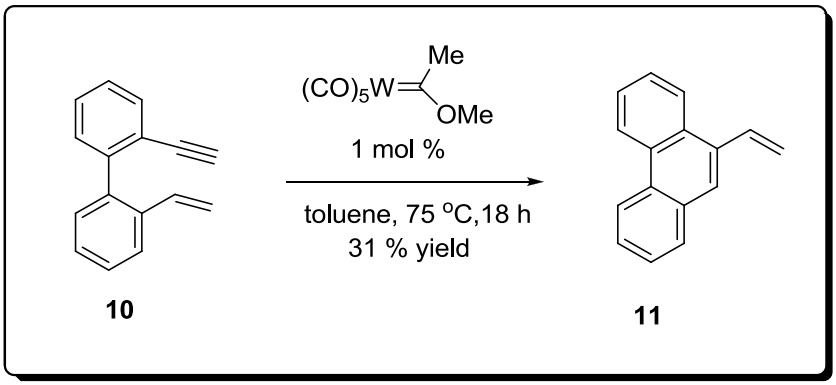
1.9.2. Enyne Metathesis

Enyne metathesis is an important method for synthetic organic chemistry in terms of formation of conjugated dienes. It is defined as rearrangement of covalent bonds between alkene and alkyne units to form a 1,3-diene systems [35]. In enyne metathesis reaction, double bonds and triple bonds are broken and two new double bonds are formed at the same time (Scheme 4) [46]. After metathesis reaction is completed, triple bonds are converted to single bonds and double bonds are inserted into alkyne carbon to form 1,3-diene systems. This is called as "skeletal re-organization"



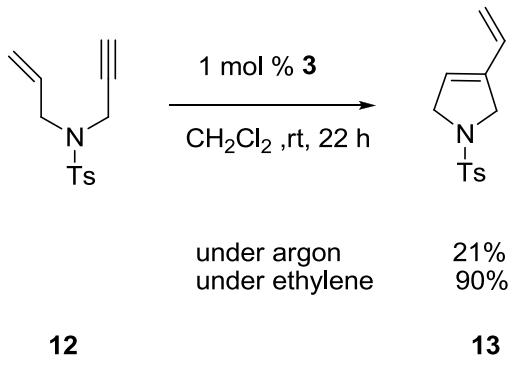
Scheme 4. An example of ring closing enyne metathesis

Enyne metathesis was discovered by Katz in 1985 *via* Fisher tungsten carbene. Compound **10** was treated with catalytic amount of tungsten carbene and 1,3-conjugated diene was observed in 31% yield (Scheme 5) [47].



Scheme 5. First example of enyne metathesis

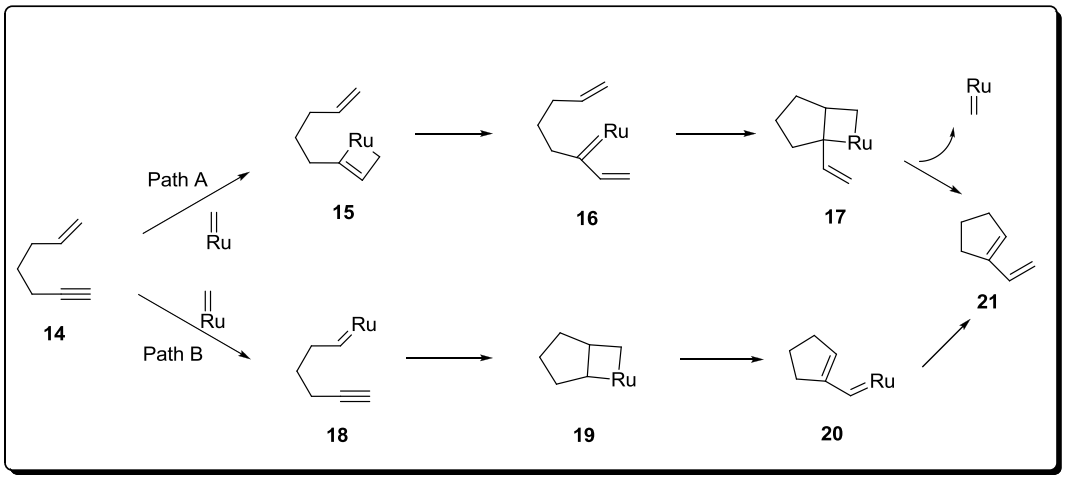
Grubbs and coworkers have discovered well-defined Ru-carbene. After this development, enyne metathesis has become important. Although these Ru-carbene complexes were developed for olefin metathesis, they are used to catalyze ring closing enyne metathesis [40]. By using these Ru-carbenes; five up to nine membered rings can be synthesized. In 1994, intramolecular enyne metathesis was achieved *via* Grubbs catalyst firstly by Mori. Reaction of compound **12** with first generation Grubbs catalyst gave five membered cyclic diene (Scheme 6) [48].



Scheme 6. An example of RCEM by using Grubbs catalyst

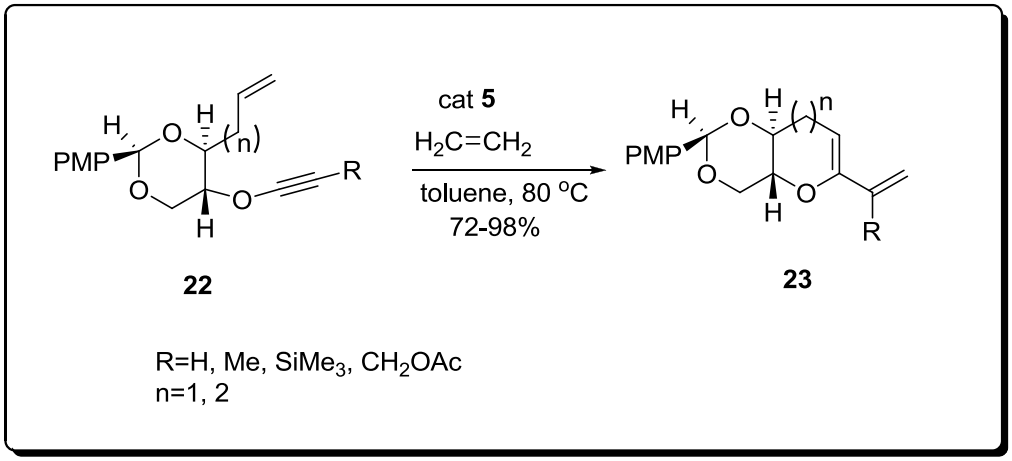
There are generally two types of possible mechanisms of enyne metathesis. If the reaction goes through path A, enyne **14** reacts with ruthenium carbene at the

alkyne to generate metallocyclobutane **15**. After electrocyclic ring opening, diene **16** is obtained. Another metallocyclobutane **17** is formed by [2+2] cycloaddition. Compound **17** opens to produce 1,3-diene **21** and active ruthenium catalyst. In another possible mechanism (path B), alkene reacts with ruthenium carbene and carbenoid **18** is obtained. Intramolecular cycloaddition of this carbenoid gives bicyclic metallocyclobutane **19**. It converts to carbenoid **20**. The enyne **14** is reacted again with the carbenoid **20** to afford target 1,3-diene **21** (Scheme 7) [49].



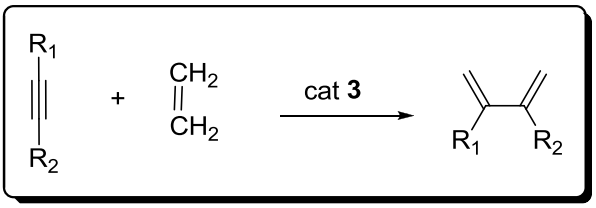
Scheme 7. Possible reaction mechanisms of enyne metathesis

RCEM is also important step for total synthesis of natural compounds. Clark and coworkers have prepared six and seven membered cyclic enol ethers *via* RCEM and Ru-carbene complex [50]. These cyclic enol ethers are potential precursor for the synthesis of marine polyether natural products. (Scheme 8) [50].



Scheme 8. Synthesis of cyclic enol ethers *via* RCEM

In addition to intramolecular enyne metathesis, intermolecular enyne metathesis is also possible. However, it is very difficult since it includes different types of metathesis reactions namely; olefin, enyne and diyne metathesis. It means that, several olefins, dienes and polymers can be obtained by intermolecular enyne metathesis [51]. Mori has developed a method where, ethylene was used as alkene and 1,3-dienes were observed from alkyne (Scheme 9) [46].

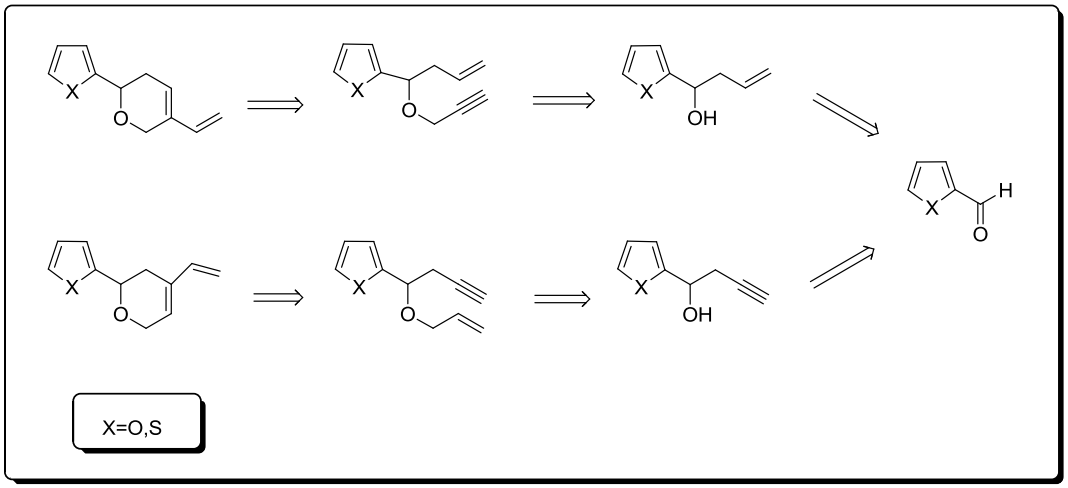


Scheme 9. An example of intermolecular enyne metathesis

1.10. Aim of the Work

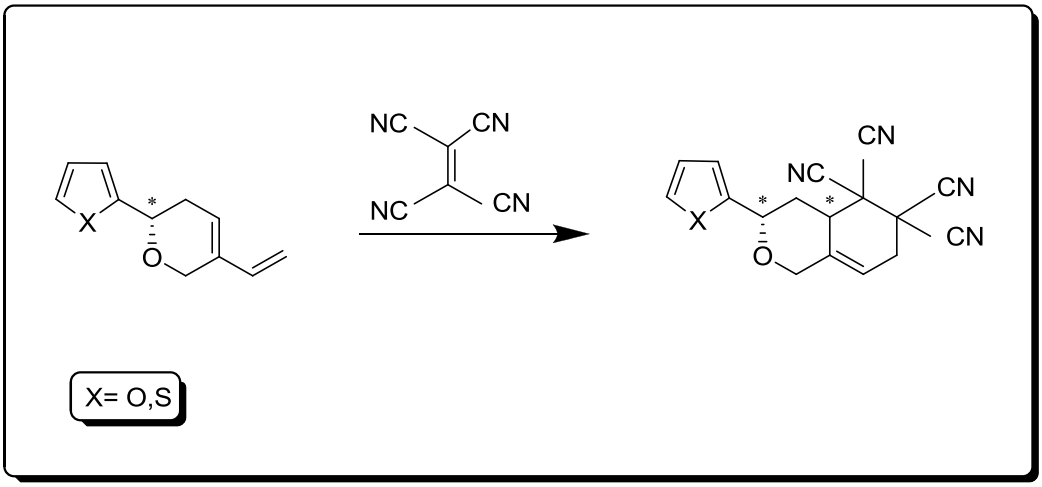
After development of well-defined ruthenium carbene complex, ring closing enyne metathesis has become important method. An alkyne reacts with alkene part to form 1,3-diene system. These diene systems can be valuable candidates for various organic reactions such as Diels-Alder reaction. In addition, unsaturated carbon and heterocycles are achieved from acyclic starting materials. Ring closing enyne metathesis is also an important key step of total synthesis of several natural compounds.

We planned to synthesize chiral heteroaryl substituted 1,3-diene systems *via* ring closing enyne metathesis. Furan and thiophene substituted aldehydes were chosen as starting materials. Secondary homoallylic and homopropargylic alcohols were synthesized from these aldehydes. These alcohols are appropriate precursors for asymmetric induction by using enzymatic resolution. *O*-allylation and *O*-propargylation of these chiral alcohols afford suitable backbone for RCEM (Scheme 10). Grubbs 1st generation catalyst was used for all metathesis reactions.



Scheme 10. Retrosynthetic pathway of the work

1,3-Diene systems were not highly stable. In order to form more stable substances and to search the stereoselectivity, 1,3-dienes were subjected to Diels-Alder reaction. Tetracyanoethylene was used as a dienophile. Only one diastereomeric Diels-Alder adducts were observed (Scheme 11).



Scheme 11. Diels-Alder applications of diene systems

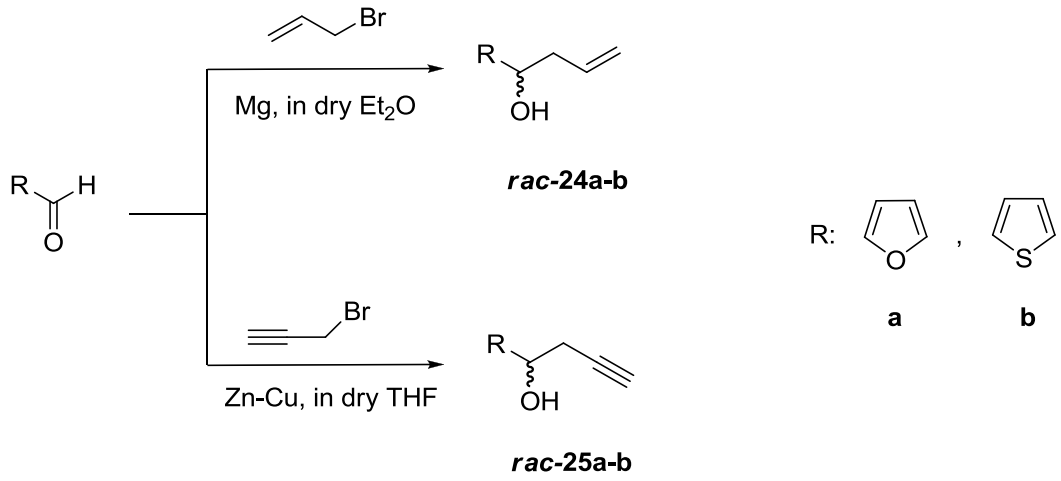
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Racemic Homoallylic and Homopropargylic Alcohols

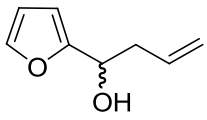
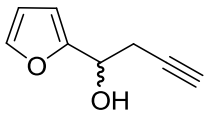
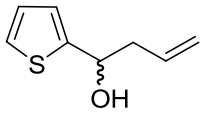
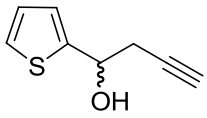
Homoallylic and homopropargylic alcohols are used in the synthesis of several natural and biologically active compounds like micro antibiotics and alkaloids [52]. In the literature, homoallylation and homopropargylation of aldehydes by using organometallic reagents is a changeable method in terms of nucleophilic addition of different metals to carbonyl groups [53].

The first part of this work is composed of synthesis of racemic homoallylic and homopropargylic alcohols *via* Grignard and a type of Reformatsky reaction, respectively. Starting materials were 2-heteroaryl carbaldehydes because they are commercially available and eligible towards these Grignard types of reactions. The homoallylic and homopropargylic alcohols were synthesized by the addition of *in situ* prepared allylmagnesium bromide and propargyl bromide with zinc-copper couple in dry solvents and under argon atmosphere (Scheme 12). All results are given in Table 2.



Scheme 12. Synthetic pathway of racemic homoallylic and homopropargylic alcohols

Table 2. Results of homoallylic and homopropargylic alcohols

Substrate	Product	Time(h)	Yield(%)
Furan-2-carbaldehyde	 *rac*-**24a**	12	75
Furan-2-carbaldehyde	 *rac*-**25a**	18	70
Thiophene-2-carbaldehyde	 *rac*-**24b**	7	80
Thiophene-2-carbaldehyde	 *rac*-**25b**	12	72

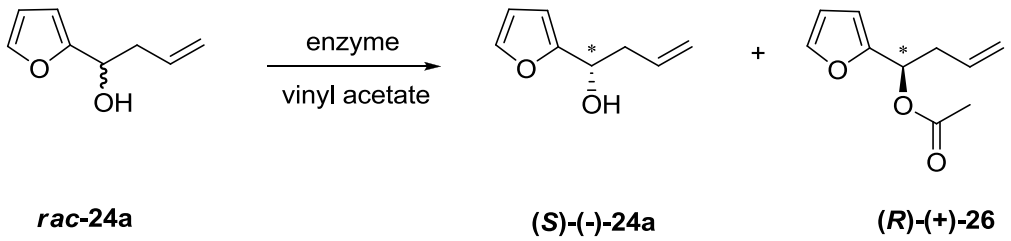
^{1}H- and ^{13}C-NMR results confirmed the structure of homoallylic and homopropargylic alcohols. NMR spectra are shown in Appendix part as Figure A1-A8. The spectra of all alcohols are in accordance with literature results [54,55].

2.2. Enzymatic Resolution of Racemic Homoallylic and Homopropargylic Alcohols

Depending upon our aim, biocatalysts were used to isolate enantiomerically enriched compounds. Furan and thiophene substituted racemic secondary alcohols were subjected to enzymatic resolution by several lipases. In order to get best results, firstly optimization was done with different enzymes (CAL A, CAL B, Lipozyme, PS-C II). Among the lipases used, lipozyme and PS-C II were found to be the most feasible biocatalysts during the course of stereoselective acetylation of homoallylic and homopropargylic alcohols. The absolute configurations of all resolved homoallylic and homopropargylic alcohols were determined as (*S*) by comparing the specific rotation values with the literature data [55].

2.2.1. Enzymatic Resolution of *rac*-1-(furan-2-yl)but-3-en-1-ol, (*rac*-24a)

Enantiomeric enrichment of furan substituted homoallylic alcohol, *rac*-**24a** was performed by using vinyl acetate as acetyl source and different enzymes. The reaction was monitored by TLC controlling and terminated when alcohol to acetyl ratio were approximately 50% (Scheme 13, Table 3).



***rac*-24a** **(*S*)-(-)-24a** **(*R*)-(+)-26**

Scheme 13. Enzymatic resolution of *rac*-1-(furan-2-yl)but-3-en-1-ol, *rac*-**24a**

Enantiomeric excess values (e.e.) of *rac*-**24a** were determined by using HPLC with OJ-H chiral column (Figure A9). The enzymatic resolution reactions were carried out in different solvents at the temperature range between 24-26 ºC. The results are summarized in Table 3. The first experiment was performed with CAL-B in THF (entry 1) and afforded 65% e.e. with 52% conversion. When the same reaction was carried out in hexane, drastic increase was observed in enantiomeric excess as 85% (entry 2). In the case of DPE as co-solvent, 75% e.e. value was obtained (entry 3). In order to find best e.e value, Lipozyme and PS-C II were also used. Lipozyme in THF afforded 79% e.e. (entry 4). As we observed drastic solvent effect on enantioselectivity in CAL-B case, Lipozyme catalyzed resolution was performed in DPE and fortunately we obtained the best e.e. value as 99% with 55% conversion (entry 5). In entry 6, PS-C II catalyzed reaction of *rac*-**24a** in THF afforded best e.e. result (99% e.e.) with 55% conversion. We did not check the effect of other solvents with PS-C II.

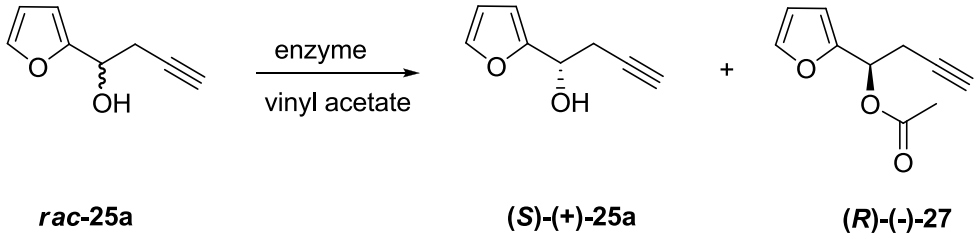
Table 3. Enzymatic resolution results of *rac*-**24a**

Entries	Enzyme	Time(h)	Temp. (ºC)	Conv(%)	E.e(%)	Co-solvent
1	CAL-B	26	26	52	65	THF
2	CAL-B	48	24	55	85	Hexane
3	CAL-B	48	24	53	75	DPE
4	Lipozyme	48	24	52	79	THF
5	Lipozyme	16	26	55	99	DPE
6	PS-C II	4	24	55	99	THF

2.2.2. Enzymatic Resolution of *rac*-1-(furan-2-yl)but-3-yn-1-ol, (*rac*-25a)

Enzymatic hydrolysis of *rac*-1-(furan-2-yl)but-3-yn-1-ol, *rac*-**25a** was catalyzed by using two different enzymes; Lipozyme and PS-C II in DPE and THF as co-solvents, respectively, since they afforded the most accessable results furan

substituted homoallylic alcohol (Scheme 4). In each case, high enantiomeric excess values were observed as 85% and 93%, respectively. The results are shown in Table 4.



***rac*-25a** **(*S*)-(+)-25a** **(*R*)-(-)-27**

Scheme 14. Enzymatic resolution of *rac*-1-(furan-2-yl)but-3-yn-1-ol, *rac*-**25a**

Table 4. Enzymatic resolution of *rac*-**25a**

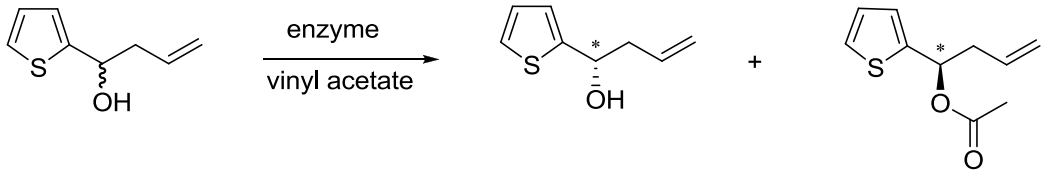
Enzyme	Time(h)	Temp.(°C)	Conv(%)	E.e(%)[a]	Co-solvent
Lipozyme	16	24	55	85	DPE
PS-C II	2	24	52	93	THF

[a] Determined by HPLC with OJ-H chiral column.

Both resolutions were carried out at 24 ^{o}C. Lipozyme needed longer reaction time than PS-C II.

2.2.3. Enzymatic Resolution of *rac*-1-(thiophen-2-yl)but-3-en-1-ol, (*rac*-24b)

Thiophene substituted homoallylic alcohol substrate *rac*-**24b** was subjected to enzymatic resolution with Lipozyme and PS-C II (Scheme 15). Lipozyme catalyzed resolution afforded 99% e.e in DPE as well as furan substituted homoallylic alcohol *rac*-**24a**. When the same substrate was resolved with PS-C II, 95% e.e. was observed (Table 5). By comparing the results of thiophene substituted substrate with furan substituted one, we observed a slight decrease in e.e. from 99 to 95%. However, drastic difference in reaction time was indicated.



***rac*-24b** **(*S*)-(-)-24b** **(*R*)-(+)-28**

Scheme 15. Enzymatic resolution of *rac*-1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**24b**

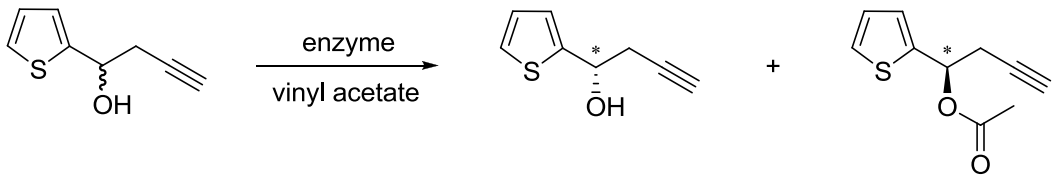
Table 5. Enzymatic resolution of *rac*-**24b**

Enzyme	Time(h)	Temp.(°C)	Conv(%)	E.e(%)[a]	Co-solvent
Lipozyme	18	26	54	99	DPE
PS-C II	20	24	56	95	THF

[a] Determined by HPLC with OJ-H chiral column

2.2.4. Enzymatic Resolution of *rac*-1-(thiophen-2-yl)but-3-yn-1-ol, (*rac*-25b)

In the enzymatic resolution of rac-1-(thiophen-2-yl)but-3-yn-1-ol, the conditions for furan substituted homopropargyl alcohol was applied (Scheme 16). The results are summarized in Table 6. In both cases, we obtained excellent e.e. values as 99% by comparing the e.e. values of substrate *rac*-**25a** as 85% and 93% e.e. with Lipozyme and PS-C II, respectively.



rac-**25b** (*S*)-(+)-**25b** (*R*)-(-)-**29**

Scheme 16. Enzymatic resolution of *rac*-1-(thiophen-2-yl)but-3-yn-1-ol, *rac*-**25b**

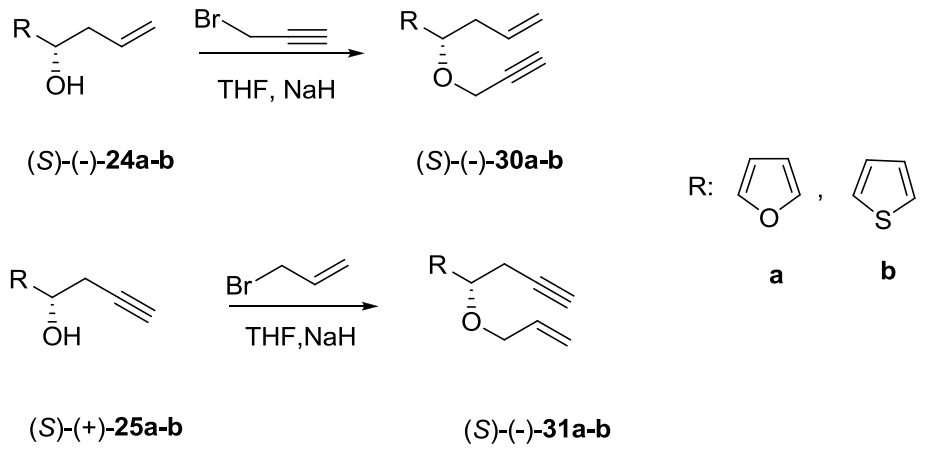
Table 6. Enzymatic resolution of *rac*-**25b**

Enzyme	Time(h)	Temp.(°C)	Conv(%)	E.e(%)[a]	Co-solvent
Lipozyme	20	26	55	99	DPE
PS-C II	2	24	53	99	THF

[a] Determined by HPLC with OJ-H chiral column

2.3. Construction of Chiral Enyne Skeleton

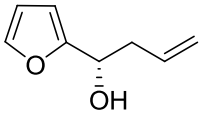
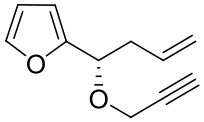
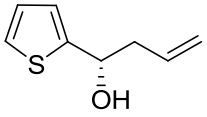
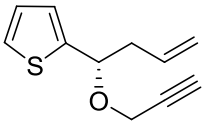
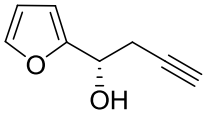
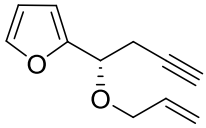
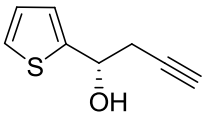
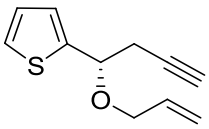
As it was indicated in the "Aim of the Work" part, the purpose of this study is to synthesize chiral diene systems anchored to dihydropyran ring system *via* ring closing enyne metathesis (RCEM). Until now, chiral inductions of homoallylic and homopropargylic alcohols were achieved by enzymatic resolution method. RCEM reactions needed an enyne unit on the main backbone. Because of this reason, feasible alkene and alkyne moieties were anchored to chiral homoallylic alcohols (*S*)-(-)-**24a-b** and homopropargylic alcohols (*S*)-(+)-**25a-b** by the well-known *O*-propargylation and *O*-allylation procedure, respectively (Scheme 17). During the course of the reactions, configuration of stereogenic centers kept constant. No racemization was observed. Therefore, all chiral enyne compounds (-)-**30a-b** and (-)-**31a-b** have (*S*) configuration. All the results are given in table 7.



