EGE UNIVERSITY
GRADUATE SCHOOL OF
NATURAL AND APPLIED SCIENCES

(MASTER THESIS)

PREPARATION OF NEW CHIRAL LIGANDS DERIVED FROM AMINO ACIDS

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Code of discipline: 405.02.01
Date of presentation: 03.09.2010

Bornova-İZMİR

2010

Murat Desde tarafından Yüksek lisans tezi olarak sunulan “Preparation of New Chiral Ligands Derived From Amino Acids (Amino Asitlerden Yeni Kiral Ligandların Hazırlanması)” başlıklı bu çalışma E.Ü. Lisansüstü Eğitim ve Öğretim Yönetmeliği ile E.Ü. Fen Bilimleri Enstitüsü Eğitim ve Öğretim Yönergesi’nin ilgili hükümleri uyarınca tarafımızdan değerlendirilerek savunmaya değer bulunmuş ve 03.09.2010 tarihinde yapılan tez savunma sınavında aday oybirliği/oyçokluğu ile başarılı bulunmuştur.

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ÖZET

AMİNO ASİTLERDEN YENİ KİRAL LİGANDLARIN HAZIRLANMASI

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Ağustos 2010, 107 sayfa

Yeni üç dişli kiral ligandları sentezlemek için 2-aminofenol ile basit amino asitler (L-Valin, L-ter-lösin, L-isolösin) arasındaki coupling reaksiyonu yöntemleri araştırıldı. Coupling reaktifi olarak DCC'nin ve NH_2 grubunu korumak için BOC koruyucu grubunun kullanılmasıyla ürünler için en iyi verimler elde edildi. Sentezlenen kiral ligandların katalitik aktiviteleri, Cu(II) iyonlarının varlığında Henry reaksiyonunda incelendi. L-Valinden elde edilen ligandın türevlendirilmesi, amid grubunun BH_3-THF kompleksi ile indirgenmesiyle ve koruyucu grubun fosforik asit ile çıkarılmasıyla yapıldı. Ürünlerin yapıları spektroskopik analizler (IR, ^{1}H-NMR, ^{13}C-NMR) ile karakterize edildi.

Anahtar sözcükler: Amino asit, kiral ligand, 2-aminofenol, asimetrik sentez, Henry reaksiyonu.

ABSTRACT

PREPARATION OF NEW CHIRAL LIGANDS DERIVED FROM AMINO ACIDS

DESDE, Murat

MSc in Chemistry Department
Supervisor: Assoc. Prof. Dr. Stephen T. ASTLEY
August 2010, 107 pages

Methods to synthesize novel tridentate chiral ligands by coupling reactions between simple amino acids (L-valine, L-tert-leucine and L-isoleucine) with 2-aminophenol were investigated. The best yields of products were obtained by using BOC to protect the NH_2 group and by using DCC as a coupling reagent. Catalytic activities of these chiral ligands were investigated in Henry reactions in the presence of Cu(II) ions. Modification of the ligand obtained from L-valine was carried out by reduction of the amide group using borane-THF complex and removal of the protection group using phosphoric acid. The products were characterized by spectroscopic methods. (IR, ^{1}H-NMR, ^{13}C-NMR)

Keywords: Amino acids, chiral ligands, 2-aminophenol, asymmetric synthesis, Henry reactions.

ACKNOWLEDGEMENT

I would like to express my gratitude to Assoc. Prof. Dr. Stephen T. ASTLEY and Prof. Dr. Demet ASTLEY as they encouraged me to support in this study. I wish to thank them for their directions and all kinds of helps during my studies.

I wish to thank to Gamze DOĞANER KOZ, Leman ALKAN KARADENİZ and Neslihan KORKMAZ for their help, sharing their support during this work.

Special thanks to my dear friends Ahmet Abuş, Bekir Soner Zeybek, Sadık İlhan, İbrahim Gereli, Ümit Barış Bakan, Salih Günnaz, Erkan Halay, Kadir Özek, Ahmet Aykaç, Didem Taşel, Ömer Yaşarikiz, Emre Yavuz, Emre Seyyal, Harika Topallar, Sevilen Yılmaz, Duygu Yapıcı, Raif İlktaç, Burak Beran, Neşe Çevirim, Ela Kılıç, Sinem Toksabay, Özgür Tağ, Gökhan Şenel, Miray Kavas, Yasemin İşlek, Kemal Volkan Özdokur, İrem Çakar, Korcan Korba for everything.

I also wish to thank my family for their encouragement and infinite support in any step of my study and my life.

