CHEMOENZYMATIC SYNTHESIS OF ENANTIOMERICALLY ENRICHED GAMMA AND DELTA LACTONES

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ABSTRACT

CHEMOENZYMATIC SYNTHESIS OF ENANTIOMERICALLY ENRICHED GAMMA AND DELTA LACTONES

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The major subject of this thesis is the synthesis of enantiomerically enriched gamma and delta lactones *via* Ring Closing Metathesis (RCM). Furan and thiophene substituted aldehydes were transformed to the corresponding heteroaryl substituted allylic and homoallylic alcohols by using vinyl and allylmagnesium bromide, respectively and then resultant racemic alcohols were resolved by hydrolase type enzymes (PSC-II, Lipozyme, CAL-B) with high enantiomeric excess values. Since the absolute configuration of alcohols were known, it was possible to determine the configuration of the synthesized compounds. After the enantiomeric enrichment of the alcohols, subsequent acylation with acryloyl and methacryloyl chloride afforded feasible diene system that was subjected to ring closing metathesis reaction 1st and 2nd generation Grubbs' catalysts were used. These lactones were used to test their biological activities.

Key words: Gamma and delta lactones, ring closing metathesis, Grubbs catalyst

ÖZ

ENANTİYOMERCE ZENGİNLEŞTİRİLMİŞ GAMA VE DELTA LAKTONLARIN KEMOENZİMATİK SENTEZLERİ

Şardan, Melis

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Tezin ana konusu kiral gama ve delta laktonların halka kapamalı metatez yoluyla sentezlenmesidir. Furan ve tiyofen sübtitue aldehitler vinil ve alilmagnezyum bromürle tepkimeye sokularak alil ve homoalil alkol türevleri sentezlenmiştir. Elde edilen rasemik alkoller çeşitli hidrolaz tipi enzimlerle (PSC-II, Lipozyme, CAL-B) yüksek ee değerleriyle enantiyomerce zengin hale getirilmiştir. Alkollerin konfigürasyonları bilindiği için sentezlenen bileşiklerin konfigürasyonuna karar vermek mümkün olmuştur. Enantiyomerce zenginleşmiş alkollerin akriliol ve metakriloil klorür ile asillenmesi sonucu uygun dienler elde edilmiş ve halka kapamalı metatez tepkimesine sokularak hedef gama ve delta laktonlar elde edilmiştir. Metatez tepkimeleri sırasında birinci ve ikinci tip Grubbs katalizörleri kullanılmıştır. Sentezlenen laktonların biyolojik aktivitelerine bakılmıştır.

Anahtar Kelimeler: Gama ve delta laktonlar, halka kapamalı metatez, Grubbs katalizörü

Dedicated to my precious parents and lovely brother Mustafa...

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LIST OF ABBREVIATIONS

CAL-A: Lipase A from *Candida antartica*

CAL-B: Lipase B from *Candida antartica*

CRL: *Candida frugosa* lipase

DCM: Dichloromethane

DPE: Diisopropylether

PSC-II: *Psedomonas cepacia* lipase on ceramics

THF: Tetrohydrofuran

DMSO: Dimethyl sulfoxide

DPPH: 1,1-Diphenyl-2-Picrylhydrazyl

TBDPS: Tert-butyldiphenylsilyl

CHAPTER 1

INTRODUCTION

1.1. What is Chirality?

The word *chiral* connotes hand, which comes from Greek word *cheir*. If the molecule is nonsuperimposable on its mirror image, it is called chiral. A chiral molecule does not have any second order symmetry elements (improper), center of symmetry (σ), mirror plane (i), and rotation-reflection axis (S). If, for instance, amino acids (Figure 1) are considered, they can exist in two forms which show tetrahedral arrangement as (*S)*-amino acid and (*R*)-amino acid called enantiomers. These two arrangements are mirror images to each other [1].

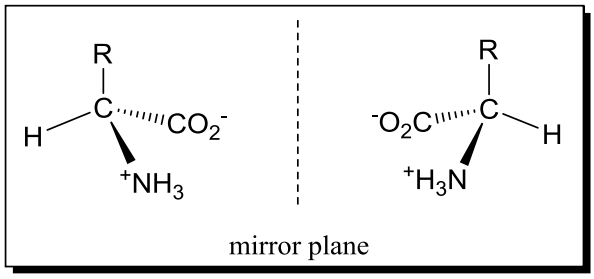


Figure 1. Chirality of the amino acid is represented with models of its two forms. Two enantiomers of the amino acid.

Enantiomers have both distinct and identical properties. While they possess the same melting and boiling point, refraction index, solubility, reaction rate, IR and NMR spectra, these enantiomeric pairs show different behaviour towards plane-polarized light. Although both rotate the plane-polarized monochromatic light

while the light passes through them, the difference comes from the direction of the rotation (clockwise or counterclockwise direction). Therefore, they are called optically active compounds.

1.2. The Significance of the Chirality

"The world is chiral"[2]. Most of the natural products are found as a single stereoisomer. Proteins, enzymes, DNA, RNA, and nucleic acids exist as only one chiral form. Since a molecule has two forms in the universe, it may show distinct interaction with the receptor and it results in observing various activities [3]. Enantiomers have also dissimilar odor, taste, pharmocological effects, etc. which have been concluded after their interaction with the human body [4]. For example, aspartame (Figure 2) is sold as a sweetener. Some interactions occur between a sweetener and the mouth. However, the interaction takes place if the isomer is derived from the *L*-amino acids [5].

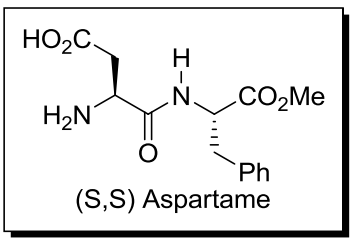


Figure 2. Structure of the aspartame.

Especially, pharmaceuticals are figuring large in human health due to their chirality. Most of benefical drugs are sold as a single enantiomeric forms because of the higher efficiency than its mirror image enantiomer and displaying better fit to its receptor. In addition, it may even be encountered with harmful results with the other enantiomer. For example, one of the enantiomeric form of the Thaliomide (Figure 3) is calmative which was sold in 1960's to pregnants to avoid

nausea, whereas the other form is teratogenic which causes terrible birth defects [6,7]. Moreover, there are several chiral pharmaceuticals such as penicillamine [8], timolol [9], ketamine [10], which exhibits discrete pharmacological activity.

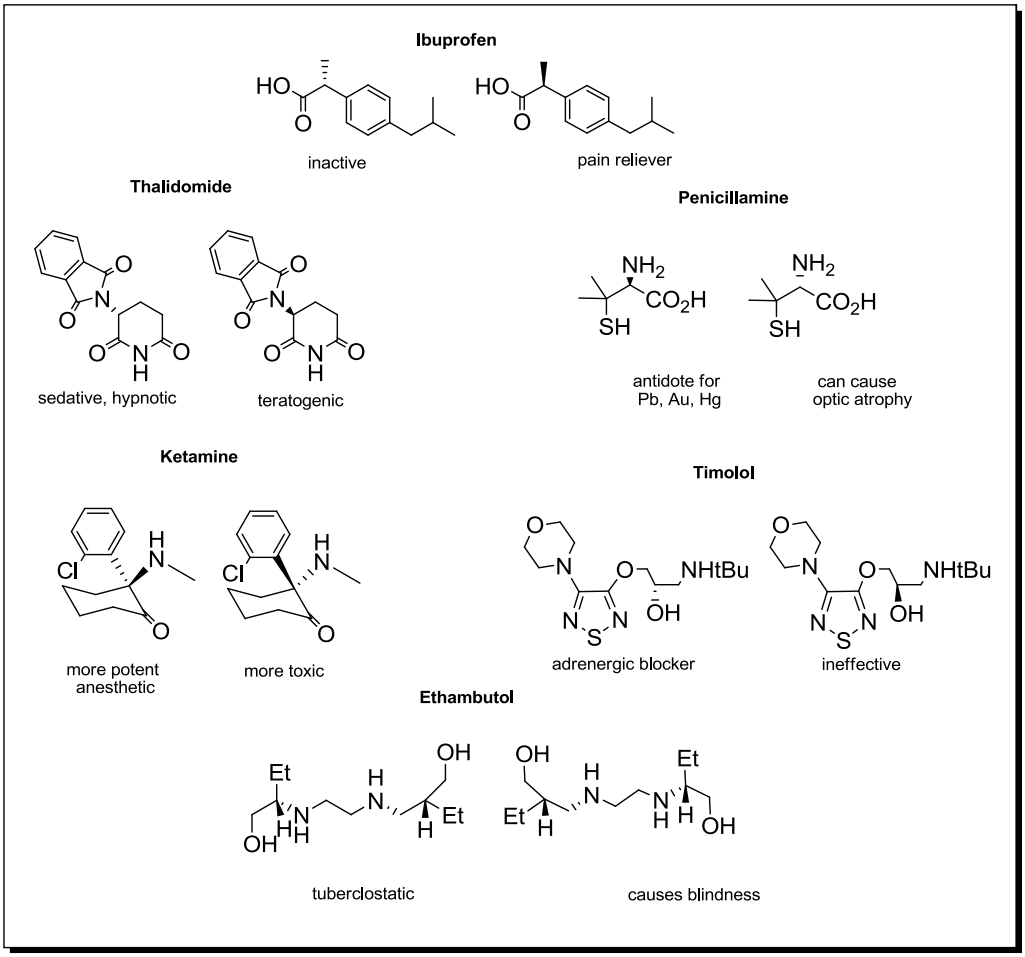


Figure 3. The structure and the pharmacological effects of the enantiomers of some chiral molecules.

1.3. Asymmetric Synthesis

The first and the most quoted definition of the asymmetric synthesis was made by Marckwald in 1904: " 'Asymmetric' syntheses are those which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials, but with the avoidance of any separation" [11]. After a few decades, Morrison and Mosher enhanced the definition in 1971 and it was defined 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" [12].

Asymmetric synthesis is very crucial for the research and industry; also, the compounds which are formed by asymmetric synthesis have created great interest in recent years [13]. Since natural products are chiral and exist as a single enantiomer, it is needed to synthesize enantiomerically pure compounds. In this way, asymmetric synthesis provides to obtain Nature-identical material [14].

There are three main methods to obtain enantiomerically pure compounds which can be listed as chiral pool, prochiral compounds, and seperation of racemates (Figure 4) [15].

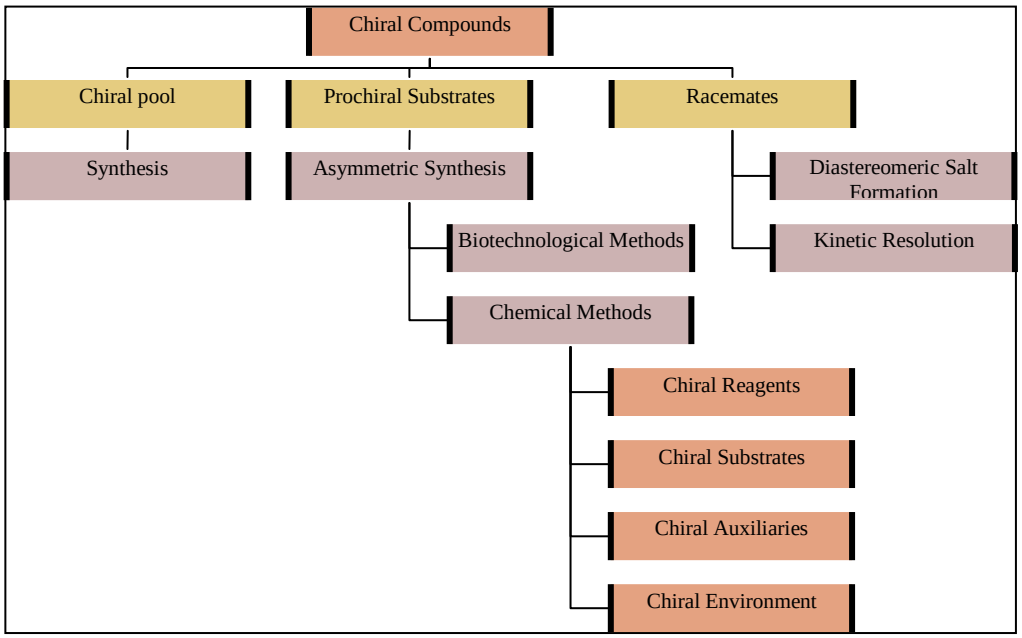


Figure 4. Methods to produce chiral compounds.

1.4. Chiral Pool

Chiral pool is a method of producing compounds as single enantiomers by using enantiopure natural products as a starting material in order to get desired compound [16]. High stereoselectivity is required for gaining enantiomeric and diastereomeric purity. The starting material is used stoichiometrically and the stereochemistry of the natural product remains same after the synthesis. This method has both advantages and disadvantages. Although the technique is considered as economic, it is confronted with some restrictions in terms of natural resource and cost of their isolation. Carbohydrates, amino acids, and terpenes can be exemplified for chiral pool substances from the nature (Figure 5).

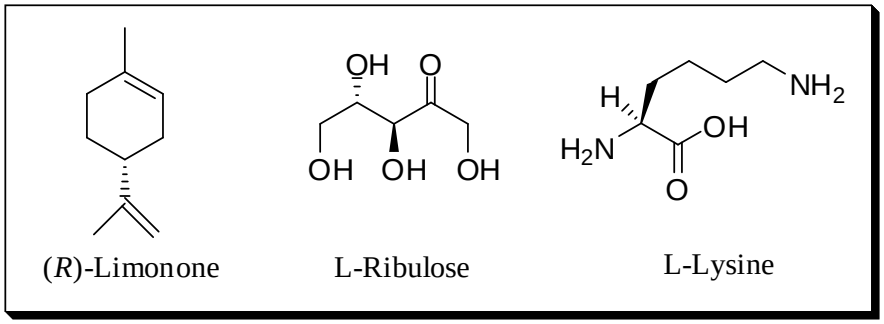


Figure 5. Specific examples for chiral pool products.

1.5. Prochiral Subtrates

If an achiral molecule can be converted into the chiral form in a single step reaction, the molecule is said to be prochiral. sp^3-hybridized atom having two identical substituents turns into chiral form after change of one of these substituents. This process is also called asymmetric synthesis. Asymmetric synthesis techniques can be divided into two subgroups as chemical and biotechnological.

1.5.1. Chemical Methods

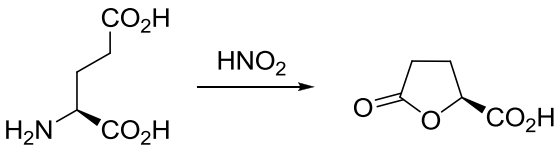
In order to succeed in these methods, chiral compound can be synthesized by controlling the conditions of reagent (chiral reagents, chiral catalysts) or substrate (chiral substrates, chiral auxiliaries).

- **Chiral Reagents**

In this method, enantiomerically enriched compound is produced after the treatment of the prochiral subtance with a chiral reagent. Since the chiral reagent is used stoichiometrically during the synthesis, the method is not suitable due to the high cost. Therefore, the nature benefits from this technique through enzymes [17].

- **Chiral Substrates**

In this case, the stereoselection of the reaction is controlled by the chiral starting material. The "chiral pool" is generated by the chiral compounds which are produced by nature. However, it may be experienced with difficulties in terms of the availability of the natural product and its price. The conversion of the L-glutamic acid to the optically active butyrolactone is an example for this kind of synthesis (Scheme 1) [18].



Scheme 1. An example of the use of a natural product for a starting material.

- **Chiral Auxiliaries**

The deficiency in convenient natural products, expensive reagents, and the number of steps required to obtain useful intermediate in the synthesis are main drawbacks of previous methods. Hence, chiral groups have been designated that can be

bonded to an achiral unit. These developed groups bring about selectivity in the reaction in order to afford diastereoselectivity [19]. Reusability of the auxiliary and the ease of purification of major diastereomer are the advantages of this method [20].

- **Chiral Environment**

It is feasible to form the environment of a reaction chiral by making good use of chiral additives or solvents [19].

1.5.2. Biotechnological Methods

Apart from chemical methods, biological techniques are also influential and practical to synthesize optically active compounds from prochiral substances. Enzymes, cell cultures, and the microorganisms are used to carry out the method [21].

1.6. Racemates

The separation of the racemate called resolution is a technique to obtain enantiomers after the separation of the racemic molecules [22]. According to this method, a molecule ought to contain a functional group which can give a reaction with any chiral agent to form diastereomers. Moreover, the agent used to separate racemates should be discarded from the medium after reaction. Resolution can be applied in two different ways; diastereomeric salt formation and kinetic resolution.

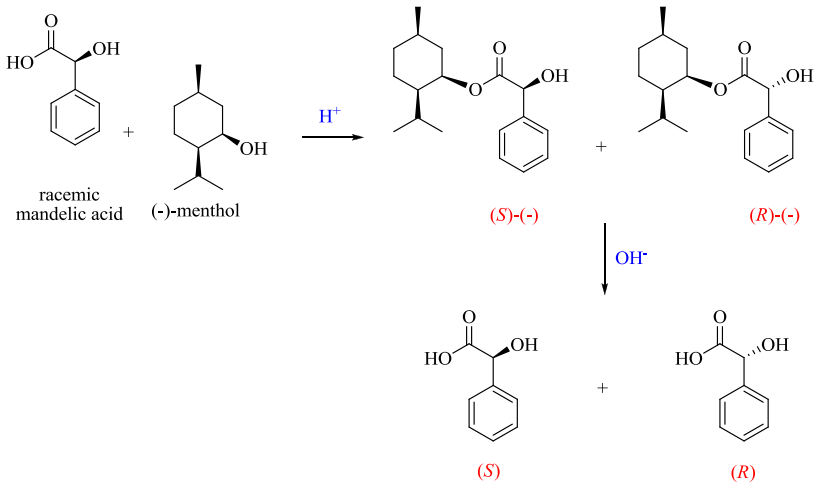
1.6.1. Diastereomeric Salt Formation

In this type resolution, diastereomeric derivatives are formed and physical properties which are boiling point, chromatographic adsorption, and solubility in crystalline derivative can be used as a separation method for these diastereoisomers [23].

1.6.2. Kinetic Resolution

Kinetic resolution is a process where two enantiomers of racemate react with the chiral reagent with different reaction rate. In other words, formation of one diastereomer is observed earlier than the other [4]. Generally, while the enantiomeric excess of the starting material increases during the reaction, enantiomeric excess of the product reduces [19].

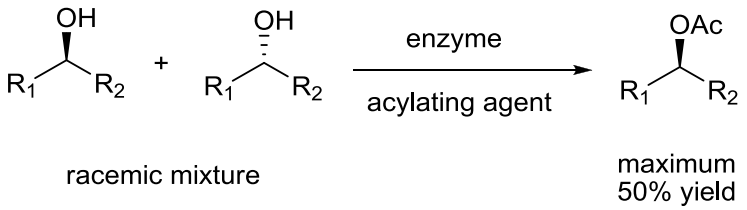
Kinetic resolution has been used to apply in the synthesis of the chiral molecules. This technique was first developed by Marckwald and McKenzie in 1899 while performing esterification reaction of racemic mandelic acid with chiral (-)-menthol (Scheme 2) [24].



Scheme 2. An example for kinetic resolution.

Kinetic resolution can be carried out both chemical and enzymatic means. Due to the catalytic process, enzymatic resolution is preferred than the chemical method.

In enzymatic resolution, while one of the enantiomers of a racemic compound is selectively converted to product, the other remains same (Scheme 3). At the end of this kind of resolution, maximum theoretical yield can reach to 50%. However, this problem can be solved by the usage of meso compounds or prochiral substrates; stereoinversion of the left enantiomer; and dynamic kinetic resolution (DKR) [25].



Scheme 3. Enzymatic resolution of an alcohol.

1.7. Enzymes

Enzymes are proteins and they function as biological catalysts of remarkable efficiency [26]. They speed up reactions by factors of 10^8 - 10^{12} and their activity depends on the concentration of products, substrates or other species in the solution. Also, they decrease the activation energy of reaction. These biocatalysts have both advantages and disadvantages [21, 27, 28].

1.7.1. Advantages of Enzymes

- The turnover number is higher than any catalyst; in other words, it is very effective.
- In opposition to chemical catalyst which bear metal ions to work properly, enzymes are environment-friendly.
- They can function under mild conditions.
- Since they have three dimensional structure, they possess enhanced stereoselectivity.
- As the compatibility is seen among enzymes, multienzyme systems can be conducted to simplfy the process.

1.7.2. Disadvantages of Enzymes

- Since enzymes are natural products, they exist in single enantiomeric form. They can only be derived from L-amino acids.
- Despite the fact that enzymes performing under harsh conditions is considered as an advantage, it may raise some difficulties. Thus, they need narrowing the parameters.
- Although water is not preferable solvent for most organic reactions, enzymes show highest catalytic activity in aqueous medium.

1.7.3. Mechanistic View

Main principle of enzymes is based on “Lock and Key” model. The interaction between enzyme and its substrate resembles the relation between lock and key. This idea was first proposed by Emil Fisher in 1894 who won the Nobel Prize in Chemistry in 1902. The model illustrates that enzyme and substrate have unique shapes which show compatibility with one another (Figure 6) [29].

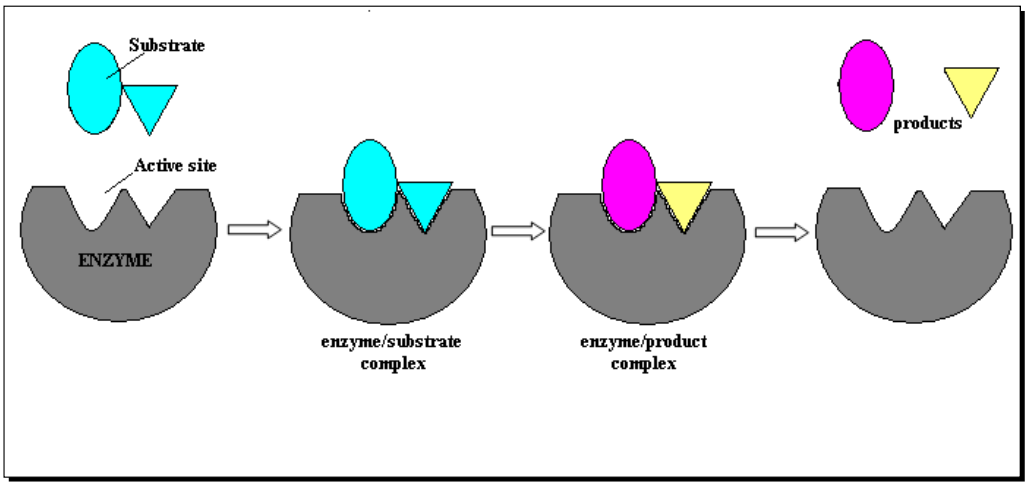


Figure 6. Lock and Key model.

1.7.4. Factors Affecting the Enzyme Reaction Rate

The major factors that influence the reaction rate of enzymes can be listed as enzyme concentration, substrate concentration, inhibitors, activators, temperature, and pH.

- **Effect of Enzyme Concentration**

As the enzyme concentration increases, the rate of a reaction also increases, theoretically. These two parameters show paralellism. However, in some cases like at high enzyme concentrations, deviation in the linearity can be observed. Also, in the presence of the activators or inhibitors during enzyme preparation, a falling off from linearity can occur [30].

- **Effect of Substrate Concentration**

The substrate concentration is one of the most significant factor that influences enzymatic reaction rate. As the amount of enzyme is kept constant and substrate concentration is increased, there is an increase in reaction rate until maximum velocity has reached. After reaching the maximum rate, the substrate concentration does not have any effect on the enzymatic reaction rate. Moreover, at high substrate concentration, the rate of a reaction can decline [31].

- **Effect of Inhibitors**

Inhibitors are molecules that attach to enzymes and diminish their activities. Also, a decrease in the reaction rate is observed after the interaction between enzyme and inhibitor or substrate and inhibitor.

There are two kinds of inhibitors; reversible and irreversible. In the former case, the activity of the enzyme reaches to the initial level after the inhibitor is removed. On the other hand, in the irreversible case, enzyme activity is lost when any interaction between inhibitor and enzyme takes place. Also, inhibition increases continuously by increasing the inhibitor concentration and continues until all the inhibitor reacts with the enzyme [32, 33].

- **Effect of Activators**

The rate of the reaction increases by adding a small amount of substance which is called activator. The activity of the enzyme changes enormously in the presence of activators. At low concentrations, the reaction rate of the enzyme is proportional

to the activator concentration. Besides, the rate of the reaction does not depend on the quantity of activator at higher concentrations [34].

- **Effect of Temperature**

Enzymatic reactions contain three unseperable steps; the generation of enzyme-substrate complex, conversion to enzyme-product complex, and separation of the product and enzyme. All the steps are affected from the temperature. At very high temperatures, the enzyme loses its activity, but it can be recovered if the temperature decreases.

- **Effect of pH**

Enzymes can generally function at a narrowed range of pH. The most effective point of enzyme activity is called optimum pH. It shows alterability from enzyme to enzyme. For example, as pepsin is very effective at pH 1.5-1.6, urease shows its maximum activity at pH 7 [35]. Most of the enzymes may lose their effectiveness either at higher or lower pH values. Furthermore, the structure and the ionization state of enzymes and reactants can be changed by monitoring the reaction pH.

1.8. Enzymes in Asymmetric Synthesis

Various kinds of enzymes are used to synthesize organic compounds. For instance, hydrolase type enzymes are the most widely used ones. They do not need any coenzyme or cofactor to become activated and they possess a wide range of substrate [36]. They are responsible for hydrolyzing the chemical bonds. Moreover, similar to hydrolases; proteases, lipases, acylases, amylases and esterases are from the same class of enzyme [37].

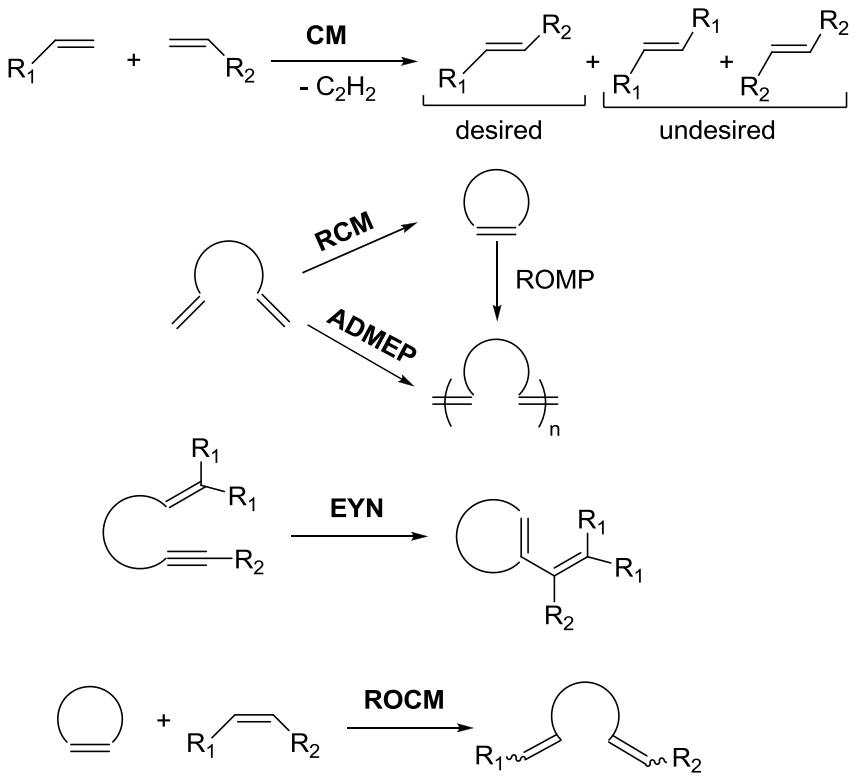
Proteases enable to hydrolyze peptide bonds, whereas esterases and lipases are capable of hydrolyzing ester groups of triglycerites. Lipases are especially used in the preparation of enantiomerically enriched products. In acyl transfer reactions, racemic substance (amine or alcohol) and achiral acyl donor (acid or ester) react in the presence of lipases and enantiomerically enriched compound is obtained after kinetic resolution [38]. *Candida sp. Lipases* (*Candida lipotyca,* CAL-B, CRL) and *Pseudomonas sp. Lipases* (*Pseudomonas fluorescens, Pseudomonas cepacia)* are commonly used lipases.

1.9. General Survey to Metathesis

Metathesis which is derived from Greek words meta (change), and thesis (position), means the exchange of parts of two substances [39]. It comprises industrial and pharmaceutical methods which are more effective less polluting [40]. Metathesis reactions have become very popular due to being effective tool for carbon-carbon bond formation in the natural-product based organic synthesis. These reactions are catalyzed by alkylidene complexes which provide both high activity and wide functional group tolerance. In metathesis process, the reactions can be classified according to the bearing unsaturated functional group type as diene, enyne, and diyne. Also, another type of classification is based on the structural variations during the metathesis reactions [41]. These reactions can be listed as

- Ring-closing Metathesis (RCM)
- Cross Metathesis (CM)
- Acyclic Diene MetathesisPolymerization (ADMEP)
- Ring-opening Metathesis Polymerizatioin (ROMP)
- Enyne Metathesis (EYN)
- Ring-opening Cross Metathesis (ROCM)

Among these kinds of metathesis, RCM has captured the attention in natural-product synthesis despite of the low stereoselectivity of macrocyclic series . In CM, intermolecular coupling between two different olefins yields three new alkenes as shown in Scheme 4. Coupling selectivity can affect the efficiency of the cross metathesis. Therefore, some optimizations should be performed to decrease the unproductive alkenes formed by self-metathesis and to increase the productive cross-metathized alkene [42].