Scheme 17. *O*-allylation and *O*-propargylation of chiral homoallylic and homopropargylic alcohols

The structure elucidation of enyne systems was done with ^{1}H and ^{13}C NMR. In ^{1}H NMR of compound (*S*)-(-)-**30a**, AB system methylene protons next to the oxygen atom, appear as doublet of doublets at 4.06 and 3.85 ppm with the coupling constants values J =16 and 2.4 Hz due to the geminal coupling and the coupling with terminal acetylenic proton. Terminal acetylenic proton resonates at 2.31 ppm as triplet with the coupling constant value of J =2.4 Hz.

Table 7. *O*-allylation and *O*- propargylation results of chiral homoallylic and homopropargylic alcohols

Substrate	Product	Configuration	Time(h)	Yield (%)
	 (*S*)-(-)-**30a**	*S*	2	83
	 (*S*)-(-)-**30b**	*S*	2	89
	 (*S*)-(-)-**31a**	*S*	4	80
	 (*S*)-(-)-**31b**	*S*	4	85

Compound (*S*)-(-)-**30b** has also similar propargyl unit AB system methylene protons signals appear at 4.15 and 3.92 ppm as doublet of doublets with the

coupling constant values J =15.6 and J =2.4 Hz and at 2.39 ppm as triplet for acetylenic proton. Partial ^{1}H NMR discussion given above strongly confirmed the attachment of propargyl unit to homoallylic systems.

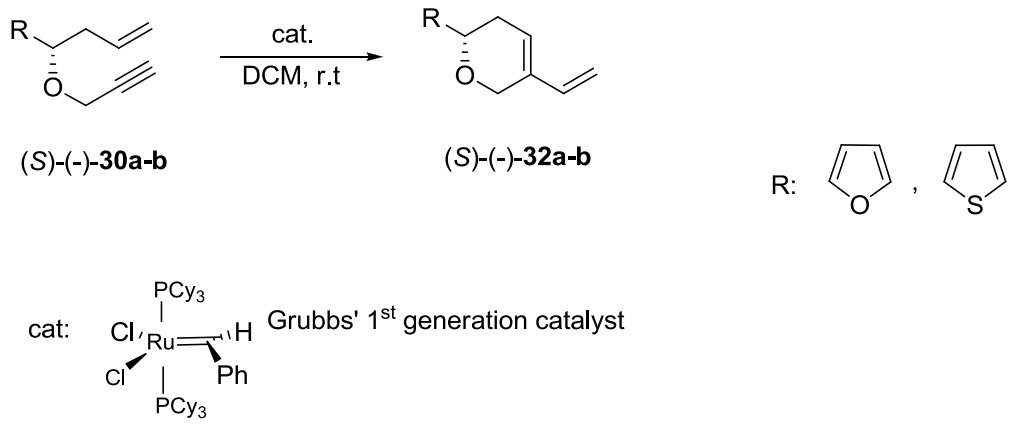
In contrast to the homoallylic enyne backbone ^{1}H NMR characterization, homopropargylic type enyne systems structure elucidations were mainly based on the new attached allyl unit signals. In ^{1}H NMR spectrum of compound (S)-(-)-**31a** methylene protons neighboring to the oxygen atom resonates as AB system which appears as two doublet of doublet of triplets at 3.94 ppm with coupling constant values J =12.8, 5.1 and 1.5 Hz and at 3.82 ppm with J =12.8, 6.2 and 1.3 Hz. Methine proton of olefinic unit gives a characteristic signal at 5.80 ppm as doublet of doublet of triplet with the coupling constant values J =17, 10.4 and 5.2 Hz. One of the olefinic methylene protons resonates at 5.20 ppm as doublet of quartet with the coupling constant values J =17.2 and 1.6 Hz whereas the other olefinic proton resonates at 5.11 as doublet of quartet with J = 10.3 and 1.3 Hz. By comparing the coupling constants values, it is possible to indicate the *trans* relation of the signal appeared at 5.20 ppm with olefinic methine proton due to larger J value (17.2 Hz) than the other one.

^{1}H NMR of (*S*)-(-)-**31b** shows similar signal set for the attached allylic unit as well as furan substituted enyne system (*S*)-(-)-**31a**. Complete NMR data are given in experimental part.

2.4. Ring Closing Enyne Metathesis (RCEM) Studies

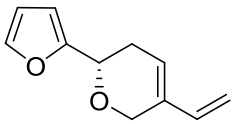
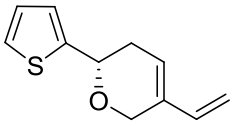
Ring closing enyne metathesis is an useful method in terms of formation of 1,3-diene systems. After Ru-carbenes were found by R.H. Grubbs, enyne metathesis has become more important. Grubbs' 1st generation catalyst is widely used for ring closing enyne metathesis since it is stable in air and compatible with many functional groups. In this step, we planned to synthesize heteroaryl substituted chiral 1,3-diene systems *via* RCEM reactions.

RCEM reactions of *O*-propargyl anchored substrates (*S*)-(-)-**30a-b** were carried out with 5% of Grubbs' 1st generation catalyst (Scheme 18). Enyne system (*S*)-(-)-**30a-b** afforded corresponding 1,3-diene system with the yield of 76% and 80%, respectively. These results are given in Table 8.



Scheme 18. RCEM reactions of (*S*)-(-)-**30a-b**

Table 8. Results of RCEM reactions (*S*)-(-)-**30a-b**

Substrate	Product	Configuration	Time(h)	Yield (%)
(*S*)-(-)-**30a**	 (*S*)-(-)-**32a**	*S*	8	76
(*S*)-(-)-**30b**	 (*S*)-(-)-**32b**	*S*	8	80

The structure elucidation of compound (*S*)-(-)-**32a** was done with ^{1}H and ^{13}C NMR. (*S*)-(-)-**32a** reveals four olefinic protons at 6.19 ppm as doublet of doublet,

5.81 ppm as broad doublet, 4.89 and 4.86 ppm as doublet. The methine proton of olefinic unit, which belongs to the dihydropyran ring, gives a signal at 5.81ppm as broad doublet with the coupling constant value J =2.4 Hz. The vinyl unit attached to the dihydropyran ring possesses characteristic olefinic signals; the methine proton resonates at 6.19 ppm as doublet of doublet with J =17.9 and 11.2 Hz and methylene protons of vinyl unit give signals at 4.88 and 4.86 ppm as doublet with the coupling constant values J =11.0 and 17.9 Hz, respectively. By the help of COSY spectrum, interactions of all protons were clearly explained (Figure 7). The diastreotopic methylene protons of dihydropyran ring next to the stereogenic center resonated at the highest field with respect to the all other protons (δ 2.60 and 2.33-2.27 ppm) have the cross-peaks with the olefinic methine proton of the dihydropyran ring (δ 5.81 ppm), stereogenic center methine proton (δ 4.53 ppm) and also with the other methylene protons of the ring (δ 4.37 ppm). ^{13}C NMR spectrum reveals eleven signals as expected. DEPT, HSQC (directly bond interaction) and HMBC (longer coupling interaction) techniques also supported structure of (*S*)-(-)-**32a**. (Figure A27-30)

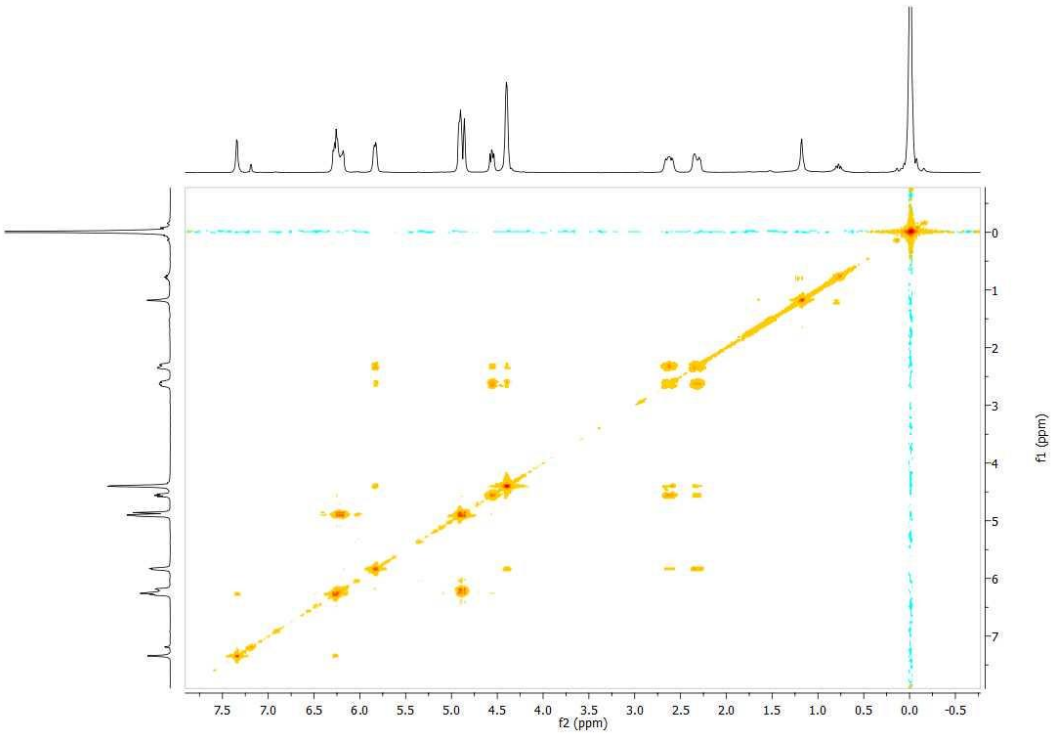
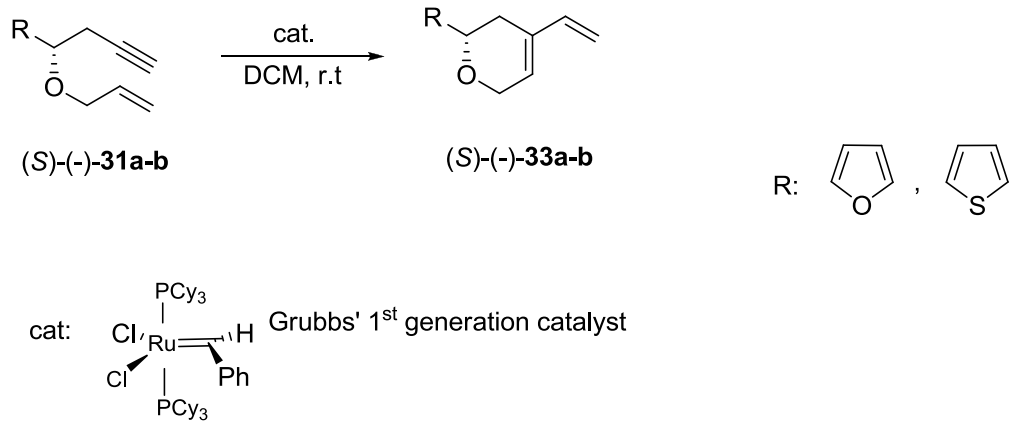


Figure 7. COSY spectrum of (*S*)-(-)-**32a**

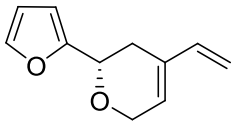
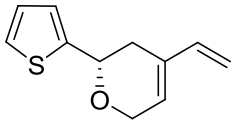
In ^{1}H NMR spectrum thiophene substituted derivative (*S*)-(-)-**32b** reveals diastereotopic methylene protons next to the stereogenic center as two different sets of signals appeared at 2.57-2.49 ppm as multiplet and at 2.43 ppm as doublet of multiplet. The other methylene protons of the ring appear as two different sets of signals at 4.46 ppm as doublet (J =15.6 Hz) and at 4.40 ppm as doublet of doublet (J =15.6, 2.0 Hz). The stereogenic center methine proton resonates at 4.72 ppm as doublet of doublet with the coupling constant values J =9.6 and 3.6 Hz. Dihydropyran ring attached vinyl unit shows the characteristic signals at 4.90 ppm as doublet J =11.0 Hz denoted as *cis* and at 4.88 ppm as doublet J =17.9 Hz as *trans* with respect to internal olefinic methine proton resonated at 6.21 as doublet of doublet (J =17.9 and 11.2 Hz). ^{13}C NMR, eleven signals confirm the structure. The HRMS measurements of (*S*)-(-)-**32b** also strongly supported the structure found for $(M+H)^{+}$: 193.0726 and calculated value for $(M+H)^{+}$: 193.0609

RCEM reactions of *O*-ally anchored compounds (*S*)-(-)-**31a-b** were performed by Grubbs' 1st generation catalyst (Scheme 19). The amount of catalyst for substrate (*S*)-(-)-**31a** was 5%, whereas 8% of Grubbs' 1st generation catalyst was used for substrate (*S*)-(-)-**31b**. Enyne systems (*S*)-(-)-**31a-b** produced conjugated dienes (*S*)-(-)-**33a-b** as structural isomers of (*S*)-(-)-**32a-b** with the yield of 70% and 78% respectively. All results are summarized in table 9.



Scheme 19. RCEM reactions of (*S*)-(-)-**31a-b**

Table 9. Results of RCEM reactions (*S*)-(-)-**31a-b**

Substrate	Product	Configuration	Time(h)	Yield (%)
(*S*)-(-)-**31a**	 (*S*)-(-)-**33a**	*S*	12	70
(*S*)-(-)-**31b**	 (*S*)-(-)-**33b**	*S*	8	78

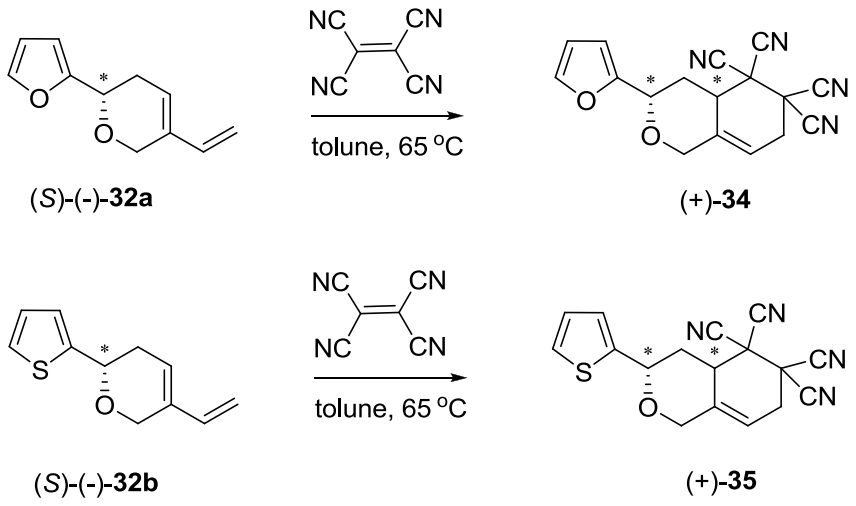
In ^{1}H NMR spectrum of (*S*)-(-)-**33a**, methylene protons next to the oxygen atom show AB system signals at 4.34 ppm as doublet of doublet (*J* =17.6 and 2.4 Hz) and at 4.26 ppm as doublet of multiplet (*J* =17.6 Hz), stereogenic methine proton appears as doublet of doublet at 4.59 ppm with the coupling constants *J* =9.6 and 3.6 Hz. The newly formed vinyl unit reveals the characteristic signal sets for one of olefinic methylene protons at 4.96 ppm as doublet (*J* =10.8 Hz) for the other methylene proton at 5.11 ppm as doublet (*J* =17.6 Hz) and for methine olefinic proton at 6.32 ppm as doublet of doublet (*J* =17.6 and 10.8 Hz). ^{13}C NMR spectrum reveals eleven signals.

^{1}H NMR of compound (*S*)-(-)-**33b** possesses olefinic methine signals at 6.32 and 5.71 ppm as doublet of doublets with the coupling constant *J* =17.6, 10.8 Hz and multiplet for vinyl unit and dihydropyran olefinic unit, respectively. The methylene protons resonate at 5.10 ppm and 4.96 ppm as doublet with the coupling constants *J* =17.2 and 10.8 Hz indicated as H_{trans} and H_{cis}, respectively. Stereogenic center attached proton shows the signal at 4.78 ppm as doublet of doublets (*J* =9.2 and 4.0 Hz). ^{13}C NMR shows again eleven signals. All other results are given in experimental part in detail.

2.5. Diels-Alder Application of Chiral Diene Systems

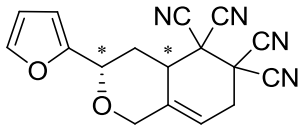
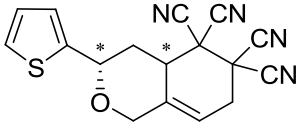
Ring closing enyne metathesis is an important method for the formation of several precursors which are used in total synthesis of some natural compounds. The product of RCEM, 1,3-conjugated diene systems are valuable candidates for various organic reactions. One of the important reactions among them is Diels-Alder reaction. According to our synthetic pathway, final step is the Diels-Alder reaction of previously synthesized chiral diene systems with a powerful dienophile. The aim of this step is to form more stable compounds because 1,3-dienes were not highly stable. Tetracyanoethylene was chosen as a dienophile for Diels-Alder applications. It is one of the most feasible dienophile due to its strong electron withdrawing cyano substituents. In addition, a new stereogenic center was formed as a result of Diels-Alder cycloaddition reaction. By this way, it is possible to make a comment about stereoselectivity.

Diels-Alder reaction was applied to two chiral diene systems (*S*)-(-)-**32a-b**. As it was mentioned before, tetracyanoethylene was used a dienophile and the reaction was carried out in dry toluene (Scheme 20). Diels-Alder adducts of chiral diene systems (+)-**34** and (+)-**35** were produced with the yield of 72% and 63% respectively (Table 10).



Scheme 20. Diels-Alder application of (*S*)-(-)-**32a-b**

Table 10. Results of Diels-Alder reactions

Substrate	Product	Time(h)	Yield(%)
(*S*)-(-)-**32a**	 (+)-**34**	18	72
(*S*)-(-)-**32b**	 (+)-**35**	24	63

The structure elucidation of compounds (+)-**34** and (+)-**35** were done with ^{1}H and ^{13}C NMR. In proton NMR of compound (+)-**34**, four olefinic protons of diene (*S*)-(-)-**32a** disappeared, while new signals are observed at 5.58-5.62 ppm as multiplet which belongs to the newly formed double bond of Diels-Alder adduct. The methylene protons located between two stereogenic centers appear as AB system at 2.63 and 2.33 ppm as doublet of doublets and doublet of triplets, respectively. ^{13}C NMR shows seventeen signals as expected.

The COSY spectrum strongly supports our suggestion for the structure of cyclo-adduct (+)-**34**. In the COSY spectrum, we focused our attention to diastereotopic methylene protons located between two stereogenic centers. They possess cross-peaks with the signal resonated at 3.60 ppm as doublet belonging to newly generated stereogenic center and the signal resonated at 5.20 ppm as doublet denoted as already formed stereogenic center. In addition to these relations, we also observed the cross-peaks between newly formed olefinic proton at 5.58-5.62 as multiplet and the diastereotopic methylene protons of newly cyclic system resonated at 3.16 and 3.06-3.00 ppm, as doublet of doublets and multiplet, respectively (Figure 8).

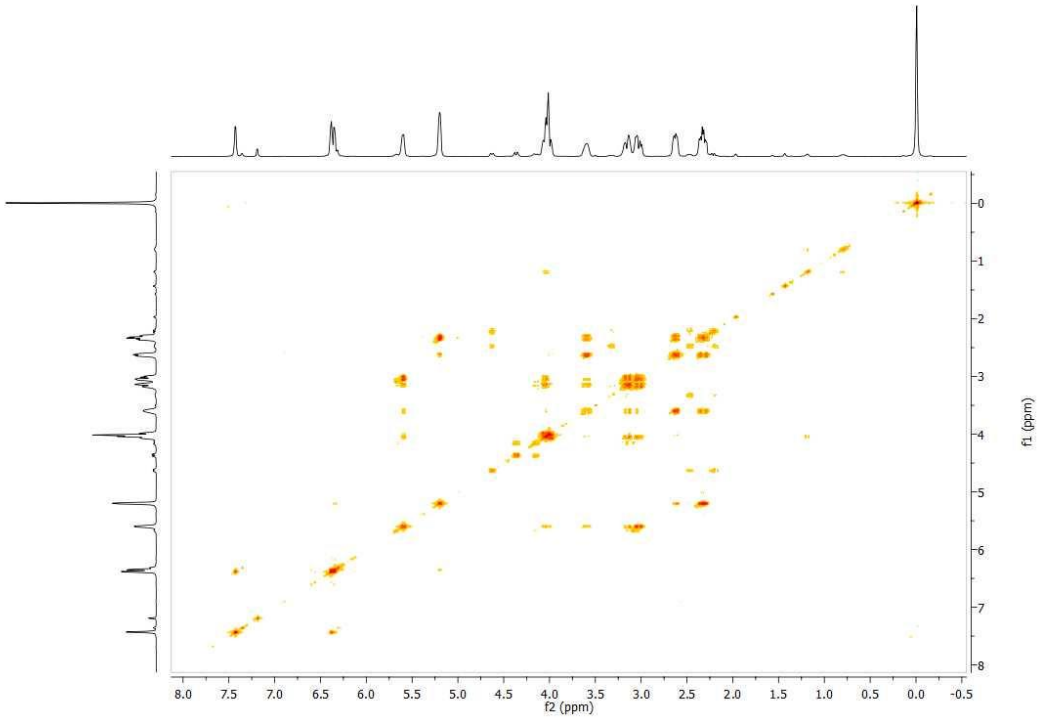


Figure 8. COSY spectrum of (+)-**34**

^{1}H NMR of compound (+)-**35** gives a signal at 5.60 ppm as doublet of doublet which belongs to the olefinic proton. The protons which are neighbor to the stereogenic centers have signals at 2.75 ppm as doublet of doublets of doublets and 2.43 ppm as triplet of doublets. The proton attached to the newly formed stereogenic center possesses a signal at 3.45 ppm as doublet. Diastereotopic methylene protons next to the oxygen atom reveals two signal sets resonated at 4.24 and 4.03 ppm as doublet. Seventeen peaks are observed in ^{13}C NMR. Four peaks at 109.6-107.6 belong to the cyano carbons.

In the COSY spectrum of (+)-**35**, (δ = 2.75 and 2.43 ppm as doublet of doublet of doublet and triplet of doublet, respectively) diastereotopic methylene protons located between stereogenic centers have cross-peaks with newly formed stereogenic center proton (δ = 3.45 ppm) and with the other stereogenic center proton (δ = 5.44 ppm) (Figure 9).

