ASYMMETRIC SYNTHESIS OF NORBORNENE BASED 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN ASYMMETRIC DIETHYLZINC REACTIONS

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ABSTRACT

ASYMMETRIC SYNTHESIS OF NORBORNENE BASED 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN ASYMMETRIC DIETHYLZINC REACTIONS

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The asymmetric synthesis of chiral norbornene based 1,4-aminoalcohols and their applications in asymmetric diethylzinc addition reactions was perfomed starting from *meso*-anhydride **50.** The desymmetrization of this *meso*-anhydride **50** was done by the usage of quinine or quinidine cinchona alkaloids with very high enantiomeric excess values (up to 98% ee) and chemical yields. The Quinidine-mediated desymmetrization of *meso*-anhydride **50** with methanol gave (2*R*,3*S*)-(+)-*cis*-monoester **51**. The amination of this resulting compound with HMPTA was performed and by keeping the amine group constant, the amidoester was transformed into chiral ligands with Grignard reaction followed by LAH reduction.

The effectiveness of 1,4-aminoalcohol type ligands, (2*R,*3*S*)-(-)-**57**, (2*R*,3*S*)-(-)-**58**, (2*R*,3*S*)-(-)-**59** and (2*S,*3*R*)-(+)-**60** as chiral catalysts in asymmetric diethylzinc addition reaction to benzaldehyde were examined and the ligand **60** gave the highest enantioselectivity (69% e.e.)

Key words: Amino alcohol, chiral ligand, asymmetric reaction, diethylzinc

ÖZ

NORBORNEN TEMELLİ 1,4-AMİNO ALKOL TÜREVLERİNİN
ASİMETRİK OLARAK SENTEZİ VE ASİMETRİK
DİETİLÇİNKO REAKSİYONLARINDA KULLANIMI

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Norbornen temelli cis-1,4-aminoalkollerin asimetrik olarak sentezi ve bunların ligand olarak asimetrik dietilçinko reaksiyonlarındaki uygulamaları *meso*-anhidrit **50**'den başlanarak tamamlanmıştır. Anhidritin kinin veya kinidinli ortamda metanolle verdiği tepkime sonucunda (2*R*,3*S*)-(+)-*cis*-monoester **51** maddesi (98 % e.e.) oluşmuştur. Oluşan bu madde HMPTA kullanılarak aminlenip, amin grubu sabit tutularak çeşitli Grignard reaksiyonlarında denenmiştir. Oluşan ürünler lityum alüminyum hidrat kullanılarak indirgenip kiral ligandlar elde edilmiştir.

Sonuç olarak, sentezlenen kiral ligandların, (2*R,*3*S*)-(-)-**57**, (2*R*,3*S*)-(-)-**58**, (2*R*,3*S*)-(-)-**59**, (2*S,*3*R*)-(+)-**60,** kiral katalizör olarak asimetrik dietilçinko reaksiyonları üzerindeki etkilerine bakılmıştır. Kullanılan bu aminoalkoller içerisinde en yüksek enantioseçiciliği kiral ligand **60** göstermiştir. (69% e.e.)

Anahtar Kelimeler: Amino alkol, kiral ligand, asimetrik tepkime, dietilçinko

To My Family

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THF: Tetrahydrofurane

DCC: Dicyclohexylcarbodiimide

DMAP: Dimethylaminopyridine

HMPTA: Hexamethylenephosphoroustriamide

DCM: Dichloromethane

LAH: Lithium aluminum hydride

CHAPTER 1

INTRODUCTION

1.1. Importance of Asymmetric Synthesis

Compounds occur in nature are mainly optically active since living organisms produce only a single enantiomer of given molecule. The asymmetry of these molecules arises from the inherent chirality of enzymes, which are responsible for their production. The development of methods for the asymmetric synthesis of chiral compounds has been an area of intense research over the last decade. The interest in the preparation of chiral compounds in enantiomerically pure form has greatly increased lately due to several factors; enantiospecificity shown by most biological systems in their responses to drugs, the regulatory pressure on the pharmaceutical industry to market chiral drugs as single enantiomers, and the strong drive for synthetic efficiency.

Organic compounds play an important role in modern life, not at least in the area of pharmaceuticals, agrochemicals, and other materials which possess useful biological activity. Often such biological activity arises through the interaction of the organic compound with a biomolecule such as an enzyme or a receptor [1].

The synthesis of optically active compound is one of the most important problems of contemporary chemistry. Pure enantiomers gain increasing commercial interest, especially in the field of pharmaceutical products.

Carbon atoms carrying four different substituents possess a unique property. The substituents can be arranged in two alternative ways to bring about two forms of the molecule with the same constitution. The two forms of the molecule are related to each other, being non-superimposable mirror images of each other. In such a case there are two possible forms of the same object, which are called enantiomers and thus these two forms are said to be enantiomeric with each other. They are also called chiral and the central carbon atom is known as the chiral or stereogenic center [2].

In enantiomeric case, the whole molecule does not possess any element of symmetry and the molecule is also asymmetric. However, asymmetry is not a necessary requirement for chirality. Dissymmetric molecules which lack one or more elements of symmetry can also be chiral. To take a simple example, tartaric acid can be obtained in two enantiomers, (+)-tartaric acid and (-)-tartaric acid in Figure 1, which are non-superimposible mirror images of each other. These tartaric acid salts are dissymmetric and one rotates the plane polarized light to the left while the other one rotates the polarized light to the right.

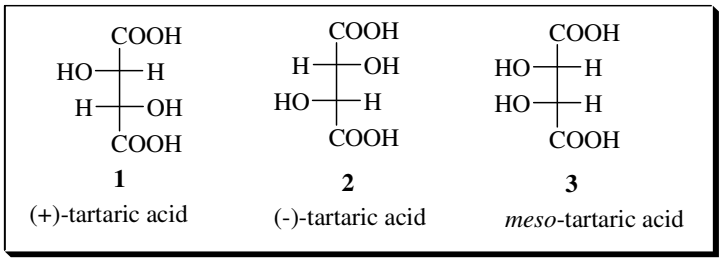


Figure 1. The two enantiomeric and *meso* form of tartaric acid

Enantiomers have identical physical and chemical properties in the absence of an external chiral influence. So these two enantiomers, (+)-tartaric acid and (-)-tartaric acid have the same solubility, melting point, infrared spectroscopy (IR), chromatographic retention time and nuclear magnetic resonance (NMR) spectra.

If the molecule contains more than one chiral center, there emerges the possibility of another form of stereoisomerism. Stereoisomeric molecules which can not be superimposed by any symmetry operations are called diastereomers; two pairs of enantiomeric compounds and two pairs of diasteromeric compounds. In Figure 1 the *meso*-tartaric acid is an achiral compound because of its symmetry plane and it is the diastereomer of two (+) and (-) tartaric acids.

Chirality is a property which often determines the actions and behavior of molecules in rather unexpected ways. Lemons and oranges both contain limonene, the different enantiomers giving rise to subtle changes in the aroma properties of these fruits. One isomer (*R*) of limonene smells of oranges, the other (*S*) of lemons. (Figure 2).

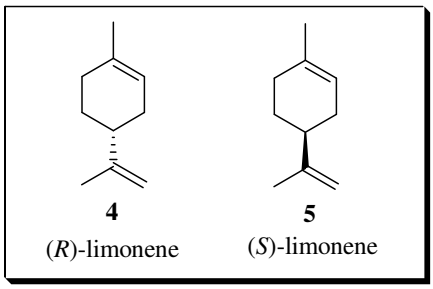


Figure 2. (*R*) and (*S*) limonene

Similarly, *R*- and *S*- carvone in Figure 3, have different tastes, the former tasting spearmint and the letter of caraway [3].

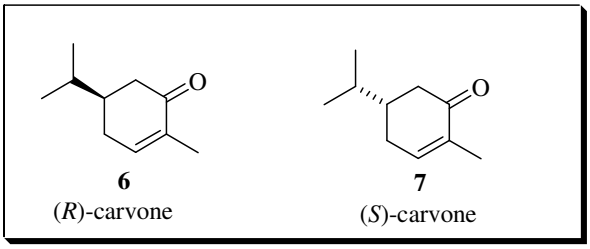


Figure 3. (*R*) and (*S*)-carvone

Synthesis of optically pure compounds is important since they are more effective than their racemic mixtures. As natural products and their derivatives they find wide use in our everyday life. An increasing number of drugs, food additives and flavouring agents are prepared by total synthesis and asymmetric synthesis is a convenient way to get optically active compounds. And most of the biological macromolecules of living systems occur in nature in one enantiomeric form only.

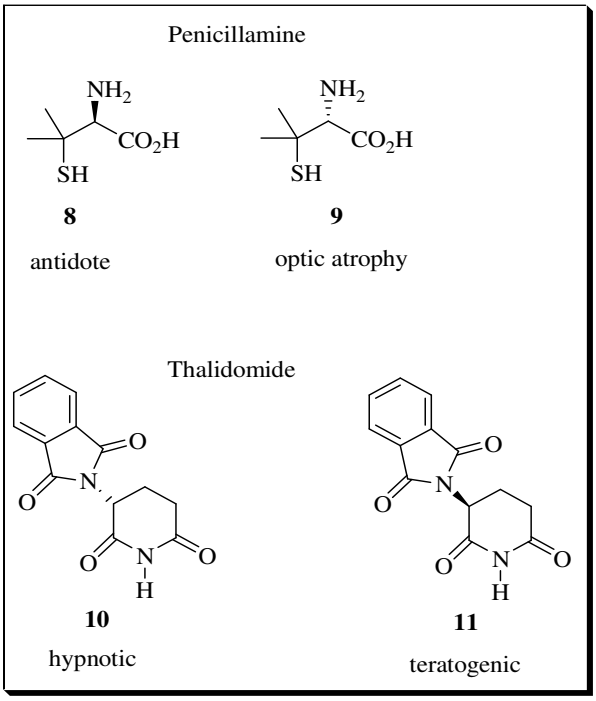


Figure 4. Pencillamine and Thalidomide

It is well known, that the interactions between chiral molecules change dramatically when one molecule is replaced by its mirror image. This chiral specificity is the basis of a major industry producing chiral drugs [4].

The two enantiomers of a drug molecule cannot bind equally well to the receptor and therefore cause different biological responses. Therefore understanding of chirality is extremely important in the preparation of therapeutic drugs.

For example, one enantiomer of penicillamine (Figure 4) is a potent anti-arthritic agent whereas the other enantiomer is highly toxic [4].

Perhaps the most startling example of the difference in activity between enantiomers is Thalidomide (Figure 4).

This drug was seen as a panacea for the treatment of morning sickness in pregnant women, and indeed one enantiomer reliably has this effect. The other enantiomer, unfortunately, has been associated with the well-characterized birth defects that arose from use of Thalidomide.

The importance of enantiomerically pure compounds comes from the central role of enantiomer recognition in biological activity. There are many examples of pharmaceutical drugs, agrochemicals, and other chemical compounds where the desired biological property is related to the absolute configuration.

The desirable reasons for producing optically pure materials include:
(i) Biological activities associated with one enantiomer.
(ii) Enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable: production of only one enantiomer allows separation of the effects.
(iii) The unwanted isomer is at best isomeric ballast gratuitously applied to the environment.
(iv) The optically pure compound may be more than twice as active as the racemate because of antangonism.
(v) Registration constraints; production of material as the required enantiomer is now question of law of certain countries, the unwanted enantiomer being considered as an impurity.
(vi) Where the switch from racemate to enantiomer is feasible, there is the opportunity to effectively double the capacity of an industrial process; alternatively where the optically active component of the synthesis is not the most costly, it may allow significant savings to be made in some other achiral but very expensive process intermediate.
(vii) Improved cost-efficacy
(viii) The physical characteristics of enantiomers versus racemate may confer processing or formulation advantages.

1.2. Obtaining Optically Active Compounds

Excluding the isolation of natural products, the production of optically pure materials has generally presented a significant challenge bearing in mind that, to be of practical large scale use, enantiomeric excesses ought to be at least 70% and preferably greater than 80% for the crude material which is initially produced.

In order to achieve asymmetric synthesis, at least one component of the reaction must be chiral and non-racemic. If there is no asymmetric component in the reaction, then transition states which lead to enantiomers will themselves be enantiomeric, equal in energy, and a racemate must be formed. In principle, the use of chiral, non-racemic substrate, reagent, solvent or catalyst should learn to asymmetric synthesis. In general terms, any feature of the reacting system which would cause the possible transition states for the reaction to be diasteromeric (where they would be enantiomeric) could lead to the preferential formation of one diastereomer or enantiomer. This follows because transition states which are diasteromeric need not be of the same energy and consequently one of the possible products could be formed more rapidly.

Approaches which may be applied are: (i) utilization of chiral pool materials; (ii) general synthetic methodologies.

1.2.1. The Chiral Pool

The chiral pool customarily refers to relatively inexpensive, readily available optically active natural products. The chiral pool substances are used as building blocks. In some enantiomer synthesis of target molecules, optically pure starting materials are incorporated directly. The supply of enantiopure starting materials for this purpose is sometimes referred to as the chiral pool [5].

They are incorporated into the target structure with any necessary modification in order to achieve the desired chiral features. Some representative materials are:

- Ascorbic acid
- (+)-Calcium pantothenate
- (-)-Carvone
- Anhydrous dextrose
- Ephedrine hydrochloride
- (+)-Limonene
- L-Lysine
- Mannitol
- Monosodium glutamate
- Norephedrine hydrochloride
- Quinidine sulphate
- Quinine sulphate
- Sorbitol
- L-Threonine
- L-Tryptophan (Figure 5)

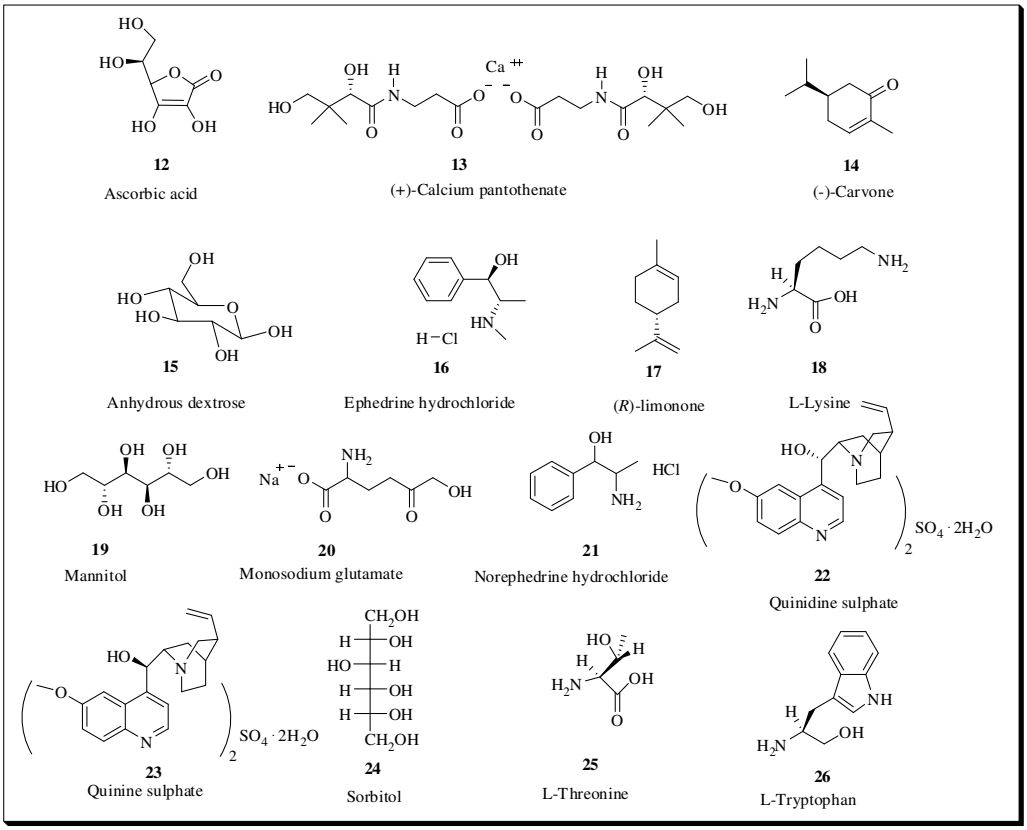


Figure 5. Examples of chiral pool substances

1.2.2. General Synthetic Methodologies

Obtaining optically active substances in solution can be obtained only through the intervention of some chiral reagent to give some diasteromeric transition states, products, or complexes. In the sense of this statement, ‘‘chiral reagent’’ must include a chiral physical force, such as a circularly polarized light which would lead to an absolute asymmetric synthesis. The general processes whereby optically active substances are obtained from optically inactive materials can be achieved by one of the following methods [6]:

1. Physical separation via enantiomeric crystalline forms
    a. Physical sorting of enantiomeric crystals
    b. Selective seeding of a solution racemate with crystals of one enantiomer (or isomorphous crystal)
    c. Preferential incorporation of one enantiomer in an inclusion compound
2. Resolution based on separation of diasteromeric forms
    a. Classical resolution. Stable diastereomer formation (including molecular complexes) followed by physical separation based upon crystallization, chromatography, distillation etc.
    b. Selective association on a chiral adsorbent or selective solvent extraction using a chiral solvent or solution
3. Thermodynamically controlled asymmetric transformations of stereochemically labile diastereomers
4. Kinetically controlled asymmetric transformations
    a. Reactions of racemic substrates with chiral reagents
    b. Reactions of achiral substrates with chiral reagents
    c. Absolute asymmetric degradation and synthesis
    d. Derivation from optically active natural products
    e. Enantiomeric resolution of an intermediate or final product
    f. Chemical or biochemical asymmetric synthesis.

1.3. Asymmetric Synthesis

‘‘Asymmetric synthesis are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes [7].’’

-W. Marckwald

According to this historically important definition, an asymmetric synthesis must start with an achiral substance.

The broader definition specifies a symmetric but prochiral center or group which may be incorporated into either a chiral or an achiral molecule. However most planned studies of asymmetric synthesis have concentrated on cases in which an achiral starting material is transformed into a chiral compound by the action of a chiral reagent, a chiral catalyst or a chiral auxiliary under conditions whereby the original chiral group subsequently is removed, leaving behind a chiral product.

Asymmetric organic reactions have proved to be very valuable in the study of reaction mechanisms, in the determination of relative and absolute configurations, and in the practical synthesis of optically active compounds. The pharmaceutical industry, in particular, has shown markedly increased interest in asymmetric organic reactions. Currently, an expanding number of drugs, food additives, and flavoring agents are being prepared by synthetic methods. Most often, the desired compound is obtained through resolution of the corresponding racemic species performed at the end of the synthetic sequence. Because only one optical antipode is useful, half of the synthetic product is often discarded. Obviously, this is a wasteful procedure from the preparative point of view. Even if the wrong isomer can be converted to the active form via racemization and resolution, extensive work is required. Also, resolution is usually a tedious, repetitious, and laborious process. It is economically appealing to exclude the unwanted optical isomers at the earliest possible stage through the asymmetric creation of chiral centers. In the interest of effective use of raw material, it is wise to choose an early step in the synthetic sequence for the asymmetric operation and to consider carefully the principles of convergent synthesis.

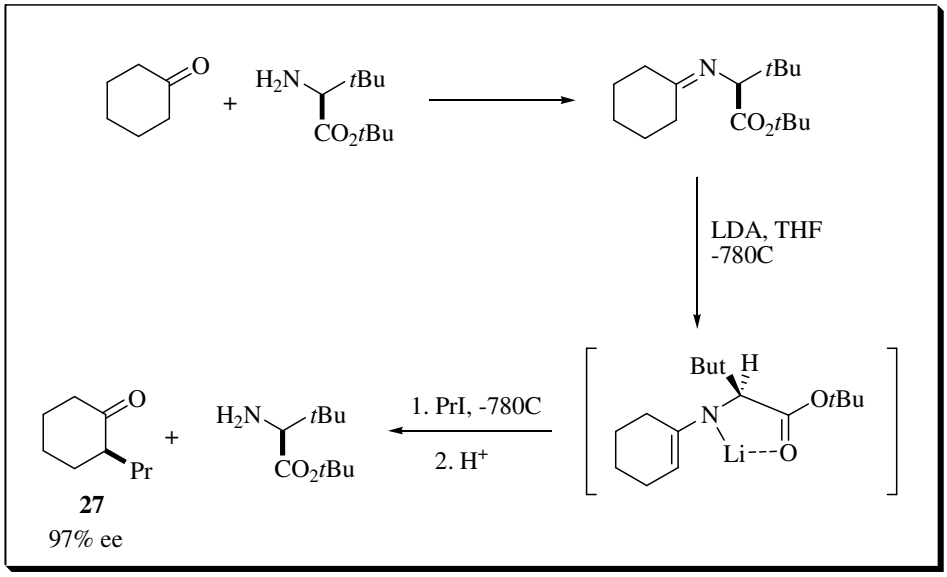
In an asymmetric reaction, substrate and reagent combine to form diasteromeric transition states. One of the two reactants must have a chiral element to induce asymmetry at the reaction site. Nowadays asymmetric synthesis is used for reactions capable of giving rise to enantiopure products, which is certainly the most important and possess the greatest challenge. In principle this can be achieved by using a chiral, non-racemic substrate, reagent, solvent or catalyst.

