ASYMMETRIC SYNTHESIS OF N-ARYL SUBSTITUTED CHIRAL 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN VARIOUS ASYMMETRIC TRANSFORMATION REACTIONS

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

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ABSTRACT

ASYMMETRIC SYNTHESIS OF N-ARYL SUBSTITUTED CHIRAL 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN VARIOUS ASYMMETRIC TRANSFORMATION REACTIONS

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June 2007, 102 pages

The asymmetric synthesis of N-aryl substituted chiral 1,4-aminoalcohols and their applications in asymmetric borane reduction and enantioselective diethylzinc addition to benzaldehyde reactions were performed starting from *meso*-anhydride **51** that is the cycloadduct of cyclopentadiene and maleic anhydride. The desymmetrization of *meso*-anhydride **51** was achieved by using quinine or quinidine with very high enantiomeric excess value (up to 98% ee) and with high chemical yield. The quinine-mediated desymmetrization of *meso*-anhydride **51** with methanol gave (2*S*,3*R*)-(-)-*cis*-monoester **52**. The hemiester was subjected to chemoselective amidation with various types of *N*-aryl substituted amines and then, it was treated with LAH and followed by hydrogenation in the presence of palladium catalyst to get the chiral 1,4-amino alcohols. The catalytic effectiveness of these chiral 1,4-amino alcohol ligands, (2*S,*3*R*)-**60**, (2*S*,3*R*)-**61**, (2*S*,3*R*)-**62** and (2*S,*3*R*)-**63** were examined in asymmetric borane reduction and enantioselective diethylzinc addition to benzaldehyde reactions.

Keywords: Amino alcohol, chiral ligand, asymmetric reaction, borane reduction, diethylzinc addition

ÖZ

N-AROMATİK SÜBSÜTİENTLİ KİRAL 1,4-AMİNOALKOL TÜREVLERİNİN ASİMETRİK OLARAK SENTEZİ VE ÇEŞİTLİ ASİMETRİK TRANSFORMASYON REAKSİYONLARINDA KULLANIMI

ODABAŞ, SERHAT

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Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Haziran 2007, 102 sayfa

N-Aril sübstitüe kiral cis-1,4-amino alkollerin asimetrik olarak sentezi ve kiral ligand olarak asimetrik boron indirgeme ve enantiyoseçici dietilçinko katılma reaksiyonlarındaki uygulamaları; siklopentadien ve maleik anhidritin siklokatılma ürünü *meso*-anhidrit **51**'den başlanarak tamamlanmıştır. Anhidritin, kinin ortamında metanolle verdiği desimetrizasyon tepkimesi sonucunda (2*S*,3*R*)-(-)-*cis*-monoester **52** bileşiği yüksek seçicilik (98 % e.e.) ve yüksek verimle elde edilmiştir. Bu bileşik N-arilamin türevleri ile kemoseçici amidasyon tepkimelerine sokulmuş ve LAH ile indirgenmiştir. Ardından Pd katalizörlüğünde hidrojenleme tepkimesine sokularak kiral ligandlar elde edilmiştir. Sonuç olarak, sentezlenen kiral ligandların, (2*S,*3*R*)-**60**, (2*S*,3*R*)-**61**, (2*S*,3*R*)-**62** ve (2*S,*3*R*)-(+)-**63,** kiral katalizör etkileri asimetrik boron indirgeme ve enantiyoseçici dietilçinko katılma reaksiyonlarında incelenmiştir.

Anahtar Kelimeler: Amino alkol, kiral ligand, asimetrik tepkime, boron indirgemesi, dietilçinko katılması

To My Family

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THF: Tetrahydrofurane

DCC: Dicyclohexylcarbodiimide

DMAP: 4-Dimethylaminopyridine

DCM: Dichloromethane

LAH: Lithium aluminum hydride

CHAPTER 1

INTRODUCTION

1.1. Importance of Asymmetry

Organic compound play an important part in modern life, not at least in the area of pharmaceuticals, agrochemicals, and other materials, which possess biological activity [1]. Symmetry and asymmetry relations play an important role in almost all physical sciences, especially in chemistry and physics. According to the definition of Hermann Weyl, an object is symmetrical, if one can subject it to an operation and it appears exactly the same after the operation as before [2]. A chemist usually deals with the symmetry of molecules with respect to chirality, or left and right handedness.

In 1848, Louis Pasteur achieved to resolve the ammonium sodium tartrate into its enantiomers [3] and it can safely be stated that the huge developments that occurred in the field of asymmetric synthesis during the 20^{th} century rose on the shoulders of Pasteur's discoveries [4]. Now, with the help of the recent discoveries, the universe seems to possess asymmetry with respect to chirality at all levels [5] confirming Pasteur's famous statement, "L'universe est dissymetrique".

Chirality is a fundamental property of many three-dimensional objects. An object is chiral if it cannot be superimposed on its mirror image. 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. To take a simple example, tartaric acid can be obtained in two forms or enantiomers, (+)-tartaric acid

and (-)-tartaric acid in (Figure 1), which are clearly enantiomeric in that they are related as mirror images that cannot be superimposed on each other.

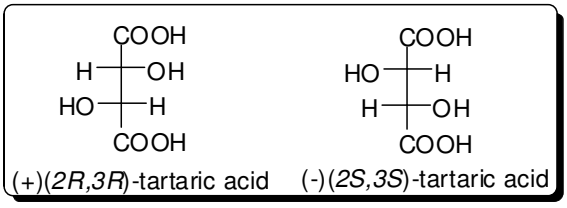


Figure 1. The two enantiomers of tartaric acid

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

Examples of property differentiation within enantiomer pairs are numerous and often dramatic. A selection is given is in Figure 2.

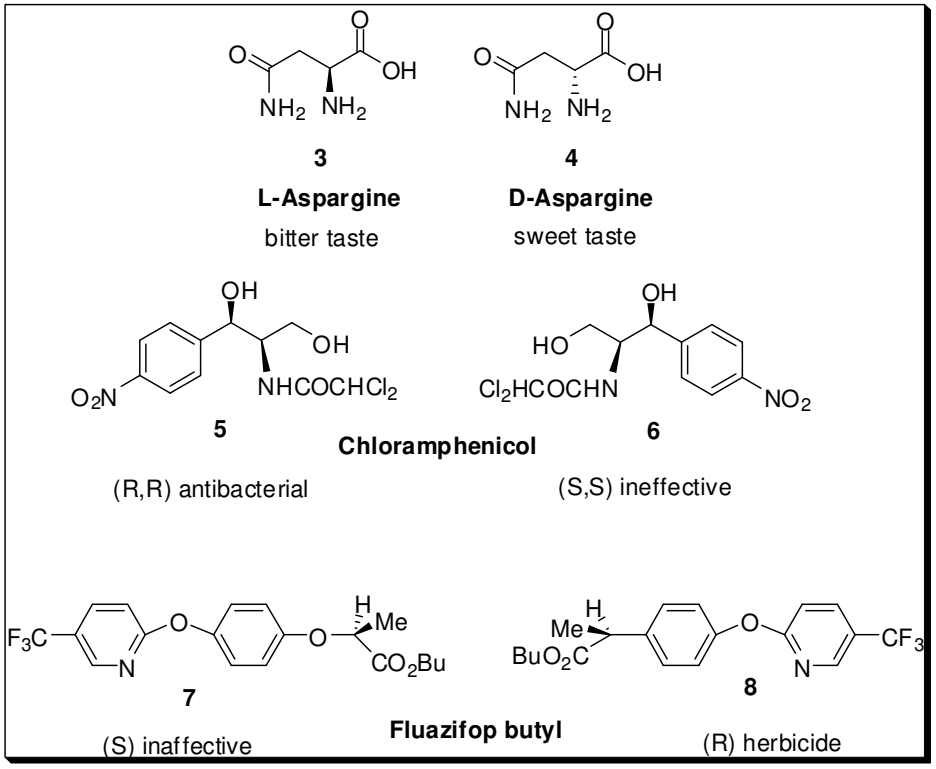


Figure 2. Examples of the Different Behaviours of Enantiomers

From a pharmacological point of view, the situation is very similar. More than half of all useful drugs appear to exist in enantiomeric forms and generally, one of these enantiomers is much more effective than its mirror image enantiomer, exhibiting a better fit to its receptor. For example, the S enantiomer of methacholine, a parasymphathomimetic drug, is over 250 times more potent than the R enantiomer. Penicillamine, ketamine, timolol and the well-known drug thalidomide, can be given as further examples to chiral drugs whose enantiomers exhibit different pharmacological effects (Figure 3). Furthermore, the more active enantiomer at any receptor type may be less active at another type. Carvedilol, is such an example: Its S enantiomer is a potent beta receptor blocker, while the R enantiomer is 100-fold weaker at the beta receptor. However, both enantiomers are approximately equipotent as alpha receptor blockers [6].

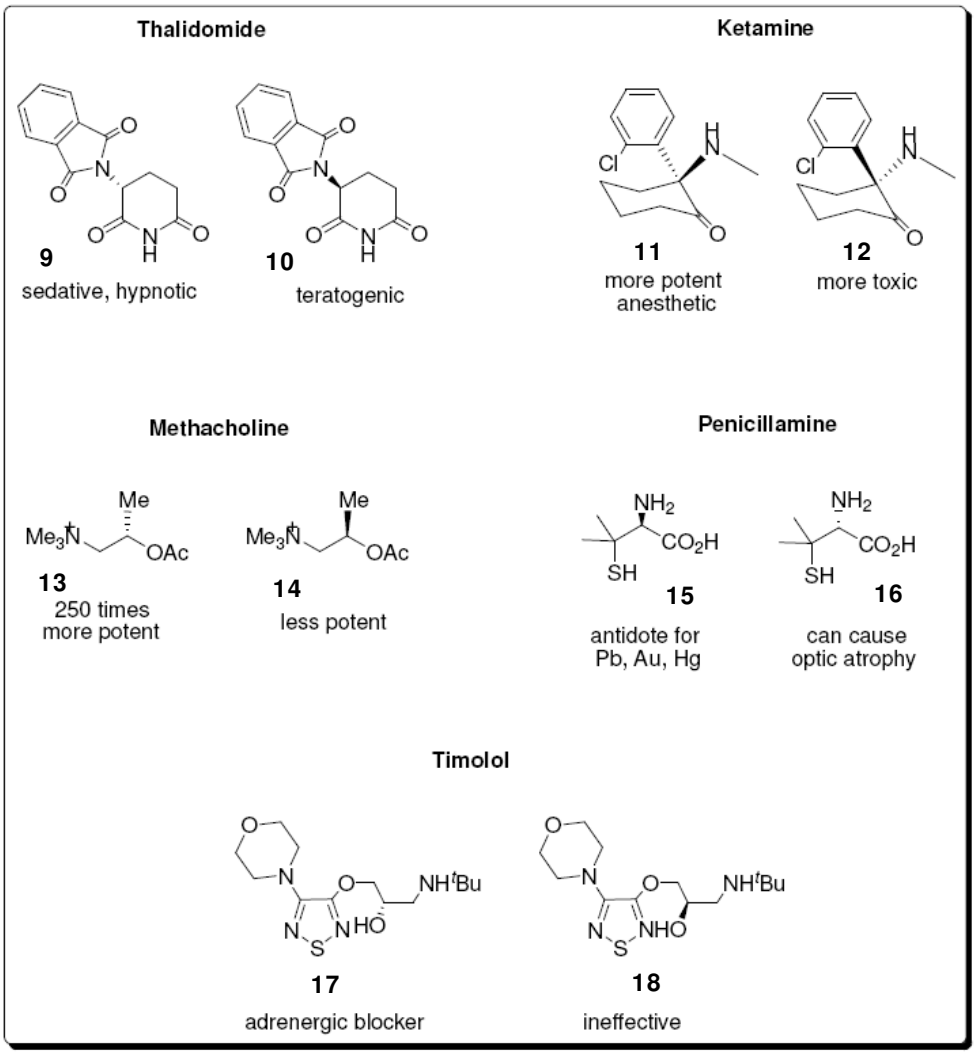


Figure 3. The structures and pharmacological effects of the enantiomers of some biologically active chiral molecules

1.2. Asymmetric Synthesis

There are many definitions of asymmetric synthesis but most are unwieldy to state [7]. The asymmetric synthesis has been used to describe a wide variety of transformations.

In its original definition, coined by Marckwald in 1904, asymmetric synthesis was described as the process for the formation of optically active compound through reaction of an achiral substrate with a chiral reagent. This definition was expanded by Morrison and Mosher in 1971 to cover wider range reactions. Their definition describes asymmetric synthesis as a reaction where an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the streoisomeric products are formed in unequal amounts [8].

Asymmetric synthesis has become more and more important in research and industry, which is partly due to the always increased need for enantiopure chiral drugs. This leads to a strong and fast growing range of new chiral building blocks, chiral catalysts and the increased use of chiral biotransformations in organic synthesis.

In general, there are three routes to enantiopure compounds (Figure 4). They can be obtained from the chiral pool, from prochiral substrates or from a racemic mixture [9], [10].

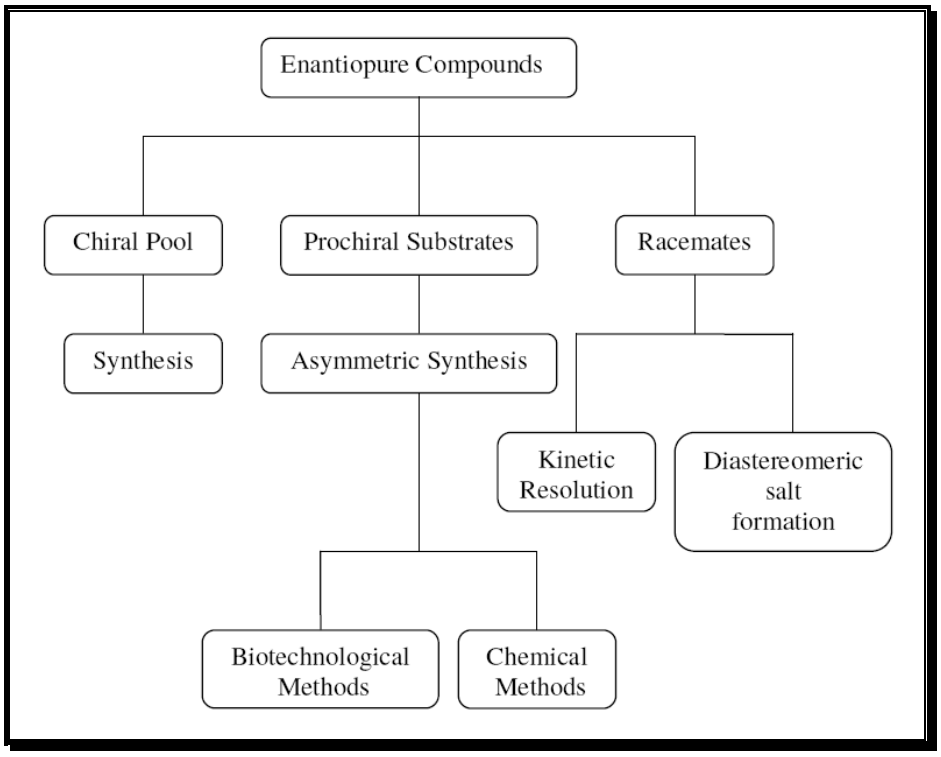


Figure 4. How to obtain enantiopure compounds

1.3. Chiral pool

An economical way of making compounds as single enantiomers is to manufacture them using an enantiomerically pure natural product as a starting material [11]. These 'synthons' are transformed into the desired product via synthetic methods. Examples of chiral synthons from nature are amino acids, carbohydrates and terpenes. Clearly, all transformations should be carried out with high stereoselectivity in order to maintain the original enantiomeric or diastereomeric purity. The natural compound is used stoichiometrically and the stereochemistry of the starting material determines the stereochemistry of the product which is a limitation of this approach as one can only synthesize one of the enantiomers.

1.4. General Methods for Asymmetric Synthesis

In order to obtain enantioselective synthesis, at least one of the agents in the system must be chiral. Asymmetric synthesis involves the introduction of chirality by action of a chiral reagent, auxiliary or catalyst which is not incorporated in the final product. This process is probably the choice which provides the widest of possibilities [8].

A molecule is said to be prochiral if it can be converted to a chiral molecule in a single reaction step. If a carbon atom is sp^2-hybridized and bears three different substituents, the two sides of the carbon available for addition of a fourth substituent are prochiral. A tetrahedral carbon with two identical substituents is prochiral and replacement or change of one of these substituents leads to a chiral compound. Prochirality can only be recognized in a chiral operation.

Mainly there are two methods for asymmetric synthesis; chemical and biotechnological.

1.4.1. Chemical Methods

In order to prepare optically pure compounds through synthesis, chemists make use of either reagent-controlled (chiral reagents, chiral catalysts) or substrate controlled (chiral substrates, chiral auxiliaries) conditions [12].

1.4.2. Chiral Reagents

In this approach, the prochiral substrate is treated with a chiral reagent in order to obtain enantiomerically enriched product. The chiral reagent is used stoichiometrically which is usually rather costly. In many ways, this is the approach of choice as nature utilizes this methodology through enzymes.

The reagent must be selective both in terms of induction and functional group specificity. The need for protection should be carefully considered as this could lead to the introduction of extra steps [13].

1.4.3. Chiral Substrates

In the chiral substrate case the stereoselection of the reaction is controlled after having a chiral starting material in the beginning. Nature produces chiral compounds that make up the "chiral pool". This approach is often limited to the amount of the natural product available and its price. With a chiral starting material in hand, a well-designed synthesis should then reduce to the control of relative stereochemistry, the natural product's chirality inducing the appropriate stereochemistry at the new center(s).

1.4.4. Chiral Auxiliaries

As it stated in the previous sections the number of useful natural products available is not large, or the number of steps necessary to convert a cheap, readily available one to a useful intermediate in a synthesis may require many steps [11].

Though, a number of chiral groups have been developed that can be attached to an achiral molecule. These groups then induce selectivity through a subsequent chemical reaction to afford diastereoselectivity. Removal of chiral auxiliary then provides the product enriched in one enantiomer. However, this type of approach introduces two extra steps; the attachment and removal of the auxiliary. A good chiral auxiliary should be recovered at the end of the sequence so that they can be reused.

1.4.5. Chiral Environments

It is possible to make the environment of a chemical reaction chiral. The majority of examples in this class are chiral solvents and chiral additives.

1.4.6. Chiral Catalysts

On using a catalyst, two diastereomeric transition states are involved and an excess of one product will be delivered via the lowest energy transition state. Often transition metal catalysts are used and these have the advantage that the catalyst properties can be carefully tuned by changing the ligands around the metal atom. There are some examples of important chiral catalyst shown in the Figure 5.

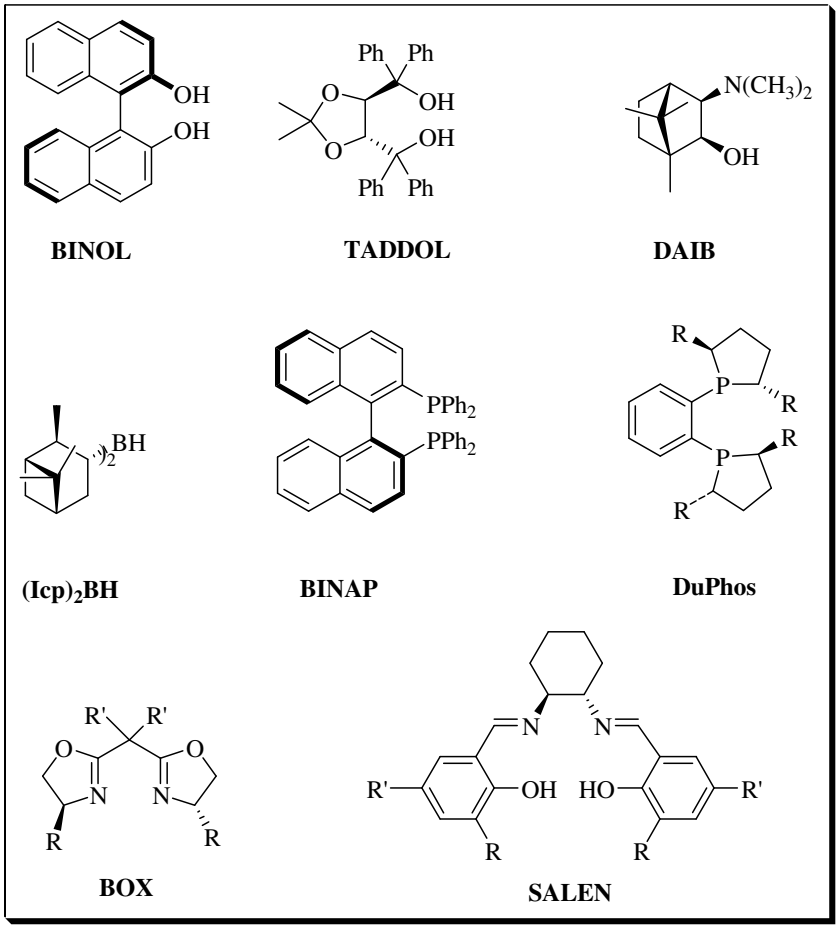


Figure 5. Some important chiral ligands

1.4.7. Biotechnological methods

Apart from chemical methods; biological transformations using enzymes, cell cultures, or whole microorganisms are also practical and powerful means of access to enantiomerically pure compounds from prochiral precursors, even though the scope of such reactions is limited due to the highly specific action of enzymes. Enzymes are chiral molecules and their active sites include chiral molecules. Lock and key model is the main principle of enzymes and according to this rule only right handed or left handed product is formed [14].

The “Lock and Key” mechanism is the first proposal for a general mechanism of enzymatic action which was developed by E. Fischer in 1894. According to this mechanism, an enzyme acts as a lock, while the substrate acts as a key [15].

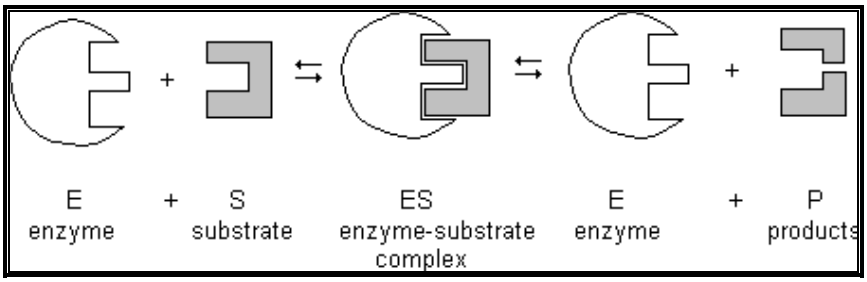


Figure 6. “Lock and Key” Model

1.4.8. Kinetic Resolution

In this approach a substrate is acted on by a chiral agent to produce one enantiomer or diastereomer of the product at a much faster rate than the other isomer. The transition states have to be of significant energy difference for this method to be viable. It is an economical way but with less satisfactory. The attractiveness of this method is diminished by the fact that a maximum 50 % yield can be obtained. A further disadvantage is that the other enantiomer often ends up in waste [16].

1.4.9. Diastereomeric Salt Formation

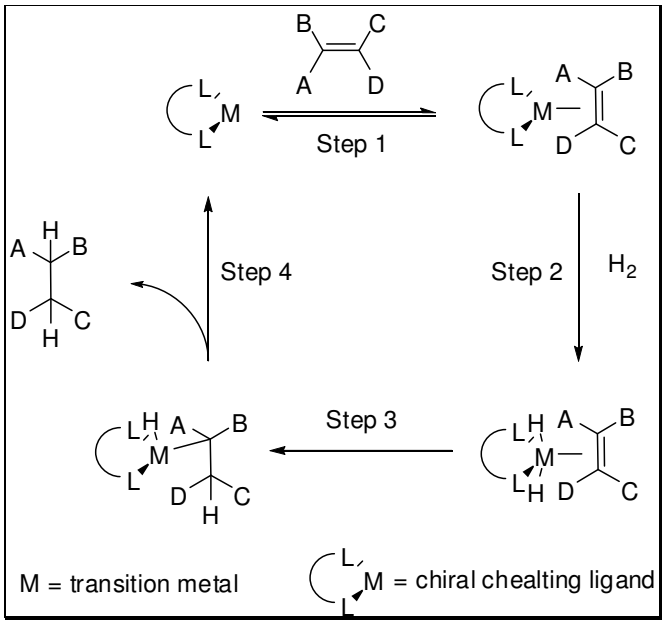
Resolution of a racemic pair is most generally carried out by formation of a diastereomeric derivative, which can then be separated by virtue of some differences in physical properties. Most generally this is a difference in solubility of a crystalline derivative such as an alkaloid salt, but differences in boiling point; in chromatographic adsorption, as well as in gas chromatographic retention times can be employed. A common way is allowing the solution of racemic mixture in

methanol or water react with a pure enantiomer, thereby forming a mixture of diastereomers that can be separated by crystallization [17].

1.5. Asymmetric Transformation Reactions

1.5.1. Asymmetric Catalytic Hydrogenation Reactions

Asymmetric hydrogenation has been studied intensively for a relatively long time [18]. In its usual form the reaction involves the addition of hydrogen to a double bond in the presence of a transition metal catalyst and a chiral, non-racemic ligand. As with many enantioselective reactions which involve catalysis, a substrate, ligand, metal atom and stoichiometric reagent are all involved in the transition state of the rate determining step. A typical catalytic cycle for asymmetric hydrogenation is shown schematically in Scheme 1.



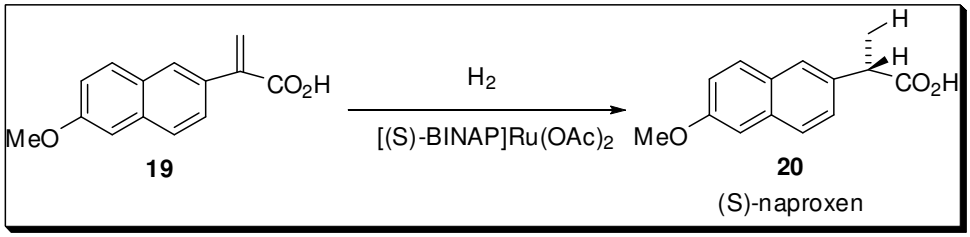
Scheme 1. . Mechanism of asymmetric hydrogenation

In this schematic representation the chiral ligand, usually a chelating diphosphine remains attached to the metal throughout the cycle. The complex binds to the substrate to form intermediate. Oxidative addition of molecular hydrogen to the metal produces, and is followed by hydrogen atom transfer to the substrate to give the product of step 3. Transfer of the second hydrogen atom and subsequent decomplexation of the fully reduced product regenerate the catalyst and completes the cycles [19].

Before 1960s, heterogeneous catalysis was a topic of indisputable importance in chemical research. The first asymmetric reaction was the application of chiral supports in the catalytic dehydrogenation of racemic 2-butanol by Schwab in 1932. Attempts to hydrogenate olefins with the aid of heterogeneous catalysts produced chiral products with only 10-15 % e.e. in the 1950's, it was becoming apparent that heterogeneous catalysts in general were not capable of providing satisfactory results in the hydrogenation of prochiral olefins.

A new approach to asymmetric hydrogenation emerged in the late 1960's. In 1965, Wilkinson discovered a practical homogeneous catalyst, Rh(PPh3)3Cl, which showed very high activity in the hydrogenation of alkenes under mild conditions [20].

Here is a simple example; the asymmetric synthesis of the analgesic drug naproxen (Scheme 2).