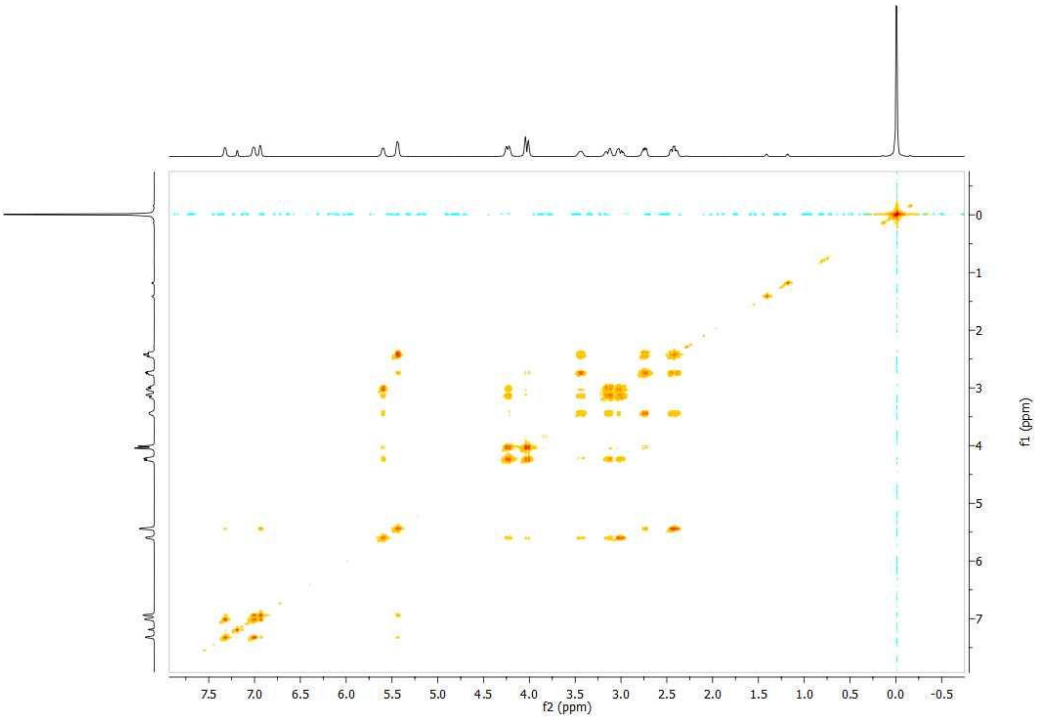


Figure 9. COSY spectrum of (+)-**35**

Both ^{1}H and ^{13}C NMR spectrum of (+)-**34** and (+)-**35** indicate the formation of single diastereomeric form for each one depending upon the only one sets of signals. This finding can show the excellent diastereoselectivity of the cycloaddition reaction.

CHAPTER 3

CONCLUSION

In this study, four heteroaryl substituted homoallylic and homopropargylic alcohols were successfully synthesized. Commercially available aldehydes (furan-2-carbaldehyde and thiophene-2-carbaldehyde) were chosen as starting material. These homoallylic and homopropargylic alcohols were enantiomerically enriched by enzymatic resolution method by using various enzymes with the high enantiomeric excess value. All the absolute configurations of alcohols were defined as (*S*) by comparing the literature. As a result of very well-known *O*-allylation and *O*-propargylation reactions of enantiomerically enriched alcohols, enyne moieties were produced which were used as precursors of Ring Closing Enyne Metathesis (RCEM). The resultant chiral diene systems were synthesized via RCEM with Grubbs' catalyst in high yield. During the course of the metathesis reaction, absolute configuration of chiral center was preserved. This is an advantage for the determination of absolute configuration of the Diels-Alder adduct. Only one diastereomeric cyclo adducts were observed as a result of Diels-Alder application of diene systems (*S*)-(-)-**32a-b.**

In our group, there were similar studies about exploring the control of remote stereochemistry in intramolecular Pausan-Khand Reaction (PKR) of enynes tethered to chiral 2-furyl homoallylic and homopropargylic alcohols [55]. In this study, it was explained why only one form of diastereomers was obtained; the most favorable chair conformation of pyran ring which can control the configuration of newly formed stereogenic center. By looking these results, it is possible to make a comment about our Diels-Alder adducts configuration. X-Ray analysis studies are still ongoing.

CHAPTER 4

EXPERIMENTAL

Following instruments and materials were used for the purification and characterization of products during the study.

NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are expressed in ppm. downfield from tetramethylsilane, which is used as internal standard; the ^{1}H-NMR data are presented in the order value of the signal, peak multiplicity (abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad) and coupling constants in Hertz integrated number of protons.^{13}C-NMR spectra were measured at 100 MHz and the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter at specified temperatures.

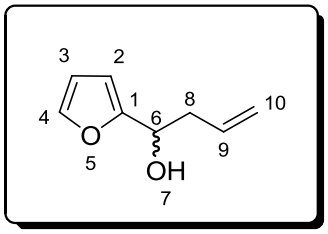
HPLC measurements were performed with ThermoFinnigan Spectra System instrument. Separations were carried out on Chiralcel OJ-H analytical column (250 x 4.60 mm) with hexane/2-propyl alcohol as eluent.

Flash column chromatography was employed using thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck Silica Gel PF-254), visualized with UV-light, polymolybden phosphoric acid in methanol, ninhydrin and anisaldehyde. The relative portions of solvents are in volume:volume ratio used in column chromatography as eluent.

4.1. General Procedure for Synthesis of Racemic Homoallylic Alcohols, *rac*-24a-b

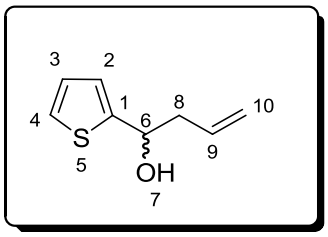
Mg (17.6 mmol, 1.7 eq.) and a few crystal of I_2 were mixed in dry Et_2O (10 mL). Then, allybromide (12.4 mmol, 1.2 eq.) was added to the mixture dropwise, reflux was observed. After 30 minutes mixing the solution, the temperature was cooled down to 0 °C in an ice bath. Corresponding aldehyde (1.0 eq.) was added this solution dropwise. The mixture was stirred at room temperature until all the starting material has finished by TLC controlling. 1 N HCl (9 mL) and saturated NH_4Cl (15 mL) solutions were added and the mixture was extracted with ether (3x15). The organic phase was separated and dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude *rac*-**24a-b** were purified with flash column chromatography using mixture of ethyl acetate and hexane 1:6 for *rac*-**24a-b**.

4.1.1-(Furan-2-yl)but-3-en-1-ol, *rac*-24a



Colorless oil (75% yield). ^{1}H NMR: δ 7.23 (dd, J=1.6 and J=0.8 Hz, 1H, H_4), 6.19 (dd, J=3.2 and J=2 Hz, 1H, H_3), 6.10 (d, J=3.2 Hz, 1H, H_2), 5.71-5.60(m, 1H, H_8) 4.99 (td, J=10.4 and J=0.8 Hz, 2H, H_{10}), 4.56 (t, J=2.4 Hz, H_6), 2.97(bs, 1H, H_7), 2.49-2.45(m, 2H, H_5); ^{13}C-NMR: δ 155.9, 141.4, 133.5, 117.7, 109.7, 105.7, 66.7, 39.7. (Figure A1-2)

4.1.2. 1-(Thiophen-2-yl)but-3-en-1-ol, *rac*-24b

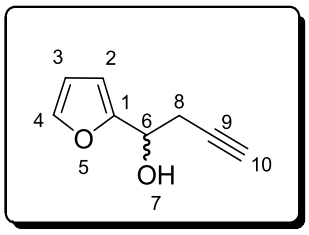


Yellow oil (80% yield). ^{1}H-NMR: δ 7.17 (dd, J=4.6 and J=1.7 Hz, 1H, H_4), 5.88-5.91 (m, 2H, H_2, H_3), 5.68-5.81 (m, 1H, H_9), 5.06-5.14 (m, 2H, H_{10}), 4.88-4.93 (m, 1H, H_6), 2.51-2.57 (m, H_8), 2.22 (d, J=4.3 Hz, 1H, H_7); ^{13}C-NMR: δ 147.9, 133.9, 126.6, 124.6, 123.7, 118.8, 69.4, 43.785. (Figure A3-4)

4.2.General Procedure for Synthesis of Racemic Homopropargylic Alcohols, *rac*-25a-b

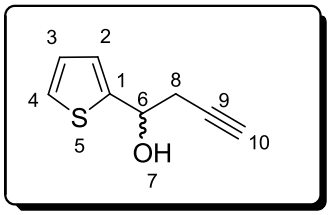
A Zn-Cu couple reagent was prepared as the following. Zinc dust (6.5 g, 100 mmol) was mixed with distilled water (10 ml) and added to the solution of acidic cupric chloride (0.15M in 5% hydrochloric acid, 22 ml). The solution was stirred vigorously. When the gas evolution ended, the suspension was filtered and black solid was washed twice with dry acetone. Freshly prepared Zn-Cu (79.6 mmol, 1.1 eq) and corresponding aldehyde (1.0 eq.) were mixed in dry THF (20 ml). Then, propargylbromide (79.6 mmol, 1.1 eq.) was added to the mixture dropwise at 0 ^{o}C. The mixture was refluxed until all aldehyde was consumed by TLC controlling. 1 N HCl (8 mL) and saturated NH_4Cl (15 mL) solutions were added and the mixture was extracted with ether (3x30 ml). The organic phase was separated and anhydrous $MgSO_4$ was used for drying and evaporated under reduced pressure.

4.2.1. 1-(Furan-2-yl)but-3-yn-1-ol, *rac*-25a



Yellow oil (70% yield) ^{1}H-NMR: δ 7.30 (dd, J=1.6 and J=1.2 Hz, 1H, H_4), 6,26 (d, J=1.6 Hz, 2H, H_2, H_3), 4.79 (dd, J=12.0 and J=6.0 Hz, 1H, H_6), 2.70 (d, J=2.8 Hz, 1H, H_8), 2.68 (d, J=2.8 Hz, 1H, $H_{8'}$), 2.38 (brs, 1H, H_7), 1.97 (t, J=2.8 Hz, 1H, H_{10}); ^{13}C-NMR: δ 154.7, 142.2, 110.2, 105.6, 79.9, 71.2, 66.1, 26.1. (Figure A5-6)

4.2.2. 1-(Thiophen-2-yl)but-3-yn-1-ol, rac-25b



Yellow oil(72% yield) ^{1}H-NMR: δ 7.19 (dd, J=4.8 and J=1.2 Hz, 1H, H_4), 6,96 (dd, J=3.6 and J=0.8 Hz, 1H, H_2), 6.90 (dd, J=5.2 and J=3.6 Hz, 1H, H_3), 5.05 (dd, J=11.2 and J=6.0 Hz, 1H, H_6), 2.69 (dd, J=6.4 and J=2.8 Hz, 2H, H_8), 2.37 (d, J=4.4, 1H, H_7), 2.01 (t, J=2.4 Hz, 1H, H_{10}); ^{13}C-NMR: δ 145.1, 125.6, 123.8, 123.0, 78.9, 70.5, 67.5, 28.6. (Figure A7-8)

4.3. General Procedure for Enzymatic Resolution of Homoallylic Alcohols and Homopropargylic Alcohols

Racemic alcohols *rac*-**24a-b** and *rac*-**25a-b** (1.0 mmol), vinyl acetate (0.9 mL, 10mmol) and corresponding cosolvent were mixed in a round bottom flask. Then, corresponding enzyme was added to this solution and stirred at constant temperature (26 ^{o}C). The reaction was monitored by TLC. When the alcohol to acetyl ratio became 50%, reaction was ended. Enzyme was filtered. The acetylated product and the alcohol were separated by column chromatography (silica gel, EtOH/hexane 1:5). (*S*)- alcohols and (*R*)-acetates were afforded.

4.3.1. (*S*)-(-)-1-(Furan-2-yl)but-3-en-1-ol, (*S*)-(-)-24a

$[\alpha]_D^{27}$= -21.6 (c 5.0, CH_2Cl_2) for 99% e.e., in lit.[58] $[\alpha]_D^{27}$= -32.6 (*c* 0.50 CH_2Cl_2 for 84%, HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=26.01 (Figure A10).

4.3.2. (*S*)-(-)-1-(Thiophene-2-yl)but-3-en-1-ol, (*S*)-(-)-24b

$[\alpha]_D^{27}$= -24.2 (c 1, CH_2Cl_2) for 99% e.e., in lit.[58] $[\alpha]_D^{27}$= -8.2 (*c* 1.2 CH_2Cl_2) for 80% e.e. , HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=12.98 (Figure A12).

4.3.3. (*S*)-(+)- 1-(Furan-2-yl)but-3-yn-1-ol, (*S*)-(+)-25a

$[\alpha]_D^{25}$= +6.7 (c 3.1, MeOH) for 93% e.e., in lit.[56] $[\alpha]_D^{28}$ = -6.61 (*c* 2.4 MeOH) for 95% e.e., HPLC analysis: OJ-H colomn, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=23.15 (Figure A14)

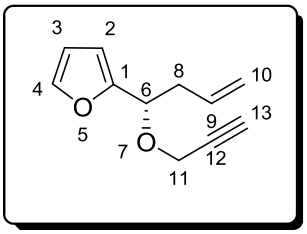
4.3.4. (*S*)-(+)- 1-(Thiophen-2-yl)but-3-yn-1-ol, (*S*)-(+)-25b

$[\alpha]_D^{29}$= +12.4 (c 1.3, MeOH) for 99% e.e., in lit.[57] $[\alpha]_D^{20}$ = +0.3 (*c* 7.86 EtOH) for 99% e.e., HPLC analysis: OJ-H colomn, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=35.57 (Figure A16)

4.4. General Procedure for *O*-propargylation Reaction

To a solution of enantiomerically pure alcohol (*S*)-(-)-**24a-b** in dry freshly distilled THF (10 ml), NaH (2.5 eq.) was added. This mixture was stirred for 15 minutes. Then, propargylbromide (2.5 eq.) was added dropwise under argon atmosphere. The reaction was refluxed until all the alcohol was consumed. For quenching the reaction, distilled water (5 ml) was added. Ether (3x15 ml) was used for extraction of aqueous layer. Then, all organic layers were combined and washed with brine (2x10 ml), dried over $MgSO_4$. The solvent was evaporated in vacuum and targeting products were obtained.

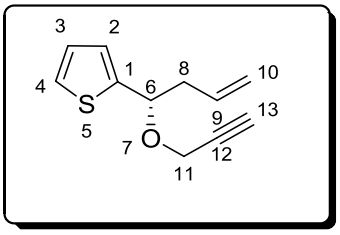
4.4.1. (*S*)-2-(1-(Prop-2-ynyloxy)but-3-enyl)furan, (*S*)-(-)-30a



Yellow oil(83% yield) $[\alpha]^{25}_D$ = -78.5 (*c*, 2.7, CH_2Cl_2); IR(neat) cm^{-1} : 3301, 1747, 1440, 1073, 737. H-NMR: δ 7.32 (dd, *J*=1.6 and *J*=0.8 Hz, 1H, H_4), 6.26-6.24 (m, 2H, H_2, H_3), 5.67 (ddt, *J*=17.1, *J*=10.2 and *J*=7.0 Hz, 1H, H_9), 5.02 (dq, J_{trans}=17.1, *J*=1.6 Hz, 1H, H_{10}), 4.96 (dm, J_{cis}=10.2 1H, $H_{10'}$), 4.51 (t, *J*=3.2 Hz, 1H, H_6), 4.06 (dd, *J*=16 and *J*=2.4 Hz, 1H, H_{11}), 3.85 (dd, *J*=16 and *J*=2.4 Hz, 1H, $H_{11'}$), 2.61 (dtt, *J*=14.3, *J*=7.0 and *J*=1.2 Hz, 1H, H_8), 2.53 (ddt, *J*=14.3, *J*=7.0

and *J*=1.2 Hz, 1H, $H_{8'}$), 2.31 (t, *J*=2.4 Hz, 1H, H_{13}); ^{13}C-NMR: δ 152.9, 142.5, 133.8, 117.4, 110.0, 108.9, 79.7, 72.8, 55.4, 38.3 (Figure A17-18).

4.4.2. (*S*)-2-(1-(Prop-2-ynyloxy)but-3-enyl)thiophene, (*S*)-(-)-30b

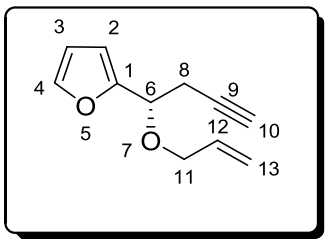


Yellow oil (89% yield) $[\alpha]^{29}_{D}$ = -135.9 (*c*, 1, CH_2Cl_2); IR(neat) cm^{-1} : 3053, 2877, 1264, 736. ^{1}H-NMR: δ 7.28 (dd, *J*=5.2 and *J*=0.8 Hz, 1H, H_4), 7.00 (dd, *J*=3.6 and *J*=0.8 Hz 1H, H_2), 6.95 (dd, *J*=5.2 and *J*=3.6 Hz 1H, H_3), 5.78 (ddt, *J*=17.2, *J*=10.2 and *J*=6.9 Hz, 1H, H_9), 5.10 (dq, J_{trans}=17.2 and 1.5 Hz, 1H, H_{10}), 5.04 (ddt, J_{cis}=10.2, *J*=1.8 and *J*=1.1 Hz, 1H, $H_{10'}$), 4.83 (t, *J*=2.8 Hz, 1H, H_6), 4.15 (dd, *J*=15.8 and *J*=2.4 Hz, 1H, H_{11}), 3.92 (dd, *J*=15.8 and *J*=2.4 Hz, 1H, $H_{11'}$), 2.63 (dtt, *J*=14.3, *J*=7.0 and *J*=1.2 Hz, 1H, H_8), 2.53 (dtt, *J*=14.3, *J*=6.7 and *J*=1.3 Hz, 1H, $H_{8'}$), 2.39 (t, *J*=2.4 Hz, 1H, H_{13}); ^{13}C-NMR: δ 144.2, 134.0, 126.3, 126.2, 125.5, 117.5, 79.7, 75.4, 74.4, 55.2, 42.4 (Figure A19-20).

4.5. General Procedure for *O*-allylation Reaction

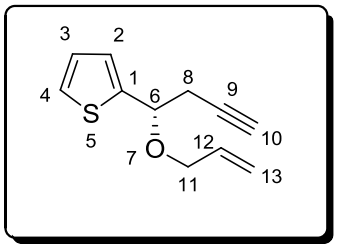
To a solution of enantiomerically pure alcohol (*S*)-(-)-**25a-b** in dry freshly distilled THF (10 ml), NaH (2.5 eq.) was added. This mixture was stirred for 15 minutes. Then, allybromide (2.0 eq.) was added dropwise under argon atmosphere. The reaction was refluxed until all the alcohol was finished. For quenching the reaction, distilled water (5 ml) was added. Ether (3x15 ml) was used for extraction of aqueous layer. Then, all organic layers were combined and washed with brine (2x10 ml), dried over $MgSO_4$. The solvent was evaporated in vacuum and target products were obtained.

4.5.1. (*S*)-2-(1-(Allyloxy)but-3-ynyl)furan, (*S*)-(-)-31a



Yellow oil (80 % yield) $[\alpha]^{29}_{D}$ = -103.4 (*c*, 1.0, CH_2Cl_2); IR(neat) cm^{-1} : 3301, 1725, 1685, 1077, 733. ^{1}H-NMR: δ 7.33 (t, *J*=1.2 Hz, 1H, H_4), 6.28-6.26 (m, 2H, H_2, H_3), 5.80 (ddt, *J*=17.0, *J*=10.4 and *J*=5.2 Hz, 1H, H_{12}), 5.20 (dq, J_{trans}=17.2 and *J*=1.6 Hz, 1H, H_{13}), 5.11 (dq, J_{cis}=10.3 and *J*=1.3 Hz, 1H, $_{H13'}$), 4.45 (t, *J*=6.8 Hz, 1H, H_6), 3.94 (ddt, *J*=12.8, *J*=5.2, *J*=1.5 Hz, 1H, H_{11}), 3.82 (ddt, *J*=12.8, *J*=6.2 and *J*=1.3 Hz, 1H, $H_{11'}$), 2.70 (t, *J*=2.4 Hz, 1H, H_8), 2.68 (t, *J*=2.6 Hz, 1H, $H_{8'}$), 1.86 (t, *J*=2.4 Hz, 1H, H_{10}); ^{13}C-NMR: δ 151.9, 141.4, 133.3, 116.3, 109.0, 107.4, 79.1, 71.3, 68.9, 68.7, 23.5 (Figure A21-22)

4.5.2. (*S*)-2-(1-(Allyloxy)but-3-ynyl)tiophene, (*S*)-(-)-31b



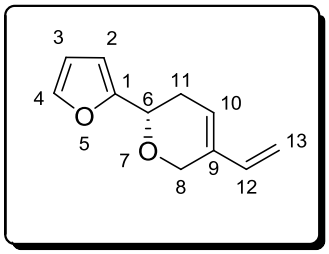
Yellow oil (85% yield) $[\alpha]^{29}_{D}$ = -35.3 (*c*, 1.0, CH_2Cl_2); IR(neat) cm^{-1} : 3301, 2973, 1088, 1047, 880. 1H-NMR: δ 7.19 (dd, *J*=4.8 and *J*=0.8 Hz, 1H, H_4), 6.94 (dd, *J*=3.2 and *J*=0.8 Hz, 1H, H_2), 6.89 (dd, *J*=5.2 and *J*=3.6 Hz, 1H, H_3), 5.81 (ddt, *J*=17.0, *J*=10.4 and *J*=5.2 Hz, 1H, H_{12}), 5.20 (dq, *J*=17.2 and *J*=1.6 Hz, 1H, H_{13}), 5.11 (dq, *J*=10.3 and *J*=1.3 Hz, 1H, $H_{13'}$), 4.67 (t, *J*=6.8 Hz, 1H, H_6), 3.97 (ddt, *J*=12.8, *J*=5.2 and *J*=1.6 Hz, 1H, H_{11}), 3.81 (ddt, *J*=12.8, *J*=6.0 and *J*=1.2 Hz, 1H, $H_{11'}$), 2.71 (ddd, *J*=16.8, *J*=6.4 and *J*=2.8 Hz, 1H, H_8), 2.56 (ddd, *J*=16.8, *J*=6.8

and *J*=2.8 Hz, 1H, $H_{8'}$), 1.89 (t, *J*=2.8 Hz, 1H, H_{10}); ^{13}C-NMR: δ 144.5, 134.4, 126.4, 125.6, 125.2, 117.3, 80.4, 75.4, 70.4, 69.7 (Figure A23-24)

4.6. General Procedure of RCEM Reaction

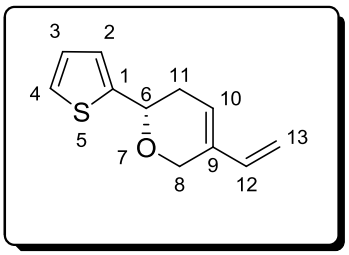
To a solution of enyne system (*S*)-(-)-**30a-b** and (*S*)-(-)-**31a-b** in CH_2Cl_2 (8 ml), Grubbs' first generation catalyst (5% and 8%) was added and stirred at room temperature until all starting compound was consumed. Purification was done with a short column choromotography (EtOAc/hexane: 1:15 for all products)

4.6.1. (*S*)-2-(Furan-2-yl)-5-vinyl-3,6-dihydro-2H-pyran, (*S*)-(-)-32a



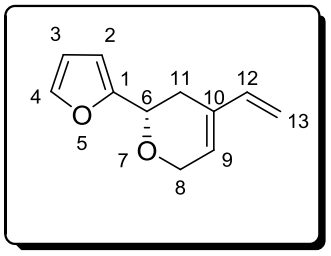
Pale yellow oil (76% yield) $[\alpha]^{27}_D$ = -50.1 (*c*, 1.0, CH_2Cl_2); IR(neat) cm^{-1}: 3054, 2986, 1265, 737, 704. ^{1}H-NMR: δ 7.31 (dd, *J*=2.0 and *J*=0.8 Hz, 1H, H_4), 6,25 (dd, *J*=3.2 and *J*=1.6 Hz, 1H, H_3), 6.21 (d, *J*=3.2 Hz, 1H, H_2), 6.19 (dd, *J*=17.9 and *J*=11.2 Hz, 1H, H_{12}), 5.81 (brd, *J*=2.4 Hz, 1H, H_{10}), 4.88 (d, *J*=11.0, 1H, H_{13}), 4.86 (d, *J*=17.9 Hz, 1H, $H_{13'}$), 4.53 (dd, *J*=10.0 and *J*=4.0 Hz 1H, H_6) 4.37 (brs, 2H, H_8), 2.60 (ddd, *J*=17.4, *J*=9.8 and *J*=2.4 Hz, 1H, H_{11}), 2.33-2.27 (m, 1H, $H_{11'}$); ^{13}C-NMR: δ 152.0, 140.1, 133.5, 132.8, 122.6, 109.1, 107.9, 104.7, 66.7, 63.0, 26.8 (Figure A25-26)

4.6.2. (*S*)- 2-(Thiophen-2-yl)-5-vinyl-3,6-dihydro-2H-pyran, (*S*)-(-)-32b



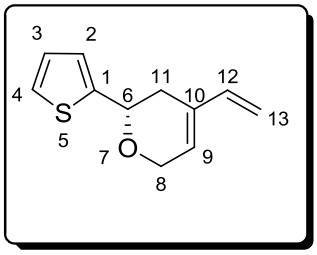
Yellowish oil (80% yield). $[\alpha]^{25}_{D}$ = -107.1 (*c*, 1.0, CH_2Cl_2); IR(neat) cm^{-1}: 3054, 2879, 1716, 1264, 702. ^{1}H-NMR: δ 7.18 (dd, *J*=4.8 and *J*=1.2 Hz, 1H, H_4), 6.91 (d, *J*=3.2, 1H, H_2), 6.90 (dd, *J*=4.8 and *J*=3.6 Hz, 1H, H_3), 6.21 (dd, *J*=17.9 and *J*=11.2 Hz, 1H, H_{12}), 5.82 (brd, *J*=2.0 Hz, 1H, H_{10}), 4.90 (d, *J*=11.0 Hz, 1H, H_{13}), 4.88 (d, *J*=17.9 Hz, 1H, $H_{13'}$), 4.72 (dd, *J*=9.6 and *J*=3.6 Hz, 1H, H_6), 4.46 (d, *J*=15.6 Hz, 1H, H_8), 4.40 (dd, *J*=15.6 and *J*=2.0 Hz, 1H, $H_{8'}$), 2.57-2.49 (m, 1H, H_{11}), 2.43 (dm, *J*=17.8 Hz, 1H, $H_{11'}$); ^{13}C-NMR: δ 144.1, 134.6, 134.0, 125.4, 123.9, 123.7, 122.8, 110.3, 70.5, 64.5, 31.9 (Figure A31-32)

4.6.3. **(*S*)- 2-(Furan-2-yl)-4-vinyl-3,6-dihydro-2H-pyran, (*S*)-(-)-33a**



Yellow oil (70 % yield) $[\alpha]^{29}_{D}$ = -17.9 (*c*, 1.0, CH_2Cl_2); ^{1}H-NMR: δ 7.33 (dd, *J*=1.6 and *J*=0.8 Hz, 1H, H_4), 6,32 (dd, *J*=17.6 and *J*=10.8 Hz, 1H, H_{12}), 6.27 (dd, *J*=3.2 and *J*=1.6 Hz, 1H, H_3), 6.25 (d, *J*=3.2 Hz, 1H, H_2), 5.69 (m, *J*=1.1 Hz, 1H, H_9), 5.11 (d, *J*=17.6, 1H, H_{13}), 4.96 (d, *J*=10.8 Hz, 1H, $H_{13'}$) 4.59 (dd, *J*=9.6 and *J*=3.6 Hz, 1H, H_6), 4.34 (dd, *J*=17.6 and *J*=2.4 Hz, 1H,H_8) 4.26 (dm, *J*=17.6 Hz, 1H, $H_{8'}$), 2.59-2.50 (m, 1H, H_{11}), 2.39 (dm, *J*=16.5, 1H, $H_{11'}$); ^{13}C-NMR: δ 153.2, 141.2, 136.8, 132.1, 125.1, 110.6, 109.1, 105.9, 67.8, 64.6, 26.6 (Figure A33-34)

4.6.4. (*S*)-2-(Thiophen-2-yl)-4-vinyl-3,6-dihydro-2H-pyran, (*S*)-(-)-33b

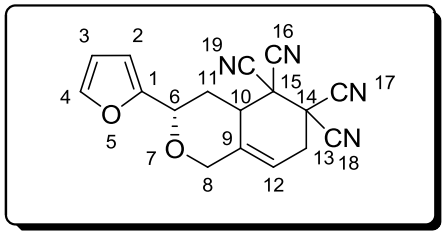


Yellow oil (78% yield) $[\alpha]^{25}_{D}$ = -5.8 (*c*, 1.0, CH_2Cl_2); ^{1}H-NMR: δ 7.20 (dd, *J*=5.2 and *J*=1.2 Hz, 1H, H_4), 6,95 (dt, *J*=3.2 and *J*=1.2 Hz, 1H, H_2), 6.91 (dd, *J*=5.2 and *J*=3.2 Hz, 1H, H_3), 6.32 (dd, *J*=17.6 and *J*=10.8 Hz, 1H, H_{12}), 5.71-5.70 (m, 1H, H_9), 5.10 (d, *J*=17.2, 1H, H_{13}), 4.96 (d, J_{cis}=10.8 Hz, 1H, $H_{13'}$), 4.78 (dd, *J*=9.2 and *J*=4.0 Hz, 1H, H_6), 4.37-4.34 (m, 2H, H_8), 2.53-2.41 (m, 2H, H_{11}); ^{13}C-NMR: δ 144.3, 136.7, 132.3, 125.4, 125.2, 123.7, 122.8, 110.6, 70.4, 65.0, 30.7 (Figure A35-36)

4.7. General Procedure of Diels-Alder Reaction

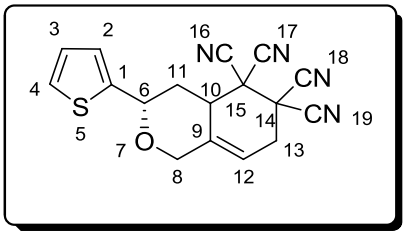
To a solution of diene ststem (*S*)-(-)-**31a** and (*S*)-(-)-**32b** in dry toluene (8 ml), tetracyanoethylene (1.2 eq.) was added and the reaction was stirred at 65 ^{o}C under argon atmosphere until all the diene was consumed. For purification column chromotography was used (EtOAc/hexane: 1:3 for each product).

