SYNTHESIS OF CHIRAL HETEROARYL SUBSTITUTED DIHYDROFURAN AND DIHYDROPYRAN DERIVATIVES BY "GREEN CHEMISTRY APPROACH"

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

SEMA DEMİRCİ

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

SEPTEMBER 2009

Approval of the thesis:

SYNTHESIS OF CHIRAL HETEROARYL SUBSTITUTED DIHYDROFURAN AND DIHYDROPYRAN DERIVATIVES BY "GREEN CHEMISTRY APPROACH"

submitted by **SEMA DEMİRCİ** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen _____
Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. Ahmet M. Önal _____
Head of Department, **Chemistry**

Prof. Dr. Cihangir Tanyeli _____
Supervisor, **Chemistry Dept., METU**

Examining Committee Members:

Prof. Dr. Metin Balcı _____
Chemistry Dept., METU

Prof. Dr. Cihangir Tanyeli _____
Chemistry Dept., METU

Prof. Dr. Canan Ünaleroğlu _____
Chemistry Dept., Hacettepe University

Prof. Dr. Özdemir Doğan _____
Chemistry Dept., METU

Assis. Prof. Dr. Fazilet Devrim Özdemirhan _____
Chemistry Dept., Abant İzzet Baysal University

Date: 09.09.2009

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name : Sema Demirci

Signature :

ABSTRACT

SYNTHESIS OF CHIRAL HETEROARYL SUBSTITUTED DIHYDROFURAN AND DIHYDROPYRAN DERIVATIVES BY "GREEN CHEMISTRY APPROACH"

Demirci, Sema

M.S., Department of Chemistry

Supervisor: Prof. Dr. Cihangir Tanyeli

September 2009, 94 pages

The thesis subject is mainly involved in *Green Chemistry* approach. Thiophene, furan and pyridine carboxaldehydes were chosen as starting compounds and vinylation and allylation with Grignard reaction afforded the corresponding racemic heteroaryl substituted allylic and homoallylic alcohols. Subsequent resolution with enzymes (PS-Amano II, Lipozym and Novazym 435) gave enantiomerically enriched alcohols with the e.e. values varied between 65 and 99%. The absolute configurations of all substrates are known. As a result of *O*-allylation with the common procedure formed the feasible carbon backbone for the ring closing metathesis reaction. All ring closing metathesis reactions were performed by Grubbs' catalyst with just 5% catalyst loading. The absolute configurations of dihydrofuran and dihydropyran derivatives are known, since the chiral center configurations of all substrates are preserved throughout all the applied processes.

Key words: Green Chemistry, enzymatic resolution, ring closing metathesis

ÖZ

KİRAL HETEROARİL SUBSTİTUE
DİHİDROFURAN VE DİHİDROPİRAN TÜREVLERİNİN
"GREEN CHEMISTRY" YAKLAŞIMI İLE SENTEZİ

Demirci, Sema
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Eylül 2009, 94 sayfa

Tezin konusu temel olarak Green Chemistry yaklaşımını içermektedir. Tiyofen, furan ve piridin karbaldehitleri başlangıç bileşikleri olarak seçilmiş ve ilgili rasemik heteroaril substitue allilik ve homoallilik alkoller için vinilleme ve allilleme Grignard reaksiyonu ile gerçekleştirimiştir. Daha sonra, çeşitli enzimlerle (PS Amano II, Lipozyme ve Novozyme435) yapılan rezolüsyon çalışmaları, e.e. değerleri % 65 ile 99 arasında değişen enantiomerce zenginleştirilmiş alkolleri vermiştir. Tüm zenginleştirilmiş başlangıç bileşiklerinin mutlak konfigurasyonu bilinmektedir. Yaygın olarak kullanılan yöntem uygulanarak yapılan *O*-allilleme çalışmalarının sonucunda, halka kapama metatez reaksiyonları için uygun karbon ana iskeleti oluşturulmuştur. Bütün halka kapama metatez reaksiyonları, sadece %5 Grubbs' katalizörü kullanımı ile gerçekleştirilmiştir.Tüm uygulanan işlemlerde, başlangıç bileşiklerinin kiral merkez konfigurasyonlarının korunmasından dolayı heteroaril substitue dihidrofuran ve dihidropiran türevlerinin mutlak konfigurasyonu bilinmektedir.

Anahtar kelimeler: Green Chemistry, enzimatik rezolüsyon, halka kapama metatezi

To my dear parents and sister...

ACKNOWLEDGEMENTS

I would like to express my greatest appreciations to my supervisor Prof. Dr. Cihangir Tanyeli for his guidance, encouragement, patience and advices throughout this study.

I would also thank to Serdar Sezer for his support, encouragement, help and interesting scientific discussions.

Moreover, I would like to thank to Seda Karayılan and Zehra Uzunoğlu for NMR spectra.

I would like to give special thanks to Kayahan Uzun for his support, understanding, unlimited tolerance and endless love every time.

Very special thanks to Funda Oğuzkaya for her valuable support, interesting scientific discussion and close friendship throughout my graduate education. Also, thank to Yasemin Gümrükçü for her helpful manner and kind friendship.

My deepest gratitude is for my best friends Tuğba Efe, Nazmiye Bihter Akça and Ezgi Yavuz. During this study, they have always motivated me with their friendship, encouragement, help and understanding.

In addition, I want to thank to my lab mates from D-251, D-254 and D-255 and also Serhat Odabaş and Esen Çakır Odabaş for their friendship.

Finally, I owe great thanks to my parents and my sister for their endless love, support, patience and unquestionable belief in me; I dedicate this thesis to them.

TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

LIST OF SCHEMES

SCHEMES

LIST OF ABBREVIATIONS

CCL: Candida cylindrical lipase

DCM: Dichloromethane

DPE: Diisopropylether

HLE: Human leulcocyte elastase

LDA: Lithiumdiethylamide

NMP: N-methyl pyrolidine

PLE: Pig liver esterase

PPL: Porcine pancreatic lipase

PSC-II: Psedomonas cepacia lipase on ceramics

THF: Teatrahydrofuran

CHAPTER 1

INTRODUCTION

1.1. Green Chemistry

Green chemistry is a methodology which aims to prevent environmental pollution. It designs products and processes that reduce or eliminate the use and generation of hazardous substances or byproducts [1].

In the modern industrial age, numerous scientific inventions and industrial developments brought significant increase in standard of living, efficiency in production and greed for technical innovation. However, these technological changes accelerated the destruction of the environment, since the need for hazardous chemicals and the consumption of natural resources have been increased. The technological improvements should be implemented without avoiding the fact that our natural resources which we as human beings rely on for survival are limited and not renewable. Otherwise, we won't be able to sustain our and all other living being's existence on Earth [2].

Throughout the 1990s, many scientists and producers in industry have begun to pull out of old approaches about product processes and using hazardous chemicals to use eco-friendly one which is economically beneficial and more scientifically based approach known as green chemistry [3] .

The major research areas of Green Chemistry are environmentally benign solvents and auxiliaries, catalysis [4], supercritical fluids [5], atom [6] and step economy [7], some techniques such as microwave [8-10], real time analysis for pollution prevention. Paul Anastas, then of the United States Environmental

Protection Agency, and John C. Warner developed 12 principles of green chemistry, which help to explain what the definition means in practice [11] . The principles include such concepts as:

- the design of processes to increase the amount of atom economy and to decrease the number of steps in reactions,
- the use of environment-benign substances, including solvents,
- the design of energy efficient processes,
- the best form of waste disposal: do not create it in the first place.

"Paul Anastas stated that the 12 principles are:

1. *Prevent waste:* Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. *Design safer chemicals and products:* Design chemical products to be fully effective, yet have little or no toxicity.
3. *Design less hazardous chemical syntheses:* Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. *Use renewable feedstock:* Use raw materials and feedstock that are renewable rather than depleting. Renewable feedstock are often made from agricultural products or are the wastes of other processes, depleting feedstock are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
5. *Use catalysts, not stoichiometric reagents:* Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. *Avoid chemical derivatives:* Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. *Maximize atom economy:* Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

8. *Use safer solvents and reaction conditions:* Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals. If a solvent is necessary, water is good medium as well as certain eco-friendly solvents that do not contribute to smog formation or destroy the ozone.
9. *Increase energy efficiency:* Run chemical reactions at ambient temperature and pressure whenever possible.
10. *Design chemicals and products to degrade after use:* Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
11. *Analyze in real time to prevent pollution:* Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. *Minimize the potential for accidents:* Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment" [11].

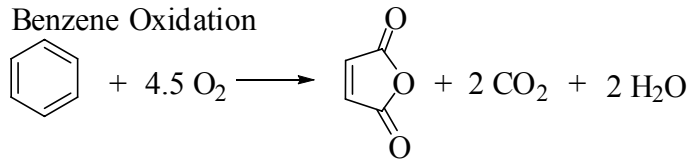
The Environmentally Factor (E Factor) which is one of the most important terms defined as mass ratio of waste to product in the Green Chemistry concept [12-17]. It is important to calculate this value so that the efficient process is designed to prevent waste. It is defined as:

$$E\ Factor = \frac{Total\ Waste\ (kg)}{Product\ (kg)} \quad (1)$$

The ideal E factor is zero. A higher E factor than zero means more waste and greater negative effect for the environment.

One of the most important principles of Green Chemistry is that of *atom economy* [18]. This is a measure of reactants end up in desired product and how many end up in by products or waste. Unlike the E factor, atom economy is a theoretical number which is provided to prevent waste. The atom economy value can be calculated as 100 times the relative molecular mass of all atoms used to make

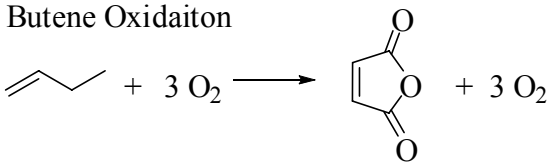
wanted product divided by the molecular relative mass of all reactants. Scheme 1 shows how to calculate the atom economy values for the representative reactions [2].



Formula weights

78 4.5 x 32 = 144 98

% atom economy = 100 x 98 / (78 + 144) = 100 x 98 / 222 = 44.1%



Formula weights

56 3 x 32 = 96 98

% atom economy = 100 x 98 / (56 + 96) = 100 x 98 / 152 = 64.5%

Scheme 1. Atom economy for maleic anhydride production routes

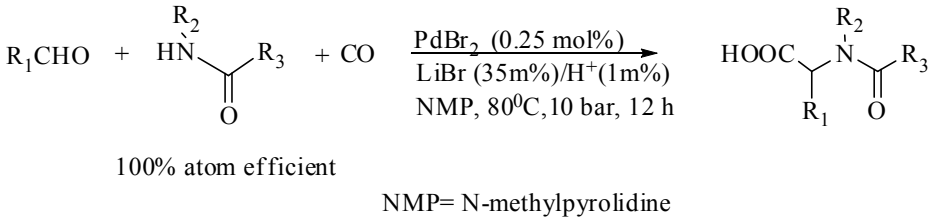
The types of widely used applications in Green Chemistry approach are given below.

Today many catalysts are used in chemical, refining and pharmaceutical processes. Catalysts supply the great economic benefits with their activity. There are three important parameters that impact on both the commercial viability and the greenness of a particular catalyst:

i. *Selectivity:* The amount of substrate converted to the desired product as a percentage of total consumed substrate.

ii. *Turnover frequency:* The number of moles of product produced per mole of catalyst per second.
iii. *Turnover number:* The amount of product is produced per mole of catalyst.

Catalytic C-C bond formation is a methodology which is widely used synthesis of bulk chemicals. Since, atom economy value is nearly 100% in such reactions, this method is suitable green chemistry concept. It is given an example (Scheme 2) which is the palladium catalyzed, one step, 100% atom efficient synthesis of α-amino acid derivatives from an aldehyde, CO and an amide [19].

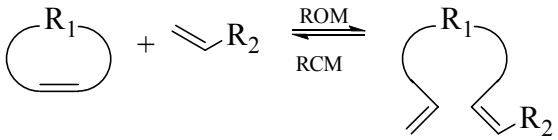


Scheme 2. Palladium Catalyzed Amidocarbonylation

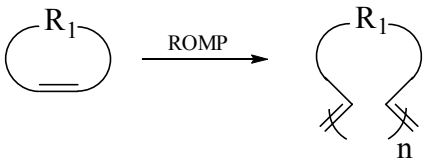
Olefin metathesis which is a type of C-C bond formation reactions has many forms: cross metathesis (CM), ring closing metathesis (RCM), ring opening metathesis (ROM), ring opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) (Scheme 3) [20].

Cross Metathesis

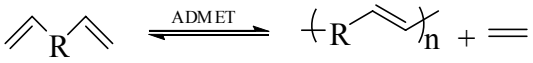
Ring Opening / Ring Closing Metathesis



Ring Opening Metathesis Polymerization



Acyclic Diene Metathesis



Catalysts: Mo, W, Re and Ru complexes

Scheme 3. Olefin Metathesis Reaction

Chauvin, Grubbs and Schrock were awarded with 2005 Nobel Prize in Chemistry for the development of the olefin metathesis reaction under mild condition. With these works, olefin metathesis reactions have been regarded as “a great step forward for green chemistry”.

Throughout 1990s, waste minimization was becoming an important case enantiomeric purity of biologically active agents especially researches on pharmaceuticals and pesticides [21]. When a chiral molecule exhibits bioactivity, the desired activity generally belongs to one of the enantiomers and the other enantiomer does not contribute the desired effect as well known example being thalidomide tragedy in the 1960s. Consequently, in the last two decades there have been chiral pharmaceuticals and pesticides as pure enantiomers in marketing. This situation

generated a need for economically viable methods for their synthesis. Enantioselective catalysis, using enzymes, chiral metal complexes or more recently organocatalysts have become increasing attention in this perspective [22]. Knowles, Noyori and Sharpless received the 2001 Nobel Prize in Chemistry for their contributions to enantioselective catalysis [23].

Biocatalysis has many advantages with mild reaction conditions(pH and temperature), an environmentally compatible, enzyme and solvent combined with high activities and chemo-, regio- and stereoselectivities in reactions of multifunctional molecules in *green chemistry* concept. Furthermore, use of enzymes generally avoids the protection and deprotection steps required in traditional organic syntheses. These processes which are shorter and generate less waste are both environmentally and economically more efficient than the classical methods.

1.2. Chirality and Its Importance

The word chiral stems from ‘cheir’ meaning hand in Greek. If a molecule cannot be superimposed on its mirror image, it is called chiral. Chiral molecules have property of rotating the plane-polarized monochromatic light that is passed through it. The name of this phenomenon is optical activity.

Chirality is a fundamental property of many three-dimensional molecules. In such a case, a chiral molecule has two different arrangements which are called enantiomers (Figure 1). Enantiomers have the identical chemical and physical properties except their effects on rotating of plane-polarized light. One isomer rotates the light to the clockwise direction, (+), and the other one rotates this light to the counter clockwise, (-), for the same number of degrees. This (+) and (-) nomenclature must not be confused *R* and *S* nomenclature. On the other hand, they have the same melting point, solubility, chromatographic retention time, IR and NMR spectra.

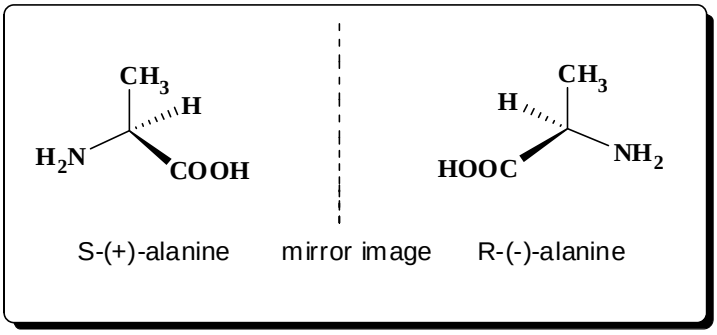


Figure 1. Two enantiomers of the alenine

Chirality is important in terms of biological macromolecules of living systems. All living material in our cells, like amino acids therefore peptides, proteins, enzymes, DNA and RNA prefer to be only one of the two mirror images form. The two mirror images of a chiral unit may interact differently with the receptor and can display various activities [24]. Thus the enzymes in our cells are chiral, as are other receptors that play an important part in cell machinery. In other words, they prefer to bind to one of the enantiomers. Because of the selectivity of receptor, only one of the enantiomers fits the receptor's site.

Most drugs consist of chiral molecules. And since a drug must match the molecules it should bind to itself in the cells, it is often only one of the enantiomers that is of interest. In certain cases the other form may even be harmful (Figure 2).

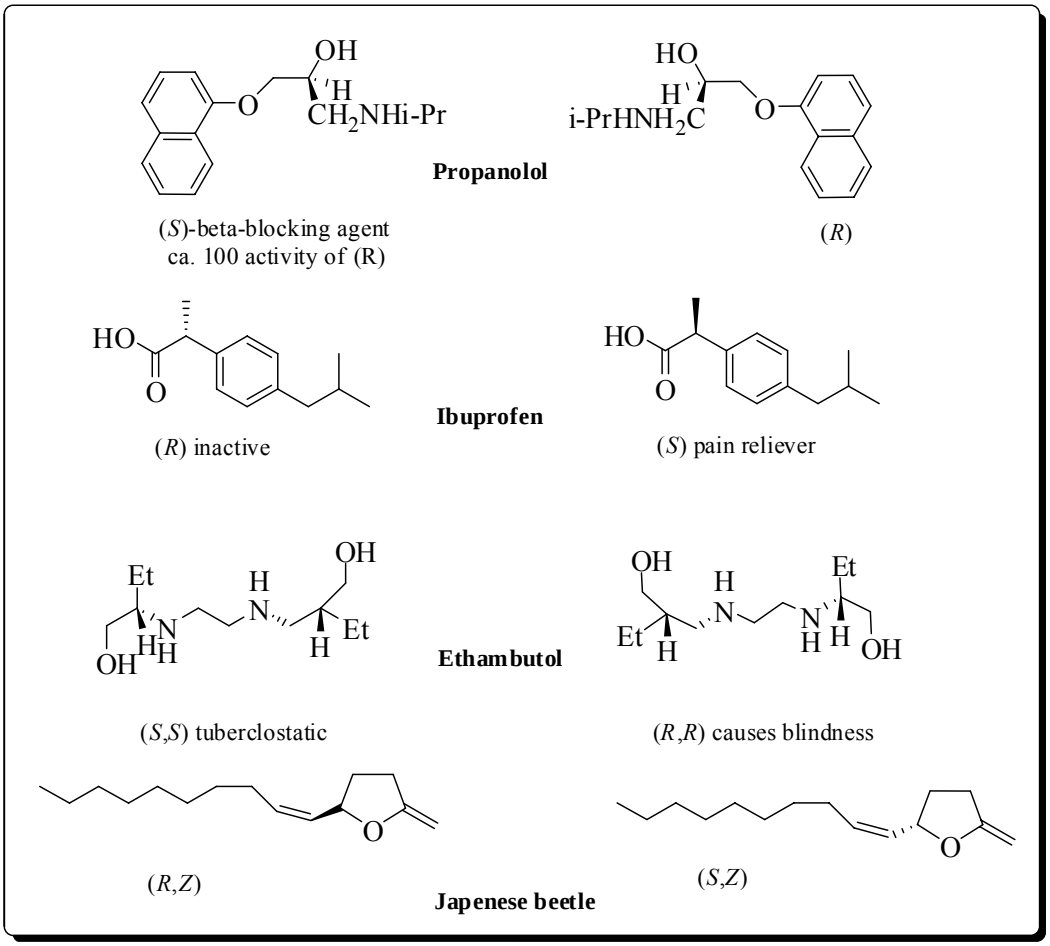


Figure 2. The structures and pharmacological effects of the enantiomers of some biologically active chiral molecules

Since the two enantiomers of a chiral molecule often have totally different effects on cells, it is important to be able to produce each of the two enantiomers in pure form.

1.3. General Aspects of Asymmetric Synthesis

According to Marckwald "Asymmetric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes." [25]. In addition to this definition, today, asymmetric synthesis is described as the conversion of an achiral unit in a molecule to a chiral unit such that stereoisomers are formed in unequal amounts [26].

Asymmetric synthesis has become more important to obtain enantiomerically pure products in terms of research and industry which is especially due to increased need for enantiomerically enriched drugs.

It is given three different routes to get enantiopure compound in Figure 3. It is seen that they can be obtained from chiral pool, from prochiral substrate or from racemates [27-28].

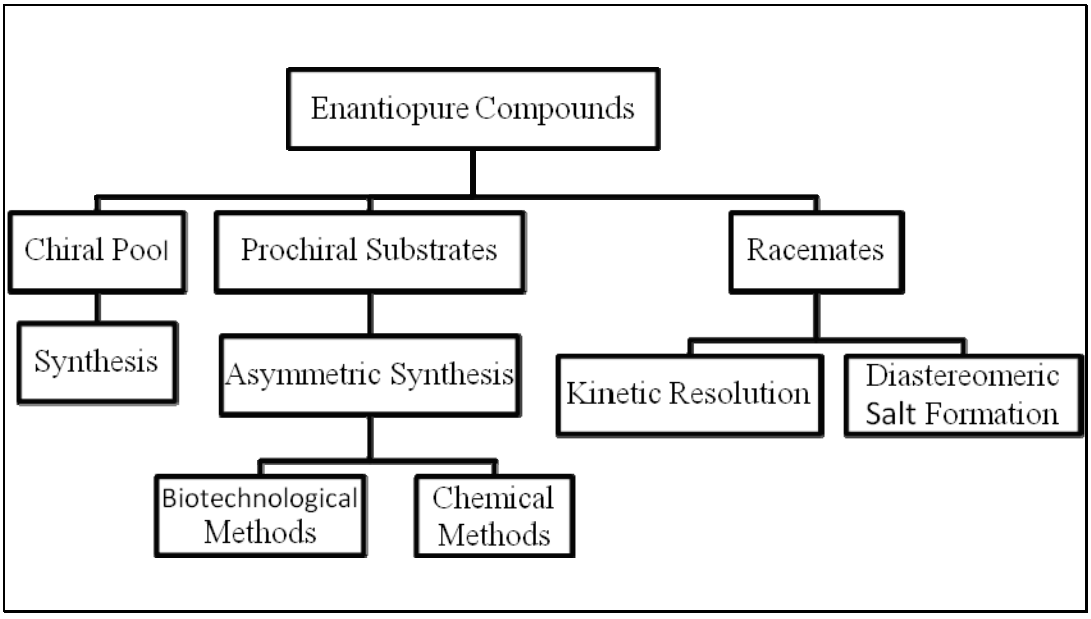


Figure 3. How to obtain enantiopure compound

It is widely preferred to use any enantiopure natural product as a chiral starting material in the synthesis of any target compound *via Chiral Pool* method [29]. This method has some limitations due to the natural sources and their isolation cost. On the other hand, this method which has potential to eliminate resolutions or the other enantioselective transformation is favorable in terms of the number of steps. Some common examples to chiral pool substances are given in Figure4.

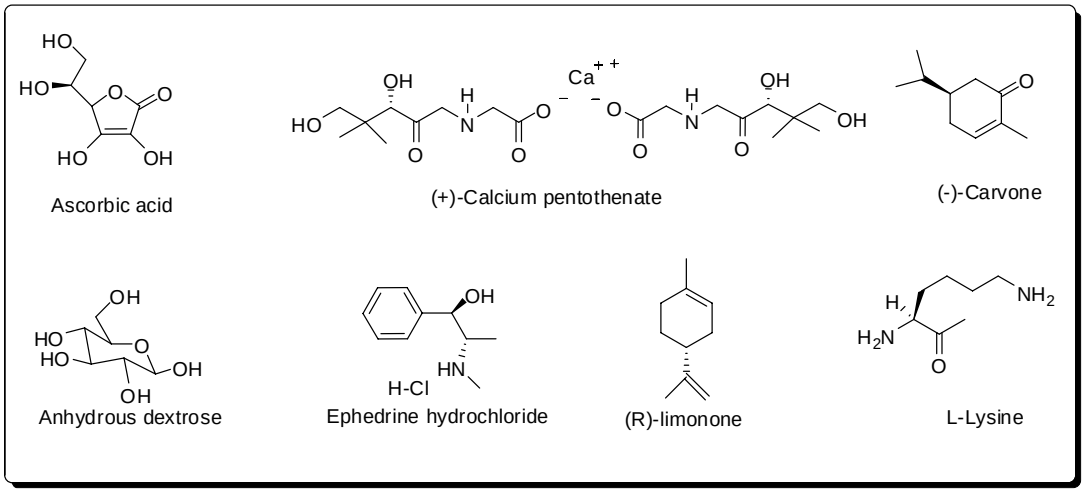
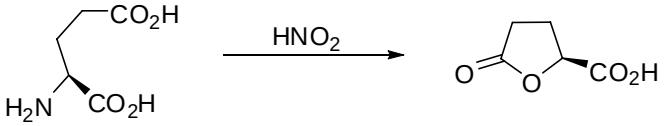


Figure 4. Examples of Chiral Pool Subtances

One example for the use of a natural product as a starting compound is the conversion of L-glutamic acid to the chiral butyrolactone (Scheme 4) [30].



Scheme 4. An example for a Chiral Substrates in Asymmetric Synthesis

In the beginning of an asymmetric synthesis, how a chiral center will be generated on a molecule should be considered. Advantages and disadvantages of each approach should be inspected so that the synthetic pathway has greatest success. There are mainly two methods for asymmetric synthesis, chemical and biotechnological. In this sense, the route of them is studied on case by case in this part.

1.3.1 Chemical Methods

In order to prepare enantiomerically or diastereomerically enriched compounds, the chemists make use of either reagent-controlled (chiral reagents, chiral catalysts) or substrate controlled (chiral substrates, chiral auxiliaries) conditions given below:

i. Chiral Reagents:

In many ways, this is the approach of choice as nature utilizes this methodology through enzymes. The reagent must be selective both in terms of induction and functional group specificity. The need for protection should be carefully considered as this could lead to the introduction of extra steps. The chiral reagent should allow for the inexpensive cost component to be recycled, if necessary, or have a very high turnover number. However, the use of a chiral catalyst that can induce the desired asymmetry in a large number of substrate molecules has great cost implications In this approach, the prochiral substrate is treated with a chiral reagent in order to obtain enantiomerically enriched product [31].

ii. Chiral Catalysts:

Chiral catalysts cause one enantiomer to be selectively converted or only one enantiomer to be obtained. Enantioselective catalysis using chiral transition metal

complexes appears as one of the most efficient methods since a small amount of material can produce a large amount of optically active product. In transition metal catalyzed enantioselective processes, the chirality is commonly introduced by the presence of chiral ligands bound to the transition metal.

The major advantage of this approach is that only catalytic amounts of the chiral mediator or required, which provides economic and practical advantages. With an efficient method, the expense of the catalysts can become irrelevant as so little is required, which means that fairly lengthy catalyst preparations and/or expensive sources of chirality might be feasible. The major drawbacks at present are that relatively few catalysts which give both a high enantiomeric excess and accept a wide range of substrates are available, and that the products are enantiomer mixtures so enantiomeric enrichment could be difficult. Some important chiral ligands are shown in Figure 5 [32].

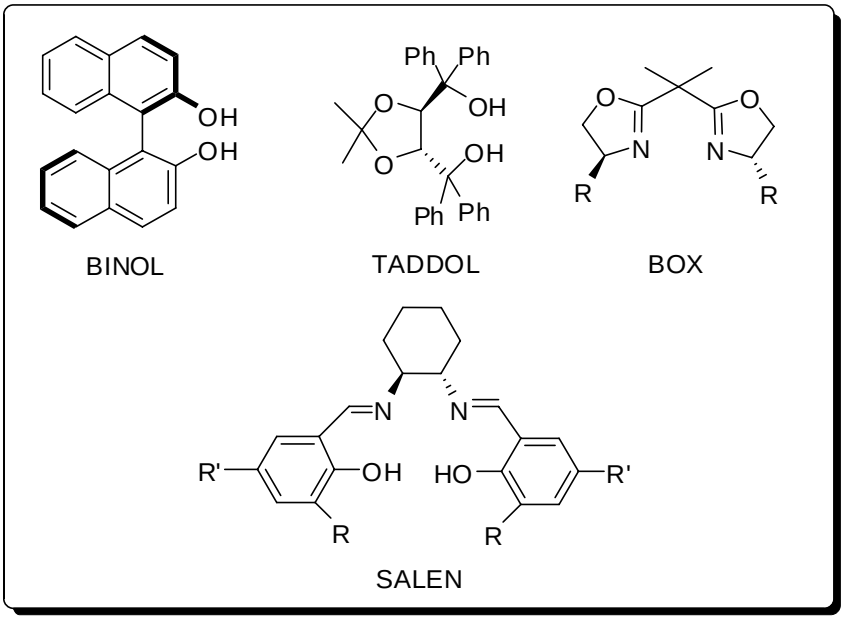
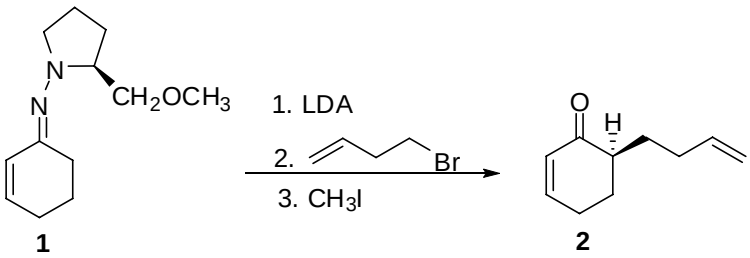


Figure 5. Some Important Chiral Ligand

iii. Chiral Auxiliaries:

Another general approach to the asymmetric synthesis involves the use of chiral auxiliaries. This approach offers significant advantages, provided that the chiral auxiliaries fulfill all the necessary conditions. The auxiliaries can be recycled and it is easy to purify major diastereoisomer. They are easily separated from product and recovered. Since the absolute configuration of the chiral auxiliary is known, it is possible to determine the absolute configuration of the product by X-ray analysis. It must be stressed that the optical purity of the product can depend upon the optical purity of the chiral auxiliary or reagent [33]. A linear relationship between these two variables is often assumed and significant deviations from linearity are known [34]. An example to the use of chiral auxiliaries in an asymmetric synthesis is given in Scheme 5 [35].



Scheme 5. An example of a chiral auxiliary in an asymmetric synthesis

iv. Chiral Environment:

It is possible to make the environment of a chemical reaction chiral. The majority of examples in this class utilizes chiral solvents or additives. They may cause the differentiation of the free energies of the diastereomeric transition states, and hence provide useful chiral induction, these additives should be closely

associated with the reaction center. In most cases, this has not been fruitful, as in the use of chiral solvents [36-38].

1.3.2 Biotechnological Methods

Besides all of the chemical methods have been mentioned previously, biocatalysts can also be used to obtain enantiomerically enriched products from prochiral substances. Biotechnological methods involve the reactions catalyzed by bacteria, fungi or their true catalytic components, enzymes [39]. Enzyme catalyzed chemical transformations have been recognized as the partial alternatives to conventional organic synthesis. Two problems now facing organic synthesis are the development of techniques for preparing complex, water-soluble biochemicals, and the development of environmentally acceptable synthetic processes that are also economically acceptable. Enzymes are able to contribute to the resolution of both of these issues, and they should be considered as one useful class of catalysts to be used, when appropriate, for organic synthesis [40].

1.4 Kinetic Resolution

Kinetic resolution is a kind of separation (or partial separation) technique of enantiomers due to a difference in the reaction rate of a racemic mixture components with a chiral reagent. It can be performed both using chemical catalyst and biocatalyst [41]. Enzymes are proteins that are capable of accelerating reactions under mild reaction conditions (pH range about 5-8 and in a temperature range of 20-40°C). Other advantages are the high degrees of substrate-, chemo-, regio- and stereoselectivity and high efficiency. This selectivity of enzymes can be explained by their three dimensional complex structures. The molecular recognition between the enzyme and its substrate occurs the active site of enzyme. The electronic and steric properties of enzymes active site are rather important in terms of the reaction mechanism [42].

Enzymes function as catalysts by forming complexes with the reacting molecules, by increasing the local concentration of the molecule, by orienting the molecule correctly so that reaction can take place most efficiently and by distorting the shape of the molecule slightly, thereby changing their energy content and helping them react the transition state. Enzymes can enhance the rate of reactions by factors of 10^8 - 10^{12} than those of the corresponding uncatalyzed reaction [43].