Murat DESDE

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SYMBOLS AND ABBREVIATIONS

Abbreviations	Explanations
NMR	Nuclear Magnetic Resonance
$NaBH_4$	Sodium borohydride
$LiBH_4$	Lithium borohydride
Me_3SiCl	Trimethylsilylchloride
Me_2S	Dimethyl sulfide
BOC	t-butyloxycarbonyl
Cbz	benzyloxycarbonyl
t-BuOH	t-butyl alcohol
THF	Tetrahydrofuran
$(BOC)_2O$	Di-tert-butyldicarbonate
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
HCl	Hydrochloric acid
TFA	Trifluoroacetic acid
MeOH	Methanol
TBDMS	t-butyldimethylsiloxy
EtOAc	Ethylacetate
DCC	Dicyclohexylcarbodiimide

DCU	Dicyclohexylurea
CDI	Carbonyldiimidazole
BINOL	1,1'-Bi-2-naphthol
EtOH	Ethanol
TLC	Thin Layer Chromatography
UV	Ultraviolet
FT-IR	Fourier Transformation Infrared
HPLC	High Pressure Liquid Chromatography
BH_3-THF	Borane-tetrahydofuran complex
CH_2Cl_2	Dichloromethane
KBr	Potassium hydroxide
Ee	Enantiomeric excess
s	singlet
m	multiplet
d	doublet
t	triplet

1.INTRODUCTION

1.1 The Significance Of Chirality And Stereoisomeric Discirimination

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. (Lin et al., 2001)

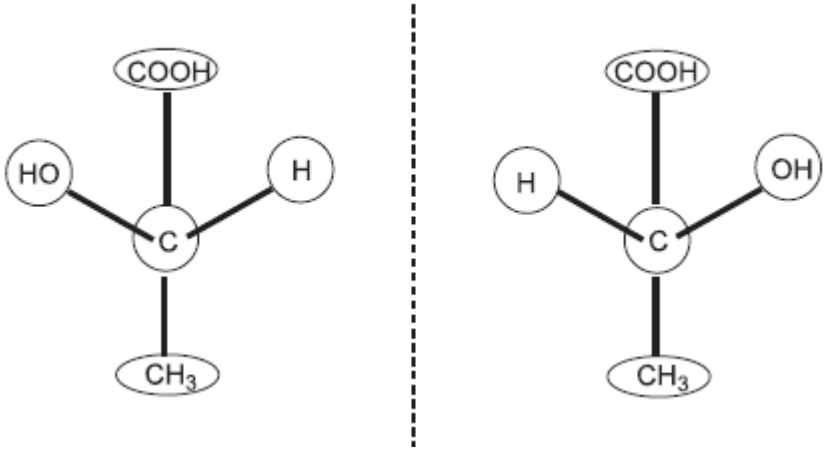


Fig. 1.1 Mirror images of lactic acid. (Lin et al., 2001)

To take a simple example, lactic acid can be obtained in two forms or enantiomers (Fig. 1.1) which are clearly enantiomeric in that they are related as mirror images that cannot be superimposed on each other. (Lin et al., 2001)

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. This means that two enantiomers of lactic acid have the same melting point, solubility, chromatographic retention time, infrared spectroscopy (IR), and nuclear magnetic resonance (NMR) spectra. However, there is one property in which chiral compounds differ from achiral compounds and in which enantiomers differ from each other. This property is the direction in which they rotate plane-polarized light, and this is called optical activity or optical rotation. Optical rotation can be interpreted as the outcome of interaction between an enantiomeric compound and polarized light. Thus, enantiomer on the right side in Fig.1.1, which rotates plane-polarized light in a clockwise direction, is described as (+)-lactic acid, while enantiomer on the left side in Fig.1.1, which has an equal and opposite rotation under the same conditions, is described as (-)-lactic acid. (Lin et al., 2001)

Chirality is of prime significance, as most of the biological macromolecules of living systems occur in nature in one enantiomeric form only. A biologically active chiral compound interacts with its receptor site in a chiral manner, and enantiomers may be discriminated by the receptor in very different ways. Thus it is not surprising that the two enantiomers of a drug may interact differently with the receptor, leading to different effects. Indeed, it is very important to keep the idea of chiral discrimination or stereoisomeric discrimination in mind when designing biologically active molecules. (Lin et al., 2001)

As human enzymes and cell surface receptors are chiral, the two enantiomers of a racemic drug may be absorbed, activated, or degraded in very different ways, both in vivo and in vitro. The two enantiomers may have unequal degrees or diferent kinds of activity. For example, one may be therapeutically effective, while the other may be ineffective or even toxic. (Stinson, 1995, 1997)

Stereoisomeric discrimination is very striking in biological systems, and for this reason chirality is recognized as a central concept. If we consider the biological activities of chiral compounds in general, there are four different behaviors: (1) only one enantiomer has the desired biological activity, and the other one does not show significant bioactivity; (2) both enantiomers have identical or nearly identical bioactivity; (3) the enantiomers have quantitatively different activity; and (4) the two enantiomers have different kinds of biological activity. Figure 1.2 presents a number of examples of differences in the behavior of enantiomers. (Lin et al., 2001)

