SYNTHESIS OF HETEROCYCLIC AMINE SUBSTITUTED NOVEL 1,4-AMINOALCOHOLS AND APPLICATIONS IN VARIOUS ASYMMETRIC TRANSFORMATIONS

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Approval of the Graduate School of Natural and Applied Science

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ABSTRACT

SYNTHESIS OF HETEROCYCLIC AMINE SUBSTITUTED NOVEL 1,4-AMINOALCOHOLS AND APPLICATIONS IN VARIOUS ASYMMETRIC TRANSFORMATIONS

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May 2007, 101 pages

Aminoalcohols are very important compounds used in various asymmetric transformations as chiral ligands or chiral auxiliaries. In this thesis, four novel heterocyclic amine substituted chiral 1,4-aminoalcohols were synthesized.

In the synthetic strategy, amide esters were synthesized from (2*S,* 3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid by DCC coupling method. Subsequent reduction of these amide esters lead to target 1,4-aminoalcohols.

The activities of these novel chiral 1,4-aminoalcohols were tested in enantioselective diethylzinc addition, Mukaiyama aldol and Diels-Alder reactions. The enantioselectivities were measured by HPLC.

All the products were identified by ^{1}H NMR and ^{13}C NMR spectroscopy

Key words: 1,4-aminoalcohols, enantioselective diethylzinc addition reaction, catalytic asymmetric Mukaiyama aldol reaction, catalytic asymmetric Diels-Alder reaction

ÖZ

HETEROSİKLİK AMİN İÇEREN YENİ 1,4-AMİNOALKOLLERİN SENTEZLENMESİ VE ÇEŞİTLİ ASİMETRİK TRANSFORMASYONLARDA KULLANILMASI

KESKİN, EDA

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Mayıs 2007, 101 sayfa

Aminoalkoller çeşitli asimetrik transfomasyonlarda kiral ligand ve kiral yardımcı olarak kullanılan önemli maddelerdir. Bu tezde, heterosiklik amin içeren 4 tane yeni kiral 1,4-aminoalkol sentezlenmiştir.

Sentezleme aşamasında, uygun amit esterler (2*S,* 3*R*)-3-metoksikarbonilbisiklo[2.2.1]-hept-5-en-2-karboksilik asite DCC bağlama yöntemiyle elde edilmiştir. Bunu takip eden indirgeme reaksiyonu sonucunda hedeflenen 1,4-aminoalkollere ulaşılmıştır.

Yeni 1,4-aminoalkollerin aktiviteleri enantiyoseçici dietil çinko, Mukaiyama aldol ve Diels-Alder reaksiyonlarında denenmiştir. Enantiyoseçiciclik HPLC yöntemiyle belirlenmiştir.

Tüm ürünlerin yapısı ^{1}H NMR ve ^{13}C NMR spektroskopisi ile tanımlanmıştır.

Anahtar kelimeler: 1,4-aminoalkoller, enantiyoseçici dietilçinko reaksiyonu, katalitik asimetrik Mukaiyama aldol reaksiyonu, katalitik asimetrik Diels-Alder reaksiyonu

To my parents;

Şahin & Ülkü Keskin

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DCC: N, N'-Dicyclohexyl-carbodiimide

DMAP: 4-dimethylaminopyridine

THF: Tetrahydrofuran

CHAPTER 1

INTRODUCTION

1.1 Chirality

One of the main features of the living world is its chirality [1, 2, 3, 4]. All the building blocks of the human body, such as amino acids, carbohydrates and nucleic acids, have chiral centers. These biomolecules are made up of units that have the same sense of chirality — the 21 essential amino acids are all L-enantiomers, whereas most carbohydrates have the D-configuration [1]. As a result, the interaction of the two enantiomers of the biomolecule with an organic molecule is different so the biological response. Not only these biomolecules, but also drugs, vitamins, flavors and fragrances are enantiomerically pure compounds. Especially purity of the drugs are very important because while one enantiomer is effective, the other one is toxic or ineffective. For instance, thalidomide caused handicapped births since its racemate was brought onto the markets instead of its R-(+) enantiomer in 1950s.

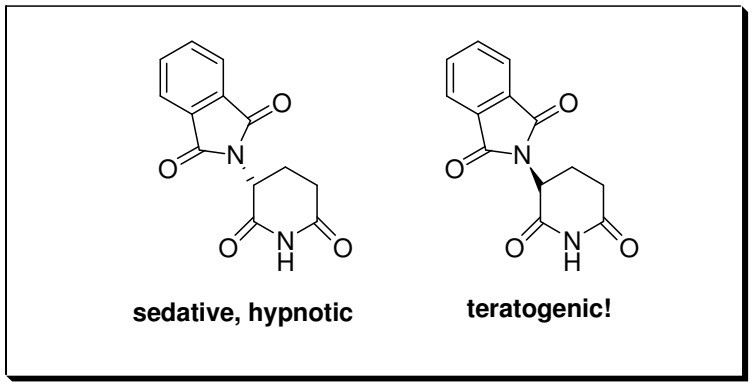


Figure 1 Enantiomers of Thalidomide

The studies about chirality started with Louis Pasteur in 1848. He discovered that two tartaric acid molecules with otherwise identical properties different in sign of optical rotation [5, 6]. So he stated that tartaric acid has an asymmetric form and it is chiral.

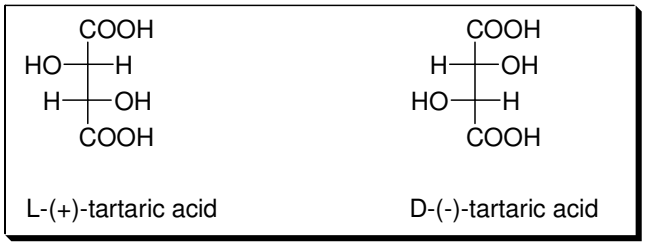


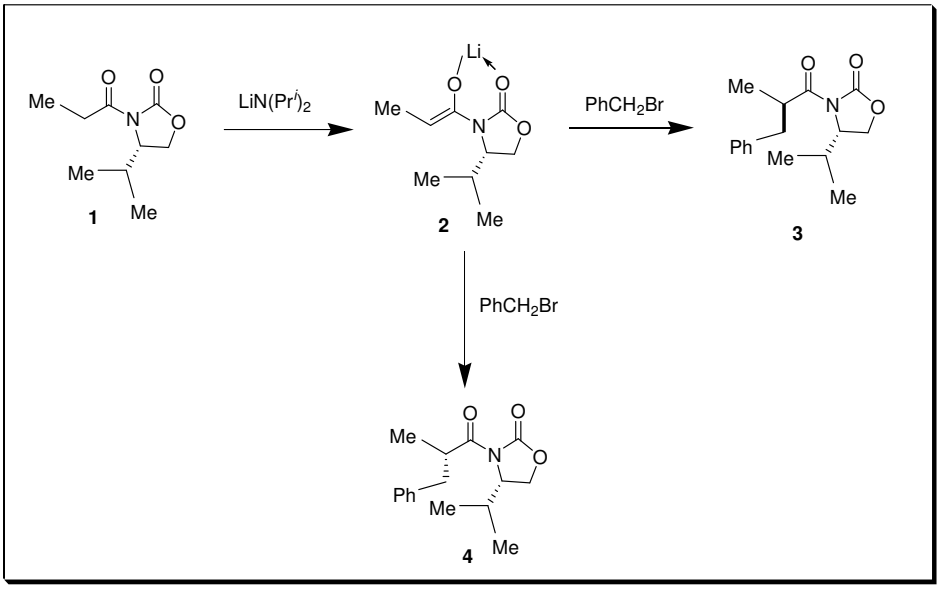
Figure 2 Enantiomers of Optically Active Tartaric Acid

Chirality is a Greek word which means handedness. Properties of molecules and molecular arrays depend on chirality [7]. Molecular communication in the body, the effects of optical and electronic materials and bulk properties arise from this phenomena [8, 9, 10, 11, 12, 13]. Although chirality is very important, obtaining enantiomerically pure compounds has been very difficult until recently. By the advances in catalytic asymmetric sythesis, large amount of chiral products can be synthesized by using small amount of chiral catalysts.

1.2 Asymmetric Synthesis

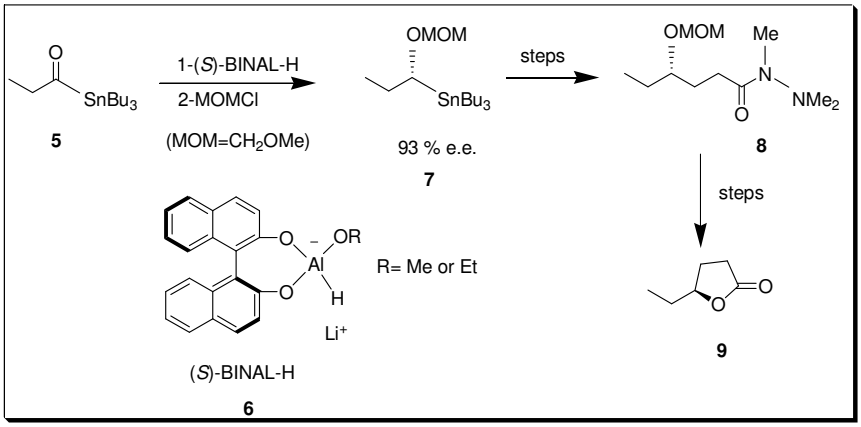
According to Marckwald "Asymmeric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes." [14]. By the help of this definition, today, asymmetric synthesis is defined as the conversion of an achiral unit in a molecule to a chiral unit such that stereoisomers are formed in unequal amounts.

The first method in order to obtain chiral substances is the usage of chiral, non-racemic substrate. The example is shown in the scheme 1[15].



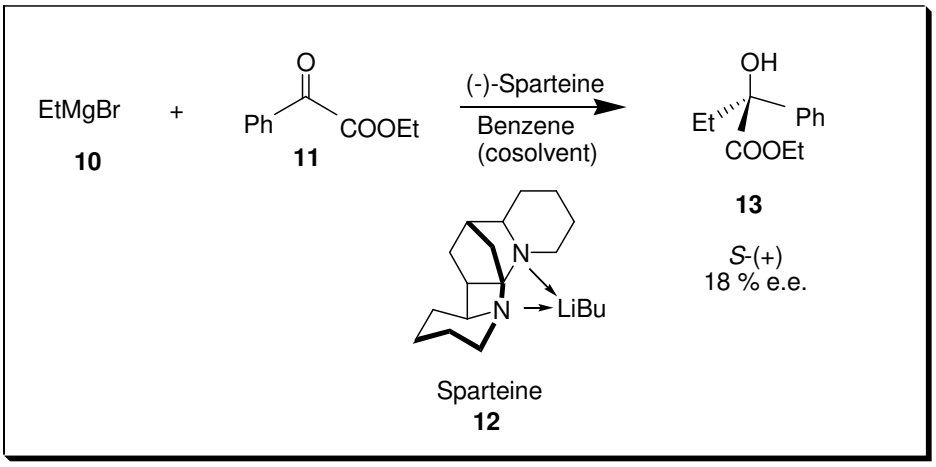
Scheme 1 Usage of chiral, non-racemic substrate

Obtaining chiral alcohol from a prochiral ketone can be achieved by using chiral, non-racemic reagent. For the achiral reagent, a racemic mixture is formed since the transition states need the same amount of energy. On the other hand, when the chiral reagent is used, transition states differ in energy and the one with lower energy transition state is formed [15]. The example is shown in the scheme 2 [16].



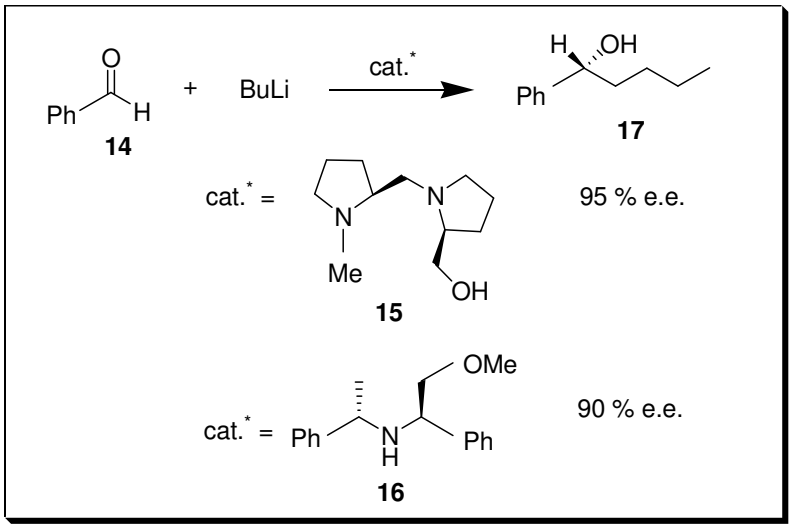
Scheme 2 Usage of chiral, non-racemic reagent

Another way for achieving asymmetric synthesis is the usage of chiral solvent if it is possible to involve in the transition states. However, because of its low and unpredictable level of stereoselectivity, this approach is rarely used. On the contrary, use of chiral, non-racemic solvating agents (in a normal solvent) is more popular [15]. The example is shown in the scheme 3 [17].



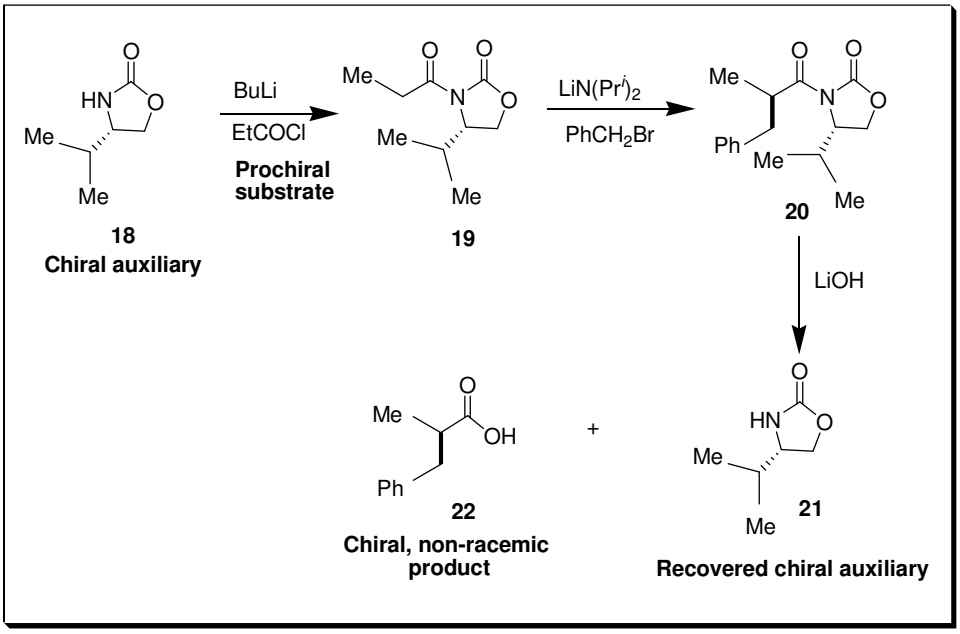
Scheme 3 Usage of chiral, non-racemic solvent

The most attractive approach for asymmetric synthesis is the usage of chiral, non-racemic catalysts. By using catalytic amount of chiral ligands together with metals, stoichiometric amount of product can be obtained. The example is shown in the scheme 4 [16].



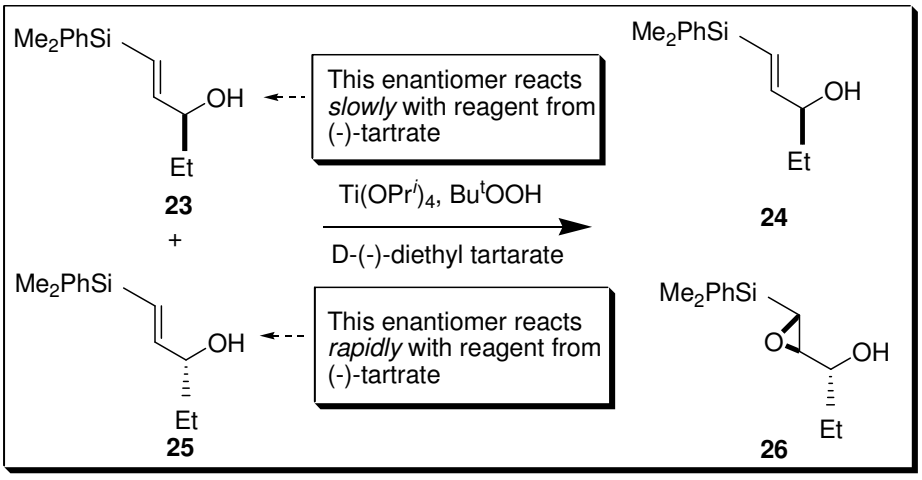
Scheme 4 Usage of chiral, non-racemic catalyst

Chiral auxiliaries are the alternative for asymmetric synthesis. Prochiral substrate and the chiral auxiliary is attached to each other before the reaction. Two diastereoisomeric products are formed but one of them is in excess. After the reaction, the major one is isolated and the chiral auxiliary is removed. Because of this, chiral auxiliary has the property of easy removal without loss of diastereoisomeric or enantiomeric purity. Beside this, it should be cheap and its control of stereoselectivity should be high and predictable [15]. The example is shown in the scheme 5 [15].



Scheme 5 Usage of chiral, non-racemic auxiliary

Kinetic resolution is an another approach to asymmetric synthesis. In this approach, the rates of reactions of individual enantiomers of the racemate must be different. The differece is so great that one enantiomer reacts rapidly whereas other one remains as the same [15]. The example is shown in the scheme 6 [15].



Scheme 6 An example of kinetic resolution

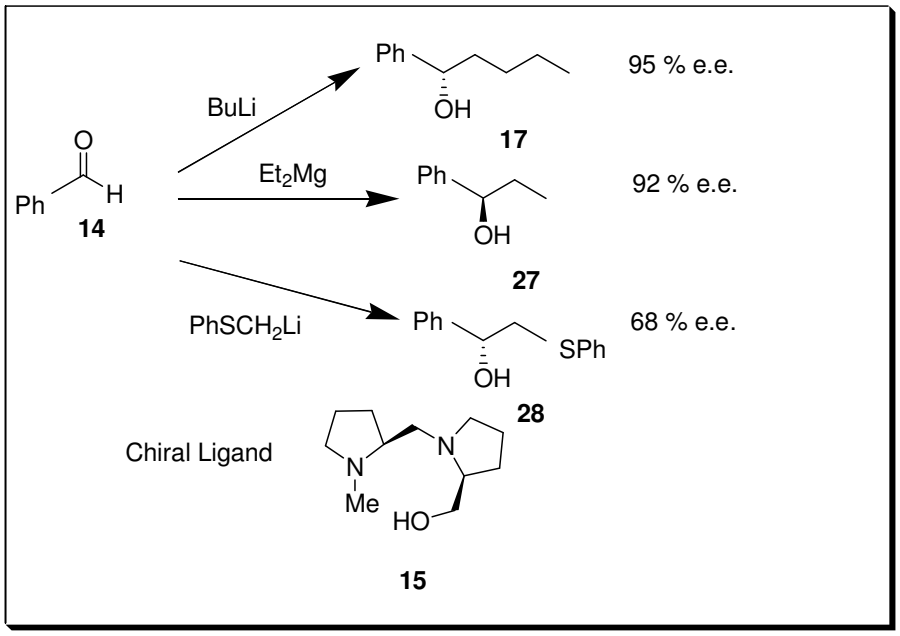
1.2.1 Catalytic Asymmetric Transformations

It is well known that chiral molecules such as pharmaceuticals are complex and multifunctional compounds. In order to synthesize these compounds, multistep reactions are needed [5]. Catalytic asymmetric transformations are useful processes which can be used to obtain large amount of compounds in a short time. Catalytic asymmetric hydrogenation and oxidation are very popular reactions. In this section, dialkyl zinc addition, aldol and Diels-Alder reactions will be shown as examples.

1.2.1.1 Enantioselective Addition of Dialkylzinc to Aryl Aldehydes

One of the most important carbon-carbon bond formation reaction is the enantioselective addition of dialkyl zinc to aryl aldehydes [18-20]. By using different chiral ligands, enantiomerically pure and enriched secondary alcohols, which are very valuable intermediates for synthesizing bioactive compounds and natural products [21], can be obtained.

Firstly, Oguni [22] reported that 1,2-aminoalcohols are effective in ethylation of benzaldehyde with diethylzinc. After that, many chiral ligands containing mostly β-aminoalcohols were synthesized and used [21 a-c , 22, 23, 24]. However, the best result was obtained by Noyori [25] later. He proved the efficiency of (−)-3-*exo*-dimethylaminoisoborneol (DAIB) in diethyl zinc addition reaction. The examples of enantioselective dialkylzinc addition reaction are given in the scheme 7 [21 c].



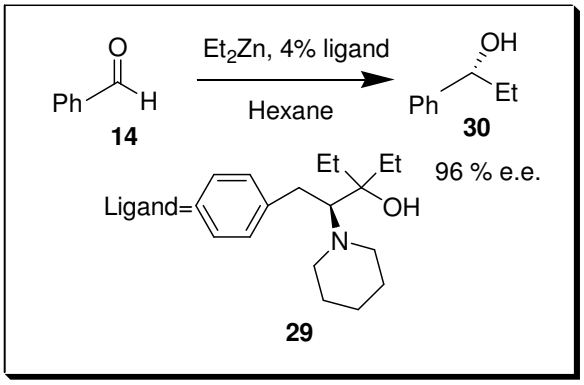
Scheme 7 Enantioselective dialkylzinc addition reaction

Their enantioselectivities were explained by the flexible [26] but not rigid [27, 28] groups on the carbon atom of the hydroxyl group [29]. In addition to their effectiveness, easy handling and being economical made them more popular [27, 30].