Enzymes have a particular shape with an active site. The active site is the place where the substrate (the reactant molecule) fits. The substrate comes into contact with the active site and the active site induces a fit around the substrate like a key that fits a lock (This metaphor comes from another Nobel Laureate in Chemistry, Emil Fischer, who was awarded the Prize in 1902.) This action is called the induced fit hypothesis (Figure 6) [44].

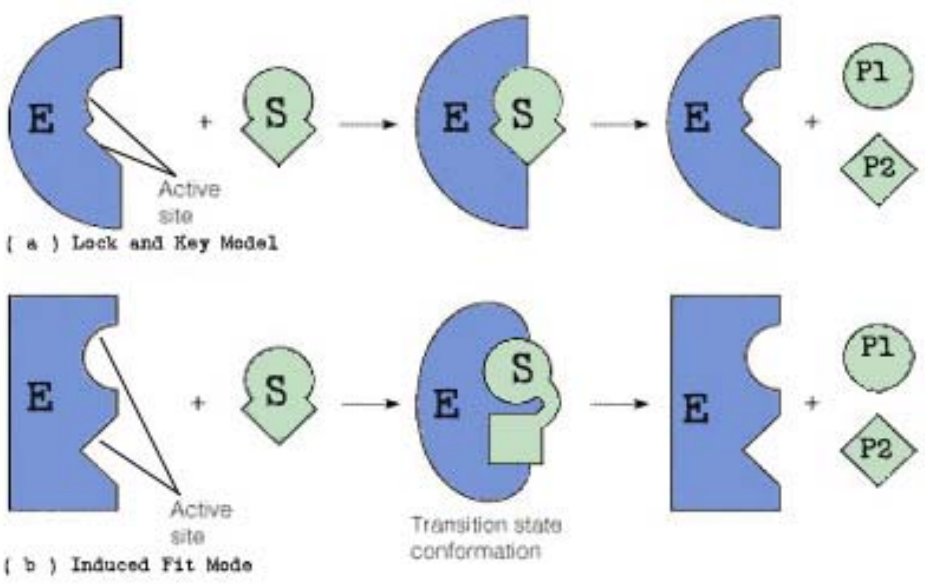


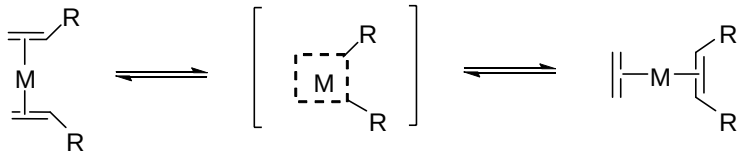
Figure 6. (a) Lock and Key Model

(b) Induced Fit Model

During the biocatalyst catalyzed processes three major types of selectivity are displayed. In chemoselective reactions purifications of product(s) from impurities is easier and side reactions can be omitted. Thus reactions are generally cleaner. As mentioned before because of their three-dimensional structure, enzymes can distinguish functional groups, which are chemically situated in different regions of the same substrate, so they can show regioselectivity and diastereoselectivity. Biocatalysts are also enantioselective because they are chiral catalysts. So any type of chirality present in the substrate is recognized and prochiral compound is transformed into optically active product. Stereoselectivity in an enzymatic reaction can be accomplished through kinetic control. This means that one enantiomer reacts faster than the other. The enantioselective performance of enzymes is expressed as the enantiomeric ratio E, which is a measure for the selectivity of an enzyme for one of the enantiomers of a substrate [45].

1.5 Olefin Metathesis

Olefin metathesis is a transition metal catalyzed reaction which formally a mutual exchange of alkylidene groups between two substituted alkenes occurs (Scheme 6) [46-48]. In other words, the metathesis constitutes a catalytic method for both breaking and forming C-C double bonds.

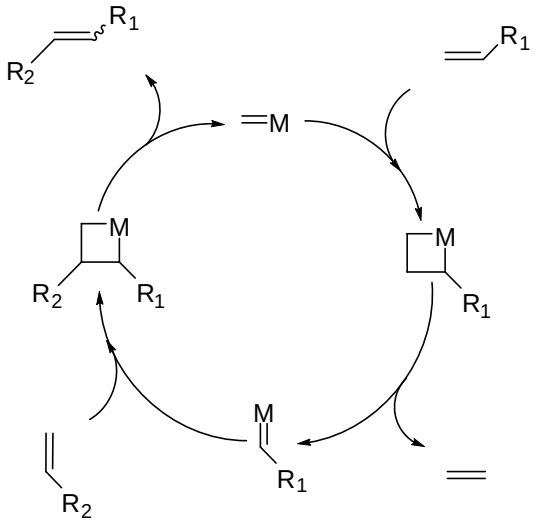


Scheme 6. General Principle of Olefin Metathesis of Symmetrically Substituted Olefins

Robert H. Grubbs, Richard R. Schrock, Yves Chauvin received the Nobel Prize in 2005 in Chemistry for their works in the field of olefin metathesis. This represents a great step forward for "*green chemistry*", reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment.

1.5.1. Mechanism of Olefin Metathesis

In 1971 Chauvin and his student Louis Hérisson published as their metathesis mechanism illustrated modified form in Scheme 7 [49].



Scheme 7. The Chauvin Catalytic Cycle

The metal methylene (metal alkylidine) reacts with the olefin forming a metallocyclobutane intermediate. This intermediate then cleaves, yielding ethylene

and a new metal alkylidine. The ethylene formed contains one methylene from the catalyst and one from the starting olefin. The new metal alkylidine contains the metal with its ligands and alkylidine from the substrate alkene. This metal alkylidine reacts with a new substrate alkene molecule to occur another metallocyclobutane intermediate. On decomposition in the forward direction this intermediate yields the product internal alkene and metal methylene. This metal alkylidine is ready now to enter another catalytic cycle. Thus each step in the catalytic cycle involves exchange of alkylidines- metathesis [50].

Chauvin and co-workers also presented experimental support for the mechanism which could not be explained by the other proposed mechanisms. The mechanism has also experimental support by Grubbs, T.J. Katz, Schrock and others and is now generally accepted as the mechanism for metathesis.

1.5.2. Well-Defined Catalyst Systems in Olefin Metathesis Reactions

Schrock and his group have afforded to find the stable molecular alkylidene and alkylidyne complexes of molydmenum and tungsten metals. The search eventually produced a whole family of molydmenum- and tungsten-alkylidene complexes of the general formula [M(=CHMe2Ph)(=N-Ar)(OR2)] , R being bulky groups. These compounds are at present the most active of the alkene metathesis catalysts known (Figure 7) [51-53].

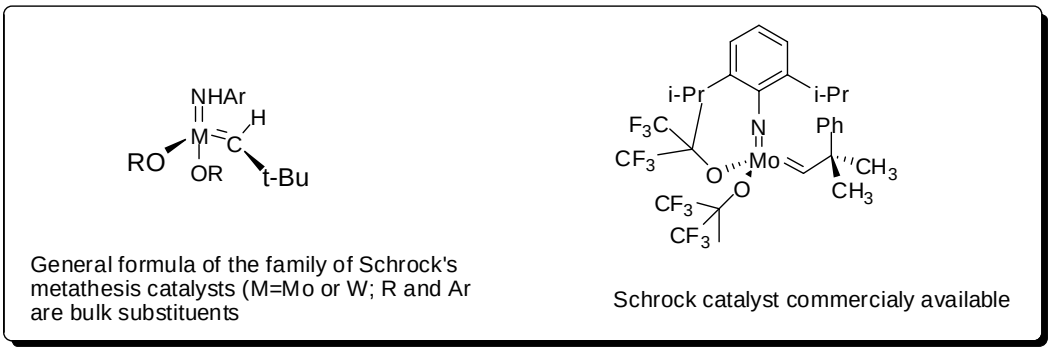


Figure 7. Well-Defined Olefin Metathesis Schrock Catalysts [47]

Grubbs and co-workers 1992 reported their first molecularly well-defined ruthenium-carbene complex that was not only active towards polymerization of norbornene but was also stable in the presence of protic solvents [54-56]. The complex was of the vinylidene type [$RuCl_2$ (PR_3)(=CH-CH=CPh_2)] with R=Ph (Figure 8).

In 1995 Grubbs reported new molecularly-well-defined catalysts [Ru(=CHPh)Cl_2(PR_3)$_2$], R=Ph or Cy (cyclohexyl) [57-58]. These structures are closely related to the vinylidene ones. The compound with R=Cy [Ru(=CHPh)Cl_2(PCy_3)$_2$] has been commercialized and is known as the first-generation Grubbs catalyst (Figure 8). This compound is still the most common metathesis catalyst used by organic chemists, because of its stability in air and compatibility with a large variety of groups.

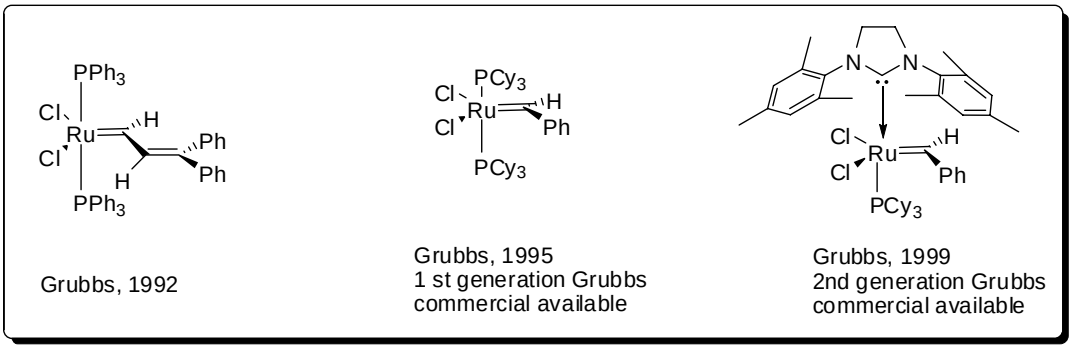


Figure 8. Well-Defined Olefin Metathesis Grubbs Catalyst

In a number of difficult ring-closing reactions, the lifetime of the catalyst was insufficient to give high yields of products with reasonable catalyst loadings. Apparently catalysts with improved properties were needed. Detailed mechanistic studies led Grubbs` group to conclude that the reaction first involved the dissociation of one of the phosphines to generate the reactive ruthenium intermediate. To accelerate the dissociation Grubbs replaced one of the phosphines with a cyclic bis-amino carbene ligand. The new, more reactive, catalysts are called second generation Grubbs` catalysts. It is currently used catalyst in particular for the efficient cross-metathesis reactions [59]. This new ruthenium catalyst, with its greater thermal stability is now also commercially available.

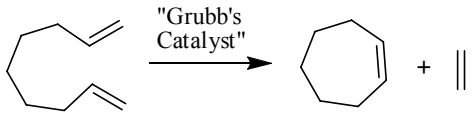
Grubbs and Schrock catalysts offer synthetic chemists novel opportunities. Their widespread use in organic chemistry is due to their tolerance of a large variety of functional groups, combined with their efficiency and, for Grubbs` catalysts, their ease of handling in air [60-61].

1.5.3 Ring Closing Metathesis

Olefin metathesis can be utilized in three closely related type of reactions, ring- opening metathesis polymerization (ROMP), acyclic cross metathesis which

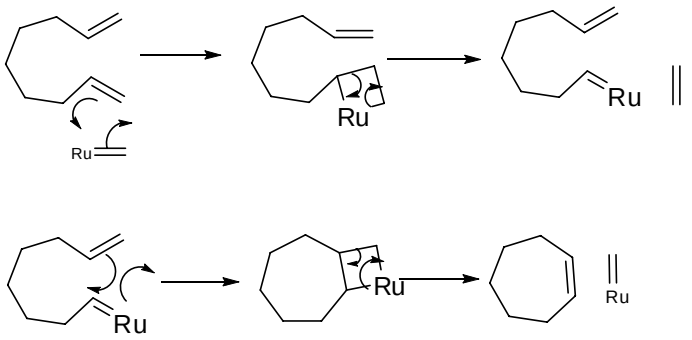
carried out on diolefins results in polymers (ADMET) and ring closing metathesis [62].

Ring Closing Metathesis (RCM), a term coined by Robert Grubbs is a variant of the olefin metathesis reaction. The reaction allows the closing of previously hard to make rings (in particular 7-8 member rings) [63]. RCM is simply an intramolecular olefin metathesis *via* Grubbs' catalyst, yielding to cycloalkene and volatile alkene is shown in Scheme 8.



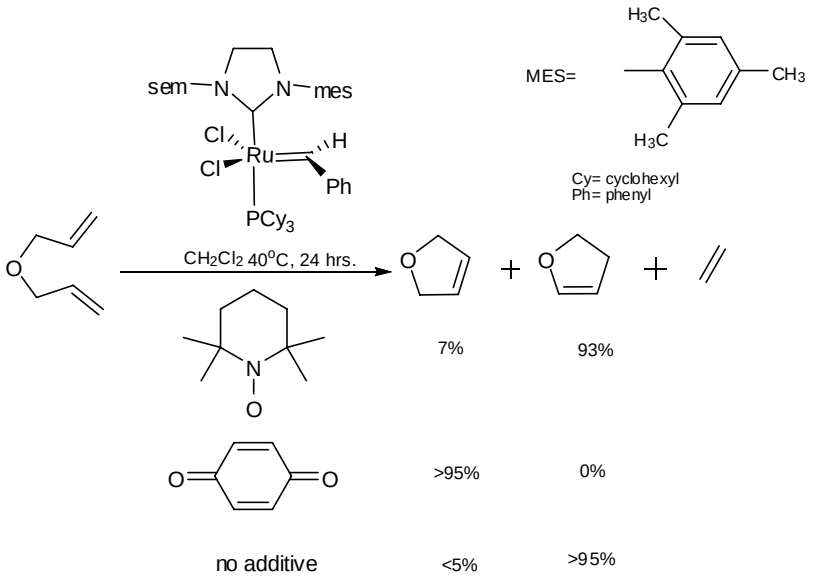
Scheme 8. A example of Ring Closing Metathesis reaction

The mechanism of this reaction was proposed by Grubbs (Scheme 9).



Scheme 9. Mechanism of Ring Closing Metathesis

Many metathesis reactions with ruthenium catalyst are hindered by undesired isomerization of the newly formed double bond and it is believed that ruthenium hybrides are responsible that form as a side reaction. It is found that isomerization is suppressed in the RCM reaction of the diallyl ether with specific additive capable of removing these hydrides [64]. Without an additive, the reaction product is 2,3-dihydrofuran and not the expected 2,5-dihydrofuran (together with the formation of ethylene gas). Radical scavengers such as TEMPO or phenol as an additive show the same picture but with additives such as 1, 4-benzoquinone or acetic acid on the other hand isomerization is absent. Both additives are able to oxidize the ruthenium hydrides which may explain their behavior.

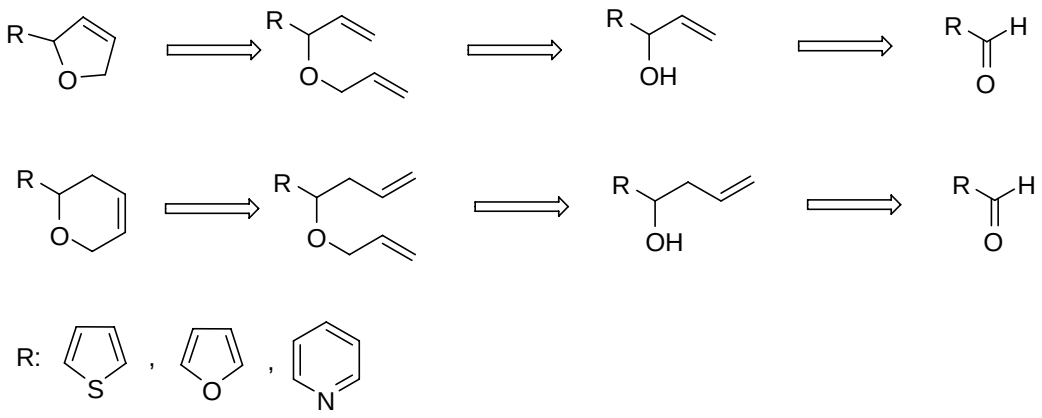


Scheme 10. RCM of diallyl ether with selective additive

1.6 Aim of the Work

In the recent years, chiral heterocyclic compounds have become popular in the synthesis of various natural products. Transition metal catalyzed olefin metathesis is used as a suitable method in the synthesis of the biologically active natural products which are comprised heterocycles. In this field ruthenium carbene catalysts are the most convenient ones in terms of their stability, functional group tolerance, easy handling and commercially availability.

In this work, we planned to synthesize chiral heteroaryl substituted dihydro furan and pyran derivatives *via* ring closing metathesis. Retrosynthetic analysis of the target systems shows that heteroaryl substituted secondary allylic and homoallylic alcohols could be suitable precursors in the enzymatic resolution methods for the asymmetric induction (Scheme 11). Subsequent *O*-allylation might afford the feasible backbone for ring closing metathesis (RCM) reactions by Grubbs first generation catalyst. During the course of all synthesis we have considered Green Chemistry approach in terms of atom economy, E factor, olefin metathesis type reaction and biocatalysts.



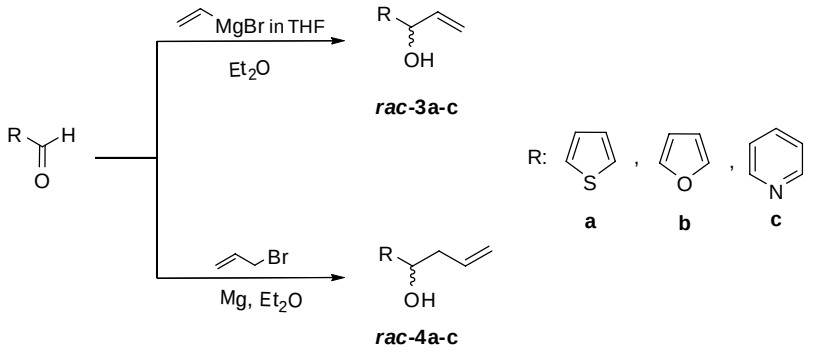
Scheme 11. Retrosynthetic approach of the work

CHAPTER 2

RESULTS AND DISCUSSION

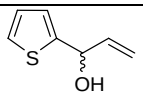
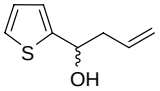
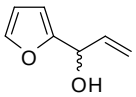
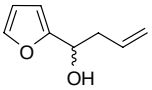
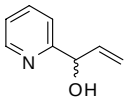
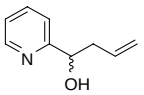
2.1. Synthesis of Racemic Allylic and Homoallylic Alcohols

Allylic and homoallylic alcohols are widely used in the synthesis of natural products, bioactive compounds and many complex molecules [65]. In the literature, allylation of aldehydes by organometallic reagents is a versatile synthetic method which involves the nucleophilic addition of allyl In, Mg, Zn to the carbonyl groups [66]. In the first part of the work, it was planned to synthesize racemic allylic and homoallylic alcohols. The 2-heteroaryl substituted carbaldehydes were chosen as starting materials because of their commercially availabilities and eligibilities in Grignard reactions. The reactions were performed using commercially available vinylmagnesium bromide and *in situ* prepared allylmagnesium bromide in dry solvents (ether or THF) under argon atmosphere to afford corresponding 2-heteroaryl substituted allylic and homoallylic compounds, respectively (Scheme 12). All the results are summarized in Table 1.



Scheme 12. Synthetic pathway of heteroaryl substituted allylic and homoallylic alcohols

Table 1. Results of allylic and homoallylic alcohol synthesis

Substrate	Product	Time(h)	Yield (%)
Thiophene-2-carbaldehyde	 *rac*-**3a**	3	85
Thiophene-2-carbaldehyde	 *rac*-**4a**	7	80
Furan-2-carbaldehyde	 *rac*-**3b**	5	90
Furan-2-carbaldehyde	 *rac*-**4b**	12	84
Pyridine-2-carbaldehyde	 *rac*-**3c**	4	78
Pyridine-2-carbaldehyde	 *rac*-**4c**	8	75

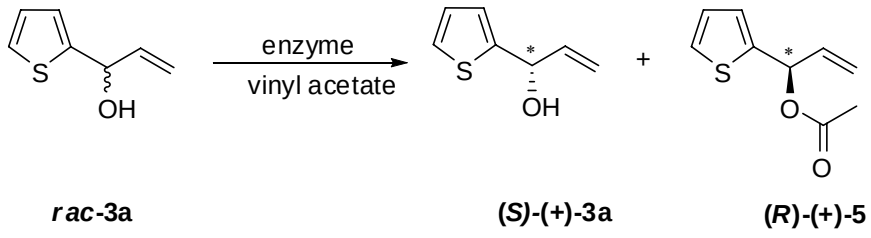
The structure elucidation of all racemic alcohols was done by ^{1}H and ^{13}C NMR spectroscopy. The spectra are all in accordance with the literature data and given in appendix (Figure A1-6) [67].

2.2. Enzymatic Resolution of Racemic Allylic and Homoallylic Alcohols

Racemic 2-heteroaryl substituted secondary alcohols were enantiomerically enriched by enzymatic resolution approach. Screening reactions were first completed with various lipases (i.e. CCL, PLE, HLE, PPL, PS-C II, Lipozyme and Novozyme435) using substrate: enzyme ratios varied from 1:1 to 1:0.5. Among the lipases studied, PS-C II, Lipozyme and Novozyme435 proved suitable for the enantioselective acetylation of these substrates. PS-C II, Lipozyme and Novozyme435 catalyzed reactions of all racemic allylic and homoallylic substrates *rac*-**3a-c** and *rac*-**4a-c** afforded (*S*) configured alcohols with different enantioselectivities. Absolute configuration of the products was determined by comparing with the literature data [67-68].

2.2.1. Enzymatic Resolution of *rac*-(thiophen-2-yl)prop-2-en-1-ol, *rac*-3a

Enzymatic hydrolysis of *rac*-(thiophen-2-yl)prop-2-en-1-ol *rac*-**3a** was separately carried with Novozyme435 and PS-C II. The resolution was monitored by TLC. When the conversion of alcohol to acetyl derivative was approximately 50%, the reaction was ended (Scheme 13).



***rac*-3a** **(*S*)-(+)-3a** **(*R*)-(+)-5**

Scheme 13. Enzymatic resolution of *rac*-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**3a**

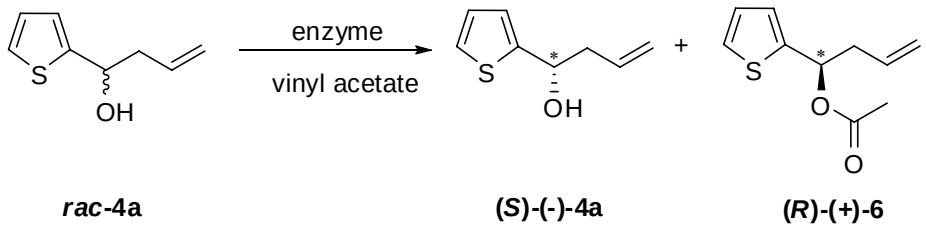
Enantiomeric excess e.e. value of allyl alcohol (+)-**3a** was determined by using HPLC with OJ-H chiral column (Figure A14). The enzymatic resolution results are given in Table 2. According to ee values, Novozyme435 showed higher enantioselectivity than PS-C II for the substrate *rac*-**3a**. Both resolution reactions were carried out at 26 ^{o}C in THF and completed in a very short period of time around 1h.

Table 2. Enzymatic resolution results of *rac*-**3a**

Substrate	Enzyme	Time(min.)	Temp. (°C)	Conv.(%)	E.e. (%)	Co-solvent
***rac*-3a**	Novozyme435	65	26	56	97	THF
***rac*-3a**	PS-C II	75	26	47	84	THF

2.2.2. Enzymatic Resolution of r*ac*-(thiophen-2-yl) but-3-en-1-ol, *rac*-4a

Enantiomeric enrichment of thiophenyl substituted homoallylic alcohol *rac*-**4a** was carried out through the resolution by Lypozyme and PS-C II under the conditions given below (Scheme 14, Table 3).



***rac*-4a** **(*S*)-(-)-4a** **(*R*)-(+)-6**

Scheme 14. Enzymatic resolution of *rac*-(thiophen-2-yl)but-3-en-1-ol, *rac*-**4a**

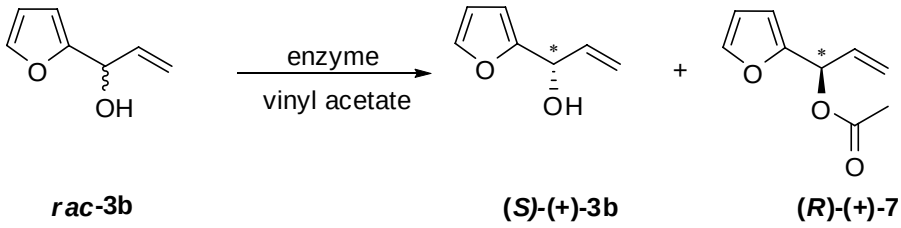
Enantiomeric excess values were determined by using HPLC with OJ-H chiral column (Figure A16). PS-C II and Lipozyme resolution reactions were carried out in the presence of co-solvents, THF and DPE, and afforded 95% and 99% e.e. values, respectively. Although PS-C II resolution completed for 20 h which has shorter reaction time than Lipozyme resolution, the latter gave excellent e.e. value.

Table 3. Enzymatic resolution results of *rac*-**4a**

Substrate	Enzyme	Time(h)	Temp. (°C)	Conv.(%)	E.e(%)	Co-solvent
***rac*-4-a**	PS-C II	20	24	56	95	THF
***rac*-4-a**	Lipozyme	27	26	54	99	DPE

2.2.3. Enzymatic Resolution of *rac*-(furan-2-yl)prop-2-en-1-ol, *rac*-3b

Screening reactions of furyl substituted allylic alcohol *rac*-**3b** done with various lipases showed that PS-C II and Novozyme435 were the most suitable enzymes (Scheme 15).



***rac*-3b** **(*S*)-(+)-3b** **(*R*)-(+)-7**

Scheme 15. Enzymatic resolution of *rac*-(furan-2-yl)prop-2-en-1-ol, *rac*-**3b**

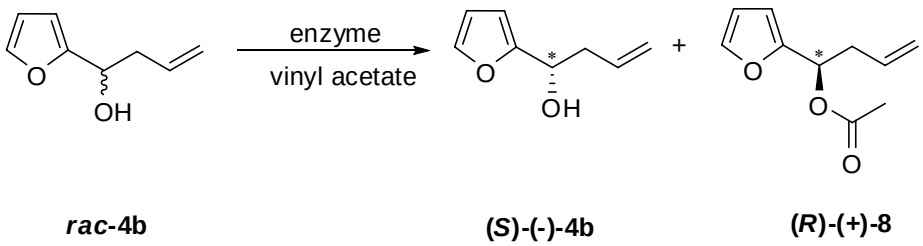
Rac-**3b** was first resolved with PS-C II at 27 ^{o}C in vinyl acetate without any co-solvent and as a result of 40% conversion afforded 51% e.e. (Table 4, entry 4). Further investigations on PSC-II were done by using THF as co-solvent and sharp increasing from 51% to 77% was observed in e.e. values (entry 3). The conversion ratio was increased up to 48%, too. This result directed us towards the thorough screening on the conversion parameter. Actually, increasing the conversion to 54%, drastic increase in the e.e. value was observed as 92% (entry 2). Final attempt with 60% conversion afforded the (*S*)-configurated alcohol (+)-**3b** in 98% e.e. value (entry 1). Novozyme435 was also used as resolving catalyst (entry 5) and gave the highest e.e. value as well as entry 1.

Table 4. Enzymatic resolution results of *rac*-**3b**

Entry	Substrate	Enzyme	Time(min)	Temp. (°C)	Conv.(%)	E.e(%)	*Co-solvent*
1	*rac*-**3b**	PS-C II	70	26	60	*98*	THF
2	*rac*-**3b**	PS-C II	65	27	54	*92*	THF
3	*rac*-**3b**	PS-C II	55	27	48	*77*	THF
4	*rac*-**3b**	PS-C II	55	27	40	*51*	-
5	*rac*-**3b**	Novozyme435	75	26	56	*98*	THF

2.2.4. Enzymatic Resolution of *rac*- (furan-2-yl)but-3-en-1-ol, *rac*- 4b

Tanyeli and coworkers reported the first enzymatic resolution of various furylcarbinols with excellent enantioselectivities [69]. Herein, we described the highly efficient resolution of the allyl substituted furylcarbinol *rac*-**4b** with PS-C II, Lipozyme and Novozyme435 (Scheme 16).



Scheme 16. Enzymatic resolution of *rac*-(thiophen-2-yl)but-3-en-1-ol, *rac*-**4b**

The resolutions required co-solvents as THF and DPE for PS-C II, Novozyme435 and Lipozyme, respectively, to afford high e.e. values varied from 93% to 99%. The reactions done with PS-C II and Novozyme435 completed in 4 h whereas the resolution with Lipozyme took place in 15.5 h. All three cases can be applied to get enantiomerically enriched (*S*)-(-)-**4b** (Table 5).

Table 5. Enzymatic resolution results of *rac*-**4b**

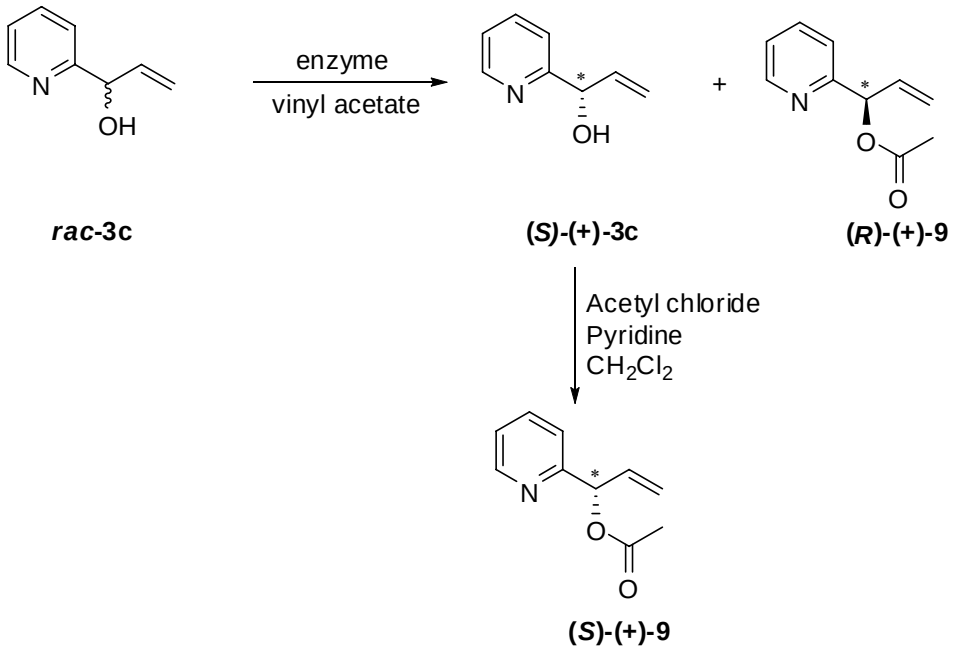
Substrate	Enzyme	Time(h)	Temp. (°C)	Conv.(%)	E.e.(%)	*Co-solvent*
***rac*-4b**	PS-C II	4	24	55	99	THF
***rac*-4b**	Lipozyme	15.5	27	60	99	DPE
***rac*-4b**	Novozyme435	4	24	52	93	THF

2.2.5. Enzymatic Resolution of r*ac*-(pyridine-2-yl)prop-2-en-1-ol, *rac*-3c

Enzymatic resolution of pyridine substituted allyl alcohol system *rac*-**3c** was tested with various lipases. Among the lipases, only Novozyme435 showed activity

in THF as co-solvent and afforded 60% e.e. as a result of 46% conversion for 12.5 h (Scheme 17).