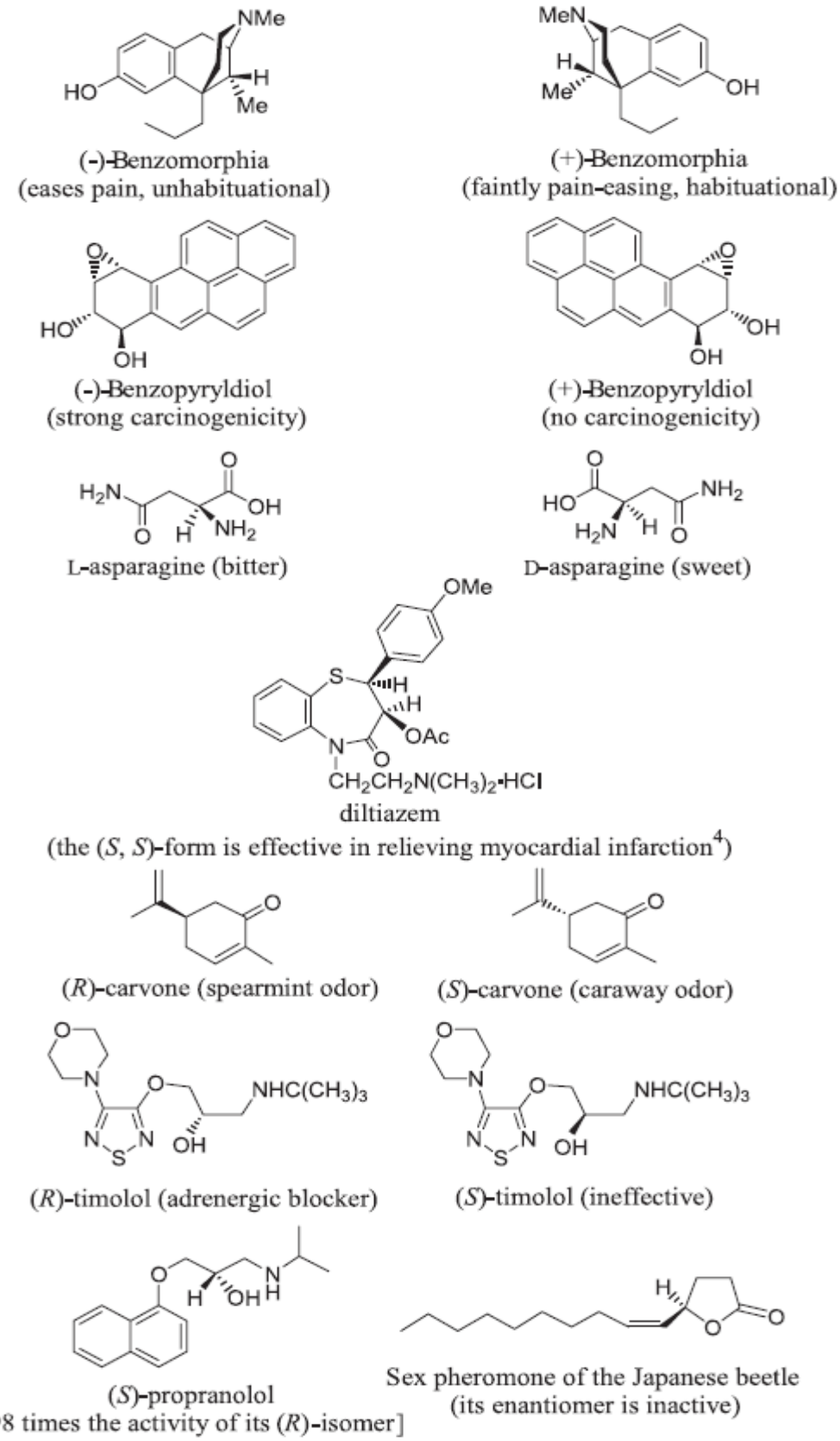


Fig. 1.2 Examples of the Different Behaviors of Enantiomers. (Lin et al., 2001)

1.2 Asymmetric Synthesis

Asymmetric synthesis refers to the conversion of an achiral starting material to a chiral product in a chiral environment. It is presently the most powerful and commonly used method for chiral molecule preparation. Thus far, most of the best asymmetric syntheses are catalyzed by enzymes, and the challenge before us today is to develop chemical systems as efficient as the enzymatic ones.

The resolution of racemates has been an important technique for obtaining enantiomerically pure compounds. Other methods involve the conversion or derivatization of readily available natural chiral compounds (chiral pools) such as amino acids, tartaric and lactic acids, terpenes, carbohydrates, and alkaloids. 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. Organic synthesis is characterized by generality and flexibility. During the last three decades, chemists have made tremendous progress in discovering a variety of versatile stereoselective reactions that complement biological processes.

In an asymmetric reaction, substrate and reagent combine to form diastereomeric transition states. One of the two reactants must have a chiral element to induce asymmetry at the reaction site. Most often, asymmetry is created upon conversion of trigonal carbons to tetrahedral ones at the site of the functionality. Such asymmetry at carbon is currently a major area of interest for the synthetic organic chemists.