Although there are many examples of 1,2-aminoalcohols in the literature, few applications contain 1,4-aminoalcohols as chiral ligands. One of the well known study done by Tanyeli et al. [27] contains the application of 1,4-aminoalcohols with norbornene backbone in enantioselective addition of diethylzinc to benzaldehyde.

High results were explained by the more flexible structure of the 1,4-aminoalcohols with respect to 1,2-aminoalcohols. So better complexation results in more stable complex.

In addition to aminoalcohols, naturally occuring amino acids are commercially available and are used as a source of cheap chiral ligands [29] Moreover, their derivation lead to highly efficient chiral ligands and catalysts [31]. An example is shown in the scheme 8 [29].



Scheme 8 L-Phenylalanine derived chiral ligand

1.2.1.2 Catalytic Asymmetric Aldol Reactions

Aldol reaction is one of the most powerful method for the formation of carbon-carbon bonds [32]. It is highly atom economic but chemo- and regioselectivity are the biggest problems [33].

Traditionally, pre-conversion of carbonyl pro-nucleophile to corresponding more active enolate or enol ether with the help of stoichiometric amount of Lewis acid [34] or Lewis base [35] is needed in order to control the stereochemistry of the aldol reaction [36]. However, usage of chiral catalyst is the most popular strategy in the point of atom economy. Shibasaki [37, 38, 39] design the first such catalyst based on novel BINOL complexes formed by the self-assembly of BINOL in the presence of lanthanide and base. So the aldol adducts can be easily obtained. This process is used in order to synthesize the intermediate for the anticancer agents, epothilones.

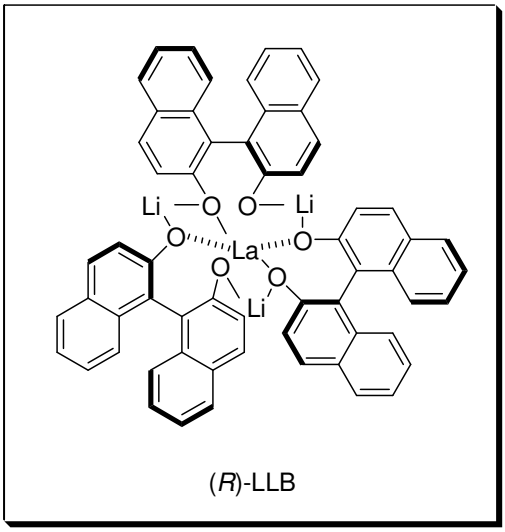
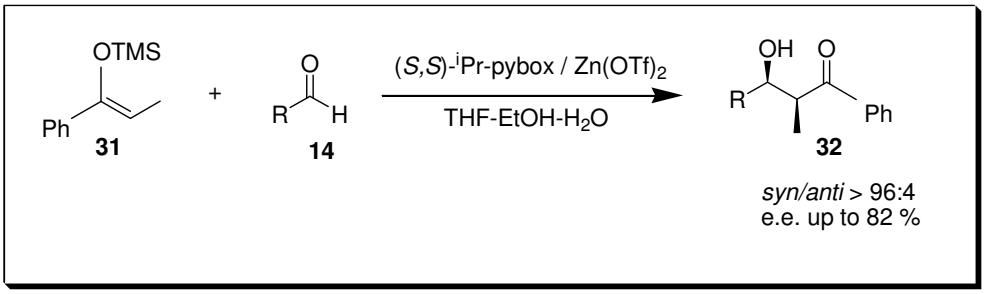


Figure 3 First catalyst designed by Shibasaki

In 1990, the first asymmetric aldol reaction of silyl enol ethers catalyzed by chiral diamine/$Sn(OTf)_2$ was reported by Mukaiyama [40]. However, the reaction took place at low temperatures and in aprotic anhydrous solvents. Recently, studies focused on organic reactions in aqueous media [41]. Kobayashi and co-workers [42] obtained excellent results by using $Cu(OTf)_2$, $Pb(OTf)_2$ and $Ln(OTf)_3$ in asymmetric Mukaiyama aldol reactions in aqueous ethanol (ethanol:water = 9:1). An example of Mukaiyama aldol reaction in aqueous media is given in scheme 9 [43].



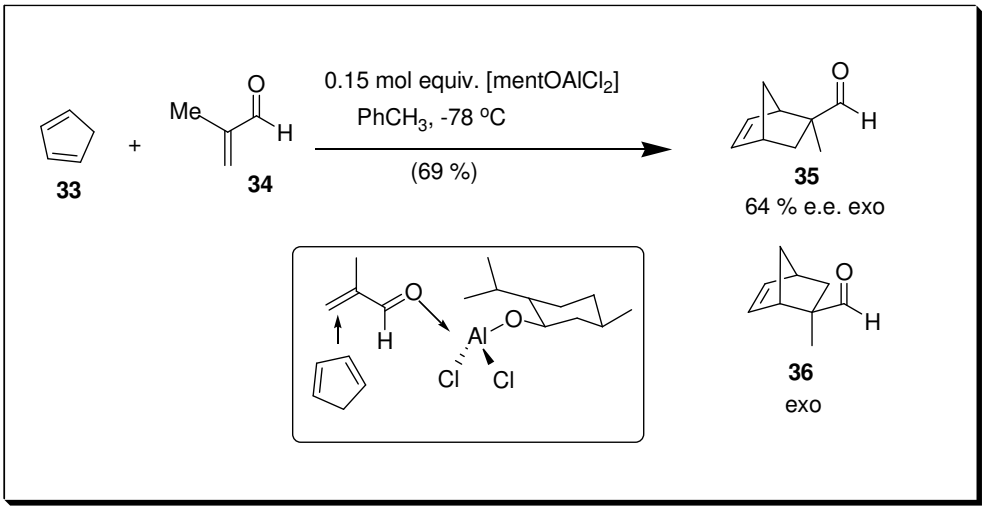
Scheme 9 Mukaiyama aldol reaction in aqueous media

These reactions attract many scientists since damaging and expensive organic solvents is not needed [41 c].

1.2.1.3 Catalytic Asymmeric Diels-Alder Reactions

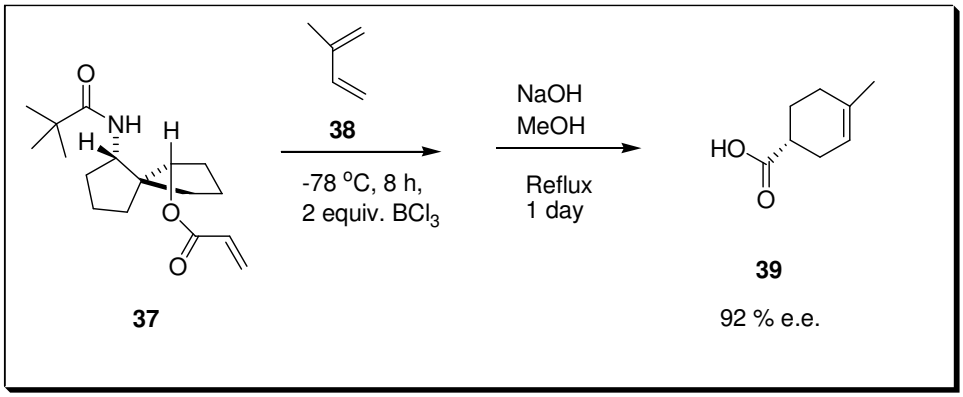
Another important carbon carbon bond formation reaction is the Diels-Alder reaction which results in six membered ring formation [44]. Because of the formation of the cyclic transition state, control of stereochemistry is possible and afford to high regio- and stereoselectivity [15]. Beside this, four new stereogenic centers are formed.

The studies about asymmetric Diels-Alder reaction was firstly initiated by the introduction of removable chiral auxiliary on the dienophile [45, 46, 47, 48]. Then, it was found that Lewis acids allow the reaction to occur in very mild conditions [49]. The first catalytic asymmetric Diels-Alder reaction by using chiral Lewis acid is shown in the scheme 10 [50].



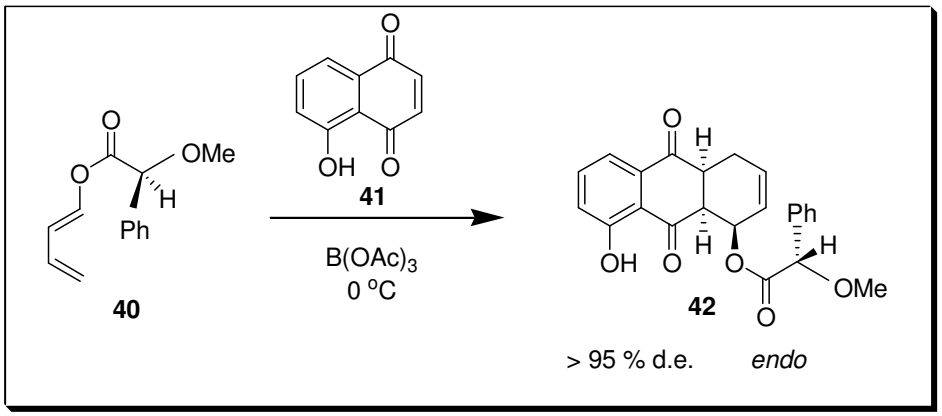
Scheme 10 The first positive catalytic asymmetric Diels-Alder reaction

In the literature, 1,1- and 1,2- aminoalcohols were used in many asymmetric transformations as chiral auxiliaries [51, 52]. However, 1,3-aminoalcohols are not very popular. In 2000, Keay et al. [53] used 1,3-aminoalcohol derivative, *cis, trans*- spiro-amido-alcohol, in Diels-Alder reaction as a chiral auxiliary. The example is shown in the scheme 11.



Scheme 11 Catalytic asymmetric Diels-Alder reaction with 1,3-aminoalcohol derivative

The examples in the schemes 10 and 11 contain a chiral Lewis acid and a chiral dienophile, respectively. In addition to these, chiral dienes can also be used in Diels-Alder reaction as shown in the scheme 12 [15].

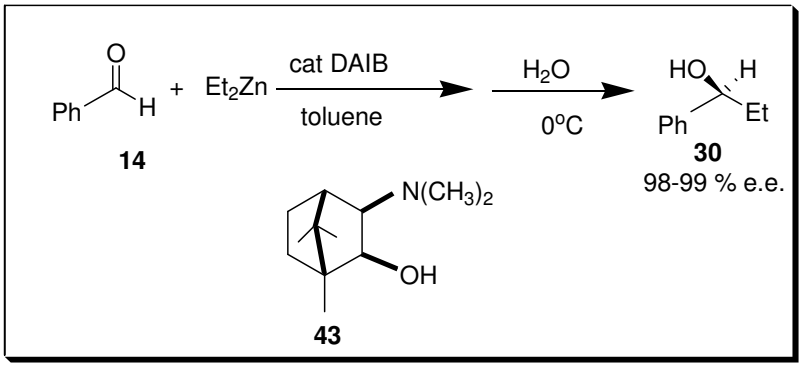


Scheme 12 Usage of chiral diene

1.3 Aminoalcohols

Aminoalcohols are very valuable compounds as both chiral ligands and auxiliaries in asymmetric synthesis since two heteroatoms allow flexibility while one or two of them bound to a Lewis acid, transition metal or achiral starting material [54]. Moreover, they are building blocks of natural products and have wide application in pharmaceuty [55].

As it was mentioned before, popularity of the aminoalcohols was started with the demonstration of high activity of DAIB by Noyori [25].



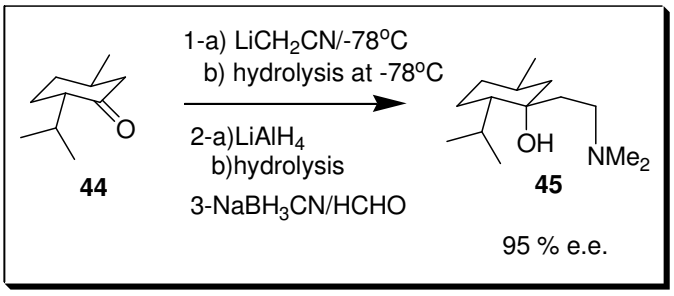
Scheme 13 Enantioselective diethylzinc addition reaction with DAIB

Until recently, there has been few examples for the preparation of γ- [56] and δ-aminoalcohols [57, 58]. However, scientists started to interest in γ-aminoalcohols and used them enantioselctive diethylzinc addition reactions [59].

1.3.1 1,2-Aminoalcohols

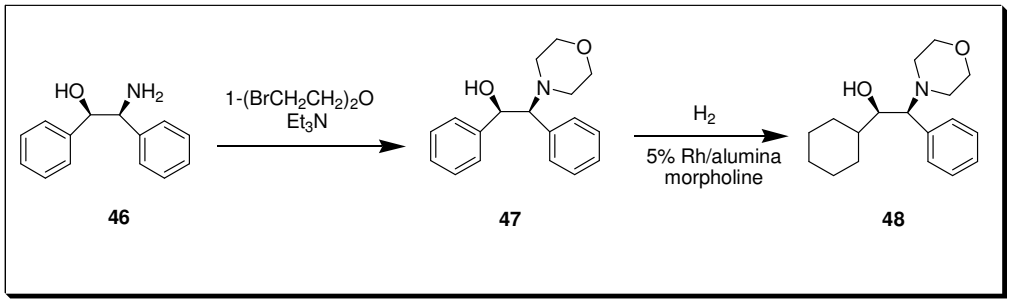
The most popular aminoalcohol is the β-aminoalcohols since they are easily obtained, effective and economical chiral catalysts [27, 60]. They can be prepared from aminoacids [61] or chiral aminocarbonyl compounds [62].

There are many examples of β-aminoalcohols in the literature. For instance, Dimitrov et al. [63] synthesize various β-aminoalcohols starting from (-)-menthone and obtain up to 95 % e.e. in enantioselective diethylzinc addition reactions.



Scheme 14 Synthesis of 1,2-aminoalcohol starting from (-)-menthone

Another scientist Nugent [64] synthesize morpholine substituted 1,2-aminoalcohol starting from commercially available (1*R,* 2*S*)-2-amino-1,2-diphenylethanol and its enantioselectivities in enantioselective diethylzinc addition reactions is up to 99 % e.e.

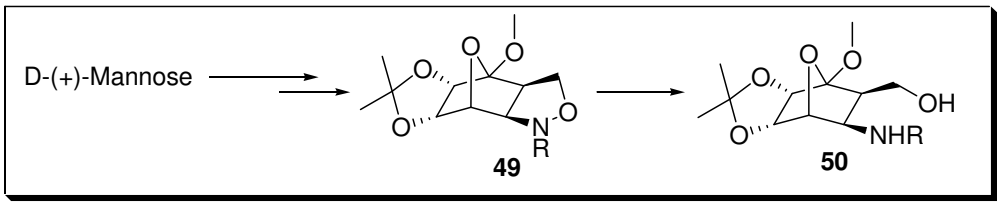


Scheme 15 Synthesis of 1,2-aminoalcohol starting from (1*R,* 2*S*)-2-amino-1,2-diphenylethanol

1.3.2 1,3-Aminoalcohols

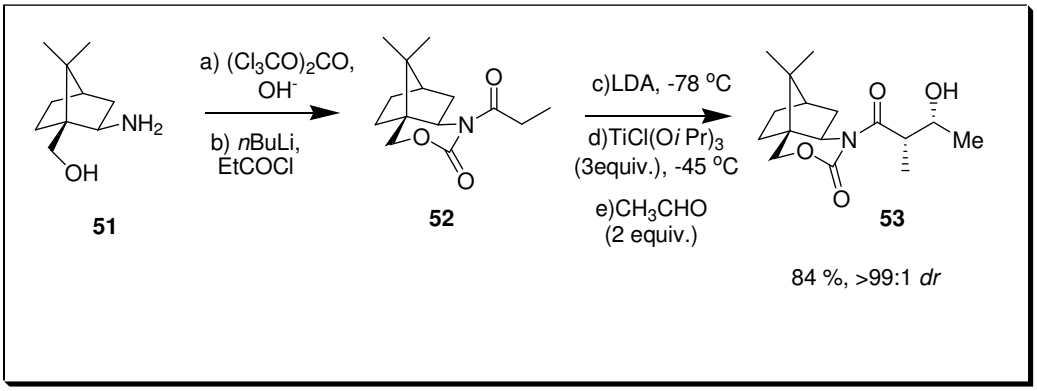
Many synthetic [65] and natural products [66] composed of 1,3-aminoalcohols and they have potent biological activity. Not only are they used as chiral ligands or auxiliaries, they have been utilized as resolving agents and phase transfer catalysts [54].

Although 1,2-aminoalcohols can be prepared by the reduction of amino acids, synthesis of 1,3-aminoalcohols need N-O bond clevage [67]. For instance, Das et al. [67] started from D-(+)-mannose in order to synthesize corresponding 1,3-aminoalcohol.



Scheme 16 Synthesis of 1,3-aminoalcohols starting from D-(+)-mannose

In 1992, 1,3-aminoalcohol derived from camphor was used as chiral auxiliary in aldol [68] reaction and up to 84 % e.e. was obtained.



Scheme 17 Synthesis of camphor derived 1,3-aminoalcohols

1.3.3 1,4-Aminoalcohols

As it was mentioned before, although 1,2-aminoalcohols have been used extensively, less examples can be found for 1,4-aminoalcohols. These compounds can be more selective due to their flexibility and better complexation with metals [27].

In a research done by Widhalm et al. [69] ferrocene substituted 1,4-aminoalcohols were synthesized and tested in enantioselective diethylzinc addition reactions.

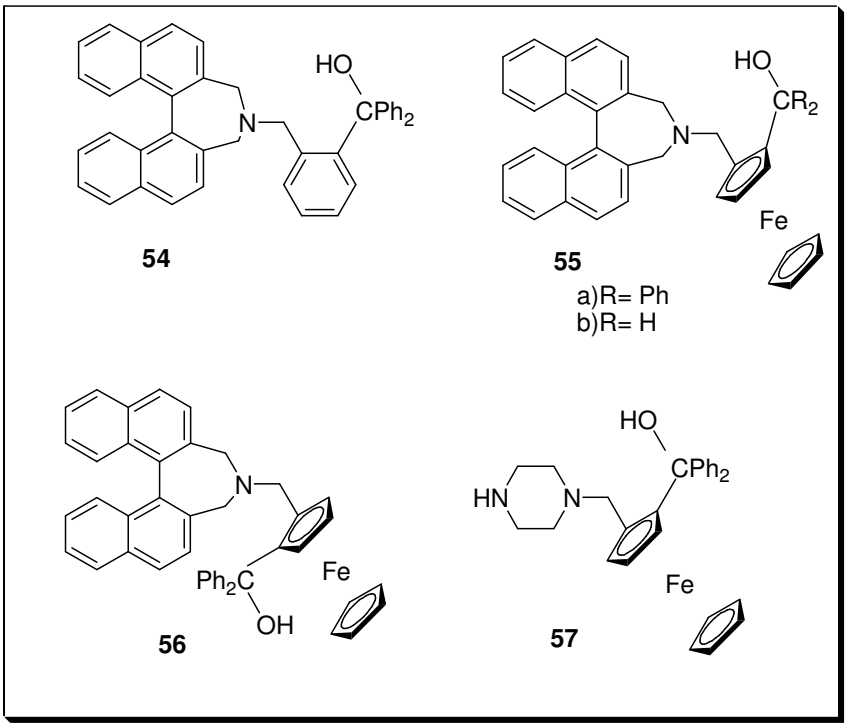


Figure 4 Chiral 1,4-aminoalcohols

Ligand **55a** had the e.e. value above 90 %. However, e.e. value of ligand **56** is very low because of the wrong metollecene configuration.

Synthesis of 1,4-aminoalcohols based on (+)-camphor and (-)-fenchone was done by Fujita et al. [59 b].

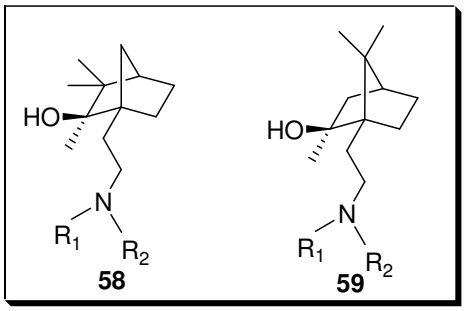


Figure 5 (+)-camphor and (-)-fenchone derived 1,4-aminoalcohols

The highest enantiomeric excess was 95 % obtained with N,N-dipropyl substituted **58** aminoalcohol.

In 1956, Campell et al. [70] synthesized 1,4-aminoalcohols using acetylenic amines with carbonyl compounds.

