SYNTHESIS OF 1,2-AMINO ALCOHOLS HAVING TERTIARY ALCOHOL MOIETY

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Approval of the Graduate School of Natural and Applied Sciences.

_____

Prof. Dr. Canan Özgen

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

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Prof. Dr. Hüseyin işçi

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

SYNTHESIS OF 1,2- AMINO ALCOHOLS HAVING TERTIARY ALCOHOL MOIETY

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June 2006, 70 pages

An applicable method for the racemic synthesis of 1,2-amino alcohols having tertiary alcohol moiety was developed. This method can be used as a general method for the synthesis of various 1,2-amino alcohols with various tertiary alcohol moieties by changing chloroacetone with different monohalo ketones, and with different aryl halides or alkyl halides. The resultant racemic 1,2-amino alcohols were tried to resolve by using various hydrolase type enzymes under different conditions by changing the parameters i.e. solvent, temperature and substrate: enzyme ratios. Finally, poorly resolved amino alcohol **20** with 21 % was used as chiral ligand in diethylzinc addition to benzaldehyde and afforded (R)-1-phenylpropan-1-ol almost with 21 % e.e..

Keywords: 1,2-Amino alcohol, enzymatic resolution, diethylzinc addition

ÖZ

ÜÇÜNCÜL ALKOL GRUBU İÇEREN 1,2-AMİNO ALKOLLERİN SENTEZİ

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Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli
Haziran 2006, 70 sayfa

Üçüncül alkol grubu içeren rasemik 1,2-amino alkollerin sentezi için uygulanabilir bir metot geliştirilmiştir. Bu metotun, çeşitli tersiyeri alkol grubu içeren 1,2-amino alkollerin sentezi için genel bi yöntem olarak kullanilabileceği, kloroaseton yerine çeşitli monohalojenür ketonlar ve çeşitli aril halojenürler veya ceşitli alkil halojenürler kullanılarak gösterilmiştir. Elde edilen rasemik 1,2-amino alkollerin sıcaklık, çözücü ve enzim: substrat oranı gibi parametreleri değiştirilerek farklı koşullarda çeşitli hidrolaz tipi enzimlerle enzimatik rezolüsyona tabi tutulmuştur. Sonuç olarak %21 enantiyomerik zenginliğe sahip amino alkol **20**, benzaldehit'e dietilçinko katılma tepkimesinde kiral ligand olarak kullanılmıştır. (R)-1-fenilpropan-1-ol yaklaşık %21 enantiomerik zenginlikle sentezlenmiştir.

Anahtar kelimeler: 1,2-Amino alkol, enzimatik rezolüsyon, dietilçinko katılması

To My Family

ACKNOWLEDGEMENT

I would like to express my sincere thanks to my supervisor Prof.Dr. Cihangir Tanyeli for his patience, guidance, support through the study

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THF: Tetrahydrofurane

DMSO: Dimethyl sulfoxide

DIE: Diisopropyl ether

DCM: Dicholoromethane

MBE: Methyl t-butyl ether

VA: Vinyl acetate

CALB: Candia antartica lipase type B (novozyme 435)

CCL: Candida cylindracea lipase

AL PS-C II: Amano Lipase PS-C II

CHAPTER 1

INTRODUCTION

1.1. 1,2-Amino Alcohols

Amino alcohols are widely used in organic chemistry as building blocks. They can be used in asymmetric synthesis as chiral ligands. Amino alcohols are one of the major components of biosystems. Moreover, amino alcohols are used in pharmaceutical industry.

Chiral 1,2-amino alcohol motif has an important role in pharmaceutical industry. Especially, 1,2-amino alcohol motif used as; inhibitors of aspartyl proteases, hence this inhibition treatments for HIV **7** [1]**,** anti-inflammatory **1** [2], anti-obesity **5** [3]**,** treatment of bronchial asthma **2**, **3**, **4** [4], antidepressant **6** [5], dual action agonists/antagonists for the T-type calcium channel **8** [6]. Structures of these compounds are shown in figure 1. As consequence, notable pharmaceutical companies work on new drugs which containing 1,2-amino alcohol motif.

In asymmetric chemistry amino alcohols can be used as chiral auxiliaries [7]. Chiral 1,2-amino alcohols are one of the most important ligands used in diethylzinc addition reactions [8], (S)-DIAB is one of the most famous one, **9**. With catalytic amounts of 1,2-amino alcohols, diethylzinc can react with benzaldehyde in toluene which gave optically active 1-phenylpropan-1-ol with high enantiomeric excess [9].

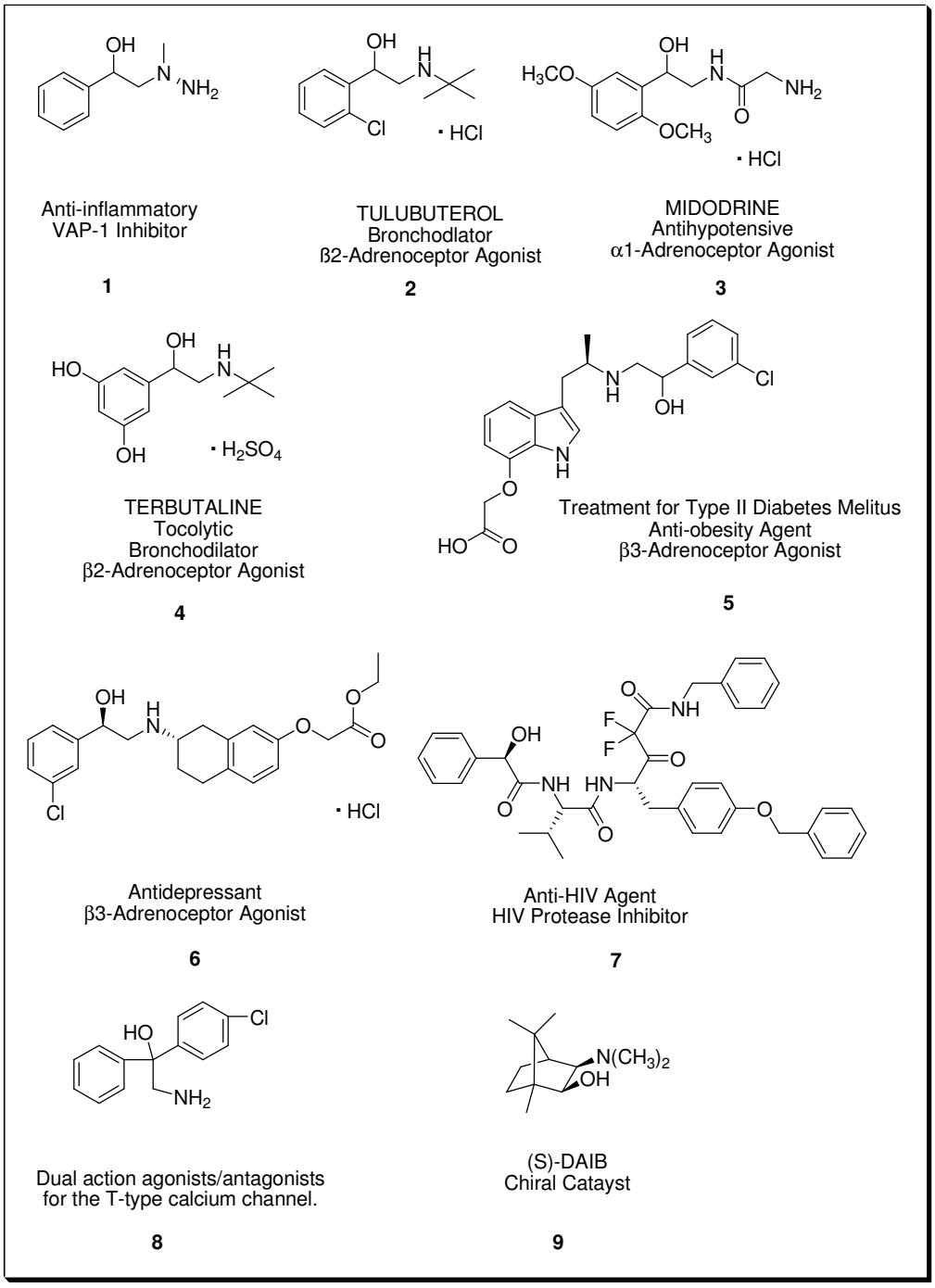
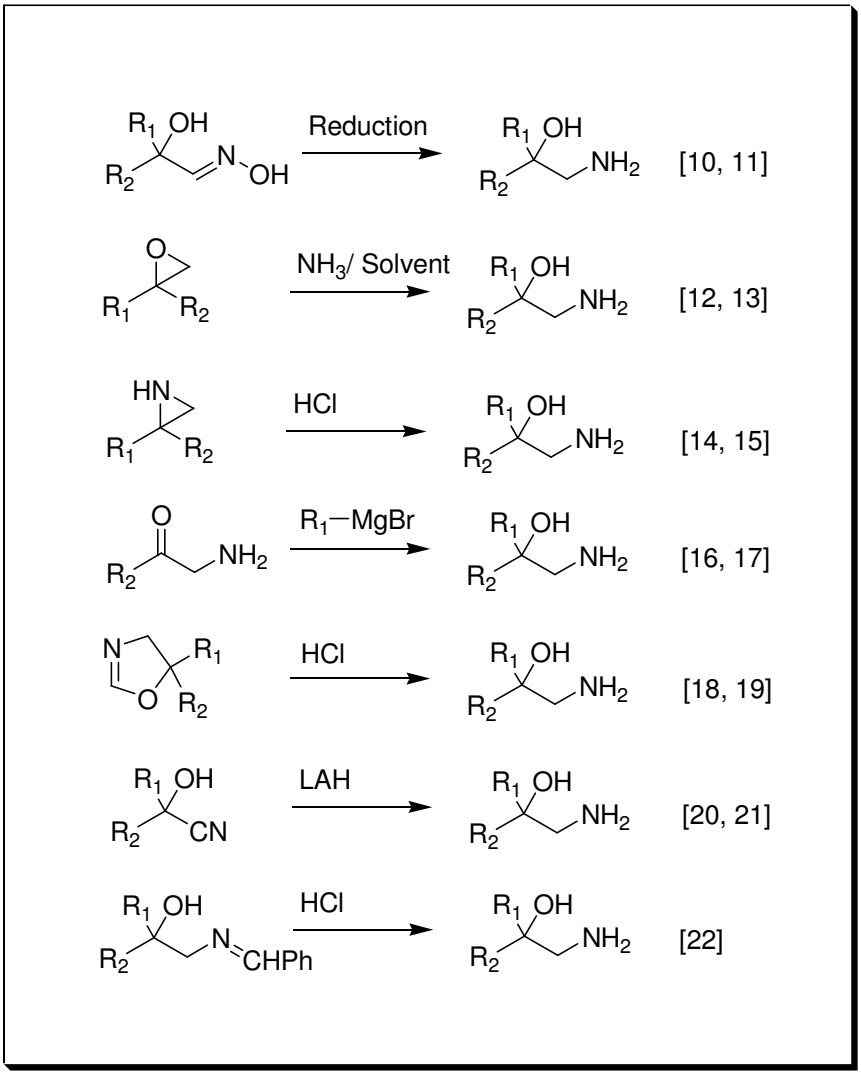


Figure 1. Some important 1,2-amino alcohols

There are several ways for synthesis of 1,2-amino alcohol derivtives. 1,2-amino alcohols having tertiary alcohol moiety, are one of the most important classes among amino alcohols. The first synthetic method was statedted by Campbell, where oximes have been used as precursor for amino alcohol synthesis [10]. In the following years other examples of this method have been reported in literature [11]. In 1941, Cairns founded a new synthetic method from the corresponding epoxide, where ammonia was used as the amine source [12]. In time more studies were reported about epoxide ring opening with ammonia in literature [13]. In 1953, Kissman discovered a method in which the aziridine ring opening reaction with acid was used [14]. There are several works reported about these studies [15]. In 1959, House informed a Grignard reaction of amino ketone with alkyl bromide for this type of amino alcohol synthesis [16]. In literature several more examples was shown [17]. In 1976, Schoellkopf informed a ring opening reaction of 4,5-dihydrooxazole with acid to obtain 1,2-amino alcohols having tertiary alcohol moiety [18, 19]. In 1975, Markaryan applied a reduction procedure for cyanide group with Lithium aluminum hydride [20], and related examples were found in literature [21]. In 1977, Kaufman synthesized amino alcohols from corresponding N-methylene amine with acid [22]. Summary of these reaction are given in Scheme 1.



Scheme 1. Summary of synthesis methods for 1,2-amino alcohols having tertiary alcohol moiety

1.2 General Methods for Optically Active Compounds

Optically active molecules are also called as chiral molecules. In daily life chiral molecules are important because stereoisomers have different chemical properties; for instance human body can only use L- amino acids but not D- amino acids.. As a result of this, chemists try to synthesize pure enantio-rich molecules or try to separate the two enantiomers from each other.

Enantiomers are separated via producing a diastereomeric transition states as products or complexes. There are four major separation methods for producing optically active compounds; a) Physical separation via Enantiomeric Crystalline Forms, b)Resolution Based upon separation of Diastereomeric Forms, c) Thermodynamically Controlled Asymmetric Transformations of Stereochemically Labile Diastereomers, Kinetically Labile Diastereomers, d) Kinetically Controlled Asymmetric Transformations [23].

1.2.1 Kinetically Controlled Asymmetric Transformations.

Diastereomeric transition states or intermediates are the controlling factors in the stereochemical course of the reaction. By all kinetically controlled asymmetric transformations, the reactants have the same ground state free energy however the free energies of activation of the two pathways determine the changes. As a consequence of this, kinetically controlled asymmetric transformations only depend on the differences in the free energies of the competing pathways [23]. There are three kinds of kinetically controlled asymmetric transformations; chiral auxiliaries, chiral ligands and chiral environment.

1.3 Enzymes

Enzymes are proteins or RNA molecules which catalyze or accelerate a chemical reaction. The word enzyme comes from the Greek word énsimo where én means, in simo means yeast. This Greek term is used because of the Josesph Gay Lussac's research on fermentation at 1810, where ethanol and carbon dioxide are the products of sugar decomposition by yeast. So this term refers the substance in yeast by Frederich Wilheim Kühne in 1878. Most of the enzymes used in chemistry are proteins.

The catalytic characteristics of enzymes can be listed as; they accelerate the rate of reactions, and operate under mild conditions. They are highly selective for substrates. Moreover, they are stereoselective in reactions they catalyze. They may be subjected to regulation; that is, the catalytic activity may be strongly influenced by the concentrations of substrates, products or the other species present in solution. They normally catalyze reactions under the same or similar conditions, since they are generally present in the same environment with other enzymes. They are generally unstable (relative to man-made catalysts.). They are chiral, and can show high enantiodifferentiation [24]. These catalytic characteristics make enzymes an important source for asymmetric transformations, where they can be used as chiral catalyst.

Enzymes are large polar macromolecules with molecular mass in a range 10^4 to 10^6 Dalton. Enzymes are made of amino acids where amino acids form large polymers through peptide bonds. There are 20 amino acids used in enzymes. The chemical properties of enzymes depend on binding order of these 20 amino acids, and folding of these protein chains. Enzymes have quaternary structures. The three-dimensional structure of a protein composed of a single polypeptide chain or covalently linked chains is known as tertiary structure. Many enzymes are composed of subunits that are not covalently

linked together. The overall organization of these subunits is known as quaternary structure [25]. Quaternary structure of enzymes formed by relatively weak forces as a result of this, many factors such as solvent, temperature, can easily change the conformation of the enzymes.

As a consequence of protein structure, enzymes are highly specific for their substrates. In 1894 Emil Fisher discovered that glycolytic enzymes can distinguish between steroisomeric sugars. This led him to propose his Lock and Key model: The specificity of an enzyme (the lock) for its substrate (the key) arises from their geometrically complementary shapes. This mechanism is shown in Figure 2. However, today we know that this model is not totally correct. It is known that enzymes are specific for specific substrate structures like lipases, where lipases acetylate both amine and alcohol functional groups. So, lock can be opened with similar kind of keys not always with same one.

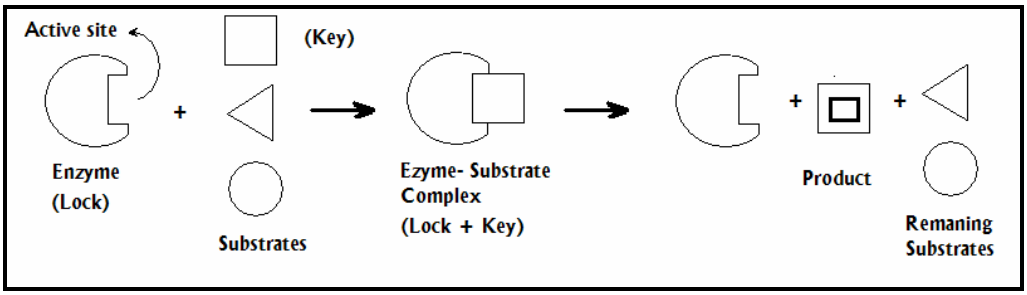


Figure 2. Lock and Key model.

When target substrate binds on enzyme, an enzyme substrate complex is formed. Some enzymes undergo major changes in three dimensional shapes when a substrate molecule binds. Enzymes change their shape from inactive to active form. Activation of an enzyme by a substrate- initiated conformation is called induced fit.

There are compounds called inhibitors that bind to enzymes, and interfere with their activity by preventing either formation of enzyme substrate complex or its breakdown to enzyme product. There are four types of inhibitions; classical competitive inhibition, non-clasical competitive inhibition, uncompetitive inhibition, noncompetitive inhibition.

Inhibitors competing with substrate for active site source classical competitive inhibition. Inhibitors bind to enzyme substrate complexes and cause non-classical competitive inhibition. Inhibitors which bind to free enzyme and change the active site of enzyme are responsible for uncompetitive inhibition. Inhibitors, which bind both the free enzyme and the enzyme substrate complex and by doing so inactivate the enzyme, are referred to as noncompetitive inhibition.

Some enzymes need some molecules to change their inactive form to active. These activator molecules are called cofactors which are ions or non-protein molecules generally. The enzyme possessing its cofactor is called holoenzyme, and if the cofactor is absent it is called apoprotein.

1.3.1 Specificity

The major importance of enzymes in chemistry, and in biosystems is their stereoselectivity. Enzymes are large chiral molecules with unique stereo-structures in their active site so they can easily select certain types of substrate structures and reactions. Useful types of enzyme- catalyzed reactions include; the chemoselective reaction of one of several different functional groups in a molecule, the regioselective reaction of one of the same or similar groups in a molecule, the enantioselective reaction of one enantiomer of a racemic pair or one of the enantiotopic faces or groups, and the diasteroselective reaction of one or a mixture of diastereomers or one of the diastereomeric faces or groups [24]. If the prochiral or chiral reactants form diastereomeric enzyme- transition

state complexes that differ in transition – state energy, selective reactions occur during a reaction.

Although the stereoselectivity in most enzymatic reactions is dictated by the particular tertiary structure of the catalyst, it is difficult to predict the stereochemistry of a reaction and a change over in the sense of the stereoselectivity from one substrate to another is not uncommon [26]. According to Wong and Whitesides, only approach to the prediction of stereoselectivity at present is to develop a reliable, empirical active- site model for enzyme. Using computer graphics analysis to develop such a model is commonly used in literature; Horse liver alcohol dehydrogenase [27], and pig liver esterase [28] are among such examples. Models are now available that are simple and reasonably reliable both for prediction of new reactions and for rationalization of literature results. Empirical models are particularly useful for enzymes for which X- ray crystal structures are not available.