4.7.1. (3*S*)-3-(Furan-2-yl)-4,4a-dihydro-1H-isochromene-5,5,6,6(3H,7H)-tetracarbonitrile, (+)-34



White crystal (72% yield). $[\alpha]^{27}_{D}$ =+98.1 (*c*, 1.0, CH_2Cl_2), m.p.: 113-114 ^{o}C IR(neat) cm^{-1} : 2932, 2255, 1291,761. ^{1}H-NMR: δ 7.43 (d, *J*=1.6 Hz, 1H, H_4), 6,39 (dd, *J*=3.2 and *J*=1.6 Hz, 1H, H_3), 6.35 (d, *J*=3.2 Hz, 1H, H_2), 5.58-5.62 (m, 1H, H_{12}), 5.20 (d, *J*=6.0 Hz, 1H, H_6), 4.06 (d, *J*=14.4, 1H, H_8), 4.00 (d, *J*=13.6 Hz, 1H, $H_{8'}$), 3.60 (d, *J*=12.0 Hz, 1H, H_{10}), 3.16 (dd, *J*=18.4 and *J*=2.8 Hz, 1H, H_{13}), 3.06-3.00 (m, 1H, $H_{13'}$), 2.63 (dd, *J*=13.2 and *J*=5.2 Hz, 1H, H_{11}), 2.33 (dt, *J*=12.8 and *J*=6.0 Hz, 1H, $H_{11'}$); ^{13}C-NMR: δ 150.1, 142.2, 131.2, 113.3, 109.8, 109.6, 109.4, 109.0, 108.8, 107.6, 66.7, 63.4, 43.4, 43.1, 36.9, 31.2, 28.5 (Figure A37-38)

4.7.2. (3*S*)-3-(Thiophen-2-yl)-4,4a-dihydro-1H-isochromene-5,5,6,6(3H,7H)-tetracarbonitrile, (+)-35



White crystal (63 % yield). $[\alpha]^{27}_{D}$ = +85.17 (*c*, 1.0, CH_2Cl_2), m.p.;151-153 ^{o}C IR(neat) cm^{-1}: 3062, 2323, 1257, 727. ^{1}H-NMR: δ 7.32 (d, *J*=5.2 Hz, 1H, H_4), 7,01 (dd, *J*=5.2 and *J*=3.6 Hz, 1H, H_3), 6.95-6.93 (m, 1H, H_2), 5.60 (dd, *J*=5.2 and *J*=2.0 Hz, 1H, H_{12}), 5.44 (d, *J*=5.6 Hz, 1H, H_6), 4.24 (d, *J*=14.0, 1H, H_8), 4.03 (d, *J*=14.0 Hz, 1H, $H_{8'}$), 3.45 (d, *J*=12.4 Hz, 1H, H_{10}), 3.18-3.11 (m, 1H, H_{13}), 3.05-2.98 (m, 1H, $H_{13'}$), 2.75 (ddd, *J*=13.2, *J*=4.8 and *J*=1.2 Hz, 1H, H_{11}), 2.43 (td, *J*=12.8 and *J*=5.6 Hz, 1H, $H_{11'}$); ^{13}C-NMR: δ 140.1, 131.2, 126.6, 125.7, 124.6, 113.1, 109.6, 109.4, 108.9, 107.6, 69.1, 62.7, 43.0, 36.8, 36.5, 31.1, 30.0 (Figure A43-44).