1.3.1. The Methods Applied in Asymmetric Synthesis

Asymmetric synthesis involves the formation of a new stereogenic unit in the substrate under the influence of a chiral group ultimately derived from a naturally occurring chiral compound. These methods can be divided into four major classes, depending on how this influence is exerted: (1) substrate controlled methods; (2) auxiliary-controlled methods; (3) reagent-controlled methods, and (4) catalyst-controlled methods.

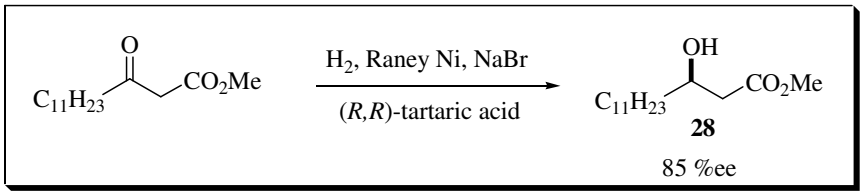
The substrate-controlled reaction is often called the first generation of asymmetric synthesis. It is based on intramolecular contact with a stereogenic unit that already exists in the chiral substrate. Formation of the new stereogenic unit most often occurs by reaction of the substrate with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit.

The auxiliary-controlled reaction (Scheme 1) is referred to as the second generation of asymmetric synthesis. This approach is similar to the first generation method in which the asymmetric control is achieved intramolecularly by a chiral group in the substrate. The difference is that the directing group, the ‘‘chiral auxiliary’’, is deliberately attached to the original achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary will be removed once the enantioselective transformation is completed.



Scheme 1. Example for the chiral auxiliary in asymmetric synthesis [8].

Although second-generation methods have proved useful, the requirement for two extra steps, namely, the attachment and the removal of the chiral auxiliary, is a cumbersome feature. This is avoided in the third-generation method in which an achiral substrate is directly converted to the chiral product using a chiral reagent. In contrast to the first- and second-generation methods, the stereocontrol is now achieved intramolecularly.



Scheme 2. Example for the use of chiral reagent in asymmetric synthesis [8].

In all three of the above-mentioned chiral transformations, stoichiometric amounts of enantiomerically pure compounds are required.

An important development in recent years has been the introduction of more sophisticated methods that combine the elements of the first-, second-, and third-generation methods and involves the reaction of a chiral substrate with a chiral reagent. The method is particularly valuable in reactions in which two new stereogenic units are formed stereoselectively in one step.

The most significant advance in asymmetric synthesis in the past three decades has been the application of chiral catalysts to induce the conversion of achiral substrates to chiral products. In ligand-accelerated catalysis, the addition of a ligand increases the reaction rate of an already existing catalytic transformation. Both the ligand-accelerated and the basic catalytic process operate simultaneously and complement each other. The nature of the ligand and its interaction with other components in the metal complex always affect the selectivity and rate of the organic transformation catalyzed by such a species.

Among the types of asymmetric reaction, the most desirable and the most challenging one is the catalytic asymmetric synthesis that only small amounts of chiral catalysts are needed to generate large quantities of chiral products just as enzymes do in biological systems. The enormous economic potential of asymmetric catalysis has made it one of the most extensively explored areas of research in recent years.

1.4. Catalytic Asymmetric Transformation Reaction

A catalyst can affect both reactivity and selectivity of organic transformations, and affords the possibility of conducting organic synthesis in a highly controlled manner. The chiral catalysts in figure 6 were chosen because of their low cost and high effectiveness in the catalytic asymmetric synthesis.

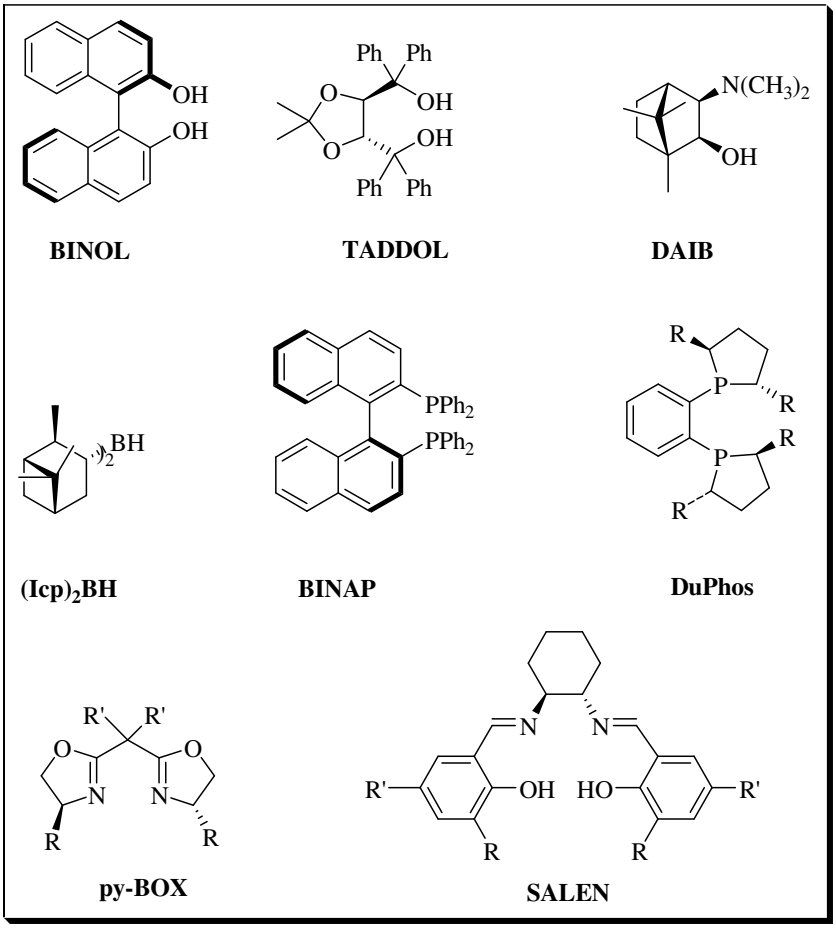


Figure 6. Some Important Chiral Catalysts

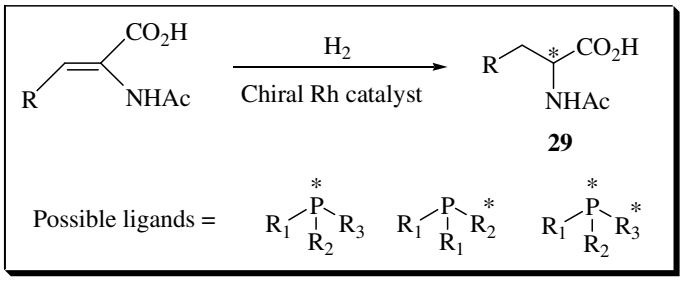
In this part different types of asymmetric reactions based on asymmetric catalytic hydrogenations, asymmetric aldol reactions, asymmetric oxidations, Diels- Alder reactions are discussed.

1.4.1. Asymmetric Catalytic Hydrogenation

The asymmetric additions of hydrogen to carbon-carbon double bonds may be divided into two main classes.

The alkene may contain a chiral center which mediates the hydrogenation process so that one diastereotopic face of the alkene is preferentially saturated; alternatively, the hydrogen may be transferred from a catalyst that is chiral with the result that enantiotopic faces of an achiral alkene are selectively saturated via diasteromeric transition states which incorporate the catalyst. Unsaturated bonds like C=C, C=O, C=N are converted to the corresponding saturated CH-CH, CH-OH, CH-NH bonds. These reactions are mainly used in industry for the production of pure amino acids, flavor, fragrance materials and many important agrochemicals and pharmaceuticals.

A new approach to asymmetric hydrogenation emerged in the late 1960s. In 1965, Wilkinson discovered a practical homogenous catalyst, $Rh(PPh_3)_3Cl$ [9, 10], which showed very high activity in the hydrogenation of alkenes under mild conditions, and more attention has since been focused on modifying this catalyst by replacing the common triphenyl phosphine with chiral phosphine ligands.



Scheme 3. Possible Chiral Phosphine Ligands and Asymmetric Hydrogenation Reaction

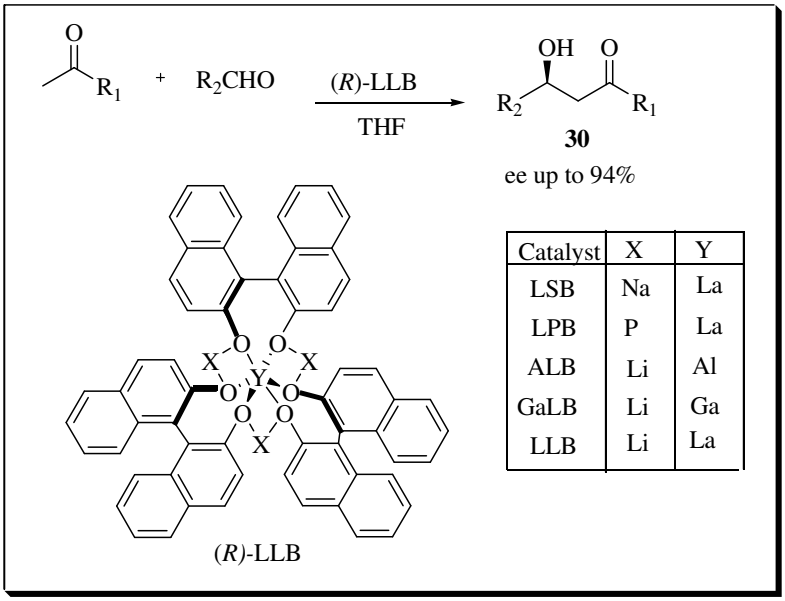
1.4.2. Asymmetric Aldol Reactions

The addition of an enolate to a ketone or aldehyde, often refers to as an aldol reaction, having studied for many years from both the synthetic and mechanistic points of view [11].

The aldol reaction is of great value in asymmetric synthesis, given good methods for stereochemical control.
Two common types of synthetic units are combined by C-C bond formation, with the simultaneous formation of two new chiral centers.

The aldol reaction has emerged as one of the most utilized transformations in modern synthetic chemistry. The reaction, which forms a carbon-carbon bond along with the potential concomitant formation of two vicinal stereocenters, is an efficient method to rapidly construct complex molecules from small building blocks. With the current emphasis on enantioselective synthesis, it is not surprising that numerous, highly successful asymmetric versions of this reaction have been developed. Noncatalytic asymmetric versions involve the use of stoichiometric amounts of a chiral auxiliary in diastereoselective aldol reactions. Small molecule catalyzed aldol reactions [12] typically involve the use of a chiral Lewis acid for aldehyde activation or a chiral Lewis base for donor activation. While these methods have found widespread use in the synthesis of complex molecules, the search for more efficient methods continues.

In 1997 Shibasaki found that unmodified ketones could successfully be subjected to a direct catalytic asymmetric aldol reaction. In presence of (*R*)-LLB (lanthanum-lithium-(*R*)-BINOL) (Scheme 4), a variety of aldehydes and ketones directly afforded aldol products in up to 94% ee [13].



Scheme 4. Shibasaki's direct catalytic asymmetric Aldol reaction with (*R)*-LLB

However the stereochemical control in the aldol reaction is likely to be a challenging problem and there are many approaches for the stereochemical control in aldol reactions. The first one is the substrate control, referring to the addition of an achiral enolate to a chiral aldehyde; the second one is the reagent control which involves the addition of chiral enolate to an achiral aldehyde and finally the addition of chiral enolate to a chiral aldehyde.

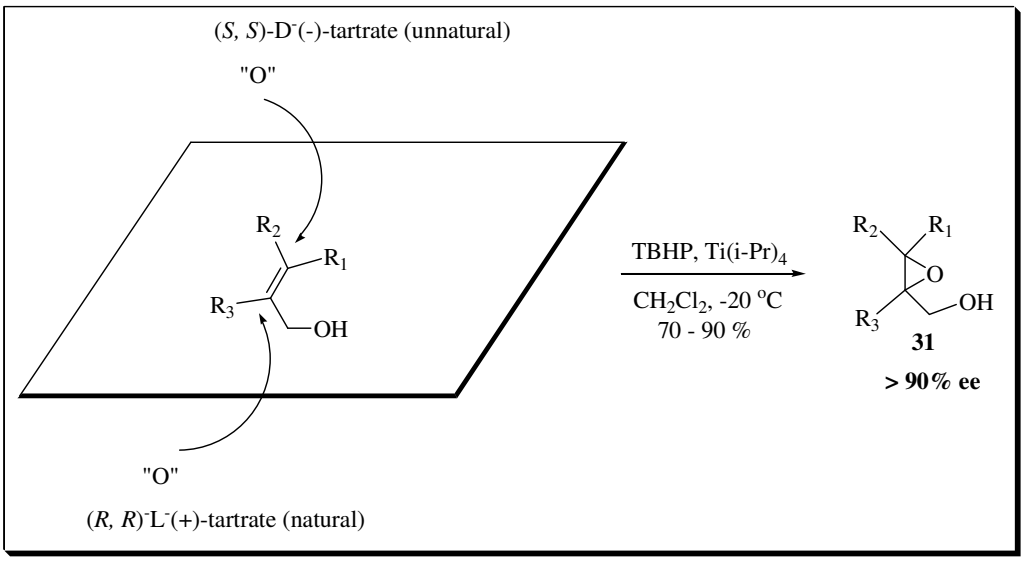
1.4.3 Asymmetric Oxidation Reactions

The asymmetric oxidation of organic compounds, especially the epoxidation, dihydroxylation, aziridination and related reactions have been extensively studied and found widespread applications in asymmetric synthesis of many important compounds.

Asymmetric Epoxidation of olefins is one of the most important processes in organic synthesis and the preparation of biologically active compounds; therefore many efforts have been directed toward the exploitation of highly enantioselective epoxidation reactions of olefins [14].
Epoxidation of an olefin leads to the addition of the epoxide oxygen on one face of the molecule. The regioselectivity of the epoxide opening can usually be predicted quite simply by classical means (inductive effects or polarity control) [15] and necessarily invokes an inversion of stereochemistry at the carbon being attacked by the nucleophile.

In the case of allyl alcohols, one can utilize the existing chirality either as directing group or as blocking group [16]. Careful choice of the oxidant gives one the option to choose either an intramolecular delivery of the oxygen to give the *syn* addition product [17], or pre-blocking the allylic hydroxyl with a suitable protecting group to protect this same face from the attack of the oxidant, giving rise to the *anti* product.

In the 1980's Sharpless *et al.* have discovered an enantioselective titanium-tartarate-catalyzed epoxidation of a wide variety of allylic alcohols, which is the only restriction of this method. Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product. The basic mechanism of the reaction is shown in Scheme 5 [18].

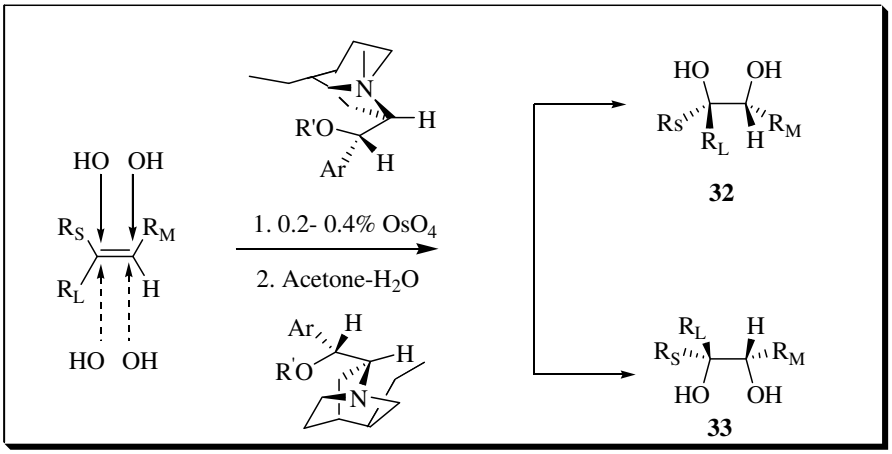


Scheme 5. Basic mechanism for Sharpless epoxidation

The first attempt to affect the asymmetric *cis*-dihydroxylation of olefins with osmium tetroxide was reported in 1980 by Hentges and Sharpless [19]. Taking into consideration that the rate of osmium(VI) ester formation can be accelerated by nucleophilic ligands such as pyridine. However, the diols obtained in this way, were of low enantiomeric excess (3±18% ee only). The low ee was attributed to the instability of the osmium tetroxide chiral pyridine complexes. As a result, the naturally occurring cinchona alkaloids quinine and quinidine were derived to dihydroquinine and dihydroquinidine acetate and were selected as chiral auxiliaries.

Because the bonding of osmium tetroxide to quininuclidine nitrogen is much tighter than the bonding of chiral pyridine, the diols obtained were in reasonably high enantiomeric excess.

In the work of Sharpless' group, improved enantioselectivities were observed with potassium ferricyanide as the primary oxidant under alkaline (K_2CO_3) conditions in aqueous *t*-butanol.



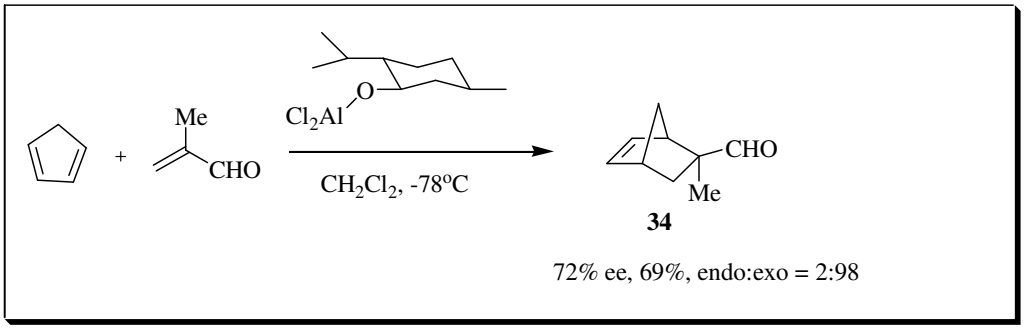
Scheme 6. Asymmetric dihydroxylation reaction

1.4.4 Asymmetric Diels- Alder Reactions

The Diels-Alder reaction is one of the most useful synthetic reactions for the construction of the cyclohexane framework. Four contiguous stereogenic centers are created in a single operation, with the relative stereochemistry being defined by the usually *endo*-favoring transition state. Asymmetric Diels-Alder reactions using a dienophile containing a chiral auxiliary were developed more than 20 years ago. Although the auxiliary-based Diels-Alder reaction is still important, it has two drawbacks, additional steps are necessary, first to introduce the chiral auxiliary into the starting material, and then to remove it after the reaction. At least an equimolar amount of the chiral auxiliary is, moreover, necessary.

After the discovery that Lewis acids catalyze the Diels-Alder reaction, the introduction of chirality into such catalysts has been investigated. The Diels-Alder reaction utilizing a chiral Lewis acid is truly a practical synthetic transformation, not only because the products obtained are synthetically useful, but also because a catalytic amount of the chiral component can, in theory, produce a huge amount of the chiral product.

The pioneering work in the chiral Lewis-acid promoted Diels-Alder reaction was that of Koga, reported in 1979, in which the first catalytic asymmetric reaction proceeding in high enantioselectivities was realized [20] (Scheme 7)



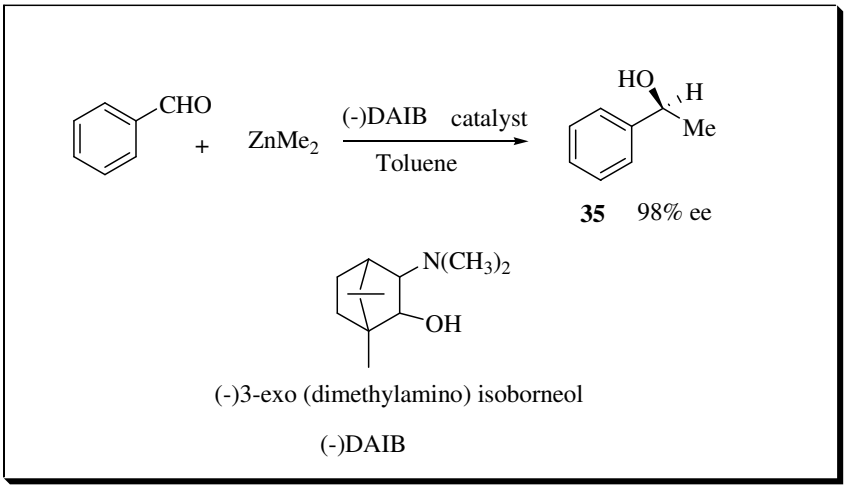
Scheme 7. The chiral Lewis acid catalyzed Diels-Alder Reaction

1.5. Asymmetric Diethylzinc Additions to Aldehydes

Enantioselective carbon-carbon bond formation is one of the most extensively studied areas in catalytic asymmetric synthesis. The catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention because of its simplicity and usefulness in the preparation of variety of high value chiral alcohols.

Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols. The optically active secondary alcohols are components of many naturally occurring compounds and biologically active compounds [21].