1.3.2 Enzyme Classifications

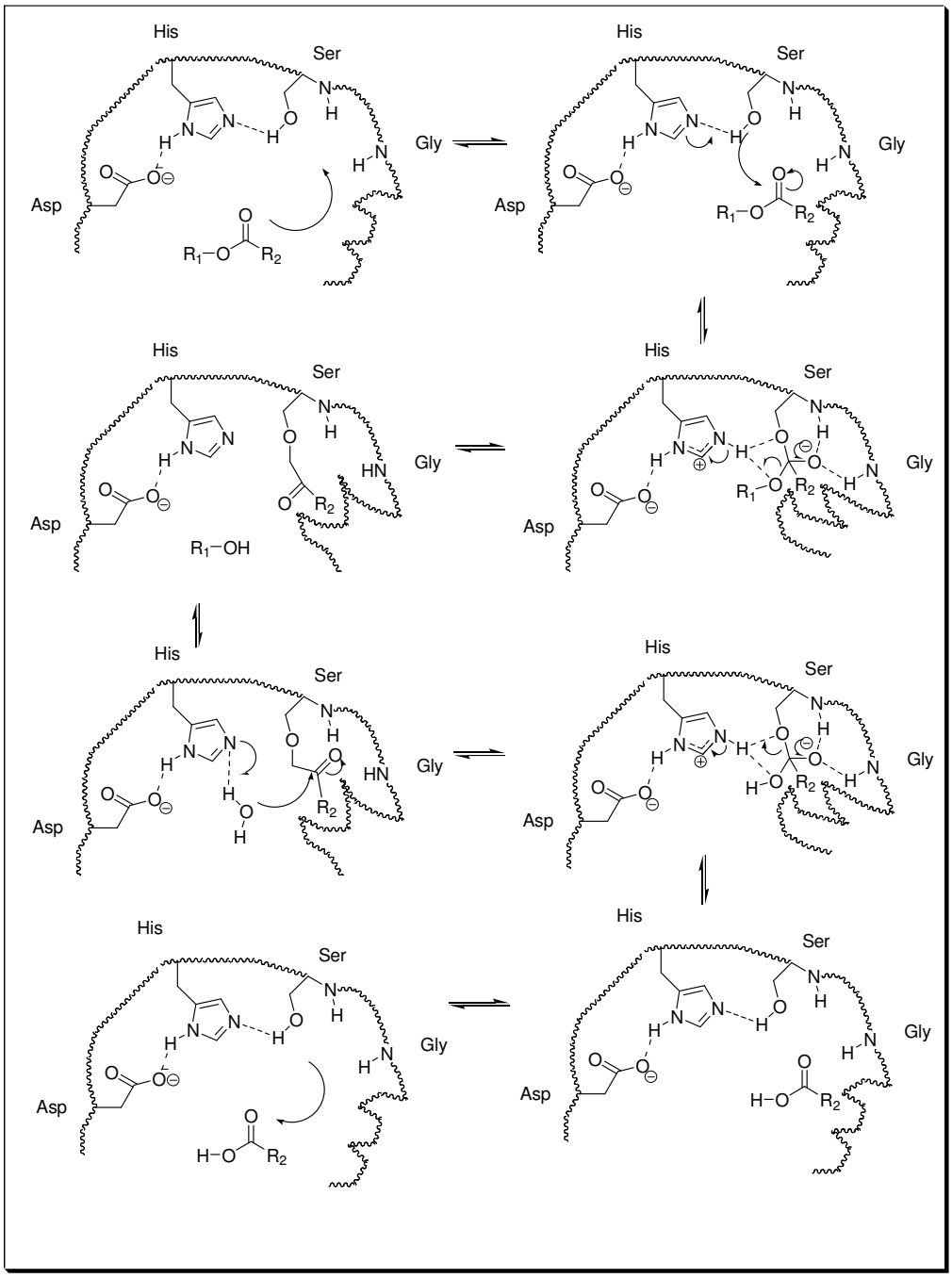
International Union of Biochemistry (UIB) had published and maintained a classification scheme that categorizes enzymes into six major groups according to the general class of organic chemical reactions they catalyze [29].

1. Oxidoreductases catalyze group-transfer reactions. Many require the presence of coenzymes is known as dehydorgenases, but some are called oxidases, peroxidases, oxygenases, or reductases.
2. Transferases catalyze group- transfer reactions. Many require the presence of coenzymes. A portion of the substrate molecule usually binds covalently to these enzymes or their coenzymes. This group includes the kinases.

3. Hydrolases catalyze hydrolysis. They are a special class of transferases, with water serving as the acceptor of the group transferred.
4. Lyases catalyze nonhydrolytic and nonoxidative elimination reaction, or lysis, of a substrate, generating a double bond. In the reverse direction, lyases catalyze addition of one substrate to a double bond of a second substrate. A lyase that catalyzes an addition reaction in cells is often termed a synthase.
5. Isomerases catalyze isomerization reactions. Because these reactions have only one substrate and one product, they are among the simplest enzymatic reactions.
6. Ligases catalyze ligation, or joining, of two substrates. These reactions require the input of the chemical potential energy of a nucleoside triphosphate such as ATP. Ligases are usually referred to as synthetases.

1.3.3 Hydrolytic Enzymes

Hydrolytic enzymes catalyze the hydrolysis and formation of ester and amide bonds. On account of this chemists usually use these type enzymes for kinetic resolution of alcohols and amines. There are 6 main type of this enzymes; amidases, proteases, esterases, lipases, nitrales, phosphates, epoxide hydrolases. Amidases usually are used to break amide bonds. Proteases are used in peptide synthesis. Esterases are used in kinetic resolution of esters where a racemic ester gives back a chiral ester and a chiral alcohol as product. Main usage of lipases is enantioselective hydrolysis of alcohols, and amines. Nitrales catalyze hydrolysis of nitriles. Phosphates have been used as deprotecting agents in the hydrolysis of phosphates to alcohols. Finally, epoxide hydrolases selectively hydrolyses epoxides.



Scheme 2. A simple mechanism for ester hydrolyze with catalytic triad.

The most common enzymes used in asymmetric synthesis are lipases. The most widely used lipase in asymmetric synthesis is the porcine pancreatic lipase (PPL) [30], and Candida cylindracea lipase (CCL) [31], and also recombinant form of Candida antartica lipase (SP435 is available from NOVO) [24]. About 30 different lipases are commercially available [32]. Most of them are serine hydrolyses containing a serine residue in their active- site featuring presumably the triad Ser….His…. Asp. A simple mechanism for catalytic triad is given in Scheme 2.

1.3.4 Amplification and Alteration of Enzyme Specificity

The formation of diastereomeric transition states that are different in free energy is the main reason of the enantioselectivity of an enzyme catalyzed reaction. The ratio of two enantiomeric products is equal to the ratio of the two corresponding second order rate constants. Increase in free energy results in increase in enantiomeric excess. This magnitude of free energy is equivalent to one or two hydrogen bonds and reaction conditions can often be altered to improve the enantioselectivity of a given reaction. Another method for amplification of enantiomeric excess is to modify the substrate by applying different substitiuents or protecting groups. There are three major alteration conditions that proves useful in synthesis. They range from increasing the amount of organic solvent [33], to an adjustment in pH [34], and, occasionally, even a change in reaction temperature [35].

The changes in conformation or ionization status of an enzyme are directly affected by the pH variation of enzymatic reaction. This conformational change have a chance to change the enzyme activity or substrate selectivity, but only if there is a major change occurred in active sites of the enzyme. However, it is known that an optimal pH is important to maximize the enantioselectivity and the substrate selectivity.

The change of solvent from water to organic solvent, changes enzyme activity significantly. As a result of this, stereoselectivity of the enzyme is altered too. In water, the hydrophilic parts of enzymes form hydrogen bonds so that the enzyme is stabilized at a form, and only pH changes this conformation. However, organic solvents disturb or change these hydrogen bonds and create other types of weak bonds so this changes the shape of enzyme. So in every different solvent enzyme has different shape, but these may or may not be so different. In different words, in organic solvents, the enantioselectivity drops substantially and hydrophilic substrates becomes more reactive than hydrophobic substrates. This phenomenon, solvent induced change of substrate selectivity, can be often rationalized in terms of differences in partitioning of the substrate between the active side and medium; this change is reflected in the Km values [24].

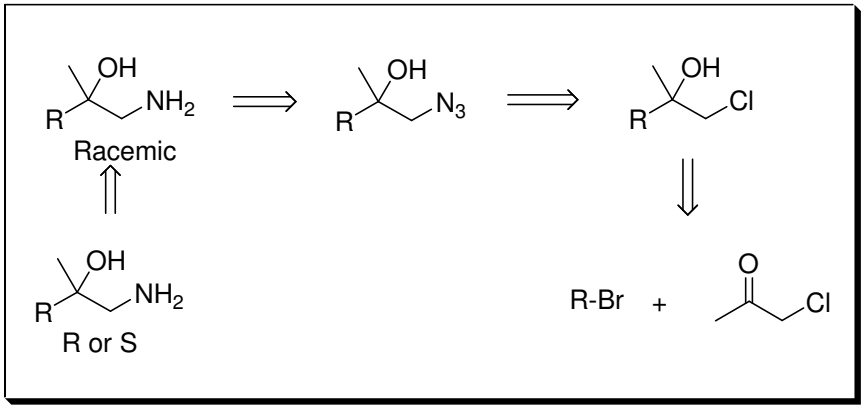
Enzymes are temperature-labile, so to achieve an optimum stereoselectivity, changing temperature is a rare method. There are some examples of enzymes that show a linear relation between the temperature and the difference in transition-state energies of the two enantiomers. Since free energy is related to the ratio of specicity constants, free energy could be determined from the values of k_{cat} and K_m of each enantiomer at different temperatures.

1.4 Aim of the Work

The main subject of this thesis is to develop a short and an effective method for racemic synthesis of 1,2-amino alcohols having tertiary alcohol moiety. This study also includes the enzymatic resolution of racemic 1,2-amino alcohols to their enantiomerically enriched forms. The last part involves the use the enantiomerically enriched 1,2-amino alcohols as chiral ligands in diorganozinc reactions.

In our retrosynthetic approach, 1,2-azido alcohol is the key precursor, which can be reduced via a simple hydrogenation reaction with the help of the Pd(C) catalyst to afford corresponding amino alcohol. Our second precursor is 1,2-chloro alcohols where the chloromethylene part is chosen as potent center for amine formation. Chloroacetone and aryl bromide (and benzyl bromide) are used as starting compounds, where chloroacetone and aryl bromides (and benzyl bromide) can undergo the well common Grignard reaction to get 1,2-chloro alcohols. Chloroacetone is chosen as the starting compound since it is cheap and available for our purpose. The carbonyl and chloride moieties of it are susceptible to nucleophilic attack. The carbonyl part of chloroacetone is used as a source to tertiary alcohol motif of the target amino alcohols.

At final the step of this study, it is thought that the resultant racemic amino alcohols can be resolved by enzymatic hydrolysis to get their enantiomerically enriched forms. Retrosynthetic analysis is shown in Scheme 3.



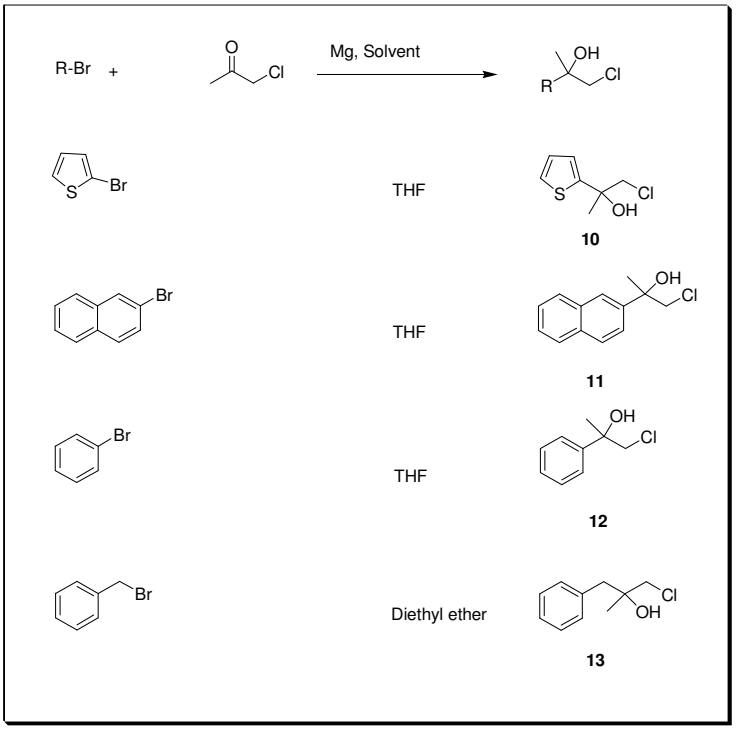
Scheme 3. Retrosynthetic pathway of the study

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 1,2-chloro alcohol derivatives

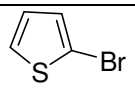
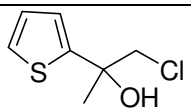
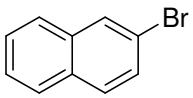
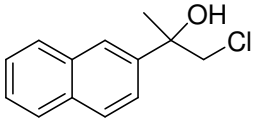
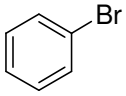
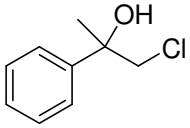
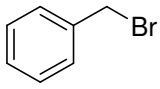
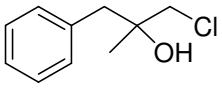
The first part of this thesis involves the synthesis of 1,2-chloro alcohol derivatives. Grignard reaction has quite high chemo selectivity towards carbonyl over chloromethylene group and we used different aryl bromides and benzyl bromide for the reaction with chloroacetone. The summary of Grignard reactions is shown in Scheme 4.



Scheme 4. Synthesis summary of 1,2-chloro alcohols

In this reaction THF was used as solvent because the chemical yield in THF was higher than that in diethyl ether except benzyl bromide. In all Grignard reactions, iodoethane and iodine were used to activate metallic magnesium. The solution was refluxed in the entire Grignard reagent formation step, and the chloroacetone addition was done at 0 ^{o}C. All the reactions were controlled with TLC, and the reactions were stopped by the addition of ammonium chloride at the depletion of the starting compound. The standard workup procedure with ammonium hydroxide was applied. The purification of the products was done with the column chromatography and detailed information is given in the experimental part.

Table 1. The results of Grignard reaction of chloroacetone and aryl bromides and benzyl bromide

Reactants	**Time**	**Products**		**Isolated Yields**
	30 min		**10**	70 %
	30 min		**11**	66 %
	30 min		**12**	75 %
	30 min		**13**	37 %

In all reactions the yield seems much more in TLC, however, in purification step there was a considerable loss because of the product and

stationary phase interactions. The structure elucidation of the products was done by NMR. Summary of all Grignard reactions is given in Table 1.

2.1.1 1-Chloro-2-(thiophen-2-yl)propan-2-ol, (10)

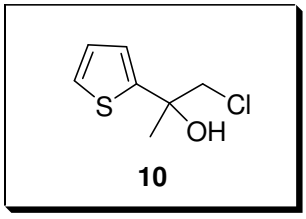


Figure 3. 1-chloro-2-(thiophen-2-yl)propan-2-ol, (**10)**.

In the ^{1}H-NMR spectrum of 1-chloro-2-(thiophen-2-yl)propan-2-ol **(10),** methyl protons are observed as a singlet at 1.72 ppm. The hydroxide proton of compound **10** can be seen at 2.80 ppm where it was controlled with D_2O. The two doublets at 3.73 ppm and 3.83 ppm correspond to the diastereotopic methylene protons. The signals at 6.97 ppm and 7.24 ppm are corresponding to the protons at 5th, 4th and 3rd positions of thiophene ring, respectively. The peaks observed from ^{13}C-NMR spectrum are; 27.9 which belong to methyl carbon, 55.3 is belong to methylene carbon; 73.1 is belonging to tertiary carbon and 123.4, 124.8, 126.9, and 148.9 belong to thienyl carbons. The NMR spectra of compound **10** are given in Appendix A.

2.1.2 1-Chloro-2-(naphthalen-2-yl)propan-2-ol, (11)

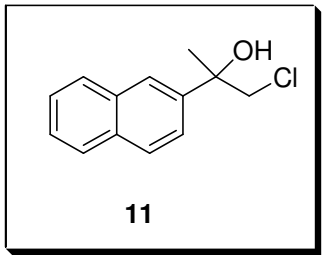


Figure 4. 1-chloro-2-(naphthalen-2-yl)propan-2-ol, (**11**).

In the ^{1}H-NMR spectrum of 1-chloro-2-(naphthalen-2-yl)propan-2-ol .(**11),** methyl is observed as a singlet at 1.92 ppm. The hydroxide proton of compound **11** can be seen at 2.42 ppm where it is controlled with D_2O. The doublets at 3.98 ppm and 4.34 ppm correspond to the diastereotopic methylene protons. The rest of the protons can be shown in a range between 7.26 ppm and 8.48 ppm, belong to the naphtyl. The peaks observed from ^{13}C-NMR spectrum are; 28.1 which belong to methyl carbon, 56.0 for methylene carbon; 76.0 is belonging to quaternary carbon and the rest of the carbon peaks belong to the naphtyl as range between 123.6 and 139.8. The NMR spectra of compound **11** are given in Appendix A.

2.1.3 1-Chloro-2-phenylpropan-2-ol, (12)

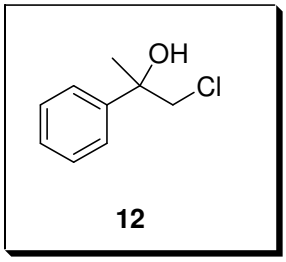


Figure 5. 1-Chloro-2-phenylpropan-2-ol, (**12**).

This compound was already synthesized and its physical properties are compared with the data given in the literature [36]. The NMR spectra of compound **12** are given in Appendix A.

2.1.4 1-Chloro-2-methyl-3-phenylpropan-2-ol, (13)

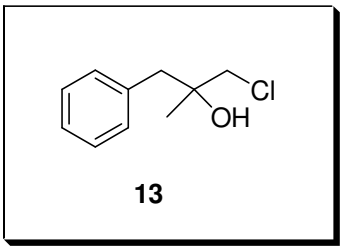


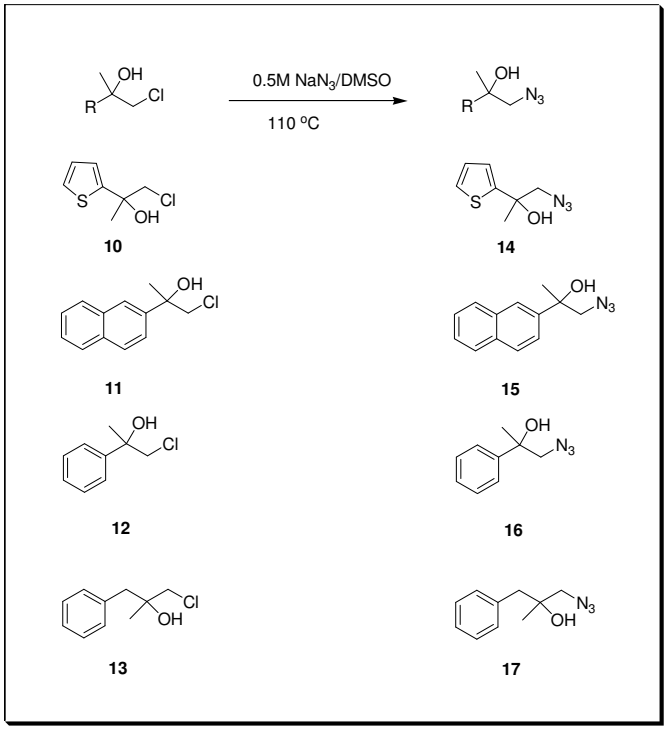
Figure 6. 1-Chloro-2-methyl-3-phenylpropan-2-ol, (**13**).

