SYNTHESIS OF 2-HETEROARYL SUBSTITUTED CHIRAL FUSED CYCLOPENTA[C]PYRIDINE DERIVATIVES VIA PAUSON-KHAND REACTION

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SYNTHESIS OF 2-HETEROARYL SUBSTITUTED CHIRAL FUSED CYCLOPENTA[C]PYRIDINE DERIVATIVES VIA PAUSON-KHAND REACTION

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ABSTRACT

SYNTHESIS OF 2-HETEROARYL SUBSTITUTED
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The racemic homoallylic and homopropargylic alcohol derivatives were resolved by applying chemoenzymatic method using various lipase type enzymes *i.e.*, PS-C II, Lipozyme, CAL-B. The enantiomeric excess values of the resultant alcohols were determined by HPLC. These enantiomerically enriched homoallylic and homopropargylic alcohols were subjected to *N*-propargylation and *N*-allylation, respectively, by S_N2 and modified Mitsunobu reactions. During the course of all reactions, stereochemistry of the chiral centers were under controlling according to the known reaction mechanisms. The resultant chiral *N*-tosylated enyne derivatives afforded the corresponding chiral fused cyclopenta[*c*]pyridinone derivatives (**69, 73, 75** and **77**) with acceptable chemical yields and excellent diastereoslectivity depending upon the conformational effect on the complete remote stereochemical control for the newly generated chiral centers. The chemoenzymatic applications done with biocatalysis (lipases) and the Pauson-Khand reaction are involved in "*Green Chemistry*" approach.

Key words: Pauson-Khand reaction, enzymatic resolution, "Green Chemistry"

ÖZ

2-HETEROARİL SUBSTİTUE KİRAL SİKLOPENTA[C]PİRİDİN TÜREVLERİNİN PAUSON-KHAND REAKSİYONU İLE SENTEZİ

Gümrükçü, Yasemin
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Ekim 2009, 114 sayfa

Racemik homoalilik ve homoproparjilik alkol türevlerinin kemoenzimatik rezolüsyonu çeşitli lipaz tipi enzimler, PS-C II, Lipozyme ve CAL-B, kullanılarak yapılmıştır. Elde edilen alkollerin enantiyomerce zenginlikleri HPLC ile belirlenmiştir. Bu enantiyomerce zengin homoalilik ve homoproparjilik alkoller S_N2 ve Mitsunobu tipi reaksiyonlarla *N*-proparjilik ve *N*-alilik sistemleri oluşturmuştur. Tüm bu reaksiyonlar boyunca, stereokimyaları bilinen kiral merkezler reaksiyon mekanizmalarıyla kontrol altında tutulmaktadır. Kiral *N*-tosil enin sistemleri hedeflenen kiral içerikli siklopenta[*c*]piridin türevlerini (**69**, **73**, **75** ve **77**) mükemmel diastereoseçicilikle ve kabul edilebilir kimyasal verimlerle oluşturmaktadır. Diastreoseçicilik, konformasyona bağlı uzaktan streokimyasal kontrol ile sağlanmaktadır. Biokatalizörler ile yapılan kemoenzimatik uygulamalar ve Pauson-Khand tepkimesi "*Çevre uyumlu kimya*" yaklaşımını içermektedir.

Anahtar kelimeler: Pauson-Khand reaksiyonu, enzimatik rezülosyon, "Çevre uyumlu kimya"

To my dear family...

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LIST OF ABBREVIATIONS

PKR: Pauson-Khand Reaction

DME: Dimethoxyethane

NMO: *N*-methylmorpholine *N*-oxide

TMO: Trimethylamine *N*-oxide

TMANO: Trimethylamine *N*-oxide

DEAD: Diethyl azodicarboxylate

TPP: Triphenylphosphine

4-NBA: 4-Nitrobenzoic acid

DIAD: Diisopropyl azodicarboxylate

THF: Tetrahydrofuran

DPE: Diisopropyl ether

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

CHAPTER 1

INTRODUCTION

1.1 Green Chemistry

Green chemistry involves a reduction or elimination of the use of hazardous or toxic substances in the design, manufacture and application of chemical products in order to prevent environmental pollution [1]. The main purpose is preventing the pollution rather than the waste remediation by designing new chemicals and chemical processes.

The revolution of green chemistry is providing a wide range of challenges to those who practice chemistry in industry, education and research. However, there are numerous opportunities to discover and apply new chemistry, to improve the economics of chemical manufacturing [2]. Thus, significant progress is being made in numerous research areas such as catalysis, designing safer chemicals and environmentally harmless solvents, and developing renewable feedstocks. On the other hand, all the green chemistry research, education, industrial implementation, awards and outreach are based on the fundamental definition of green chemistry and the set of criteria, principles and methodologies, developed by Paul T. Anastas and John C. Warner as 12 principles of green chemistry [3].

"Paul Anastas stated out that the 12 principles are [1];

1. *Prevention:* Preventing waste is better than the treating or cleaning up waste after it is formed.

2. *Atom Economy:* New synthetic methods should be developed for maximizing the final product without any waste.
3. *Less hazardous chemical syntheses:* Synthetic methodologies are designed with little or no toxicity to humans and the environment.
4. *Designing safer chemicals:* Effective chemical products with less or no toxicity are designed.
5. *Safer solvents and auxiliaries:* The usage of auxiliaries such as solvents, separation agents etc. should be minimized and if necessary should be replaced with greener ones.
6. *Designing synthesis for energy efficiency:* Energy requirements should be arranged by considering the environmental and economic impacts of the chemical processes.
7. *Use of renewable feedstocks:* Raw materials and feedstocks should be designed as renewable if only it is technically and economically practicable.
8. *Reduce Derivatives:* Use of blocking or protecting groups or any temporary modifications for processes should be avoided to prevent additional reagents and waste.
9. *Use of catalyst:* Catalysts are preferable to stoichiometric reagents since they can enhance the selectivity of the reaction, reduce the temperature of a transformation, reduce reagent wastes and prevent unwanted side reactions.
10. *Design for degradation:* Chemical products should be designed for breaking down into innocuous substances at the end of the reaction.
11. *Real time analysis for pollution prevention:* Synthesis should be monitored for a real time in order to prevent formation of hazardous substances.
12. *Accident prevention:* The potential of chemical accidents should be avoided by designing new substances."

The environmental factor (E factor) is a useful measurement for environmental acceptability of chemical processes along with atom economy. Whereas the terms of atom economy [4] covers the highest yield and product selectivity in a chemical

synthesis, in the E factor [5-9] the chemical yields cover the reagents, solvent losses, all process aids and, in principle, even fuel (Figure 1) [10]. In addition, a higher E factor implies more waste and, so, greater negative environmental impact. In ideal case, E factor is zero.

$$E\text{-}factor = \frac{Total\ waste\ (kg)}{Product\ (kg)}$$

$$Atom\ Economy = \frac{Molecular\ weight\ of\ desired\ product}{Molecular\ weight\ of\ all\ products} \times 100\%$$

Figure 1. Equation of the atom economy and E-factor yields

The impact of the E-factor is not the inhibition of the chemical industry but also the measurement of the efficiency of the chemical industry. For instance, when a chiral molecule shows biological activity, always one of the enantiomer is the only desired ones and for economic and environmentally viability, processes should be have atom economy and low E-factors which means they should employ catalytic methodologies. The common methods for the enantioselective catalysis are the enzymes, the method which was used in our work, chiral metal complexes and biocatalyst (enzymes) [12].

Besides, the Pauson-Khand [13] and the Mitsunobu [14] reactions also have atom efficiency and low E-factors in ideal cases. Thus, the ideal Pauson-Khand and Mitsunobu reactions are catalytic in nature. Whereas the catalytic age of Pauson-Khand reaction was progressed by designing new transition-metal complexes such as, titanium, rhodium, ruthenium, etc. [15], for the Mitsunobu reaction it was with the stoichiometric oxidant and reductant generating innocuous by-products [16]. However, these catalytic, economic and environmentally friendly syntheses have several challenges which will be resolved in coming years.

1.2 Pauson-Khand Reaction

The Pauson-Khand reaction (PKR) is utilized for construction of a variety of cyclopentenones [13]. It is a [2+2+1] cycloaddition reaction via an alkene, an alkyne and carbon monoxide mediated by transition metal complex (Figure 2) [17].

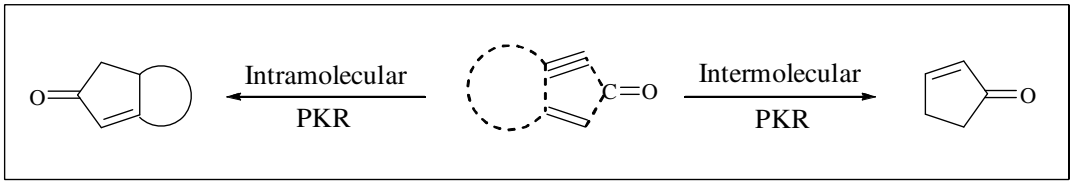
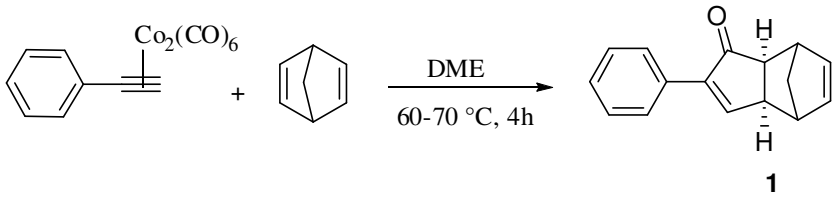


Figure 2. The Pauson-Khand Reaction

The reaction was found out by I. U. Khand and P. L. Pauson in 1973 as a coincidence result in search for the new organometallic cobalt complexes [18- 22]. The conversion of norbornene with the phenylacetylene–hexacarbonyldicobalt complex to give the corresponding cyclopentenone **1** in 45% yields was the first successful PKR (Scheme 1) [18].



Scheme 1. First example of Pauson-Khand reaction

At the beginning there were some limitations for the PKR. For instance, to obtain acceptable yields, long reaction times and high temperatures were required and all alkynes were useful except for propynoic acid derivatives. Besides, under the original reaction conditions, only strained olefins were reacted efficiently.

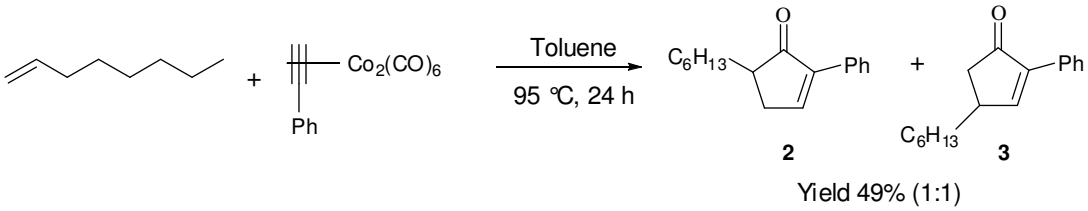
Moreover, if unsymmetrical alkynes and alkenes were used, the reactions typically gave a mixture of regioisomers. In addition, until the nineties dicobalt octacarbonyl was the only cluster used to mediate the reaction [17].

Furthermore, the Pauson-Khand reaction is one of the most attractive methods for the synthesis of cyclopentenone compounds. The efficiency and atom economy of the reaction were progressed in years. Nevertheless, the reaction was discovered as an intermolecular reaction, the reactivity and selectivity of the alkene components has always been limited. These brought about the development of intramolecular form of the Pauson-Khand reaction which was in good yields with complete control of regioselectivity.

Since the discovery of the PKR, the investigations have been kept on extensively. Nowadays, the transformation of the simple components into the cyclopentenone systems in a single step with perfect stereochemical and regiochemical control are provided both by intermolecular and intramolecular Pauson-Khand reaction [23].

1.2.1 The Intermolecular Pauson-Khand Reaction

The Pauson-Khand reaction was discovered as an intermolecular reaction in 1971 [13]. In early studies unsymmetrical alkynes and alkenes were responsible from low yields and poor selectivity (Scheme 2) [24].

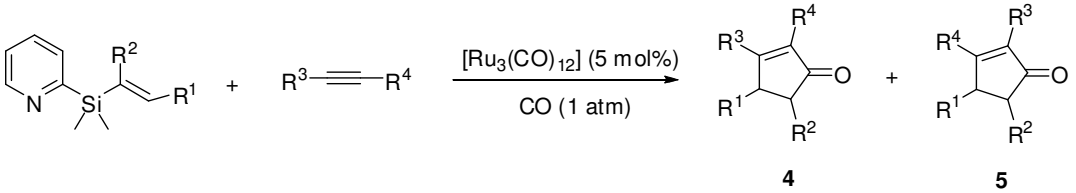


Scheme 2. An intermolecular Pauson–Khand reaction of a terminal alkene.

Besides, in order to synthesize synthetically useful and selective cyclopentenone compounds, symmetrical and active alkenes were used in these years. According to regioselectivity, the bulkier substituent of the alkyne is placed to the carbonyl in the cyclopentenone product.

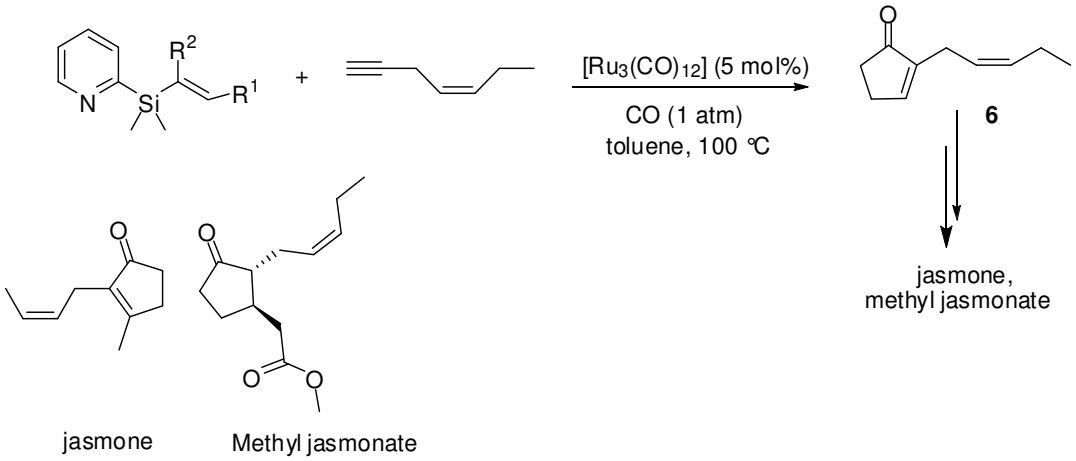
Moreover, fundamental improvement of the intermolecular form of PKR was started in 1988 by Krafft [25]. Krafft and co-workers, by considering the proposed mechanism, investigated that a heteroatom tethered to the alkene by a carbon chain which coordinate to cobalt, and control the regioselectivity of the reaction. As well, bidentate olefinic ligands led to an increase in yields of products. According to this study, oxygen, sulfur and nitrogen substituted alkenes have better yields and regiocontrol than the alcohols and methoxymethyl ethers substituted alkenes. Apart from, the outcome of the chain length extension between the heteroatom and the alkene was decline in regioselectivity [25].

Furthermore, there were no further elegant investigations until 2002. Itami and Yoshida declared the use of alkenyldimethyl 2-pyridylsilanes as an alkene for the catalytic ruthenium catalyzed intermolecular Pauson–Khand reaction (Scheme 3) [26]. Although the regiocontrol problems solved by a heteroatom tethered to the olefins, the removal of the directing groups after PKR became a disturbing problem. The most important part of this reaction is that, the pyridylsilyl group serves as a removable directing group, which generates desilylated cyclopentenones, **4** and **5**, in excellent yields [24].



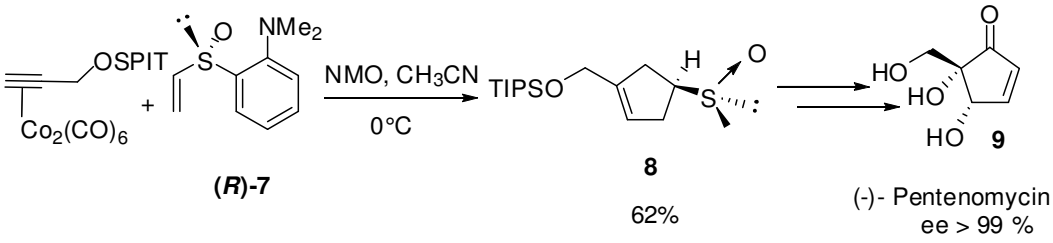
Scheme 3. The pyridiylsilyl-directed Pauson–Khand reaction

According to these studies, syntheses of natural and unnatural cyclopentanoid products were developed. For example, jasmone, methyl jasmonate, and epijasmonate, was synthesized via single step from an enyne and dimethyl(2-pyridyl)(vinyl)silane with 60% yield and 63% regioselectivity (Scheme 4) [26].



Scheme 4. Natural product synthesis with intramolecular PKR

In addition, another inspired study was reported by Carretero and co-workers in 2003. This study was reported as the first asymmetric synthesis of Pauson-Khand reaction via chiral sulfoxides [27]. The study also originated in substrate directed intermolecular Pauson-Khand reactions. The use of chiral 2-(*N*, *N*-dimethylamino) phenyl vinyl sulfoxide as an alkene constitutes high steroselective and regioselective products. Series of racemic vinyl sulfoxides with different substituents were prepared in order to control the applicability of this study. In addition, highly efficient and the shortest enantioselective synthesis of the antibiotic (-)-pentenomycinI **9** was developed *via ortho*-amino-substituted sulfoxide **(*R*)-7** (Scheme 5) [27].



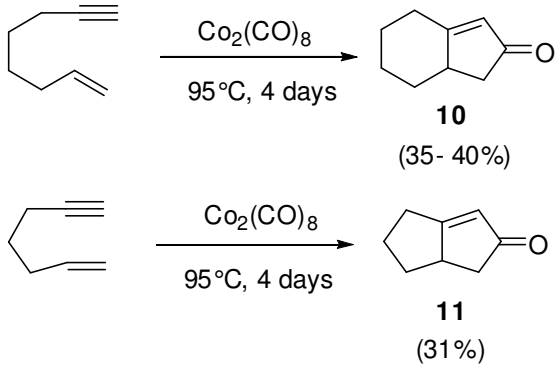
Scheme 5. Synthesis of (-)-pentenomycinI

Eventually, there is much work to be done to attain the efficient, versatile, environmentally friendly, asymmetric and catalytic intermolecular Pauson-Khand reaction. So the progress of intermolecular method will be kept on [24].

1.2.2 The Intramolecular Pauson-Khand Reaction

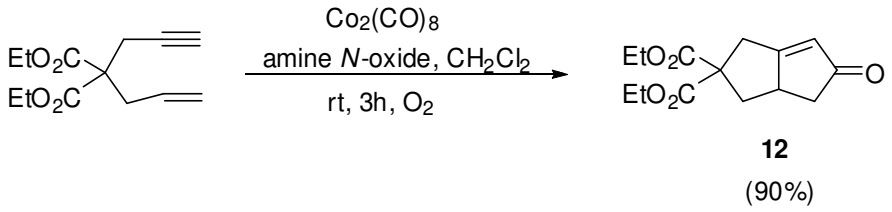
After the discovery of the Pauson-Khand reaction in 1973, there were some problems such as; to obtain useful yields; stoichiometric amount of catalyst and strained olefins had to be used, unsymmetrical alkynes and alkenes gave mixture of regioisomers and to attain full conversion, long reaction times and high temperatures were necessary [28].

An important improvement was reported by Schore and Croudace in 1981 that is the first example of intramolecular Pauson-Khand reaction. In this study, the functionalized derivatives of bicyclo[3.3.0]octane ring system,**10** and **11**, which are in sort of biologically active natural products, were synthesized directly from acyclic starting materials with complete regioselectivity (Scheme 6) [29].



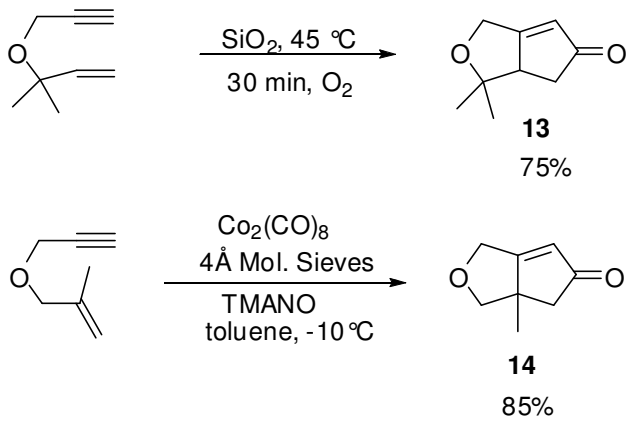
Scheme 6. Intramolecular Pauson-Khand reaction

According to these developments in the Pauson- Khand reaction, there were still some fundamental problems in reaction conditions that required high temperatures (60-120°C) and long reaction times (6h-4 days) [30]. The solution of these problems was reported by two independent groups of Jeong [31] and Schreiber [32]. The addition of *N*-methylmorpholine *N*-oxide (NMO) and trimethylamine *N*-oxide (TMO) as PKR accelerating agents brought about high yield cyclopentenone **12** synthesis at room temperature (Scheme 7). The NMO and TMO could readily remove CO from the transition metals oxidatively as CO_2 [28, 30].



Scheme 7. Effect of additives to the PKR

Furthermore, other promoters and additives were reported such as silica gel [33], molecular sieves [34], alkyl methyl sulfides [35], primary amines [36], etc. These reagents also facilitate enormously the intramolecular Pauson-Khand reaction (Scheme 8) [30, 34].



Scheme 8. The intramolecular Pauson–Khand cycloaddition reactions

Additionally, the structure of the alkenes and the alkynes still constitute the most important part of the synthesis. That is to say, all simple alkynes are good substrates in spite of the yields are depend on the degree of substitution and bulkiness of substituents. Ethyne and terminal alkynes are the most common substrates, in order to constitute high yield cyclopentenones, whereas the internal alkynes give lower yields. Besides, strained cyclic alkenes are the best substrates such as norbornadiene, norbornene, and cyclobutene. Apart from cyclopentenes and cyclohexenes are simple acyclic alkenes, suitable substrates. Moreover, the important detrimental effect on the formation of cyclopentenones is the steric hindrance around the double bond. As the number of substituents of the alkene or steric bulk of the substituents at the carbon atom of attachment increases, carbon-cobalt bond insertion becomes more difficult [30].

1.2.3 Mechanism

The mechanistic pathway of the Pauson-Khand reaction was proposed by Magnus in 1985 (Figure 3) [37]. Ever since several theoretical studies support this mechanism while it explains the regiochemical and stereochemical results. The initial complex **15** formed with alkyne and transition metal complex $Co_2(CO)_8$.

Then the first step would be the loss of one CO ligand and formation of complex **16**. This step is the rate determining step, strongly endothermic, and almost certainly reversible. In the amine *N*-oxide promoted reaction, CO_2 released in this step and the step becomes irreversible. Consequently, this also explains why the high yield products are synthesized *via* promoters. Then the alkene coordinates to the cobalt **17** and inserted into a Co-C bond, and the cobaltacycle **18** formed. After that, by CO insertion the complex **19** and by reorganization the complex **20** formed. The final step is formation of cyclopentenone **21** by reductive elimination of the $Co_2(CO)_6$ complex.

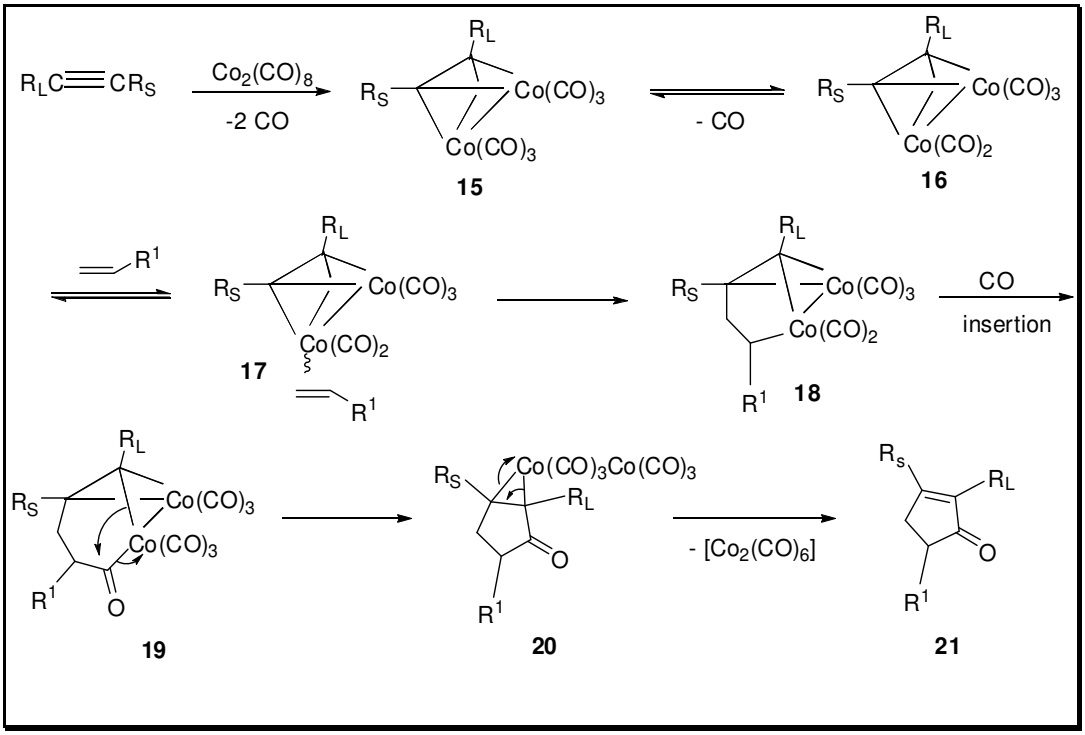


Figure 3. Proposed mechanism of the Pauson-Khand reaction

The effect of additives and promoters, as already mentioned, are observed in the first step, in the formation of complex **16**. While the amine *N*-oxides act oxidizing one CO ligand to CO_2, the addition of sulfides and sulfoxides act helping the displacement of a CO ligand and stabilizing the intermediates. In addition, the

molecular sieves act to absorb the enyne and stabilize the transition state which increases the conversion [17].

1.2.4 Asymmetric Pauson- Khand Reaction

The Pauson-Khand cyclization is a powerful synthetic tool in organic synthesis. In particular in the natural product synthesis, the stereoselectivity is important. After the latest nineties the progress of asymmetric PKR begins and several methods were developed, shown in Figure 4 [17]. In these approaches the most effective and useful methods are the followings:

- The chiral substrate
- The chiral auxiliary
- The chiral metal complex
- The chiral promoter.

In these methods, chiral substrates and chiral auxiliaries give the best results whereas the chiral metal complex method still in progress [38].

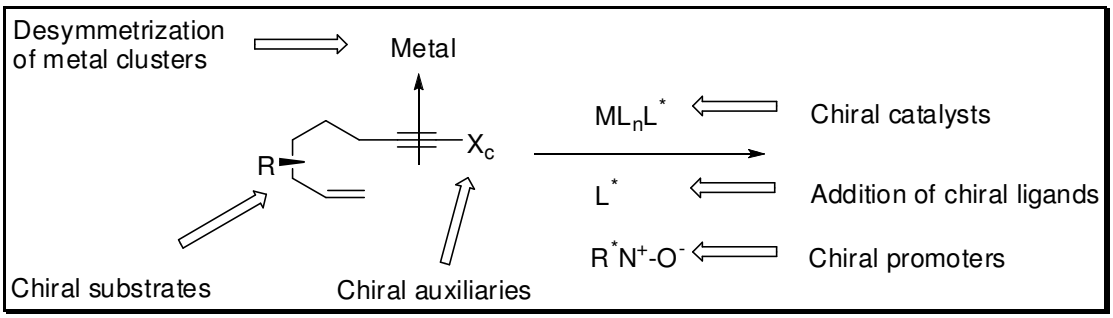
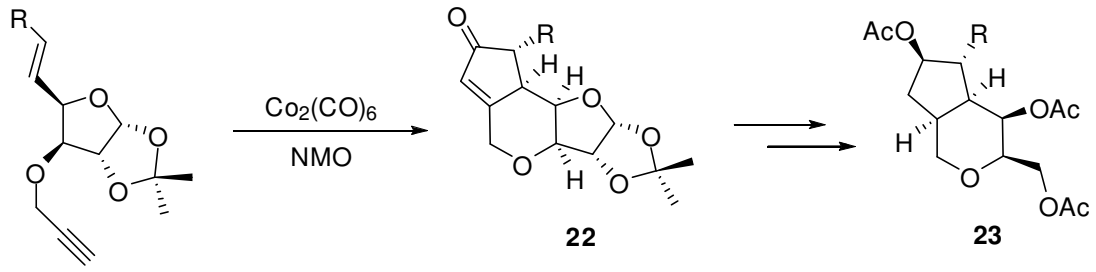


Figure 4. General methods for Asymmetric PKR

1.2.4.1 The chiral substrate approach

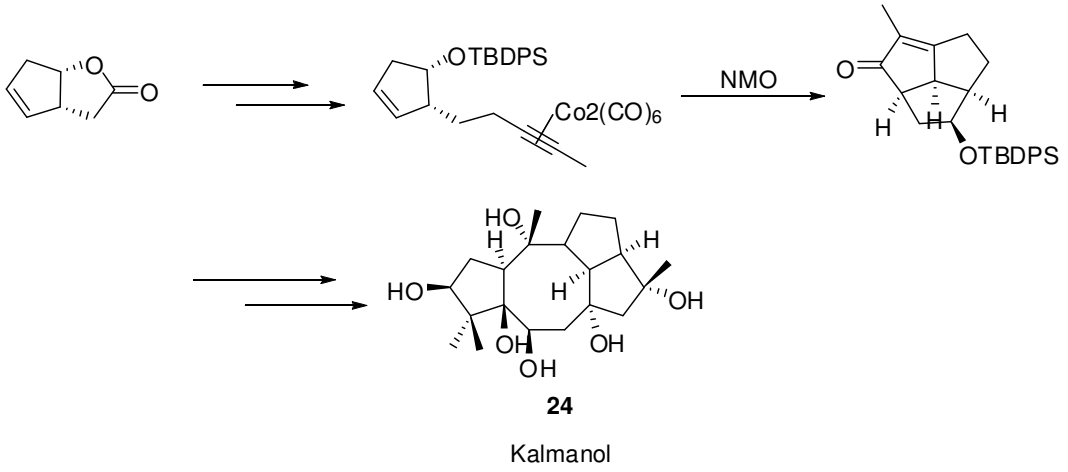
This approach uses chiral substrates as starting materials, which have generally been made from chiral pools, by transfering their chirality to the final product.

For the synthesis of chiral enynes, the carbohydrates have been used widely instead of amino acids. The isopropylidenedioxyfuran has been used as a skeleton to obtain a series of enynes, which are transformed into cyclopenta[*c*]pyranes **22** and subsequently into compound **23** (Scheme 9) [38].



Scheme 9. Transferring chirality from the substrate

Another example for this approach is the total synthesis of Kalmanol [39], natural product, which exhibits significant cardiotoxic activity.



Scheme 10. Total synthesis of Kalmanol *via* PKR

1.2.4.2 The chiral auxiliary approach

The chiral auxiliary method was developed by Pericàs' group. They worked with chiral sulfur moieties like 10-methylthioisoborneol that is coordinate with the metal, improving the diastereoselection of the reaction. Oppolzer's camphorsultam **25** or chiral oxazolidinones **26** which are other chiral auxiliaries gave excellent results in the selectivity and the yields. Conversely, chiral alkynylthiols like **27** gave good stereochemical results in both intermolecular and intramolecular PKR, in spite of not working well when sulfur is substituted by oxygen, and the chiral sulfoxides like **28** only reacted when an absolute connection to the alkyne, even so gave mixtures of regioisomers with partial loss of the enantiomeric excess (Figure 5) [38].

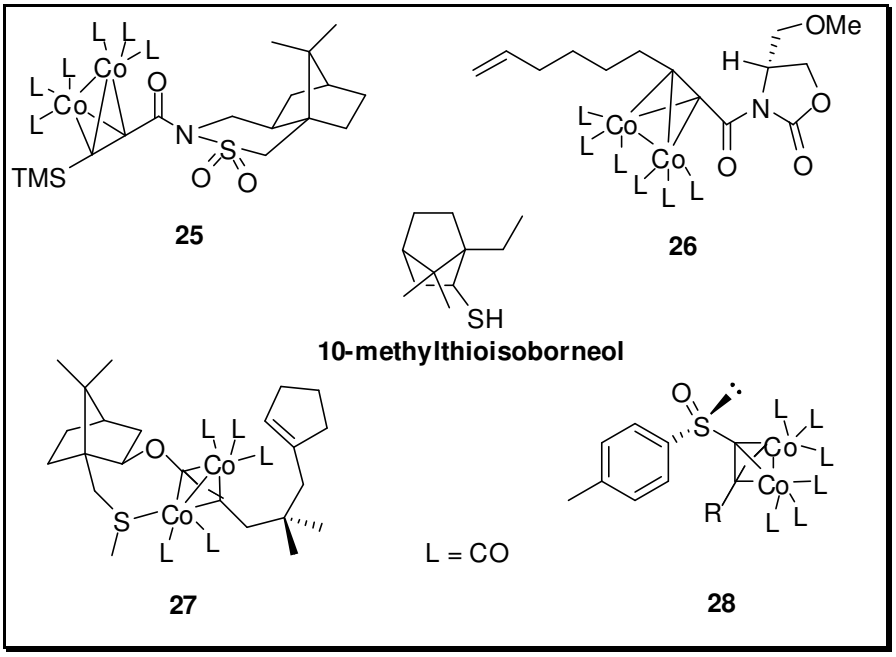


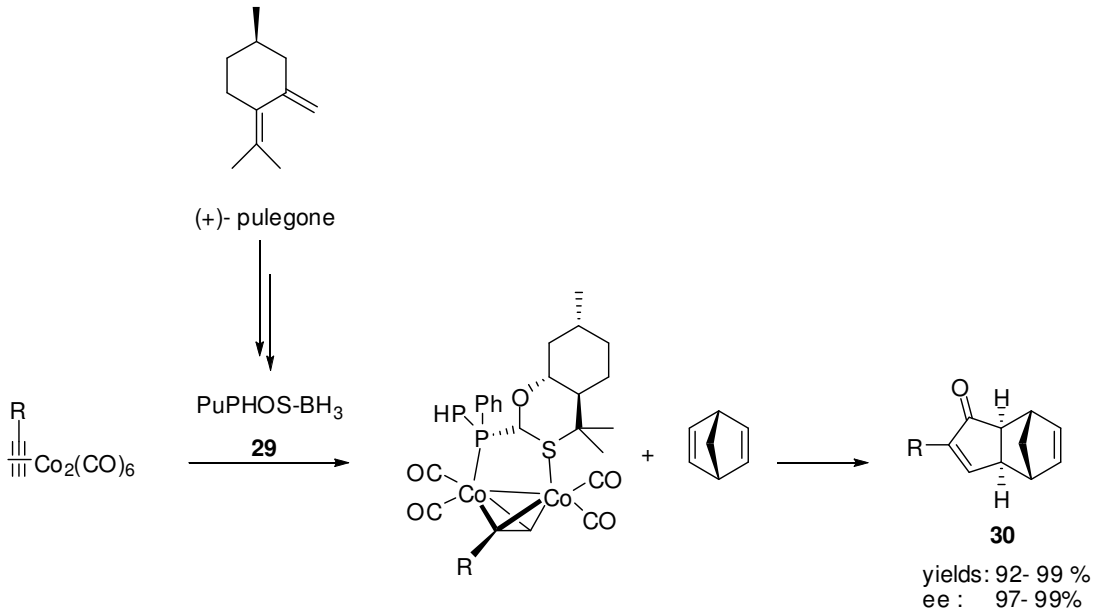
Figure 5. The structures of some chiral auxiliaries

Moreover, chiral sulfoxides, with different electronic withdrawing groups, were used as chiral auxiliaries by Carretero's group. The main point is the proximity of the chiral sulfur to the reaction centre, gives high enantiomeric excess [40].

1.2.4.3 The chiral metal complex approach

The first approach is reported by Greene as addition of chiral ligand to the metal complexes, forms chiral aggregates. Although the ligands used are well known for their success in other chemical reactions, only good enantioselectivities were reported, in some examples, for PKR. Consequently, the same methodology was applied to the different transition metal catalyst such as titanium, ruthenium and rhodium catalyst [38].

Furthermore, Pericàs lean his studies on this methodology and synthesized different chiral complexes using bidentate (P, N) and (P, S) ligands. Then, one of the ligand, called PuPHOS **29**, shows excellent results which is readily obtained from natural product (+)-pulegone. This ligand reacted with cobalthexacarbonyl-alkyne complexes and gave diastereomerically-enriched mixtures of chiral complexes. The reaction with norbornadiene gave excellent results in yields and stereoselectivities of compound **30** (Scheme 11) [41].

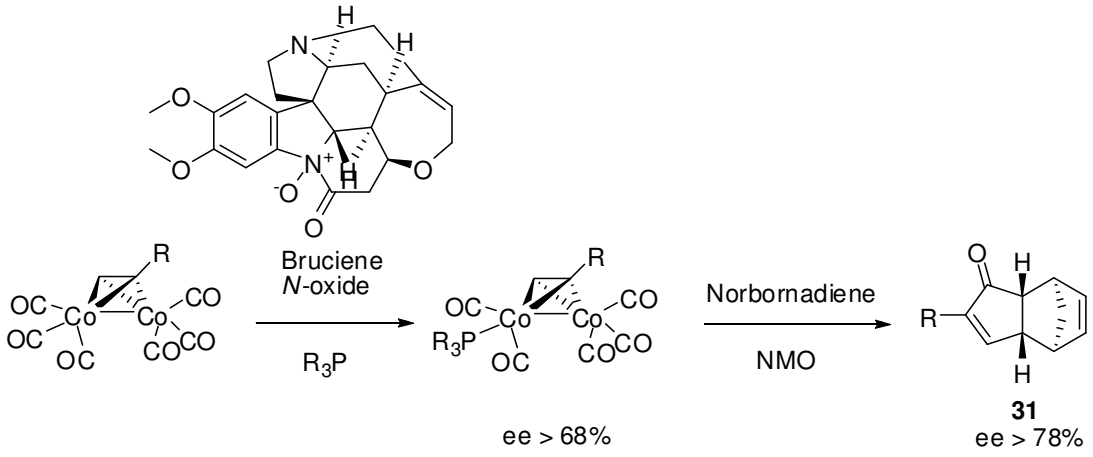


Scheme 11. Transferring chirality from metal complexes

Consequently, whereas the chiral auxiliary approach gives excellent yields and disasteroselectivities, it is more expensive method than the metal cluster. This method, chiral transition metal catalyst, is more convenient method for the synthesis of enantiomerically pure cyclopentenones [28].

1.2.4.4 The chiral promoter

Chiral promoters, amine *N*-oxides such as; NMO, TMO, are generally derived from natural alkaloids. The important point for the chiral promoter is that, the one carbonyl of the cobalt cluster should be made a selective decarbonylation. This selectivity provides a constitution for enantiomerically enriched cyclopentenones after the cyclization. However, the enantiomeric excesses of cyclopentenones were very low untill the modification of this approach by Kerr [42]. This modification based on preparing a desymmetrised cobalt complex by using chiral *N*-oxide which gives selective substitution of one carbonyl by a phosphine. Consequently, sterically and electronically different cobalt complexes lead high enantiomeric excesses in final products. For example, in the presence of norbornadiene and chiral amine *N*- oxide enantiomerically enriched products **31** synthesized successfully (Scheme 12) [38].



Scheme 12. Transferring chirality from promoters

In conclusion, the most effective method, the chiral substare approach, was the method which we have used in our synthesis for asymmetric Pauson-Khand reaction. There are plenty of ways for chiral compund generation. One of the most

common methods, the enzymatic resolution, is the method which was used in our work.

1.3 Enzymatic Resolution

The enzymatic resolution method is one of the methods to obtain optically pure compounds. In our study, chiral homoallylic and homopropargylic alcohols are the starting compounds which were synthesized from racemic alcohols *via* kinetic resolution.

In kinetic resolutions of racemic alcohols, vinyl acetate or isopropenyl acetate are the most common acyl donors. In both cases, a byproduct is formed as a vinyl alcohol and isopropenyl alcohol, respectively. Although the reactions become irreversible in both cases by the help of these byproducts, they present different effects. The vinyl alcohol undergoes keto-enol tautomerization and forming acetaldehyde whereas isopropenyl alcohol tautomerize to acetone [43].