The first study about the diethylzinc addition reactions to aldehydes was done by Oguni and Omi in 1984 with the usage of catalytic amount of (*S*)-leucinol and moderate enantiomeric excess values were obtained. Then in 1986 Noyori and co-workers synthesized (*S*)-1-phenylethanol from the dimethylzinc addition reaction with benzaldehyde and obtained high enantiomeric excess values (up to 98%) [21-b]. In this study catalytic amount of (-)-3-*exo*-dimethylaminoisoborneol [(-)-DAIB] was used as in Scheme 8.



Scheme 8. Example of dialkyl zinc addition by Noyori

In recent years the addition reaction of diethylzinc to benzaldehyde becomes a classical test in the synthesis of new ligands and a large number of chiral catalyst were synthesized and high enantioselectivities were obtained.

Among these, amino alcohols constitute an important part of the chiral ligands developed for dialkyl zinc additions to aldehydes [22, 23].

1.6. Chiral Amino Alcohols

Amino alcohols have been used as classic ligands for the asymmetric diethylzinc addition reactions since the discovery of the first effective catalyst to this type of reactions by Noyori and his coworkers.

Optically pure 1,2 and 1,3-amino alcohols have found wide applications as chiral ligands in asymmetric synthesis [24]. These ligands have primarily been used in enantioselective additions of dialkyl zinc to α,β-unsaturated ketones [25] to prochiral ketones [24a, 26].

Even though 1,2-amino alcohols are among the most versatile and successful chiral ligands in this area, design and synthesis of highly enantioselective optically active 1,2-amino alcohols continue to be the aim of many research groups on account of the necessary for highly effective, easily obtained and economical chiral catalysts [27]. In addition, researches on relationship between asymmetric catalytic activity and structural information of chiral ligand are very important and interesting in order to search for optimized asymmetric catalysts. .

One example of the usage of 1,2 amino alcohols, is the application of piperdine based 1,2-amino alcohols (36, 37) in diethylzinc addition reaction to benzaldehyde, giving ee values up to 98% [28].

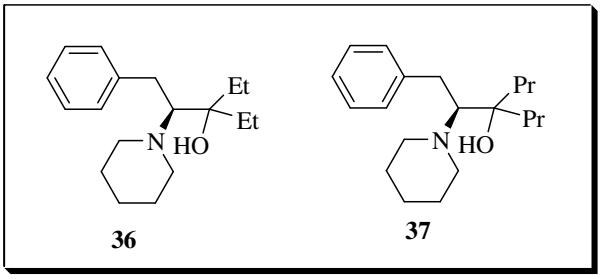
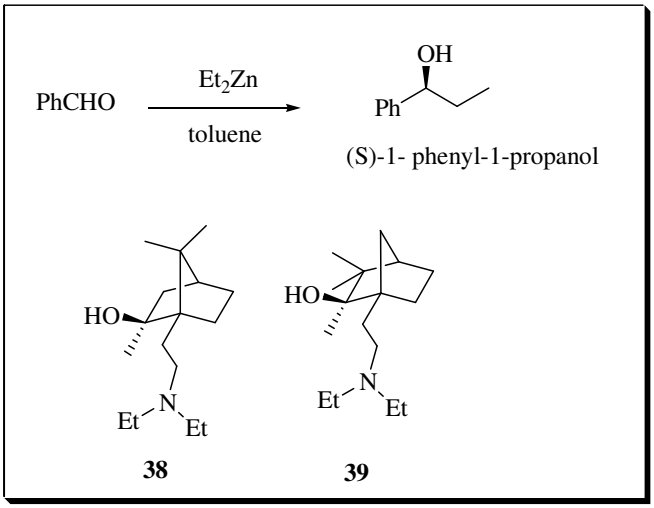


Figure 7. Example of 1,2 amino alcohols in diethylzinc addition reactions

It is known that chiral 1,2-amino alcohols show high catalytic activity for this enantioselective alkylation; however, only a few examples using chiral 1,4-amino alcohols have been reported. Recently, 1,4-amino alcohols **38** and **39** prepared from (+)-camphor was an efficient chiral catalyst for the ethylation of aldehydes by diethylzinc (Scheme 9) [29].



Scheme 9. Example of 1,4 amino alcohols in diethylzinc reaction with benzaldehyde

Here are the some examples of 1,2 and 1,4 amino alcohol type ligands used in diethylzinc addition reactions to aldehydes [30-34].

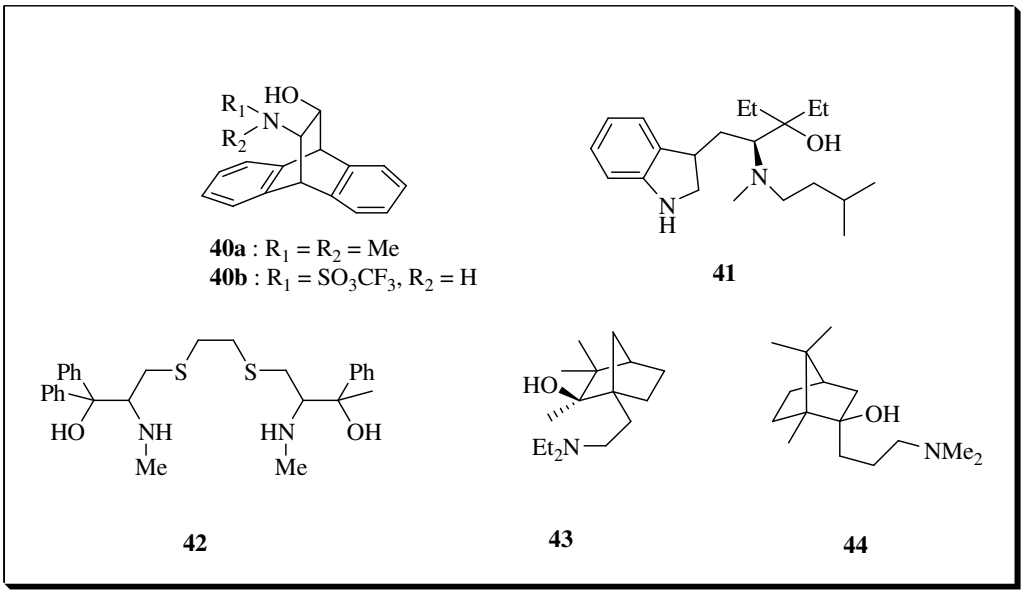


Figure 8. Examples of 1,2 and 1,4 amino alcohols in diethylzinc addition reactions to aldehydes

1,3-Amino alcohols are important and versatile synthetic intermediates for many natural products [35] possessing potent biological activity such as nucleoside antibiotics [35a-d] or in alkaloids [35e]. They also possess relevance in the development of new enzyme inhibitors and the HIV protease inhibitor, ritonavir and lopinavir [36]. Consequently, these compounds became targets for the synthetic chemists, with different methodologies for their synthesis.

1,3-amino alcohols derived from (+)-pulegone, [37, 38], camphor, (-)-fenchone [39] and (-)-menthone have successfully been applied as chiral catalysts, but their application is limited, as in most cases, only one of the enantiomers of the starting

material is available commercially. Some examples of the applications of 1,3-amino alcohols in diethylzinc addition reaction is as follows;

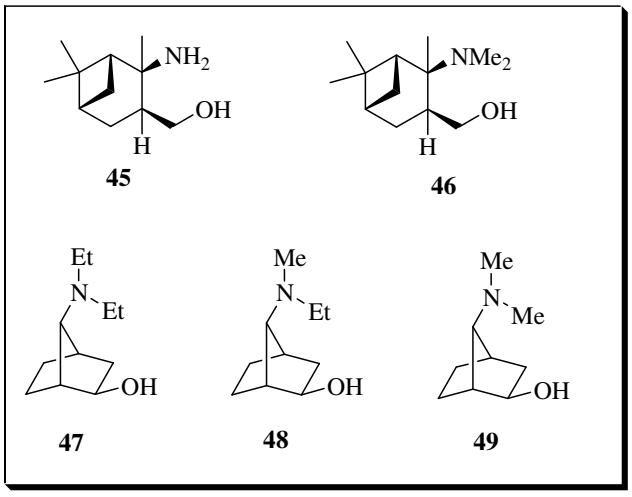


Figure 9. Examples of 1,3-amino alcohols in diethylzinc addition reactions [41a-b]

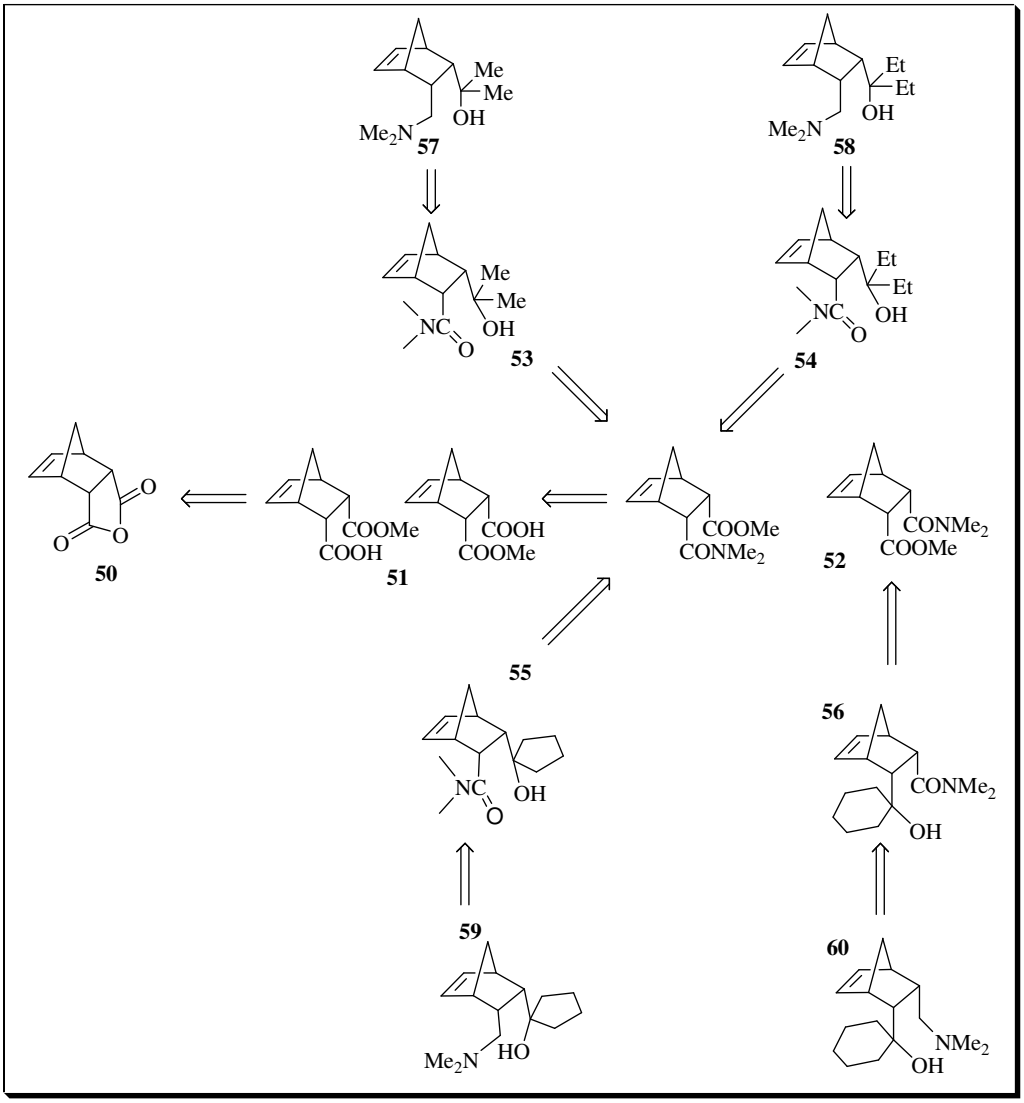
1.7. Aim of the Work

The design of new chiral ligands has become an important issue to improve enantioselectivity of organic reactions during the development of asymmetric synthesis. There are a lot of researchers who work for the synthesis of novel chiral ligands.

Among various types of chiral ligands, 1,4-amino alcohols are attracting more attention.

In this study, we aimed to synthesize novel chiral 1,4-amino alcohol type ligands and to test their effectiveness in diethylzinc addition reaction to benzaldehyde.

Retrosynthetic analysis of target chiral 1,4-amino alcohols are shown in Scheme 10.



Scheme 10. Retrosynthesis of the Work

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Perspective of the Work

Development of an asymmetric transformation process to get selectively one of the enantiomers with the desired absolute configuration is an important subject dealt with by organic chemists specializing in the synthesis. In particular, asymmetric synthesis based on the use of catalytic amount of an asymmetric catalyst is a very attractive research subject. The asymmetric alkylation of an aldehyde by dialkyl zinc using a chiral amino alcohol as the asymmetric catalyst has become one of the most challenging and common area in synthetic organic chemistry. Optically active amino alcohols are not only versatile chiral building blocks in asymmetric synthesis [42], but also important chiral ligands developed for enantioselective addition of dialkyl zinc to aldehydes, which is one of the most widely studied areas in asymmetric C-C bond formation [43]. Among various chiral ligands, such as diols [44], amino thiols [45], and amino sulfides [45], amino alcohols are the most investigated ligands and prominent for asymmetric dialkyl zinc addition to aldehydes. Usually, 1,2-amino alcohols are highly efficient and the most popular whereas 1,4-amino alcohols are rarely used due to their multi-step synthesis and, in order to guarantee good enantioselectivities, they require complicated rigid structures, they are less appealing than most simple and commercially available 1,2-amino alcohols.

2.2. Asymmetric Synthesis of 1,4-Amino Alcohol Ligands

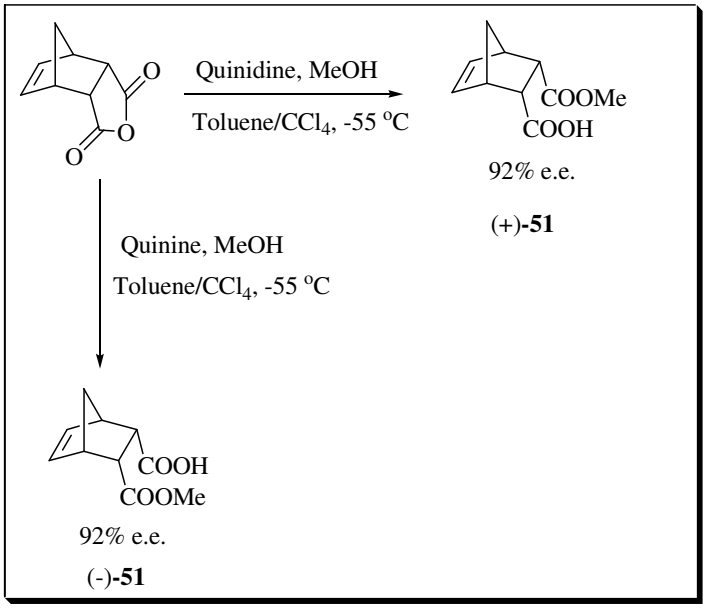
In our synthetic work, we have chosen norbornene based hemi-ester as the starting material. The aim of choosing this compound is to see the effects of rigidity of the backbone on 1,4-amino alcohols. As it is well known in literature the alkene moiety of this rigid norbornene system is a potent material in ring opening metathesis polymerization (ROMP) reaction using the Grubbs catalyst. So the synthesis of norbornene based 1,4-amino alcohols was originated from *cis*-monoester (+)-**51**.

2.2.1. Desymmetrization of Meso-Anhydride

In this project, cheapest and the most available *meso*-anhydride **50** was chosen for the synthesis of hemi-ester. Enantioselective desymmetrization of *meso*-anhydrides has been recently reported by Bolm et al [46]. In this study the desymmetrization of *meso*-anhydride was done with cinchona alkaloid-mediated ring opening with methanol. Both enantiomers are obtained with the usage of quinine or quinidine cinchona alkaloids with very high enantiomeric excess values (up to 92% e.e.) and chemical yields.

This step is actually the most important part of the project since the chirality source of all target ligands depends upon it. The stereoselectivity of cinchona alkaloid mediated desymmetrization directly influences the optical purity of the related chiral ligands.

The quinidine-mediated desymmetrization of *meso*-anhydride **50** with methanol gave *cis*-monoester (+)-**51**. (Scheme 11)



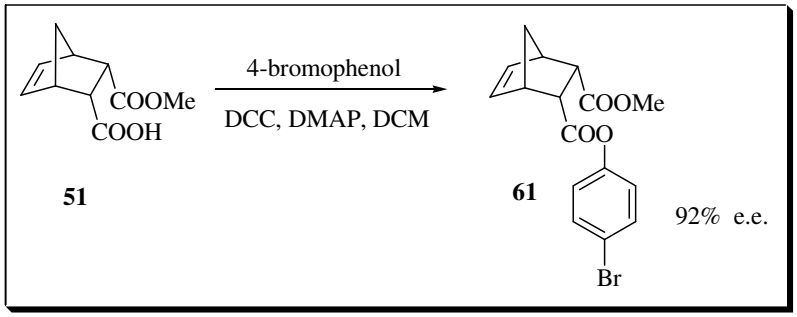
Scheme 11. Synthesis of *cis*-monoester (+)-**51** and **(-)-51**

In this reaction one mole of MeOH reacted enantioselectively with the one carbonyl group of the *meso*-anhydride. The identification of the product (+)-**51** was done with NMR spectroscopy. The ^{1}H-NMR spectrum showed that the starting compound completely lost its symmetry and the following peaks are observed: olefinic protons showed two doublet of doublets at 6.26 (1H) and 6.16 (1H) ppm; methoxy protons appeared at 3.54 (3H) ppm as a singlet; there are also two doublet of doublets at 3.28 (1H) and 3.22 (1H) ppm belonged to H_2 and H_3 methine protons respectively; H_1 and H_4 bridgehead protons showed two broad singlets at 3.14 (1H) and 3.11 (1H) ppm; two doublets at 1.43 (1H) and 1.28 (1H) ppm belonged to the H_7 bridge protons (In Appendix Figure 24). ^{13}C-NMR spectrum showed the following peaks; 177.8 (C_9) carbonyl carbon of carboxylic acid group; 173.1 (C_8) carbonyl carbon of ester group; 135.6 and 134.4 belonged to C_5 and C_6 double bond carbons; 51.6 (C_{10}) belonged to –O**C**H$_3$; there are two methine carbons at 48.8 and 48.2 ppm for C_2 and C_3; bridgehead carbons showed peaks at 47.9 and 46.6 ppm for C_1 and C_4; and finally 46.1 (C_7) ppm belonged to bridge carbon (Figure 25).

2.2.2. Enantiomeric Excess Determination of the Hemiester, 51

The *cis*-monoester is a very polar substance and additionally has very low UV activity. Thus it was converted to its *p*-bromophenyl ester derivative with bromophenol, to decrease its polarity and increase its UV activity to be detected with UV detector.

The *cis*-monoester (+)-**51** was reacted with 4-bromophenol with DCC and DMAP to give the corresponding diester structure **61** (Scheme 12), which was then analyzed by HPLC for the enantiomeric excess determination (Figure 10). The absolute configuration of starting compound **51**, was determined as (2*R*,3*S*) by comparing specific rotation sign determined at equal concentration in the same solvent given in the literature for *cis*-monoester (+)-**51** [47].