This compound is common and its properties are accordance with the literature data [37]. It was already synthesized by Malinovskii et. al. with Grignard reaction of benzyl bromide and chloroacetone. In their work they got

40 % chemical yield [38]. In benzyl bromide reactions, extra attention should be paid since fast addition of reagents cause formation of different dimerization products. The NMR spectra of compound **13** are given in Appendix A.

2.2 Synthesis of 1,2-azido alcohol derivatives

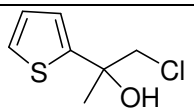
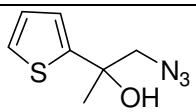
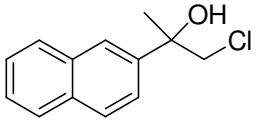
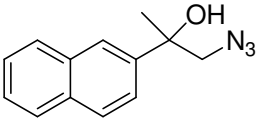
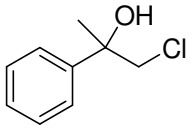
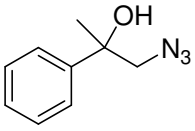
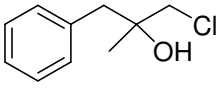
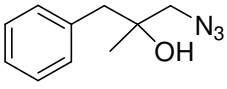
Azide, generally, is a good and applicable precursor for amine [39]. Azide group can easily undergo S_N2 type reaction with alkyl halides [40]. Alvarez et al. had reported a highly efficient method for azide addition reaction to alkyl bromides [41]. In our halo systems, chloromethylene parts are susceptible to S_N2 reactions. The procedure, which was reported by Alvarez et. al., was used for our systems. The summary of S_N2 reactions was shown in Scheme 5.



Scheme 5. Synthesis of 1,2-azido alcohols

DMSO was used as solvent. In this method, 1,2-chloro alcohol derivatives didn't react with azide until temperature reached to 110 ^{0}C. The reaction was completed in 3 hours, and the standard work-up procedure with water and ethyl acetate was applied. All of the reactions were controlled with TLC and the reaction was stopped in the absence of the 1,2-chloro alcohol. The purification of the crude products was done with column chromatography, and detailed information is given in experimental part. In crude NMR, there are two more elimination products seen in aryl substituted 1,2-chloro alcohol derivatives. Elimination products could occur because of the high temperature. The structure determination of products was done by ^{1}H-NMR, ^{13}C-NMR, and IR spectra. By IR spectroscopy, characteristic azide stretching was observed approximately at 2100 cm^{-1}. Summary of all of these S_N2 reactions is given in Table 2.

Table 2. The results of S_N2 reactions

Reactants	Time	Products		Isolated Yields
	180 min		**14**	63 %
	180 min		**15**	60 %
	180 min		**16**	65 %
	180 min		**17**	95 %

2.2.1 1-Azido -2-(thiophen-2-yl)propan-2-ol, (14)

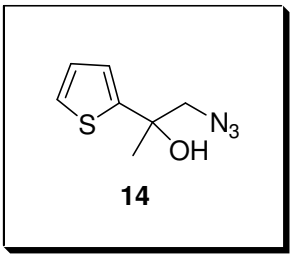


Figure 7. 1-Azido -2-(thiophen-2-yl)propan-2-ol, (**14)**

The ^{1}H-NMR spectrum of 1-azido -2-(thiophen-2-yl)propan-2-ol **(14)** is slightly different from the ^{1}H-NMR spectrum of 1-chloro-2-(thiophen-2-yl)propan-2-ol **(10).** The characteristic difference is observed in the chemical shift values of two doublets of the diastereotopic methylene protons. In the ^{1}H-NMR spectrum of compound **10**, these two hydrogens appears at 3.73 ppm and 3.83 ppm. On the other hand, in the ^{1}H-NMR spectrum of compound **14**, they shift to 3.64 ppm and 3.74 ppm. The rest of the peaks at 7.01 ppm, 7.06 ppm, and 7.30 ppm correspond to protons at the 5th, 4th and 3rd positions of thiophene ring, respectively. In the ^{13}C-NMR spectrum, the most distinct change becomes visible in the methylene carbon, where it shifts from 55.3 to 66.0. The NMR spectra of compound **14** are given in Appendix A

2.2.3 1-Azido-2-(naphthalen-2-yl)propan-2-ol, (15)

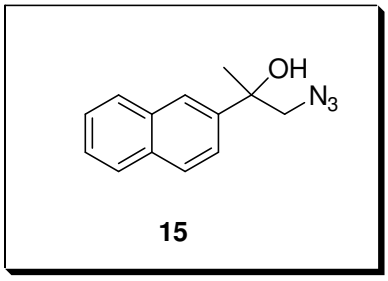


Figure 8. 1-Azido-2-(naphthalen-2-yl)propan-2-ol, (**15)**

The distinguishing difference between the ^{1}H-NMR spectrum of 1-azido-2-(naphthalen-2-yl)propan-2-ol (**15)** and ^{1}H-NMR spectrum of 1-chloro-2-(naphthalen-2-yl)propan-2-ol (**11)** is the chemical shifts of two doublets of the diastereotopic methylene protons. In the ^{1}H-NMR spectrum of compound **11**, these two hydrogens show the signals at 3.98 ppm and 4.34 ppm, however in the ^{1}H-NMR spectrum of compound **15**, they shift to 3.72 ppm and 4.10 ppm. In the ^{13}C-NMR spectrum, the change can be seen in the methylene carbon where it shifts from 56.0 to 61.0. The NMR spectra of compound **15** are given in Appendix A

2.2.4 1-Azido-2-phenylpropan-2-ol, (16)

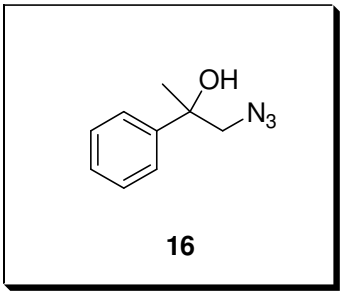


Figure 9. 1-Azido-2-phenylpropan-2-ol, (**16)**

The physical properties of 1-azido-2-phenylpropan-2-ol (**16)** are compared with the data given in literature [42]. The NMR spectra of compound **16** are given in Appendix A.

2.2.5 1-Azido-2-methyl-3-phenylpropan-2-ol, (17)

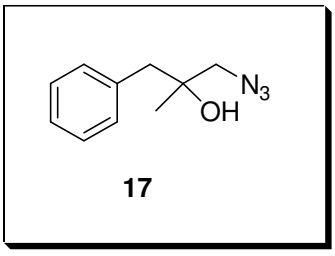


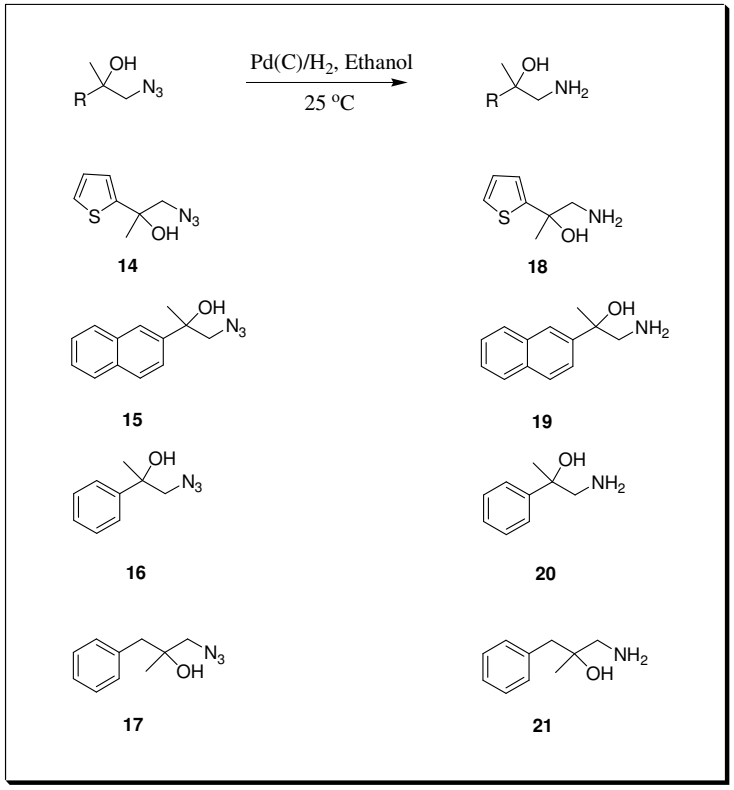
Figure 10. 1-Azido-2-methyl-3-phenylpropan-2-ol, (**17)**

In the ^{1}H-NMR spectrum of 1-azido-2-methyl-3-phenylpropan-2-ol **(17)**, there are two different sets of diastereotopic methylene protons. The

drastic difference is at the diastereotopic benzylic methylene protons, where two doublets shift from 2.83 ppm and 2.92 ppm to 2.63 ppm and 2.67 ppm, respectively. Another significant difference is observed at diastereotopic methylene protons joined to the carbon having azide, where they shift from 3.42 ppm and 3.46 ppm to 3.04 ppm to 3.14 ppm, respectively. The aromatic protons are observed as multiplet between 7.08- 7.26 ppm. The shift of the methylene carbon having the azide group from 52.9 to 60.0 is the most important variant in the ^{13}C-NMR spectrum. The NMR spectra of compound **17** are given in Appendix A

2.3 Synthesis of 1,2-amino alcohols

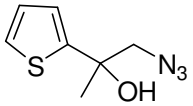
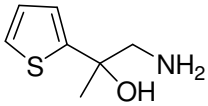
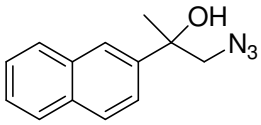
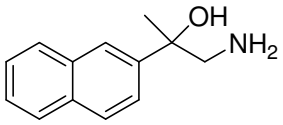
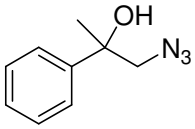
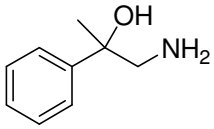
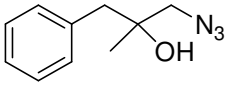
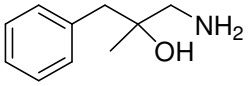
The best way of conversion of azide group to amine group was found to be the molecular hydrogenation with the aid of Pd(C) catalyst. Quantitative conversion was observed. Summary of the hydrogenation reactions is shown in Scheme 6.



Scheme 6. Synthesis of 1,2-amino alcohol derivatives

In our method ethanol was used as solvent and 0.1: 1 Pd(C) to 1,2-azido alcohol (w/w) was applied. The reaction was controlled by TLC and stopped when all the 1,2-azido alcohol was converted to the 1,2-amino alcohol. After separation of catalyst with filtration, 1,2-amino alcohol was obtained. The characterization of 1,2-amino alcohols was done by NMR. Summary of all of these hydrogenation reactions is given in Table 3.

Table 3. The Summary of hydrogenation reaction

Reactants	Time	Products	
	10 h		**18**
	9 h		**19**
	11 h		**20**
	10 h		**21**

2.3.1 1-Amino-2-(thiophen-3-yl)propan-2-ol, (18)

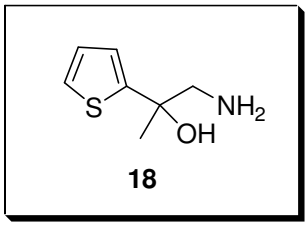


Figure 11. 1-Amino-2-(thiophen-3-yl)propan-2-ol, (**18)**

In the comparison ^{1}H-NMR spectrums of 1-azido -2-(thiophen-2-yl)propan-2-ol (**14)** and 1-amino-2-(thiophen-3-yl)propan-2-ol **(18)**, the diastereotopic methylene protons shift from 3.64 ppm and 3.74 ppm to 3.40 ppm and 3.48 ppm, respectively. The presence of the amine and the hydroxide protons were controlled with D_2O. In the ^{13}C-NMR spectrums the methylene

carbon shifts from 66.0 to 55.8. The NMR spectra of compound **18** are given in Appendix A

2.3.2 1-Amino-2-(naphthalen-2-yl)propan-2-ol, (19)

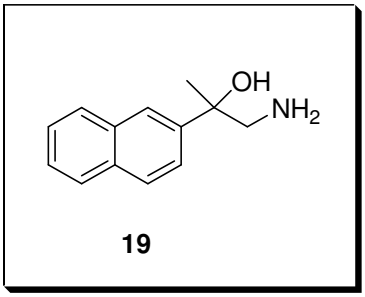


Figure 12. 1-Amino-2-(naphthalen-2-yl)propan-2-ol, (**19)**

In the ^{1}H-NMR spectrum of 1-amino-2-(naphthalen-2-yl)propan-2-ol **(19)**, diastereotopic methylene protons show two doublets at 2.82 ppm to 3.37 ppm, in the ^{1}H-NMR spectrum of 1-azido-2-(naphthalen-2-yl)propan-2-ol **(15)**, they show two doublets at 3.72 ppm and 4.10 ppm. In the ^{13}C-NMR spectrum of compound **19**, most specific difference can be seen at the methylene carbon where it shifts from 61.0 to 51.3. The NMR spectra of compound **19** are given in Appendix A

2.3.3 1-Amino-2-phenylpropan-2-ol, (20)

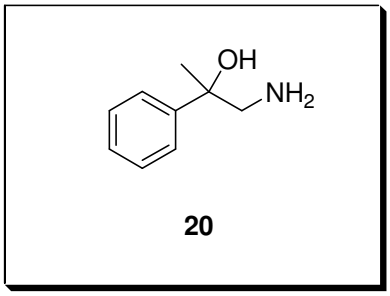


Figure 13. 1-Amino-2-phenylpropan-2-ol, (**20**).

All physical properties of 1-amino-2-phenylpropan-2-ol **(20)** are in accordance with the literature data [43]. The NMR spectra of compound **20** are given in Appendix A.

2.3.4 1-Amino-2-methyl-3-phenylpropan-2-ol, (21)

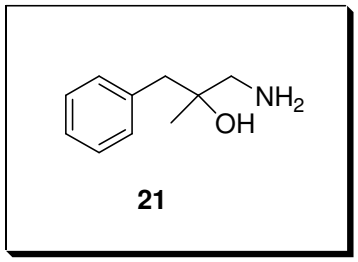


Figure 14. 1-Amino-2-methyl-3-phenylpropan-2-ol, (**21**).

The ^{1}H-NMR spectrum of 1-amino-2-methyl-3-phenylpropan-2-ol **(21)** was taken in CD_3OD. The methylene protons show the main difference in the ^{1}H-NMR spectrums of 1-azido-2-methyl-3-phenylpropan-2-ol **(17)** and

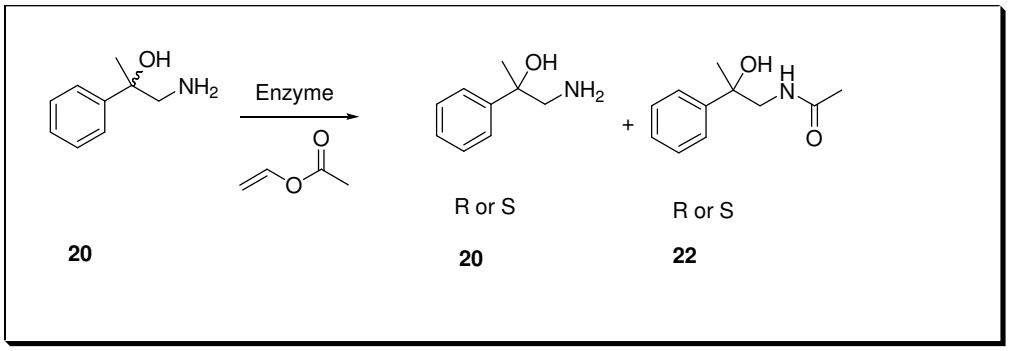
compound **21**. The two doublets of diastereotopic methylene protons which attached to nitrogen atom shift from 3.04 ppm and 3.14 ppm to 2.82 ppm and 2.83 ppm, respectively. The ^{13}C-NMR spectrum of compound **21** and the ^{13}C-NMR spectrum of compound **17,** are distinguished by the methylene carbon attached to azide, which shifted from 60.0 (in 17) to 49.5. The NMR spectra of compound **21** are given in Appendix A

2.4 Enantiomeric resolution studies of 1,2-amino alcohols.

In our study, we focused our attention to only one of the 1,2-amino alcohols synthesized, to optimize the conditions. Kinetic resolution using enzymes is one of the easiest methods to produce enantiomerically enriched amines out of racemic mixture [44]. In our research three hydrolytic enzyme types were used; CCL, CALB, AL PS-C II. The other variables used in this study are solvent effect, temperature and enzyme amount.

2.4.1 Enzymatic resolution studies of 1-amino-2-phenylpropan-2-ol, (20)

At the beginning, vinyl acetate was chosen as acetylating agent. The kinetic resolution of compound **20** with vinyl acetate is shown in scheme 7.



Scheme 7. Enzymatic resolution of 1-amino-2-phenylpropan-2-ol (**20)** with vinyl acetate.

CALB was used as biocatalyst and solvent effect was examined. In vinyl acetate, compound **20** did not give any reaction. In DIE, CALB produced racemic N-(2-hydroxy-2-phenylpropyl)acetamide **(22)**. When THF was used as solvent, CALB produced racemic N-(2-hydroxy-2-phenylpropyl)acetamide **(22)** in low chemical yield. In hexane, compound **20** did not give any reaction.

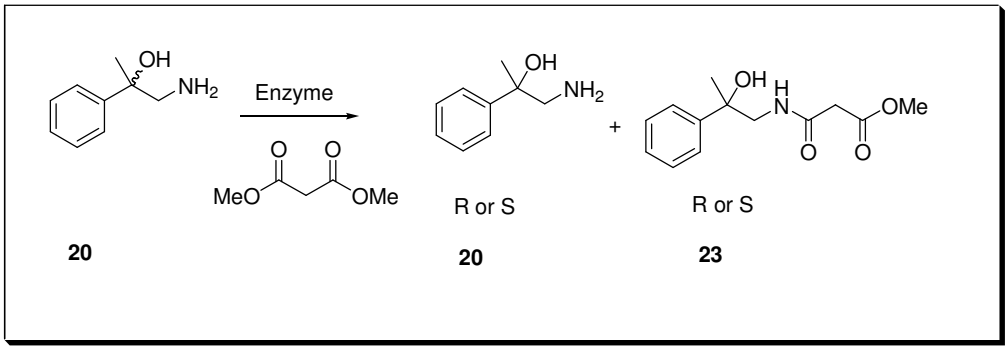
The enzyme was then changed to CCL. In DIE, CCL slightly amplifies enantiomeric excess. Therefore, temperature and enzyme amount decreased. These two changes did not affect the enantiomeric excess value. Hence, hexane was used as solvent; this was increased chemical yield but, sadly, resulted in racemic mixture of compound **22**. Finally, solvent changed to THF, unfortunately, no product formation observed.