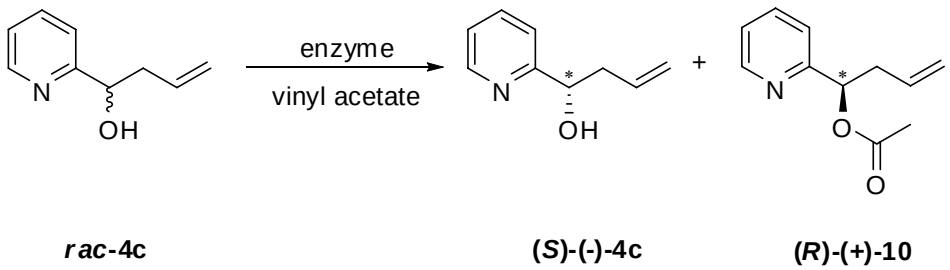
During the determination of enantiomeric excess value of allylic alcohol (*S*)-(-)-**3c**, no feasible HPLC separation condition could be found. Fortunately, *O*-acetylated derivative *rac*-**9** was separated with OJ-H chiral column. For this purpose, (*S*)-(-)-**3c** was chemically transformed into the corresponding *O*-acetylated derivative (*S*)-(-)-**9**.



Scheme 17. Enzymatic resolution of *rac*-(pyridine-2-yl)prop-2-en-1-ol, *rac*-**3c.**

2.2.6. Enzymatic Resolution of *rac*-(pyridine-2-yl)but-3-en-1-ol, *rac*-4c

Enzymatic resolution studies of pyridine substituted homoallylic alcohol *rac*-**4c** were performed with three different enzymes (PS-C II, Lipozyme and Novozyme435) (Scheme 18).



***rac*-4c** **(*S*)-(-)-4c** **(*R*)-(+)-10**

Scheme 18. Enzymatic resolution of r*ac*-(pyridine-2-yl)but-3-en-1-ol, *rac*-**4c**

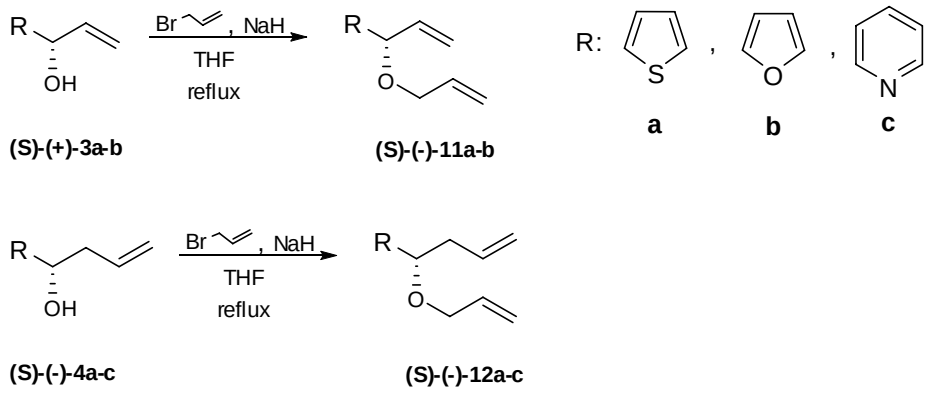
Among the lipases studied, PS-C II gave the best result as 98% e.e. in THF (Table 6). Lipozyme also showed acceptable selectivity in DPE (85% e.e.) whereas Novozymedid not catalyze (< 20% conversion) and the e.e. value could not be determined.

Table 6. Enzymatic resolution results of *rac*-**4c**

Substrate	Enzyme	Time(h)	Temp.(°C)	Conv.(%)	E.e(%)	*Co-solvent*
***rac*-4c**	PS-C II	24	24	55	98	THF
***rac*-4c**	Lipozyme	49	31	51	85	DPE
***rac*-4c**	Novozyme435	72	30	<20	n.d.	-

2.3. Construction of Chiral Diene Carbon Skeleton

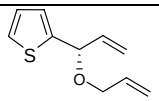
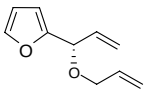
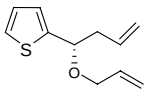
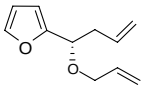
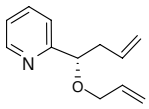
As it was mentioned before in "Aim of the Work" part, we planned to synthesize chiral heteroaryl substituted dihydrofuran and pyran derivatives *via* ring closing metathesis (RCM) reaction. So far, excellent level of chiral induction was achieved on the allylic and homoallylic alcohol backbone by enzymatic resolution approach. Ring closing metathesis (RCM) reactions required an isolated diene unit on the main skeleton. For this purpose, the second feasible alkene unit as allyl moiety was anchored to the chiral allylic (*S*)-(+)-**3a-b** and homoallylic alcohols (*S*)-(-)-**4a-c** from their oxygen atom by the very well known *O*-allylation procedure (Scheme 19). During the course of these reactions, applied procedure did not cause any racemization on the chiral center. Thus, all isolated diene compounds (-)-**11a-b** and (-)-**12a-c** possess (*S*) configuration. All the results are summarized in Table 7.



Scheme 19. *O*-Allylation of chiral allylic and homoallylic alcohols

Characterization of all isolated diene compounds was done by ^{1}H and ^{13}C NMR spectroscopy and the data are given in the experimental part in detail.

Table 7. *O*-Allylation results of (*S*)-(+)-**3a-b** and (*S*)-(-)-**4a-c**

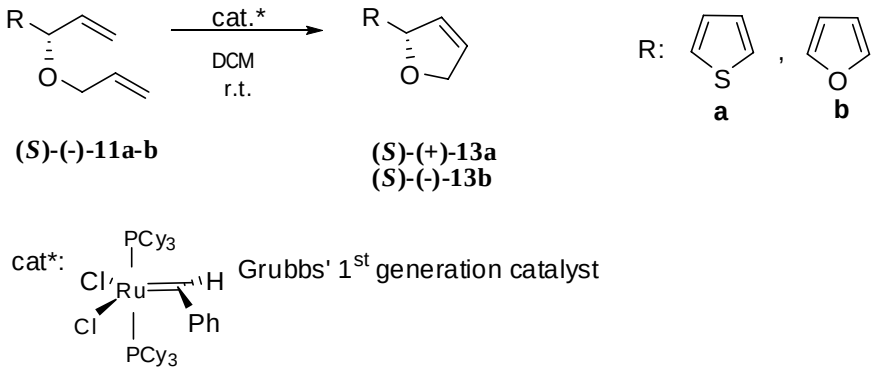
Substrate	Product	Configuration	Time (h)	Yield(%)
(*S*)-(+)-**3a**	 (*S*)-(-)-**11a**	*S*	1	95
(*S*)-(+)-**3b**	 (*S*)-(-)-**11b**	*S*	1.5	93
(*S*)-(-)-**4a**	 (*S*)-(-)-**12a**	*S*	1	92
(*S*)-(-)-**4b**	 (*S*)-(-)-**12b**	*S*	1	90
(*S*)-(-)-**4c**	 (*S*)-(-)-**12c**	*S*	75 min.	95

2.4. Ring Closing Metathesis (RCM) Studies

Ring closing metathesis (RCM) reaction initiated by Robert H. Grubbs has been widely used to form the cyclic systems in particular 7-8 member rings. Grubbs' 1st generation catalyst is quite feasible for RCM applications due to its high reactivity, stability in air and the compatibility with a large variety of groups. Depending upon our synthetic strategy, the final step involved the construction of chiral dihydrofuran and dihydropyran ring systems *via* RCM reaction.

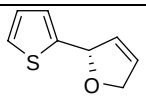
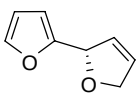
2.4.1. Synthesis of Chiral 2-Heteroaryl Substituted 2,5-Dihydrofuran Derivatives

RCM reactions of *O*-allyl anchored substrates (*S*)-(-)-**11a-b** were performed with 5% of Grubbs' 1st generation catalyst in DCM. (*S*)-(-)-**11b** gave the corresponding dihydrofuran in 85% yield whereas (*S*)-(-)-2-(2,5-dihydrofuran-2-yl)furan in 82% chemical yield (Scheme 20). The results are summarized in Table 8.



Scheme 20. RCM reactions of (*S*)-(-)-**11a-b**

Table 8. Results of RCM reactions

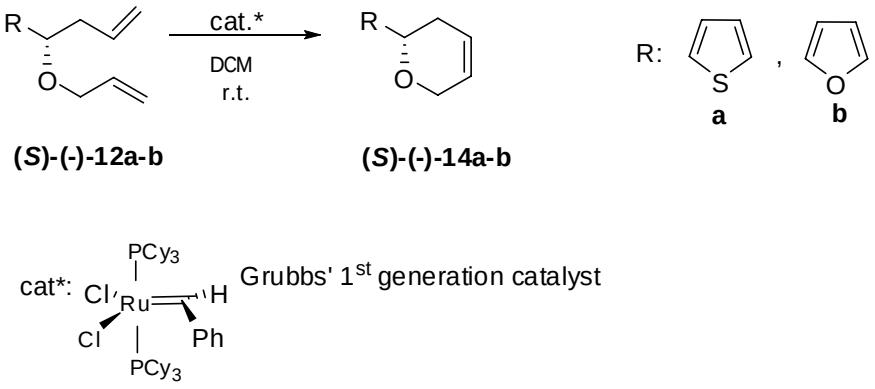
Substrate	Product	Configuration	Time(h)	Yield(%)
(*S*)-(-)-**11a**	 (*S*)-(+)-**13a**	*S*	2	82
(*S*)-(-)-**11b**	 (*S*)-(-)-**13b**	*S*	75 min.	85

The structure elucidation of compounds (*S*)-(+)-**13a** and (*S*)-(-)-**13b** was done by ^{1}H and ^{13}C NMR spectroscopy. (*S*)-(+)-**13a** reveals two olefinic protons at 6.00-6.03 and 5.85-5.88 ppm as multiplet. The methine proton attached to chiral center resonates at 5.95-5.98 ppm and its position shifts to down field (4.96 ppm to 5.95-5.98 ppm) by comparing with acyclic precursor (*S*)-(-)-**11a** as expected. ^{13}C NMR spectrum shows the characteristic eight signals.

The chiral center attached proton of (*S*)-(-)-**13b** resonates at 6.02 ppm as doublet (*J*=6.1 Hz), whereas double bond protons of dihydrofuran moiety show the signals at 5.78-5.84 and 5.70-5.75 ppm as multiplet. Diasteretopic methylene protons are observed as AB system at 4.72 and 4.62 ppm as doublet and doublet of doublet, respectively. ^{13}C NMR spectrum reveals the characteristic eight signals which are discussed in experimental part in detail.

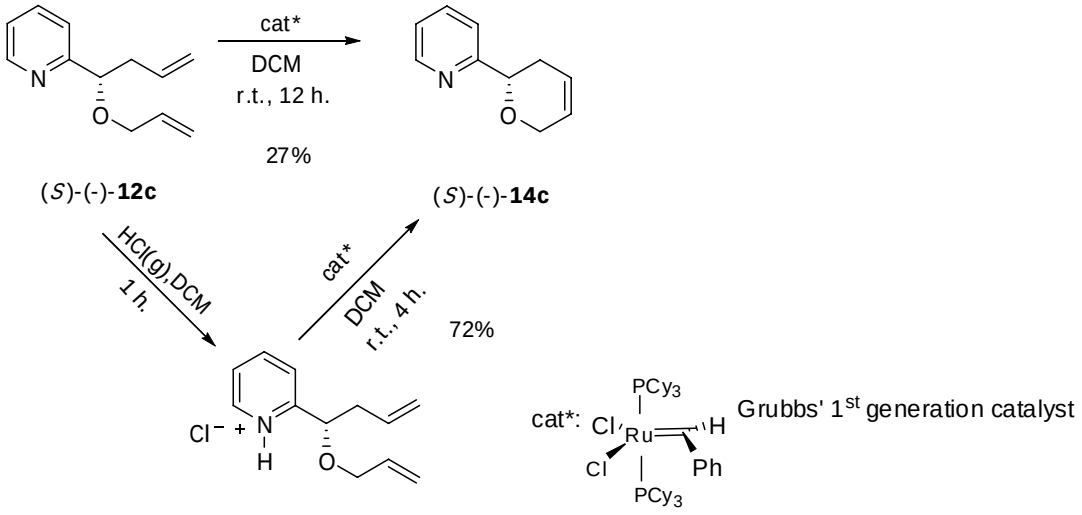
2.4.2. Synthesis of Chiral 2-heteroaryl Substituted 3,6-dihydro-*2H*-pyran Derivatives

Ring closing metathesis reactions of *O*-allyl anchored homoallylic substrates (*S*)-(-)-**12a-c** were carried out with 5% of Grubbs' 1st generation catalyst in DCM as well as allylic substrates. (*S*)-(-)-**12a** and (*S*)-(-)-**12b** afforded the corresponding dihydropyran derivatives (*S*)-(-)-**14a** and (*S*)-(-)-**14b** in 86% and 88% chemical yields, respectively(Scheme 21).



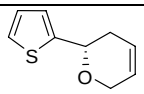
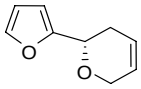
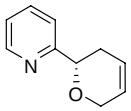
Scheme 21. RCM reactions of (*S*)-(-)-**12a-b**

Pyridine substituted starting compound (*S*)-(-)-**12c** gave the RCM dihydropyran product (*S*)-(-)-**14c** just with 27% chemical yield (Scheme 22). This low chemical yield could be presumably due to the possible interaction between the available free electrons of pyridine unit and the Grubbs' catalyst. In order to avoid the deactivation of catalyst, we tried to block the free electrons by HCl salt formation. Fortunately, the chemical yield was raised up to 72%. The results are summarized in Table 9.



Scheme 22. RCM reactions of (*S*)-(-)-**12**

Table 9. Results of RCM reactions of (*S*)-(-)-**12a-c**

Substrate	Product	Configuration	Time(h)	Yield(%)
(*S*)-(-)-**12a**	 (*S*)-(-)-**14a**	*S*	1	86
(*S*)-(-)-**12b**	 (*S*)-(-)-**14b**	*S*	1.5	88
(*S*)-(-)-**12c**	 (*S*)-(-)-**14c**	*S*	4	72

The structure elucidation of all dihydropyran derivatives (*S*)-(-)-**14a-c** was done by ^{1}H and ^{13}C NMR spectroscopy.

Olefinic proton attached to 4th position of (*S*)-(-)-**14a** resonates at 5.84 ppm as ddd, whereas the 5th position attached proton shows the signal at 5.72 as dt. The chiral center attached methane proton is observed at 4.15 ppm as dd. The characteristic diastereotopic methylene protons next to oxygen unit appear as two different sets at 4.27-4.35 and 4.21-4.26 ppm as dm. Another diastereotopic methylene protons are observed as two different sets at 2.40-2.49 and 2.26-2.36 ppm as dm. In ^{13}C NMR, two signals in the aromatic region are overlapped and the spectrum shows eight signals.

Proton NMR of (*S*)-(-)-**14b** shows the signals at 5.76-5.82 and 5.66 ppm which belong to double bond attached protons. The chiral center methine proton reveals the signal at 4.53 ppm as dd. Diastereotopic methylene protons next to oxygen atom resonate as a one set of signals at 4.17 ppm as dd. ^{13}C NMR possesses nine signals.

Pyridine substituted diyhydropyran derivative (*S*)-(-)-**14c** shows the signal at highly down field region 8.46 ppm as doublet for the pyridine ring attached proton next to nitrogen atom. The position of the other aromatic protons is varied between 7.10-7.60 ppm with the expected splitting pattern. Olefinic protons of dihydropyran unit are observed at 5.82-5.90 as multiplet and at 5.73 ppm as dt. The signal at 4.60 ppm as dd belongs to chiral center attached methine proton. Diastreotopic methylene protons next to pxygen atom resonate as a one set of signals as multiplet at 4.25-4.75 ppm, whereas another diastereotopic methylene protons appear as two different sets at 2.36-2.46 ppm and 2.20-2.32 ppm, respectively. ^{13}C NMR spectrum shows ten carbon signals.

CHAPTER 3

CONCLUSION

In this thesis, totally six heteroaryl substituted allylic and homoallylic systems were successfully synthesized starting with commercially available heteroarylcarbaldehydes by applying the very well-known Grignard reaction. The resulting racemic heteroaryl substituted allylic *rac*-**3a-c** and homoallylic alcohols *rac*-**4a-c** were enantiomerically enriched by the enzymatic resolution method which is involved in "*Green Chemistry"* approach. The absolute configurations of all substrates are known. This knowledge would help us to determine the absolute configurations of the target dihydrofuran (*S*)-(+)-**13a**, (*S*)-(-)-**13b** and dihydropyran (*S*)-(-)-**14a-c** molecules. The second part of the subject consists of ring closing metathesis method done with Grubbs' catalyst which is also strongly recommended in "*Green Chemistry"*.

In the enzymatic resolution part of the thesis, all the racemic substrates were resolved in >90% e.e. except pyridine substituted allylic derivative (*S*)-(+)-**3c**. In the ring closing metathesis reactions, we had only the problem in the cyclization of pyridine derivative (*S*)-(-)-**14c**. Fortunately, we overcame that problem by transforming it into the HCl salt. Since all the chiral products synthesized may have potent bioactivity, their tests are carried out with a joint research group.

CHAPTER 4

EXPERIMENTAL

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

NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are expressed in ppm.and tetramethylsilane (TMS) is used as an 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, br, 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.

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.

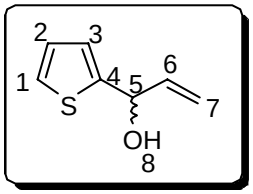
Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter at specified temperatures.

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

4.1. General Procedure for Synthesis of Racemic Allylic Alcohols, *rac*-3a-c

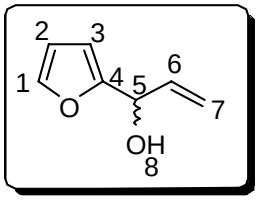
To a stirred solution of vinylmagnesium bromide in THF (1.0 N stock solution, 1.2 eq.), was added drop wise corresponding 2-heteroaryl substituted carbaldehyde (1 eq.) diluted with dry ether (5 mL) at 0 °C. The reaction was allowed to proceed under argon atmosphere until no aldehyde remained by TLC monitoring at room temperature. After the completion of reaction, 1 N HCl (9 mL) and saturated NH_4Cl (15 mL) solutions were added and the resulting mixture was extracted with Et_2O (3x15). Solvent was dried over $MgSO_4$ and then concentrated under reduced pressure to give *rac*-**3a-c**, purified with column chromatography (silica gel, EtOH/Hexane, 1:15 for *rac*-**3a,** 1:6 for *rac*-3**b** and 1:2 for *rac*-**3c**).

4.1.1. 1-(Thiophene-2-yl)prop-2-en-1-ol, *rac*-3a.



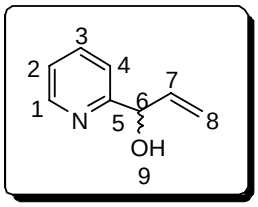
Colorless oil (85% yield). ^{1}H NMR: δ 7.13-7.15 (m, 1H, H_1), 6.84-6.86 (m, 2H, H_2 *and* H_3), 5.99 (ddd, 1H, J=17.1, 10.3 and 5.6 Hz, H_6), 5.24-5.30 (m, 2H, H_5 and H_{7cis}), 5.12 (dt, 1H, J=10.3 and 1.2 Hz, H_{7trans}), 2.61 (brs, 1H, H_8). ^{13}C NMR: δ 146.7, 139.4, 126.7, 125.2, 124.3, 115.6,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

4.1.2. 1-(Furan-2-yl)prop-2-en-1-ol, *rac*-3b.



Colorless oil (90% yield). ^{1}H NMR: δ 7.30 (dd, 1H, J=1.7 and 0.7 Hz, H_1), 6.25 (dd, 1H, J=3.2 and 1.8 Hz, H_2), 6.15 (d, 1H, J=3.2 Hz, H_3), 6.02 (ddd, 1H, J=17.3, 10.6 and 6.0 Hz, H_6), 5.3 (bd, 1H, J=17.3 Hz, H_5), 5.19 (bd, 1H, J=10.6 Hz, H_7), 5.12 (bt, 1H, J=4.7 Hz, H_7), 2.23 (brs, 1H, H_8). ^{13}C NMR: δ 155.3, 142.3, 136.9, 116.4, 110.3, 106.6, 68.5.

4.1.3. 1-(Pyridine-2-yl)prop-2-en-1-ol, *rac*-3c.

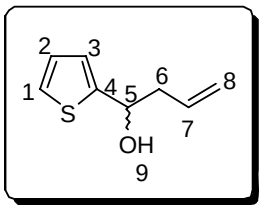


Colorless oil (90% yield). ^{1}H NMR: δ 8.40-8.44 (m, 1H, H_1), 7.60 (bt, 1H, J=7.7 Hz, H_3), 7.22 (d, 1H, J=8.0 Hz, H_4), 7.07-7.13 (m, 1H, H_2), 5.83-5.93 (m, 1H, H_7), 5.32 (dd, 1H, J=17.0 and 1.2 Hz, H_8), 5.07-5.14 (m, 2H, H_6 and H_8), 4.91 (brs, 1H, H_9). ^{13}C NMR: δ 160.4, 148.1, 139.6, 136.7, 122.3, 120.8, 116.6, 74.3.

4.2. General Procedure for Synthesis of Racemic Homoallylic Alcohols, *rac*-4a-c

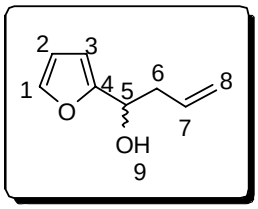
Dry Et_2O (10 mL) was added to the mixture of Mg (17.6 mmol, 1.7 eq.) and a few crystall of I_2. After dropwise addition of allylbromide (12.4 mmol, 1.2 eq.) to the mixture, reflux was observed. The solution was mixed for 30 minutes and the temperature was cooled down to 0 °C in an ice bath for dropwise addition of corresponding aldehyde (1.0 eq.). The mixture was allowed to stir at room temperature until all the starting material has finished by TLC controlling. 1 N HCl (9 mL) and saturated NH_4Cl (15 mL) solutions were added and the resulting mixture was extracted with ether (3x15). The organic layer was separated and dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude *rac*-**4a-c** were purified with flash column chromatography using mixture of ethyl acetate and hexane 1:6 for *rac*-**4a**, 2:1 for *rac*-**4b** and 2:1 for *rac*-**4c**.

4.2.1. 1-(Thiophene-2-yl)but-3-en-1-ol, *rac*-4a



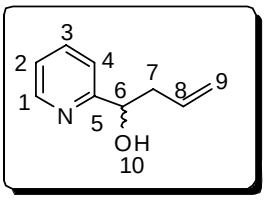
Colorless oil (80% yield). ^{1}H NMR: δ 7.17 (dd, 1H, J=4.6 and 1.7 Hz, H_1), 5.88-5.91 (m, 2H, H_2 and H_3), 5.68-5.81 (m, 1H, H_7) 5.06-5.14 (m, 2H, H_8), 4.88-4.93 (m, 1H, H_5), 2.51-2.57 (m, 2H, H_6), 2.22 (d, 1H, J=4.3 Hz, H_9). ^{13}C NMR: δ 147.9, 133.9, 126.6, 124.6, 123.7, 118.8, 69.4, 43.785.

4.2.2. 1-(Furan-2-yl)but-3-en-1-ol, *rac*-4b



Colorless oil (84% yield). ^{1}H NMR: δ 7.22-7.24 (m, 1H, H_1), 6.19 (dd, 1H, J=3.1 and 1.9 Hz, H_2), 6.10 (d, 1H, J=3.1 Hz, H_3), 5.66 (ddt, 1H, J=17.2, 14.1, 10.2 and 7.0 Hz, H_7), 4.97-5.00 (m, 2H, H_5 and H_{8trans}), 4.56 (t, 1H, J=6.6 Hz, H_{8cis}), 2.98 (brs, 1H, OH), 2.40-2.53 (m, 2H, H_6). ^{13}C NMR: δ 155.9, 141.4, 133.6, 117.7, 109.7, 105.7, 66.58, 39.69.

4.2.3. 1-(Pyridine-2-yl)but-3-en-1-ol, *rac*-4c



Colorless oil (75% yield). ^{1}H NMR: δ 8.53 (dm, 1H, J=5.0 Hz, H_1), 7.68 (td, 1H, J=7.7 and 1.7 Hz, H_3), 7.31 (d, 1H, J=7.7 Hz, H_4), 7.19 (dd, 1H, J=7.7 and 5.0 Hz, H_2), 5.77-5.90 (m, 1H, H_7), 5.08-5.14 (bd, 1H, J=10.4 Hz, H_8), 5.13-5.60 (m, 1H, H_8), 4.81 (dd, 1H, J=7.1 and 2.0 Hz, H_6), 4.29 (s, 1H, H_9), 2.49 (ddm, 1H, J=14.1 and 7.1 Hz, H_7), 2.60-2.68 (m, 1H, H_7). ^{13}C NMR: δ 161.6, 148.3, 136.6, 134.2, 122.3, 120.3, 117.9, 72.4, 42.9.

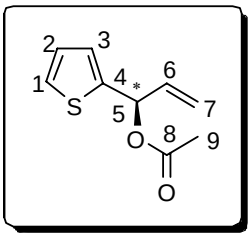
4.3. General Procedure for Enzymatic Resolution of Allylic and Homoallylic Alcohols

To a solution of the *rac*-**3a-c** and *rac*-**4a-c** (1 mmol) in corresponding co-solvent and vinyl acetate (0.9 ml, 10 mmol) in a 25 mL round bottom flask, was added corresponding enzyme (1 eq. w/w). The reaction mixture was stirred at constant temperature (26 °C for *rac*-**3a**, *rac*-**4a** and *rac*-**3b**, 24 ℃ for *rac*-**4b**, *rac*-**3c**, *rac*-**4c**) and monitored by TLC. On achieving the desired conversion the reaction was stopped by filtering the enzyme. The filtrate was concentrated and purified with flash column chromatography (silica gel, EtOH/hexane 1:15 for **3a,** 1:6 for 3**b** and 1:2 for **3c**, 1:6 for **4a**, 2:1 for **4b** and 2:1 for **4c**) afforded (*R*)-acetates and (*S*)-alcohols.

4.3.1. (*S*)-(+)-1-(Thiophene-2-yl)prop-2-en-1-ol, (*S*)-(+)-3a

$[\alpha]_D^{29}$= +2.74 (*c* 1.00, $CHCl_3$) for 97% e.e., in lit.[67a] $[\alpha]_D^{26}$= +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 A14).

4.3.2. (*R*)-(+)-1-(Thiophene-2-yl)allyl acetate, (R)-(+)-5



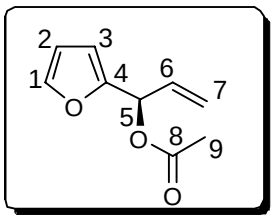
$[\alpha]_D^{33}$= +89,4 (c=1,CH_2Cl_2). ^{1}H NMR: δ 7.20 (dd, 1H, *J*=5.0 and 1.2 Hz, H_1), 7.00 (dm, 1H, *J*=3.6 Hz, H_2), 6.89 (dd, 1H, *J*=5.0 and 3.6 Hz, H_3), 5.95-6.04 (m, 1H, H_5),

6.0 (ddd, 1H, *J*=17.1, 10.4 and 6.0 Hz, H_6), 5.32 (dt, 1H, *J*=17.1 and 2.4 Hz, H_7), 5.22 (dt, 1H, *J*=10.4 and 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.

4.3.3. (*S*)-(+)-1-(Furan-2-yl)prop-2-en-1-ol, (*S*)-(+)-3b

$[\alpha]_D^{29}$= +1.08 (*c* 2.24, $CHCl_3$) for 98% e.e.., in lit.[67a] $[\alpha]_D^{26}$= +1.14 (*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_S=18.87, t_R=19.81.

4.3.4. (*R*)-(+)-1-(Furan-2-yl)allyl acetate, (R)-(+)-7

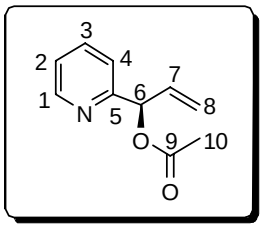


$[\alpha]_D^{33}$= +64,7 (c=1,CH_2Cl_2) ^{1}H NMR: δ 7.33-7.34 (m, 1H, H_1), 6.24-6.30 (m, 3H, H_2, H_3 and H_5), 5.94-6.02 (m, 1H, H_6), 5.32 (dt, 1H, *J*=17.2 and 1.2 Hz, H_7), 5.26 (dt, 1H, *J*=10.4 and *1*.2 Hz, H_7), 2.03 (s, 3H, H_9). ^{13}C NMR: δ 169.8, 151.7, 143.1, 133.2, 118.6, 110.6, 109.2, 69.2, 21.3.

4.3.5. (*S*)-(+)-1-(Pyridine-2-yl)prop-2-en-1-ol, (*S*)-(+)-4c

$[\alpha]_D^{29}$= +54.8 (*c* 1.84, $CHCl_3$) for %65 e.e., HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 99:1, flow rate 0.5 mL min^{-1}, λ=254 nm, t_R=28.03, t_S= 30.27.

4.3.6. (*R*)-(+)-1-(Pyridine-2-yl)allyl acetate, (*R*)-(+)-9

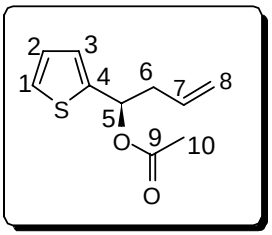


$[\alpha]_D^{27}$= +40.2 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 8.49 (d, 1H, *J*=4.1 Hz, H_1), 7.58 (td, 1H, *J*=7.7 and 1.8 Hz, H_3), 7.26 (d, 1H, *J*=7.7 Hz, H_4), 7.10 (ddd, 1H, *J*=5.6, 4.9 and 0.9 Hz, H_2), 6.20 (d, 1H, *J*=6.3 Hz, H_6), 6.03-5.95 (m, 1H, H_7), 5.26 (bd, 1H, *J*=17.2 Hz, H_8), 5.16 (bd, 1H, *J*=10.4 Hz, H_8), 2.02 (s, 3H, H_{10}). ^{13}C NMR: δ 169.6, 158.0, 149.1, 137.0, 135.0, 123.0, 121.2, 117.6, 76.7, 21.0.

4.3.7. (*S*)-(-)-1-(Thiophene-2-yl)but-3-en-1-ol, (*S*)-(-)-4a

$[\alpha]_D^{29}$= -17.1 (c 1.2, CH_2Cl_2) for %99 e.e., in lit.[67c] $[\alpha]_D^{27}$= -8.2 (*c* 1.2 CH_2Cl_2) for 80% e.e. , HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=12.21.

4.3.8. (*R*)-(+)-1-(Thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-6

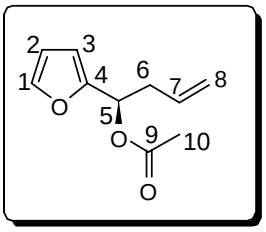


$[\alpha]_D^{32}$= + 64.81 (c=1,$CHCl_3$). ^{1}H NMR: δ 7.18 (dd, 1H, *J*=5.1 and 1.2 Hz, H_1), 6.95-6.96 (bd, 1H, *J*=3.5 Hz, H_2), 6.87 (dd, 1H, *J*=5.1 and 3.5 Hz, H_3), 6.01 (t, 1H, *J*=8.5 Hz, H_7), 5.58-5.70 (m, 1H, H_5), 5.03-5.08 (bd, *J*=17.1 Hz, 1H, H_8), 4.97-5.02 (bd, 1H, *J*=8.5 Hz, H_8), 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.

4.3.9. (*S*)-(-)-1-(Furan-2-yl)but-3-en-1-ol, (*S*)-(-)-4b

$[\alpha]_D^{29}$= -40.0 (c 5.0, CH_2Cl_2) for 99% e.e., in lit.[67c] $[\alpha]_D^{27}$= -32.6 (*c* 0.50 CH_2Cl_2 for 84%, HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 96:4, flow rate 1 mL min^{-1}, λ=230 nm, t_S=27.51.

4.3.10. (*R*)-(+)-1-(Furan-2-yl)but-3-enyl acetate, (*R*)-(+)-8

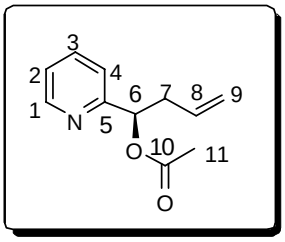


$[\alpha]_D^{32}$= +94,36 (c=1,$CHCl_3$). ^{1}H NMR: δ 7.30 (brs, 1H, H_1), 6.24 (brs, 2H, H_2 and H_3), 5.80 (t, 1H, *J*=7.14 Hz, H_7), 5.58-6.65 (m, 1H, H_5), 5.04 (dd, 1H, *J*=17.1 and 1.4 Hz, H_8), 5.00 (bd, 1H, *J*=10.2 Hz, H_8), 2.63 (t, *J*=7.0 Hz, 2H, H_6), 2.00 (s, 3H, H_{10}). ^{13}C NMR: δ 170.1, 143.2, 133.2, 126.8, 126.2, 125.6, 118.8, 70.7, 41.0, 21.4.