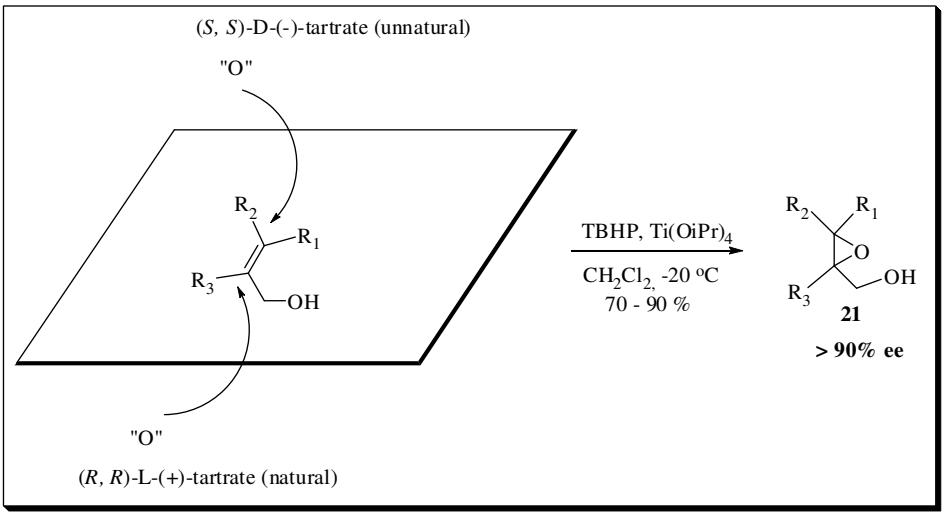
Scheme 2. Synthesis of naproxen

The principle is quite simple; the catalyst selects a single enantiotopic face of the double bond and adds hydrogen across it. In common with many other ligands in asymmetric hydrogenation, BINAP is a chelating diphosphine; the metal sits between the two phosphorous anchored in a chiral environment [21]

1.5.2. Asymmetric Epoxidation

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 [22]. Synthesis of optically active epoxides is the very important objective in organic synthesis

In 1980, a highly enantioselective epoxidation of allylic alcohols was first reported by Katsuki and Sharpless [23]. The Sharpless epoxidation of allylic alcohols by tert-butyl hydroperoxide under catalysis with chiral titanium complexes is a very popular method that has frequently been used in many total organic syntheses of important compounds (Scheme 3).



Scheme 3. Asymmetric Epoxidation

After Sharpless attempt, Jacobsen and Katsuki have suggested a new methodology in the 1990's. They have used catalytic amounts of chiral, C_2-symmetric Mn(III)- salen complexes of general structure of **22** in the presence of a stoichiometric oxidation agent, meanwhile over 100 complexes of this kind have been reported [24]. The most efficient and the most widely used one as mentioned before is N,N-bis(3,5-di-t-butylsalycilydene)-1,2-cyclohexanediamino manganese(III)chloride, the so called Jacobsen catalyst (Figure 7). This complex stable under air and can be stored for long period of time without decomposition [25].

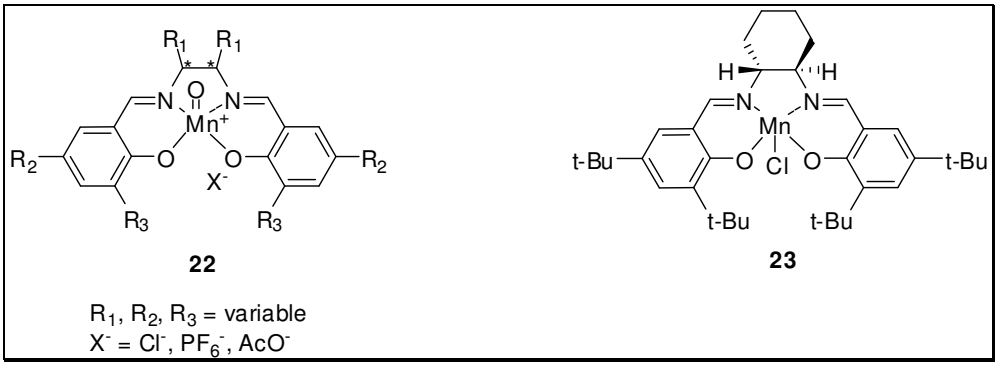
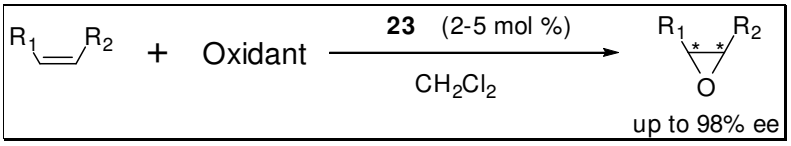


Figure 7. Jacobsen Catalyst for Asymmetric Epoxidation

This complex is currently the most efficient catalyst available for the enantioselective epoxidation of unfunctionalized olefins as well as of conjugated olefins. The method involves 2 to 5 mol % of catalyst in an organic solvent such as CH_2Cl_2. The source of oxygen used can be either aqueous oxidant such as sodium hypochlorite or an organic peracid, for example m-chloroperbenzoic acid [26] (Scheme 4).



Scheme 4. General example for epoxidation reactions

1.5.3. Asymmetric Borane Reduction

Chiral oxazaborolidines catalyze the chiral reduction of prochiral ketones and allow efficient enantioselective preparation of secondary with desired configuration.

Several amine boranes have been found to be highly selective reducing agents for aldehydes and ketones under mild conditions [27]. Their thermal and hydrolytic stability and solubility in a wide variety of solvents are advantages of their usage [28].

Oxazaboralidines derived from chiral β-amino alcohols have proven to be an important class of reagents and catalysts for the enantioselective reduction of prochiral ketones. Corey et al [29] developed CBS process for the asymmetric reduction of prochiral ketones to optically active alcohols with oxazaborolidines. The CBS process is an enantioselective reduction of borane or catecholborane as stoichiometric reductant. The catalyst is an oxazaborolidines that behaves like an enzyme since it binds both the ketone and the hydride and releases them after reduction.

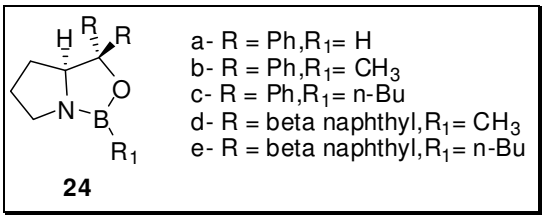
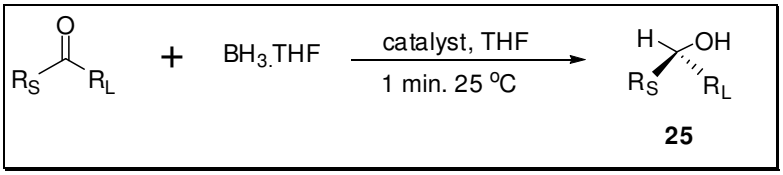


Figure 8. CBS catalyst

A good catalyst for the reduction of ketones is the oxazaborolidine made with R=Ph, R1=H **24a** (Figure 8). It is prepared form (S)-(-)-2-(diphenylhydroxymethyl) pyrolidine by heating at reflux with 3 equivalent BH_3.THF in THF. Up to 100 % chemical and optical yields are obtained with a variety of ketones, and the catalyst precursor is easily recovered upon workup.



Scheme 5. General example for asymmetric borane reductions

In the oxazaborolidine-catalyzed borane reduction, the molecular recognition, two-point binding of borane and the oxygen atom of ketone by the oxazaborolidine, assembles a trimolecular complex which provides the high enantiomeric excess. This reaction may occur by the following sequence:

(a) complexation of borane to the nitrogen;
(b) coordination of the ketone oxygen to the boron of oxazaborolidine;
(c) hydrogen transfer from the coordinated borane to the carbonyl *via* a six-membered cyclic transition state [30] (Figure 9).

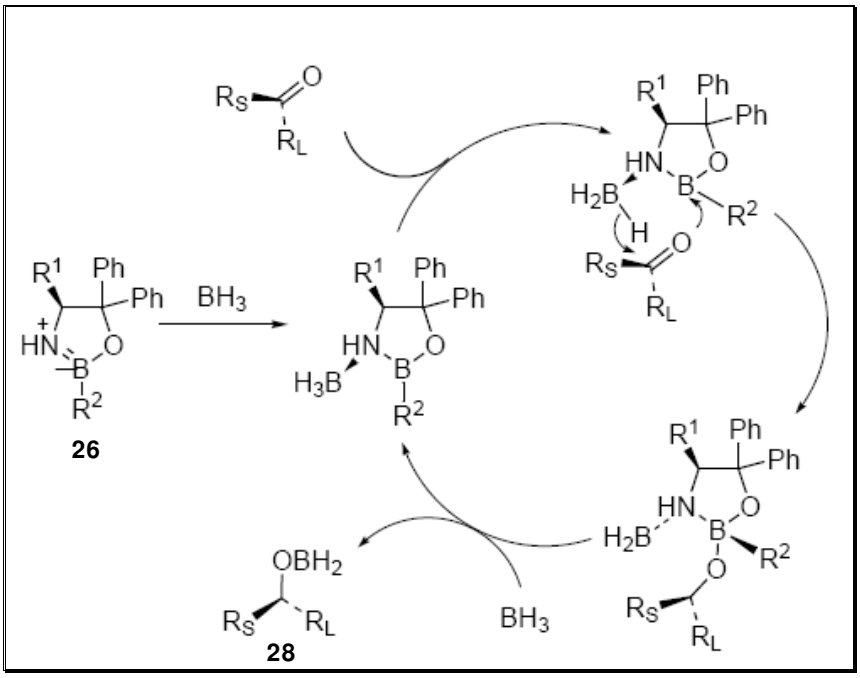


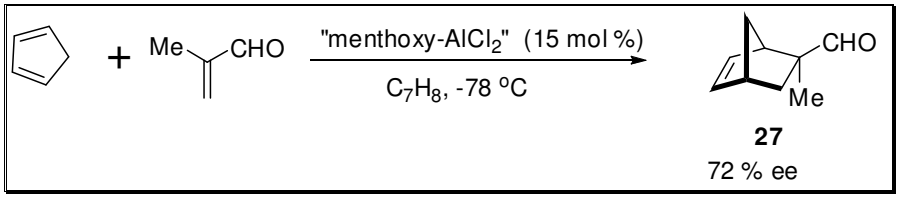
Figure 9. Mechanism of Borane Reduction

In many stereoselective reactions, the effect of temperature on the selectivity is as expected, with better results being obtained at lower temperature. A lower temperature is often required to increase the selectivity. From the practical point of view, one of the most attractive feature of this enantioselective reduction is that excellent enantioselectivity is obtained at a relatively high temperature such as room temperature. In some cases, the selectivity of the oxazaborolidine catalyzed borane reduction increases with increasing temperature until an optimal range is reached (30–50 ˚C) where the selectivity then begins to decrease [31]. Interpretation of this phenomena is not so easy. The amount of catalyst dimer that exists in a temperature-dependent equilibrium with the monomeric form might have an effect on the selectivity.

1.5.4. Asymmetric Diels Alder Reaction

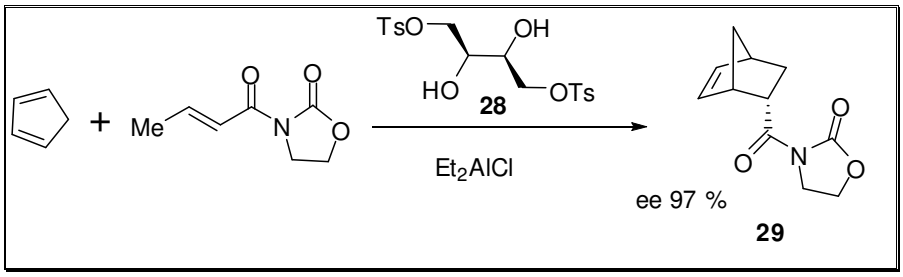
The Diels-Alder reaction is the most popular [4+2] cycloaddition, and it has been used to elaborate the carbon backbone of many natural products [32]. The Diels-Alder reaction occurs between a diene and a dienophile and is often catalyzed by Lewis acids. Normal Diels-Alder reactions occur between electron-rich dienes and electron-poor dienophiles, and inverse electron demand Diels-Alder reactions occur between electron-poor dienes and electron-rich dienophiles. The hetero-Diels-Alder reaction is a useful method to elaborate heterocycles [33], [34], [35].

Chirality can be introduces on the Lewis acid catalyst, on the dienophile or on the diene. The first chiral Lewis acid was designed and applied in asymmetric Diels-Alder reaction by Idris Mecidoglu Akhmedov et.al. [36] in 1976. The enantioselectivity was poor but the first step was accomplished. Then in 1979, Koga and coworkers disclosed the practical example of a catalytic enantioselective Diels-Alder reaction [36] promoted by a Lewis acidic complex, presumed to be "menthoxyaluminum dichloride", derived from menthol and ethylaluminum dichloride, whose structure remains undefined [37]. This complex catalyzed the cycloaddition of cyclopentadiene with acrolein, methyl acrylate, and methacrolein with enantioselectivities as high as 72% ee (Scheme 6).



Scheme 6. Cycloadditon of cyclopentadiene with acrolein

Kagan and coworkers used methacrolein as dienophile at -100 ^{o}C with a catalyst shown below [38] (Scheme 7).



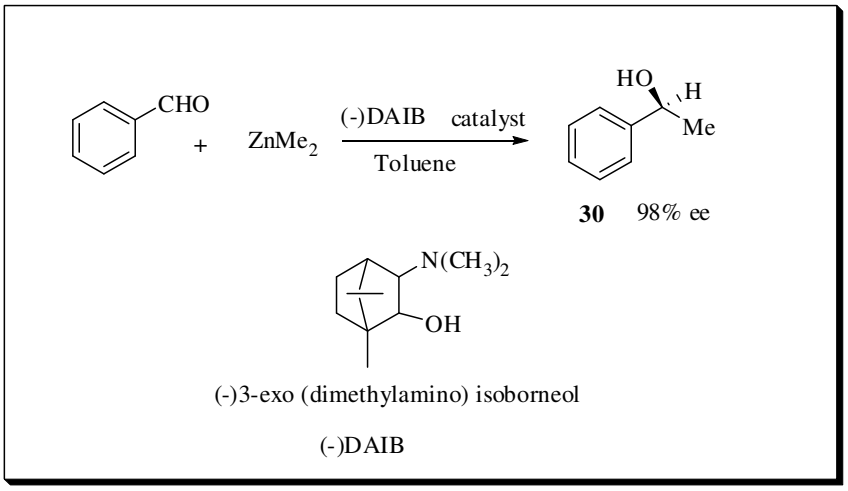
Scheme 7. Example of Kagan's work

1.5.5. Enantioselective Diethylzinc Addition to Aldehydes

Nucleophilic addition of metal alkyls to carbonyl compounds in the presence of a chiral catalyst has been one of the most extensively explored reactions in asymmetric synthesis. Various chiral amino alcohols as well as diamines with C_2 symmetry have been developed as excellent chiral ligands in the enantioselective catalytic alkylation of aldehydes with organozincs. Although dialkylzinc compounds are inert to ordinary carbonyl substrates, certain additives can be used to enhance their reactivity.

The first clean nucleophilic addition of diethylzinc to benzaldehyde was reported by Mukaiyama et al. [39] In the presence of β-amino alcohol derived from (S)-proline. β-amino alcohol accelerates the carbon-carbon bond forming reaction to afford 1-phenylpropanol in 76 % yield. No asymmetric induction was reported. Oguni and Omi [40] used (S)-leucinol as a chiral catalysts and first obtained optically active compound with moderate yield. (49 % ee).

The first highly enantioselective catalytic addition of dialkylzinc to aromatic aldehydes was reported by Noyori et al. [41]. (-)-3-exo-(dimethylamino)isoborneol (Scheme 8) catalyzes the addition of diethylzinc to benzaldehyde to afford (S)-1-phenylpropanol with 99% ee and with 98 % chemical yield. The catalyst is also effective for other aromatic aldehydes but the enantioselectivity, fort he aliphatic aldehydes, is moderate (61 % ee).



Scheme 8. Dialkylzinc addition using DAIB

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 [41], [42].

1.6. Chiral Amino alcohols

Using amino alcohols as chiral auxiliaries found wide spread applications in various organic synthesis. Reagents that encompass both the alcohol and the amine functional groups of a commercially available amino alcohol are very useful.

1.6.1. 1,2-amino alcohols

The 1,2-amino alcohol motif is a common structural component in bioactive natural products and many pharmaceutical agents; it is also present in useful synthetic intermediates, auxiliaries, and ligands in catalysis.

Enantiomerically pure beta-amino alcohols play an increasingly important role in both the treatment of a wide variety of human disorders and as chiral auxiliaries in organic synthesis. β-amino alcohols can be found as important subunits of many bioactive compounds such as α/β-adrenergic agents or antagonists [43], HIV protease inhibitor [44], and antifungal or antibacterial peptides [45]. For this reason, many attempts have been made at the asymmetric construction of β-amino alcohol subunits [46].

The two heteroatoms allow flexibility while one or two of them bound to a Lewis acid, transition metal or achiral starting material. The 1,2-amino alcohol unit has been found in a number of bioactive natural products [47] such as alkaloids, amino sugars, enzyme inhibitors, and antibiotics. Also, they are frequently employed in asymmetric synthesis as chiral auxiliaries or chiral catalysts [48], [49]. Here are some examples of chiral 1,2-amino alcohols (Figure 10).

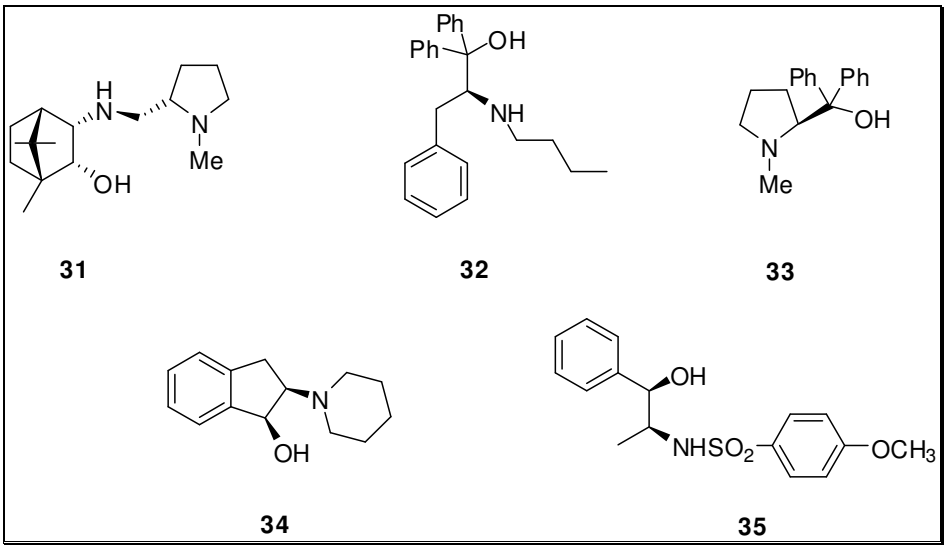
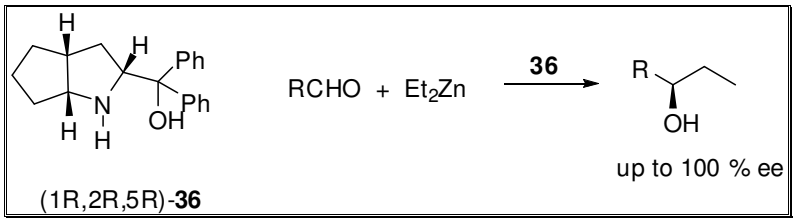


Figure 10. Examples of chiral 1,2-amino alcohols

Martens et. al. [50] reported that, the optically active β-amino alcohol (1R,3R,5R,)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane derived from bicyclic praline analogue catalyzes the enantioselective addition of diethylzinc to various aldehydes. The resulting chiral alcohols are obtained in high optical yields up to 100 % e.e. under mild conditions (Scheme 9).



Scheme 9. Diethylzinc addition by using β-amino alcohols

1.6.2. 1,3-amino alcohols

While frequently overlooked in favor of the more common 1,2-amino alcohols, a wide variety of 1,3-amino alcohols and their derivatives have been used for asymmetric induction in organic synthesis, but 1,3-amino alcohols are less abundant than 1,2-amino alcohols. They range from small linear compounds to multicyclic structures and heterocyclic derivatives [51]. Here are some examples of chiral 1,3-amino alcohols (Figure 11)

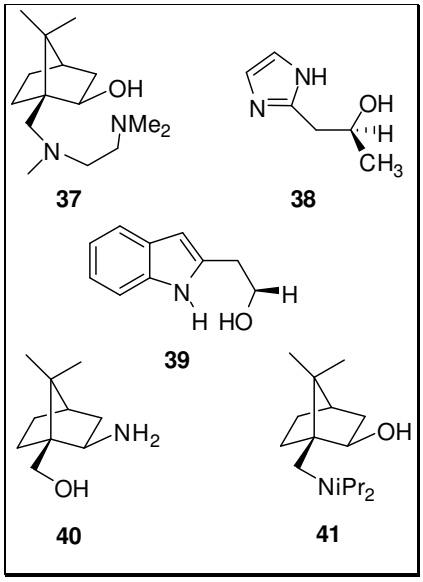
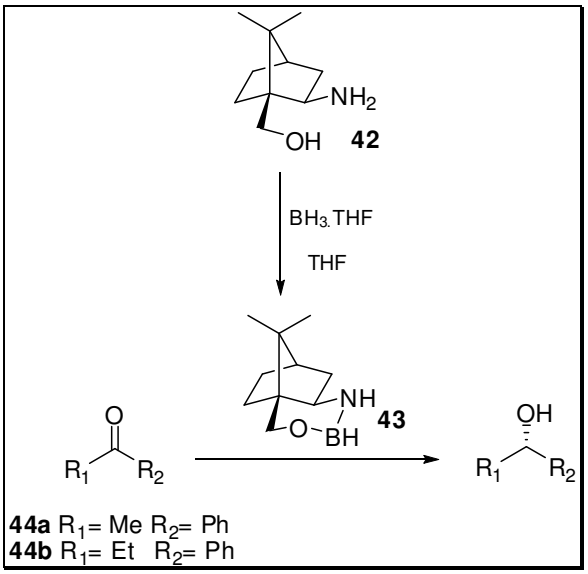


Figure 11. Examples of chiral 1,3-amino alcohols

Some are derived from common natural products such as menthol, camphor, and sugars while others are entirely synthetic in structure. 1,3-amino alcohols have been used as chiral auxiliaries for Diels-Alder reactions and other cycloadditions, for sigmatropic rearrangements, for aldol reactions and alkylation of anions, for radical cyclizations, and for addition of organometallic reagents to ketals and carbonyl groups. They have been chelated to transition metals and other catalysts including B, Al, Zn, Ti, Pd, Cu, and Zn species.

The resulting chiral catalysts have been used for Diels-Alder reactions, for allylic alkylation and Heck reactions, for carbenoid cyclopropanation reactions, for reduction of enamines and carbonyl groups, for trimethylsilylcyanations, and for addition of organometallic reagents to carbonyl groups. 1,3-Amino alcohols have a rich history in asymmetric organic synthesis and, given their usefulness and adaptability, they will likely have a rich future as well [52].

Amino alcohol **42** was used in 1999 as a chiral ligand for ketone reduction. Complexation of **42** with BH_3 gave **43**, which was used *in situ* to catalyze reduction of ketones **44** to corresponding alcohol. Increasing reaction temperature from 0 to 50 ^oC improved the e.e. of **44a** from 58:42 to 94:6 (Scheme 10).



Scheme 10. Asymmetric Borane Reduction using 1,3-Amino Alcohol

1.6.3. 1,4-amino alcohols

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

1,4-Amino alcohols have more flexible structures with respect to 1,2-amino alcohols for complexation with various types of metals and thus may form more stable and selective catalysts in the reaction. Here are some examples of chiral 1,4-amino alcohols (Figure 12)

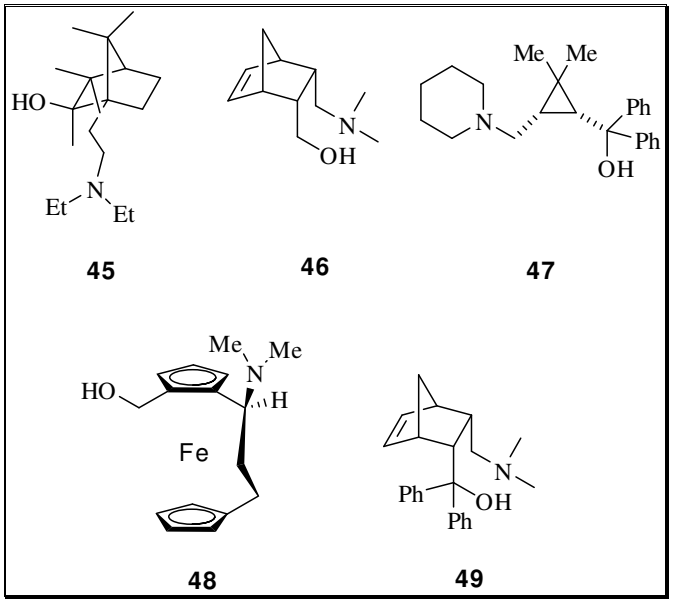
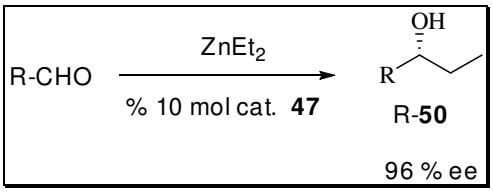


Figure 12. Examples of some chiral 1,4-amino alcohols

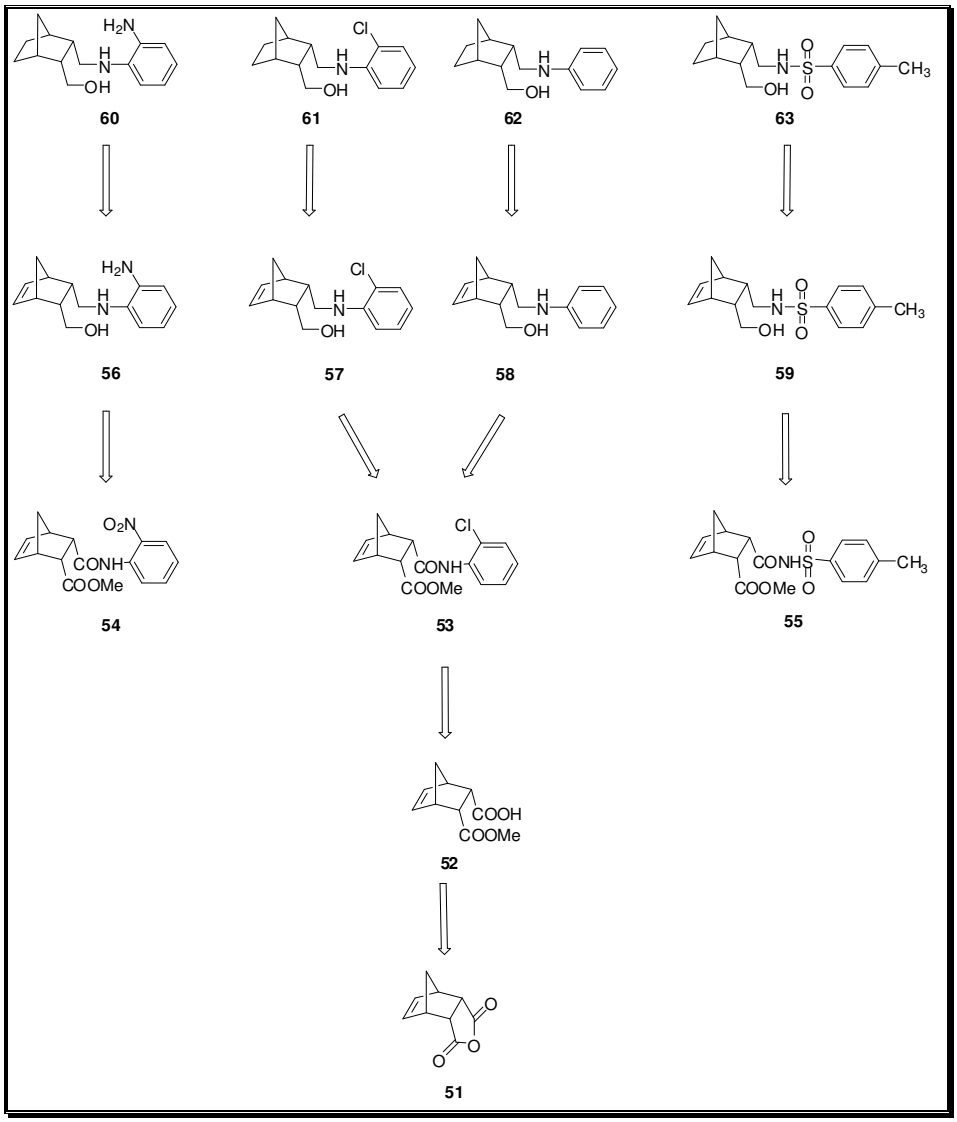
Zhong et. al. [54] used the 1,4-amino alcohol **47** in 2006 as a chiral ligand for enantioselective diethylzinc addition to aromatic ketones to afford chiral secondary alcohol (Scheme 11). The reaction was completed with high optical purity with 96 % e.e. value (R enantiomer).