In DIE, AL PS-C II afforded racemic N-(2-hydroxy-2-phenylpropyl)acetamide **(22)** as product. Finally, THF was used with AL PS-C II, unluckily this also didn't give any reaction. The enzymatic resolution of compound **20** with vinyl acetate failed. The summary of the enzymatic resolution experiments is shown in Table 4.

Table 4. The summary of the enzymatic resolutions using vinyl acetate as acetylating agent.

Enzyme	20/ Enzyme (w/w)	Solvent	Temp.	Time	Chemical Yield %	Ee %
CALB	1: 0.16	VA	RT	5h	-	NR
CALB	1: 0.25	DIE	RT	2h	15	Rac
CALB	1: 0.25	THF	RT	3h	15	Rac
CALB	1: 0.20	Hexane	RT	2h	-	NR
CCL	1: 0.3	DIE	RT	8h	10	6.2
CCL	1: 0.12	DIE	10	8h	10	7.3
CCL	1: 0.13	Hexane	RT	2h	60	Rac
CCL	1: 0.20	THF	RT	60h	-	NR
AL PS-C II	1: 0.06	DIE	RT	5h	45	Rac
AL PS-C II	1: 0.07	THF	RT	60h	45	NR

Gotor et al. has recently reported a highly efficient method [45]. Dimethyl malonate was used as acylating agent in dry dioxane. The kinetic resolution of compound **20** with dimethyl malonate is shown in Scheme 8.



Scheme 8. Enzymatic resolution of compound **20** with dimethyl malonate.

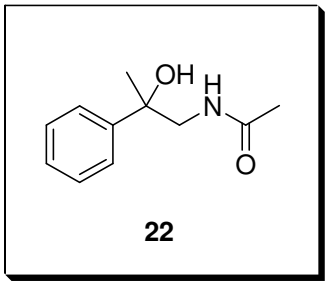
When CALB was used in dry dioxane at room temperature, 23 % enantiomeric excess was obtained. To get better results temperature was decreased however this only caused to increase the reaction time. Next, THF was used as solvent. Unfortunately the enantiomeric excess was no more than 21 %. Then, the solvent changed to DIE, but CALB produced nearly racemic methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate **(23)**. When EtOH was used as solvent, CALB didn't give any reaction. Finally, CALB in MBE, sadly, gave racemic methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate **(23)**. When AL PS-C II in CCL was used and resultant products were unluckily nearly racemic.

Table 5. The summary of the enzymatic resolutions using dimethyl malonate

Enzyme	**20/ Enzyme (w/w)**	**Solvent**	**Temp. (^{0}C)**	**Time**	**Chemical Yield %**	**Ee %**
CALB	1: 0.6	Dioxane	RT	2h	55	23
CALB	1: 0.05	Dioxane	15	3h	53	20.4
CALB	1: 0.05	Dioxane	5	8h	56	21.7
CALB	1: 0.09	THF	RT	2h	52	21
CALB	1: 0.06	DIE	RT	2h	53	7
CALB	1: 0.05	EtOH	RT	60h	-	NR
CALB	1: 0.06	MBE	RT	2h	47	Rac
CCL	1: 0.09	Dioxane	RT	60h	-	NR
AL PS-C II	1: 0.07	THF	RT	2h	58	4.6

The reason for the quite low selectivity of the enzymes used in all resolution experiments is presumably due to the crowded tertiary alcohol moiety of the substrate. In all reactions, substrates and solvents are mixed at first, and then the enzymes are added. The reactions were monitored by TLC.

The resultant mixtures were purified with column chromatography and detailed information given in experimental part.



22

Figure 15. N-(2-hydroxy-2-phenylpropyl)acetamide, (**22**)

For optimizing the HPLC conditions to separate its enantiomers, N-(2-hydroxy-2-phenylpropyl)acetamide **(22)**, was synthesized in racemic form. Compound **20** was treated with acetylchloride in DCM. Compound **22** had already been synthesized and its physical properties are compared with the data given in the literature [46].

HPLC analysis is carried out by using chiral OJ-H column at room temperature by using n-hexane/2-propanol (90:10) as eluent, flow rate is 0.5 mL/min and the wavelength is 254 nm. [t_1= 9.0 min t_2= 12.6 min].

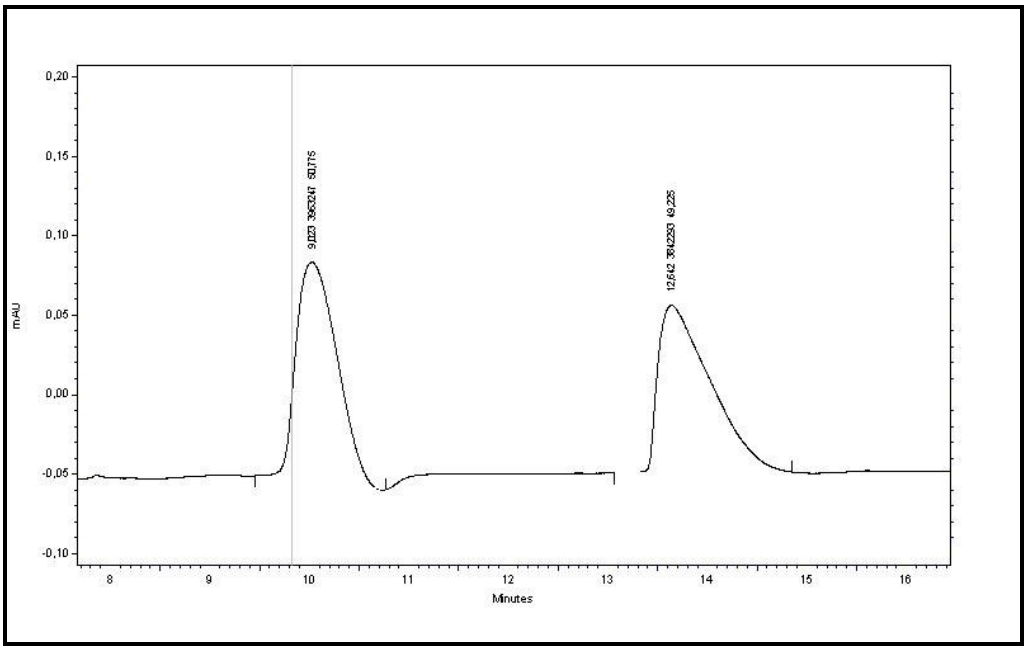
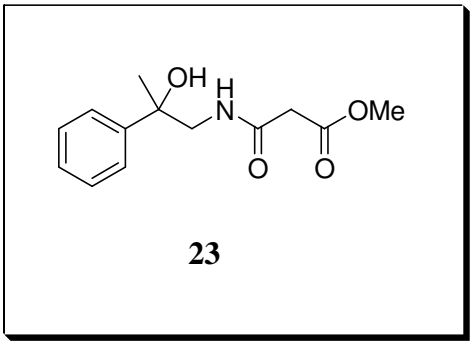


Figure 16: HPLC Chromatogram of racemic compound **22**.

Staskun et. al. was proposed a good method, for aniline and dimethyl malonate fusion [47]. At 180 ^{o}C dimethyl malonate and compound **20** were reacted to give methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate (**23)** with 95% chemical yield.



23

Figure 17. Methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **(23)**

The methoxy protons are observed at 3.63 ppm. Methylene protons between carbonyls give singlet at 3.20 ppm in the ^{1}H-NMR spectrum of methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate (**23**). The two doublet of doublet of diastereotopic methylene protons of compound **23** shift from 3.57 ppm and 3.42 ppm to 3.66 ppm to 3.42 ppm, respectively, when compared with the two doublet of doublet of diastereotopic methylene protons of N-(2-hydroxy-2-phenylpropyl)acetamide (**22**).. The NMR spectrum of compound **23** can be seen in Appendix A.

HPLC analysis is carried out by using chiral OJ-H column at room temperature by using n-hexane/2-propanol (87:13) as eluent system, flow rate is 0.5 mL/min and the wavelength is 254 nm. [t_1= 15.2 min t_2= 21.6 min].

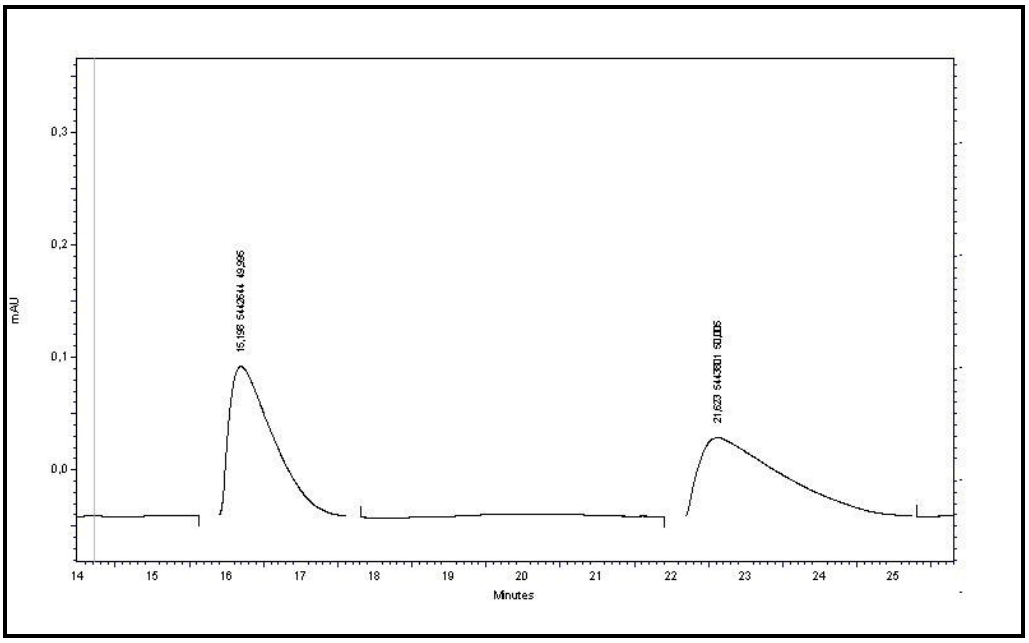


Figure 18. HPLC Chromatogram of racemic compound **23**.

2.5 Diethyl Zinc Experiments

Usually in asymmetric synthesis, enantioselectivity of the reaction linearly depends of the enantiomeric purity of catalyst. Initial rate of the reaction depends on the catalyst concentration but not to the S or R configuration and concentration of the catalyst. However, this is not always valid. Noyori et .al reported that there is a nonlinearity exists in some cases [48]. A simple model for the generation of nonlinear phenomena is shown in Figure 19.

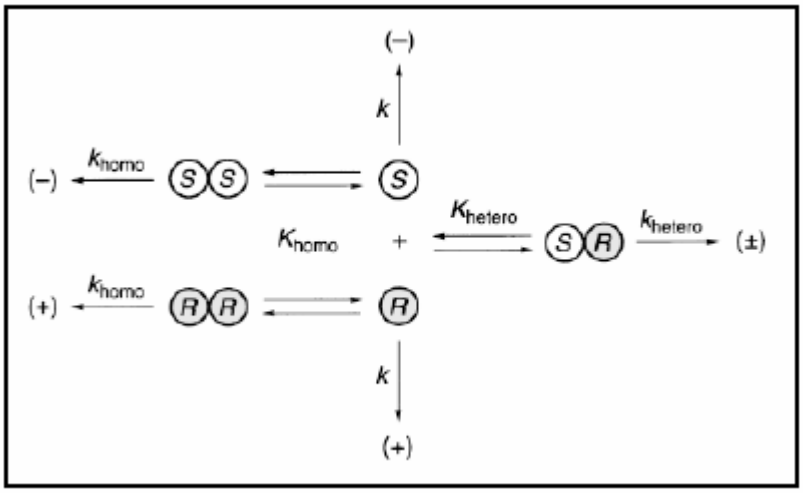


Figure 19.The simplest system generating nonlinear effects which are controlled by two thermodynamic and three kinetic parameters [48].

According to Noyori et. al. the homochiral and heterochiral interaction of enantiomeric S and R leads to SS or RR (homochiral) and SR (heterochiral). Then the reaction may be catalyzed by the monomers and/or dimers to give either a nonracemic or racemic product, depending on the situation. The interplay between the thermodynamics (K_{homo} and K_{hetero}) and kinetics (k, k_{homo}, and k_{hetero}) results in various non-classical aspects. If in this model one

of the homochiral active ligand complex gives much more faster reaction then other this leads to an enantiomeric enrichment in product, so this is called nonlinear effect [48].

Therefore, this information led us to think that enantiomerically enriched compound **20** could be used as chiral ligand in diethyl zinc addition reaction. The resultant compound **20** was used as chiral ligand. The reaction was carried out in dry toluene and at 0 ^{o}C and afforded compound **24** with 70% chemical yield and revealed 20.6% enantiomeric excess. Since there wasn't a drastic increase in the enantiomeric excess of compound **24,** we can say that our ligand didn't show any (+) nonlinear effect. Asymmetric diethylzinc addition reaction to benzaldehyde is given in Scheme 9.

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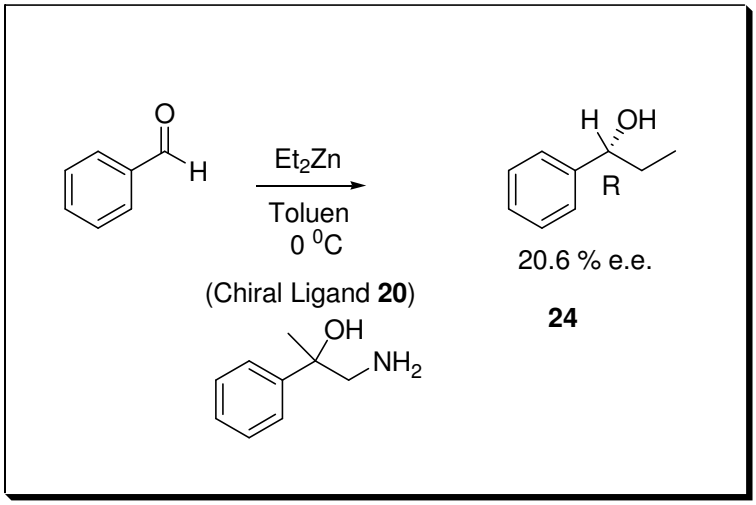

Scheme 9. Asymmetric diethylzinc addition

CHAPTER 3

EXPERIMENTAL

In this study, structures of the compounds are characterized with the instruments below.

By the ^{1}H-NMR and ^{13}C-NMR spectra $CDCl_3$ and CD_3OD were used as solvents in a Bucker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield form tetramethyl silane. Apparent splittings are given in all cases. Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet)

Infrared spectra were done in Varian 1000 FT-IR Scimitar Series, on KBr pellets.

HPLC chromatograms are done in ThermoFinnigan Spectra System instrument. Samples run through on Chiracel OJ-H analytical column (250 x 4.60 mm) with hexane/ 2-propanol as eluent.

Column chromatography was performed on silica gel (60- Mesh, Merck). TLC studies were carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates.

All extracts were dried over anhydrous magnesium sulphate and solutions were concentrated under vacuum.

3.1 General procedure for synthesis of 1,2- chloro alcohols.

Iodine, iodomethane (0.1 mL), and dry THF (2 mL) was added on Mg (0.27 mg. 11.1 mmol). Aryl bromide or benzyl bromide (11.0 mmol) in THF (10 mL) was added on the solution drop-wise under reflux. The resulted Grignard reagent was cooled down to 0 ^{o}C. Then chloroacetone (12.5 mmol) was added in THF (20 mL) drop-wise on the solution. After 30 min, solution was hydrolyzed with saturated NH_4OH solution (20 mL). Organic phase was extracted with ethyl acetate (3x 10 mL) and dried over $MgSO_4$. The resultant 1,2-chloro alcohol was purified with column chromatography (1:6; ethyl acetate: hexane). The resultant solution was concentrated with vacuum and 1,2-chloro alcohol was obtained.

3.1.1 1-Chloro-2-(thiophen-2-yl)propan-2-ol, (10)

1-Chloro-2-(thiophen-2-yl)propan-2-ol was obtained as yellowish oil (1.37 g, 70 %). ^{1}H-NMR: δ 7.24 (dd, J=1.6, 2.7 Hz 1H), 6.97 (s, 2H), 3.83 (d, J= 11.1 Hz 1H), 3.73 (d, J= 11.1 Hz 1H), 2.80 (br, 1H) 1.72 (s, 3H); ^{13}C-NMR: δ 148.9, 126.9, 124.8, 123.4, 73.1, 55.3, 27.9.

3.1.2 1-Chloro-2-(naphthalen-2-yl)propan-2-ol, (11)

1-Chloro-2-(naphthalen-2-yl)propan-2-ol was obtained as yellowish oil (1.60 g, 66 %). ^{1}H-NMR: δ 8.48 (d, J= 8.3 Hz 1H), 7.71 (d, J= 7.9 Hz 1H), 7.63 (d, J= 8.2 Hz 1H), 7.42 (d, J= 7.3 Hz 1H), 7.53-7.41 (m, 2H), 7.26 (t, J= 9.8 Hz, 2H), 4.34 (d, J= 11.4 Hz 1H), 3.98 (d, J= 11.4 Hz 1H), 2.42 (br, 1H) 1.92 (s, 3H); ^{13}C-NMR: δ 139.8, 135.2, 130.1, 128.7, 127.6, 125.8, 125.3, 124.9, 124.4, 123.6, 76.0, 56.0, 28.1.

3.1.3 1-Chloro-2-phenylpropan-2-ol, (12)

1-Chloro-2-phenylpropan-2-ol was obtained as colorless oil. (1.41 g, 75 %). ^{1}H-NMR: δ 7.36 (d, J= 7.5 Hz 2H), 7.27 (t, J= 7.4 2H), 7.19 (t, J= 7.1 Hz), 3.71 (d, J= 11.1 Hz 1H), 3.63 (d, J= 11.1 Hz 1H), 2.60 (br, 1H) 1.53 (s, 3H); ^{13}C-NMR: δ 144.3, 128.5, 127.6, 125.0, 73.9, 55.4, 27.3.

3.1.4 1-Chloro-2-methyl-3-phenylpropan-2-ol, (13)

1-Chloro-2-methyl-3-phenylpropan-2-ol was obtained as colorless oil. (0.75 g, 37 %). ^{1}H-NMR: δ 7.34- 7.24 (m, 5H), 3.46 (d, J= 11.1 Hz 1H), 3.42 (d, J= 11.1 Hz 1H), 2.92 (d, J= 13.4 Hz 1H), 2.87 (d, J= 13.4 Hz 1H), 2.03 (br, 1H) 1.27 (s, 3H); ^{13}C-NMR: δ 136.4, 130.3, 128.4, 126.9, 72.2, 52.9,45.0, 24.7.

3.2 General procedure for synthesis of 1,2-azido alcohol derivatives

NaN_3 (6 mmol) was added to DMSO (11 mL) then solution was mixed for 24 h. 1,2-chloro alcohol (6 mmol) was added to the solution. The resulted solution was heated to 110 ^{o}C and in 3 h. the reaction was completed. Water (30 mL) was added to solution and the mixture was extracted with ethyl acetate (3x 15 mL). Then solution was dried over $MgSO_4$. 1,2-azido alcohol was purified with column chromatography (1:4; ethyl acetate: hexane). Resultant solution was concentrated under vacuum.