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APPENDIX A

SUPPORTING INFORMATION

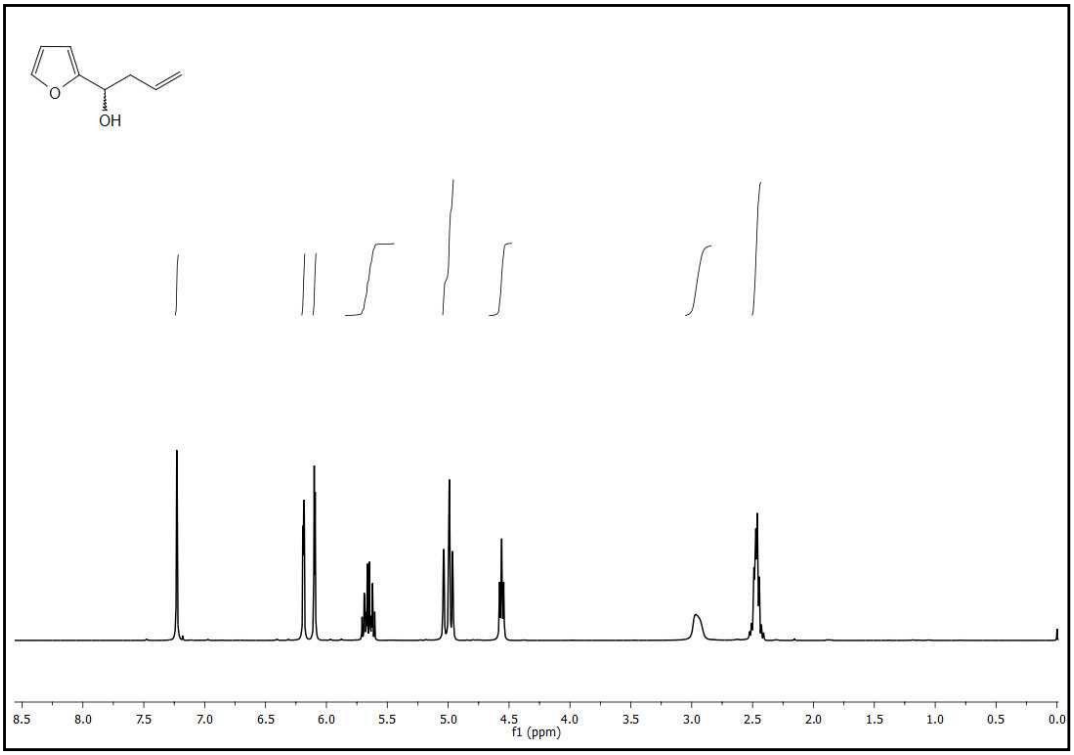

Figure A1. ^{1}H NMR spectrum of *rac*-**24a**

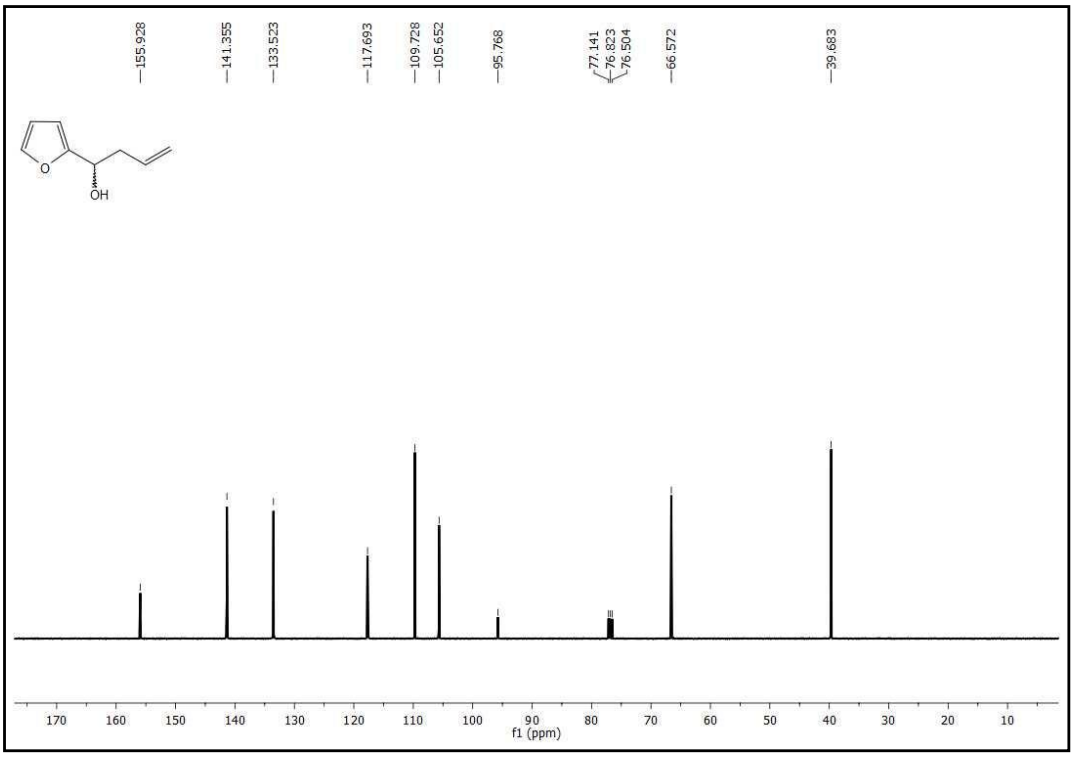

Figure A2. ^{13}C NMR spectrum of *rac*-**24a**

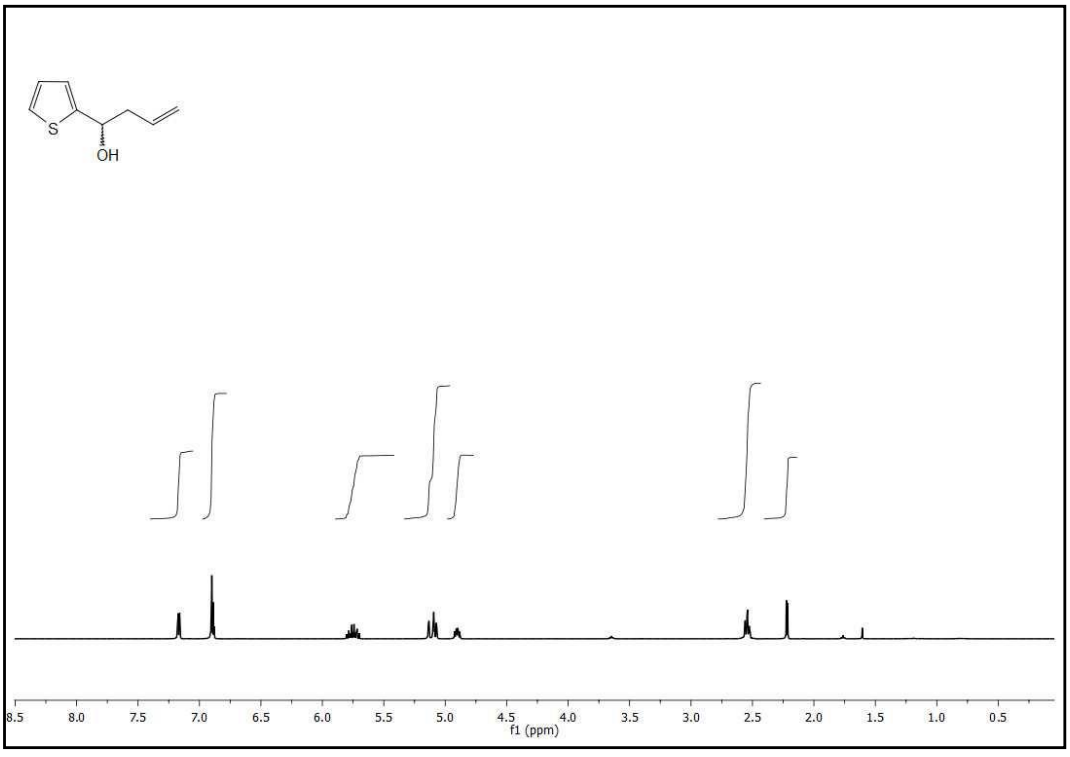

Figure A3. ^{1}H NMR spectrum of *rac*-**24b**

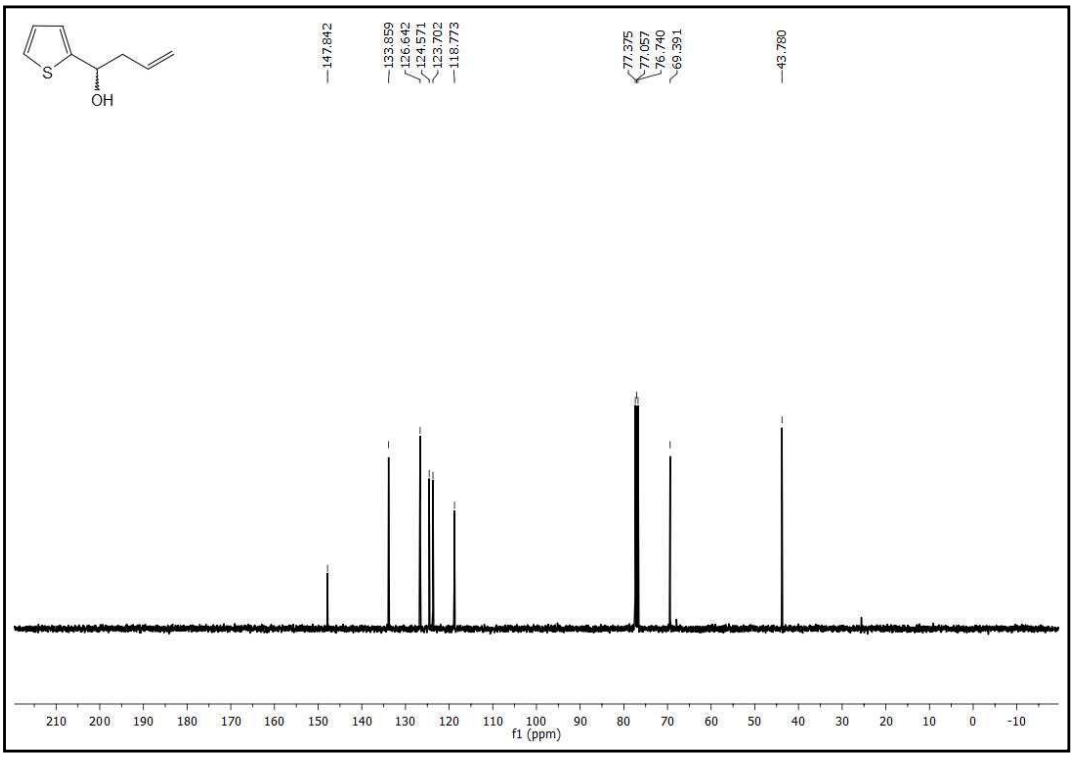

Figure A4. ^{13}C NMR spectrum of *rac*-**24b**

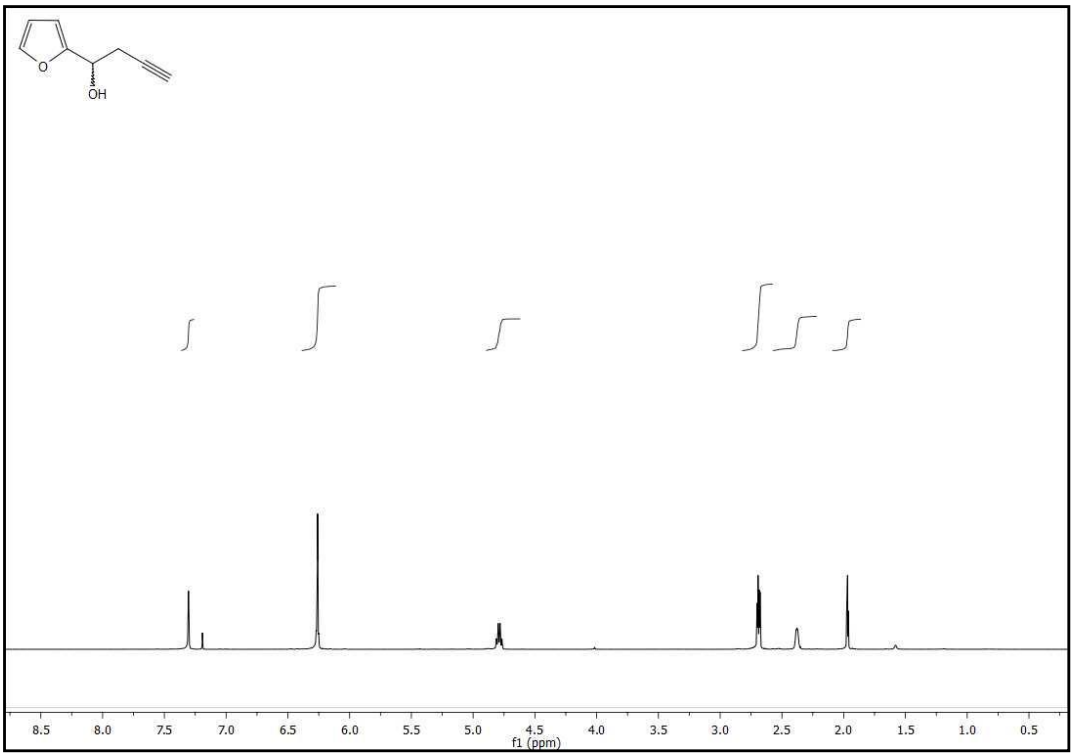

Figure A5. ^{1}H NMR spectrum of *rac*-**25a**

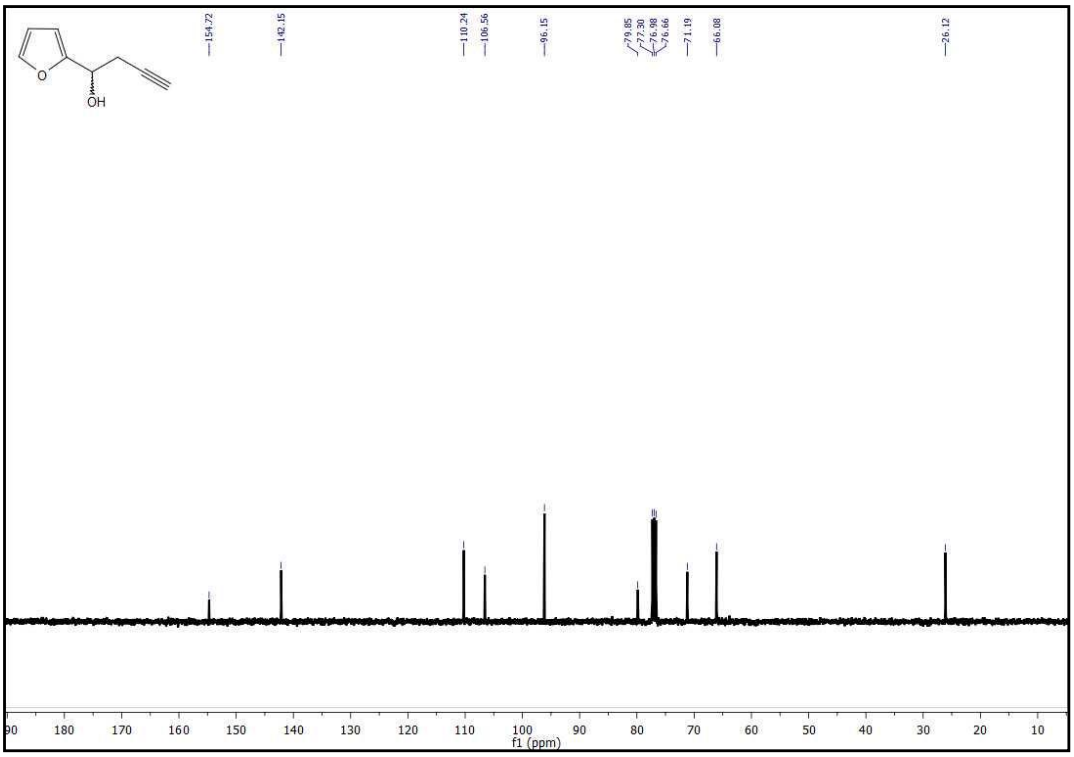

Figure A6. ^{13}C NMR spectrum of *rac*-**25a**

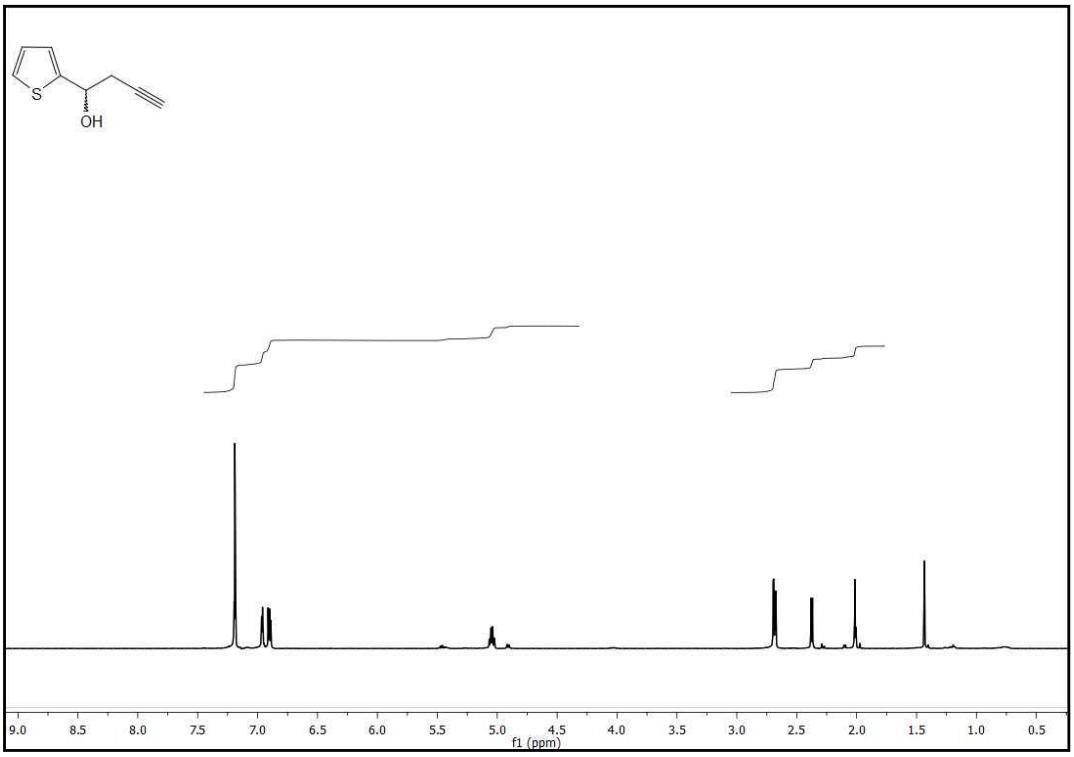

Figure A7. ^{1}H NMR spectrum of *rac*-**25b**

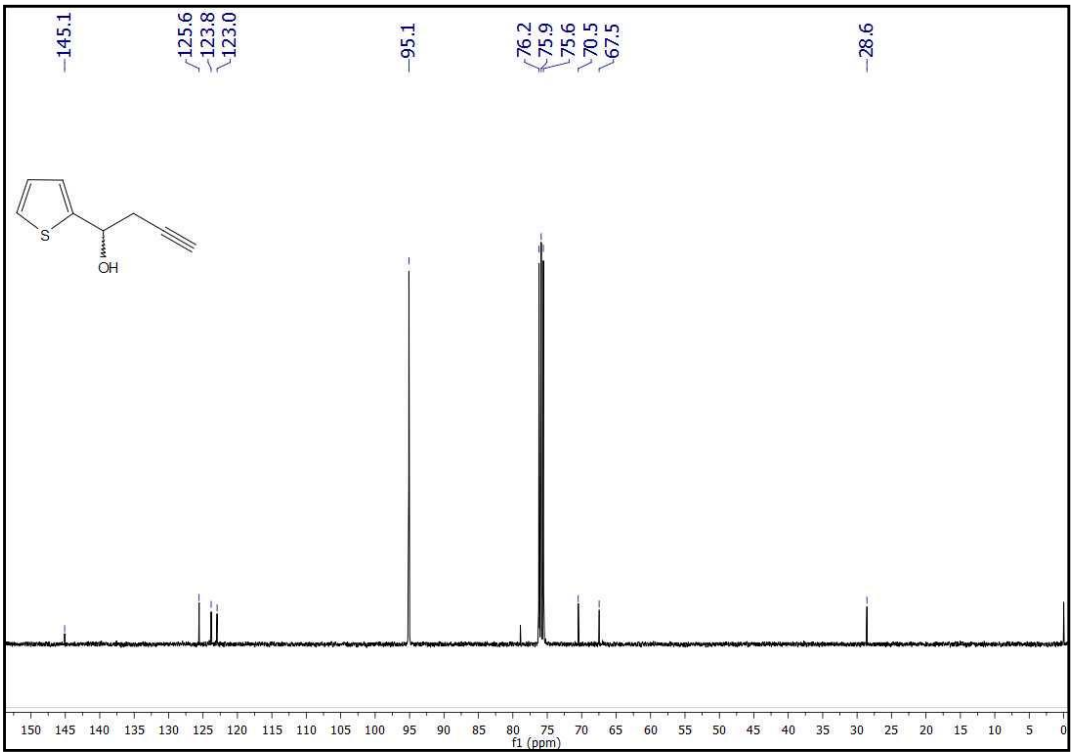

Figure A8. ^{13}C NMR spectrum of *rac*-**25b**

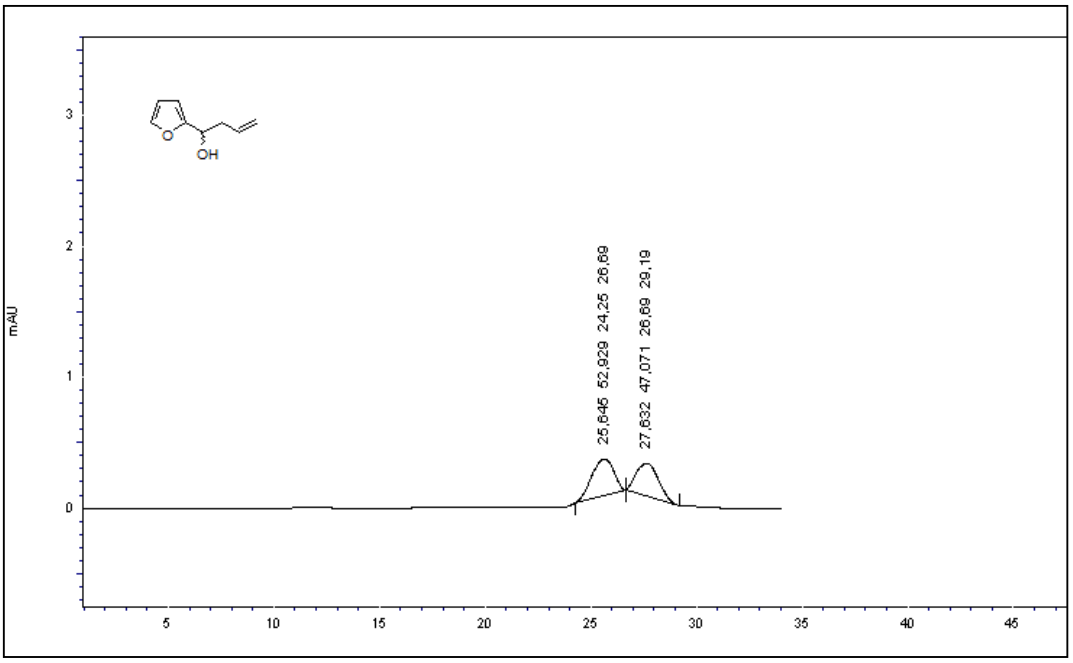

Figure A9. HPLC chromatogram of *rac*-**24a**

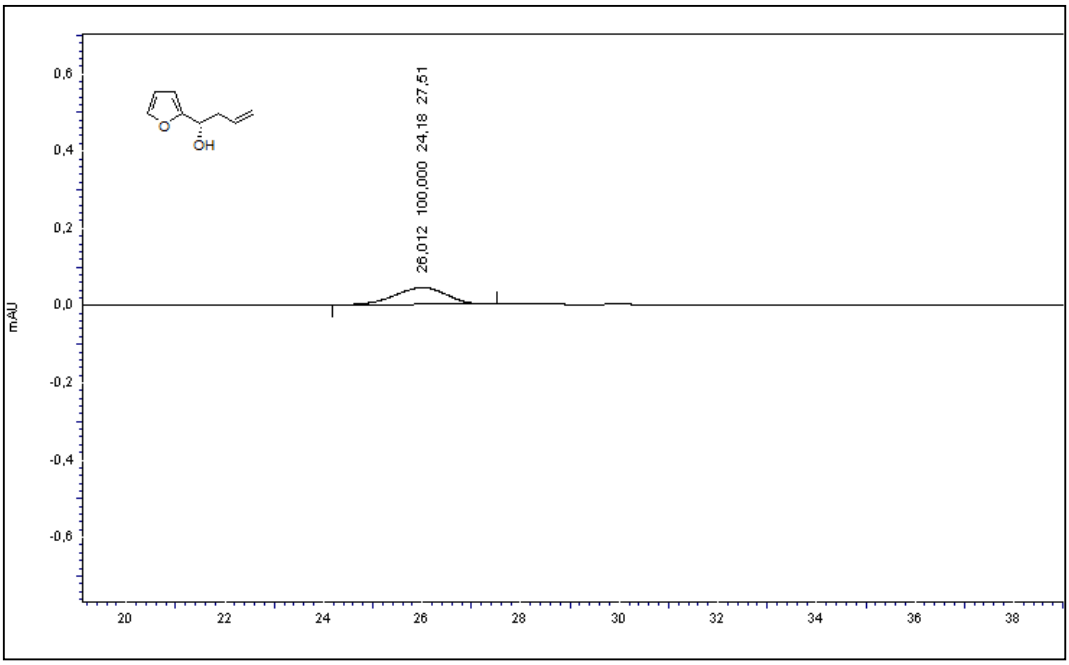

Figure A10.HPLC chromatogram of (*S*)-(-) **24a**

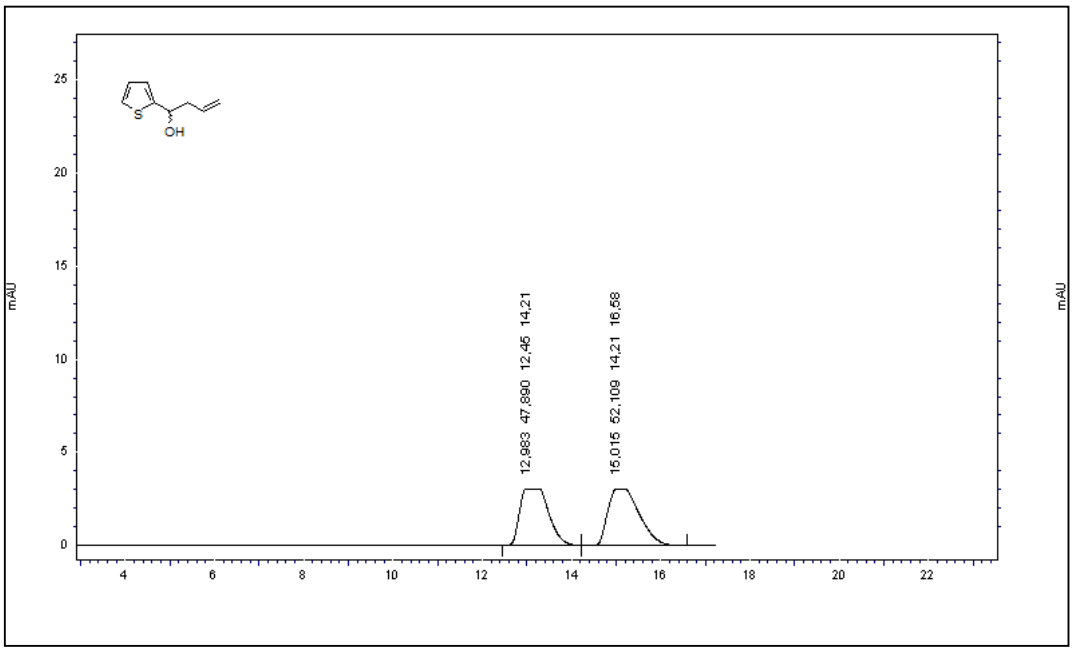

Figure A11. HPLC chromatogram of *rac*-**24b**

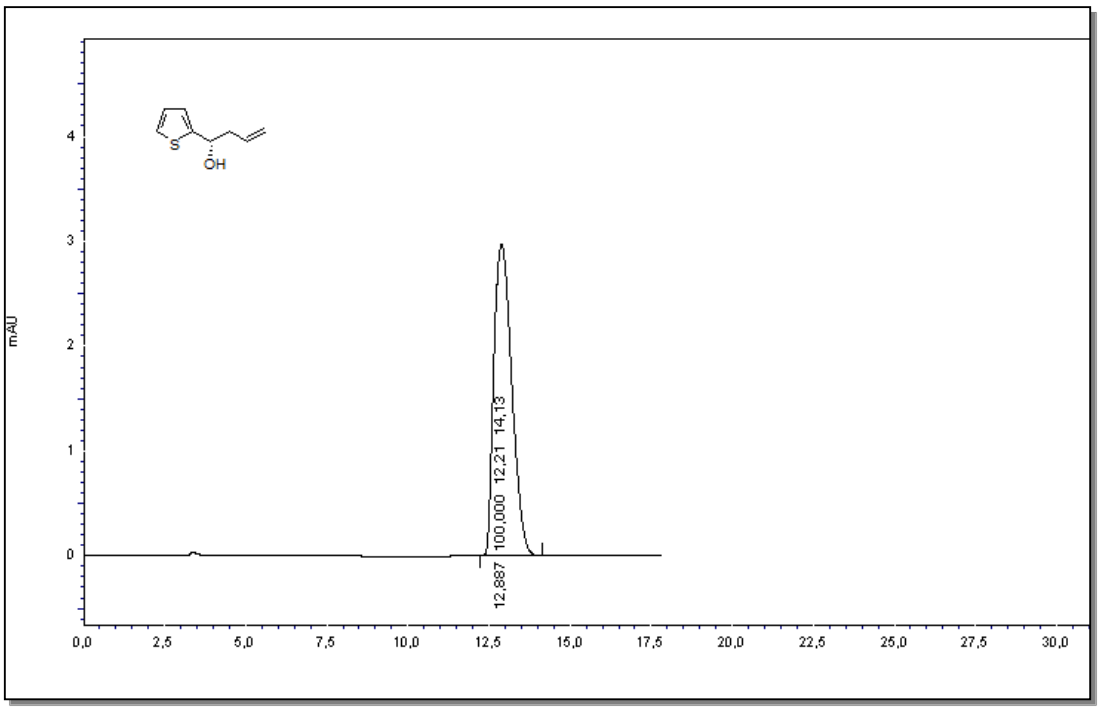