1.2.1 The Chiral Pool

The chiral pool is that collection of available natural products considered cheap enough to use as starting materials for organic synthesis. The chiral pool strategy is the incorporation of part or all of one of these compounds into the target molecule. Chiral pool compounds were used as resolving agents and derivatives of them will be used as reagents, catalysts and chiral auxiliaries.

1.2.2 The Amino Acids

The α-amino acids found in proteins are widely available and reasonably priced - many indeed are cheap. They have the general structure, where R can be alkyl, cycloalkyl and functionalised alkyl or aryl. (Fig. 1.3) They are all (*L)*, most are also *(S)* (all except cysteine and cystine), and some are (+) and some (-).Some are also available as the (*D*) enantiomer, usually more expensive, but the synthesis of (*D*) amino acids is making them cheaper.

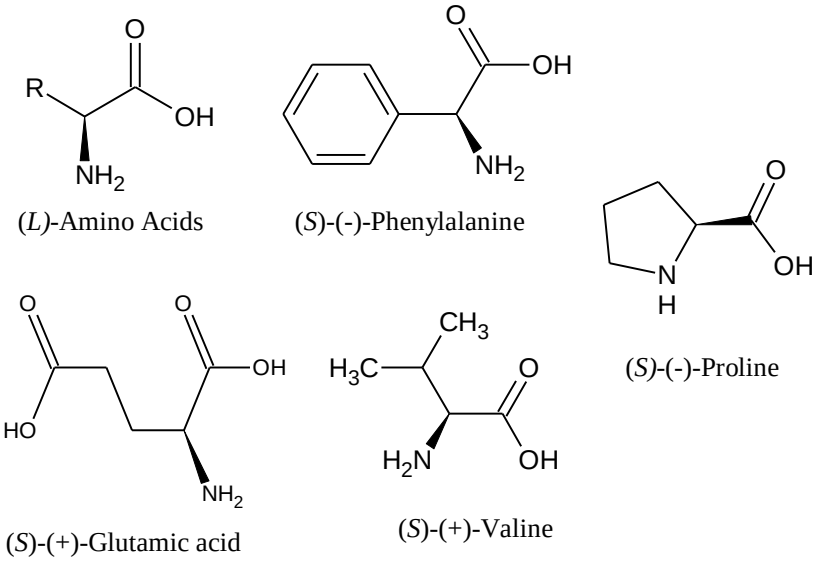


Fig. 1.3 Some important amino acids.

1.2.2.1 <u>Important reactions of amino acids</u>

Diazotisation of amino acids gives diazonium salts such as derived from valine. This reaction obviously goes with retention as the chiral centre is not affected. The internal CO_2H group is the best nucleophile and displaces N_2^+ with inversion. Any nucleophile now opens the α-lactone by S_N^2 displacement at the alkyl centre, again with inversion to give the final product with overall retention from the original amino acid. (Fig. 1.4) Most lactones react with nucleophiles at the carbonyl group but α-lactones react at saturated carbon as that relieves the strain of the 3-membered ring. (Kolasa and Miller, 1987)

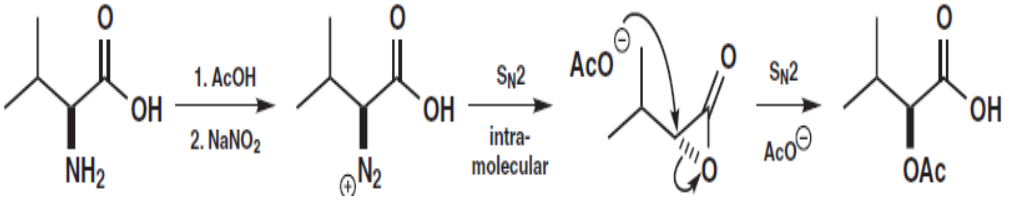


Fig. 1.4 Yield of the product is 98%

This type of reaction can be used to invert the natural series to give a rare and expensive (*R*)-amino acid. Phenylalanine is converted into the hydroxyacid with retention. Displacement of triflate with inversion and removal of the benzyl ester gives Boc-protected (*R*)-Phe. (Fig. 1.5) (Degerbeck et al., 1993)