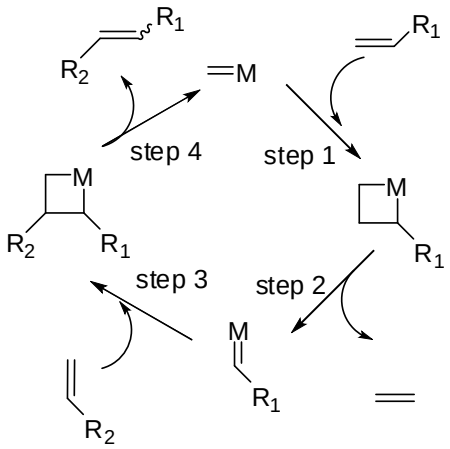


Scheme 4. Different metathesis reactions.

1.10. Olefin Metathesis

Metal-catalyzed olefin metathesis is the most commonly used organometallic transformation for both breaking and forming carbon-carbon bond in organic chemistry. Therefore, Yves Chauvin, Robert H. Grubbs, and Richard Schrock won the Nobel Prize in chemistry in 2005 for developing the metathesis method in organic synthesis [41].

The olefin metathesis, in which an exchange of alkylidene groups between two substituted alkenes occurs in the presence of metal carbene, has general proposed mechanism shown in Scheme 5.



Scheme 5. Chauvin Mechanism / Catalytic Cycle.

According to the mechanism, metallocyclobutane intermediate is formed by the reaction between the metal alkylidene and the alkene molecule (step 1). After the cleavage, ethylene and new metal alkylidene are produced (step 2). The formed metal alkylidene reacts with new olefin and formation of the new metallocyclobutane intermediate occurs (step 3). Finally, the intermediate decomposes and alkene product and metal methylene are evolved (step 4).

Chauvin and co-workers proved the mechanism by experimental results and it is also supported by Grubbs, T. J. Katz, Schrock and others [43].

1.10.1 Well-Defined Useful Catalyst for Olefin Metathesis

Chauvin mechanism accelerates the generation of high performance, stable, tolerant catalysts. Tungsten or molybdenium alkylidene complexes designed by Schrock and co-workers and ruthenium carbene complexes developed by Grubbs and co-workers are the most widely known ones. All the reagents are commercially available (Figure 7) [44].

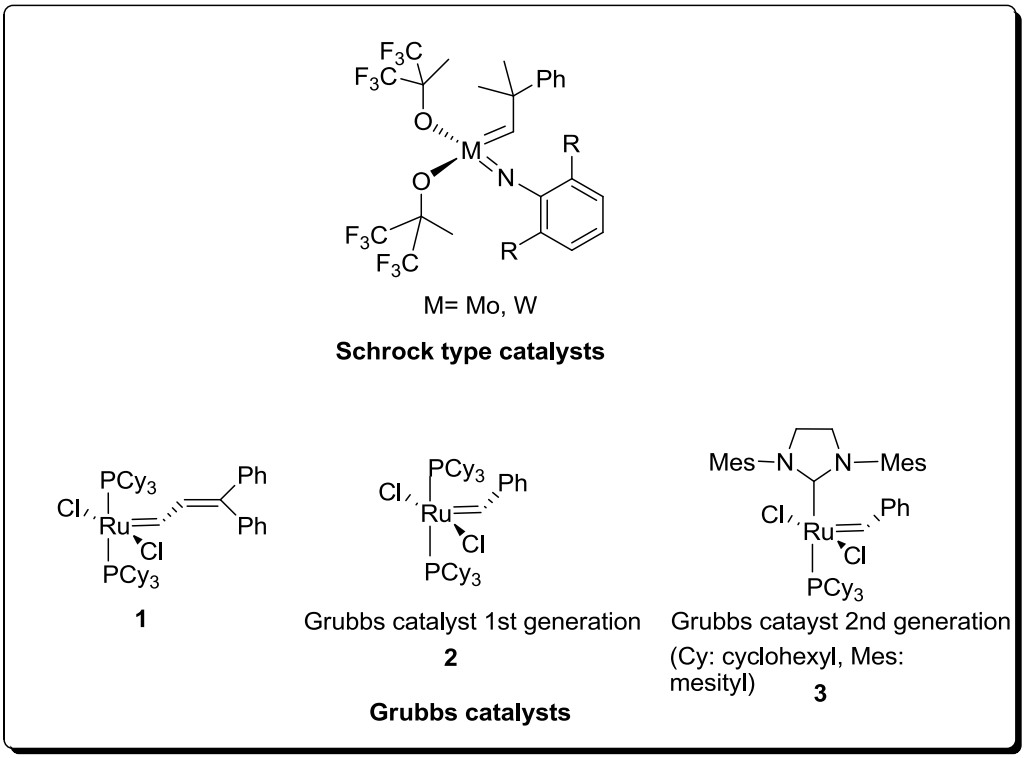


Figure 7. Some typical metathesis catalysts.

Olefin metathesis became a most effective synthetic method for carbon-carbon bond formation with the development of well-defined molybdenum and ruthenium alkylidene complexes. Schrock type catalysts having the general formula [M(=CH(Me)$_2$Ph)(=N-Ar)((OR)$_2$)] show more reactivity towards highyl substituted olefins and electron-rich double bonds; however, they are unstable against air and moisture. Also, their preparation is expensive. On the other hand, ruthenium-based carbene complexes have more tolerance to polar functional groups and they are more resistant to mild conditions. Although the activity of Grubbs catalysts is lower, range of substrates is very broad in applications [45].

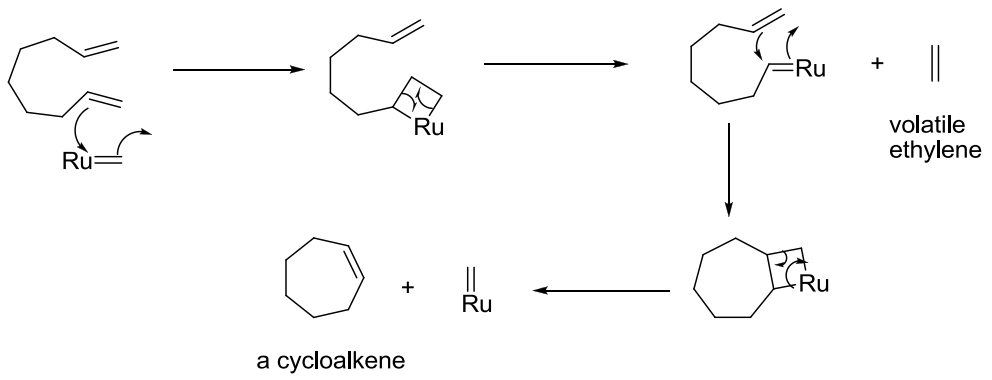
Grubbs and his co-workers designed their first Ru-based carbene complex in 1992 which has a structure of [RuCl$_2$(PR$_3$)(=CH-CH=CPh$_2$)] with R=Ph. Despite of low reactivity towards polymerization of norbornene, they had stability in protic solvent medium. In 1995, the most commonly used metathesis catalyst synthesized called first generation Grubbs catalyst. It was discovered that bulky tricyclohexylphosphine ligand are more reactive than triphenylphosphine ligand in the Ru-catalyzed metathesis. In 1999, additional changes were done on the structure of the catalyst and one of the phospine ligands on the first generation of Grubbs catalyst was replaced with an N-heterocyclic carbene (NHC) ligand. This new well-defined catalyst called second-generation Grubbs catalyst results in an increased rate of catalyst turnover by making use of electron donation and steric bulk of the NHC ligand [46].

1.10.2. Ring Closing Metathesis

There are three essential aspects to the success of ring closing metathesis (RCM) as a tool;

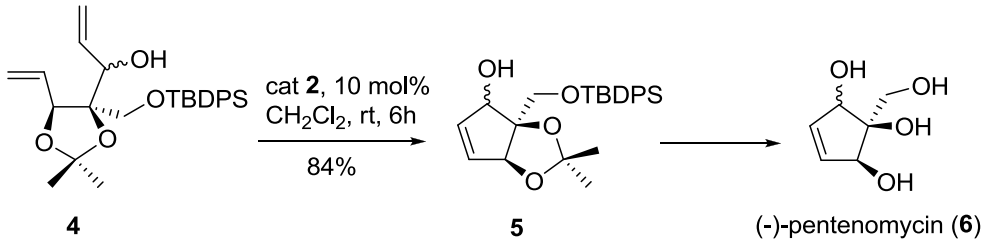
- the availability of molybdenum and ruthenium pre-catalysts bearing well-defined electronic and coordinative unsaturation to permit usability and high turnover performance
- diversity in the functional groups
- one's capability for macrocyclization.

However, oligomerization is the competing reaction in RCM. The rate of the oligomerization can be minimized by a decrease in diene concentration or by adding the substrate dropwise. Moreover, ring closure is favored at higher temperatures [47]. Small-, medium-, and large-ring systems can be formed by RCM. The general mechanism of RCM proposed by Grubbs is illustrated in Scheme 6.



Scheme 6. General Mechanism of Ring Closing Metathesis.

RCM can be a very fundamental step for the total syntheses of natural products. For instance, (-)-pentenomycin shown in Scheme 7 was synthesized by the help of the first generation of Grubbs catalyst [48].



Scheme 7. Synthesis of (-)-pentenomycin.

1.11. Lactones

The word lactone is derived from the cyclic compound lactide. Lactone is also a kind of cyclic ester which can be obtained by the condensation of the alcohol group and carboxylic acid group existing in the same molecule. Intermolecular esterification occurs in acidic medium to yield desired lactones. Its nomenclature is based on a *-lactone* suffix and a Greek letter prefix that denotes the number of carbons in the heterocyle. The Greek letters designates the size of the lactone ring; α-lactone means 3-membered ring, β-lactone is 4-membered, γ-lactone is 5-membered, etc. [49].

Various natural products contain a lactone core in their structures. The lactones possess a wide variety of biological activities often depending on the substituents which are mainly on the pyran skeleton. Five- or six- membered rings are the most naturally occuring lactones because of the stability [50]. Vitamin C, (*R*)-Goniothalamin [51], Yangonin [52], (*R*)-Kavain, and Jerangolid D [50] are some examples for lactone containing natural products (Figure 8).

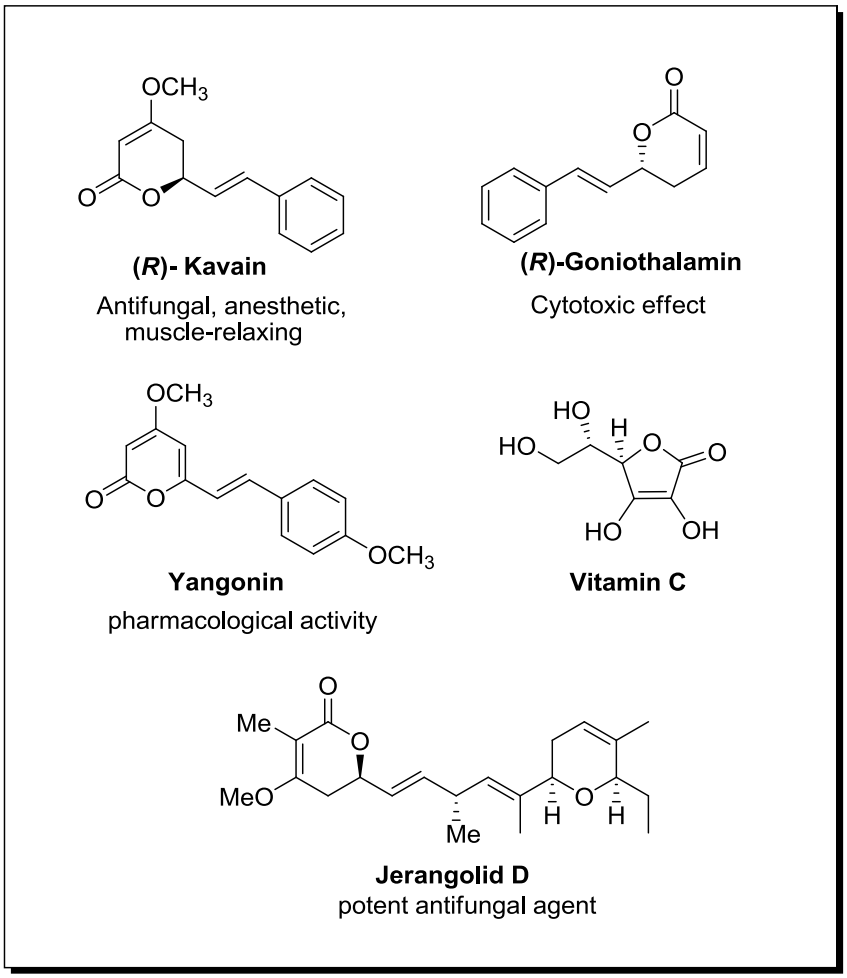
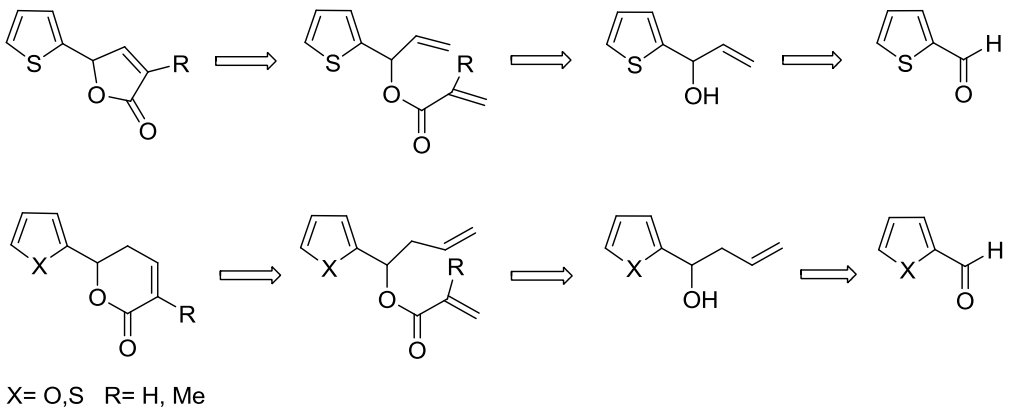


Figure 8. The structures of some bioactive lactones.

1.12. Aim of the Work

In the last decade, natural products containing chiral heterocyclic compounds have been very popular. Therefore, we aimed to synthesize highly enantiomerically enriched 2-heteroaryl substituted α,β-unsaturated γ- and δ-lactones. We followed the retrosynthetic pathway in which racemic secondary homoallylic and allylic alcohols were chosen as proper backbone as shown in Scheme 8.

For the constructions of these carbon skeletons, we thought to apply well-known Grignard type coupling reaction between heteroaryl carbaldehydes and allyl and vinyl magnesium bromides. We planned to get high enantiomeric enrichment *via* enzymatic resolution method by using various lipases. Subsequently, enantiomerically enriched alcohols could be acylated with acryloyl and methacryloyl chlorides to afford proper diene systems which can be available substrates for RCM reaction done with first- and second-generation Grubbs' catalysts. After completing the syntheses, target γ- and δ-lactones will be subjected to some bioactivity tests.



Scheme 8. Retrosynthetic pathway of the work.

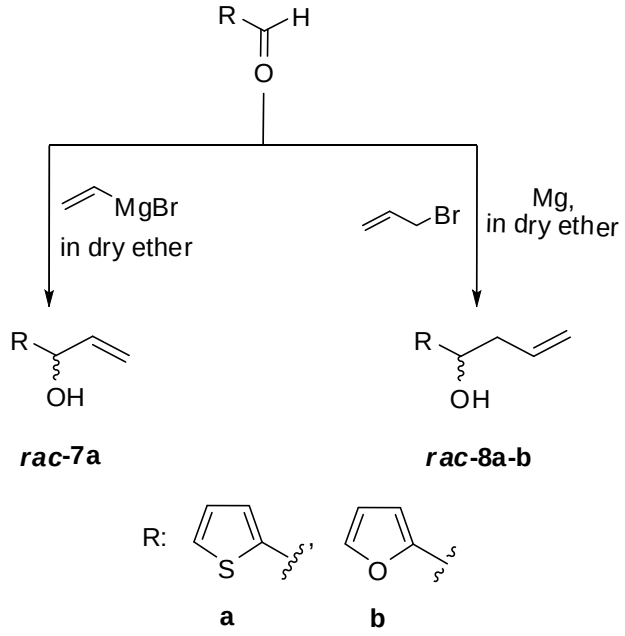
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of Racemic Allylic and Homoallylic Alcohols

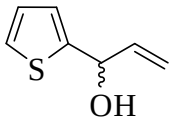
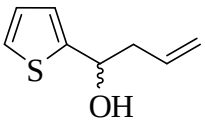
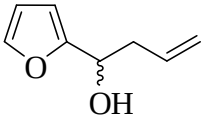
In the synthesis of natural products, optically active molecules including enantiopure 1,3-diols, antitumor macrolides, alkoloids, α,β-unsaturated lactones, and chiral epoxy alcohols, it is utilized from allylic and homoallylic alcohols. In literature, allylation of aldehydes by using various allylmetal reagents (allyl In, Mg, Zn) is an outstanding synthetic method [53-54].

As indicated in the synthetic pathway, firstly, racemic allylic and homoallylic alcohols were synthesized. For this purpose, commercially available 2-heteroaryl substituted carbaldehydes were chosen as starting materials. These carbaldehydes were commonly used in Grignard reactions. In order to afford 2-heteroaryl substituted allylic alcohols, commercially available vinylmagnesium bromide in dry ether was used under argon atmosphere. On the other hand, 2-heteroaryl substituted homoallylic alcohols were synthesized by using *in situ* prepared allylmagnesium bromide under the conditions given above (Scheme 9). The reaction durations and the chemical yields are summarized in Table 1.



Scheme 9. Synthetic pathway for the preparation of racemic allylic and homoallylic alcohols.

Table 1. Synthesis of allylic and homoallylic alcohols.

Substrate	Product	Time (h)	Yield (%)
Thiophene-2-carbaldehyde	 *rac*-**7a**	3	85
Thiophene-2-carbaldehyde	 *rac*-**8a**	7	80
Furan-2-carbaldehyde	 *rac*-**8b**	12	84

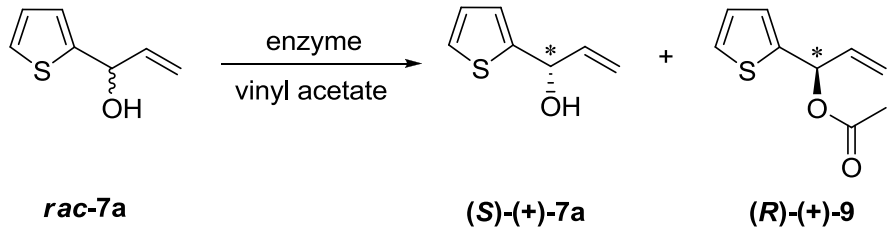
The structure of allylic and homoallylic alcohols were proved by ^{1}H- and ^{13}C-NMR spectroscopy. These spectra shown in appendix (Figure A1-6) are consistent with the literature data [54,55].

2.2. Enzymatic Resolution of Allylic and Homoallylic Alcohols

In order to afford enantiomerically enriched 2-heteroaryl substituted secondary alcohols, we preferred to choose enzymatic resolution approach. Various lipases were used in enzymatic resolution of furan and thiophene substituted racemic secondary alcohols. Among the lipases tested, CAL-B, lipozyme, and PS-C II gave the optimum results for the enantioselective acetylation of these secondary alcohols. All racemic alcohols (*rac*-**7a,** *rac*-**8a-b**) were configured as (*S*) after the resolution. The absolute configurations were determined by checking the specific rotation values with the literature data [56].

2.2.1. Enzymatic Resolution of *rac*-(thiophen-2-yl)prop-2-en-1-ol (*rac*-7a)

Thiophene substituted allylic alcohol was enantiomerically enriched by using CAL-B and PS-C II enzymes separately in the presence of vinyl acetate used as acetyl source. The reaction was monitored by TLC and it was ended as the conversion of alcohol to acetyl derivative observed approximately 50% (Scheme 10).



Scheme 10. Enzymatic resolution of *rac*-(thiophen-2-yl)prop-2-en-1-ol (*rac*-**7a**).

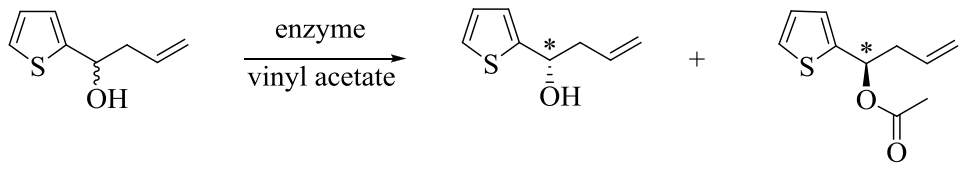
Enantiomeric excess (ee%) values of allyl alcohol (+)-**7a** were determined by HPLC using OJ-H chiral column (Figure A8). All reactions were performed at 26 ^{o}C in THF and went to completion in a very short period of time as 1h. According to the enzymatic resolution results demonstrated in Table 2, higher ee value was obtained by the usage of CAL-B rather than PS-C II for the substrate *rac*-**7a**.

Table 2. Enzymatic resolution results of *rac*-**7a**.

Substrate	Enzyme	Co-solvent	Temp. (°C)	Time (min.)	Conv. (%)	e.e. (%)
***rac*-7a**	CAL-B	THF	26	65	56	97
***rac*-7a**	PS-C II	THF	26	75	47	84

2.2.2. Enzymatic Resolution of r*ac*-(thiophen-2-yl) but-3-en-1-ol (*rac*-8a)

Among lipases tested in enzymatic resolution of substrate *rac*-**8a** (Scheme 11), Lipozyme and PS-C II were found as the most feasible biocatalysts.



***rac*-8a** **(*S*)-(-)-8a** **(*R*)-(+)-10**

Scheme 11. Enzymatic resolution of *rac*-1-(thiophen-2-yl)but-3-en-1-ol (*rac*-**8a**).

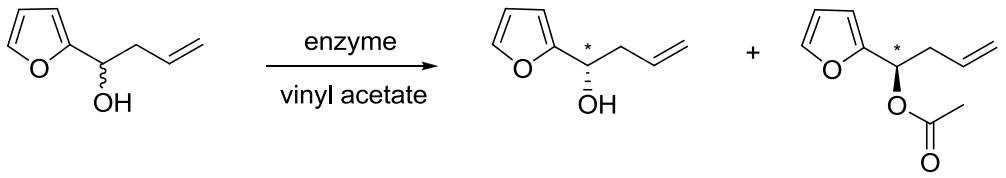
As shown in Table 3, 99% e.e. value was achieved by Lipozyme catalyzed resolution in DPE. When PS-C II was used, ee value decreased to 95% in THF which is the best solvent in most cases. Despite the fact that PS-C II catalyzed resolution has faster reaction rate than Lipozyme resolution reaction, the latter afforded optimum e.e. value. HPLC with OJ-H chiral column was used to determine ee values (Figure A12).

Table 3. Enzymatic resolution results of *rac*-**8a**.

Substrate	Enzyme	Co-solvent	Temp. (°C)	Time (h)	Conv. (%)	e.e. (%)
rac-**8a**	Lipozyme	DPE	26	18	54	99
rac-**8a**	PS-C II	THF	24	20	56	95

2.2.3. Enzymatic Resolution of *rac*-(Furan-2-yl)prop-2-en-1-ol, *rac*-8b

Racemic furan substituted homoallylic alcohol, *rac*-**8b** was subjected to enzymatic hydrolysis by CAL-B, Lipozyme, and PS-C II (Scheme 12).



***rac*-8b** **(*S*)-(-)-8b** **(*R*)-(+)-11**

Scheme 12. Enzymatic resolution of *rac*-(furan-2-yl)prop-2-en-1-ol, *rac*-**8b**.

The enzymatic resolution reactions were conducted in various solvents at 24-26 °C. The results are summarized in Table 4. Solvent and temperature were changed while keeping the enzyme same to find good ee values. Among CAL-B catalyzed resolutions, the best result which is 85% ee with 55% conversion was obtained when the reaction performed at 24 °C in hexane (entry 3). In order to increase the enantiomeric excess value, Lipozyme and PS-C II were also tested. In Lipozyme catalyzed resolution, THF and DPE were used as solvent and the determined ee values are 79% (entry 4) and 99% (entry 5), respectively. Changing the solvent affected the enantioselectivity of the reaction as previous case. Moreover, the best result required shorter reaction duration as 16 h rather than 48 h. For PS-C II case, since the resolution in the presence of THF at 24 °C afforded 99% ee value with 55% conversion, there was no need to search for other conditions. The enantiomeric excess values were determined by HPLC with OJ-H chiral column (Figure A16).

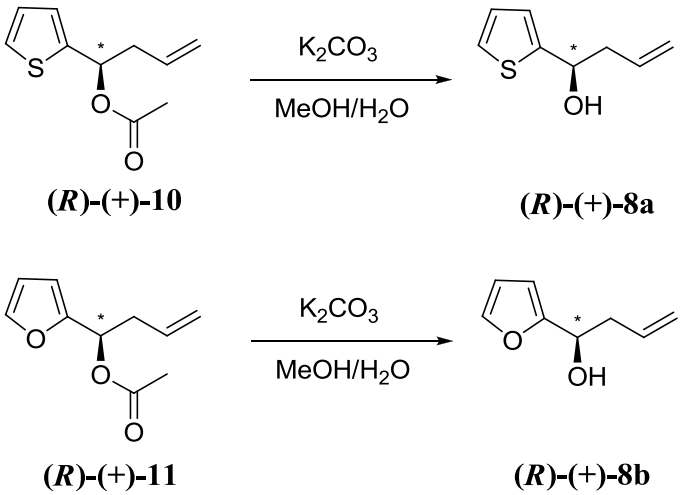
As it is seen from the results, 99% enantiomeric excess was obtained in DPE for both thiophene substituted racemic homoallylic alcohol, *rac*-**8a,** and furan substituted racemic homoallylic alcohol, *rac*-**8b**. However, ee value decreased from 99% to 95% in THF for the latter case and big difference in reaction time was observed.

Table 4. Enzymatic resolution of *rac*-**8b**.

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

2.3. Hydrolysis of (*R*)-acetate Derivatives of Heteroaryl Substituted Homoallylic Alcohols

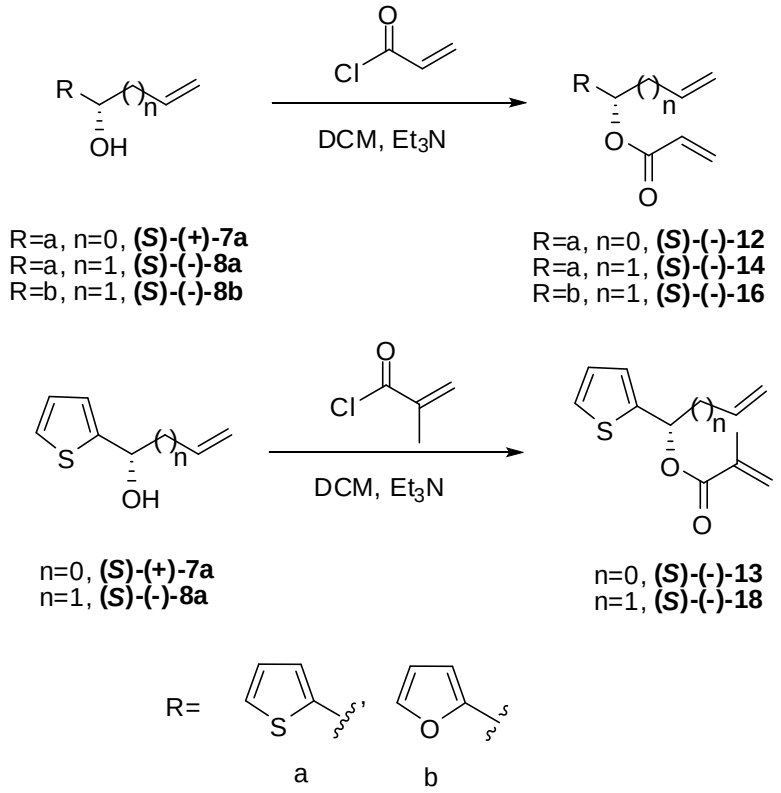
As it was mentioned in the introduction part, natural compounds are mostly chiral and they may show biological activity. In order to understand whether our desired product is biologically active or not, it is needed to synthesize both (*S)* and (*R*) configured compounds because as one of the enantiomers may have biological activity, other enantiomer may not possess this activity. Therefore, in the beginning of the synthesis, (*R*)- acetate derivatives of heteroaryl substituted homoallylic alcohols were converted to (*R*) configured heteroaryl substituted homoallylic alcohols by chemical hydrolysis (Scheme 13).



Scheme 13. Hydrolysis of (*R*)-acetates.