4.3.11. (*S*)-(-)-1-(Pyridine-2-yl)but-3-en-1-ol, (*S*)-(-)-4c

$[\alpha]_D^{29}$= -42.9 (c 0.86, CH_2Cl_2) for 98% e.e., in lit. [67b] $[\alpha]_D^{27}$= -46.4 (*c* 0.86 CH_2Cl_2) for 95% e.e. , HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 99:1, flow rate 0.3 mL min^{-1}, λ=254 nm, t_S=63.747, t_R= 58.75.

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



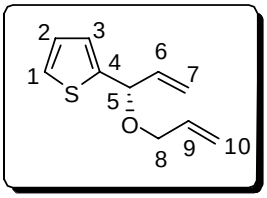
$[\alpha]_D^{32}$= +58,36 (c=1,$CHCl_3$). ^{1}H NMR: δ 8.51-8.54 (m, 1H, H_1), 7.59 (bt, 1H, *J*=7.7 Hz, H_3), 7.22 (bd, 1H, *J*=9.3 Hz, H_4), 7.10-7.15 (m, 1H, H_2), 5.77-5.82 (m, 1H), 5.61-5.80 (m, 1H, H_9), 5.03-4.98 (m, 1H, H_8), 4.98 (brs, 1H, H_6), 2.65 (ddm, 2H, *J*=27.0 and 14.2 Hz, H_7), 2.05 (brs, 3H, H_{11}). ^{13}C NMR: δ 170.3, 158.8, 149.4, 136.5, 133.1, 122.7, 121.2, 118.1, 75.7, 39.1, 21.1.

4.4. General Procedure for *O*-Allylation Reaction

Enantiomerically enriched alcohol (*S*)-(+)-**3a-b** and (*S*)-(-)-**4a-c** was dissolved in freshly distilled THF (10 mL). NaH (1.5 eq.) was added to the solution at a rate maintained gently reflux. After the solution was stirred for 15 minutes, allyl bromide (1.5 eq.) was added dropwise under argon atmosphere. The reaction was monitored by TLC and then quenched with distilled water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x15 mL) and the combined organic layers were washed with brine (2x15 mL), dried over MgSO4, and the solvent was removed in *vacuo*. At

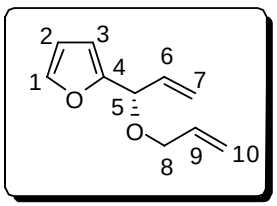
the end of these processes, the desired pure products were obtained without any purification step.

4.4.1. (*S*)-(-)-2-(1-(Allyloxy)allyl)thiophene, (*S*)-(-)-11a



Colorless oil (95% yield). $[\alpha]_D^{22}$= -12.06 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 7.17 (t, 1H, *J*=3.2 Hz, H_1), 6.80 (m, 2H, H_2 and H_3), 5.79-5.98 (m, 2H, H_9 and H_{10}), 5.22 (dm, 1H, *J*=16.8 Hz, H_{10}), 5.21 (m, 2H, H_7 and H_{10}), 5.10 (ddm, 1H, *J*=10.4 and 1.5 Hz, H_7), 4.96 (d, 1H, *J*=6.7 Hz, H_5), 3.90-4.00 (m, 2H, H_8). ^{13}C NMR: δ 144.4, 137.7, 134.2, 126.1, 124.9, 124.4, 116.6, 116.5, 76.2, 68.7.

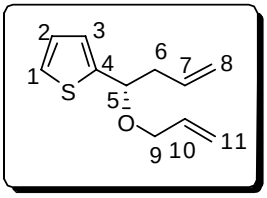
4.4.2. (*S*)-(-)-2-(1-(allyloxy)allyl)furan, (*S*)-(-)-11b



Colorless oil (93% yield). $[\alpha]_D^{26}$= -23.35 (*c*=1, $CHCl_3$). ^{1}H NMR: δ 7.32 (dd, 1H, *J*=1.8 and 0.8 Hz, H_1), 6.25 (dd, 1H, *J*=3.2 and 1.8 Hz, H_2), 6.19 (d, 1H, *J*=3.2 Hz,

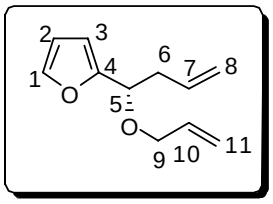
H_3), 5.95 (ddd, 1H, J=10.5, 6.6 and 3.7 Hz, H_9), 5.83 (ddd, 1H, J=16.0, 10.5 and 5.6 Hz, H_6), 5.29 (dt, J=17.2 and 1.4 Hz, 1H, H_{10}), 5.24-5.23 (m, 1H, H_7), 5.20 (bd, 1H, J=6.4 Hz, H_{10}), 5.11(bd, 1H, J=10.4 Hz, H_7), 4.78 (d, J=6.6 Hz, 1H, H_5), 3.93 (bd, 2H, J=5.6 Hz, H_8). ^{13}C NMR: δ 153.6, 142.4, 135.4, 134.6, 117.6, 117.1, 110.1, 107.8, 75.0, 69.2.

4.4.3. (*S*)-(-)-2-(1-(Allyloxy)but-3-enyl)thiophene, (*S*)-(-)-12a



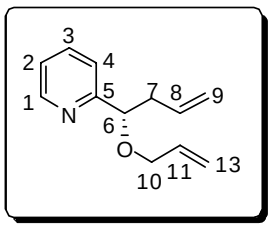
Colorless oil (92% yield). $[\alpha]_D^{19}$= -55.03 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.18-7.20 (m, 1H, H_1), 7.85-7.90 (m, 2H, H_2 and H_3), 5.65-5.88 (m, 2H, H_7 and H_{10}), 5.15-5.22 (dm, 1H, J=17.3 Hz, H_{11}), 5.07-5.12 (bd, 1H, J=10.5 Hz, H_{11}), 4.99-5.04 (dm, 1H, J=17.3 Hz, H_8), 4.94-4.99 (dm, 1H, J=10.3 Hz, H_8), 4.53 (t, 1H, J=17.3 Hz, H_5), 3.93 (ddm, 1H, AB system diastereotopic CH_aH$_b$, J_{AB} =12.8 and 5.1 Hz, H_9), 3.80 (ddm, 1H, AB system diastereotopic CH$_a$$H_b$, J_{AB} =12.8 and 5.1 Hz, H_9), 2.58-2.68 (m, 1H, H_6), 2.40-2.50 (m, 1H, H_6). ^{13}C NMR: δ 145.8, 134.7, 134.3, 126.3, 125.2, 125.0, 117.3, 117.1, 76.5, 69.4, 42.8.

4.4.4. (*S*)-(-)-2-(1-(Allyloxy)but-3-enyl)furan, (*S*)-(-)-12b



Colorless oil (90% yield), $[\alpha]_D^{32}$= -35.42 (*c* 0.5, $CHCl_3$).^{1}H NMR: δ 7.29 (dd, 1H, *J*=1.8 and 0.7 Hz, H_1), 6.23 (dd, 1H, *J*=3.2 and 1.8 Hz, H_2), 6.16 (d, 1H, *J*=3.24 Hz, H_3), 5.62 -5.82 (m, 2H, H_7 and H_{10}), 5.13-5.18 (bd, 1H, *J*=17.2 Hz, H_{11}), 5.05-5.08 (dm, 1H, *J*=8.8 Hz, H_{11}), 4.96-5.02 (bd, 1H, *J*=17.1 Hz, H_8), 4.92-4.95 (dm, 1H, *J*=10.7 Hz, H_8), 4.28 (t, 1H, *J*=7.1 Hz, H_5), 3.86-3.91 (ddm, 1H, AB system diastereotopic CH_aH_b, J_{AB} =12.8 and 5.2 Hz, H_9), 3.72-3.78 (ddm, 1H, AB system diastereotopic CH_aH_b, J_{AB} =12.8 and 5.1 Hz, H_9), 2.55-2.62 (m, 1H, H_6), 2.46-2.53 (m, 1H, H_6). ^{13}C NMR: δ 154.2, 142.1, 134.7, 134.1, 117.2, 116.6, 109.9, 107.9, 73.8, 69.4, 39.7.

4.4.5. (*S*)-(-)-2-(1-(Allyloxy)but-3-enyl)pyridine, (*S*)-(-)-12c



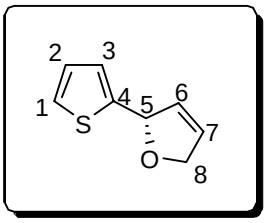
Colorless oil (95% yield), $[\alpha]_D^{29}$= -69.8 (*c* 1.00, EtOH). ^{1}H NMR: δ 8.45 (dm, 1H, *J*=4.8 Hz, H_1), 7.57 (td, 1H, *J*=7.6 and 1.6 Hz, H_3), 7.32 (d, 1H, *J*=7.8 Hz, H_4), 7.06

(bt, 1H, *J*=6.1 Hz, H_5), 5.68-5.85 (m, 2H, H_8 and H_{11}), 5.16 (dd, 1H, *J*=17.3 and 1.6 Hz, H_{12}), 5.05 (dd, 1H, *J*=10.4 and 1.2 Hz, H_{12}), 4.92 (m, 1H, H_9), 4.91 (bd, 1H, *J*=17.1 Hz, H_9), 4.41 (t, 1H, *J*=6.3 Hz, H_6), 3.80 (dd, 1H, AB system diastereotopic CH_aH_b, J_{AB}=12.8 and 5.1 Hz, H_{10}), 3.89 (dd, 1H, AB system diastereotopic CH_aH_b, J_{AB}=12.8 and 5.1Hz, H_{10}), 2.47 (bt, 2H, *J*=6.6 Hz, H_7). ^{13}C NMR: δ 161.8, 148.8, 136.3, 134.5, 134.2, 122.1, 120.3, 117.0, 116.6, 81.9, 70.0, 40.9.

4.5. General Procedure for Ring Closing Metathesis

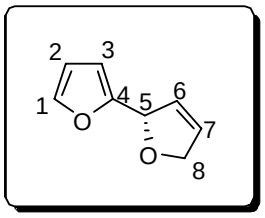
O-Allyl anchored substrate (*S*)-(+)-**11a**, (*S*)-(-)-**11b** and (*S*)-(-)-**12a-c** was dissolved in DCM (10 mL) and Grubbs' first generated catalyst (5%) was added to the solution. The reaction was monitored by TLC. The crude product was concentrated and purified with short column chromatography (cellite, EtOAc/hexane 1:15 for (*S*)-(-)-**13a-b** and (*S*)-(-)-**14a-b**, 1:2 (*S*)-(-)-**14c**).

4.5.1. (*S*)-(+)-2-(Thiophene-2-yl)-2,5-dihydrofuran, (*S*)-(+)-13a



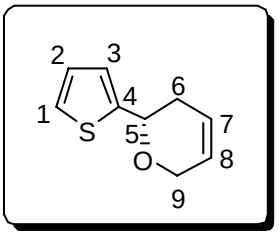
Colorless oil (82% yield). $[\alpha]_D^{28}$= +12.06 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.18-7.19 (m, 1H, H_1), 6.88-6.92 (m, 2 H, H_2 and H_3), 6.00-6.03 (m, 1 H, olefinic H), 5.95-5.98 (m, 1H, H_5), 5.85-5.88 (m, 1 H, olefinic H), 4.73-4.78 (bd, *J*=12.8 Hz, 1H, H_8), 4.61-4.66 (dm, 1H, *J*=12.8 Hz, H_8). ^{13}C NMR: δ 146.3, 130.0, 128.0, 127.0, 125.7, 124.9, 83.2, 75.4.

4.5.2. (*S*)-(-)-2-(2,5-Dihydrofuran -2-yl)furan, (*S*)-(-)-13b



Colorless oil (85% yield). $[\alpha]_D^{27}$= -42.14 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.30-7.33 (brs, 1H, H_1), 6.23-6.27 (m, 1H, H_2), 6.18 (d, 1H, *J*=3.0 Hz, H_3), 6.02 (d, 1H, *J*=6.1 Hz, H_5), 5.78-5.84 (m, 1H, H_6), 5.70-5.75 (m, 1H, H_7), 4.72 (d, 1H, AB system diastereotopic CH_aH$_b$, J_{AB}=12.7 Hz, H_8), 4.62 (dd, 1H, AB system diastereotopic CH$_a$$H_b$, J_{AB}=12.7 and 5.6 Hz, H_8). ^{13}C NMR: δ 154.1, 142.6, 128.6, 126.4, 110.2, 107.3, 80.5, 75.2.

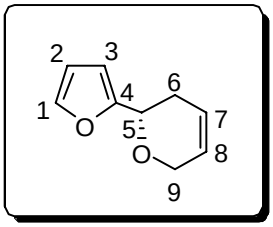
4.5.3. (*S*)-(-)-2-(Thiophene-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-14a



Colorless oil (86% yield). $[\alpha]_D^{26}$= -17.8 (*c* 1.00, EtOH). ^{1}H NMR: δ 7.19 (dd, 1H, *J*=5.0 and 1.3 Hz, H_1), 6.92-6.94 (bd, 1H, *J*=3.6 Hz, H_2), 6.80-6.91 (bd, 1H, *J*=11.5 Hz, H_3), 5.84 (ddd, 1H, *J*=5.4, 3.8 and 2.3 Hz, H_7), 5.72 (dt, 1H, *J*=10.3 and 1.3 Hz, H_8), 4.27-4.35 (dm, 1H, AB system diastereotopic CH_aH$_b$, J_{AB}=17.3 Hz, H_9), 4.21-4.26 (bd, 1H, AB system diastereotopic CH$_a$$H_b$, J_{AB}=17.3 Hz, H_9), 4.15 (dd, 1H, *J*=

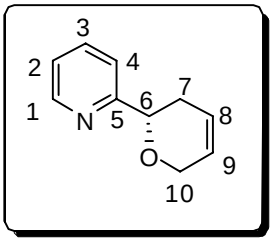
9.7 and 3.7 Hz, H_5), 2.40-2.49 (bd, 1H, AB system diastereotopic CH_aH$_b$, J_{AB}=16.5 Hz, H_6), 2.26-2.36 (bd, 1H, AB system diastereotopic CH$_a$$H_b$, J_{AB}=16.5 Hz, H_6). ^{13}C NMR: δ 146.5, 126.5, 126.4 (overlapped), 124.8, 123.8, 71.5, 66.8, 32.7.

4.5.4. (*S*)-(-)-2-(Furan-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-14b



Colorless oil (88% yield). $[\alpha]_D^{25}$=-77.22 (*c* 1.00, CH_2Cl_2). ^{1}H NMR: δ 7.25-7.26 (brs, 1H, H_1), 6.20-6.25 (m, 1H, H_2), 6.15-6.25 (m, 1H, H_3), 5.76-5.82 (m, 1H, H_7), 5.66 (bd, 1H, *J*=10.2 Hz, H_8), 4.53 (dd, 1H, *J*= 9.7 and 3.6 Hz, H_5), 4.17 (dd, 2H, diastereotopic CH_aH_b, *J*=36.0 and 16.5 Hz, H_9), 2.15-2.51 (m, 2H, H_6). ^{13}C NMR: δ 154.5, 141.9, 126.3, 123.6, 110.1, 106.6, 68.7, 65.5, 28.7.

4.5.5. (*S*)-(-)-2-(3,6-Dihydro-*2H*-pyran -2-yl)pyridine, (*S*)-(-)-14c



Before RCM, in order to avoid the complexation of Grubbs' catalyst with the free electrons of pyridine ring system, it was transformed into the corresponding HCl salt by passing HCl gas through the DCM solution of (*S*)-(-)-**12c**. At the end of RCM reaction, the product was isolated as in the free form. The reaction was monitored by TLC. Colorless oil (72% yield). $[\alpha]_D^{26}$= -18.8 (*c* 1.00, EtOH). ^{1}H NMR: δ 8.46 (d, 1H, *J*=10.3 and 3.5 Hz, H_1), 7.60 (t, 1H, *J*=7.7 Hz, H_3), 7.41 (d, 1H, *J*=8.1 Hz, H_4), 7.10 (dd, 1H, *J*=7.5 and 5.1 Hz, H_2), 5.82-5.90 (m, 1H, H_8), 5.73 (dt, 1H, *J*=10.3 and 1.2 Hz, H_9), 4.60 (dd, 1H, *J*=10.3 and 3.5 Hz, H_6), 4.25-4.75 (m, 2H, H_{10}), 2.36-2.46 (bd, 1H, AB system diastereotopic CH_aH$_b$, J_{AB}=17.3 Hz, H_7), 2.20-2.32 (bd, 1H, AB system diastereotopic CH$_a$$H_b$, J_{AB}=17.3 Hz, H_7). ^{13}C NMR: δ 162.0, 149.0, 136.8, 126.5, 124.7, 122.5, 120.3, 76.5, 66.7, 31.7.

REFERENCES

1) Ahluwalia, V.K. *Green Chemistry*, Ane Books, India, **2008**.

2) Lancastar, M. *Green Chemistry: an İntroductory Text*, RCS, **2002**.

3) Hjeresen, L. D.; Anastas, P.; Ware S., Kirchhof M. *Environmental Science &Technology,* **2001**, 115 A.

4) Li, C. *Chem. Rev*., **1993**, *93,* 2023 and **2005**, *105*, 3095.

5) Jessop, P.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH:Weinheim, **1999**.

6) Trost, B. *Acc. Chem. Res*., **2002**, *35*, 695.

7) Wender, P. A.; Croatt M. P.; Witulski, B. *Tetrahedron*, **2006**, *62*, 7505.

8) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* , **2002**, 1578.

9) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum A. *Green Chem*, **2004**, *6*, 128.

10) Larhed, M.; Olofsson, K. Topics in Current Chemistry: Microwave Methods in Organic Synthesis, Springer: Berlin, **2006**.

11) Anastas, P. T.; Warner, J. C. *Green Chemistry Theory and Practice*, Oxford University Press Inc., New York, **1998**.

12) Sheldon, R. A. *Chem Ind.*, London, **1992**, 903.

13) Sheldon, R. A. *Chemtec*, **1994**, 38.

14) Sheldon, R. A. *Chem Ind*., London, **1997**, 12.

15) Sheldon, R. A. *J. Chem. Technol. Biotechnol.*, **1997**, *68*, 381.

16) Sheldon, R. A. *Pure Appl. Chem*., **2000**, *72*, 1233.

17) Stinson, S. C. *Chem Eng. News*, **1997**, *75 (42)*, 38.

18) Trost, B. M. *Angew. Chem. Int. Ed*., **1995**, *34*, 259.

19) Gördes, D.; Neumann, H.; Jacobi, Van Wangelin, A.; Fischer C.; Drauz K.; Krimmer, H. P.; Beller, M., *Adv. Synth. Catal.*, **2003**, *345*, 510.

20) Fürstner, A.; Grubbs, R. H.; Schrock, R. R. *Adv. Synth. Catal*., *Olefin Metathesis Issiue* , **2002**, *344*, 6 .

21) Sheldon, R. A. *Chirotechnology: the Industrial Synthesis of Optically Active Compunds,*Maecel Dekker, New York, **1993**.

22) Berkessel, A.; Groerger, H. *Asymmetric Organocatalysis,* Wiley-VCH, Weinheim, **2005**.

23) Noyori, R. *Nobel Lecture*, **2001**.

24) Morrison, J. D.; Mosher, S. H. *Asymmetric organic Reactions* , Prentice- Hall New Jersey, **1971**.

24) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis,* Elsevier, **1996**.

25) Marcwald, W. *Ber. Desch. Chem. Ges*. , **1904**, *37*, 1368.

26) Ager, D. J.; East, M. B. *Asymmetric synthesis Methodology*, CRC Press, **1995**.

27) Crosby, J. *Tetrahedron ,* **1991**, *47*, 4789.

28) Kotha, S. *Tetrahedron* , *50* , 3639.

29) Clayden, J. *Organic Chemistry,* Oxford **2000**, 1224.

30) Gringore, O. H.; Rouessac F. P. *Org. Synth.,* **1984**, *63*, 121.

31) Noyori, R. *Science* , **1990**, *248*, 1194.

32) Scott, J. S. In Asymmetric Synthesis, J. D. Morrison Ed., Academic Press **1984**, Vol. *4*, pp 1.

33) Blaser, H.-U. *Chem Rev.* , **1992**, *9*, 935 .

34) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc*., **1986**, *108*, 2353.

35) Pennanen, S. I. *Acta Chem.Scand,* B35, 555, **1981**.

37)Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.,* **1987**, *52*, 3174.

38) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett*. , **1979**, 447.

39)Wong, C.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*, **1995**, London, 25.

40)Itoh, T.; Takagi, K.; Tsukube, H. *J. Mol. Catal. B: Enzyme* ,**1997**, *3*, 259 .

41) Tomioka, K. Synthesis , 1990, 541 .

42) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *J. Am. Chem. Soc*. , **1979**, *101*, 1455.

43) Noyori, R.; Kitamura, M. *Angew. Chem*. , Int. Ed. Engl. , **1991**, *30*, 49.

44) Faber, K. *Biotransformations in organic Chemistry (4th ed.)* , Springer-Verlag, Berlin Heidelberg,**1999**.

45) Nogradi, M. *Stereoselective Synthesis , A Practical Approach* , VCH Publisher Inc. , New York, **1995**, 15.

46) Raban, M.; Mislov, K. *in Topics in Stereochemistry* , ed. E. Eliel and N. Allinger, (New York NY. : Interscience Pub.) , **1967**, *2*, 199-230.

47) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* , **1997**, *36*, 2036 .

48) Grubbs, R. H. *Tetrahedron*, **2004**, *60*, 7117 .

49) Chauvin, Y. *Adv. Synth.Catal.* , **2007**, *349*, 27 .

50) Murdzek, J.S.; Schrock, R.R. *Organometallics*, **198** , *6*, 1373.

51) Schrock, R.R.; Krouse, S.A.; Knoll, K.; Feldman, J.; Murdzek, J.S.; Yang, D.C. *J. Mol. Catal* , **1988**, *46*, 243 .

52) Schrock, R.R.; Murdzek, J.S.; Barzan, G.C.; Robbins, J.; DiMare, M.; O`Regan, M. *J. Am. Chem. Soc.* , **1990**, *112*, 3875.

53) Bazan, C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. J. Am. Chem. Soc., **1991**, *113(18)*, 6899 .

54) Wu, Z; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. *J. Am. Chem. Soc*., **1995** , *117* , 5503 .

55) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. *J. Am. Chem. Soc*., **1993**, *115*, 9858 .

56) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* , **1995**, 34.

55) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* , **1995**, 107, 2197.

57) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R. H. *J. Am. Chem. Soc.* , **1996**, *118*, 100.

58) Scholl, M.; Trnka, T.M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* , **1999**, *40*, 2247.

59) Grubbs, R. H. *Handbook of Metathesis* , Ed. Wiley-VCH , New York , **2003** .

60)Grubbs, R. H. *Angew. Chem. Int. Ed.*, **2006**, *45*, 3760.

61) Grubbs, R.H.; Scott, J. M.; Gregory, C. F. *Acc. Chem. Res*. , **1995**, *28*, 446.

62) Hong, H. Y.; Sanders, D. P.; Lee, C. L.; Grubbs, R. H. *J. Am. Chem. Soc*., **1995**, *127 (49)*: 17160.

63) (a) Fürstner, A. *Angew. Chem*., Int. Ed., **2000**, *39*, 3012.

(b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* , **2001**, *34*, 18.

(c) Connon, S. C.; Blechert, S. *Angew. Chem. Int. Ed*., **2003,** *42*, 1900.

64) a) Yamamoto, Y.; Asao, N. *Chem. Rev.* , **1993**, *93*, 2207.

b) Kennedy, J. W. J.; Hall, D. G. Angew. *Chem*. , **2003**, *115*, 4480.

c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed*., **2003**, *42*, 4732.

65) Bodenteich, M.; Marquez, V. H.; Hallows, W. H.; Goldstein, B. M. *J. Org. Chem*, **1992**, *57(7)*, 2071.

66) Mignani, G.; Mansouri, S.; Arthaud, S.; Vidal, T. *PCT Int. Appl*., **2008**, 24.

67) a) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.*, **2006**, *45*, 6204.

b) Uenishi, J.; Hiraoka, T.; Hata, S.; Kenji, N.; Yonemitsu, O.; Nakamura, K.; Tsukube, H. *J. Org. Chem.*, **1998**, *63*, 2481.

c) Singh, S.; Kumar, S.; Chimni, S. *Tetrahedron: Asymmetry*, **2002**, *13*, 2679.

68) Sezer, S.; Özdemirhan, D.; Tanyeli, C. *Tetrahedron: Asymmetry*, **2006**, *17*, 2981

69) Tanyeli, C.; Akhmedov, I. M.; Özdemirhan, D. *Enantiomer*, **2001**, 259.

APPENDIX A

SUPPORTING INFORMATION

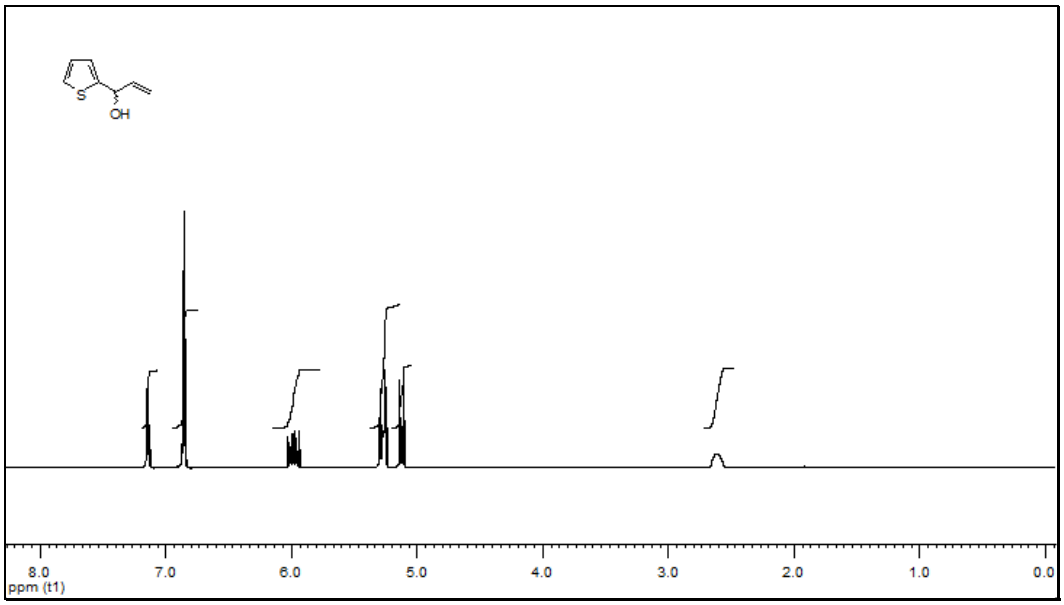


Figure A1. ^{1}H-NMR spectrum of 1-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**3a**

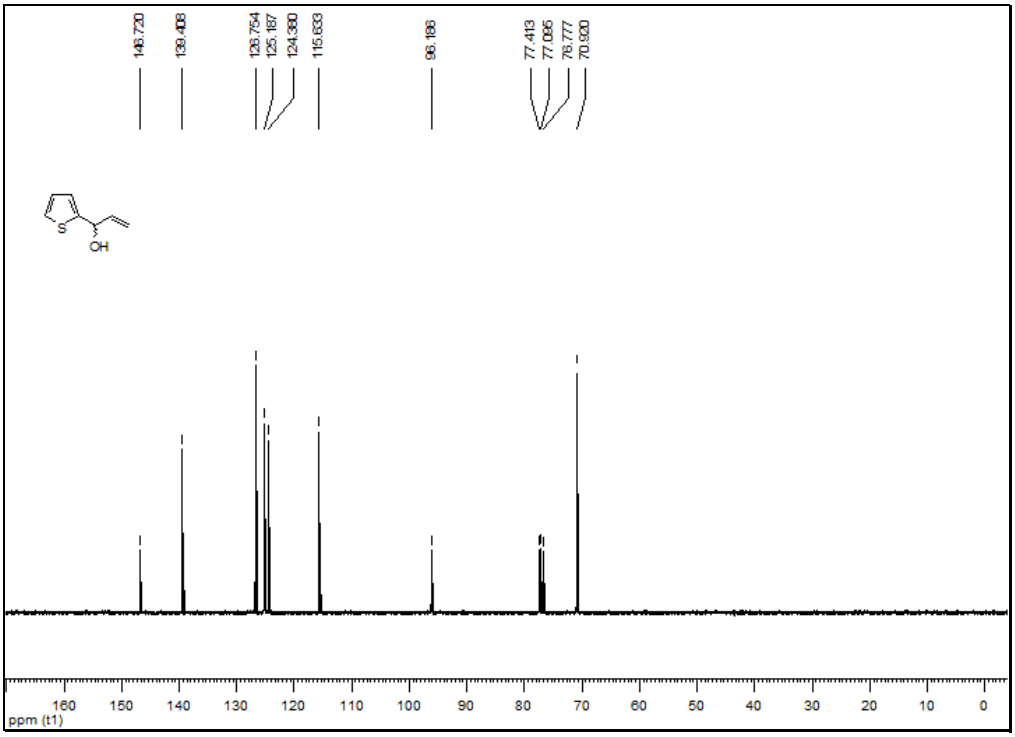


Figure A2. ^{13}C-NMR spectrum of 1-(thiophen-2-yl)prop-2-en-1-ol,*rac*- **3a**

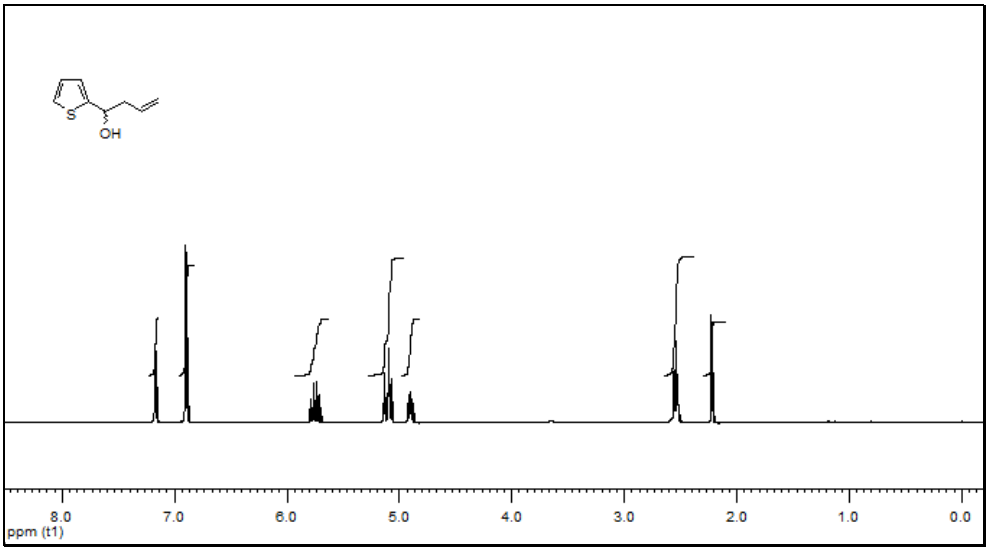


Figure A3. ^{1}H-NMR spectrum of 1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**4a**