Figure A12. HPLC chromatogram (*S*)-(-)-**24b**

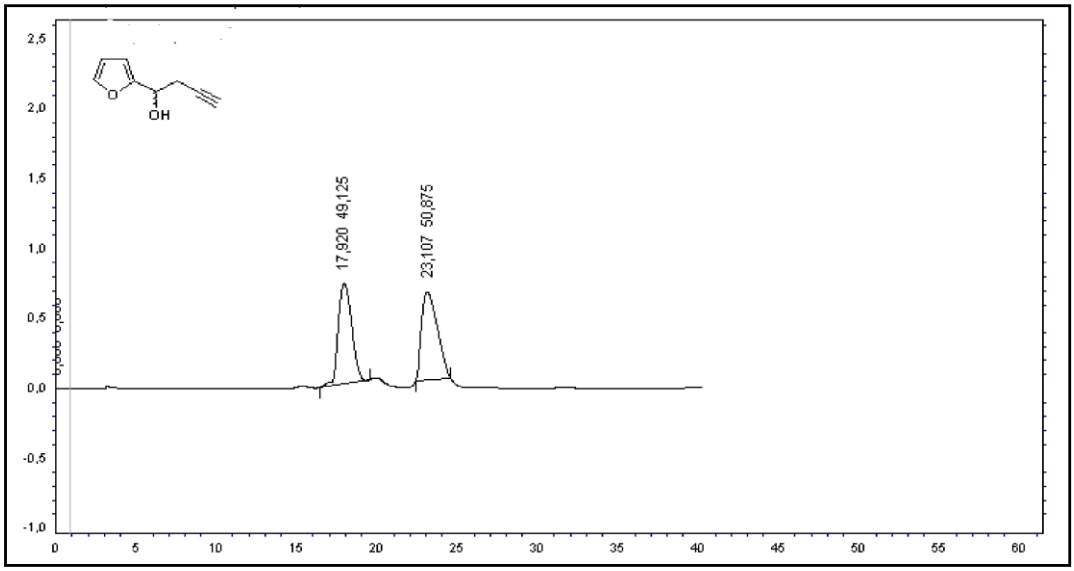

Figure A13. HPLC chromatogram of *rac*-**25a**

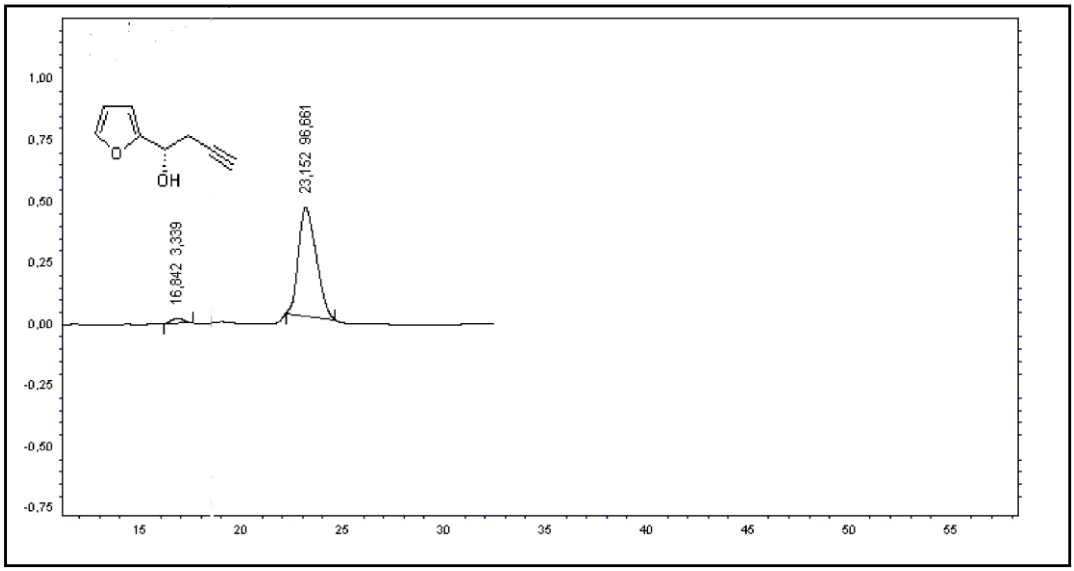

Figure A14. HPLC chromatogram of (*S*)-(+)-**25a**

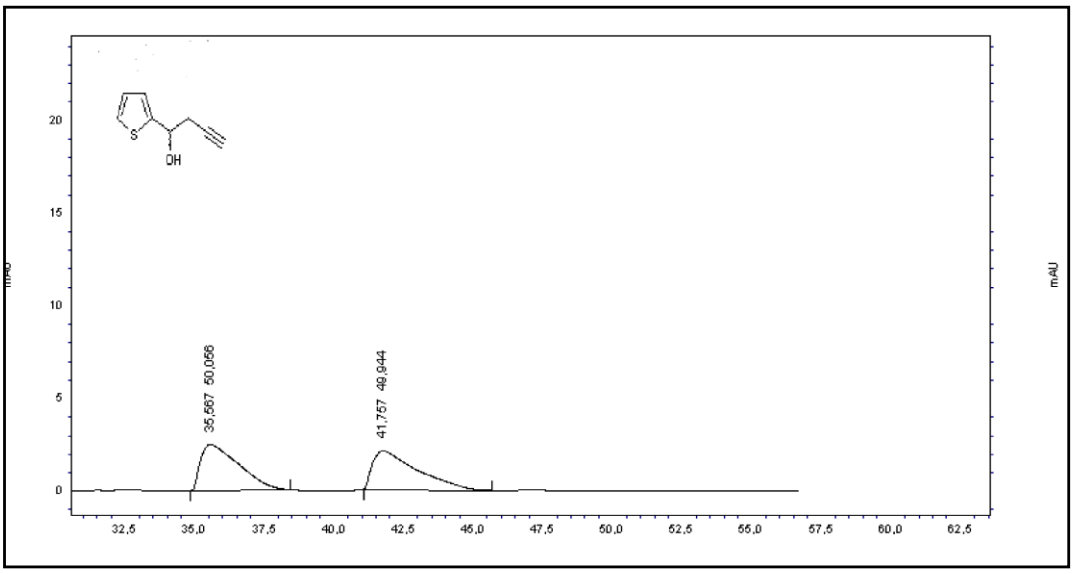

Figure A15. HPLC chromatogram of *rac*-**25b**

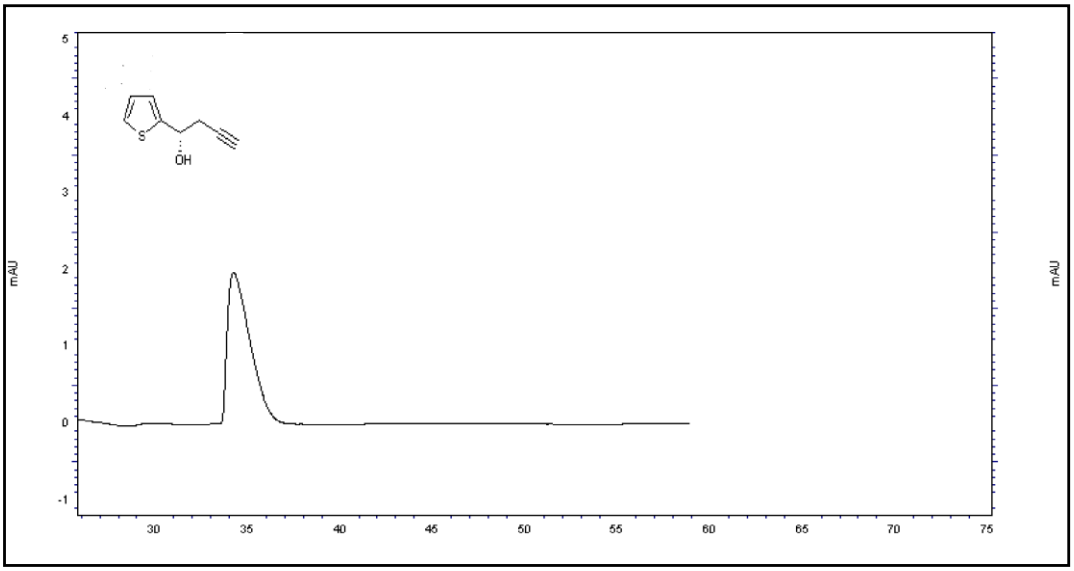

Figure A16. HPLC chromatogram of (*S*)-(+)-**25b**

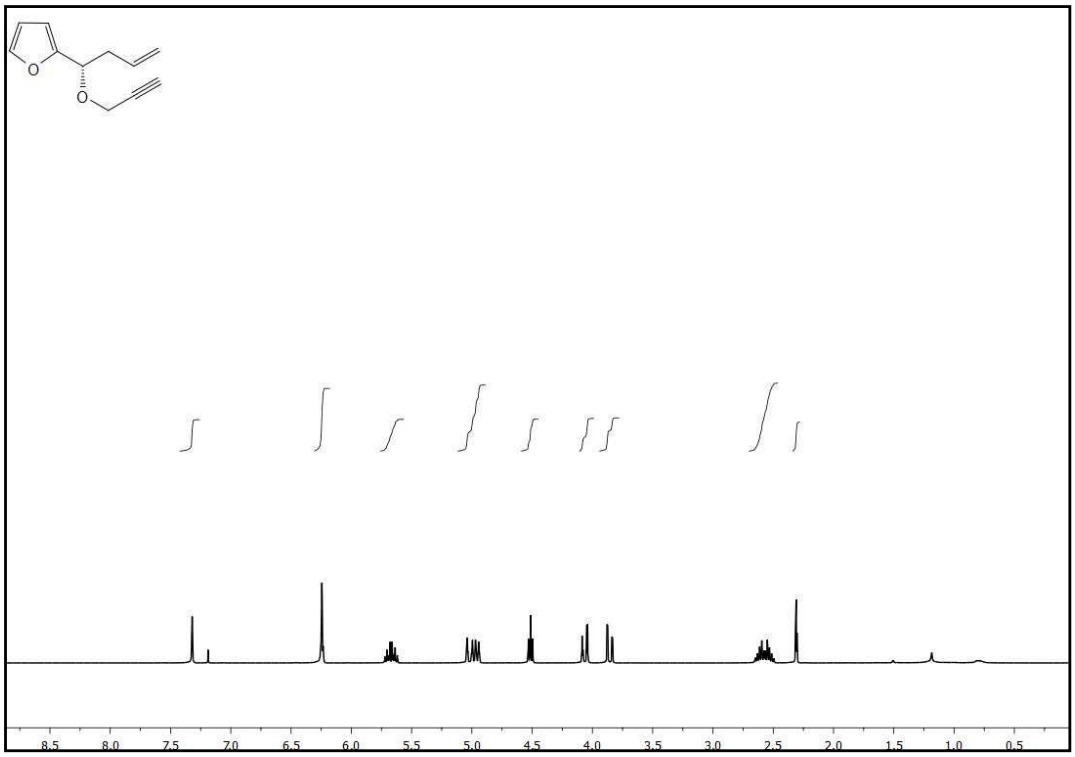

Figure A17. ^{1}H NMR spectrum of (*S*)-(-)-**30a**

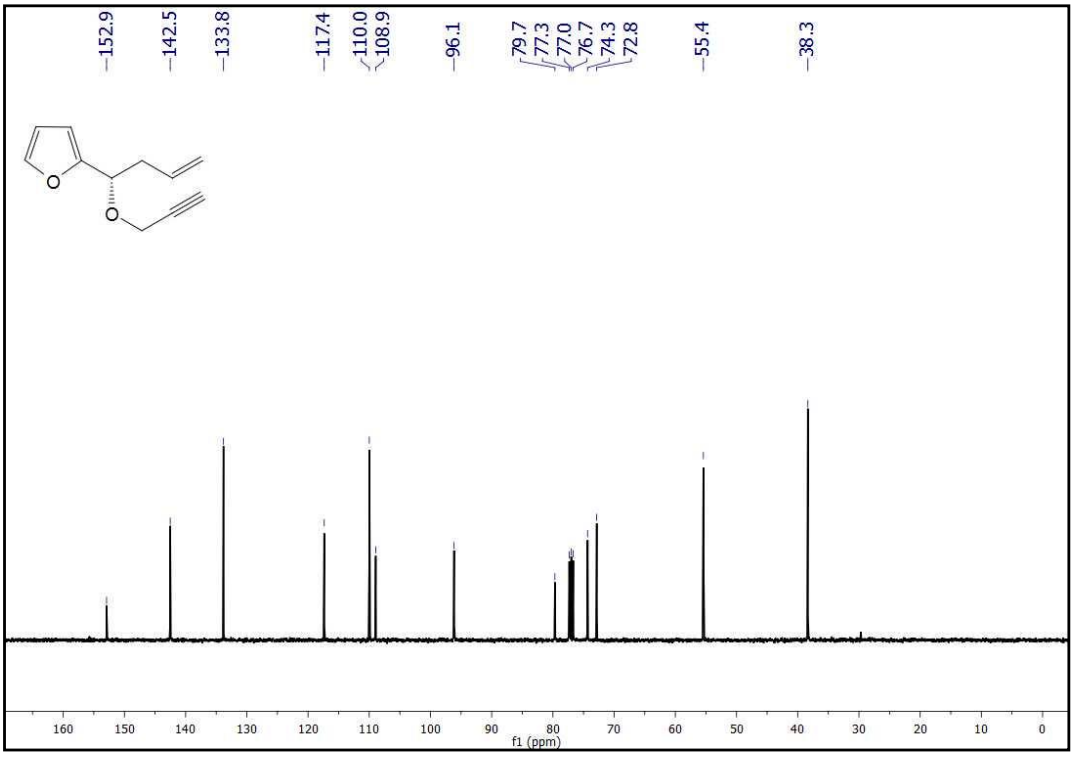

Figure A18. ^{13}C NMR spectrum of (*S*)-(-)-**30a**

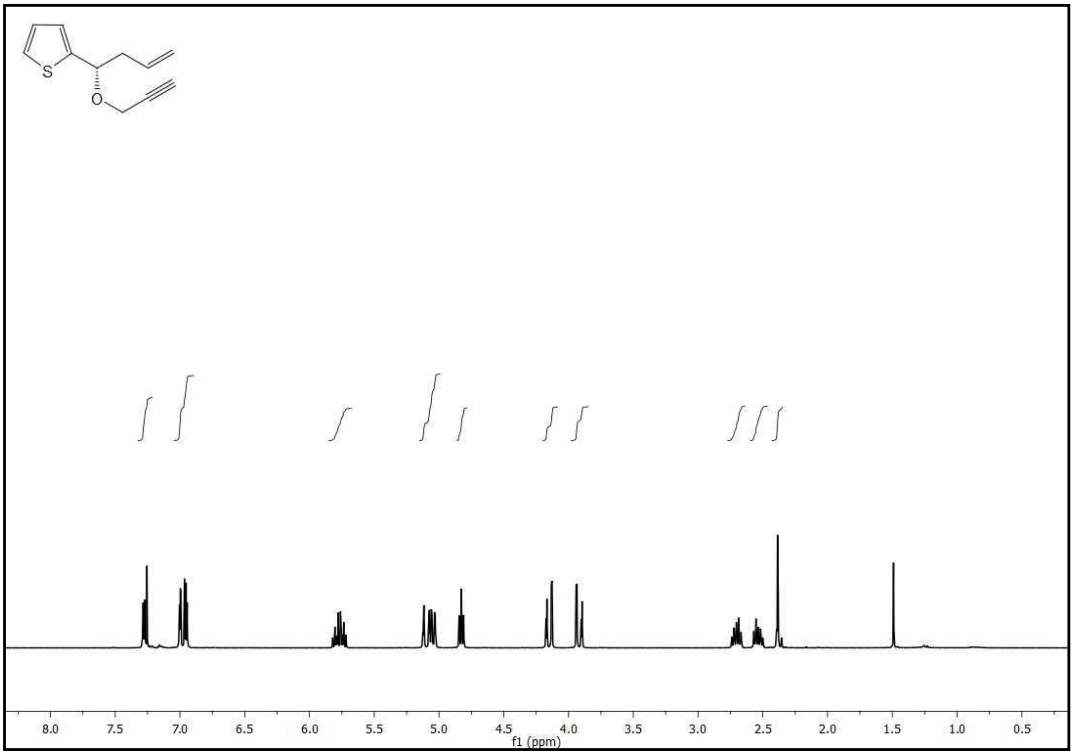

Figure A19. ^{1}H NMR spectrum of (*S*)-(-)-**30b**

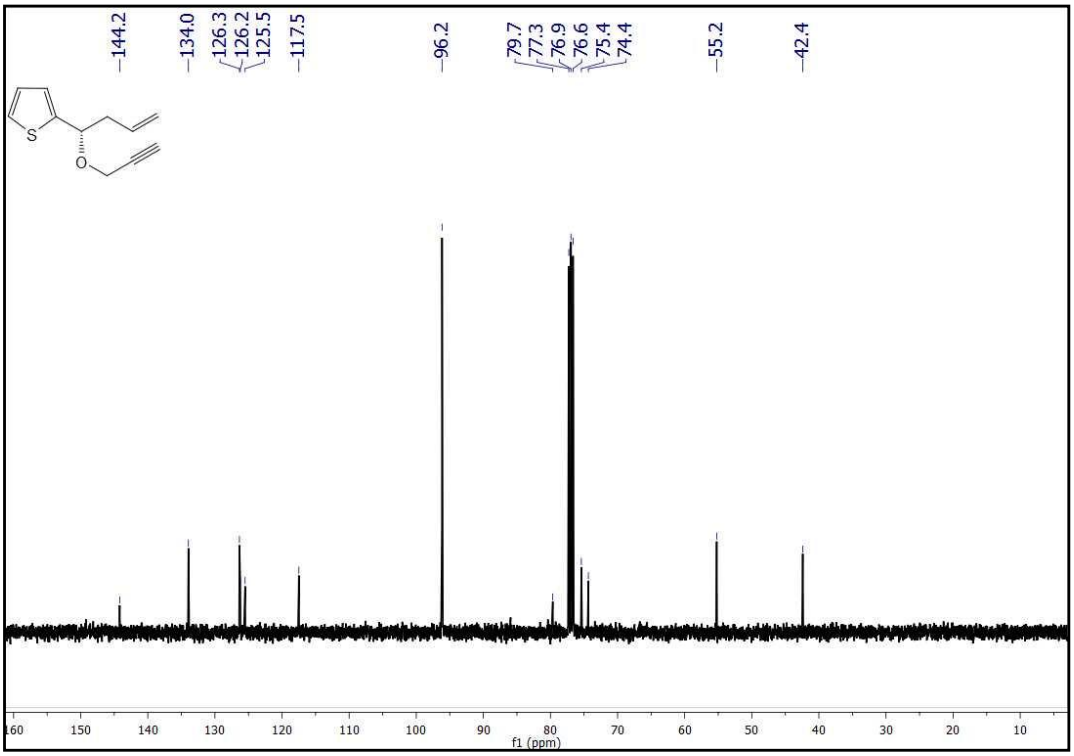

Figure A20. ^{13}C NMR spectrum of (*S*)-(-)-**30b**

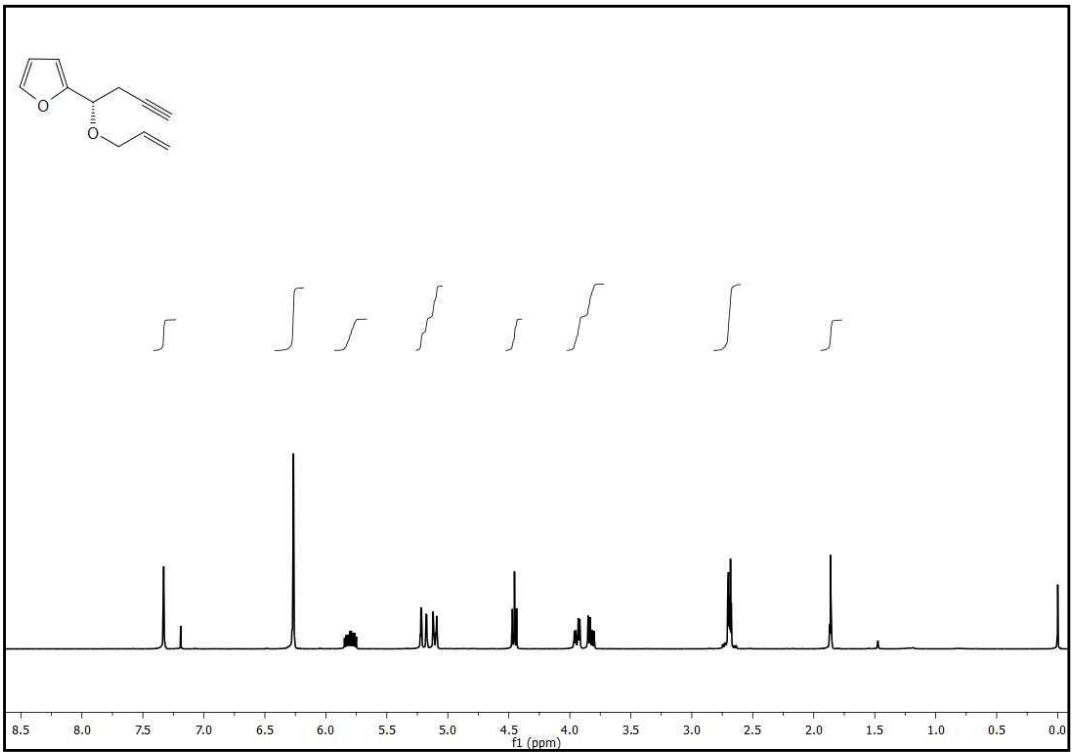

Figure A21. ^{1}H NMR spectrum of (*S*)-(-)-**31a**

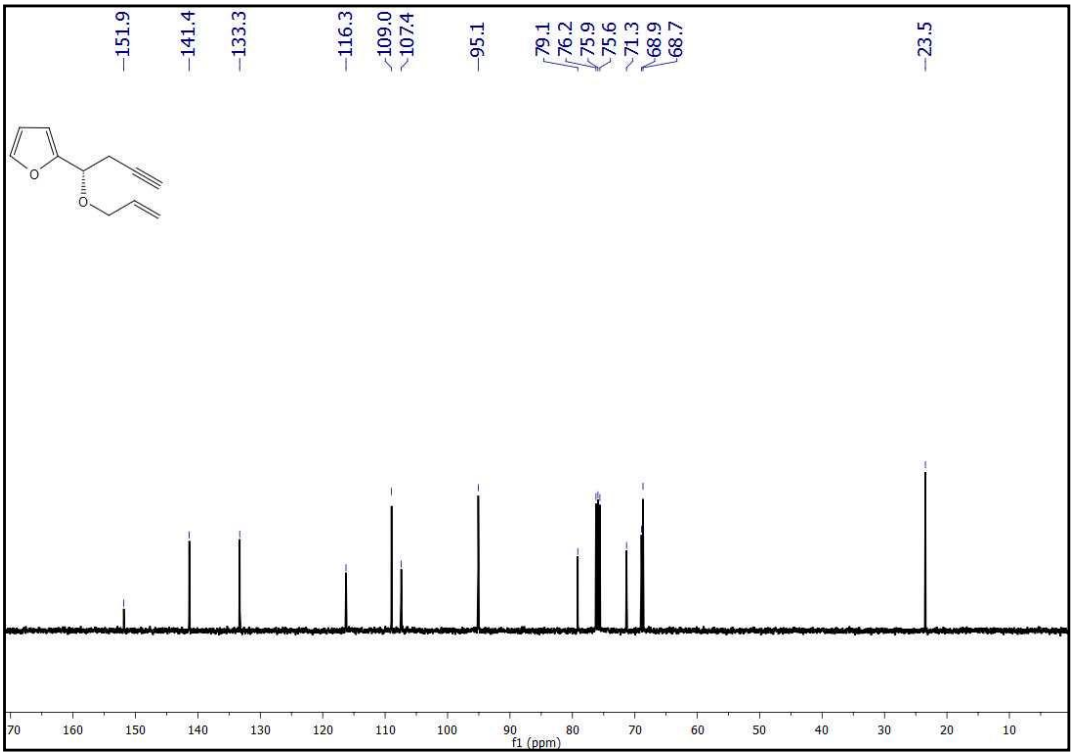

Figure A22. ^{13}C NMR spectrum of (*S*)-(-)-**31a**

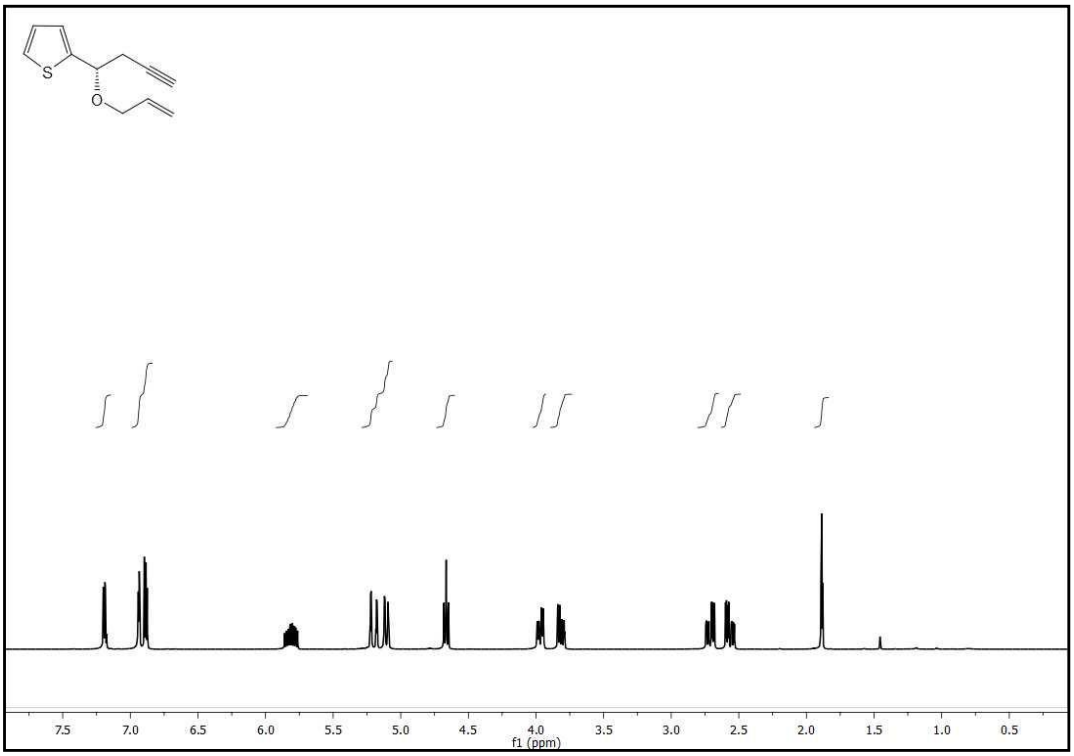

Figure A23. ^{1}H NMR spectrum of (*S*)-(-)-**31b**

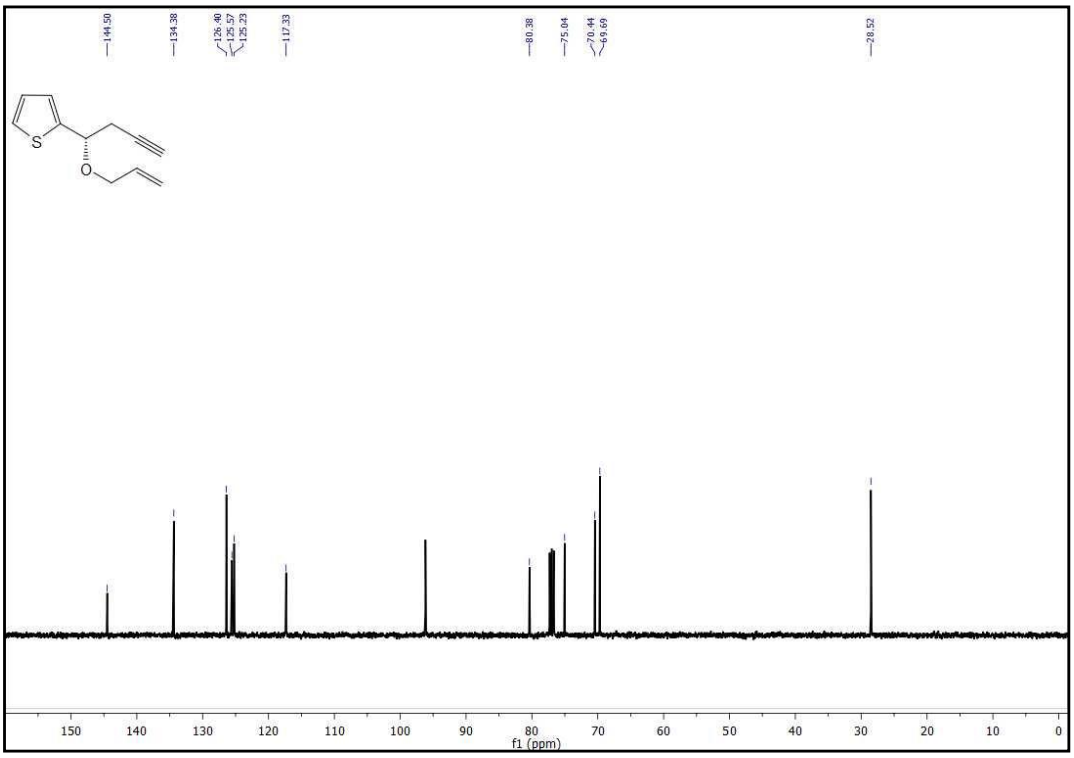