2.4. Construction of Chiral Diene Carbon Skeleton

According to our synthetic pathway mentioned in the previous chapter, it was aimed to synthesize chiral 2-heteroaryl substituted α,β-unsaturated γ- and δ-lactones from optically active heteroaryl substituted diene systems *via* ring closing metathesis (RCM) reaction. These diene units on the main skeleton were suitable for RCM type reaction. Therefore, acryloyl and methacryloyl units were anchored to the allylic (*S*)-(+)-**7a** and homoallylic alcohols (*S*)-(-)-**8a-b**,and (*R*)-(+)-**8a-b** to generate second alkene unit in the skeleton by *O*-acylation procedure (Scheme 14). During the course of the reactions, any racemization did not take place; *i.e.*, all configurations of the chiral centers kept constant. The results are shown in Table 5.

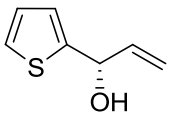
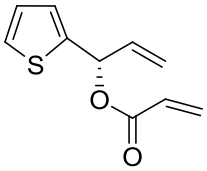
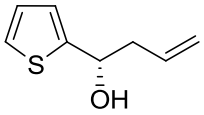
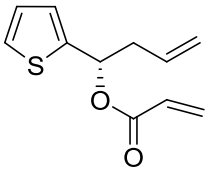
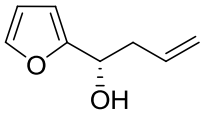
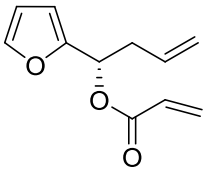
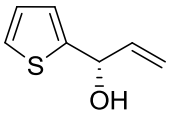
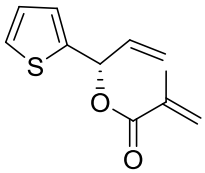
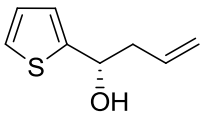
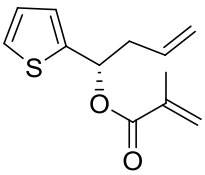


Scheme 14. *O*-acylation of chiral allylic and homoallylic alcohols.

The structure elucidation of all acrylate esters was done with ^{1}H and ^{13}C NMR. Since all acrylate and methacrylate esters almost possess the similar carbon backbone except heteroaryl units, herein one representative example is given for each. For instance, in ^{1}H NMR of compound (*S*)-(-)-**14**, methine proton of olefinic unit next to the carbonyl group appears as doublet of doublet at 6.05 ppm with the coupling constants J = 17.3 and 10.4 Hz due to the trans- and cis couplings with the terminal methylene protons of olefinic unit. These metylene protons resonate as doublet of doublets at 6.35 and 5.76 ppm with J = 17.3 and 1,4 Hz, and J = 10.4 and 1.4 Hz, respectively. Diastereotopic methylene protons next to stereogenic center show AB system at 2.72 ppm as doublet of triplet of triplet with the coupling constant values J = 14.3, 7.3, and 1.1 Hz and at 2.64 ppm as doublet of triplet of triplet with the coupling constant values J = 14.3, 6.5, and 1.2 Hz. The

stereogenic center methine proton resonates at 6.01 ppm as triplet with J = 6.9 Hz. ^{13}C NMR spectrum possesses eleven carbon signals. Characteristic carbonyl signal appears at 165.5 ppm.

Table 5. *O*-acylation results of allylic and homoallylic alcohols.

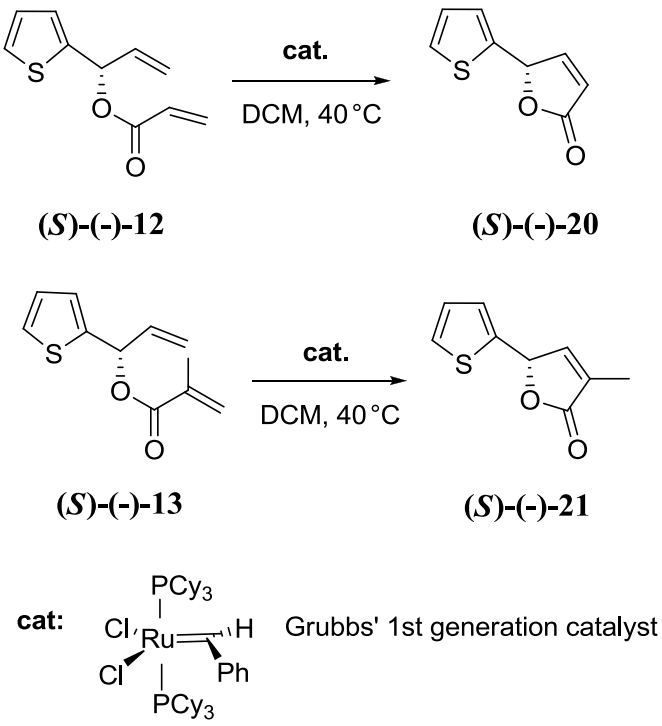
Substrate	Product	Configuration	Time (h)	Yield (%)
		*S*	3	60
		*S*	1.5	81
		*S*	1.5	70
		*S*	3	61
		*S*	2	75

In ^{1}H NMR of compound (*S*)-(-)-**18**, methyl protons of methacrylate unit resonates at 1.85 ppm as singlet. AB system is observed on the diastereotopic methylene protons next to stereogenic center at 2.70 ppm as doublet of triplet of triplet with the coupling constant values J = 14.3, 7.2, and 1.2 Hz and at 2.63 ppm as doublet of triplet of triplet with the coupling constant values J = 14.2, 6.5, and 1.4 Hz. The stereogenic center methine proton appears at 5.48 ppm as triplet with J = 1.6 Hz. In ^{13}C NMR, carbonyl carbon has characteristic signal at 165.1 ppm.

2.5. Synthesis of Enantiomerically Enriched γ-Lactones *via* Ring Closing Metathesis (RCM) Reaction

Ring closing metathesis is one of the most suitable method to synthesize γ-lactones especially after the invention of Ru-carbene complexes by R. H. Grubbs. One of his designed catalysts, first generation Grubbs catalyst, was used in our reactions to get desired final products. In the last step of our synthetic strategy, enantiomerically enriched 2-heteroaryl substituted acrylate and methacrylate esters were converted to 2-heteroaryl substituted α,β-unsaturated γ-lactones.

Two kinds of γ-lactones were synthesized from *O*-acyl anchored substrates (*S*)-(-)-**12** and (*S*)-(-)-**13** by using 10% and 15% of Grubbs' 1st generation catalyst, respectively (Scheme 15). Target γ-lactones, (*S*)-(-)-**20** and (*S*)-(-)-**21** were obtained in 60% and 24% yields, respectively.



Scheme 15. RCM reactions of (*S*)-(-)-**12** and (*S*)-(-)-**13**.

The structural determination of (*S*)-(-)-**20** was done with ^{1}H and ^{13}C NMR. (*S*)-(-)-**20** has two olefinic protons at 7.49 and 6.19 ppm as doublet of doublets. β-Position methine proton of the olefinic unit resonates at 7.49 ppm as doublet of doublet with the coupling constant values J = 1.7 Hz and 5.6 Hz. α-Position methine proton gives a signal at 6.19 ppm as doublet of doublet with the coupling constants J = 2.1 Hz and 5.6 Hz. The stereogenic center proton appears as triplet at 6.16 ppm with the coupling constant J = 1.7 Hz. All interactions of protons can be explained by COSY spectrum (Figure 9). ^{13}C NMR spectrum shows eight signals as expected. The peak at 170.7 ppm belongs to the γ-lactone carbonyl group. The structure of (*S*)-(-)-**20** was also proved by the help of DEPT, HSQC (directly bond interaction) and HMBC (longer coupling interaction) techniques (Figure A31-34).

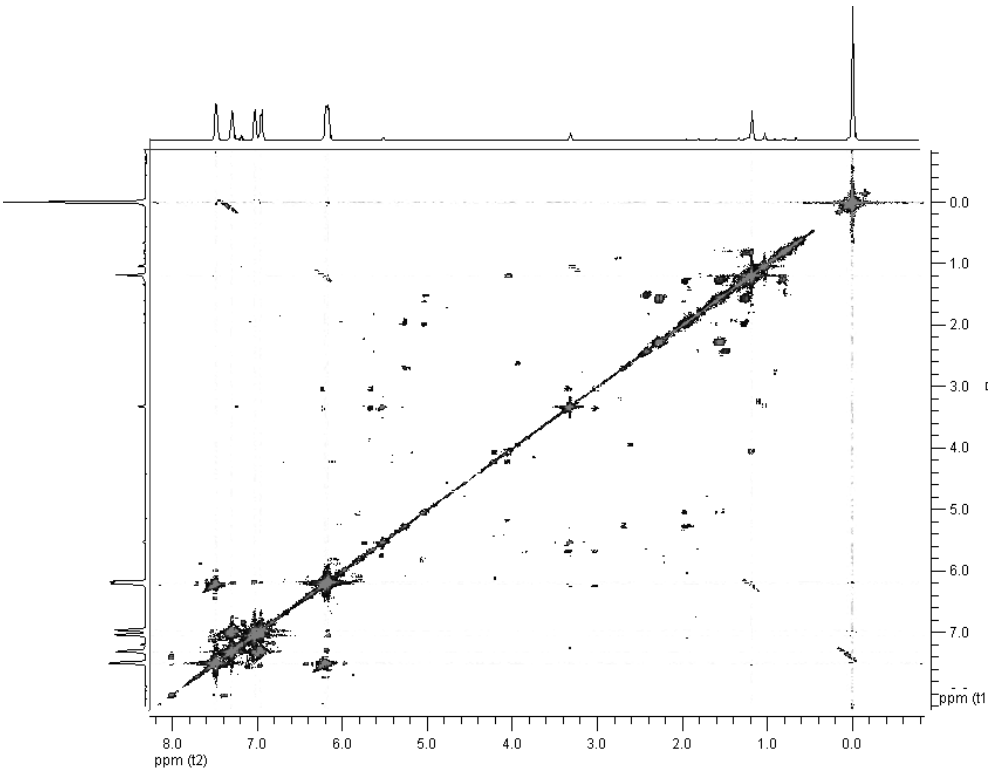


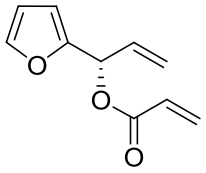
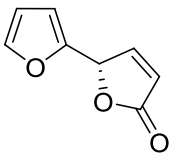
Figure 9. COSY spectrum of (*S*)-(-)-**20**.

According to ^{1}H NMR spectrum of methyl substituted derivative (*S*)-(-)-**21**, methyl protons appear as triplet at 1.95 ppm with the coupling constant value of *J* = 1.8 Hz due to long range coupling interactions. Similar interactions are observed for olefinic proton and stereogenic center proton resonated at 7.07 ppm and 6.02 ppm, respectively as multiplet. ^{13}C NMR spectrum reveals nine signals in which seven signals correspond to unsaturated carbons and the rest belongs to the saturated carbons. γ-Lactone carbonyl signal is observed at 172.0 ppm Also, HRMS measurements strongly supported the structure measured for $[M]^-$: 179.0166 and calculated value for $[M]^-$: 179.0167.

We also tried to synthesize furan substituted α,β-unsaturated γ-lactone *via* RCM reaction. Furan substituted acrylate ester could not be purified due to the vinylic components of the structure. Since it is not stable, RCM reaction was carried out

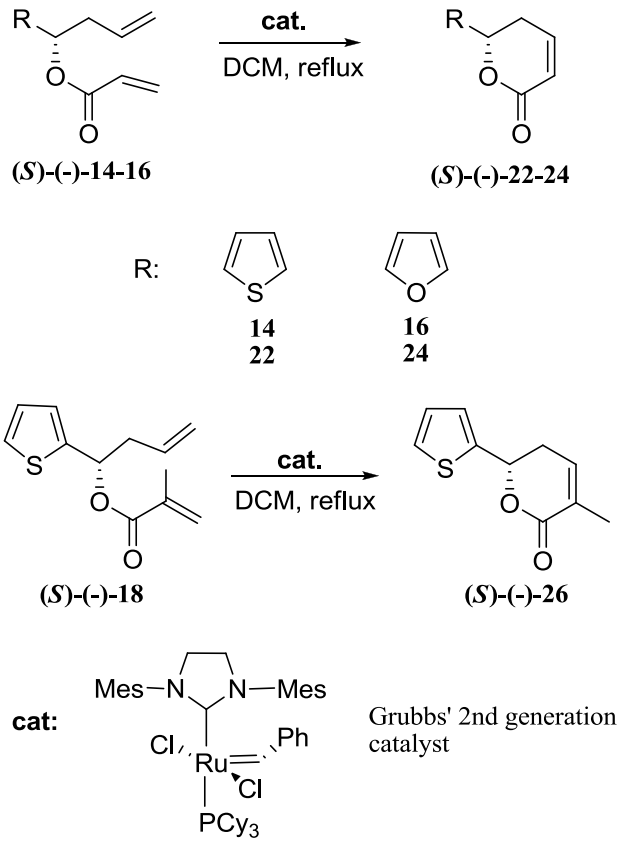
immediately. Although furan substituted acrylate ester could be synthesized, lactonization *via* RCM could not be achieved. We only observed some decomposition products. The applied RCM conditions are given in Table 6.

Table 6. Conditions for RCM reaction to afford furan substituted γ-lactone.

Substrate	Product	Catalyst (%)	Temp. (°C)
		10% Grubbs' 1st generation	40
		15% Grubbs' 1st generation in the presence of $Ti(OiPr)_4$	40
		5% Grubbs' 2nd generation	80
		10% Grubbs' 2nd generation	80

2.6. Synthesis of Enantiomerically Enriched δ-Lactones *via* Ring Closing Metathesis (RCM) Reaction

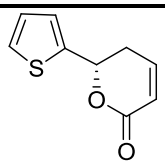
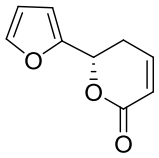
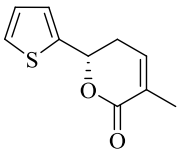
Optically active α,β-unsaturated δ-lactones, (*S)*-(-)-**22**-**24**-**26** were synthesized from heteroaryl substituted chiral *O*-acyl anchored homoallylic substrates *via* ring closing metathesis reaction. For this purpose, 2nd generation Grubbs catalyst was used instead of 1st generation Grubbs catalyst due to its thermal stability. Previous γ-lactones were formed at 40°C, whereas δ-lactones were synthesized at 80°C (Scheme 16). Results are summarized in Table 7.



Scheme 16. RCM reaction of (*S*)-(-)-**14**, (*S*)-(-)-**16**, (*S*)-(-)-**18**.

In ^{1}H NMR spectrum of (*S*)-(-)-**22**, methylene protons, which have interaction with all protons except the aromatic protons, resonate between 2.63 and 2.79 ppm as multiplet. The methine proton of the stereogenic center gives a signal at 5.62 ppm as doublet of doublet with the coupling constants J = 4.6 and 10.6 Hz because of the coupling with methylene protons. β-Position olefinic proton resonates at 6.88 ppm as doublet of doublet of doublet (J = 2.9, 5.5, and 9.7 Hz) due to the interaction with diastereotopic metylene protons and α proton of olefinic unit. The COSY spectrum clearly shows all the interactions between protons and supports our explanations (Figure 10). In addition, ^{13}C NMR spectrum shows nine expected signals. Characteristic δ-lactone carbonyl group appears at 163.4 ppm.

Table 7. Results of RCM reaction of (*S*)-(-)-**14**, (*S*)-(-)-**16**, (*S*)-(-)-**18**.

Substrate	Product	Grubbs' 2nd gen. catalyst (%)	Time (h)	Yield (%)
(*S*)-(-)-**14**		5	1.5	55
(*S*)-(-)-**16**		5	1.5	65
(*S*)-(-)-**18**		7	4	23

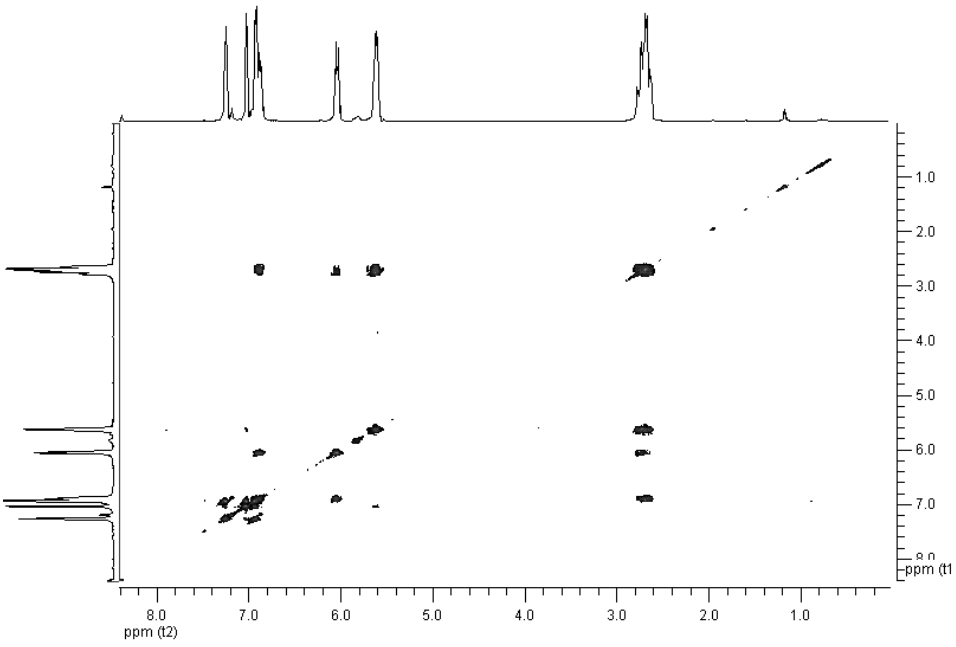


Figure 10. COSY spectrum of (*S*)-(-)-**22**.

The structure elucidation of (*S*)-(-)-**26** was done with ^{1}H and ^{13}C NMR. The stereogenic center methine proton resonates at 5.58 ppm as doublet of doublet with the coupling constants J = 4.1 and 11.0 Hz due to the interaction with diastereotopic methylene protons. Olefinic proton appears at 6.57 ppm as doublet of doublet of doublet (J = 1.5, 2.9, and 5.8 Hz). All proton interactions can be clearly seen in COSY spectrum (Figure 11). Moreover, ^{13}C NMR shows ten signals which supports the structure. HRMS measurement also proves the formation of the lactone found for $[M\text{-}H]^{+}$: 179.0166 and calculated for $[M\text{-}H]^{+}$: 179.0167.

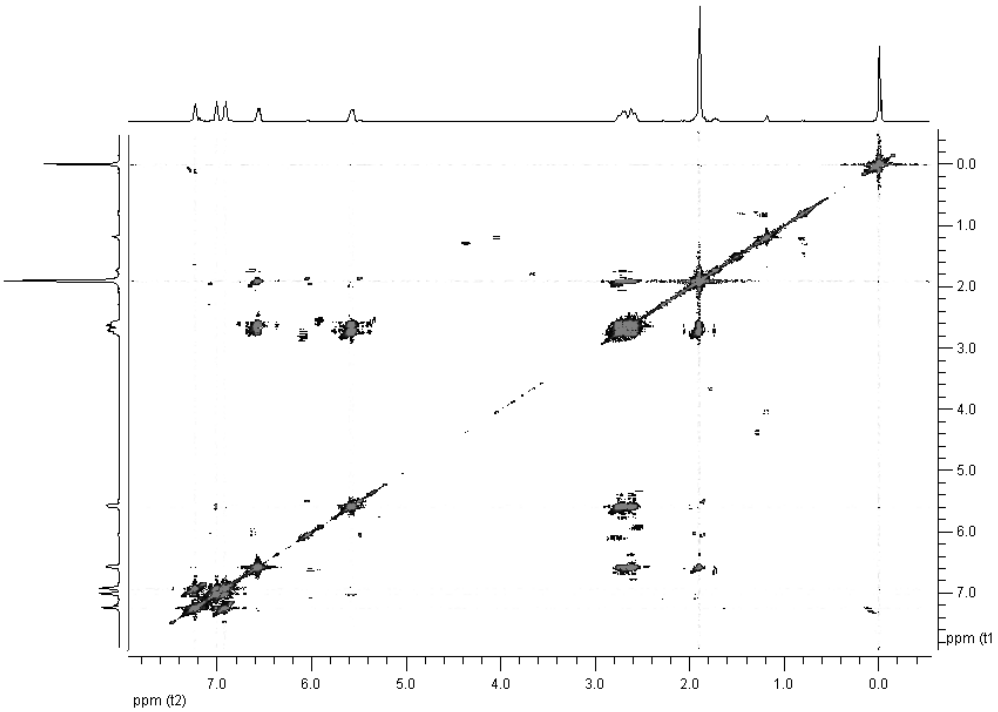
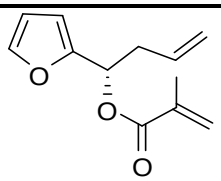
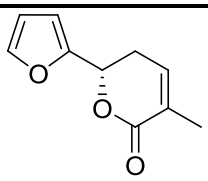


Figure 11. COSY spectrum of (*S*)-(-)-**26**.

Furan substituted derivative of compound **18** could not be synthesized with the conditions listed in Table 8. The furan substituted acrylate ester, *rac*-**27** was synthesized and its ^{1}H-NMR and ^{13}C-NMR were given in Appendix A (Figure A56-57).

Table 8. Tested conditions to synthesize furan substituted δ-lactone.

Substrate	Product	2nd gen. Grubbs catalyst	Temp. (°C)	Solvent
		6	80	Toluene
		6	110	Toluene
		6	40	DCM
rac-**27**		7.5	40	DCM

CHAPTER 3

BIOACTIVITY TEST RESULTS

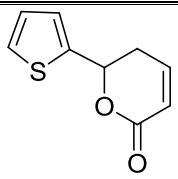
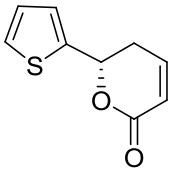
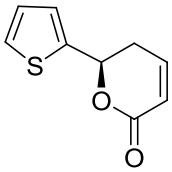
After completing the synthesis of target γ- and δ-lactones, it was aimed to study on their antimicrobial activity because of their potent biological activities. The antimicrobial activity of the target compounds were tested on different strains of bacteria and strain of yeast. All the strains were obtained from American Type Culture Collection (ATTC). As a gram-positive bacteria *Staphylococcus aureus* ATTC 6538, *Bacillus subtilis* ATTC 6633 were used and as a gram-negative bacteria *Escherichia coli* ATTC 3509, *Pseudomonas aeruginosa* ATTC 9027 were used and as a fungi *Candida albicans* ATTC 10231 were used.

- **Antibacterial Activity**

A modified version of the disc diffusion method (Rasoanaivo-Urverg, 1993) was used in order to detect the antimicrobial activity and Minimal Inhibitory Concentration (MIC) of the compounds. The bacteria cultures (as a gram-positive bacteria *Staphylococcus aureus* ATTC 6538, *Bacillus subtilis* ATTC 6633 were used, and as a gram-negative bacteria *Escherichia coli* ATTC 3509, *Pseudomonas aeruginosa* ATTC 9027 were used, and as a fungi *Candida albicans* ATTC 10231) were grown in Luria-Bertani (LB) medium at 37°C for overnight. Each microorganism, at a concentration of 106 cells/mL, was inoculated on the surface of LB agar plates. The compounds were diluted with different concentrations (10-100 mg/mL). Subsequently, filter paper discs (6mm in diameter) were saturated either with compounds (50 μL) were placed on surface of each inoculated plate. The plates were incubated at 37°C for 24 h. After this period, it was possible to

observe the inhibition zone. Overall, cultured bacteria with inhibition zones equal or greater than 7 mm were considered as susceptible to compounds. DMSO was used to dissolve the compounds. The control was the solvent DMSO used for each compound and it had showd no inhibitions in preliminary studies.The positive control was antibiotic discs that were Gentamicine (10 mg/mL) and streptomycine (10 mg/mL) discs for *B. subtilis* and *P. aeriginosa*, *E. coli* and *S. aureus* respectively. In addition, nystatin (10 mg/mL) is used for *C. albicans*. The Minimum Inhibition Concentration of the compounds was considered as the concentration that gave the lowest zone (bigger than 6 mm, smaller than or equal to 7 mm) on the inoculated agar (Table 9) [57,58].

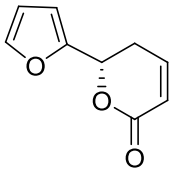
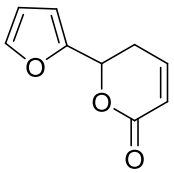
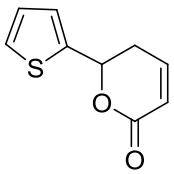
Table 9. MIC of the compounds that gave the inhibition zones bigger than 6 mm, smaller than or equal to 7 mm.

Compound	*C. Albicans* (mg/mL)	*E. Coli* (mg/mL)	*S. aereus* (mg/mL)	*B. Subtilis* (mg/mL)	*P. Aerogenesa* (mg/mL)
	25	20	30	10	-
	30	30	50	20	-
	40	50	40	50	-

- **Antioxidant Activity**

The free radical scavenging activity was determined by the DPPH assay described by Blois in 1958. In its radical form, DPPH absorbs at 517 nm, but upon reduction by an antioxidant or a radical species its absorption decreases. Briefly, 0.1 mM solution of DPPH in methanol was prepared and 150 µL of this solution was added to 50 µL of sample solutions in methanol at different concentrations (10-80 µM). Thirty minutes later, the absorbance was measured at 517 nm. Lower absorbance of the reaction mixture indicates higher free radical scavenging activity. Alpha tocopherol was used as standard [59].

Table 10. DPPH scavenging effect (%) of the compounds.

Substance	10 µM	20 µM	40 µM	60 µM	80 µM
	23.41±2.43	34.22±0.61	37.11±0.89	37.93±0.77	38.05±1.54
	21.23±1.14	32.38±0.84	37.75±0.59	38.6±1.29	38.1±0.39
	31.44±1.60	33.31±1.78	39.90±1.32	38.61±0.89	34.02±4.08
Alpha tocopherol	28.69±0.60	36.89±1.43	40.64±1.63	58.52±0.82	66.21±1.21

CHAPTER 4

CONCLUSION

In this study, the syntheses of three heteroaryl substituted allylic (*rac*-**7a**) and homoallylic alcohols (*rac*-**8a**-**b**) were achieved *via* Grignard reaction by using commercially available aldehydes (furan-2-carbaldehyde and thiophene-2-carbaldehyde) as starting materials. These alcohols were enantiomerically enriched with various type of enzymes by the help of the enzymatic resolution resulted in high enantiomeric excess values. Since the absolute configurations of corresponding alcohols were checked with the literature, we were able to determine the absolute configuration of all synthesized compounds because during the course of the reactions the configurations were preserved. After the chiral induction, *O*-acylation reaction proceeded to get diene system required for the target γ- and δ-lactones *via* Ring Closing Metathesis (RCM) reaction in the presence of Grubbs catalysts. Finally, biological activities (antibacterial and antioxidant activities) of desired γ- and δ-lactones were tested and good results were obtained in lower concentrations when compared with a standard.

CHAPTER 5

EXPERIMENTAL

Following materials and instruments were used to purify and identify the products during the study.

NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are expressed in ppm. and tetramethylsilane (TMS) 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.

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) and aluminum oxide TLC plates, visualized with UV-light, polymolybden phosphoric acid in ethanol. The relative portions of solvents are in volume:volume ratio used in column chromatography as eluent.

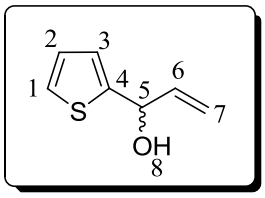
Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter at specified temperatures.

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.

5.1. Synthesis of Racemic Allylic Alcohol, *rac*-7a

Vinyl magnesium bromide in THF (1.0 N stock solution, 1.2 eq.) was placed in a 100 ml- round bottomed flask. Thiophene-2-carbaldehyde (1 eq.) diluted with dry ether was added dropwise at 0°C. The mixture was stirred under argon atmosphere at room temperature until all the aldehyde was consumed which was controlled by TLC. After completing the reaction, 1N HCl (2 mL) and saturated NH_4Cl (15 mL) were added and the aqueous layer was extracted with EtO_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The column chromatography (silica gel, EtOAc/ Hexane, 1:5) was used to purify *rac*-**7a**.