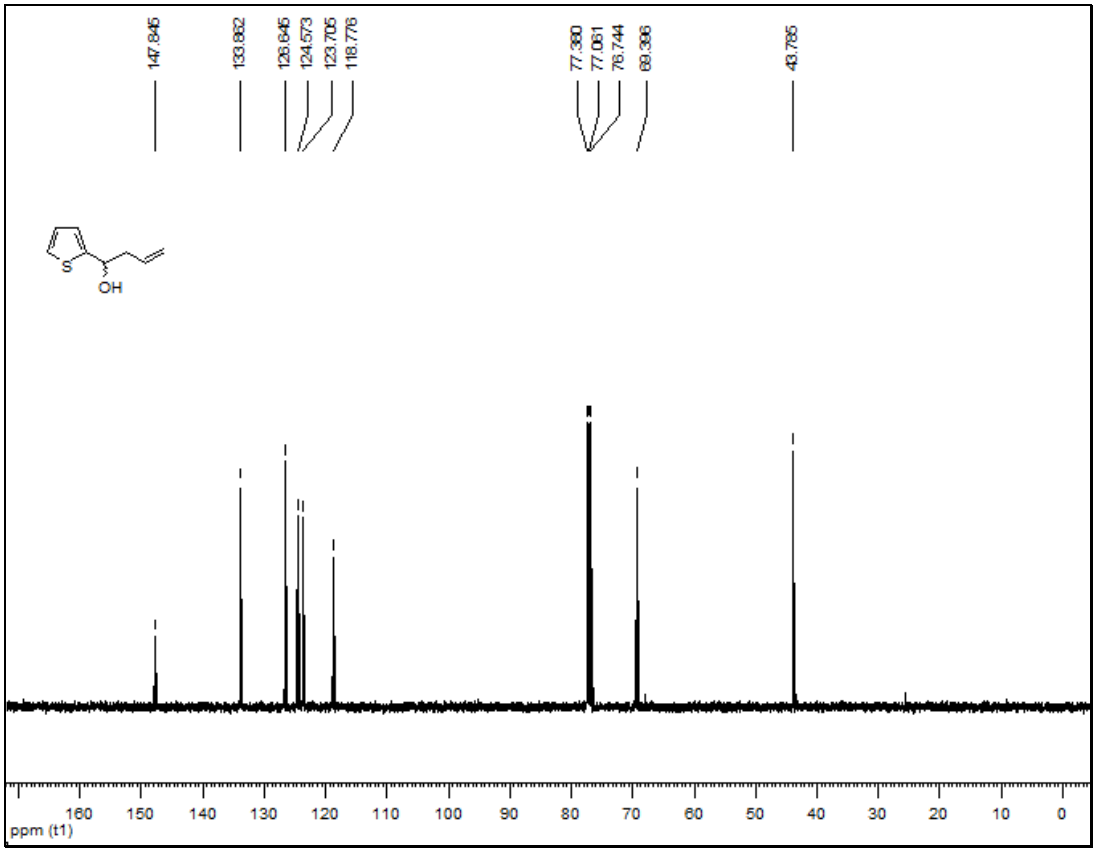


Figure A4. ^{13}C-NMR spectrum of 1-(thiophen-2-yl)but-3-en-1-ol,*rac*- **4a**

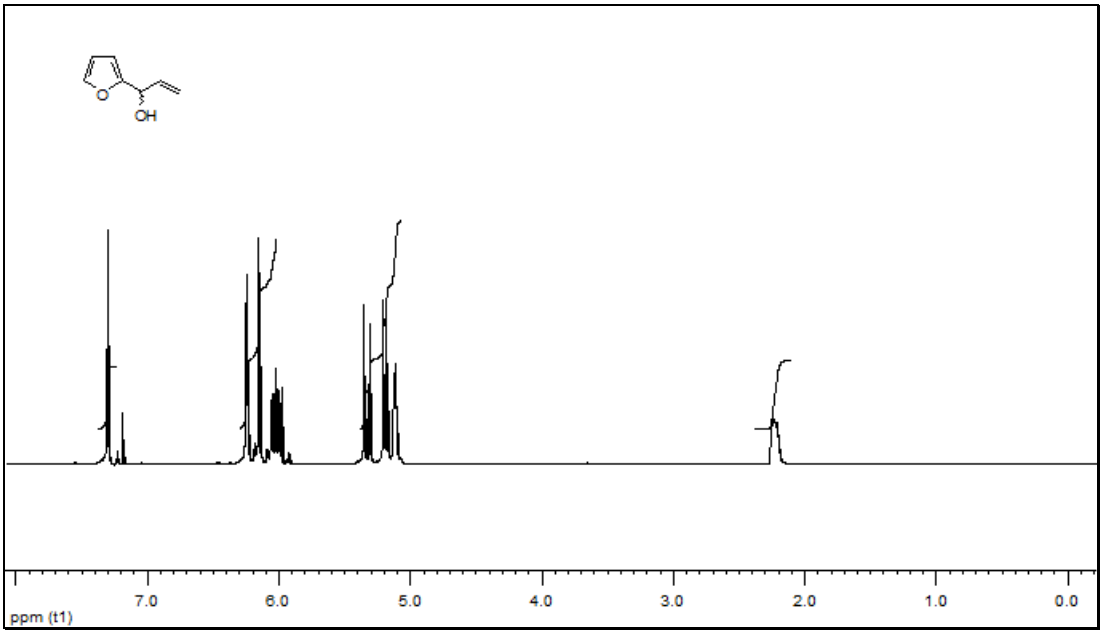


Figure A5. ^{1}H-NMR spectrum of 1-(furan-2-yl)prop-2-en-1-ol, *rac*-**3b**

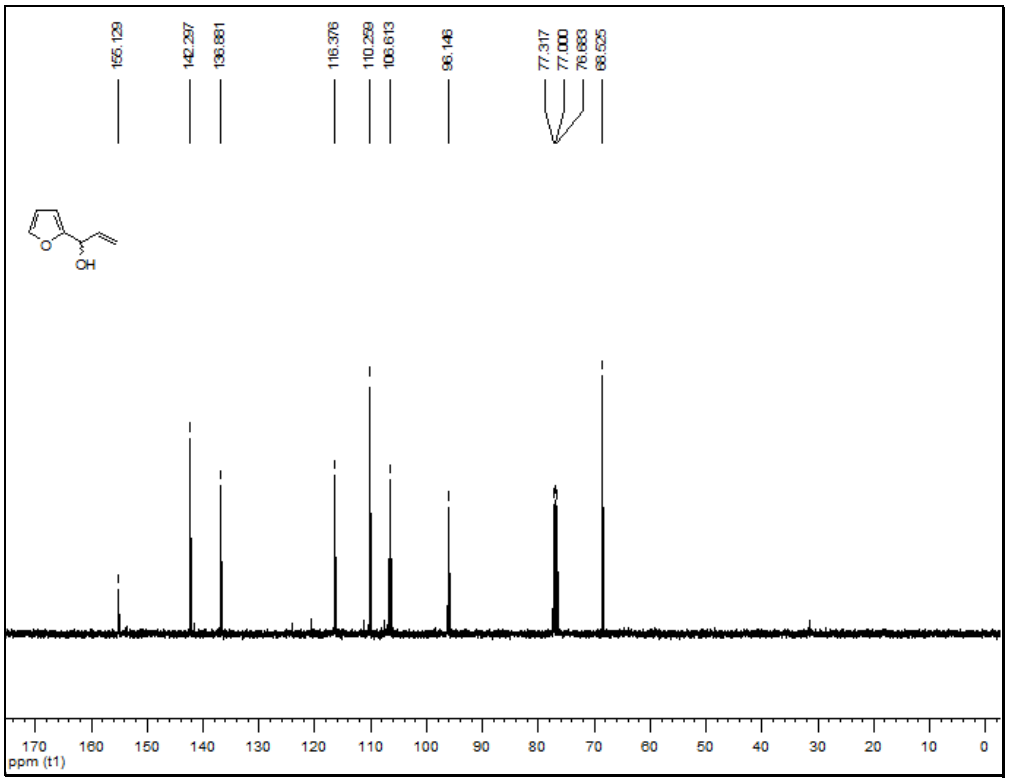


Figure A6. ^{13}C-NMR spectrum of 1-(furan-2-yl)prop-2-en-1-ol,*rac*- **3b**

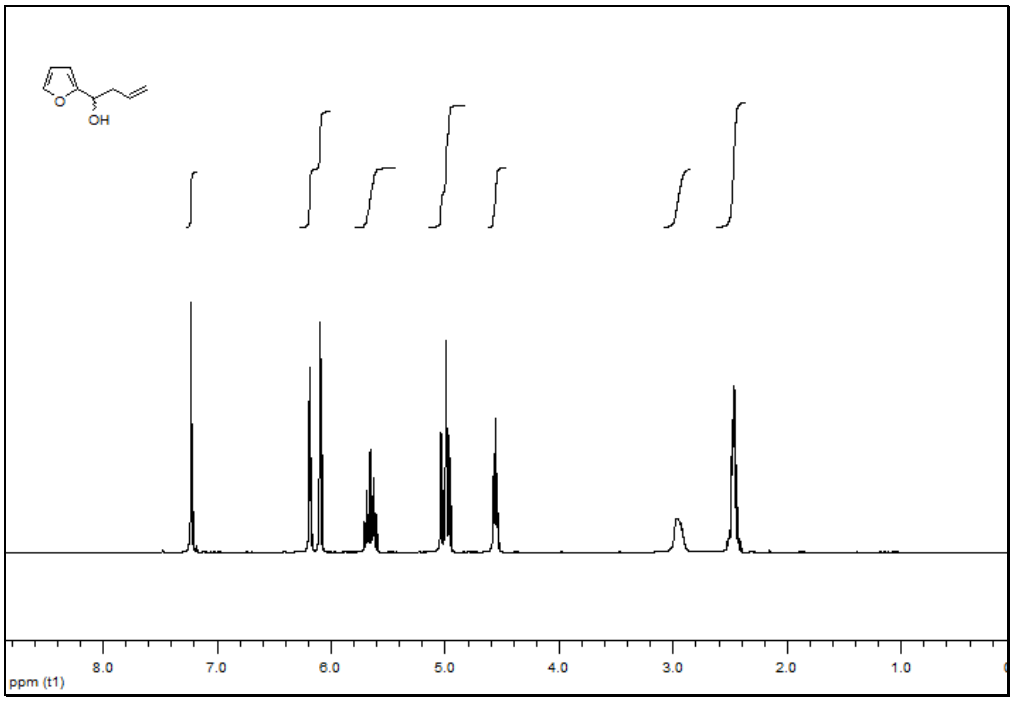


Figure A7. ^{1}H-NMR spectrum of 1-(furan-2-yl)prop-2-en-1-ol, *rac*-**4b**

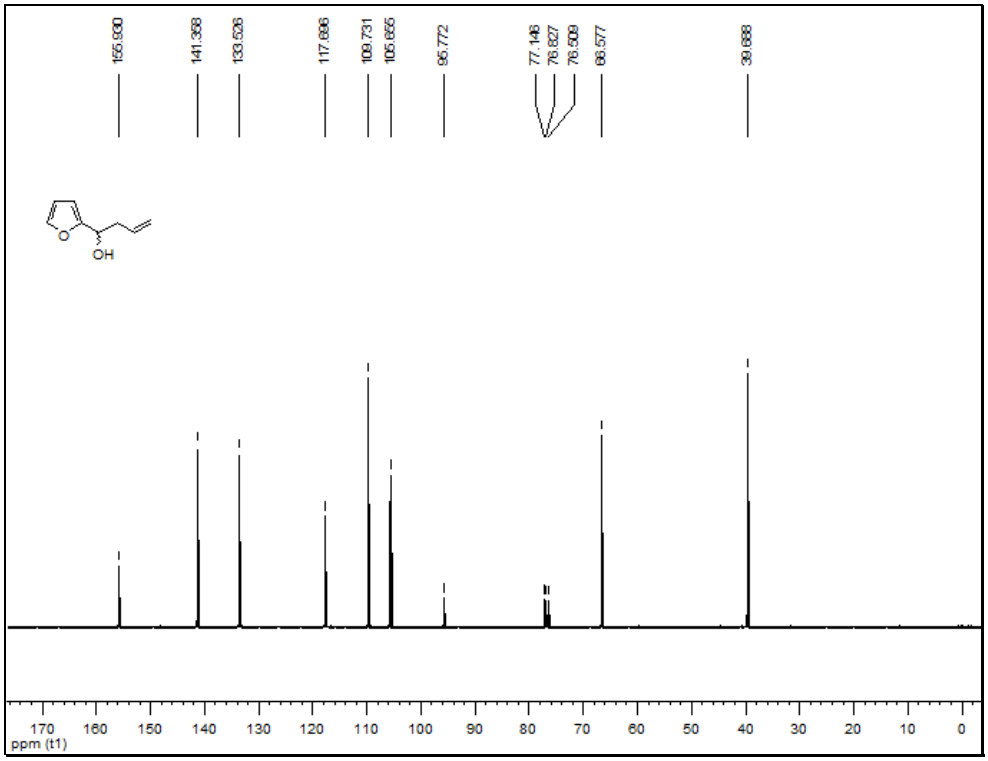


Figure A8. ^{13}C-NMR spectrum of 1-(furan-2-yl)but-3-en-1-ol,*rac*- **4b**

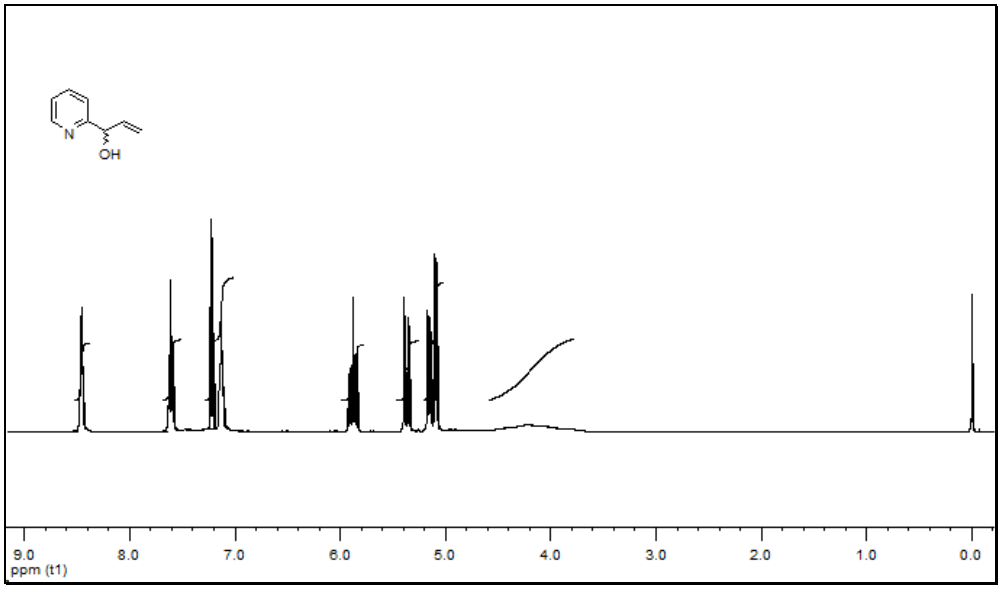


Figure A9. ^{1}H-NMR spectrum of 1-(pyridine-2-yl)prop-2-en-1-ol, *rac*-**3c**

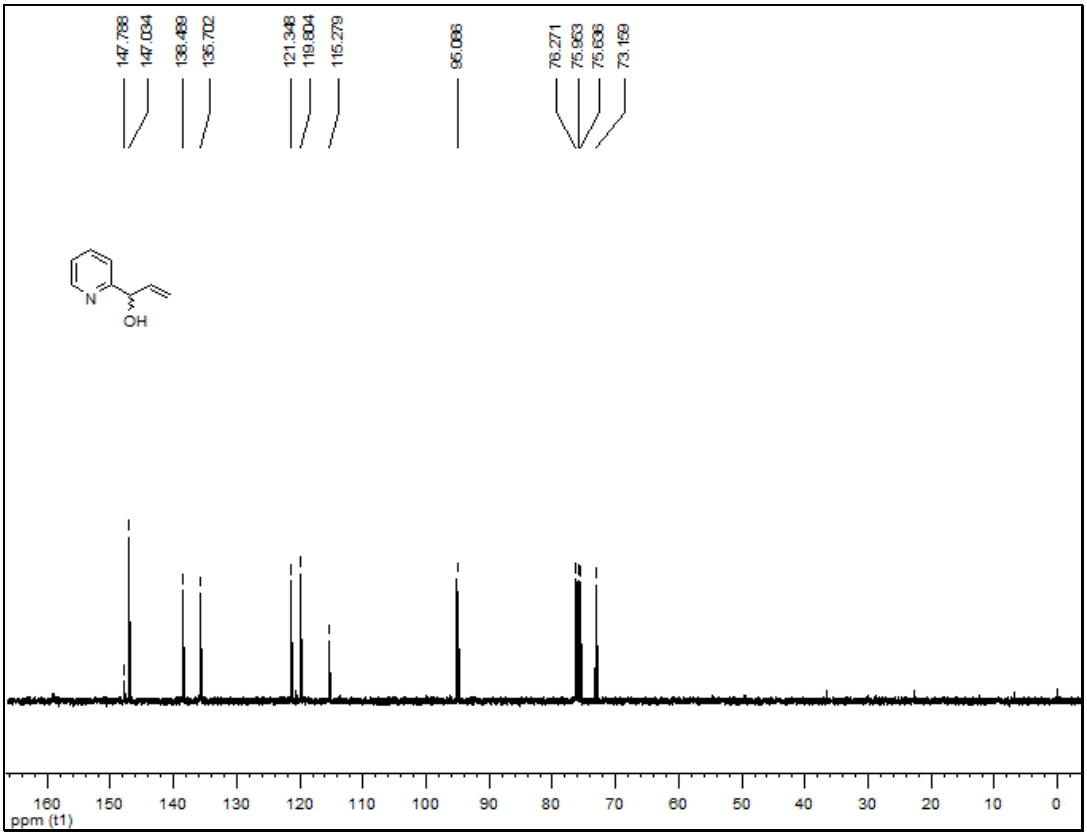


Figure A10. ^{13}C-NMR spectrum of 1-(pyridine-2-yl)prop-2-en-1-ol,*rac*- **3c**

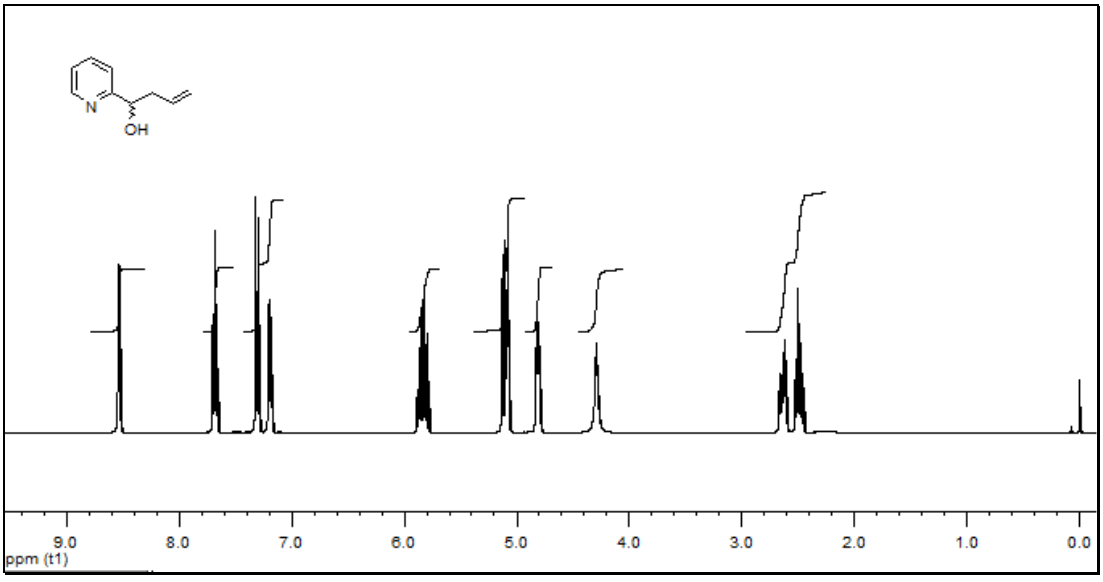


Figure A11. ^{1}H-NMR spectrum of 1-(pyridine-2-yl)but-3-en-1-ol, *rac*-**4c**

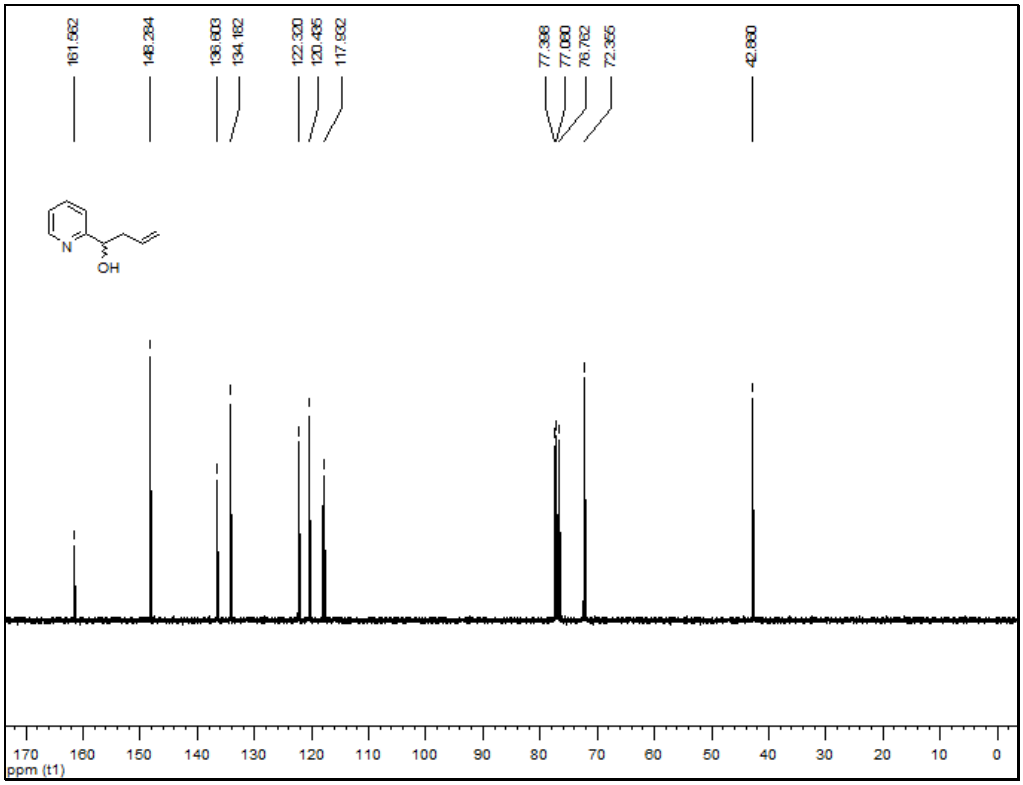


Figure A12. ^{13}C-NMR spectrum of 1-(pyridine-2-yl)but-3-en-1-ol,*rac*- **4c**

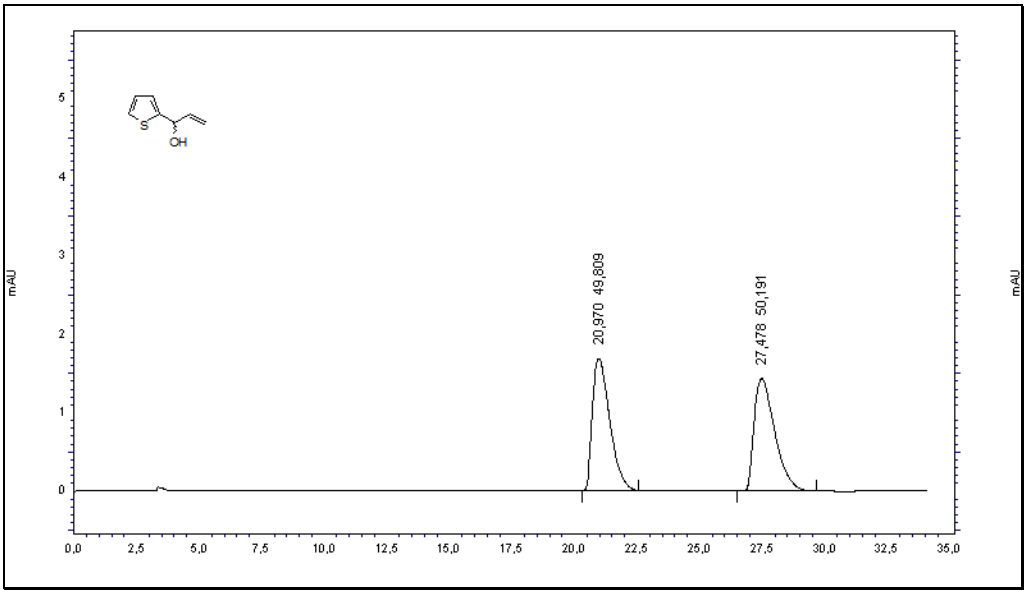


Figure A13. HPLC chromatogram of 1-(thiophen-2-yl)prop-2-en-1-ol, *rac*-**3a**

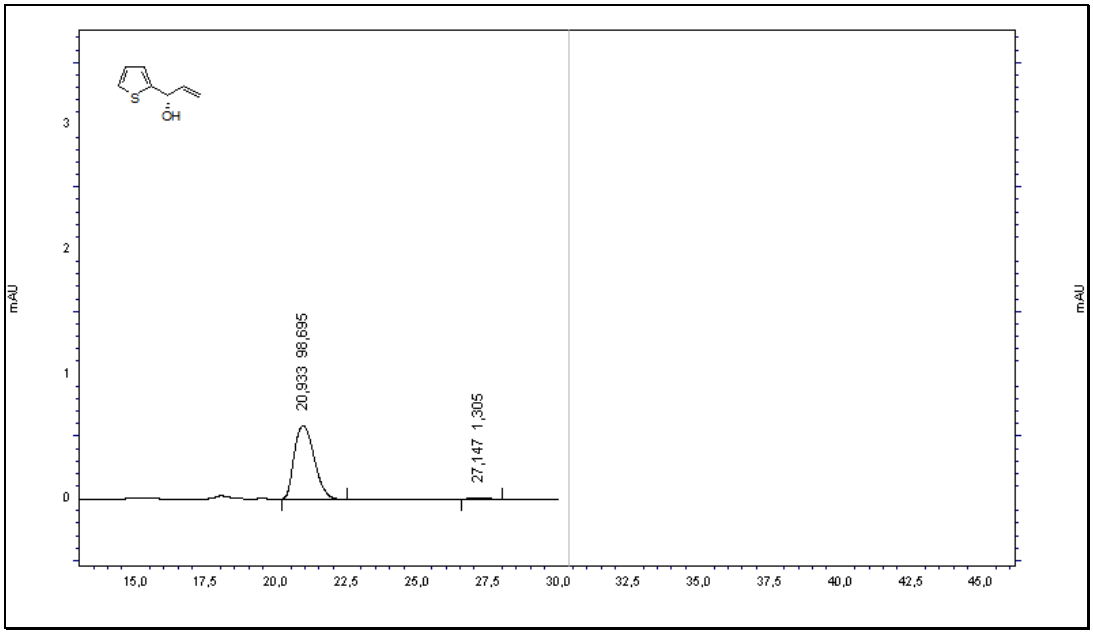


Figure A14. HPLC chromatogram of (*S*)-(+)-1-(thiophene-2-yl)prop-2-en-1-ol, (*S*)-(+)-**3a**

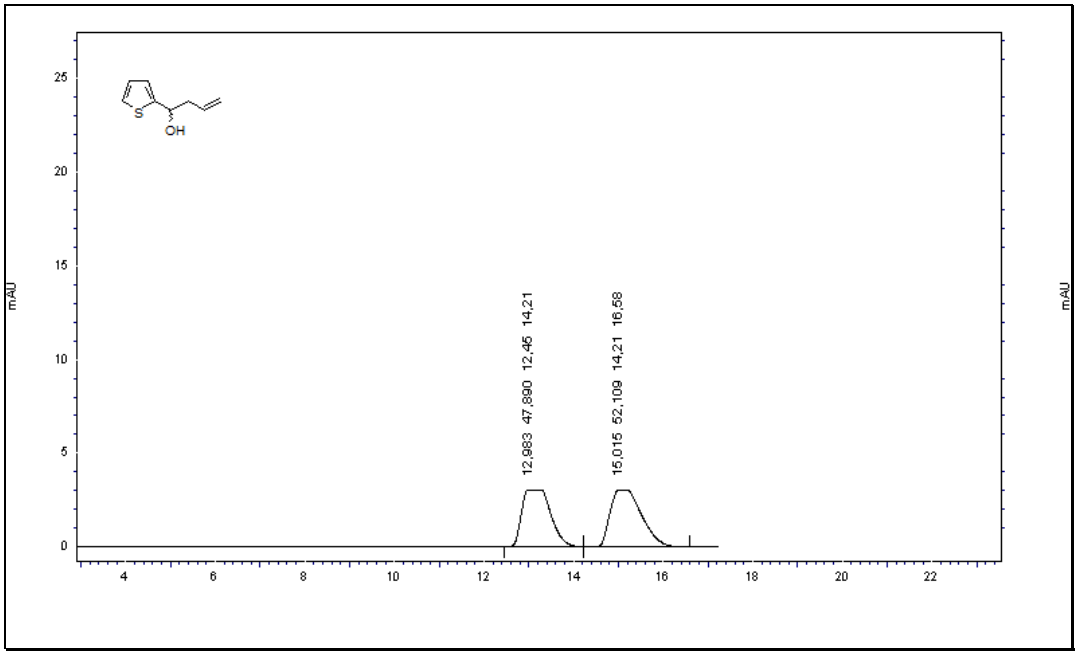


Figure A15. HPLC chromatogram of 1-(thiophen-2-yl)but-3-en-1-ol, *rac*-**4a**

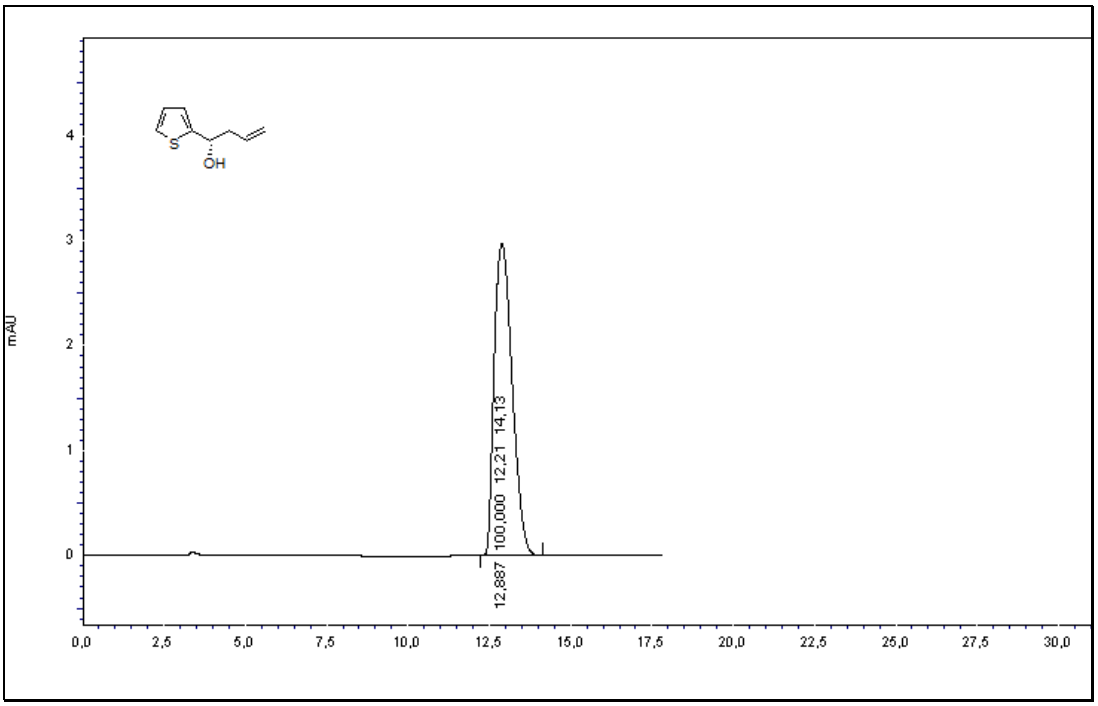


Figure A16. HPLC chromatogram of (*S*)-(-)-1-(thiophene-2-yl)but-3-en-1-ol, (*S*)-(-)-**4a**