Scheme 11. Zhong work

1.7. Aim of Work

The aim of this project is to synthesize new chiral N-aryl substituted chiral 1,4-amino alcohol ligands and test their effectiveness in various asymmetric transformation reactions.



Scheme 12. Retrosynthesis of the work

CHAPTER 2

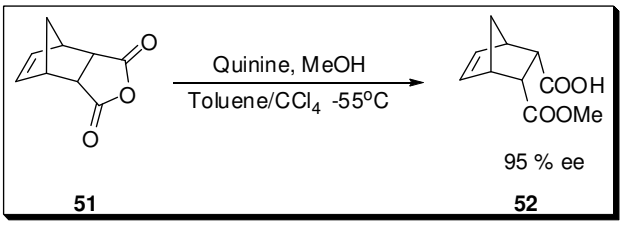
RESULTS AND DISCUSSION

2.1. Asymmetric Synthesis of Amino Alcohol Ligands

2.1.1. Desymmetrization of Meso-Anhydride

In 1999, Bolm et al. [55] have reported a highly efficient way for enantioselective desymmetrizaton of *meso*-anhydrides via cinchona alkaloid-mediated ring opening with methanol. Quinine or quinidine are used as chiral directing agents and both enantiomers of the corresponding *cis*-monoester can be obtained with very high enantiomeric excess values (up to 99% e.e.) and chemical yield.

Quinine-mediated desymmetrization of anhydride **51** with methanol resulted *cis*-monoester **(-)-52** (Scheme 13). The synthetic route starts with this *cis*-monoester. The 1,4-amino alcohols which are going to synthesize depends on the key structure of the *cis*-monoester.

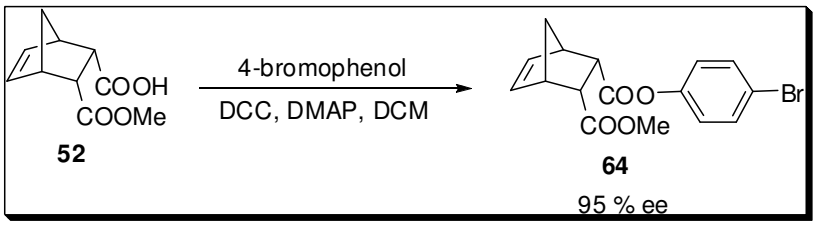


Scheme 13. Desymmetrization of Meso-Anhydride

Carbonyl group of the anhydride reacted with MeOH in an enantioselective way to produce chiral hemiester. The product was identified using NMR spectroscopy. After completing the reaction the compound lost its symmetry and the following peaks are observed in ^{1}H-NMR: the characteristic singlet at 3.54 (3H) ppm belongs to $-OCH_3$; there are two doublet of doublets at 6.26 (1H) and 6.16 (1H) ppm belongs to double bonds hydrogens; two doublet of doublets at 3.28 (1H) and 3.22 (1H) ppm belongs to methine protons; two broad singlets at 3.14 (1H) ppm belongs to bridge head methine protons; two doublets at 1.43 (1H) and 1.25 (1H) ppm belongs to bridge protons. ^{13}C-NMR spectroscopy gave the following signals: the carbonyl carbons gave signals at 177.8 and 173.1; the olefinic carbons gave two signal at 135.6 and 134.4; at 51.6 there is a signal belongs to ester carbon; the carbons next to the carbonyl groups gave signals at 48.8 and 48.2; the signals at 47.9 and 46.6 were corresponding to bridge head carbons; and finally the bridge carbon gave a signal at 46.1. The melting point of the compound **(-)-52** is 75-78 ^{o}C and has $[\alpha]_D^{20}$ is equal to -7.8 (c 4.0 CCl_4). These data are in accordance with the literature [56,57].

2.1.2. Enantiomeric Excess Determination of the Hemiester

Monoester (-)-**52** was reacted with *p*-bromophenol via DCC coupling method to produce corresponding diester **64** (Scheme 14), which was then analyzed by HPLC for enantiomeric excess determination. HPLC analysis of the methyl 4-bromophenyldiester was carried out by using Chiralcel OD-H column and the process was done at room temperature by using n-hexane/2-propanol = 98:2 system, the flow rate was 0.5 mL/min and the wavelength of the detector was 254 nm [t_1=20.3 min (major), t_2= 23.2 min (minor)].



Scheme 14. Enantiomeric Excess Determination of the Hemiester

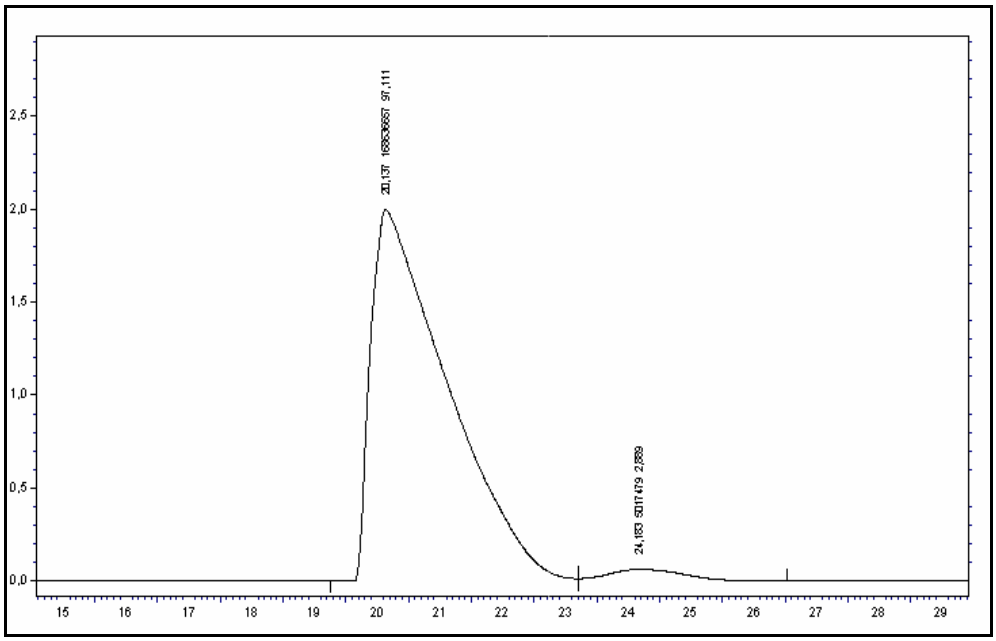


Figure 13. HPLC Chromatogram of compound **64**

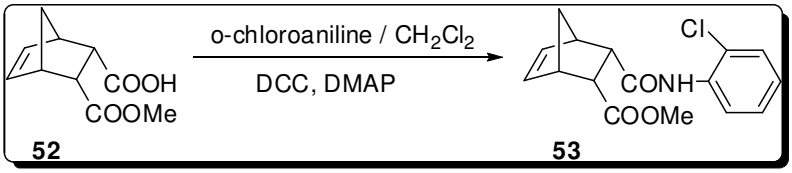
In this reaction, carboxylic acid group of the compound **(-)-52** was activated with DCC and then reacted with 4-bromophenol to afford the product **64**. The product was identified by using NMR spectroscopy.

From the ^{1}H-NMR, the following peaks was observed: a singlet at 3.55 (3H) ppm belonging to -OCH_3; two doublet of doublets at 6.32 (1H) and 6.15 (1H) ppm belonging to the double bond hydrogens; two doublets at 7.37 and 6.92 ppm

belonged to aromatic protons respectively; two doublets at 1.40 and 1.33 ppm belonging to the hydrogens; one broad singlets at 3.39 belonging to protons attached to the carbonyls and; two broad singlets at 3.20 and 3.17 ppm belonging bridge protons. From the ^{13}C-NMR spectroscopy, following peaks were observed. The carbonyls showed peaks at 173.0 and 171.2; and the aromatic and olefinic carbons gave signals at 150.3; 135.9, 135.0, 132.7, 123.8; 119.0 ppm; the methoxy carbon gave signal at 52.2 ppm; and the rest of them are belonging to norbornene carbons at 49.1, 48.7, 48.5, 47.2, 46.6 ppm.

2.1.3. Synthesis of Amide-Ester, (+)-53

Since our synthetic route depends on the construction of 1,4-amino alcohol moiety on norbornene backbone, firstly carboxylic acid group was transformed to corresponding amide using an arylamine**.** The monoester was first chemoselectively activated with DCC and then reacted with *o*-chloroaniline to afford corresponding *cis*-amide ester product **(+)-53** with a 68 % yield and $[\alpha]_D^{20}$=+58.9 (Scheme 15).



Scheme 15. Synthesis of Amide-Ester **(+)-53**

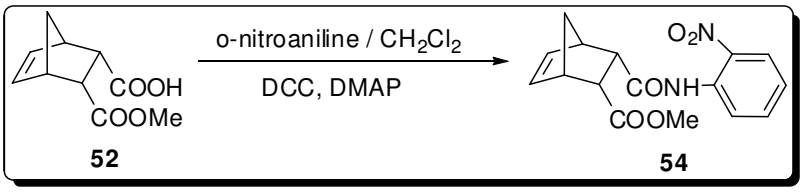
NMR spectroscopy technique was used to identify the product. From the ^{1}H-NMR the following peaks are observed; since there is no change in the ester moiety, the characteristic singlet signal belonging to -OCH_3 group came at 3.61 (3H) ppm, and also the olefinic protons gave doublet of doublets at 6.19 (1H) and 6.07 (1H), respectively. In the chlorophenyl moiety, there are 4 different protons and has the following chemical shift values; one doublet at 8.25 ppm belongs to

the hydrogen in α position with respect to amide group; another doublet at 7.25 ppm belongs to hydrogen next to the chloride group; two triplets at 7.16 ppm and 6.91 ppm corresponding to hydrogens at second and third positions with respect to amide group, respectively. Methine protons next to carbonyl groups show an overlapped doublet at 3.18 ppm whereas the bridgehead proton on the ester side has a broad singlet at 3.01 ppm and the other bridgehead proton has a triplet at 2.64 ppm. The bridge protons show two doublets at 1.70 and 1.44 ppm. In the ^{13}C-NMR spectroscopy, the ester and the amide carbonyl carbons gave signals at 174.0 ppm and 172.4 ppm. The 6 different carbon atoms of the benzene ring yielded the corresponding signals; the α carbon with respect to amide at 137.7 ppm; the carbon atom at the *para*-position with respect to amide at 133.2 ppm, at 127.6 ppm and 124.5 ppm the carbons at β and α position from the chloride group, respectively, the carbons at λ and β from the amide gave signals at 122.8 ppm and 121.7 ppm, respectively. The olefinic carbons showed the characteristic signals at 135.9 ppm and 135.0 ppm. Methoxy carbon of the ester group had a signal at 49.8 ppm. The methine carbons next to the carbonyl groups showed the signals at 49.8 ppm and 48.9 ppm. The bridgehead carbons were observed at 47.7 ppm and 47.5 ppm whereas the bridge carbon was observed at 46.2 ppm.

2.1.4. Synthesis of Amide-Ester, (+)-54

In this project, it was aimed to test the electronic effects of the substituents attached to aryl part of the target chiral ligands in asymmetric transformation reactions. For this purpose, *o*-nitroaniline was chosen as another arylamine moiety source. The amide-ester **(+)-54** was synthesized by using general DCC coupling method (Scheme 16).

The product was isolated with 60 % chemical yield and with the optical rotation value $[\alpha]_D^{20}$=+ 7.9 (c. 2.0 $CHCl_3$).

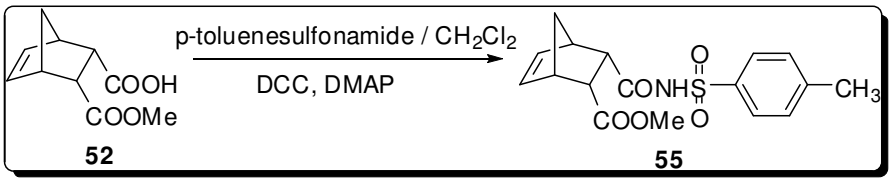


Scheme 16. Synthesis of Amide-Ester, **(+)-54**

The structure of **(+)-54** was elucidated by using NMR spectroscopy. The following results were obtained by careful analysis of ^{1}H-NMR. The norbornene backbone did not change so the characteristic signals were almost similar with the amide-ester product **(+)-53.** The only noticeable change was in the aromatic region. The nitro group has more electron withdrawing effect than the chloride group, therefore the protons on the benzene ring shifted to the more downfield. Similar to **(+)-53**, the *o*-nitro substituted amide ester had also 4 different protons and showed two doublets and two triplets. In ^{13}C-NMR spectroscopy, the main difference arose in the aromatic carbon signals due to the high electronegative effect of nitro group that causes to shift the carbon signals to the downfield.

2.1.5. Synthesis of Amide-Ester, (+)-55

In our synthetic strategy, we decided that increasing the acidity of the amide hydrogen could have some positive effects in the asymmetric transformation reactions i.e. making much better complexation with metals**.** Therefore, **t**he amide ester **(+)-55** was synthesized by general DCC coupling method using *p*-toluenesulfonamide as an amine source with 82% chemical yield and with an optical rotation $[\alpha]_D^{20}$=+ 16.7 (c. 2.0 $CHCl_3$) (Scheme 17).

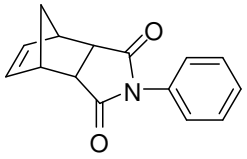
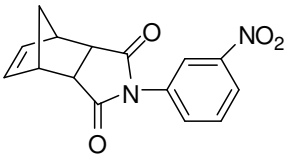
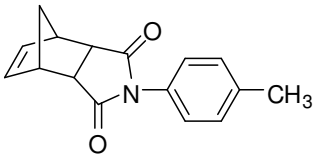
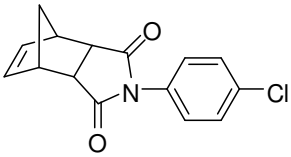
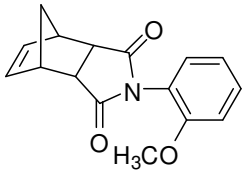


Scheme 17. Synthesis of Amide-Ester, **(+)-55**

NMR spectroscopy techniques helped us to investigate the product. The norbornene backbone did not change for that reason the characteristic signals were almost similar in ^{1}H-NMR with the amide-ester products **(+)-53** and **(+)-54.** The methyl group attached to the benzene ring is an electron donating group so the protons belonging to benzene ring were shifted to the relatively highfield. The *para*-substituted benzene ring has symmetry and the symmetric α and α' protons with respect to SO_2 group gave a doublet at 7.88 ppm; and the symmetric β and β' proton gave another doublet at 7.24 ppm. Also, the methyl group attached to benzene ring gave a singlet at 2.36 ppm. Moreover, in the ^{13}C-NMR spectroscopy, the benzene ring characteristically afforded 4 different carbon signals due to the symmetry; the SO_2 attached carbon atom gave a signal at 144.8 ppm; the methyl attached carbon atom gave a signal at 137.5 ppm and the other carbon atoms which are at α and β positions with respect to methyl group gave signals at 128.3 ppm and 129.5 ppm, respectively. Also, the methyl carbon gave a signal at 33.8 ppm.

In addition to *o*-substituted aryl amide-ester derivatives, various *m*- and *p*-substituted aryl amines were used to get the desired amide-ester products. Unfortunately, they afforded imide type products. The reason should be presumably due to the sterical effect of the *o*-substitutents which can prevent the imide formation. There is only one exceptional case in which *o*-methoxy aniline afforded the corresponding imide structure. This unusual behavior can be explained by the high activity effect of electron donating substituent on the amide nitrogen. The results are shown in Table 1.

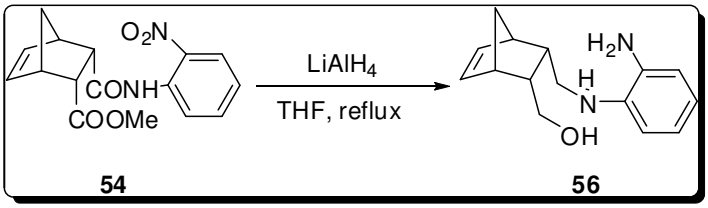
Table 1. Norbornene Dicarboxy Imide Type Products

Amine Derivative	Product
aniline	 **65**
m-nitroaniline	 **66**
p-toluidine	 **67**
p-chloroaniline	 **68**
o-anisidine	 **69**

2.1.6. Reduction of Amide-Ester (+)-54, with LAH

The second part of our synthetic route involves the transformation of ester and amide functionality to the corresponding alcohol and amine moieties, respectively. $LiAlH_4$ was chosen as a feasible reducing agent due to its high reducing agent ability and THF was chosen as the solvent to carry out the reactions

in much elevated temperatures. The amide-ester **(+)-54** was subsequently reduced by using $LiAlH_4$ to afford corresponding norbornene based 1,4-amino alcohol **(-)-56** (Scheme 18). The isolated yield was 71 % and optical rotation value is $[\alpha]_D^{20}$ = -202.90 (c 0.5 $CHCl_3$).



Scheme 18. Reduction of Amide-Ester **(+)-54**, with LAH

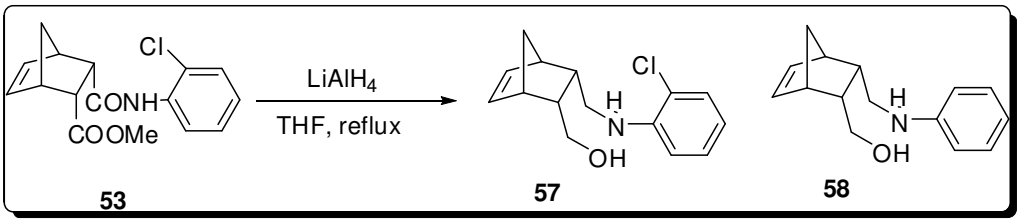
Spectroscopic techniques were used to elucidate the structure of the product. By using ^{1}H-NMR spectrum we have seen that the methoxy group was disappeared and the carbonyl groups were turned out to be methylene protons after the reduction. As a result of this; the methine protons which were already next to the carbonyl groups shifted to the highfield and gave a doublet of doublets at 1.39 ppm. The newly formed methylene protons, one set is attached next to hydroxyl group and one is attached next to arylamine moiety showed two doublet of doublets at 3.50 and 3.15 ppm, and two triplets at 2.82 and 2.72 ppm, respectively. In addition, the bridge head methine protons were shifted to the highfield due to loss of carbonyl groups. In the aromatic region the proton signal were shifted about 2.0 ppm to the highfield by comparing with the starting amide-ester product **(+)-54**.

By concerning the ^{1}H-NMR results we can say that the $-NO_2$ group was turned to $-NH_2$ at the end of the reaction. The olefinic proton signals were nearly comparable with the starting amide-ester product **(+)-54**. From the ^{13}C-NMR spectroscopy the following peaks were observed: The carbonyl signals were disappeared. Instead of them, two new methylene carbons were appeared in the NMR and these carbons showed signals at 66.5 ppm which is next to -OH group and

49.6 ppm which is next to –NH group. Six different carbons belonging to benzene ring gave the corresponding signals: at 133.5 ppm carbon attached to –NH group; at 133.2 carbon attached to -NH_2 group, at 120.9 ppm carbon β position with respect to–NH group, and the rest of three carbon in the benzene ring showed signals at 116.4, 117.8 and 111.0 ppm.

2.1.7. Reduction of Amide-Ester (+)-53, with LAH

The amide-ester **(+)-53** was subsequently reacted with $LiAlH_4$ to afford corresponding amino alcohol. The reduction afforded two different products, one with expected chlorinated and the other with dechlorinated (Scheme 19). Using excess $LiAlH_4$ and increasing the reaction time mainly afforded the removal of chloride from the ring. The product ratio depends on the reaction time. In our case (5 eq LAH and 24 h reflux), the ratio between chlorinated and dechlorinated was 2:1.



Scheme 19. Reduction of Amide-Ester **(+)-53**, with LAH

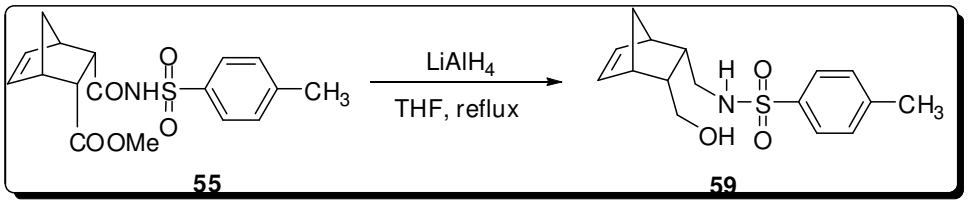
The obtained products are similar each other except one –Cl group but the dechlorinated product have an internal symmetry in the ring. Thus, the products were elucidated using NMR spectroscopy. From the ^{1}H-NMR spectrum of chlorinated product the following results were obtained; since the backbone structure had similarities with the previous amino alcohol **(-)-56**, the characteristic signals that come form the norbornene backbone were approximately similar. The differences were arising from the different electron withdrawing abilities of attached groups.

For the chlorinated product **(+)-57,** there are 4 different protons in the aromatic region and they show 4 different integrals in the ^{1}H-NMR spectroscopy; a doublet at 7.15 ppm belongs to proton that is attached to next to the halogenated carbon; a triplet at 7.04 ppm corresponds to proton that is at the β position with respect to amine side; and the other two protons were overlapped each other due to poor resolution and gave doublet of doublet at 6.53 ppm. There were 6 different carbons in the aromatic region belonging to chlorinated product **(+)-57** and they showed six different signals in the ^{13}C-NMR spectrum: at 144.4 ppm carbon attached to nitrogen; at 129.1 ppm fifth position carbon that was next to –Cl attached carbon. The carbon at the third position with respect to nitrogen had a signal at 127.8 ppm; the carbon in the *para* position concerning with nitrogen gave a peak at 119.1 ppm; 116.8 ppm was belonged to carbon attached to –Cl group and finally 111.1 ppm corresponded to the second position carbon regards to nitrogen.

For the dechlorinated product **(+)-58,** there were only 3 different sets of protons in the aromatic region. Therefore, in the ^{1}H-NMR spectroscopy; they gave only 3 different integrals with 2:2:1 ratio. There were no electron withdrawing groups attached to benzene ring like –Cl or –NO_2, the aromatic signals were shifted to the realtively highfield. A triplet at 7.07 ppm belonged to protons at the third and fifth positions. These proton signals overlapped each other due to the symmetry; a triplet at 6.60 ppm corresponded to hydrogen at the *para* position and lastly the protons at the second and sixth position gave a doublet at 6.51 ppm. These protons also overlapped each other due to the symmetry. The other signals are very similar with the chlorinated product **(+)-57**. From the ^{13}C-NMR spectroscopy the following peaks were observed: the dechlorinated product **(+)-58** has only 4 different carbons belonged to benzene ring and they gave the corresponding signals; at 148.7 ppm carbon attached to nitrogen; the symmetric carbons at the third and fifth position gave a signal at 129.3; the carbon at the *para* position has a signal at 117.3 ppm finally the other two symmetric carbons gave a peak at 112.9 ppm.

2.1.8. Reduction of Amide-Ester (+)-55, with LAH

The synthesis of chiral 1,4-amino alcohol **(-)-59** was achieved by the reduction of amide-ester **(+)-55** using $LiAlH_4$ with a chemical yield 78 % (Scheme 20).

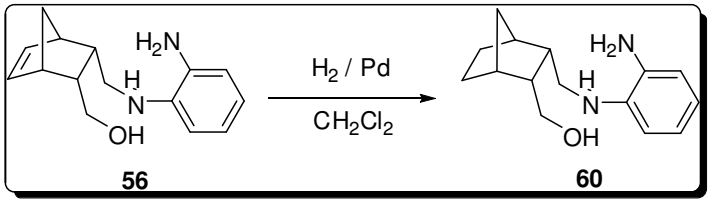


Scheme 20. Reduction of Amide-Ester **(+)-55**, with LAH

Identification of the reduction product was performed by using ^{1}H-NMR and ^{13}C-NMR spectroscopy. From the ^{1}H-NMR spectroscopy the methoxy group was disappeared and the carbonyl groups were turned out to be methylene protons after the reduction. As a result of this; the methine protons shifted to the highfield. The other characteristic signals coming from the norbornene backbone were similar with the product **(-)-56**. The product had totally four aromatic protons giving two different integrals with a ratio of 2:2. This is because of the internal symmetry. The protons at the second and sixth positions gave a doublet at 7.76 ppm and the other two symmetric protons gave a doublet at 6.60 ppm. The amine proton gave a broad singlet at 6.21 ppm. From the ^{13}C-NMR spectroscopy the following peaks were observed: the product **(-)-59** has 4 different carbons corresponded to benzene ring due to the symmetry and they gave the corresponding signals between 143.1 and 127.1 ppm.

2.1.9. Hydrogenation of Amino Alcohol (-)-56

In asymmetric transformation reactions, amino alcohols having secondary amine moieties are generally used in borane reductions. Since, norbornene backbone undergoes a classical hydroboration reaction with BH_3 unit; the double bond must be saturated to avoid this possible side reaction. For this purpose, norbornene backbone was subjected to hydrogenation reaction with H_2 in the presence of Pd/C to afford norbornane based amino alcohol **(-)-60** with 90% chemical yield (Scheme 21).

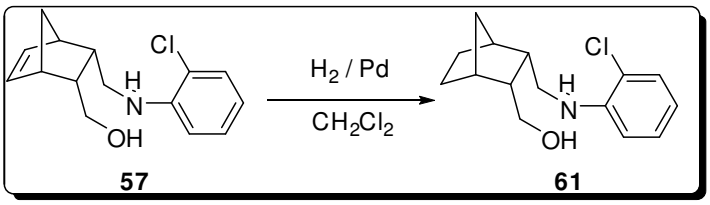


Scheme 21. Hydrogenation of Amino Alcohol **(-)-56**

In ^{1}H-NMR spectrum, the disappearance of olefinic protons and the appearance of new methylene protons at 1.39 and 1.18 ppm were observed. Similar to these results, in ^{13}C-NMR spectrum, the disappearance of olefinic carbon signals and the appearance of new methylene carbons at 30.1 and 25.9 ppm strongly support the expected structure.

2.1.10. Hydrogenation of Amino Alcohol (+)-57

Norbornane based chiral 1,4-amino alcohol **(+)-61** was synthesized by hydrogenation of amino alcohol **(+)-57** with H_2 in the presence of Pd/C catalyst. The chemical yield was 87 % (Scheme 22).

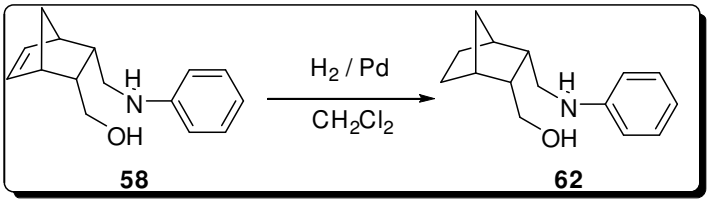


Scheme 22. Hydrogenation of Amino Alcohol **(+)-57**

New methylene protons were appeared and the olefinic protons were disappeared in the ^{1}H-NMR. The newly appeared methylene protons gave two multiplets between 1.39-1.24 and 1-13-1.06. The ^{13}C-NMR spectroscopy strongly supports the hydrogenation of the product. The olefinic signals were disappeared and new methylene carbons were appeared and showed peaks at 37.3 and 29.9.

2.1.11. Hydrogenation of Amino Alcohol (+)-58

The amino alcohol **(+)-58** was subsequently reacted with H_2 in the presence of Pd/C to afford the norbornane based chiral 1,4-amino alcohol **(+)-62**. The chemical yield was 88 % (Scheme 23).