51 61

Scheme 12. Synthesis of **61**

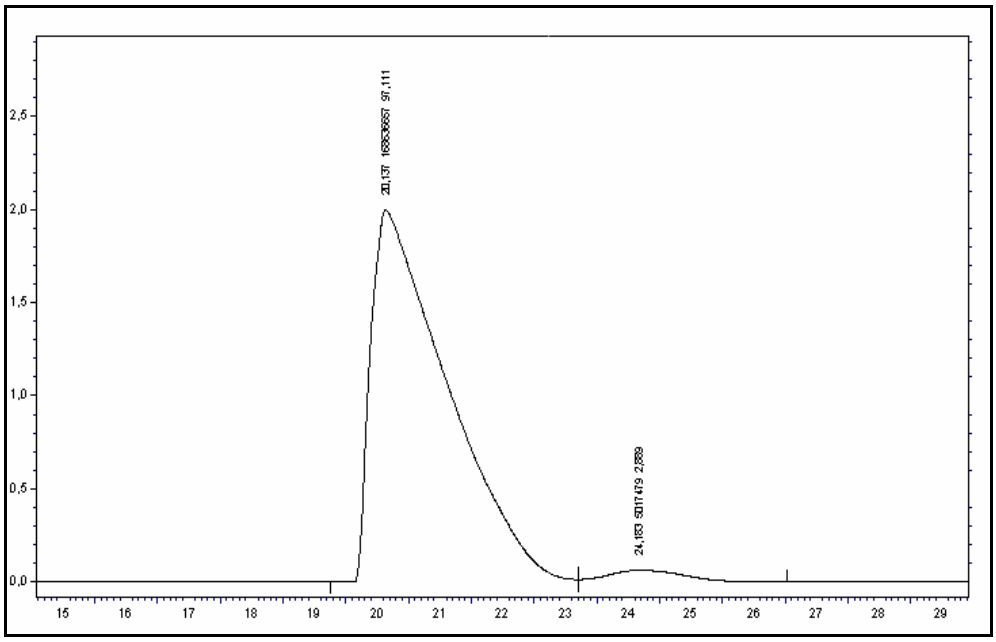
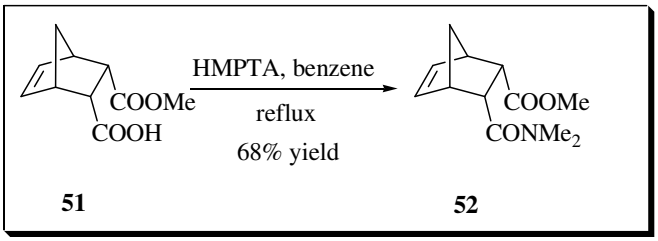


Figure 10. HPLC Chromatogram of Compound **61**

The structure elucidation of the compound **61** was done by NMR spectroscopy. In the ^{1}H-NMR spectrum, there are two doublets at 7.37 (2H) and 6.92 (2H) ppm belonged to aromatic protons H_{12} and H_{13} respectively; the double bond hydrogens showed two doublet of doublets at 6.32 (1H) and 6.15 (1H) ppm; singlet appeared at 3.55 (3H) ppm for methoxy protons; one broad singlet at 3.39 (2H) ppm belonged to H_2 and H_3 methine protons; H_1 and H_4 bridgehead protons observed at 3.20 (1H) and 3.17 (1H) ppm as two broad singlets; and finally two doublets at 1.40 (1H) and 1.33 (1H) ppm belonged to the H_7 bridge protons (Figure 26). In the ^{13}C-NMR spectrum, following peaks are observed: 173.0 (C_8) carbonyl carbon of methyl ester group; 171.2 (C_9) carbonyl carbon of *p*-bromophenyl ester group; 150.3, 123.8, 119.0 and 132.7 belonged to C_{11}, C_{12}, C_{13} and C_{14} benzene carbons and 135.9 and 135.0 belonged to C_5 and C_6 double bond carbons; methoxy carbon showed a peak at 52.2 (C_{10}) ppm; C_2 and C_3 methine carbons appeared at 49.1 and 48.7 ppm; 48.5 and 47.2 belonged to C_1 and C_4 bridgehead carbons; and finally bridge carbon observed at 46.6 (C_7) ppm (Figure 27). HPLC analysis of the methyl 4-bromophenyldiester: Chiralcel OD-H at room temperature, n-hexane/2-propanol = 98:2, 0.5 mL/min, 254 nm, 92% e.e., t_1=20.3 min (major), t_2= 23.2 min (minor).

2.2.3. Synthesis of Amide-Ester, 52

For the construction of 1,4-amino alcohols, in order to introduce the amine moiety, it was aimed to convert carboxylic acid group to amide structure, without touching the ester group. Monoester (+)-**51** was reacted with hexamethylphosphorous triamide (HMPTA) in benzene to give the corresponding amide ester structure **52** with 68% yield [48] and used further as a versatile starting compound (Scheme 13).



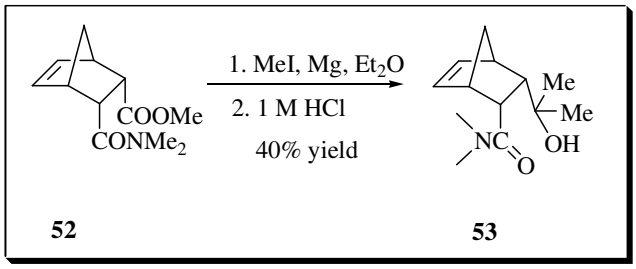
Scheme 13. Synthesis of amide-ester, **52**

The identification of the product **52** was done by NMR spectroscopy. In the ^{1}H-NMR spectrum, olefinic protons showed two doublet of doublets at 6.30 (1H) and 6.12 (1H) ppm; singlet at 3.52 (3H) ppm belonged to -OC**H**$_3$; H_2 and H_3 methine protons appeared at 3.19 (1H) and 3.35 (1H) ppm as two doublet of doublets; two broad singlets at 3.12 (1H) and 3.04 (1H) ppm belonged to the H_1 and H_4 bridgehead protons whereas; two singlets at 2.81 (3H) and 2.95 (3H) ppm belonged to methyl groups attached to the nitrogen atom; the characteristic bridge protons (H_7) appeared at 1.38 (1H) and 1.27 (1H) ppm as two doublets (Figure 28).

^{13}C-NMR spectrum showed the following peaks: 173.3 (C_8) carbonyl carbon of methyl ester; 172.4 (C_9) carbonyl carbon of amide; 136.6 and 133.9 belonged to C_5 and C_6 olefinic carbons; 51.9 (C_{10}) belonged to –O**C**H$_3$; 49.2 and 48.9 for C_{11} and C_{12} two methyl groups attached to the nitrogen; C_2 and C_3 methine carbons showed peaks at 47.3 and 47.0 respectively; 46.9 and 37.3 for C_1 and C_4 bridgehead carbons and finally 36.0 (C_7) ppm belonged to bridge carbon (Figure 29).

2.2.4. Grignard Reaction of Amide-Ester 52 with Iodomethane

As indicated in the aim of the work part of the thesis, the target 1,4-amino alcohol involved tertiary alcohol moieties. The construction of these moieties was accomplished by applying the classical Grignard reaction at this step. The ester group of the amide-ester structure **52** was reacted with methyl magnesium iodide to afford compound **53** with Grignard reaction (Scheme 14). Although the monitoring of the reaction with TLC showed us high conversion of the starting material to product, it was isolated with 40% yield. This is due to the isolation problem in column chromatography.

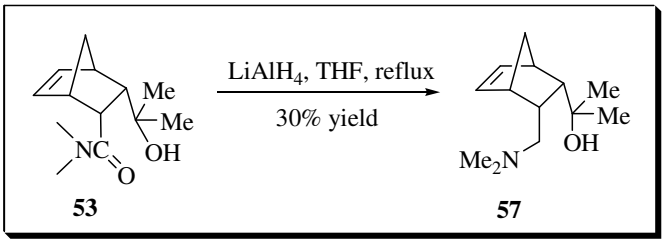


Scheme 14. Grignard Reaction of Amide-Ester, 52

The structure elucidation of the compound was done by NMR spectroscopy. In ^{1}H-NMR spectrum, olefinic protons were observed as doublet of doublets at 6.46 (1H) and 5.87 (1H) ppm; hydroxy proton showed a broad singlet at 5.76 (1H) ppm; one doublet of doublet at 3.45 (1H) and one doublet at 2.36 (1H) ppm belonged to H_2 and H_3 methine protons respectively; one of the bridgehead proton H_1 was observed at 3.09 ppm (1H) as a singlet; one of the N-attached methyl signal appeared at 3.20 ppm (3H) as a singlet; and the other one was overlapped with H_4 bridgehead proton at 2.96 ppm (4H) as a singlet; two doublets at 1.39 (1H) and 1.32 (1H) ppm belonged to the H_7 bridge protons whereas; two singlets observed at 1.26 (3H) and 1.09 (3H) ppm for H_{13} and H_{14} hydrogens, two methyl protons in alcohol moiety (Figure 30). In the ^{13}C-NMR spectrum, characteristic ester carbon at about 170 ppm was disappeared and two newly formed carbon peaks were observed; C_{13} and C_{14} were appeared at 31.1 and 30.9 ppm for the attached methyl groups in alcohol moiety and 49.6 (C_8) ppm belonged to carbon atom with two methyl groups in alcohol moiety (Figure 31).

2.2.5. Reduction of 53, with LAH

The final step to construct the related 1,4-amino alcohol structure involved the reduction of amide function into corresponding amine moiety with LAH. Similar isolation problem was observed for this step too. One of the target 1,4-amino alcohol **57** was obtained from **53** by subsequent $LiAlH_4$ reduction in THF with 30% yield (Scheme 15).



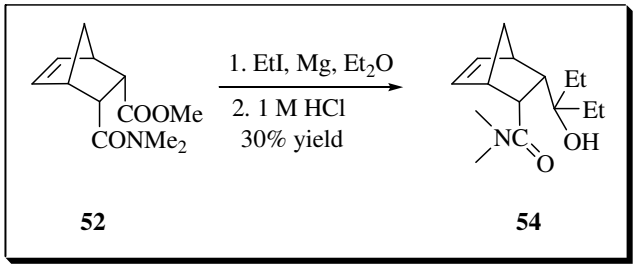
Scheme 15. Reduction of 53, with LAH

The product was identified by NMR spectroscopy. The characteristic difference of compound **57** from compound **53** was observed as the presence of two new sets of broad singlets at 2.71 (1H) and 2.63 (1H) ppm for diastereotopic H_9 methylene protons, which confirms that the carbonyl was converted to methylene group**;** methyl protons H_{11} and H_{12} attached to the nitrogen atom gave one singlet, instead of two separate singlets at 2.16 (6H) ppm, as expected; H_7 bridge protons showed one quartet at 1.37 (2H) ppm for the ^{1}H-NMR spectrum (Figure 32). In the ^{13}C-NMR spectrum, disappearance of carbonyl carbon in amide moiety, confirms that the reduction is succeeded. Here different from the previous part, there is an additional methylene carbon at 60.0 (C_9) ppm (Figure 33).

2.2.6. Grignard Reaction of Amide-Ester 52 with Iodoethane

In the former case, two methyl groups were introduced whereas in this case, we introduced two ethyl groups on the tertiary alcohol moiety in order to see their effects on selectivity.

The amide-ester structure **52** was reacted with ethyl magnesium iodide giving the corresponding compound **54** with 30 % yield by the application of Grignard method (Scheme 16).

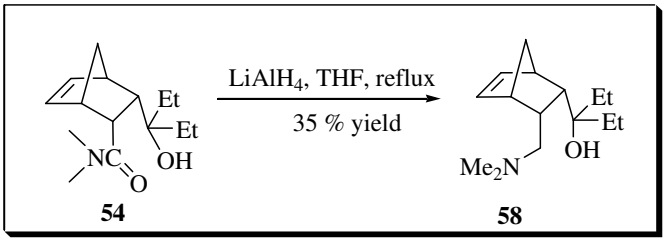


Scheme 16. Grignard Reaction of Amide-Ester **52** with Iodoethane

The structure elucidation of compound **54** was done by NMR spectroscopy. In the ^{1}H-NMR spectrum, it was understood that, the ester group was converted to alcohol from the following peaks; hydroxy proton showed a broad singlet at 5.56 (1H) ppm; two sets of multiplets at 1.65-1.55 (2H) and 1.45-1.36 (2H) ppm belonged to the newly formed H_{15} and H_{16} methylene protons; H_{13} and H_{14} methyl protons in alcohol moiety observed as multiplet at 0.78-0.72 (6H) ppm (Figure 34). In the ^{13}C-NMR spectrum; there is no carbonyl carbon in ester moiety whereas; there is one new carbon C_8 at 73.5 ppm; carbon atom with two ethyl groups in alcohol moiety; two newly formed C_{15} and C_{16} methylene carbons observed at 30.8 and 30.1 ppm; C_{13} and C_{14} two methyl carbons in alcohol moiety appeared at 8.3 and 7.9 ppm respectively which strongly support the structure (Figure 35).

2.2.7. Reduction of 54, with LAH

In this part similar route was followed and 1,4-amino alcohol **58** was obtained from **54** by subsequent $LiAlH_4$ reduction in THF with 35% yield (Scheme 17).

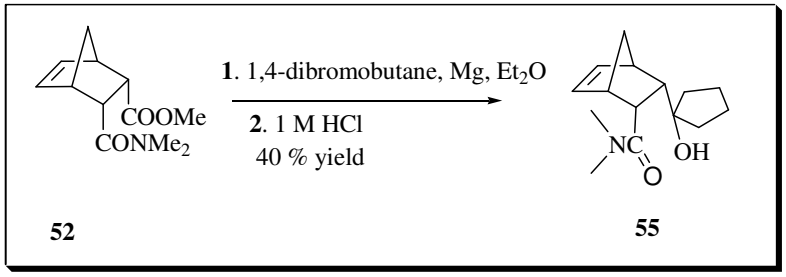


Scheme 17. Reduction of **54**, with LAH

The reduction of compound **54** was achieved successfully and the characterization was done with NMR spectroscopy. ^{1}H-NMR spectrum showed one multiplet at 3.54-3.51 and one broad singlet at 3.12 ppm belonged to diastereotopic H_9 methylene protons, which confirms that the carbonyl was converted to methylene group; two multiplets observed at 1.59-1.48 (2H) ppm for the newly formed H_{16} methylene protons and at 1.40-1.18 (4H) ppm for the H_7 bridge protons together with H_{15} methylene protons respectively; H_{13} and H_{14} methyl protons in alcohol moiety showed one triplet at 0.89 (6H) ppm (Figure 36). In the ^{13}C-NMR spectrum, there is no carbonyl carbon, which indicates that amide was converted to amine group and there is an additional methylene carbon at 61.0 (C_9) ppm (Figure 37).

2.2.8. Grignard Reaction of Amide-Ester 52 with 1,4-dibromobutane

In this part, it was tried to construct cyclic structure on the tertiary alcohol moiety to see their effects on stereoselectivity. Grignard method was used here too, however this time dihalo type reagents were used. In order to construct a five-membered ring by functionalizing amide-ester **52** with 1,4-dibromobutane and compound **55** was obtained with 40 % yield (Scheme 18).

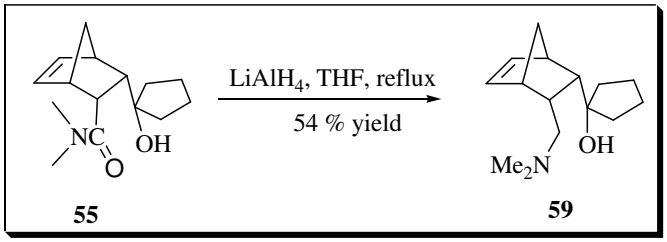


Scheme 18. Grignard Reaction of Amide-Ester, **52**, with 1,4-dibromobutane

For the characterization of the product **55** we benefited from their NMR spectroscopy. In the structure elucidation by ^{1}H-NMR spectrum, characteristic –CH_2 protons on cyclopentyl were helpful to understand whether the product was formed or not at first glance. They are two multiplets at 1.76-1.65 ppm (4H) belonged to H_{13} methylene protons and 1.50-1.38 ppm (4H) belonged to H_{14}, the other methylene protons on cyclopentyl ring. The first methylene group is close to –OH group, so they were shifted to downfield. H_7 bridge protons appeared at 1.25 (1H) and 1.22 (1H) ppm as two doublets (Figure 38). ^{13}C-NMR spectrum showed that carbonyl carbon in ester moiety was disappeared and C_8 carbon atom with cyclopentyl group in alcohol moiety was observed at 80.8 ppm and finally 38.2 and 36.4 ppm belonged to C_{13}, 24.3 and 24.1 ppm belonged to C_{14} newly formed methylene carbons on the ring (Figure 39).

2.2.9. Reduction of 55, with LAH

The compound **59** was obtained from amide-alcohol **55** by subsequent $LiAlH_4$ reduction in THF with 54% yield (Scheme 19).



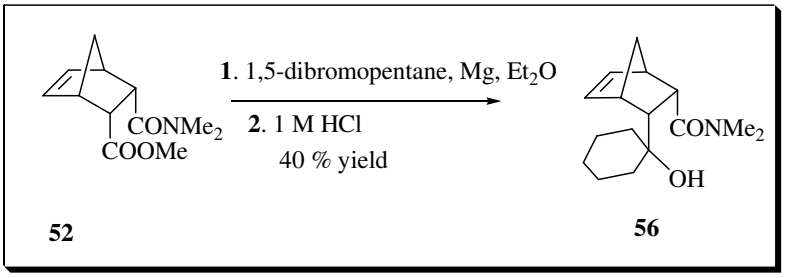
Scheme 19. Reduction of **55,** with LAH

The structure identification of the product **59** was done by NMR spectroscopy. In the ^{1}H-NMR spectrum, following peaks are observed: olefinic protons showed two quartets at 6.10 (1H) and 5.99 (1H) ppm and the hydroxy proton appeared at 2.73 (1H) ppm as one broad singlet; one doublet at 2.64 (1H) ppm belonged to H_1 bridgehead proton; one doublet at 2.61 (1H) ppm belonged to the H_2 methine proton; H_9 methylene protons showed one multiplet at 2.59-2.51 (1H) ppm and one triplet at 2.30 (1H) ppm, which confirms that the carbonyl was converted to methylene group by the reduction process; H_4 bridgehead proton overlapped with the two methyl group attached to nitrogen and gave one broad singlet (7H) at 2.15 ppm; the other methine proton H_3 showed one doublet of doublet at 1.95 (1H) ppm; one multiplet at 1.80-1.40 (8H) ppm belonged to the cyclopentyl protons in alcohol moiety and finally one doublet at 1.35 (2H) ppm belonged to the H_7 bridge protons (Figure 40). ^{13}C-NMR spectrum showed that there is no carbonyl carbon in amide moiety whereas a new peak was appeared at 61.3 ppm belonged to C_9 methylene carbon (Figure 41).

2.2.10. Grignard Reaction of Amide-Ester 52 with 1,5-dibromopentane

Analog to the cyclopentane moiety, in this part it has been tried to construct a six-membered ring on alcohol moiety by choosing 1,5-dibromopentane as the reactant.

Again by the help of Grignard method, the ester group was functionalized to give the corresponding compound **56** with 40% yield (Scheme 20). In this part of the thesis, the other enantiomer desymmetrized with Quininine was used and the configuration of the compound **56** was changed.

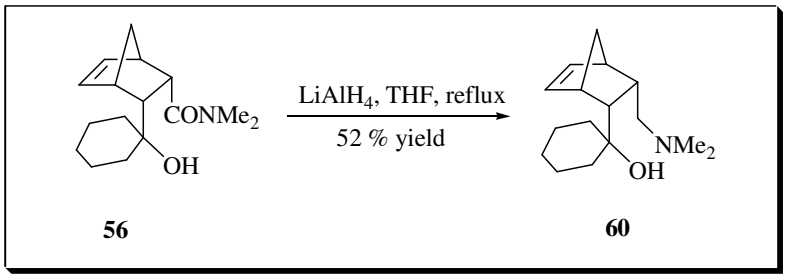


Scheme 20. Grignard Reaction of Amide-Ester, **52**, with 1,5-dibromopentane

The structure elucidation of compound **56** was done by NMR spectroscopy. From the ^{1}H-NMR spectrum, it was understood that, the ester group was converted to alcohol and five methylene protons on the cyclohexyl ring overlapped with H_7 bridge protons and showed a multiplet at 1.75-1.08 ppm (Figure 42). ^{13}C-NMR spectrum showed no peak belonged to carbonyl carbon of ester moiety, instead C_8 carbon with cyclohexyl ring in alcohol moiety appeared at 70.1 ppm, in addition to this newly formed methylene carbons on the ring observed at 38.3 and 36.6 ppm (C_{13}); 26.2 ppm (C_{15}); and finally 22.2 and 21.9 ppm for C_{14} (Figure 43).

2.2.11. Reduction of 56, with LAH

The 1,4-amino alcohol **60** was obtained from amide-alcohol **56** by subsequent $LiAlH_4$ reduction in THF with 52% yield (Scheme 21).



Scheme 21. Reduction of **56**, with LAH

For the characterization of the product **60** we benefited from their NMR spectroscopy. In the structure elucidation by ^{1}H-NMR spectrum, one multiplet at 2.62-2.55 (2H) ppm belonged to the bridgehead proton H_1 and one of the H_9 methylene protons which confirms that the reduction was achieved and one triplet at 2.39 (1H) ppm belonged to the other H_9 methylene proton; the two H_{11} and H_{12} methyl protons attached to the nitrogen observed at 2.15 (6H) ppm as one broad singlet; other bridgehead proton H_4 appeared at 2.12 (1H) ppm as one singlet; two multiplets at 1.79-1.16 (6H) and 1.07-0.95 (4H) ppm belonged to the methylene protons on cyclohexyl ring respectively (Figure 44). ^{13}C-NMR spectrum showed that, there is no carbonyl carbon of the amide group; however new methylene carbon observed at 61.5 (C_9) ppm (Figure 45).