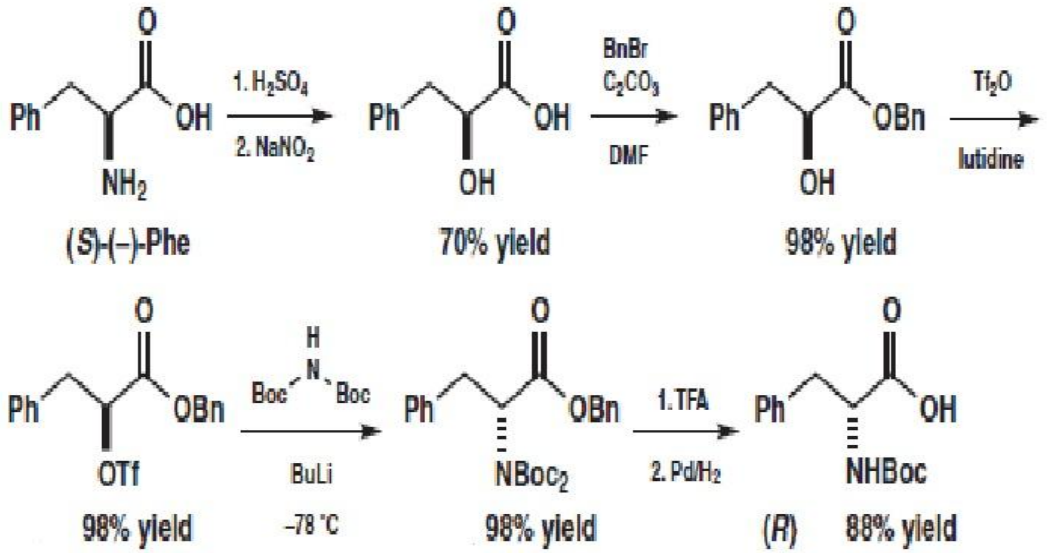


Fig. 1.5 Inversion of phenylalanine

1.2.2.2 Reduction of amino acids

Reduction of the carboxyl group of the amino acids gives a range of amino alcohols, usually named after the parent acid such as valinol and prolinol. It is important that the reduction does not threaten racemisation. Various methods have been used such as $NaBH_4$ in acid solution (no doubt producing borane *in situ*) and $LiBH_4$ with Me_3SiCl. (Abiko and Masamune, 1992; Quagliato et al., 2000)

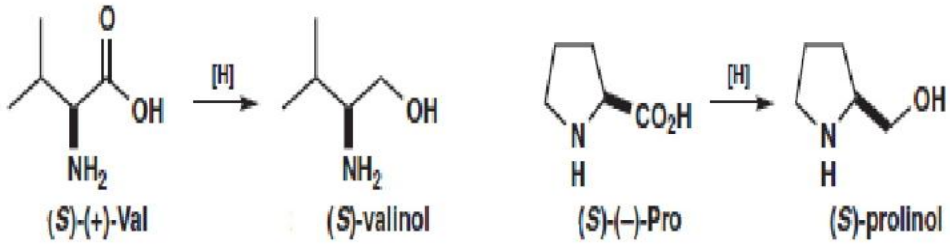


Fig. 1.6 Reduction of (*S*)-Valine and (*S*)-Proline.

Valinol and phenylalaninol are used to make the Evans chiral auxiliaries used in asymmetric aldol reactions and Evans prefers reduction with borane itself as its complex with Me_2S. The phenylalanine based auxiliary (Fig. 1.7) is generally preferred as the compounds are more likely to be crystalline and can easily be made on a 150 g scale. (Gage and Evans, 1990)

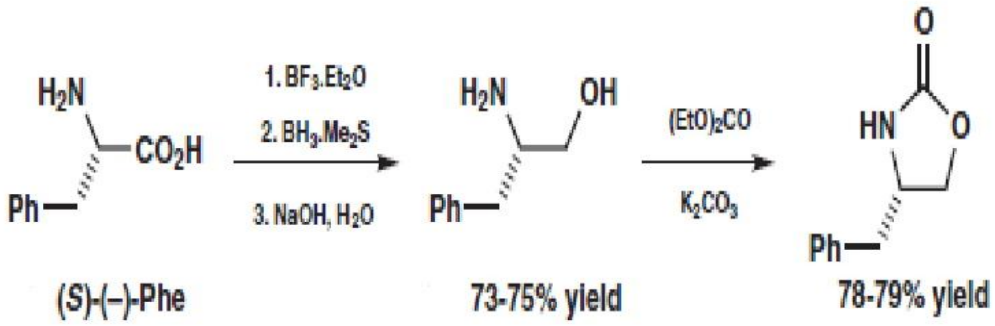


Fig. 1.7 Phenylalanine based chiral auxiliary.

1.3 Protection For The Amino Group

A great many protective groups have been developed for the amino group, including carbamates (>NCO_2R), used for the protection of amino acids in peptide and protein syntheses, and amides (NCOR), used more widely in syntheses of alkaloids and for the protection of the nitrogen bases adenine, cytosine and guanine in nucleotide syntheses. Carbamates are formed from an amine with a wide variety of reagents, the chloroformate being the most common; amides are formed from the acid chloride. *N*-alkyl carbamates are cleaved by acid-catalyzed hydrolysis; *N*-alkylamides are cleaved under forcing conditions by acidic or basic

hydrolysis at reflux, as well as by ammonolysis in cases where the amine is not very basic such as in heterocyclic amine derivatives. (Greene and Wuts, 2007)

1.3.1 Carbamates

Carbamates can be used as protective groups for amino acids to minimize racemization in peptide synthesis. Racemization occurs during the base-catalyzed coupling reaction of an *N*-protected, carboxyl-activated amino acid, and it takes place in the intermediate oxazolone that forms readily from an *N*-acyl protected amino acid. (Fig. 1.8)