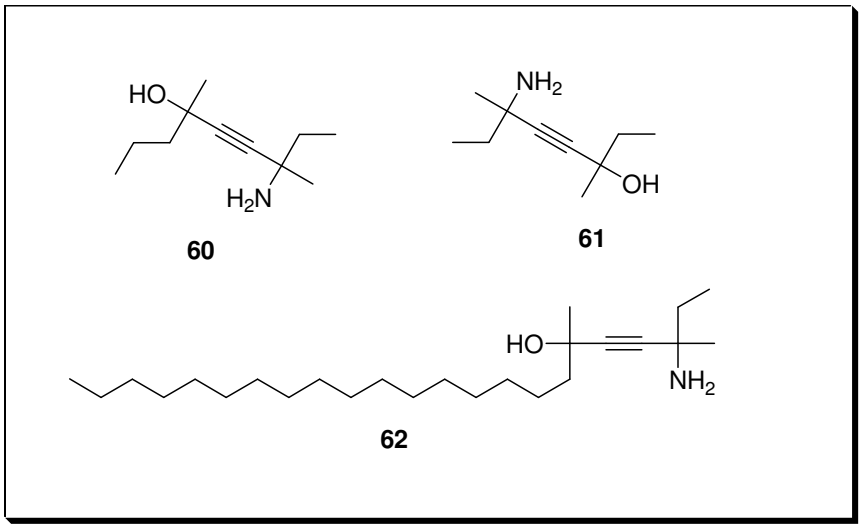


Figure 6 Acetylenic 1,4-aminoalcohols

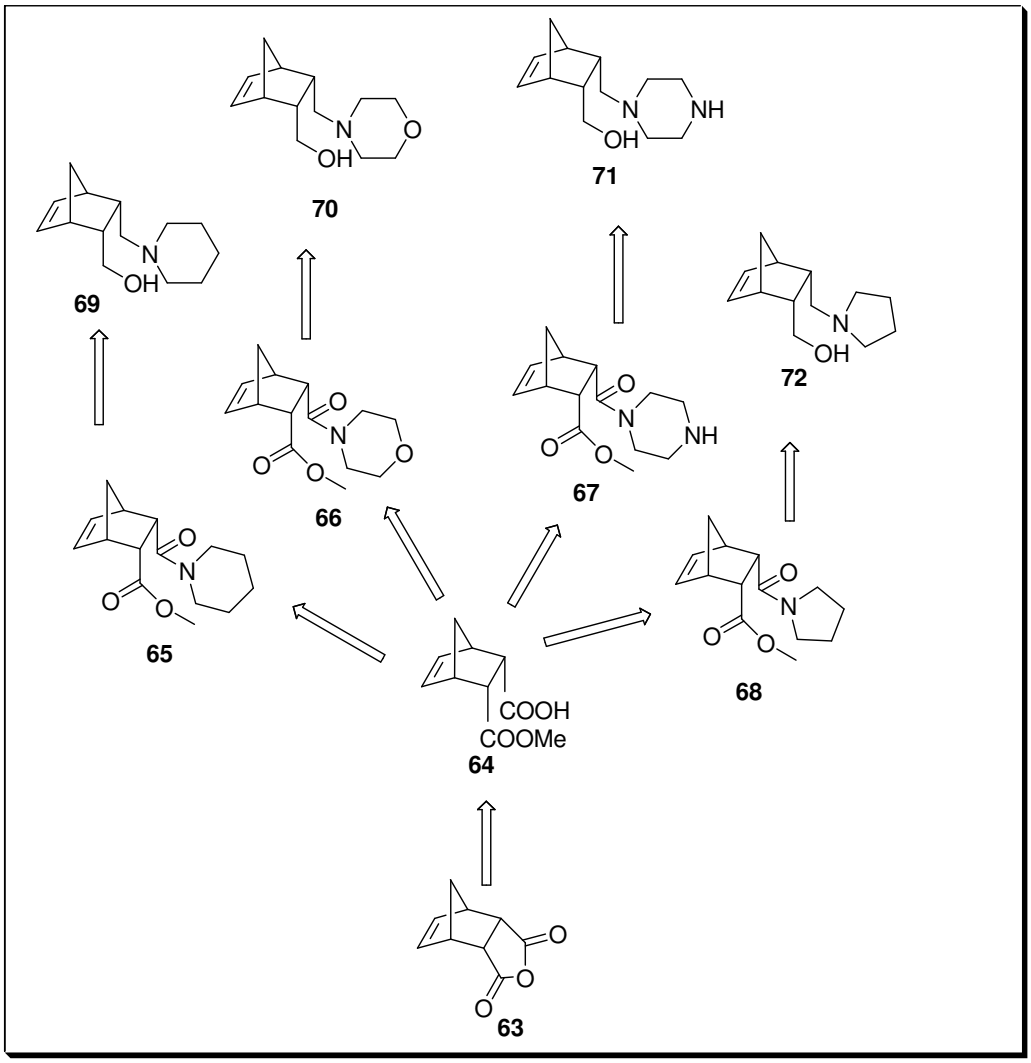
Since they were synthesized as racemate, they were not tested in any asymmetric reaction.

1.4 Aim of the work

The subject of this thesis involves the synthesis of novel chiral 1,4-aminoalcohols with norbornene backbone and determination of their effectiveness in some asymmetric transformations.

Meso anhydride **63** is a feasible, the cheapest and commercially available starting material. It is well known from the literature that desymmetrization of meso anhydrides with cinchona alkaloids gives high enantiomeric excess.

In our synthetic strategy, carboxylic acid part of the hemiester can easily be functionalized by cyclic amine structure i.e. piperidine, morpholine, piperazine and pyrrolidine. Subsequent reduction of the amide ester produce the corresponding 1,4-aminoalcohols. Retrosynthetic pathway of the study is shown in the scheme 18.



Scheme 18 Retrosynthetic pathway of the study

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Perspective of the work

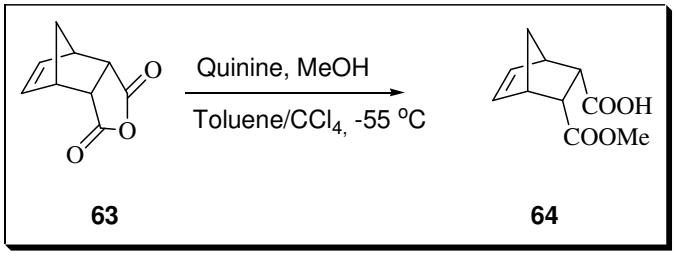
Chiral aminoalcohols are widely found as essential structural units in natural products and are of great importance in pharmaceutical research [71]. After Noyori and co-workers [25] demonstrated the high catalytic activity of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) in enantioselective diethylzinc addition reaction, many scientists focus on the synthesis of β-aminoalcohols since they can be obtained in enantiomerically pure form from the natural precursors easily. However, only few examples about 1,4-amino alcohols are found in the literature. 1,4-aminoalcohols have more flexible structures with respect to 1,2-aminoalcohols for complexation with various types of metals and thus may form more stable and selective catalysts in the reaction [27]. This motivate us to synthesize new chiral 1,4-aminoalcohols containing heterocyclic amine with norbornene backbone and use them in catalytic asymmetric transformations.

2.2 Asymmetric Synthesis of Aminoalcohols

Meso anhydride was chosen as the starting compound in order to synthesize 1,4-aminoalcohols since it is feasible, cheap and commercially available. Subsequent desymmetrization of meso-anhydride with cinchona alkaloids results in the formation of hemiester. Introduction of various cyclic amines to the compound and successive reduction lead to the corresponding 1,4-aminoalcohols.

2.2.1 Desymmetrization of Meso -Anhydride, 63

Enantioselective desymmetrization of meso-anhydrides was done by Bolm et al. [72] with cinchona alkaloids. In this study, quinine was chosen as the directing agent since it is cheaper than quinidine. The usage of meso-anhydride with quinine in the presence of methanol and CCl_4/toluene mixture affords to (2*S,* 3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid, **63**

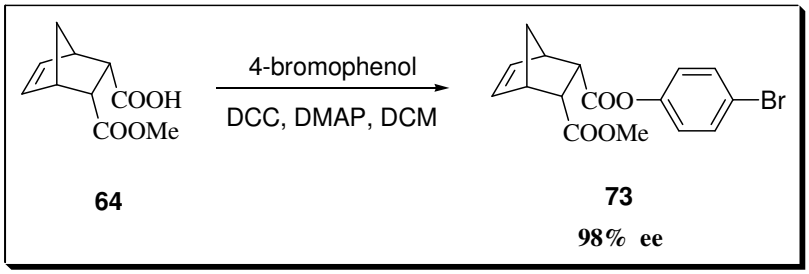


Scheme 19 Desymmetrization of **63**

The NMR results confirm the structure. Two doublets of doublets at 6.26 (1H) and 6.16 (1H) ppm belong to the hydrogens of the double bond. Methoxy protons appear as singlet at 3.54 (3H) ppm. Two doublet of doublets at 3.28 (1H) and 3.22 (1H) ppm correspond to hydrogens neighbouring to carbonyl groups. Two broad singlets at 3.14 (1H) and 3.11 (1H) ppm are the characteristic of bridgehead protons. Bridge protons give signals at 1.43 (1H) and 1.28 (1H) ppm as doublets. In the carbon NMR, characteristic carbonyl signals appear at 177.8 and 173.1 ppm. Signals at 135.6 and 134.4 ppm correspond to carbons of the double bond. Remaining carbons have the signal between 51.6-46.1 ppm.

2.2.2 Determination of Enantiomeric Excess of (2*S*,3*R*)-3 methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid, 73

Determination of the enantiomeric excess of (2*S*, 3*R*)-hemiester **64** was done by the substitution of 4-bromophenol. Since the UV activity of (2*S*, 3*R*)-hemiester **64** is so low and the polarity is so high, derivation of the carboxylic acid part of the compound was done with 4-bromophenol by DCC coupling method in order to obtain more UV active and less polar diester **73**. Next, the HPLC analysis was done in OD-H column. The conditions were *n*-hexane/2-propanol = 98:2 and the flow rate was 0.5 mL/min. The wavelength of the detector was 254 nm. [t_1=20.3 min (major), t_2=23.2 min (minor)]

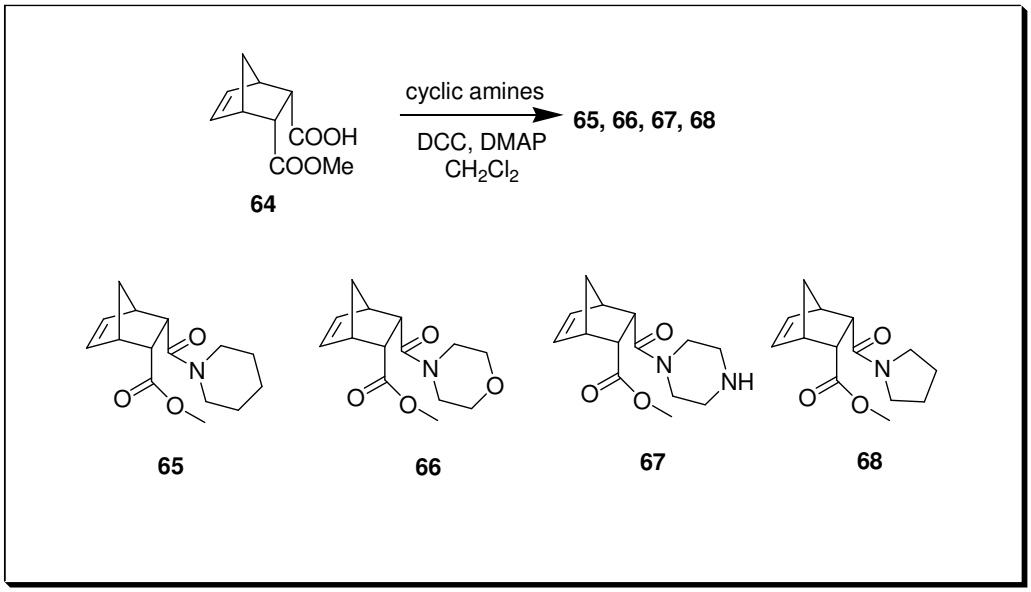


Scheme 20 Synthesis of **73**

NMR results confirm the compound **73.** Different from the ^{1}H- and ^{13}C-NMR spectrum of (2*S*, 3*R*)-hemiester **64,** there were signals at 7.37 (2H) and 6.92 (2H) ppm and the region between 150.3-132.7 ppm which correspond to aromatic hydrogens and carbons, respectively. Other signals remain as the same as in (2*S*, 3*R*)-hemiester **64.**

2.2.3 Synthesis of Amide Ester

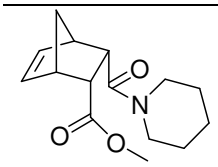
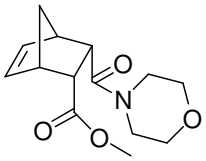
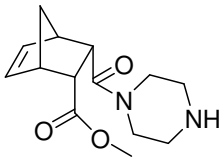
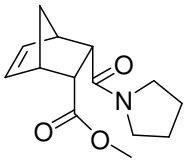
In the construction of target 1,4-aminoalcohols, enantiomerically enriched (2*S*, 3*R*)-hemiester **64** was transformed into corresponding amide ester by the substitutiton of cyclic amines piperidine, morpholine, piperazine and pyrrolidine via DCC coupling method. The structures are shown in the scheme 21.



Scheme 21 Synthesis of amide esters

Each compound was monitored by TLC. Yields and physical data are given in table 1

Table 1 Yields and physical data of amide esters

Compound	Cpd. No[a]	t[b]	T[c]	Yield % (isolated)	mp[d] °C	$[\alpha]_D^{20}$
	**65**	24 h	RT[e]	88	77.3	-21,95 MeOH
	**66**	24 h	RT[d]	74	88	-32,22 MeOH
	**67**	24 h	RT[d]	32	210	-55,9 $CHCl_3$
	**68**	24 h	RT[d]	39	51.6	-24,65 MeOH

[a] compound number

[b] reaction time

[c] temperature

[d] melting point

[e] room temperature

Although yields of compound **65** and **66** are acceptable, compound **67** and **68** have very low yields. This is because of the isolation problems in flash column chromatography. In addition to this, dicyclohexylurea formed in the reaction medium can not be completely removed by filtration.

All the compounds were characterized by ^{1}H and ^{13}C NMR.

In compound **65**, due to the partial double bond of the amide ester, α-protons give signal as multiplet between 3.61-3.10 ppm (overlap with methoxy and methine signals). Other 6 protons in piperidine cycle appear as multiplet in the region between 1.54-1.43 ppm. Methoxy, bridgehead and bridge protons correspond to singlet, doublet of doublet and doublet signals, respectively nearly in the same region like in the spectrum of (2*S*, 3*R*)-hemiester **64**. In ^{13}C spectrum, carbonyl carbons and carbons of the double bond shift to the upper field comparing to (2*S*, 3*R*)-hemiester **64** because of the introduction of less electronegative nitrogen to the compound. In addition to this, there are signals of methylene and methine carbons between 51.3-25.0 ppm.

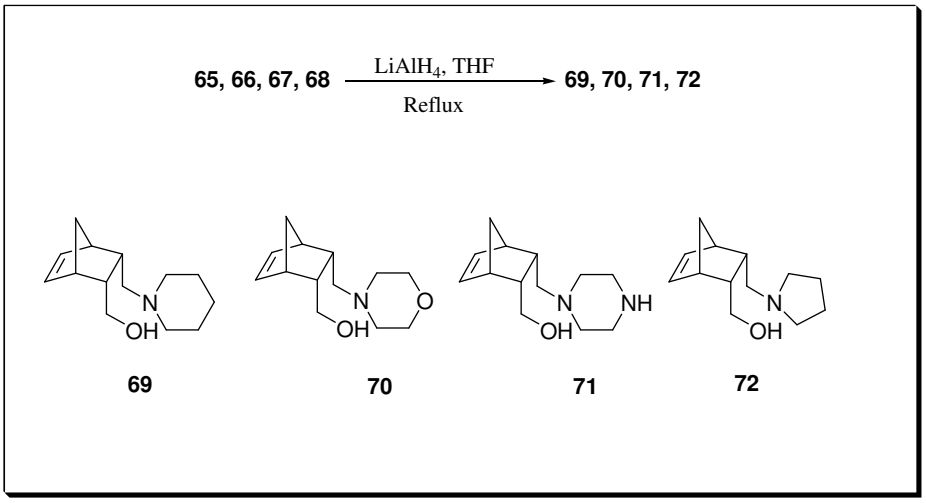
^{1}H NMR spectrum of **66** shows that methylene protons neigbouring oxygen appear as multiplet between 3.72-3.50 ppm (overlap with methoxy signals). Other methylene protons in the ring correspond to multiplet between 3.48-3.33 ppm (overlap with methenyl protons). ^{13}C NMR also confirms the structure. Carbonyl carbons and carbons of the double have characteristic signals. Moreover, there are signals of remaining carbons between 66.8-42.2 ppm.

^{1}H NMR of the compound **67** differs from compound **65** in this way: methylene protons in the ring have signals between 3.56-3.50 ppm (overlap with methoxy signal). In ^{13}C NMR 51.5-41.4 ppm contains the signal of the carbons except carbonyl carbons and carbons of the double bond.

The last amide ester **68** have more clear ^{1}H NMR spectrum than others. Methylene protons neighbouring nitrogen appear as two doublet of triplets between 3.46-3.40 ppm different from compounds **65**, **66** and **67**. Other multiplets between 2.00-1.80 ppm correspond to remaining protons on the pyrrolidine ring. In ^{13}C NMR, carbons other than having double bond character have signals between 51.4-24.2 ppm

2.2.4 Reduction of Amide Esters

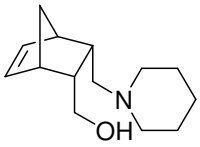
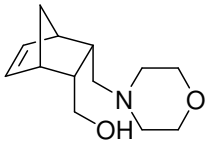
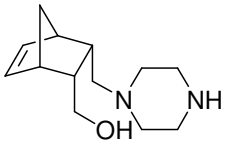
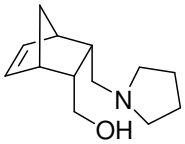
This part of the work covers the reduction of amide esters in order to obtain target 1,4-aminoalcohols. Although $NaBH_4$ is an excellent reducing agent for aldehydes and ketones, it is very slow for amides and carboxylic acids [73] With the combination of various metal halides, its reduction power can be enhanced [73-83]. In an another study in 1992, Periasamy [84] reported that reduction of amides with $NaBH_4$-I_2 system in THF give yields between 70-76 %. Compared to $NaBH_4$, $LiAlH_4$ is a more powerful reagent for the reduction of carboxylic acids and amides, and it was used as the reducing agent for amide esters. The structures of the resulting 1,4-aminoalcohols are given in the scheme 22.



Scheme 22 Reduction of amide esters

Each compound was monitored by TLC. Yields and physical data are given in table 2.

Table 2 Yields and physical data of 1,4-aminoalcohols

Compound	Cpd[a]. No	t[b]	T[c]	Yield % (isolated)	mp[d] °C	$[\alpha]_D^{20}$
	**69**	24 h	RT[e]	89	61.4	-3.625
	**70**	24 h	RT[e]	70	-	-4.3
	**71**	24 h	RT[e]	90	229	-8.59
	**72**	24 h	RT[e]	95	65.1	0.157

[a] compound number

[b] reaction time

[c] temperature

[d] melting point

[e] room temperature

As it is shown in the table, all the compounds have acceptable yields and ^{1}H and ^{13}C NMR spectrums of them confirm the structures.

The basic difference of ^{1}H NMR of compounds **69, 70, 71** and **72** from the corresponding amide esters is the disappearance of the methoxy signal at about 3.50 ppm and appearance of methylene signals as doublet and triplet. This difference can be seen in ^{13}C NMR with the removal of signals corresponding to carbonyl carbons between 170-172 ppm. In addition to this, protons of the double bond do not give a doublet of doublets any more. In this study, they can be seen as a singlet at more than 6.0 ppm.

In the ^{1}H spectrum of compond **69**, methylene protons neighbouring the hydroxyl group appear as a doublet a and triplet at 3.50 (1H) and 3.21 (1H) ppm, respectively. Other methylene protons next to nitrogen have signals between 2.28-2.17 ppm as multiplets. Moreover, all the remaining protons shift to the lower field with respect to corresponding amide ester **65**. In ^{13}C NMR, carbons have signals between 63.1-24.2 ppm, in slightly upper field.

The difference of ^{1}H NMR of compound **70** from compound **69** is the signal at about 3.66 ppm which correspond to methylene protons neighbouring to oxygen in the ring. Other protons have signal at expected fields. ^{13}C NMR also confirms the structure by giving signals between 66.0-29.7 ppm except for the signals of carbons belonging to double bond.

Compound **71** has nearly same ^{1}H NMR spectrum as compound **70**. However, while methylene protons neighbouring to oxygen appears in lower field, methylene protons neighbouing to nitrogen give signal between 2.51-2.39 ppm which is at a higher field.

In the ^{1}H NMR of compound **72**, methylene protons appear as multiplet and triplet at 3.68-3.66 (1H) ppm and 3.22 (1H) ppm, respectively. Other methylene protons next to the nitrogen give signals as multiplet between 2.51-2.44 ppm (overlap with methylene protons neighbouring to nitrogen on the pyrrolidine ring). ^{13}C NMR agrees with the ^{1}H NMR. Signals between 63.0-23.3 ppm belong to the saturated carbons.

2.3 Test Reactions

Enantioselective diethylzinc addition reaction, Mukaiyama aldol reaction and Diels-Alder reaction are very important carbon carbon bond formation reactions.

Enantioselective diethylzinc addition reaction is very important in this point of view, chiral secondary alcohols, which are important intermediates for the synthesis of natural products [21], can be obtained. Various aminoalcohols are used as chiral ligands in this reaction and very high selectivity can be obtained.

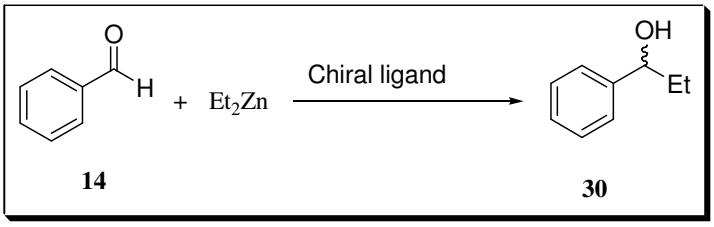
Mukaiyama aldol reaction is also very popular, since it is highly atom economic [33]. In addition to this, the reaction can occur in aqueous media [41] so it is less harmful to the environment.

Diels-Alder reaction is the third carbon carbon bond formation reaction which occurs in the presence of a diene and a dienophile. Since the transition state is cyclic, control of the stereochemistry is easy [15]. Beside this, four stereogenic centers can be obtained.

By taking these information into account, novel chiral 1,4-aminoalcohols were tested in the reactions mentioned above.

2.3.1 Enantioselective Diethylzinc Addition Reaction

The effectiveness of novel chiral ligands were tested firstly in enantioselective diethylzinc addition reaction. The reaction took place in the presence of benzaldehyde, diethylzinc and chiral ligand as shown in the scheme 23.



Scheme 23 Enantioselective diethylzinc addition reaction

The results are summarized in table 3

Table 3 Effect of different ligands to diethylzinc addition reaction

Entry	Ligand[a]	Ee %
1	**69**	40
2	**70**	63
3	**72**	20

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

As it is shown in table 3, the highest e.e. value was obtained from morpholine substituted chiral ligand **70**. Piperidine substituted one **69** gave the second highest result.