Figure A24. ^{13}C NMR spectrum of (*S*)-(-)-**31b**

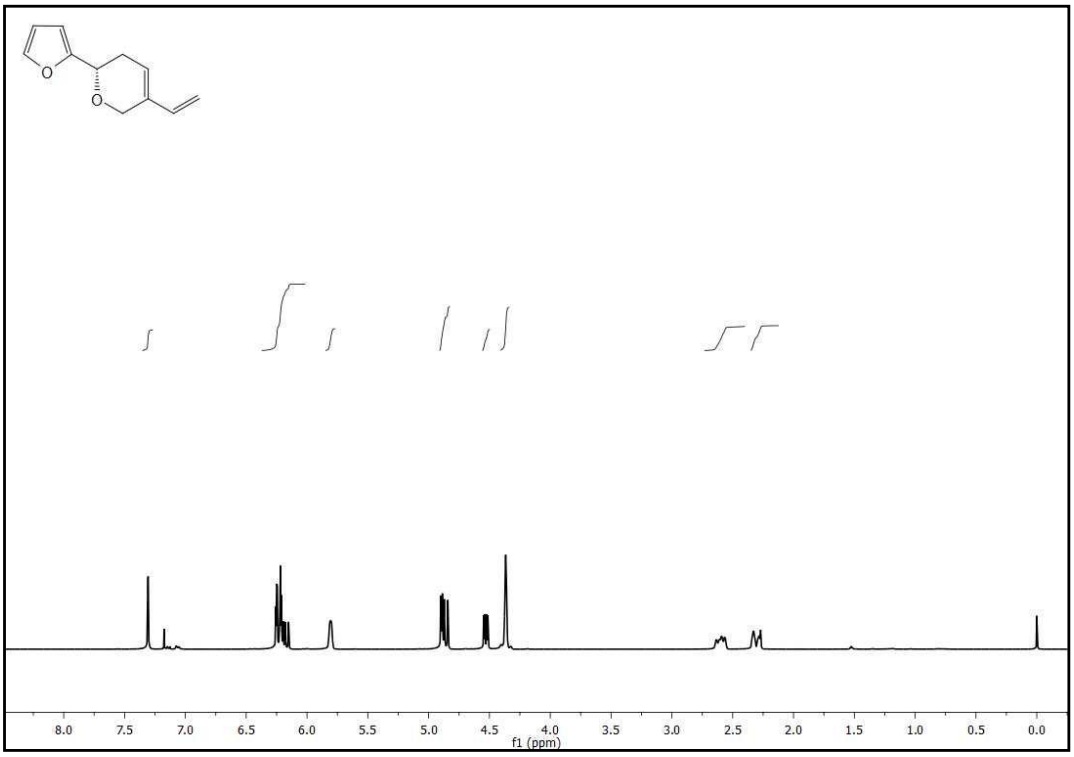

Figure A25. ^{1}H NMR spectrum of (*S*)-(-)-**32a**

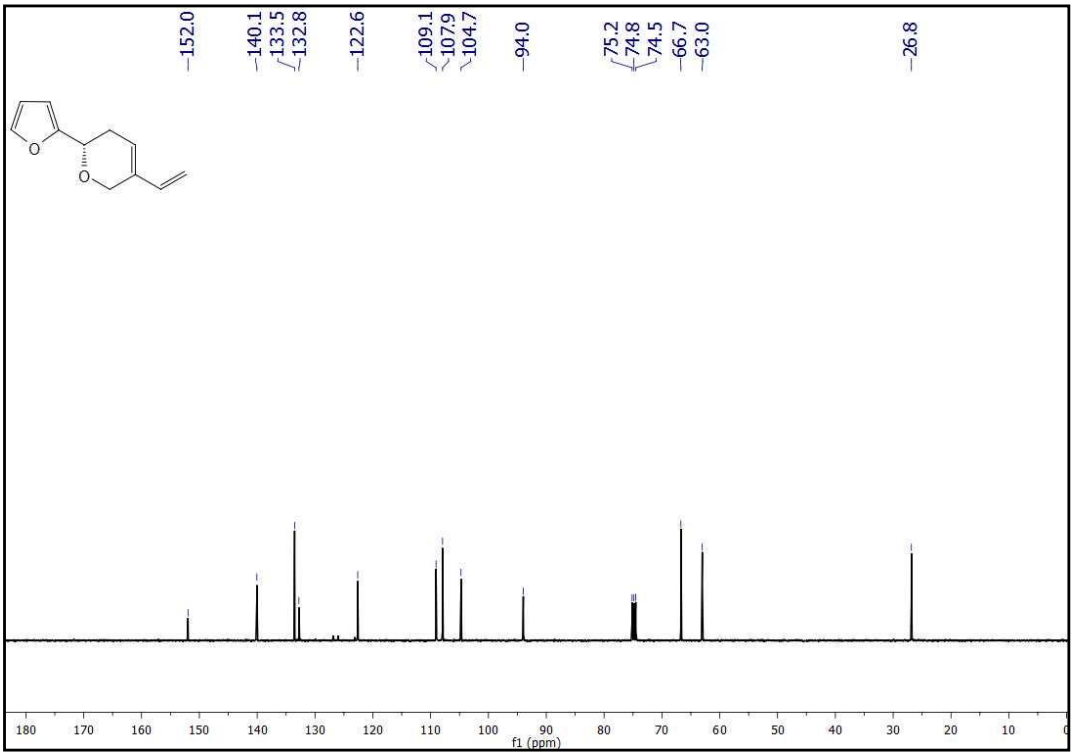

Figure A26. ^{13}C NMR spectrum of (*S*)-(-)-**32a**

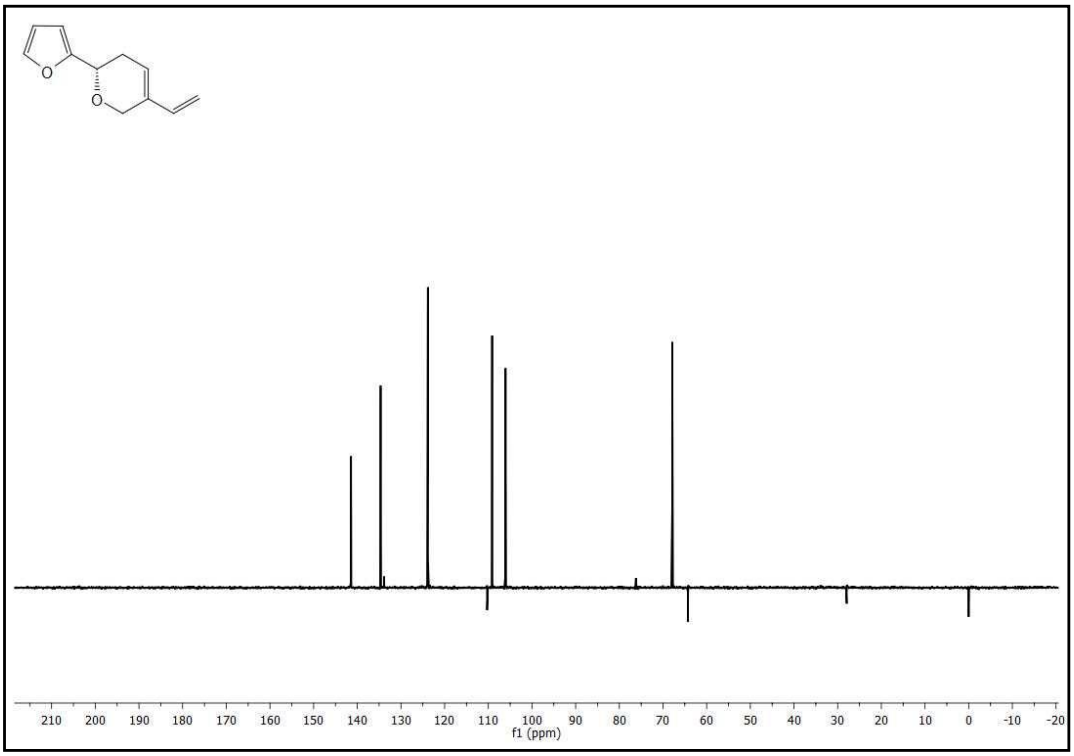

Figure A27. DEPT-90 spectrum of (*S*)-(-)-**32a**

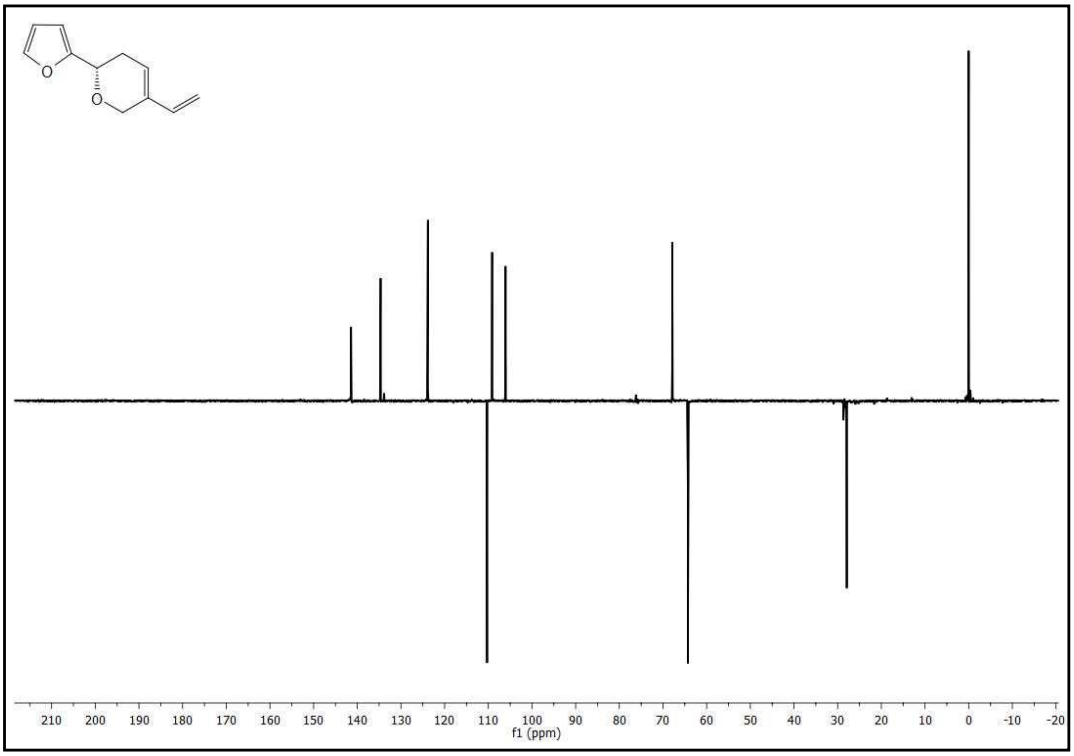

Figure A28. DEPT-135 spectrum of (*S*)-(-)-**32a**

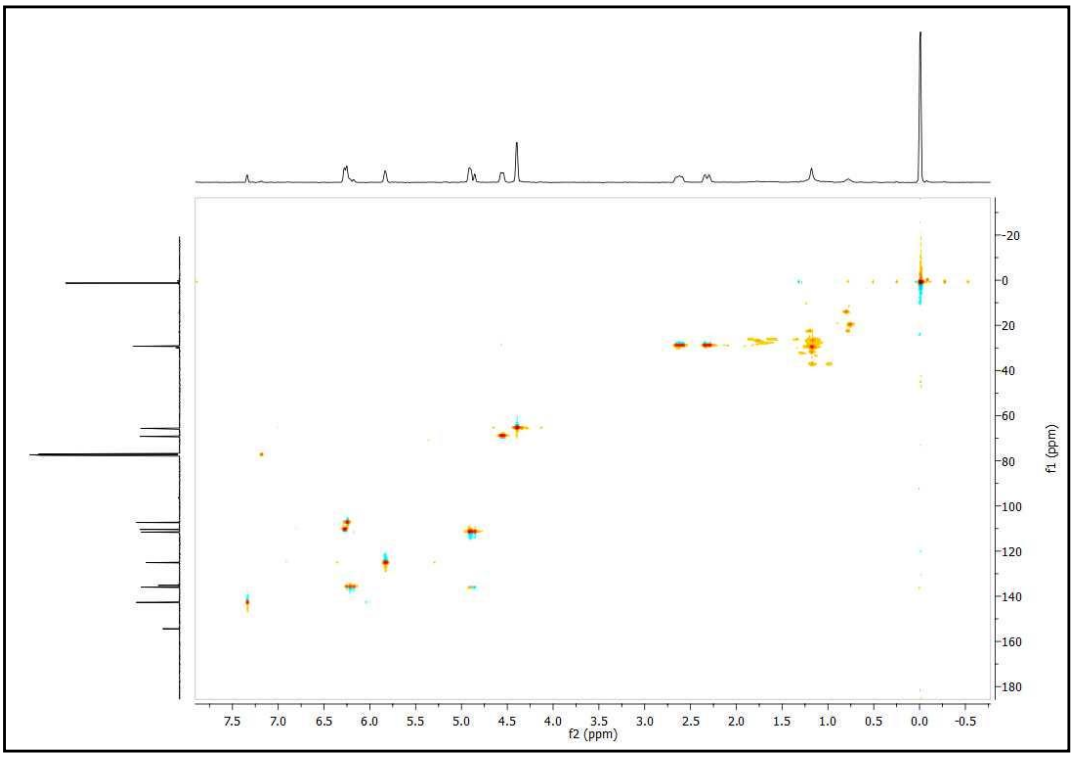

Figure A29. HSQC spectrum of (*S*)-(-)-**32a**

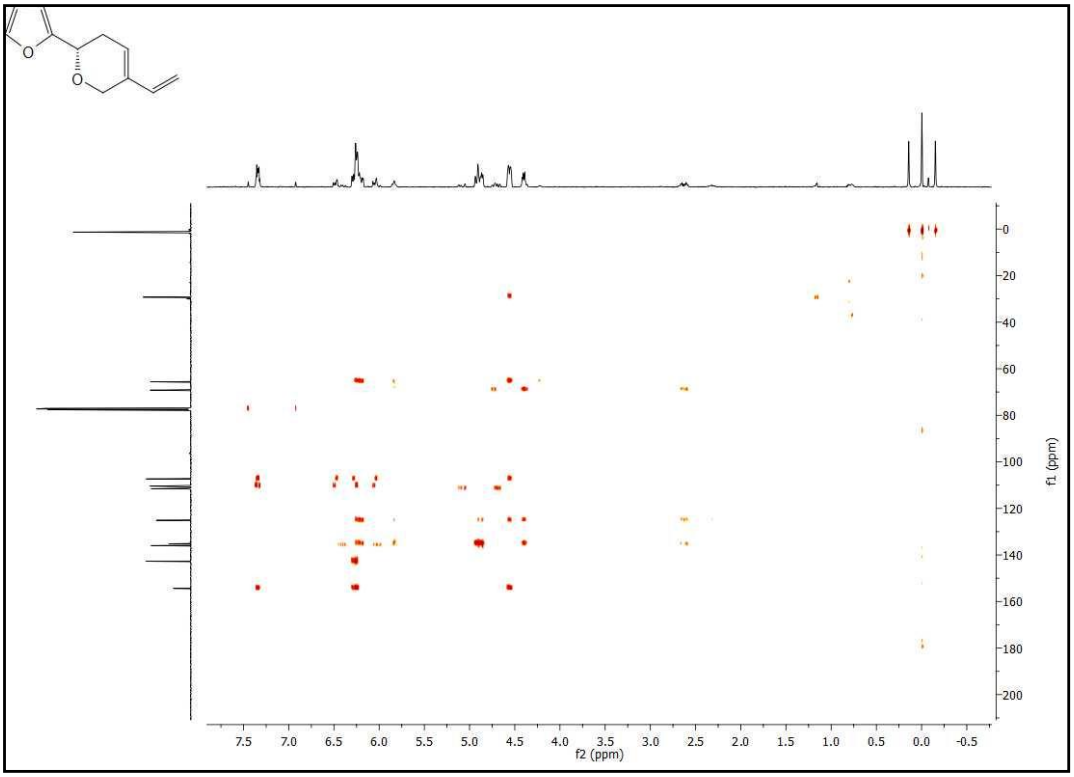

Figure A30. HMBC spectrum of (*S*)-(-)-**32a**

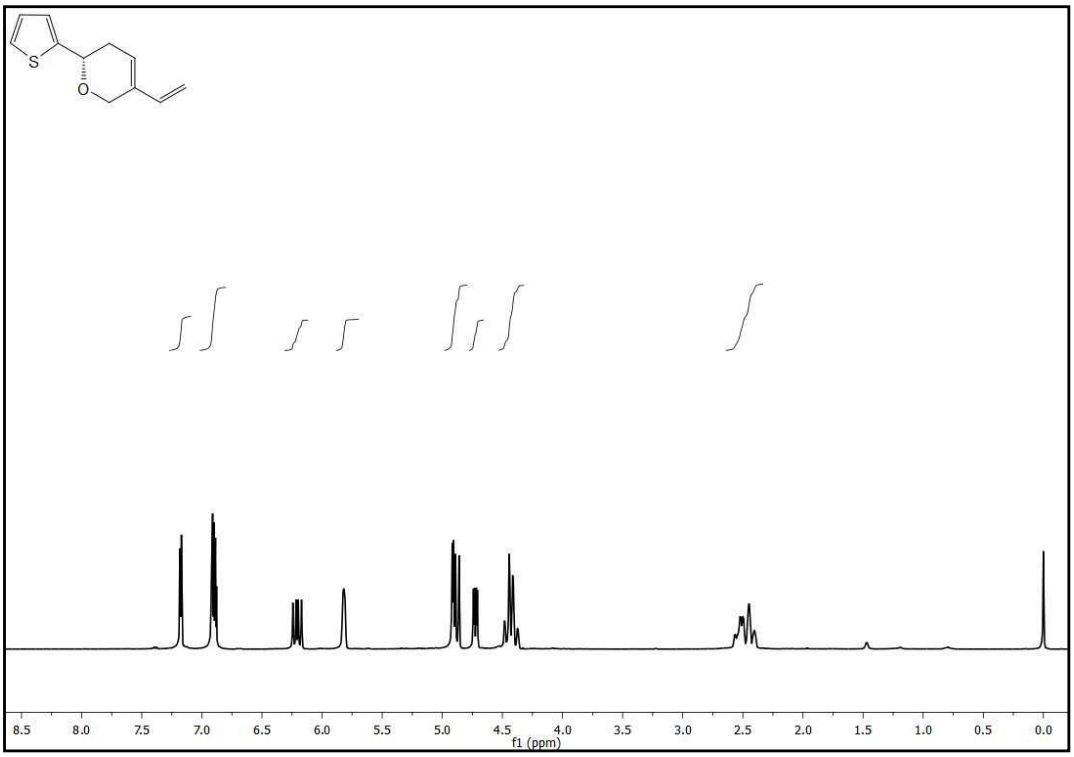

Figure A31. ^{1}H NMR spectrum of (*S*)-(-)-**32b**

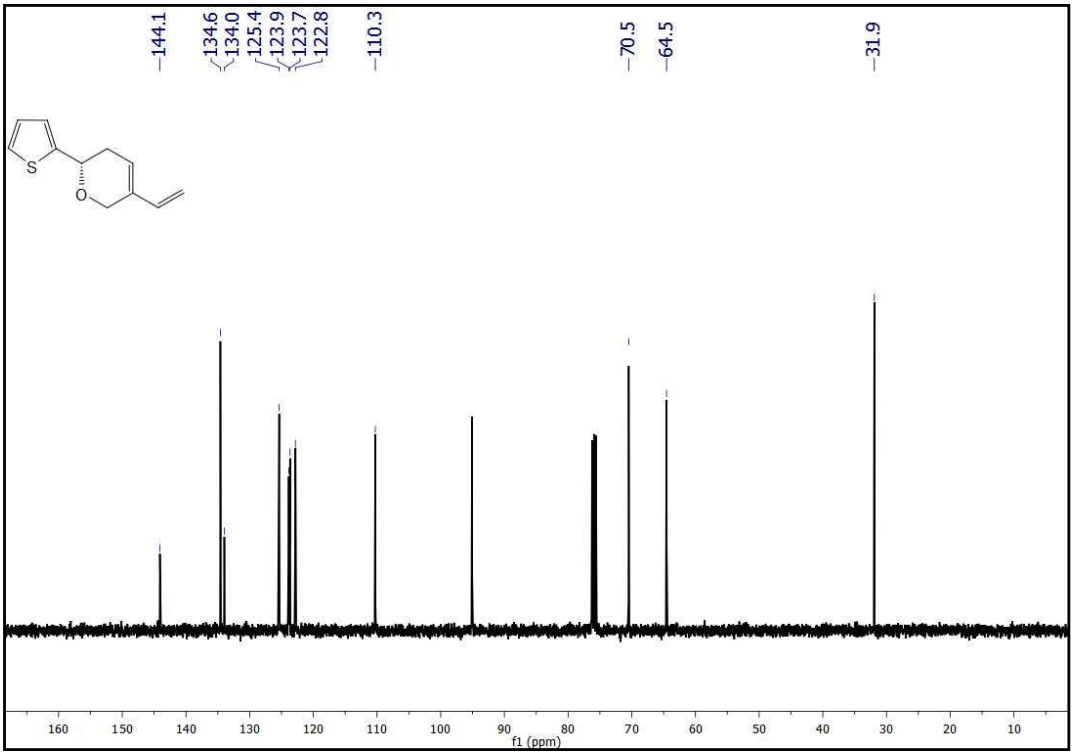

Figure A32. ^{13}C NMR spectrum of (*S*)-(-)-**32b**

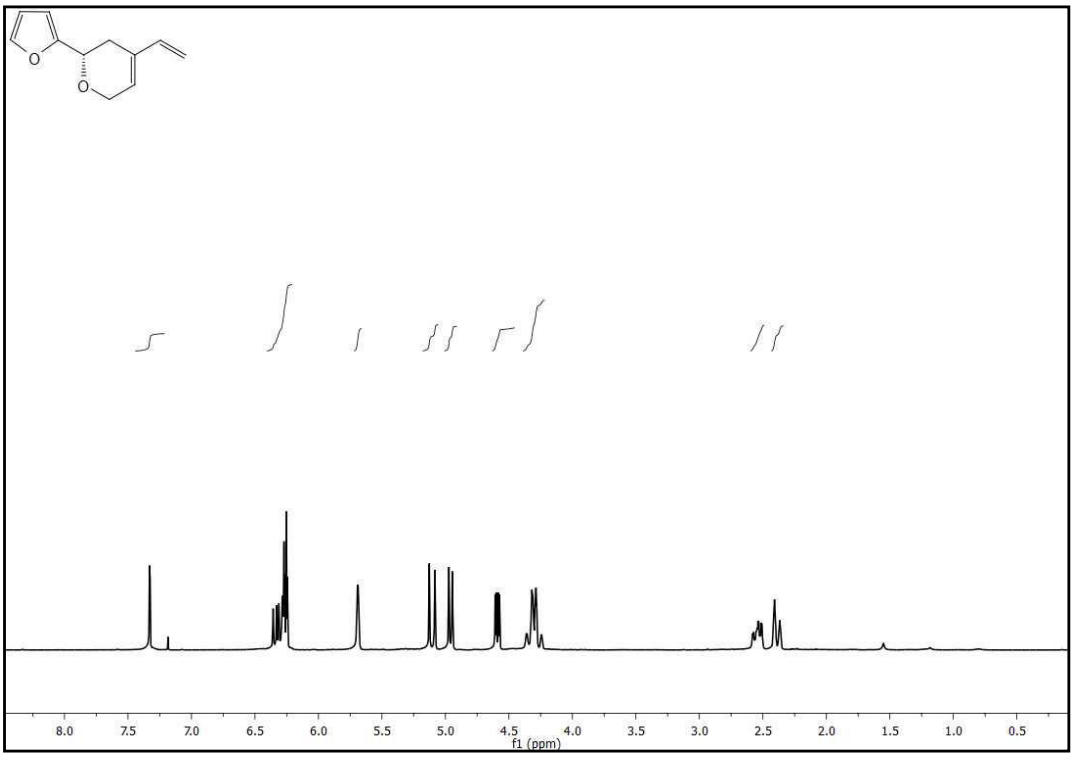

Figure A33. ^{1}H NMR spectrum of (*S*)-(-)-**33a**

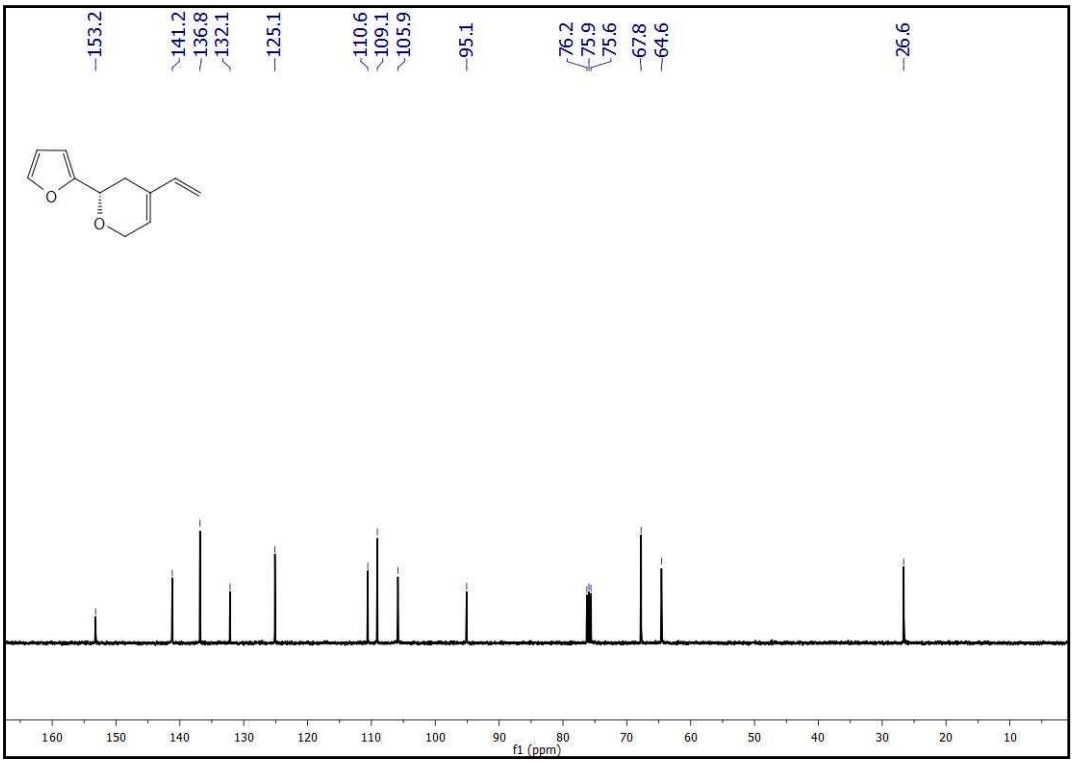

Figure A34. ^{13}C NMR spectrum of (*S*)-(-)-**33a**

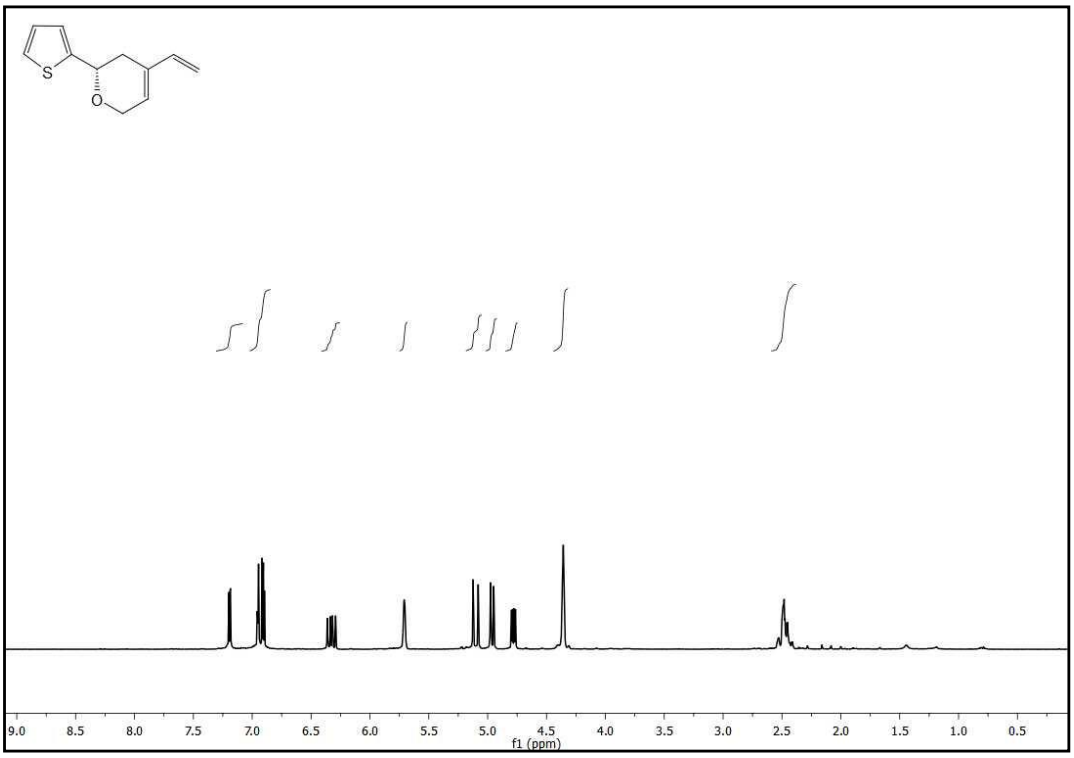

Figure A35. ^{1}H NMR spectrum of (*S*)-(-)-**33b**