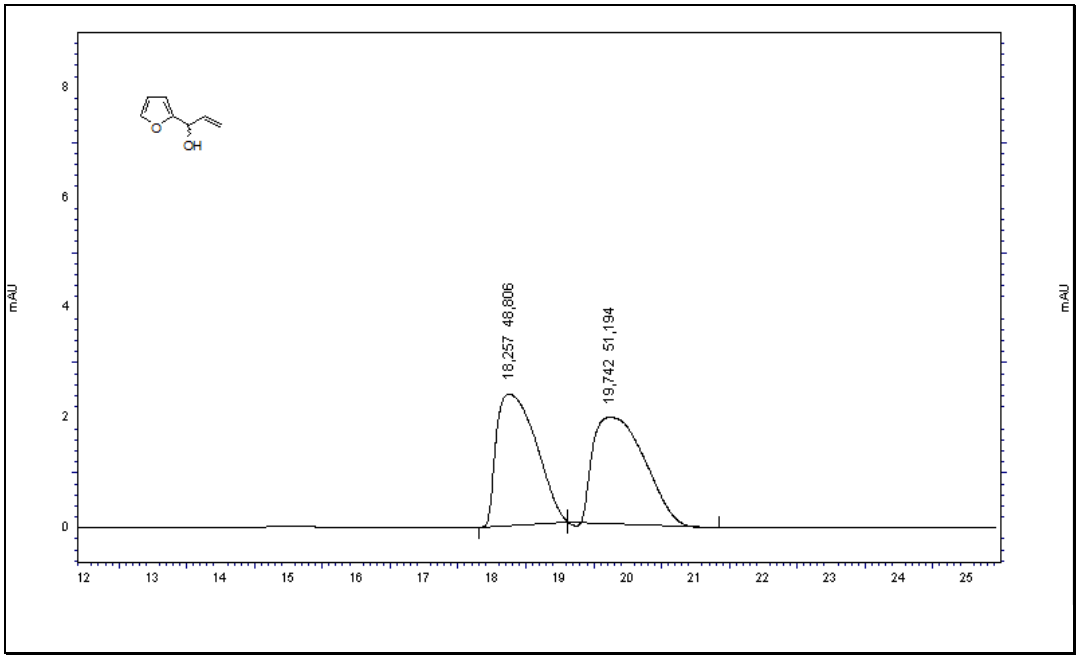


Figure A17. HPLC chromatogram of 1-(furan-2-yl)prop-2-en-1-ol, *rac*-**3b**

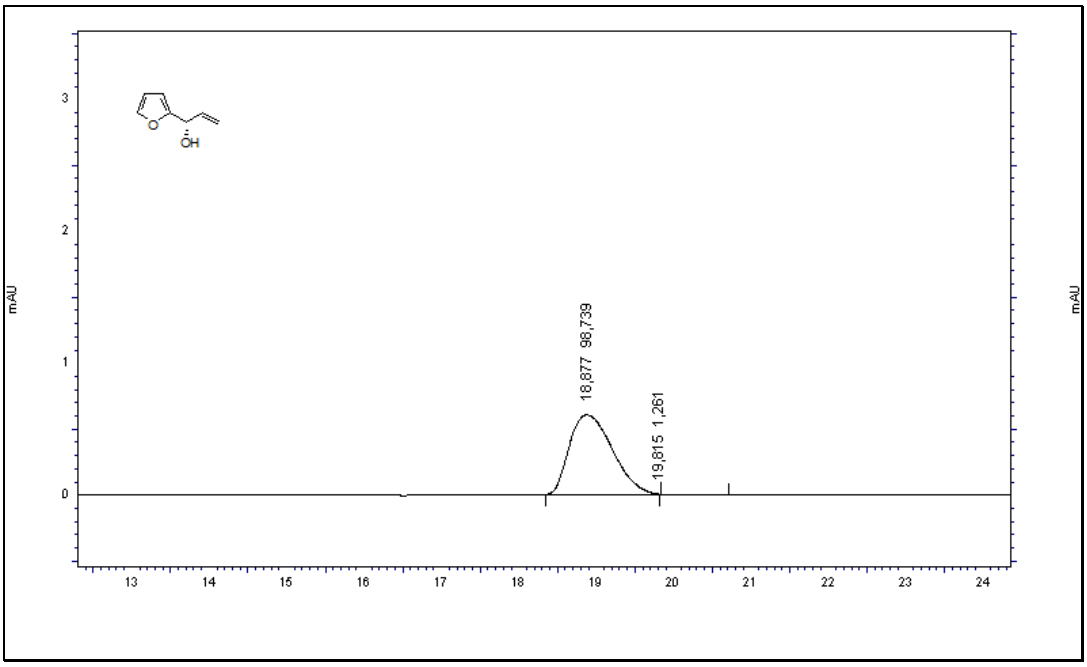


Figure A18. HPLC chromatogram of (*S*)-(+)-1-(furan-2-yl)prop-2-en-1-ol, (*S*)-(+)-**3b**

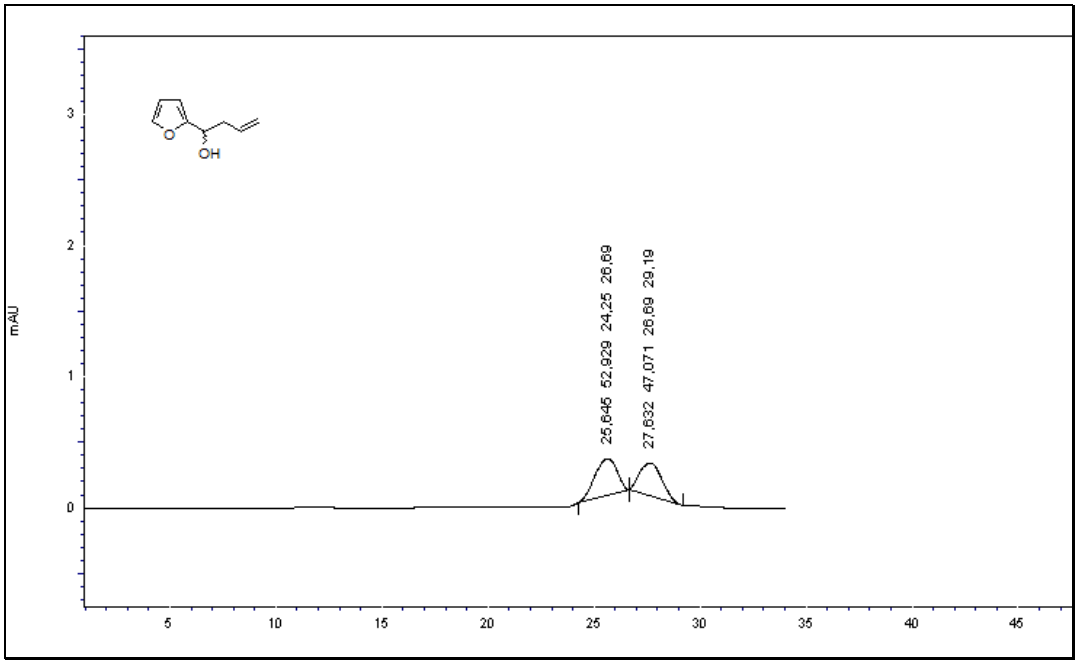


Figure A19. HPLC chromatogram of 1-(furan-2-yl)but-3-en-1-ol, *rac*-**4b**

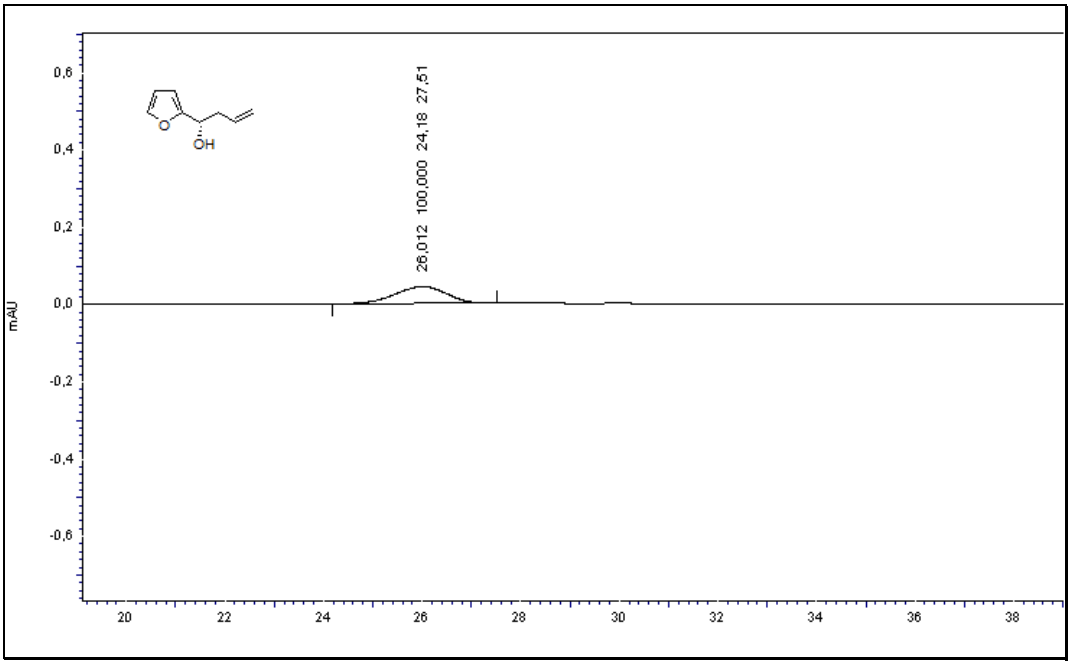


Figure A20. HPLC chromatogram of (*S*)-(-)-1-(furan-2-yl)but-3-en-1-ol, (*S*)-(-)-**4b**

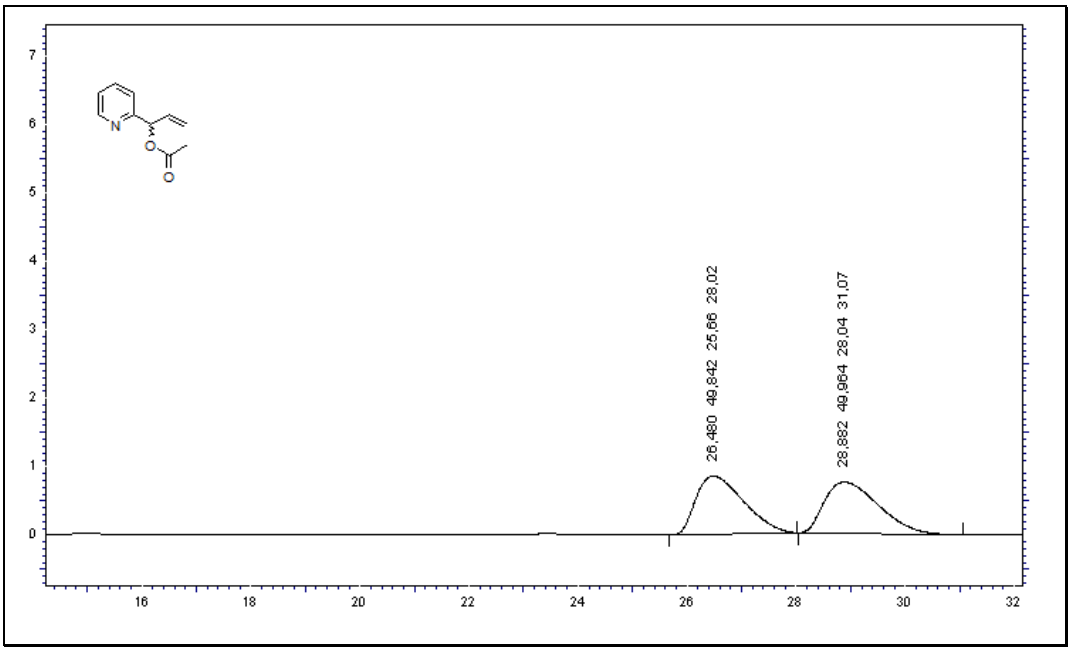


Figure A21. HPLC chromatogram of 1-(pyridine-2-yl)allyl acetate, *rac*-**9**

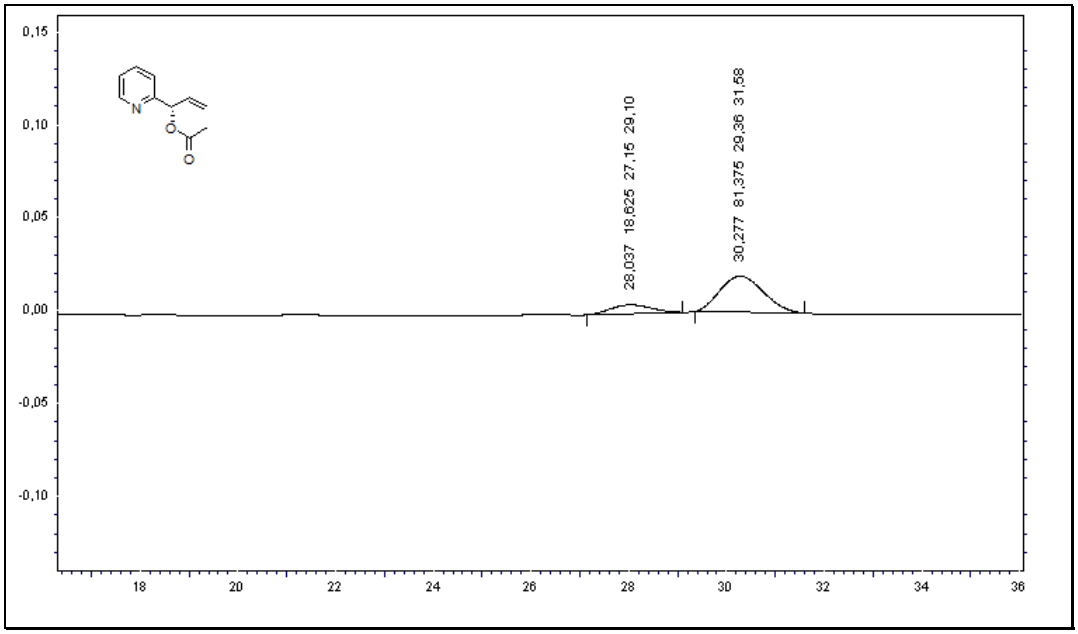


Figure A22. HPLC chromatogram of (*S*)-(-)-1-(pyridine-2-yl)allyl acetate, (*S*)-(-)-**9**

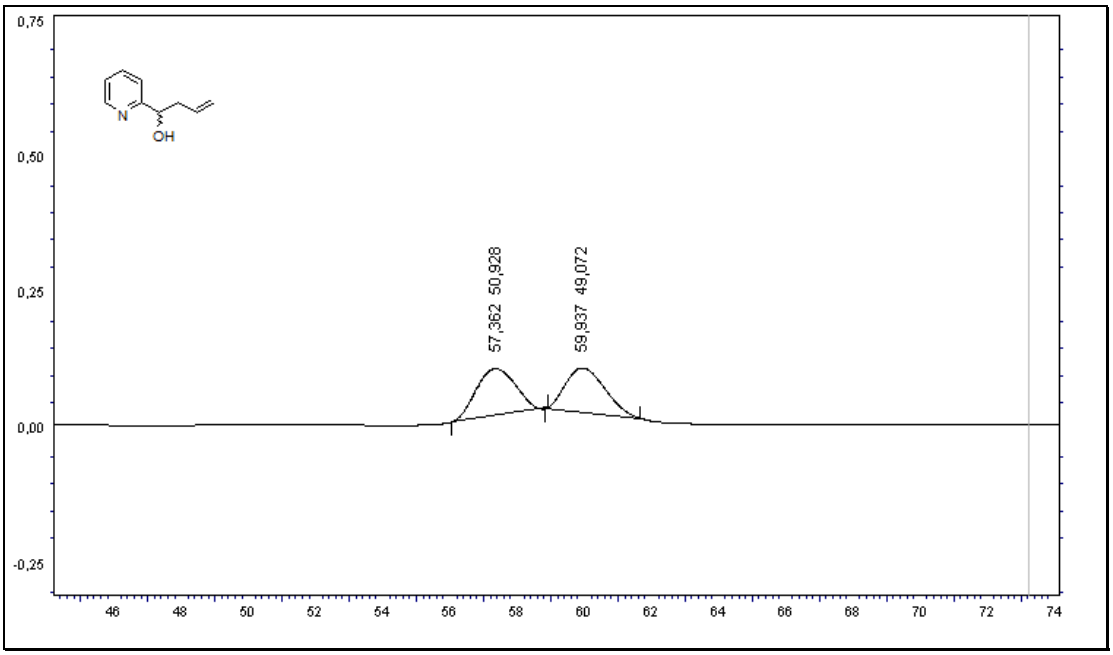


Figure A23. HPLC chromatogram of 1-(pyridine-2-yl)but-3-en-1-ol,*rac*- **4c**

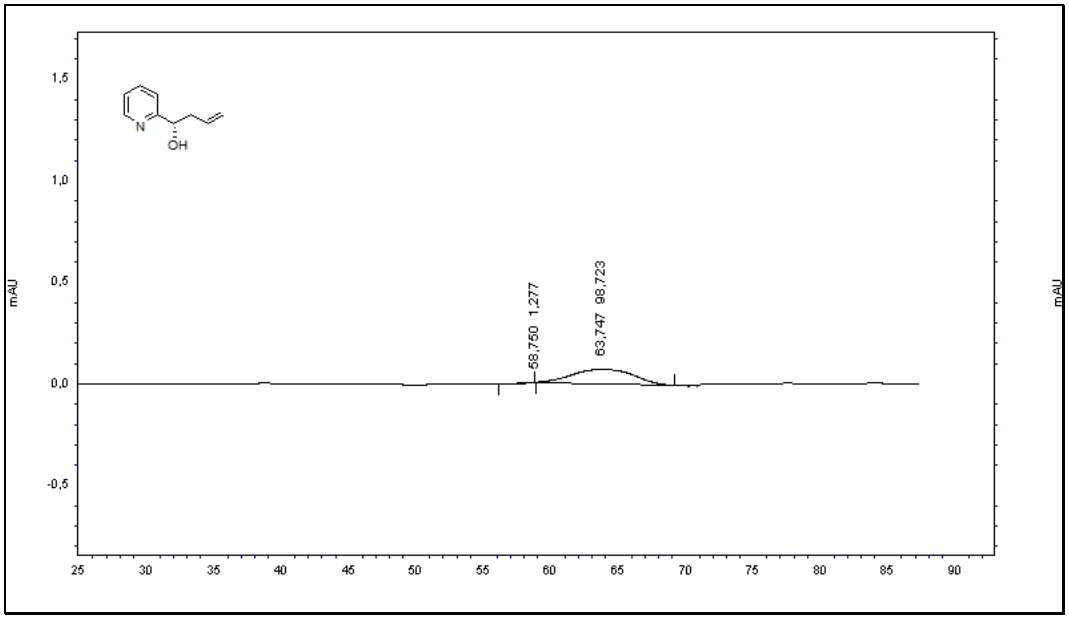


Figure A24. HPLC chromatogram of (*S*)-(-)-1-(pyridine-2-yl)but-3-en-1-ol, (*S*)-(-)-**4c**

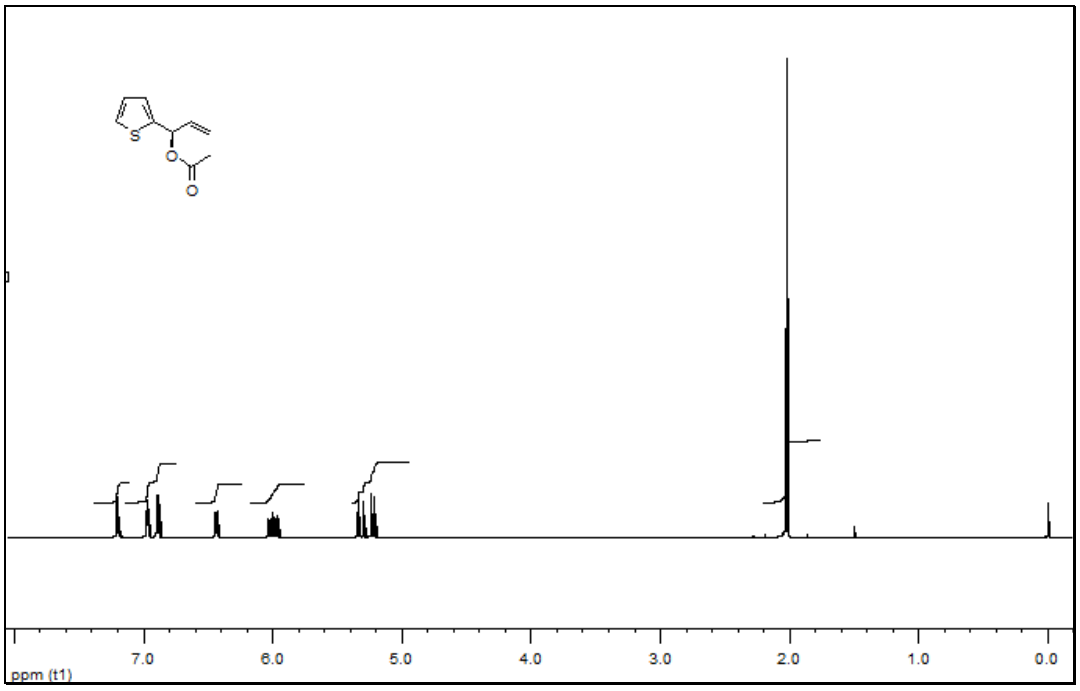


Figure A25. ^{1}H-NMR spectrum of (*R*)-(-)-1-(thiophene-2-yl)allyl acetate, (R)-(-)-**5**

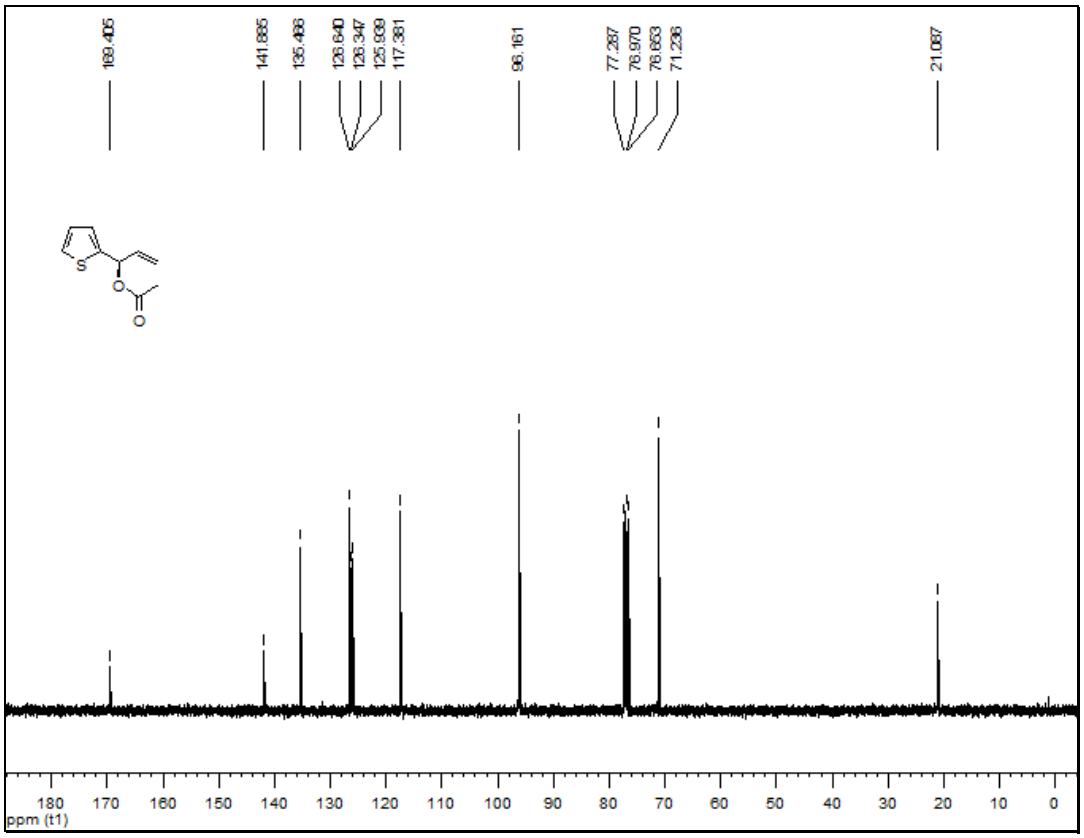


Figure A26. ^{13}C-NMR spectrum of (*R*)-(-)-1-(thiophene-2-yl)allyl acetate, (R)-(-)-**5**

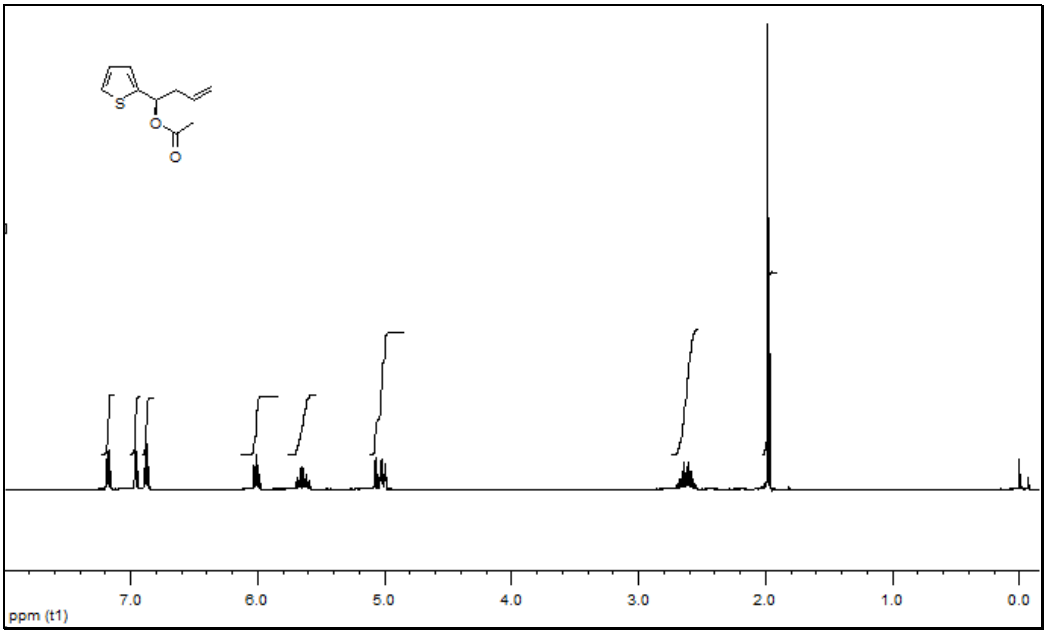


Figure A27. ^{1}H-NMR spectrum of (*R*)-(+)-1-(thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-**6**

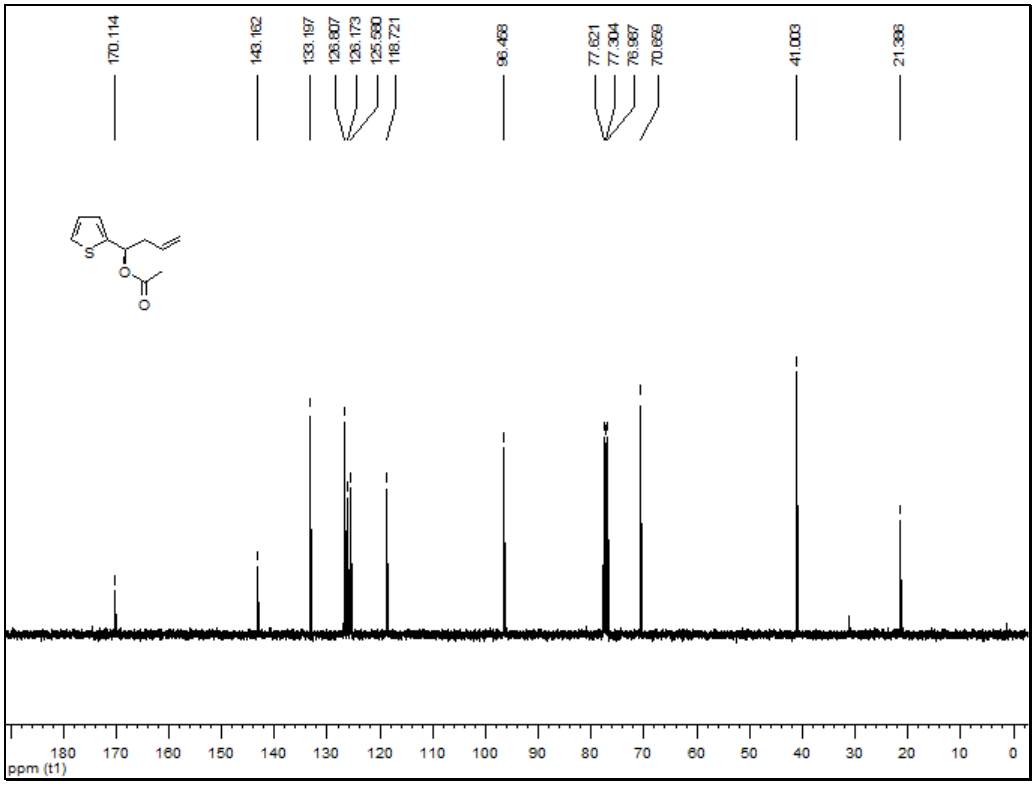


Figure A28. ^{13}C-NMR spectrum of (*R*)-(+)-1-(thiophene-2-yl)but-3-enyl acetate,(*R*)-(+)-**6**

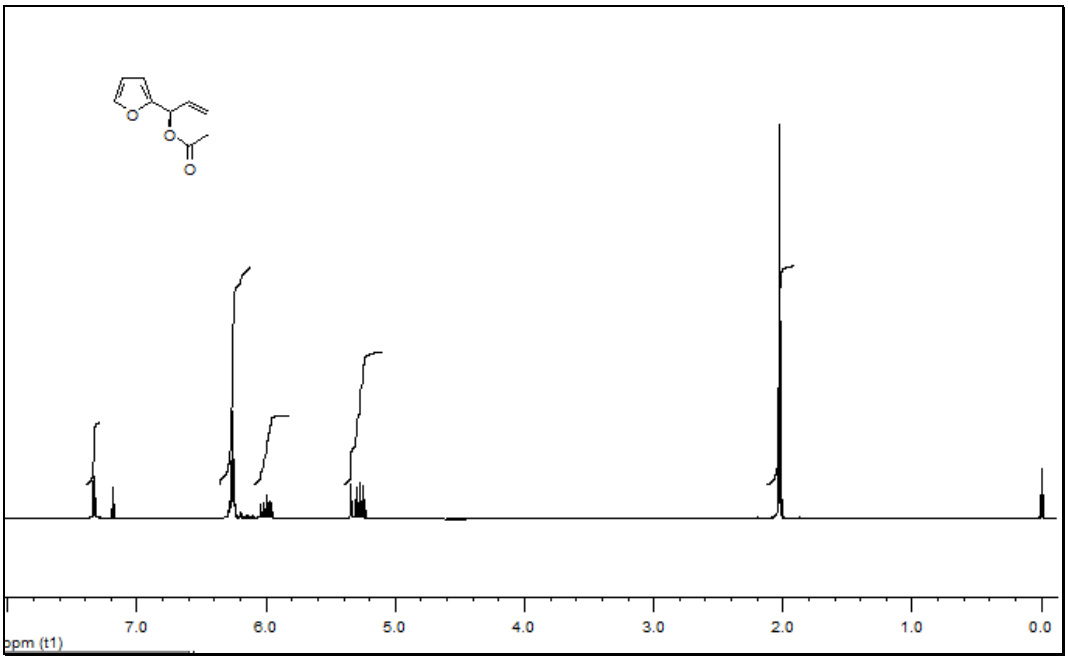


Figure A29. ^{1}H-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)allyl acetate, (*R*)-(+)-**7**