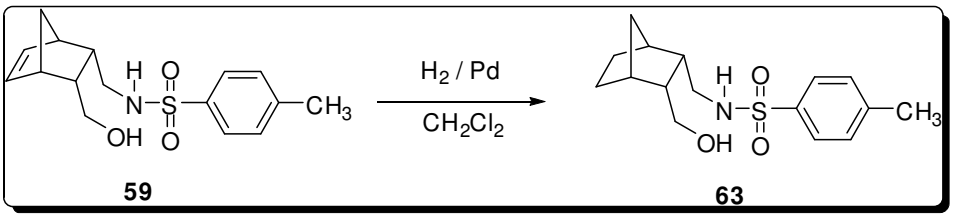
Scheme 23. Hydrogenation of Amino Alcohol **(+)-58**

The characteristic backbone signals coming from the norbornene were changed obviously because the olefinic protons were saturated by hydrogenation. The olefinic signals were disappeared and new methylene protons were appeared

in the ^{1}H-NMR and had two multiplet signals between 1.32-1.22 ppm and 1.12-1.10 ppm. In addition, the olefinic signals were also disappeared in the ^{13}C-NMR and the new formed methylene protons gave signals at 38.9 and 37.3 ppm**.**

2.1.12. Hydrogenation of Amino Alcohol (-)-59

Synthesis of norbornane based chiral 1,4-amino alcohol **(-)-63** was performed by hydrogenation of the amino alcohol **(-)-59** with H_2 in the presence of Pd/C catalyst. The chemical yield was 91 % (Scheme 24).



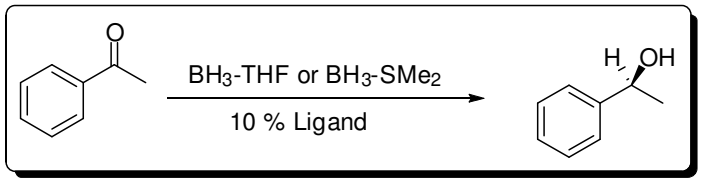
Scheme 24. Hydrogenation of Amino Alcohol **(-)-59**

The product was identified by using NMR spectroscopy. The saturation of double bonds afforded to disappear of olefinic signals thus the norbornene backbone was changed upon the reduction. Generally the signals were shifted to the more highfield. After the saturation of olefinic protons, the methylene protons showed signal between 1.23-1.13 ppm as multiplet. When the ^{13}C-NMR spectrum was examined it was seen that the olefinic signals were disappeared and the new formed methylene protons gave signals at 28.9 and 21.5.

2.2. Application of Chiral Ligands in Asymmetric Transformation Reactions

2.2.1. Asymmetric Borane Reduction

The first application for testing the catalytic effectiveness of the synthesized ligands **(-)-60**, **(+)-61**, **(+)-62**, **(-)-63** is the asymmetric borane reduction (Scheme 25). The results are summarized in the following section.



Scheme 25. Asymmetric Borane Reduction

In general for any reaction, first of all the optimized conditions must be determined for the desired reaction. For this reason, all the ligands were tested with BH_3-THF in various solvents using 10% ligand molar ratio at room temperature. The ligands, except **(-)-60**, afforded low e.e. results. The highest enantiomeric excess value is 54% with the ligand **(-)-60** in toluene at room temperature. Then, the activity differences between BH_3-THF and BH_3-SMe_2 were tested but the same results were obtained. Although the results were low, the solvent effect should be seen. In the entries 2 and 3, the enantiomeric excess value decreased and the reaction time increased by changing the solvent from toluene to dichloromethane (Table 2).

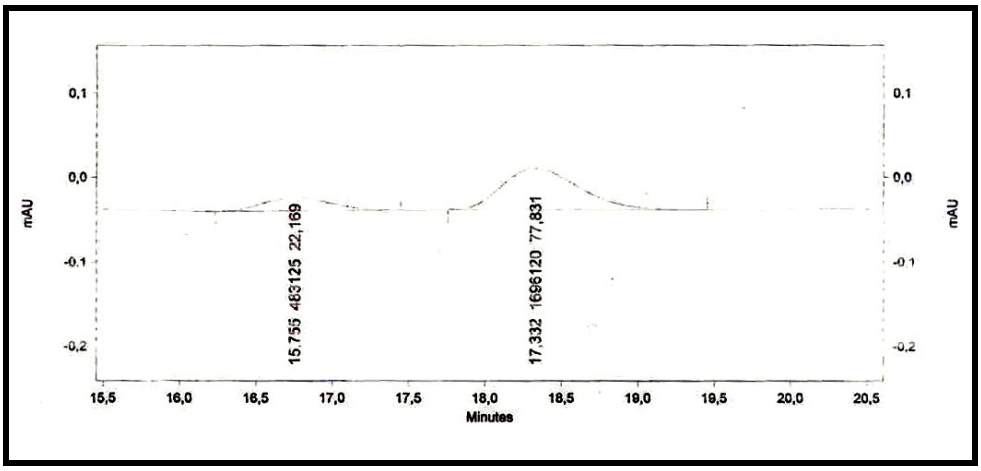


Figure 14. HPLC Chromatogram of 1-phenylethanol using compound **(-)-60**

Table 2. Asymmetric Borane Reduction by using BH_3.THF or $BH_3.SMe_2$

Entry	Ligand	Solvent	Time (h)	e.e. (%)
1	60	Toluene	8	**54**
2	61	Toluene	6	16
3	61	DCM	12	8
4	62	Toluene	12	31
5	63	THF	12	8
6	63	Toluene	12	12

Then the strategy was changed. Firstly, $B(OMe)_3$ reagent that is more reactive than BH_3 was allowed to react and to form the oxazaborolidine complex with the desired ligand and then continue the reduction process. Moreover, in the complex formation part, the procedure was performed at the reflux temperature of the solvent to give the energy to the system in order to overcome the activation energy barrier for forming the oxazaborolidine complex. Although, we expect much higher enantiomeric excess values with this strategy, the results were below of our expectations (Table 3).

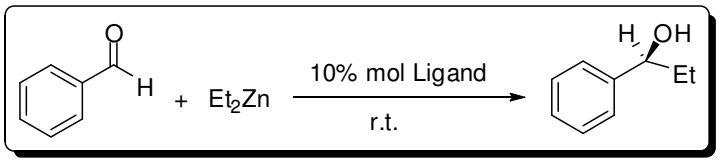
Table 3. Asymmetric Borane Reduction using $B(OMe)_3$

Entry	Ligand	Temp. (°C)	Solvent	Time (h)	e.e. (%)
1	61	r.t.	Toluene	8	10
2	62	r.t.	Toluene	8	12
3	62	0	Toluene	12	6

The reason is that the asymmetric borane reduction is absolutely dependent on the oxazaborolidine complex formation. The lower e.e. values could be associated with this fact. In the absence of any oxazaborolidine complex, the reaction can also go the completion itself**.** Therefore, if the complex was not formed, high enantiomeric excess values would not be obtained.

2.2.2. Diethyl Zinc Addition Reactions

The second application for testing the catalytic effectiveness of the synthesized ligands **(-)-60**, **(+)-61**, **(+)-62**, **(-)-63** was the enantioselective diethyl zinc addition to benzaldehyde (Scheme 26). The results are summarized in the following section.



Scheme 26. Enantioselective Diethylzinc Addition to Benzaldehyde

In this application, two different solvents were used as toluene and hexane. All the ligands exhibited acceptable and high enantioselectivities (up to 97% e.e.) and afforded 1-phenylpropanol in good yields. All the ligands gave the product with the *S* configuration.

The best result was obtained with the amino alcohol **(-)-63**, which is the sulfonamide derivative.

Table 4. Enantioselective Diethylzinc Addition to Benzaldehyde

Entry	Ligand	Solvent	Time (h)	e.e. (%)	Configuration
1	60	Hexane	48	**91**	S
2	60	Toluene	48	**95**	S
3	61	Hexane	48	76	S
4	61	Toluene	48	80	S
5	62	Hexane	48	84	S
6	62	Toluene	48	**92**	S
7	63	Hexane	40	**97**	S
8	63	Toluene	40	**96**	S

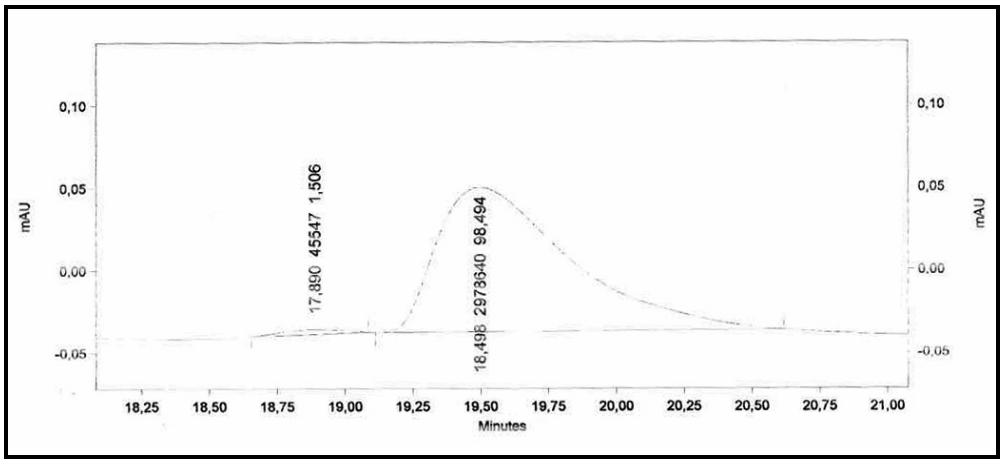


Figure 15. HPLC Chromatogram of 1-phenyl-1-propanol Using Compound **(-)-63**

In our project, the aim was to examine the electronic effects of the substituents attached to aryl part of the target chiral ligands in asymmetric transformation reactions.

However, the effect of the substituent could not be observed. The dechlorinated amino alcohol **(+)-62** gave higher enantiomeric excess values than the chlorinated one **(+)-61**, but lower e.e. values than **(-)-60**. This finding leads us to a conclusion that by decreasing or increasing the electron density on the ring might not have any noticeable effect on the enantiomeric excess values. In fact; heterogeneity could be a possible drawback. In the application reactions, the chlorinated amino alcohol gave inhomogeneous solutions both in toluene and hexane; however, the dechlorinated amino alcohol gave homogeneous mixtures with the solvents.

Furthermore, adding SO_2 group between the nitrogen and the ring increases the acidity of the hydrogen attached to amine group. This causes to increase the effectiveness of the ligand. Besides, for all the ligand except **(-)-63**, amino alcohols gave higher results in toluene than in hexane and for the ligand **(-)-63** they gave nearly same e.e. value (Table 4).

CHAPTER 3

EXPERIMENTAL

In this study, the structure elucidation of the compounds was done with the instruments as written.

NMR spectra were recorded on a Brucker DPX 400 spectrometer. Chemical shifts are expressed in ppm. downfield from tetramethylsilane, which is used as internal standard; the ^{1}H-NMR data is presented in the order: _ value of the signal, peak multiplicity (abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and coupling constants in Hertz integrated number of protons.^{13}C-NMR spectra were measured at 100 MHz and the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

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

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.

Flash column chromatography was employed using thick-walled glass columns with a flash grade silica-gel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck Silica Gel PF-254), visualized with UV-light, polymolybden phosphoric acid in methanol and $KMnO_4$ solution as appropriate. The relative portions of solvents are in volume: volume ratio used in column chromatography as eluent.

3.1. Synthesis of (2*S*,3*R*)-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene-3-carboxylic acid, 52

MeOH (0.63 mL, 15.6 mmol) was added dropwise to a stirred solution of the *meso*-anhydride **51** (0.85 g, 5.20 mmol) and quinine (1.85 g, 5,72 mmol) in a 1:1 mixture of toluene (60 mL) and carbontetrachloride (60 mL) at -55 oC 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 ethylacetate, the organic layer was dried over MgSO4, filtered, and concentrated providing the monoester **52** (0.94 g, 92 %).

$[\alpha]_D^{20}$ = -7.8 (*c* 4.0, CCl_4), lit.[56],[57]
m.p. 75–78 °C, lit.[56], [57] 74 °C (racemic);

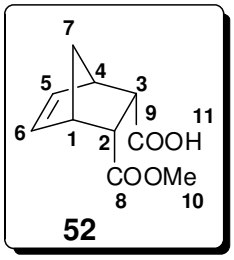


Figure 16

^{1}H-NMR (400 MHz, $CDCl_3$): 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= 1.56, 8.67Hz, 1H, H_7),

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

^{13}C-NMR (100 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*S*,3*R*)-3-(4-bromophenoxy)-2- (methoxycarbonyl)bicyclo [2.2.1]hept-5-ene, 64

4-Bromophenol (0.088 g, 0.51 mmol) and monoester 31 (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. DCC precipitated as dicyclohexylurea. The mixture was filtered and filtrate was washed with first 5% HOAc, then 1 N NaOH and finally brine. The organic phase was dried over $MgSO_4$ and evaporation of the solvent afforded the compound 38 (0.16 g, 89%). 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)

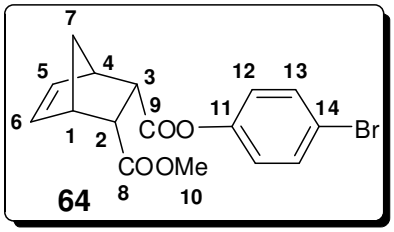


Figure 17

^{1}H-NMR (400 Mhz, $CDCl_3$): 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, 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 (100 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. General DCC coupling method to synthesize amide esters

Monoester **52** (1 eq.) and amine (1 eq.) were dissolved in CH_2Cl_2 at 0 ^{o}C under argon atmosphere. Then, DCC (1,1 eq.) and DMAP (0,25 eq) were added simultaneously at this temperature. The mixture were slowly come to room temperature and stirred overnight at room temperature. DCC precipitated as dicyclohexylurea. The mixture was filtered and filtrate was washed with first with 1 N HCl then 1 N $NaHCO_3$ and finally brine. The organic phase was dried over MgSO4 and evaporation of the solvent afforded the desired amide ester product.

3.4. Synthesis of *(2S,3R)*-2-(2-clorobenzenecarboxyamido)-3-(methoxy carbonyl)bicyclo[2.2.1]hept-5-ene, 53

Yield % 68

m.p. 78 ^{o}C

$[\alpha]_D^{20}$ = +58.9 (*c* 2.0, $CHCl_3$)

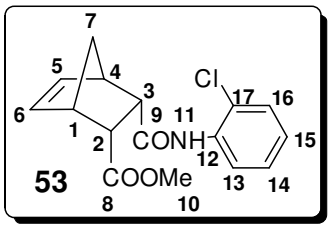


Figure 18

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

8.25 (d, *J*=8.06 Hz, 1H, H_{13}),

8.20 (s, 1H, H_{11}),

7.25 (d, *J*= 7.90 Hz, 1H, H_{16}),

7.16 (t, *J*= 8.0 Hz, 1H, H_{15}),

6.91 (t, *J*=7.8 Hz, 1H, H_{14}),

6.19 (dd, *J*=2.90, 5.28 Hz, 1H, H_5),

6.07 (dd, *J*=2.95, 5.32 Hz, 1H, H_6),

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

3.18 (d, *J*=4.57 Hz, 2H, H_2, H_3),

3.01 (bs, 1H, H_1),

2.64 (t, *J*=1.63 Hz, 1H, H_4),

1.70 (d, *J*=7.95 Hz, 1H, H_7),

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

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

174.0, 172.4, 137.7, 135.9, 135.0, 133.2, 127.6, 124.5, 122.8, 121.7, 49.8, 49.8, 48.9, 47.7, 47.5, 46.2.

3.5. Synthesis of *(2S,3R)*-2-(2-nitrobenzenecarboxyamido)-3-(methoxy carbonyl)bicyclo[2.2.1]hept-5-ene, 54

Yield % 60

m.p. 96 °C

$[\alpha]_D^{20}$ = +7.9 (*c* 2.0, $CHCl_3$)

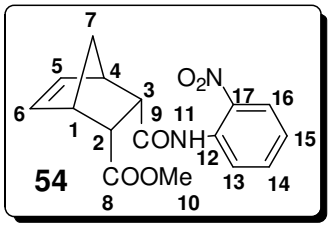


Figure 19

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

10.52 (s, 1H, H_{11}),

8.74 (d, *J*=8.54 Hz, 1H, H_{16}),

8.21 (d, *J*=6.96 Hz, 1H, H_{13}),

7.64 (t, *J*=7.14 Hz, 1H, H_{15}),

7.18 (t, *J*=7.83 Hz, 1H, H_{14}),

6.33 (dd, *J*=5.41, 2.90 Hz, 1H, H_5),

6.19 (dd, *J*=5.37, 2.70 Hz, 1H, H_6),

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

3.37 (t, *J*=4.1 Hz, 1H, H_2),

3.31 (bs, 1H, H_3),

3.20 (bs, 1H, H_1),

2.72 (t, *J*=2.34 Hz, 1H, H_4),

1.80 (d, *J*=8.75 Hz, 1H, H_7),

1.55 (dd, *J*=8.80, 1.45 Hz, 1H, H_7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm:

173.5, 173.2, 137.5, 136.7, 136.1, 135.7, 134.8, 125.7, 123.2, 122.5, 52.1, 50.6, 49.3, 47.5, 47.0, 45.0.

3.6. Synthesis of *(2S,3R)*-2-(4-methylbenzenesulfoncarboxyamido)-3-(methoxycarbonyl)bicyclo[2.2.1]hept-5-ene, 55

Yield % 82

m.p. 76 °C

$[\alpha]_D^{20}$ = +16.7 (*c* 2.0, $CHCl_3$)

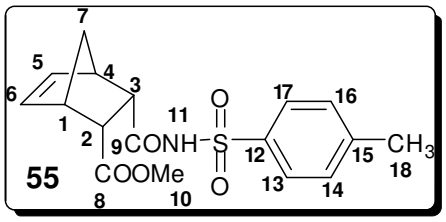


Figure 20

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.88 (d, J=8.28 Hz, 2H, H_{17}, H_{13}),

7.24 (d, J=8.15 Hz, 2H, H_{16}, H_{14}),

6.12 (dd, J=3.20, 5.42 Hz, 1H, H_5)

6.01 (dd, J=3.17, 5.48 Hz, 1H, H_6),

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

3.14 (bs, 1H, H_2),

3.10 (t, *J*=4.26 Hz, 1H, H_3),

2.98 (bs, 1H, H_1),

2.38 (d, *J*=4.82 Hz, 1H, H_4),

2.36 (s, 3H, H_{18}),

1.50 (dd, *J*=8.95, 17.40 Hz, 1H, H_7).

1.33 (dd, *J*=8.62, 16.85 Hz, 1H, H_7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

174.3, 171.8, 144.8, 137.5, 136.0, 135.7, 129.5, 128.3, 52.3, 49.2, 48.5, 47.3, 46.2, 44.9, 33.8,

3.7. General procedure for the reduction of amide ester by LAH.

Amide ester (1 eq) was added dropwise to a suspension solution of LAH (5 eq) in anhydrous THF after it starts to reflux gently. The mixture was continued to reflux until the starting compound is disappeared on TLC. The reaction is quenched with 1 ml distilled water in an ice bath. The precipitated was filtered and washed with THF for several times. Evaporation of solvent afforded to desired product.

3.8. Synthesis of *(2S,3R)*-3-(2-aminobenzeneaminomethyl)-2-(hydroxymethyl) bicyclo[2.2.1]hept-5-ene, 56

Yield = % 71

m.p. = oily

$[\alpha]_D^{20}$ = -202.90 (c .0.5 $CHCl_3$)

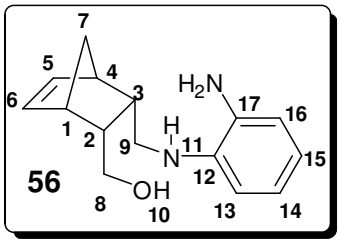


Figure 21

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

6.67 (t, J= 7.9 Hz, 1H, H_{15}),

6.52 (t, J=7.3 Hz, 2H, H_{14}, H_{16}),

6.45 (d, J=7.6 Hz, 1H, H_{13}),

6.02 (dd, J= 2.95, 5.43 Hz, 1H, H_5),

5.82 (dd, J=2.95, 5.43 Hz, 1H, H_6),

3.50 (dd, J=4.74, 9.98 Hz, 1H, H_8),

3.15 (dd, J= 4.82, 10.66 Hz, 1H, H_8),

2.82 (t, J=10.15 Hz, 1H, H_9),

2.72 (t, J=9.56 Hz, 1H, H_9),

2.60 (bs, 1H, H_1),

2.55 (bs, 1H, H_4)

1.77 (dd, J=5.10, 9.02 Hz, 1H, H_7)

1.39 (dd, J=8.34, 21.18 Hz, 2H, H_3, H_2),

1.26 (dd, J=5,48, 10.64 Hz, 1H, H_7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

137.9, 137.7, 133.5, 133.2, 120.9, 117.8, 116.4, 111.0, 66.5, 49.6, 48.7, 48.6, 47.2, 46.5,44.7.

3.9. Synthesis of *(2S,3R)*-3-(2-clorobenzeneaminomethyl)-2-(hydroxymethyl) bicyclo[2.2.1]hept-5-ene, 57

Yield = % 78

m.p. = oily

$[\alpha]_D^{20}$ = +7.65 (c 2.0 $CHCl_3$).

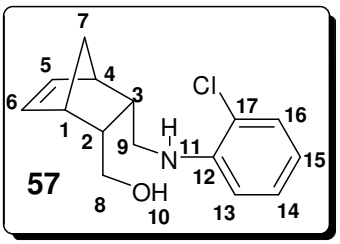


Figure 22

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.15 (d, J=7.88 Hz, 1H, H_{16}),

7.04 (t, J=7.25 Hz, 1H, H_{13}),

6.53 (dd, J=8.00, 15.5 Hz, 2H, H_{14}, H_{15}),

6.15 (dd, J=3.20, 5.55 Hz, 1H, H_5),

5.93 (dd, J=3.20, 5.90 Hz, 1H, H_6),

3.51 (dd, J=5.29, 9.01 Hz, 1H, H_8),

3.17-3.09 (m, 2H, H_8, H_9),

2.98 (dd, J=9.08, 11.35 Hz, 1H, H_9),

2.75 (bs, 1H, H_1),

2.61 (bs, 1H, H_4),

1.88-1.83 (m, 1H, H_2),

1.44 (dd, J=7.59, 14.89 Hz, 2H, H_7, H_7),

1.35-1.30 (m, 1H, H_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

144.4, 137.7, 133.8, 129.1, 127.8, 119.1, 116.8, 111.1, 66.4, 49.2, 48.4, 46.9, 46.1, 44.4, 43.3.

3.10. Synthesis of *(2S,3R)*-3-(2-phenoxyaminomethyl)-2-(hydroxymethyl) bicyclo[2.2.1]hept-5-ene, 58

Yield = % 81

m.p. = 77.1 ^{o}C

$[\alpha]_D^{20}$ = +3.85 (c 2.0 $CHCl_3$)

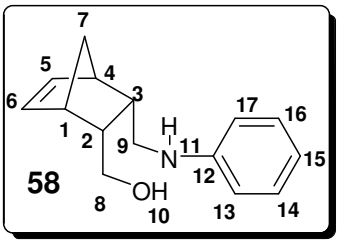


Figure 23

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.07 (t, J=7.9 Hz, 2H, H_{17}, H_{16}),

6.60 (t, J=6.95 Hz, 1H, H_{15}),

6.51 (d, J=7.92 Hz, 2H, H_{13}, H_{14}),

6.12 (dd, J=3.17, 5.49 Hz, 1H, H_5)

5.89 (dd, J=3.17, 5.49 Hz, 1H, H_6),

3.46 (dd, J=5.94, 10.04 Hz, 1H, H_8),

3.11 (dd, J=6.00, 11.40 Hz, 1H, H_8),

3.02 (t, J=9.60 Hz, 1H, H_9),

2.87 (t, J=9.56 Hz, 1H, H_9),

2.71 (s, 1H, H_1),

2.56 (s, 1H, H_4),

1.78 (dd, J=2.98, 6.95 Hz, 1H, H_7),

1.41 (dd, J=8.68, 16.63 Hz, 2H, H_2, H_3),

1.24 (dd, J=4.88, 9.46 Hz, 1H, H_7).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

148.7, 137.8, 133.7, 129.3, 117.3, 112.9, 66.4, 49.6, 48.5, 46.9, 46.1, 44.5, 43.9.

3.11. Synthesis of *(2S,3R)*-3-(4-methylphenoxysulfonaminomethyl)-2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene, 59

Yield % 77

m.p. 121 °C

$[\alpha]_D^{20}$ = -12.8 (*c* 2.0, $CHCl_3$)

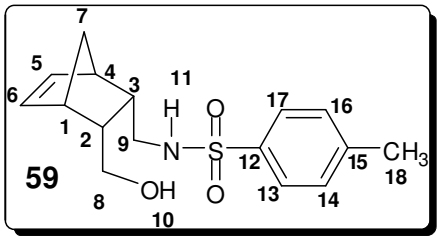


Figure 24

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.76 (d, J=8.02 Hz, 2H, $H1_3$, H_{17}),

6.60 (d, J=8.10 Hz, 2H, H_{14}, H_{16}),

6.21 (bs, 1H, H_{11}),

6.14 (dd, J=3.16, 5.43 Hz, 1H, H_5)

5.94 (dd, J=3.17, 5.60 Hz, 1H, H_6),

3.62 (dd, J=5.30, 9.77 Hz, 1H, H_8),

3.10 (dd, J=5.40, 11.14 Hz, 1H, H_8),

3.03 (t, J=9.60 Hz, 1H, H_9),

2.72 (t, J=8.40 Hz, 2H, H_9, H_1),

2.50 (s, 1H, H_4),

2.41 (s, 3H, H_{18}),

1.73-1.68 (m, 1H, H_2),

1.36 (dd, J=8.38, 23.35 Hz, 2H, H_7, H_7),

1.24-1.17 (m, 1H, H_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

143.1, 137.5, 136.9, 133.6, 129.6, 127.1, 47.9, 47.8, 46.8, 45.9, 44.5, 43.7, 21.5, 20.7.

3.12. General Procedure for Hydrogenation of olefins

The compound was put into a 2 necked reaction vessel and solved in CH_2Cl_2. Then 10 % (wt/wt) Pd was added to this mixture and H_2 gas is allowed to pass into the reaction vessel. The reaction is continued until the starting compound is consumed by monitoring on TLC. The mixture was filtered with celite and washed with CH_2Cl_2 several times. Evaporation of solvent afforded to desired product.

3.13. Synthesis of *(2S,3R)*-3-(2-aminobenzeneaminomethyl)-2-(hydroxy methyl)bicyclo[2.2.1]hept-5-ene, 60

Yield % 90

m.p. 85 °C

$[\alpha]_D^{20}$ = -116.0 (*c* 0,1 $CHCl_3$)

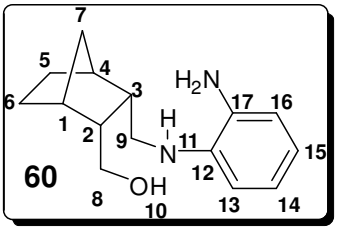


Figure 25

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

6.72 (t, J= 6.25 Hz, 1H, H_{15}),

6.58 (dd, J=1.42, J=7.41 Hz, 1H, H_{14}),

6.54 (d, J=7.30 Hz, 1H, H_{16}),

6.50 (d, J= 4.40 Hz, 1H, H_{13}),

3.54 (dd, J=4.89, 10.06 Hz, 1H, H_8),

3.27 (t, J=9.93 Hz, 1H, H_8),

3.02 (dd, J=5.22, 10.79 Hz, 1H, H_9),

2.60 (t, J=10.60 Hz, 1H, H_9),

2.10 (bs, 1H, H_2),

1.99 (d, J=4.06 Hz, 1H, H_3),

1.52 (dd, J=4.54 Hz, 9.11, 1H, H_1),

1.51-1.43 (m, 1H, H_4),

1.39 (d, J=9.60 Hz 1H, H_6),

1.25-1.18 (m, 1H, H_6),

1.18 (bs, 1H, H_7),

1.12 (bs, 1H, H_7),

1.12-1.10 (m, 1H, H_5)

1.04-0.98 (m, 1H, H_5)

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

138.1, 133.2, 120.9, 117.6, 116.3, 111.0, 49.3, 49.2, 48.1, 41.3, 39.4, 37.6, 30.1, 25.9, 22.7.