2.2.12. Absolute Configuration Determination

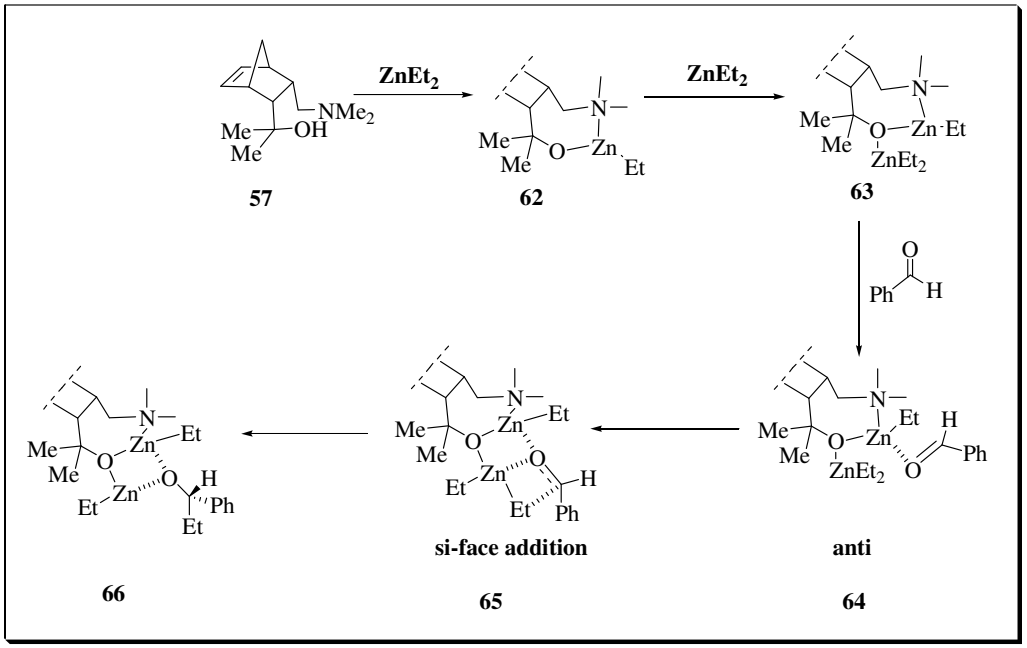
The absolute configuration of starting compound **51**, the *cis*-monoester was determined as (2*R*,3*S*) by comparing the specific rotation sign determined at equal concentration in the same solvent given in the literature for *cis*-monoester (+)-**51** [47]. And the absolute configurations of **(-)-57**, **(-)-58** and **(-)-59** were determined as (2*R*,3*S*) by comparing specific rotation signs determined at equal concentration in the same solvent with *cis*-monoester **(+)-51** that has been reported in the literature [46, 49].

Since transformation of *cis*-monoester **(+)-51** to chiral ligands **57**, **58** and **59** has no effect on the stereocenters of the norbornene backbone, the absolute configuration of each ligand was not changed during transformation reactions. For **(+)-60**, the absolute configuration was determined as (2*S*,3*R*) because of the desymmetrization with quinine, the configuration of the compound was changed.

2.3. Diethylzinc Experiments

Enantioselective addition of diethylzinc reagents to benzaldehyde affords optically active secondary alcohols. The reaction is one of the most important and fundamental asymmetric reactions.

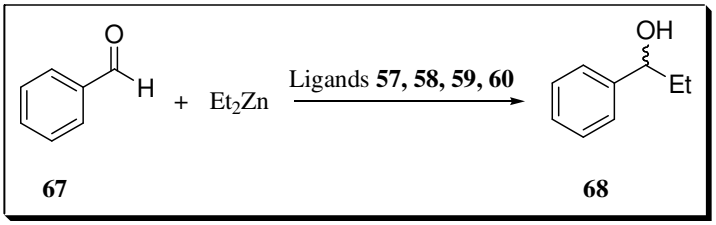
The mechanism of diethylzinc addition with 1,4-amino alcohol **57** can be explained as in Scheme 22 [50].



Scheme 22. The mechanism of diethylzinc addition to benzaldehyde with 1,4-amino alcohol **57**

In the first step, compound **57** reacts with diethylzinc to generate the zinc complex **62**. It was found that 1 equiv of **62** cannot react with benzaldehyde. That is, the Zn-Et group of **62** cannot add to an aldehyde and a second equivalent of diethylzinc is needed [51]. The alkoxy oxygen atom in **62** coordinates with diethylzinc to give **63**. Coordination of benzaldehyde with **63** generates **64**. Molecular orbital calculations indicate that the anti coordination of benzaldehyde (with respect to the chiral ligand) in **64** and a tricyclic transition state **65** are most favorable. In transition state **65**, ethyl migrates to the *si* face of the aldehyde to form **66** and aqueous workup gives (*S*)-1-phenylpropanol.

In our synthetic strategy, the four newly synthesized norbornene based 1,4-amino alcohols **57**, **58**, **59** and **60** were used in diethylzinc addition reaction to benzaldehyde (Scheme 23) and the results were shown in the following parts.



Scheme 23. Asymmetric Diethylzinc Addition to Benzaldehyde Using **57, 58, 59** and **60**

2.3.1. Effect of Different Ligands

The ligands **57**, **58**, **59** and **60** gave moderately good enantioselectivities (up to 69% e.e.) and yields, in diethylzinc addition reaction to benzaldehyde producing 1-phenylpropanol.

The highest result was obtained with aminoalcohol **60**, which has cyclohexyl substituent on alcohol moiety. The catalysts **57**, **58** and **59** having the dimethyl, diethyl and cyclopentyl groups on hydroxymethylene carbon gave lower yields and enantiomeric excess values with respect to ligand **60** (Table 1).

Table 1. Asymmetric Diethylzinc Addition Reaction to Benzaldehyde Using Norbornene Based 1,4-Aminoalcohol Catalysts

Entry	Ligand[a]	Yield (%)[b]	Ee (%)[c]
1	**57**	78	53
2	**58**	38	15
3	**59**	89	11
4	**60**	70	65

[a] 10 mol % of chiral catalysts were used. Toluene was used as solvent. All reactions were done at 0 ^{o}C.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has R configuration.

2.3.2. Effect of Solvent and Temperature

These results prompted us towards the investigation of new conditions to increase the enantioselectivity and yield of the chiral ligand **57** in diethylzinc addition reaction to benzaldehyde. So the effect of different temperatures and different solvents on enantioselectivities was investigated with the usage of chiral ligand **57**.

The asymmetric diethylzinc addition reaction to benzaldehyde was carried out with the same amount of chiral ligand **57** (10 mol%) in toluene at –10 ^{o}C and in hexane at 0 ^{o}C separately (Table 2).

At -10^{o}C in toluene, the catalyst gave 1-phenylpropanol with 35% e.e and 41% chemical yield. When this result compared with the result of entry 1 in table 1, it can be seen that this value is lower in both enantioselectivity and the chemical yield. When the reaction is carried out in hexane at 0 ^{o}C, enantioselectivity decreased as in the former case.

Table 2. Effect of Solvent and Temperature on the Diethylzinc Experiment with the Chiral Catalyst **57**

Entry[a]	Temperature	Solvent	Yield(%)[b]	Ee (%)[c]
1	**-10**	Toluene	41	35
2	**0**	Hexane	52	33

[a] 10 mol % of chiral catalyst **57** was used.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has R configuration.

We also examined the effect of solvent using toluene, hexane, THF and DCM with the chiral catalyst **58**, **59** and **60** in diethylzinc addition reaction to benzaldehyde. These reactions were carried out at optimized temperature 0 ^{o}C. Results were given in Table 3. Very low e.e. values and chemical yields, with chiral catalysts **58** and **59** in DCM and THF, were obtained.

However ligand **60** gave the highest enantiomeric excess value (69%) and yield (80%) in hexane at 0°C.

Table 3. Effect of Solvent on Diethylzinc Experiment with the Chiral Catalysts **58**, **59** and **60**

Entry[a]	Ligand[a]	Solvent	Yield (%)[b]	Ee (%)[c]
1	**58**	THF	20	1
2	**58**	DCM	10	7
3	**59**	THF	15	3
4	**59**	DCM	10	13
5	**60**	Hexane	80	69

[a] 10 mol % of chiral catalyst **58, 59** and **60** was used.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has R configuration for entry 5.

2.3.3. Effect of Ligand Amount

We have examined the effect of temperature and solvent in enantioselectivities of 1-phenylpropanol; and it was found that the ligands gave the highest yields and enantioselectivities in toluene and hexane at 0 ^{o}C. Between these four chiral ligands, **57** and **60** gave the highest values. In order to improve these values, the effect of chiral ligand amount on enantioselectivity was also investigated. The amounts were changed from 5% to 15% mole for the ligand **57**, as shown in Table 4.

Table 4. Effect of Ligand Amount on Diethylzinc Experiment with the Chiral Catalysts **57**

Entry[a]	Amount of Ligand	Yield(%)[b]	Ee (%)[c]
1	5 %	49	18
2	10 %	78	53
3	15 %	60	55

[a] Chiral catalyst **57** was used. Toluene was used as solvent. All reactions were done at 0 ^{o}C.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has R configuration for entry 3. The HPLC chromatograms are as follows (Figure 11 and 12).

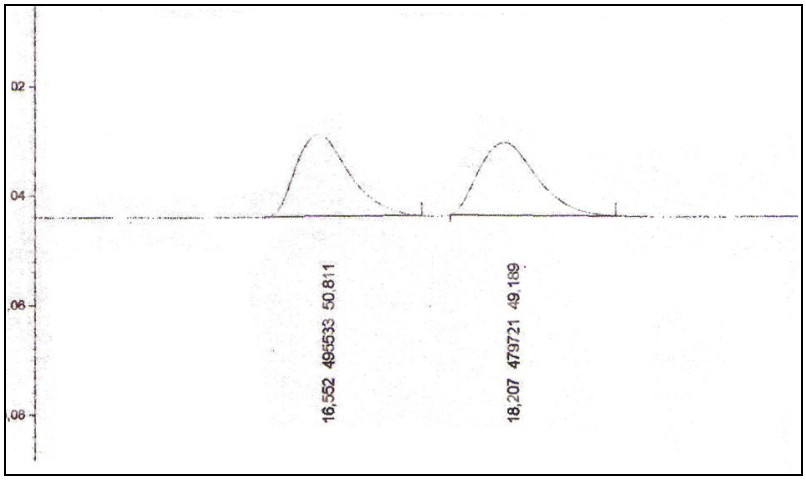


Figure 11. HPLC chromatogram of racemic 1-phenyl-1-propanol

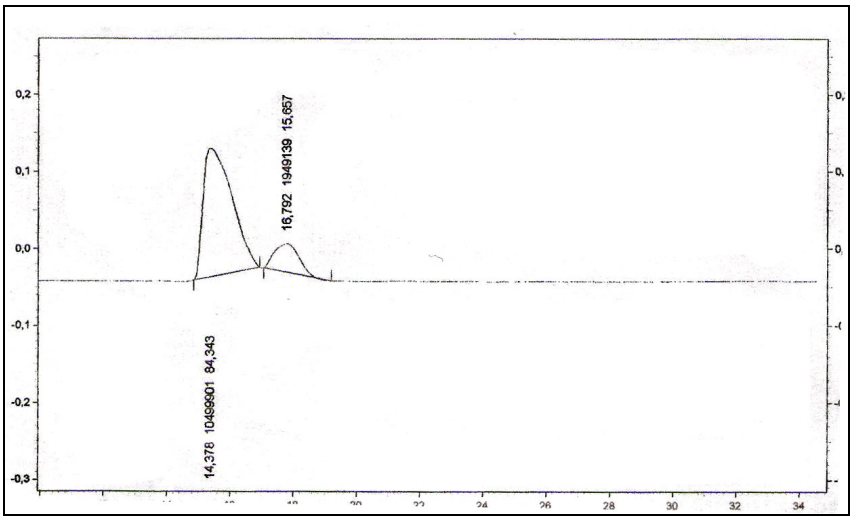


Figure 12. HPLC chromatogram of 1-phenyl-1-propanol with 69% e.e.value with chiral catalyst **60**

CHAPTER 3

EXPERIMENTAL

In this study, following instruments and materials were used for the purification and characterization of products.

The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Brucker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. Apparent splittings are given in all cases.

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

Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III, automatic polarimeter at 20 ^{o}C.

Flash column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates. Ethyl acetate/hexane mixture systems were used as eluting solvent in TLC and flash column chromatography. Solutions were concentrated under vacuum by using rotary evaporator.

3.1. Synthesis of (2*R*, 3*S*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid, 51

MeOH (0.63 mL, 36 mmol) was added dropwise to a stirred solution of the *meso*-anhydride **50** (0.85 g, 12 mmol) and quinidine (1.85 g, 13 mmol) in a 1:1 mixture of toluene (12.5 mL) and carbontetrachloride (12.5 mL) at -55 ^{o}C under argon. The reaction mixture was stirred at this temperature for 60 h. Subsequently, the resulting clear solution was concentrated in vacuo to dryness and the resulting residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 2 N HCl, and after phase separation, followed by extraction of aqueous phase with ethyl acetate, the organic layer was dried over $MgSO_4$, filtered, and concentrated providing the monoester **51** (0.8 g, 92 %).

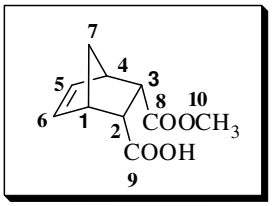


Figure 13

$[\alpha]_D^{20}$= +7.9 (*c* 4.8, CCl_4), lit. [49,52]

m.p. 76–77 °C, lit.[49,52], 74 °C (racemic)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm
6.26 (dd, *J*= 2.96, 5.50 Hz, 1H, H_5)

6.16 (dd, *J*= 2.94, 5.53 Hz, 1H, H_6)

3.54 (s, 3H, H_{10})

3.28 (dd, *J*= 3.22, 10.14 Hz, 1H, H_2)

3.22 (dd, *J*= 3.13, 10.15 Hz, 1H, H_3)

3.14 (bs, 1H, H_1)

3.11 (bs, 1H, H_4)

1.43 (d, *J*= 8.67 Hz, 1H, H_7)

1.28 (d, *J*= 8.69 Hz, 1H, H_7)

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

177.8, 173.1, 135.6, 134.4, 51.6, 48.8, 48.2, 47.9, 46.6, 46.1.

3.2. Synthesis of (2*R*,3*S*)-2-(4-bromophenoxy)-3-methoxycarbonylbicyclo[2.2.1] hept-5-ene, 61

4-Bromophenol (0.088 g, 0.51 mmol) and monoester **51** (0.100 g, 0.51 mmol) were dissolved in CH_2Cl_2 (5 mL) at 0 ^oC under argon. Then, DCC (0.105 g, 0.51 mmol) and DMAP (0.016 g, 0.13 mmol) were added simultaneously at 0 ^oC. The mixture was mixed overnight at room temperature. The mixture was filtered and filtrate was washed with first 5% HOAc, then 1 N NaOH and finally with brine. The organic phase was dried over $MgSO_4$ and evaporation of the solvent afforded the compound **61** (0.16 g, 90%). HPLC-analysis of the methyl 4-bromophenyl diester: Chiralcel OD-H at room temperature, *n*-hexane/2-propanol) = 98:2, 0.5 mL/min, 254 nm, t_1= 20.3 min (major), t_2= 23.2 min (minor).

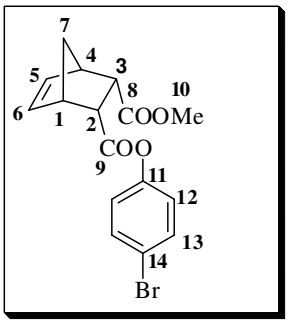


Figure 14

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

7.37 (d, *J*= 8.72 Hz, 2H, H_{12})

6.92 (d, *J*= 8.71 Hz, 2H, H_{13})

6.32 (dd, *J*= 2.91, 5.39 Hz, 1H, H_5)

6.15 (dd, *J*= 2.92, 5.41 Hz, 1H, H_6)

3.55(s, 3H, H_{10})

3.39 (s, 2H, H_2 and H_3)

3.20 (s, 1H, H_1)

3.17 (s, 1H, H_4)

1.40 (d, *J*= 8.70 Hz, 1H, H_7)

1.33 (d, *J*= 8.61, 1H, H_7)

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

173.0, 171.2, 150.3, 135.9, 135.0, 132.7, 123.8, 119.0, 52.2, 49.1, 48.7, 48.5, 47.2, 46.6.

3.3. Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylcarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 52

To the solution of monoester **51** (0.78 g, 3.9 mmol) in benzene (5 mL) was added hexamethylphosphorous triamide (0.72 mL, 3.9 mmol) at a rate that maintained reflux of the reaction. After 2h, the resulting cloudy solution was allowed to cool to room temperature and a saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with DCM. The organic solutions were combined, dried over $MgSO_4$ and concentrated to give compound **52** (0.61 g, 68%).

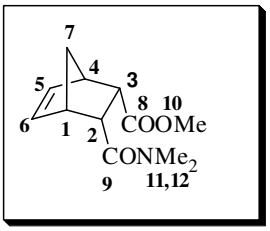


Figure 15

$[\alpha]_D^{20}$= +39.1 (*c* 2.028, $CHCl_3$);

m.p. 79-80°C [53].

^{1}H NMR (400MHz, $CDCl_3$): δ ppm
6.30 (dd, *J*= 3.03, 5.34 Hz, 1H, H_5)
6.12 (dd, *J*= 2.93, 5.39 Hz, 1H, H_6)
3.52 (s, 3H, H_{10})
3.35 (dd, *J*= 3.16, 9.91 Hz, 1H, H_3)

3.19 (dd, *J*= 3.48, 9.92 Hz, 1H, H_2)

3.12 (s, 1H, H_1)

3.04 (s, 1H, H_4)

2.95 (s, 3H, H_{11})

2.81 (s, 3H, H_{12})

1.38 (d, *J*=8.5 Hz, 1H, H_7)

1.27 (d, *J*= 8.5 Hz, 1H, H_7)

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

173.3, 172.4, 136.6, 133.9, 51.9, 49.2, 48.9, 47.3, 47.0, 46.9, 37.3, 36.0.

3.4. Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylcarboxamido)-3-(dimethylhydroxy-thyl)-bicyclo[2.2.1]hept-5-ene, 53

Iodomethane (0.48mL, 7.7 mmol) was dissolved in 10 mL of anhydrous diethyl ether and put into the addition funnel. This solution was added to magnesium (0.24 g, 10.2 mmol) turnings. Once the reaction has begun, rest of the iodomethane solution was added dropwise at a rate that maintains gentle reflux. When the addition of the iodomethane solution was complete, the mixture was refluxed for 30 min. Compound **52** (0.58 g, 2.6 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of the compound **52** solution has been added, the reaction mixture was refluxed for 3 h. The resultant mixture was cooled to 0°C and 1 mL 1N HCl and 10 mL saturated NH_4Cl was added. After the phase separation with diethyl ether, the organic phase was collected and dried over with $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc) to give compound **53** (0.38g, 40%).

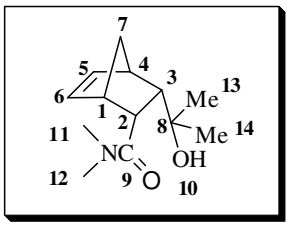


Figure 16

$[\alpha]_D^{20}$= -84.56 (*c* 1.84, $CHCl_3$)

m.p. 99-101°C

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.46 (dd, *J*= 2.9 Hz, 1H, H_5)

5.87 (dd, *J*= 2.9 Hz, 1H, H_6)

5.76 (s, 1H, H_{10})

3.45 (dd, *J*= 3.1, 9.3 Hz, 1H, H_2)

3.20 (s, 3H, H_{12})

3.09 (s, 1H, H_1)

2.96 (s, 4H, H_4 and H_{11})

2.36 (d, *J*=9.34 Hz, 1H, H_3)

1.39 (d, *J*= 8.1 Hz, 1H, H_7)

1.32 (d, *J*=8.05 Hz, 1H, H_7)

1.26 (s, 3H, H_{14})

1.09 (s, 3H, H_{13})

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

175.9, 137.4, 130.4, 69.5, 58.4, 49.6, 47.1, 46.1, 43.8, 38.3, 36.6, 31.1, 30.9.

3.5. **Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylaminomethyl)-3-(dimethylhydroxy-methyl)-bicyclo[2.2.1]hept-5-ene, 57**

To a suspension of $LiAlH_4$ (0.123 g, 3.2 mmol) in THF (10 mL) was added a solution of amide alcohol **53** (0.36 g, 1.6 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 4 h and hydrolized by the cautious addition of water at 0°C. The fine white precipitate which formed was washed with THF and discarded. The crude product was purified by column chromatography (EtOAc) to give amino alcohol **57** (0.13 g, 30%).

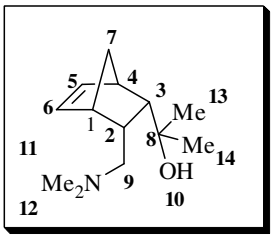


Figure 17

$[\alpha]_D^{20}$= -17.39 (*c* 1.368, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.12 (dd, *J*= 2,9, 5,7 Hz, 1H, H_5)

5.97 (dd, *J*=2,9, 5,3 Hz, 1H, H_6)

2.71 (bs, 1H, H_9)

2.63 (bs, 1H, H_9)

2,43 (s, 1H, H_4)

2.41 (s, 1H, H, H_{10})

2.35 (dd, *J*=2.7, 5.3 Hz, 1H, H_2)

2.16 (s, 6H, H_{11} and H_{12})

2.09 (s, 1H, H_1)

2.02 (dd, *J*=2.9, 12.7 Hz, 1H, H_3)

1.37 (q, *J*=6.2 Hz, 2H, H_7)

1.19 (s, 3H, H_{14})

0.95 (s, 3H, H_{13})

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

135.6, 133.0, 70.3, 60.0, 54.5, 50.3, 46.7, 45.7, 43.8, 40.7, 31.9, 27.2.

3.6. Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylcarboxamido)-3-(diethylhydroxy-thyl)-bicyclo[2.2.1]hept-5-ene, 54

Iodoethane (0.6mL, 7.5 mmol) was dissolved in 10 mL of anhydrous diethyl ether and put into the addition funnel. This solution was added to magnesium (0.26 g, 10.8 mmol) turnings.