5.1.1. 1-(Thiophen-2-yl)prop-2-en-1-ol, *rac*-7a



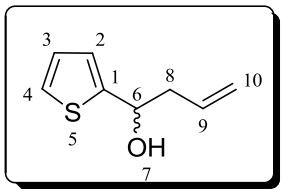
Colorless oil (85% yield). ^{1}H-NMR ($CDCl_3$): δ 7.13-7.15 (m, 1H, H_1), 6.84-6.86 (m, 2H, H_2 and H_3), 5.99 (ddd, 1H, J = 17.1, 10.3 and 5.6 Hz, H_6), 5.24-5.30 (m, 2H, H_5 and H_{7cis}), 5.12 (dt, 1H, J = 10.3 and 1.2 Hz, H_{7trans}), 2.61 (brs, 1H, H_8). ^{13}C-NMR ($CDCl_3$): δ 146.7, 139.4, 126.7, 125.2, 124.3, 115.6, 70.9. (Figure A1-2)

5.2. General Procedure for Homoallylic Alcohols, *rac*-8a-b

A crystal of I_2 and Mg (17.6 mmol, 1.7 eq.) were placed in 100 mL flask and dry ether (15 mL) was poured on it. After few minutes stirring, allylbromide (12.4 mmol, 1.2 eq.) was added dropwise and reflux was observed. The mixture was

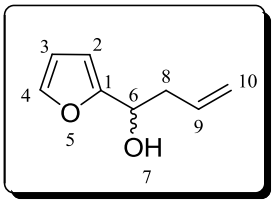
stirred for additional 30 minutes and the temperature was decreased to 0°C in an ice bath to add aldehyde (10.3 mmol, 1.0 eq.). Reaction continued until all the starting material has finished by controlling with TLC. After addition of 1 N HCl (9 mL) and saturated NH_4Cl (15 mL) solutions, the resulting mixture was extracted with ether (3x15 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude products were purified with flash column chromatography using mixture of ethyl acetate and hexane 1:6 for *rac*-**8a-b**.

5.2.1. 1-(Thiophen-2-yl)but-3-en-1-ol, *rac*-8a



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, 43.8. (Figure A3-4)

5.2.2. 1-(Furan-2-yl)but-3-en-1-ol, *rac*-8b



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 A5-6)

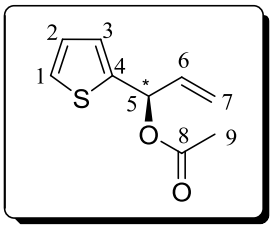
5.3. General Procedure for Enzymatic Resolution of Homoallylic Alcohols and Allylic Alcohols

Racemic alcohols *rac*-**7a** and *rac*-**8a-b** (1.0 mmol) were placed in a 50 mL round bottom flask and they were mixed with vinyl acetate (0.9 mL, 10 mmol) and corresponding cosolvent. Then, corresponding enzyme was added to this solution and the reaction was stirred at constant temperature (26 ^{o}C for *rac*-**7a** and *rac*-**8a**, 24^{o}C for *rac*-**8b**). The reaction was monitored by TLC and as the alcohol to acetylated product ratio became almost 50%, reaction was ended. Enzyme was filtered off. Separation of the acetylated product and the alcohol was performed by column chromatography (silica gel, EtOAc/hexane 1:5). (*S*)- alcohols and (*R*)-acetates were obtained.

5.3.1. (*S*)-(+)-1-(Thiophene-2-yl)prop-2-en-1-ol, (*S*)-(+)-7a

$[\alpha]_D^{29}$= +2.74 (*c* 1.00, $CHCl_3$) for 97% ee, in lit.[54] $[\alpha]_D^{26}$= +1.4 (*c* 0.5, $CHCl_3$), HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, , t_R=20.93, t_S=27.14 (Figure A8).

5.3.2. (*R*)-(+)-1-(Thiophene-2-yl)allyl acetate, (*R*)-(+)-9

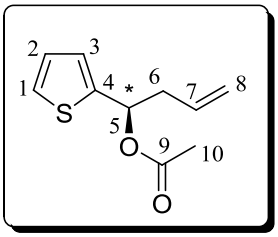


$[\alpha]_D^{33}$= +89,4 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.20 (dd, 1H, *J* = 5.0 and *J* = 1.2 Hz, H_1), 7.00 (dm, 1H, *J* = 3.6 Hz, H_2), 6.89 (dd, 1H, *J* = 5.0 and *J* = 3.6 Hz, H_3), 5.95-6.04 (m, 1H, H_5), 6.0 (ddd, 1H, *J* = 17.1, *J* = 10.4 and *J* = 6.0 Hz, H_6), 5.32 (dt, 1H, *J* = 17.1 and *J* = 2.4 Hz, H_7), 5.22 (dt, 1H, *J* = 10.4 and *J* = 1.3 Hz, H_7), 2.05 (s, 3H, H_9). ^{13}C NMR: δ 169.4, 141.9, 135.5, 126.6, 126.4, 125.0, 117.4, 71.2, 21.1. (Figure A9-10)

5.3.3. (*S*)-(-)-1-(Thiophene-2-yl)but-3-en-1-ol, (*S*)-(-)-8a

$[\alpha]_D^{27}$= -24.2 (*c* 1.00, CH_2Cl_2) for 99% ee, in lit.[55] $[\alpha]_D^{27}$= -8.2 (*c* 1.2 CH_2Cl_2) for 80% ee. 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).

5.3.4. (*R*)-(+)-1-(Thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-10

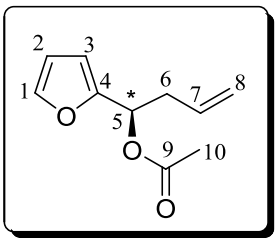


$[\alpha]_D^{23}$= + 36.6 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.18 (dd, 1H, *J* = 5.1 and 1.2 Hz, H_1), 6.95-6.96 (bd, 1H, *J* = 3.5 Hz, H_2), 6.87 (dd, 1H, *J* = 5.1 and 3.5 Hz, H_3), 6.01 (t, 1H, *J* = 8.5 Hz, H_7), 5.58-5.70 (m, 1H, H_5), 5.03-5.08 (bd, *J* = 17.1 Hz, 1H, H_8), 4.97-5.02 (bd, 1H, *J* = 8.5 Hz, H_8), 2.50-2.70 (m, 2H, H_6), 2.0 (s, 3H, H_{10}). ^{13}C NMR: δ 170.1, 143.2, 133.2, 126.8, 126.2, 125.6, 118.8, 70.7, 41.0, 21.4. (Figure A13-14)

5.3.5. (*S*)-(-)-1-(Furan-2-yl)but-3-en-1-ol, (*S*)-(-)-8b

$[\alpha]_D^{27}$= -21.6 (*c* 5.0, CH_2Cl_2) for 99% ee, in lit.[55] $[\alpha]_D^{27}$= -32.6 (*c* 0.50, CH_2Cl_2) for 84% ee. 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 A16)

5.3.6. (*R*)-(+)-1-(Furan-2-yl)but-3-enyl acetate, (*R*)-(+)-11



$[\alpha]_D^{20}$= +75,9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.30 (brs, 1H, H_1), 6.24 (brs, 2H, H_2 and H_3), 5.80 (t, 1H, *J* = 7.14 Hz, H_7), 5.58-6.65 (m, 1H, H_5), 5.04 (dd, 1H, *J* = 17.1 and 1.4 Hz, H_8), 5.00 (bd, 1H, *J* = 10.2 Hz, H_8), 2.63 (t, *J* = 7.0 Hz, 2H, H_6), 2.00 (s, 3H, H_{10}). ^{13}C NMR: δ 170.1, 143.2, 133.2, 126.8, 126.2, 125.6, 118.8, 70.7, 41.0, 21.4. (Figure A17-18)

5.4. General Procedure for Chemical Hydrolysis of the (*R*)-acetates

K_2CO_3 (1.03 g, 7.5 mmol) in 25 mL methanol and 0.5 mL H_2O were added to 7.1 mmol acetate [(*R*)-(+)-**10** or (*R*)-(+)-**11**] . The mixture was stirred for 1 h at 25°C. Ethyl acetate was used for dilution, then the mixture was washed with 1 N HCl, brine, and dried over $MgSO_4$. The crude alcohol [(*R*)-(+)-**8a** or (*R*)-(+)-**8b**] was separated by flash chromatography using ethyl acetate/hexane (1:4) as eluent.

5.4.1. (*R*)-(+)-1-(Thiophene-2-yl)but-3-en-1-ol, (*R*)-(+)-8a

$[\alpha]_D^{24}$= +11.3 (*c* 1.00, CH_2Cl_2).

5.4.2. (*R*)-(+)-1-(Furan-2-yl)but-3-en-1-ol, (*R*)-(+)-8b

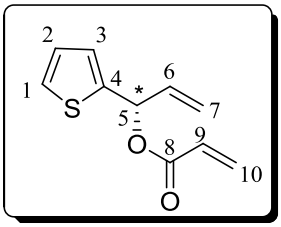
$[\alpha]_D^{20}$= +23.2 (*c* 1.00, CH_2Cl_2).

5.5. General Procedure for the Synthesis of Chiral Acrylate Esters

To a solution of homoallylic and allylic alcohols [(*S*)-(+)-**7a**, (*S*)-(-)-**8a**, and (*S*)-(-)-**8b**] (1 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Et_3N (2.96 mmol, 3 eq.). After 10 min. acryloyl chloride or methacryloyl chloride (1.48 mmol, 1.5 eq.) was added at room temperature. The mixture was stirred for 75 min. After adding 10 mL of water, the aqueous layer was extracted with CH_2Cl_2 (2x10mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. For allylic acrylate esters [(*S*)-(-)-**12**, (*S*)-(-)-**13**], the mixtures were separated by alumina oxide for chromatography using ethylacetate/hexane solvent as eluent (1:20) system. For homoallylic acrylate esters [**(*S*)-(-)-14**, (*R*)-(+)-**15**, (*S*)-(-)-**16**,

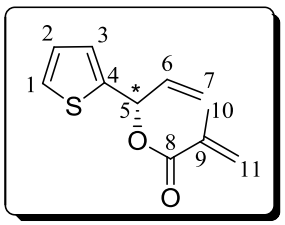
(*R*)-(+)-**17**, (*S*)-(-)-**18**, (*R*)-(+)-**19**], the crude product mixtures were separated by flash column chromatography using ethylacetate/hexane solvent as eluent (1:6) system for compounds.

5.5.1. (*S*)-(-)-1-(Thiophen-2-yl)allyl acrylate, (*S*)-(-)-12



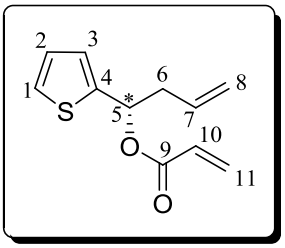
This is a pale yellow oil. (60% yield). $[\alpha]^{32}$= -52.7 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.22 (dd, *J* = 5.1 and *J* = 1.2 Hz, 1H, H_1), 7.01-6.99 (m, 1H, H_3), 6.90 (dd, *J* = 5.1 and *J* = 3.6 Hz, 1H, H_2), 6.52 (d, *J* = 6 Hz, 1H, H_5), 6.39 (dd, *J* = 17.3 and 1.4 Hz, 1H, H_9), 6.12-5.99 (m, 2H, H_{10}), 5.79 (dd, *J* = 10.4 and *J* = 1.4 Hz, 1H, H_6), 5.37- 5.23 (m, 2H, H_7). ^{13}C-NMR ($CDCl_3$): δ 163.7, 140.7, 134.3, 130.1, 127.3, 125.6, 125.4, 125.0, 116.5, 70.3. (Figure A19-20) IR (neat): 2960, 1722, 1174 cm^{-1}. MS (EI) *m/z* (rel. intensity) 194 [M^+, (39)], 123 (48), 122 (base), 121 (48), 111 (30). (Figure A21)

5.5.2. (*S*)-(-)-1-(Thiophen-2-yl)allyl methacrylate, (*S*)-(-)-13



This is a pale yellow oil. (61% yield). $[\alpha]^{23}$= -27.8 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.21 (dd, *J* = 5.2 and 1.2 Hz, 1H, H_1), 6.99 (d, *J* = 3.5 Hz, 1H, H_3), 6.90 (dd, *J* = 5.1 and 3.5 Hz, 1H, H_2), 6.50 (d, *J* = 5.9 Hz, 1H, H_{11}), 6.10 (brs, 1H, H_{11}), 6.03 (ddd, *J* = 17.0, 10.4, and 5.9 Hz, 1H, H_6), 5.52 (t, *J* = 1.6 Hz, 1H, H_5), 5.35 (dm, *J* = 17.1 Hz, 1H, H_{7trans}), 5.24 (dm, *J* = 10.4, 1H, H_{7cis}), 1.9 (s, 3H, H_{10}). ^{13}C-NMR ($CDCl_3$): δ 164.8, 140.9, 135.2, 134.5, 125.6, 125.1, 124.9, 124.8, 116.3, 70.5, 17.2. (Figure A22-23) IR (neat): 3105, 1716, 1147 cm^{-1}. MS (EI) *m/z* (rel. intensity) 208 [M^+, (20)], 180 (45), 123 [M^+-85 ($^+$OCOCHCH$_3$=CH$_2$), 122 (95, base). (Figure A24)

5.5.3. (*S*)-(-)-1-(Thiophen-2-yl)but-3-enyl acrylate, (*S*)-(-)-14

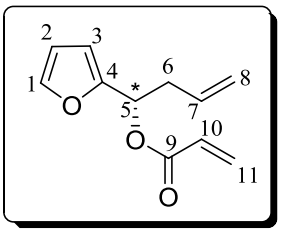


This is a pale yellow oil. (81% yield). $[\alpha]^{23}$= -108.2 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.20 (dd, *J* = 5.1 and *J* = 1.1 Hz, 1H, H_1), 7.00 (d, *J* = 3.2 Hz, 1H, H_3), 6.89 (dd, *J* = 5.1 and *J* = 3.5 Hz, 1H, H_2), 6.35 (dd, J_{trans} = 17.3 and *J* = 1.4 Hz, 1H, H_{11}), 6.10 (t, *J* = 6.9 Hz, 1H, H_5), 6.05 (dd, *J* = 17.3 and *J* = 10.4 Hz, 1H, H_{10}), 5.76 (dd, J_{cis} = 10.4 and *J* = 1.4 and Hz, 1H, H_{11}), 5.72-5.62 (m, 1H, H_7), 5.09-5.00 (m, 2H, H_8), 2.72 (dtt, *J* = 14.3, 7.3, and 1.1 Hz, 1H, H_6), 2.64 (dtt, *J* = 14.3, 6.5, and 1.2 Hz, 1H, $H_{6'}$). ^{13}C-NMR ($CDCl_3$): δ 165.5, 143.0, 133.1, 131.4, 128.7, 126.8, 126.2, 125.7, 118.8, 70.9, 40.9. (Figure A25-26) IR (neat): 3087, 2945, 1725, 833 cm^{-1}. MS (EI) *m/z* (rel. intensity) 167 [M^+- 41($^+$CH$_2$CH=CH$_2$), base]. (Figure A27)

5.5.4. (*R*)-(+)-1-(Thiophen-2-yl)but-3-enyl acrylate, (*R*)-(+)-15

$[\alpha]^{21}$= +32.5 (*c* 1.00, CH_2Cl_2).

5.5.5. (*S*)-(-)-1-(Furan-2-yl)but-3-enyl acrylate, (*S*)-(-)-16

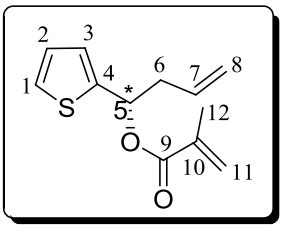


This is a pale yellow oil. (70% yield). $[\alpha]^{27}$= -108.3 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.31 (dd, *J* = 1.7 and *J* = 0.8 Hz, 1H, H_1), 6.35 (dd, J_{trans} = 17.3 and *J* = 1.5 and Hz, 1H, H_{11}), 6.27-6.24 (m, 2H, H_2 and H_3), 6.04 (dd, *J*= 10.4 and *J*=17.3 Hz, 1H, H_{10}), 5.88 (t, *J* = 7.1 Hz, 1H, H_5), 5.75 (dd, J_{cis} = 10.4 and *J* = 1.5 Hz, 1H, H_{11}), 5.68-5.58 (m, 1H, H_7), 5.08-4.98 (m, 2H, H_8), 2.68 (tt, *J* = 7.0 and *J* = 1.2 Hz, 2H, H_6). ^{13}C-NMR ($CDCl_3$): δ164.0, 151.0, 141.4, 131.6, 129.9, 127.3, 117.3, 109.1, 107.7, 66.9, 35.9. (Figure A28-29) IR (neat): 1722, 1404, 1178 cm^{-1}. MS (EI) *m/z* (rel. intensity) 151 [M^+- 41 ($^+CH_2CH{=}CH_2$), base], 91 (30). (Figure A30)

5.5.6. (*R*)-(+)-1-(Furan-2-yl)but-3-enyl acrylate, (*R*)-(+)-17

$[\alpha]^{21}$= +112.7 (*c* 1.00, CH_2Cl_2).

5.5.7. (*S*)-(-)-1-(Thiophen-2-yl)but-3-enyl methacrylate, (*S*)-(-)-18

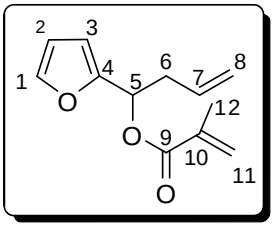


This is a pale yellow oil. (75% yield). $[\alpha]^{19}$= -67.4 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.17 (dd, *J* = 5.1 and *J* = 1.1 Hz, 1H, H_1), 6.97 (d, *J* = 3.5 Hz, 1H, H_3), 6.87 (dd, *J* = 5.1 and *J* = 3.5 Hz, 1H, H_2), 6.09-6.05 (m, 2H, H_{11}), 5.72-5.62 (m, 1H, H_7), 5.48 (t, *J* = 1.6 Hz, 1H, H_5), 5.05 (dd, J_{trans} = 17.1 and *J* = 1.5 Hz, 1H, H_8), 5.03-4.99 (m, 1H, H_8), 2.70 (dtt, *J* = 14.3, 7.2, and 1.2 Hz, 1H, H_6), 2.63 (dtt, *J* = 14.2, 6.5, and 1.4 Hz, 1H, $H_{6'}$), 1.87 (s, 3H, H_{12}). ^{13}C-NMR ($CDCl_3$): δ 165.1, 141.9, 135.2, 131.8, 125.4, 124.6, 124.1, 117.4, 69.7, 39.8, 17.2 (Figure A31-32) IR (neat): 3078, 1715, 1151 cm^{-1}. MS (EI) *m/z* (rel. intensity) 181 [M^+- 41 ($^+CH_2CH{=}CH_2$), base]. (Figure A33)

5.5.8. (*R*)-(+)-1-(Thiophen-2-yl)but-3-enyl methacrylate, (*R*)-(+)-19

$[\alpha]^{21}$= +61.1 (*c* 1.00, CH_2Cl_2).

5.5.9. 1-(Furan-2-yl)but-3-enyl Methacrylate, *rac*-28

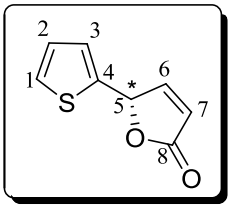


This is pale yellow oil. (65% yield). ^{1}H-NMR ($CDCl_3$): δ 7.30 (dd, J = 1.7 and J = 0.8 Hz, 1H, H_1), 6.26-6.24 (m, 2H, H_2 and H_3), 6.04 (m, 1H, H_{11}), 5.86 (t, J = 7.0 Hz, 1H, H_{11}), 5.64 (ddd, J = 17.1, J = 10.2 Hz, and J=7.0, 1H, H_7), 5.48 (t, J=1.6 Hz, 1H, H_5), 5.05 (ddd, J_{trans} = 17.1, J = 3.0 and J = 1.4 Hz, 1H, H_8), 4.99 (ddd, J_{cis}= 10.2, J = 3.1, and J=1.7 Hz, 1H, H_8), 2.69-2.66 (m, 2H, H_6), 1.86 (t, J=1.1, 3H, H_{12}). ^{13}C-NMR ($CDCl_3$): δ 165.2, 151.2, 141.3, 135.2, 131.7, 124.6, 117.2, 109.1, 107.5, 67.1, 36.0, 17.2.

5.6. General Procedure for the Synthesis of γ-Lactones *via* RCM

0.01 M CH_2Cl_2 solution of first generation Grubbs catalyst [10 mol % for (*S*)-(-)-**12**, and 15 mol % for (*S*)-(-)-**13**] was added to 0.01 M refluxing solution of acrylate ester (1 mmol) in CH_2Cl_2 by slow addition under argon atmosphere. The reaction was stirred 24 h at reflux and controlled by TLC. The solvent was evaporated in vacuum and the purification of the crude product was done by column chromatography (silica gel, EtOAc/hexane 1:3 for both products).

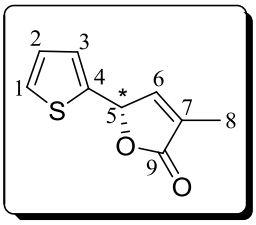
5.6.1. (*S*)-(-)-5-(Thiophen-2-yl)furan-2(5H)-one, (*S*)-(-)-20



This is a orange-brown thick liquid. (60% yield). $[\alpha]^{24.6}$= -20.1 (*c* 0.10, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.49 (dd, J = 5.6 and J = 1.7 Hz, 1H, H_6), 7.30 (dd, J = 5.1 and J = 1.1 Hz, 1H, H_1), 7.03 (d, J = 3.1 Hz, 1H, H_3), 6.96 (dd, J = 5.1 and J = 3.6

Hz, 1H, H_2), 6.19 (dd, J = 5.6 and J = 2.1 Hz, 1H, H_7), 6.16 (t, J = 1.7, 1H, H_5). ^{13}C-NMR ($CDCl_3$): δ 172.1, 154.4, 137.0, 127.7, 127.6, 127.5, 122.3, 79.7 (Figure A34-35) IR (neat): 1754, 1019, 823 cm^{-1}. HRMS, Calculated $[M]^+$ 167.0176, Measured $[M]^+$ 167.0167.

5.6.2. (*S*)-(-)-3-Methyl-5-(Thiophen-2-yl)furan-2(5H)-one, (*S*)-(-)-21



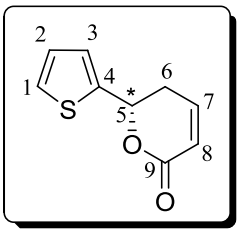
This is a dark red thick liquid. (24% yield). $[\alpha]^{23.1}$= -25.1 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.28 (dd, J = 5.1 and J = 1.1 Hz, 1H, H_1), 7.07 (m, 1H, H_6), 7.02 (d, J = 3.3 Hz, 1H, H_3), 6.96 (dd, J = 5.1 and J = 3.6 Hz, 1H, H_2), 6.02 (m, 1H, H_5), 1.95 (t, J = 1.8 Hz, 3H, H_8). ^{13}C-NMR ($CDCl_3$): δ 172.0, 145.5, 136.7, 129.7, 126.1, 126.0, 125.9, 76.1, 9.6 (Figure A40-41) IR (neat): 3088, 1752, 1035 cm^{-1}. HRMS, Calculated $[M]^-$ 179.0167, Measured $[M]^-$ 179.0166.

5.7. General Procedure for the Synthesis of δ-Lactones *via* RCM

To a solution of acrylate ester (1 mmol) [(*S*)-(-)-**14**, (*R*)-(+)-**15**, (*S*)-(-)-**16**, (*R*)-(+)-**17,** (*S*)-(-)-**18**, (*R*)-(+)-**19**] in CH_2Cl_2 (8 mL), second generation Grubbs catalyst [5% for (*S*)-(-)-**14**, (*R*)-(+)-**15**, (*S*)-(-)-**16**, (*R*)-(+)-**17** and 7 % for (*S*)-(-)-**18,** (*R*)-(+)-**19**] was added and refluxed 80 min. for (*S*)-(-)-**14**, (*R*)-(+)-**15**, (*S*)-(-)-**16**, (*R*)-(+)-**17** and 4 h for (*S*)-(-)-**18,** (*R*)-(+)-**19** substrates. The product was concentrated

and purified by column chromatography (silica gel, EtOAc/hexane 1:2 for (*S*)-(-)-**22**, (*R*)-(+)-**23**, (*S*)-(-)-**24**, (*R*)-(+)-**25** and 1:4 for (*S*)-(-)-**26,** (*R*)-(+)-**27**).

5.7.1. (*S*)-(-)-6-(Thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-22

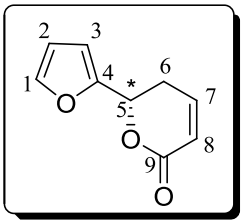


This is a light brown liquid. (55% yield). $[\alpha]^{23.6}$= -127.3 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.25 (dd, *J* = 5.1 and *J* = 1.1 Hz, 1H, H_1), 7.03 (d, *J* = 3.5 Hz, 1H, H_3), 6.93 (dd, *J* = 5.0 and *J* = 3.6 Hz, 1H, H_2), 6.88 (ddd, *J* = 9.7, *J* = 5.5 and *J* = 2.9 Hz, 1H, H_7), 6.06 (m, 1H, H_8), 5.62 (dd, *J* = 10.6 and *J* = 4.6 Hz, 1H, H_5), 2.79-2.63 (m, 2H, H_6). ^{13}C-NMR ($CDCl_3$): δ 163.5, 144.6, 141.6, 127.3, 126.5, 126.3, 122.5, 75.4, 32.0 (Figure A42-43) IR (neat): 3105, 2901, 1725, cm^{-1}. HRMS, Calculated $[M]^+$ 181.0245, Measured $[M]^+$ 181.0323.

5.7.2. (*R*)-(+)-6-(Thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*R*)-(+)-23

$[\alpha]^{22}$= +37.4 (*c* 1.00, CH_2Cl_2).

5.7.3. (*S*)-(-)-6-(Furan-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-24

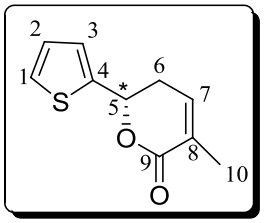


This is a light brown liquid. (65% yield). $[\alpha]^{23.5}$= -101.1 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.35 (dd, *J* = 1.8 and *J* = 0.8 Hz, 1H, H_1), 6.88 (ddd, *J* = 9.8, *J* = 5.7 and *J* = 2.8 Hz, 1H, H_7), 6.35 (d, *J* = 3.3 Hz, 1H, H_3), 6.30 (dd, *J* = 3.3 and *J* = 1.8 Hz, 1H, H_2), 6.01 (ddd, *J* = 9.8, *J* = 2.5 and *J* = 1.1 Hz, 1H, H_8), 5.41 (dd, *J* = 11.1 and *J* = 4.2 Hz, 1H, H_5), 2.90-2.52 (m, 2H, H_6). ^{13}C-NMR ($CDCl_3$): δ 161.9, 149.5, 143.3, 141.9, 120.5, 109.5, 107.9, 71.2, 26.6 (Figure A48-49) IR (neat): 3122, 2911, 1727 cm^{-1}. HRMS, Calculated $[M]^+$ 165.0473, Measured $[M]^+$ 165. 0558.

5.7.4. (*R*)-(+)-6-(Furan-2-yl)-5,6-dihydro-2H-pyran-2-one, (*R*)-(+)-25

$[\alpha]^{23}$= +67.2 (*c* 1.00, CH_2Cl_2).

5.7.5. (*S*)-(-)-3-Methyl-6-(Thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-26



This is a white-orange-brown solid. (23% yield). $[\alpha]^{21}$= -72.6 (*c* 1.00, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): δ 7.24 (dd, *J* = 5.1 and *J* = 1.2 Hz, 1H, H_1), 7.02-7.00 (m, 1H, H_3), 6.92 (dd, *J* = 5.0 and *J* = 3.6 Hz, 1H, H_2), 6.57 (ddd, *J* = 5.8, *J* = 2.9 and *J* = 1.5 Hz, 1H, H_7), 5.58 (dd, *J* = 11.0 and *J* = 4.1 Hz, 1H, H_5), 2.77-2.57 (m, 2H, H_6) 1.91-1.89 (m, 3H, H_{10}). ^{13}C-NMR ($CDCl_3$): δ 163.6, 140.4, 136.9, 128.2, 125.7, 124.8, 124.6, 73.9, 30.8, 16.1 (Figure A50-51) IR (neat): 3092, 1706, 1112 cm^{-1}. HRMS, Calculated $[M]^+$ 217.0299, Measured $[M]^+$ 217.0302. M.P. = 75-77°C.

5.7.6. (*R*)-(+)-3-Methyl-6-(Thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*R*)-(+)-27

$[\alpha]^{25}$= +36.6 (*c* 0.60, CH_2Cl_2).