3.14. Synthesis of *(2S,3R)*-3-(2-clorobenzeneaminomethyl)-2-(hydroxy methyl)bicyclo[2.2.1] hept-5-ene, 61

Yield = % 87

m.p. = oily

$[\alpha]_D^{20}$ = +10.8 (c 2.0 $CHCl_3$)

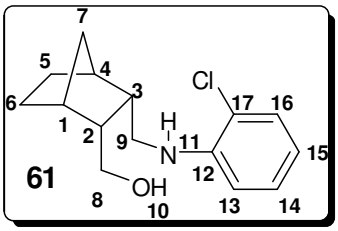


Figure 26

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.15 (dd, J=6.25 Hz, 7.3, 1H, H_{16}),

7.03 (t, J=7.07 Hz, 1H, H_{15}),

6.52 (dd, J=7.33 Hz, 13.54 2H, $H_{14,}$ H_{13}),

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

3.61 (dd, J=6.87, 9.98 Hz, 1H, H_8),

3.49 (t, J=9.41 Hz, 1H, H_8),

3.00 (dd, J=6.70 Hz, 11.62, 1H, H_9),

2.79 (dd, J=8.85, 11.47 Hz, 1H, H_9),

2.21 (s, 1H, H_2),

2.06 (s, 1H, H_3),

1.64 (bs, 1H, H_1),

1.58-1.49 (m, 1H, H_4),

1.43 (d, J=9.90, 1H Hz, H_7),

1.39-1.24 (m, 3H, H_5, H_5, H_6)

1.19 (d, J=9.76 Hz, 1H, H_7),

1.13-1.06 (m, 1H, H_5)

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

144.5, 129.1, 127.8, 119.1, 116.9, 111.2, 64.8, 49.0, 48.9, 47.2, 40.8, 38.9, 37.3, 29.9, 22.5.

3.15. Synthesis of *(2S,3R)*-3-(2-phenoxyaminomethyl)-2-(hydroxymethyl) bicyclo[2.2.1] heptane , 62

Yield = % 88

m.p. = 69.0 °C

$[\alpha]_D^{20}$ = +5.1 (c 2.0 $CHCl_3$)

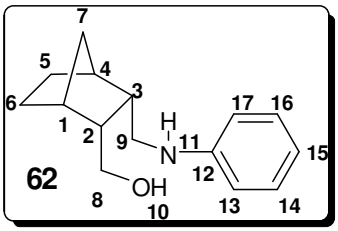


Figure 27

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.08 (t, J=7.9 Hz, 2H, H_{17} H_{13}),

6.62 (t, J=6.95 Hz, 1H, H_{15}),

6.51 (d, J=7.92 Hz, 2H, H_{16} H_{14}),

3.58 (dd, J=6.05, 10.09 Hz, 1H, H_8),

3.43 (t, J=9.51 Hz, 1H, H_8),

3.13 (bs, 1H, H_9),

3.00 (dd, J=6.21, 11.56 Hz, 1H, H_9),

2.70 (dd, J=9.22, 11.46 Hz, 1H, H_{11}),

2.19 (s, 1H, H_2),

2.02 (d, J=4.08 Hz, 1H, H_3),

1.62-1.56 (m, 1H, H_1),

1.55-1.47 (m, 1H, H_4),

1.41 (d, J=9.84 Hz, 1H, H_7),

1.32-1.22 (m, 3H, H_5, H_5, H_6)

1.17 (d, J=9.84 Hz, 1H, H_7),

1.12-1.10 (m, 1H, H_5)

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

147.7, 128.2, 116.3, 111.9, 63.9, 48.4, 48.3, 46.9, 39.8, 38.0, 36.4, 28.9, 21.5.

3.16. Synthesis of *(2S,3R)*-3-(4-methylphenoxysulfonaminomethyl)-2-(hydroxymethyl)bicyclo[2.2.1]heptane, 63

Yield = % 91

m.p. = 75.1 ^{o}C

$[\alpha]_D^{20}$ = -13.2 (c 1.0 $CHCl_3$)

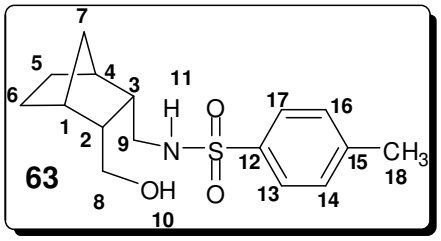


Figure 28

^{1}H-NMR (400 Mhz, $CDCl_3$): δ ppm

7.67 (d, J=8.12 Hz, 2H, H_{17}, H_{16}),

7.21 (d, J=8.10 Hz, 2H, H_{14}, H_{13}),

6.23 (bs, 1H, H_{11}),

3.61 (dd, J=4.50, 9.44 Hz, 1H, H_8),

3.36 (t, J=10.09 Hz, 1H, H_8),

2.91 (dd, J=4.65, J=15.83 Hz, 1H, H_9),

2.43 (t, J=10.96 Hz, 1H, H_9),

2.34 (s, 3H, H_{18}),

2.09 (bs, 1H, H_2)

1.85 (bs, 1H, H_3),

1.44-1.35 (m, 2H, H_1, H_4),

1.23-1.13 (m, 4H, H_5, H_5, H_6, H_6),

1.07 (dd, J=13.50, J=24.50 Hz, 2H, H_7, H_7),

^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm

142.0, 135.9, 128.6, 126.1, 63.5, 48.0, 46.7, 46.6, 39.9, 38.3, 36.4, 28.9, 21.5, 20.5.

3.17. General Procedure for Asymmetric Borane Reduction

Ligand was dissolved in desired solvent (1ml) at room temperature and BH_3.THF complex (or $BH_3.SMe_2$) (1 mmol) was added. The reaction was heated to reflux temperature of the solvent and stirring and refluxing was continued for 1 hour. Then the reaction mixture was cooled to between 30 and 40 ^oC and a THF solution of acetophenone was added dropwise via syringe during 2 h. The reaction was monitored by TLC and the reaction mixture was stirred until the starting compound is consumed. After addition of MeOH, the solvent was evaporated to give the corresponding alcohol. The compound was purified with flash column chromatography with 1:4 ethyl acetate:hexane. HPLC analysis: Chiralcel OJ-H at room temperature, *n* hexane/2-propanol = 96:4, 0.98 mL/min, 220 nm, t_1= 16.0 min, t_2= 18.5 min.

3.18. General Procedure for Diethylzinc addition to benzaldehyde reaction

Ligand (0.05 mmol) was dissolved in toluene (or hexane) (3 mL) at room temperature under argon atmosphere and diethyl zinc (2.0 mmol, 1 M in hexane) was added to this solution. The mixture was stirred for 60 minutes. Benzaldehyde (0.5 mmol) was added to this mixture and the reaction mixture was stirred for 48-60 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 OJ-H at room temperature, *n* hexane/2-propanol = 98:2, 1.0 mL/min, 254 nm, t_1= 17.3 min (*R*), t_2= 18.5 min (*S*).

CHAPTER 4

CONCLUSION

Four new different novel chiral N-aryl substituted 1,4-amino alcohol ligands **(-)-60, (+)-61, (+)-62, (-)-63** were synthesized by using chemoselective methods. Then, their effectiveness was examined in asymmetric borane reduction and enantioselective diethylzinc addition to benzaldehyde reaction. Ligands gave lower enantiomeric excess values with the asymmetric borane reduction although some optimization processes were done. Ligand **(-)-60** gave the highest ee value (54 %).

In diethylzinc experiments, ligands gave high and acceptable results in room temperature. Ligand **(-)-63** gave the highest enantiomeric excess value (97 %) in hexane. The ligands gave higher values in toluene than in hexane.

The synthesized amino alcohols are also potential chiral ligands in the various asymmetric reactions. For example, they can be used in asymmetric Aldol, Diels-Alder and Baylis-Hilman reactions. Also, they can be used as potent organocatalyst. Furthermore; the synthesized norbornene backbone amino alcohols **56**, **57**, **58**, **59** can be used in ring opening metathesis polymerization with Grubbs catalyst.

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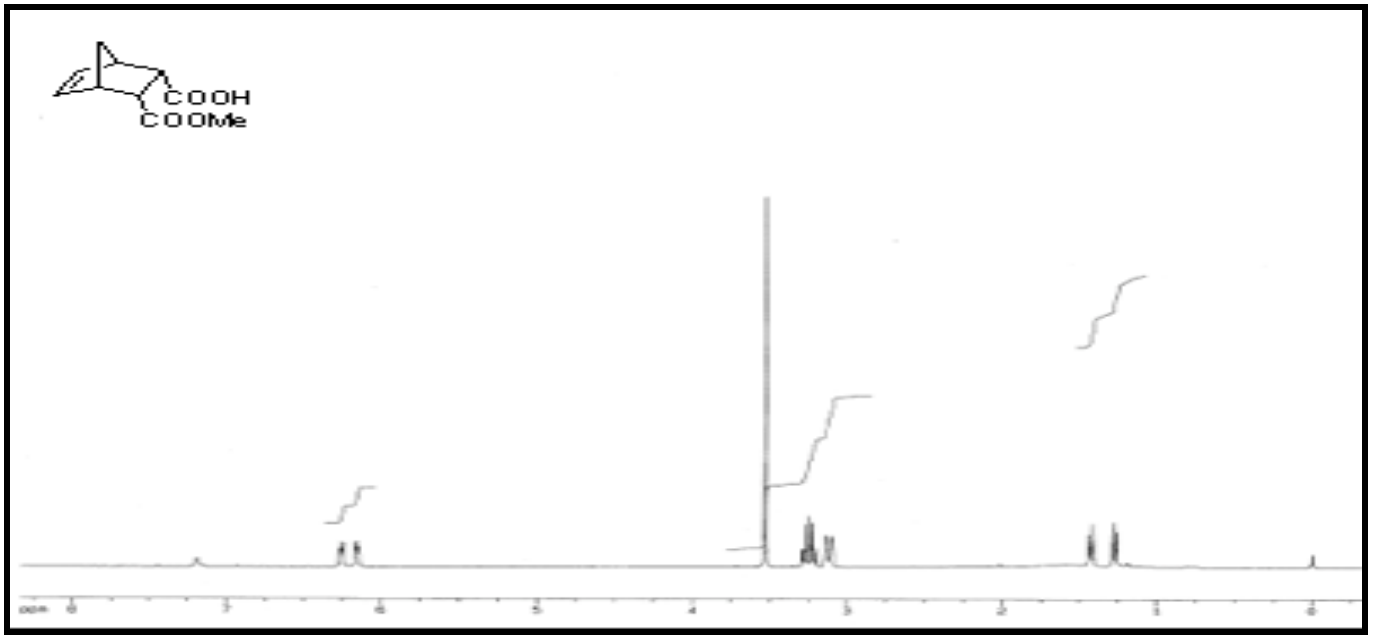