Moreover, the main point for the kinetic resolution is that the two enantiomers react at different rates with a chiral entity. The chiral entity is a biocatalyst, enzyme or a microorganism, or a chemocatalyst, chiral acid or base or even a chiral metal complex, which should be used in catalytic amounts. In addition, in ideal case one enantiomer reacts much faster than the other. For example, if only one enantiomer is reacted, the final product will be obtained as a mixture of one pure enantiomer and an unreacted one. This provides an easy separation for both enantiomers bysingle enzyme (Figure 6) [43].

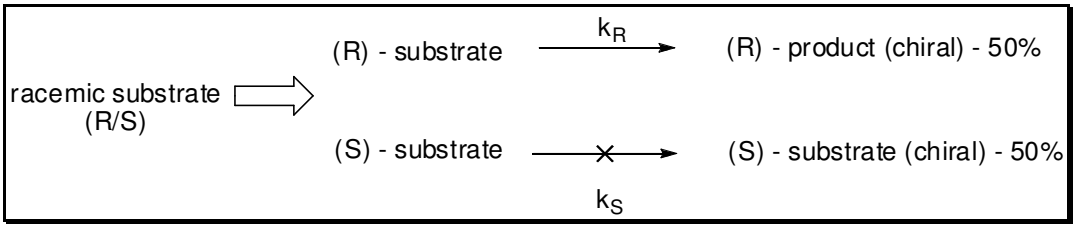


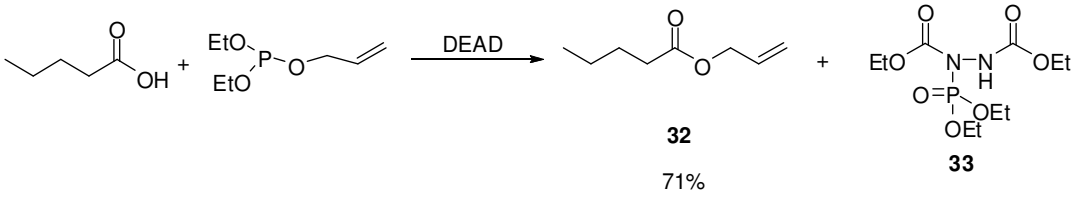
Figure 6. Kinetic resolution

The resolutions of primary, secondary and tertiary alcohols were reported by different groups in years. Thus, secondary alcohols give higher enantioselectivity with the lipase-catalyzed resolution than the primary and tertiary alcohols. There are numerous examples in literature [43]. For example, Schuring and coworkers reported the utility of isopropenyl acetate as acyl donor in lipase-catalyzed secondary alcohols [44]. Also, another comprehensive research was reported by Singh and Kumar, enzymatic resolution of heterocyclic homoallylic and homopropargylic alcohols *via* vinyl acetate [45]. Besides, our group also reported a resolution for secondary [46] and tertiary alcohols [47].

1.4 Mitsunobu Reaction

The Mitsunobu reaction is the method for the dehyrative coupling of an alcohol with an acidic pronucleophile by using an oxidizing azo reagent, diethylazodicarboxylate (DEAD), and a reducing phosphine reagent, triphenylphosphine (TPP), under mild and virtually neutral reaction conditions [14]. Carboxylic acids, phenols, diols, activated carbon acids and imides can be used as acidic pronucleophile reaction component. Besides, esters, aryl ethers, cyclic ethers, carbon–carbon and carbon–nitrogen bonds are the some products of Mitsunobu reaction [48].

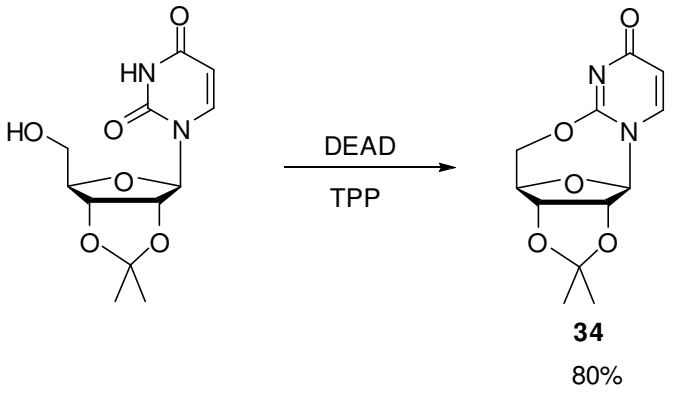
The study was published by Oyo Mitsunubo in 1967. This was the reaction of n-valeric acid with ally diethyl phosphate and DEAD to produce allyl valerate **32** and diethyl *N*-(diethyl)phosphoryl hydrazodicarboxylate **33** (Scheme 13) [14].



Scheme 13. First example of Mitsunobu reaction

Moreover, after the reaction named, other important developments also reported by Mitsunobu such as;

- to get efficient results with sterically hindered alcohols, 4-nitrobenzoic acid(4-NBA) was used [49],
- in order to synthesize amines from alcohols, phthalimide was used as an acid/ pronucleophile coupling component [50, 51],
- the intramolecular versions of the Mitsunobu reaction was developed [52], (Scheme 14) [53],
- the selectivity studies prove the primary alcohol center over the secondary in a diol [54],
- the activated methylene groups used as carbon acids [55].



34

80%

Scheme 14. Intramolecular Mitsunobu Reaction

Additionally, the conversion of thioureas into carbodiimides [56, 57], thioamides into ketenimines [58] and thiols into disulfides [59] were investigated with combination of DEAD and TPP by Mitsunobu.

1.4.1 Mechanism

Even though the Mitsunobu reaction has widespread usage in synthetic organic chemistry and the mechanistic details have been widely studied by variety of methods, it is still a subject of debate and intensive studies [60- 75]. The generally accepted mechanism with DEAD and TPP is represented by considering all experimentally observed outcomes in Figure 7 [75].

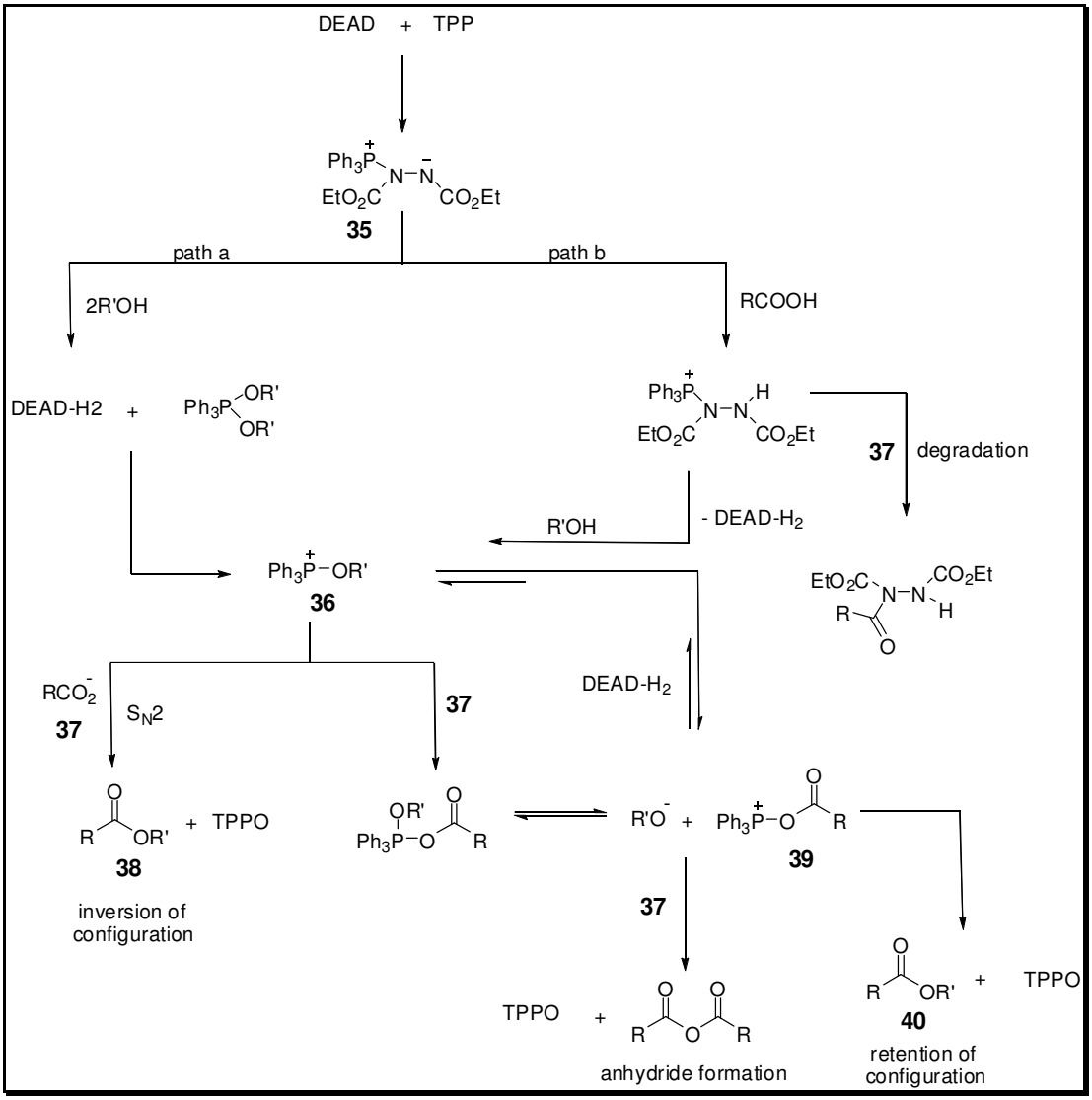


Figure 7. Mechanism of Mitsunobu reaction

In the first step, nucleophilic addition of TPP to DEAD forms the Morrison–Brunn–Huisgen betaine, **35**, [76-78]. This intermediate can then either follow the path **a** by reacting with two molecules of the alcohol to produce eventually DEAD-H_2, alkoxyphosponium species **36**, and carboxylate/ nucleophile **37**, or the path **b** by deprotonation of the acid/pronucleophile to form eventually, again, DEAD-H_2, **36**, and **37**. The product **38** has inverted stereochemistry relative

to the alcohol starting material. Besides, it was shown that **36** is in equilibrium with the corresponding acyloxyphosphonium species **39**, [63, 65, 67] and in rare cases, **39** constitute the product **40**, which retains the stereochemistry of the alcohol, and an anhydride. In addition, there is a proposed mechanism [70], which supported by experimental evidences [74,75], shows difference in first step. In this case, **39** is formed first and then converted into **36**. For example, the conversion of **39** to **36** is restricted in sterically hindered cases. This explains when steriacally hindered secondary alcohols are used as reaction substrates, they can form the product **40**, which retains configuration [79-81]. On the other hand, in general, the product **38** is favored in large extent and inversion of stereochemistry is observed. However, the formation of product **40** is very rare where retention of configuration is observed.

1.4.2 Modified Reagents and Procedures

The developments of the procedures and alternative reagents have been proceeding since the discovery of the Mitsunobu reaction. The significant drawback of this reaction is that, this reaction requires three reagents and starting materials, which are an alcohol, an acid/pro-nucleophile, a phosphine, and an azo reagent, in stoichiometric quantities thus, the isolation of the desired product is very difficult because of the excess starting materials and reagents and the reaction byproducts. Consequently, wide ranges of modified reagents and separation techniques have been developed in order to facilitate the isolation of the desired products [48]. For instance, Curran and co-workers reported a modified azo reagents such as, **41** and **42,** bis(1-adamantylmethyl) azodicarboxylate and bis(2-(1-adamantyl)ethyl) azodicarboxylate, respectively. These cyclodextrin-binding azo reagents have longer retention times on silica gel than typical Mitsunobu reaction products which facilitate the separation of desired product from the azo reagents and their byproducts (Figure 8) [82].

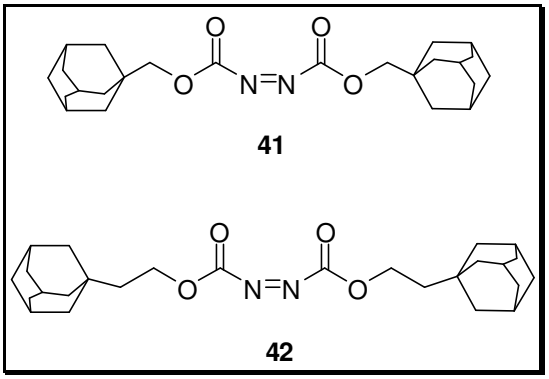
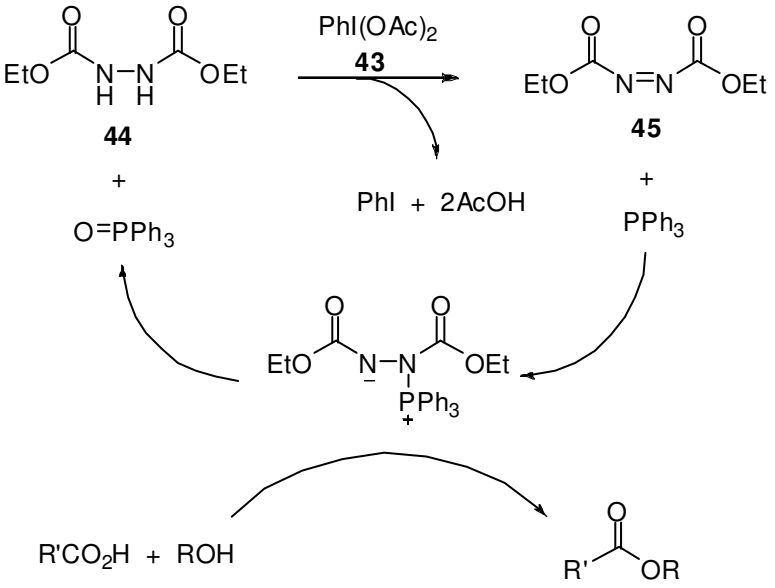


Figure 8. Azo reagents tagged with cyclodextrin-binding groups.

After the investigation of new azo reagents, the following approach is the phosphonium salts, which were used instead of triphenylphosphine to control reagent solubility and facilitate product isolation. For example, tetraarylphosphonium perchlorate and hexafluorophosphate salts are precipitate in polar solvents, which lead filtration to acquire pure product [83].

Furthermore, the significant development was achieved by Toy and co-workers as an organocatalytic Mitsunobu reaction. In this study, iodosobenzene diacetate **43** was converted the 1,2-dicarbethoxyhydrazine **44** into diethyl azodicarboxylate **45**. Thus, using **43** as the stoichiometric oxidant in Mitsunobu reactions, allow **45** to be used as a catalyst. In this study also some other azo reagents are examined to use in catalytic amount such as; (*Z*)-diiso propyldiazene-1,2-dicarboxylate, (*Z*)-diazene-1,2-diylbis(piperidin–1-ylmethanone) (Scheme 15). Whereas the former one is less expensive and easier to handle and the latter one has a wider range of use than **45**, in both reagents the yields of desired products are lower than the yields which are obtained with **45** [16].

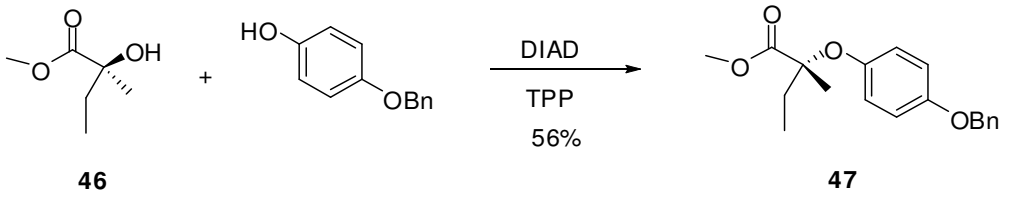


Scheme 15. Catalytic cycle of a Mitsunobu reaction

Eventually, the hypervalent iodine species are used as a stoichiometric oxidant, which leads to use azo reagents in catalytic amount. Besides, there is another advantage that the byproducts, iodobenzene and acetic acid, are easily removed [16].

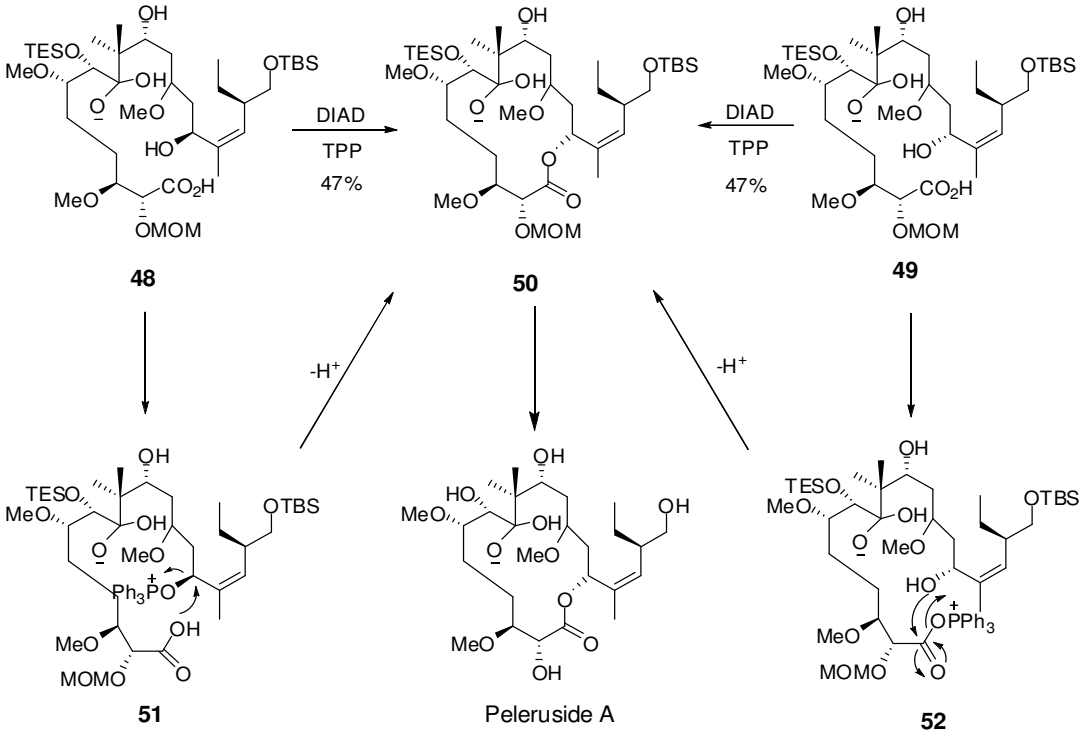
1.4.3 Synthetic Applications

The Mitsunobu reaction is widely used in organic synthesis because of its scope, stereospecifity and mild reaction conditions. In this reaction the stereochemical configuration of the products depends on the sterical environments of the alcohols. For instance, the reaction of ester- group- activated chiral tertiary alcohol **46** with phenols in the presence of TPP and DIAD forms the aryl alkyl ether **47** with inversion of configuration (Scheme 16) [84]. Besides, this was the first example of the S_N2 displacement of tertiary alcohols with phenols in Mitsunobu reaction.



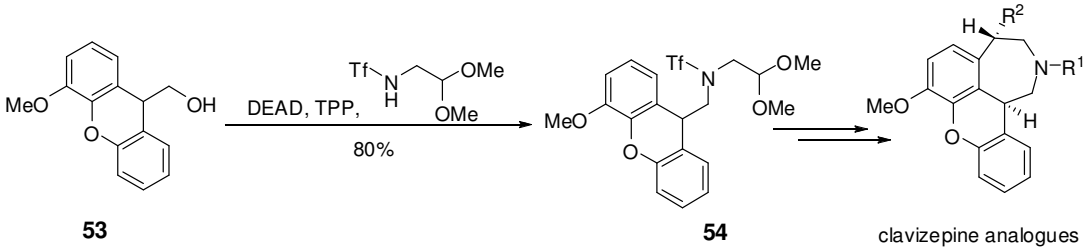
Scheme 16. Inversion of tertiary-alcohol stereochemistry

During the synthesis of naturally occurring compound Peleruside A which stabilizes microtubules and inhibits mitosis, two diastereomeric advanced intermediates, **48** and **49**, afforded the same lactone product **50** under the Mitsunobu reaction conditions (Scheme 17). This unexpected formation predicted that the intermediate **48** must form the alkoxyphosphonium intermediate **51** whereas **49** must form acyloxyphosphonium intermediate **52** to observe the product **50** [81].



Scheme 17. Synthesis of peloruside A

Furthermore, the syntheses of clavizepine analogues were reported by Dominguez and co-workers. They used an *N*-trifluoromethanesulfonamide pronucleophile to form an amine group (Scheme 18). Thus, the desired product **54** was synthesized by hydroxymethylxanthene **53** which was reacted with *N*-(dimethoxyethyl) trifluoromethanesulfonamide under standard Mitsunobu reaction conditions [85].



Scheme 18. Synthesis of clavizepine analogues

In conclusion, the Mitsunobu reaction has been versatile and applicable for a variety of organic synthesis. Since it was first reported in 1967, the developments of the reaction have been proceeded. The large numbers of modified reagents and new separation techniques have been still investigated for more atom economical and greener Mitsunobu reaction.

1.5 Aim of the Work

The aim of the work is to synthesize 2-heteroaryl substituted chiral fused cyclopenta[*c*]pyridinone derivatives *via* Pauson-Khand reaction (Figure 9). The studies on the conformational control effect of homoallyl and homopropargyl enyne systems have been done in our group [46, 86]. In these studies, complete remote stereochemical control on the newly created stereogenic centers and thus, the excellent diasteroselectivities were observed. We have chosen the heteroaryl substituted homoallyl and homopropargyl systems as the starting compounds and

planned to introduce chirality by appliying kinetic resolution with enzymes. Subsequent, propargyl and allyl amine substitution *via* S_N2 or Mitsunobu type reactions might afford the feasible *N*-containing enyne tethered system for intramolecular Pauson-Khand reactions by $Co_2(CO)_8$. During the course of all syntheses, we have considered "*Green chemistry*" approach in terms of atom economy, E- factor, asymmetric synthesis, Mitsunobu reaction and Pauson-Khand reaction.

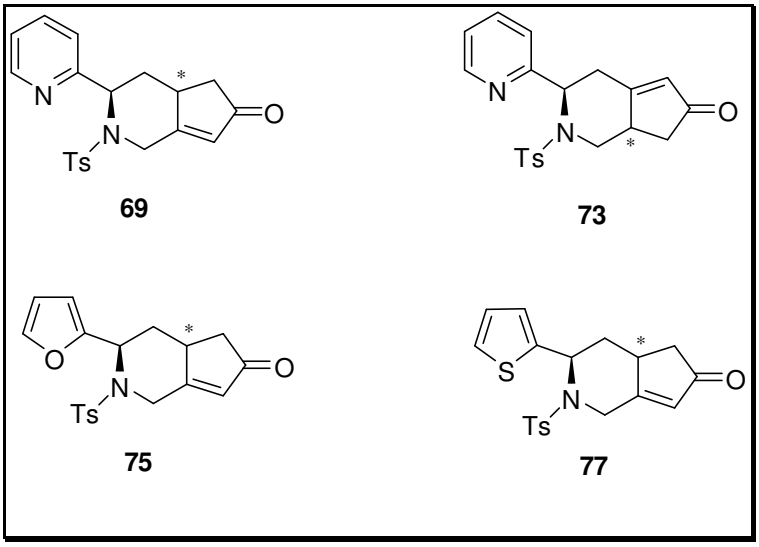


Figure 9. Target molecules

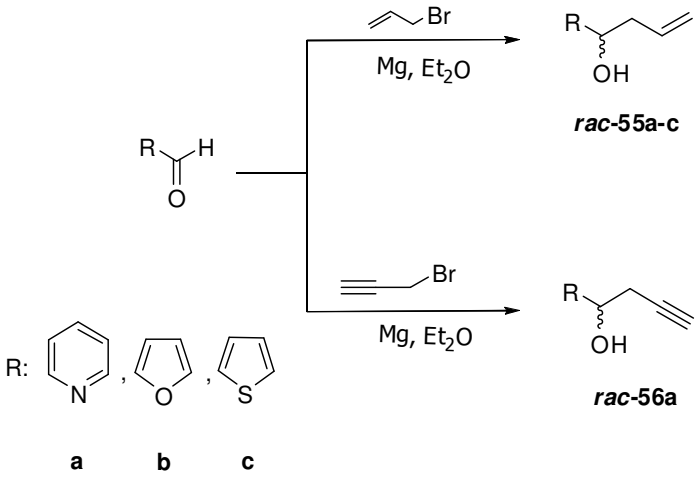
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Racemic Homoallylic and Homopropargylic Alcohols

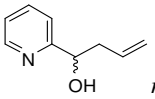
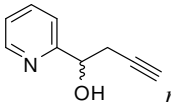
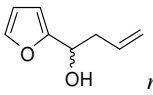
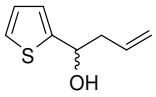
Homoallylic and homopropargylic alcohols are being used in the synthesis of various natural products and biologically active compounds such as; alkaloids, micro antibiotics etc. The addition of various homoallyl- and homopropargylmetal reagents to aldehydes is an important and useful synthetic method for the synthesis of secondary alcohols [88].

The first part of the thesis involves the synthesis of racemic homoallylic and homopropargylic alcohols *via* Grignard reaction. The commercially available 2-heteroaryl substituted carbaldehydes were chosen as the starting compound. The reaction of the carbaldehydes with the in situ prepared Grignard reagents, allylmagnesiumbromide and propargylmagnesiumbromide, afforded racemic homoallylic and homopropargylic alcohols, respectively in dry ether under argon atmosphere (Scheme 19). All the results are summarized in Table 1.



Scheme 19. Synthesis of heteroaryl substituted homoallylic and homopropargylic alcohol

Table 1. Results of heteroaryl substituted homoallylic and homopropargylic alcohols

Substrate	Product	Time(h)	Yield (%)
Pyridine-2-carbaldehyde	 *rac*-**55a**	8	78
Pyridine-2-carbaldehyde	 *rac*-**56a**	12	77
Furan-2-carbaldehyde	 *rac*-**55b**	12	84
Thiophene-2-carbaldehyde	 *rac*-**55c**	7	80

The characterization of all racemic alcohols was done by ^{1}H and ^{13}C NMR spectroscopy and the spectra are given in Appendix part as Figure A1-A8. The spectra of all compounds are in accordance with the literature data [45].

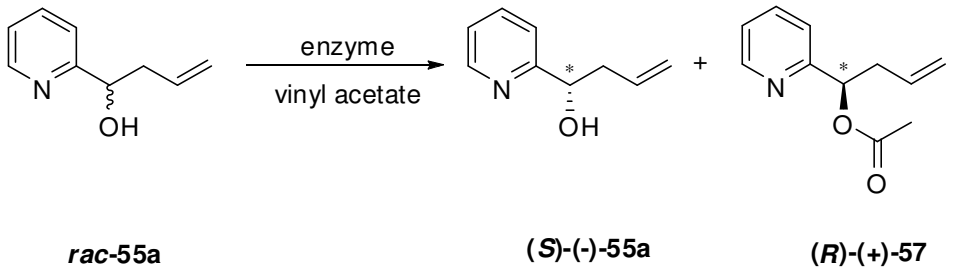
2.2 Enzymatic Resolution of Racemic Homoallylic and Homopropargylic Alcohols

Depending upon our goal, in order to synthesize the enantiomerically enriched target molecules, the racemic homoallyl and homopropargyl alcohols already synthesized were subjected to enzymatic resolution by various lipases. Among the lipases studied PS-C II, Lipozym and Novazym 435 gave the best results.

During the resolution of the substrates, the best enzyme:substrate ratio was determined as weight:weight ratio. All the resolves enantiomerically enriched alcohols possesed (*S*) configuration which was determined by comparing their α values with the literature data [45].

2.2.1 Enzymatic Resolution of *rac*- 1-(Pyridin-2-yl)but-3-en-1-ol, *rac*-55a

The resolution of *rac*-**55a** was tested with PS-C II, Lipozyme and Novazyme 435 and monitored by TLC controlling. The reaction was ended when the conversion of alcohol to acetyl became approximately 50% (Scheme 20).



***rac*-55a** **(*S*)-(-)-55a** **(*R*)-(+)-57**

Scheme 20. Enzymatic resolution of *rac*-1-(pyridin-2-yl)but-3-en-1-ol, *rac*-**55a**

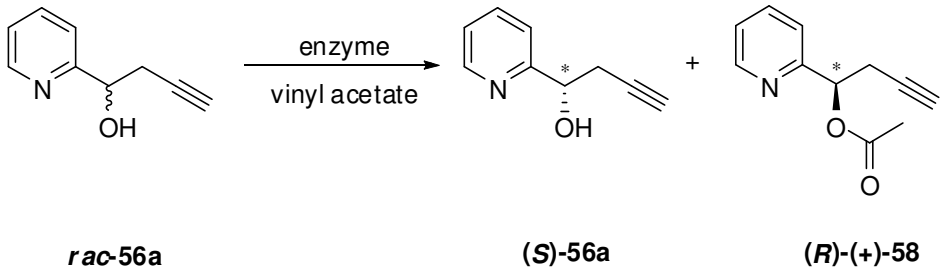
The enantiomeric excesses (ee) of *rac*-**55a** homoallyl alcohol were detected by HPLC with OJ-H chiral column and the results are given in Table 2. The highest ee value obtained with PS-C II lipase as 98% ee. Although the lipozym also have acceptable ee, the reaction time was longer than PS-C II. Since the conversion of the alcohol is very low with Novazyme 435, the ee value was not determined.

Table 2. Enzymatic resolution of *rac*-**55a**

Substrate	Enzyme	Time(h)	Temp.(^{0}C)	Conv.(%)	E.e(%)	Co-solvent
***rac*-55a**	PS-C II	24	24	55	98	THF
***rac*-55a**	Lipozyme	49	31	51	85	DPE
***rac*-55a**	Novazyme 435	72	30	<20	n.d.	-

2.2.2 Enzymatic Resolution of *rac*-1-(Pyridin-2-yl)but-3-yn-1-ol, *rac*-56a

Racemic homopropargylic alcohol *rac*-**56a** was resolved with PS-C II and Lipozyme (Scheme 21). During the resolution, THF and DPE were used as the best co-solvents for PS-C II and Lipozyme, respectively.



***rac*-56a** **(*S*)-56a** **(*R*)-(+)-58**

Scheme 21. Enzymatic resolution of *rac*-1-(pyridin-2-yl)but-3-yn-1-ol, *rac*-**56a**

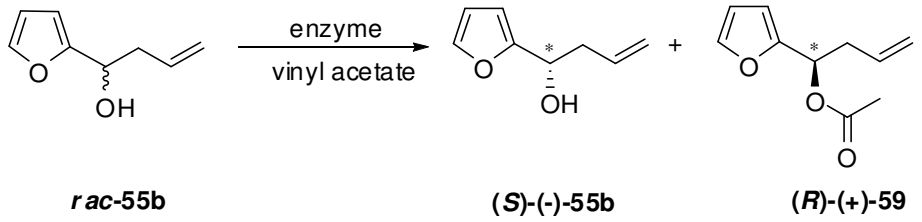
In the resolution of *rac*-**56a**, although both PS-C II and Lipozym afforded ee values as 99% and 98%, respectively, the short resolution duration of PS-C II became it preferable over Lipozym. The results are summarized in Table 3.

Table 3. Enzymatic resolution of *rac*-**56a**

Substrate	Enzyme	Time(h)	Temp.(^{0}C)	Conv.(%)	E.e(%)	Co-solvent
***rac*-56a**	PS-C II	27	24	52	99	THF
***rac*-56a**	Lipozyme	43	30	51	98	DPE

2.2.3 Enzymatic Resolution of *rac*-1-(Furan-2-yl)but-3-en-1-ol, *rac*-55b

PS-C II, Lipozyme and Novazyme 435 were the lipases used in enzymatic resolution of *rac*-**55b** (Scheme 22). In each case, highly efficient resolution of alcohol was observed with high ee values varied from 93% to 99% as shown in Table 4.



***rac*-55b** **(*S*)-(-)-55b** **(*R*)-(+)-59**

Scheme 22. Enzymatic resolution of *rac*-1-(furan-2-yl)but-3-en-1-ol, *rac*-**55b**

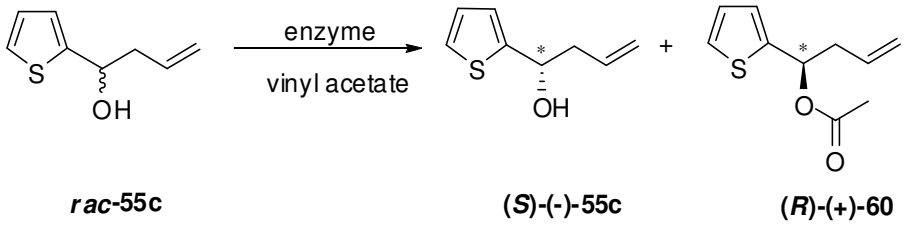
Table 4. Enzymatic resolution of *rac*-**55b**

Substrate	Enzyme	Time(h)	Temp.(^{0}C)	Conv.(%)	E.e.(%)	*Co-solvent*
***rac*-55b**	PS-C II	4	24	55	99	THF
***rac*-55b**	Lipozyme	15.5	27	60	99	DPE
***rac*-55b**	Novazyme 435	4	24	52	93	THF

For the resolution process, THF was used as co-solvent for PS-C II and Novazym 435 whereas DPE were used for Lipozym. Despite of the fact that all reactions were performed almost at the same temperature, Lipozyme required longer reaction times than the other enzymes for the high ee value. Thus, enantiomeric excess values were determined by using HPLC with OJ-H chiral column for the (*S*)-(-)-**55b** (Figure A67,A68).

2.2.4 Enzymatic Resolution of *rac*-1-(thiophen-2-yl)but-3-en-1-ol, *rac*-55c

During the resolution of *rac*-**55c**, PS-C II amona and Lipozym lipases afforded the best results. Enantiomeric excess values were 99% and 95% for the PS-C II and Lipozym, respectively.



Scheme 23. Enzymatic resolution of *rac*-1-(thiophen-2-yl)but-3-en-1-ol, ***rac*-55c**

As distrinct from the other 2-heteroaryl substituted alcohols, *rac*-**55c** gives higher ee value with Lipozyme rather than PS-C II (Table 5). The enantiomeric excess values were determined by using HPLC with OJ-H chiral column for the (*S*)-(-)-**55c** (Figure A69,A70).

Table 5. Enzymatic resolution of ***rac*-55c**

Substrate	Enzyme	Time(h)	Temp.(^{0}C)	Conv.(%)	E.e(%)	Co-solvent
***rac*-55c**	PS-C II	20	24	56	95	THF
***rac*-55c**	Lipozyme	27	26	54	99	DPE

2.3 Synthesis of 2-Pyridine Substituted Chiral Fused Cyclopenta[*c*] pyridinone Derivatives

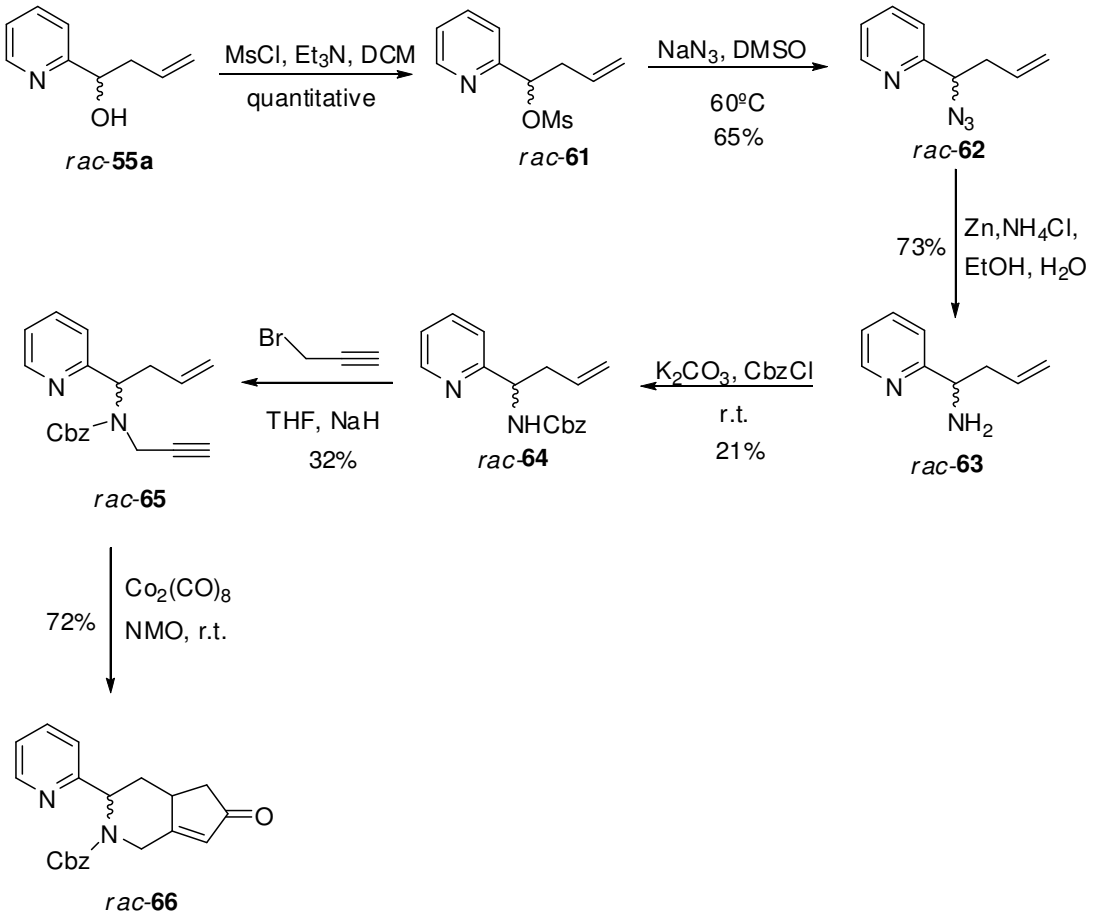
2.3.1 Synthesis of *r*ac- 3-(Pyridin-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclo penta[*c*]pyridin-6(2*H*)-one, *rac*-66

In the synthesis of pyridine substituted tetrahydro-1*H*-cyclopenta[*c*] pyridinone derivative **66**, two different synthetic pathways were followed. Since the cost of enantiomerically enriched homoallyl alcohol (*S*)-(-)-**55a** is high, all the

syntheses were carried out by *rac*-**55a**. The synthetic pathyway followed in the first part is shown in Scheme 24.

2.3.1.1 The first pathway

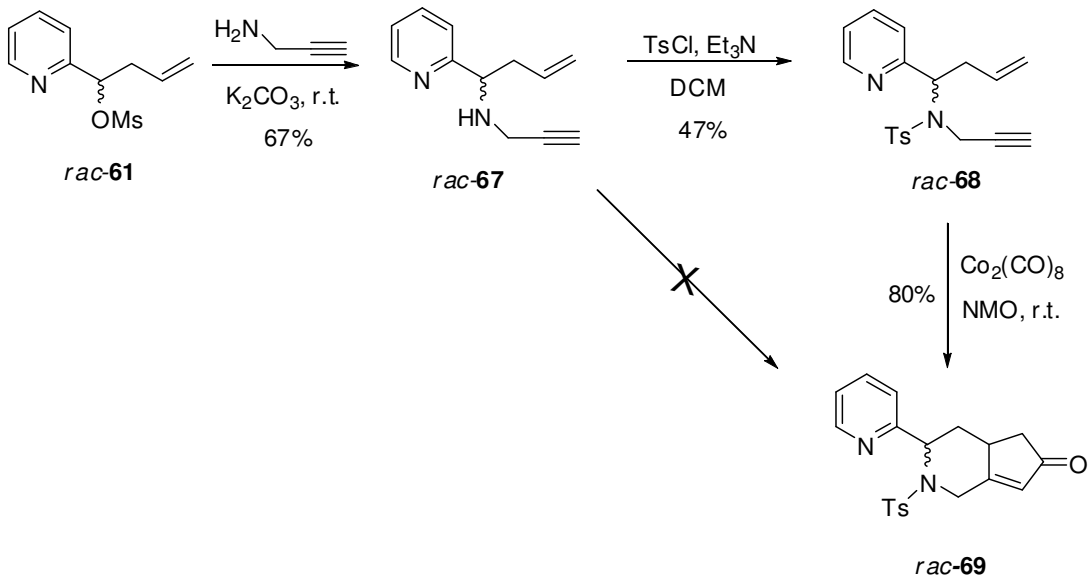
Homoallyl alcohol, *rac*-**55a** was quantitatively transformed to mesylate derivative *rac*-**61** to activate the C-O bond. In order to introduce nitrogen unit, sodium azide was chosen as the feasible reagent and as a result of substitution reaction azide derivative was isolated with 65% yield and characterized by NMR and IR. The reduction of homoallylic azide *rac*-**62** gave homoallylic amine *rac*-**63** in 73% chemical yield. Although the yields were acceptable until the amine protection step, the reaction of amine derivative *rac*-**63** with CbzCl afforded *rac*-**64** with poor chemical yield (21%). Subsequently, *rac*-**64** was propargylated under the condition given in Scheme 24. Unfortunately, the yield for that step was again low (32%). Consequently, enyne tethered system *rac*-**65** was subjected to intramolecular PKR and afforded the target compound *rac*-**66** in 72% chemical yield. Since the overall yield of this synthetic pathway was low and it was also having 7 steps, it was not preferable for our goal.