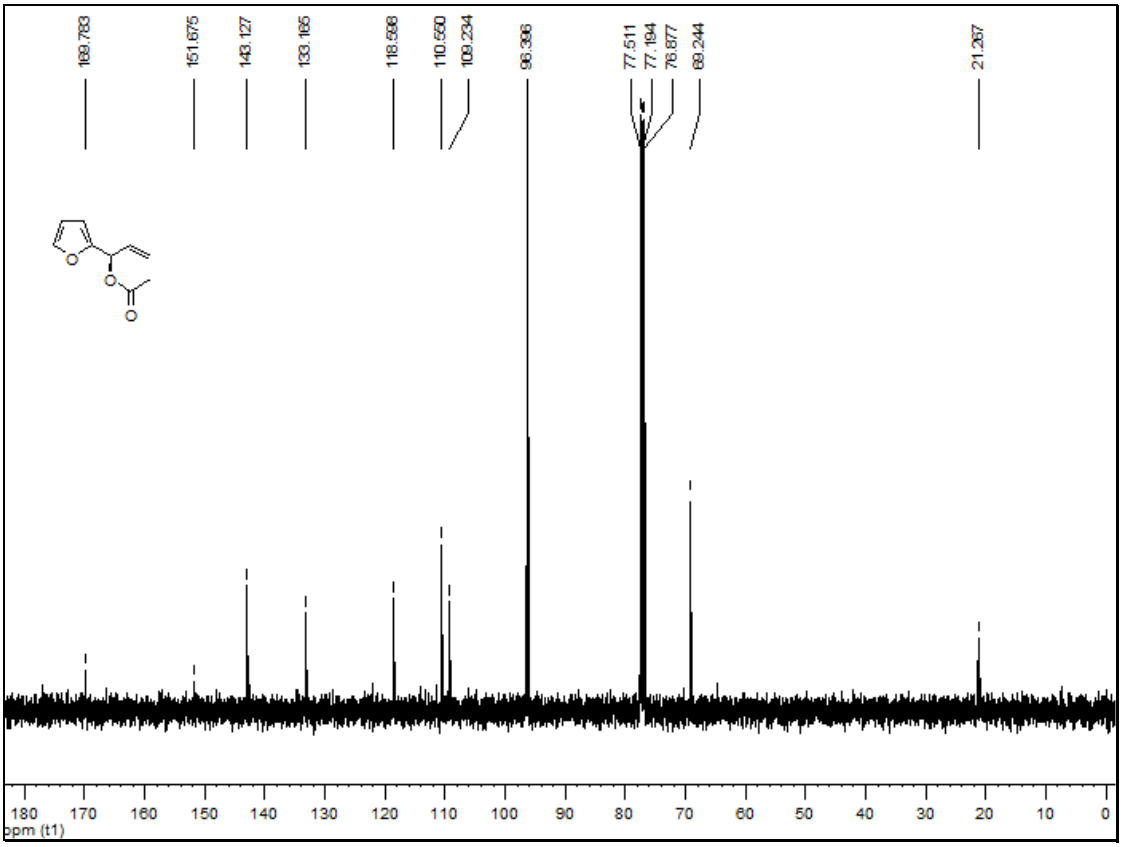


Figure A30. ^{13}C-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)allyl acetate, (*R*)-(+)-**7**

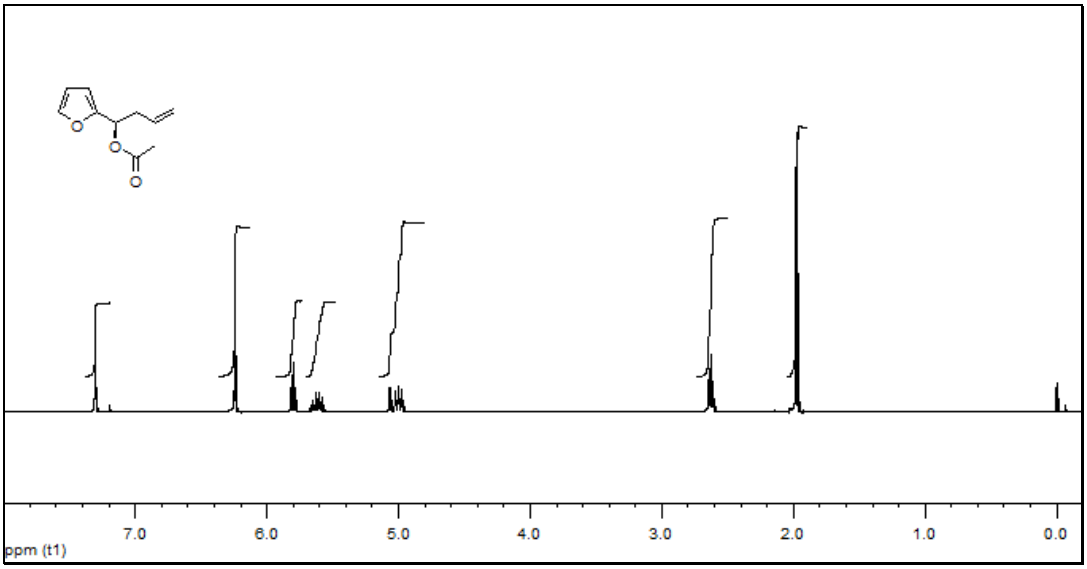


Figure A31. ^{1}H-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)but-3-enyl acetate, (*R*)-(+)-**8**

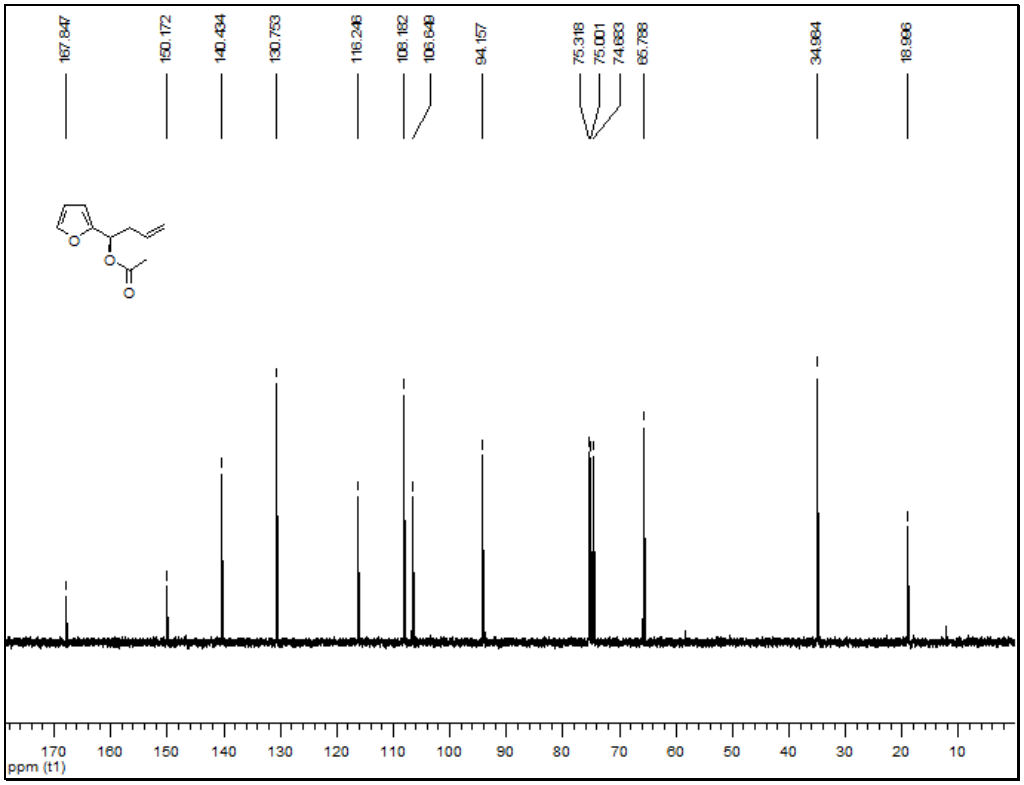


Figure A32. ^{13}C-NMR spectrum of (*R*)-(+)-1-(furan-2-yl)but-3-enyl acetate, (*R*)-(+)-**8**

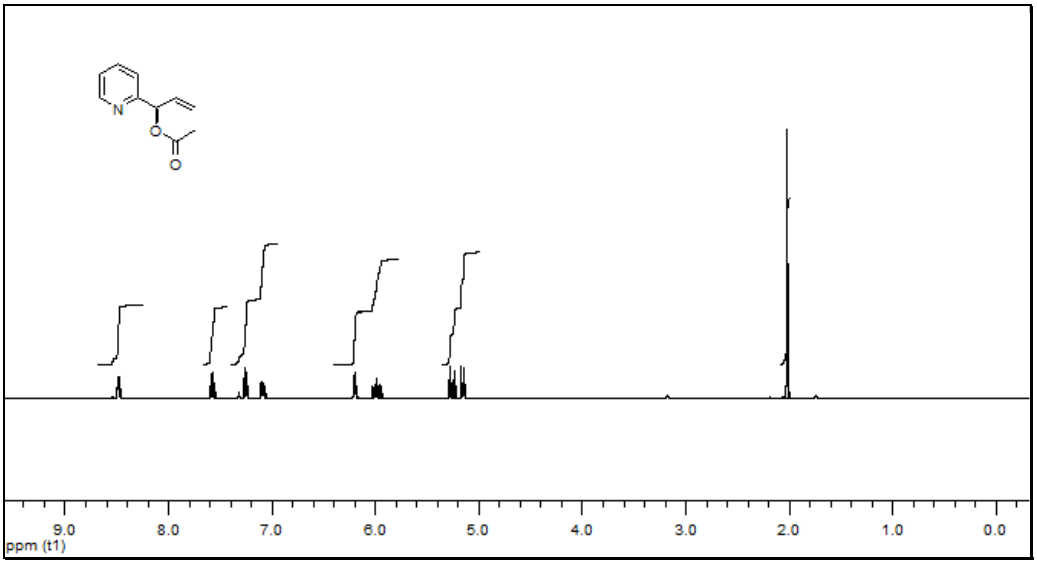


Figure A33. ^{1}H-NMR spectrum of (*R*)-(+)-1-(pyridine-2-yl)allyl acetate, (*R*)-(+)-**9**

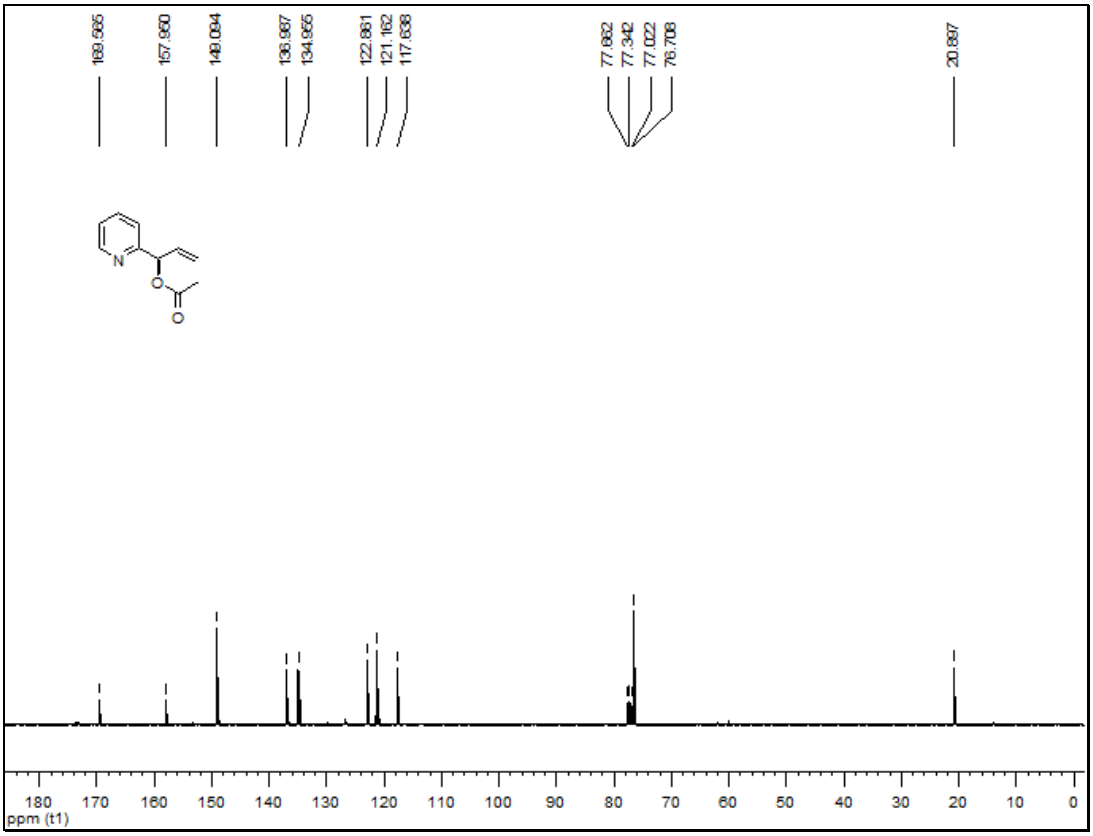


Figure A34. ^{13}C-NMR spectrum of (*R*)-(+)-1-(pyridine-2-yl)allyl acetate, (*R*)-(+)-**9**

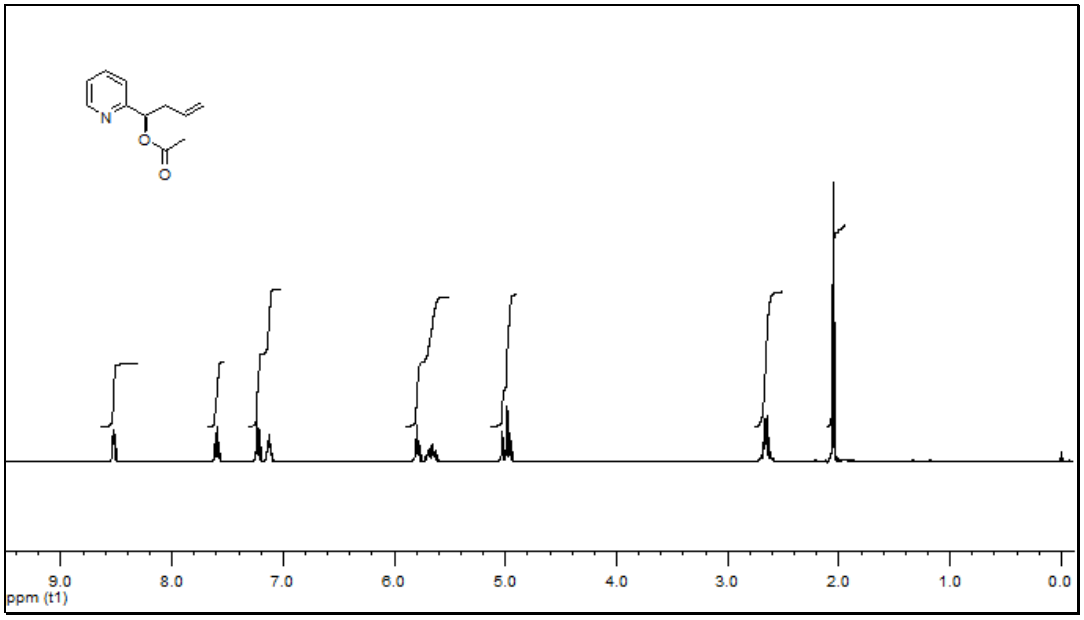


Figure A35. ^{1}H-NMR spectrum of (*R*)-(+)-1-(pyridine-2-yl)but-3-enyl acetate, (*R*)- (+)-**10**

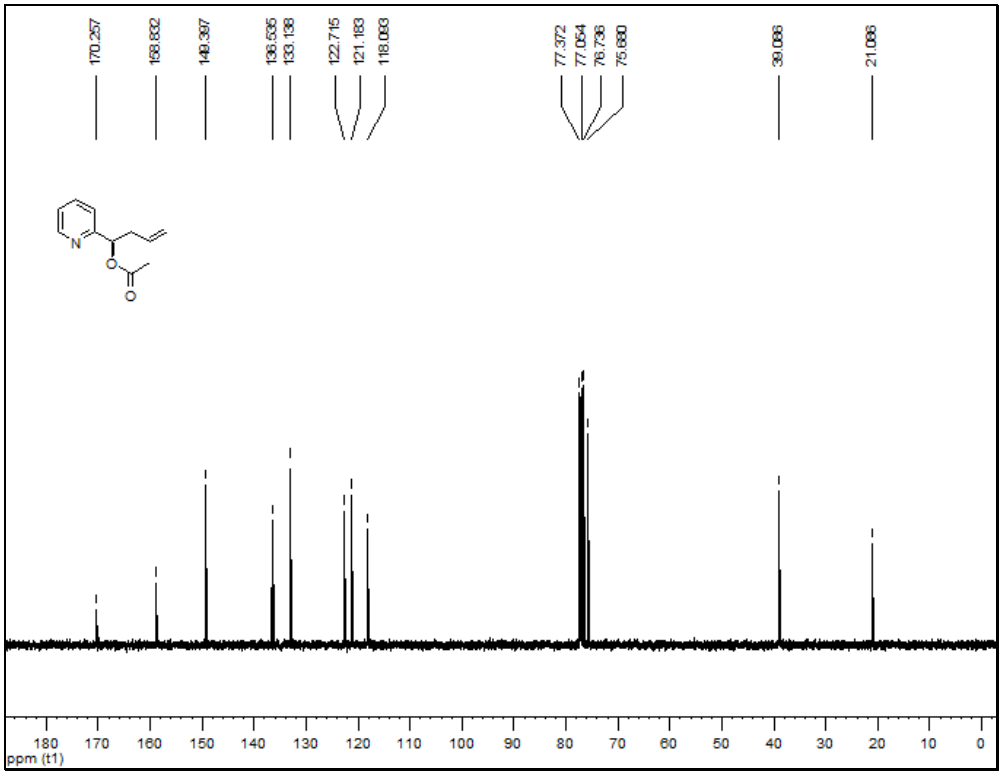


Figure A36 ^{13}C-NMR spectrum of (*R*)-(+)-1-(pyridine-2-yl)but-3-enyl acetate, (*R*)- (+)-**10**

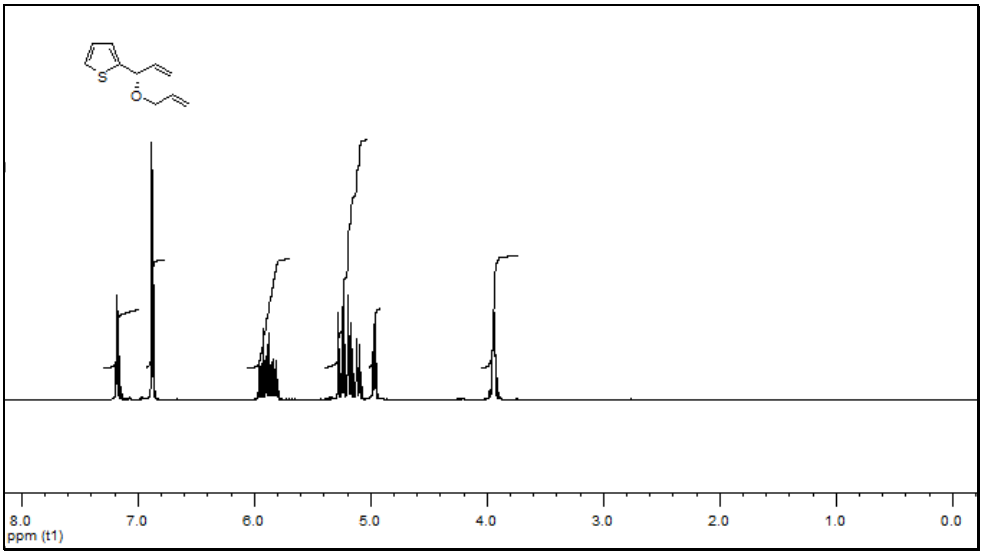


Figure A37. ^{1}H-NMR spectrum of (*S*)-(+)-2-(1-(allyloxy)allyl)thiophene, (*S*)-(+)-**11a**

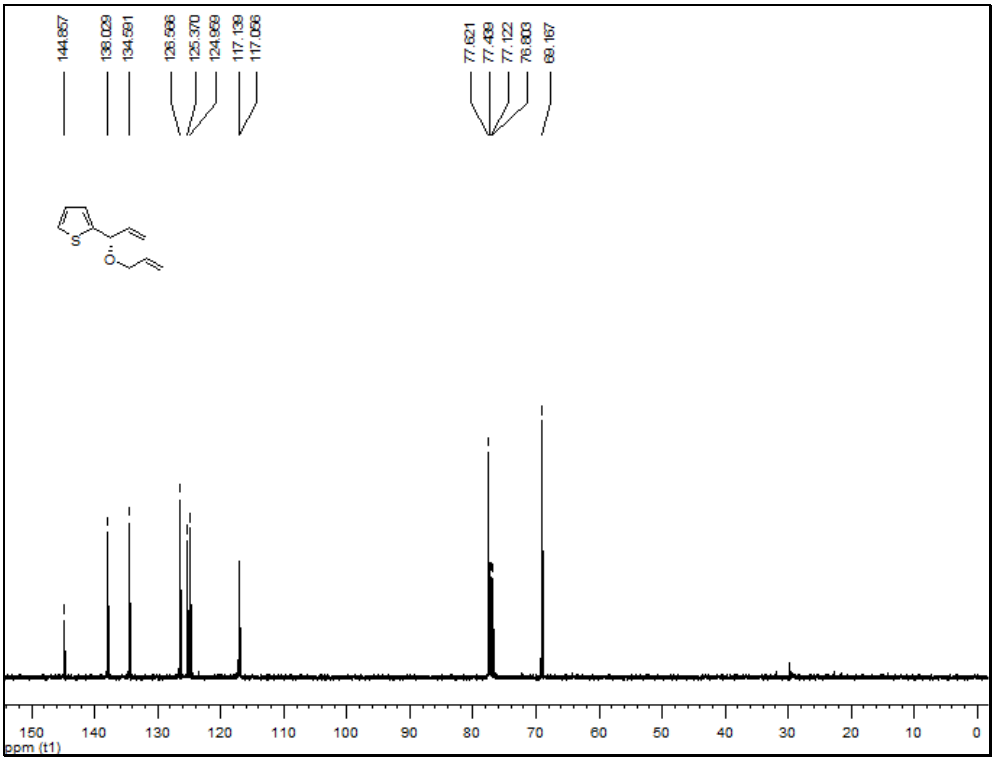


Figure A38. ^{13}C-NMR spectrum of (*S*)-(+)-2-(1-(allyloxy)allyl)thiophene, (*S*)-(+)-**11a**

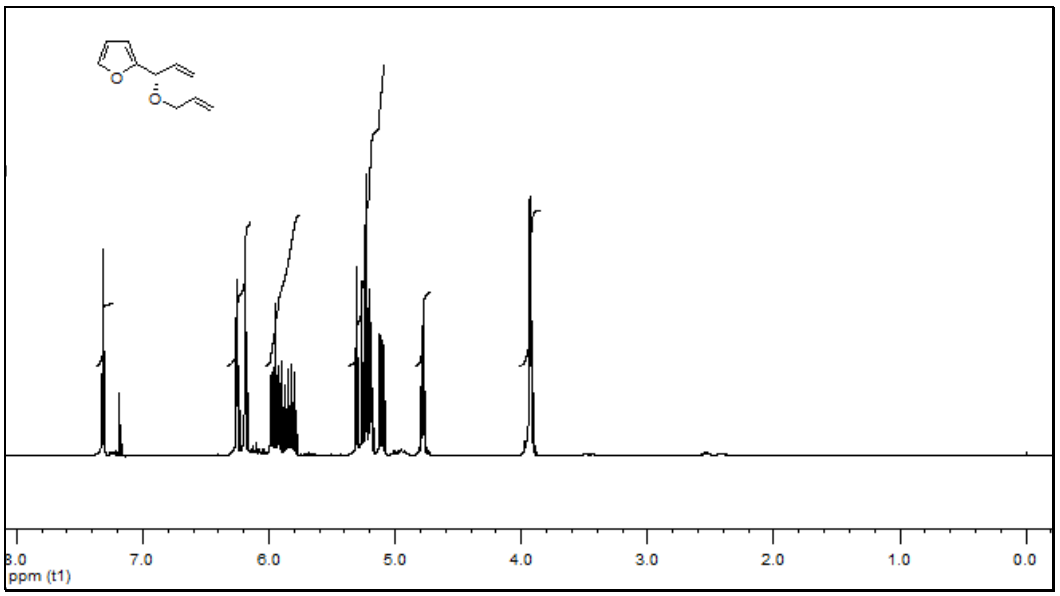


Figure A39. ^{1}H-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)allyl)furan, (*S*)-(-)-**11b**

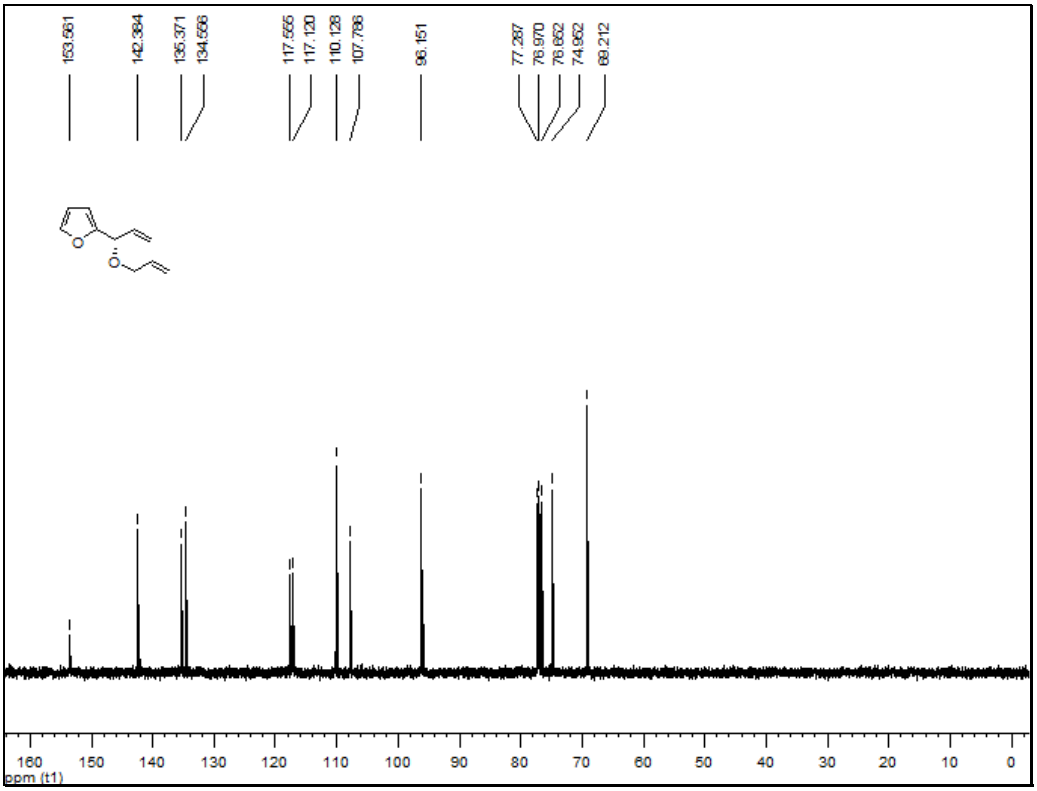


Figure A40. ^{13}C-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)allyl)furan, (*S*)-(-)-**11b**

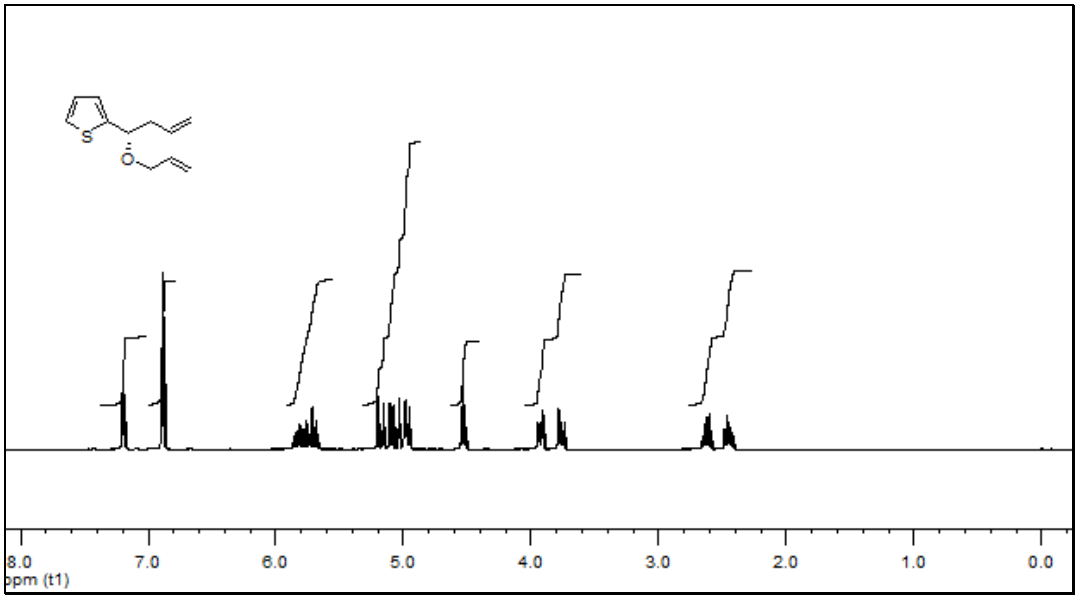


Figure A41. ^{1}H-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)thiophene, (*S*)-(-)-**12a**

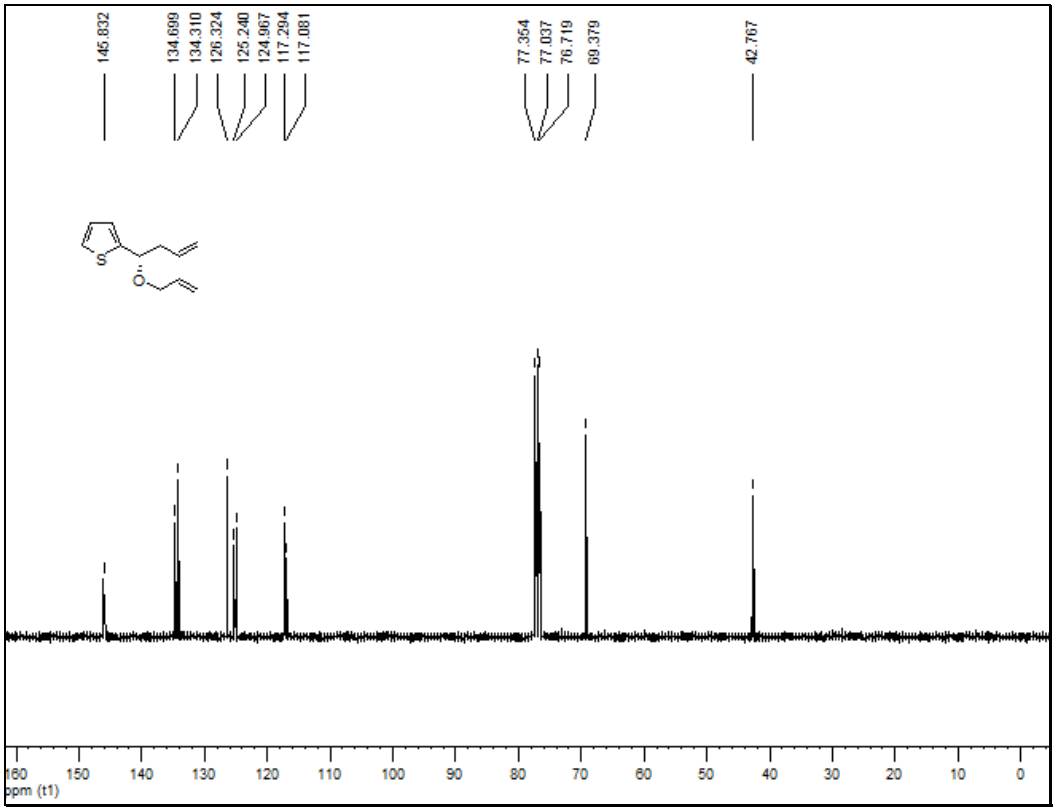


Figure A42. ^{13}C-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)thiophene,(*S*)-(-)-**12a**