3.2.1 1-Azido -2-(thiophen-2-yl)propan-2-ol, (14)

1-Azido -2-(thiophen-2-yl)propan-2-ol was obtained as yellowish oil. (0.65 g, 63 %). IR (KBr): 2110 cm^{-1}, ^{1}H-NMR: δ 7.30 (dd, J=0.8, 4.2 Hz 1H), 7.06 (d, J= 2.8 1H), 7.01 (t, J= 3.5 1H), 3.74 (d, J= 10.0 Hz 1H), 3.64 (d, J=

10.0 Hz 1H), 2.22 (br, 1H) 1.76 (s, 3H); ^{13}C-NMR: δ 144.6, 127.0, 125.6, 124.8, 70.8, 66.0, 22.4.

3.2.2 1-Azido-2-(naphthalen-2-yl)propan-2-ol, (15)

1-Azido-2-(naphthalen-2-yl)propan-2-ol was obtained as yellowish oil. (0.82 g, 60 %). IR (KBr): 2109 cm^{-1}, ^{1}H-NMR: δ 8.73 (d, J= 8.5 Hz 1H), 7.93 (d, J= 7.7 Hz 1H), 7.86 (d, J= 8.1 Hz 1H), 7.61 (d, J= 7.3 Hz 1H), 7.58-7.51 (m, 2H), 7.48 (t, J= 7.7 Hz, 2H), 4.10 (d, J= 12.4 Hz 1H), 3.72 (d, J= 12.4 Hz 1H), 2.74 (br, 1H) 1.89 (s, 3H); ^{13}C-NMR: δ 139.2, 135.0, 130.9, 129.4, 128.3, 126.3, 125.8, 125.4, 124.9, 124.1, 76.3, 61.0, 27.4.

3.2.3 1-Azido-2-phenylpropan-2-ol, (16)

1-Azido-2-phenylpropan-2-ol was obtained as yellowish oil. (0.46 g, 65 %). IR (KBr): 2108 cm^{-1}, ^{1}H-NMR: δ 7.36 (d, J=7.6 Hz 2H), 7.28 (t, J= 7.9 2H), 7.20 (t, J= 7.4 Hz), 3.49 (d, J= 12.3 Hz 1H), 3.34 (d, J= 12.3 Hz 1H), 2.35 (br, 1H) 1.49 (s, 3H); ^{13}C-NMR: δ 143.7, 127.3, 126.5, 123.9, 73.6, 61.2, 26.1.

3.2.4 1-Azido-2-methyl-3-phenylpropan-2-ol, (17)

1-Azido-2-methyl-3-phenylpropan-2-ol was obtained as colorless oil. (1.08 g, 95 %). IR (KBr): 2105 cm^{-1}, ^{1}H-NMR: δ 7.26- 7.08 (m, 5H), 3.14 (d, J= 12.2 Hz 1H), 3.09 (d, J= 12.2 Hz 1H), 2.73 (d, J= 13.4 Hz 1H), 2.67 (d, J= 13.4 Hz 1H), 1.87 (br, 1H) 1.09 (s, 3H); ^{13}C-NMR: δ 136.5, 130.5, 128.4, 126.8, 72.9, 60.0, 45.6, 24.8.

3.3 A general procedure for synthesis of 1,2-amino alcohol

1,2-Azido alcohol (0.65 g) and Pd/C (70mg) were mixed in ethanol (10 mL). Then under hydrogen atmosphere the solution was stirred for 24h. When all the 1,2-azido alcohol was converted to 1,2-amino alcohol, solution was filtered. The resulted solution was concentrated under vacuum and 1,2-amino alcohol was obtained.

3.3.1 1-Amino-2-(thiophen-3-yl)propan-2-ol, (18)

1-Amino-2-(thiophen)-3-yl)propan-2-ol was obtained as yellowish oil.(0.56g, 99 %), ^{1}H-NMR: δ 7.08 (d, J=5.1 Hz 1H), 6.09-6.87 (m, 2H), 3.48 (d, J= 10.8 Hz 1H), 3.40 (d, J= 10.8 Hz 1H), 2.46 (br, 3H) 1.44 (s, 3H); ^{13}C-NMR: δ 152.0, 127.0, 124.1, 122.9, 72.0, 55.8, 27.7.

3.3.2 1-Amino-2-(naphthalen-2-yl)propan-2-ol, (19)

1-Amino-2-(naphthalen-2-yl)propan-2-ol was obtained as yellowish oil.(0.58g, 99 %), ^{1}H-NMR: δ 8.48 (d, J= 7.9 Hz 1H), 7.71 (d, J= 7.7 Hz 1H), 7.63 (d, J= 8.1 Hz 1H), 7.42 (d, J= 7.2 Hz 1H), 7.37-7.29 (m, 2H), 7.26 (t, J= 7.8 Hz, 2H), 3.37 (d, J= 12.8 Hz 1H), 2.82 (d, J= 12.8 Hz 1H), 2.59 (br, 3H) 1.60 (s, 3H); ^{13}C-NMR: δ 141.2, 135.0, 130.9, 129.2, 128.5, 126.5, 125.3, 125.1, 125.0, 124.0, 74.7, 51.3, 27.8.

3.3.3 1-Amino-2-phenylpropan-2-ol, (20)

1-Amino-2-phenylpropan-2-ol was obtained as white solid. (0.56g, 99 %), ^{1}H-NMR: δ 7.34 (d, J=7.5 Hz 1H), 7.8 (t, J=7.8 Hz 2H), 7.17 (d, J=5.2 Hz 2H), 3.67 (br, 3H) 2.94 (d, J= 12.8 Hz 1H), 2.84 (d, J= 12.8 Hz 1H), 1.48 (s, 3H); ^{13}C-NMR: δ 146.4, 128.1, 126.5, 124.8, 73.4, 52.6, 27.5 mp 65-69 C^{0}.

3.3.4 1-Amino-2-methyl-3-phenylpropan-2-ol, (21)

1-Amino-2-methyl-3-phenylpropan-2-ol was obtained as white solid. (0.55 g, 99 %), ^{1}H-NMR: δ 7.22- 7.09 (m, 5H), 4.70 (br, 3H), 3.25 (s, 2H), 3.20 (s, 3H), 2.83 (d, J= 12.8 Hz 1H), 2.82 (d, J= 12.8 Hz 1H), 2.77 (d, J= 13.5 Hz 1H), 2.71 (d, J= 13.5 Hz 1H), 1.10 (s, 3H); ^{13}C-NMR: δ 137.7, 131.7, 129.3, 127.8, 70.7, 49.5, 47.4, 24.4. MP 144-146 C^{0}.

3.4 General procedure for enzymatic resolution of 1-amino-2-phenylpropan-2-ol (20) with vinyl acetate

10 mg of CALB (CCL, AL PS-C II) was added in one portion to a stirred solution of 1-amino-2-phenylpropan-2-ol **(20)** (100 mg, 0.7 mmol), vinyl acetate (0.1 mL, 1 mmol) and molecular sieves 4 Å (75 mg) in 10 mL solvent (DIE, THF, or hexane), under argon. The reaction mixture was stirred at 25 ^{o}C. The conversion was monitored by TLC. The products were purified by flash column chromatography (ethyl acetate).

CALB in DIE:
N-(2-hydroxy-2-phenylpropyl)acetamide **22** (20 mg, 15% yield).

CALB in THF:
N-(2-hydroxy-2-phenylpropyl)acetamide **22** (20 mg, 15% yield).

CCL in DIE:
N-(2-hydroxy-2-phenylpropyl)acetamide **22** (13 mg, 10% yield).

CCL in hexane:
N-(2-hydroxy-2-phenylpropyl)acetamide **22** (78 mg, 60 % yield).

AL PS-C II in DIE:
N-(2-hydroxy-2-phenylpropyl)acetamide **22** (59 mg, 45 % yield).

AL PS-C II in THF:

N-(2-hydroxy-2-phenylpropyl)acetamide (**22)** (60 mg, 45 % yield).

3.5 General procedure for enzymatic resolution of 1-amino-2-phenylpropan-2-ol (20) with dimethyl malonate

To a stirred solution of 1-amino-2-phenylpropan-2-ol (**20**) (100 mg, 0.7 mmol) and dimethyl malonate (0.3 mL, 1 mmol) in dioxane (10 mL DIE, THF, hexane, MBE, or EtOH), CALB (10 mg CCL, or AL PS-C II) was added in one portion under argon atmosphere. The conversion was monitored by TLC. The products were purified by flash column chromatography (ethyl acetate).

CALB in dioxane:

3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **23** (88 mg, 55 % yield). $[\alpha]_D^{20}$= -8.0

CALB in THF:

1-amino-2-phenylpropan-2-ol **20** (22 mg, 22 % yield), 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **23** (83 mg, 52 % yield). $[\alpha]_D^{20}$= -7.2

CALB in DIE:

3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **23** (85 mg, 53 % yield).

CALB in MBE:

1-amino-2-phenylpropan-2-ol **20** (23 mg, 23 % yield) 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **23** (75 mg, 47 % yield).

AL PS-C II in THF:

1-amino-2-phenylpropan-2-ol **20** (20 mg, 22 % yield) 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, **23** (93 mg, 58% yield).

3.6 Synthesis of N-(2-hydroxy-2-phenylpropyl)acetamide, (22)

1-Amino-2-phenylpropan-2-ol, (200mg, 1.3mmol) and pyridine (0.2 mL, 2.8 mmol) were added into dry DCM (10 mL) at 0 ^{o}C under argon

atmosphere. After 1 h, acetyl chloride (0.3 mL, 3.6 mmol) was added and in 30 min reaction was completed. 1N HCl was added to solution and the solution was extracted with ethyl acetate (3x 10mL). The resulted organic phase was concentrated and N-(2-hydroxy-2-phenylpropyl)acetamide was obtained as white solid. (256g, 99 %), ^{1}H-NMR: δ 7.45 (d, J=7.7 Hz 1H), 7.36 (t, J=7.8 Hz 2H), 7.26 (d, J=8.2 Hz 1H), 5.75 (br, 3H) 3.57 (dd, J=8.5 7.8 Hz 1H), 3.42 (dd, J=8.5 7.8 Hz 1H), 1.93 (s, 3H), 1.55 (s, 3H); ^{13}C-NMR: δ 172.1, 145.9, 128.5, 127.2, 125.2,75.0,51.4, 28.1, 23,2. MP 106-108 ^{o}C.

3.7 Synthesis of methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate, (23)

1-Amino-2-phenylpropan-2-ol (200 mg, 1.3 mmol) was added to refluxed. dimethyl malonate (3 mL). After 5 min reaction mixture was cooled in an ice bath. Resulted solution was purified with column chromatography. Methyl 3-(2-hydroxy-2-phenylpropylamino)-3-oxopropanoate was obtained as white solid. (0.296g, 95%), ^{1}H-NMR: δ 7.39 (d, J= 7.5 Hz 1H), 7.23 (t, J=7.4 Hz 2H), 7.19 (d, J=7.3 Hz 1H), 3.66 (dd, J=5.3 5.4 Hz 1H), 3.63 (s, 3H), 3.42 (dd, J= 6.5 7.4 Hz 1H), 3.20 (s, 2H) 3.13 (br 1H), 1.49 (s, 3H); ^{13}C-NMR: δ 169.6, 166.3, 145.5, 128.4, 127.1, 124.9, 74.8, 52.4, 51.1, 40.9, 27.7. MP 61-64 ^{o}C

3.8 Diethylzinc addition reactions

Ligand **20** (0.05 mmol) was dissolved in toluene (3 mL) at room temperature under argon atmosphere. Then diethylzinc (1.0 mmol, 1 M in hexane) was added and the solution was stirred for 1 h. The solution was cooled down to 0 ^{0}C. Benzaldehyde (0.5 mmol) was added to the mixture and the reaction mixture was stirred for 120h. at 0 ^{0}C. 1 M HCl (10 mL) was added to the solution and it was extracted with ethyl acetate (3x 10 mL). The resulted solution was purified with column chromatography and corresponding alcohol

was collected (47 mg, 70 %, 20.6 % e.e.). HPLC-analysis of 1-phenyl-1-propanol: Chiral OD-H at room temperature, n-hexane/2-propanol = 98:2, 1.0 ml/min, 254 nm, t_1= 26.3 min (R), t_2= 31.5 min (S)

CHAPTER 4

CONCLUSION

In our study, an applicable method for the racemic synthesis of 1,2-amino alcohols having tertiary alcohol moiety was developed. This method can be used as a general method for the synthesis of various 1,2-amino alcohols with various tertiary alcohol moieties by changing chloroacetone with different monohalo ketones, and with different aryl halides or alkyl halides.

Moreover, in this study, we tried to enhance enantiomeric excess of compound **20** via enzymatic resolution. However, enzymatic resolution experiments failed, and, the best result is 23 % e.e. obtained with dimethyl malonate and CALB in dioxane. The reason for the quite low selectivity of the enzymes used in all resolution experiments is presumably due to the crowded tertiary alcohol moiety of the substrate. However, the studies will be continued. In the future work, enantiomeric enrichment will be tried with diastereomeric salt formation methods.

Finally, we used one of the worst enantiomerically enriched compound **20** (21% e.e.) in diethyl zinc reaction. Ligand **20** at 0 ^{0}C in toluene afforded **(*R*)-24** (20.6 % e.e.). The result showed that our ligand didn't show any nonlinear effect. Indeed, our ligand's enantiomeric purity shows linearity with the enantioselectivity of the reaction.