Scheme 24. Synthetic pathway of the first procedure

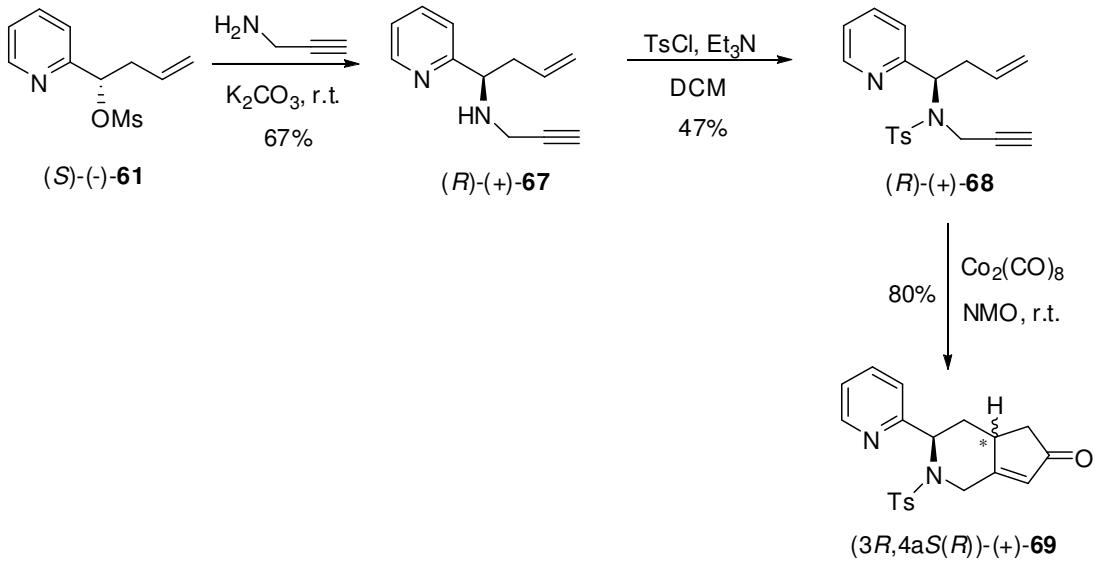
2.3.1.2 The second pathway

In the alternative synthetic pathway of target compound *rac*-**69**, the mesylate derivative *rac*-**61** was reacted with commercially available propargyl amine and K_2CO_3 in solvent free condition and afforded enyne tethered system *rac*-**67** in 67% yield which was subjected to intramolecular PKR without any purification (Scheme 25). Unfortunately, it did not afford any product. This can be presumably due to the coordination of transition metal complex $Co_2(CO)_8$ to the nitrogen. In order to overcome this problem, compound *rac*-**67** was protected with tosyl group. Consequently, *N*-tosyl protected enyne tethered system *rac*-**68** afforded the target cyclopenta[*c*]pyridinone *rac*-**69** in 80% chemical yield.



Scheme 25. Synthetic pathway of the second procedure

Depending upon the results obtained so far, stereoselective synthesis of pyridine substituted cyclopenta[*c*]pyridinone (3*R*,4a*S*(*R*))-(+)-**69** was performed by following the second pathway due to its high applicability over the first pathway (Scheme 26).



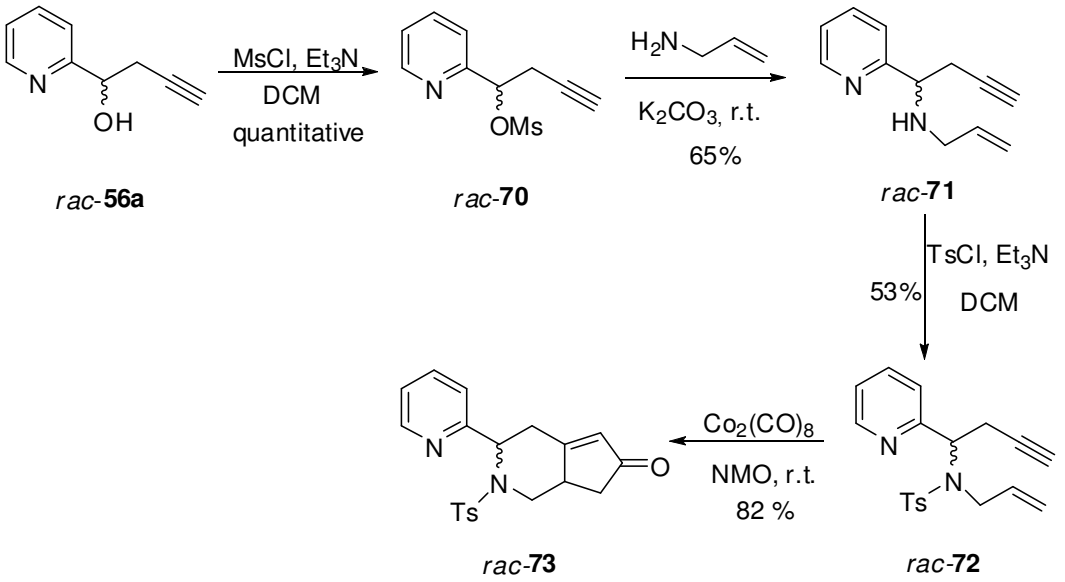
Scheme 26. Synthesis of (3*R*,4a*S*(*R*))-(+)-**69**

The first step of stereoselective synthetic route involved S_N2 type substitution of propargyl amine with mesylate group. As a result of this substitution, the absolute configuration of chiral center must be inverted from (*S*) to (*R*). Subsequent protection with tosyl group and followed by intramolecular Pauson-Khand reaction afforded (3*R*,4a*S*(*R*))-(+)-**69** as a sole diastereomer. By considering the absolute configuration of the *diast*-(+)-**69**, the compound possesses two chiral centers. The first one having direct *N*-attached unit is known, since it was originated from starting compound (*S*)-(-)-**61** which was inverted to (*R*) configuration as a result of S_N2 type reaction. Although the second newly generated chiral center absolute configuration is unknown, it can be estimated as (*S*) configuration by using the results already obtained in our group with heteroaryl substituted chiral cyclopenta[*c*]pyran derivatives [46,86]. In these studies, it was proved that pyran ring has conformational control on remote streogenic center in the intramolecular Pauson-Khand reactions and the absolute configurations were determined by X-ray analyses.

The structure determination of (3*R*,4a*S*(*R*)-(+)-**69** was done by ^{1}H, ^{13}C NMR and also with full analysis including DEPT, COSY, HSQC and HMBC (Figure A29-A35). The olefinic proton of the (3*R*,4a*S*(*R*)-(+)-**69** resonates at 5.79 ppm as a singlet. The characteristic ketone carbonyl signal was observed at 205.7 ppm in ^{13}C NMR. Chiral center methine carbons, nitrogen unit attached and at the fused position give ^{13}C signals at 55.6 ppm and 33.9 ppm, respectively, supported by DEPT-90. Three methylene carbons, next to the nitrogen, next to the carbonyl unit and between the chiral centers resonate at 42.8, 40.5 and 32.9 ppm, respectively, indicated by DEPT-135. By using HSQC spectrum, it was indicated that pyridine unit attached chiral center gives the signal at 5.26 ppm as doublet whereas another chiral center possesses the signal between 2.97-3.00 ppm as multiplet. Actually it would be expected doublet of doublet for the first chiral center. However, COSY spectrum shows the interaction of the chiral position proton with just one of the neighboring diastereotopic protons. The position of three different sets of diastereotopic methylene protons was also determined by HSQC.

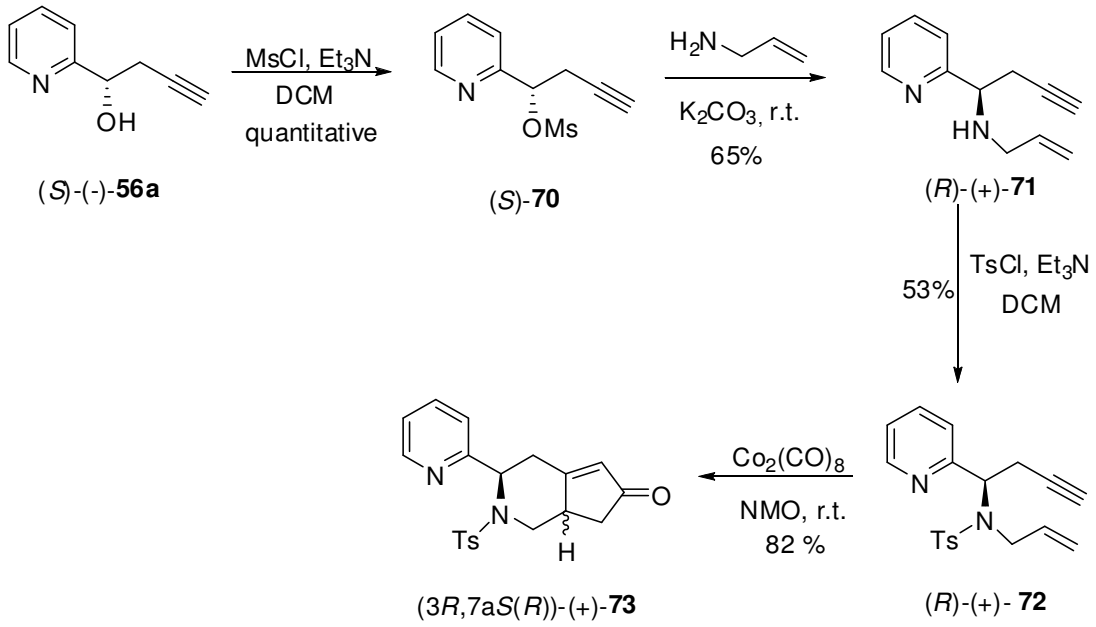
2.3.2 Synthesis of *rac*-3-(pyridin-2-yl)-2-tosyl-3,4,7,7a-tetrahydro-1*H*-cyclopenta [*c*]pyridin-6(2*H*)-one, *rac*-73

Related to the results obtained from the previous part, the second pathway was also applied to the synthesis of *rac*-**73**. The first attempt was done by using the racemic substrate (Scheme 27).



Scheme 27. Synthetic pathway of *rac*-**73**

The pyridine substituted homopropargyl alcohol *rac*-**56a** was transformed the corresponding mesylated product *rac*-**70** in quantitative yields. For the construction of the enyne tethered backbone, *rac*-**70** was reacted with allyl amine and K_2CO_3, followed by the protection of *N*-unit with tosyl group. The intramolecular Pauson-Khand reaction was again applied to get *rac*-pyridine substituted cyclopenta[*c*]pyridinone *rac*-**73** in 82% chemical yield. After the optimization of reaction conditions in the racemic synthesis, the stereoselective synthesis of (3*R*, 7a*S*(*R*))-(+)-**73** was achieved by starting with highly enantiomerically enriched (*S*)-(-)-**56a** (Scheme 28). In the first step, there was no change in the absolute configuration of *O*-mesylated compound whereas as a result of S_N2 type substitution absolute configuration of enyne tethered compound (*R*)-(+)-**71** was inverted. Depending upon the results as discussed in the absolute configuration determination of (3*R*,4a*S*(*R*)-(+)-**69**[46,86], the absolute configuration of the newly generated chiral center could be estimated as (*S*).



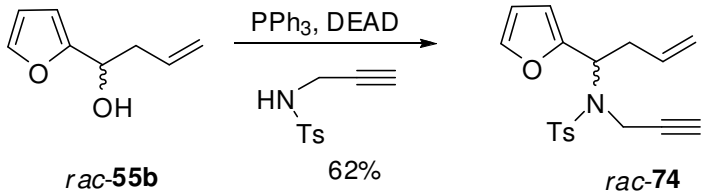
Scheme 28. Synthesis of (3*R*,7a*S*(*R*))-(+)-**73**

The structure elucidation was done by ^{1}H and ^{13}C NMR spectroscopy (Figure A40,A41). The olefinic proton of the (3*R*,7a*S*(*R*))-(+)-**73** was observed at 5.80 ppm as a singlet. The characteristic ketone carbonyl signal resonates at 206.6 ppm in ^{13}C NMR. Besides, the structure elucidation was strongly supported by full analysis results including DEPT, COSY, HSQC and HMBC (Figure A42-A46).

2.4 Synthesis of 2-Furyl Substituted Chiral Fused Cyclopenta[*c*]pyridinone Derivative

The synthesis of 2-furyl substituted chiral fused cyclopenta[*c*]pyridinone derivative was started with 2-furyl substituted homoallyl alcohol *rac*-**55b** by following the conditions found in pyridinyl substituted systems. In the first step, *rac*-**55b** was tried to be mesylated with MsCl in the presence of Et_3N in DCM at room temperature. However, we could not observe any 1-(furan-2-yl)but-3-enyl methanesulfonate product**.** Then NaOH and pyridine was separately used instead of

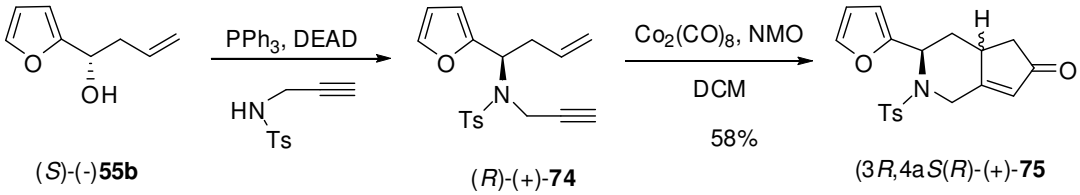
Et_3N. Unfortunately, again the desired compound was not observed. For a last trial the tosylation reaction was applied instead of mesylation. However, the results were failure. We changed the synthetic strategy and planned to apply the modificated Mitsunobu reaction. Firstly, propargyl amine was protected with TsCl in H_2O with 92% chemical yield and then subjected to Mitsunobu reaction with racemic furyl substituted homoallylic alcohol *rac*-**55b** in the presence of PPh_3 and DEAD in dry THF. The resultant enyne tethered compound *rac*-**74** was isolated in 62% yield (Scheme 29).



rac-**55b** *rac*-**74**

Scheme 29. Mitsunobu application for the synthesis of *rac*-**74**

The promising result obtained in Mitsunobu reaction was applied to the synthesis of furyl substituted cyclopenta[*c*]pyridinone derivative **75** in a stereoselective manner. (*S*)-(-)-**55b** already resolved by Lipozym lipases was subjected to Mitsunobu reaction with *N*-tosyl protected propargyl amine followed by intramolecular Pauson-Khand reaction to afford (3*R*,4a*S*(*R*))-(+)-3-(furan-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[*c*]pyridin-6(2*H*)-one-**75** in 58% chemical yield (Scheme 30).



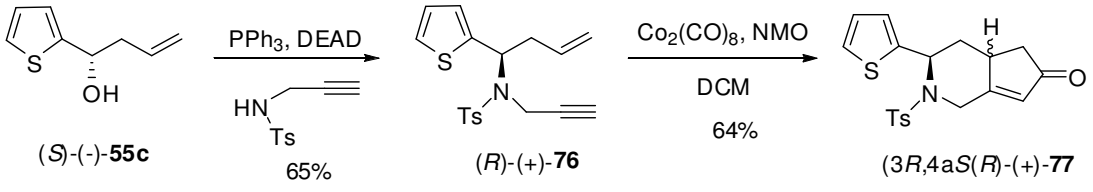
(*S*)-(-)**55b** (*R*)-(+)-**74** (3*R*,4a*S*(*R*)-(+)-**75**

Scheme 30. Synthesis of (3*R*,4a*S*(*R*))-(+)-**75**

The structure determination was done by ^{1}H and ^{13}C NMR and the full analysis, DEPT, COSY, HSQC and HMBC, spectroscopy (Figure A51-A57). The olefinic proton of the (3*R*, 4a*S*(*R*)-(+)-**75** was detected at 5.86 ppm as a singlet in ^{1}H and the specific ketone carbonyl signal was observed at 205.3 ppm in ^{13}C NMR.

2.5 Synthesis of 2-Thiophene Substituted Chiral Fused Cyclopenta[c] pyridineone Derivative

Depending upon the results found in (3*R*,4a*S*(*R*)-(+)-**75** synthesis, target compound thiophene substituted fused cyclopenta[*c*]pyridinone **77** was synthesized with the same applied procedure. By starting with the enantiomerically enriched thiophene substituted homoallyl alcohol (*S*)-(-)-**55c**, compound (3*R*,4a*S*(*R*)-(+)-**77** was afforded in 64% chemical yield *via* intramolecular Pauson-Khand reaction (Scheme 31).



(*S*)-(-)-**55c** (*R*)-(+)-**76** (3*R*,4a*S*(*R*)-(+)-**77**

Scheme 31. Synthesis of (3*R*,4a*S*(*R*)-(+)-**77**

The structure elucidation was done by ^{1}H and ^{13}C NMR and the full analysis, DEPT, COSY, HSQC and HMBC, spectroscopy (Figure A60-A). The olefinic proton resonates at 5.82 ppm as a singlet signal and the characteristic ketone carbonyl is observed at 206.2 ppm in ^{1}H and ^{13}C NMR, respectively.

CHAPTER 3

CONCLUSION

In conclusion, four 2-heteroaryl substituted chiral fused cyclopenta[*c*]pyridinone derivatives were successfully synthesized. Homoallylic and homopropargylic alcohols were chosen as the best structural component for the target molecules. Since they all gave the positive responses to the enzymatic resolution applications and also had unsaturation on the backbone which is the feasible structural unit for Pauson-Khand reactions. All racemic homoallylic and homopropargylic alcohols were resolved in >95 % ee as (*S*)-(-) alcohols and the absolute configurations were determined by comparing with the literature data. In order to construct the enyne unit on the backbone, we have applied three different approaches. One of these was the direct S_N2 type substitution of allyl or propargyl amine with the C-O bond activated with mesyl unit. The second one was the modified Mitsunobu procedure. In both cases, the configuration of the chiral center was inverted. In the final part, higly enantiomerically enriched enyne systems were subjected to intramolecular Pauson-Khand reaction and all afforded single diastereomer indicated by NMR. This result may show the effect of conformation on the remote stereochemistry control otherwise we must observe more than one diastereomer. The estimated absolute configuration will be determined by NOE analysis. The chemoenzymatic applications done with biocatalysis (lipases), and the Pauson-Khand reaction are involved in "*Green Chemistry*" approach.

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 is used as internal standard; the ^{1}H-NMR data are presented in the order value of the signal, peak multiplicity (abbreviations are mentioned as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and coupling constants in Hertz (Hz) integrated number of protons.^{13}C-NMR spectra were measured at 100 MHz and the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

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

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

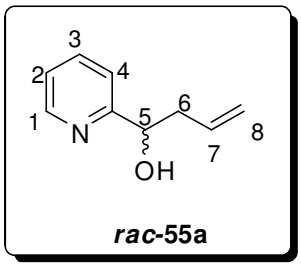
Flash column chromatography was employed using thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck Silica Gel PF-254), visualized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

anisaldehyde. The relative portions of solvents are in volume:volume ratio used in column chromatography as eluent.

4.1 General Procedure for Synthesis of Racemic Homoallylic and Homo propargylic Alcohols, *rac*-55a-c and *rac*-56a

To a stirred solution of Mg turnings (39 mmol) and a few crystals of iodine in dry diethyl ether (10 mL) at room temperature was added dropwise a mixture of allylbromide (31 mmol) and propargylbromide (33 mmol) in anhydrous diethyl ether (5mL) and a vigorous reflux was observed. The mixture was allowed to reflux 30 min. and 1h for homoallyl alcohols and homopropargyl alcohols, respectively.Then, the mixture was cooled down to 0℃ in an ice bath to add heteroaryl-2-carbaldehyde (26mmol) in dry diethyl ether (5mL). The reaction mixture was stirred at rooom temperature and ended by TLC monitoring. The mixture was hydrolyzed with 1 N HCl (5 mL) and saturated NH_4Cl (15 mL) solutions and the resulting mixture was extracted with diethyl ether (3x30 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude products *rac*-**55a-c** and *rac*-**56a** were purified by flash column chromatography using mixtures of ethyl acetate and hexane 3:1 for *rac*-**55a** and *rac*-**56a**, 2:1 for *rac*-**55b** and 1:6 for *rac*-**55c**.

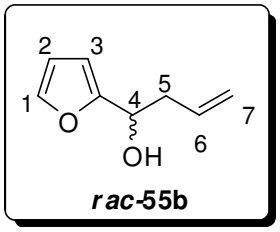
4.1.1 *rac*-1-(Pyridin-2-yl)but-3-en-1-ol, *rac*-55a



***rac*-55a**

Yellow oil (78% yield). ^{1}H-NMR: δ 8.40-8.41 (m, 1H, H_1), 7.57 (t, 1H, J = 7.6 Hz, H_3), 7.22 (d, 1H, J = 7.8 Hz, H_4), 7.06- 7.09 (m, 1H, H_2), 5.67-5.77 (m, 1H, H_7), 4.96- 5.01 (m, 2H, H_8), 4.68-4.71 (m, 1H, H_5), 4.41 (brs, 1H, O*H*) , 2.35- 2.56 (m, 2H, H_6). ^{13}C-NMR: δ 162.0, 148.4, 136.6, 134.4, 122.3, 120.6, 118.0, 72.6, 43.0. (Figure A1, A2)

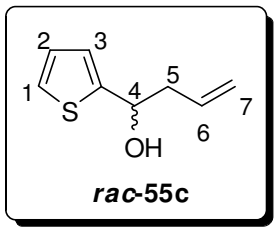
4.1.2 *rac*-1-(Furan-2-yl)but-3-en-1-ol, *rac*-55b



***rac*-55b**

Yellowish oil (84% yield). ^{1}H-NMR: δ 7.22 (d, 1H, J= 0.9 Hz, H_1), 6.18-6.19 (m, 1H, H_2), 6.09 (d, 1H, J= 3.2 Hz, H_3), 5.65 (dddd, 1H, J= 17.2, 14.1, 10.2 and 7.0 Hz, H_6), 4.96-5.03 (m, 2H, H_7), 4.56 (t, 1H, J= 6.6 Hz, H_4), 2.96 (brs, 1H, O*H*), 2.41-2.52 (m, 2H, H_5). ^{13}C-NMR: δ 155.9, 141.3, 133.5, 117.6, 109.7, 105.6, 66.5, 39.6. (Figure A3,A4)

4.1.3 *rac*-1-(Thiophen-2-yl)but-3-en-1-ol, *rac*-55c

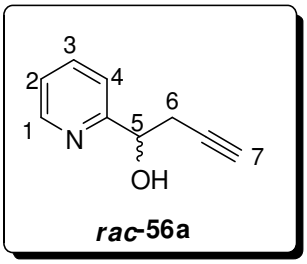


***rac*-55c**

Yellowish oil (80% yield). ^{1}H-NMR: δ 7.12 (t, 1H, J= 3.1 Hz, H_1), 6.84 (d, 2H, J= 3.4 Hz, H_2 and H_3), 5.71 (dddd, 1H, J= 17.2, 14.1, 10.2 and 7.0 Hz, H_6), 5.02-5.08

(m, 2H, H_7), 4.81- .85 (m, 1H, H_4), 2.49 (t, 2H, J= 6.7 Hz, H_5), 2.44 (brs, 1H, OH). ^{13}C-NMR: δ 147.9, 133.9, 126.5, 124.4, 123.6, 118.6,69.4, 43.7. (Figure A5, A6)

4.1.4 *rac*-1-(Pyridin-2-yl)but-3-yn-1-ol, *rac*-56a



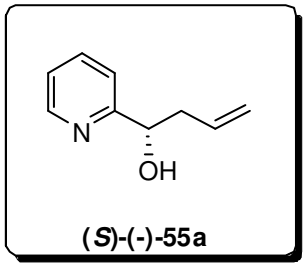
***rac*-56a**

Brown oil (77% yield). ^{1}H-NMR: δ 8.48 (d, 1H, J= 4.7 Hz, H_1), 7.63 (td, 1H, J= 1.7 and 7.6 Hz, H_3), 7.35 (d, 1H, J= 7.8 Hz, H_4), 7.16 (dd, 1H, J= 4.8 and 1.6 Hz, H_2), 4.80 (t, 1H, J= 6.4 Hz, H_5), 4.32 (brs, 1H, OH), 2.57-2.69 (m, 2H, H_6), 1.91 (t, 1H, J= 2.6 Hz, H_7). ^{13}C-NMR: δ 160.0, 148.3, 136.5, 122.7, 120.7, 80.4, 71.0, 70.8, 28.4. (Figure A7, A8)

4.2 General Procedure for Enzymatic Resolution of Homoallylic and Homopropargylic Alcohols

To a solution of the *rac*-**55a-c** and *rac*-**56** (1 mmol) in corresponding co-solvent and vinyl acetate (0.9 ml, 10 mmol) in a round bottom flask was added corresponding enzyme (1 eq. w/w). The reaction mixture was shaked at constant temperature; 24 ºC for *rac*-**55a**, *rac*-**55b** and 27 ºC for *rac*-**55c** and *rac*-**56a**. The reaction was ended by TLC monitoring when the conversion of alcohol to acetyl became approximately 50%. The enzyme was filtered and washed with ethyl acetate. The concentrated filtrate purified with flash column chromatography using mixtures of ethyl acetate and hexane (2:1 for **55a** and **56a**; 1:5 for **55b** and **55c**) afforded (*S*)-alcohols and (*R*)-acetates.

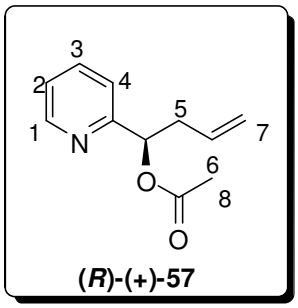
4.2.1 (*S*)-(-)-1-(Pyridin-2-yl)but-3-en-1-ol, (*S*)-(-)-55a



(*S*)-(-)-55a

$[\alpha]_D^{25}$ = -42.9 (*c* 0.86, CH_2Cl_2) for 98% e.e; in lit. [45] $[\alpha]_D^{25}$ = - 46.4 (*c* 0.86, CH_2Cl_2) for 95% ee. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 99:1, flow rate 0.3 mL min^{-1}, λ=254 nm, t_S=63.74, t_R= 58.75 (Figure A65,A66).

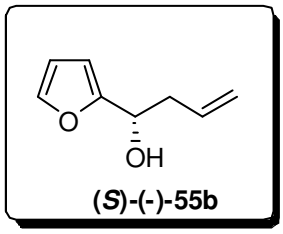
4.2.2 (*R*)-(+)- 1-(Pyridin-2-yl)but-3-enyl acetate, (*R*)-(+)-57



(*R*)-(+)-57

Light yellow oil, $[\alpha]_D^{25}$ = +58,36 (*c* 1,$CHCl_3$). ^{1}H-NMR: δ 8.51-8.52 (m, 1H, H_1), 7.59 (td, 1H, *J*= 7.6 and 1.7 Hz, H_3), 7.21 (d, 1H, *J*= 7.3 Hz, H_4), 7.10–7.13 (m, 1H, H_2), 5.76-5.79 (m, 1H, H_5), 5.59-5.69 (m, 1H, H_6), 4.93-5.00 (m, 2H, H_7), 2.57-2.69 (m, 2H, H_5), 2.03 (s, 3H, H_8). ^{13}C-NMR: δ 169.9 (C=O), 158.7, 149.1, 136.5, 133.0, 122.6, 121.1, 118.1, 75.4, 39.0, 20.9. (Figure A9, A10)

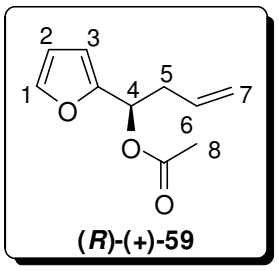
4.2.3 (*S*)-(-)-1-(Furan-2-yl)but-3-en-1-ol, (*S*)-(-)-55b



(*S*)-(-)-55b

$[\alpha]_D^{29}$ = -40.0 (*c* 5.0, CH_2Cl_2) for 99% e.e., in lit.[45] $[\alpha]_D^{27}$ = -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=11.2, t_R= 10.5 (Figure A67,A68).

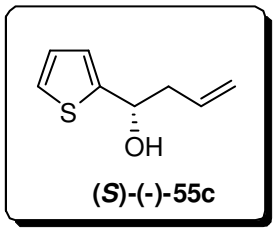
4.2.4 (*R*)-(+)-1-(Furan-2-yl)but-3-enyl acetate, (*R*)-(+)-59



(*R*)-(+)-59

Yellow oil, $[\alpha]_D^{32}$ = + 94.36 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 7.29 (brs, 1H, H_1), 6.23-6.24 (m, 2H, H_2 and H_3), 5.79 (t, 1H, *J*= 7.1 Hz, H_4), 5.60 (dddd, 1H, *J*= 17.1, 13.9, 10.1 and 6.9 Hz, H_6) , 5.03 (dd, 1H, *J*= 17.1 and 1.5 Hz, H_7), 4.97 (d, 1H, *J*= 10.2 Hz, H_7), 2.61 (t, 2H, *J*= 7.0 Hz, H_5), 1.96 (s, 3H, H_8). ^{13}C-NMR: δ 169.7 (C=O), 152.1, 142.3, 132.7, 118.1, 110.1, 108.6, 67.7, 36.9, 20.9. (Figure A11, A12)

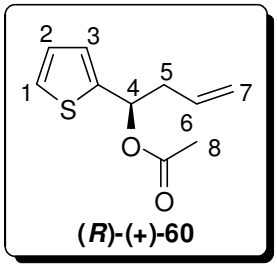
4.2.5 (*S*)-(-)-1-(Thiophen-2-yl)but-3-en-1-ol, (*S*)-(-)-55c



(*S*)-(-)-55c

$[\alpha]_D^{29}$ = -17.1 (*c* 1.2, CH_2Cl_2) for %99 e.e., in lit.[45] $[\alpha]_D^{27}$ = -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=12.09, , t_R= 13.76 (Figure A69,70).

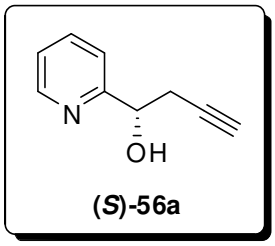
4.2.6 (*R*)-(+)-1-(Thiophene-2-yl)but-3-enyl acetate, (*R*)-(+)-60



(*R*)-(+)-60

Light yellow oil, $[\alpha]_D^{32}$ = +64.81 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 7.15 (dd, 1H, *J*= 5.1 and 1.1 Hz, H_1), 6.94 (d, 1H, *J*= 3.1 Hz, H_3), 6.83-6.86 (m, 1H, H_2), 5.99 (t, 1H, *J*= 6.9 Hz, H_4), 5.63 (dddd, 1H, *J*= 17.1, 13.8, 10.1 and 6.9 Hz, H_6), 4.97-5.05 (m, 2H, H_7), 2.53-2.67 (m, 2H, H_5), 1.95 (s, 3H, H_8). ^{13}C-NMR: δ 169.7 (C=O), 142.8, 132.9, 126.4, 125.8, 125.2, 118.3, 70.3, 40.6, 21.0. (Figure A13, A14)

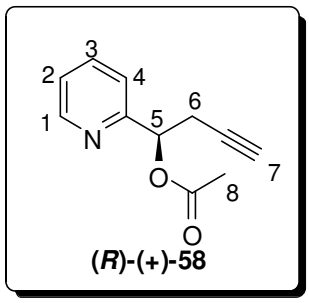
4.2.7 (*S*)-1-(Pyridin-2-yl)but-3-yn-1-ol, (*S*)-56a



(*S*)-56a

The α value cannot be determined because of the dark color of the compound, 99% ee; HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*- PrOH 99:1, flow rate 0.3 mL min^{-1}, λ=254 nm (Figure A71,A72).

4.2.8 (*R*)-(+)-1-(Pyridin-2-yl)but-3-ynyl acetate, (*R*)-(+)-58

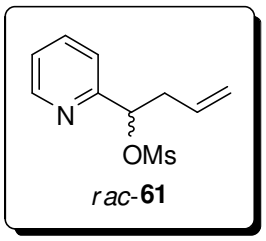


(*R*)-(+)-58

Light brown oil, $[\alpha]_D^{32}$ = +44.01 (*c* 0.5, CH_2Cl_2). ^{1}H-NMR: δ 8.53 (d, 1H, *J*= 4.0 Hz, H_1), 7.62 (td, 1H, *J*= 7.7 and 1.7 Hz, H_3), 7.30 (d, 1H, *J*= 7.8 Hz, H_4), 7.16 (ddd, 1H, *J*= 7.5, 4.8 and 1.0 Hz, H_2), 5.86 (t, 1H, *J*= 6.2 Hz, H_5), 2.77-2.92 (m, 2H, H_6), 2.09 (s, 3H, H_8), 1.82 (t, 1H, *J*= 2.6 Hz, H_7). ^{13}C-NMR: δ 169.5 (C-O), 157.3, 149.2, 136.3, 122.9, 121.4, 79.3, 73.7, 70.6, 24.2, 20.7. (Figure A15, A16)

4.3 General Procedure for Mesylation of Homoallyl and Homopropargyl Alcohols

The mesylchloride (4 mmol) solution was dropwise added at 0°C to the mixture of Et_3N (3 mmol) and corresponding 2-substituted homoallyl and homopropargyl alcohol (1 mmol) in CH_2Cl_2 (5 mL). The reaction was ended in 15 min. by TLC monitoring and the reaction mixture was extracted with water (3x10 mL), dried over anhydrous $MgSO_4$ and evaporated in vacuo. Since the mesylated compound was easily decomposed, it was used in the synthesis without purification.



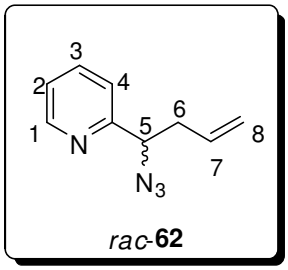
rac-**61**

Yellow oil (quantitative yield)

4.4 Synthesis of *rac*-2-(1-Azidobut-3-enyl)pyridine, *rac*-62

To a solution of mesylate *rac*-**61** (1.6 mmol) in anhydrous DMSO (5mL) was added, in one portion, NaN_3 (2.5 mmol). The resulting mixture was stirred at 60°C for 3h and then diluted with water. The mixture was extracted with diethyl ether (3x30 mL). The combined extracts were washed with brine (2x10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography with 1:1 ratio ethyl acetate- hexane gave azide compound *rac*-**62**.

4.4.1 *rac*-2-(1-Azidobut-3-enyl)pyridine, *rac*-62



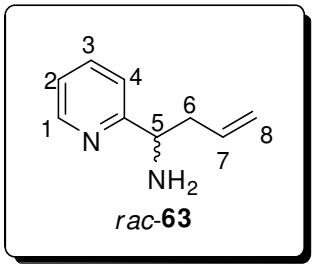
rac-**62**

Yellow oil (65% yield). IR (neat) cm^{-1}: 2095, 1455, 1248, 920. ^1H NMR: δ 8.52 (dd, 1H, *J*=4.8 and 0.7 Hz, H_1), 7.62 (td, 1H, *J*=7.7 and 1.7 Hz, H_3), 7.23 (d, 1H, *J*=7.8 H Hz, H_4), 7.15 (ddd, 1H, *J*=7.5, 4.8 and 1.0 Hz, H_2), 5.65-5.75 (m, 1H, H_7), 5.00-5.09 (m, 2H, H_8), 4.48 (dd, 1H, *J*=7.7 and 6.1 Hz, H_5), 2.55-2.69 (m, 2H, H_6). ^{13}C NMR: δ 157.6, 148.5, 135.8, 132.3, 121.9, 120.3, 117.4, 64.8, 38.0. (Figure A17, A18)

4.5 Synthesis of *rac*-1-(Pyridin-2-yl)but-3-en-1-amine, *rac*-63

To the solution of azide *rac*-**62** (12 mmol) and NH_4Cl (27 mmol) in ethyl alcohol (32 mL) and water (10 mL), zinc powder (15 mmol) was added and stirred vigorously at reflux. The reaction was ended by TLC monitoring and ethyl acetate (80 mL) and aqueous ammonia (4 mL) was added. The mixture was filtered and filtrate was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography with 5% methanol- chloroform mixture in 73% yield.

4.5.1 *rac*-1-(Pyridin-2-yl)but-3-en-1-amine, *rac*-63



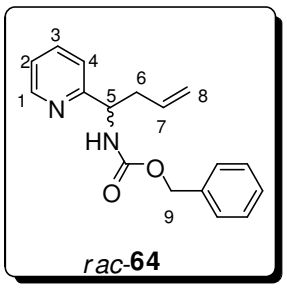
rac-**63**

Yellow oil (73% yield). ^{1}H NMR: δ 8.48 (d, 1H, *J*=3.8 Hz, H_1), 7.57 (td, 1H, *J*=7.6 and 1.5 Hz, H_3), 7.23 (d, 1H, *J*=7.7 Hz, H_4), 7.07-7.10 (m, 1H, H_2), 5.64-5.74 (m, 1H, H_7), 5.00-5.07 (m, 2H, H_8), 3.96-3.99 (m, 1H, H_5), 2.28- 2.55 (m, 2H, H_6), 1.83 (brs, 2H,NH_2). ^{13}C NMR: δ 163.0, 148.1, 135.4, 134.1, 120.9, 120.0, 116.8, 55.4, 42.2. (Figure A19, A20)

4.6 Synthesis of *rac*-Benzyl-1-(pyridin-2-yl)but-3-enylcarbamate, *rac*-64

To as solution of amine *rac*-**63** (1mmol) in dry CH_2Cl_2 (7.4 mL) at 0°C was added potassium carbonate (1 mmol) and benzyl chloroformate (1.2 mmol). After stirring at room temperature, the reaction mixture was hydrolyzed with saturated aqueous $NaHCO_3$ (4mL). The mixture was extracted with CH_2Cl_2 (3x30 mL) and dried over anhydrous $MgSO_4$, evaporated in vacuo and purified by flash column chromatography with the mixture of ethyl acetate-hexane (1:2).

4.6.1 *rac*-Benzyl-1-(pyridin-2-yl)but-3-enylcarbamate, *rac*-64



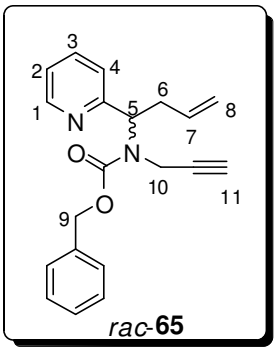
rac-**64**

White solid (21%). mp: 72-75°C. ^{1}H NMR: δ 8.44 (d, 1H, *J*=4.5 Hz, H_1), 7.50-7.54 (m, 1H, H_3), 7.19- 7.25 (m, 5H, Ph*H*), 7.04-7.12 (m, 2H, H_4 and H_2), 5.99 (brs, 1H, N*H*), 5.52-5.62 (m, 1H, H_7), 4.91-5.01 (m, 4H, H_8 and H_9), 4.77-4.82 (m, 1H, H_5), 2.52 (t, 2H, *J*=6.5 Hz, H_6). ^{13}C NMR: δ 159.6, 155.8 (C=O), 149.2, 136.6, 136.4, 133.6, 128.4, 128.0, 126.9, 122.3, 121.8, 118.2, 66.6 , 55.3, 40.7. (Figure A21, A22)

4.7 Synthesis of *rac*-Benzyl prop-2-ynyl(1-(pyridin-2-yl)but-3-enyl)carbamate, *rac*-65

NaH (2 mmol) was added to the mixture of compound *rac*-**64** (1 mmol) in freshly distilled THF (15 mL) and mixed 20 min. at room temperature. Then, propargyl bromide (2 mmol) was dropwise added and the mixture refluxed overnight. The reaction mixture hydrolyzed by the cautious addition of water and extracted with ether (3x20 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethylacetate and hexane at ratio of 1:2.