Figure 29. ^{1}H-NMR Spectrum of Compound **52**

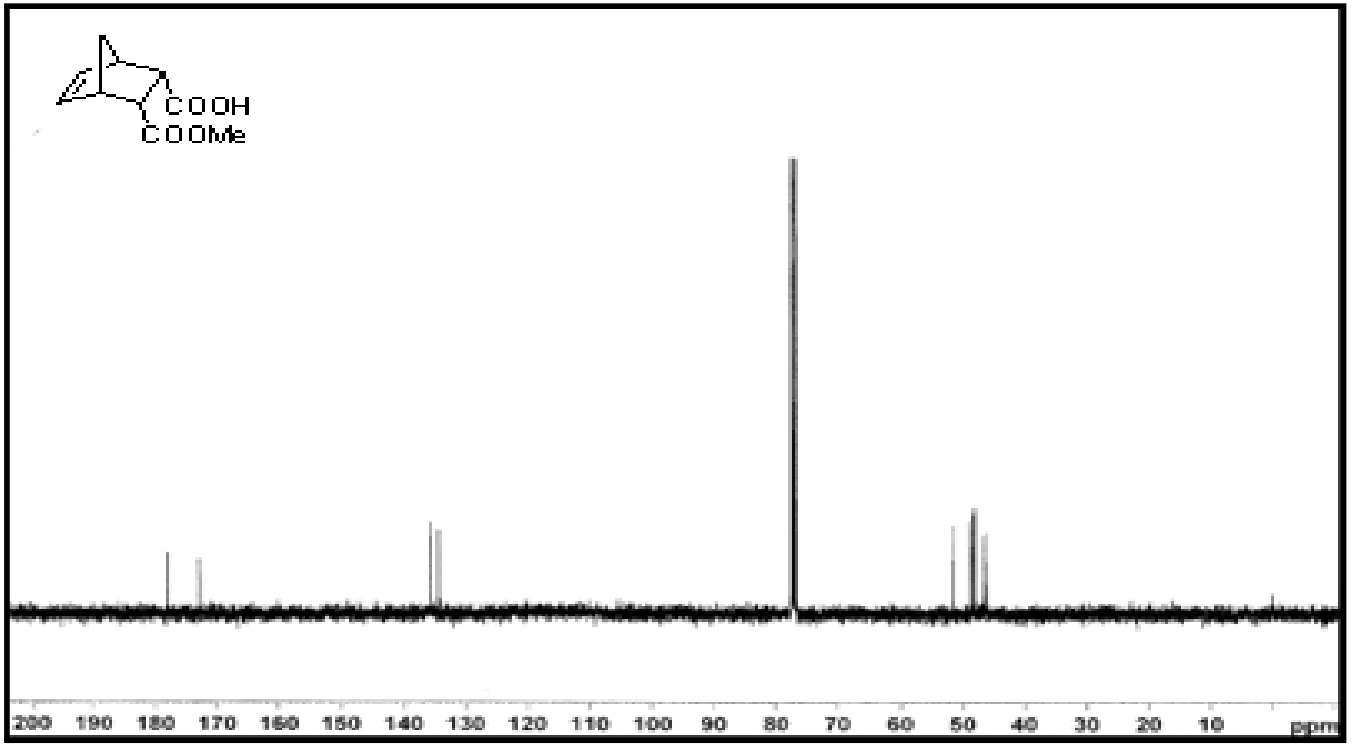

Figure 30. ^{13}C-NMR Spectrum of Compound **52**

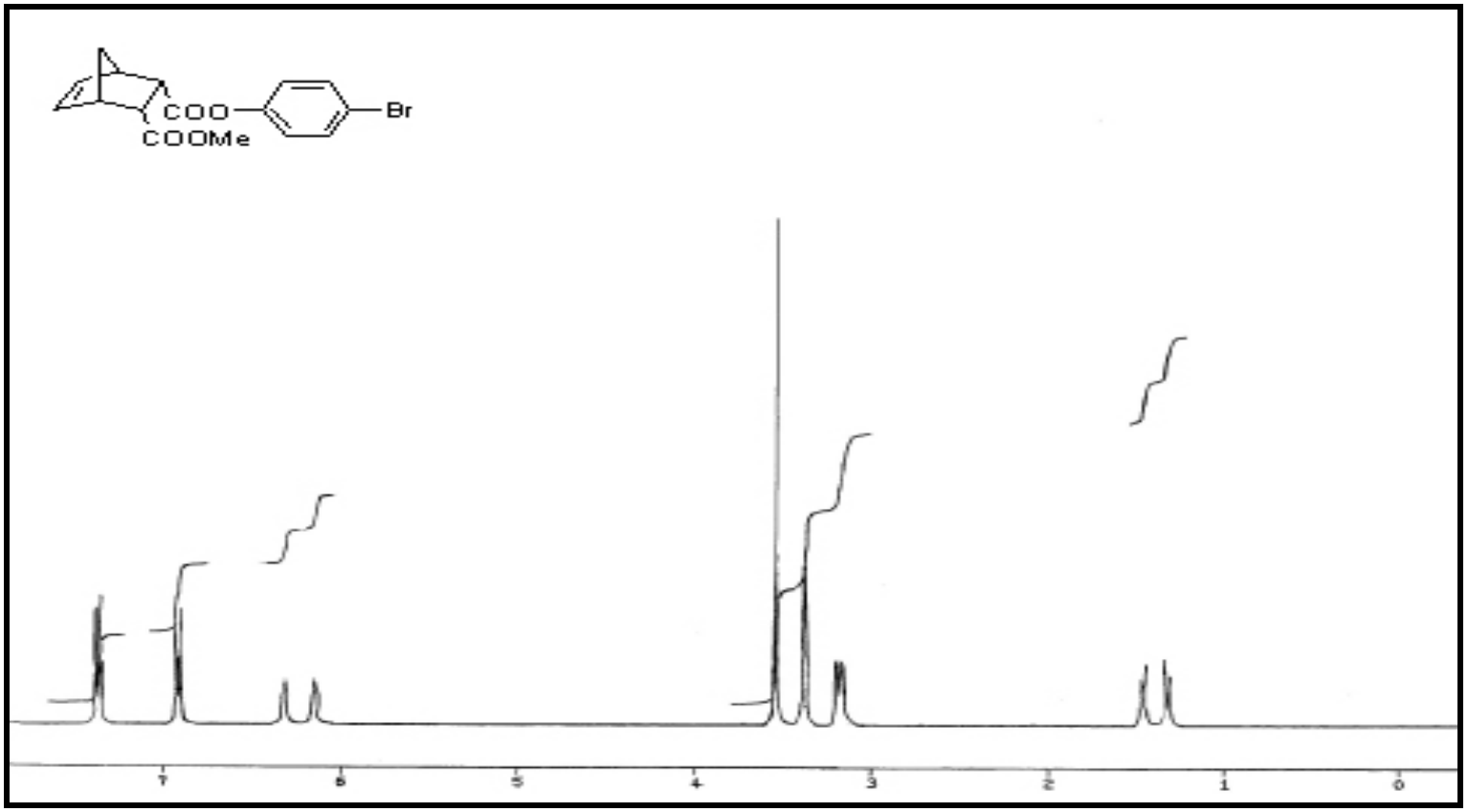

Figure 31. ^{1}H-NMR Spectrum of Compound **64**

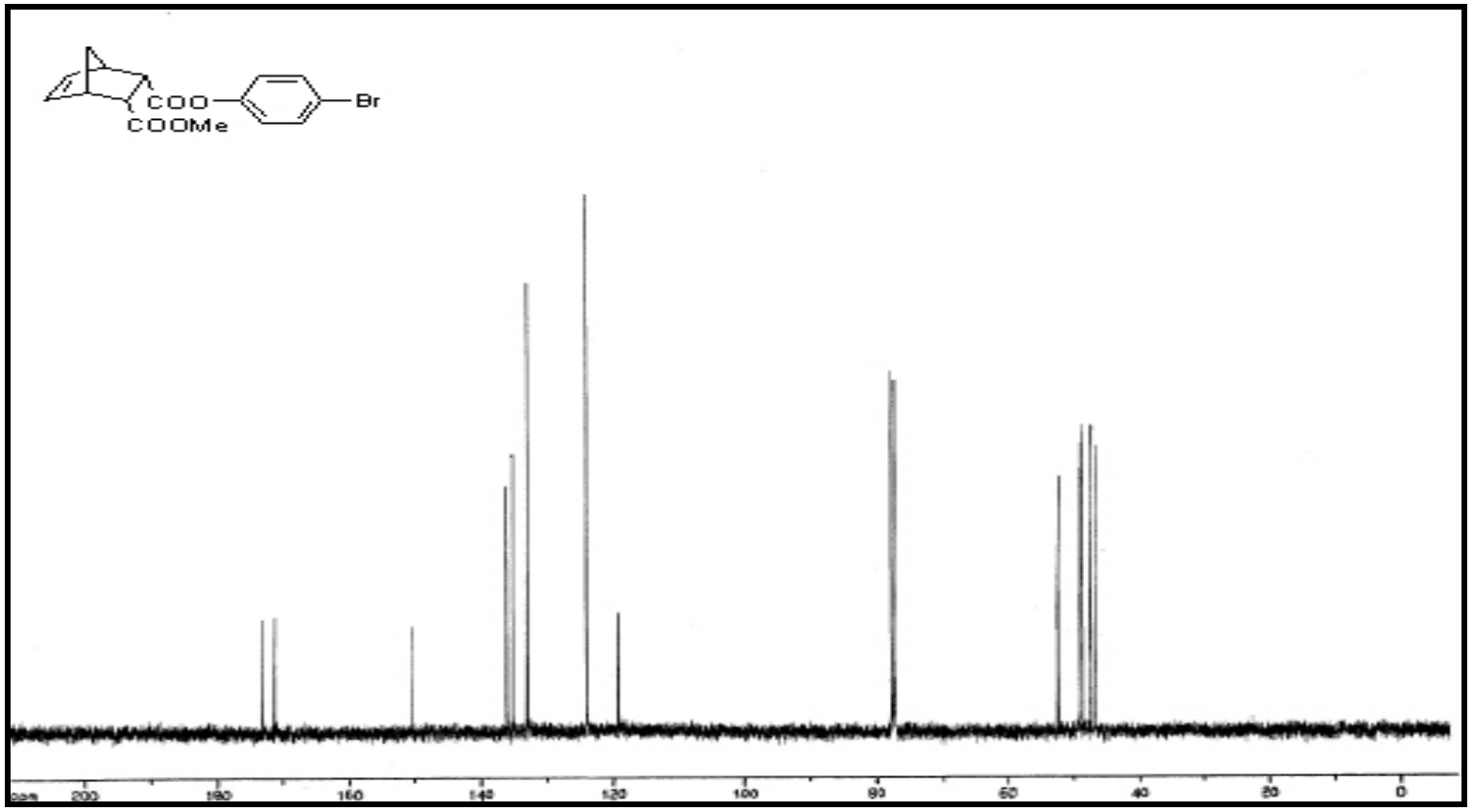

Figure 32. ^{13}C-NMR Spectrum of Compound **64**

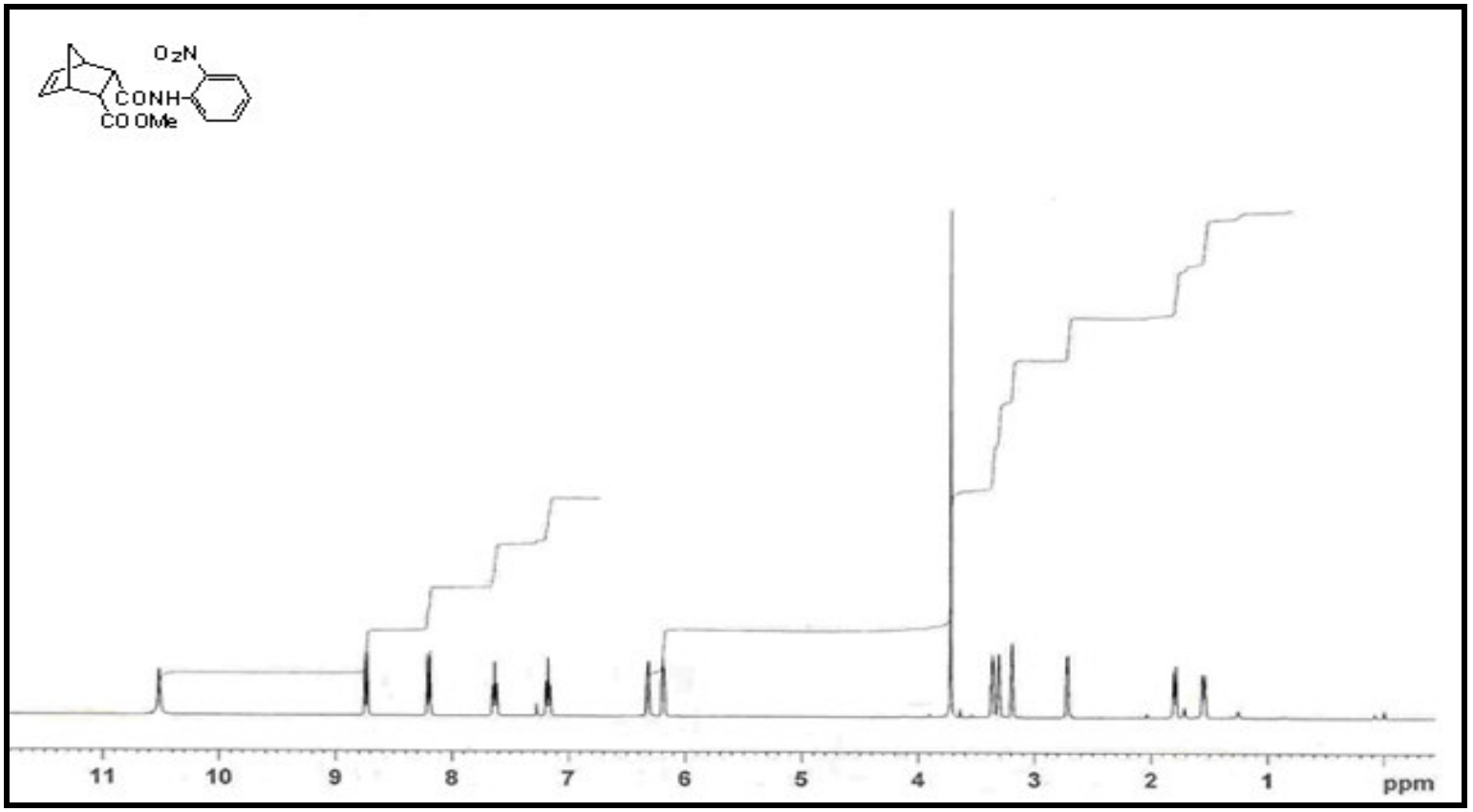

Figure 33. [1]H-NMR Spectrum of Compound **54**

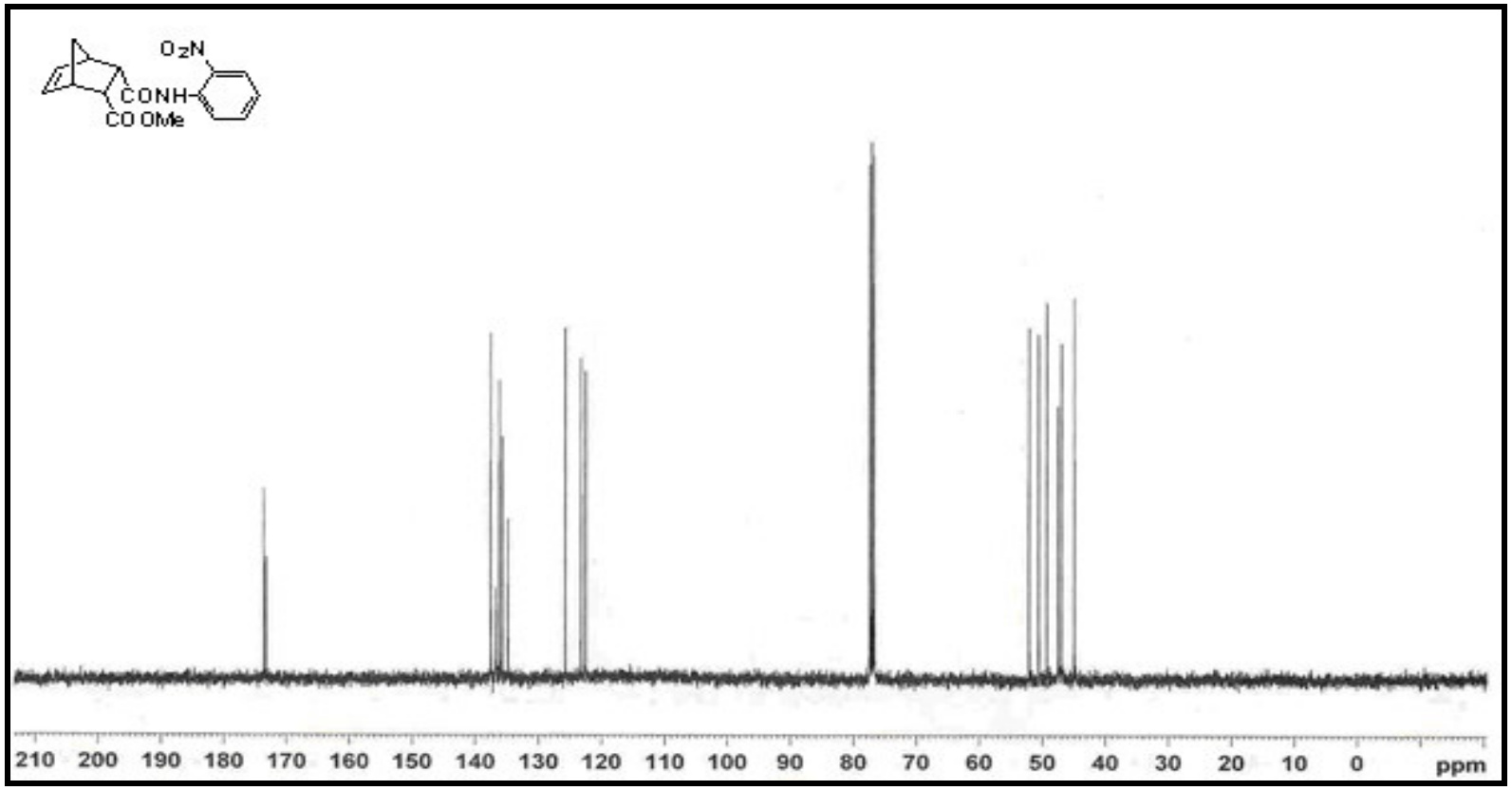

Figure 34. ^{13}C-NMR Spectrum of Compound **54**

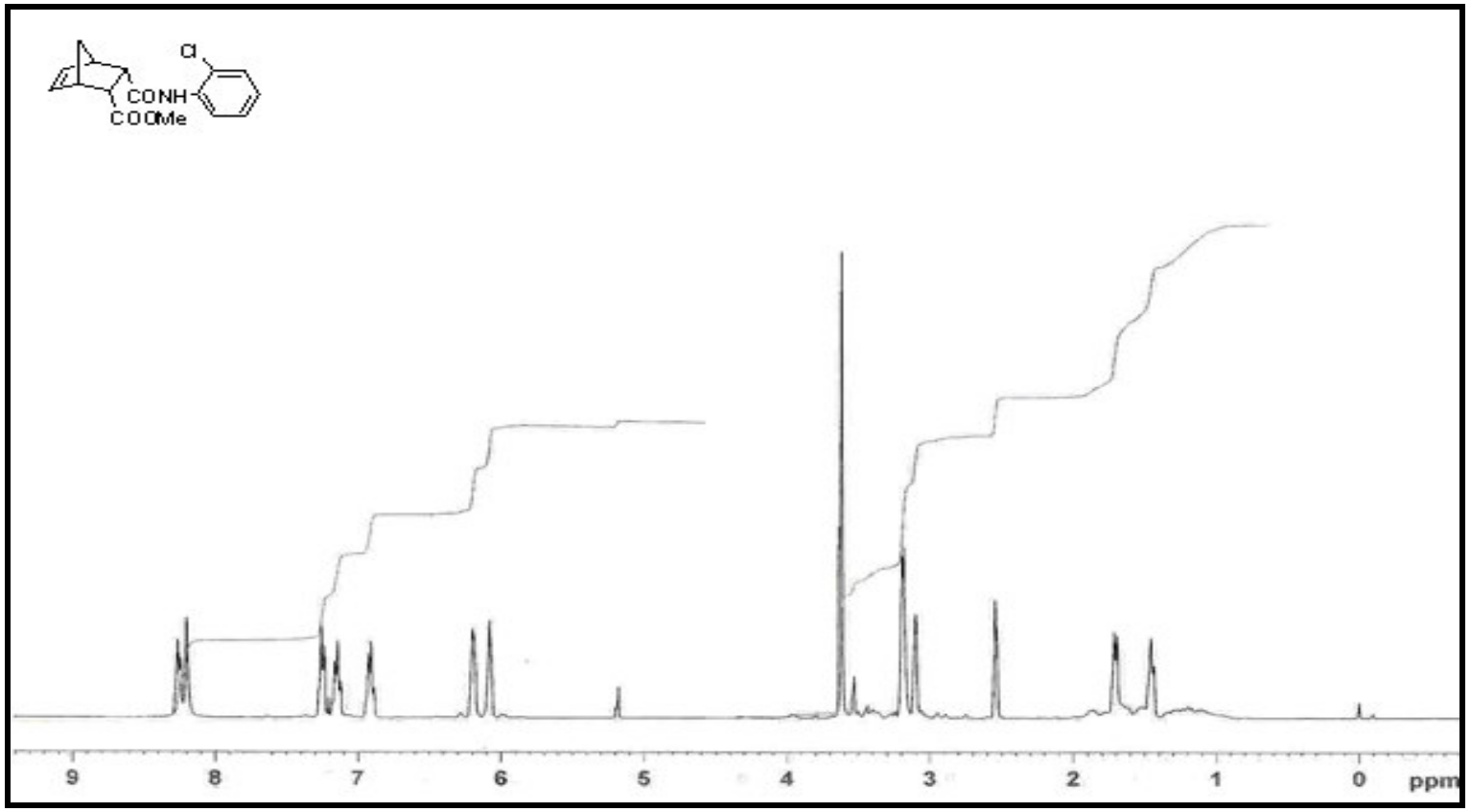

Figure 35. ^{1}H-NMR Spectrum of Compound **53**

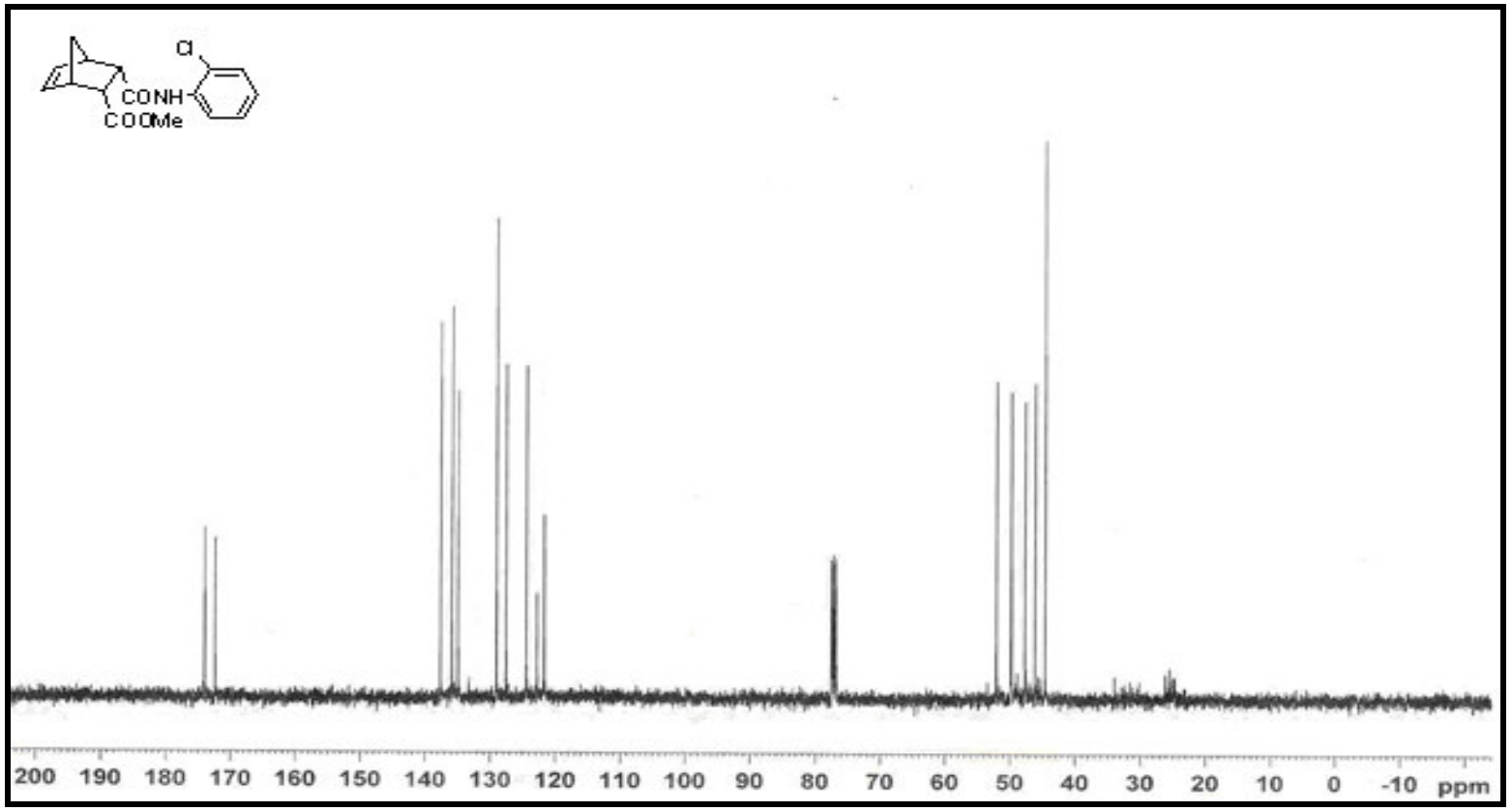

Figure 36. ^{13}C-NMR Spectrum of Compound **53**

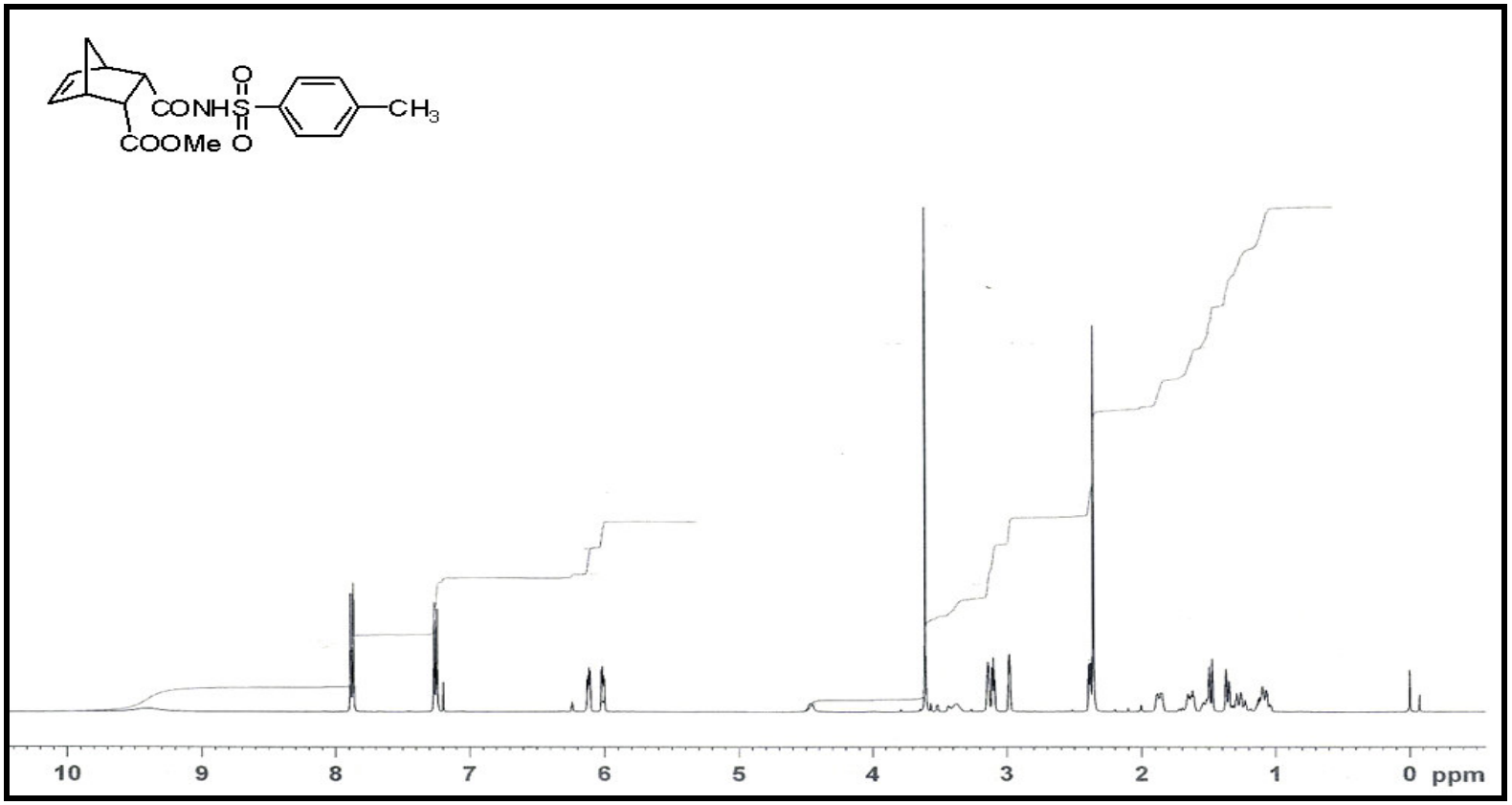

Figure 37. ^{1}H-NMR Spectrum of Compound **55**

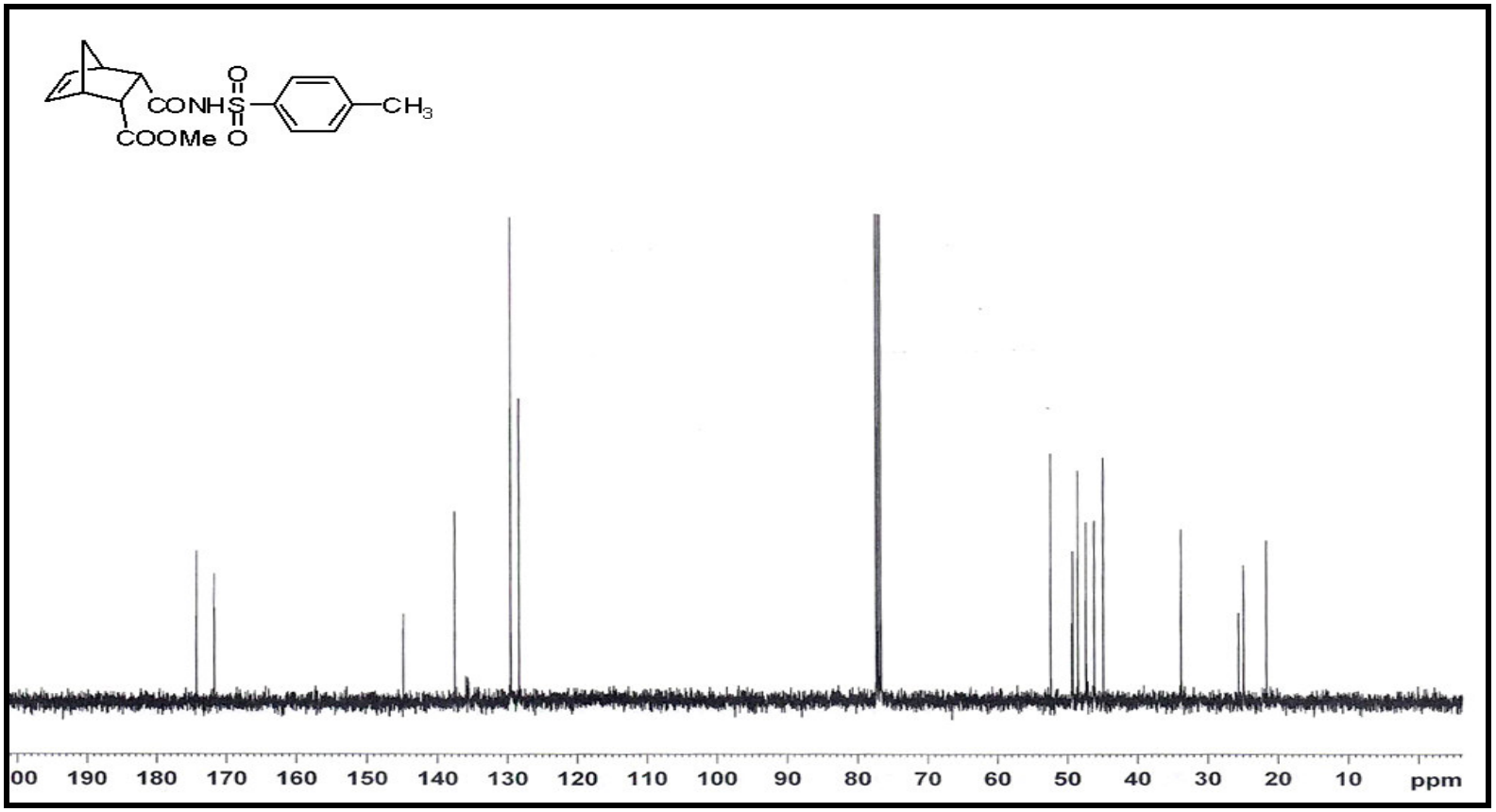