APPENDIX A

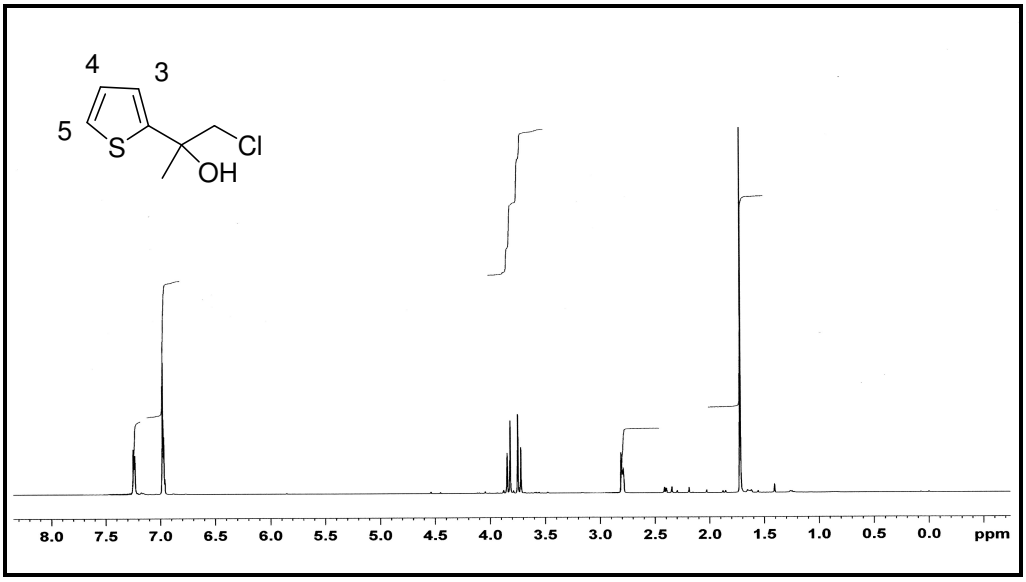

Figure 20. ^{1}H-NMR spectrum of **10** in $CDCl_3$

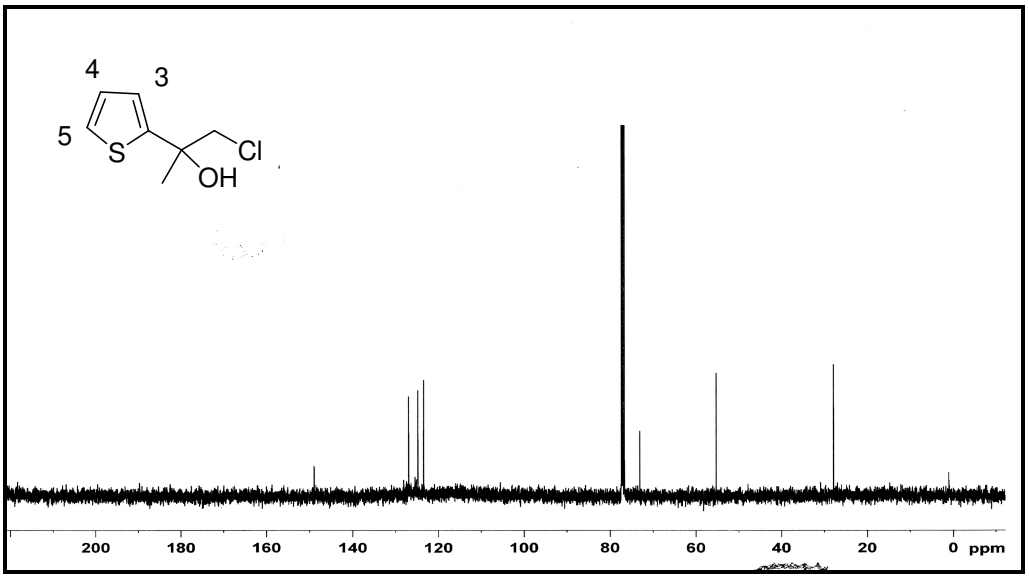

Figure 21. ^{13}C-NMR spectrum of **10** in $CDCl_3$

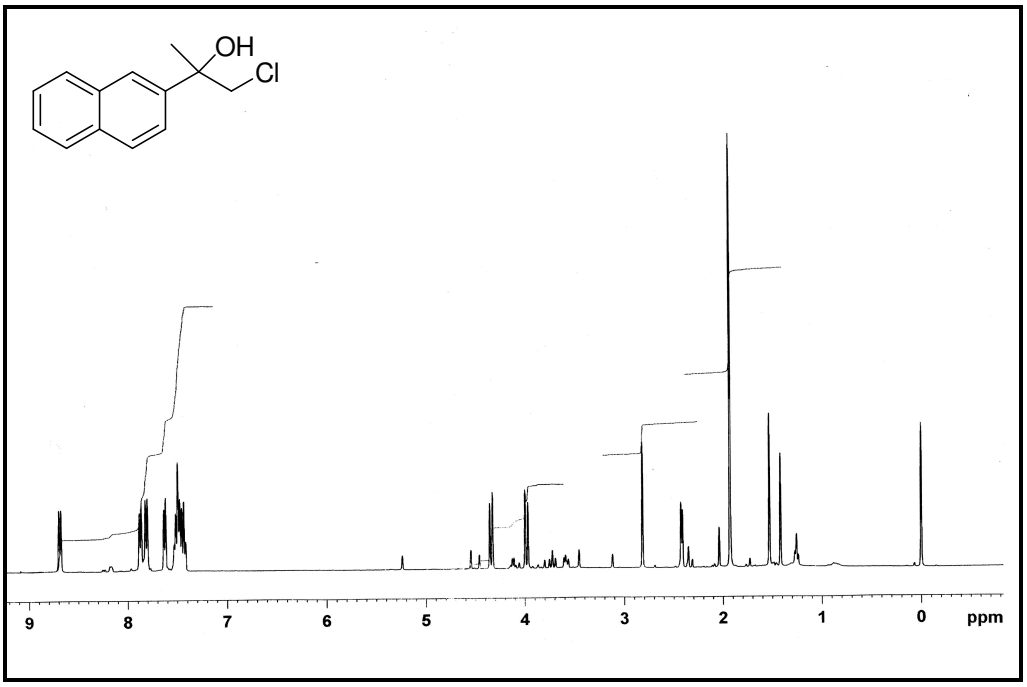

Figure 22. ^{1}H-NMR spectrum of **11** in $CDCl_3$

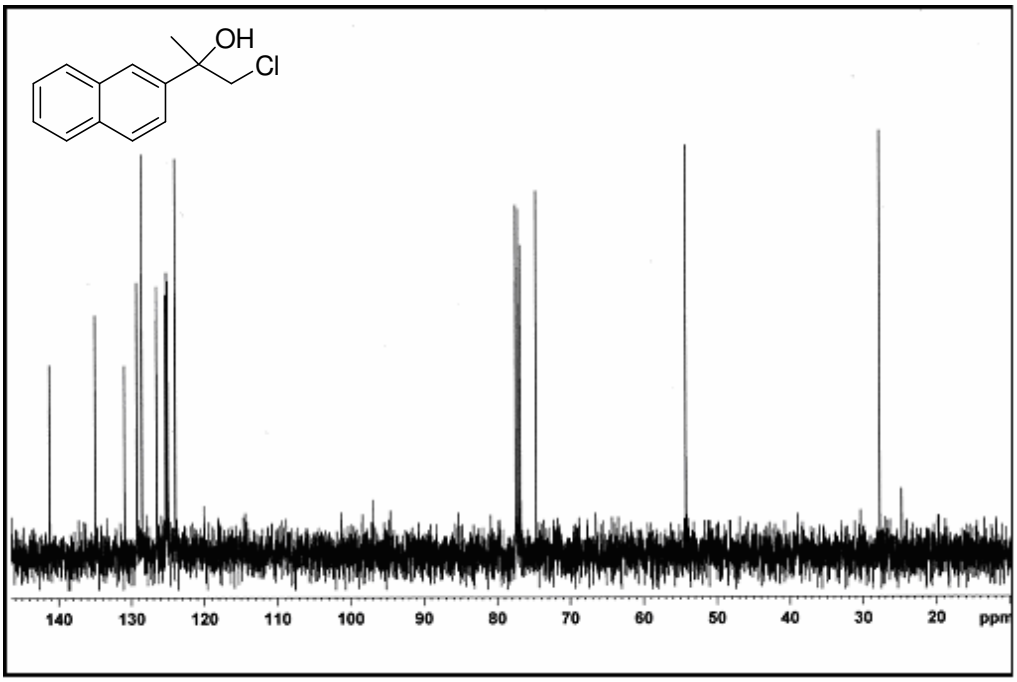

Figure 23. ^{13}C-NMR spectrum of **11** in $CDCl_3$

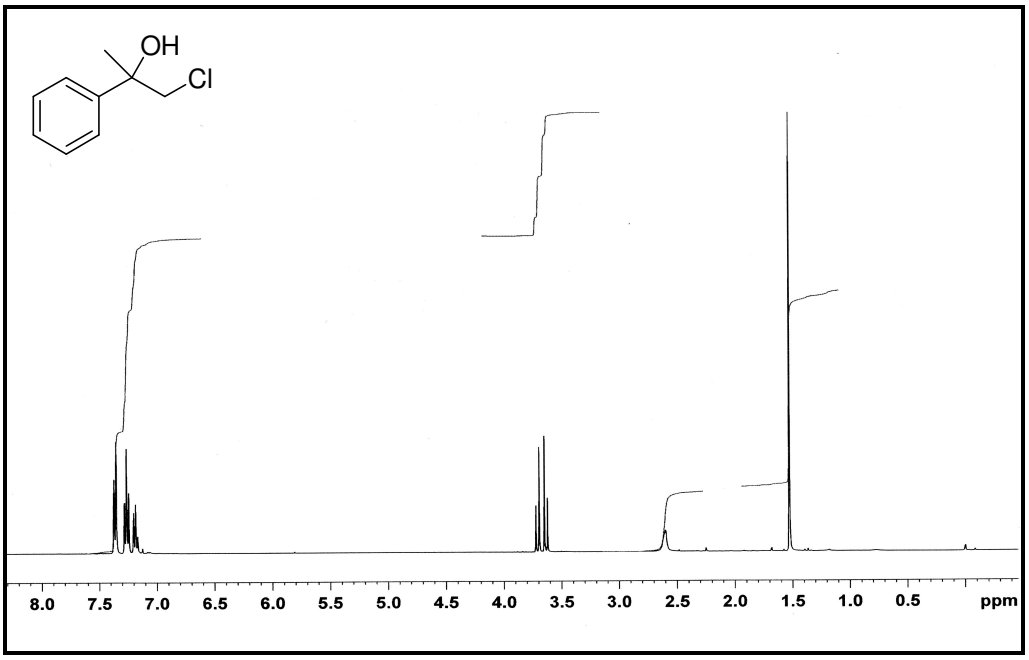

Figure 24. ^{1}H-NMR spectrum of **12** in $CDCl_3$

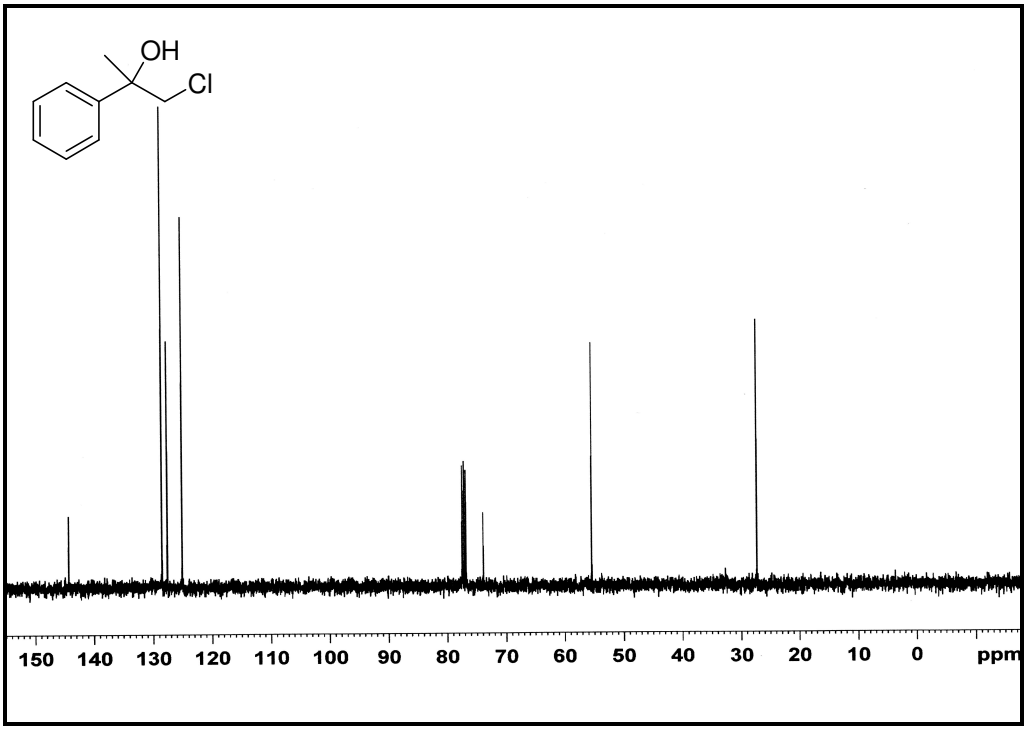

Figure 25. ^{13}C-NMR spectrum of **12** in $CDCl_3$

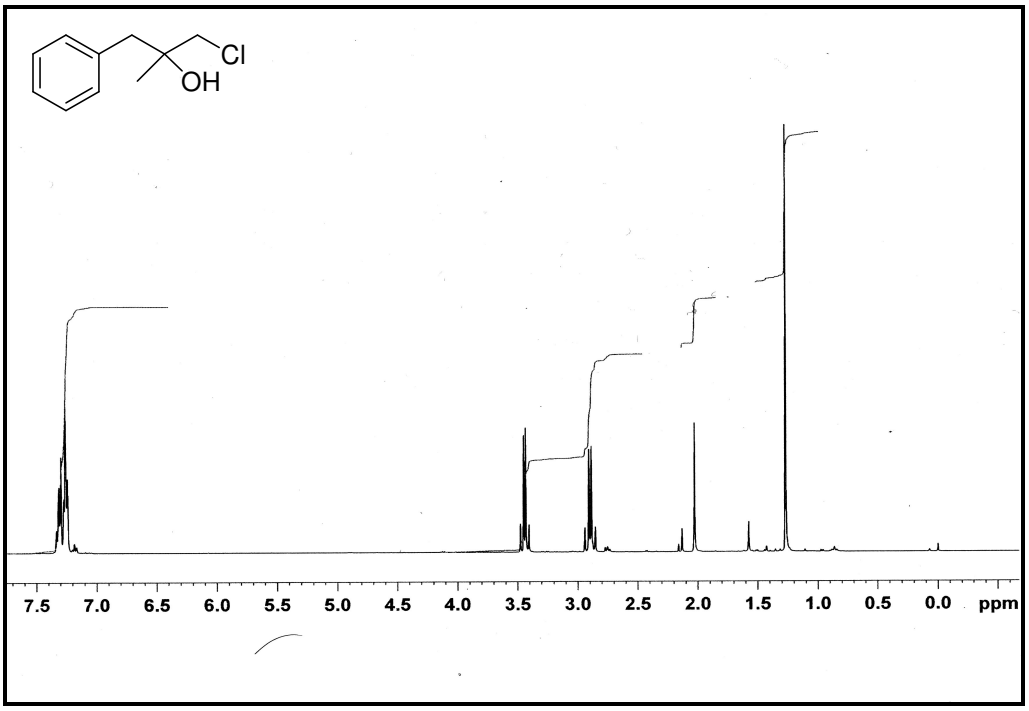

Figure 26. ^{1}H-NMR spectrum of **13** in $CDCl_3$

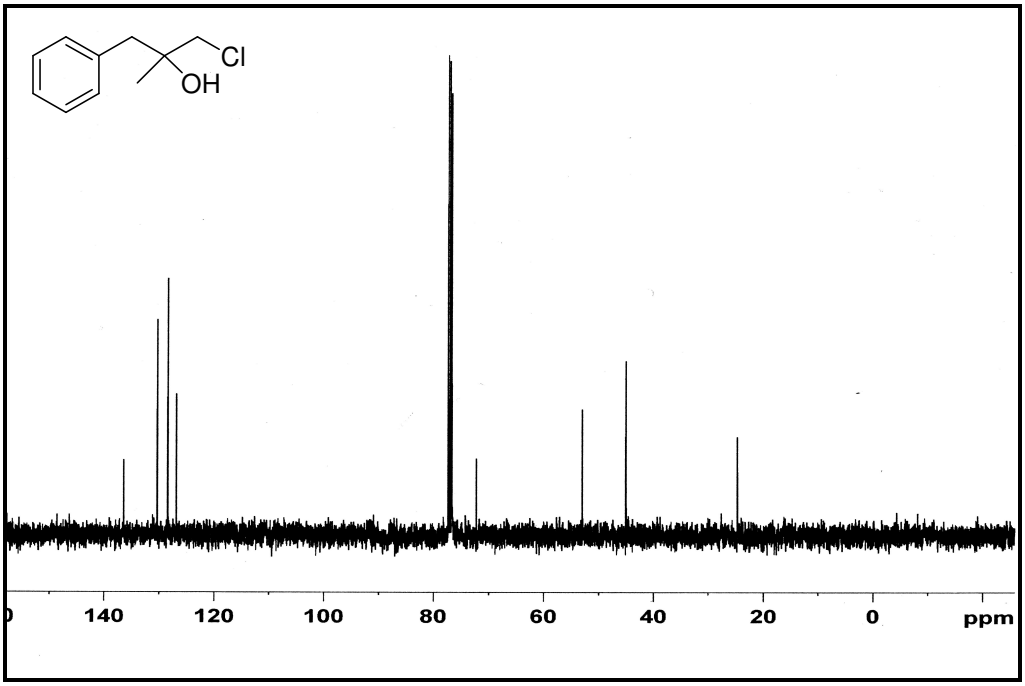

Figure 27. ^{13}C-NMR spectrum of **13** in $CDCl_3$

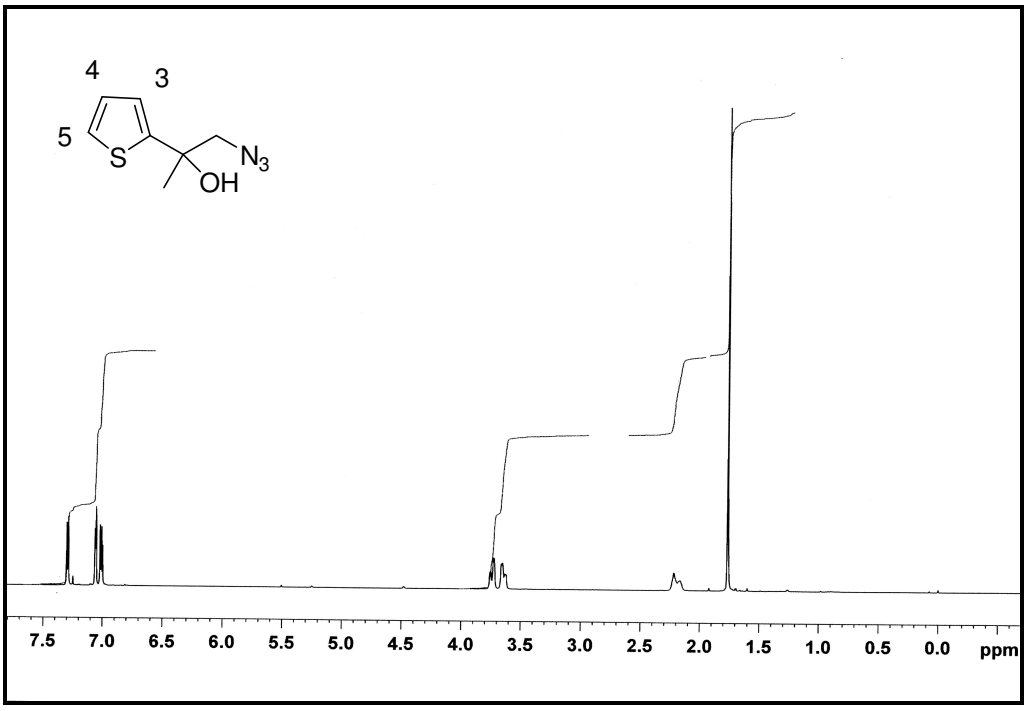

Figure 28. ^{1}H-NMR spectrum of **14** in $CDCl_3$

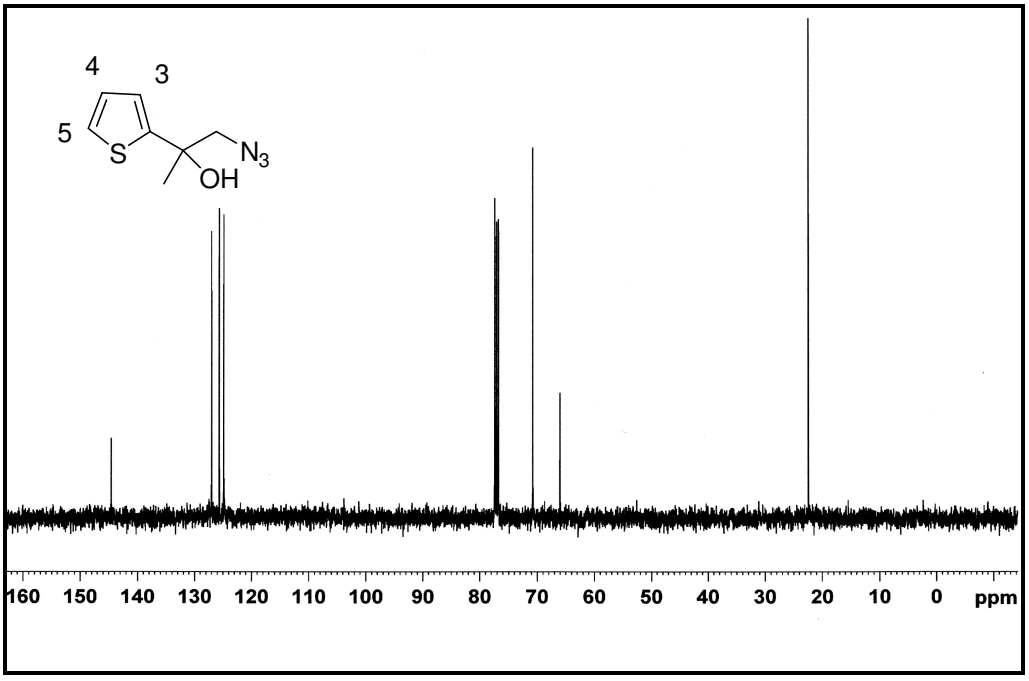