4.7.1 *rac*-Benzyl prop-2-ynyl(1-(pyridin-2-yl)but-3-enyl)carbamate, *rac*-65

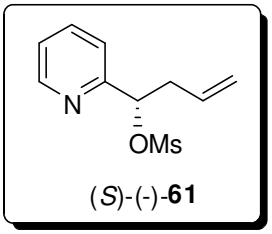


rac-**65**

Yellowish oil (32%). ^{1}H NMR: δ 8.47 (d, 1H, *J*=4.2 Hz, H_1), 7.52 (m, 1H, H_3), 7.30-7.21 (m, 6H, Ph*H* and H_4), 7.08-7.11 (m, 1H, H_2), 5.67-5.78 (m, 1H, H_7),

5.02-5.40 (m, 4H, H_8 and H_9), 4.93 (d, 1H, J=10.1 Hz, H_5), 3.92-4.02 (m, 2H, H_{10}), 2.75-2.94 (m, 2H, H_6), 1.96 (brs, 1H, H_{11}). ^{13}C NMR: δ 158.8, 156.1 (C=O), 149.2, 136.7, 134.9, 128.6, 128.1, 127.7, 124.0, 122.8, 117.7, 80.9, 70.8, 67.7, 60.0, 34.9, 33.0. (Figure A23, A24)

4.7.2 (*S*)-(-)-1-(Pyridin-2-yl)but-3-enyl methanesulfonate, (*S*)-(-)-61



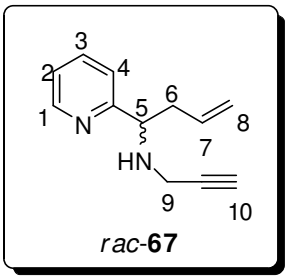
(*S*)-(-)-**61**

Yellow oil (quantitative). $[\alpha]_D^{28}$ = -37.03 (*c* 1.0, EtOH).

4.8 General Procedure for *N*-Allylation and *N*-Propargylation

To a suspension of K_2CO_3 (1.2 mmol) in allylamine (8 mmol) and propargylamine (8 mmol) was added homopropargyl and homoallyl mesylate, respectively, slowly *via* syringe addition over a period of half an hour. The solvent free reaction mixture was stirred at room temperature for 24 hours. K_2CO_3 was filtered and washed with CH_2Cl_2. Filtrate was concentrated in vacuo and purified by flash column chromatography with 5% methanol-chloroform mixture.

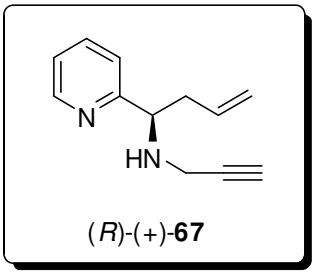
4.8.1 *rac*-*N*-(Prop-2-ynyl)-1-(pyridin-2-yl)but-3-en-1-amine, *rac*-67



rac-**67**

Light yellow oil (67% yield). ^{1}H-NMR: δ 8.48 (d, 1H, J=4.0 Hz, H_1), 7.55 (td, 1H, J=7.8 and 1.7 Hz, H_3), 7.27 (d, 1H, J=7.2 Hz, H_4), 7.07 (ddd, 1H, J=7.4, 4.8 and 1.1, H_2,), 5.61-5.72 (m, 1H, H_7), 4.96-5.03 (m, 2H, H_8), 3.94 (dd, 1H, J=7.9 and 5.6 Hz, H_5), 3.30 (dd, 1H, AB system, J_{AB}=16.9 and 2.4 Hz, H_9), 3.06 (dd, 1H, AB system, J_{AB}=16.9 and 2.4 Hz, H_9), 2.29-2.50 (m, 2H, H_6), 2.09 (t, J=2.4 Hz, 1H, H_{10}), 2.03 (brs, 1H, NH). ^{13}C-NMR: δ 162.4, 149.6, 136.4, 135.0, 122.2, 122.0, 118.0, 82.1, 71.6, 61.9, 41.5, 36.3. (Figure A25, A26)

4.8.2 (*R*)-(+)-*N*-(Prop-2-ynyl)-1-(pyridin-2-yl)but-3-en-1-amine, (*R*)-(+)-67



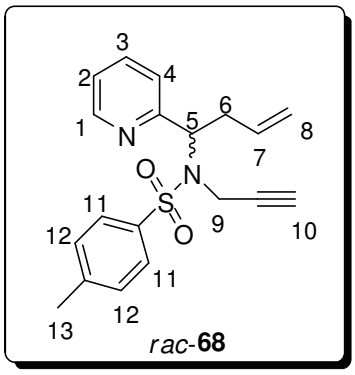
(*R*)-(+)-**67**

$[\alpha]_D^{31}$ = +79.21 (*c* 1.0, EtOH).

4.9 General Procedure for Tosylation of *N*-tethered Enyne Derivatives

To a solution of *N*-tethered enyne compound (1 mmol) in CH_2Cl_2 (20mL) was added TsCl (1.5 mmol) and Et_3N (2 mmol) at 0°C. The mixture was allowed to stir at room temperature half an hour. The reaction was ended by TLC monitoring. Then, 20 mL water was added and extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and evaporated in vacuo. Purification was done by flash column chromatography with 1:3 ratio of ethyl acetate-hexane.

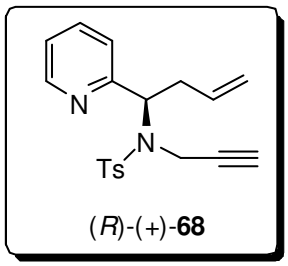
4.9.1 *rac*-4-Methyl-*N*-(prop-2-ynyl)-*N*-(1-(pyridin-2-yl)but-3-enyl)benzene sulfonamide, *rac*-68



rac-**68**

Light yellow oil (47% yield). ^{1}H-NMR: δ 8.41 (d, 1H, *J*=4.0, H_1), 7.70-7.72 (m, 2H, H_{11}), 7.51 (td, 1H, *J*=7.6 and 1.8 Hz, H_3), 7.16-7.21 (m, 3H, H_{12} and H_4), 7.09 (ddd, 1H, *J*=7.4, 4.8 and 1.0 Hz, H_2), 5.45 (dddd, 1H, *J*= 17.1, 13.9, 10.1 and 6.9 Hz, H_7), 4.93 (dd, 1H, *J*= 8.7 and 6.6 Hz, H_8), 4.87 (dd, 1H, *J*= 17.1 and 1.6 Hz, H_8), 4.76 (dt, 1H, *J*= 10.1 and 0.8 Hz, H_5), 4.19 (dd, 1H, AB system, J_{AB}= 18.5 and 2.4 Hz, H_{10}), 4.11(dd, 1H, AB system, J_{AB}= 18.5 and 2.4 Hz, H_9), 2.91-2.99 (m, 1H, H_6), 2.45-2.52 (m, 1H, H_6), 2.34 (s, 3H, H_{13}), 1.94 (t, 1H, *J*= 2.4 Hz, H_{10}). ^{13}C-NMR: δ 155.6, 146.5, 140.9, 135.6, 134.4, 132.4, 127.0, 125.6, 121.9, 120.6, 115.3, 77.7, 69.9, 59.4, 33.0, 30.7, 19.3. (Figure A27, A28)

4.9.2 (*R*)-(+)-4-methyl-*N*-(prop-2-ynyl)-*N*-(1-(pyridin-2-yl)but-3-enyl) benzene sulfonamide, (*R*)-(+)-68



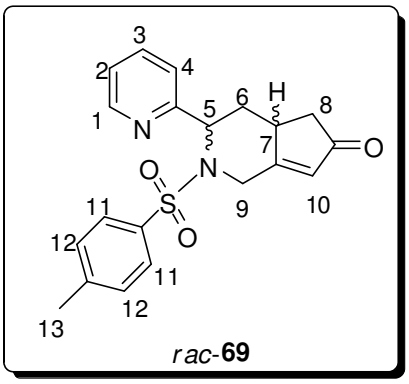
(*R*)-(+)-**68**

$[\alpha]_D^{31}$ = +83.74 (*c* 1.0, CH_2Cl_2)

4.10 General Procedure for the Intramolecular Pauson-Khand Reaction

To a solution of enyne tethered compound (1 mmol) in CH_2Cl_2 (20 mL) was added $Co_2(CO)_8$ (1.7 mmol) and stirred half an hour at room temperature. Then, NMO (9 mmol) was added to the mixture and stirred for overnight. The reaction mixture concentrated under reduced pressure and purified by flash column chromatography.

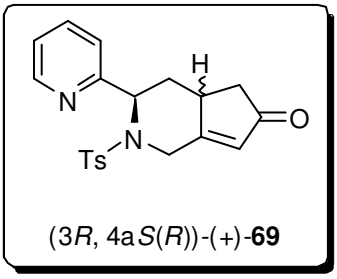
4.10.1 *rac*-3-(Pyridin-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[*c*] pyridine-6(2*H*)-one, *rac*-69



rac-**69**

White foam (80% yield). IR (neat) cm^{-1}: 2921, 1710, 1631, 1590, 1348, 1161, 1092, 690, 561. ^{1}H-NMR: δ 8.36 (d, 1H, J= 4.4 Hz, H_1), 7.65 (t, 1H, J= 7.6 Hz, H_3), 7.53-7.55 (m, 3H, H_4 and H_{11}), 7.09-7.16 (m, 3H, H_2 and H_{12}), 5.79 (s, 1H, H_{10}), 5.26 (d, 1H, J= 4.4 Hz, H_5), 4.77 (d, 1H, AB system J_{AB}= 15.4 Hz, H_9), 3.97 (d, 1H, AB system J_{AB}= 15.4 Hz, H_9), 2.97-3.00 (m, 1H, H_7), 2.77 (dd, 1H, AB system J_{AB}= 12.7 and 4.5 Hz, H_6), 2.42 (dd, 1H, AB system J_{AB}= 18.8 and 6.4 Hz, H_8), 2.33 (s, 3H, H_{13}), 1.70 (dd, 1H, AB system J_{AB}= 18.8 and 2.2 Hz, H_8), 1.22 (dt, 1H, AB system J_{AB}= 12.7 and 5.4 Hz, 1H, H_6). ^{13}C-NMR: δ 205.7 (C=O), 172.1, 156.8, 147.7, 142.5, 136.0, 135.9, 128.5, 126.9, 126.1, 121.3, 121.2, 55.6, 42.8, 40.5, 33.9, 32.9, 20.4.

4.10.2 (3*R*,4a*S*(*R*))-(+)-3-(Pyridin-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclo penta[*c*]pyridin-6(2*H*)-one, (3*R*, 4a*S*(*R*))-(+)-69



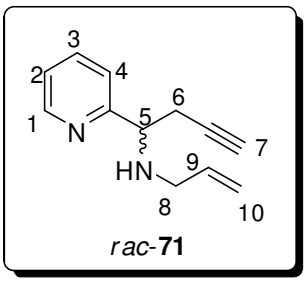
(3*R*, 4a*S*(*R*))-(+)-**69**

$[\alpha]_D^{25}$ = +55.40 (*c* 1.0, $CHCl_3$)

4.11 Synthesis of *rac*-*N*-Allyl-4-methyl-*N*-(1-(pyridin-2-yl)but-3-ynyl)benzene sulfonamide, *rac*-71

Compound *rac*-**70** afforded the *N*-tethered enyne compound *rac*-**71** with the procedure given in section 4.9.

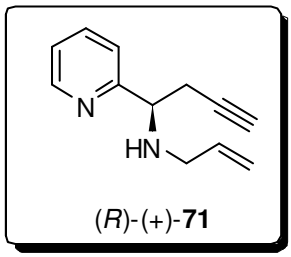
4.11.1 *rac*-*N*-Allyl-1-(pyridin-2-yl)but-3-yn-1-amine, *rac*-71



rac-**71**

Yellow oil (65% yield). ^{1}H-NMR: δ 8.49-8.50 (m,1H, H_1), 7.56-7.59 (m, 1H, H_3), 7.28 (dd, 1H, *J*= 7.7 and 0.8 Hz, H_2), 7.08-7.11 (m, 1H, H_4), 5.75-5.85 (m, 1H, H_9), 4.99-5.10 (m, 2H, H_{10}), 3.86 (t, 1H, *J*= 6.6 Hz, H_5), 3.00-3.12 (m, 2H, H_8), 2.51-2.63 (m, 2H, H_6), 2.06 (brs, 1H, N*H*), 1.86 (m, 1H, H_7). ^{13}C-NMR: δ 160.1, 148.0, 135.1, 134.7, 120.8, 120.7, 114.6, 79.8, 68.9, 60.2, 48.6, 24.8. (Figure A36, A37)

4.11.2 (*R*)-(+)- *N*-Allyl-1-(pyridin-2-yl)but-3-yn-1-amine, (*R*)-(+)-71



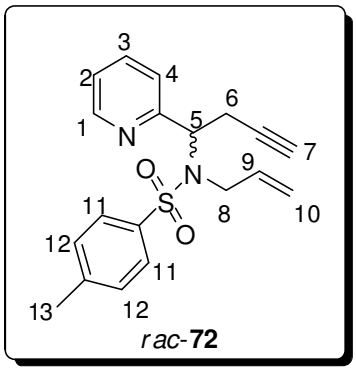
(*R*)-(+)-**71**

$[\alpha]_D^{24}$ = +25.94 (*c* 0.5, $CHCl_3$)

4.12 Synthesis of *rac*-*N*-allyl-4-methyl-*N*-(1-(pyridin-2-yl)but-3-ynyl)benzene sulfonamide, *rac*-72

Synthesis of *N*-tethered enyne compound *rac*-**72** was performed by the compound *rac*-**71** with the procedure given in section 4.10.

4.12.1 *rac*-*N*-Allyl-4-methyl-*N*-(1-(pyridin-2-yl)but-3-ynyl)benzenesulfon amide, *rac*-72

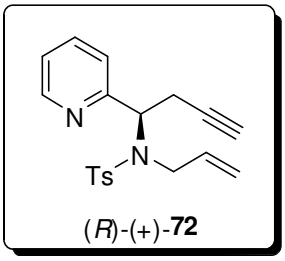


rac-**72**

Yellowish oil (53% yield). ^{1}H-NMR: δ 8.37 (d, 1H, *J*= 4.0 Hz, H_1), 7.62-7.65 (m, 2H, H_{11}), 7.51 (td, 1H, *J*= 7.6 and 1.7 Hz, H_3), 7.27 (d, 1H, *J*= 7.8 Hz, H_4), 7.13-7.15 (m, 2H, H_{12}), 7.05-7.08 (m, 1H, H_2), 5.41-5.51 (m, 1H, H_9), 5.21 (t, 1H, *J*= 7.6

Hz, H_5), 4.91 (dd, 1H, *J*= 17.1 and 1.3 Hz, H_{10}), 4.79 (dd, 1H, *J*= 10.1 and 1.2 Hz, H_{10}), 3.73-3.84 (m, 2H, H_8), 3.08 (ddd, 1H, AB system J_{AB}= 16.7, 8.1 and 2.6 Hz, H_6), 2.59 (ddd, 1H, AB system J_{AB}= 16.7, 7.1 and 2.6 Hz, H_6), 2.31 (s, 3H, H_{13}), 1.64 (t, 1H, *J*= 2.6 Hz, H_7). ^{13}C-NMR: δ 155.4, 146.8, 141.2, 136.5, 134.7, 133.4, 127.6, 125.9, 122.2, 121.1, 115.3, 79.2, 68.9, 58.9, 45.1, 19.7, 19.5. (Figure A38, A39)

4.12.2 (*R*)-(+)-*N*-Allyl-4-methyl-*N*-(1-(pyridin-2-yl)but-3-ynyl)benzenesulfon amide, (*R*)-(+)-72



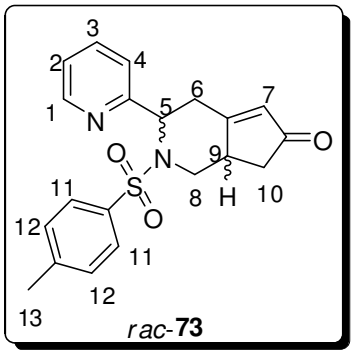
(*R*)-(+)-**72**

$[\alpha]_D^{25}$ = +41.36 (*c* 1.0, $CHCl_3$)

4.13 Synthesis of *rac*-3-(Pyridin-2-yl)-2-tosyl-3,4,7,7a-tetrahydro-1*H*-cyclo penta[*c*]pyridin-6(2*H*)-one, *rac*-73

Compound *rac*-**72** afforded the target product *rac*-**73** *via* Pauson-Khand reaction with the procedure given in section 4.11.

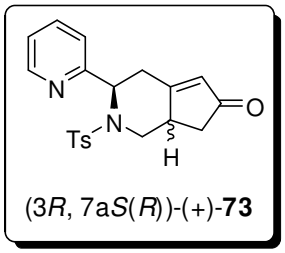
4.13.1 *rac*-3-(Pyridin-2-yl)-2-tosyl-3,4,7,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridin-6(2*H*)-one, *rac*-73



rac-**73**

White foam (82% yield). IR (neat) cm^{-1}: 2924, 1707, 1628, 1263, 1157, 1094, 947, 802, 561. ^{1}H-NMR: δ 8.36 (d, 1H, J= 4.1 Hz, H_1), 7.70-7.72 (m, 2H, H_{11}), 7.54 (td, 1H, J= 7.7 and 1.7 Hz, H_3), 7.22-7.26 (m, 3H, H_2 and H_{12}), 7.05 (dd, 1H, J= 7.4 and 4.9 Hz, H_4), 5.80 (s, 1H, H_7), 5.50 (d, 1H, J= 7.0 Hz, H_7), 4.15 (dd, 1H, J= 11.7 and 4.3 Hz, H_8), 3.72 (d, 1H, AB system J_{AB}= 13.4 Hz, H_6), 2.62-2.74 (m, 2H, H_8 and H_9), 2.54 (dd, 1H, AB system J_{AB}= 13.4 and 7.1 Hz, H_6), 2.37 (s, 3H, H_{13}), 2.31 (dd, 1H, AB system J_{AB}= 18.6 and 6.2 Hz, H_{10}), 1.68 (d, 1H, AB system J_{AB}= 18.6 Hz, H_{10}). ^{13}C-NMR: δ 206.6 (C=O), 176.9, 157.4, 149.3, 143.9, 138.2, 137.0, 130.4, 130.2, 127.4, 122.6, 121.9, 57.5, 48.1, 39.7, 38.6, 32.0, 21.8 .

4.13.2 (3*R*,7a*S*(*R*))-(+)-3-(Pyridin-2-yl)-2-tosyl-3,4,7,7a-tetrahydro-1*H*-cyclopenta[*c*]pyridin-6(2*H*)-one, (3*R*, 7a*S*(*R*))-(+)-73



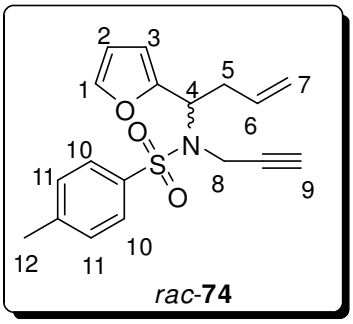
(3*R*, 7a*S*(*R*))-(+)-**73**

$[\alpha]_D^{25}$ = +124.03 (*c* 1.0, $CHCl_3$)

4.14 General Procedure for Mitsunobu Reaction

PPh_3 (1.4 mmol) in freshly distilled THF (1.8 mL) was cooled to 0°C and treated with DEAD (1.3 mmol) and stirred for 10 min. Then, to the reaction mixture was dropwise added a solution of homoallyl alcohol (1 mmol) and *N*-tosylated propargyl amine (0.7 mmol) in THF (1.8 mL). The resultant mixture was stirred at 0°C until the reaction was completed and ended by TLC monitoring. The mixture concentrated under reduced pressure and purified by flash column chromatography with ethyl acetate-hexane mixture in 1:3 ratio.

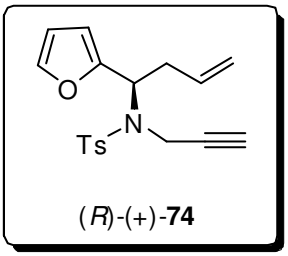
4.14.1 *rac*-*N*-(1-(Furan-2-yl)but-3-enyl)-4-methyl-*N*-(prop-2-ynyl)benzene sulfonamide, *rac*-74



rac-**74**

Yellowish oil (62% yield). ^{1}H-NMR: δ 7.69-7.71 (d, 2H, H_{10}), 7.16-7.19 (m, 3H, H_1 and H_{11}), 6.16-6.17 (m, 1H, H_2), 6.06 (d, 1H, J= 3.2 Hz, H_3), 5.63 (dddd, 1H, J= 17.1, 13.8, 10.1 and 6.9 Hz, H_6), 5.00-5.03 (m, 2H, H_7), 4.95 (m, 1H, H_4), 3.98 (dd, 1H, AB system, J_{AB}= 18.5 and 2.4 Hz, H_8), 3.72 (dd, 1H, AB system, J_{AB}= 18.5 and 2.4 Hz, H_8), 2.57-2.77 (m, 2H, H_5), 2.35 (s, 3H, H_{12}), 1.93 (t, 1H, J= 2.4 Hz, H_9). ^{13}C-NMR: δ 150.3, 142.0, 141.1, 136.6, 132.7, 128.1, 126.7, 116.9, 109.1, 108.2, 78.1, 70.7, 54.0, 34.7, 31.9, 20.4. (Figure A49, A50)

4.14.2 (*R*)-(+)-*N*-(1-(Furan-2-yl)but-3-enyl)-4-methyl-*N*-(prop-2-ynyl)benzene sulfonamide(*R*)-(+)-74



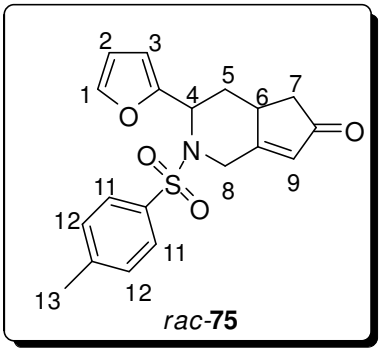
(*R*)-(+)-**74**

$[\alpha]_D^{35}$ = +10.14 (*c* 1.0, $CHCl_3$)

4.15 Synthesis of *rac*-3-(Furan-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclo pen ta[*c*]pyridin-6(2*H*)-one, *rac*-75

Target compound *rac*-**75** was afforded by *rac*-**74** *via* Pauson-Khand reaction with the general procedure given in section 4.11.

4.15.1 *rac*-3-(Furan-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[*c*]pyridin -6(2*H*)-one, *rac*-75

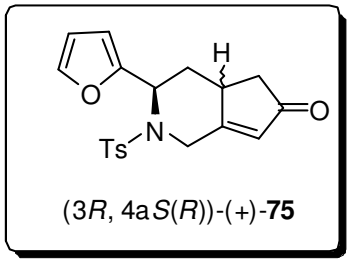


rac-**75**

White foam (58% yield). IR (neat) cm^{-1}: 2925, 1709, 1631, 1347, 1161, 1017, 1092, 699, 549. ^{1}H-NMR: δ 7.52-7.54 (m, 2H, H_1), 7.15-7.19 (m, 3H, H_1 and H_{12}), 6.23-6.24 (m, 1H, H_2), 6.15 (d, 1H, *J*= 3.2 Hz, H_3), 5.86 (s, 1H, H_9), 5.31 (d, 1H,

J= 4.3 Hz, H_4), 4.68 (d, 1H, AB system, J_{AB}= 14.9 Hz, H_8), 3.87 (d, 1H, AB system, J_{AB}= 14.9 Hz, H_8), 2.90-2.93 (m, 1H, H_6), 2.48 (dd, 1H, AB system J_{AB}= 18.7 and 6.5 Hz, H_7), 2.41 (ddd, 1H, AB system J_{AB}=13.0, 5.5 and 1.8 Hz, H_5), 2.34 (s, 3H, H_{13}), 1.82 (dd, 1H, AB system J_{AB}= 18.7 and 2.6 Hz, H_7), 1.49 (dt, 1H, AB system J_{AB}= 13.0 and 5.2 Hz, H_5). ^{13}C-NMR: δ 205.3 (C=O), 171.13, 150.6, 142.5, 141.1, 135.6, 128.5, 127.3, 126.2, 109.5, 107.2, 49.8, 42.4, 40.3, 34.6, 34.4, 20.4.

4.15.2 (3*R*,4a*S*(*R*))-(+)-3-(Furan-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclo penta[*c*]pyridin-6(2*H*)-one, (3*R*, 4a*S*(*R*))-(+)-75



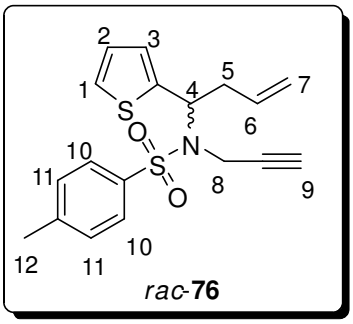
(3*R*, 4a*S*(*R*))-(+)-**75**

$[\alpha]_D^{32}$ = +13.53(*c* 1.0, $CHCl_3$)

4.16 Synthesis of *rac*-4-Methyl-*N*-(prop-2-ynyl)-*N*-(1-(thiophen-2-yl)but-3-enyl) benzenesulfonamide, *rac*-76

Compound *rac*-**76** was afforded by 2-thiophene substituted homoallyl alcohol *rac*-**55c** *via* Mitsunobu reaction. The general procedure was given in 4.15.

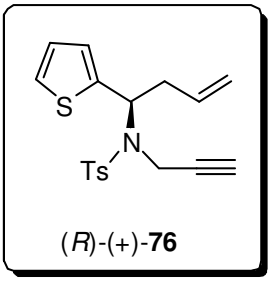
4.16.1 *rac*-4-Methyl-*N*-(prop-2-ynyl)-*N*-(1-(thiophen-2-yl)but-3-enyl)benzenesul fonamide, *rac*-76



rac-**76**

Yellowish oil (65% yield). ^{1}H-NMR: δ 7.66-7.72 (m, 2H, H_{10}), 7.18-7.21 (m, 2H, H_{11}), 7.12 (dd, 1H, J= 5.0 and 1.0 Hz, H_1), 6.87-6.88 (m, 1H, H_2), 6.81-6.84 (m, 1H, H_3), 5.50-5.71 (m, 1H, H_7), 5.18 (t, 1H, J= 7.6 Hz, H_4), 4.99 (dd, 1H, J= 17.1 and 1.5 Hz, H_7), 4.89 (d, 1H, J= 10.1 and 1.35 Hz, H_7), 4.10 (dd, 1H, AB system J_{AB}= 18.6 and 2.4 Hz, H_8), 3.62 (dd, 1H, AB system J_{AB}= 18.6 and 2.4 Hz, H_8), 2.63-2.81 (m, 2H, H_5), 2.36 (s, 3H, H_{12}), 2.02 (t, 1H, J= 2.4 Hz, H_9). ^{13}C-NMR: δ 142.1, 140.5, 136.9, 133.1, 128.3, 126.6, 125.7, 125.5, 124.7, 116.8, 78.6, 71.3, 55.9, 36.9, 31.5, 20.5. (Figure A58,A59)

4.16.2 (*R*)-(+)-4-Methyl-*N*-(prop-2-ynyl)-*N*-(1-(thiophen-2-yl)but-3-enyl) benzenesulfonamide, (*R*)-(+)-76



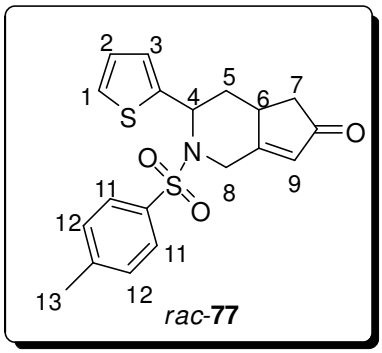
(*R*)-(+)-**76**

$[\alpha]_D^{31}$ = +9.92 (*c* 1.0, $CHCl_3$)

4.17 Synthesis of *rac*-3-(Thiophen-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[*c*]pyridin-6(2*H*)-one, *rac*-77

Target compound *rac*-**77** was synthesized from *rac*-**76** *via* Pauson-Khand reaction with the procedure given in 4.11.

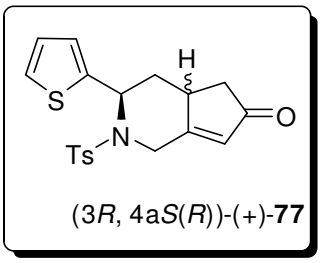
4.17.1 *rac*-3-(thiophen-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclopenta[*c*]pyridin-6(2*H*)-one, *rac*-77



rac-**77**

White foam (64% yield). IR (neat) cm^{-1}: 2926, 1703, 1629, 1344, 1160, 1092, 928, 732, 554. ^{1}H-NMR: δ 7.59-7.61 (m, 2H, H_{11}), 7.16-7.20 (m, 3H, H_1 and H_{12}), 6.89-6.90 (m, 2H, H_2 and H_3), 5.82 (s, 1H, H_9), 5.47 (d, 1H, J= 4.4 Hz, H_4), 4.74 (d, 1H, AB system J_{AB}= 15.7 Hz, H_8), 3.94 (d, 1H, AB system J_{AB}= 15.7 Hz, H_8), 2.96-2.99 (m, 1H, H_6), 2.38-2.48 (m, 2H, H_5 and H_7), 2.35 (s, 3H, H_{13}), 1.78 (dd, 1H, J= 18.7 and 2.5 Hz, H_7), 1.47 (td, 1H, J= 13.2 and 5.2 Hz, H_5). ^{13}C-NMR: δ 206.2 (C=O), 172.0, 143.8, 141.8, 137.0, 129.7, 128.2, 127.3, 127.1, 125.6, 125.5, 52.9, 42.8 , 41.3, 36.5, 34.9 , 21.5.

4.17.2 (3*R*, 4a*S*(*R*))-(+)- 3-(Thiophen-2-yl)-2-tosyl-3,4,4a,5-tetrahydro-1*H*-cyclo penta[*c*]pyridin-6(2*H*)-one, (3*R*, 4a*S*(*R*))-(+)-77



(3*R*, 4a*S*(*R*))-(+)-**77**

$[\alpha]_D^{32}$ = +10.62 (*c* 1.0, $CHCl_3$)