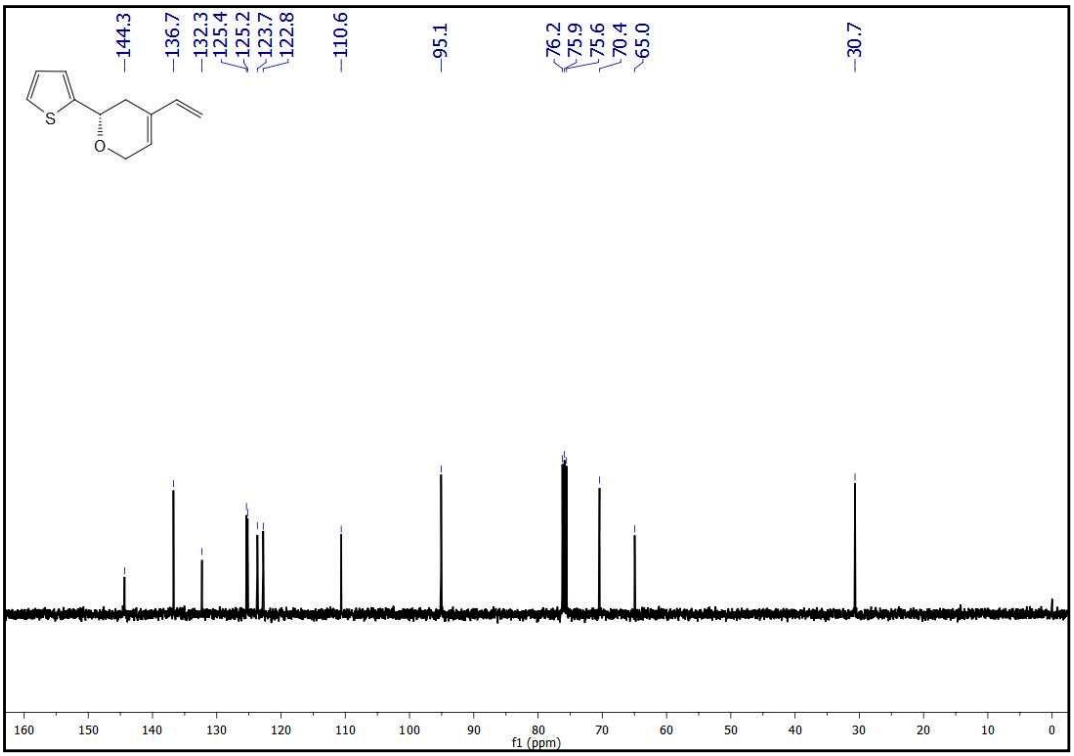

Figure A36. ^{13}C NMR spectrum of (*S*)-(-)-**33a**

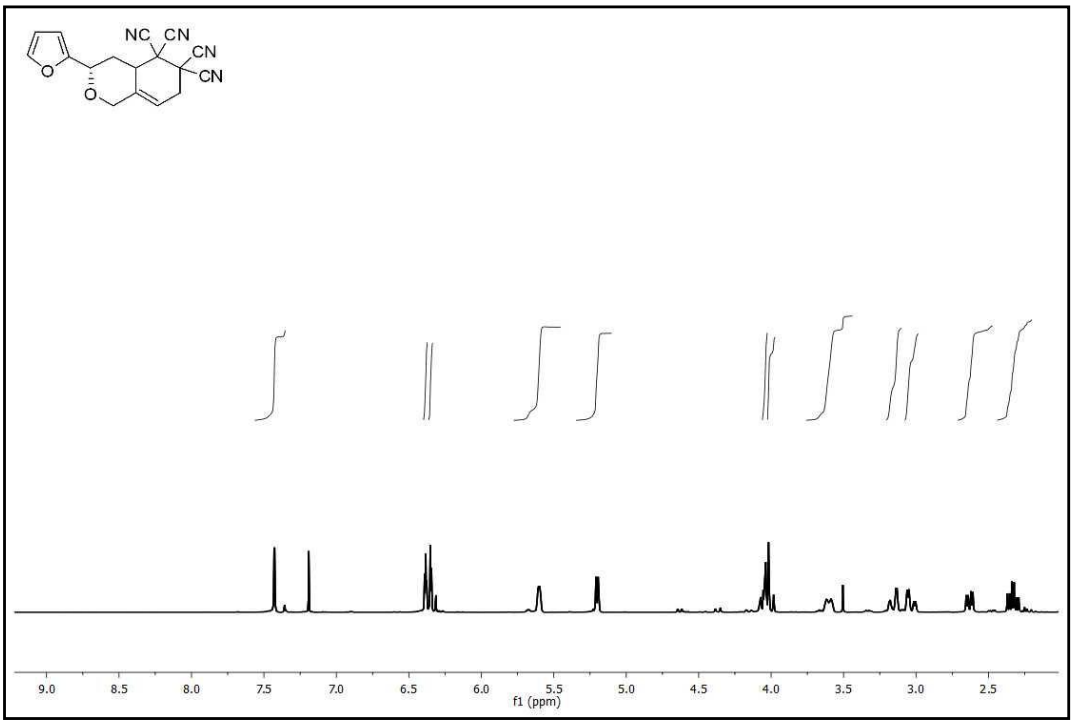

Figure A37. ^{1}H NMR spectrum of (+)-**34**

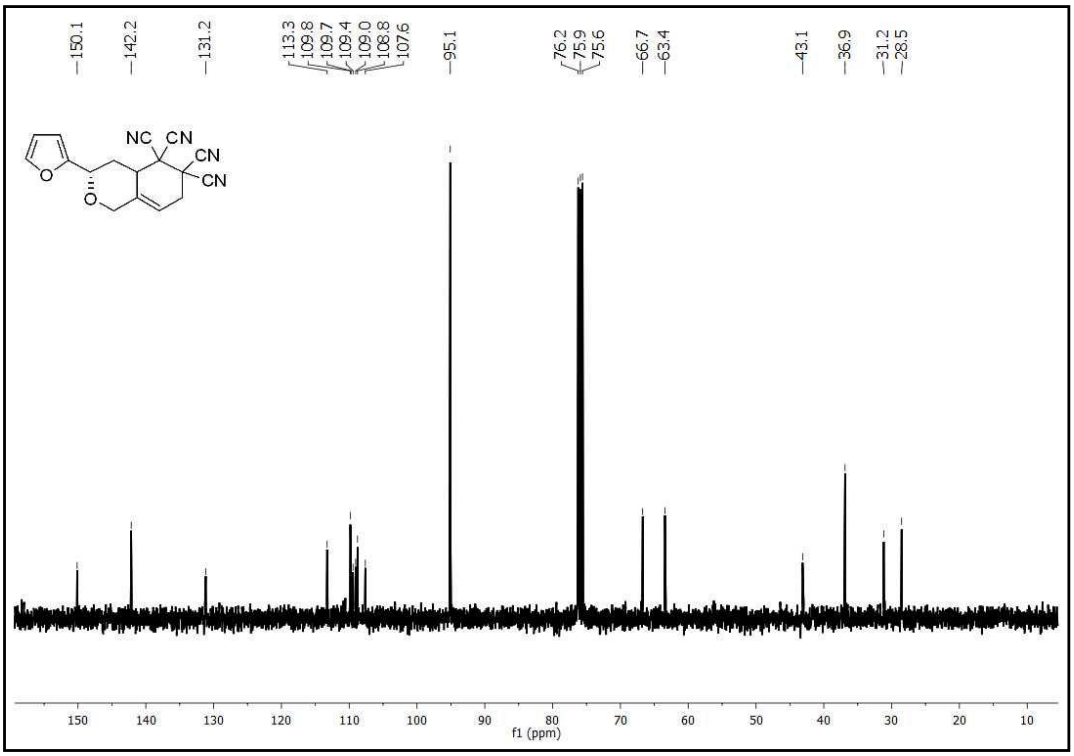

Figure A38. ^{13}C NMR spectrum of (+)-**34**

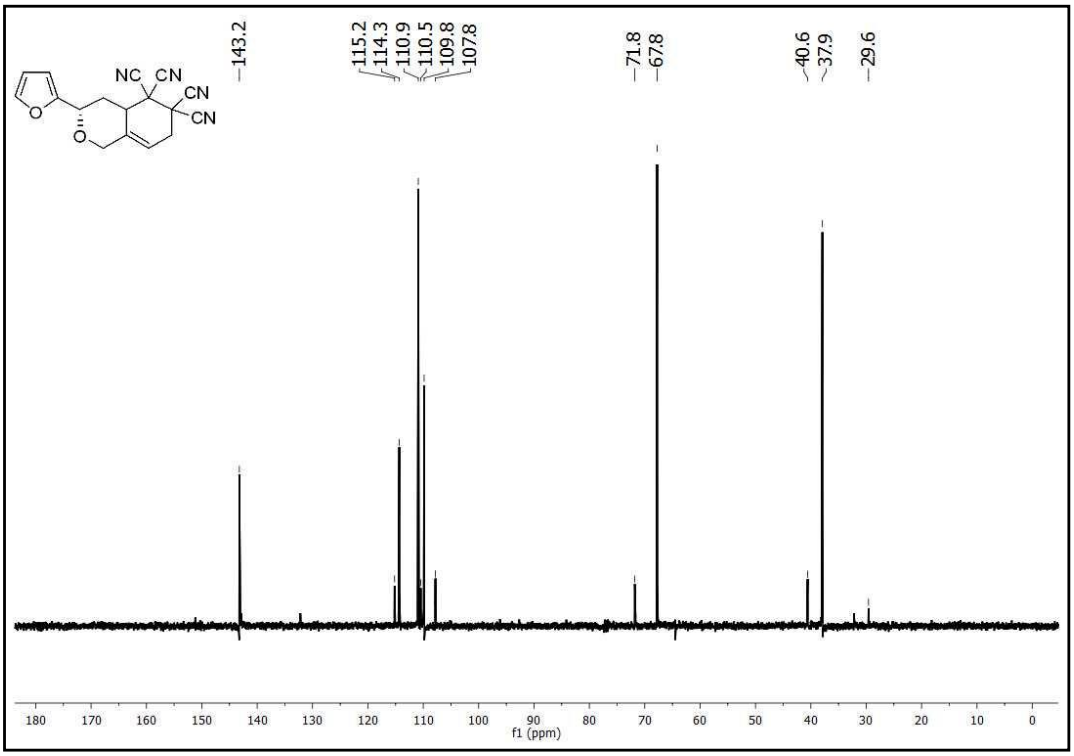

Figure A39. DEPT-90 spectrum of (+)-**34**

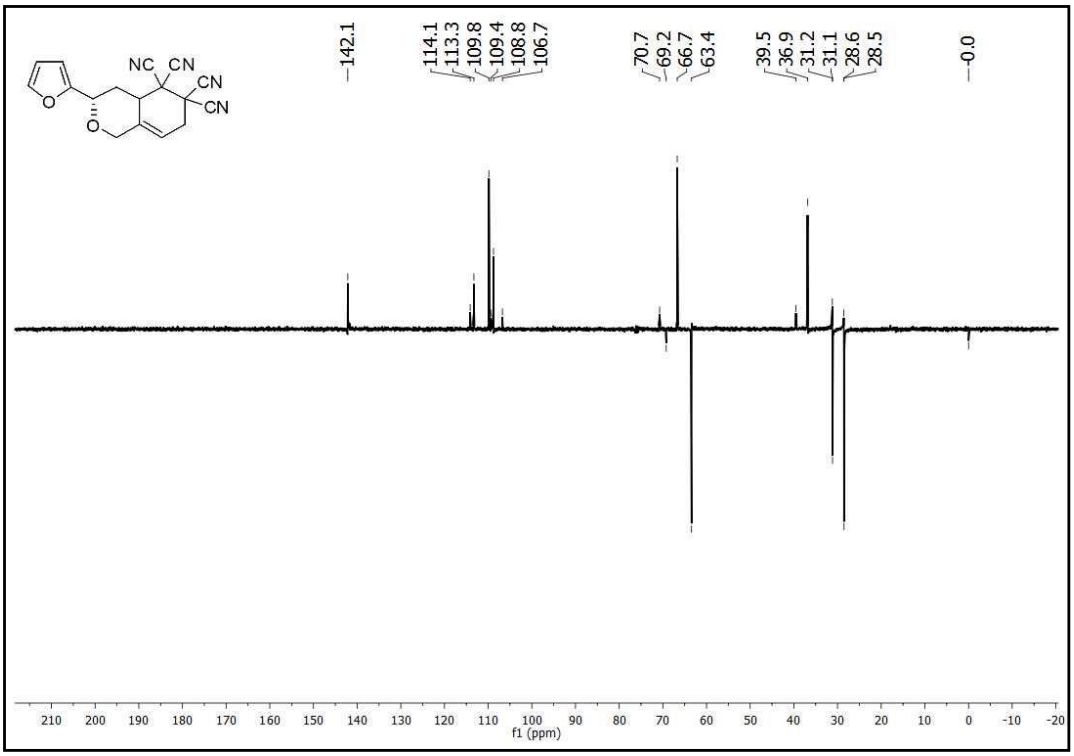

Figure A40. DEPT-135 spectrum of (+)-**34**

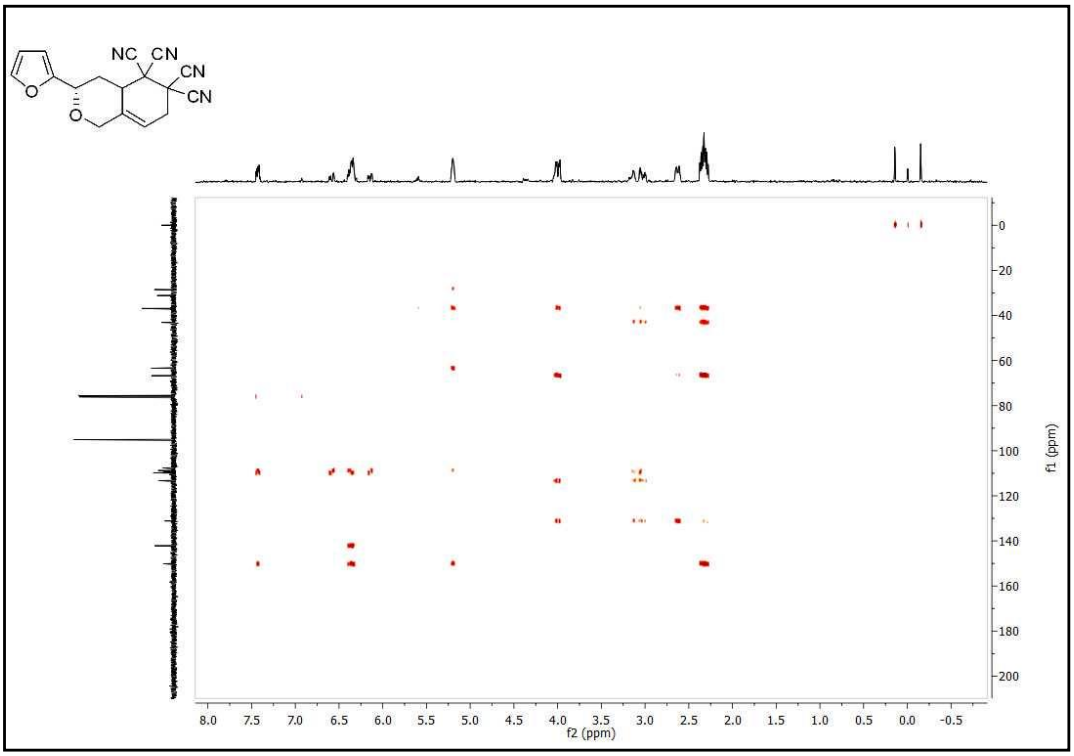

Figure A41. HMBC spectrum of (+)-**34**

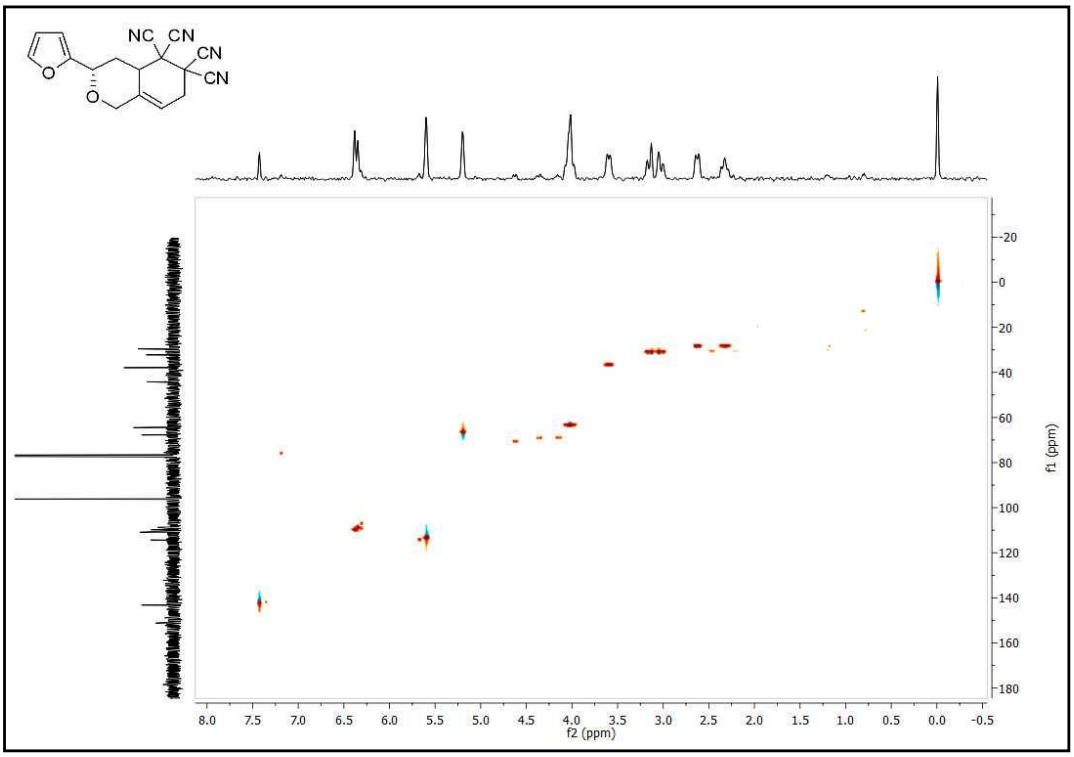

Figure A42. HSQC spectrum of (+)-**34**

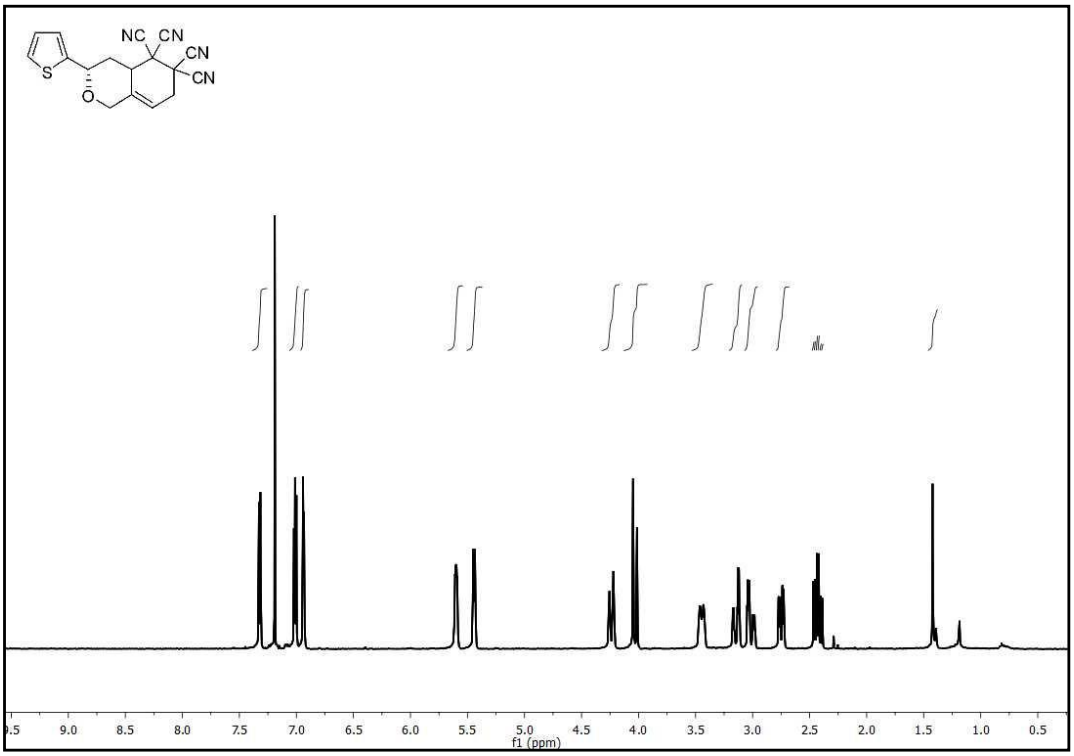

Figure A43. ^{1}H NMR spectrum of (+)-**35**

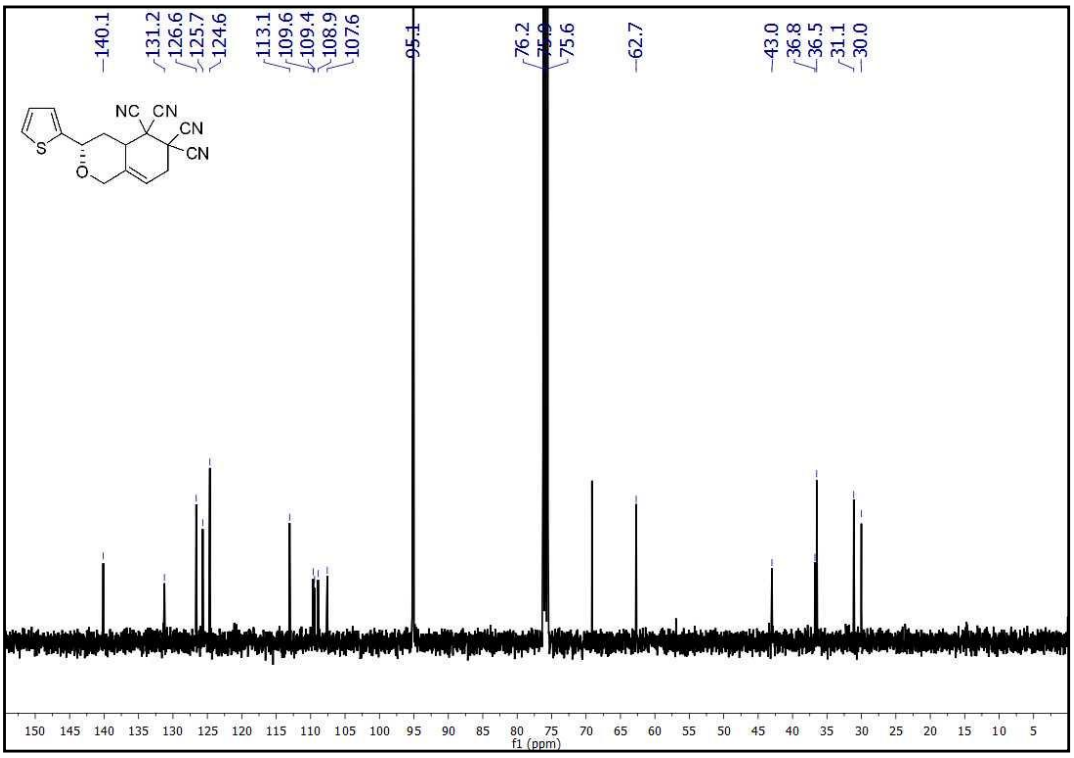

Figure A44. ^{13}C NMR spectrum of (+)-**35**

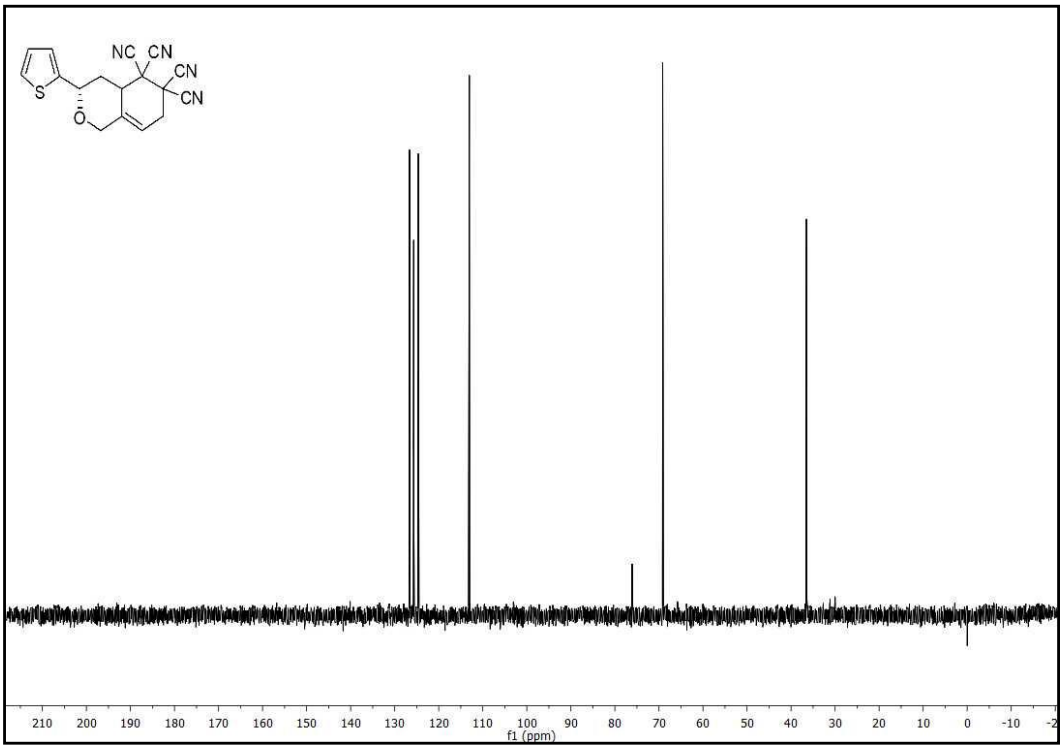

Figure A45. DEPT-90 spectrum of (+)-**35**

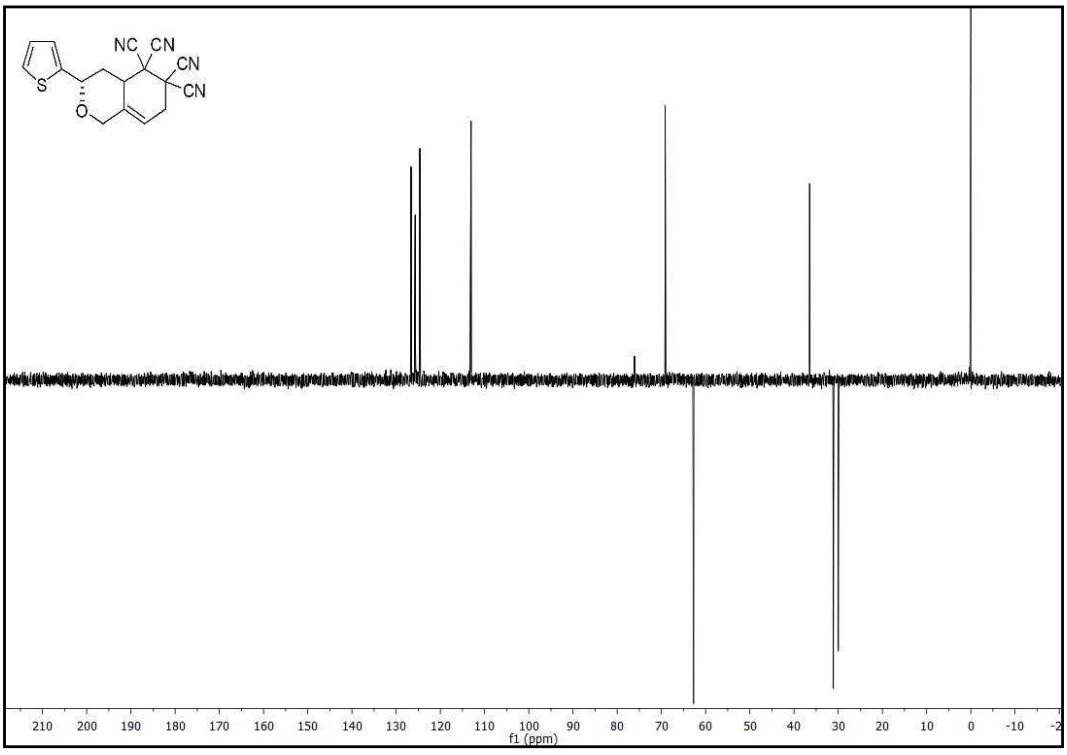

Figure A46. DEPT-135 spectrum of (+)-**35**

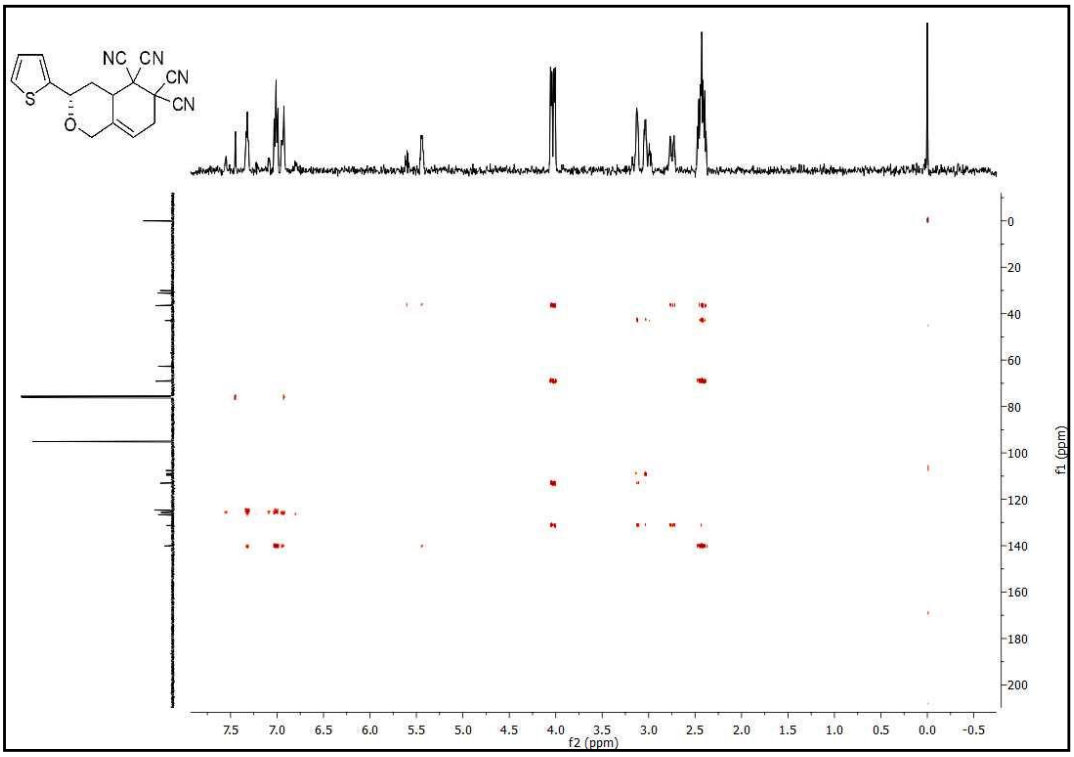

Figure A47. HMBC spectrum of (+)-**35**

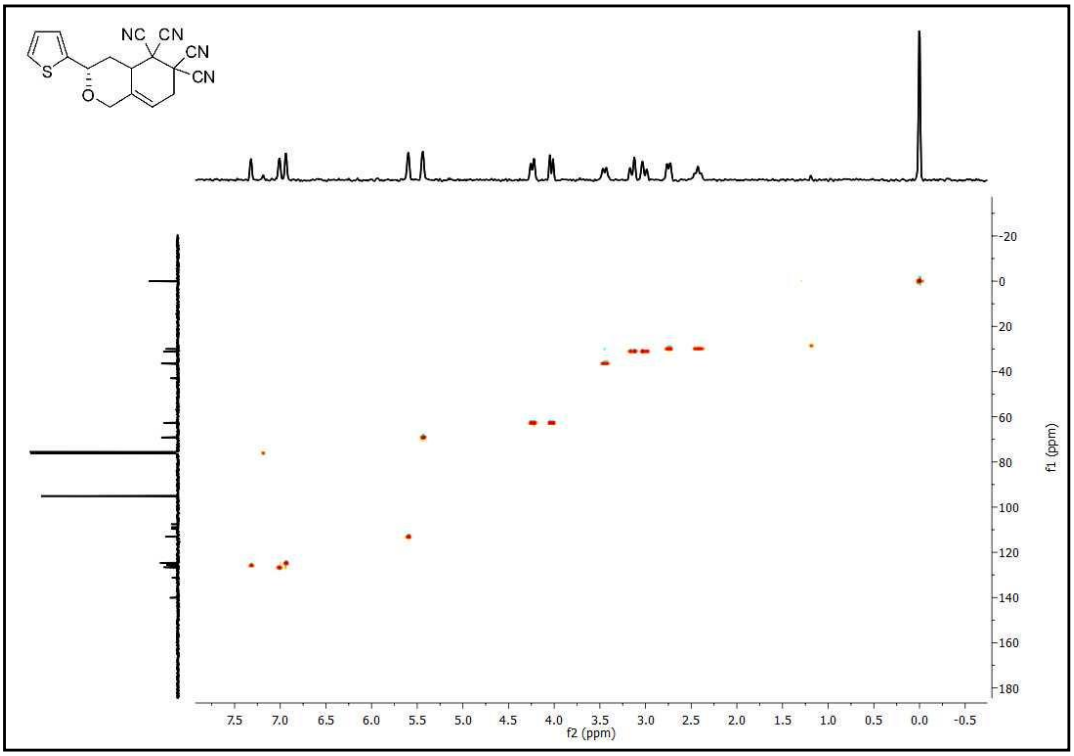

Figure A48. HSQC spectrum of (+)-**35**