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APPENDIX A

SUPPORTING INFORMATION

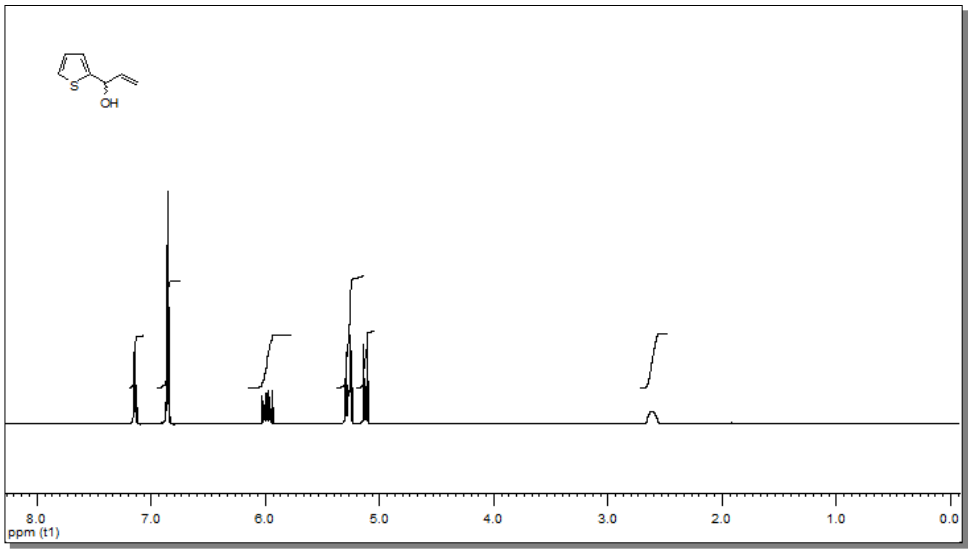

Figure A1. ^{1}H-NMR spectrum of 1-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**7a**

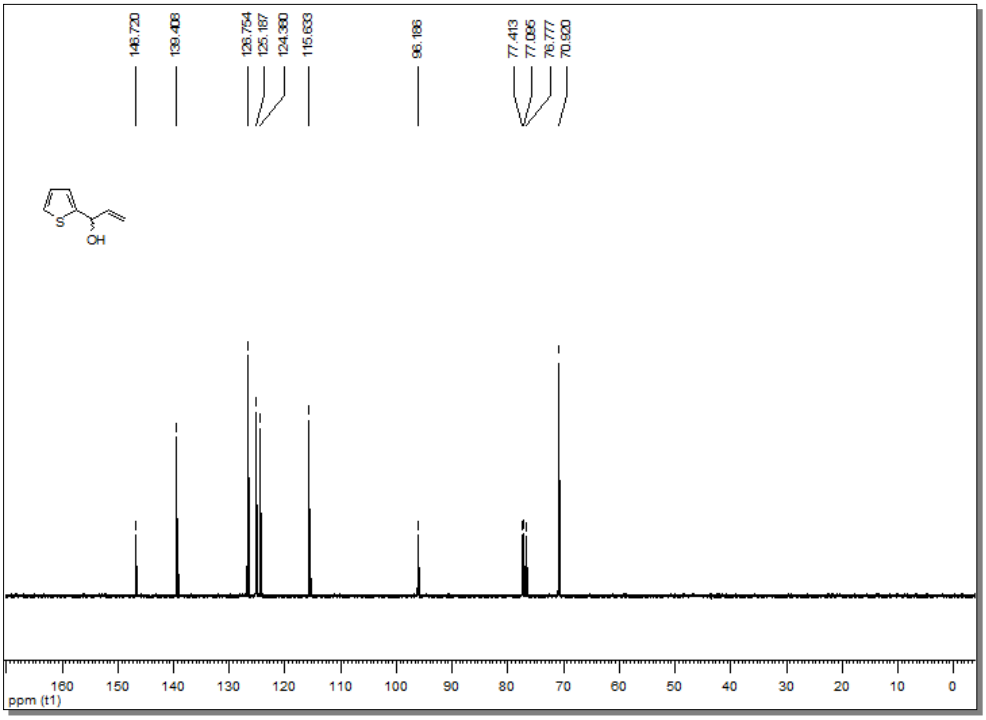

Figure A2. ^{13}C-NMR spectrum of 1-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**7a**

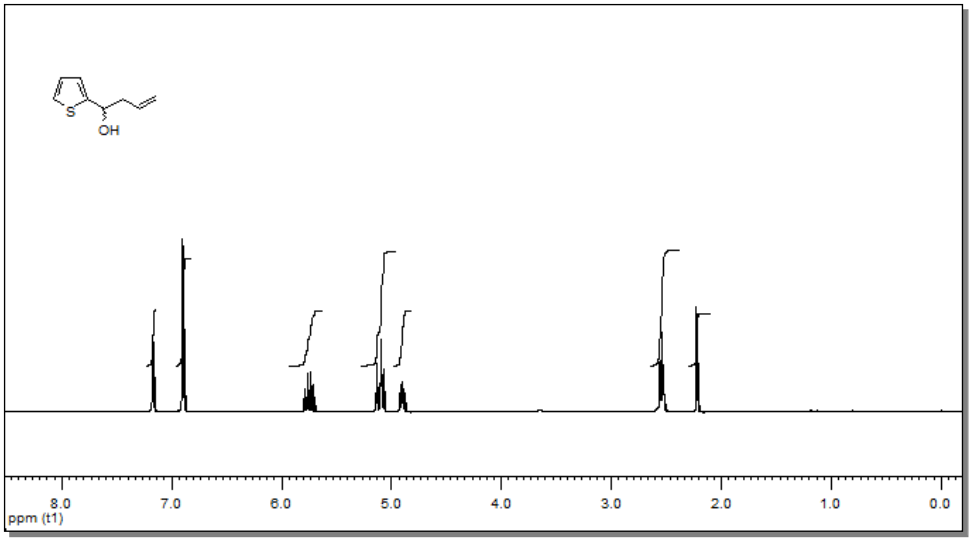

Figure A3. ^{1}H-NMR spectrum of 1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**8a**

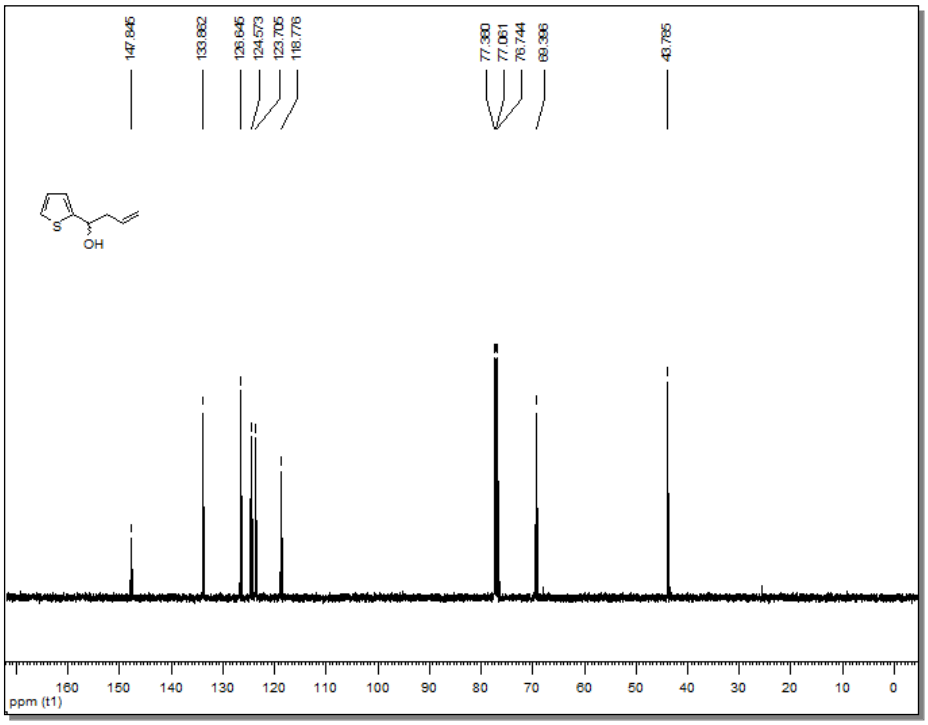

Figure A4. ^{13}C-NMR spectrum of 1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**8a**

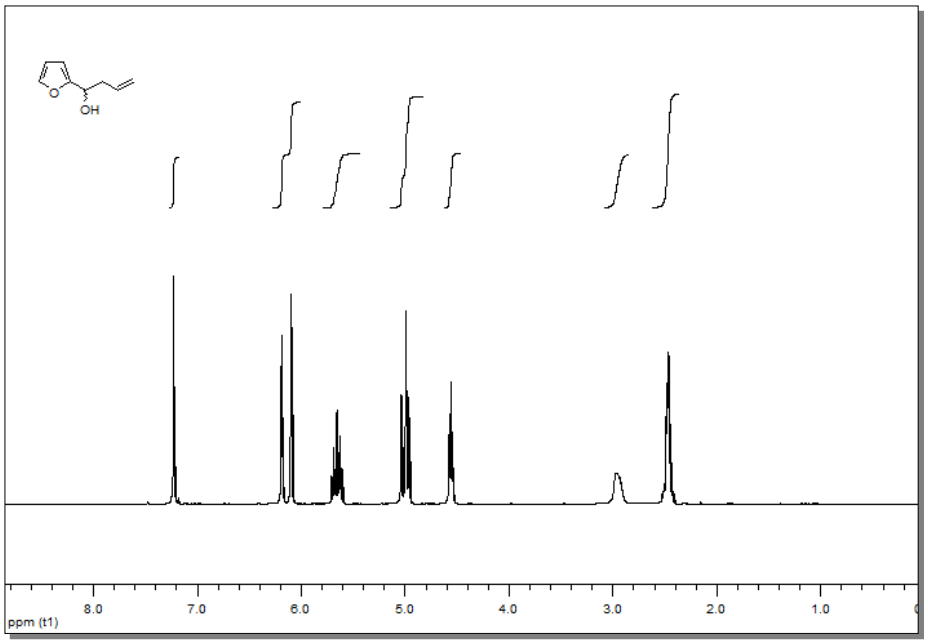

Figure A5. ^{1}H-NMR spectrum of 1-(furan-2-yl)prop-2-en-1-ol, *rac*-**7b**

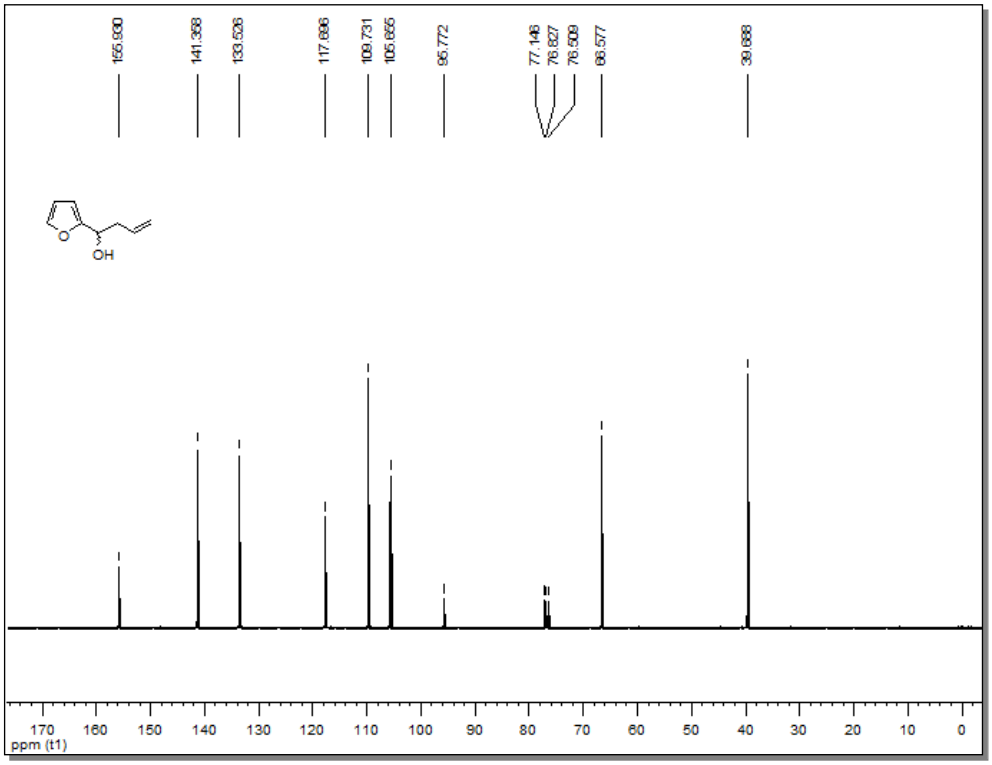

Figure A6. ^{13}C-NMR spectrum of 1-(furan-2-yl)but-3-en-1-ol, *rac*-**7b**

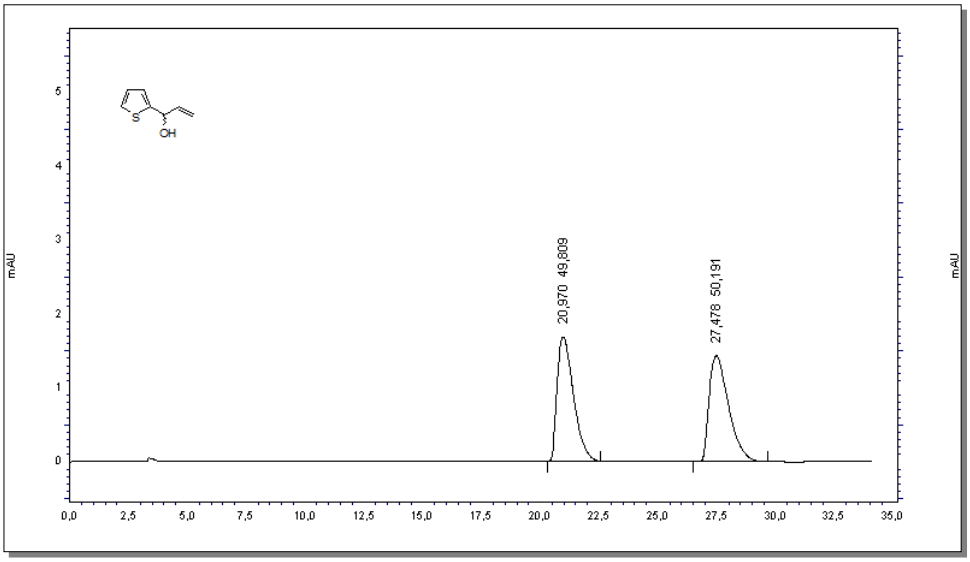

Figure A7. HPLC chromatogram of 1-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**7a**

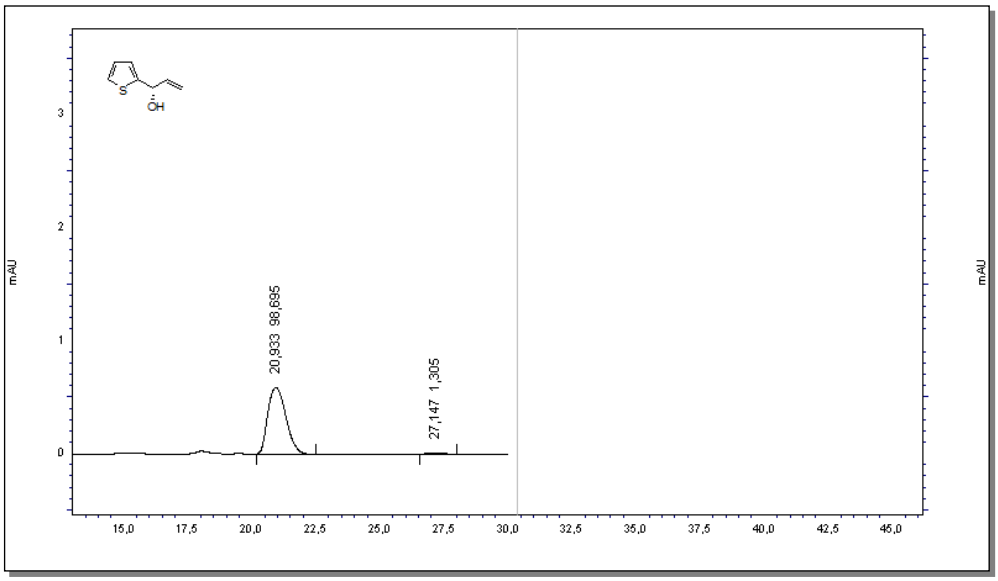

Figure A8. HPLC chromatogram of (*S*)-(+)-1-(thiophene-2-yl)prop-2-en-1-ol, (*S*)-(+)-**7a**

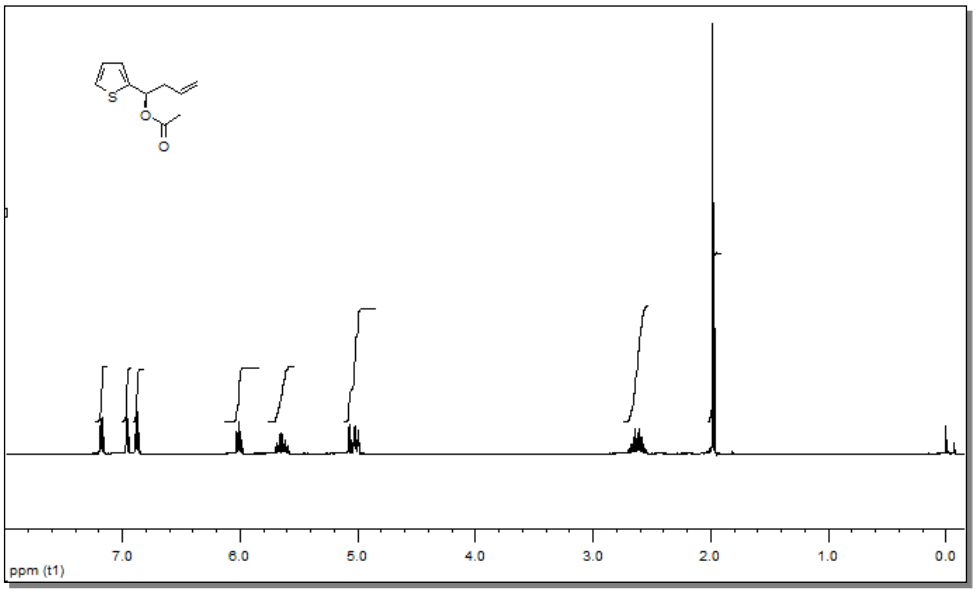

Figure A9. ^{1}H-NMR spectrum of (*R*)-(+)-1-(thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-**9**

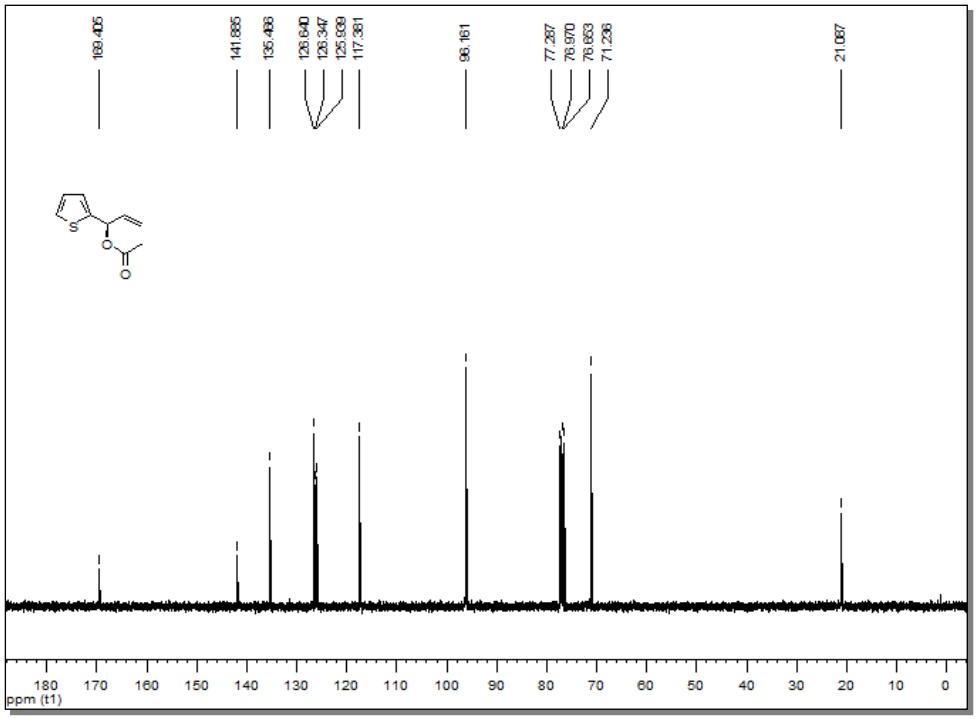

Figure A10. ^{13}C-NMR spectrum of (*R*)-(-)-1-(thiophene-2-yl)allyl acetate, (R)-(+)-**9**

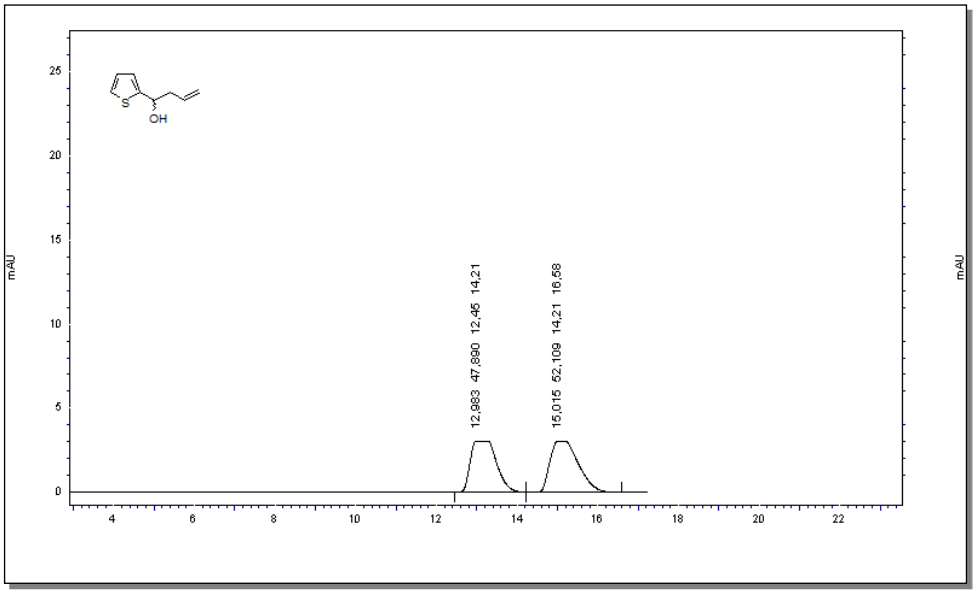

Figure A11. HPLC chromatogram of 1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**8a**

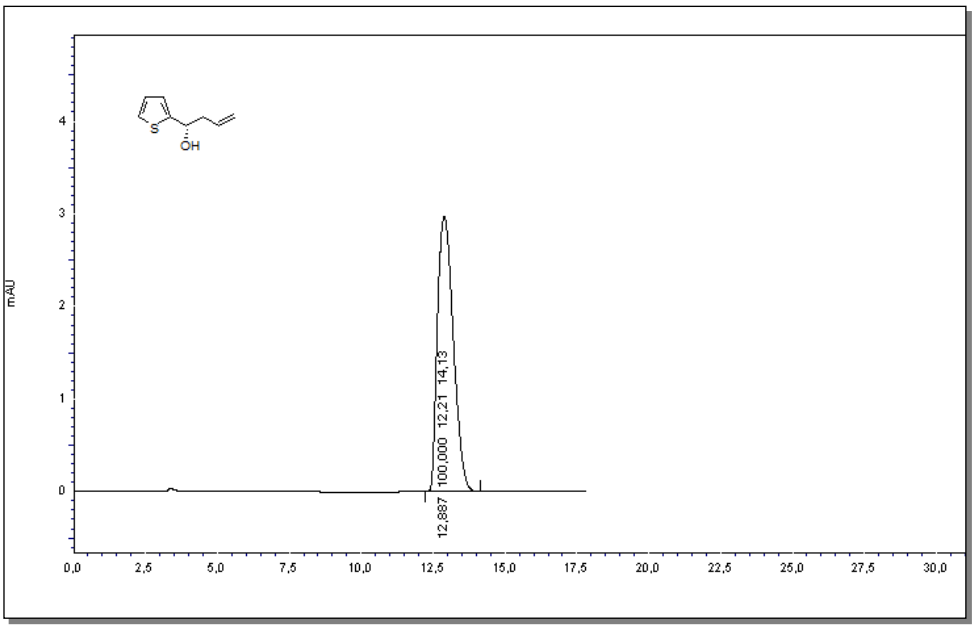

Figure A12. HPLC chromatogram of (*S*)-(-)-1-(thiophene-2-yl)but-3-en-1-ol, (*S*)-(-)-**8a**

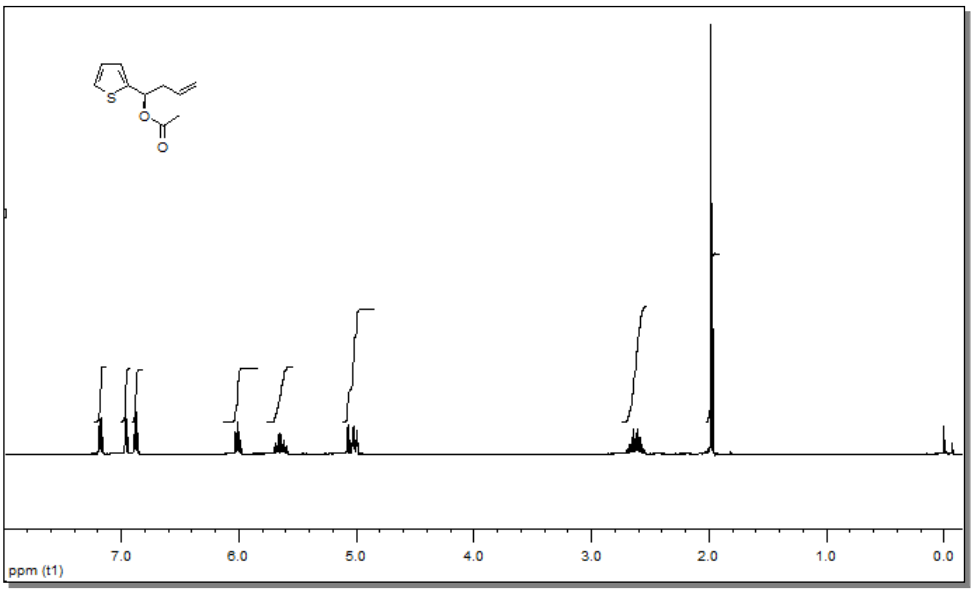

Figure A13. ^{1}H-NMR spectrum of (*R*)-(+)-1-(thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-**10**

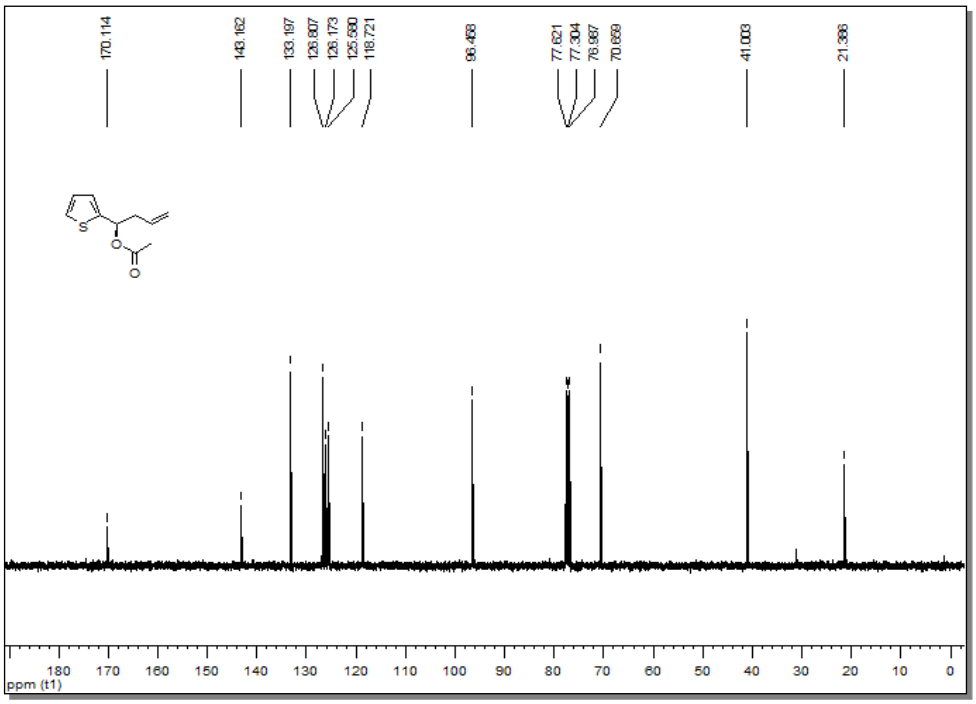

Figure A14. ^{13}C-NMR spectrum of (*R*)-(+)-1-(thiophene-2-yl)but-3-enyl acetate,(*R*)-(+)-**10**