Once the reaction has begun, rest of the iodoethane solution was added dropwise at a rate that maintains gentle reflux. When the addition of the iodoethane solution was complete, the mixture was refluxed for 30 min. Compound **52** (0.55 g, 2.4 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of the compound **52** solution has been added, the reaction mixture was refluxed for 3h- 4h. The resultant mixture was cooled to 0°C and 1 mL 1N HCl and 10 mL saturated NH_4Cl was added. After the phase separation with diethyl ether, the organic phase was collected and dried over with $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc) to give compound **54** (0.29g, 34%).

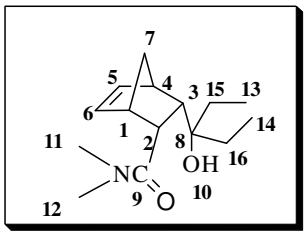


Figure 18

$[\alpha]_D^{20}$= -80.83 (*c* 2.114, $CHCl_3$)

m.p. 82-83°C

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.37 (dd, *J*= 3.1, 5.2 Hz, 1H, H_5)

5.8 (dd, *J*= 2.9, 5.3 Hz, 1H, H_6)

5.56 (s, 1H, H_{10})

3.36 (dd, *J* = 3.1, 9.3 Hz, 1H, H_2)

3.12 (s, 3H, H_{12})

2.97 (s, 1H, H_1)

2.8 (s, 4H, H_{11} and H_4)

2.38 (dd, *J*= 2.43, 9.3 Hz, 1H, H_3)

1.65–1.55 (m, 2H, H_{16})

1.45–1.36 (m, 2H, H_{15})

1.32–1.16 (m, 2H, H_7)

0.78–0.72 (m, 6H, H_{13} and H_{14}).

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

δ 176.0, 137.5, 130.2, 73.5, 54.8, 49.5, 47.1, 45.5, 43.6, 38.3, 36.6, 30.8, 30.1, 8.3, 7.9.

3.7. **Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylaminomethyl)-3-(diethylhydroxy-methyl)-bicyclo[2.2.1]hept-5-ene, 58**

To a suspension of $LiAlH_4$ (0.086 g, 2.2 mmol) in THF (10 mL) was added a solution of amide alcohol **54** (0.29 g, 1.1 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 5 h and hydrolized by the cautious addition of water at 0°C. The fine white precipitate which formed was washed with THF and discarded. The crude product was purified by column chromatography (EtOAc) to give amino alcohol **58** (0.11 g, 35%).

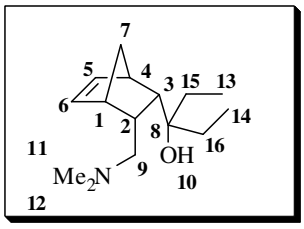


Figure 19

$[\alpha]_D^{20}$= -17.39 (*c* 1.368, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.30 (dd, *J*= 3.2, 5.3 Hz, 1H, H_5)

5.92 (dd, *J*= 3.0, 5.3 Hz, 1H, H_6)

5.53 (s, 1H, H_{10})

3.54–3.51 (m, 1H, H_9)

3.35 (dd, *J*= 3.2, 9.8 Hz, 1H, H_2)

3.12 (bs, 1H, H_9)

3.08 (s, 3H, H_{12})

2.97 (s, 1H, H_1)

2.90 (s, 1H, H_4)

2.88 (s, 3H, H_{11})

2.43–2.37 (m, 1H, H_3)

1.59–1.48 (m, 2H, H_{16})

1.40–1.18 (m, 4H, H_7 and H_{15})

0.89 (t, *J*=7,4 Hz, 6H, H_{13} and H_{14})

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

δ 136.6, 134.4, 74.6, 61.0, 51.0, 50.9, 47.2, 45.8, 44.5, 41.0, 31.8, 31.6, 30.8, 7.9, 7.7.

3.8. Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylcarboxamido)-3-(cyclopenthylhydroxy-thyl)-bicyclo[2.2.1]hept-5-ene, 55

1,4-dibromobutane (0.265mL, 2.2 mmol) was dissolved in 10 mL of anhydrous diethyl ether and put into the addition funnel. This solution was added to magnesium (0.133 g, 5.54 mmol) turnings. Once the reaction has begun, rest of the 1,4-dibromobutane solution was added dropwise at a rate that maintains gentle reflux. When the addition of the 1,4-dibromobutane solution was complete, the mixture was refluxed for 30 min. Compound **52** (0.495 g, 2.2 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of the compound **52** solution has been added, the reaction mixture was refluxed for 3h- 4h. The resultant mixture was cooled to 0°C and 1 mL 1N HCl and 10 mL saturated NH_4Cl was added. After the phase separation with diethyl ether, the organic phase was collected and dried over with $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc) to give compound **55** (0.21g, 40%).

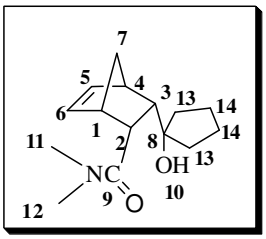


Figure 20

$[\alpha]_D^{20}$= -46.2 (*c* 2.0, $CHCl_3$)

m.p. 104-105°C

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.38 (dd, *J*= 3.6, 8.2 Hz, 1H, H_5)

5.8 (dd, *J*=3.5, 5.2 Hz, 1H, H_6)

5.26 (s, 1H, H_{10})

3.38 (dd, *J* = 3.2, 9.4 Hz, 1H, H_2)

3.12 (s, 3H, H_{12})

2.98 (s, 1H, H_1)

2.87 (s, 4H, H_{11} and H_4)

2.31 (dd, *J*= 2.53, 9.4 Hz, 1H, H_3)

1.76-1.65 (m, 4H, H_{13})

1.50-1.38 (m, 4H, H_{14})

1.25 (d, *J*= 5.5 Hz, 1H, H_7)

1.22 (d, *J*= 6.3 Hz, 1H, H_7)

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

175.0, 138.0, 129.9, 80.8, 58.3, 50.0, 47.1, 47.0, 44.3, 41.6, 41.2, 38.2, 36.4, 24.3, 24.1.

3.9. **Synthesis of (2*R*,3*S*)-2-(*N*,*N*-dimethylaminomethyl)-3-(cyclopenthylhydroxy-methyl)-bicyclo[2.2.1]hept-5-ene, 59**

To a suspension of $LiAlH_4$ (0.068 g, 1.8 mmol) in THF (10 mL) was added a solution of amide alcohol **55** (0.15 g, 0.6 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 6 h and hydrolized by the cautious addition of water at 0°C. The fine white precipitate which formed was washed with THF and discarded. The crude product was purified by column chromatography (EtOAc) to give amino alcohol **59** (0.8 g, 54%).

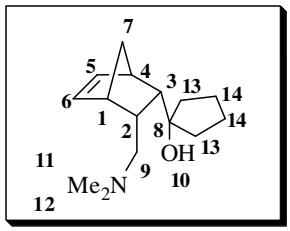


Figure 21

$[\alpha]_D^{20}$= -11.1 (c 2.56 $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.10 (q, *J*= 2.91, 5.53 Hz, 1H, H_5)

5.99 (q, *J*= 2.86, 5.53 Hz, 1H, H_6)

2.73 (bs, 1H, H_{10})

2.64 (d, *J*= 3.40 Hz, 1H, H_1)

2.61 (d, *J*= 2.55 Hz, 1H, H_2)

2.59- 2.51 (m, 1H, H_9)

2.30 (t, *J*= 12.43 Hz, 1H, H_9)

2.15 (bs, 7H, H_{11}, H_{12} and H_4)

1.95 (dd, *J*= 2.40, 12.40 Hz, 1H, H_3)

1.80- 1.40 (m, 8H, H_{13} and H_{14})

1.35 (d, *J*= 7.96 Hz, 2H, H_7)

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

135.6, 133.0, 70.3, 60.0, 54.5, 50.3, 46.7, 45.7, 43.8, 40.7, 31.9, 27.2

3.10. Synthesis of (2*S*,3*R*)-2-(*N*,*N*-dimethylcarboxamido)-3-(cyclohexylhydroxy-thyl)-bicyclo[2.2.1]hept-5-ene, 56

1,5-dibromopentane (0.515 mL, 2.2 mmol) was dissolved in 10 mL of anhydrous diethyl ether and put into the addition funnel. This solution was added to magnesium (0.13 g, 5.54 mmol) turnings. Once the reaction has begun, rest of the 1,5-dibromopentane solution was added dropwise at a rate that maintains gentle reflux. When the addition of the 1,5-dibromopentane solution was complete, the mixture was refluxed for 30 min. Compound **52** (0.5 g, 2.3 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of the compound **52** solution has been added, the reaction mixture was refluxed for 3h- 4h. The resultant mixture was cooled to 0°C and 1 mL 1N HCl and 10 mL saturated NH_4Cl was added. After the phase separation with diethyl ether, the organic phase was collected and dried over with $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc) to give compound **56** (0.28g, 40%).

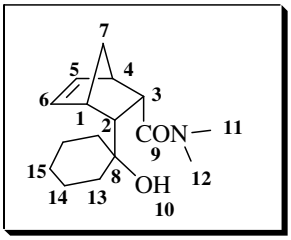


Figure 22

$[\alpha]_D^{20}$= 52.4 (*c* 2.0, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.44 (dd, *J*= 3.09, 5.3 Hz, 1H, H_5)

5.98 (dd, *J*=2.9, 5.2 Hz, 1H, H_6)

5.43 (s, 1H, H_{10})

3.34 (dd, *J* = 3.07, 9.18 Hz, 1H, H_3)

3.11 (s, 3H, H_{12})

3.02 (s, 1H, H_1)

2.88 (s, 4H, H_{11} and H_4)

2.31 (d, *J*= 9.28 Hz, 1H, H_2)

1.75-1.08 (m, 12H, H_7, H_{13}, H_{14} and H_{15})

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

176.0, 137.5, 130.2, 70.1, 57.9, 49.5, 47.0, 45.0, 43.5, 39.0, 38.8, 38.3, 36.6, 26.2, 22.2, 21.9.

3.11. **Synthesis of (2*S*,*3R*)-2-(*N*,*N*-dimethylaminomethyl)-3-(cyclohexylhydroxy-methyl)-bicyclo[2.2.1]hept-5-ene, 60**

To a suspension of $LiAlH_4$ (0.088 g, 2.3 mmol) in THF (10 mL) was added a solution of amide alcohol 56 (0.3 g, 1.14 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 6 h and hydrolized by the cautious addition of water at 0°C. The fine white precipitate which formed was washed with THF and discarded. The crude product was purified by column chromatography (EtOAc) to give amino alcohol 60 (0.135 gr, 52 %)

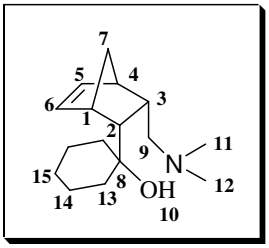


Figure 23

$[\alpha]_D^{20}$= 3.74 (c 2.16 $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm

6.15 (q, *J*= 3.08, 5.70 Hz, 1H, H_5)

5.95 (q, *J*= 2.70, 5.70 Hz, 1H, H_6)

2.75 (bs, 1H, H_{10})

2.62- 2.55 (m, 2H, H_1 and H_9)

2.39 (t, *J*= 12.83 Hz, 1H, H_9)

2.25 (dd, *J*= 2.84, 2.42 Hz, 1H, H_2)

2.15 (bs, 6H, H_{11} and H_{12})

2.12 (s, 1H, H_4)

1.99 (dd, *J*= 2.84, 2.39 Hz, 1H, H_3)

1.79- 1.16 (m, 6H, H_{13} and H_{14})

1.12 (dd, *J*= 3.93, 3.95 Hz, 2H, H_7)

1.07- 0.95 (m, 4H, H_{14} and H_{15})

^{13}C NMR (400 MHz, $CDCl_3$): δ ppm

136.7, 133.9, 71.9, 61.5, 57.2, 51.3, 47.6, 46.0, 44.6, 41.8, 39.9, 36.1, 26.1, 22.0, 21.4

3.12. General procedure for diethylzinc addition reactions

Ligand (0.05 mmol) was dissolved in toluene (or hexane) (5 mL) at room temperature under argon atmposphere and diethylzinc (1.0 mmol, 1 M in hexane) was added to this solution. The mixture was stirred for 30 minutes , then cooled to 0 ^oC. Benzaldehyde (0.5 mmol) was added to the mixture and the reaction mixture was stirred for 48 h at 0 ^oC . After adding 1 M HCl (10 mL), it was extracted with ethyl acetate (25 mL). Then the organic phase was dried over $MgSO_4$ and the solvent was evaporated to give the corresponding alcohol. HPLC-analysis of 1-phenyl-1-propanol: Chiralcel OD-H at room temperature, *n*-hexane/2-propanol = 98:2, 1.0 mL/min, 254 nm, t_1= 14.3 min (*R*), t_2= 16.7 min (*S*).

CHAPTER 4

CONCLUSION

A series of new chiral norbornene-based 1,4-aminoalcohols (2*R*,3*S*)-**57**, (2*R*,3S)-**58**, (2*R*,3*S*)-**59** and (2*S*, 3*R*)-**60** were synthesized successfully by using chemoselective methods. These 1,4-aminoalcohols were also used as chiral ligands in the asymmetric diethylzinc addition reaction to benzaldehyde. All the ligands showed selectivity toward benzaldehyde. The ligand **60** showed the highest enantioselectivity towards the benzaldehyde over the others and gave moderately good enantiomeric excess values (69%). The optimized condition for the solvent and temperature was found to be hexane and 0°C for the ligand **60**.

These 1,4-aminoalcohols were only used in asymmetric diethylzinc addition reaction to benzaldehyde. In the future they may be used as ligands toward aldehydes other than benzaldehyde and they can also be used in various asymmetric transformation reactions such as Diels-Alder, Aldol, and hydroboration reactions.

In the future these types of chiral ligands may be used in the synthesis of reusable macro molecules by the ring opening metathesis polymerization reaction with the usage of Grubbs catalyst.