In order to enhance the e.e. values, this time the reaction was done in hexane medium. The results were summarized in table 4.

Table 4 Effect of different solvents to diethylzinc addition reaction

Entry	Ligand[a]	Ee %
1	**69**	85
2	**70**	30
3	**71**	-
4	**72**	5

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

When the results are compared, it is obviously seen that there is a drastic increase in the e.e. value of the product **30** catalyzed by compound **69.** This may be due to the good solubility of the catalyst in the hexane and well coordination with diethylzinc.

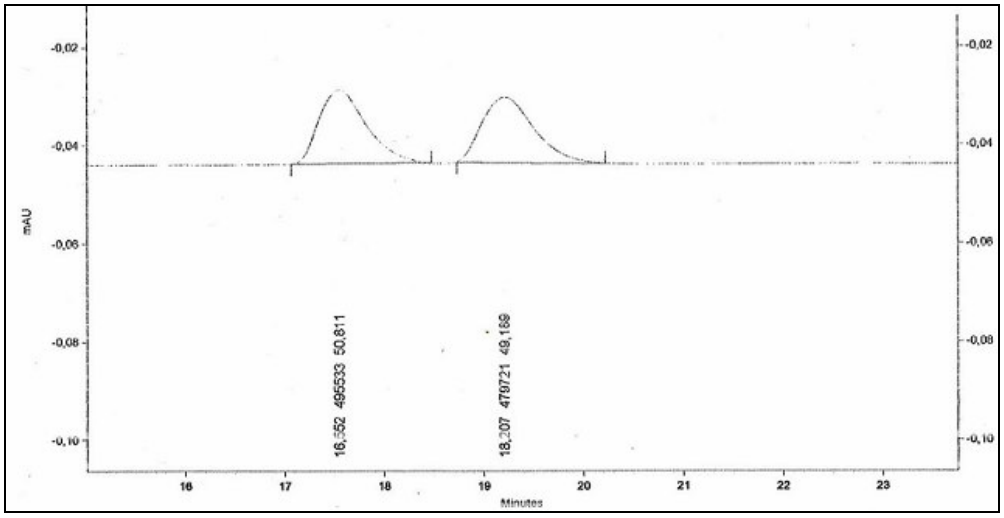


Figure 7 Chromotagram of racemic **30**

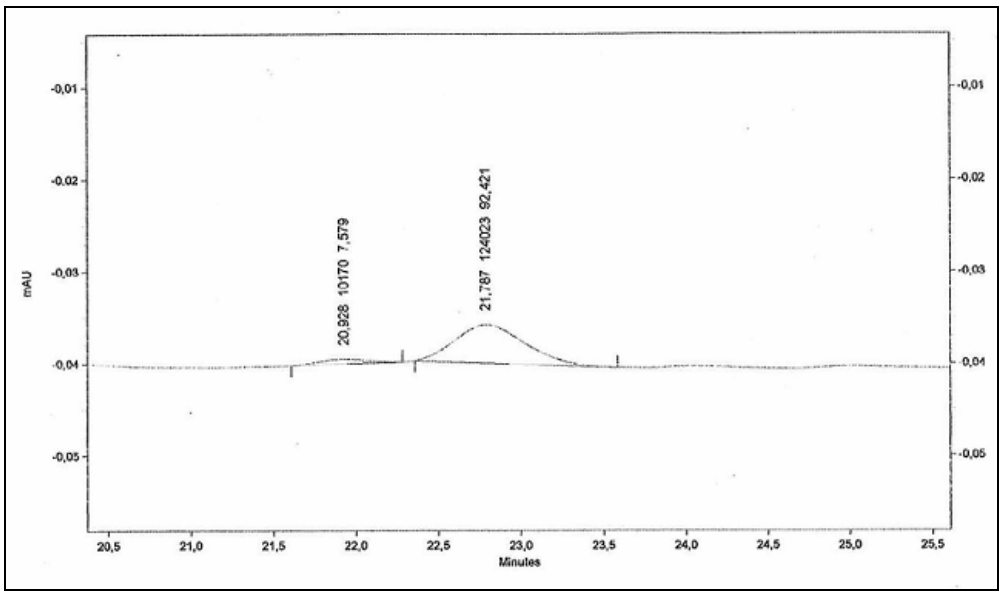
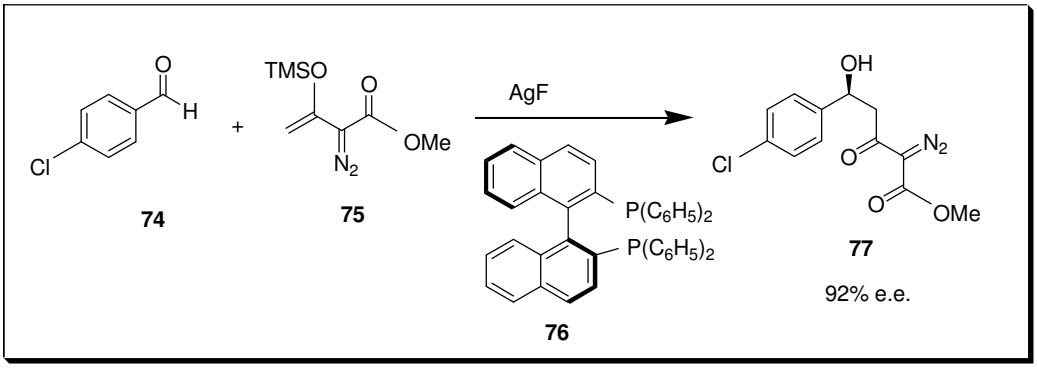


Figure 8 Chromotagram of the **30** obtained by ligand **69** in hexane

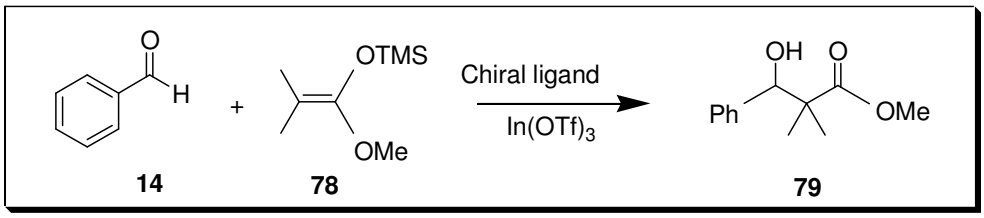
2.3.2 Catalytic Asymmetric Mukaiyama Aldol Reaction

In the literature there are many examples of Mukaiyama Aldol reaction. For example, Doyle et al. [85] synthesized chiral diazoacetoacetates, which are extensively used in metal carbene transformations in the synthesis of many natural products and pharmaceuticals [86, 87], by using 3-trimethylsilyloxy-vinyldiazoacetate **73** up to 92 % e.e.



Scheme 24 Synthesis of diazoacetoacetates

Although there are examples of Mukaiyama Aldol reaction in the literature, 1,4-aminoalcohols never used as chiral ligands. In order to test their effectiveness, benzaldehyde and (1-methoxy-2-methyl-propenyloxy)-trimethylsilane was reacted in the presence of $In(OTf)_3$ and chiral ligand at -40^0C.

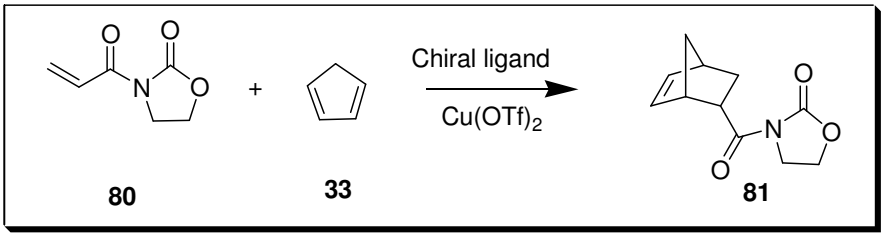


Scheme 25 Catalytic asymmetric Mukaiyama aldol reaction

However, the product was racemic in all reactions catalyzed by compounds **69, 70, 72.** Then, the reaction temparature decreased to -60 ^{0}C since this reaction usually occurs at very low temperatures. In this case, again racemic product was obtained from the reactions catalyzed by **69, 70, 71, 72.** So it is concluded that much lower temperatures are needed and metal complex may not coordinate well to the ligands.

2.3.3 Catalytic Asymmetric Diels-Alder Reaction

Diels-Alder reaction has been known for a long time and there are many applications about it. As it was mentioned before 1,3-aminoalcohols were used as chiral ligands in this reaction. However, no examples containing 1,4-aminoalcohols as chiral ligands was found. In order to test novel chiral 1,4-aminoalcohols, an oxazolidone derivative and cyclopentadiene was reacted in the presence of $Cu(OTf)_2$ and compound **69** and **70** at room temperature.



Scheme 26 Catalytic asymmetric Diels Alder reaction

The results are summarized in table 5

Table 5 Effect of different ligands to Diels-Alder reaction

Entry	Ligand[a]	Ee %
1	**69**	10
2	**70**	9

[a] 11 mol % of chiral catalyst were used. Dichloromethane was used as solvent. All the reactions were done at room temperature.

In general, this reaction occurs at room temperature without catalyst very fast. When the e.e. values are taken into account, the addition of catalyst provides some enantioselectivity. However, room temperature may not be suitable for the ligand to coordinate to the metal complex. So lower temperatures may result in higher e.e. values.

CHAPTER 3

CONCLUSION

Four novel chiral 1,4-aminoalcohols with norbornene backbone (*2S, 3R*)-**69**, (*2S, 3R*)-**70**, (*2S, 3R*)-**71** and (*2S, 3R*)-**72** were synthesized. Firstly, their effectiveness were tested in enantioselective diethylzinc addition reaction. (*2S, 3R*)-**70** gave the highest result in toluene. However, as the solvent change from toluene to hexane e.e value of the ligand (*2S, 3R*)-**69** increased from 40 to 85%. There were no increase in the values of other ligands.

While these ligands were effective in diethylzinc addition reaction, they gave racemic products in catalytic asymmetric Mukaiyama aldol reaction at both -40 ^{o}C and -60 ^{o}C in dichloromethane.

In catalytic asymmetric Diels-Alder reaction, (2*S, 3R*)-**69** and (*2S, 3R*)-**70** were used. The e.e. values were not so high but promising at room temperature. In general, this reaction occurs rapidly without catalyst. Low e.e. values obtained in the presence of catalyst showed that by lowering the temperature, more enentioselective reactions can take place.

The effectiveness of the ligands in asymmetric Mukaiyama aldol reaction and catalytic asymmetric Diels-Alder reaction were tested in specific solvent systems. Different solvents will be used in the future. In addition to this, double bond on the norbornene backbone is a potent for ring opening metathesis polymerization with Grubbs catalsyst. So a macromolecule which is a reusable catalyst can be obtained.

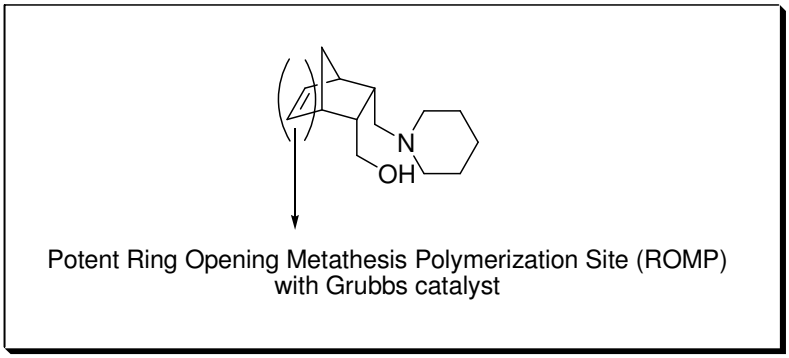


Figure 9 Ring opening metathesis polymerization with Grubbs catalyst

CHAPTER 4

EXPERIMENTAL

In this study, structure of the compounds were determined by the instruments as written.

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

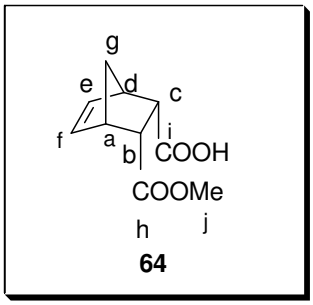
Optical rotations were measured in a 1 dm cell using Rudolph Research Analytical Autopol III Automatic Polarimeter

HPLC measurements were performed with ThermoFinnigan Spectra System instrument.

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

4.1 Synthesis of (2*S*,3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2 carboxylic acid, 64

To a stirred solution of *meso*-anhydride **63** (2.00 gr, 12 mmol) and quinine in a 1:1 mixture of toluene (120 mL) and carbontetrachloride (120 mL), MeOH (1.48 mL, 36 mmol) was added dropwise under argon atmosphere at -55 °C. The mixture has been stirred at this temperature for 60 hours. Subsequently, the solution was concentrated in vacuo in order to dry and the resulting residue was dissolved in ethyl acetate. This solution was washed with 2 N HCl. After the phase separation, extraction of the aqueous phase was done by ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to obtain monoester **64**
(2.17 g, 92 %); $[\alpha]_D^{20}$= -7.8 (*c* 4.0, CCl_4), lit.[73] $[\alpha]_D^{20}$= -7.9 (*c* 4.8, CCl_4); mp 75–78 °C, lit.[73] 74 °C (racemic)



64

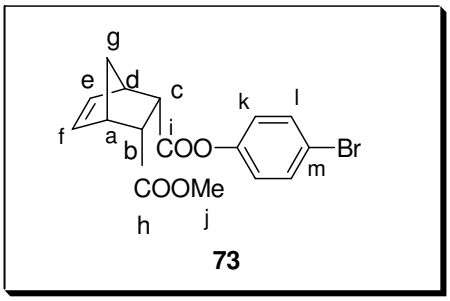
Figure 10

^{1}H NMR: δ 6.26 (dd, J= 2.96, 5.50 Hz, 1H, H_e),
6.16 (dd, J= 2.94, 5.53 Hz, H_f),
3.54 (s, 3H, H_j),
3.28 (dd, J= 3.22, 10.14 Hz, 1H, H_b),
3.22 (dd, J= 3.13, 10.15 Hz, 1H, H_c),
3.14(bs, 1H, H_a),
3.11 (bs, 1H, H_d),
1.43 (dd, J= 1.56, 8.67 Hz, 1H, H_g),
1.28 (d, J= 8.69 Hz, 1H, H_g);

^{13}C NMR: δ 177.8, 173.1, 135.6, 134.4, 51.6, 48.8, 48.2, 47.9, 46.6, 46.1.

4.2.1 Synthesis of (2*S*,3*R*)-2-(4-bromophenoxy)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 73

4-Bromophenol (0.088 g, 0.51 mmol) and hemiester **64** (0.1 g, 0.51 mmol) was dissolved in CH_2Cl_2 at 0 °C under argon atmosphere. Next, DCC (0.105 g, 0.51 mmol) and DMAP (0.016 g, 0.13 mmol) were added simultaneously at this temprature. The mixture was mixed overnight at room temperature. The mixture was filtered to remove dicyclohexylurea. The filtrate was washed with 5 % acetic acid and 1 N HCl, then $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$. Compound **73** (0.16 g, 89%) was obtained after the removal of solvent. HPLC-analysis of the methyl 4-bromophenyl diester:



73

Figure 11

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)

^{1}H NMR: δ 7.37 (d, *J*= 8.72 Hz, 2H, H_l),
6.92 (d, *J*= 8.71 Hz, 2H, H_k),
6.32 (dd, *J*= 2.91, 5.39 Hz, 1H, H_e),
6.15 (dd, *J*= 2.92, 5.41 Hz, 1H, H_f),
3.55(s, 3H, H_j),
3.39 (s, 2H, H_b, H_c),
3.20 (s, 1H, H_a),
3.17 (s, 1H, H_d),
1.40 (d, *J*= 8.70 Hz, 1H, H_g),
1.33 (d, *J*= 8.61, 1H, H_g);

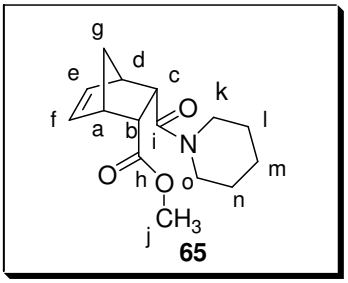
^{13}C NMR: δ 173.0, 171.2, 150.3, 135.9, 135.0, 132.7, 123.8, 119.0, 52.2, 49.1, 48.7, 48.5, 47.2, 46.6.

4.3 General procedure for the synthesis of amide ester

Monoester **44** (1g, 5.1 mmol) was dissolved in CH_2Cl_2 and amine (5.1 mmol) was added to the mixture at 0 °C under argon atmosphere. Then, DCC (1.05 g, 5.1 mmol) and DMAP (0.16 g, 1.28 mmol) were added simultaneouly at this temperature. The mixture was stirred at room temperature overnight. Next, the solution was fitered and washed with 5 % acetic acid and 1 N HCl then, $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$. The solvent was evaporated to obtain the product.

4.3.1 (2*S*,3*R*)-2-(*N*-piperidincarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 65

Using the general procedure, compound **65** was synthesized in 88% yield. $[\alpha]_D^{20}$= -21.95 (*c* 2, MeOH); mp 77.3 °C;



65

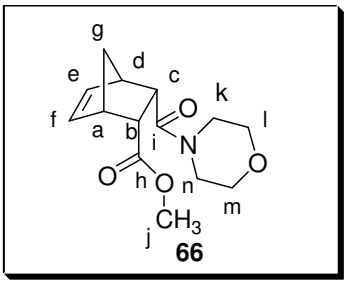
Figure 12

^{1}H-NMR: δ 6.21 (dd, *J*= 3.02, 5.19 Hz, 1H, H_e),
6.07 (dd, *J*= 2.90, 5.27 Hz, 1H, H_f),
3.62-3.58 (m, *J*= 16.7 Hz, 1H, H_k),
3.46 (s, 3H, H_j),
3.42 (s, 1H, H_k),
3.29 (dd, *J*= 2.91, 9.78 Hz, 1H, H_c),
3.10 (dd, *J*=3.12, 9.83 Hz, 3H, H_c, H_o),
3.04 (s, 1H, H_a),
2.95 (s, 1H, H_d),
1.54-1.43 (m, 6H, H_l, H_m, H_n),
1.32 (d, *J*= 7.92 Hz, 1H, H_g),
1.21 (d, *J*= 1.21 Hz, 1H, H_g);

^{13}C-NMR: 172.9, 170.0, 135.8, 133.5, 51.3, 48.8, 48.3, 46.9, 46.8, 46.6, 42.7, 33.8, 26.3, 25.4, 25.0

4.3.2 (2*S*,3*R*)-2-(*N*-morpholincarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 66

Using the general procedure, compound **66** was synthesized in 73.7% yield. $[\alpha]_D^{20}$= -32.22 (*c* 0.2, MeOH); mp 87.8-88 °C



66

Figure 13

^{1}H-NMR: δ 6.34 (dd, *J*= 3.01, 5.36 Hz, 1H, H_e),
6.10 (dd, *J*= 2.92, 5,40 Hz, 1H, H_f),
3.60 (d, *J*= 7.73, 4H, H_l, H_m)
3.50 (s, 3H, H_j),
3.47 (d, *J*= 14.35 Hz, 2H, H_k),
3.34 (d, *J*= 9.13 Hz, 2H, H_n)
3.28 (dd, *J*= 3.12, 9.84 Hz, 1H, H_b),
3.18 (dd, *J*= 3.47, 9.88 Hz, 1H, H_c),
3.12 (s, 1H, H_a),
3.02 (s, 1H, H_d),
1.40 (d, *J*=8.53 Hz, 1H, H_g),
1.26 (d, *J*=8.50 Hz, 1H, H_g);

^{13}C-NMR: δ 172.2, 170.9, 136.3, 133.4, 66.8, 66.3, 51.5, 48.8, 48.4, 46.9, 46.8, 46.7, 45.8, 42.2

4.3.3.1 (2*S*,3*R*)-2-(*N*-pyrrolidincarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 68

Using the general procedure, compound **68** was synthesized in 39% yield. $[\alpha]_D^{20}$= -24.65 (*c* 0.1, MeOH); mp 51.3-51.6 °C

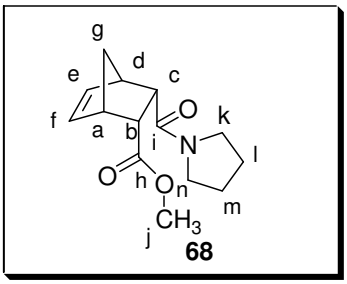


Figure 14

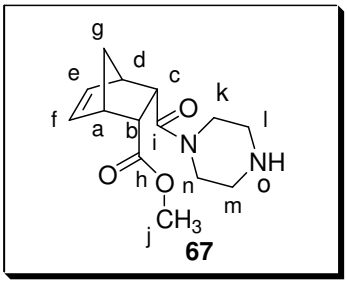
^{1}H-NMR: δ 6.32 (dd, *J*=3.00, 5.41 Hz, 1H, H_e),
6.26 (dd, *J*= 2.94, 5.42 Hz, 1H, H_f),
3.58 (s, 3H, H_j),
3.42 (dt, *J*= 8.43, 16.68 Hz, 4H, H_k, H_n),
3.33 (dd, *J*= 3.17, 10.0 Hz, 1H, H_b),
3.24 (dd, *J*= 3.40, 10.0 Hz, 1H, H_c),
3.17 (s, 1H, H_a),
3.10 (s, 1H, H_d),

1.93-1.91 (m, 2H, H_l),
1.84 (p, *J*= 6.73 Hz, 2H, H_m),
1.44, (dd, *J*= 1.42, 8.47 Hz, 1H, H_g),
1.32 (d, *J*= 8.43, 1H, H_g);

^{13}C-NMR: δ 172.8, 170.4, 135.5, 133.9, 51.4, 48.7, 48.5, 48.1, 46.3, 46.2, 45.7, 26.1, 24.2

4.3.4 Synthesis of (2*S*,3*R*)-2-(*N*-piperazincarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 67

Monoester **64** (1g, 5.1 mmol) was dissolved in CH_2Cl_2. and piperazine (0.21 g, 2.55 mmol) was added to the mixture at 0 °C under argon atmosphere. Then, DCC (1.05 g, 5.1 mmol) and DMAP (0.16 g, 1.28 mmol) were added simultaneouly at this temperature. The mixture was stirred at room temperature overnight. Next, the solution was filtered and washed with 5 % acetic acid and 1 N HCl then, $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$. The solvent was evaporated to obtain the product in 32% yield. $[\alpha]_D^{20}$= -55.9 (*c* 0.2, $CHCl_3$); mp 210 °C



67

Figure 15

^{1}H-NMR: δ 6.43 (d, *J*=2.66 Hz, 1H, H_e),
6.13 (s, 1H, H_f),
3.58 (s, 3H, H_j),
3.56-3.50 (m, 4H, H_k, H_n),
3.49-3.41 (m, 3H, H_l H_m, H_o),
3.34 (d, *J*=2.95 Hz, 1H, H_b),
3.32 (d, *J*=2.95, Hz, 1H, H_c),
3.28 (d, *J*= 2.74 Hz, 1H, H_l),
3.26 (d, *J*=3.10 Hz, 1H, H_m),
3.20 (s, 1H, H_a),
3.09 (s, 1H, H_d),
1.47 (d, *J*=8.55 Hz, 1H, H_g),
1.34 (d, *J*=8.49 Hz, 1H, H_g);

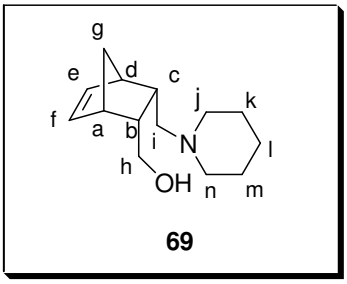
^{13}C-NMR: δ 172.5, 171.1, 136.6, 133.0, 51.5, 48.7, 48.4, 46.9, 44.7, 41.4

4.4 General procedure for the synthesis of 1,4-aminoalcohols

To a suspenesion of $LiAlH_4$ (5 eq) in anhydrous THF, amide ester (1 eq) solution was added in dry THF such a rate that the reflux was continued slowly. The mixture was refluxed for 5 hours. After the TLC control, the system was hydrolized by the addition of 1 mL distilled water. The white precipitate was washed with THF and discarded. Evaporation of the solvent afforded to 1,4-aminoalcohol.