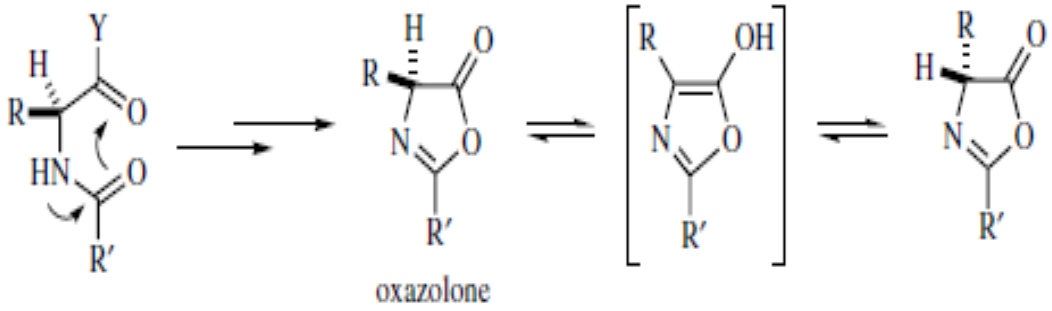


Fig. 1.8 R =alkyl, aryl R*'* = *O*-alkyl, *O*-aryl

To minimize racemization, the use of nonpolar solvents, a minimum of base, low reaction temperatures, and carbamate protective groups is effective. (Greene and Wuts, 2007)

Many carbamates have been used as protective groups. The most useful compounds are: *t*-butyl (BOC), readily cleaved by acidic hydrolysis; benzyl (Cbz or Z), cleaved by catalytic hydrogenolysis.

1.3.2 t-Butyl Carbamate (BOC group) : $(CH_3)_3COC(O)NR_2$

The BOC group is used extensively in peptide and heterocyclic synthesis for amine protection. It is not readily hydrolyzed under basic conditions and is inert to many other nucleophilic reagents. It is usually cleaved with strong acid, giving only *t*-BuOH or isobutylene and CO_2 as by-products. As a result, it is one of the most commonly used protective groups for amines. In general, it is considered nonreactive, but there are many cases in which the BOC group participates in reactions—anticipated and unanticipated. (Agami and Couty, 2002)

1.3.2.1 Formation

1. For simple amines, mixing $(BOC)_2O$ and the amine in THF with gentle heating (~40°C) to drive off CO_2 is often the simplest method for preparing BOC derivatives. If at least 2 equivalents of $(BOC)_2O$ are used, primary amines can be converted to the bis-BOC derivative ($(BOC)_2O$, THF, reflux, 92% yield). (Haug and Rich, 2004)

2. $(BOC)_2O$, NaOH, H_2O, 25°C, 10–30 min, 75–95% yield. This is one of the more common methods for introduction of the BOC group onto amino acids, but does not work efficiently for hindered amines because of reagent destruction. It has the advantage that the by-products are innocuous and are easily removed. (Tarbell et al., 1972)

3. Several amino acids have been N-protected by *tert*-butyloxycarbonyl (Boc) protecting group using Boc2O/$NaHCO_3$/THF-H_2O in nearly quantitative yields. (Shendage et al., 2004)

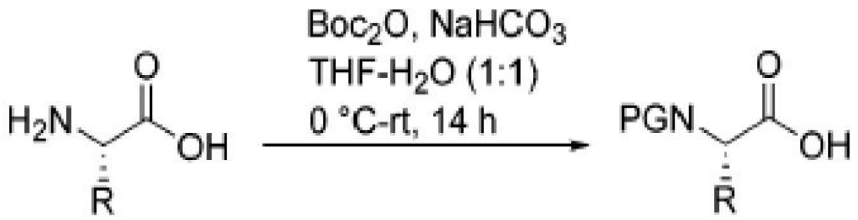


Fig. 1.9 N-protections of amino acids.

4. Treatment of *L*-hydroxyproline with di-*tert*-butyl dicarbonate in the presence of 10% aqueous NaOH provided *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-*L*-proline. (Qiu and Qing, 2002)

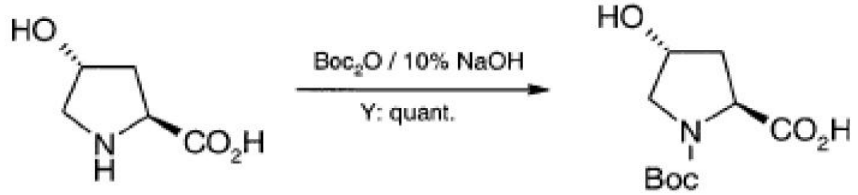


Fig. 1.10 Syntheses of *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-*L*-proline.