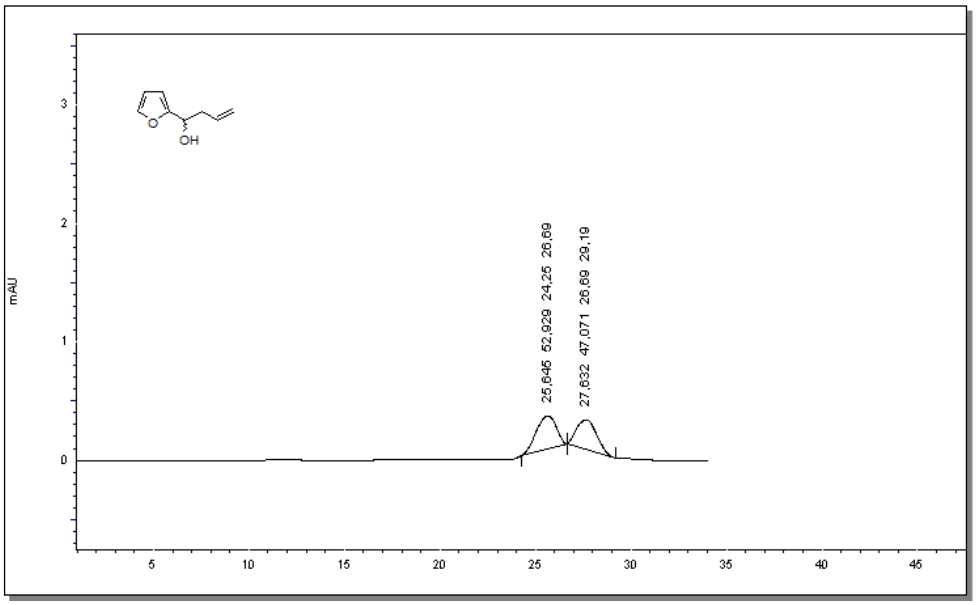

Figure A15. HPLC chromatogram of 1-(furan-2-yl)but-3-en-1-ol, *rac*-**8b**

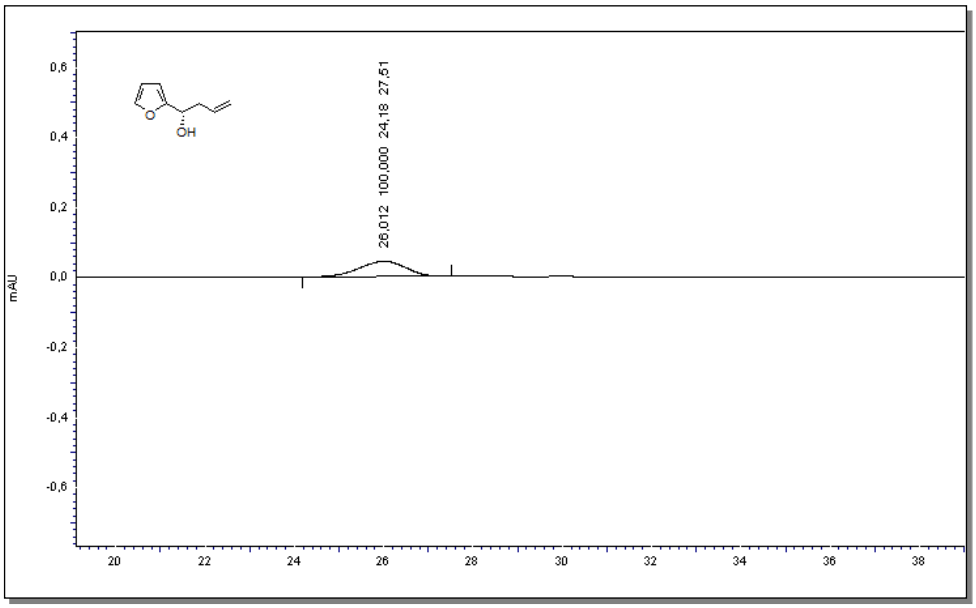

Figure A16. HPLC chromatogram of (*S*)-(-)-1-(furan-2-yl)but-3-en-1-ol, (*S*)-(-)-**8b**

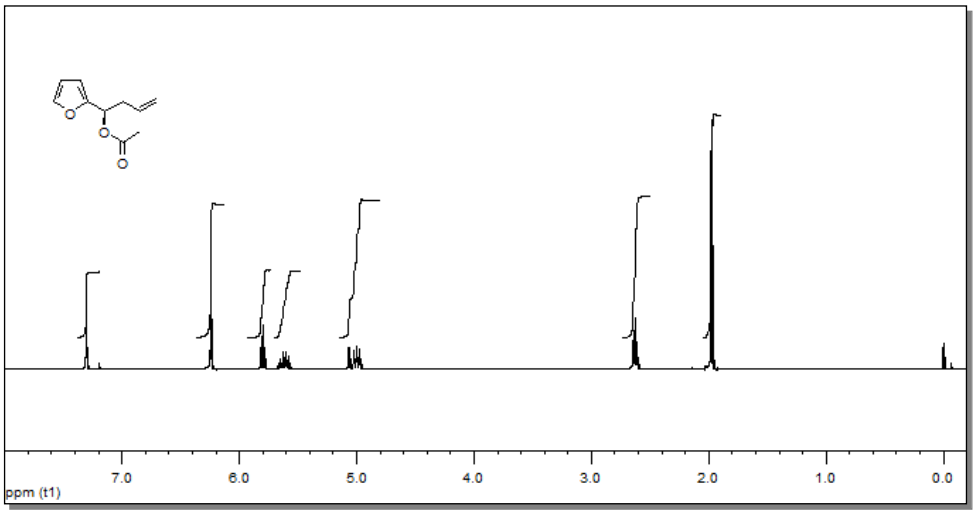

Figure A17. ^{1}H-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)but-3-enyl acetate, (*R*)-(+)-**11**

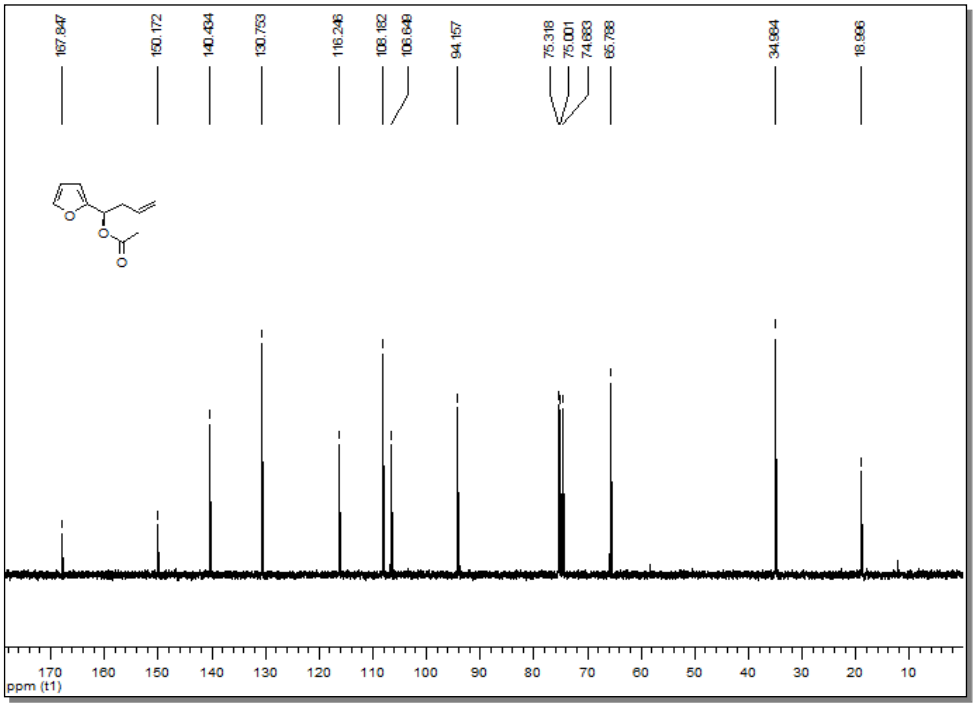

Figure A18. ^{13}C-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)but-3-enyl acetate, (*R*)-(+)-**11**

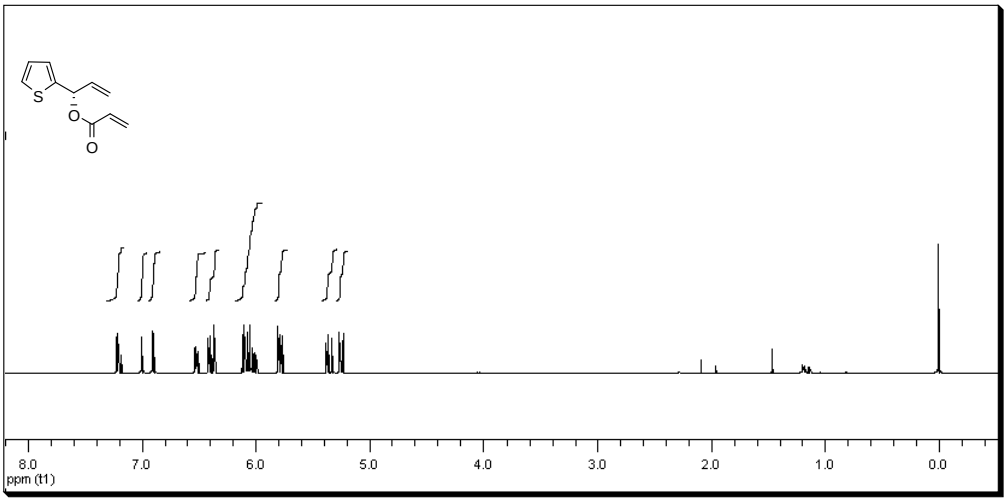

Figure A19. ^{1}H-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)allyl acrylate, (*S*)-(-)-**12**

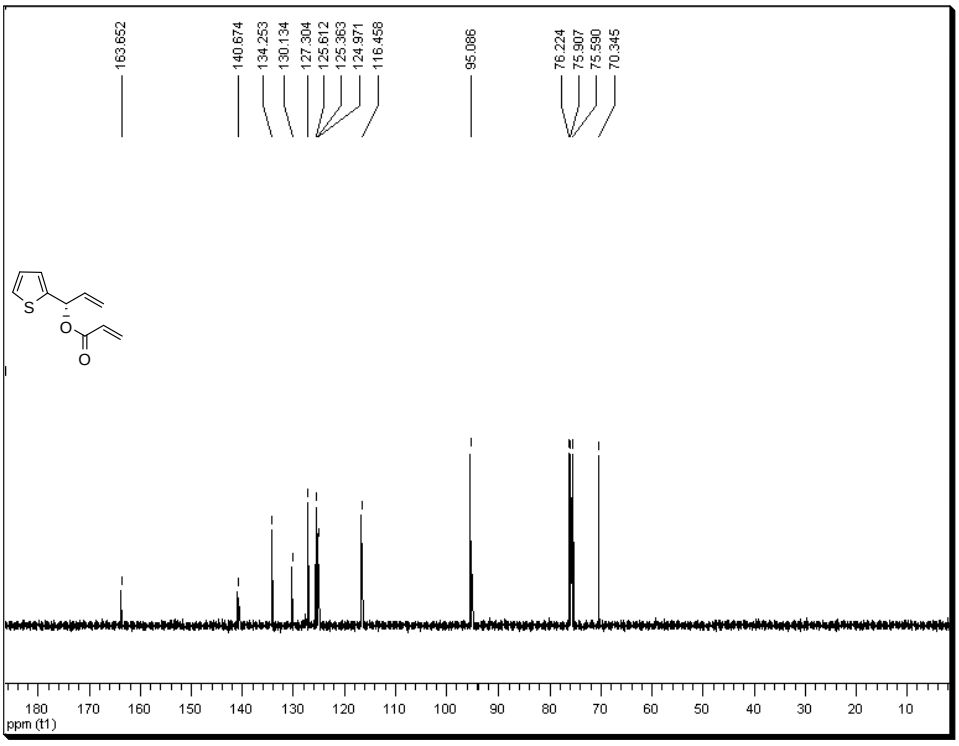

Figure A20. ^{13}C-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)allyl acrylate, (*S*)-(-)-**12**

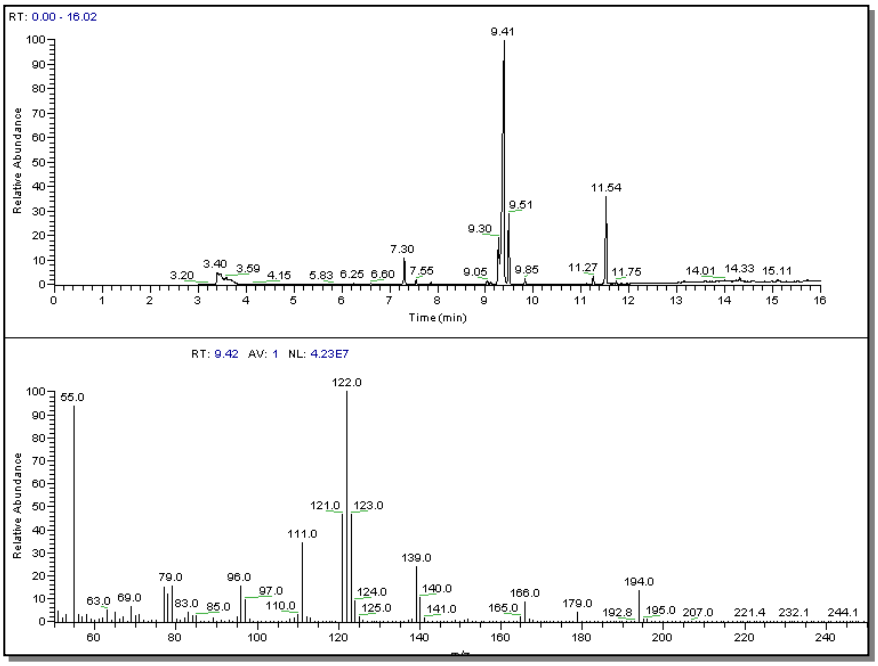

Figure A21. GC-MS result of (*S*)-(-)-**12**

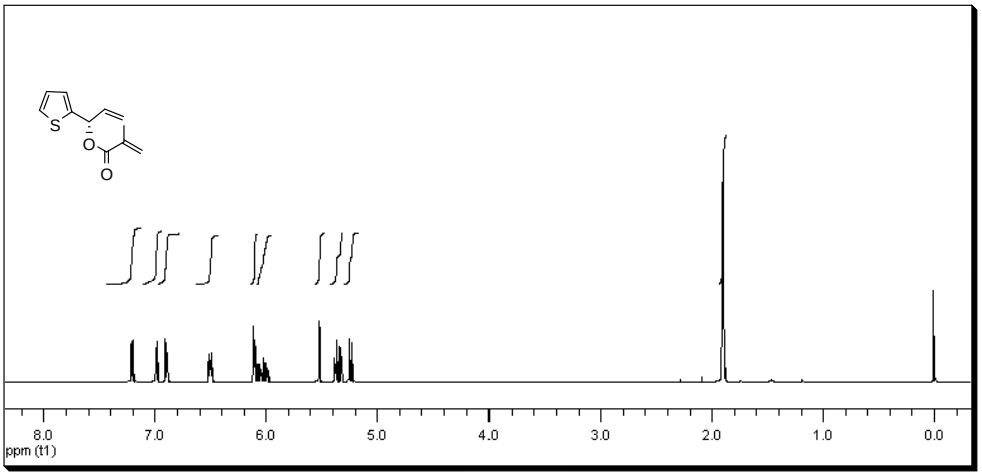

Figure A22. ^{1}H-NMR spectrum of (S)-(-)-1-(thiophen-2-yl)allyl methacrylate, (S)-(-)-**13**

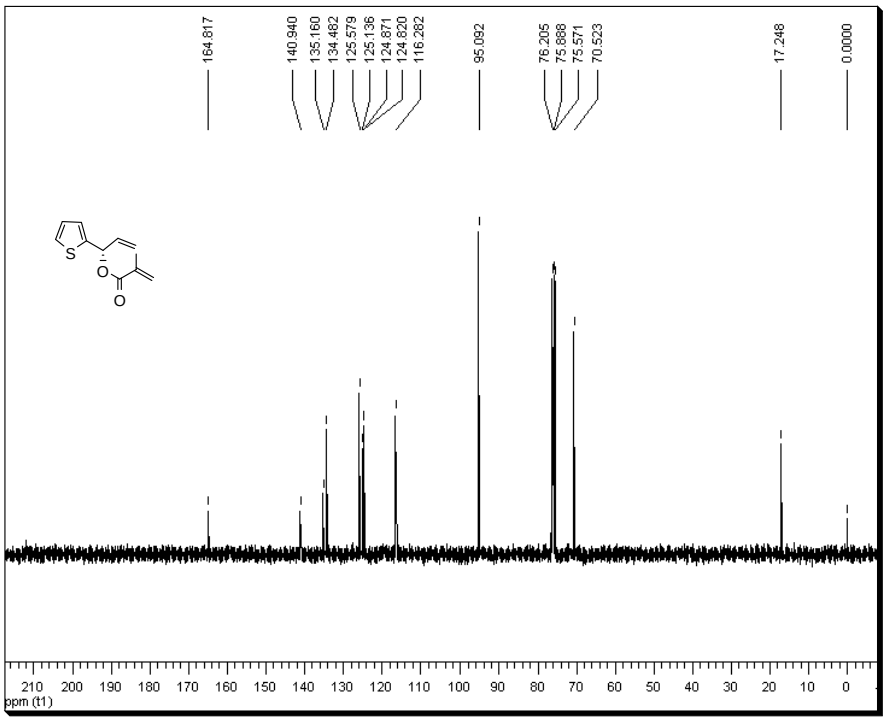

Figure A23. ^{13}C-NMR spectrum of (S)-(-)-1-(thiophen-2-yl)allyl methacrylate, (S)-(-)-**13**

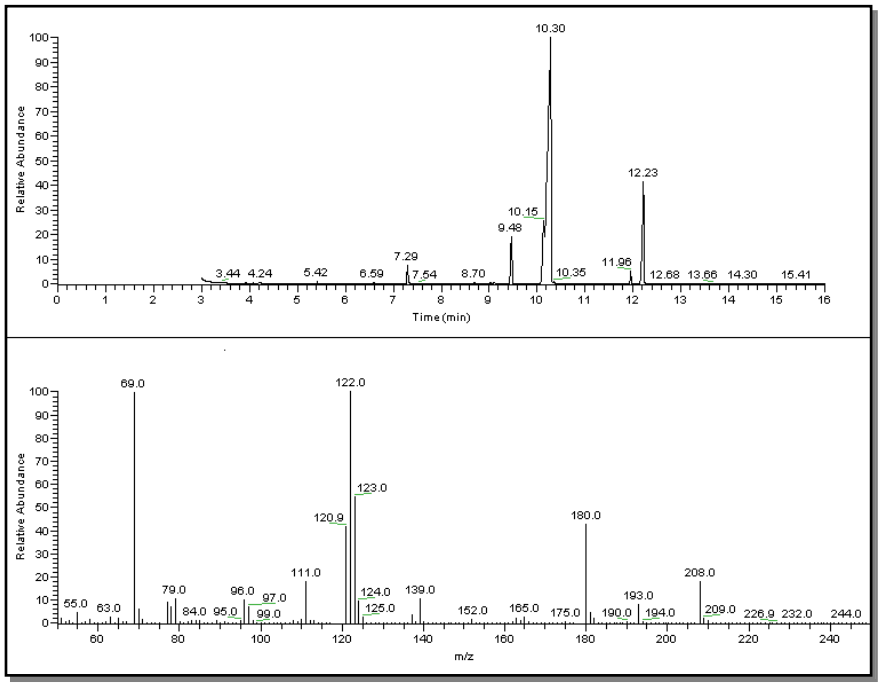

Figure A24. GC-MS result of (S)-(-)-**13**

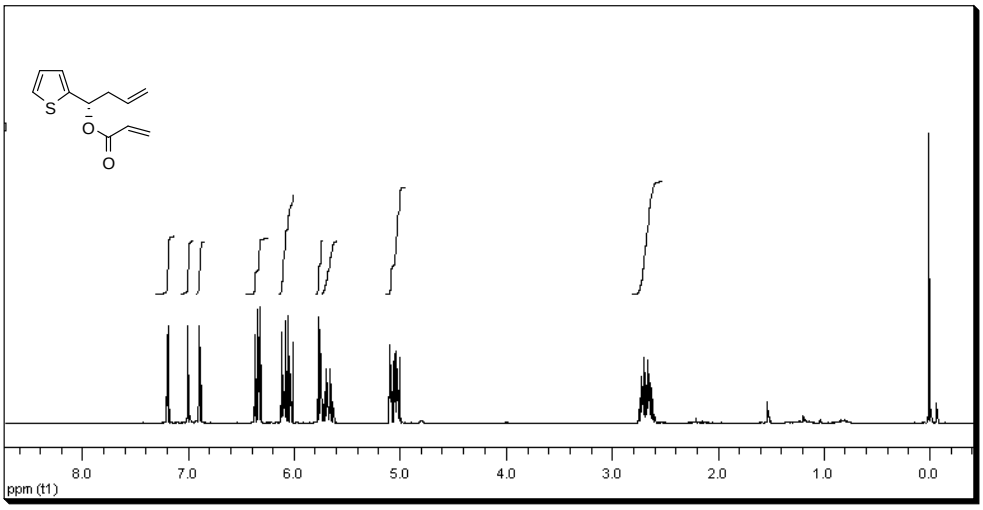

Figure A25. ^{1}H-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)but-3-enyl acrylate, (*S*)-(-)-**14**

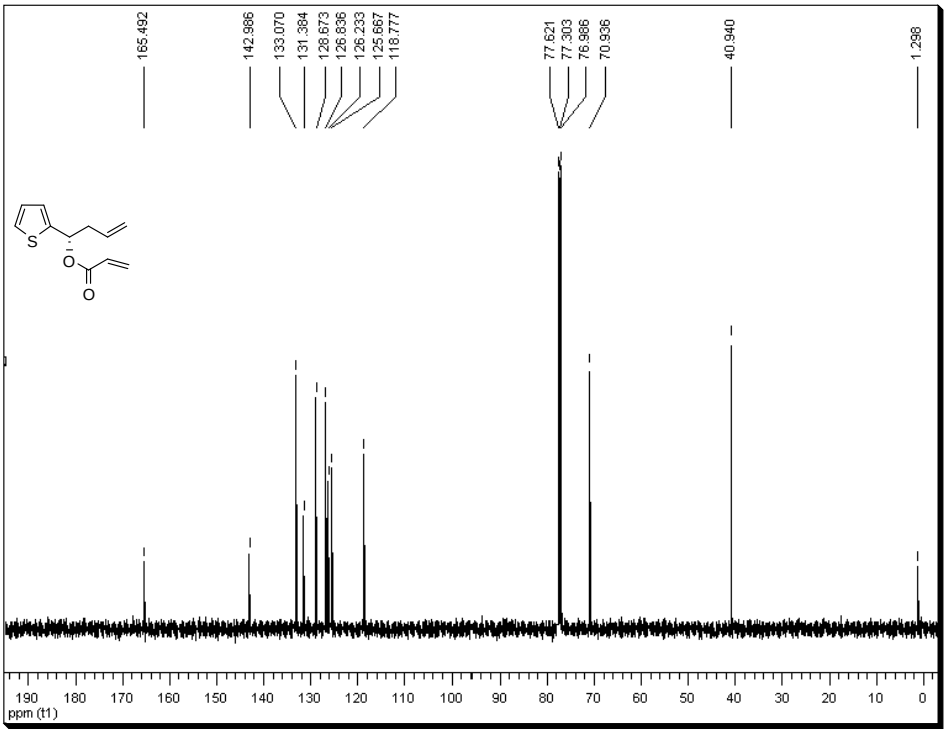

Figure A26. ^{13}C-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)but-3-enyl acrylate, (*S*)-(-)-**14**

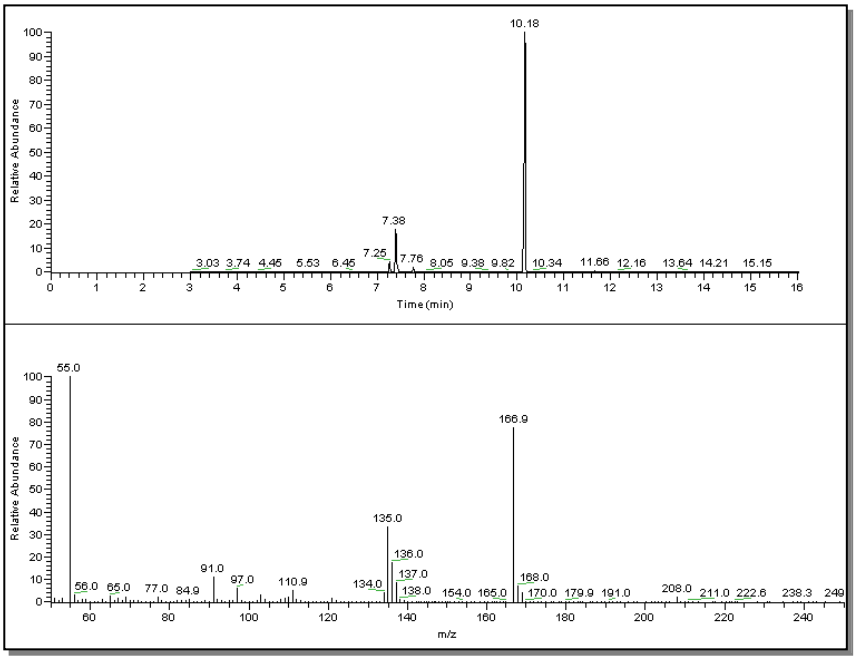

Figure A27. GC-MS result of (*S*)-(-)-**14**

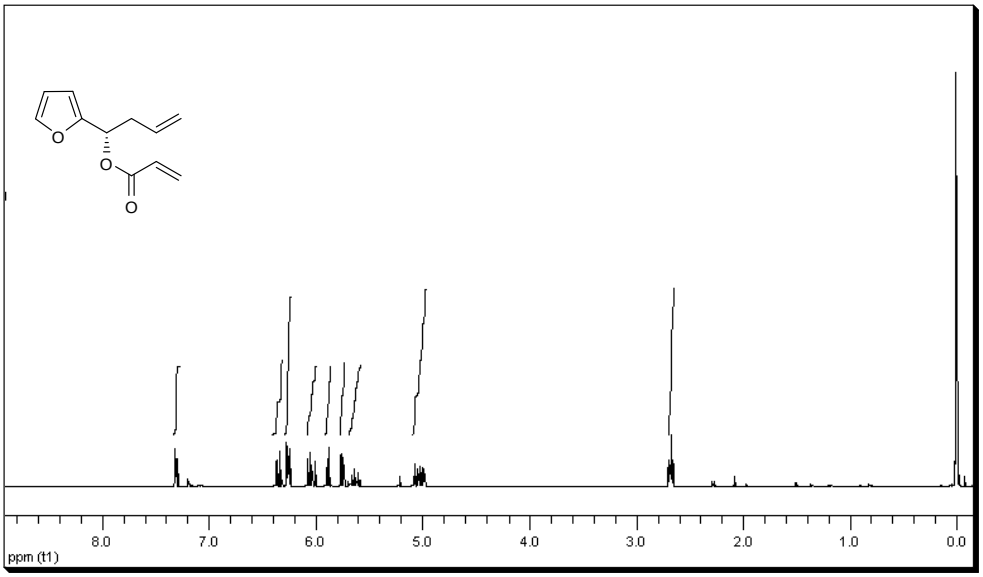

Figure A28. ^{1}H-NMR spectrum of (*S*)-(-)-1-(furan-2-yl)but-3-enyl acrylate, (*S*)-(-)-**16**

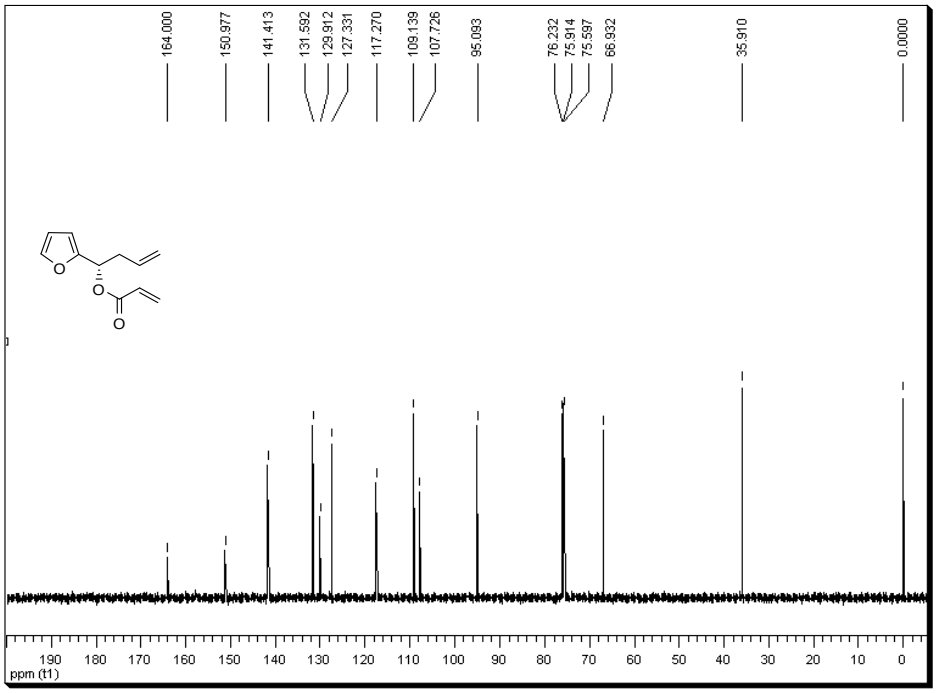

Figure A29. ^{13}C-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)but-3-enyl acrylate, (*S*)-(-)-**16**