4.5.1 (2*S*,3*R*)-2-piperdinomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 69

Using the general procedure, compound **69** was synthesized in 89% yield. $[\alpha]_D^{20}$= -3.625 (*c* 2, MeOH); mp 61.4 ^oC



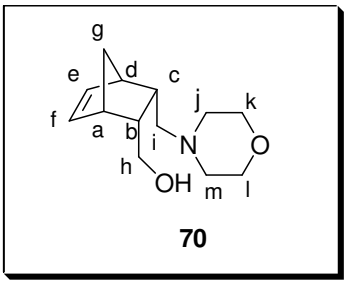
69

Figure 16

^{1}H-NMR: δ 6.05 (s, 2H, H_e, H_f),
3.50 (d, *J*= 10.65 Hz, 1H, H_h),
3.21 (t, *J*= 11.45 Hz, 1H, H_h),
2.75 (s, 1H, H_a),
2.68 (s, 1H, H_d),
2.64-2.47 (m, 4H, H_j, H_n),
2.28-2.17 (m, 4H, H_b, H_c, H_i,),
1.64-1.49 (m, 4H, H_k, H_m),
1.43-1.37 (m, 2H, H_l),
1.26 (s, 2H, H_g);
^{13}C-NMR: δ 135.3, 134.4, 63.1, 60.0, 54.6, 50.1, 47.6, 47.0, 46.4, 38.8, 29.6, 25.6, 24.2

4.5.2 (2*S*,3*R*)-2-morpholinomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 70

Using the general procedure, compound **70** was synthesized in 70% yield. $[\alpha]_D^{20}$=-4.30 (*c* 2 $CHCl_3$), oily



70

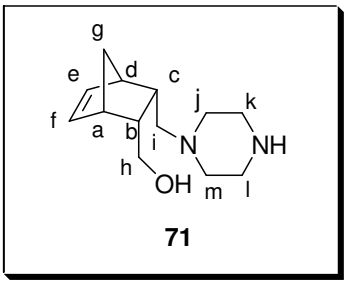
Figure 17

^{1}H-NMR: δ 6.06 (s, 2H, H_e, H_f),
3.68 (bs, 4H, H_k, H_l),
3.50 (bs, 1H, H_h),
3.21 (t, *J*= 11.21 Hz, 1H, H_h),
2.75 (s, 1H, H_a),
2.71 (s, 1H, H_d),
2.57-2.47 (m, 4H, H_j, H_m),
2.34-2.26 (m, 4H, H_b, H_c, H_i),
1.43-1.38 (m, 2H, H_g);

^{13}C-NMR: δ 134.9, 133.8, 66.0, 62.4, 59.3, 53.1, 49.5, 47.0, 46.4, 45.7, 37.6, 29.7

4.5.3 (2*S*,3*R*)-2-piperazinomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 71

Using the general procedure, compound **71** was synthesized in 90% yield. $[\alpha]_D^{20}$= -8.59 (*c* 2 $CHCl_3$); mp 229 ^oC



71

Figure 18

^{1}H-NMR: δ 5.97 (s, 2H, H_e, H_f),
3.42 (d, *J*=12.0 Hz, 1H, H_h),
3.12 (t, *J*=11.27 Hz, 1H, H_h),
2.68 (s, 1H, H_a),
2.63 (s, 1H, H_d),
2.51-2.39 (m, 4H, H_k, H_l),

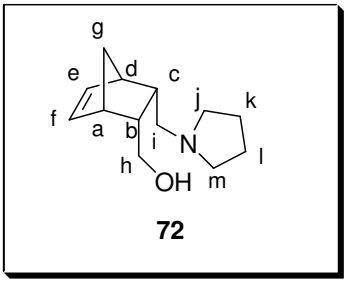
2.26-2.14 (m, 8H, H_b, H_c, H_i, H_j, H_m),

1.36-1.30 (m, 2H, H_g)

^{13}C-NMR: δ 135.4, 134.4, 63.0, 59.1, 50.0, 47.5, 46.9, 46.3, 38.7, 38.6

4.5.4 (2*S*,3*R*)-2-pyrrolidinomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 72

Using the general procedure, compound **72** was synthesized in 95% yield. $[\alpha]_D^{20}$= 0.157 (*c* 2, MeOH); mp 65.1°C



72

Figure 19

^{1}H-NMR: δ 6.05 (s, 2H, H_e, H_f),

3.50 (t, *J*= 6.87 Hz, 1H, H_h),

3.22 (t, *J*= 11.25, 1H, H_h),

2.75 (s, 2H, H_a, H_d),

2.65-2.44 (m, 7H, H_b, H_i, H_j, H_m,),
2.20 (d, *J*= 12.54 Hz, 1H, H_c),
1.76 (s, 4H, H_k, H_l),
1.40 (s, 2H, H_g);

^{13}C-NMR: δ 135.4, 134.3, 63.0, 56.8, 53.8, 49.9, 47.7, 46.9, 46.2, 41.0, 23.3

4.6 General procedure for diethylzinc addition reactions

Ligand was dissolved in dry solvent and diethylzinc solution was added at room temperature. The mixture was stirred for 30 minutes. Next, the solution was cooled to 0 °C and distilled benzaldehyde was added. The reaction mixture was allowed to stir for 48 hours at 0 °C. After the addition of 1 N HCl, the solution was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. Evaporation of the solvent gives the corresponding alcohol. HPLC-analysis of 1-phenyl-1-propanol: Chiralcel OD-H at room temperature, *n*-hexane/2-propanol = 98:2, 1.0 mL/min, 220 nm, t_1= 15.6 min (*R*), t_2= 17.8 min (*S*).

4.7 General procedure for Catalytic Asymmetric Mukaiyama Aldol Reaction

$In(OTf)_3$ (0.056 g, 0.1 mmol) was added to the oven-dried round-bottom flask equipped with magnetic stirring bar. The solid was azeotropically dried with anhydrous THF twice (2 mL x 2). Then, 1.5 mL dichloromethane and ligand (0.033 g, 0.11 mmol) were added. The mixture was stirred under nitrogen atmosphere at room temperature for 1 h. Benzaldehyde (0.05 mL, 0.5 mmol) was added to the mixture and stirred for 10 min.

Next, the mixture was cooled to desired temperature for 15 min and (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.12 mL, 0.6 mmol) was added slowly. The reaction mixture was stirred at that temperature for 24 h and quenched with 5 mL sodium bicarbonate solution. The aqueous layer was extractesd with ether (3 x 10 mL). The combined organic layer was concentrated in vacuo and treated with a mixture of THF-1M HCl (5:1 mL) solution for 20 min. The mixture was extracted with ether (3 x 10 mL) and dried over $MgSO_4$.The resultant compound was obtained by silica gel chomatography. The ee value was obtained by HPLC analysis employing a Daicel Chiracel OJ-H column (hexane:*i*-propanol, 90:10, 1mL/min: t_1= 11.5 min (*S*), t_2= 13.3 min (*R*).

4.8 Synthesis of 3-acryloyloxazolidin-2-one, 80

To a suspension of oxazolidinone, DMAP and acrylic acid in CH_2Cl_2 at 0 ^{0}C under argon atmosphere was added DCC in one portion. After 10 minutes, the temperature was raised to room temperatureand stirring was continued until no starting material has left as confirmed by TLC. The dicyclohexylurea formed was filtered and the precipitate was washed with CH_2Cl_2 (10 mL). The filtrate was washed with saturated $NaHCO_3$ (10 mL), dried with $MgSO_4$ and concentrated at reduced pressure to furnish the crude product which was purified by silica gel chromatography (30 % EtOAc in hexane).

4.9 General Procedure for Catalytic Asymmetric Diels-Alder Reaction

A tube was charged with $Cu(OTf)_2$ (0.033 mmol) and the ligand (0.036 mmol) was dissolved in CH_2Cl_2 (650 μL) was added dropwise. The solution was stirred for 2 h. Then, it was cooled to desired temperature. 3-Acryloyl-oxazolidin-2-one (0.046g, 0.33 mmol) was added as a solution in CH_2Cl_2 (650 μL) via syringe.

The resulting solution was stirred at the desired temperature for the specified amount of time. Next, the mixture was washed with saturated NH_4Cl and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The ee value was obtained by HPLC analysis employing a Daicel Chiracel OD-H column (hexane:*i*-propanol, 92:8, 0.8 mL/min: exo_1 t_r=49.1min , exo_2 t_r=51.2 min, $endo_1$ t_r 56.3 min, $endo_2$ t_r=59.9 min