1.3.2.2 Cleavage

1. Aqueous HCl, toluene, 65°C, 93% yield. This method is a commercially convenient method and has been used on a multikilogram scale. (Prashad et al., 2004)

2. The N-protected amides were subsequently hydrolyzed to free amides (peptide building blocks) using TFA/CH_2Cl_2 or to the corresponding HCl-salts by HCl-MeOH in anhydrous MeOH with high yields. (Shendage et al., 2004)

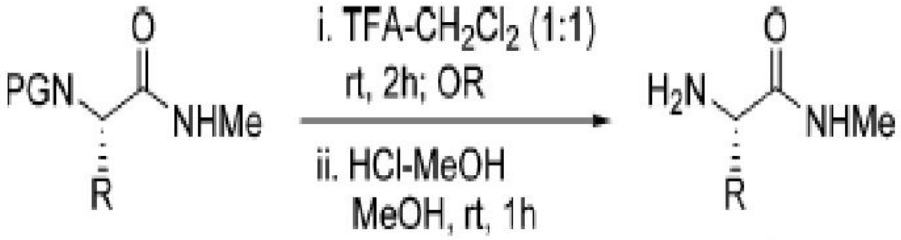


Fig. 1.11 N-Deprotection of Amides.

3. The environmentally benign aqueous phosphoric acid (85 wt%) can be used as an alternate reagent for the deprotection of *N*-BOC groups. The reaction conditions are mild and offer good selectivity among other acid sensitive groups including CBZ, benzyl and methyl esters, TBDMS and isopropylidene groups. The reaction preserves stereochemical integrity of *N*-BOC amino acids. (Li et al., 2003)

1.3.3 Benzyl Carbamate (Cbz- or Z-NR_2): $PhCH_2OC(O)NR_2$

The benzyl carbamate is one of the most popular protective groups that results largely from its facile hydrogenolysis and its orthogonality to numerous other protective groups.

1.3.3.1 Formation

1. $PhCH_2OCOCl$, MgO, EtOAc, 3 h, 70°C to reflux, 60% yield. Zinc metal can be used to scavenge the HCl produced in the protection process. $ZnCl_2$ is formed in the reaction. (Dymicky, 1989; Yadav et al., 1998)

2. β-aminopropionic acid was protected by $PhCH_2OCOCl$ with 1 N NaOH from 0°C to ambient temperature overnight. (Garcia et al., 2001)

1.3.3.2 Cleavage

1. Raney Ni (W-2), MeOH, reflux, 65% yield. (Tamura et al., 2001)

2. $PdCl_2$, MeOH, H_2, conc. HCl, rt, 100% yield. These conditions also reduce olefins, but a benzylic ether remained in tact. At 80–85°C these conditions will cleave the benzylic amine and ether. (Jain et al., 2001)

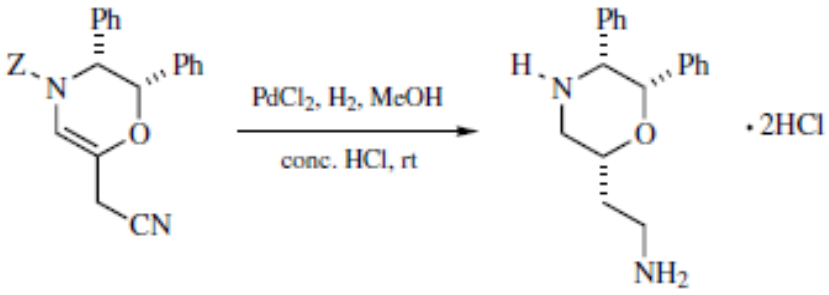


Fig. 1.12 Formation of desired all *syn*-substituted oxazine in essentially quantitative yield.

1.4 Amide Bond Formation

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs.

Amide bonds are typically synthesised from the union of carboxylic acids and amines; however, the unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures (e.g. >200°C), conditions typically detrimental to the integrity of the substrates. For this reason, it is usually necessary to first activate the carboxylic acid, a process that usually takes place by converting the –OH of the acid into a good leaving group prior to treatment with the amine (Fig. 1.13). Enzymatic catalysis has also been investigated for the mild synthesis of amides and the organic chemist may find some of these methods

useful as an alternative to traditional methods. (Gotor, 1999; Rantwijk et al., 2000)

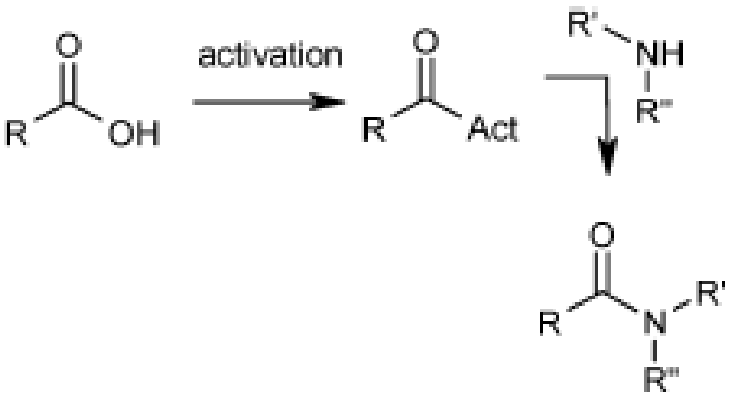


Fig. 1.13 Principle of the activation process for amide-bond formation.