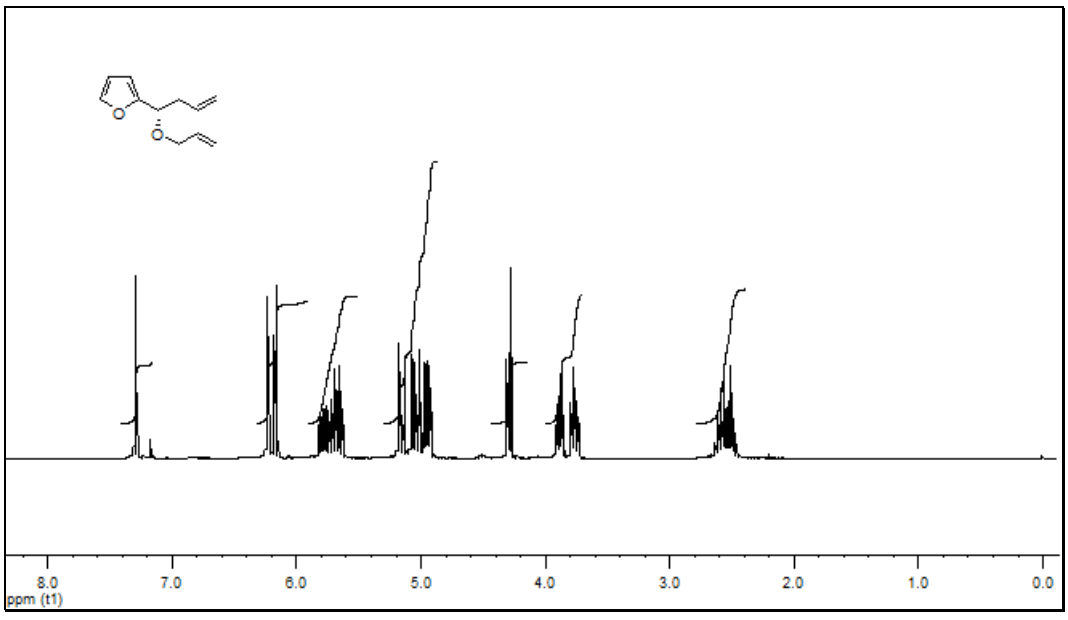


Figure A43. ^{1}H-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)furan, (*S*)-(-)-**12b**

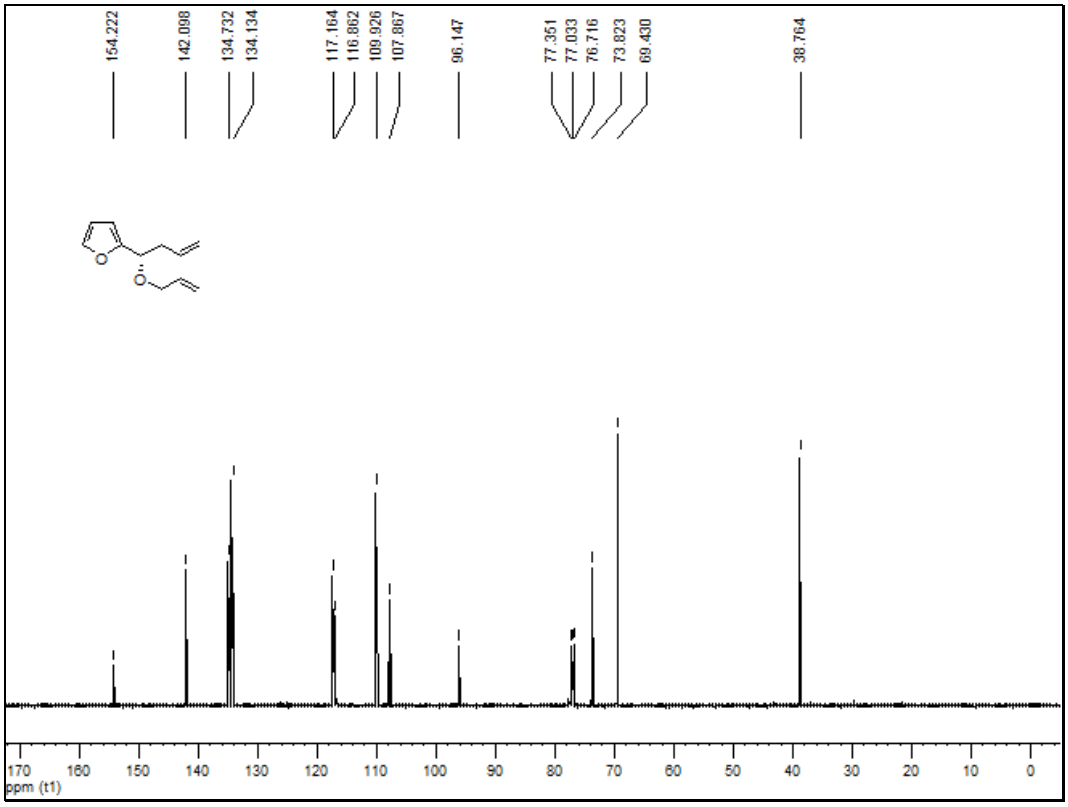


Figure A44. ^{13}C-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)furan, (*S*)-(-)-**12b**

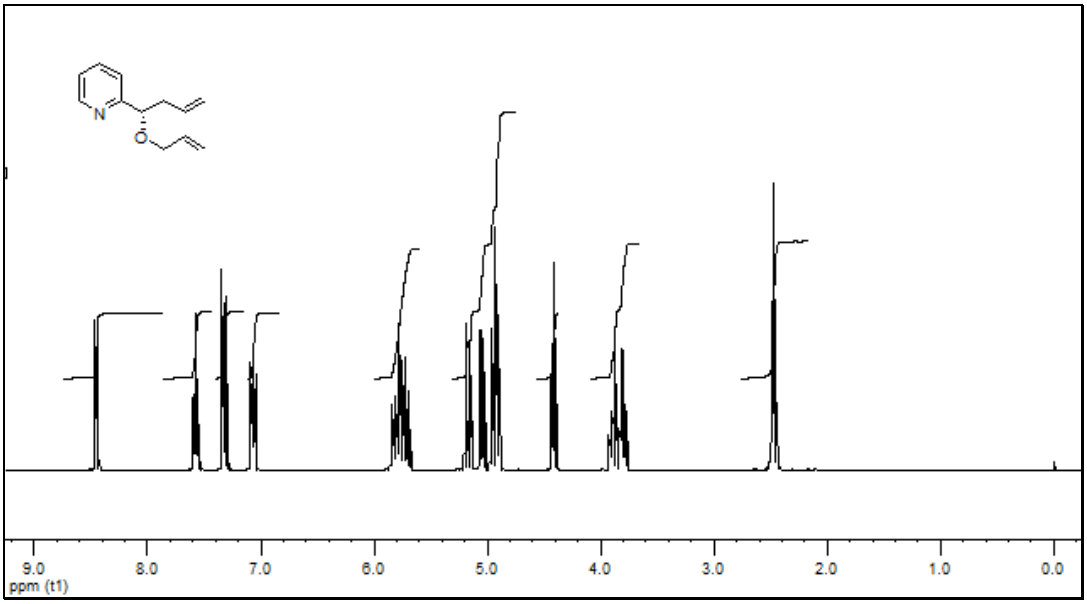


Figure A45. ^{1}H-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)pyridine, (*S*)-(-)-**12c**

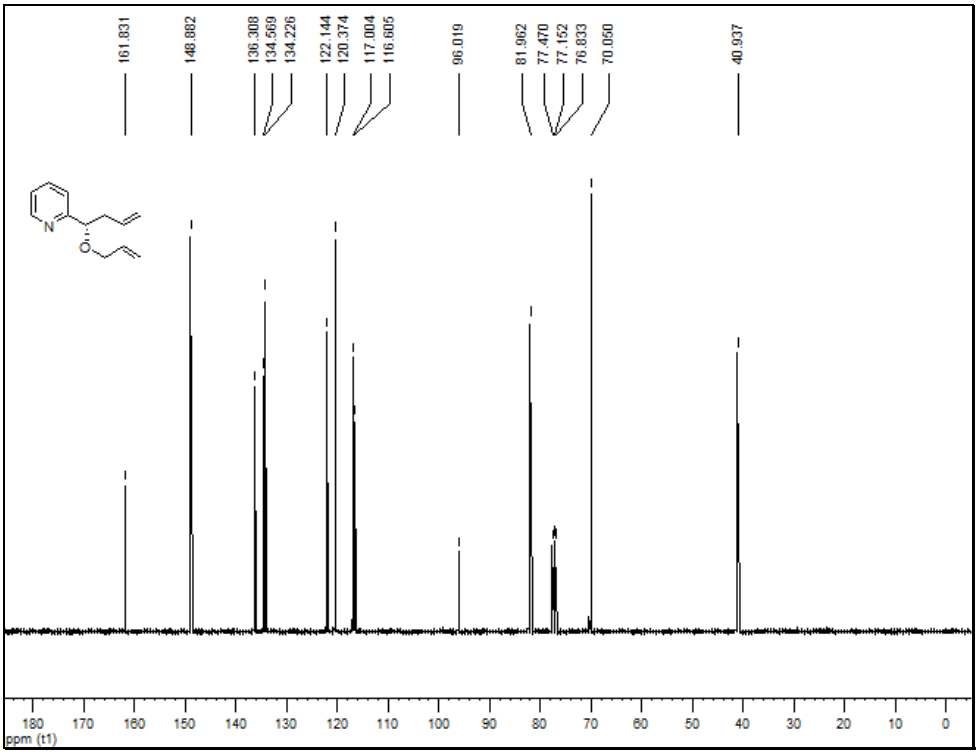


Figure A46. ^{13}C-NMR spectrum of (*S*)-(-)-2-(1-(allyloxy)but-3-enyl)pyridine, (*S*)-(-)-**12c**

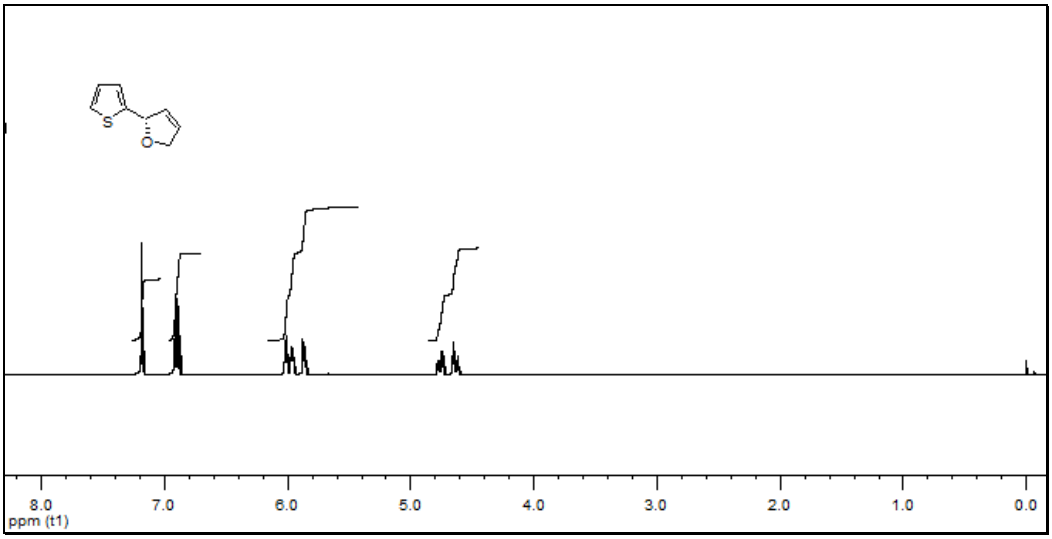


Figure A47. ^{1}H-NMR spectrum of (*S*)-(+)-2-(thiophene-2-yl)-2,5-dihydrofuran,(*S*)-(+)-**13a**

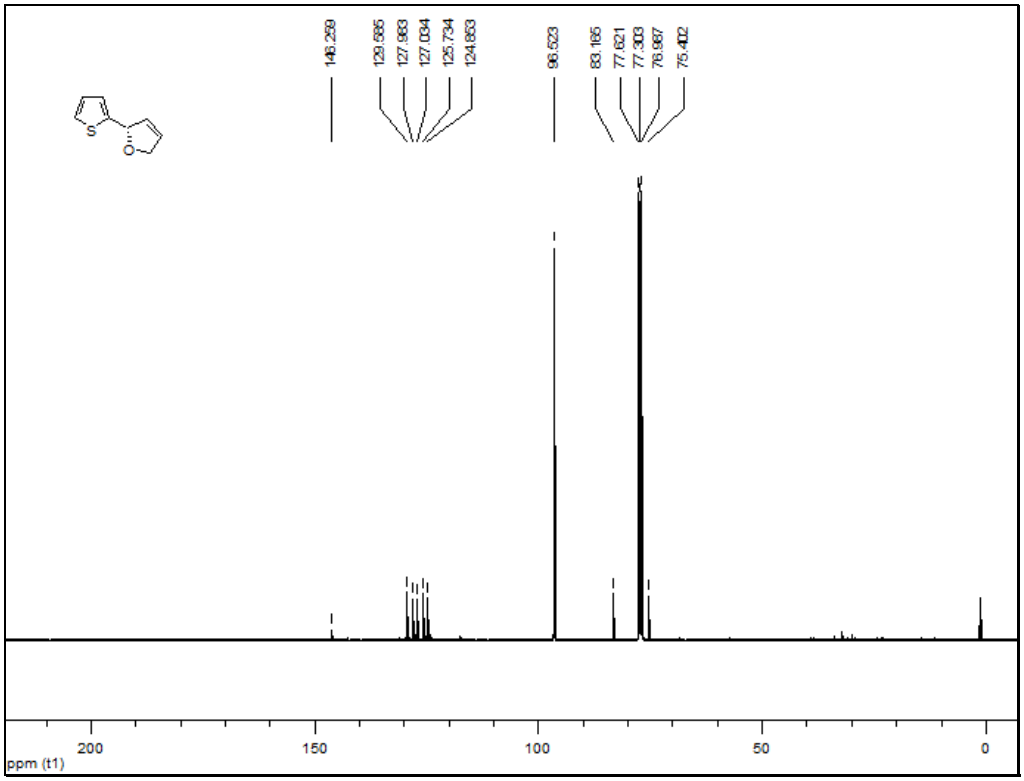


Figure A48. ^{13}C-NMR spectrum of (*S*)-(+)-2-(thiophene-2-yl)-2,5-dihydrofuran,(*S*)-(+)-**13a**

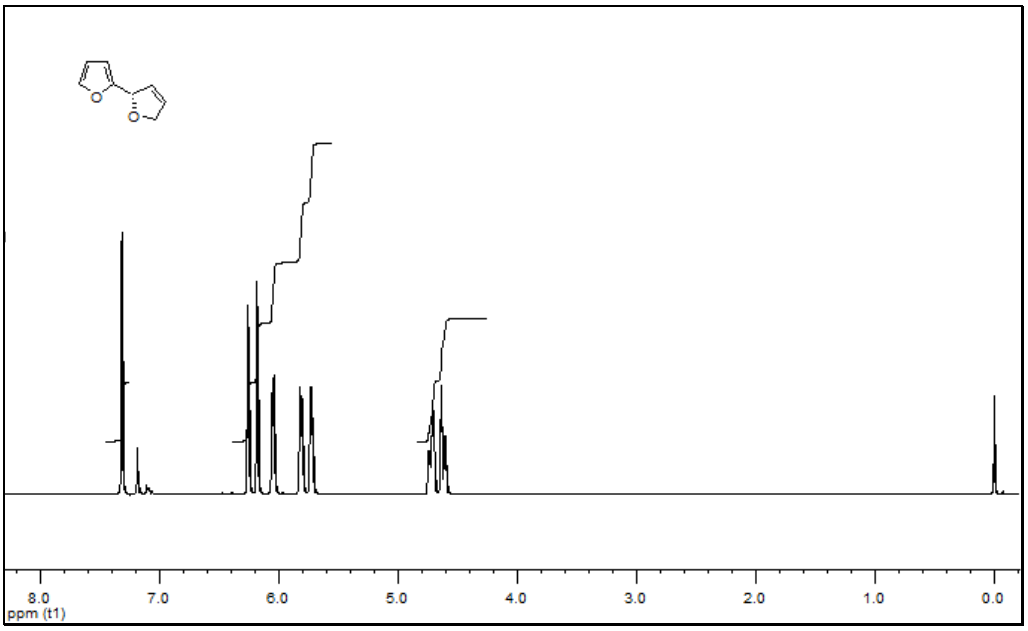


Figure A49. ^{1}H-NMR spectrum of (*S*)-(-)-2-(2,5-dihydrofuran -2-yl)furan, (*S*)-(-)-**13b**

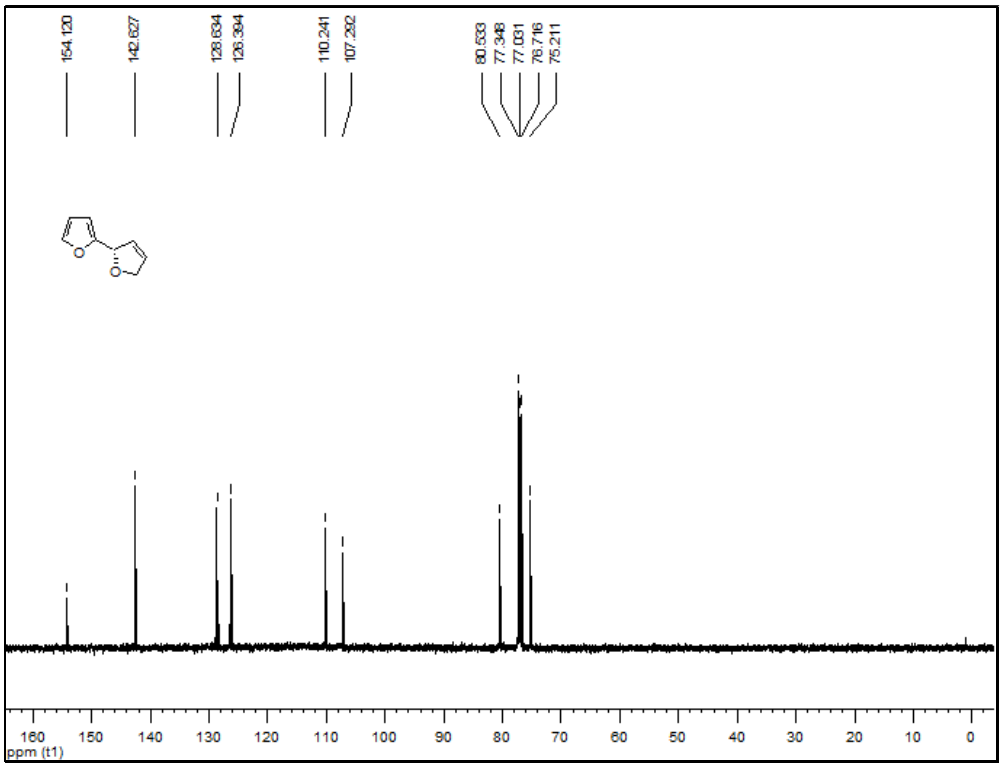


Figure A50. ^{13}C-NMR spectrum of (*S*)-(-)-2-(2,5-dihydrofuran -2-yl)furan, (*S*)-(-)-**13b**

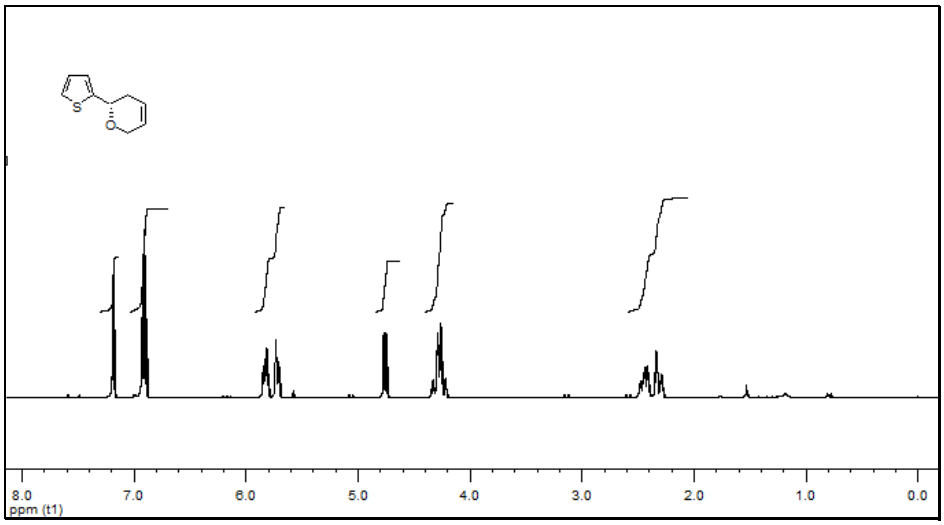


Figure A51. ^{1}H-NMR spectrum of (*S*)-(-)-2-(thiophene-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-**14a**

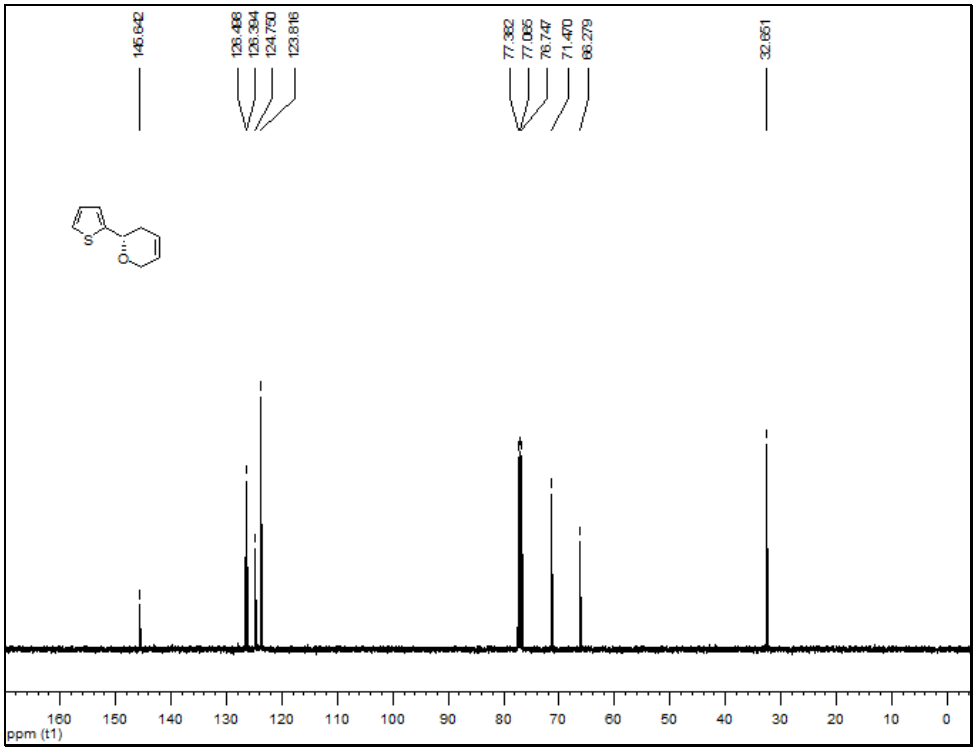


Figure A52. ^{13}C-NMR spectrum of (*S*)-(-)-2-(thiophene-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-**14a**

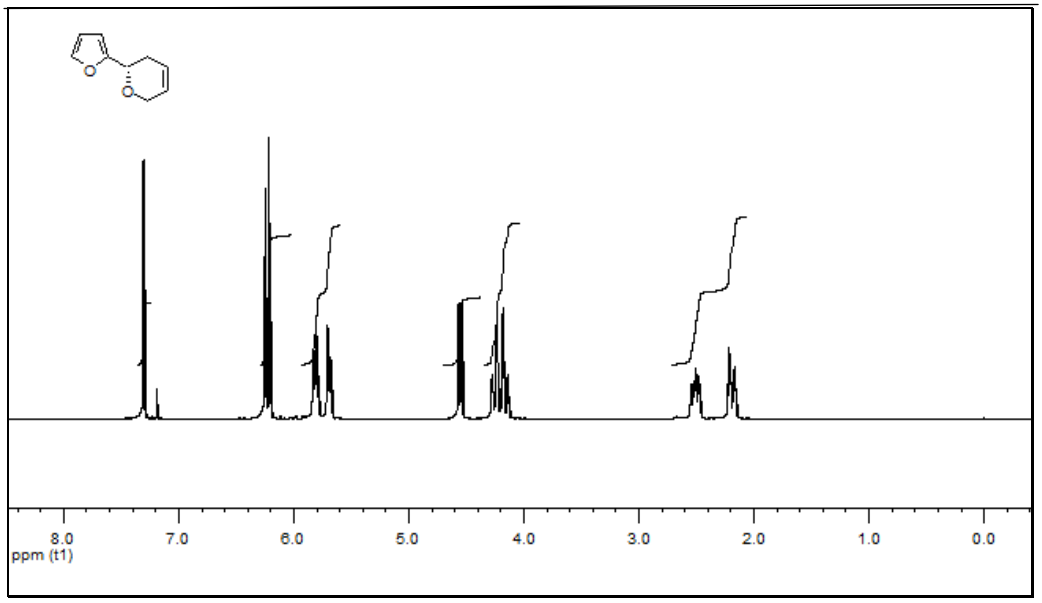
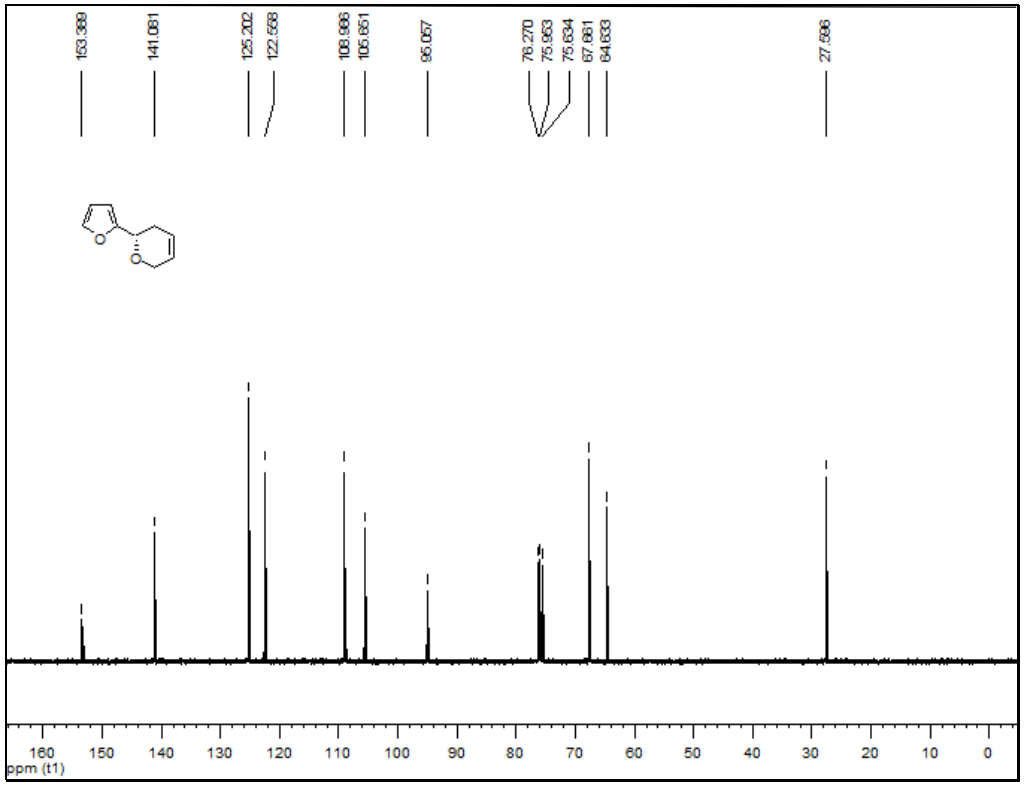


Figure A53. ^{1}H-NMR spectrum of (*S*)-(-)-2-(furan-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-**14b**



A54. ^{13}C-NMR spectrum of (*S*)-(-)-2-(furan-2-yl)-3,6-dihydro-*2H*-pyran, (*S*)-(-)-**14**

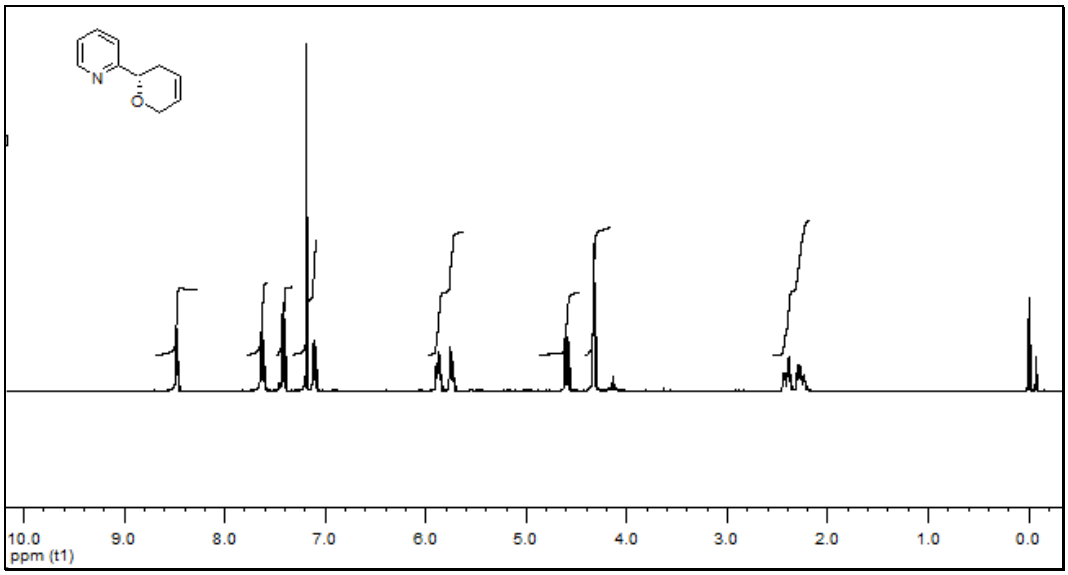


Figure A55. ^{1}H-NMR spectrum of (*S*)-(-)-2-(3,6-dihydro-*2H*-pyran -2-yl)pyridine, (*S*)-(-)-**14c**

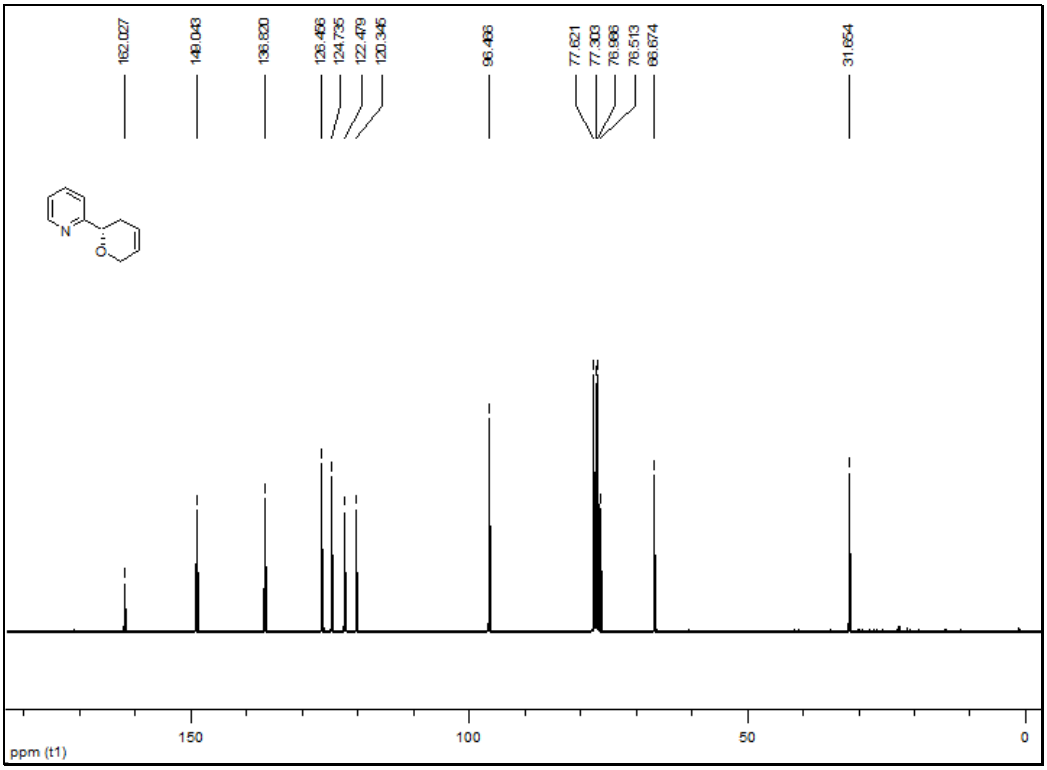


Figure A56. ^{13}C-NMR spectrum of (*S*)-(-)-2-(3,6-dihydro-*2H*-pyran -2-yl)pyridine,(*S*)-(-)-**14c**