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APPENDIX A

SUPPORTING INFORMATION

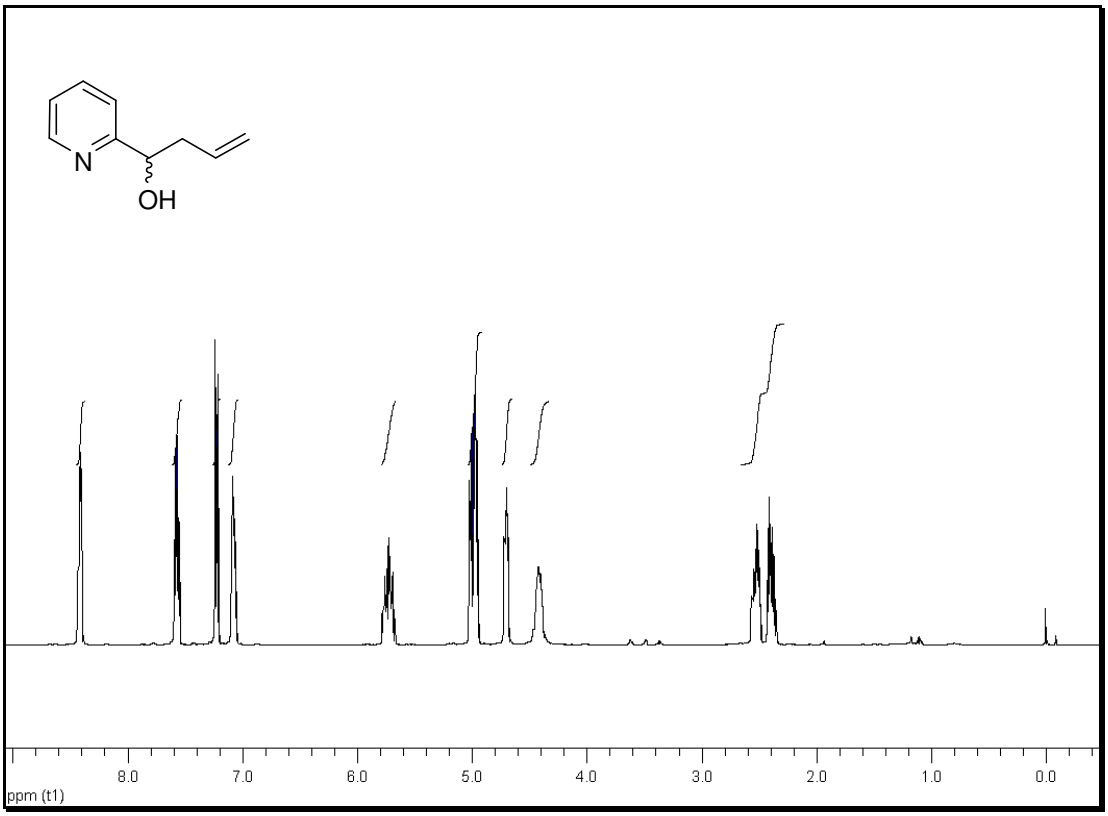

Figure A1. ^{1}H-NMR spectrum of *rac*-**55a**

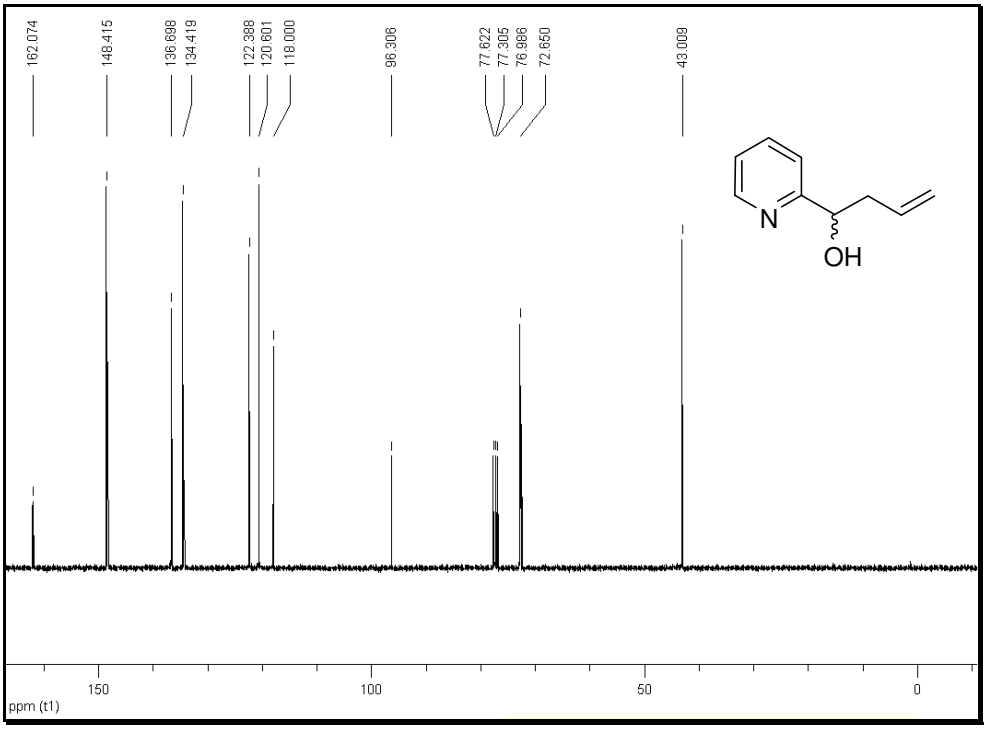

Figure A2. ^{13}C-NMR spectrum of *rac*-**55a**

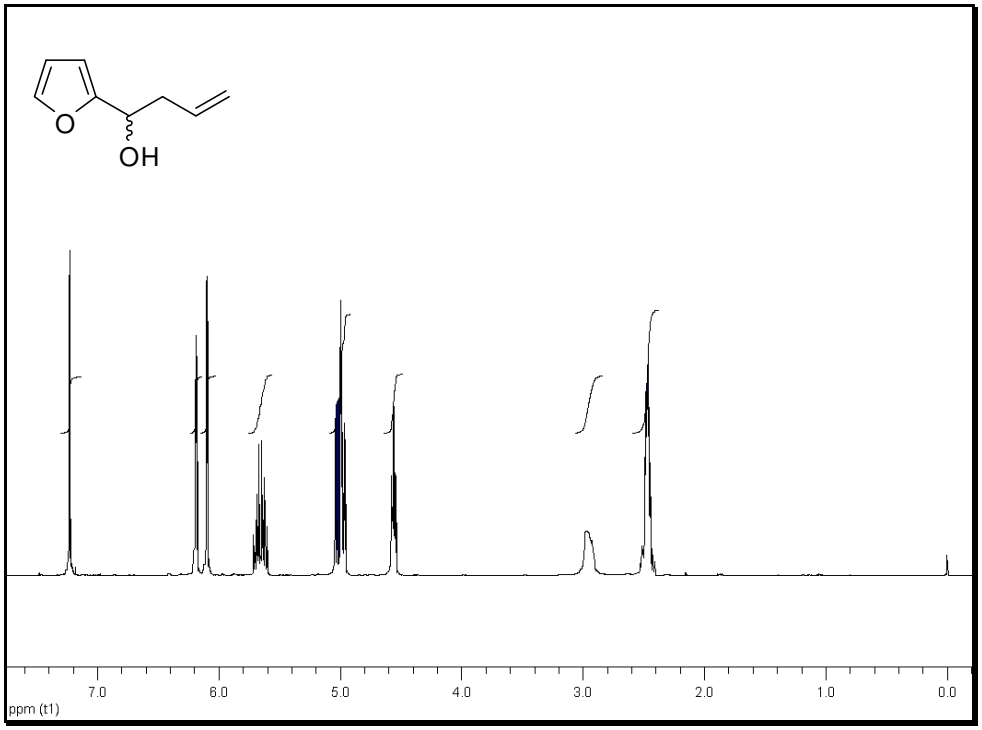

Figure A3. ^{1}H-NMR spectrum of *rac*-**55b**

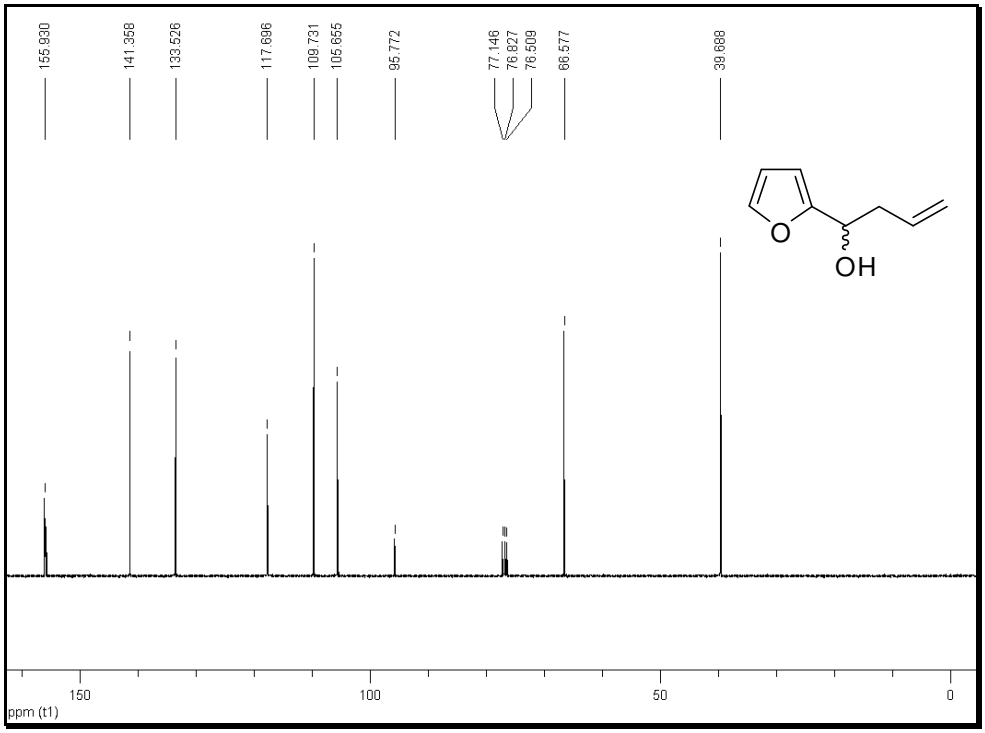

Figure A4. ^{13}C-NMR spectrum of *rac*-**55b**

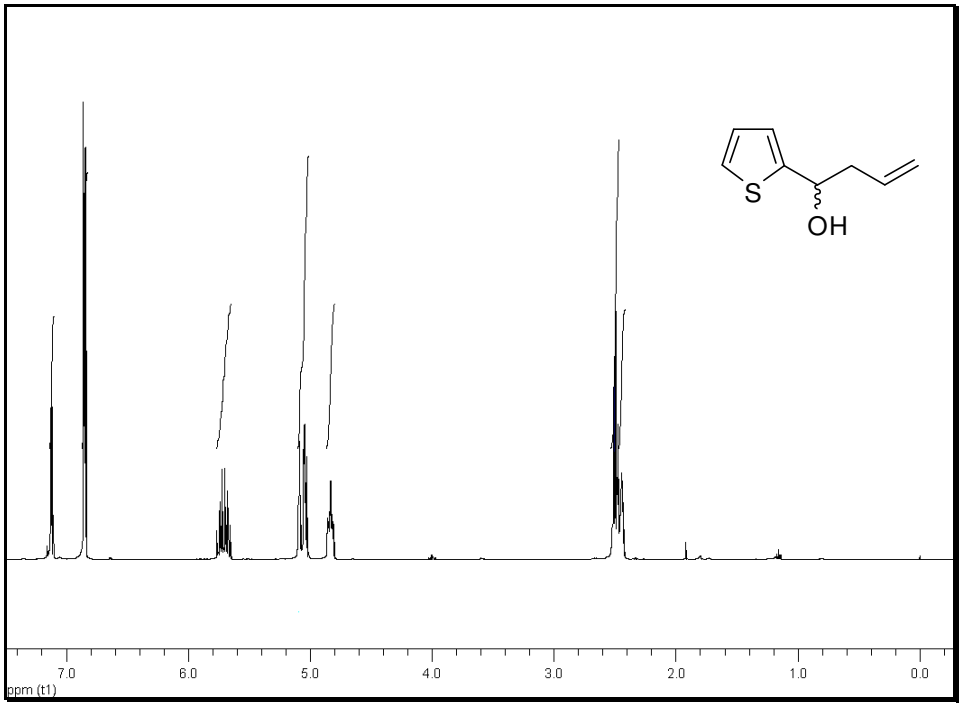

Figure A5. ^{1}H-NMR spectrum of *rac*-**55c**

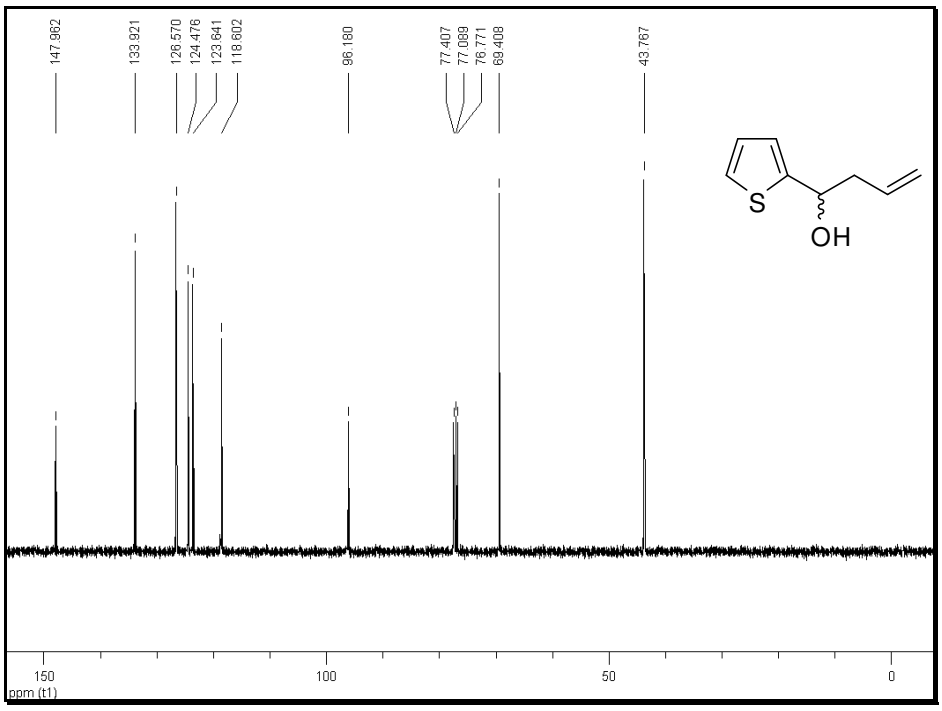

Figure A6. ^{13}C-NMR spectrum of *rac*-**55c**

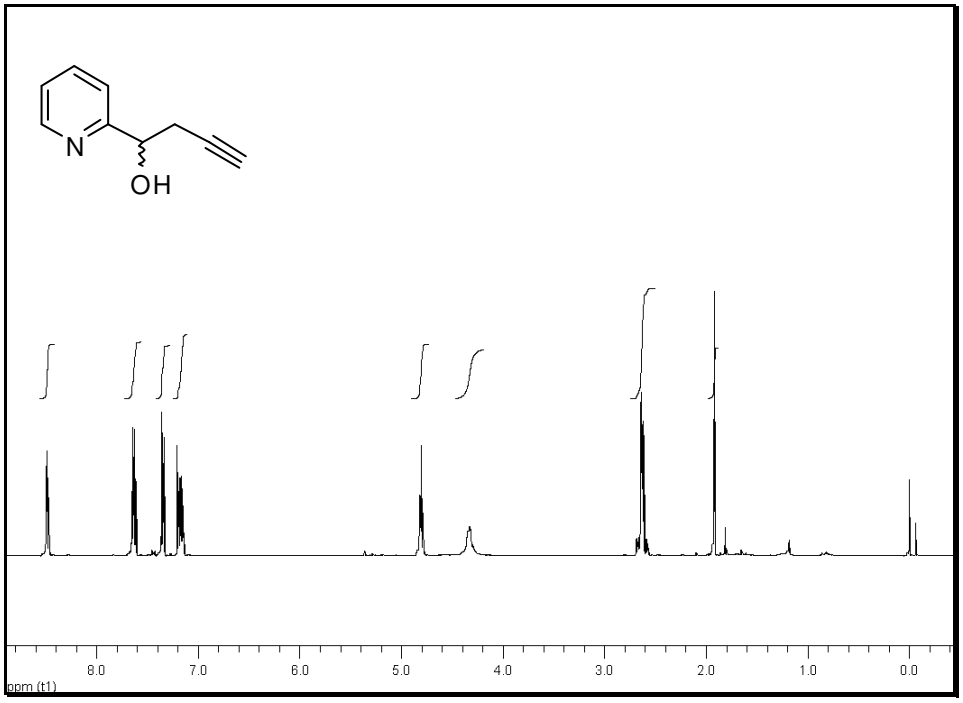

Figure A7. ^{1}H-NMR spectrum of *rac*-**56a**

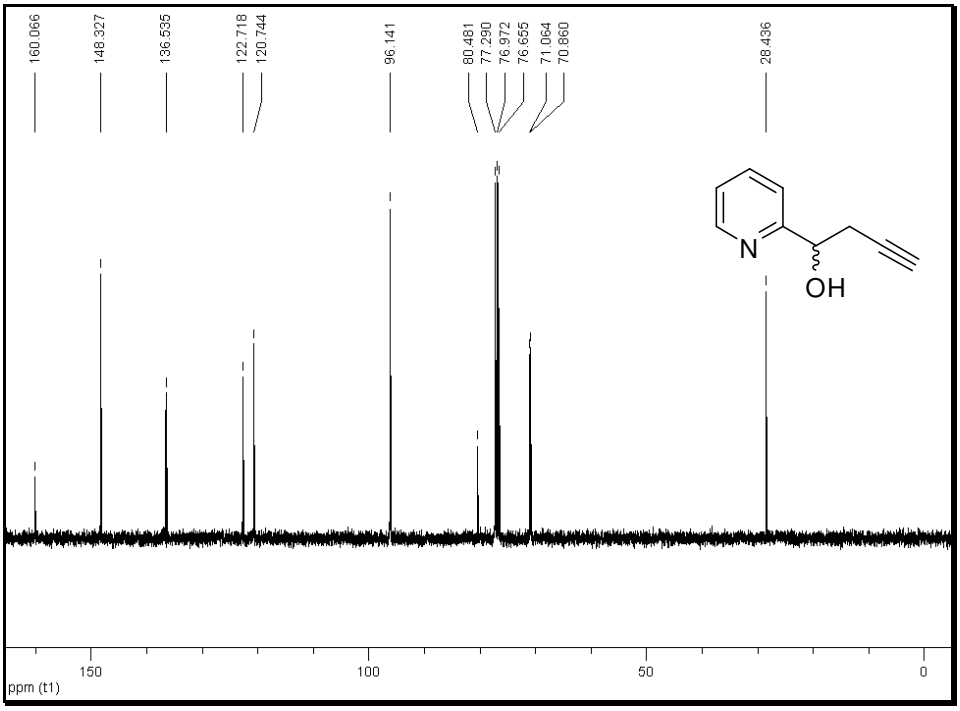

Figure A8. ^{13}C-NMR spectrum of *rac*-**56a**

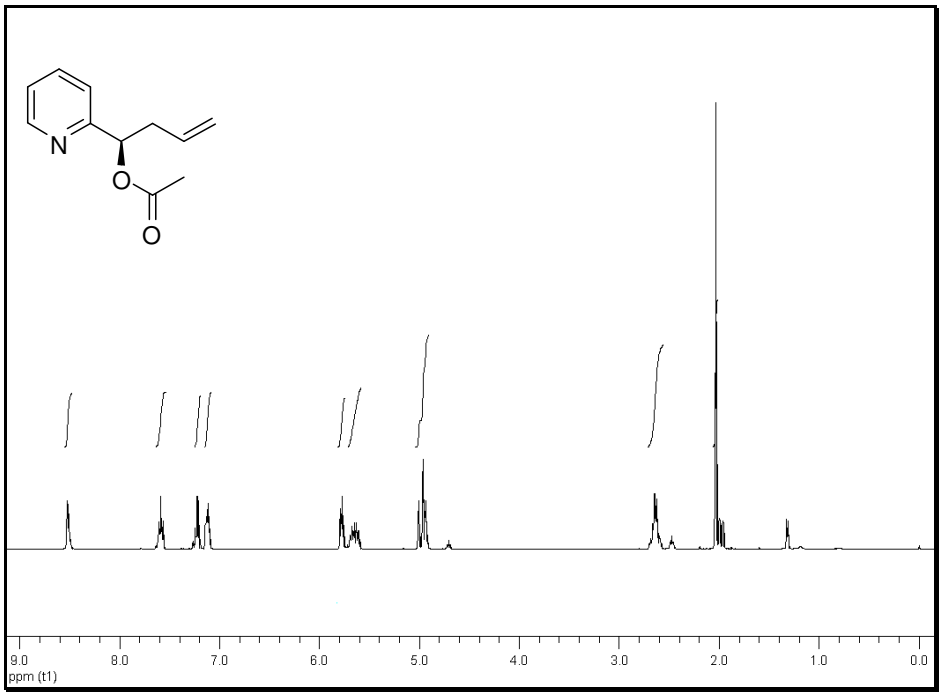

Figure A9. ^{1}H-NMR spectrum of (*R*)-(+)-**57**

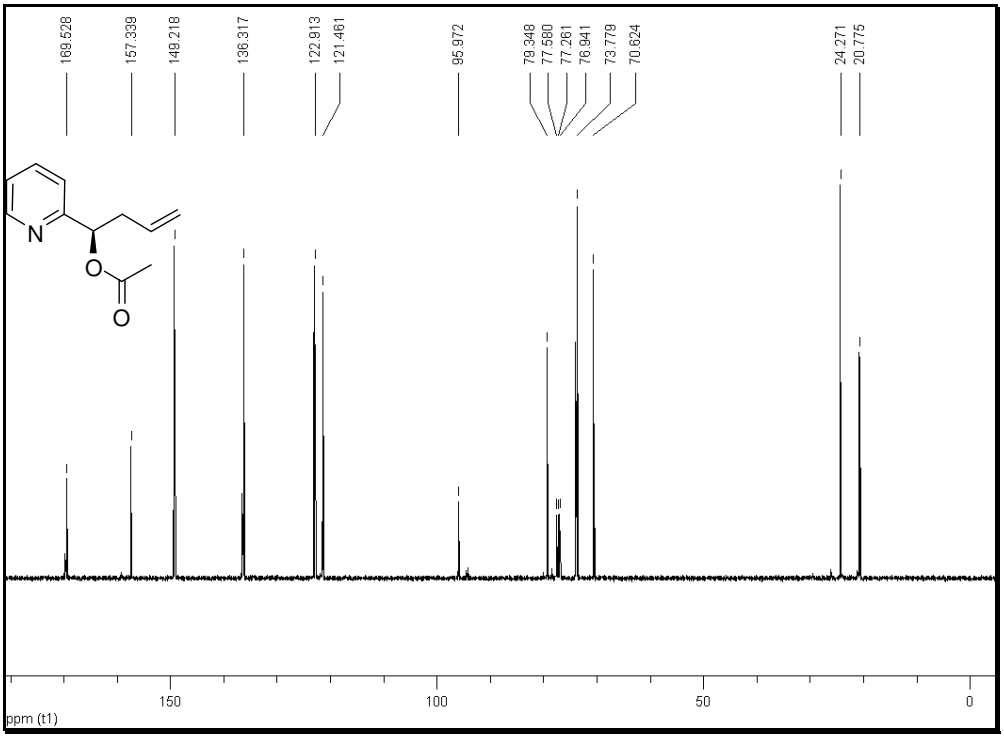

Figure A10. ^{13}C-NMR spectrum of (*R*)-(+)-**57**

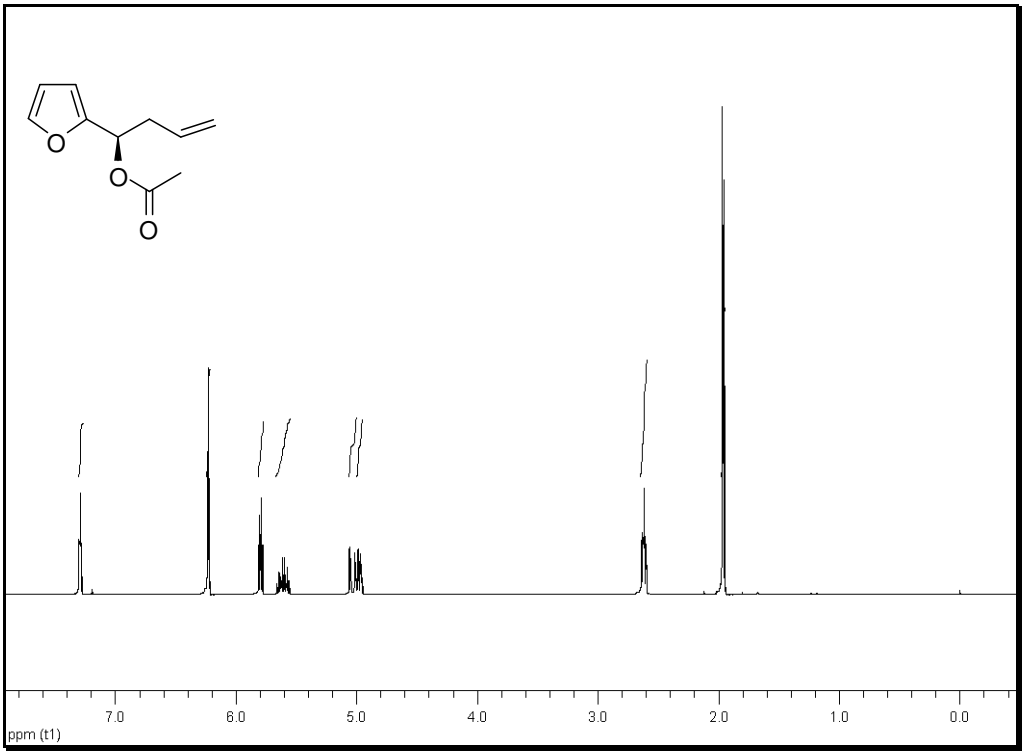

Figure A11. ^{1}H-NMR spectrum of (*R*)-(+)-**59**

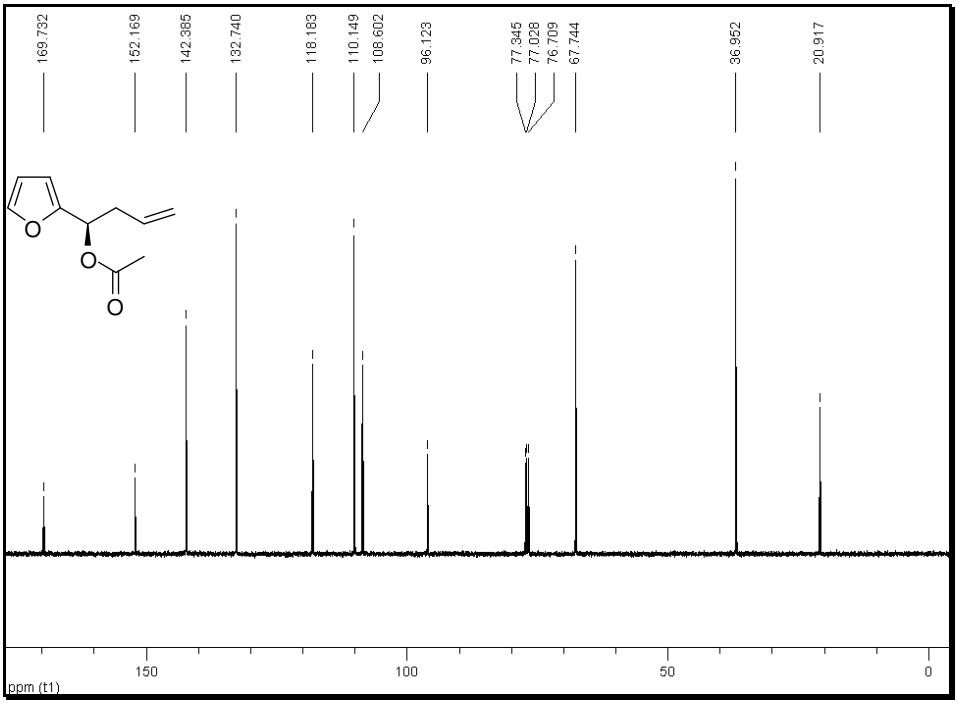

Figure A12. ^{13}C-NMR spectrum of (*R*)-(+)**59**

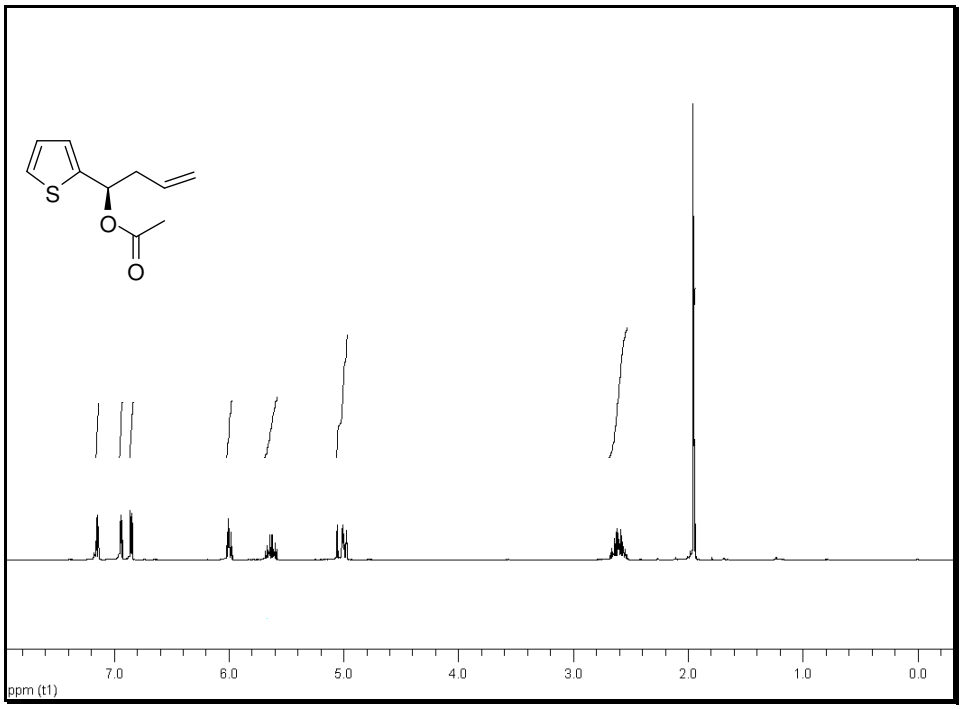

Figure A13. ^{1}H-NMR spectrum of (*R*)-(+)-**60**

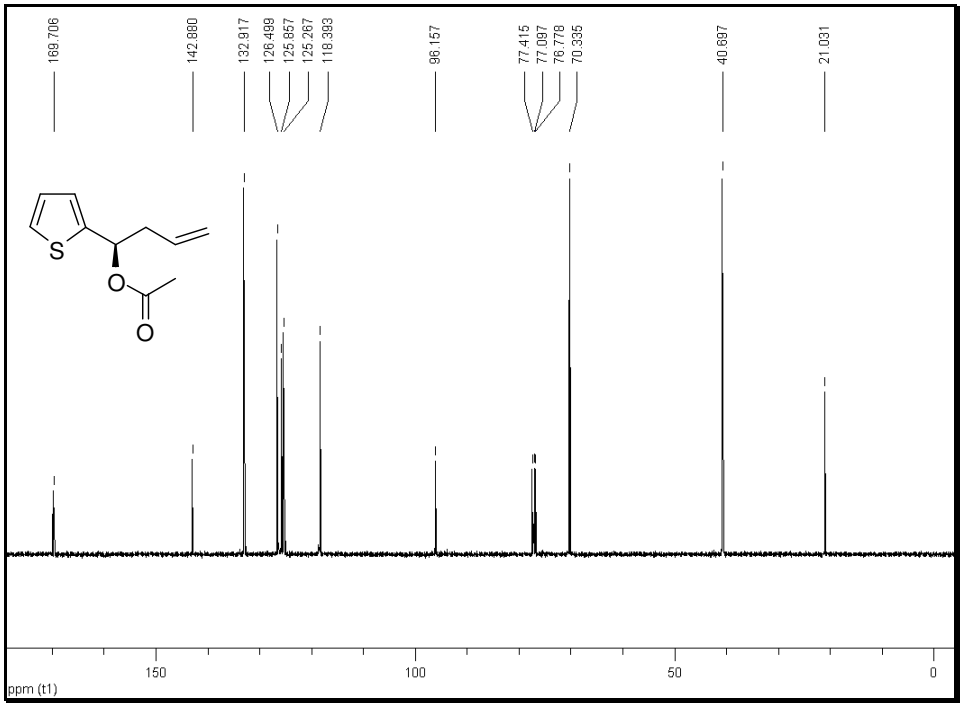

Figure A14. ^{13}C-NMR spectrum of (*R*)-(+)-**60**

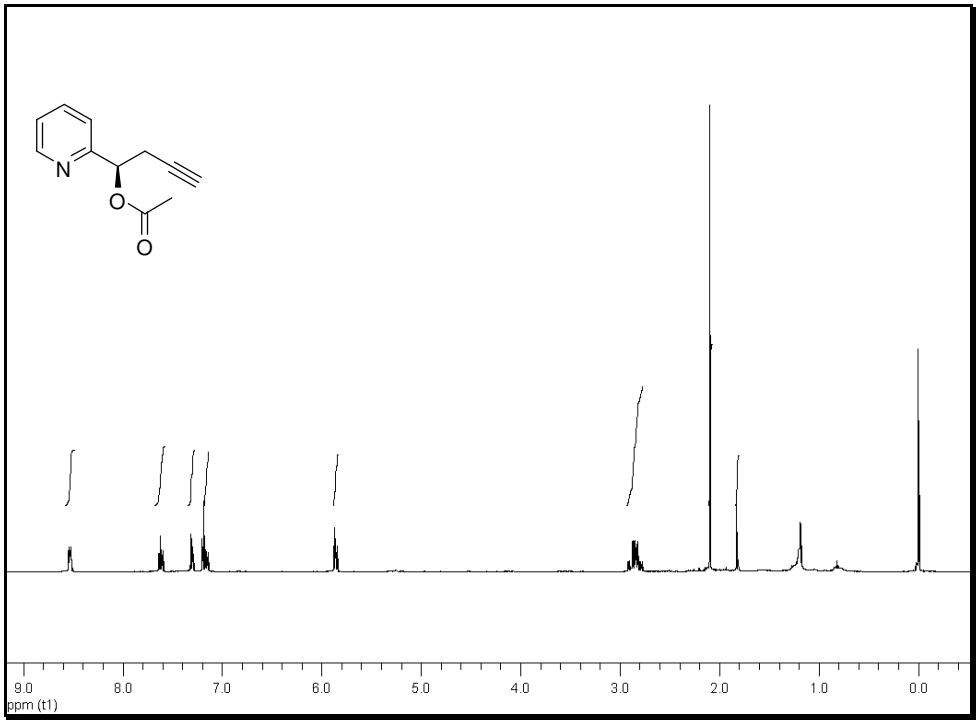

Figure A15. ^{1}H-NMR spectrum of (*R*)-(+)-**58**

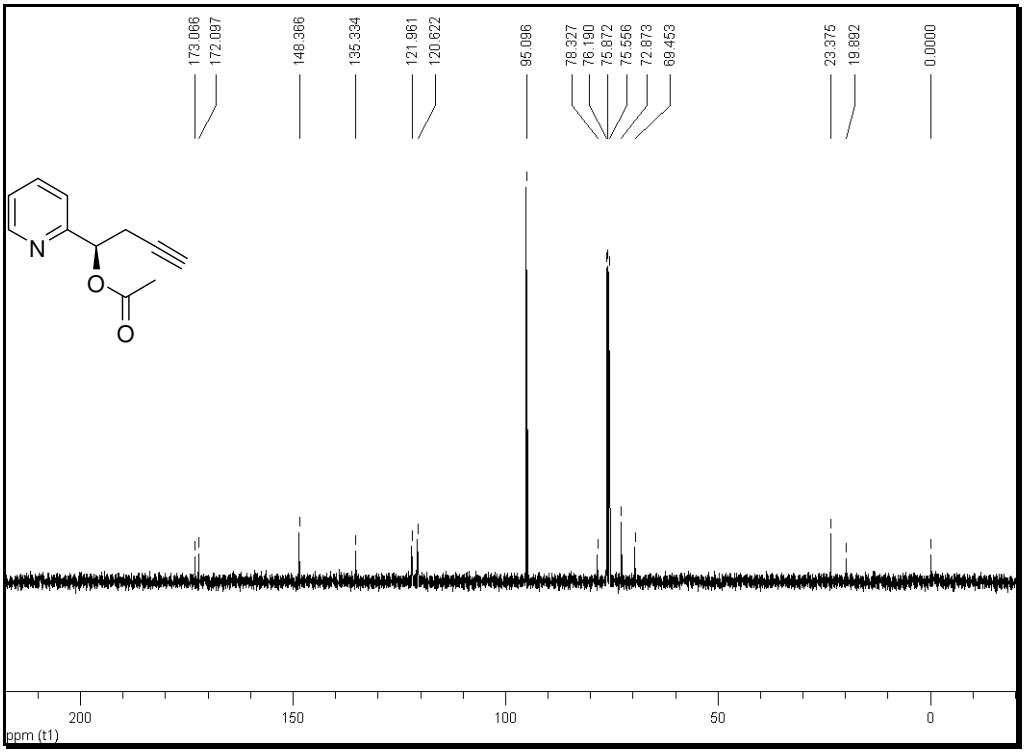

Figure A16. ^{13}C-NMR spectrum of (*R*)-(+)-**58**

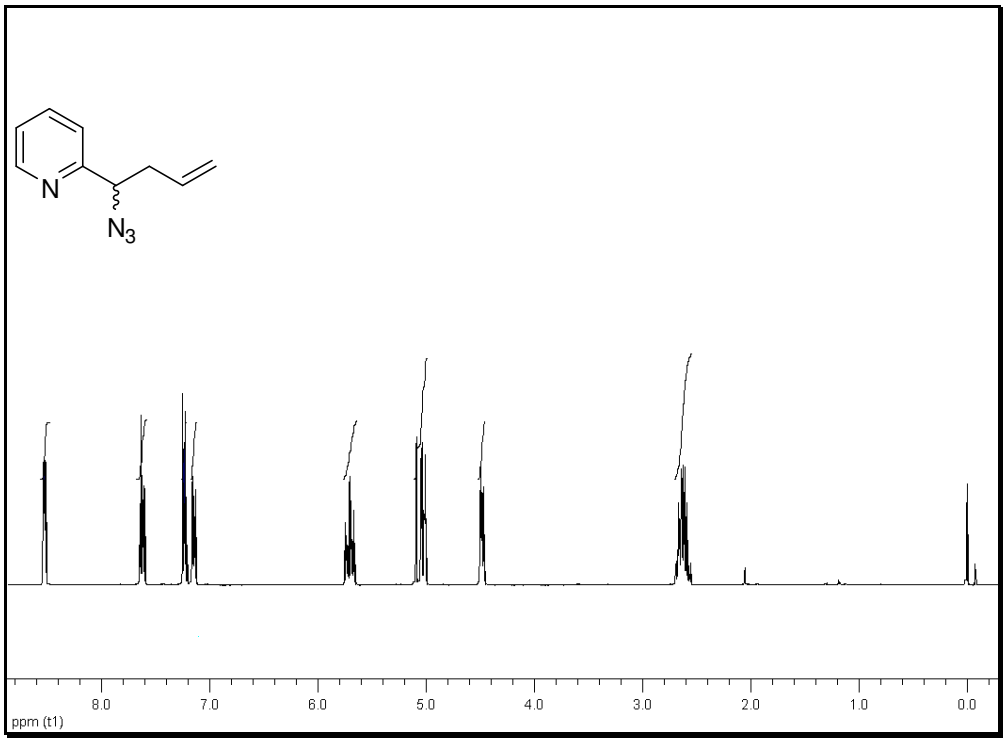

Figure A17. ^{1}H-NMR spectrum of *rac*-**62**

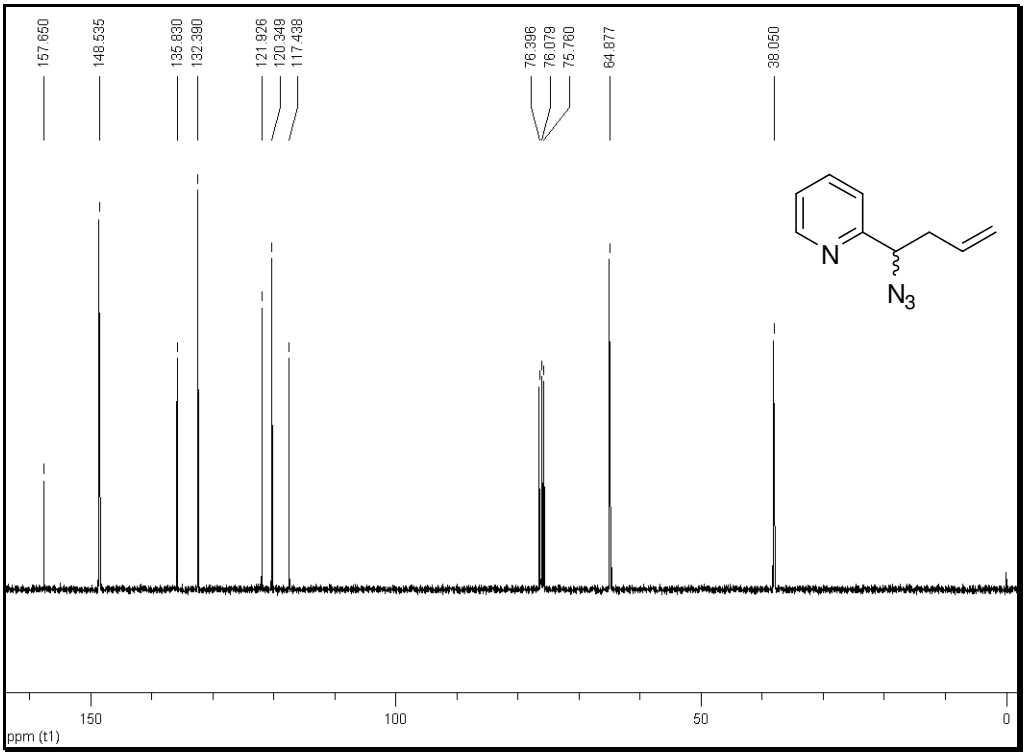

Figure A18. 13C-NMR spectrum of *rac*-**62**