Figure 38. ^{13}C-NMR Spectrum of Compound **55**

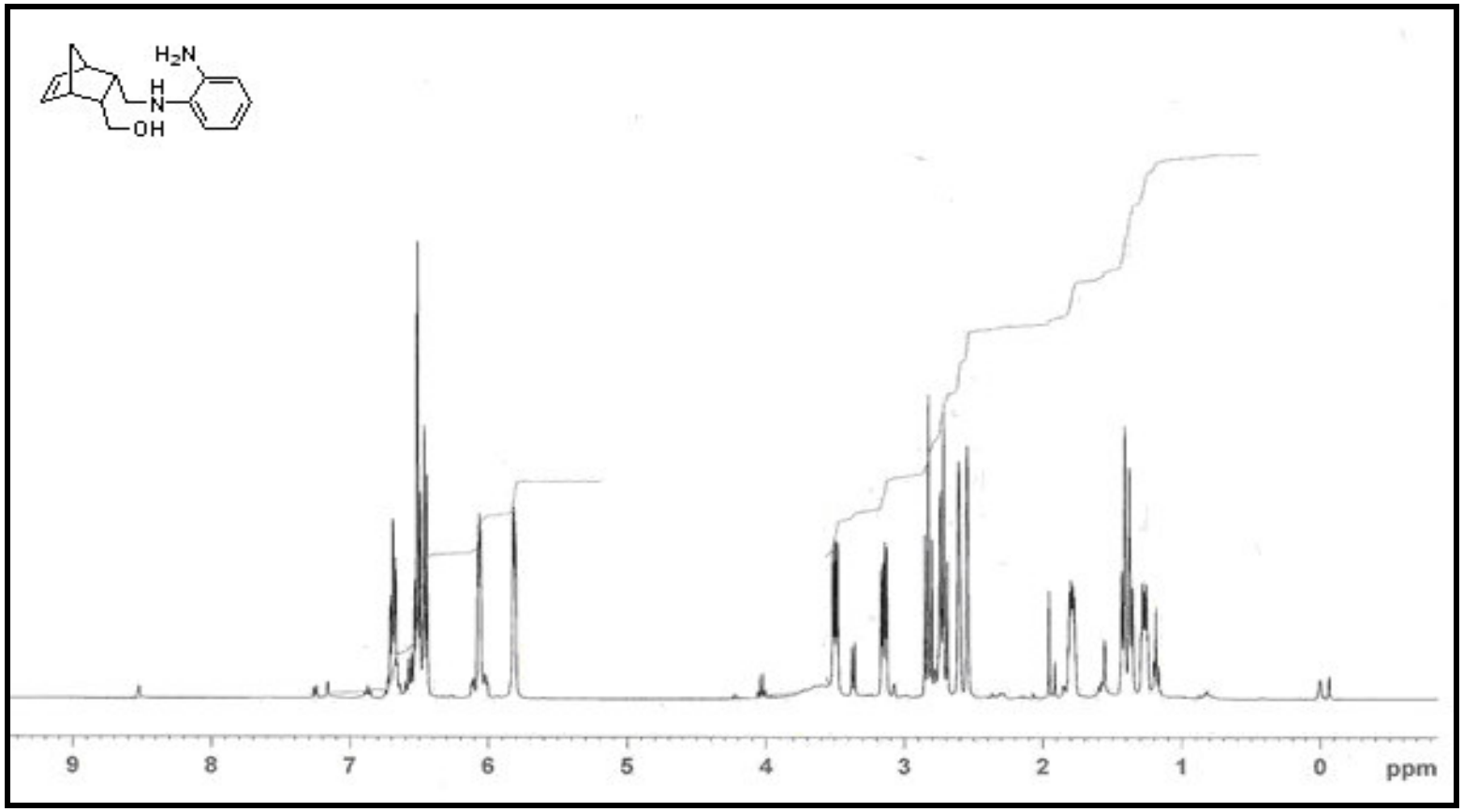

Figure 39. ^{1}H-NMR Spectrum of Compound **56**

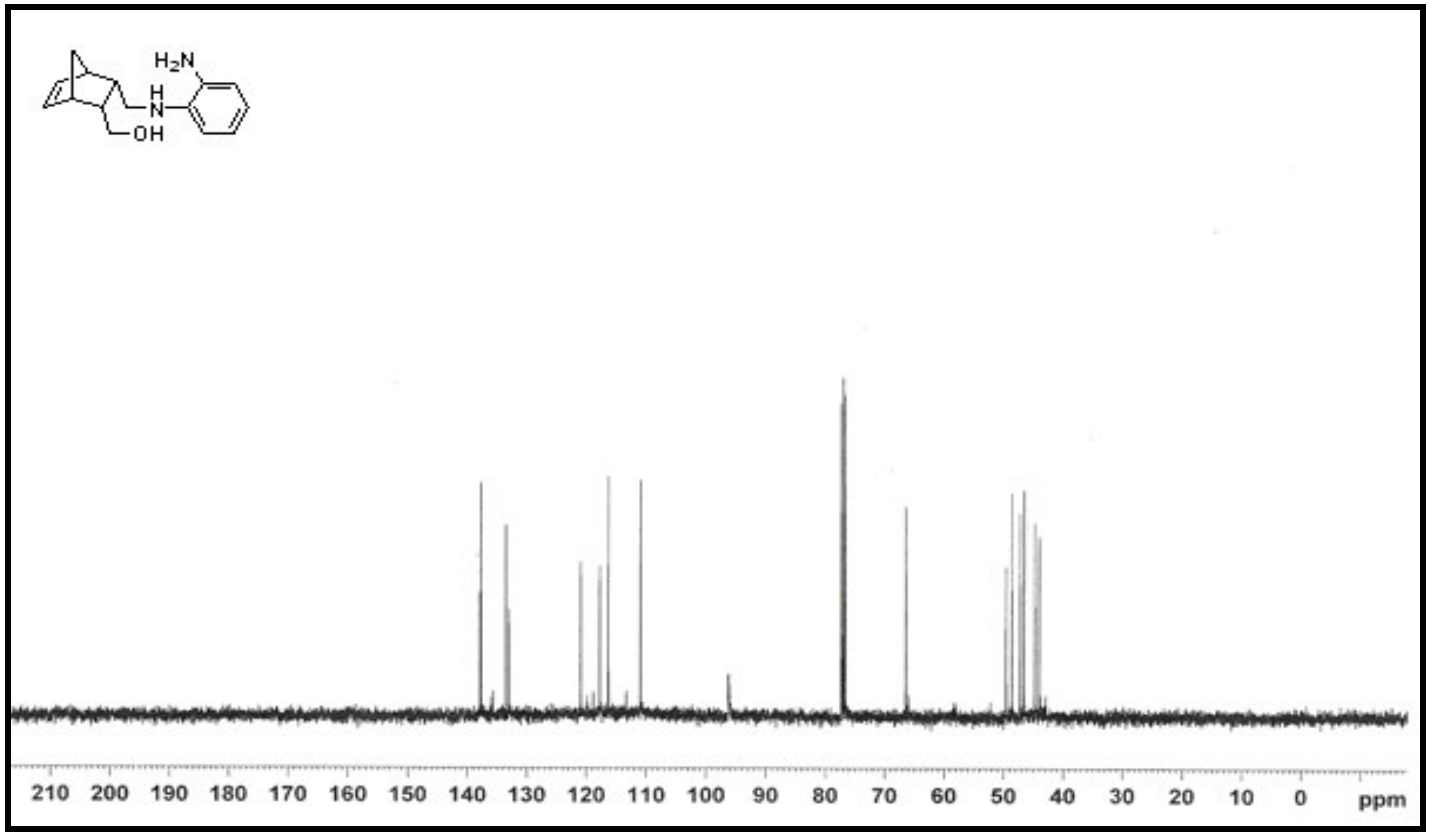

Figure 40. ^{13}C-NMR Spectrum of Compound **56**

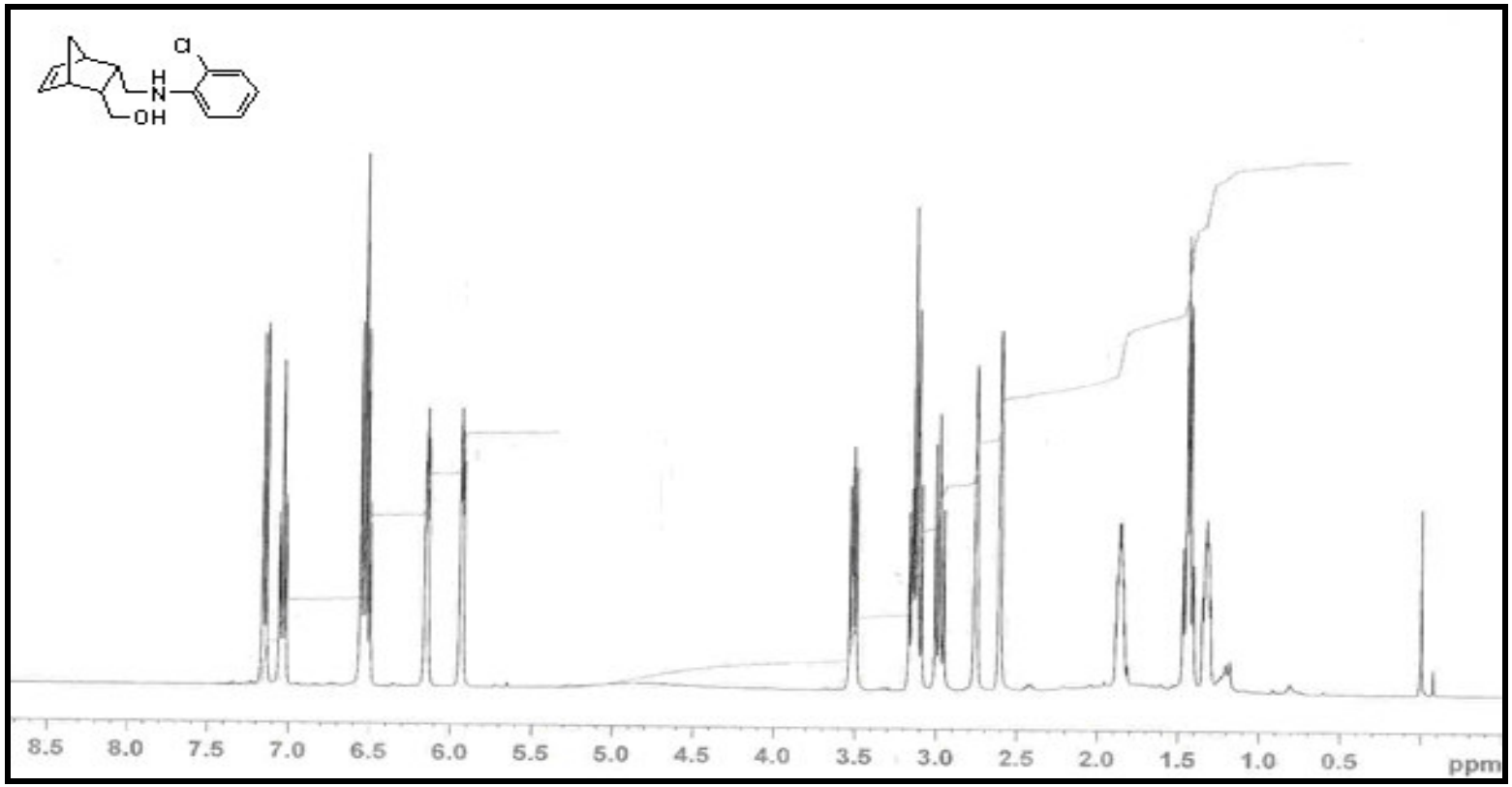

Figure 41. ^{1}H-NMR Spectrum of Compound **57**

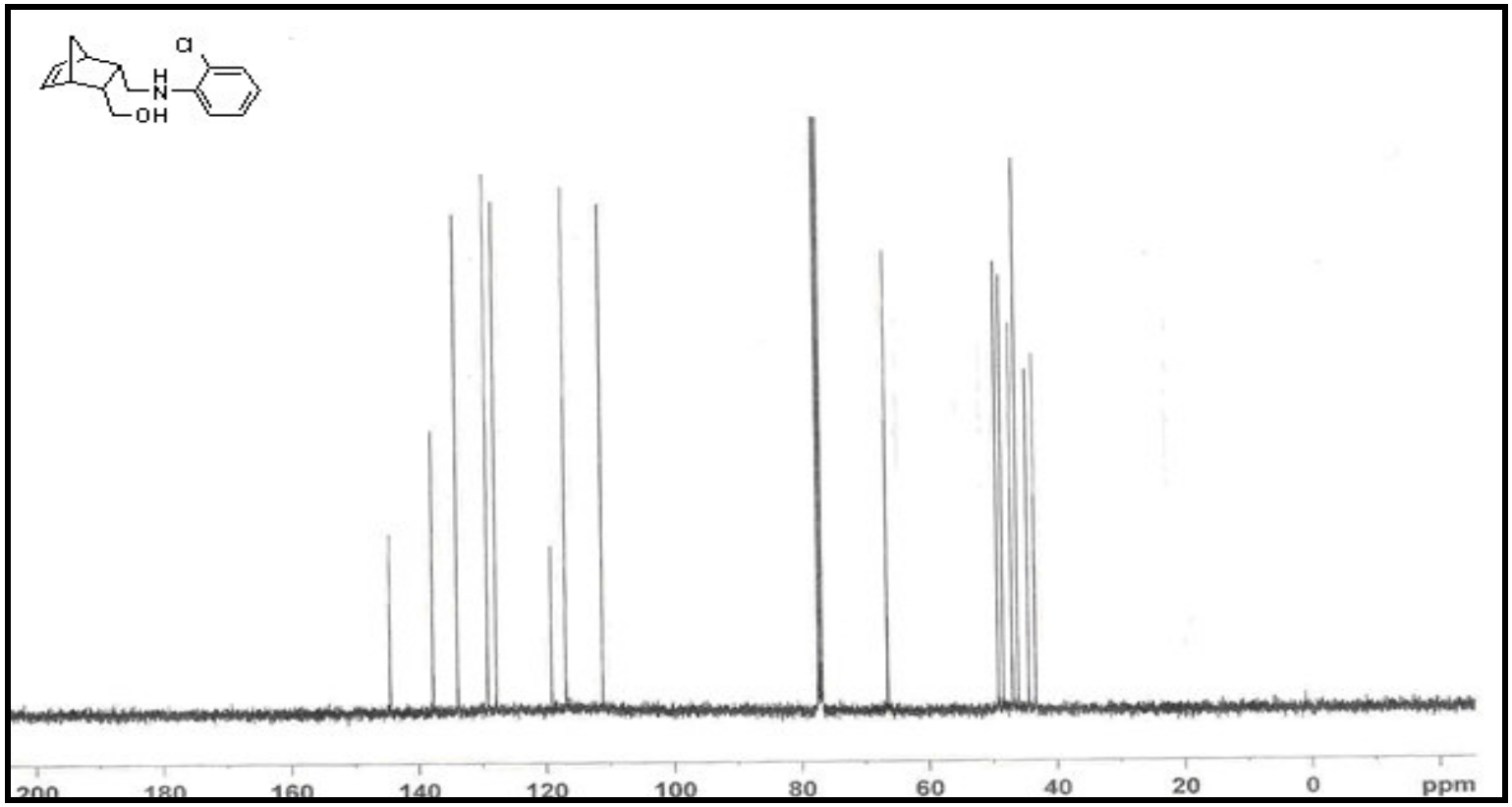

Figure 42. ^{13}C-NMR Spectrum of Compound **57**

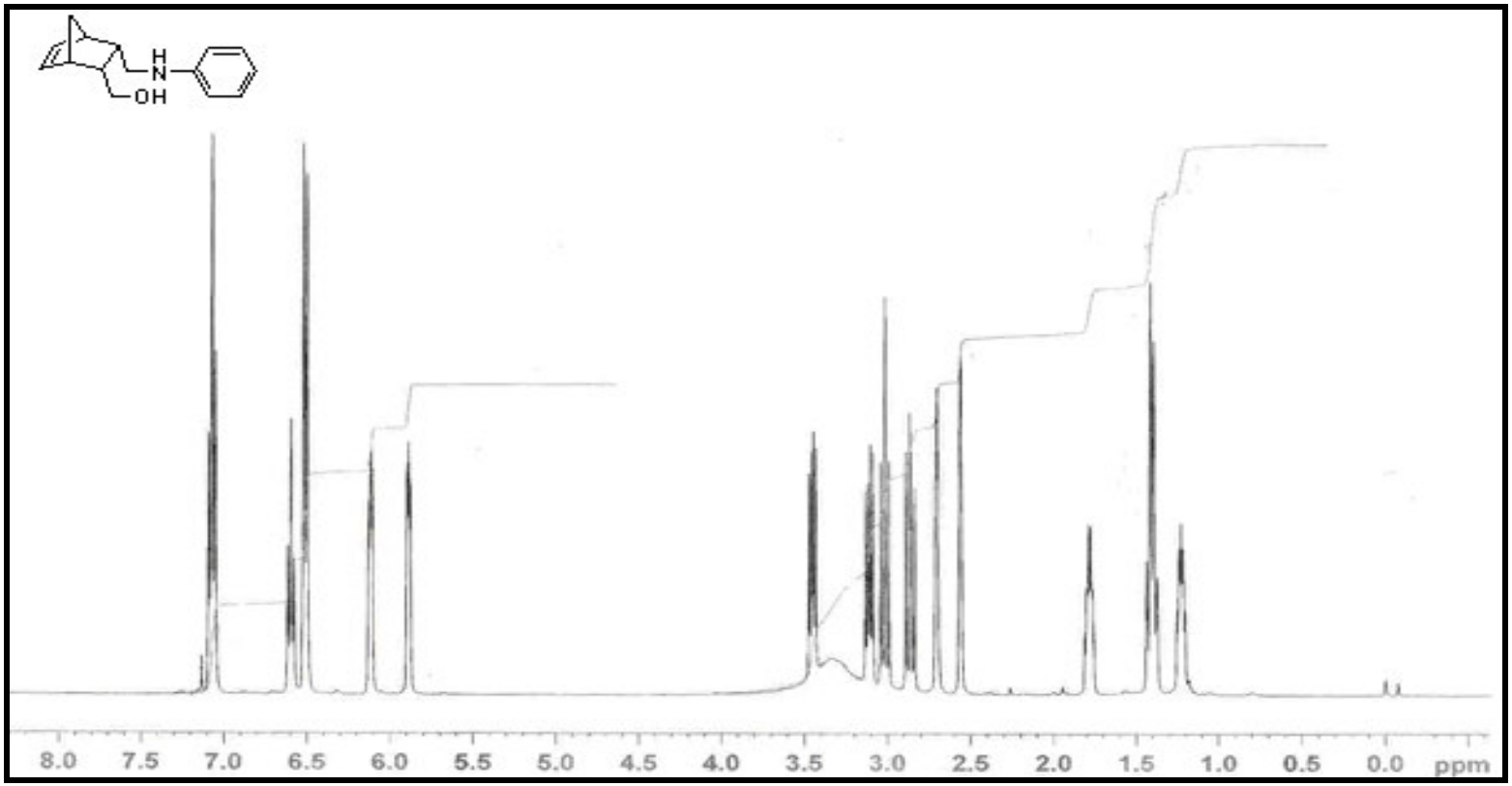

Figure 43. ^{1}H-NMR Spectrum of Compound **58**

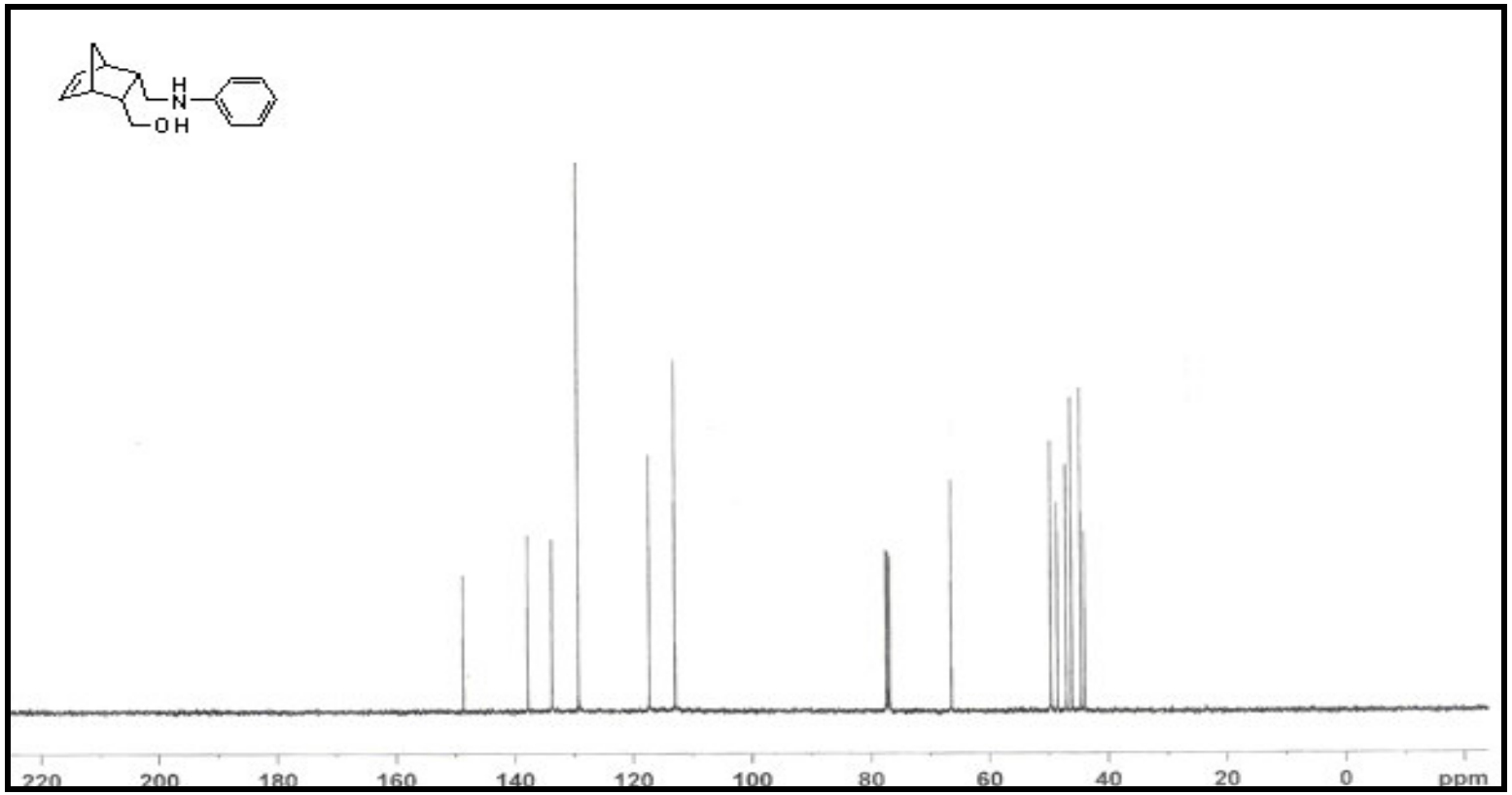

Figure 44. ^{13}C-NMR Spectrum of Compound **58**

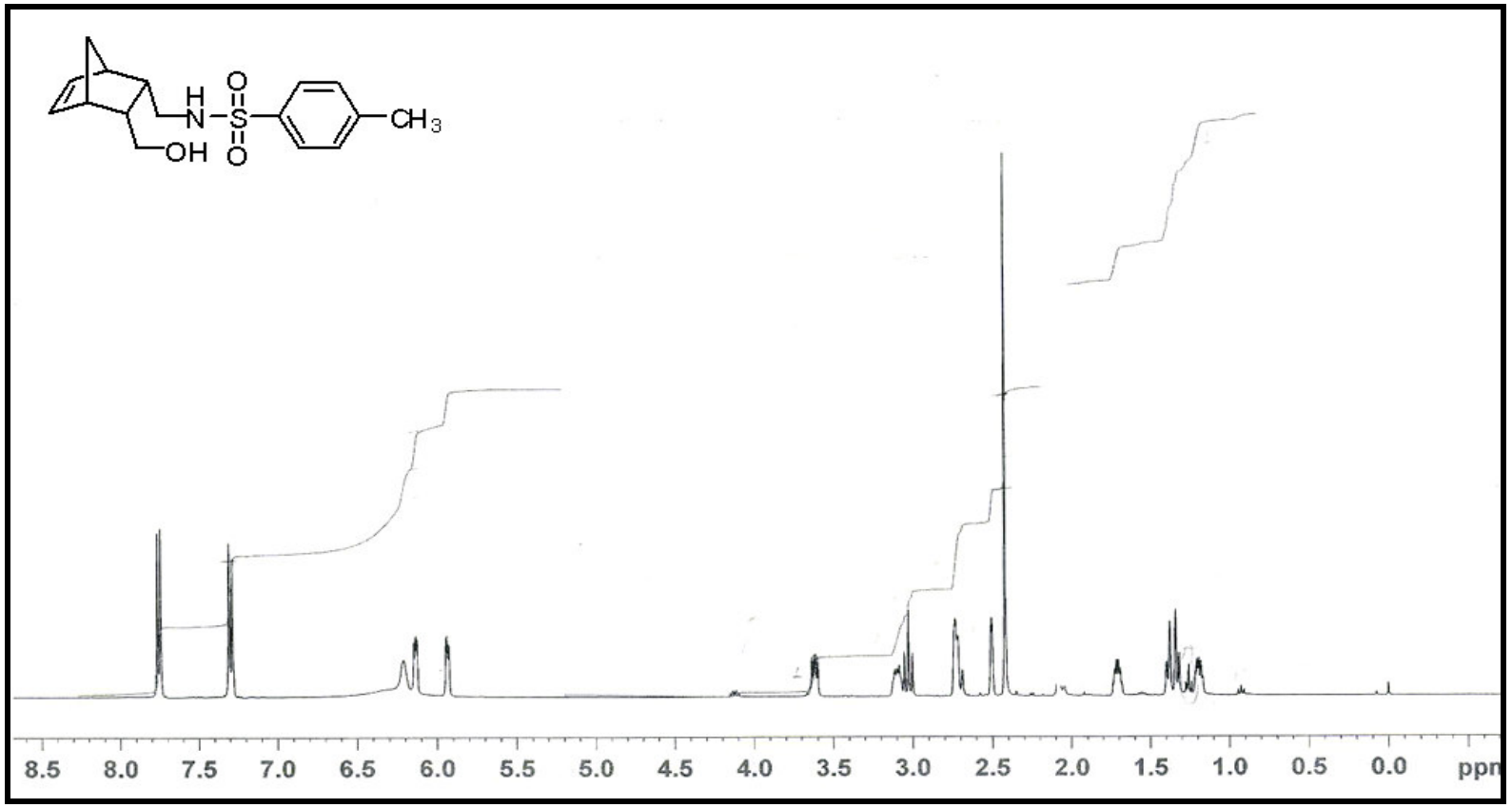

Figure 45. ^{1}H-NMR Spectrum of Compound **59**

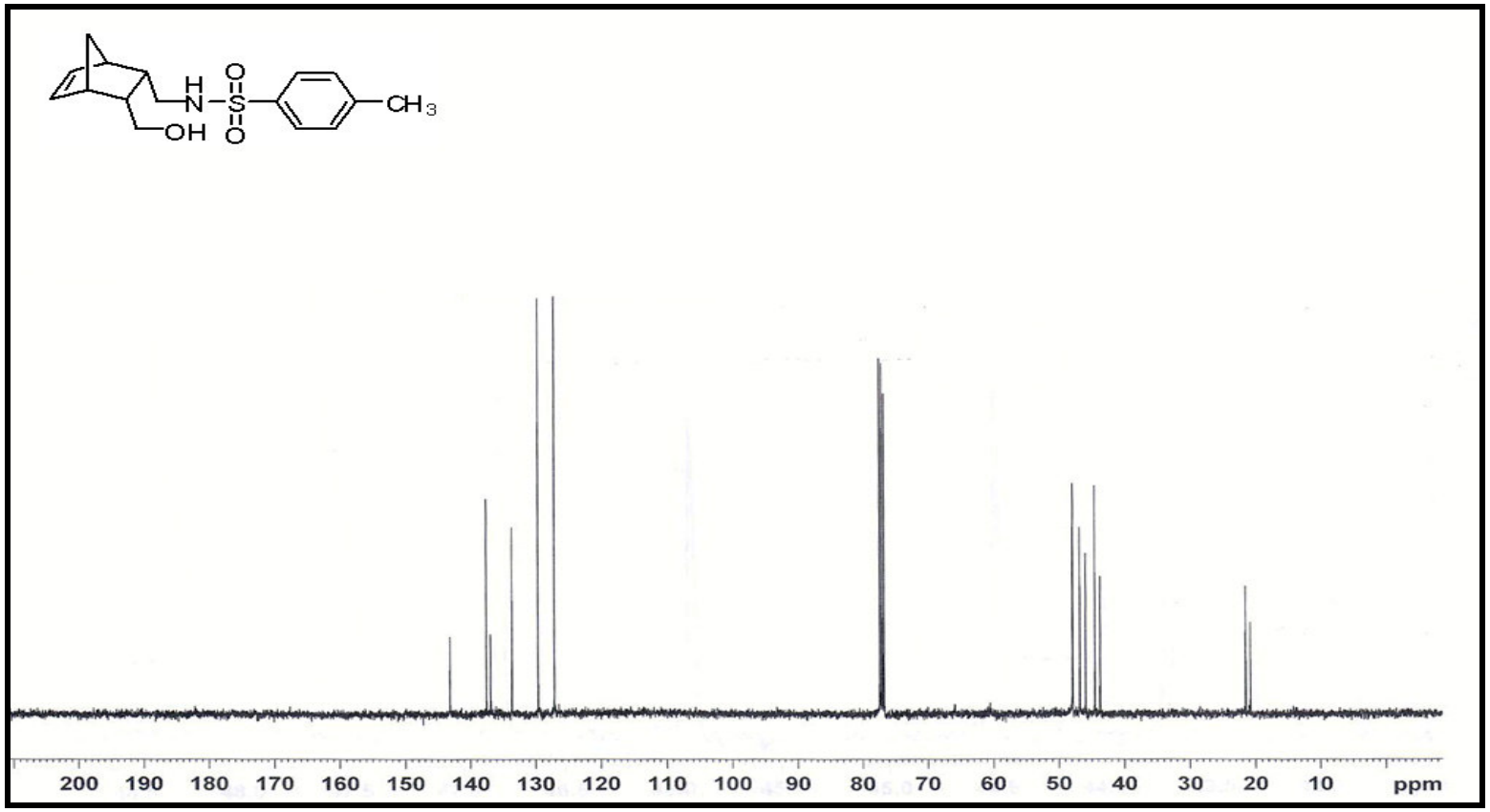

Figure 46. ^{13}C-NMR Spectrum of Compound **59**

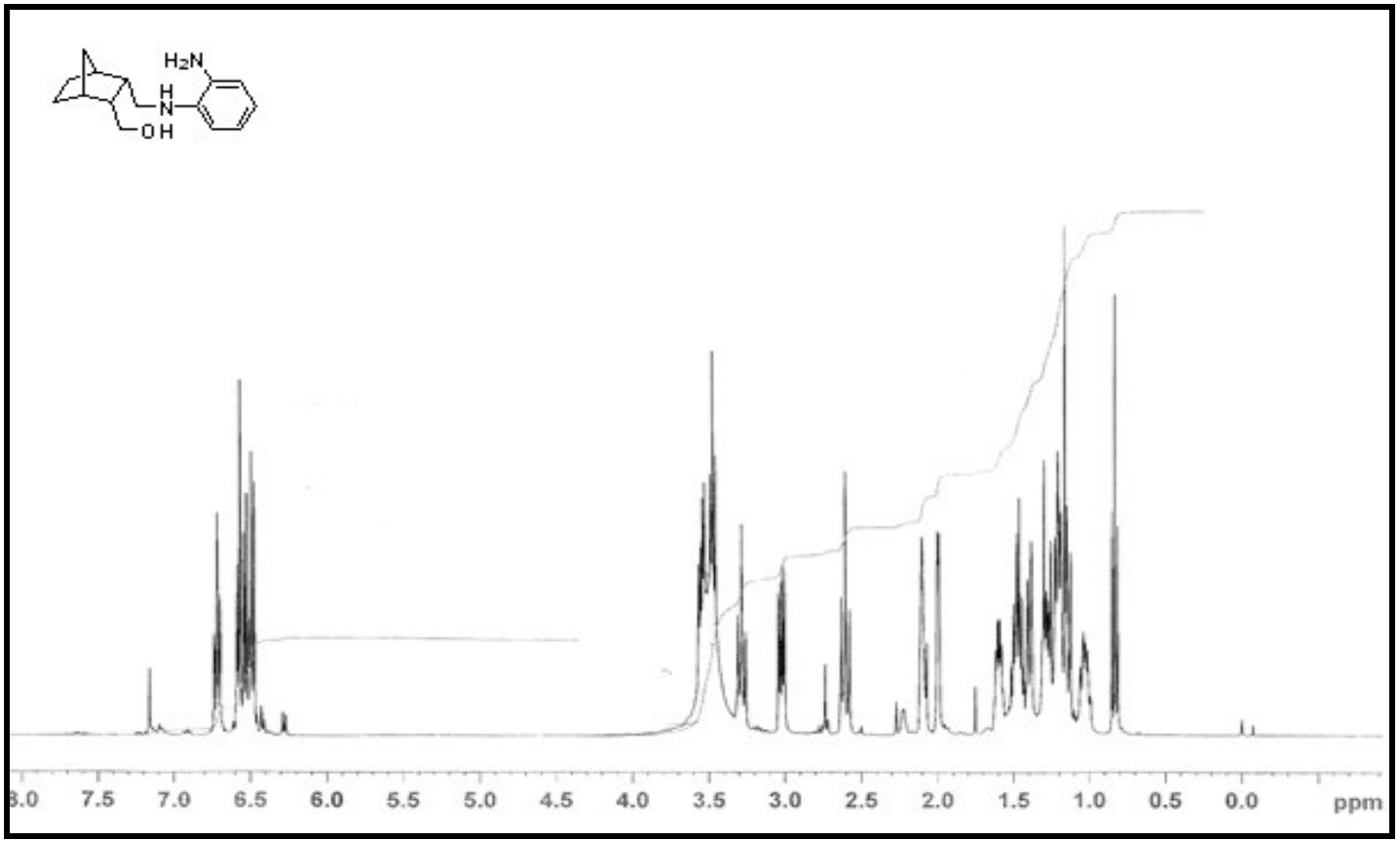

Figure 47. [1]H-NMR Spectrum of Compound **60**