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APPENDIX A

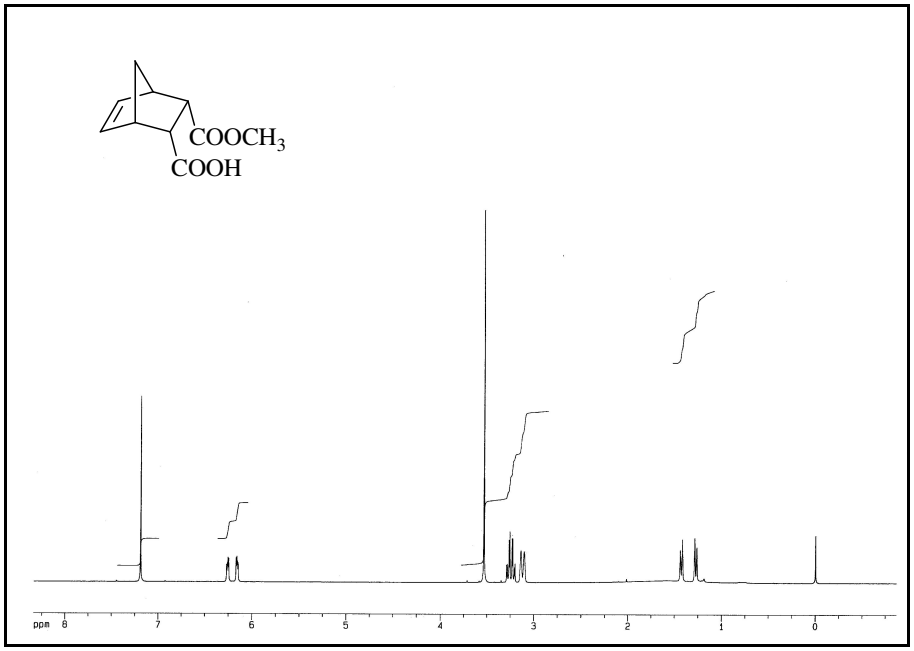

Figure 24. ^{1}H- NMR Spectrum of **51**

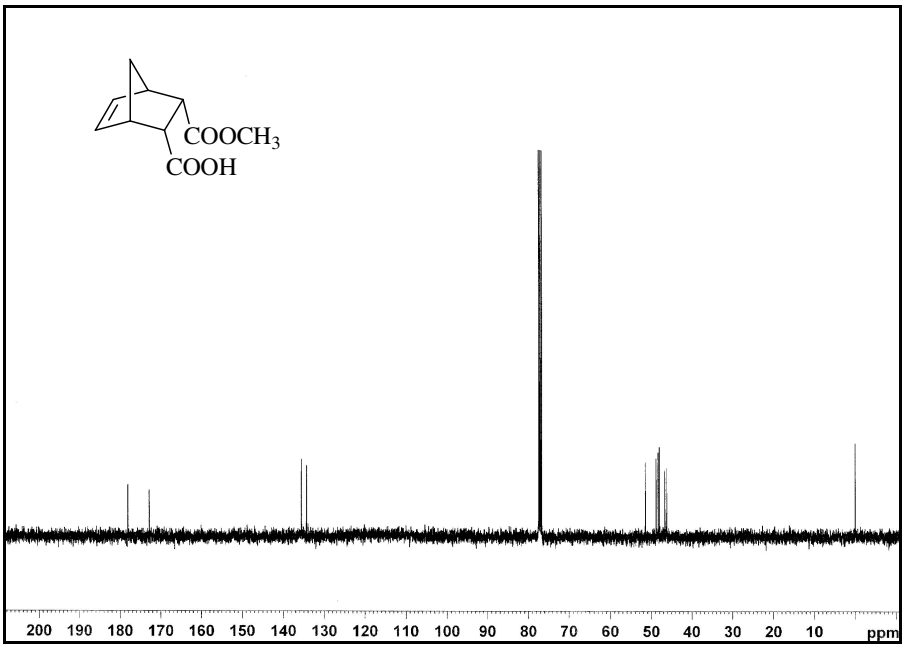

Figure 25. ^{13}C-NMR Spectrum of **51**

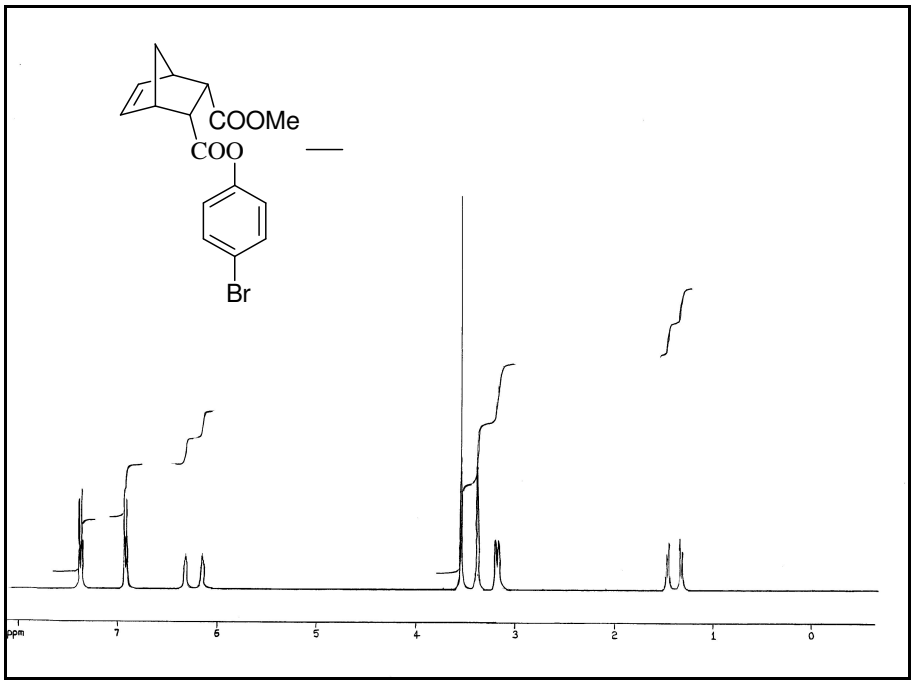

Figure 26. ^{1}H- NMR Spectrum of **61**

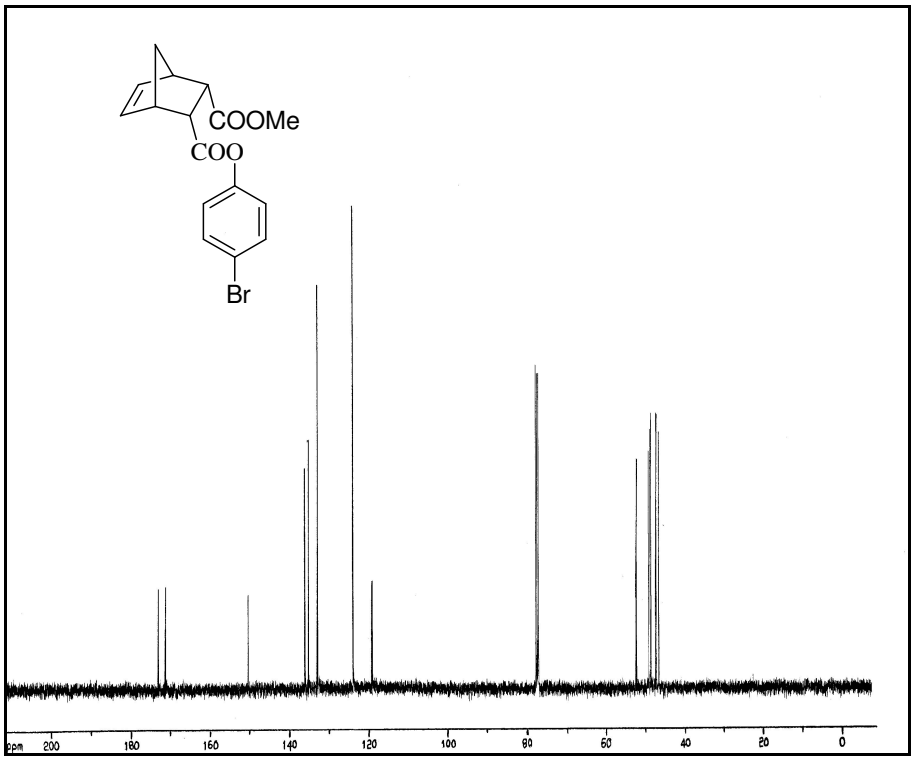

Figure 27. ^{13}C-NMR Spectrum of **61**

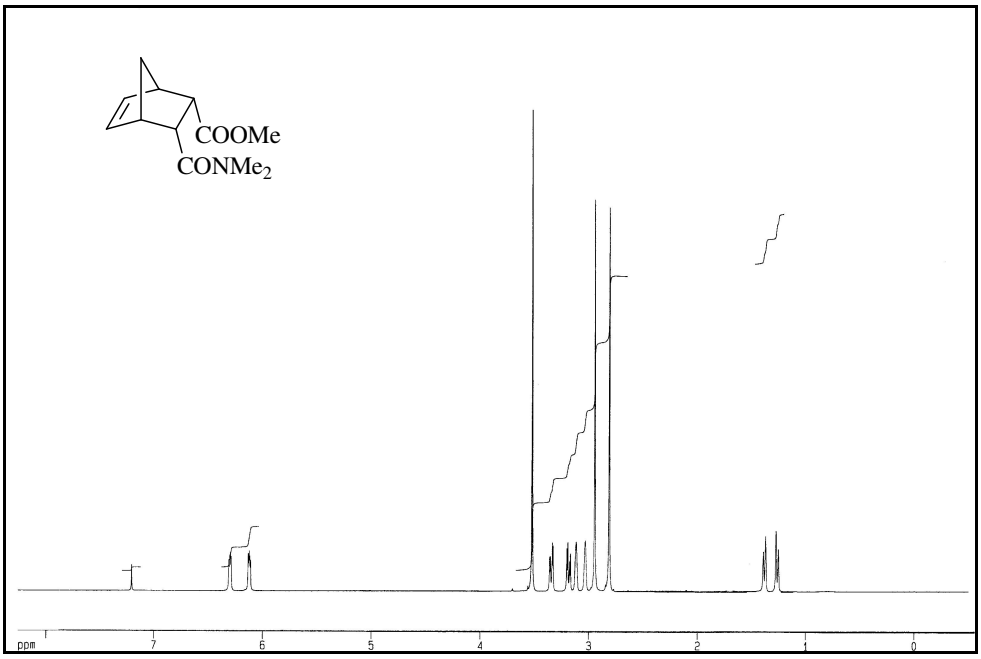

Figure 28. ^{1}H- NMR Spectrum of **52**

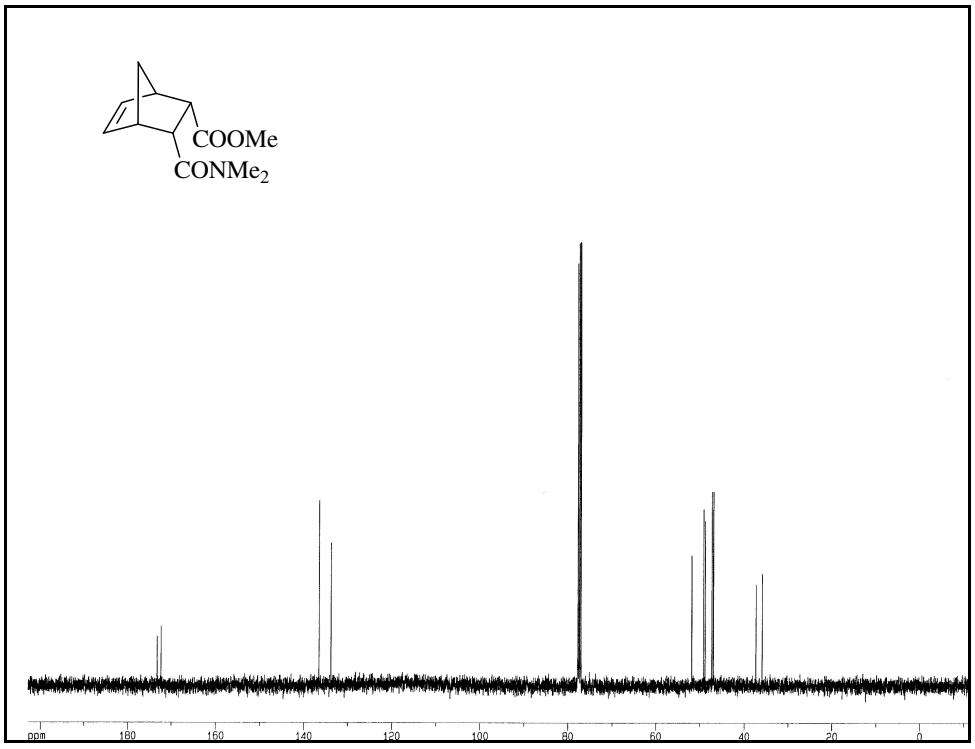

Figure 29. ^{13}C-NMR Spectrum of **52**

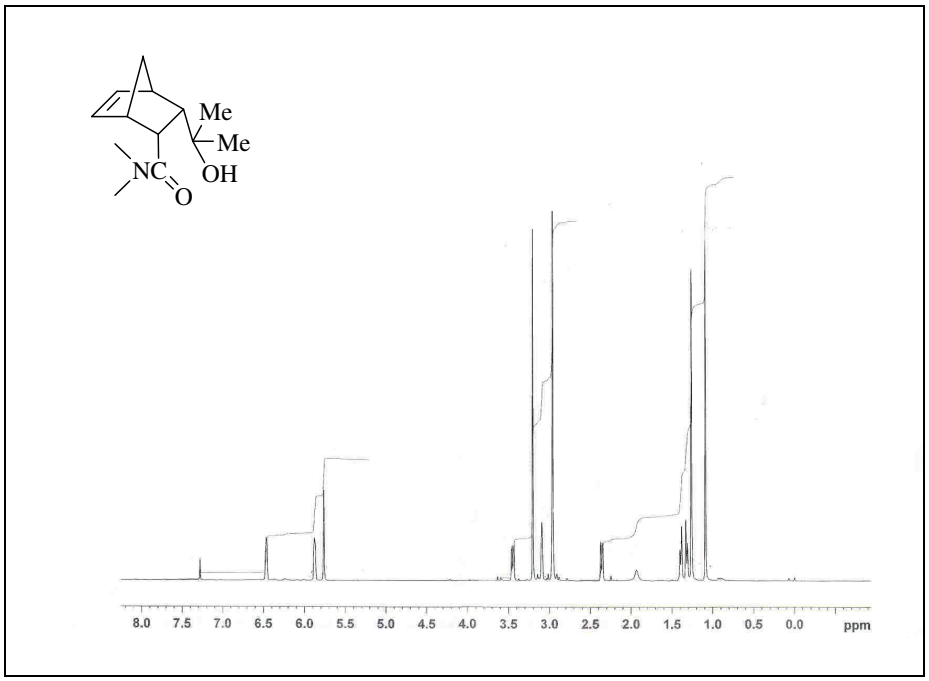

Figure 30. ^{1}H- NMR Spectrum of **53**

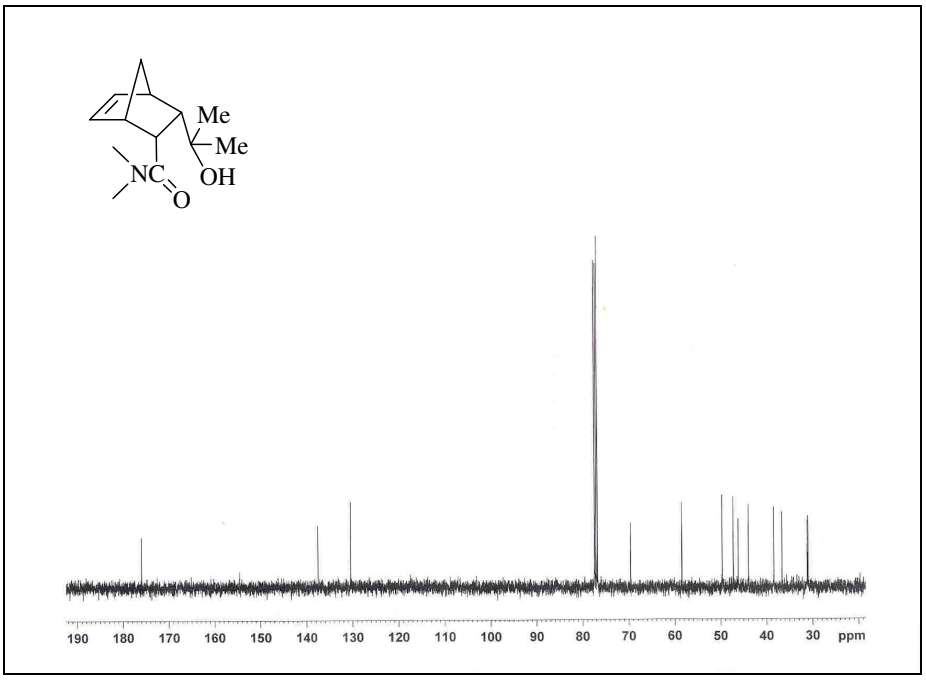

Figure 31. ^{13}C-NMR Spectrum of **53**

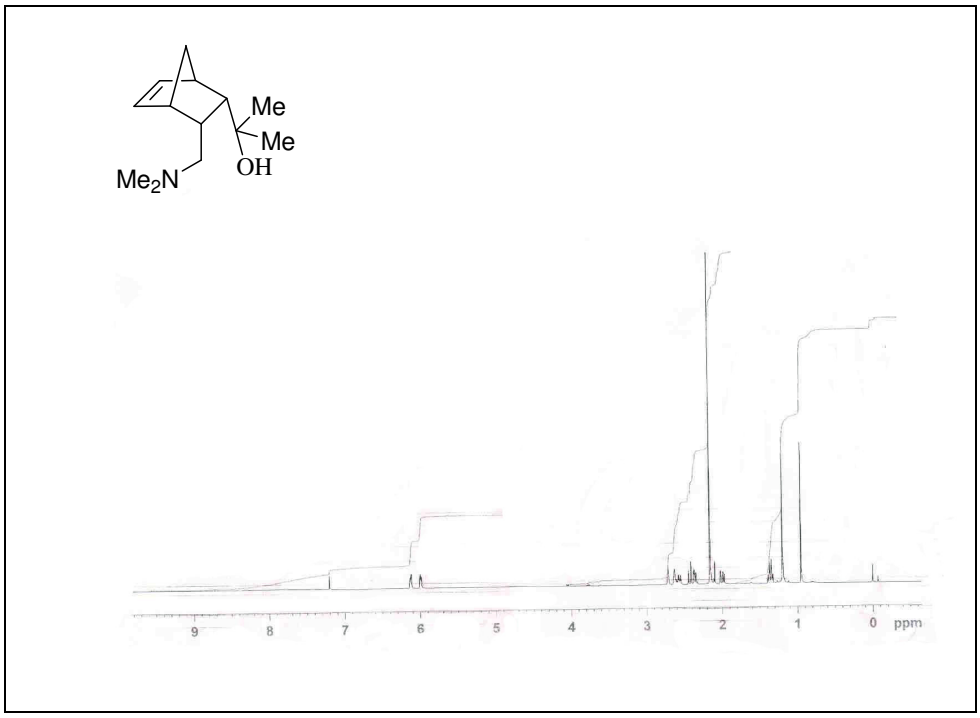

Figure 32. ^{1}H- NMR Spectrum of **57**

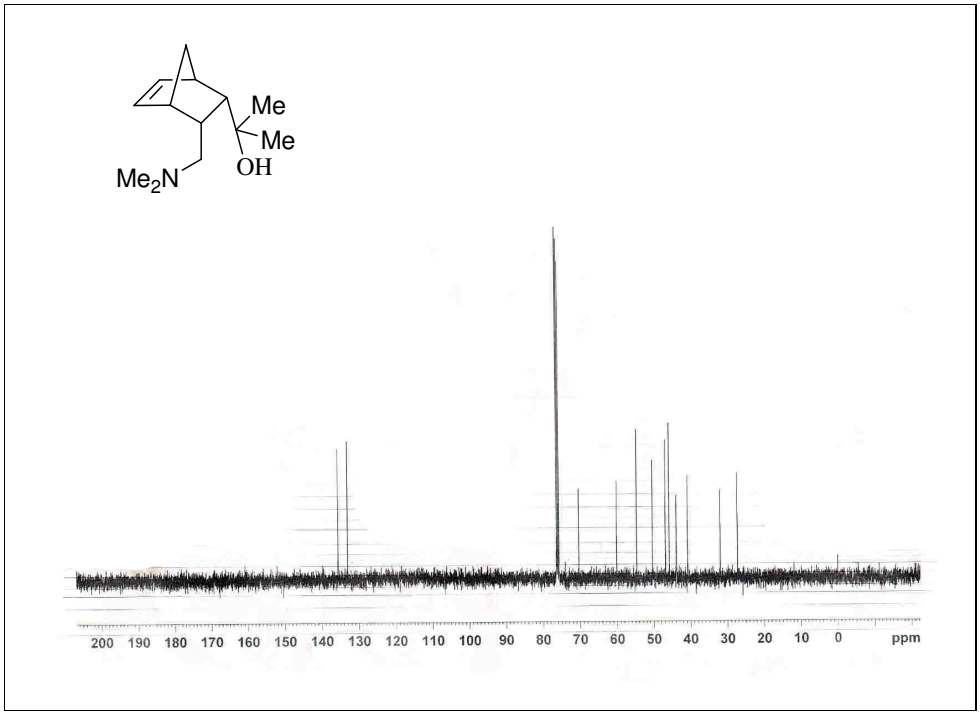

Figure 33. ^{13}C-NMR Spectrum of **57**

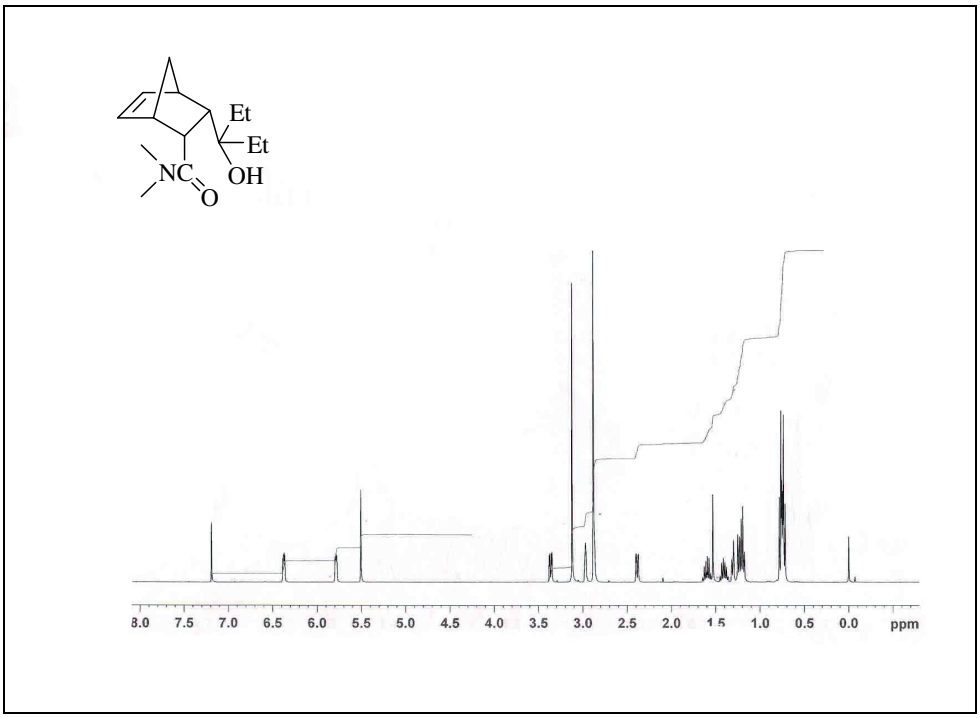