Figure 29. ^{13}C-NMR spectrum of **14** in $CDCl_3$

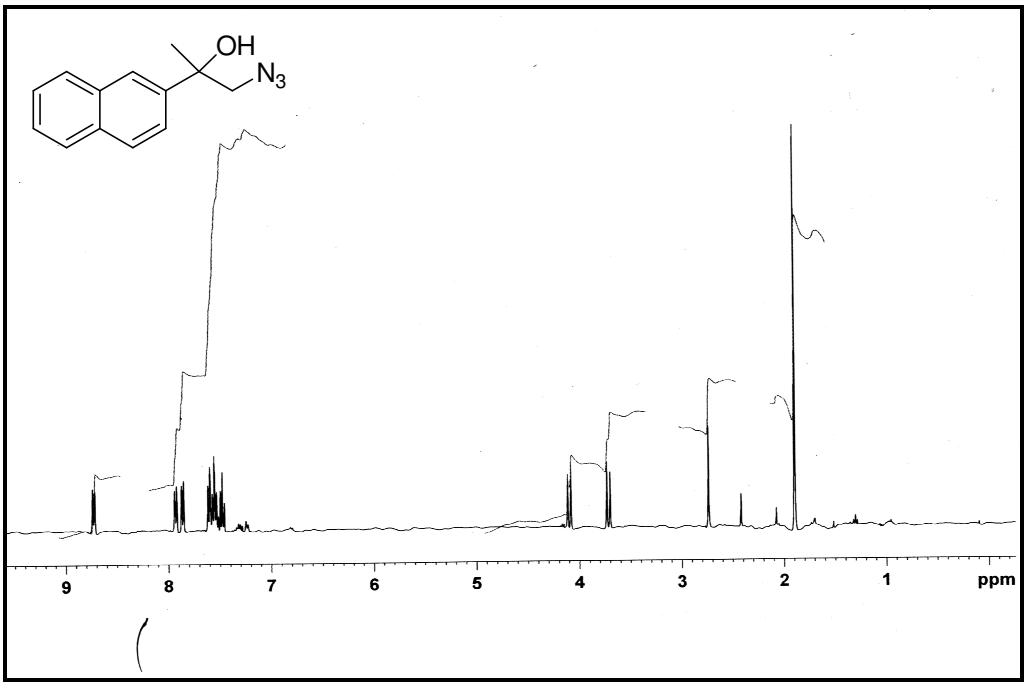

Figure 30. ^{1}H-NMR spectrum of **15** in $CDCl_3$

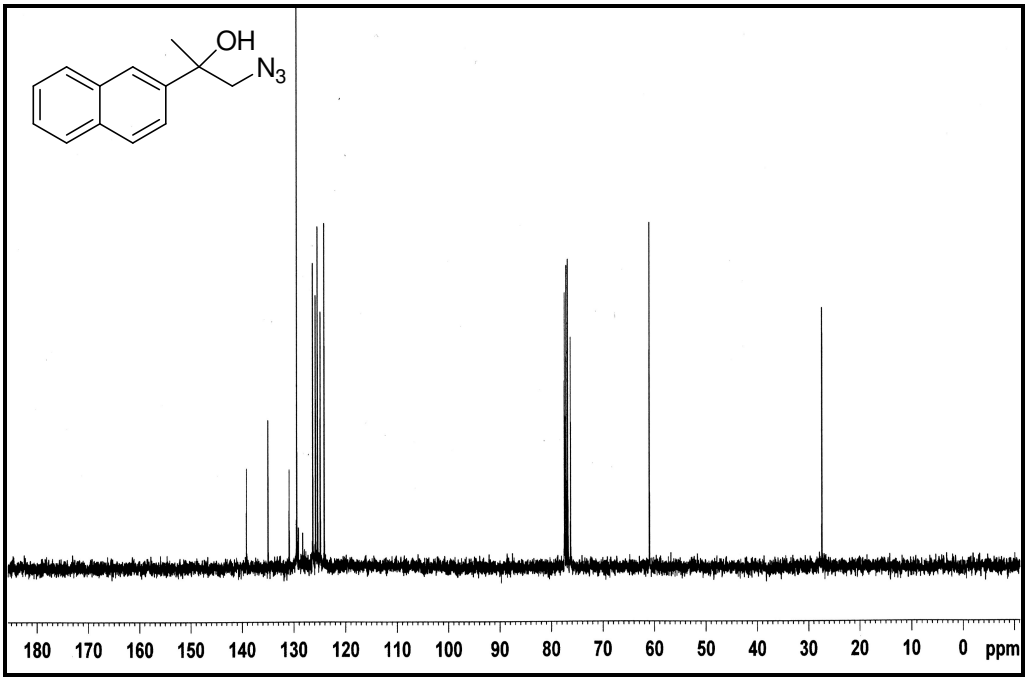

Figure 31. ^{13}C-NMR spectrum of **15** in $CDCl_3$

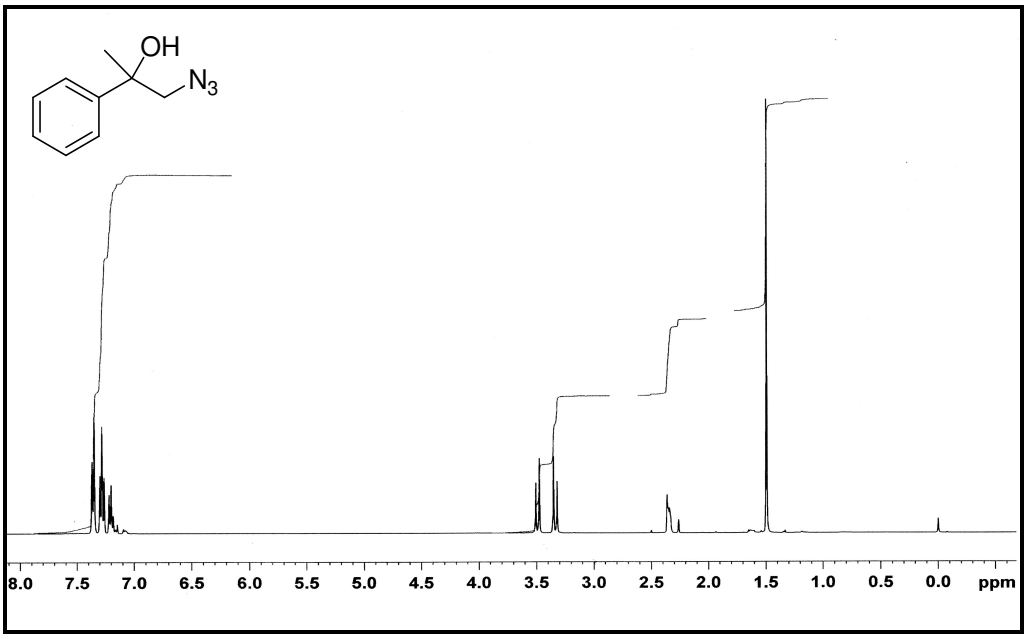

Figure 32. ^{1}H-NMR spectrum of **16** in $CDCl_3$

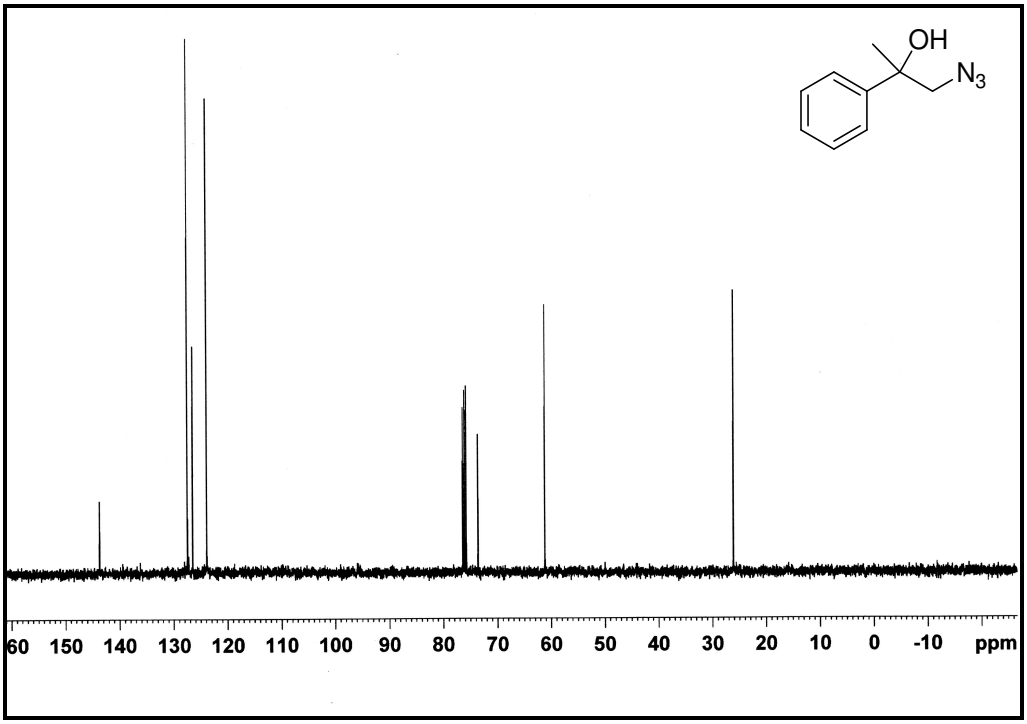

Figure 33. ^{13}C-NMR spectrum of **16** in $CDCl_3$

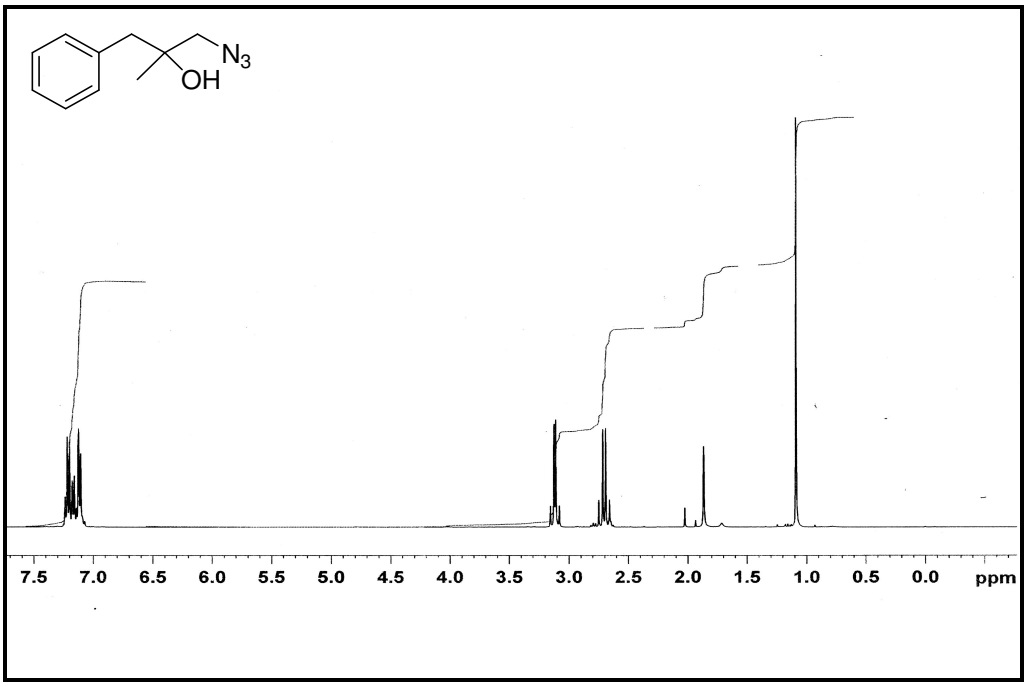

Figure 34. ^{1}H-NMR spectrum of **17** in $CDCl_3$

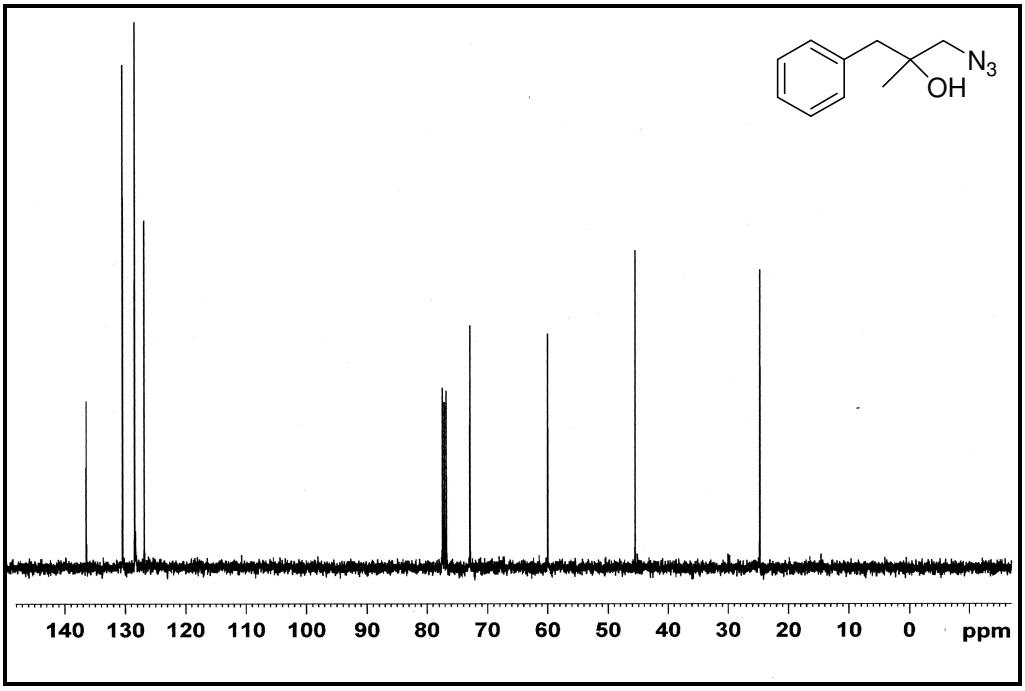

Figure 35. ^{13}C-NMR spectrum of **17** in $CDCl_3$

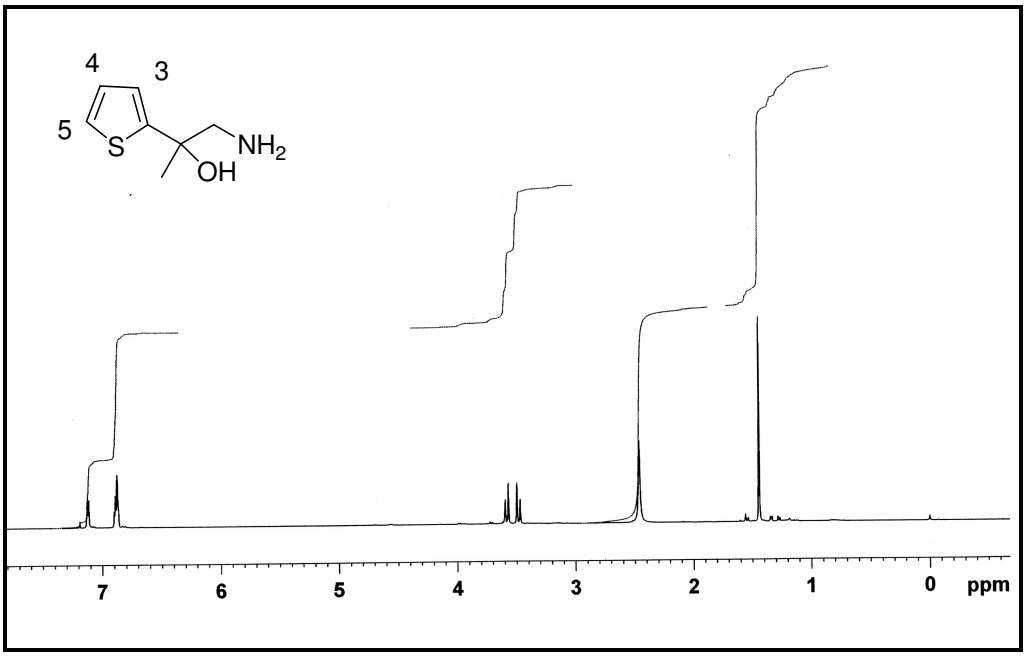

Figure 36. ^{1}H-NMR spectrum of **18** in $CDCl_3$

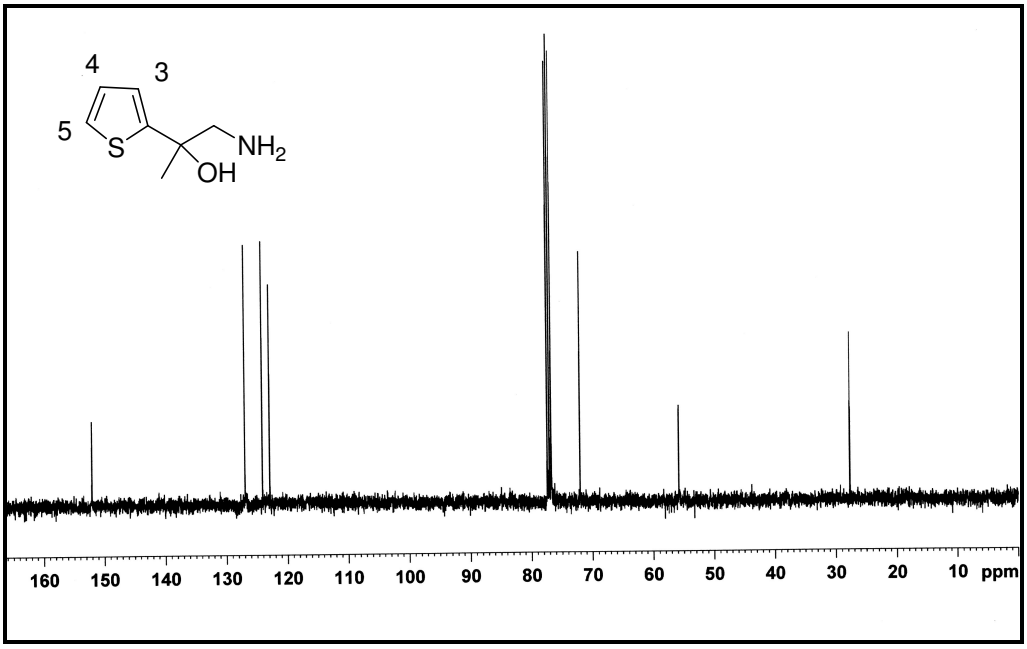

Figure 37. ^{13}C-NMR spectrum of **18** in $CDCl_3$

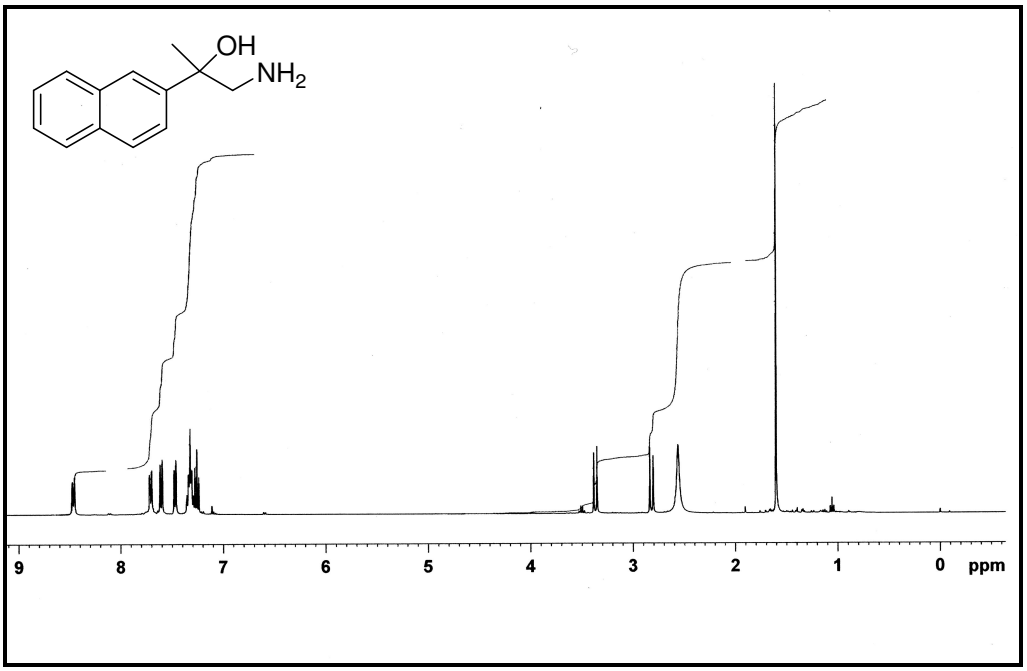

Figure 38. ^{1}H-NMR spectrum of **19** in $CDCl_3$