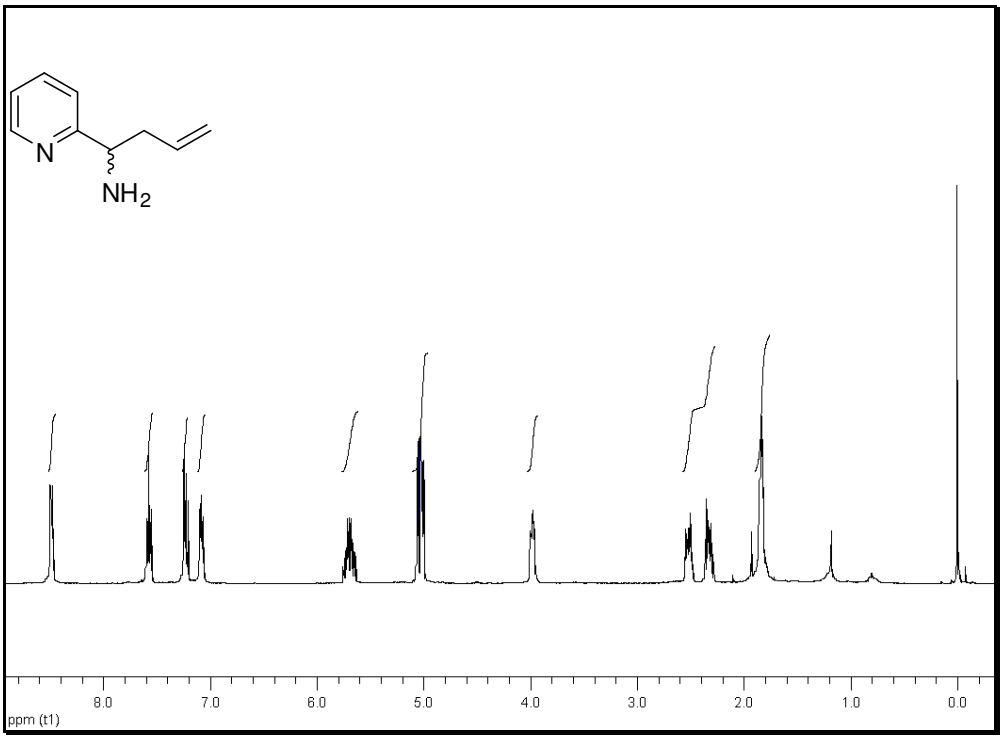

Figure A19. [1]H-NMR spectrum of *rac*-**63**

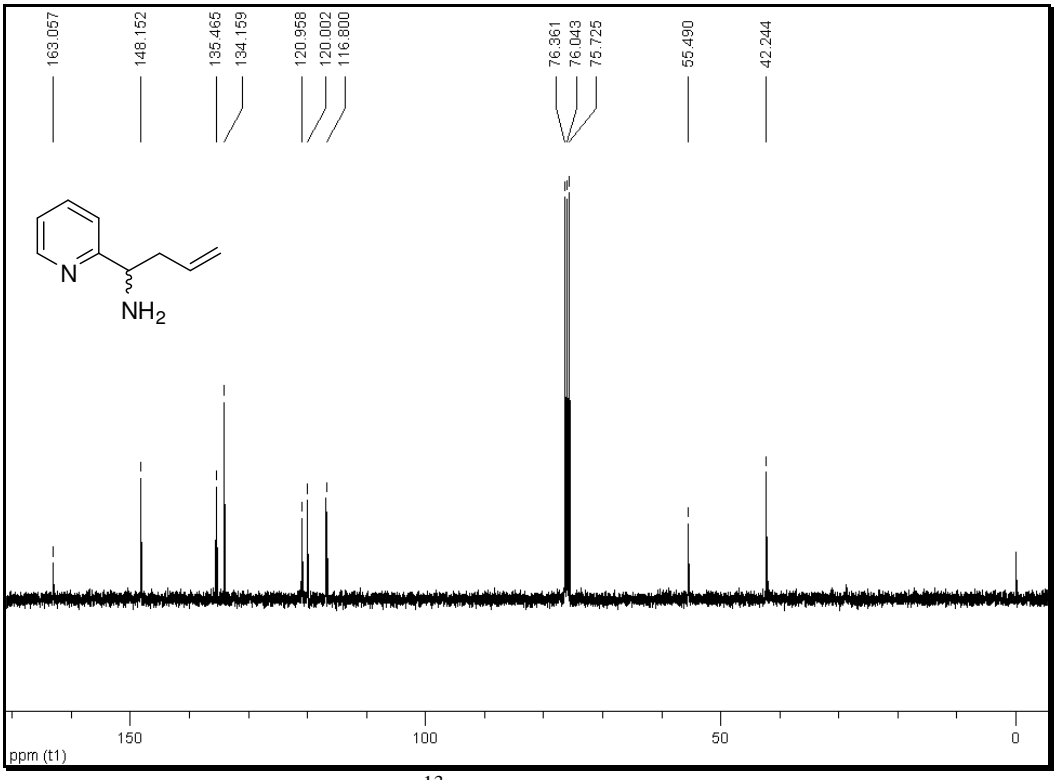

Figure A20. ^{13}C-NMR spectrum of *rac*-**63**

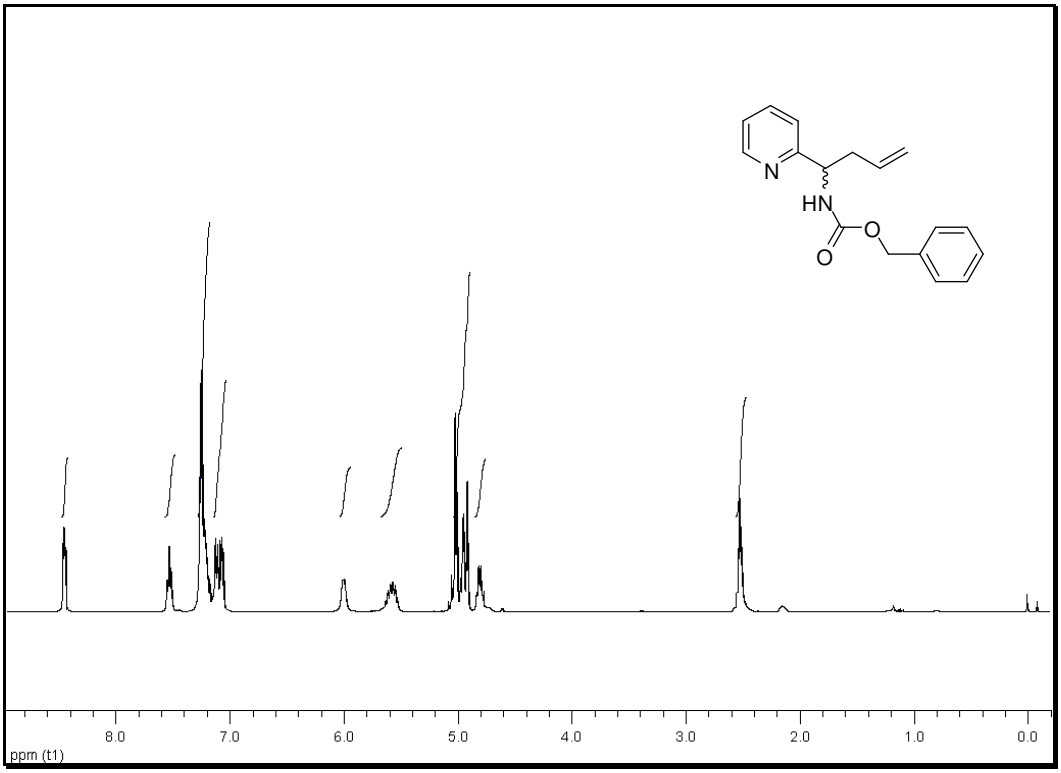

Figure A21. ^{1}H-NMR spectrum of *rac*-**64**

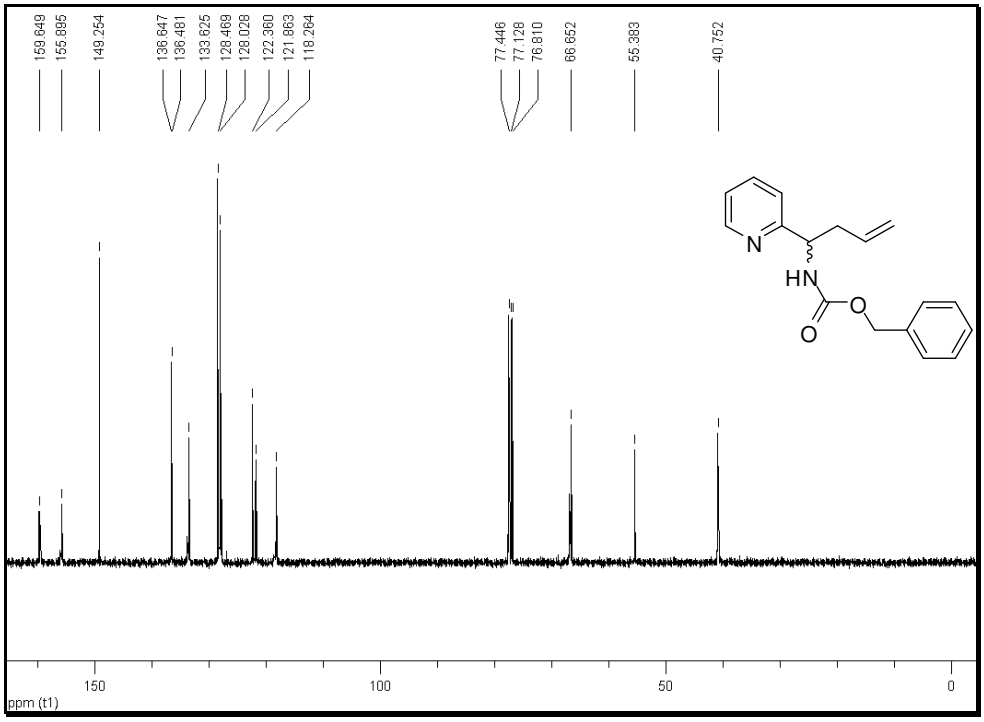

Figure A22. ^{13}C-NMR spectrum of *rac*-**64**

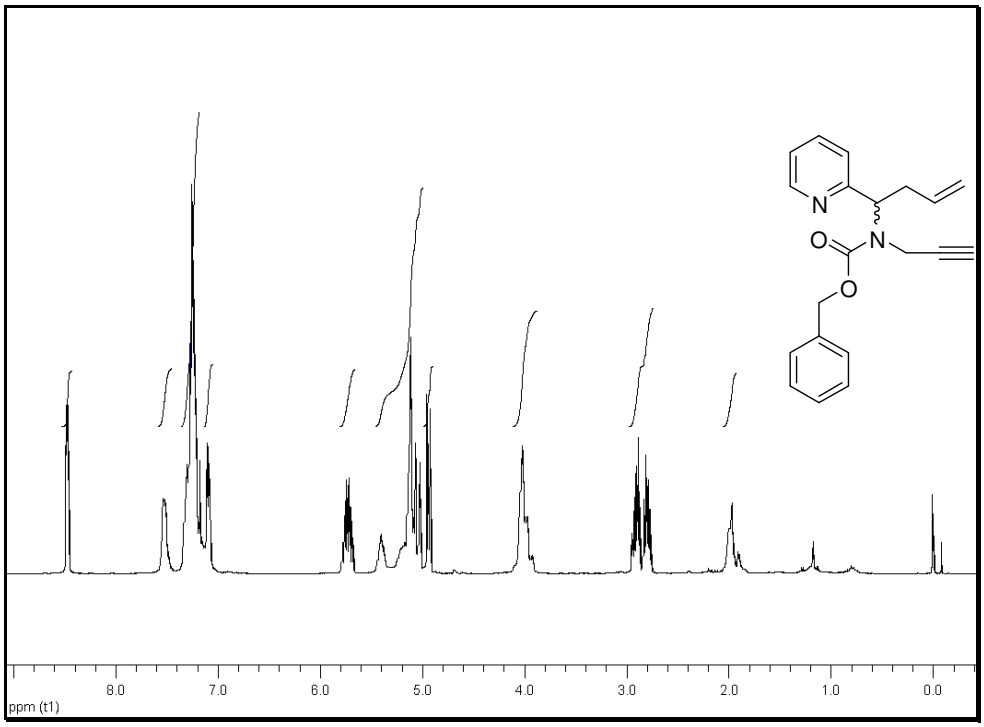

Figure A23. ^{1}H-NMR spectrum of *rac*-**65**

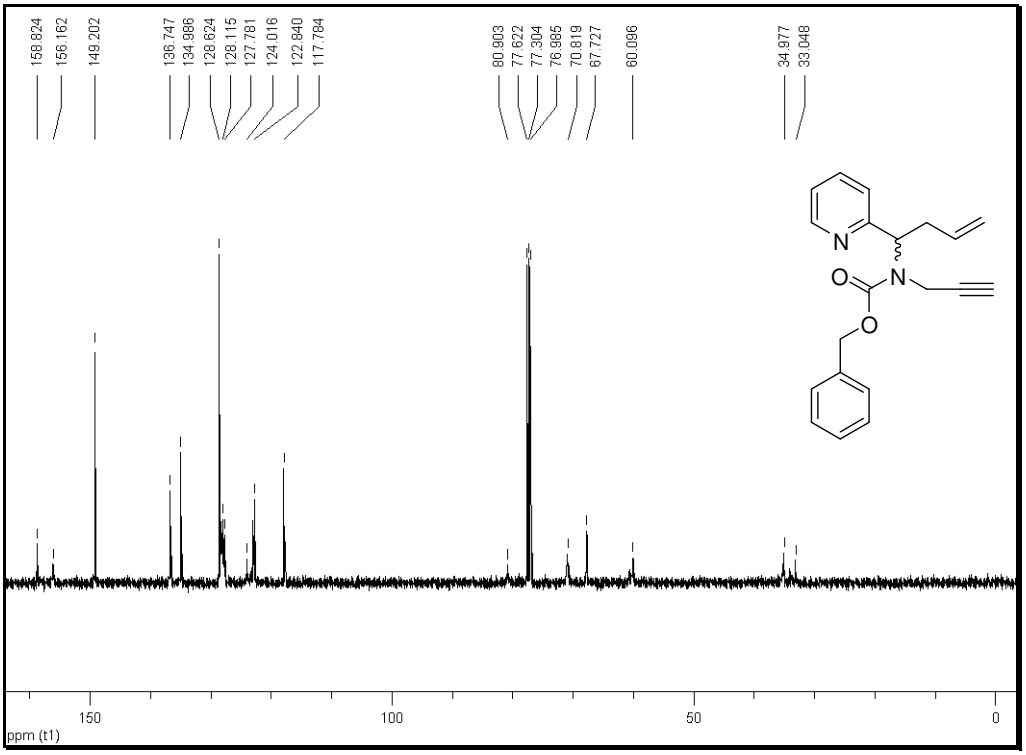

Figure A24. ^{13}C-NMR spectrum of rac-**65**

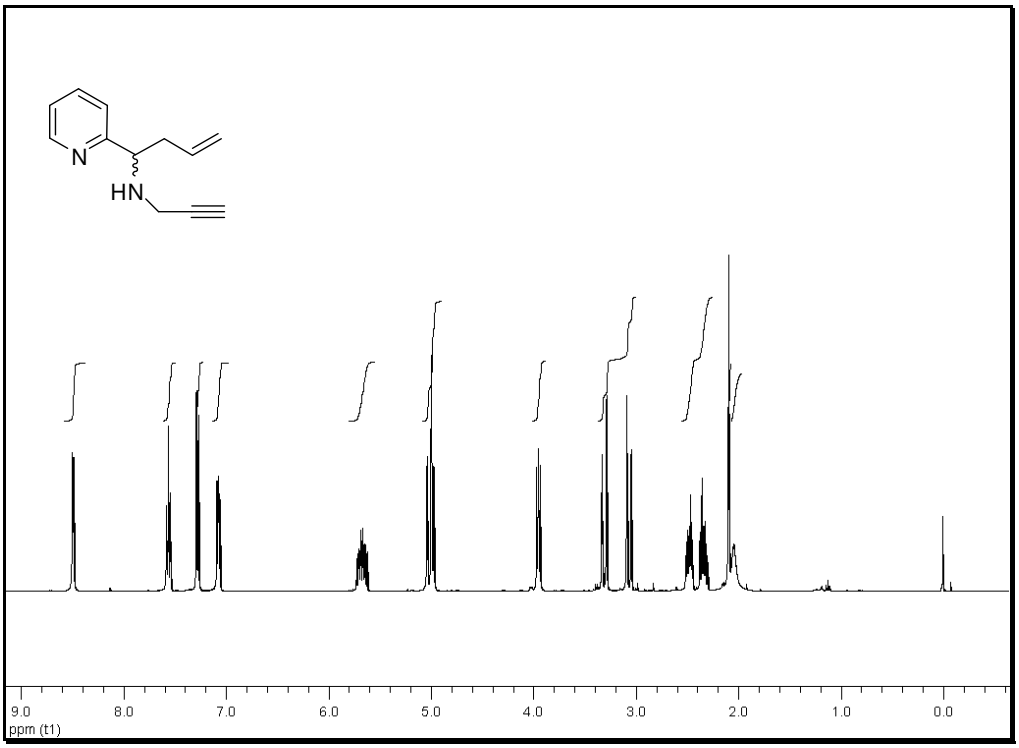

Figure A25. ^{1}H-NMR spectrum of *rac*-**67**

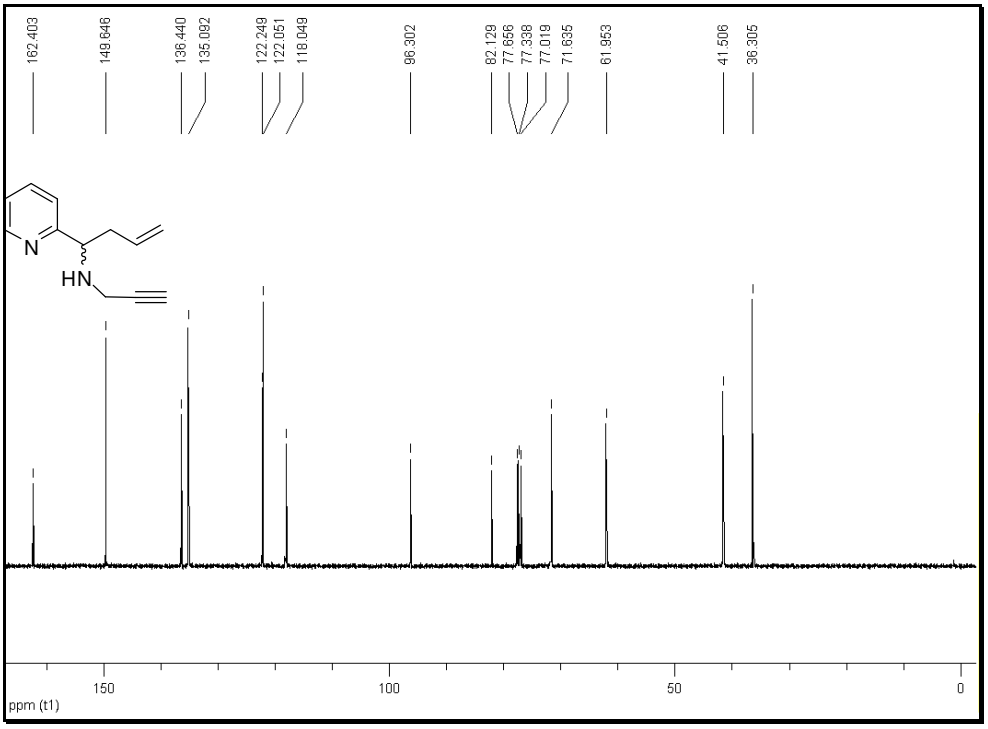

Figure A26. ^{13}C-NMR Spectrum of *rac*-**67**

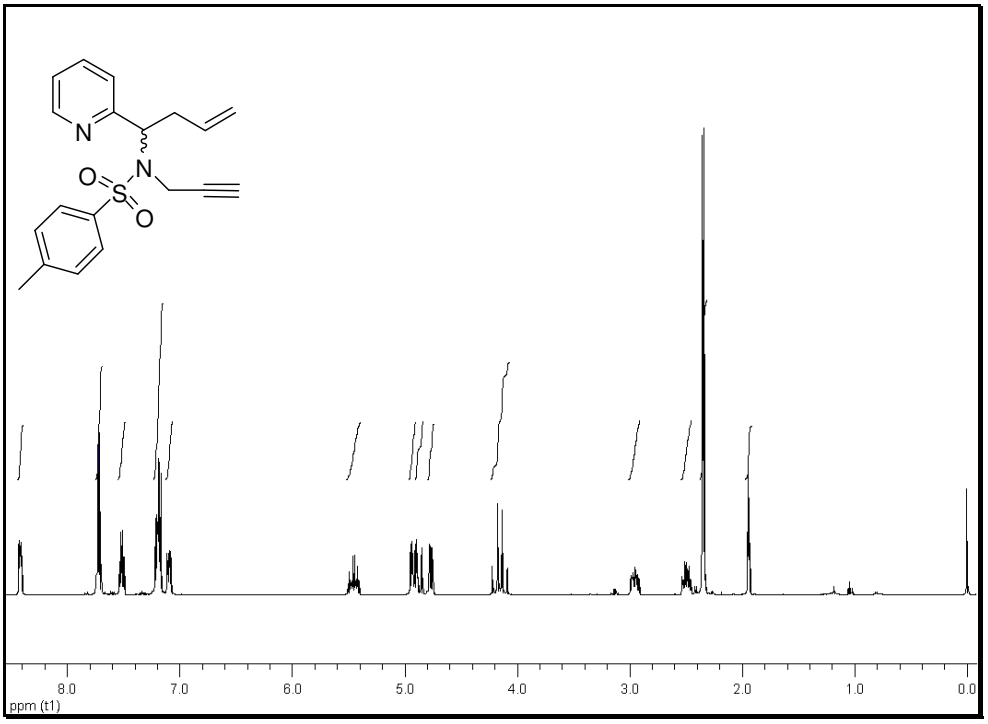

Figure A27. ^{1}H-NMR spectrum of *rac*-**68**

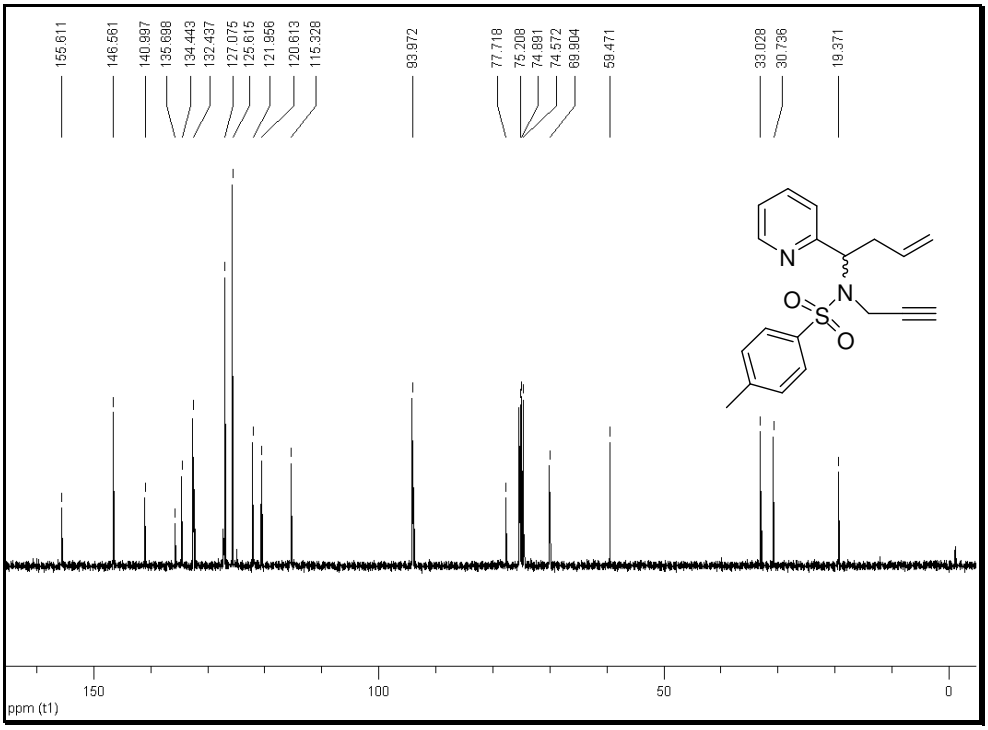

Figure A28. ^{13}C-NMR spectrum of *rac*-**68**

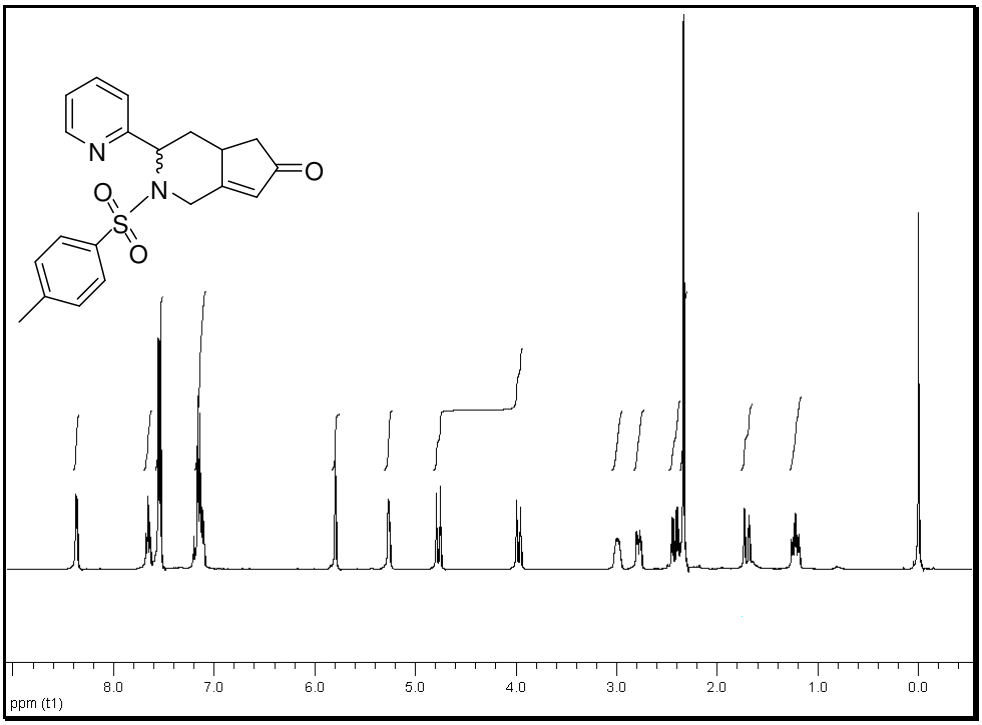

Figure A29. ^{1}H-NMR spectrum of *rac*-**69**

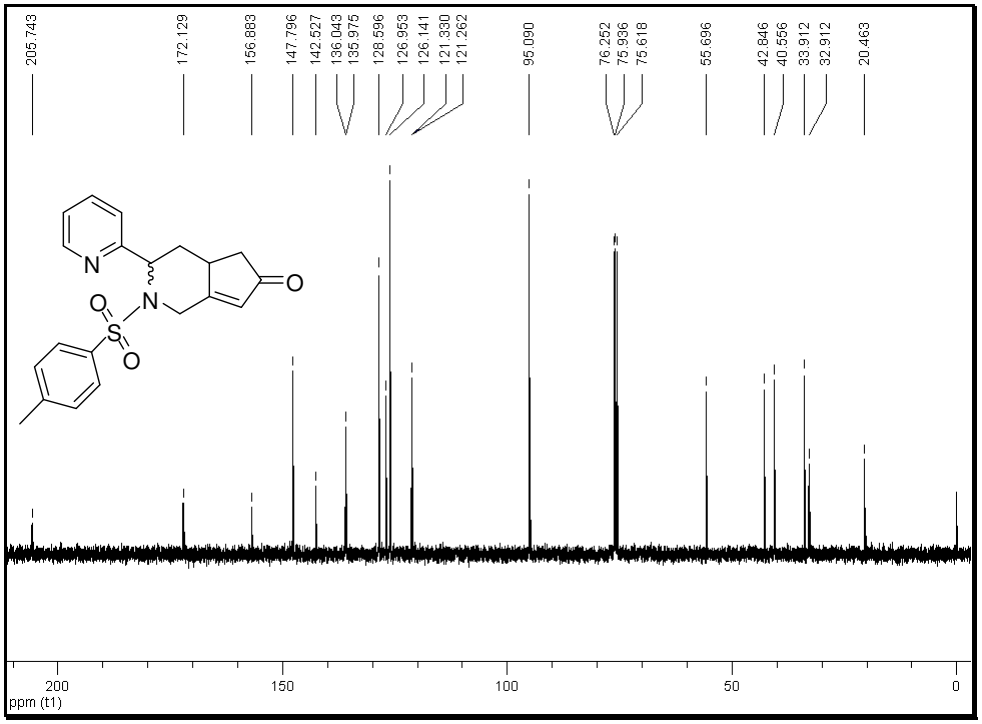

Figure A30. ^{13}C-NMR spectrum of *rac*-**69**

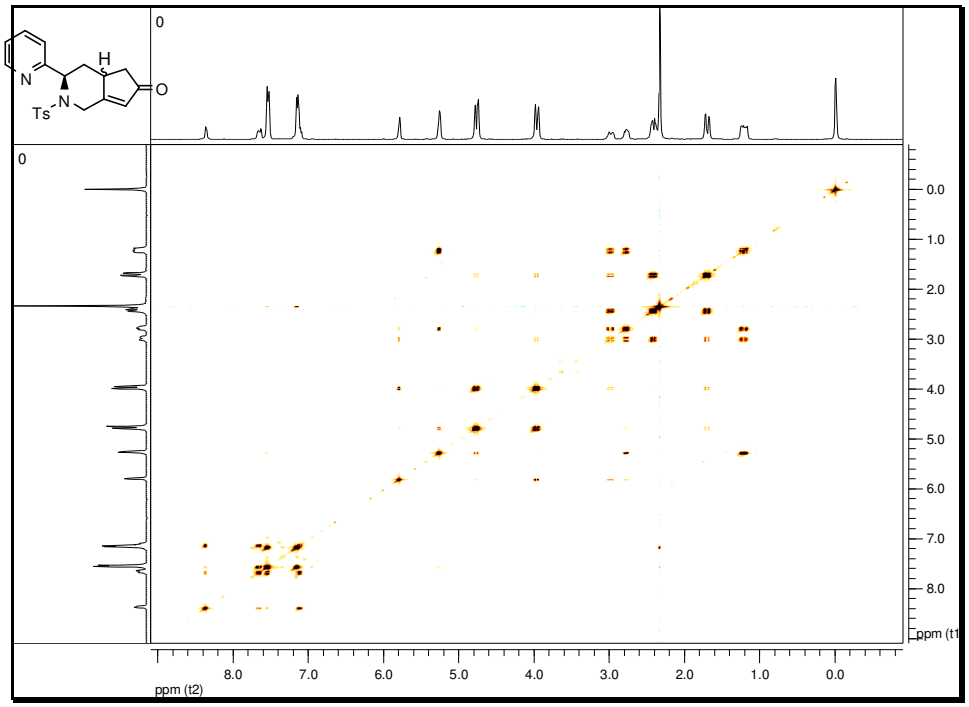

Figure A31. COSY spectrum of (3*R*, 4a*S*(*R*))-(+)-**69**

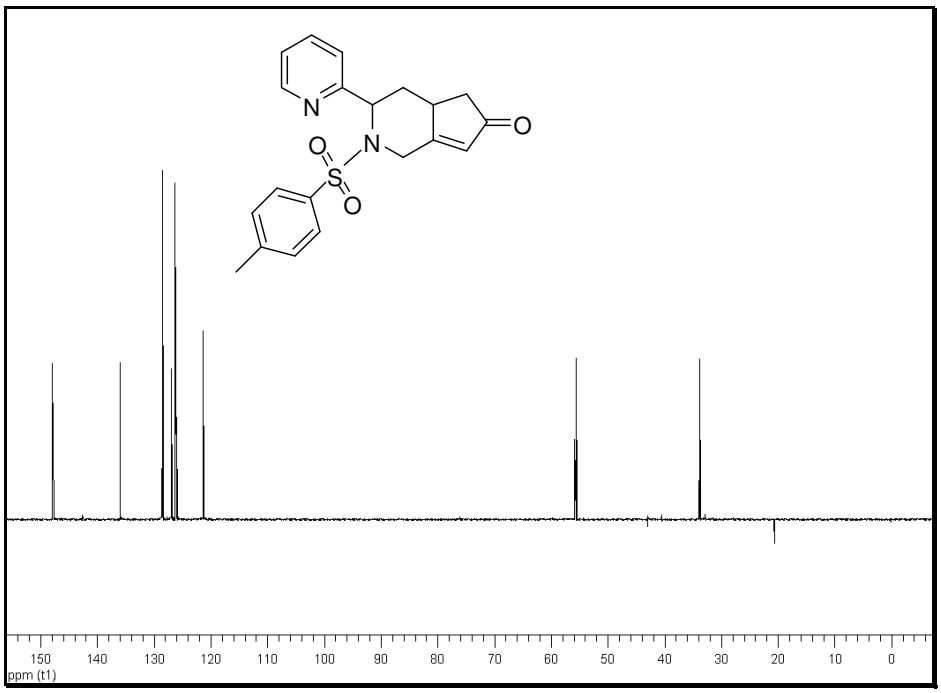

Figure A32. DEPT-90 spectrum of (3*R*, 4a*S*(*R*))-(+)-**69**

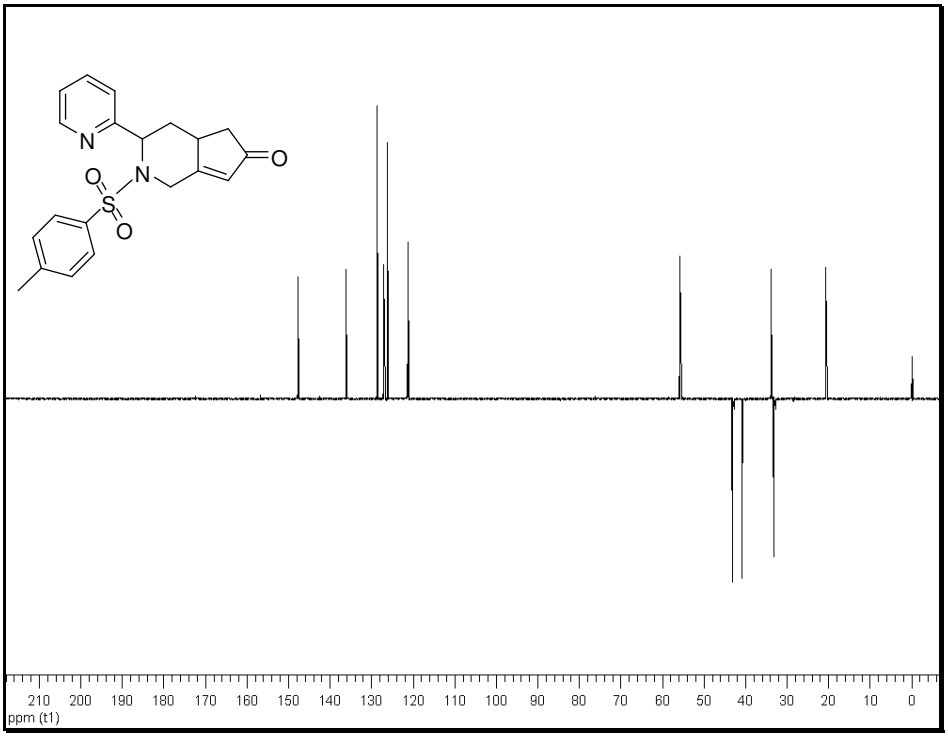

Figure A33. DEPT-135 spectrum of (3*R*, 4a*S*(*R*))-(+)-**69**

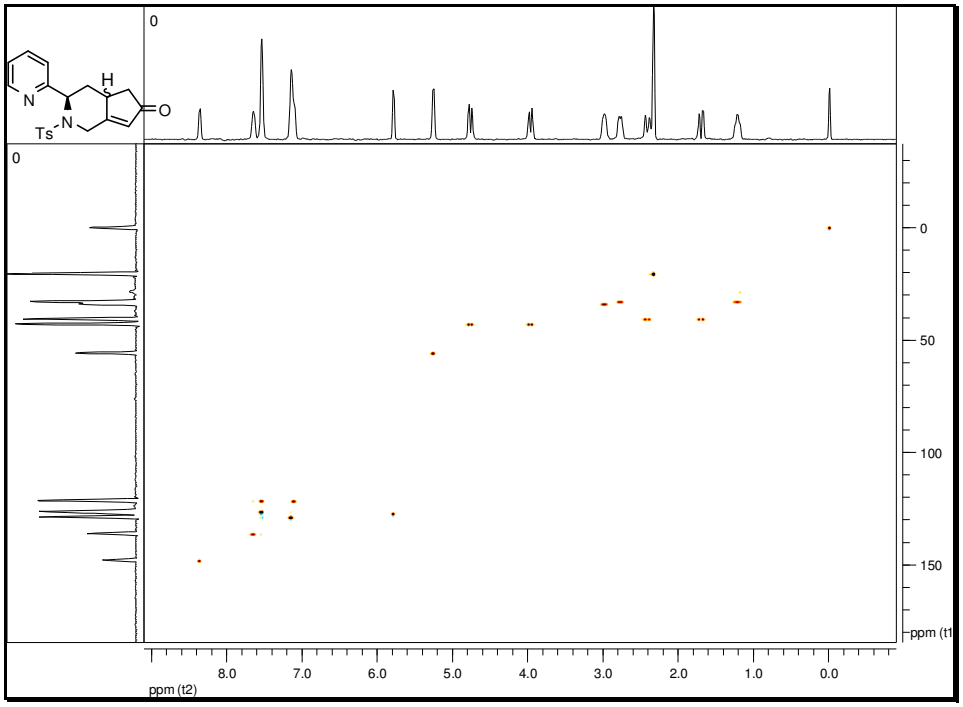

Figure A34. HSQC spectrum of (3*R*, 4a*S*(*R*))-(+)-**69**

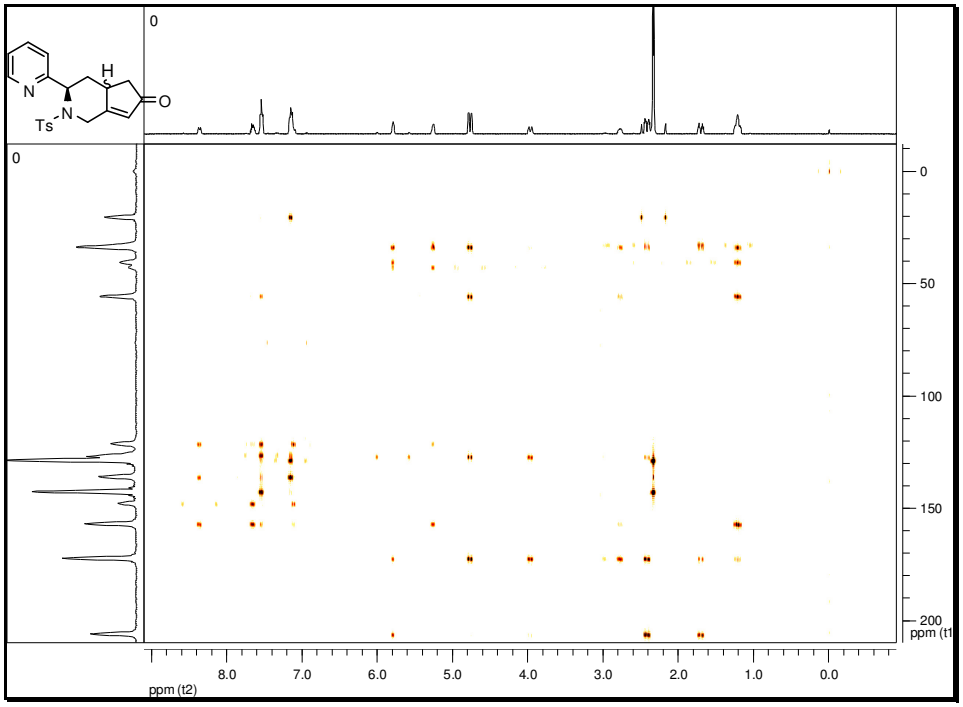

Figure A35. HMBC spectrum of (3*R*, 4a*S*(*R*))-(+)-**69**

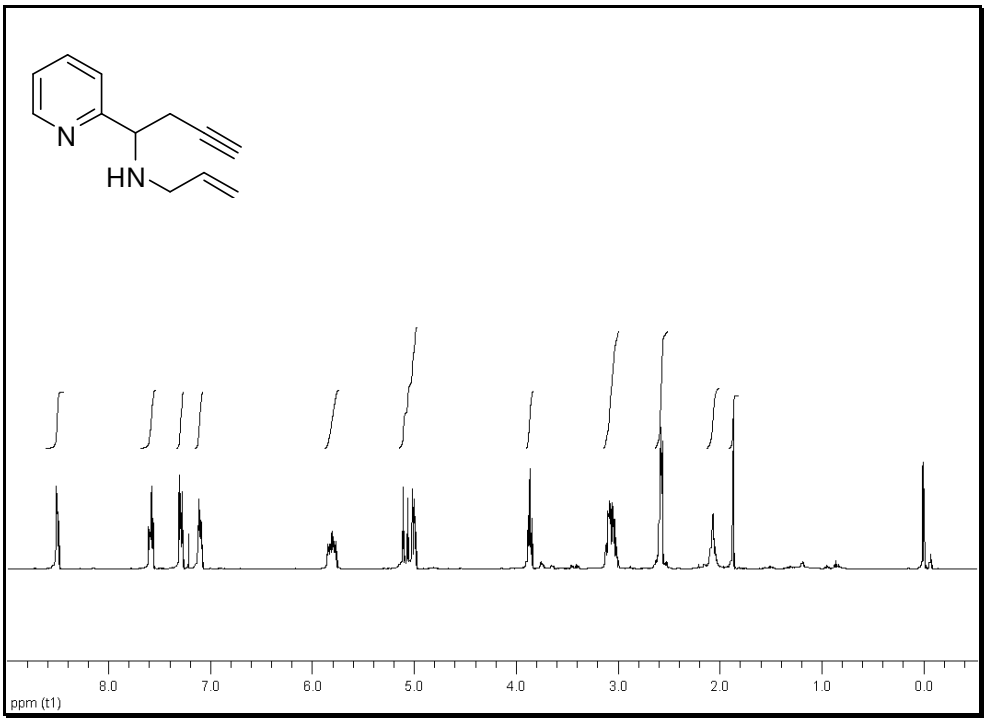

Figure A36. ^{1}H-NMR spectrum of, *rac*-**71**