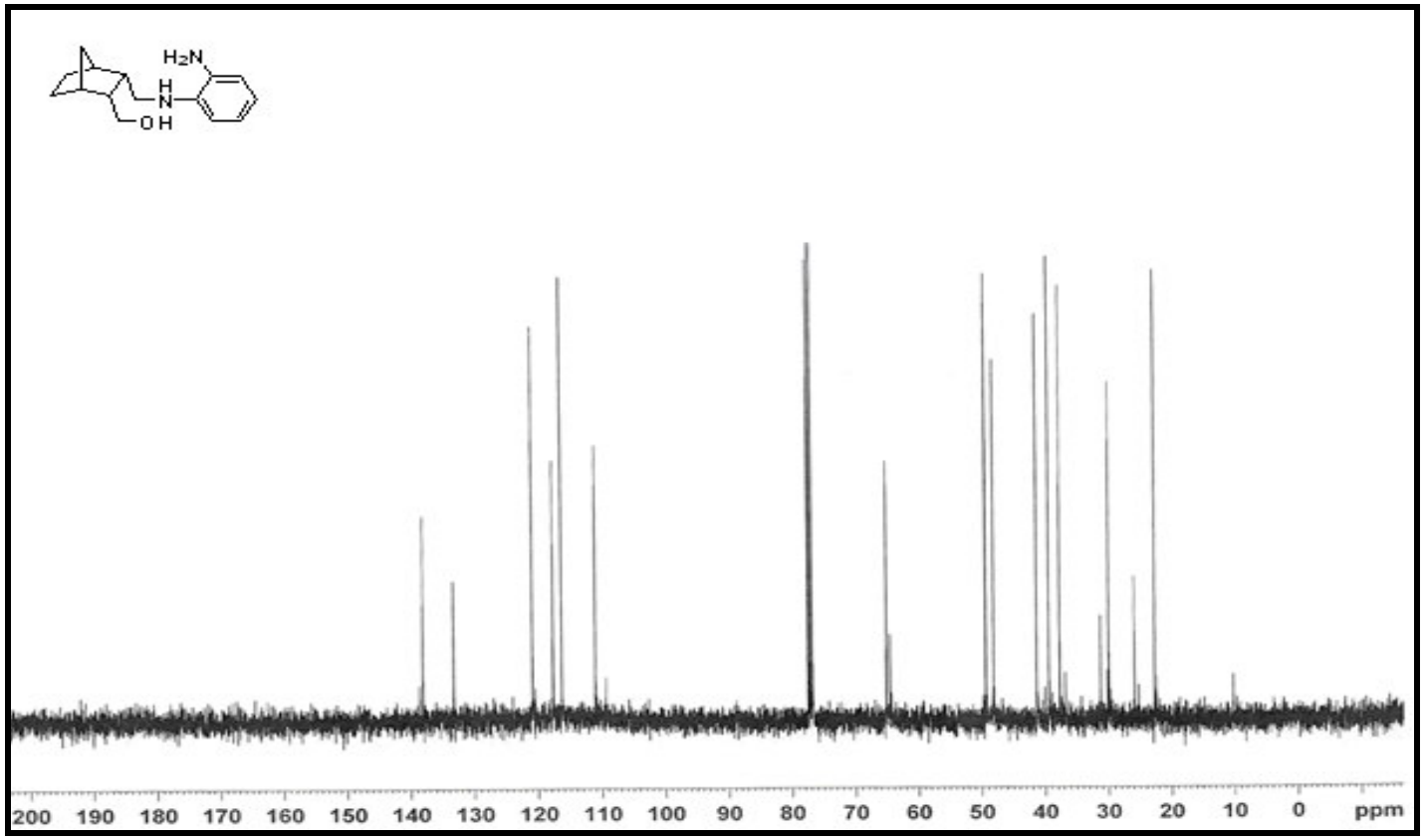

Figure 48. ^{13}C-NMR Spectrum of Compound **60**

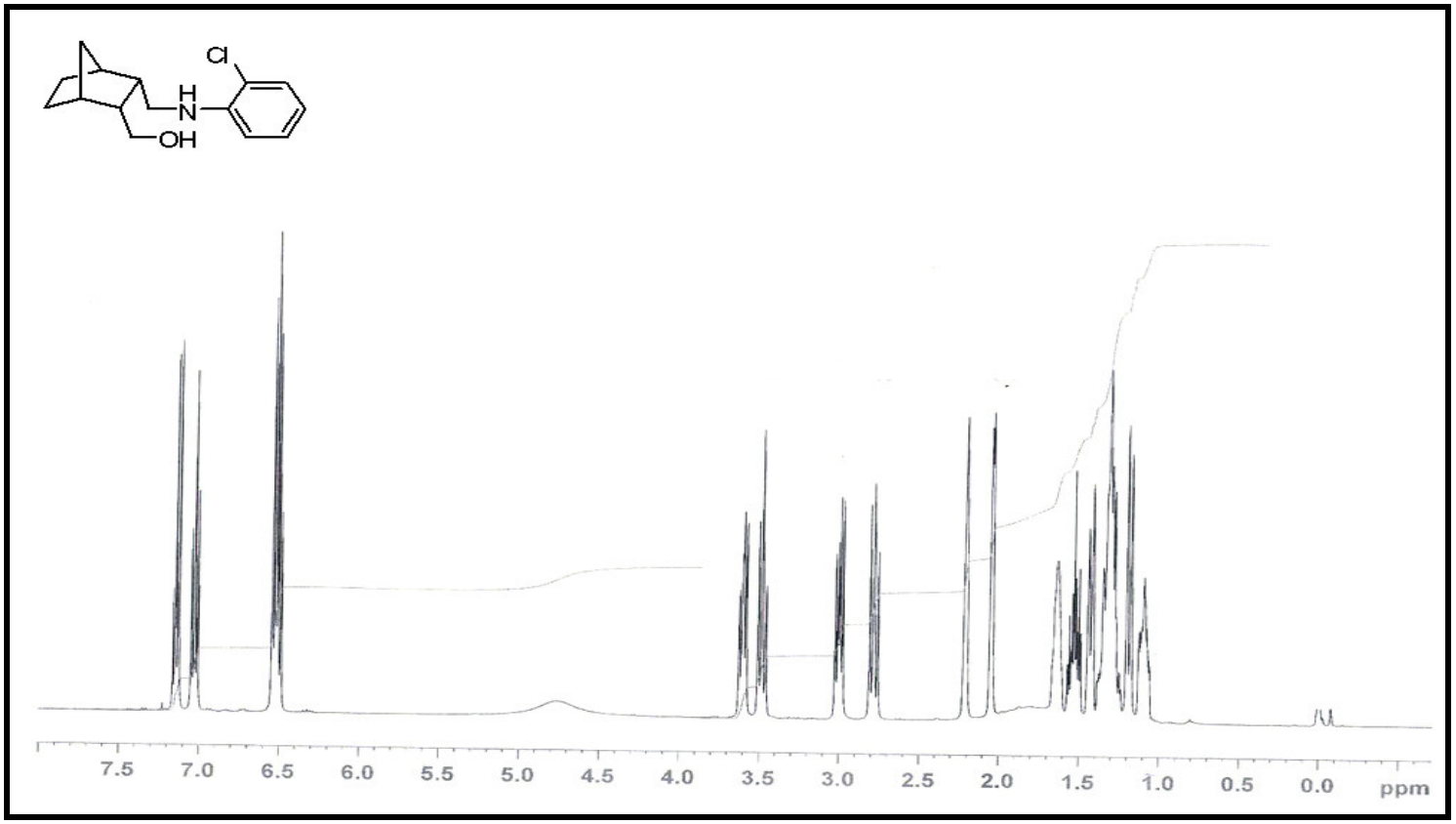

Figure 49. ^{1}H-NMR Spectrum of Compound **61**

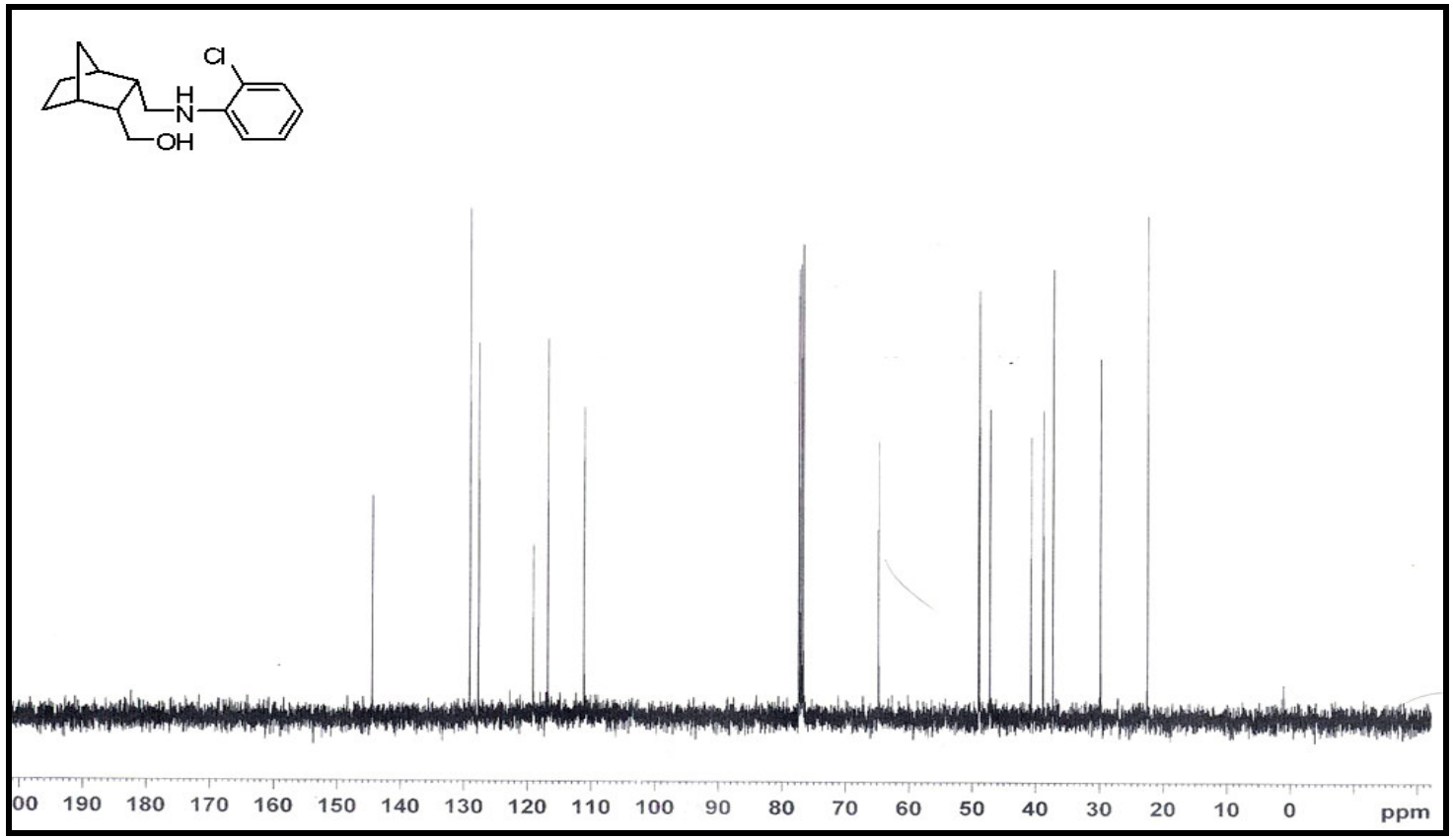

Figure 50. ^{13}C-NMR Spectrum of Compound **61**

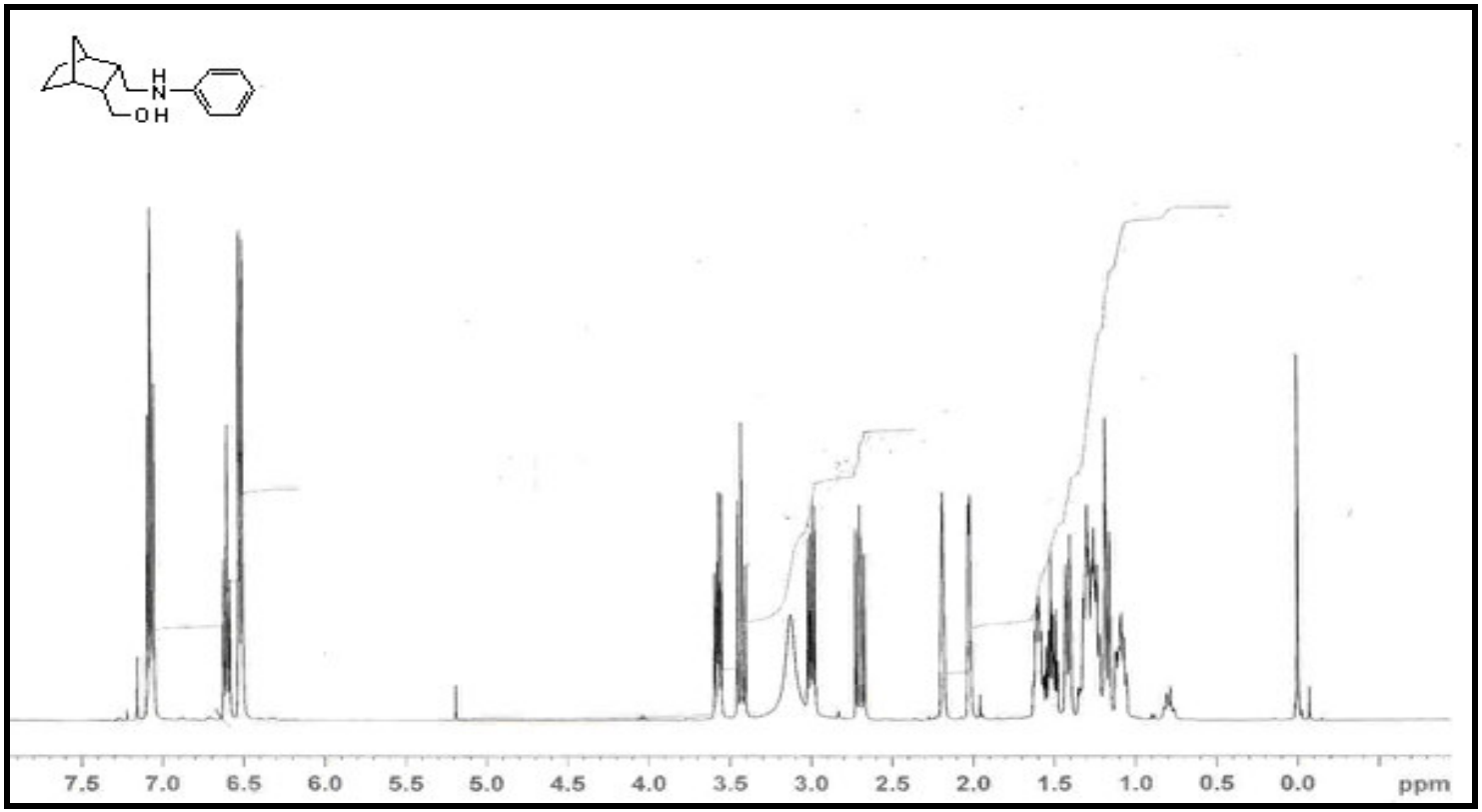

Figure 51. ^{1}H-NMR Spectrum of Compound **62**

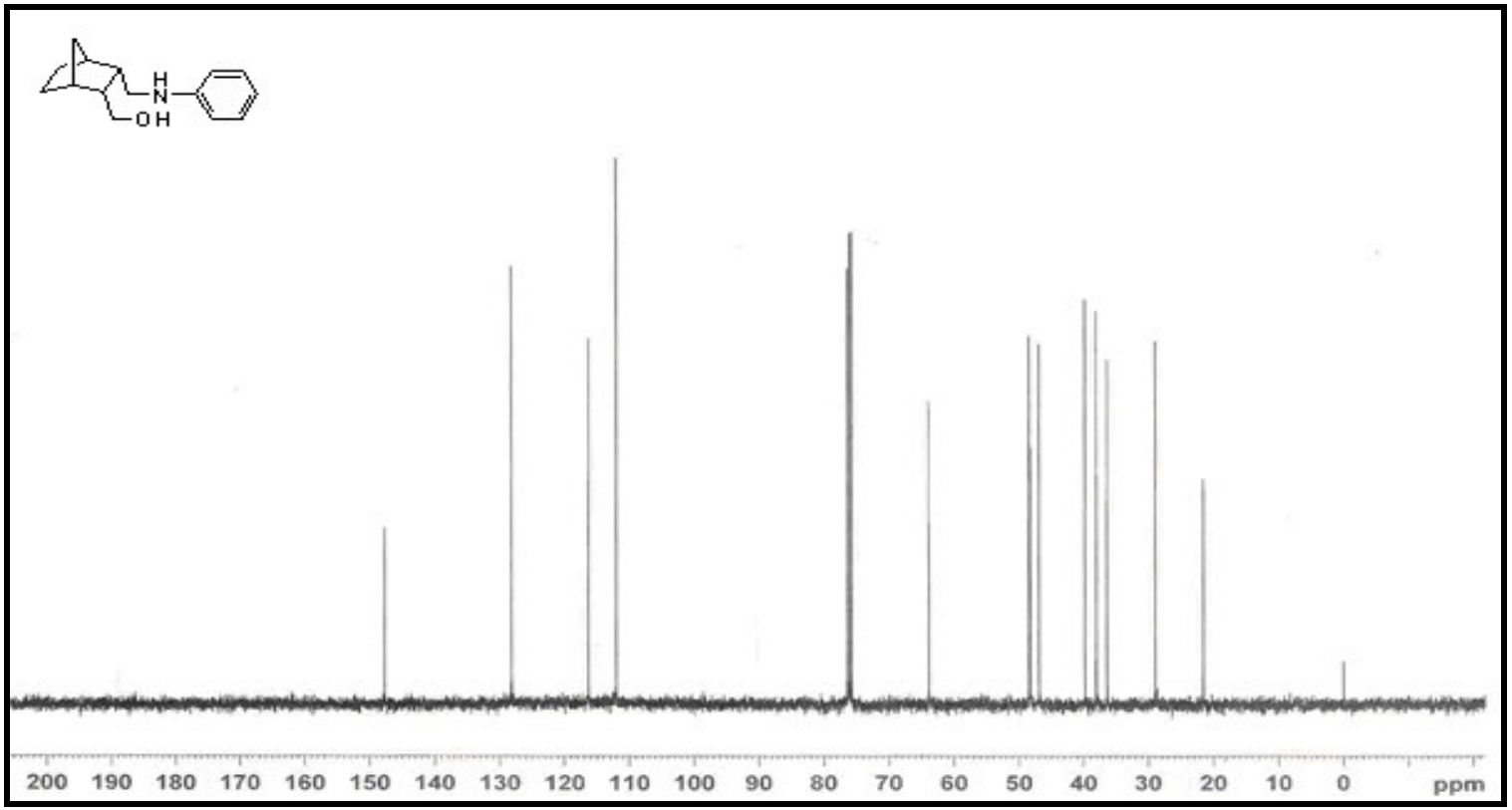

Figure 52. ^{13}C-NMR Spectrum of Compound **62**

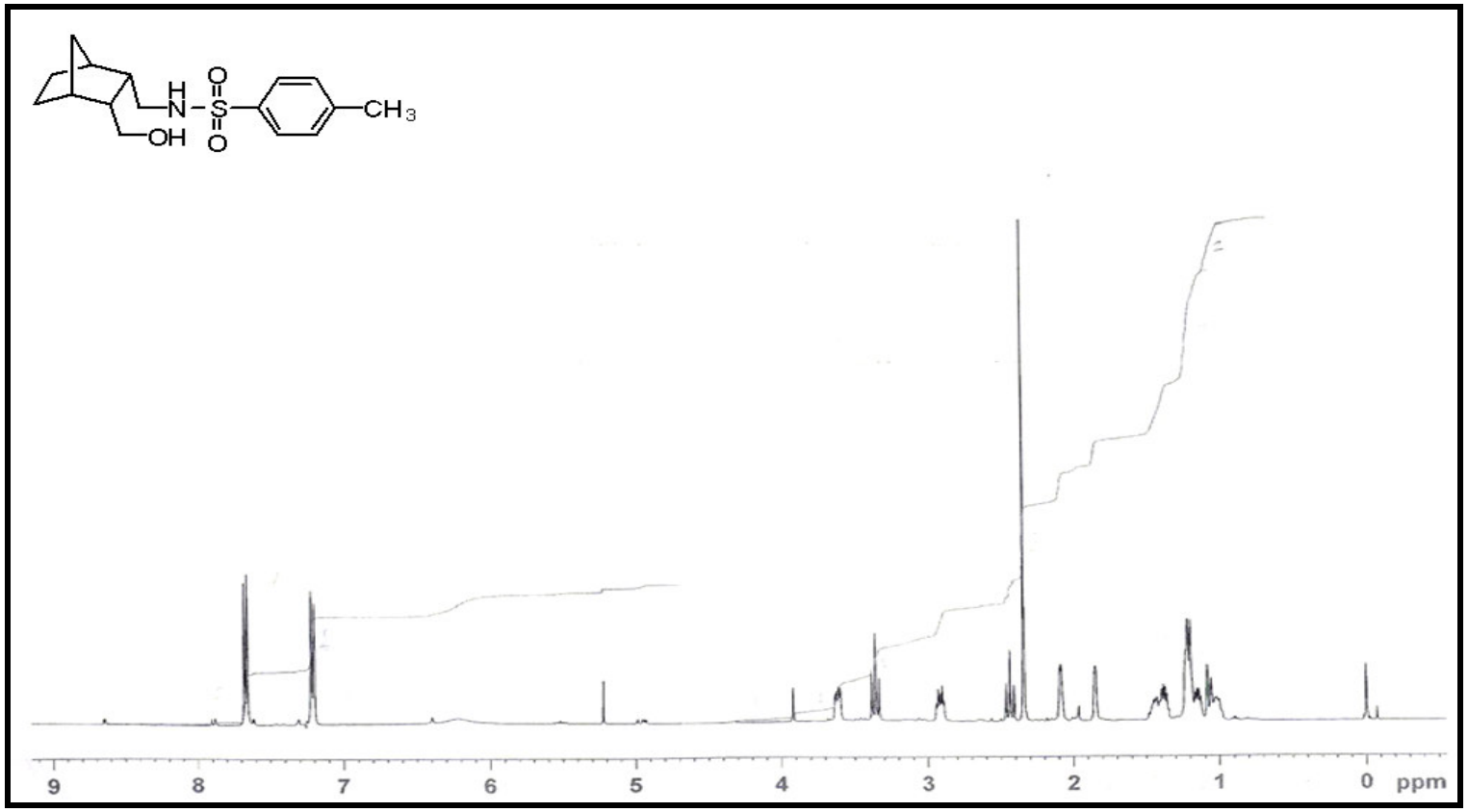

Figure 53. ^{1}H-NMR Spectrum of Compound **63**

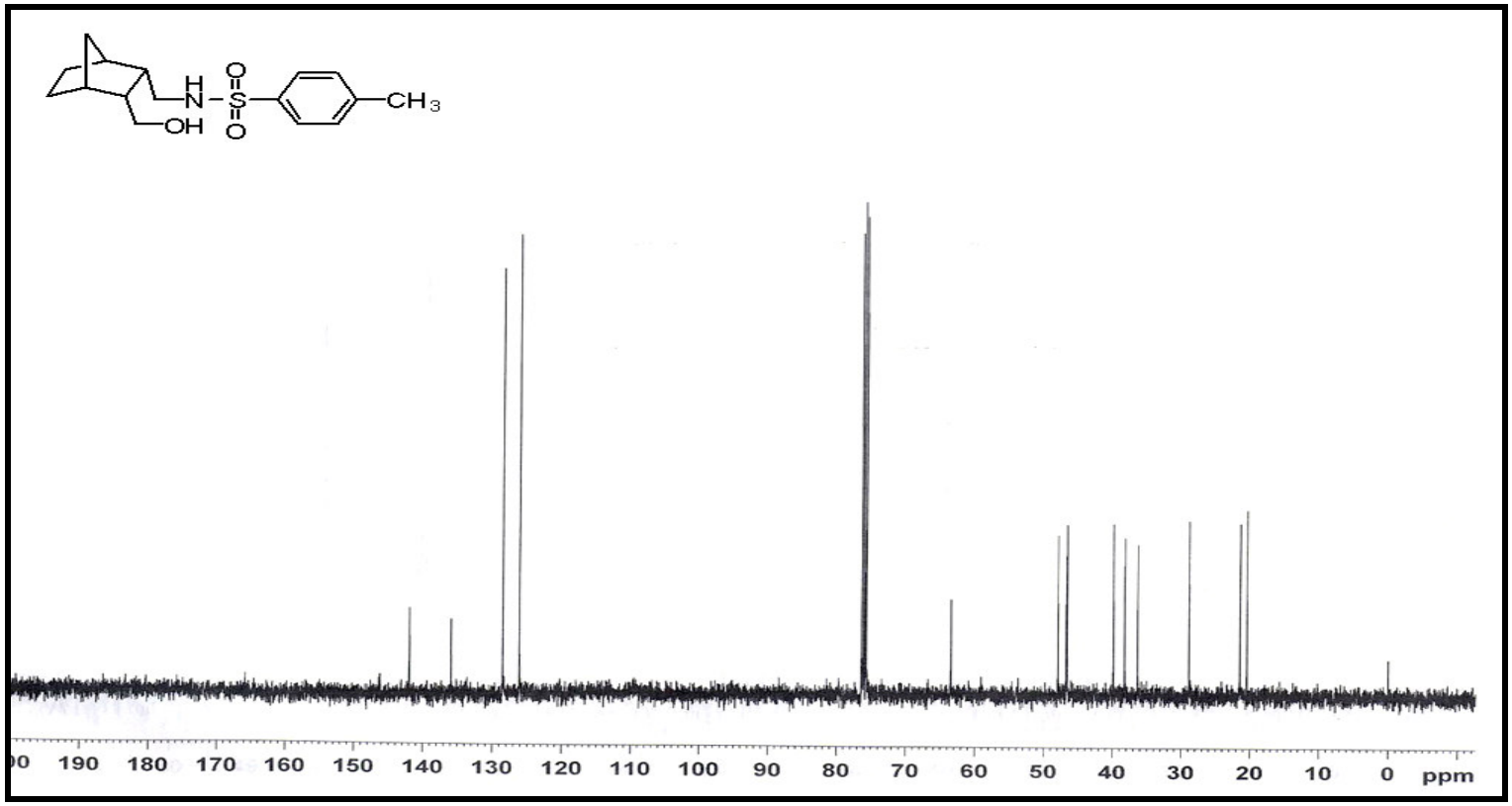

Figure 54. ^{13}C-NMR Spectrum of Compound **63**

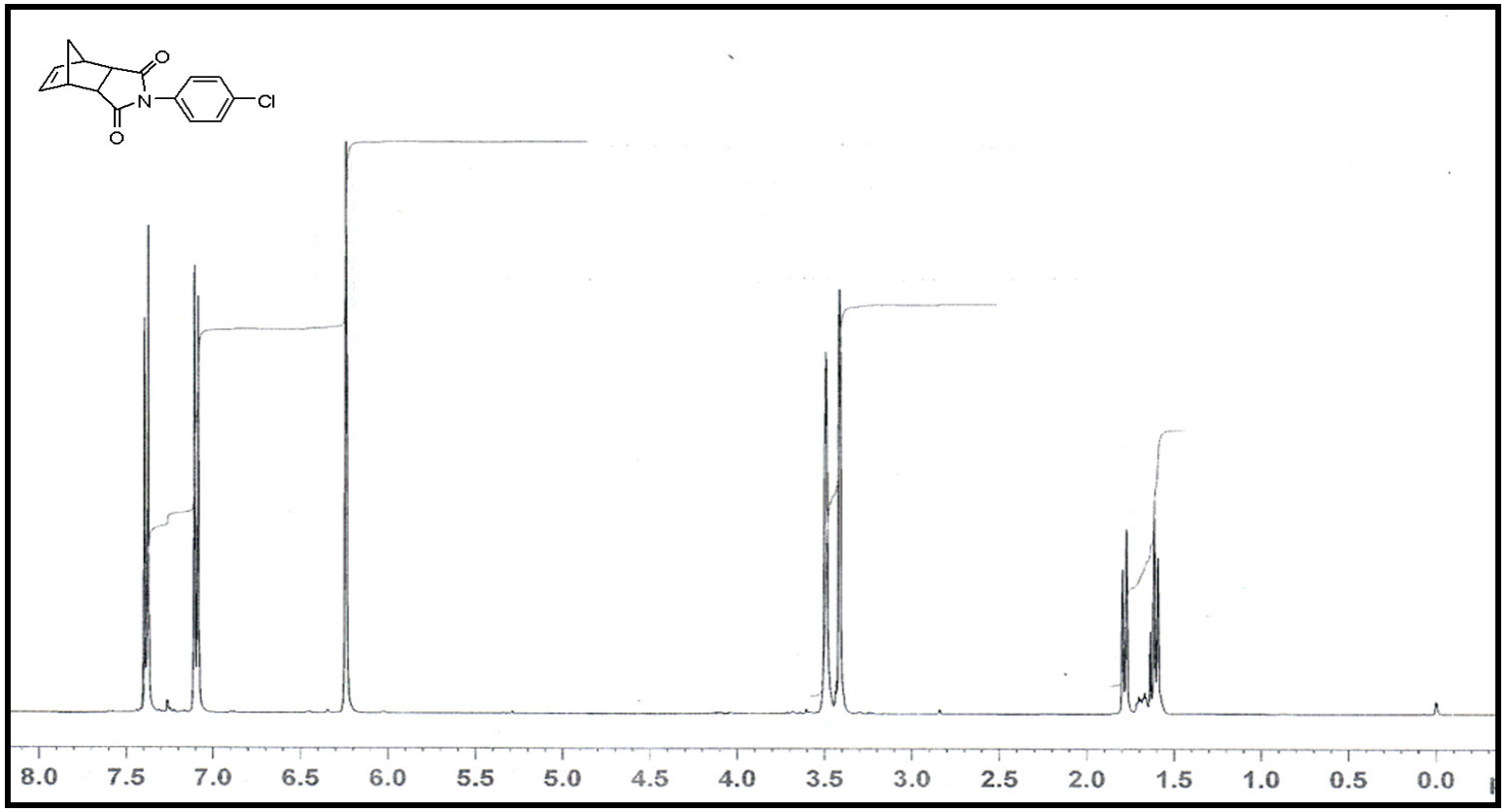

Figure 55. ^{1}H-NMR Spectrum of Compound **68**

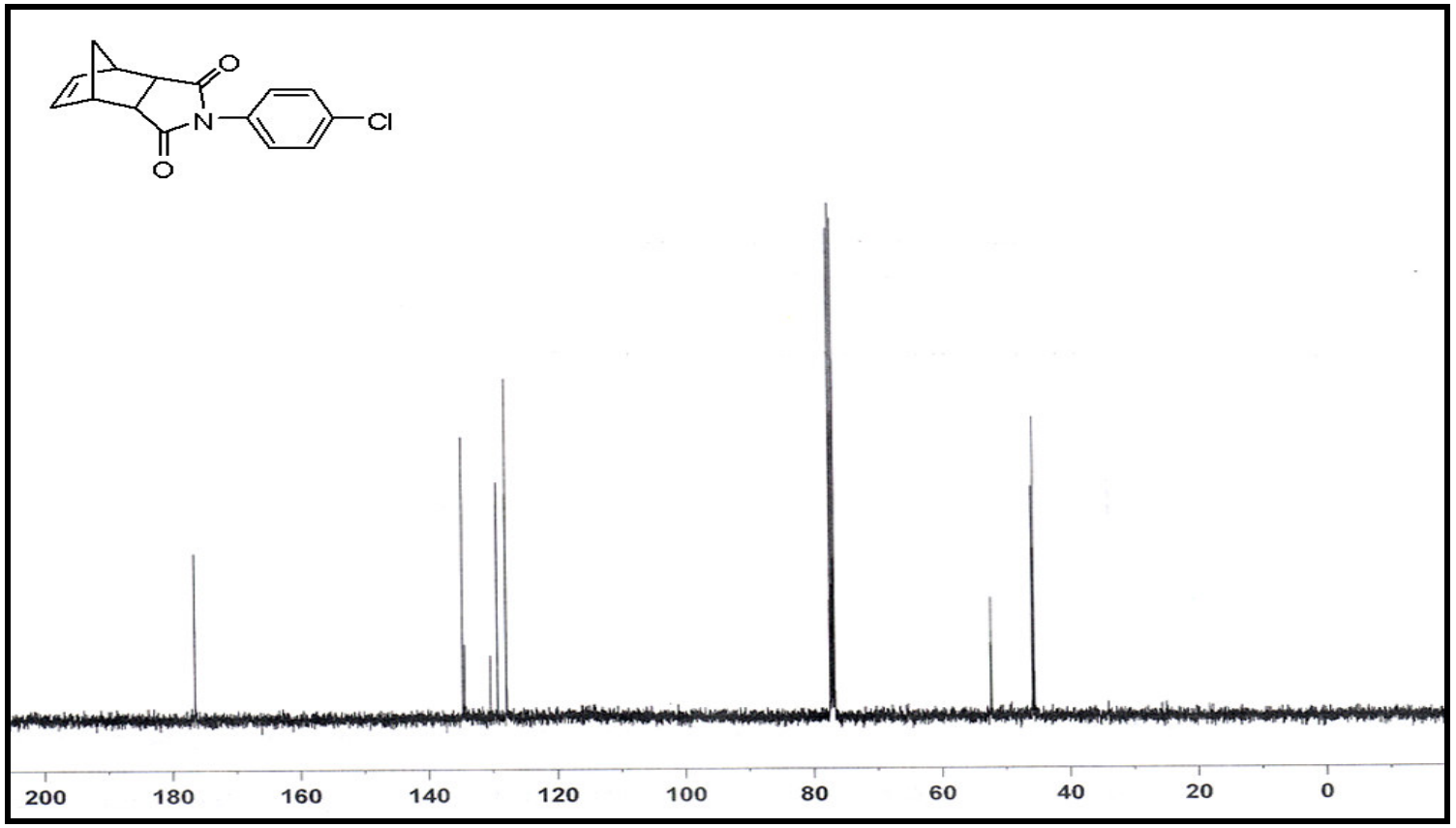

Figure 56. ^{13}C-NMR Spectrum of Compound **68**