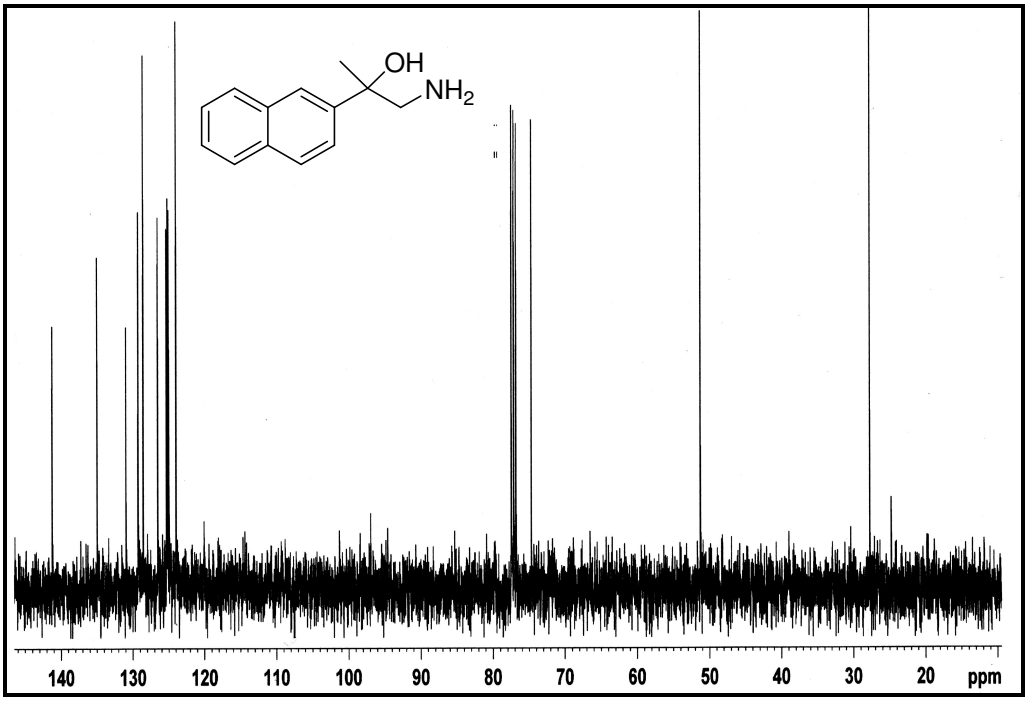

Figure 39. ^{13}C-NMR spectrum of **19** in $CDCl_3$

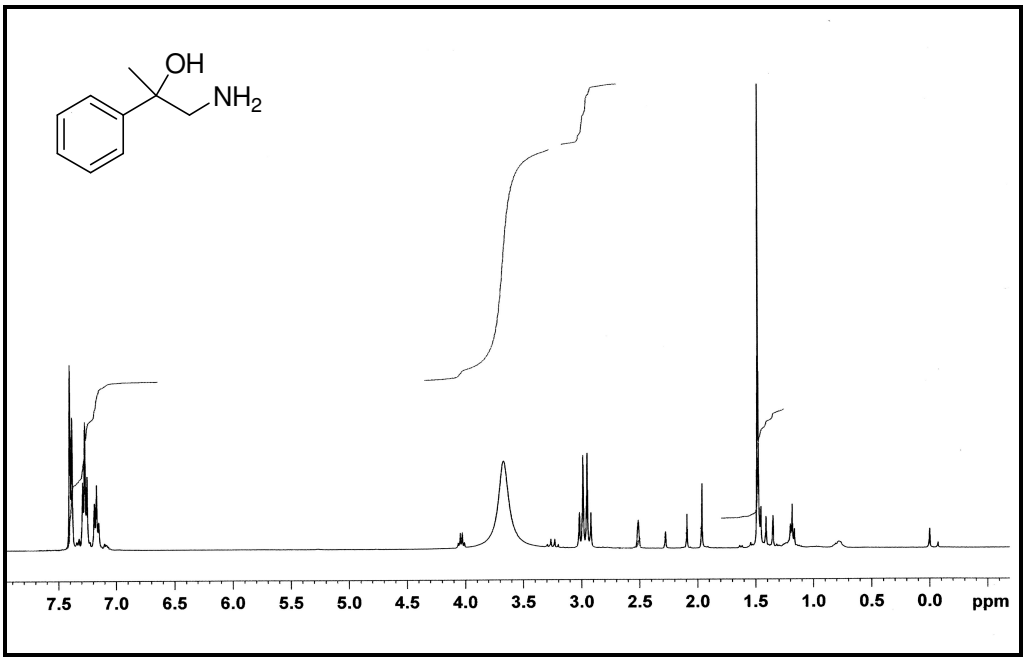

Figure 40. ^{1}H-NMR spectrum of **20** in $CDCl_3$

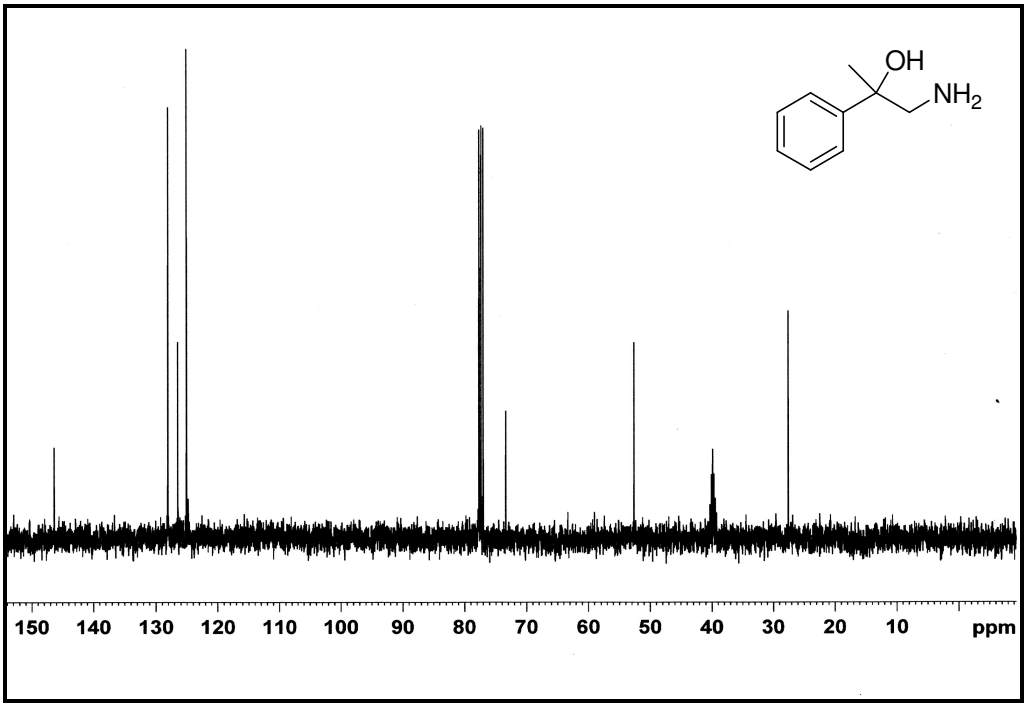

Figure 41. ^{13}C-NMR spectrum of **20** in $CDCl_3$

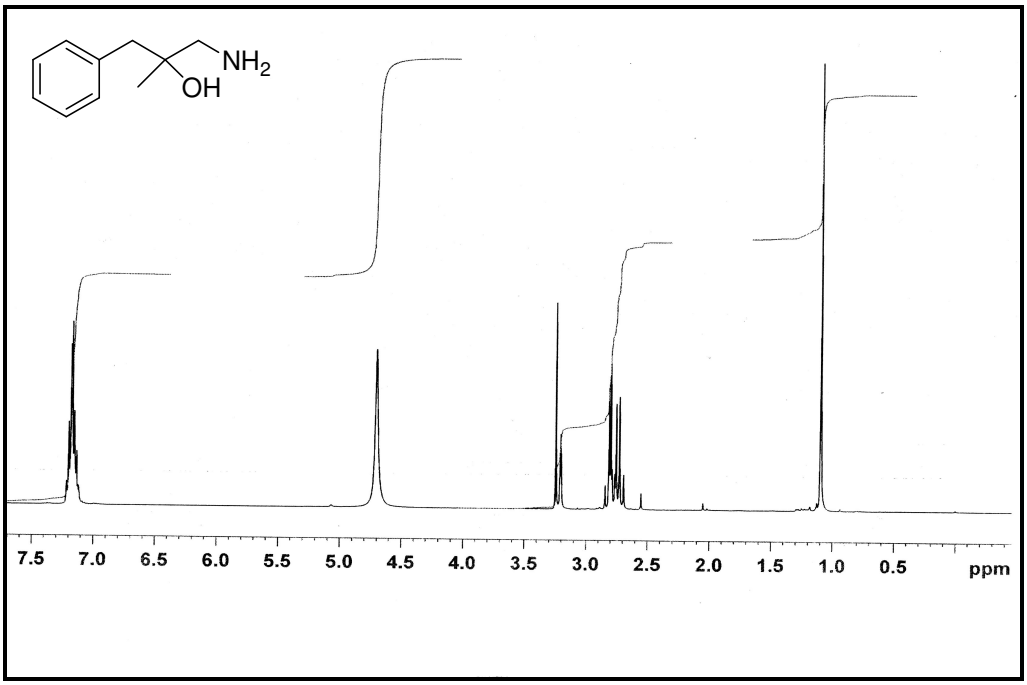

Figure 42. ^{1}H-NMR spectrum of **21** in CD_3OD

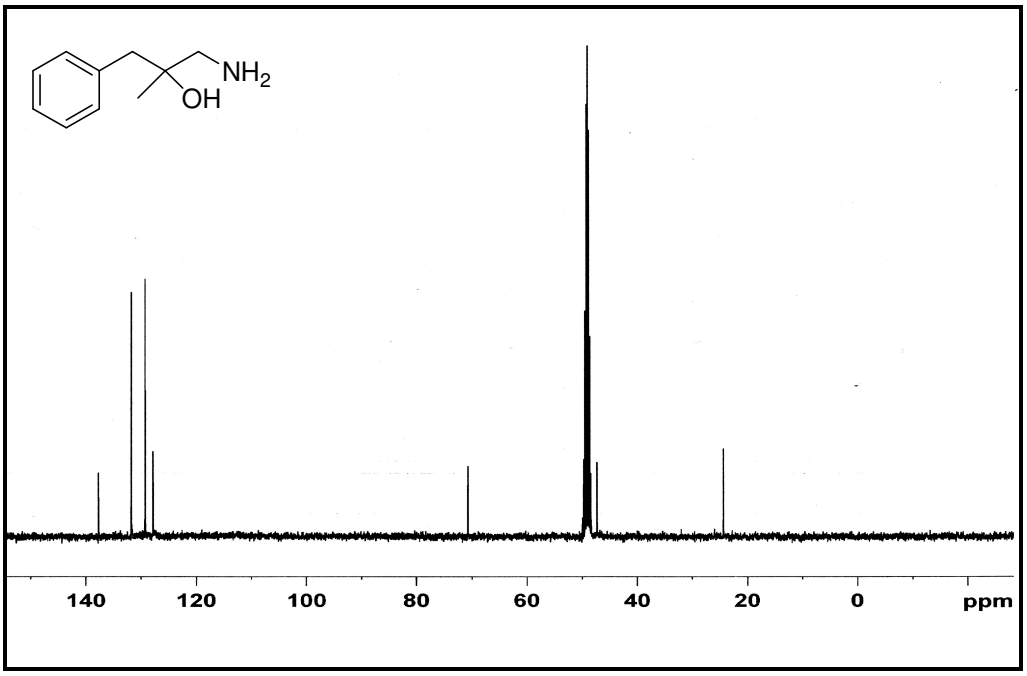

Figure 43. ^{13}C-NMR spectrum of **21** in CD_3OD

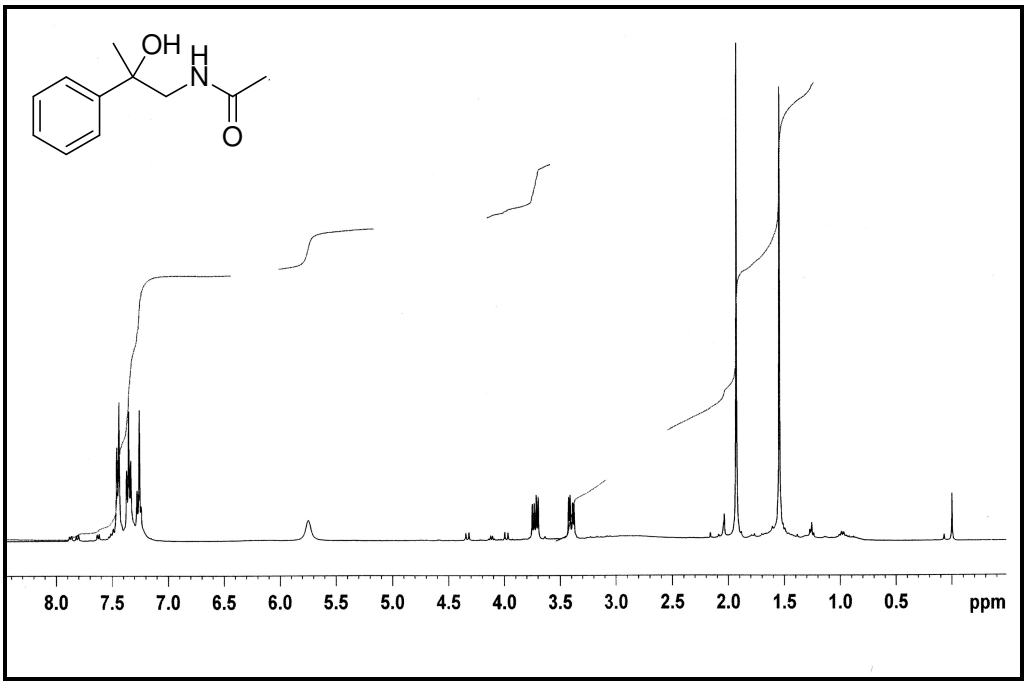

Figure 44. ^{1}H-NMR spectrum of **22** in $CDCl_3$

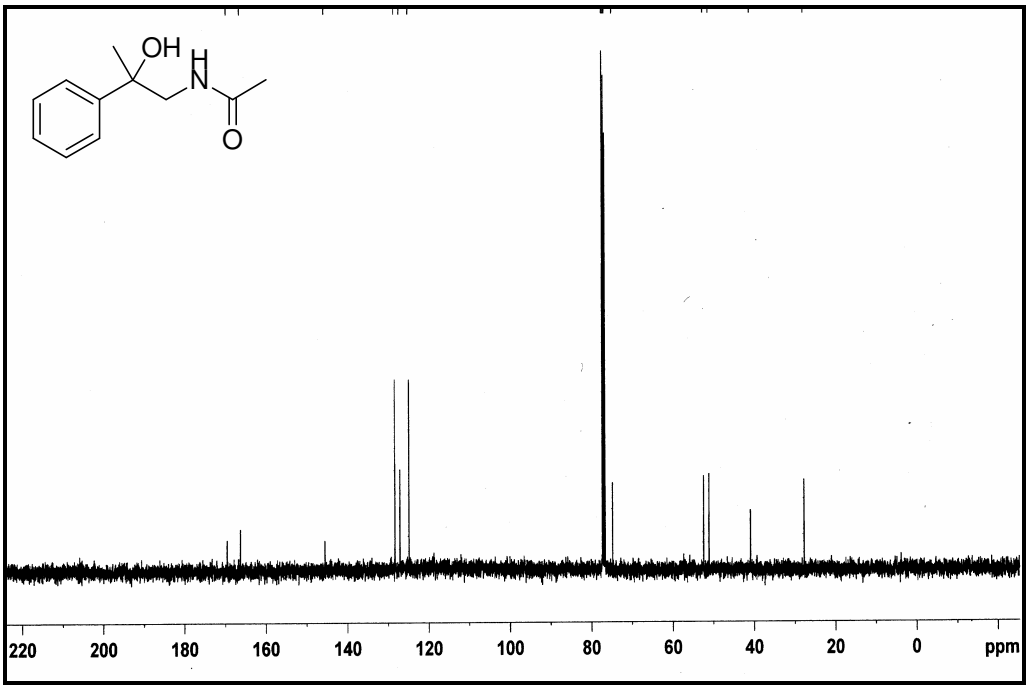

Figure 45. ^{13}C-NMR spectrum of **22** in $CDCl_3$

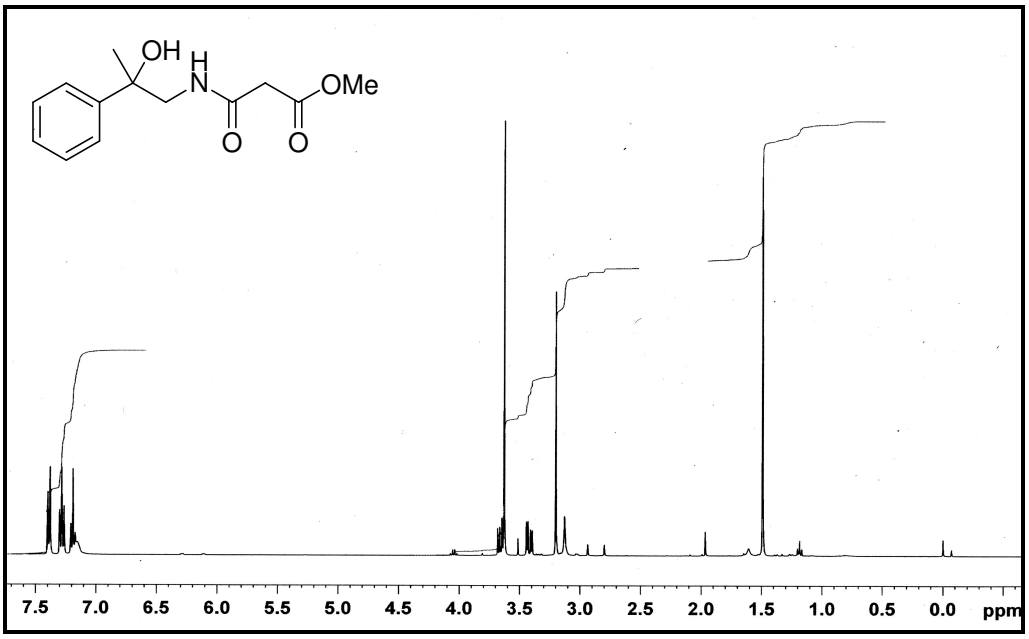

Figure 46. ^{1}H-NMR spectrum of **23** in $CDCl_3$

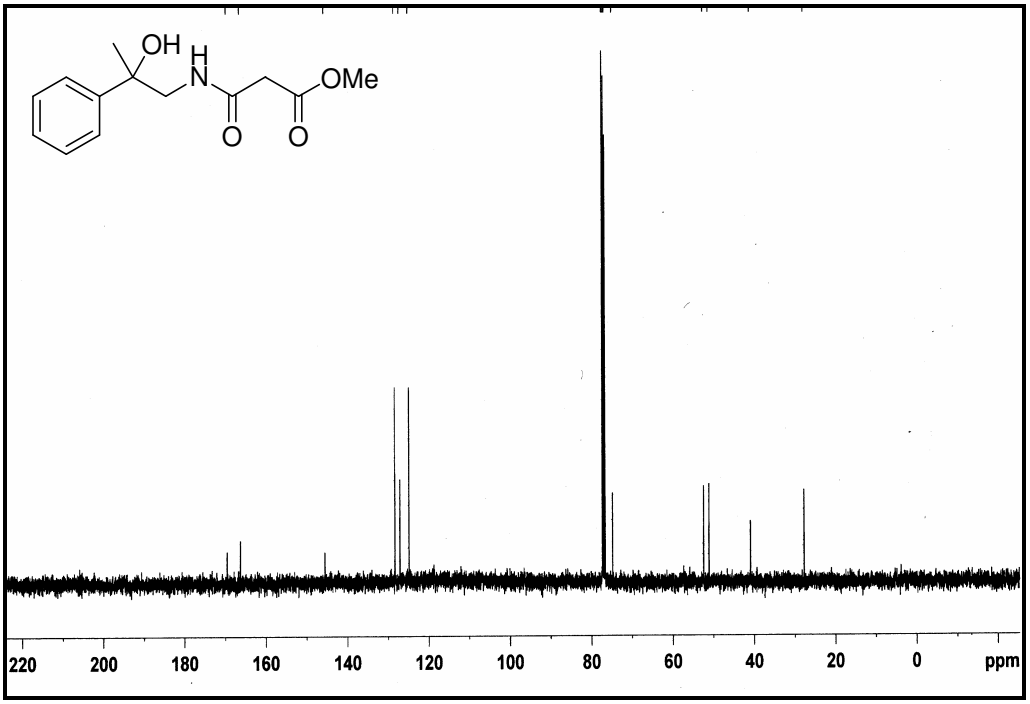

Figure 47. ^{13}C-NMR spectrum of **23** in $CDCl_3$

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