Figure 34. ^{1}H- NMR Spectrum of **54**

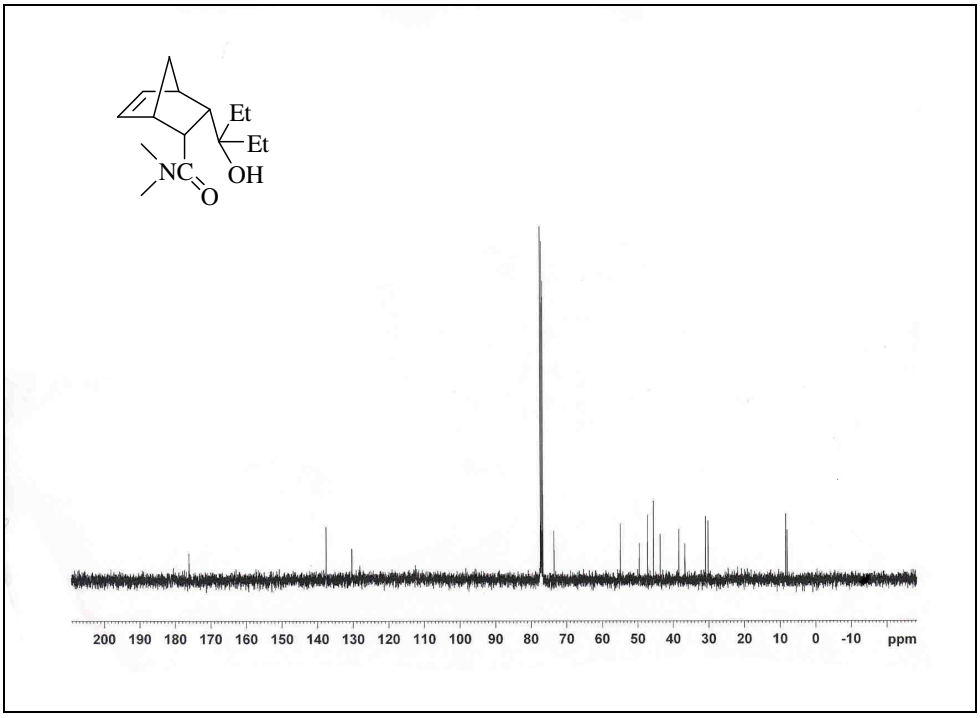

Figure 35. ^{13}C-NMR Spectrum of **54**

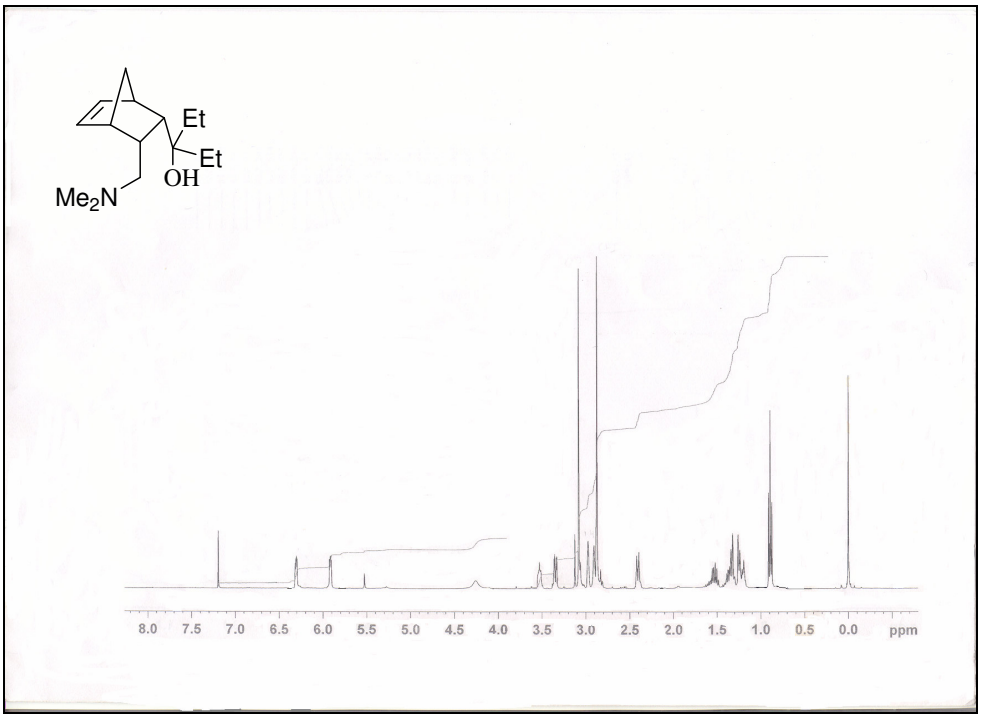

Figure 36. ^{1}H-NMR Spectrum of **58**

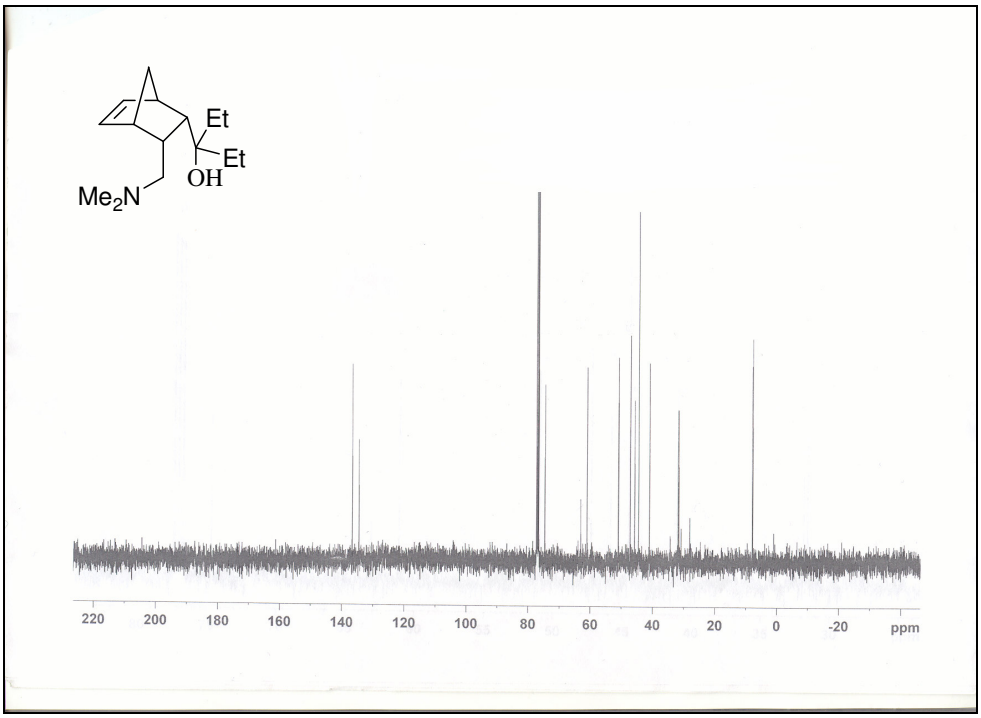

Figure 37. ^{13}C-NMR Spectrum of **58**

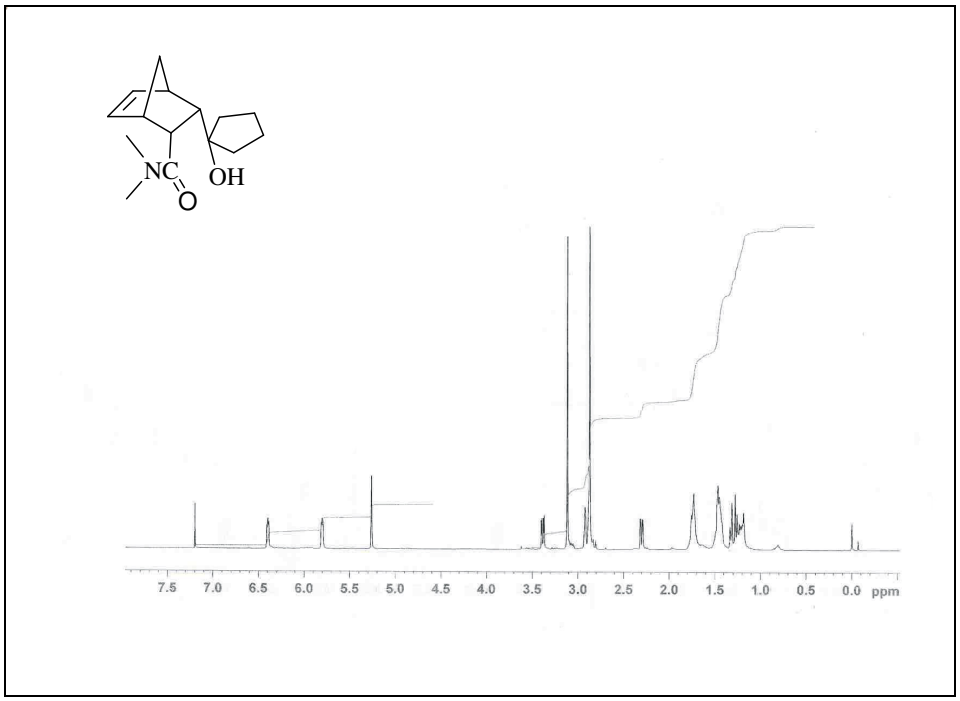

Figure 38 ^{1}H- NMR Spectrum of **55**

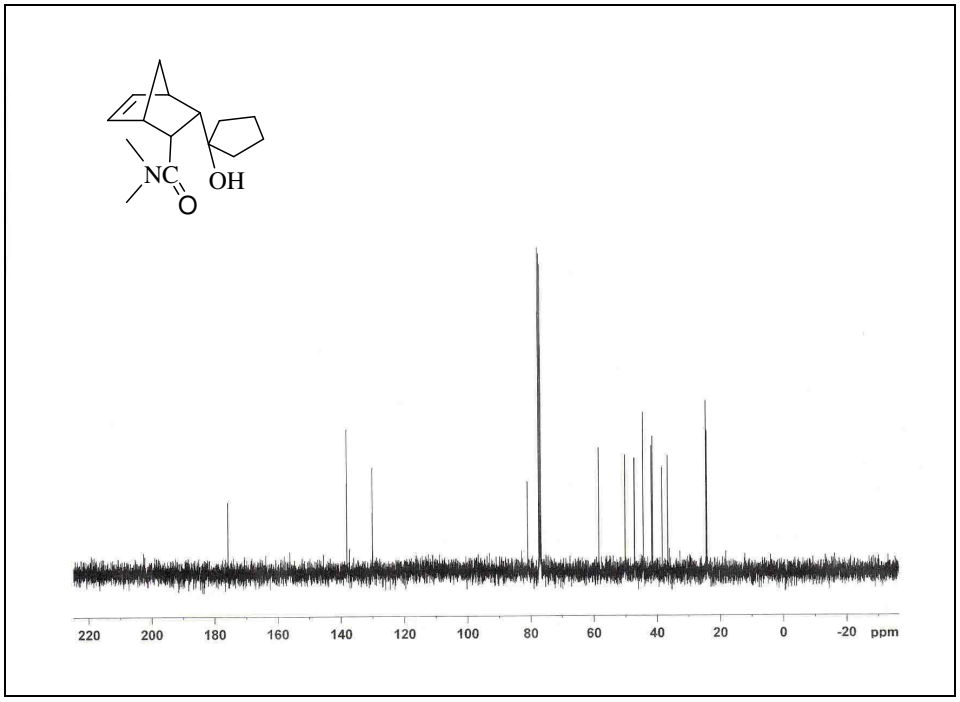

Figure 39. ^{13}C-NMR Spectrum of **55**

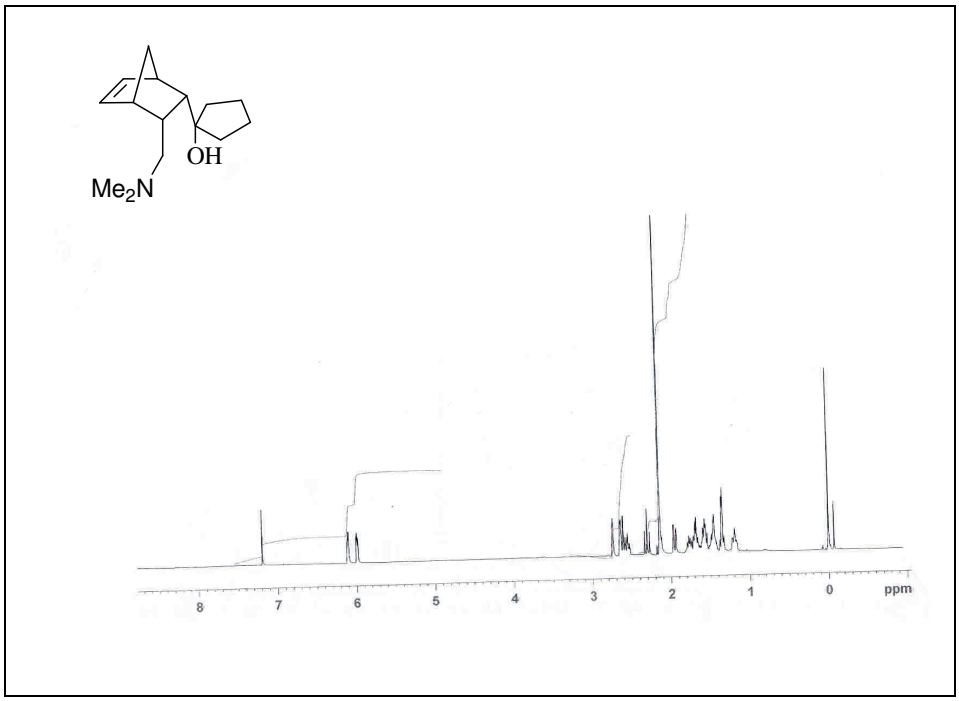

Figure 40. ^{1}H- NMR Spectrum of **59**

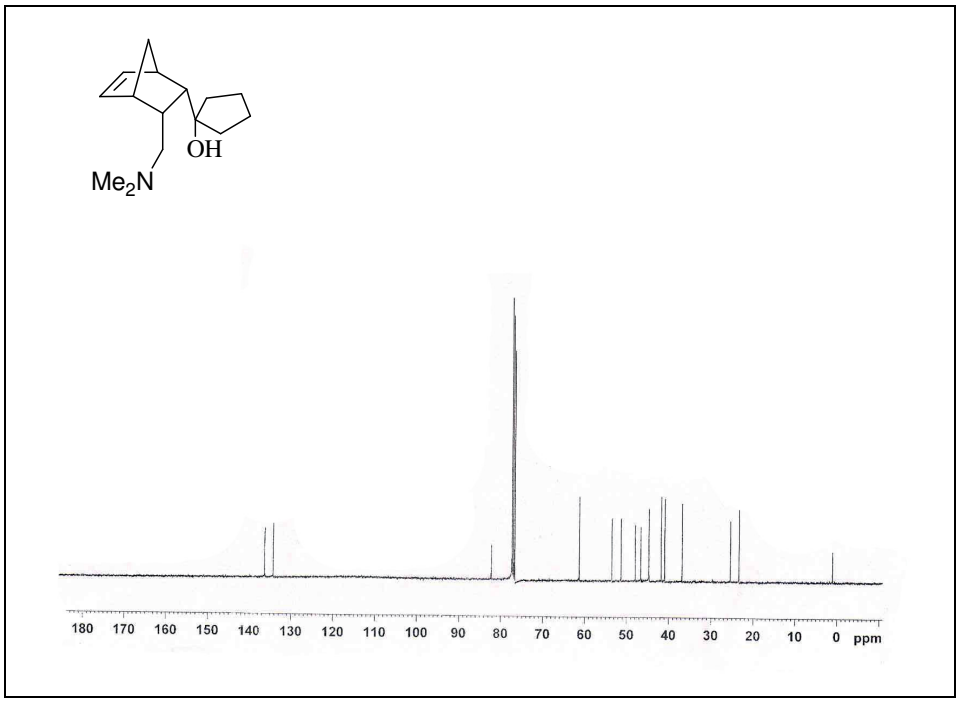

Figure 41. ^{13}C-NMR Spectrum of **59**

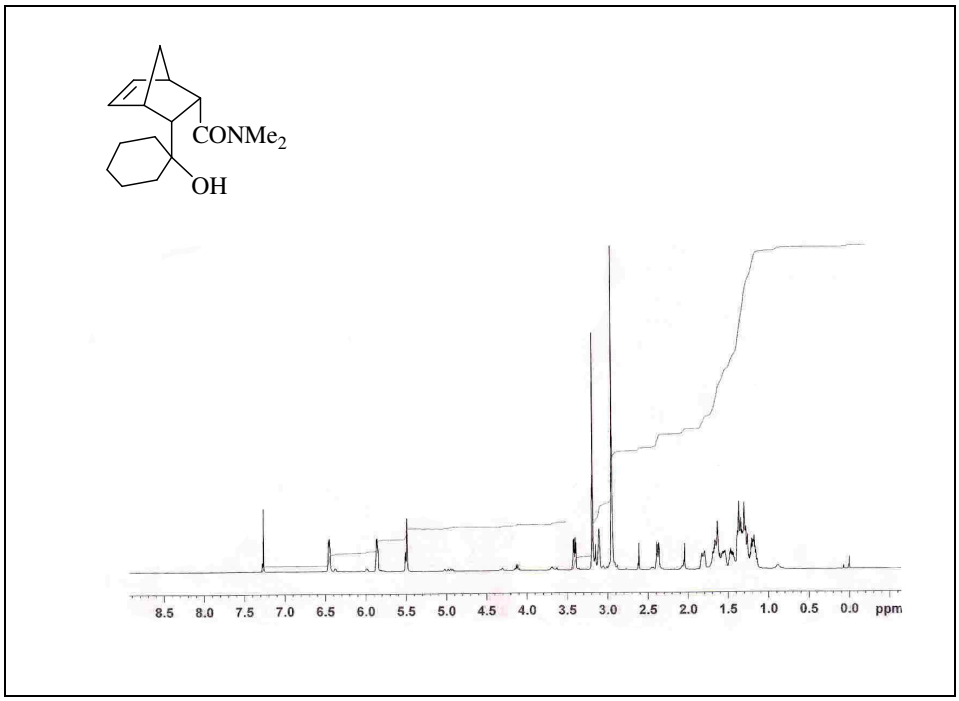

Figure 42. ^{1}H- NMR Spectrum of **56**

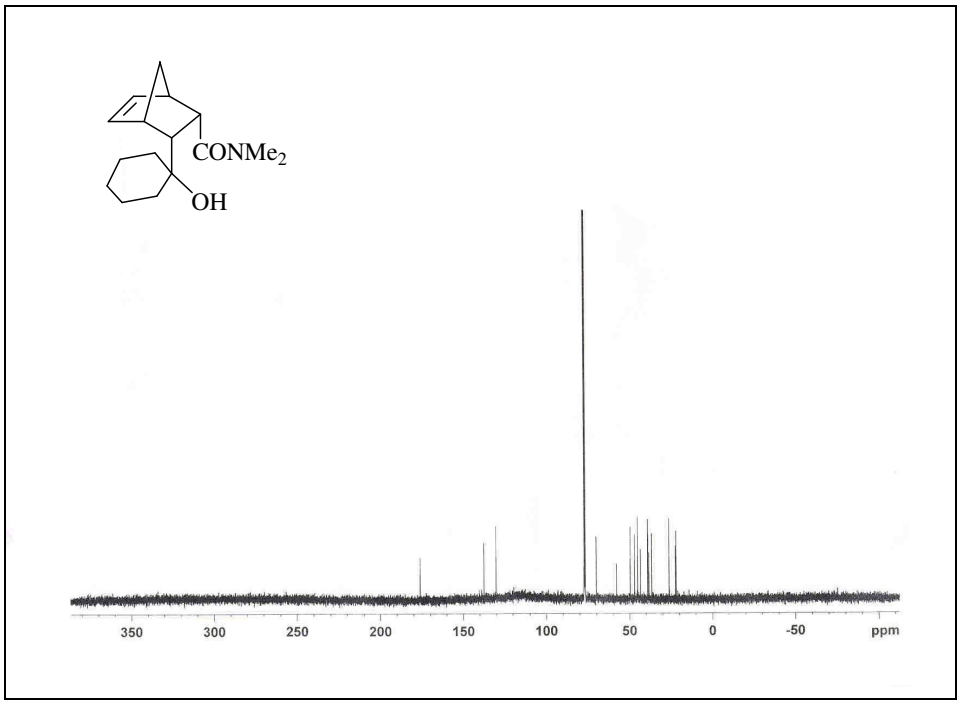

Figure 43. ^{13}C-NMR Spectrum of **56**

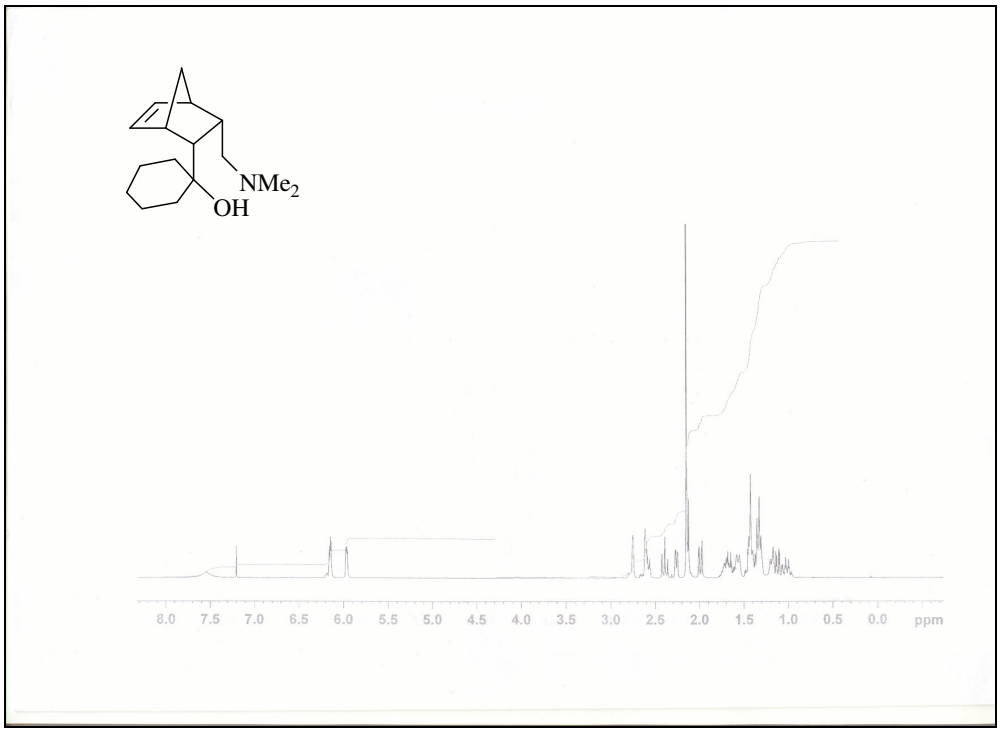

Figure 44. ^{1}H-NMR Spectrum of **60**

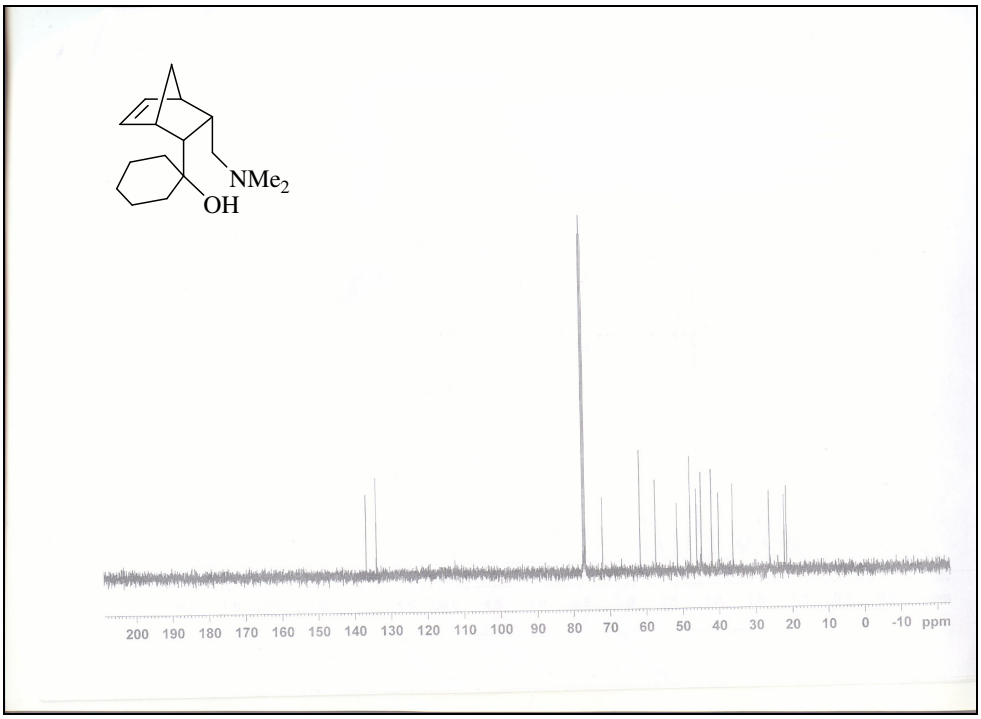

Figure 45. ^{13}C-NMR Spectrum of **60**