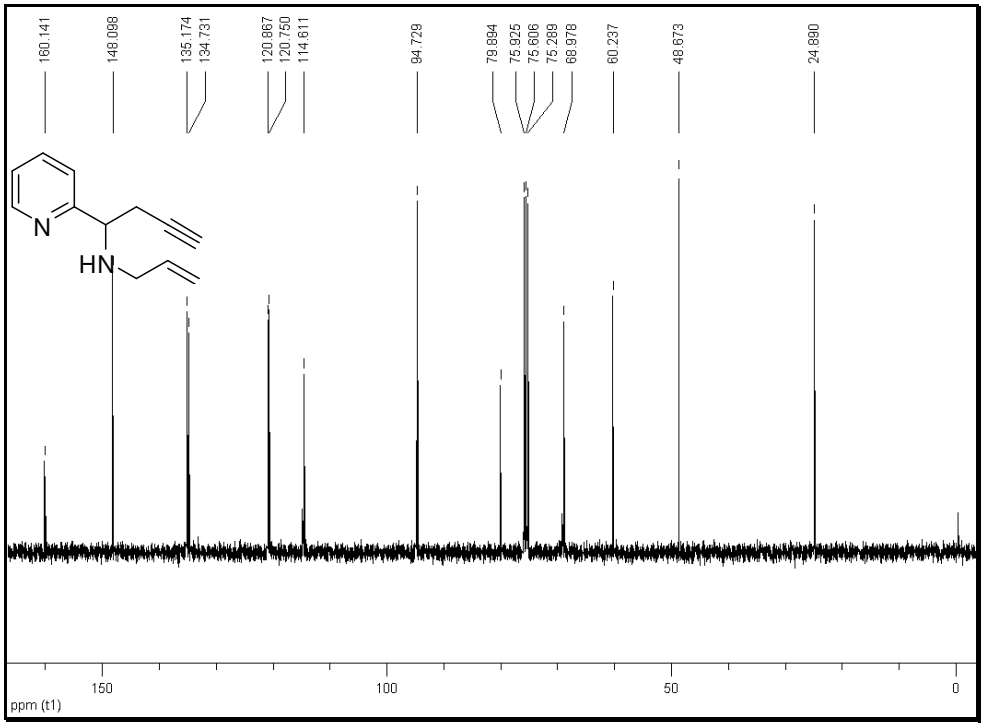

Figure A37. ^{13}C-NMR spectrum of *rac*-**71**

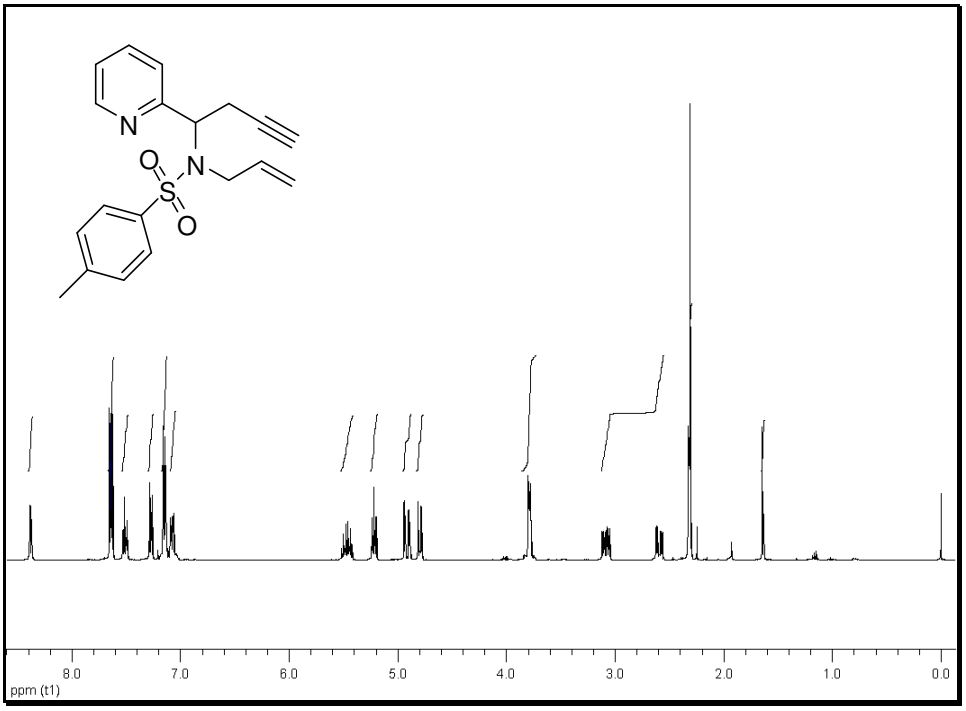

Figure A38. ^{1}H-NMR spectrum of *rac*-**72**

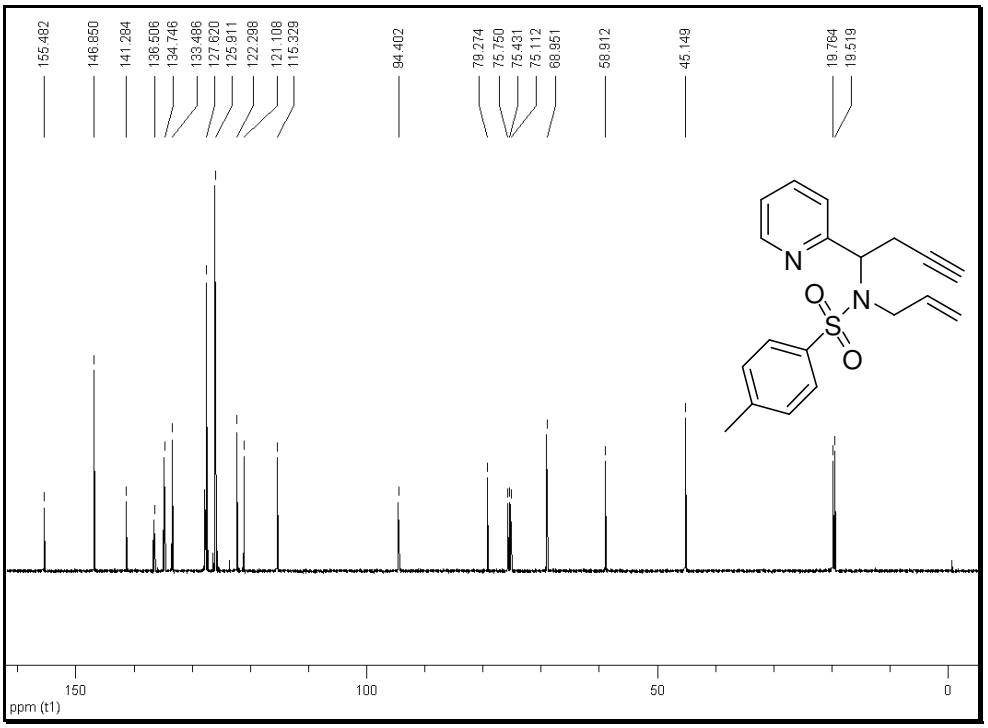

Figure A39. ^{13}C-NMR spectrum of *rac*-**72**

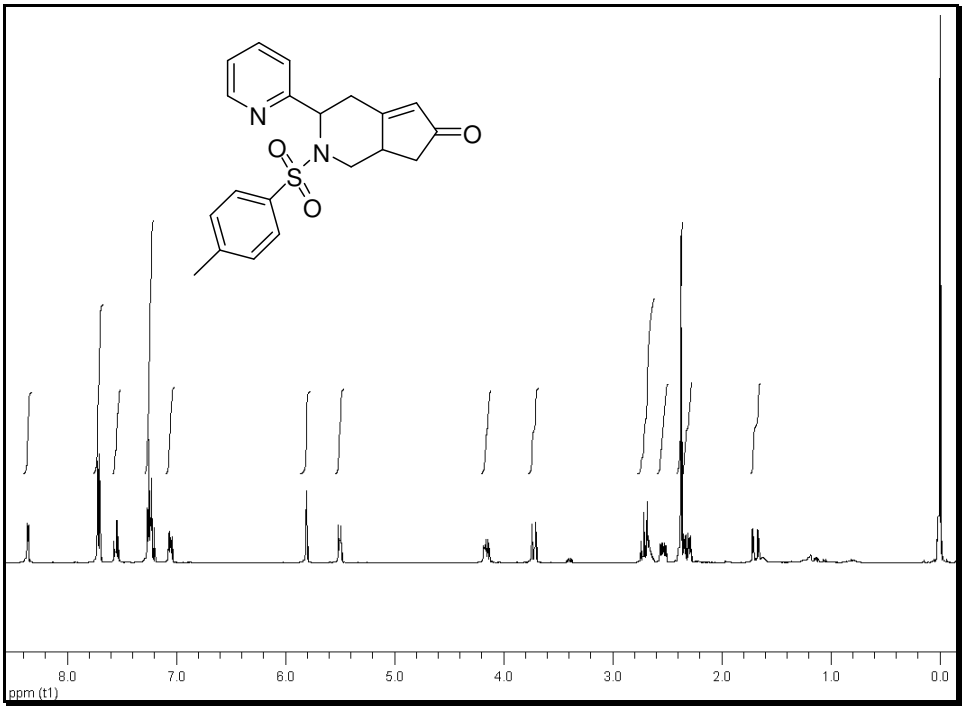

Figure A40. ^{1}H-NMR spectrum of *rac*-**73**

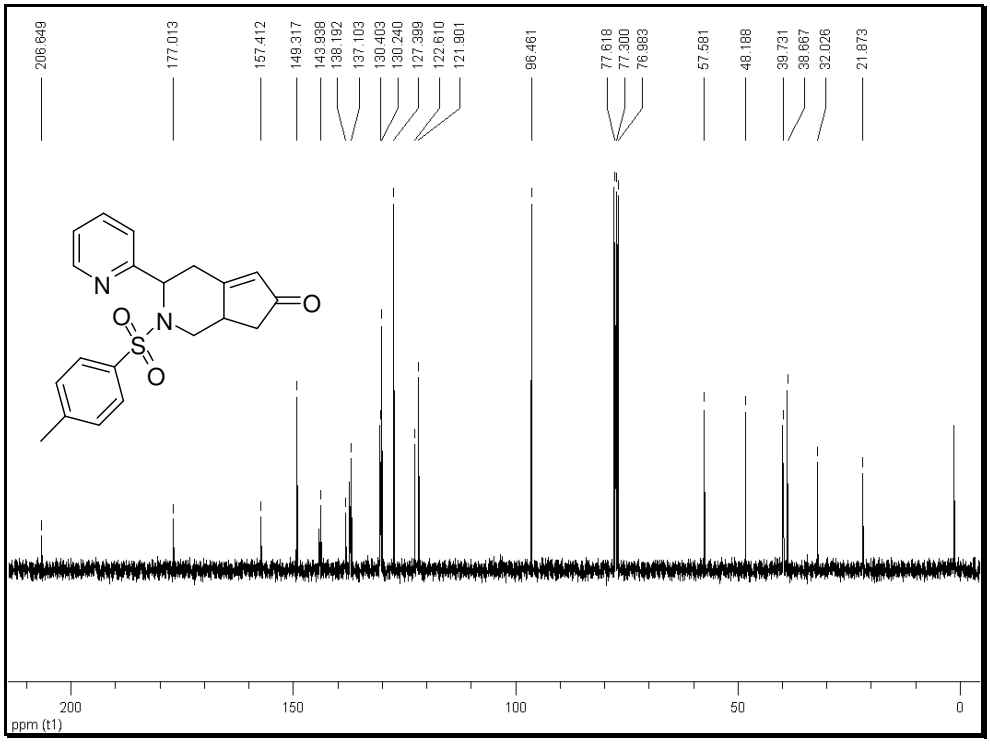

Figure A41. ^{13}C-NMR spectrum *rac*-**73**

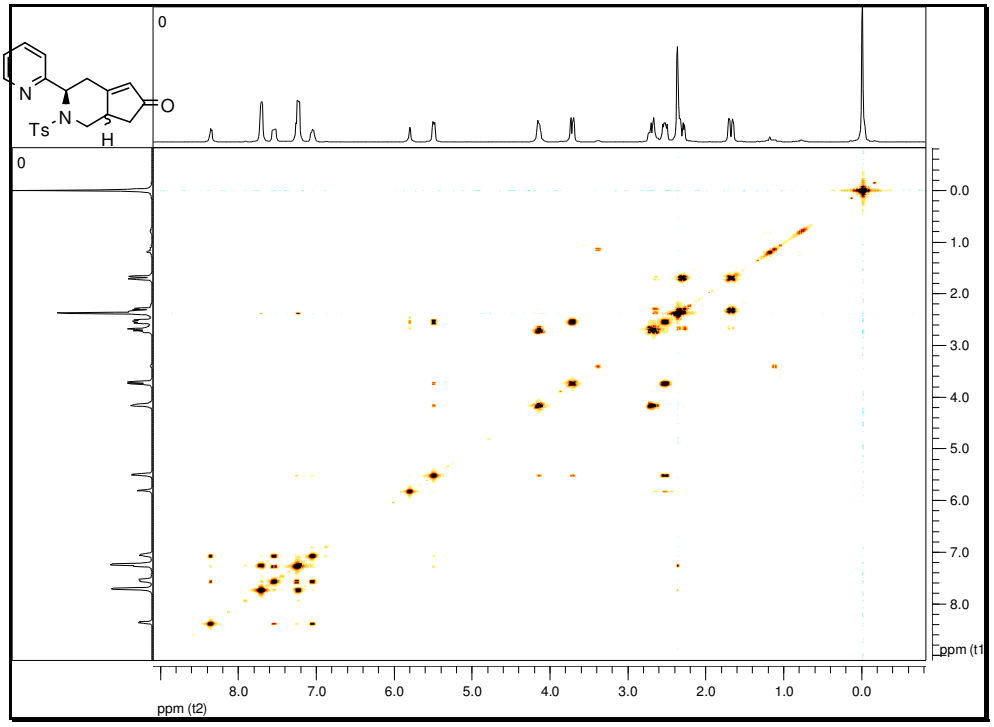

Figure A42. COSY spectrum of (3*R*, 7a*S*(*R*))-(+)-**73**

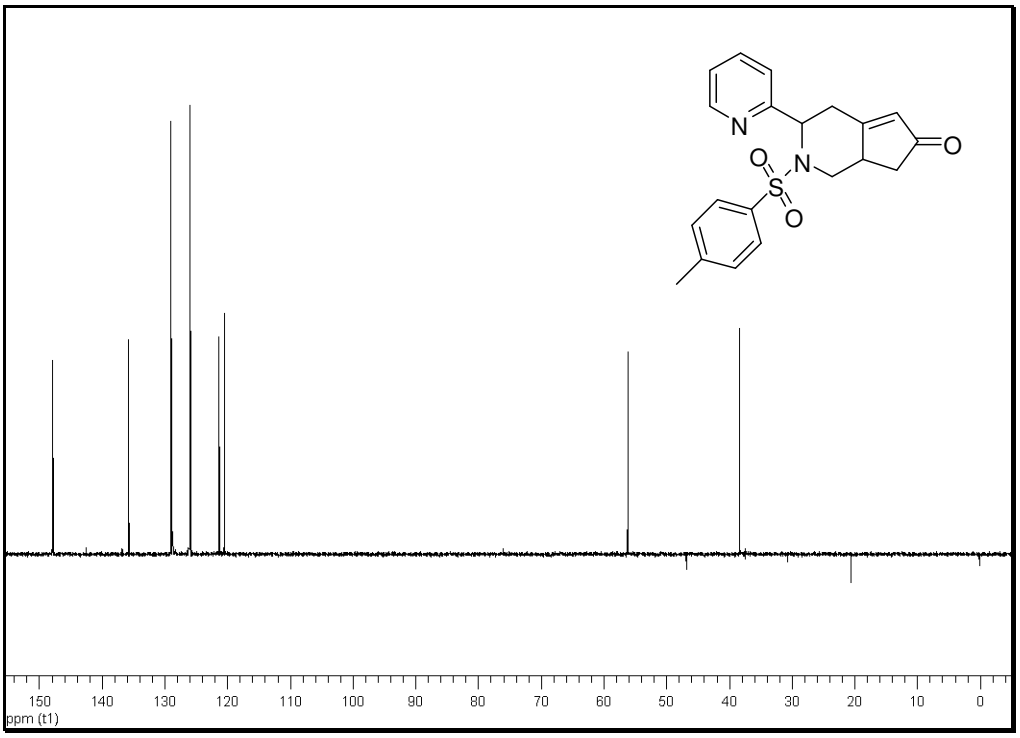

Figure A43. DEPT-90 spectrum of (3*R*, 7a*S*(*R*))-(+)-**73**

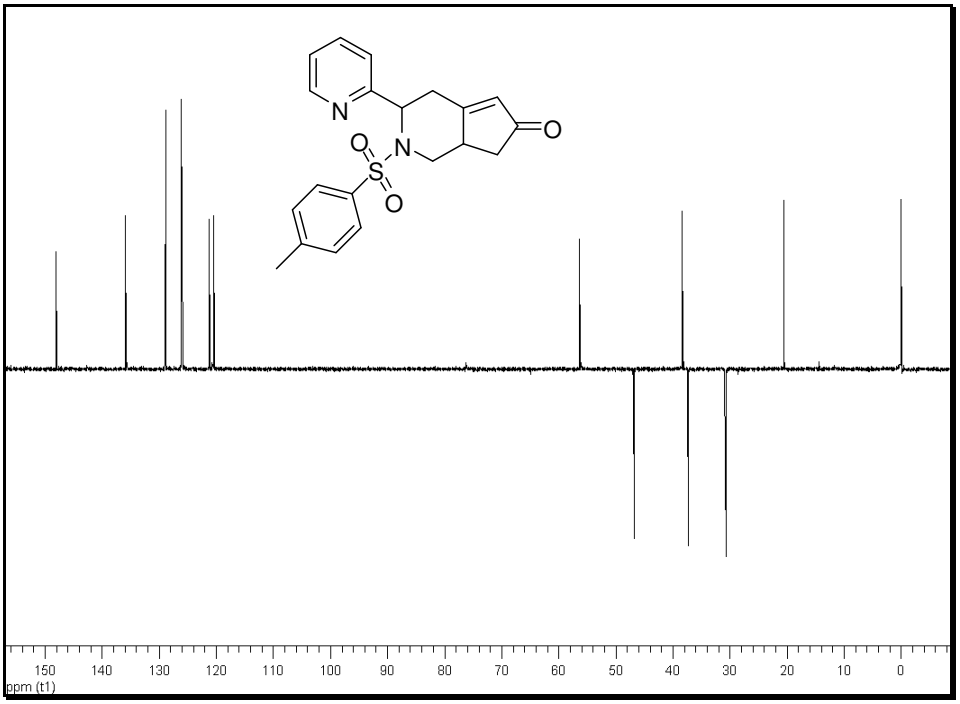

Figure A44. DEPT-135 spectrum of (3*R*, 7a*S*(*R*))-(+)-**73**

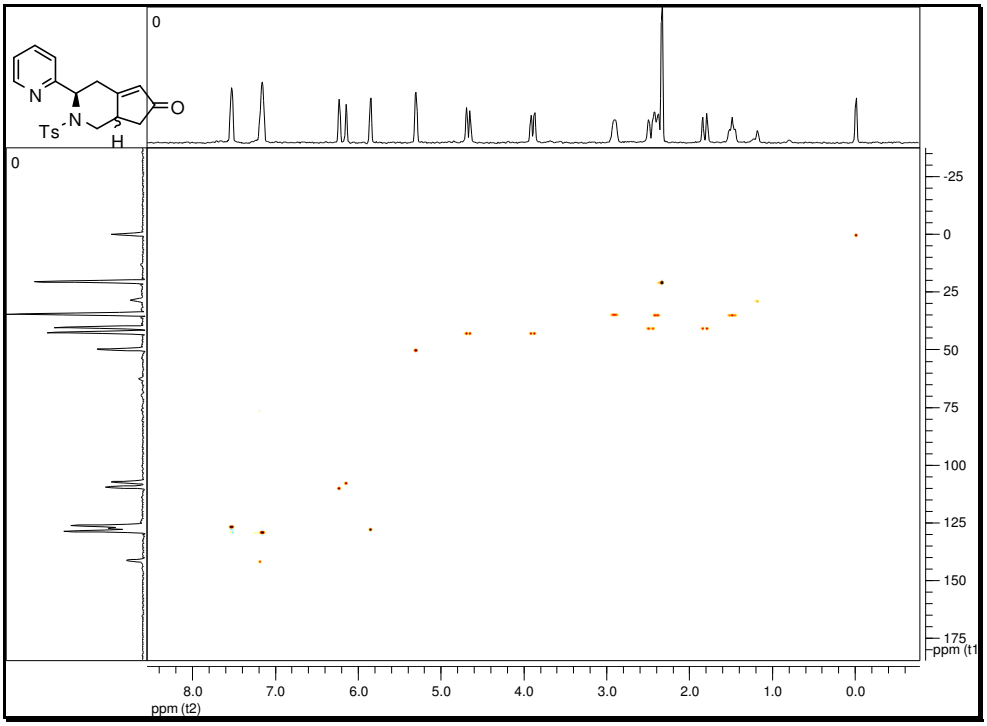

Figure A45. HSQC spectrum of (3*R*, 7a*S*(*R*))-(+)-**73**

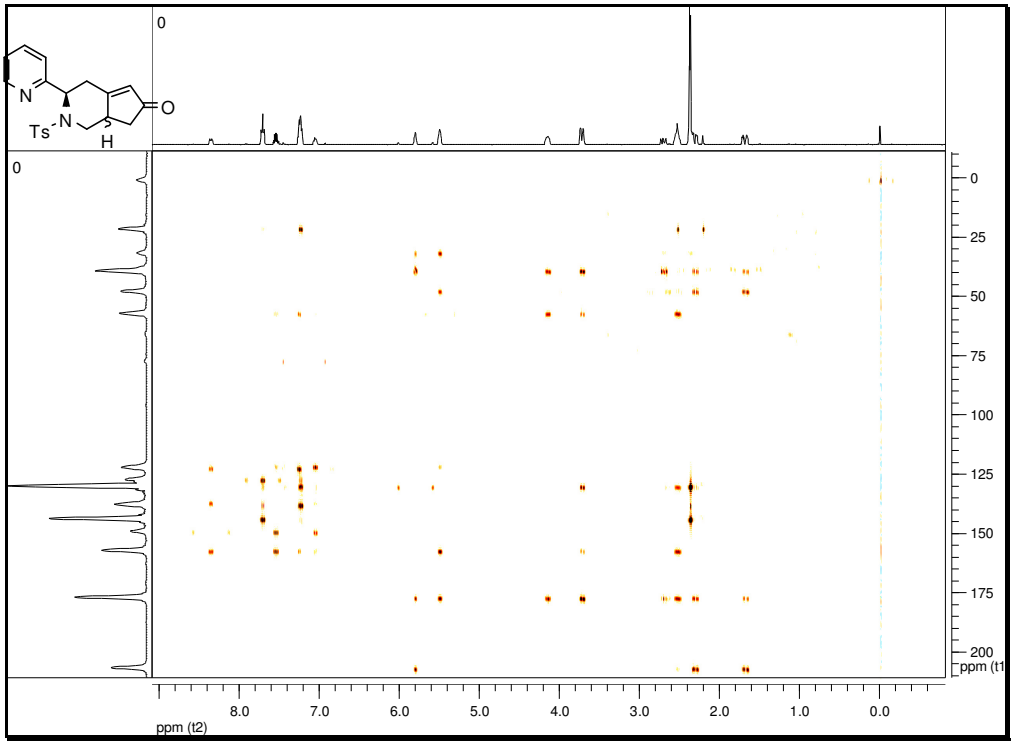

Figure A46. HMBC spectrum of (3*R*, 7a*S*(*R*))-(+)-**73**

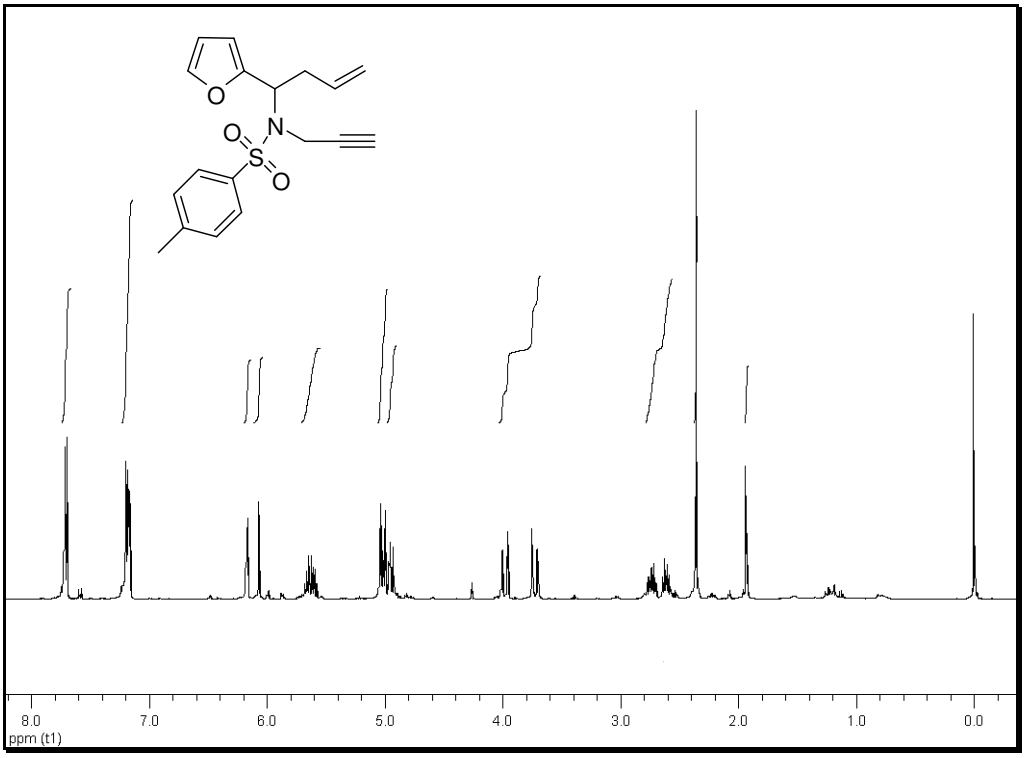

Figure A47. ^{1}H-NMR spectrum of *rac*-**75**

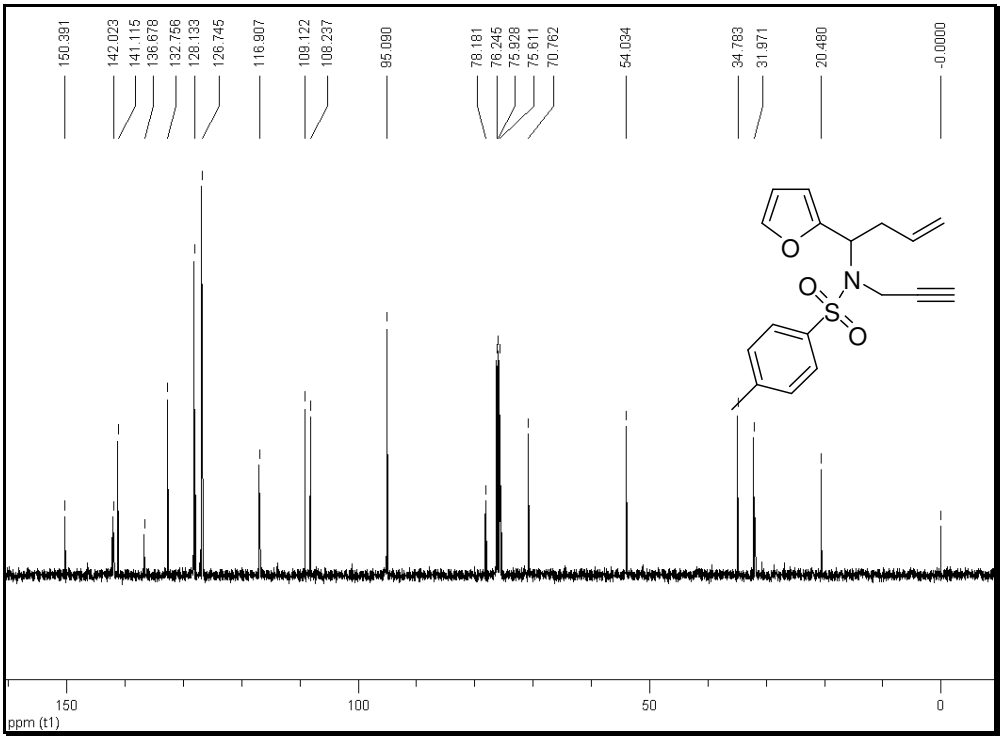

Figure A48. ^{13}C-NMR spectrum of *rac*-**75**

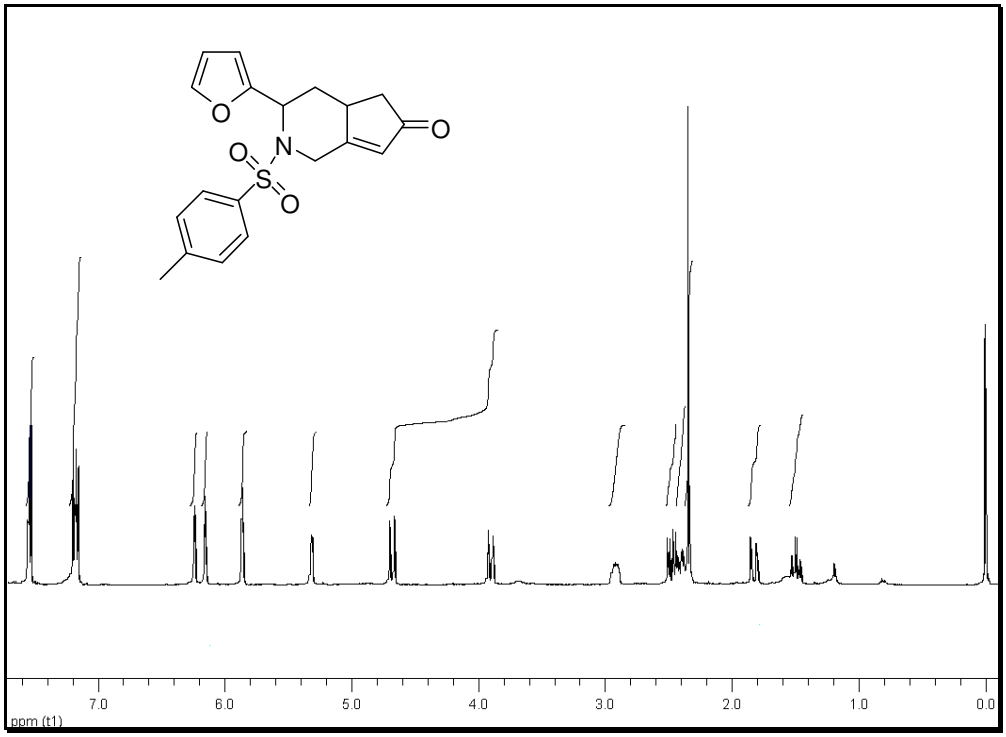

Figure A49. ^{1}H-NMR spectrum of *rac*-**76**

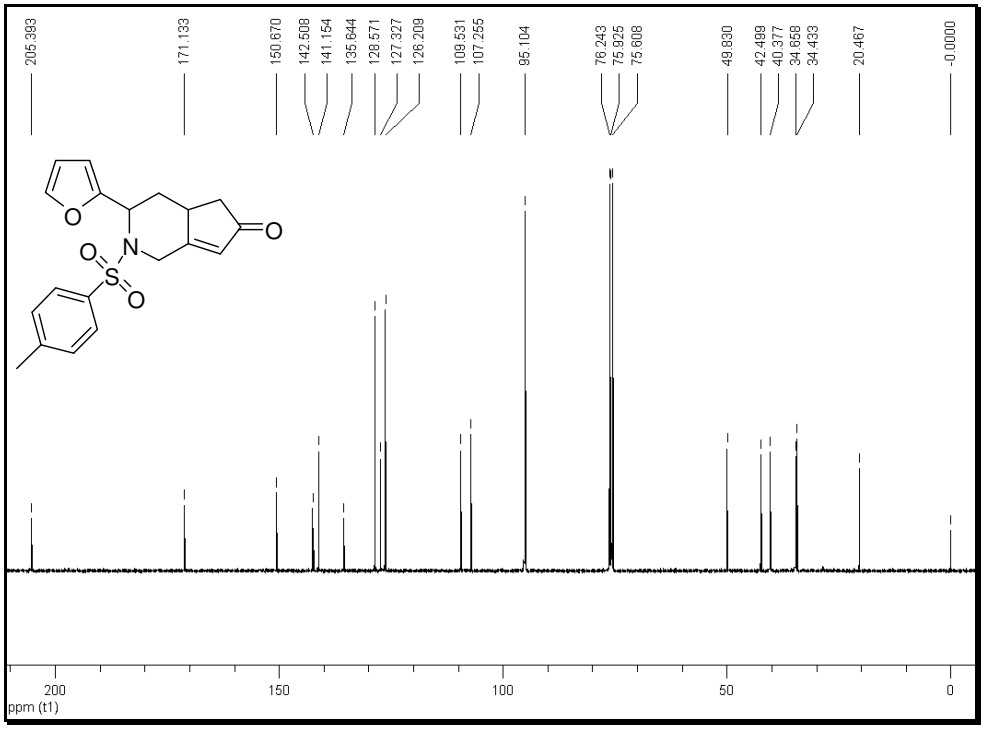

Figure A50. ^{13}C-NMR spectrum of *rac*-**76**

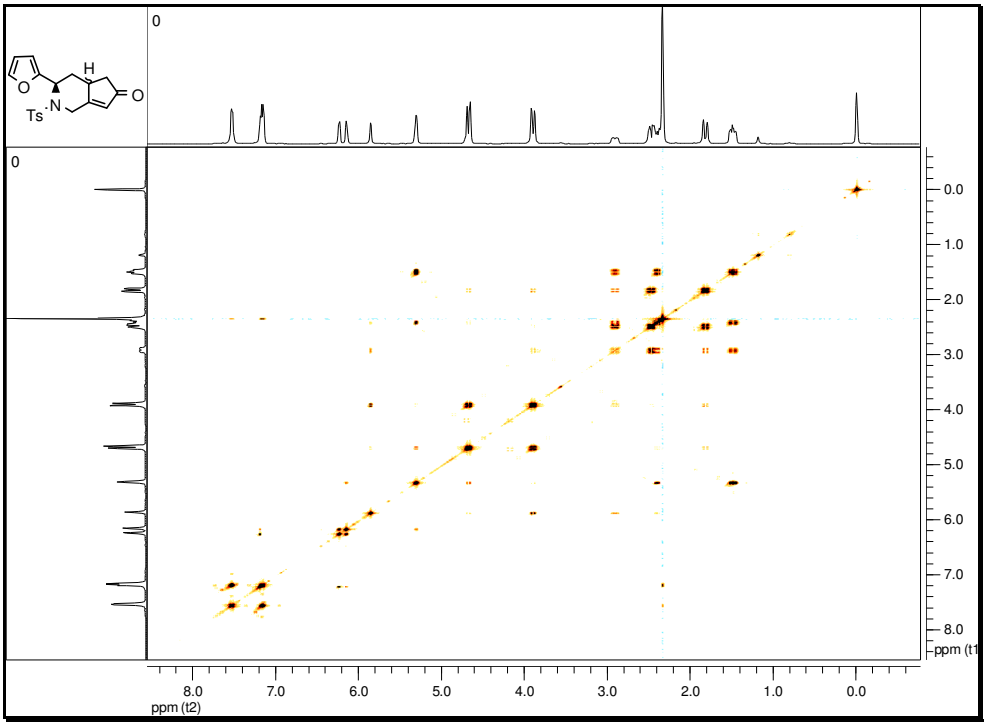

Figure A51. COSY spectrum of (3*R*, 4a*S*(*R*))-(+)-**76**

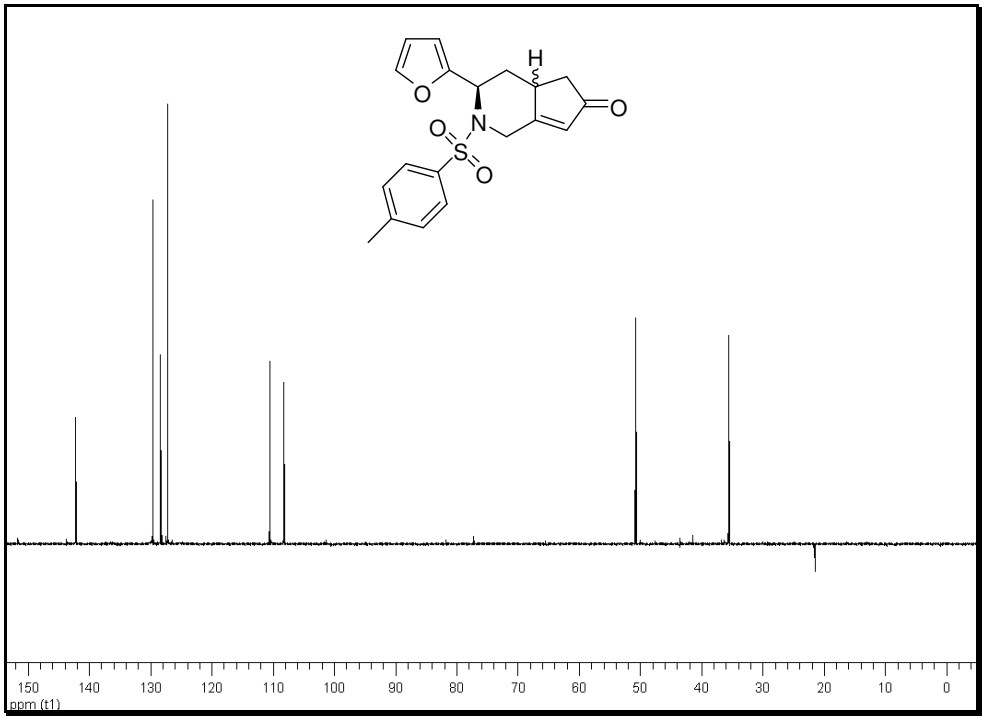

Figure A52. DEPT-90 spectrum of (3*R*, 4a*S*(*R*))-(+)-**76**

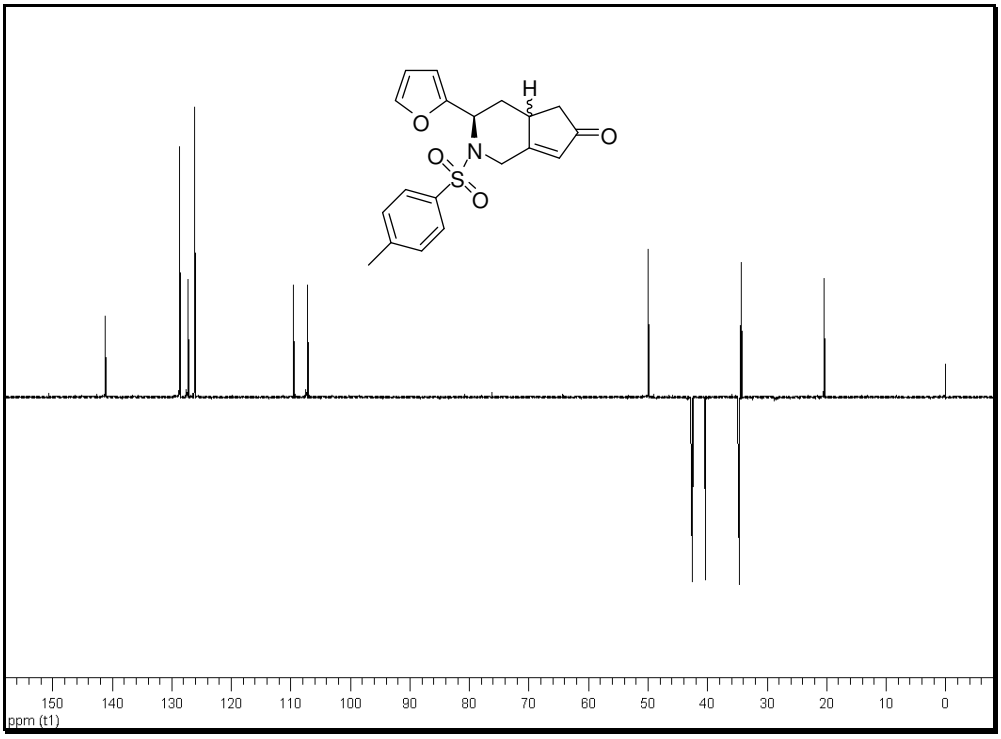

Figure A53. DEPT-135 spectrum of (3*R*, 4a*S*(*R*))-(+)-**76**

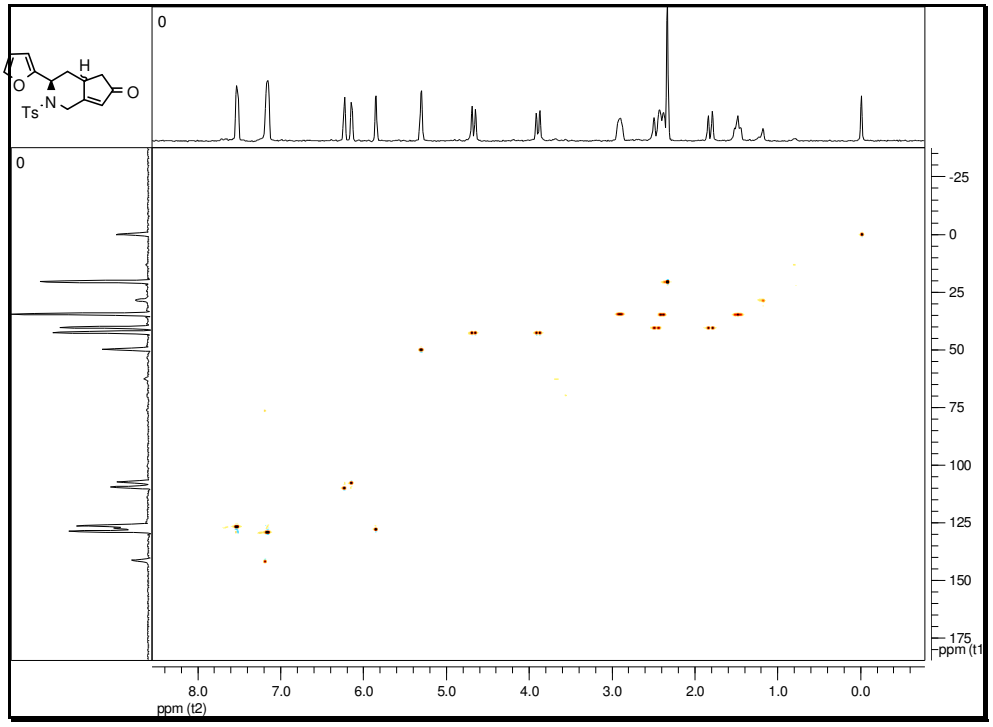

Figure A54. HSQC spectrum of (3*R*, 4a*S*(*R*))-(+)-**76**