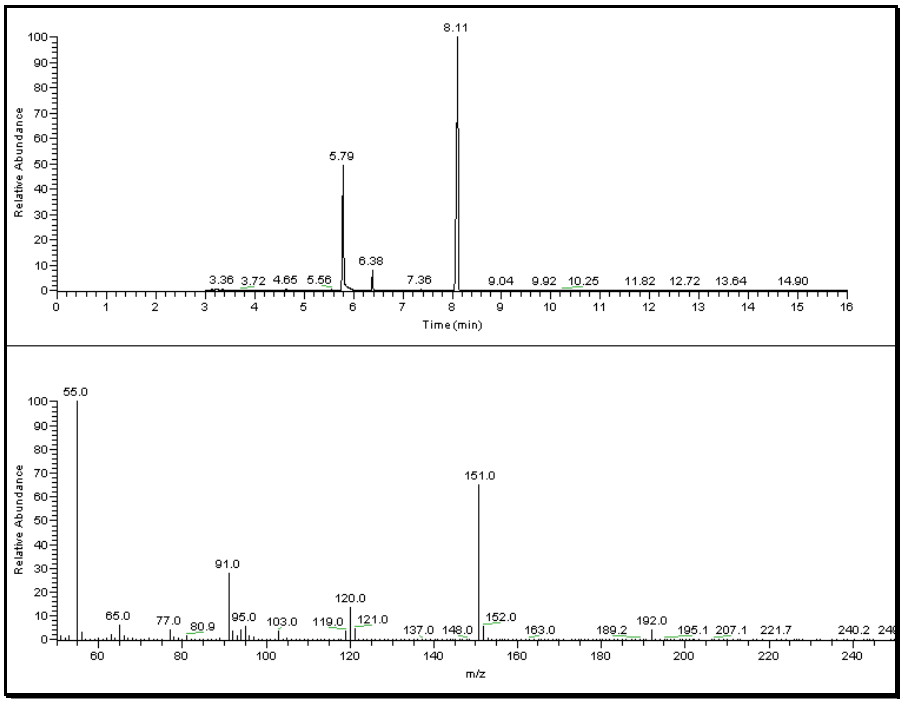

Figure A30. GC-MS result of (*S*)-(-)-**16**

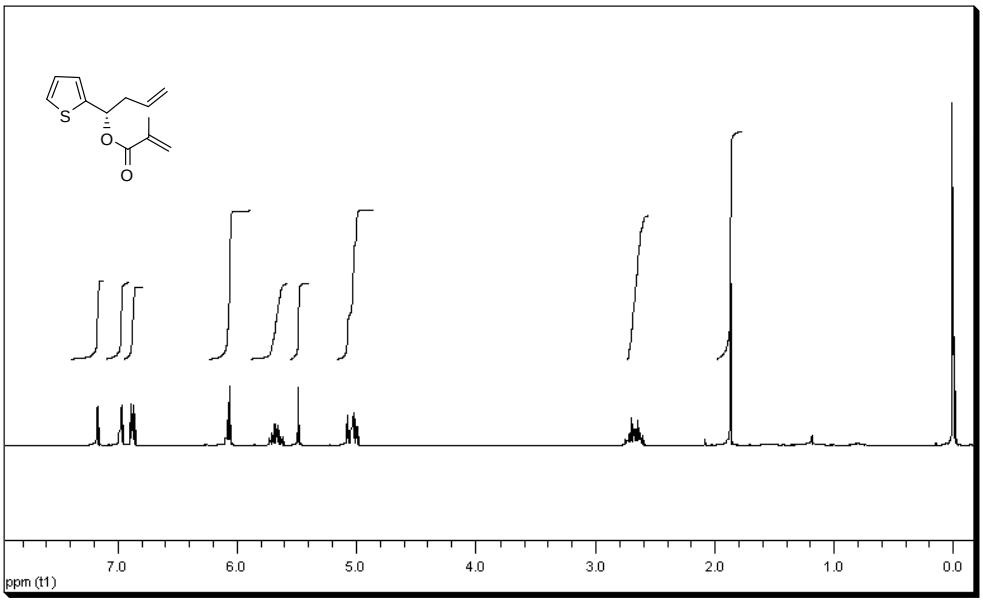

Figure A31. ^{1}H-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)but-3-enyl methacrylate, (*S*)-(-)-**18**

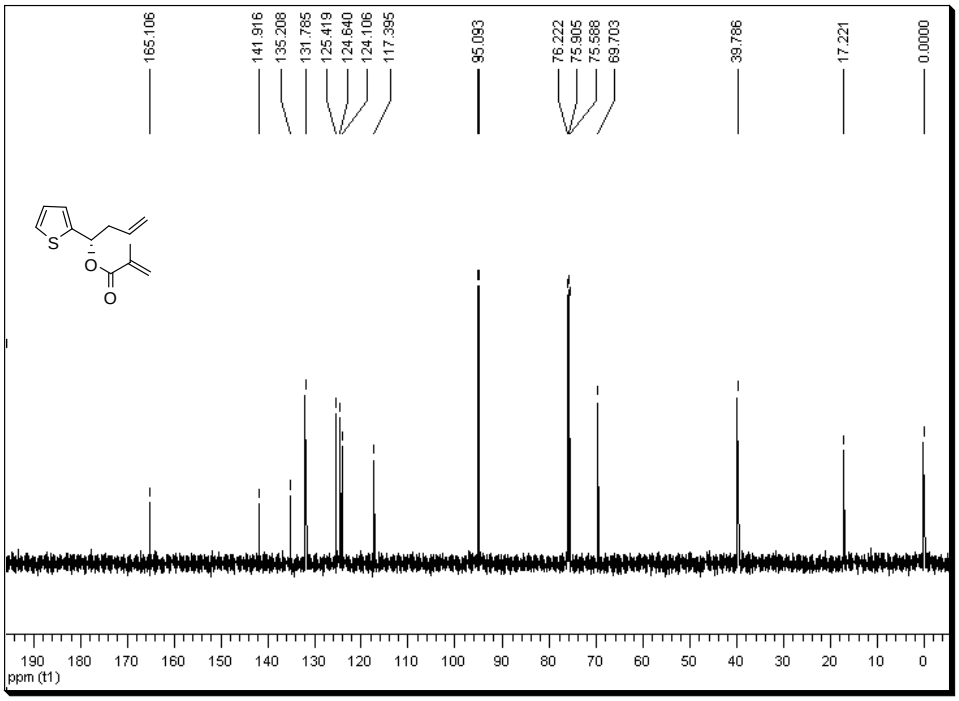

Figure A32. ^{13}C-NMR spectrum of (*S*)-(-)-1-(thiophen-2-yl)but-3-enyl methacrylate, (*S*)-(-)-**18**

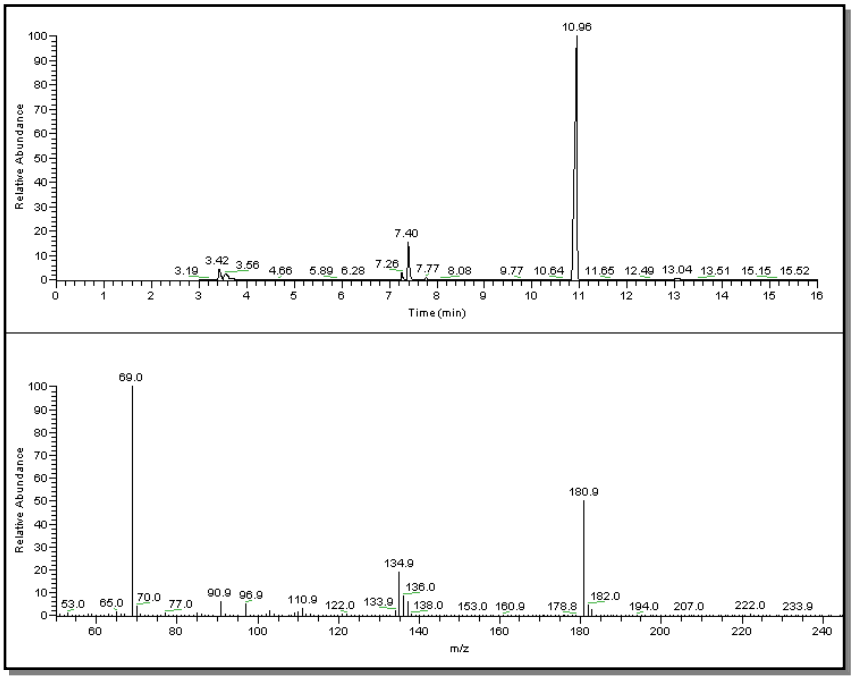

Figure A33. GC-MS result of (*S*)-(-)-**18**

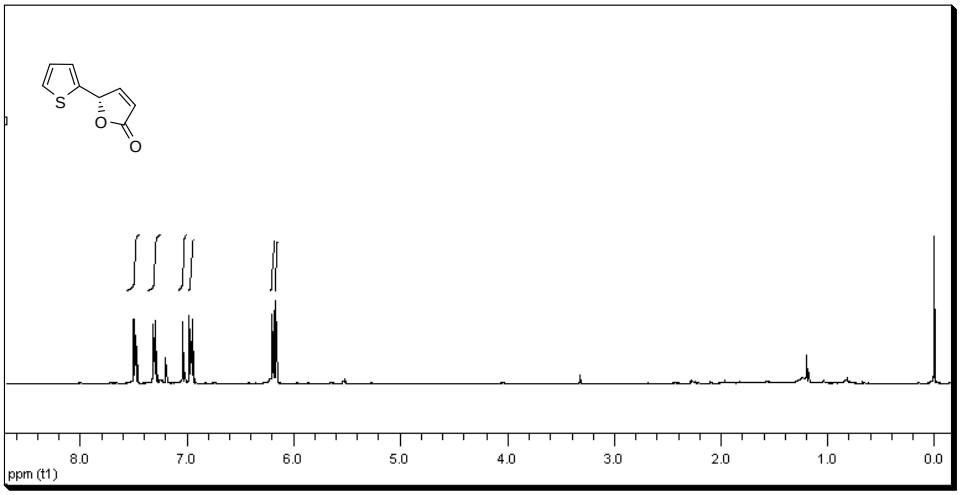

Figure A34. ^{1}H-NMR spectrum of (*S*)-(-)-5-(thiophen-2-yl)furan-2(5H)-one, (*S*)-(-)-**20**

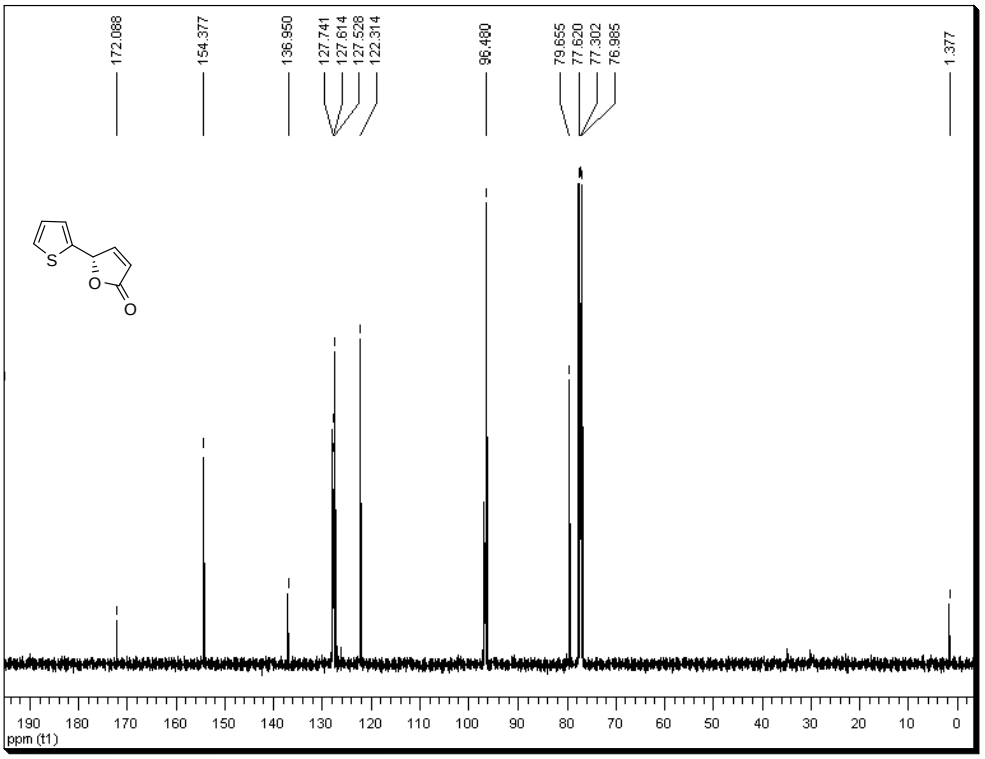

Figure A35. ^{13}C-NMR spectrum of (*S*)-(-)-5-(thiophen-2-yl)furan-2(5H)-one, (*S*)-(-)-**20**

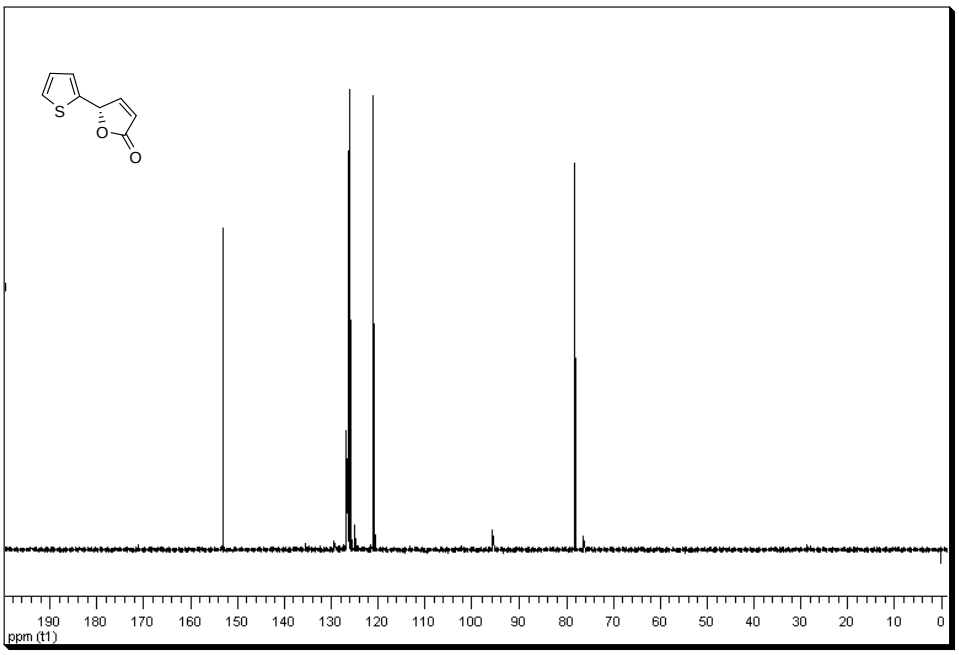

Figure A36. DEPT-90 spectrum of (*S*)-(-)-**20**

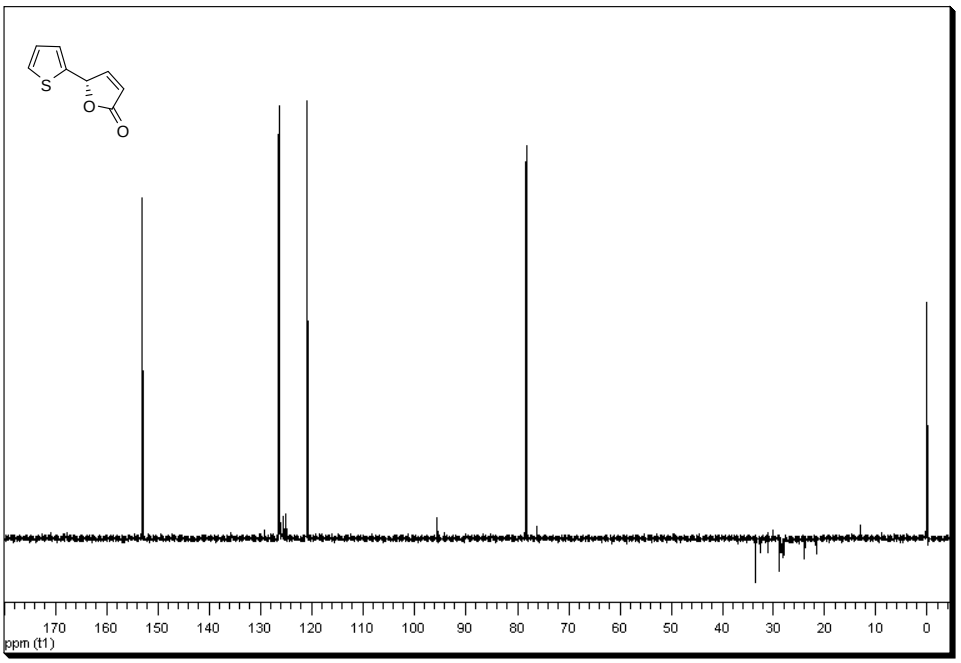

Figure A37. DEPT-135 spectrum of (*S*)-(-)-**20**

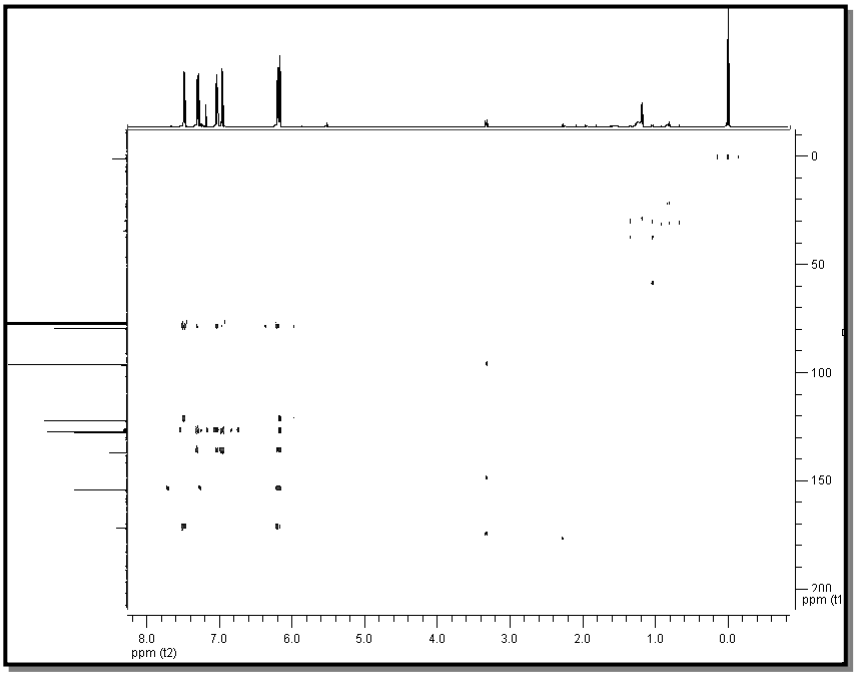

Figure A38. HMBC spectrum of (*S*)-(-)-**20**

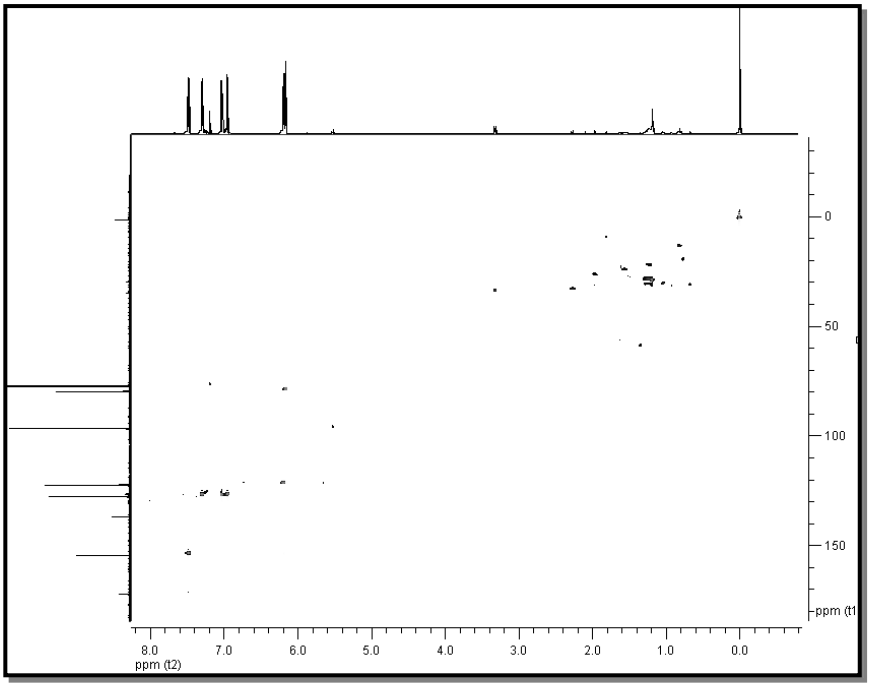

Figure A39. HSQC spectrum of (*S*)-(-)-**20**

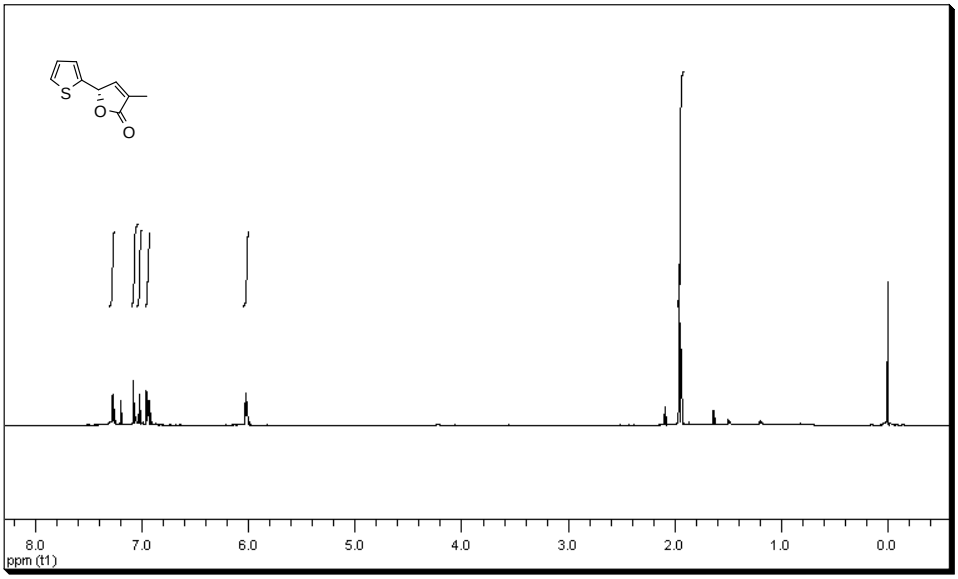

Figure A40. [1]H-NMR spectrum of (*S*)-(-)-3-Methyl-5-(thiophen-2-yl)furan 2(5H)-one, (*S*)-(-)-**21**

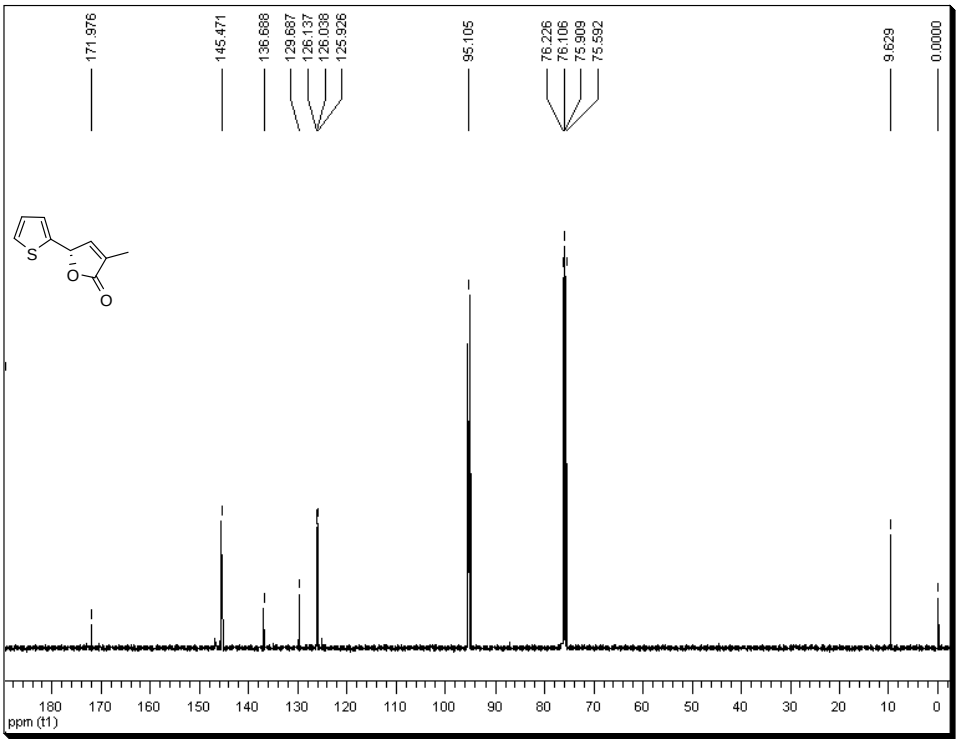

Figure A41. [13]C-NMR spectrum of (*S*)-(-)-3-Methyl-5-(thiophen-2-yl)furan 2(5H)-one, (*S*)-(-)-**21**

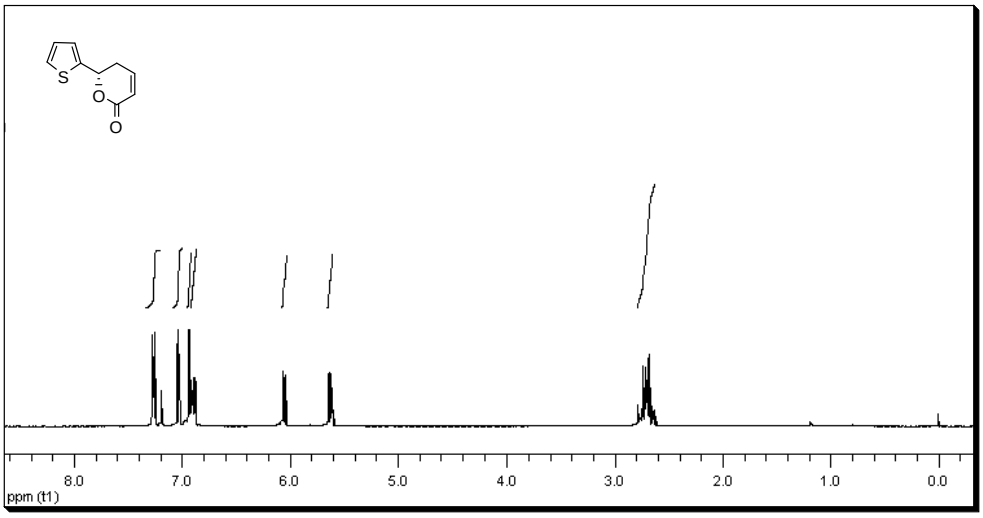

Figure A42. ^{1}H-NMR spectrum of (*S*)-(-)-6-(thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**22**

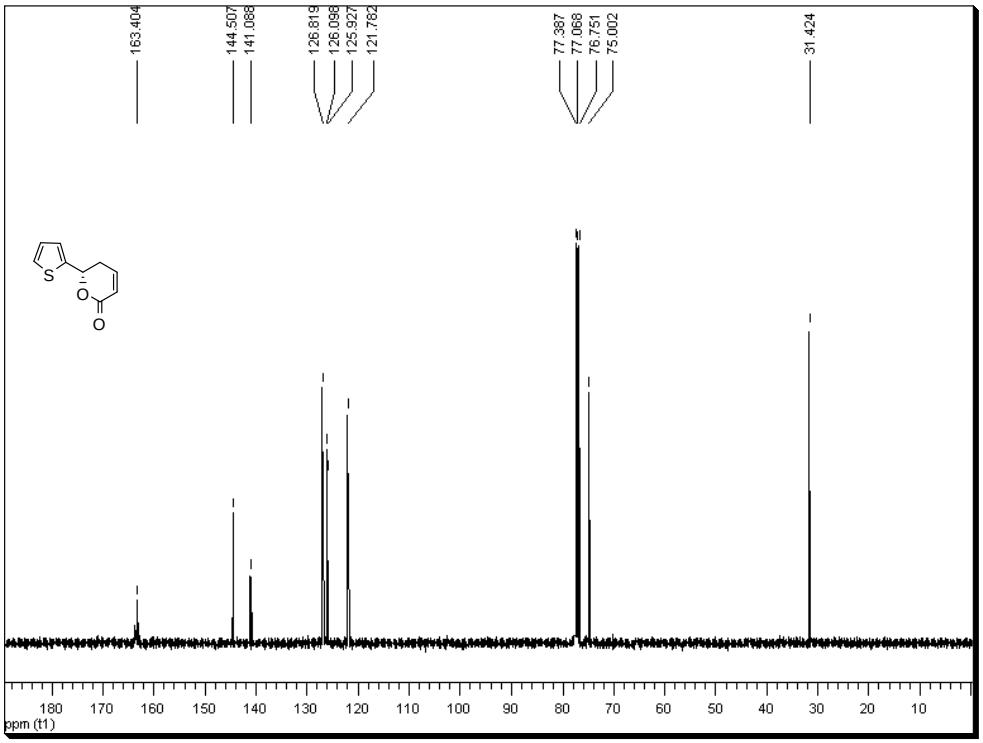

Figure A43. ^{13}C-NMR spectrum of (*S*)-(-)-6-(thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**22**