APPENDIX

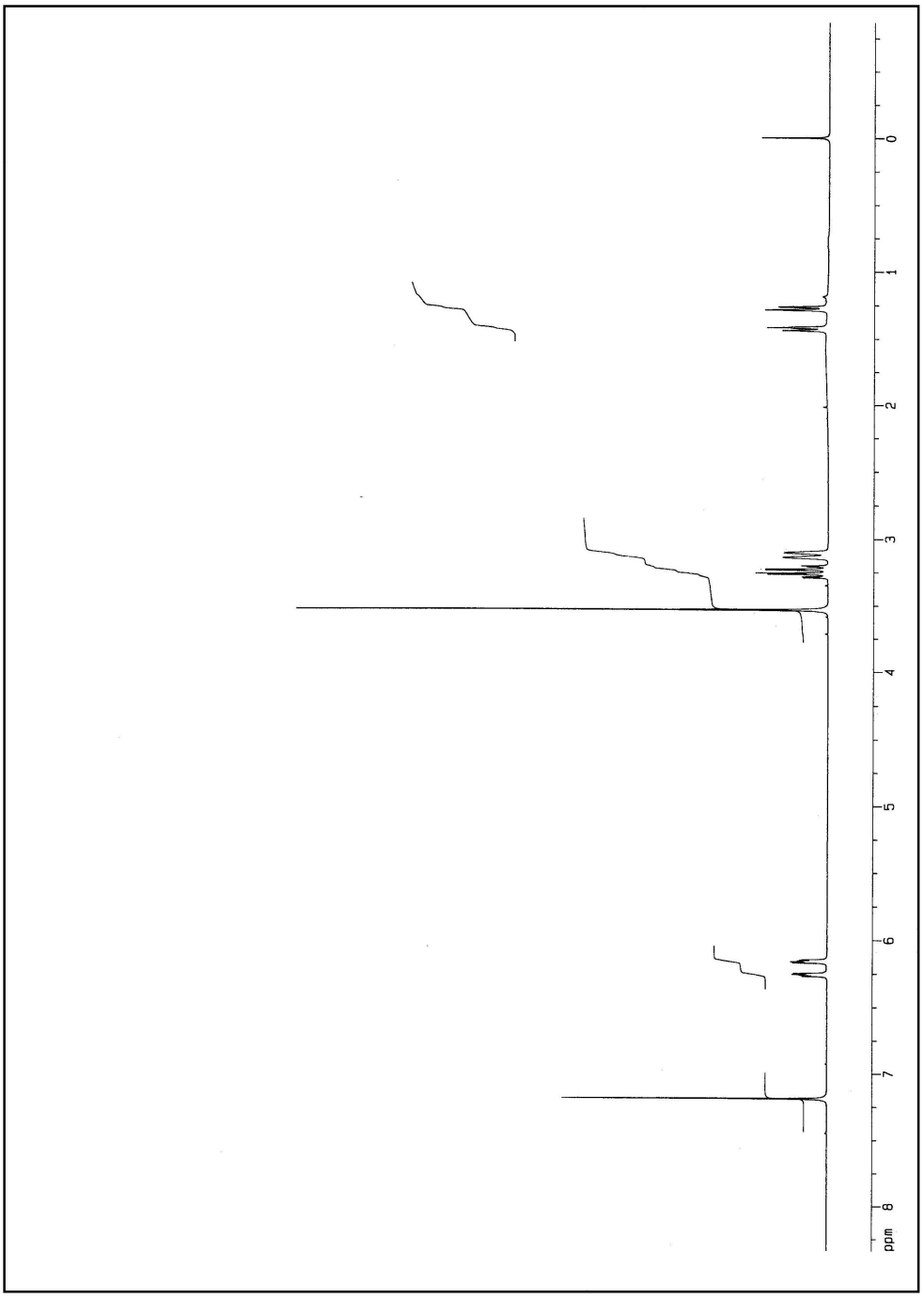


Figure 20 ^{1}H NMR of compound **64**

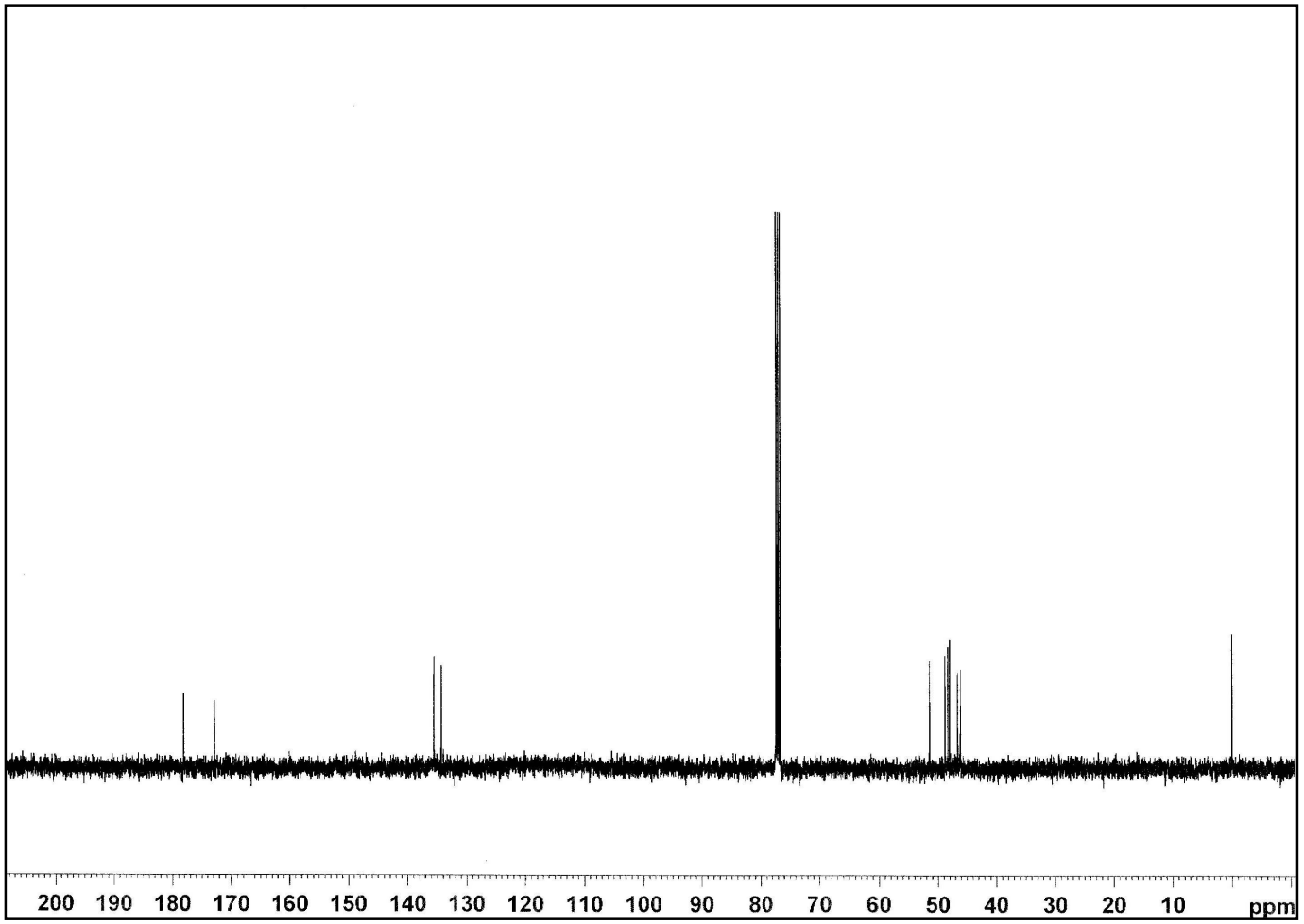


Figure 21 ^{13}C NMR of compound **64**

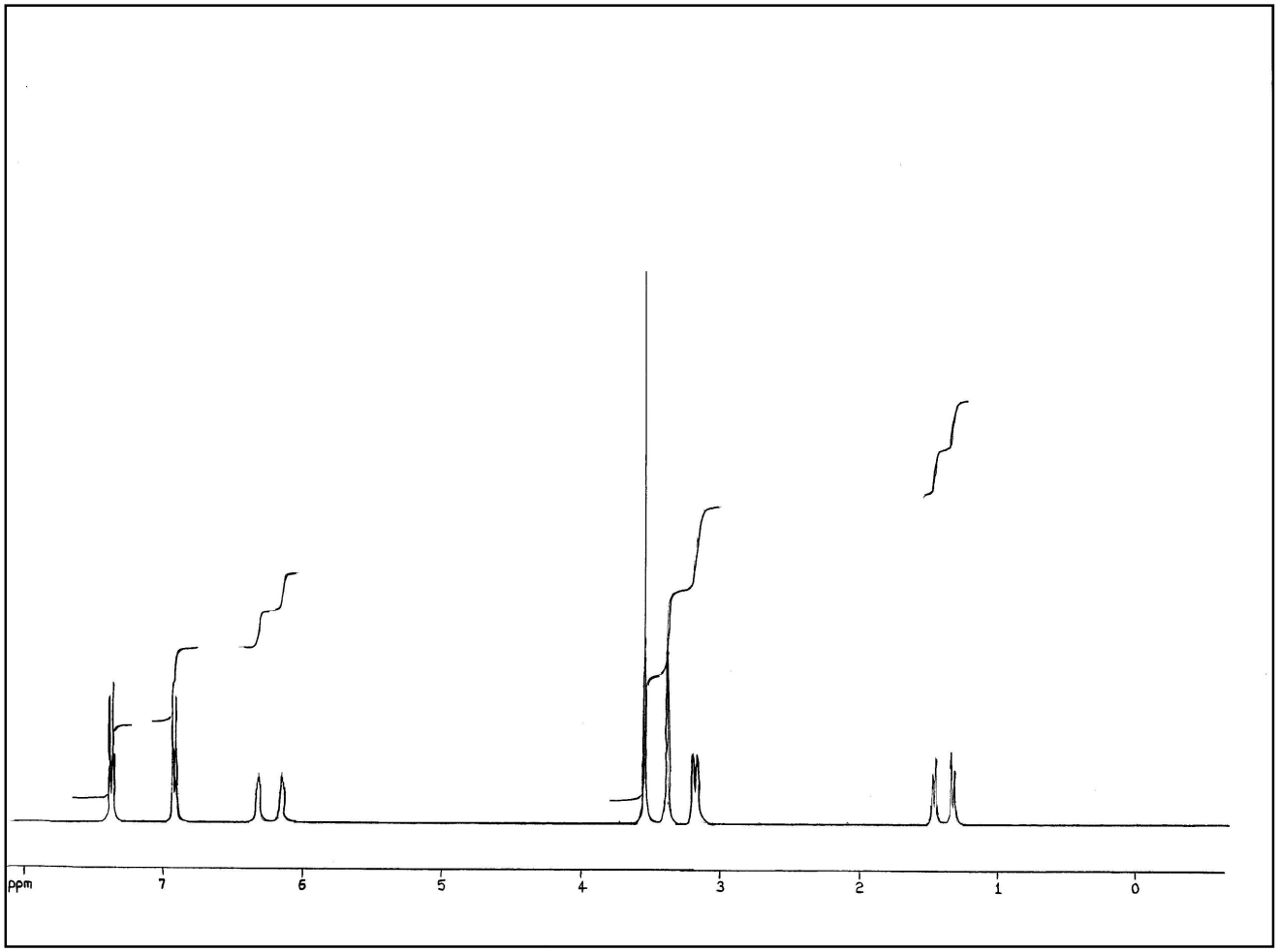


Figure 22 ^{1}H NMR of compound **73**

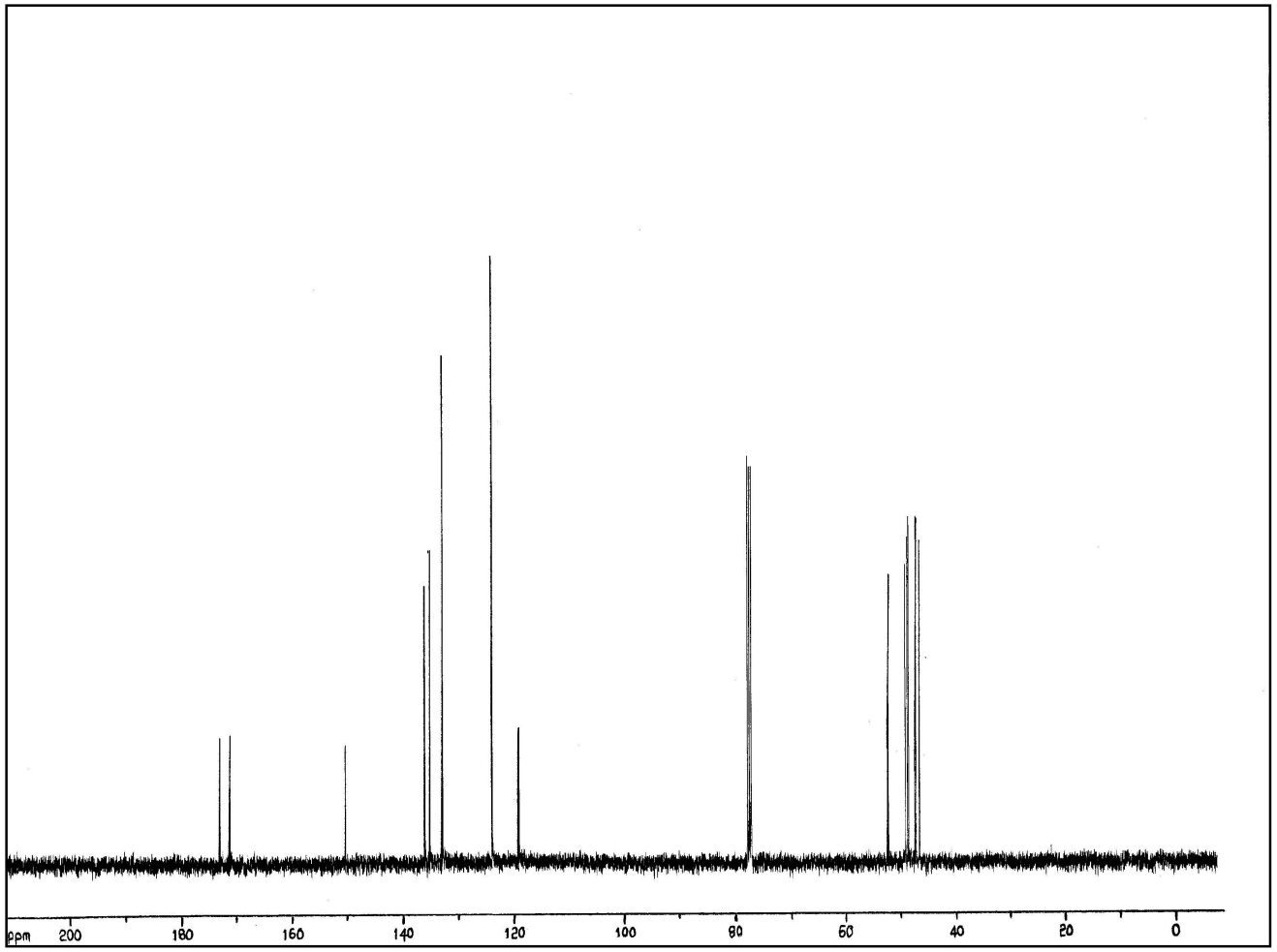


Figure 23 ^{13}C NMR of compound **73**

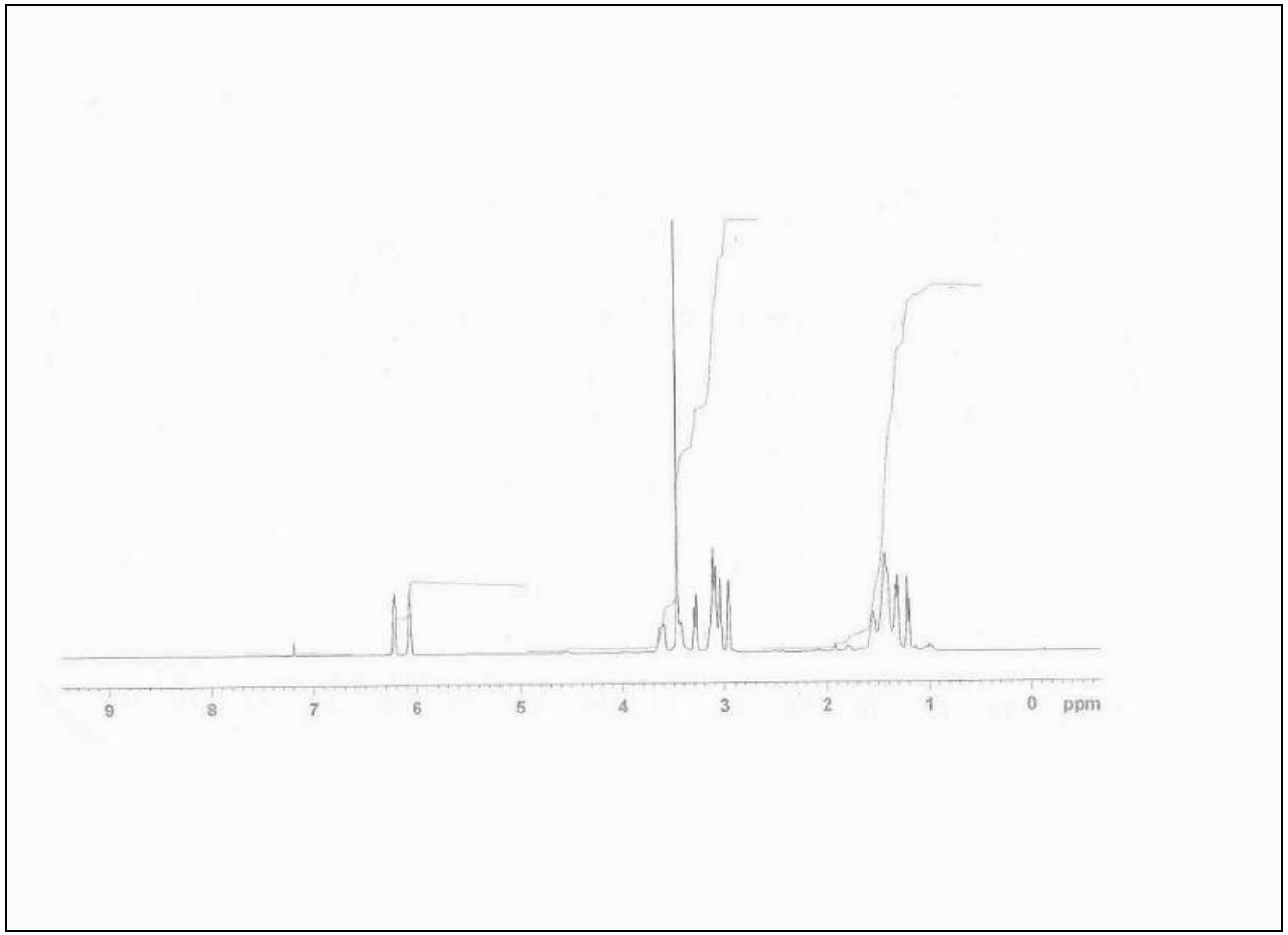


Figure 24 ^{1}H NMR of compound **65**

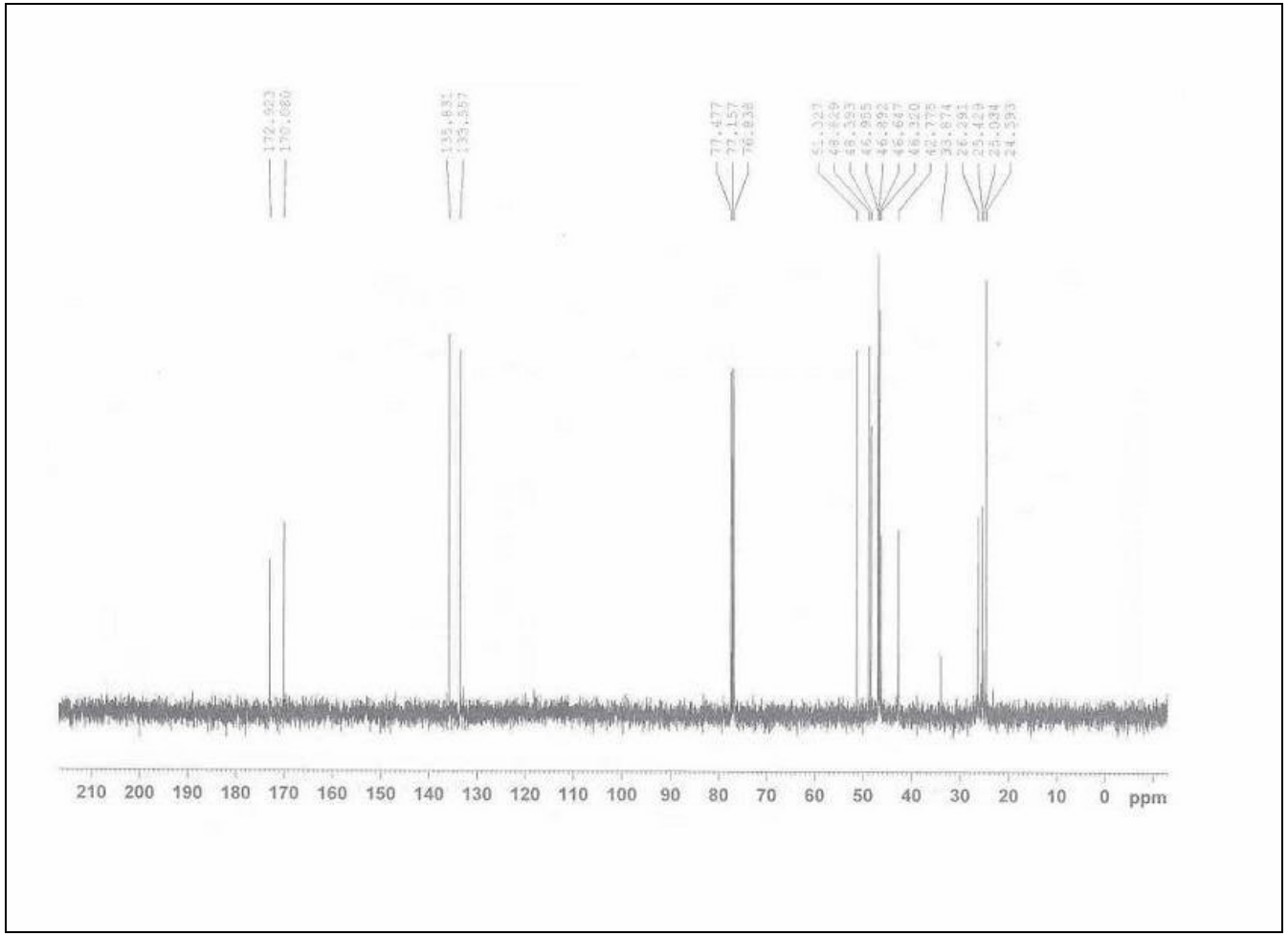


Figure 25 ^{13}C NMR of compound **65**

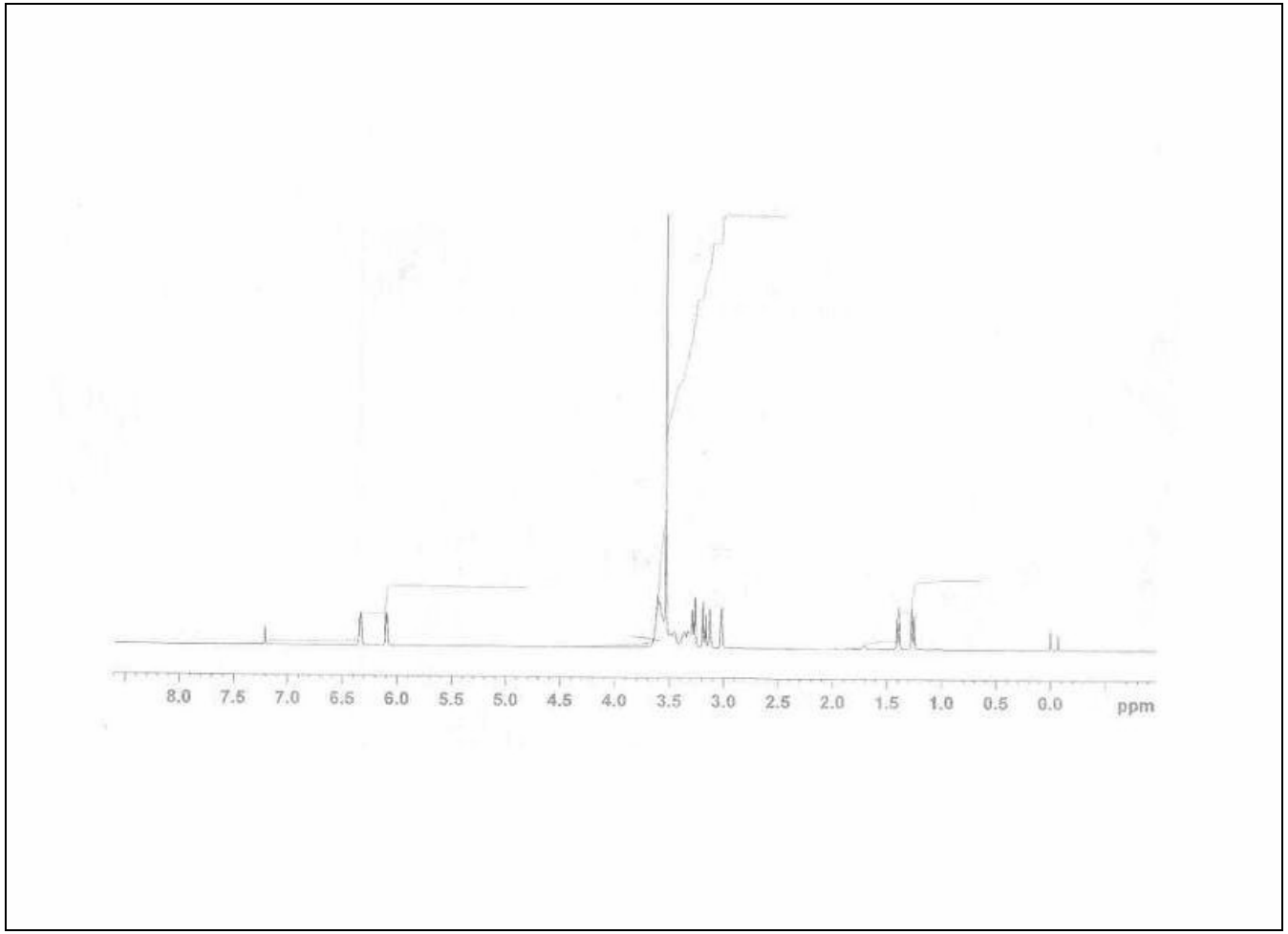


Figure 26 ^{1}H NMR of compound **66**