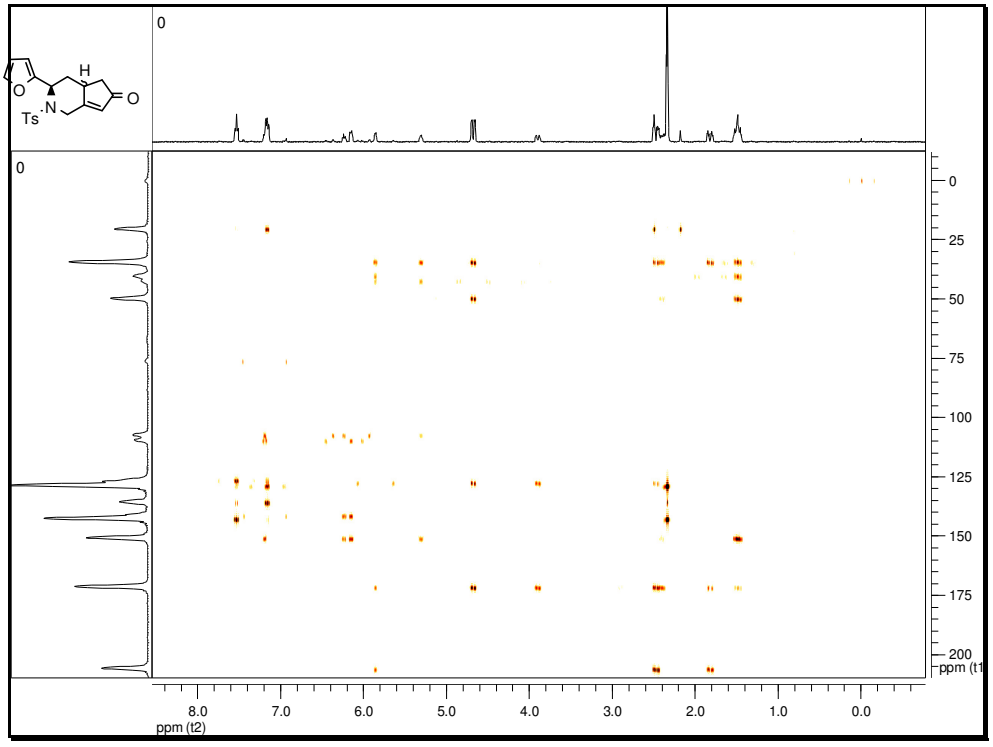

Figure A55. HMBC spectrum of (3*R*, 4a*S*(*R*))-(+)-**76**

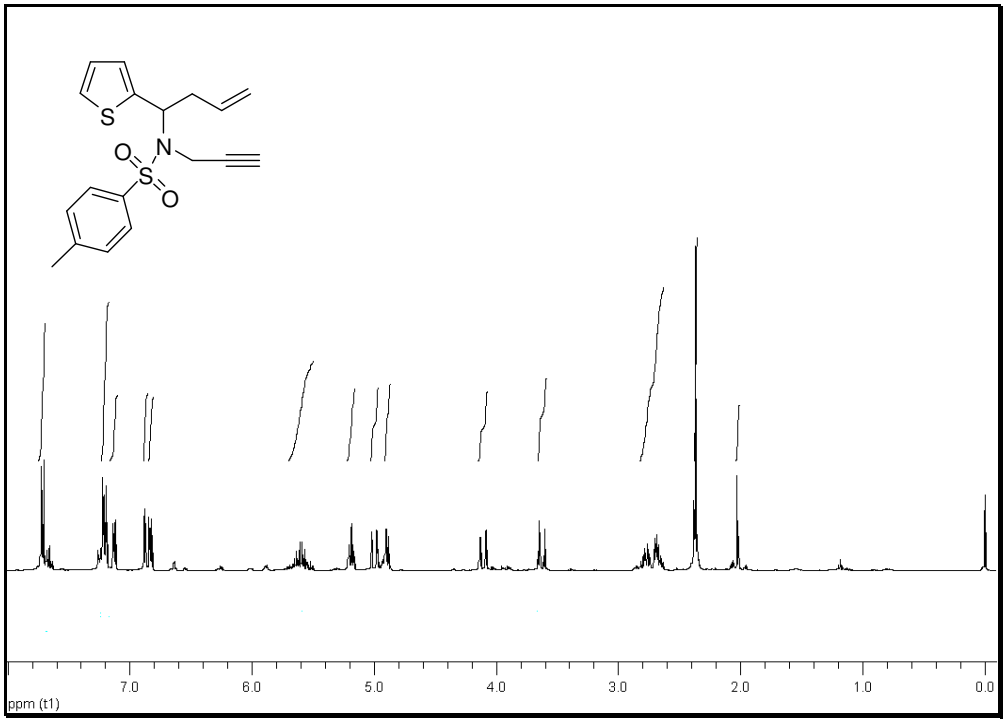

Figure A56. ^{1}H-NMR spectrum of *rac*-**77**

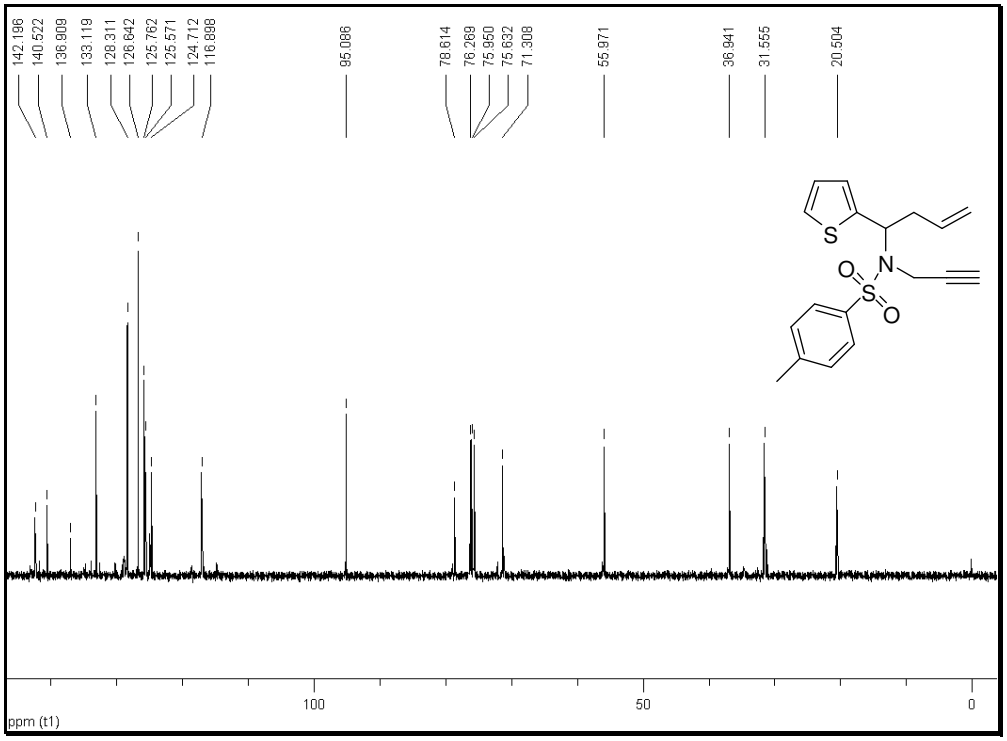

Figure A57. ^{13}C-NMR spectrum of *rac*-**77**

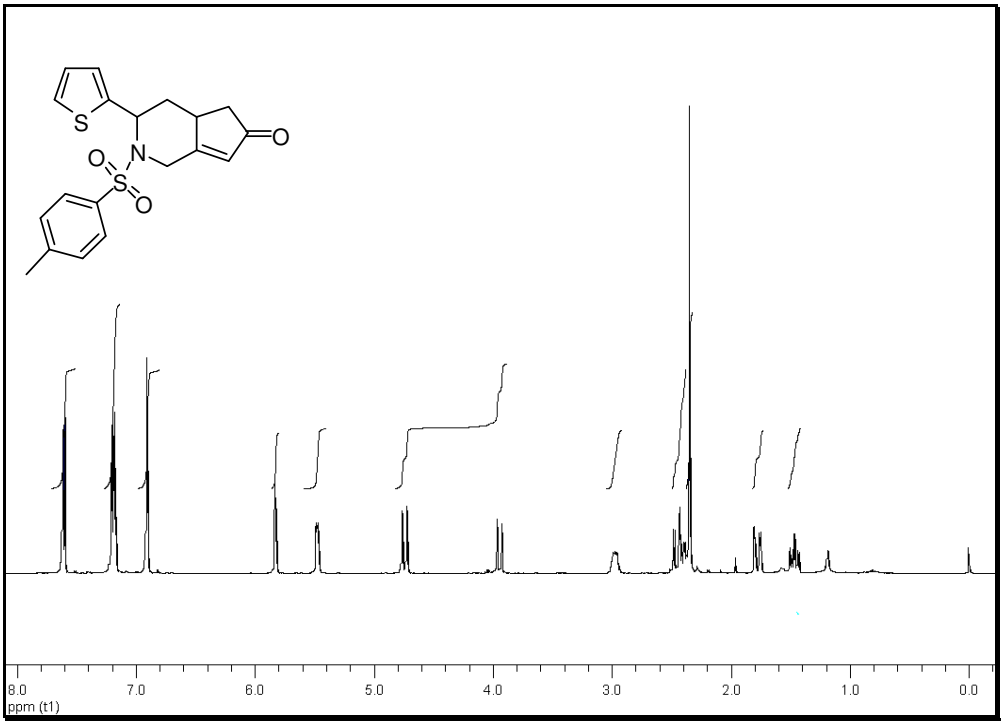

Figure A58. ^{1}H-NMR spectrum of *rac*-**78**

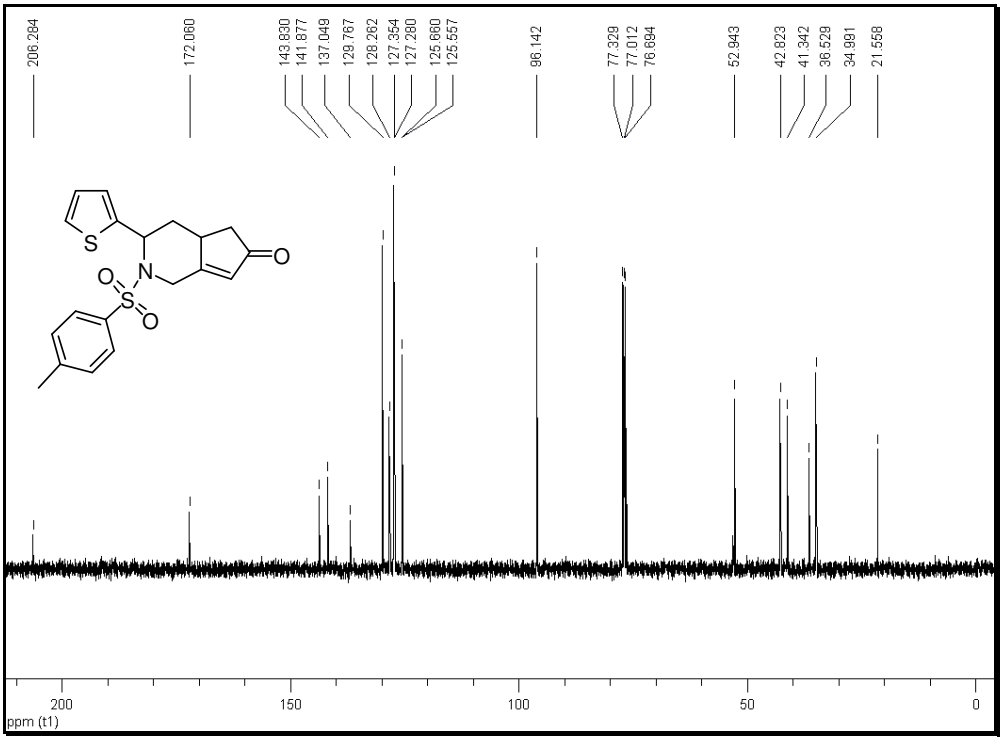

Figure A59. ^{13}C-NMR spectrum of *rac*-**78**

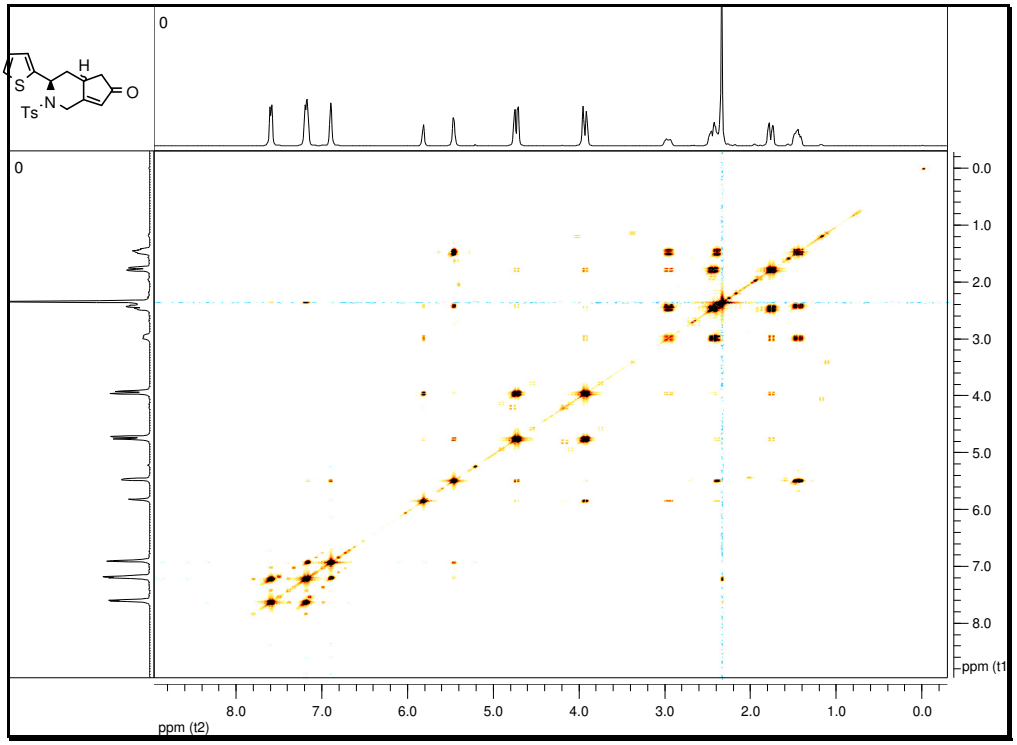

Figure A60. COSY spectrum of (3*R*, 4a*S*(*R*))-(+)-**77**

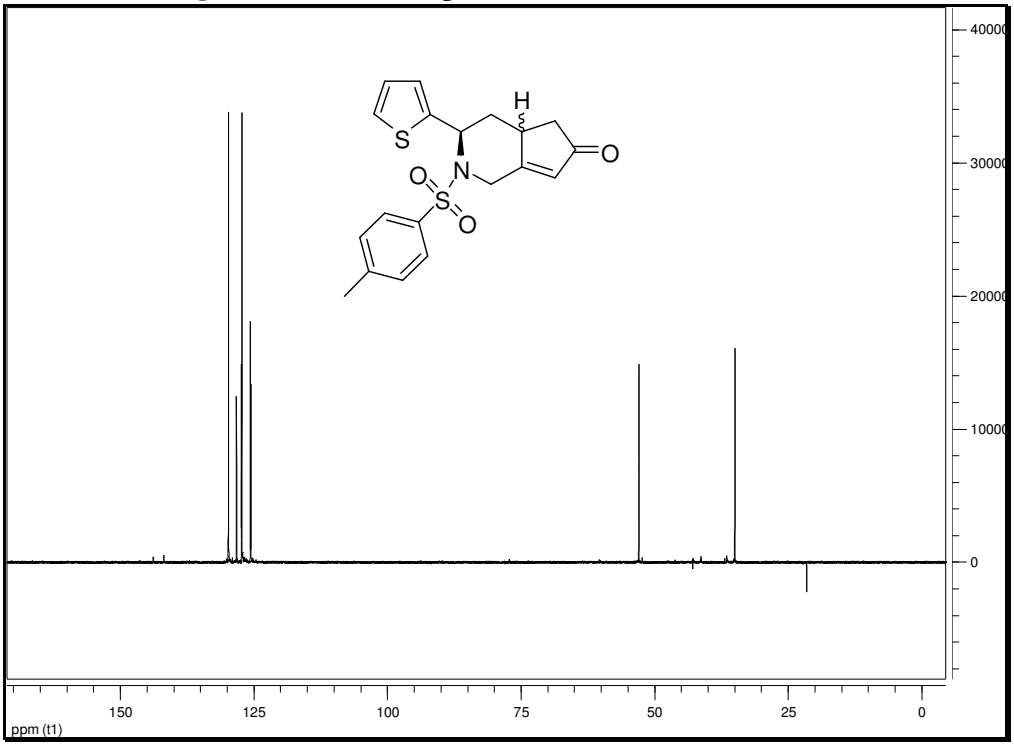

Figure A61. DEPT-90 spectrum of (3*R*, 4a*S*(*R*))-(+)-**77**

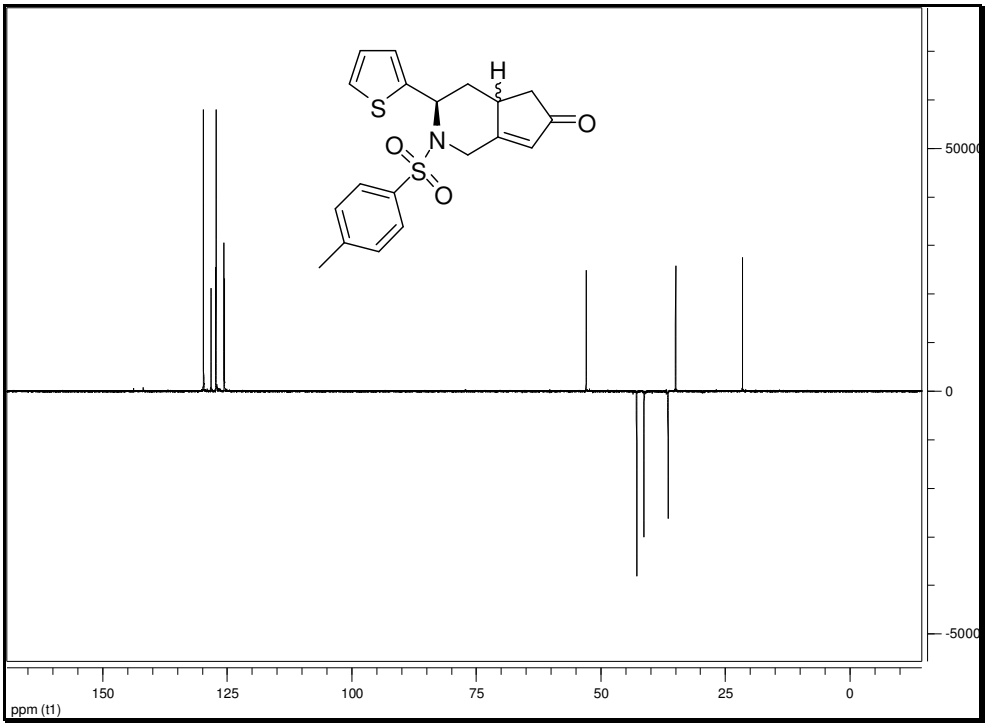

Figure A62. DEPT-135 spectrum of (3*R*, 4a*S*(*R*))-(+)-**77**

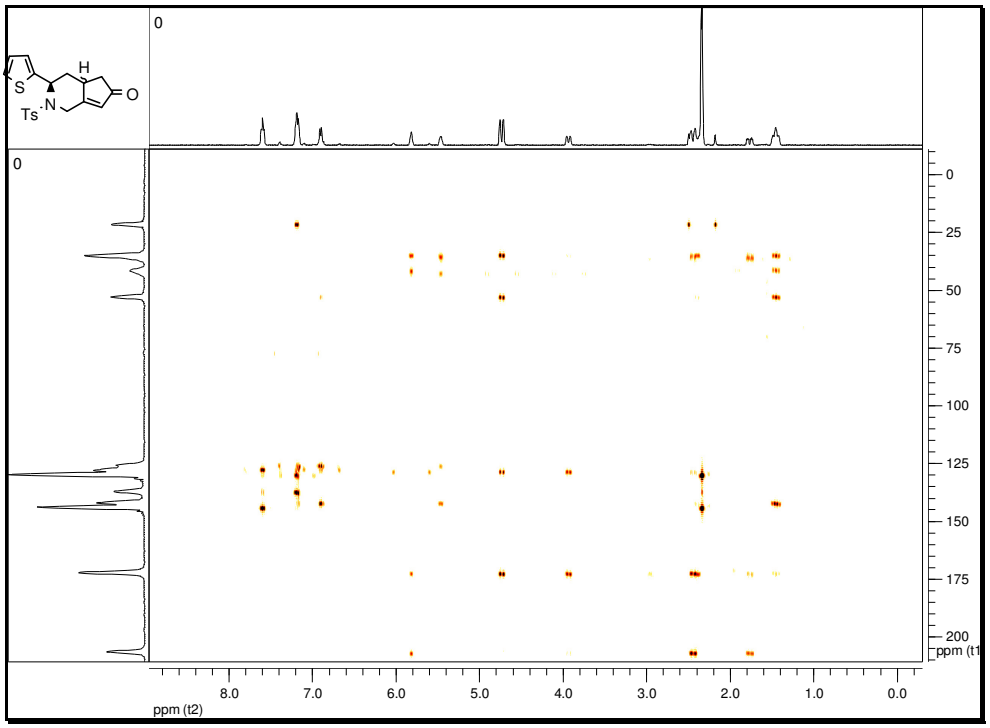

Figure A63. HMBC spectrum of (3*R*, 4a*S*(*R*))-(+)-**77**

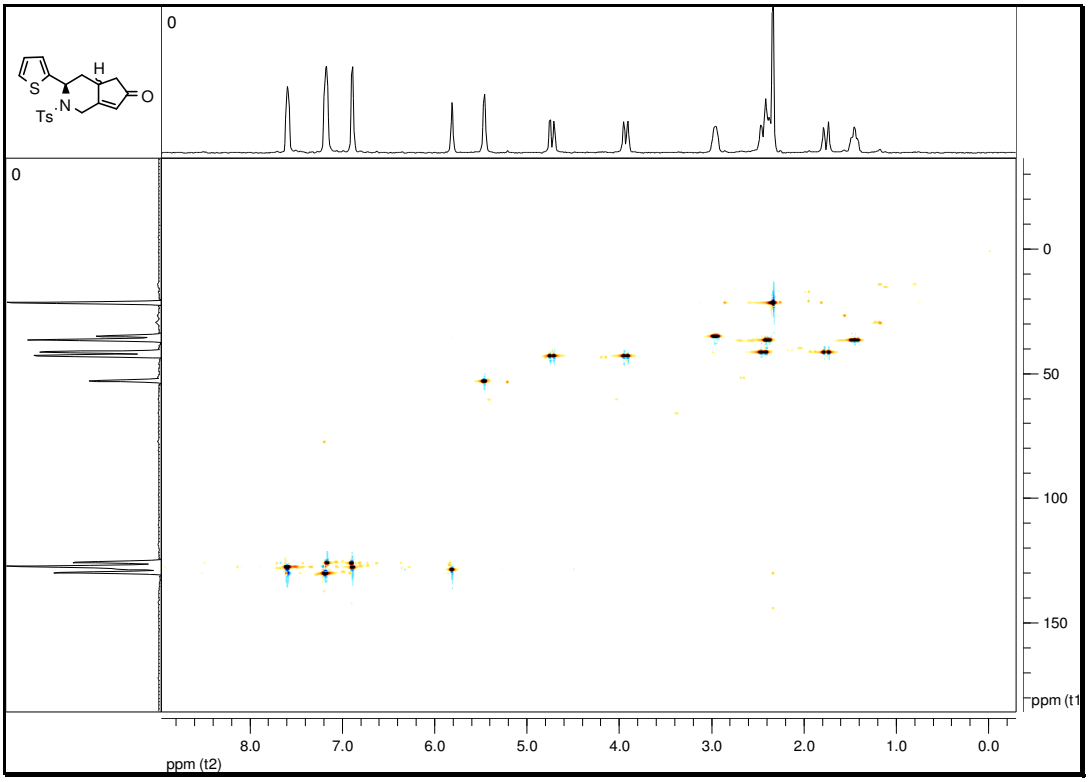

Figure A64. HSQC spectrum of (3*R*, 4a*S*(*R*))-(+)-**77**

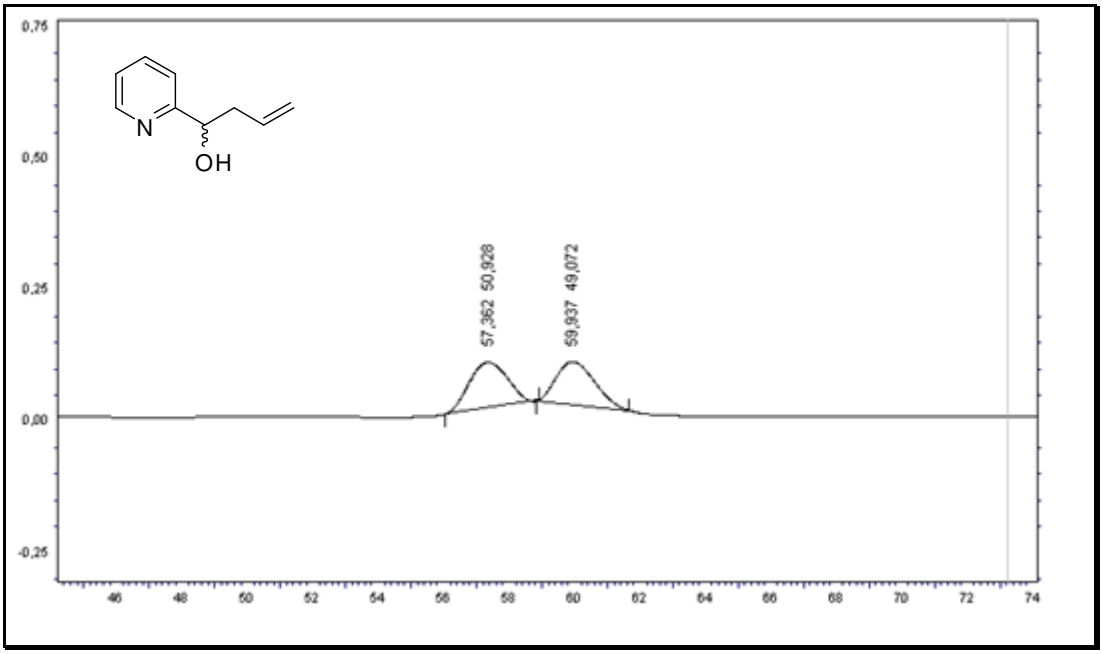

Figure A65. HPLC chromatogram of *rac*-**55a**

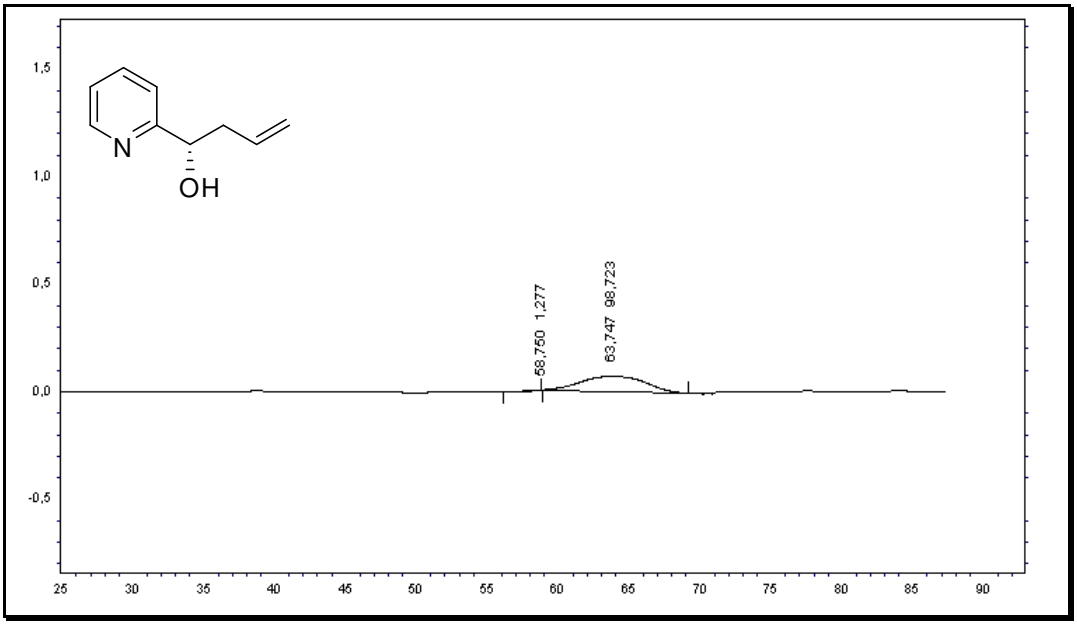

Figure A66. HPLC chromatogram of (*S*)-(-)-**55a**

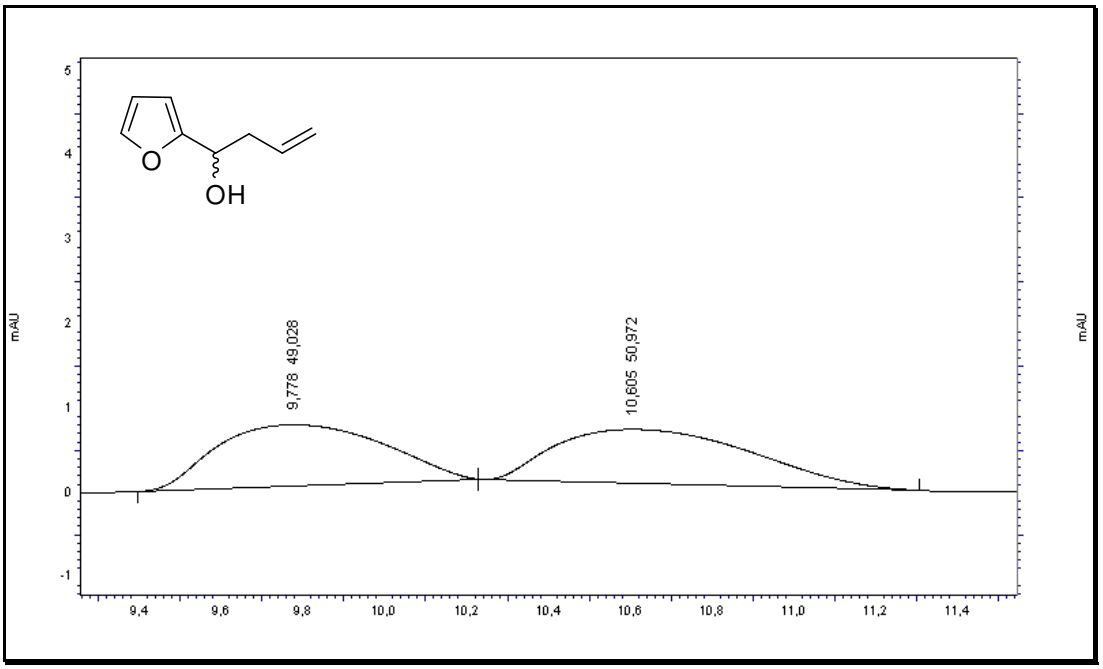

Figure A67. HPLC chromatogram of *rac*-**55b**

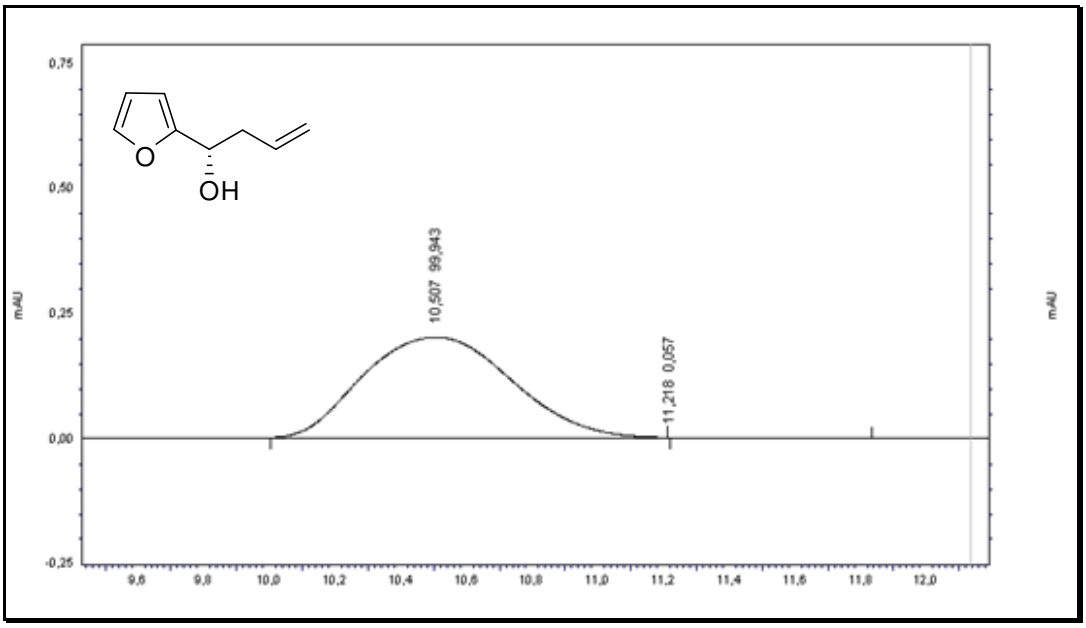

Figure A68. HPLC chromatogram of (*S*)-(-)-**55b**

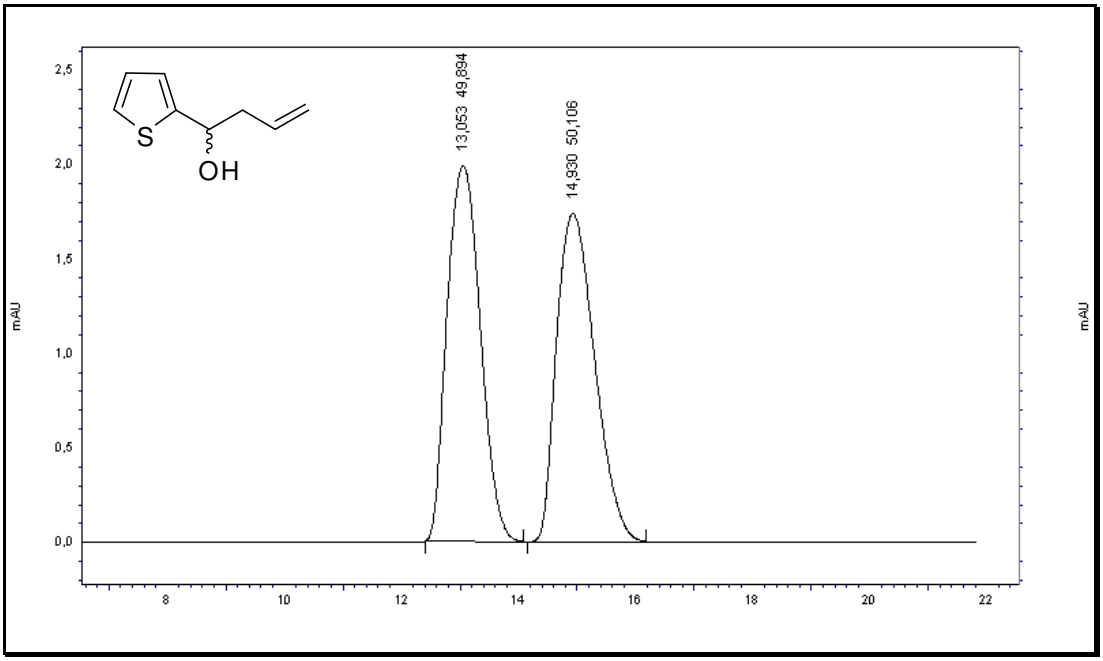

Figure A 69. HPLC chromatogram of *rac*-**55c**

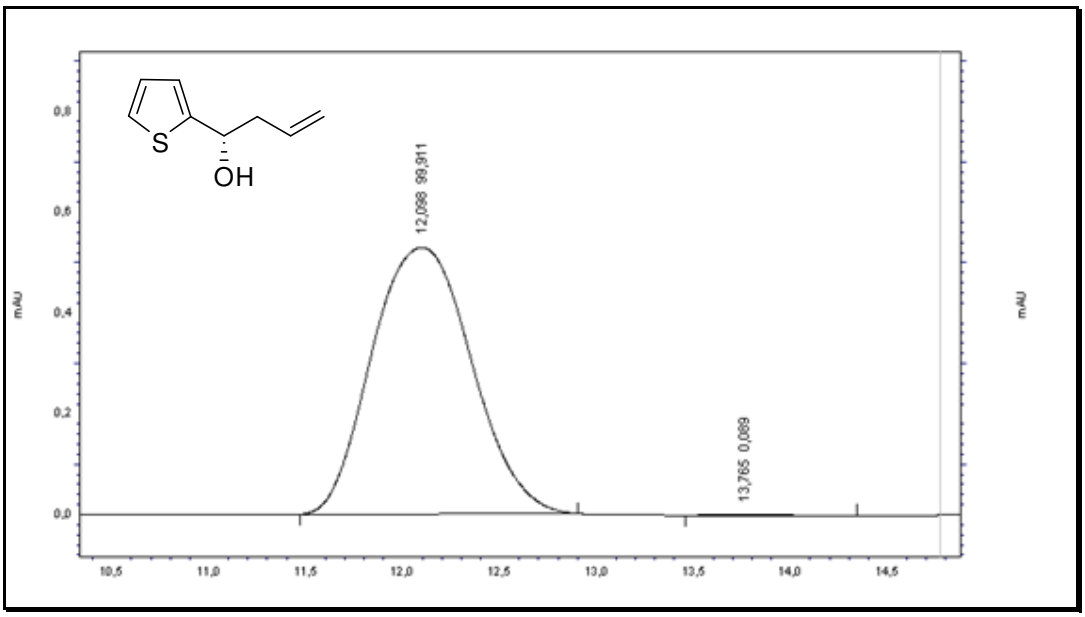

Figure A 70. HPLC chromatogram of (*S*)-(-)-**55c**

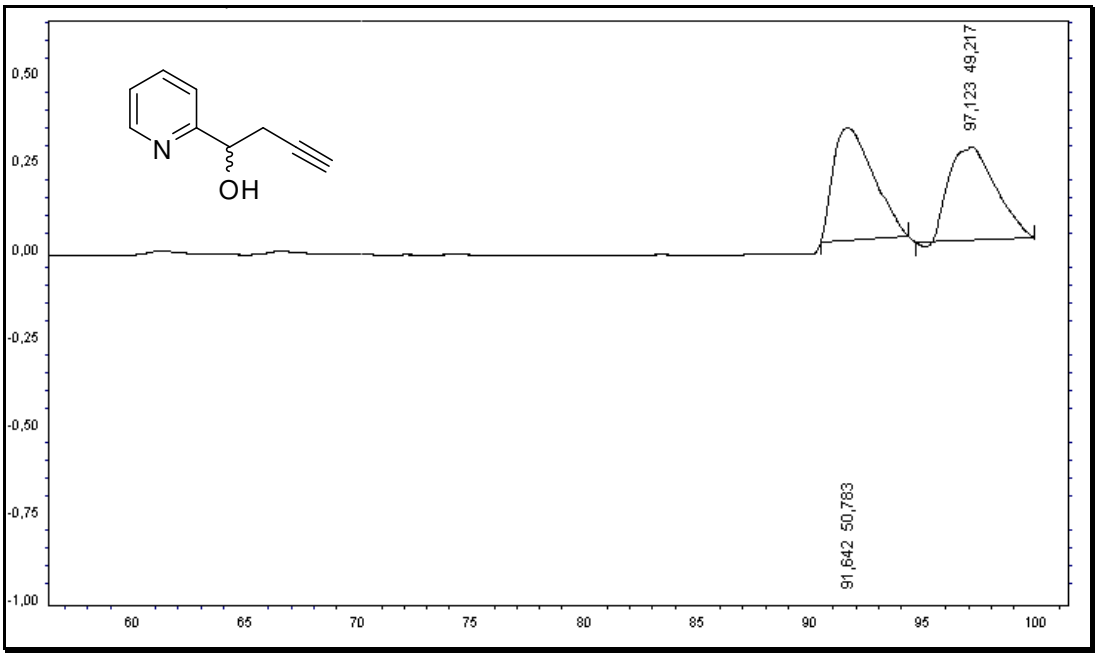

Figure A 71. HPLC chromatogram of *rac*-**56a**

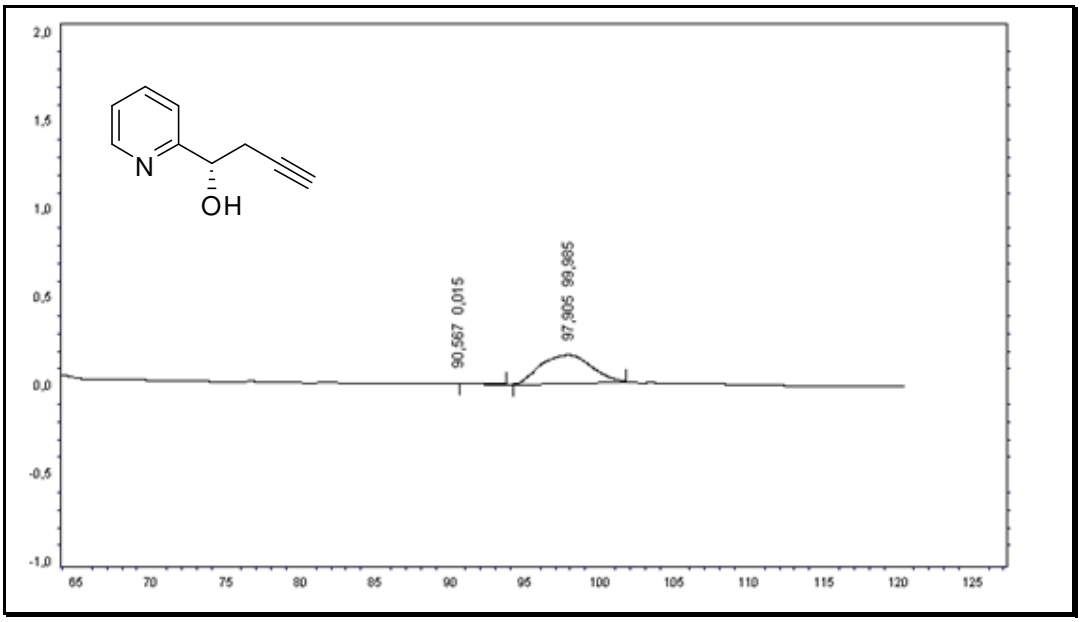

Figure A 72. HPLC chromatogram of (*S*)-(-)-**56a**