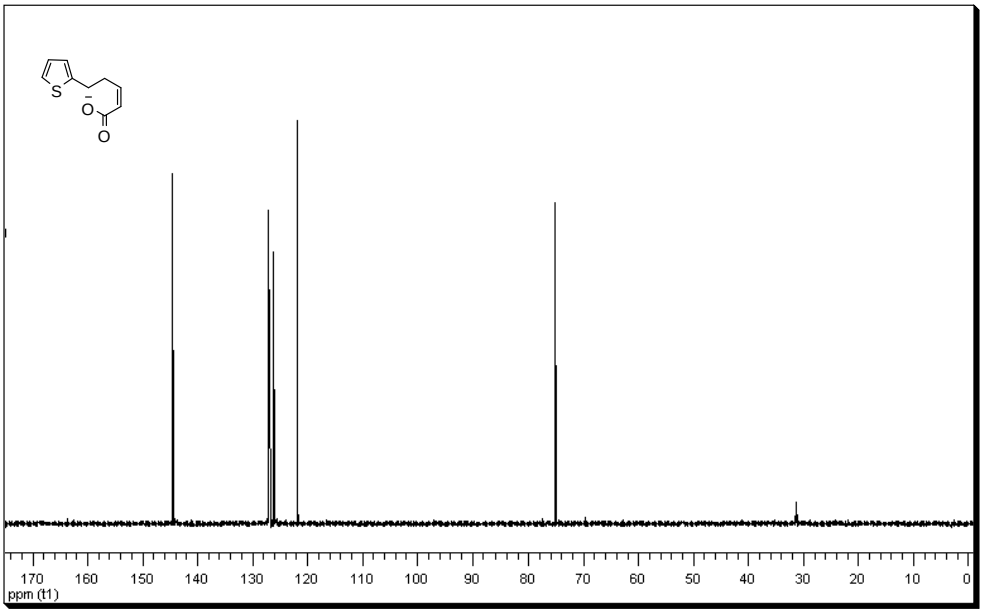

Figure A44. DEPT-90 spectrum of (*S*)-(-)-**22**

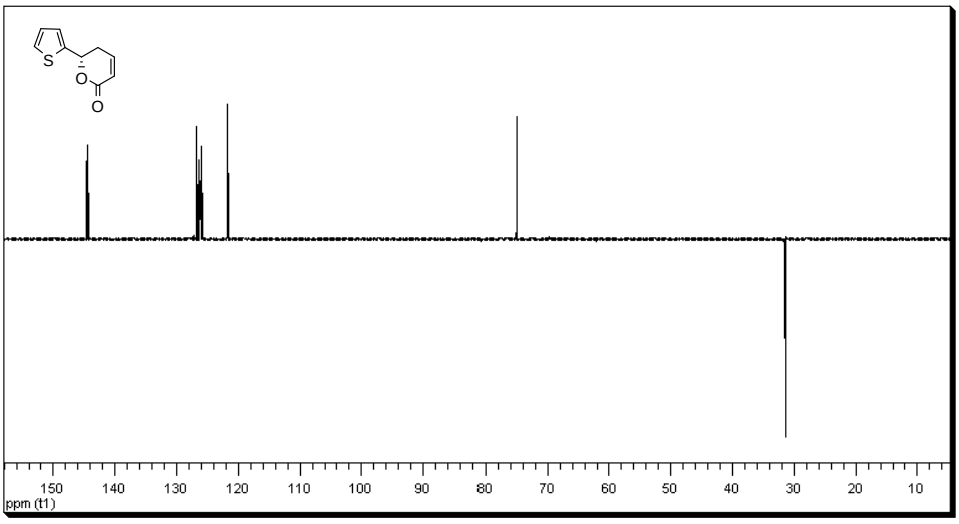

Figure A45. DEPT-135 spectrum of (*S*)-(-)-**22**

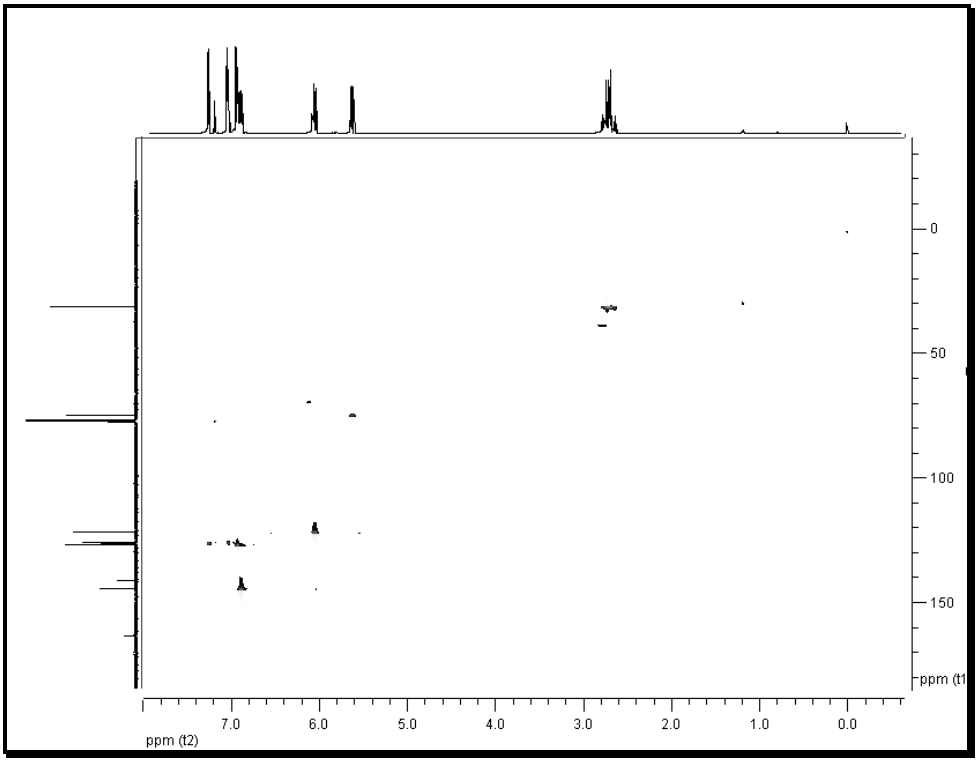

Figure A46. HMBC spectrum of (*S*)-(-)-**22**

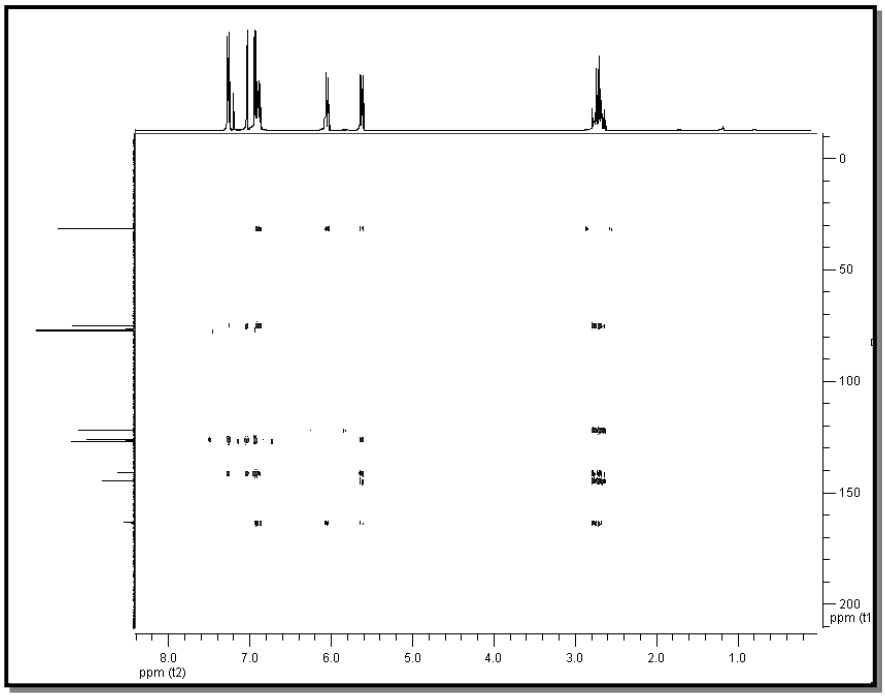

Figure A47. HSQC spectrum of (*S*)-(-)-**22**

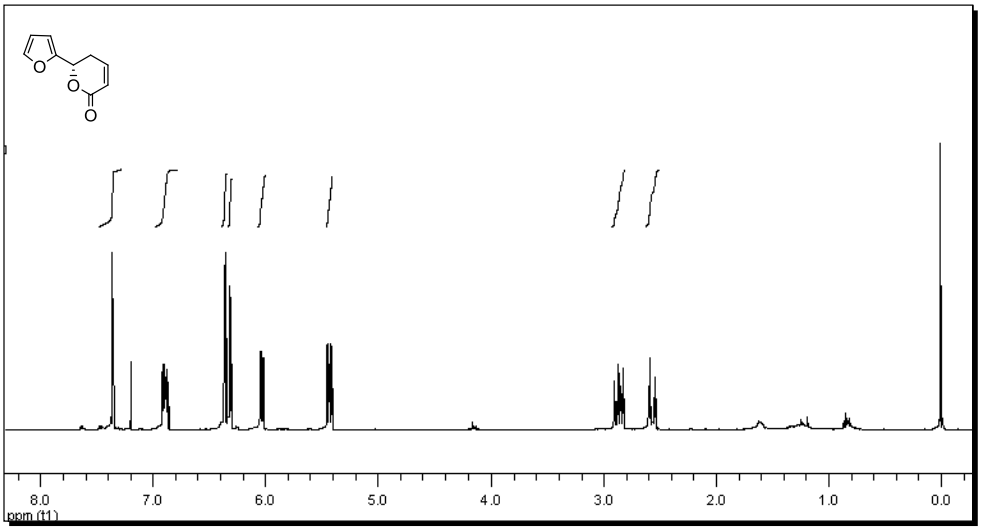

Figure A48. [1]H-NMR spectrum of (*S*)-(-)-6-(furan-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**24**

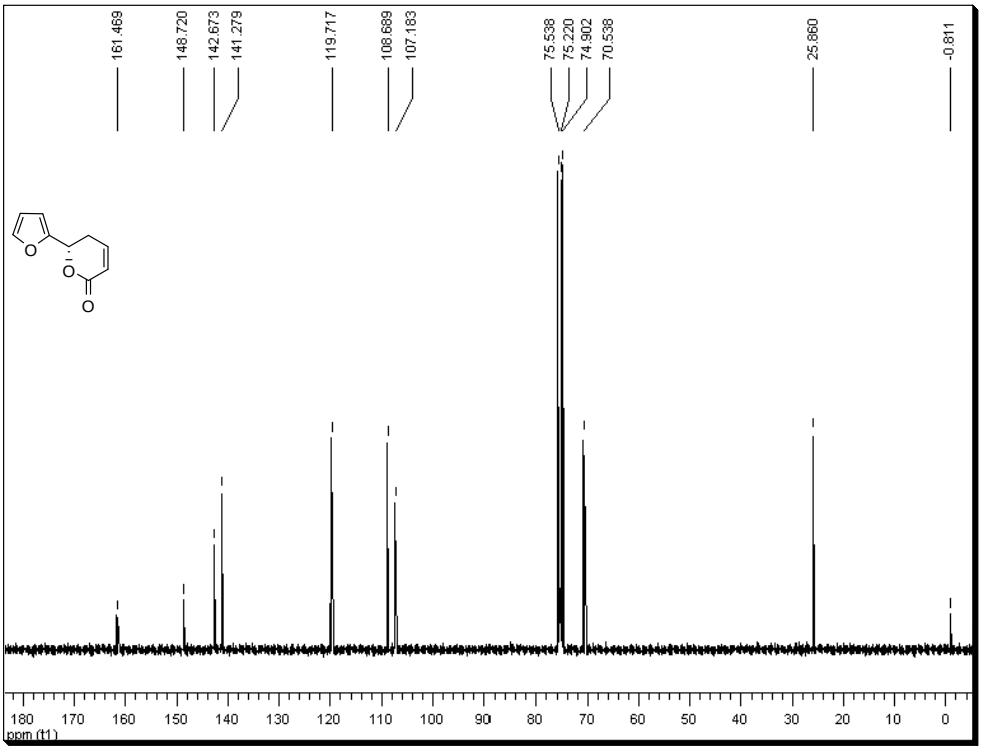

Figure A49. [13]C-NMR spectrum of (*S*)-(-)-6-(furan-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**24**

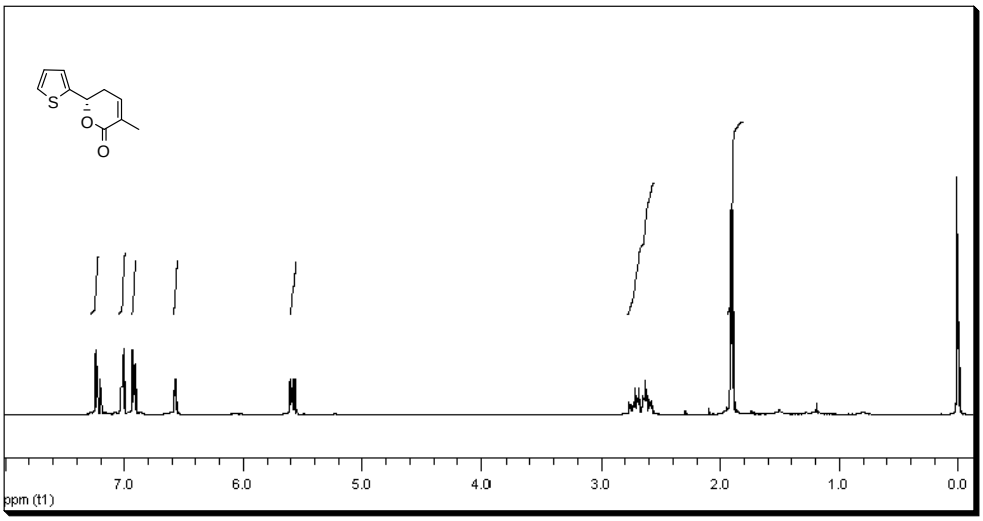

Figure A50. ^{1}H-NMR spectrum of (*S*)-(-)-3-Methyl-6-(thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**26**

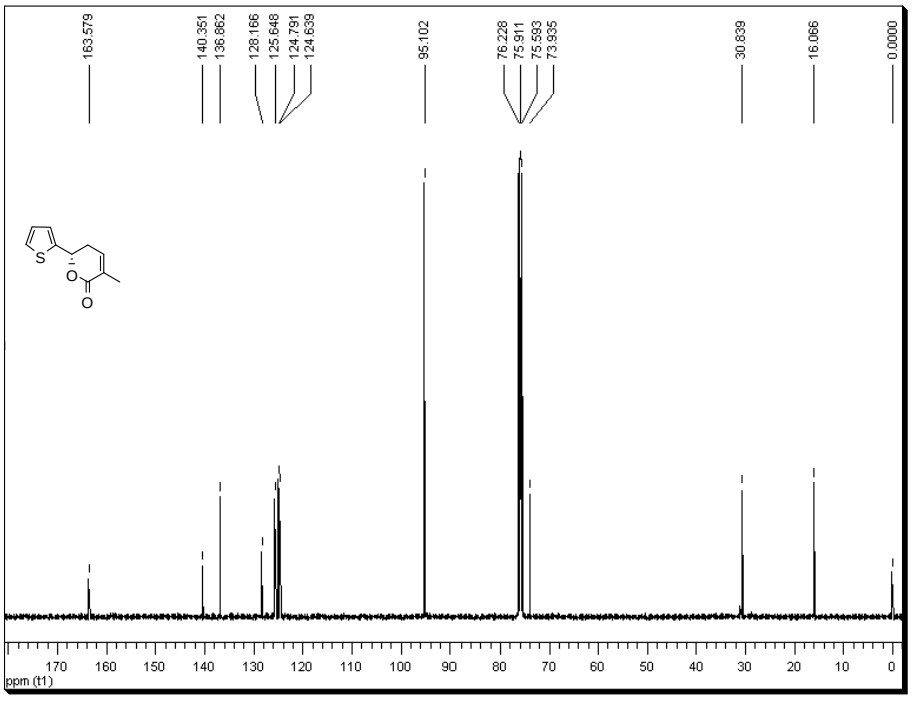

Figure A51. ^{13}C-NMR spectrum of (*S*)-(-)-3-Methyl-6-(thiophen-2-yl)-5,6-dihydro-2H-pyran-2-one, (*S*)-(-)-**26**

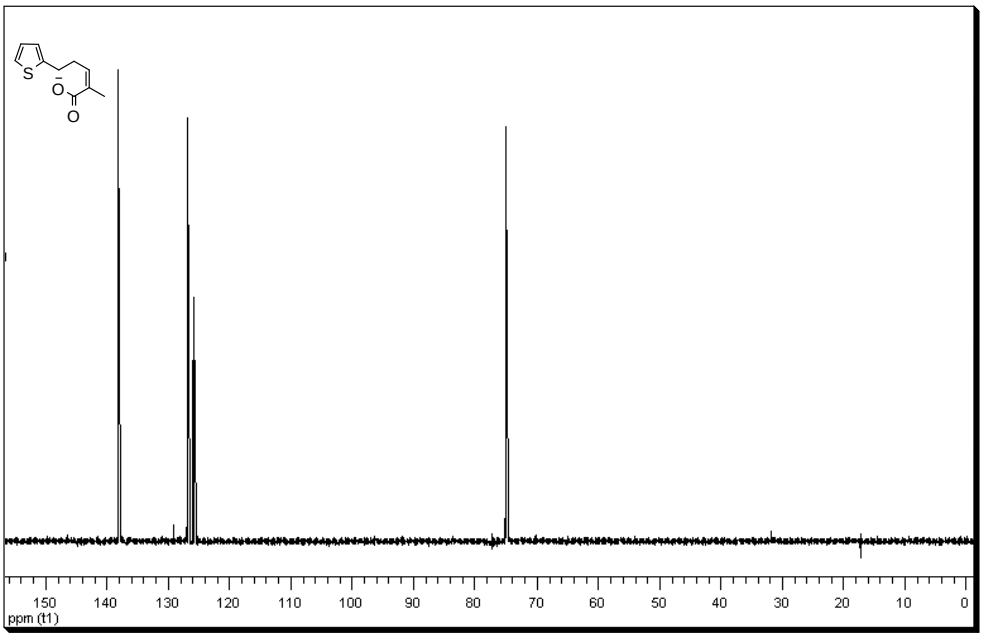

Figure A52. DEPT-90 spectrum of (*S*)-(-)-**26**

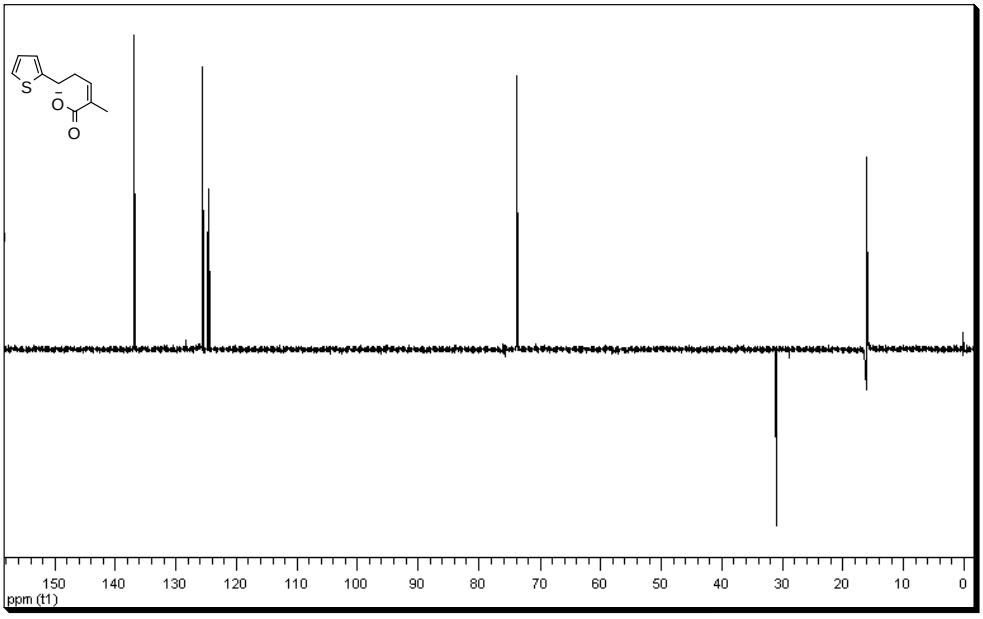

Figure A53. DEPT-135 spectrum of (*S*)-(-)-**26**

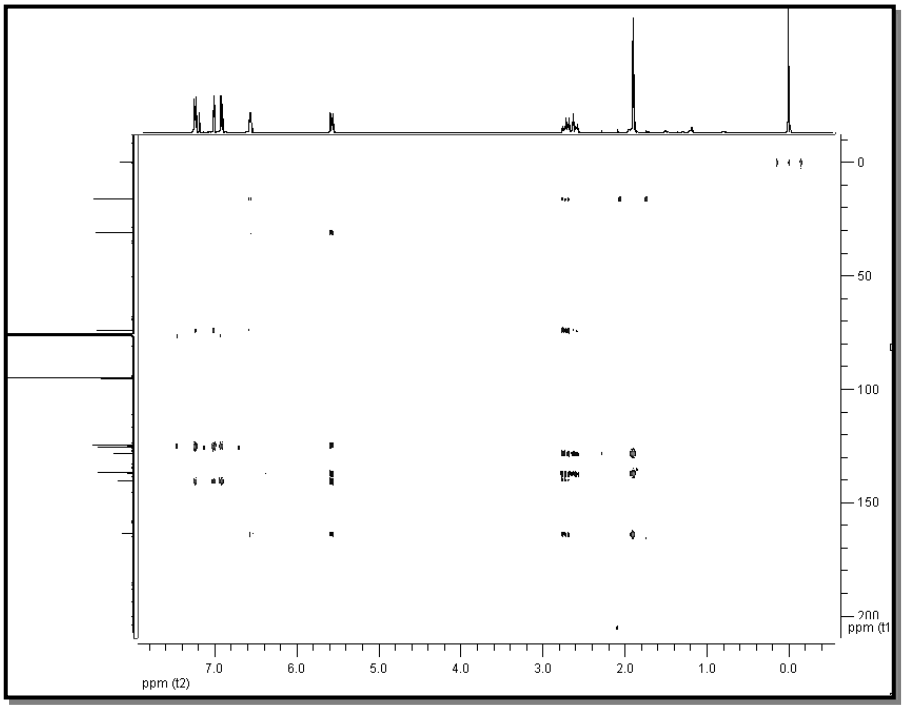

Figure A54. HMBC spectrum of (*S*)-(-)-**26**

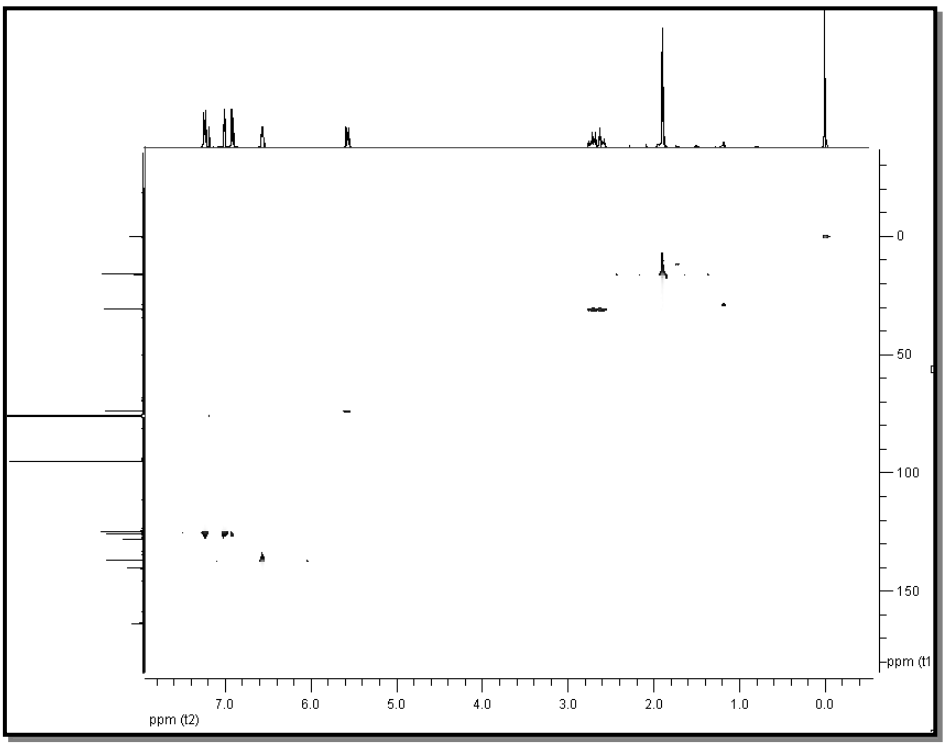

Figure A55. HSQC spectrum of (*S*)-(-)-**26**

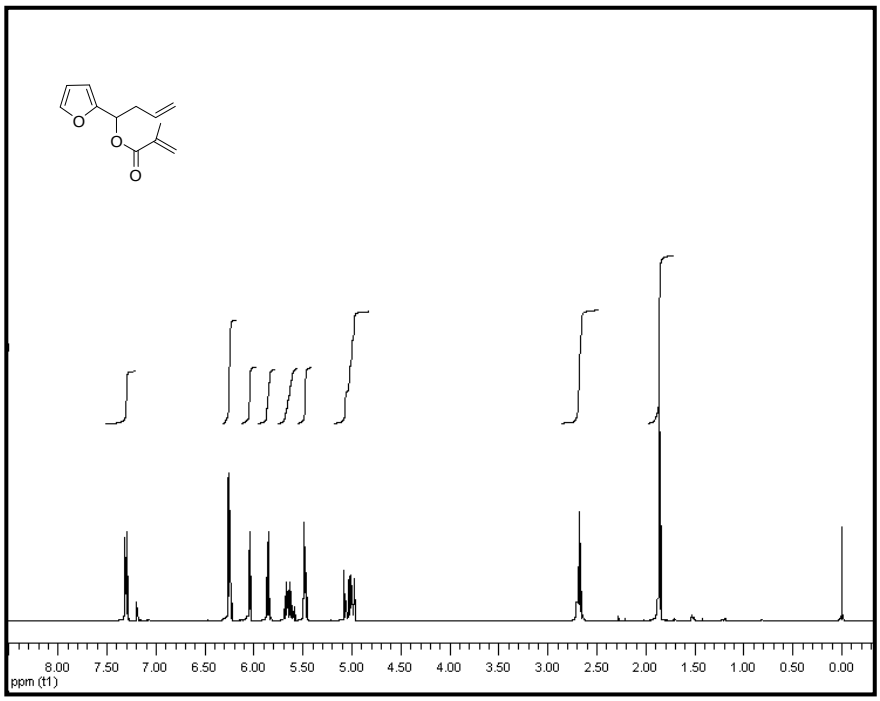

Figure A56. ^{1}H-NMR spectrum of *rac*-**28**

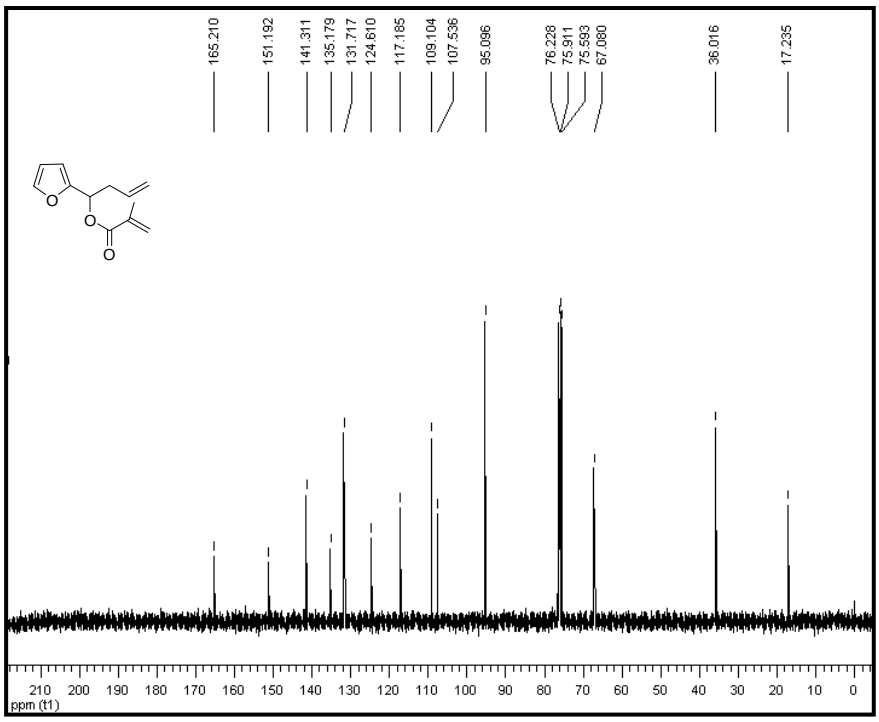

Figure A57. ^{13}C-NMR spectrum of *rac*-**28**