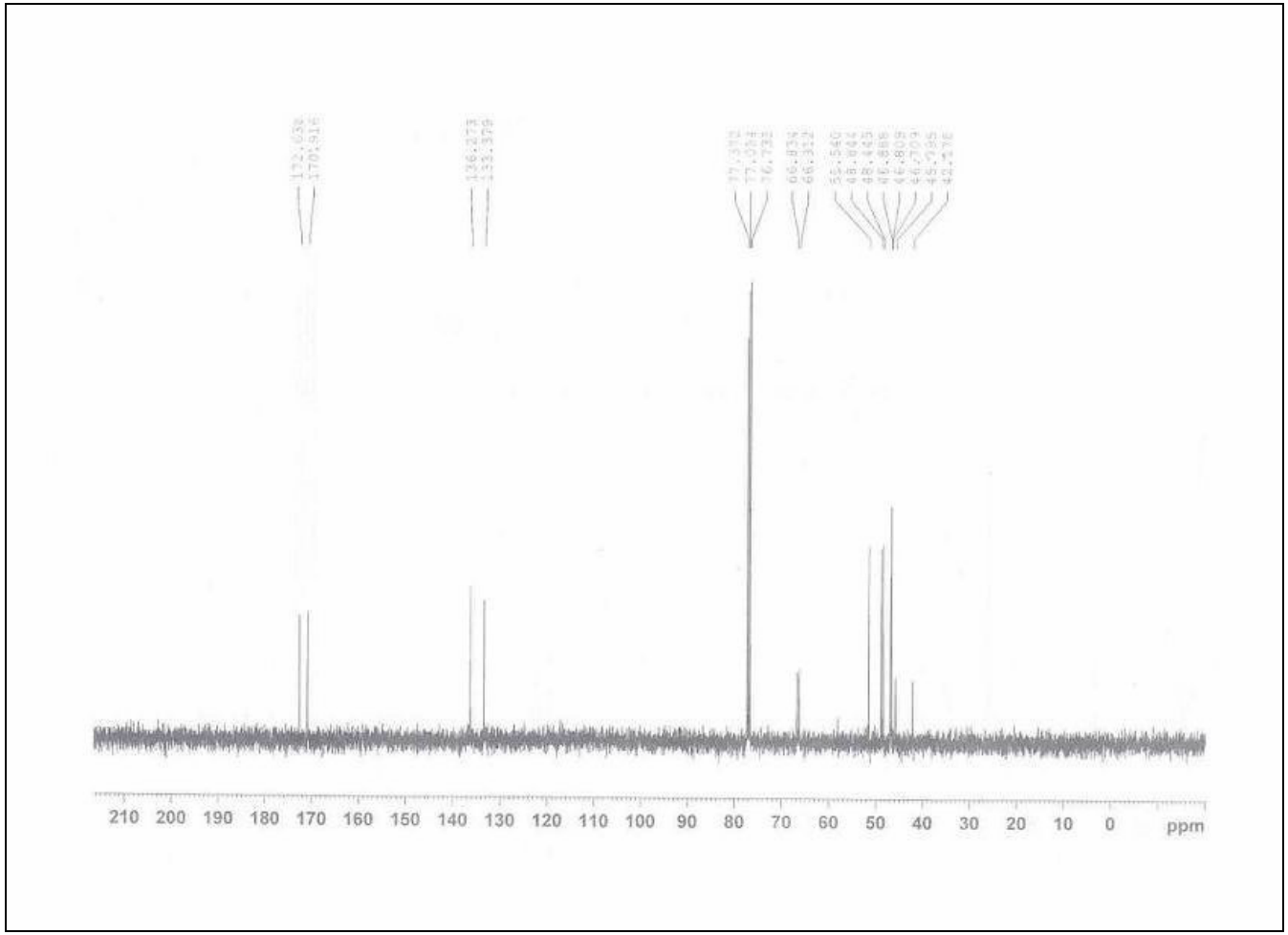


Figure 27 ^{13}C NMR of compound **66**

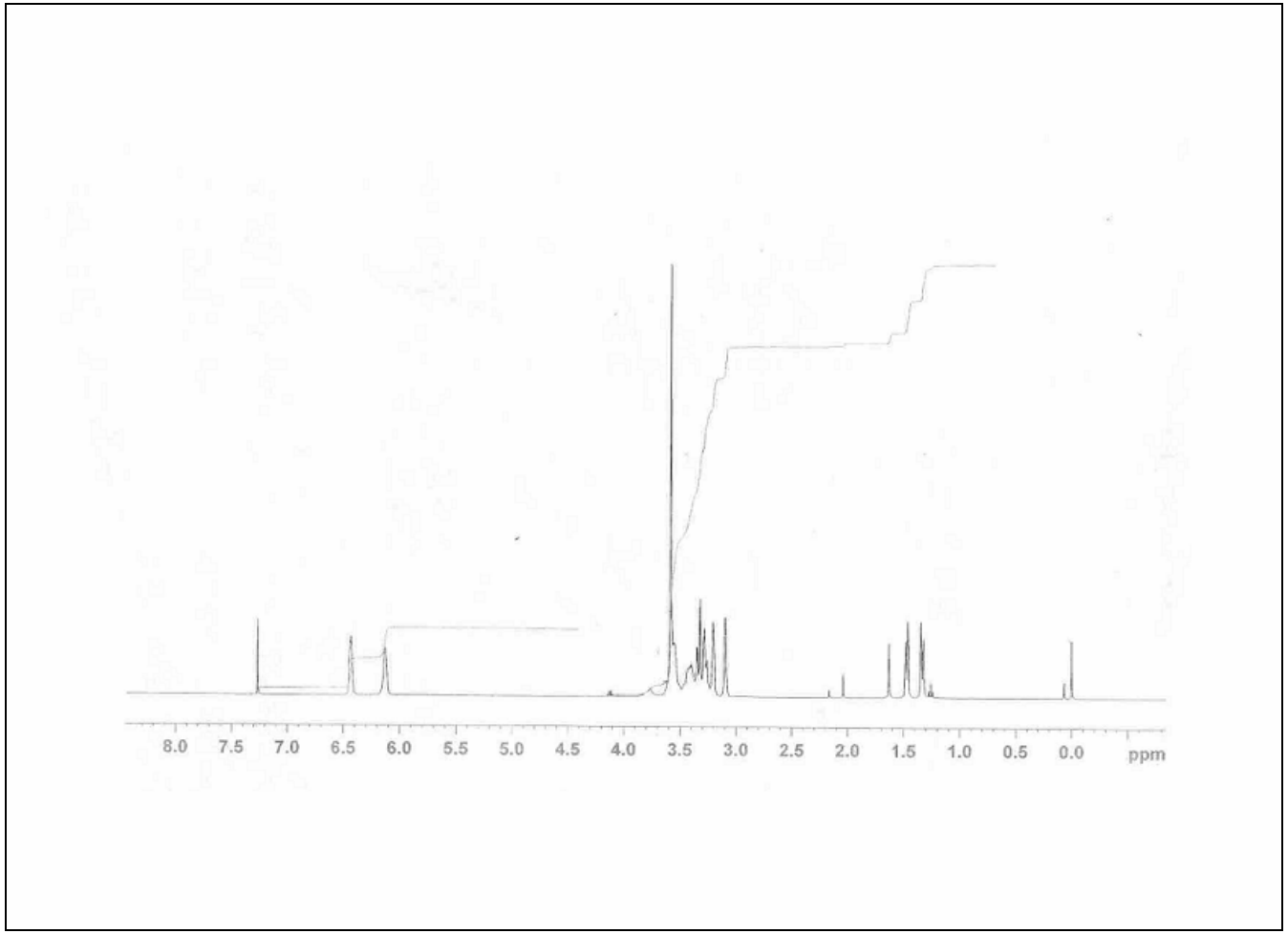


Figure 28 ^{1}H NMR of compound **67**

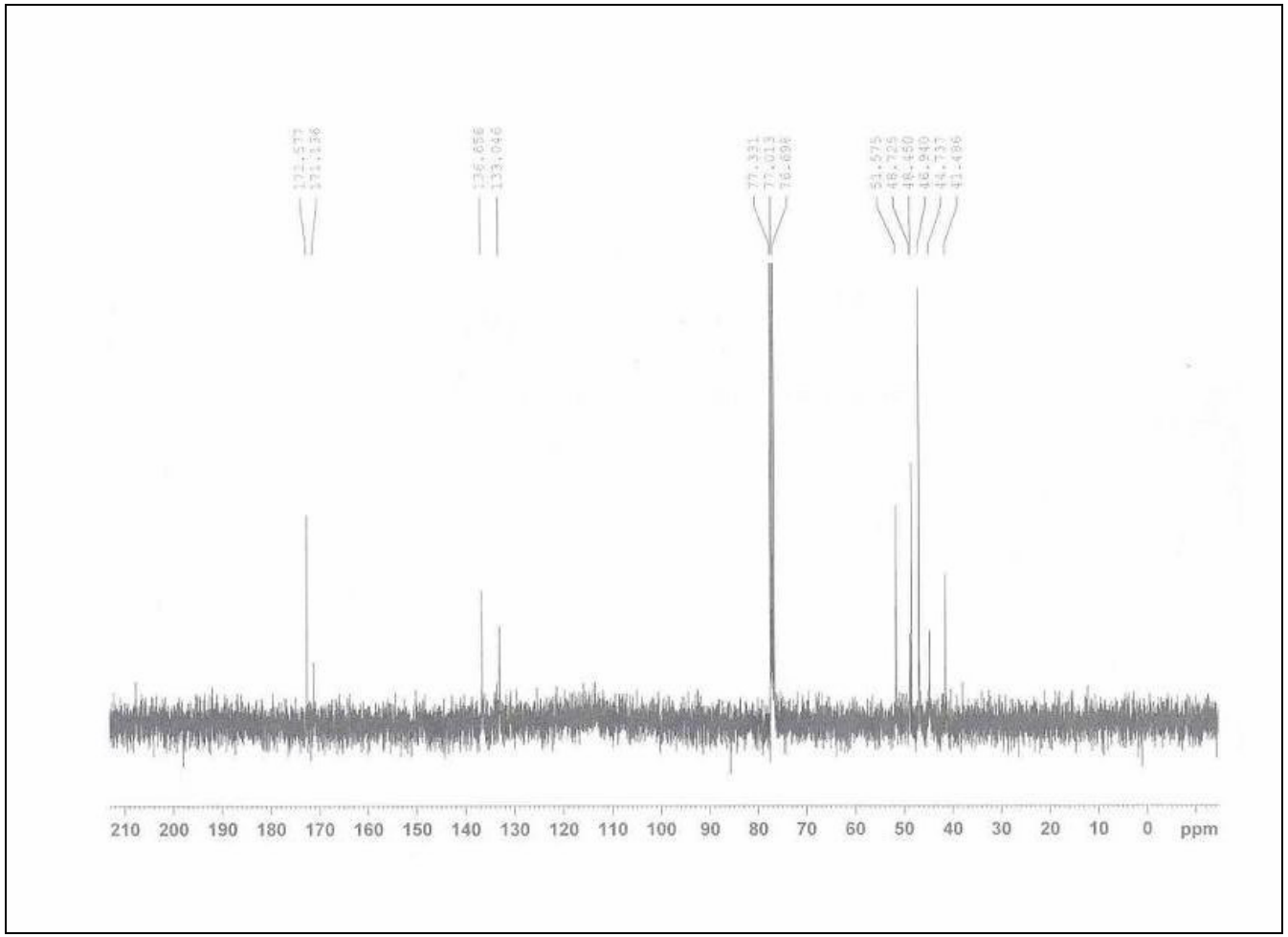


Figure 29 ^{13}C NMR of compound **67**

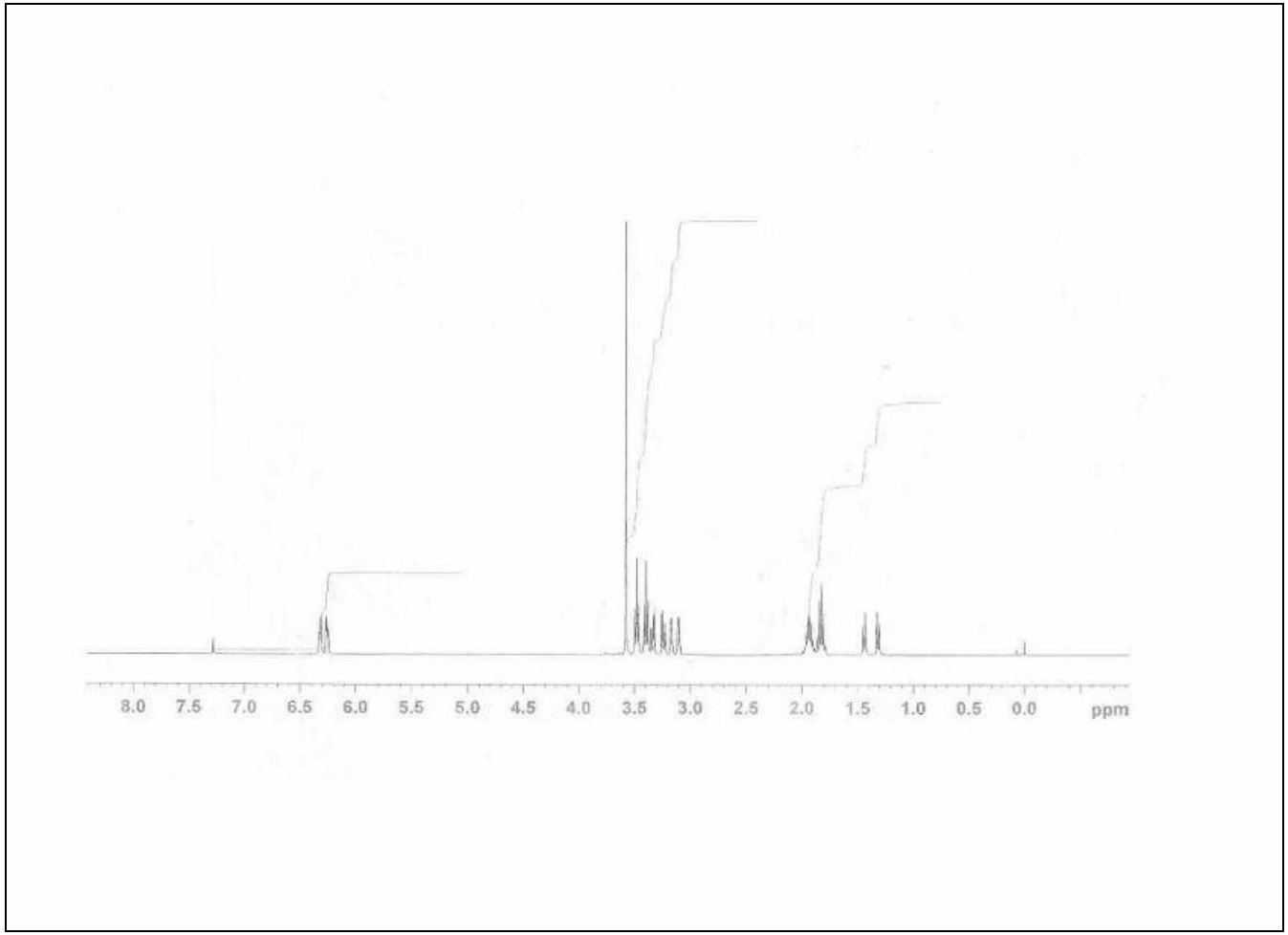


Figure 30 ^{1}H NMR of compound **68**

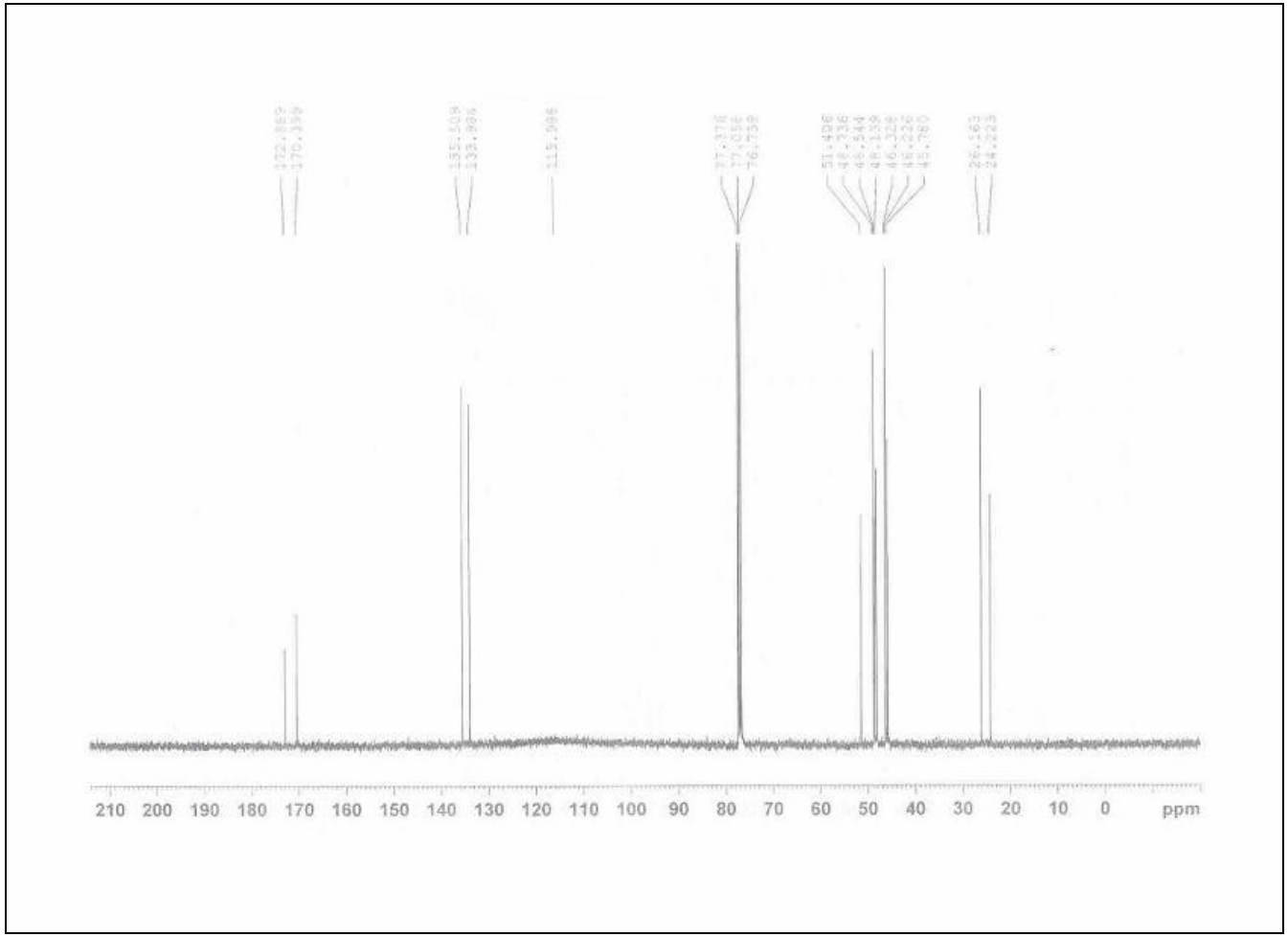


Figure 31 ^{13}C NMR of compound **68**

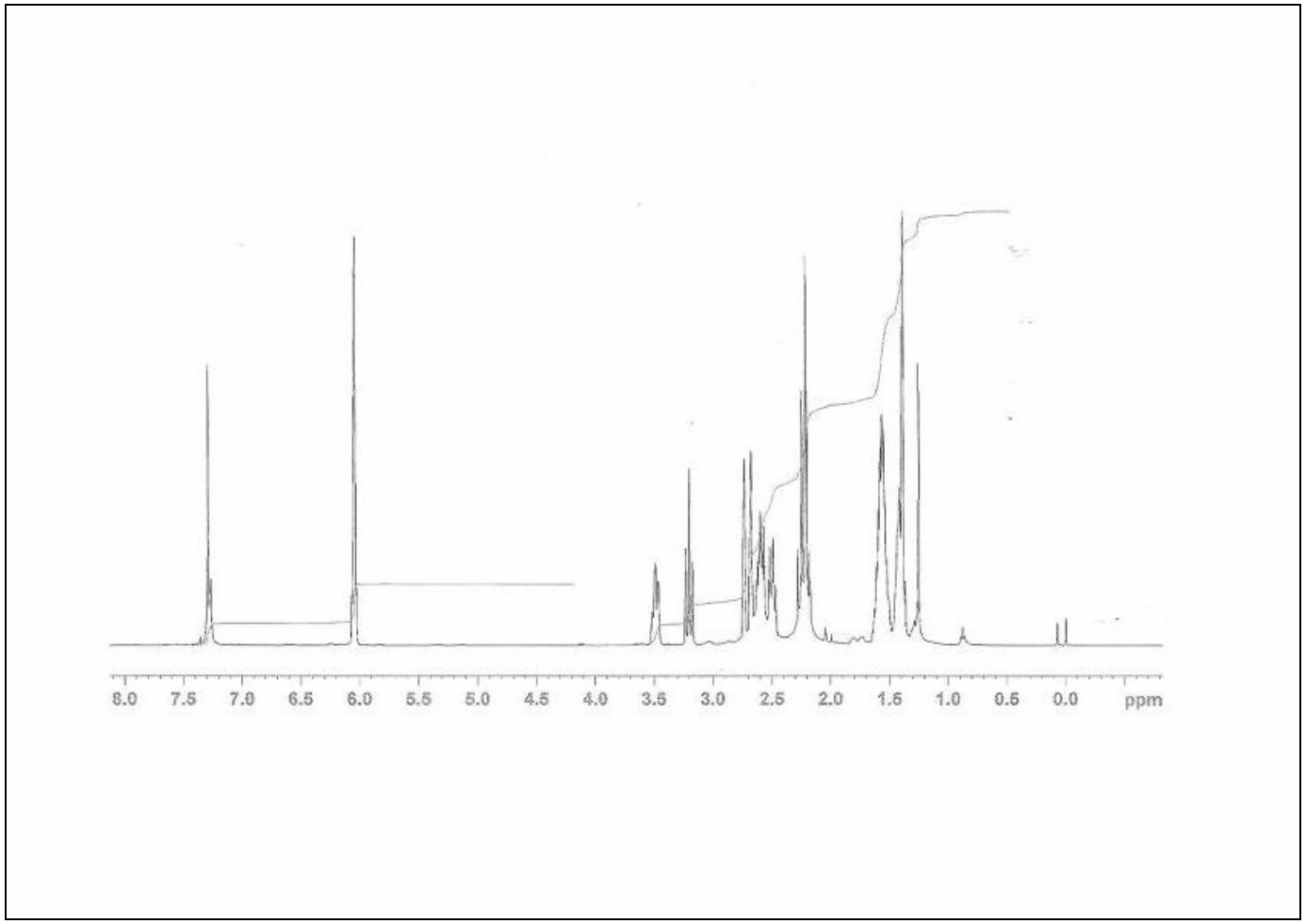


Figure 32 ^{1}H NMR of compound **69**

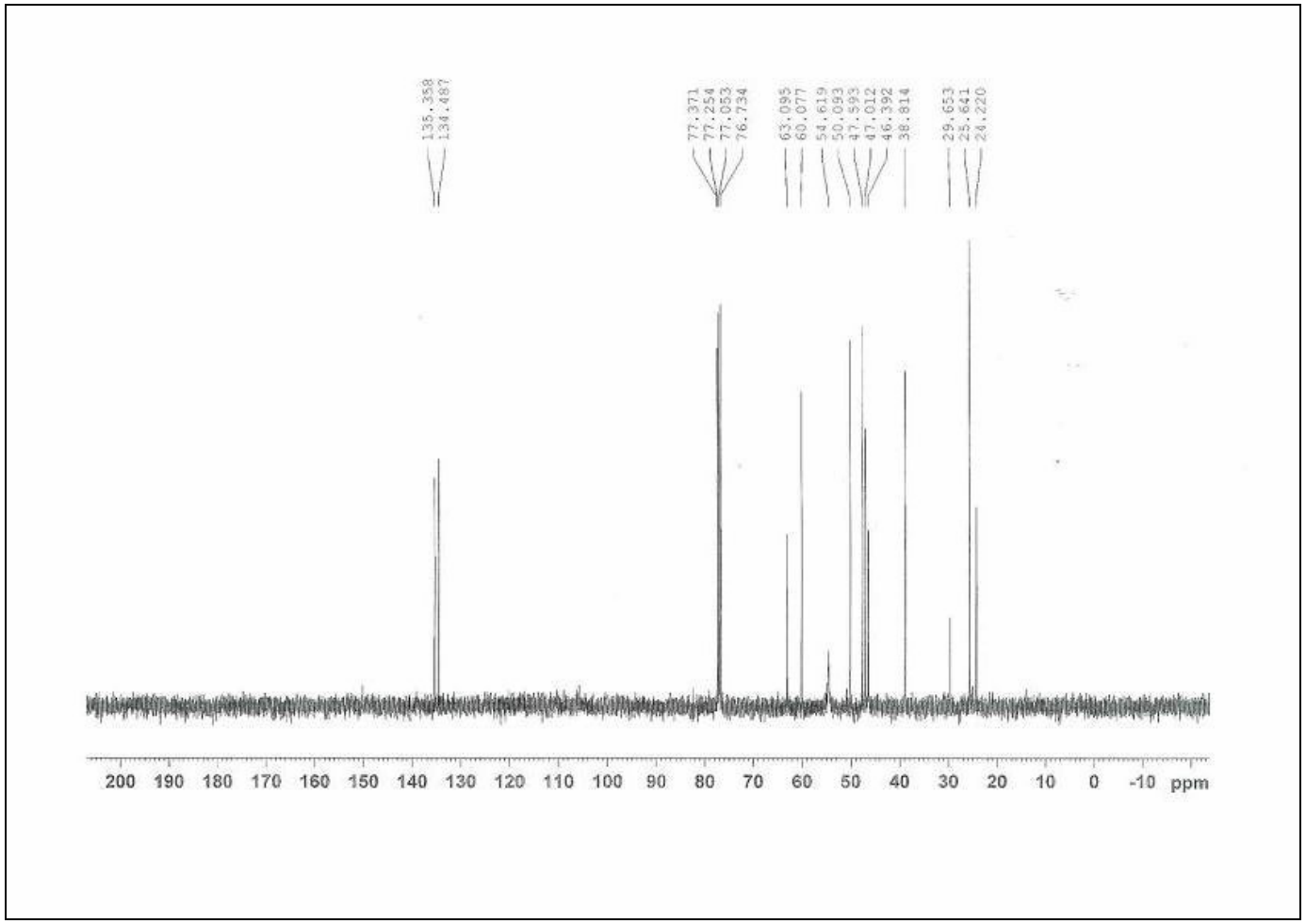


Figure 33 ^{13}C NMR of compound **69**

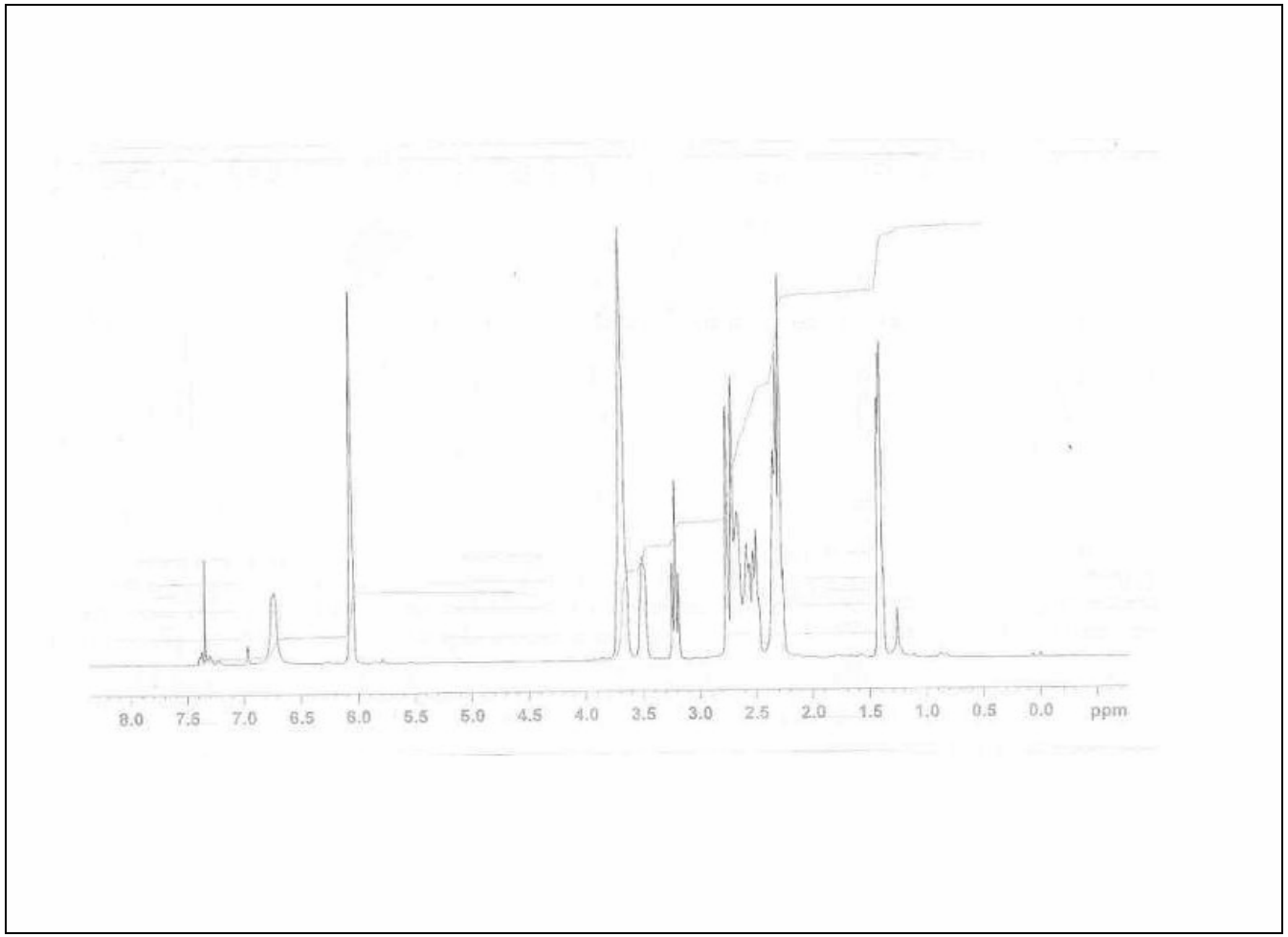


Figure 34 ^{13}H NMR of compound **70**

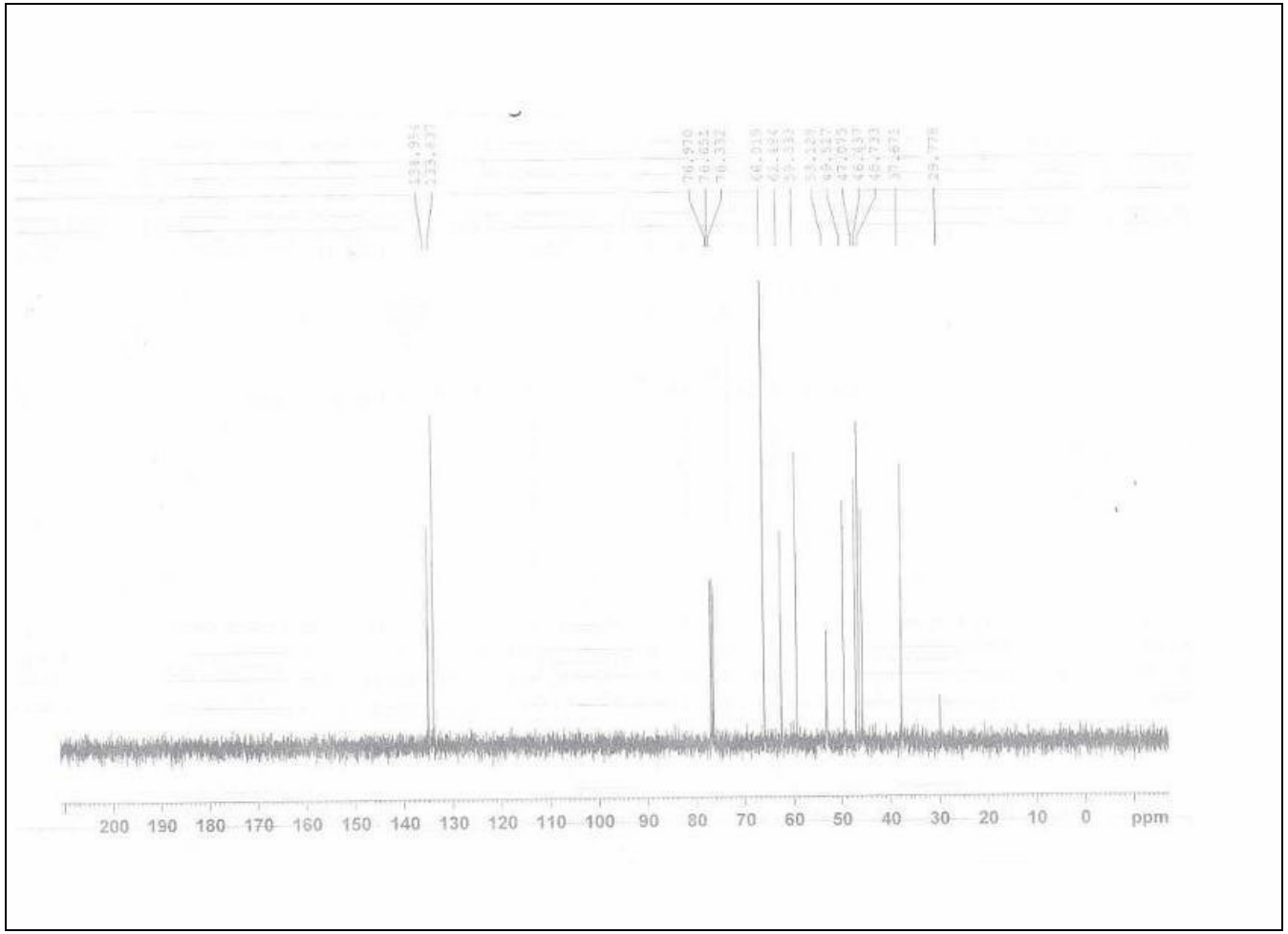


Figure 35 ^{13}C NMR of compound **70**

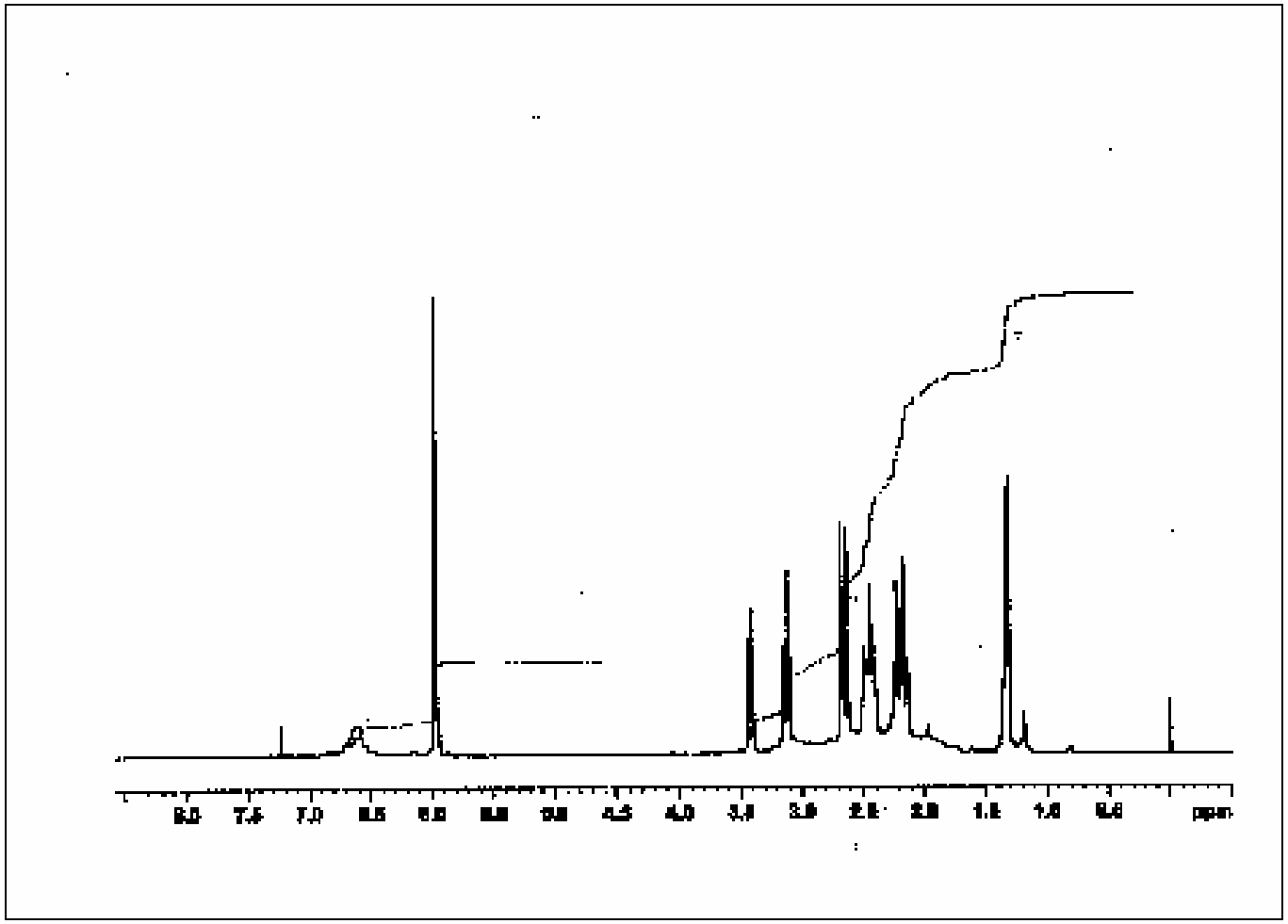


Figure 36 ^{1}H NMR of compound **71**

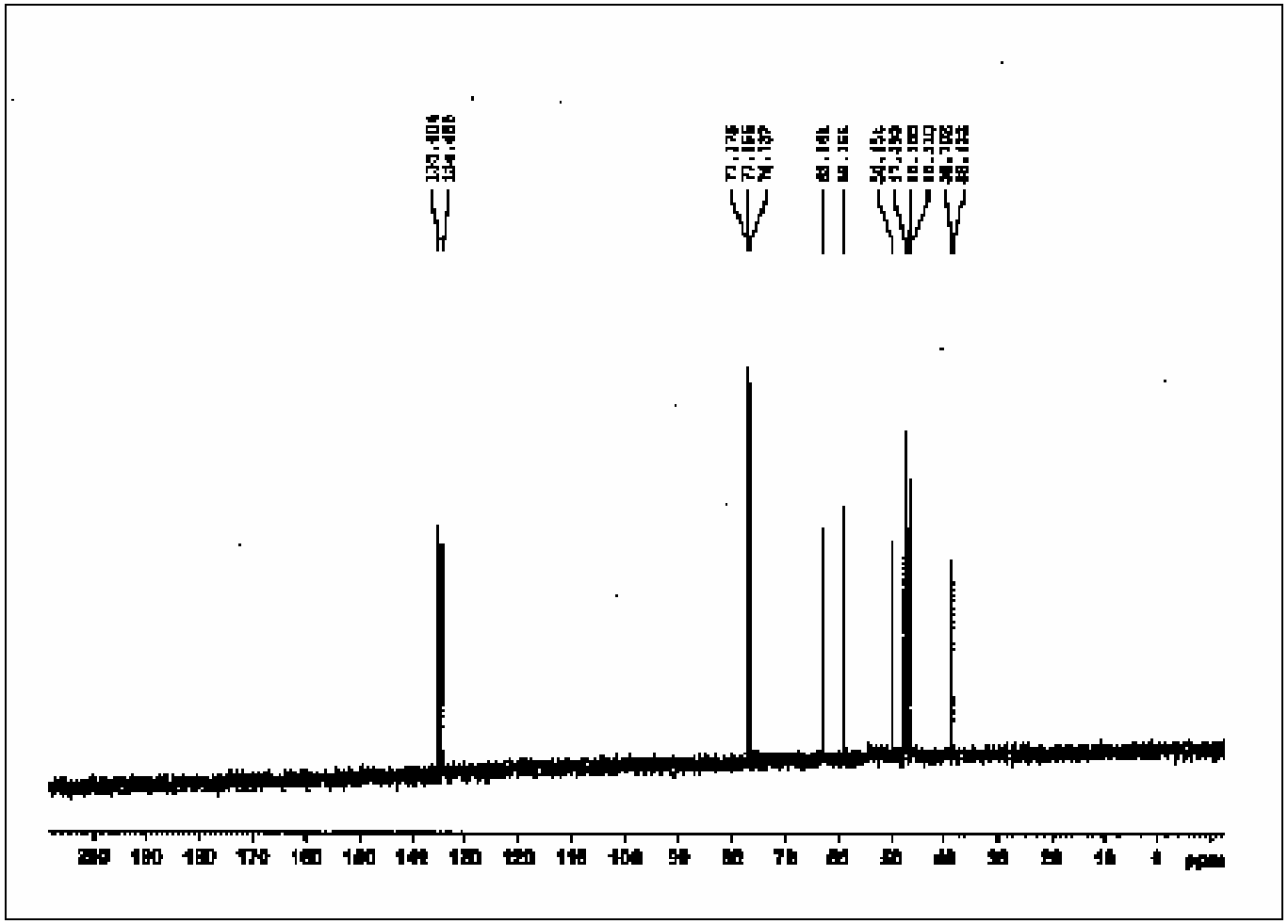


Figure 37 ^{13}C NMR of compound **71**

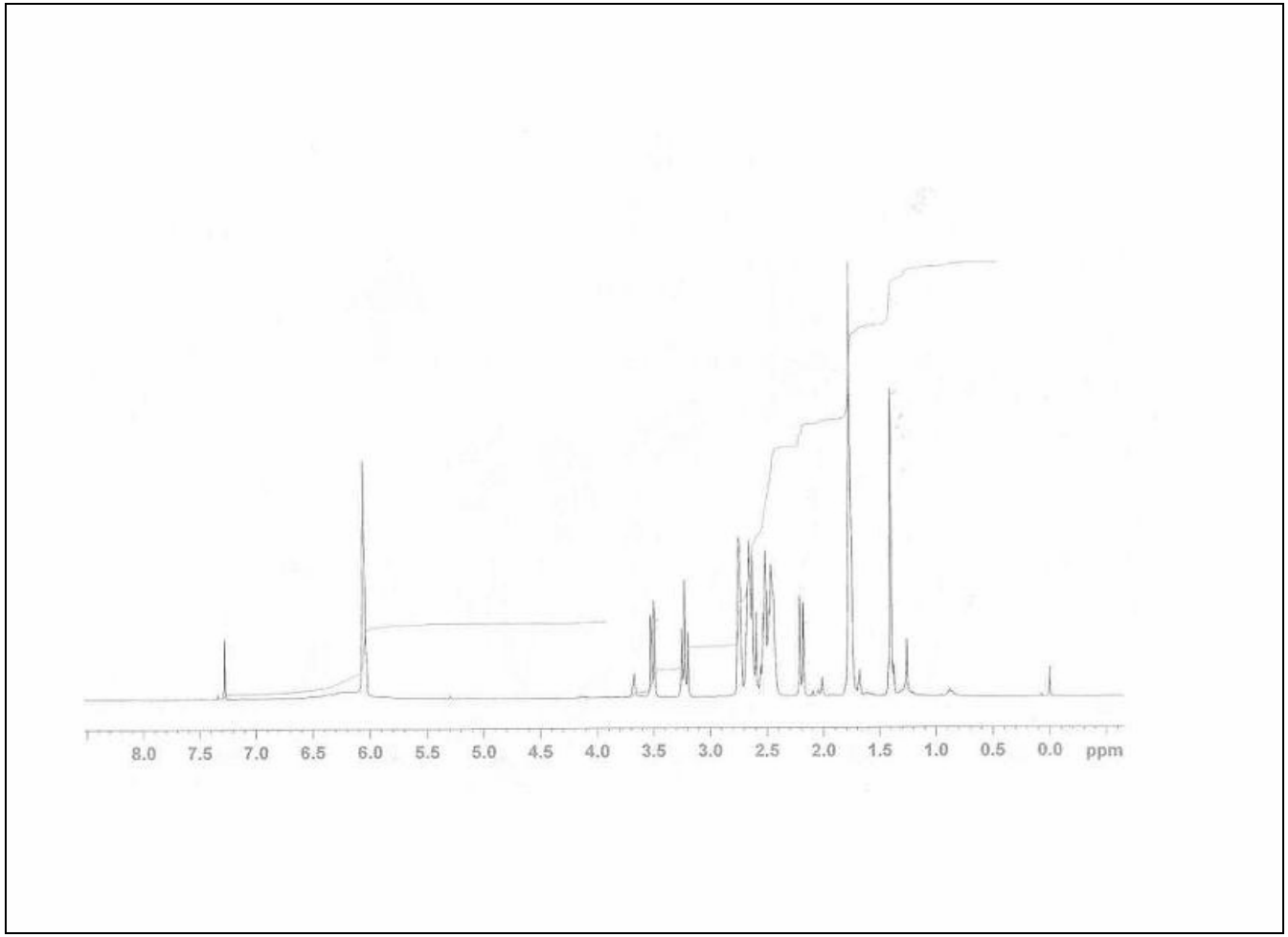


Figure 38 ^{1}H NMR of compound **72**

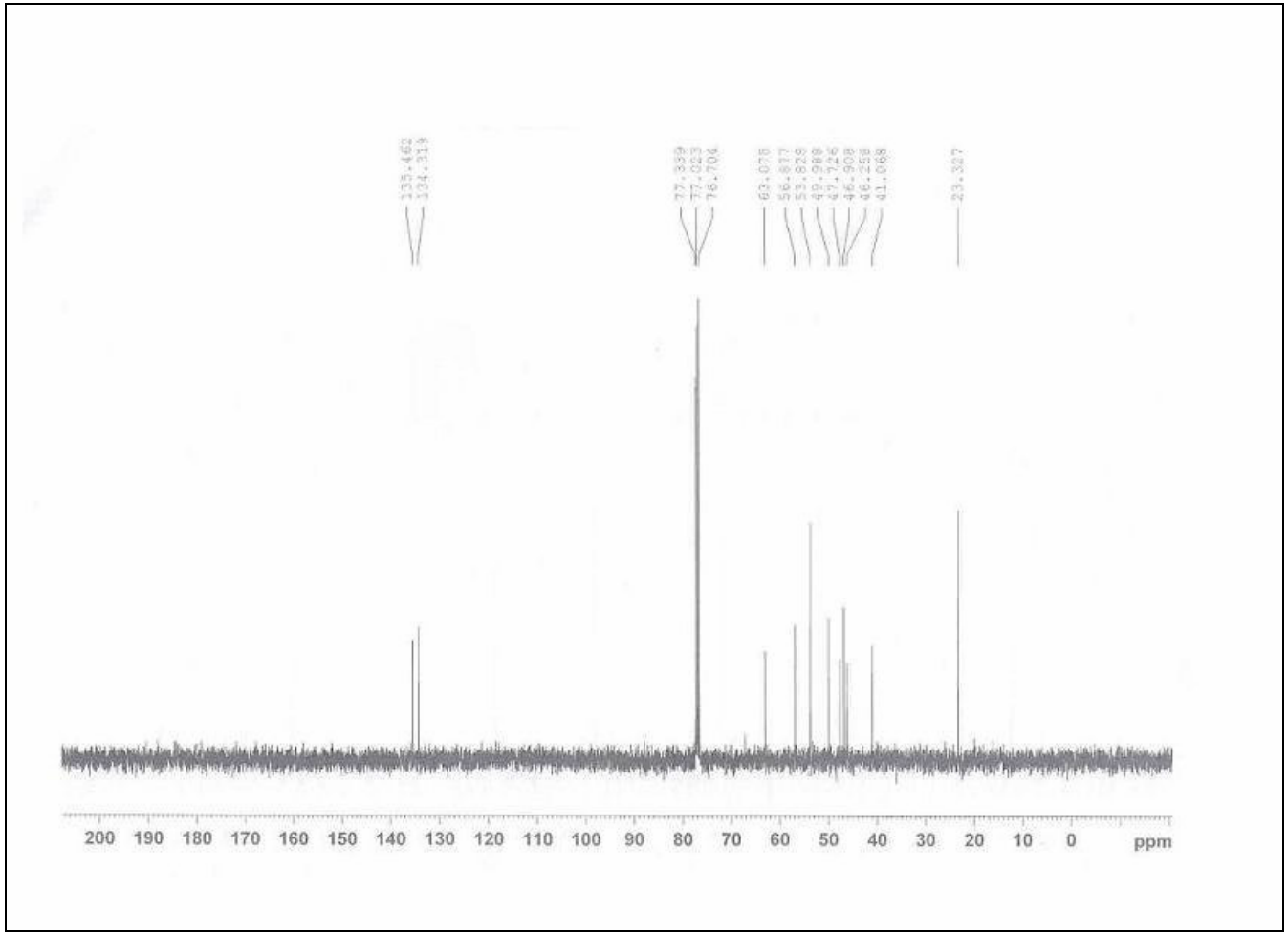


Figure 39 ^{13}C NMR of compound **72**

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