In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters.

1.4.1 Coupling using carbodiimides

1.4.1.1 <u>Dicyclohexylcarbodiimide</u>

Carbodiimides were the first coupling reagents to be synthesised. Dicyclohexylcarbodiimide (DCC) has been used for coupling since 1955, and the mechanism for coupling carboxylic acids to amines is shown in Figure 1.14. (Valeur and Bradley, 2009)

The first step involves the reaction of the carboxylic acid with DCC to form the O-acylurea. This intermediate can then yield a number of different products:

- The amide via direct coupling with the amine (the by-product formed, dicyclohexylurea (DCU), is usually insoluble in the reaction solvent and can be removed via filtration).

- Formation of an N-acylurea by-product

- Formation of the carboxylic acid anhydride which subsequently yields the amide by reaction with the amine (needs 2 equiv. of acid).

When using DCC, oxazolone formation can take place after generation of the O-acylurea leading to epimerisation, especially important when activating acid groups in the α position of an amide bond. (Valeur and Bradley, 2009)

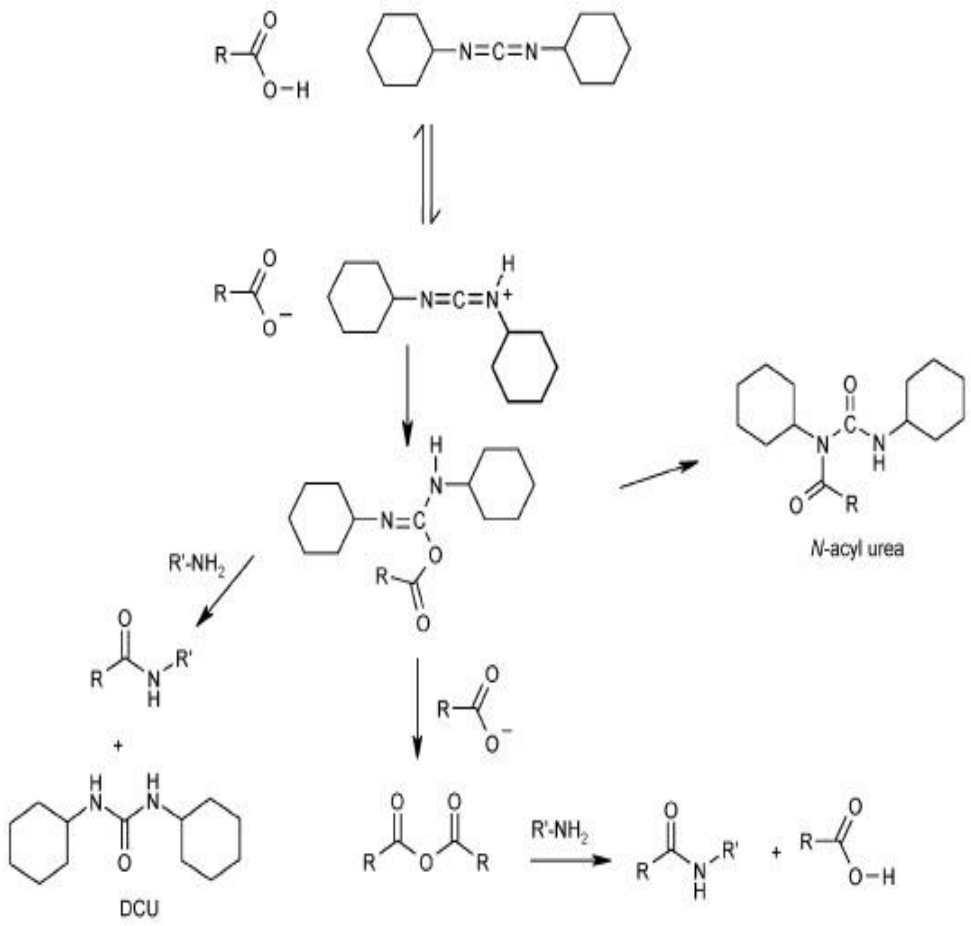


Fig. 1.14 Coupling using DCC.

1.4.1.2 Use of additives

In order to reduce the epimerisation level when using carbodiimides as coupling reagents, Koenig and Geiger introduced 1-hydroxy-1H-benzotriazole (HOBt) as an additive, showing that, when using this additive, yields were higher and epimerisation levels lower. For example, when coupling Z-Gly-Phe-OH to H-Val-OMe, the epimerisation levels dropped from 35% to 1,5%.

HOBt is believed to work by initially reacting with the O-acylurea to give the OBt active ester, which enhances the reactivity of the ‘‘activated ester’’ by encouraging/stabilising the approach of the amine via hydrogen bonding (Figure 1.15). However, HOBt can yield by-products, thus it catalyses the formation of diazetidine (Figure 1.16). (Valeur and Bradley, 2009)

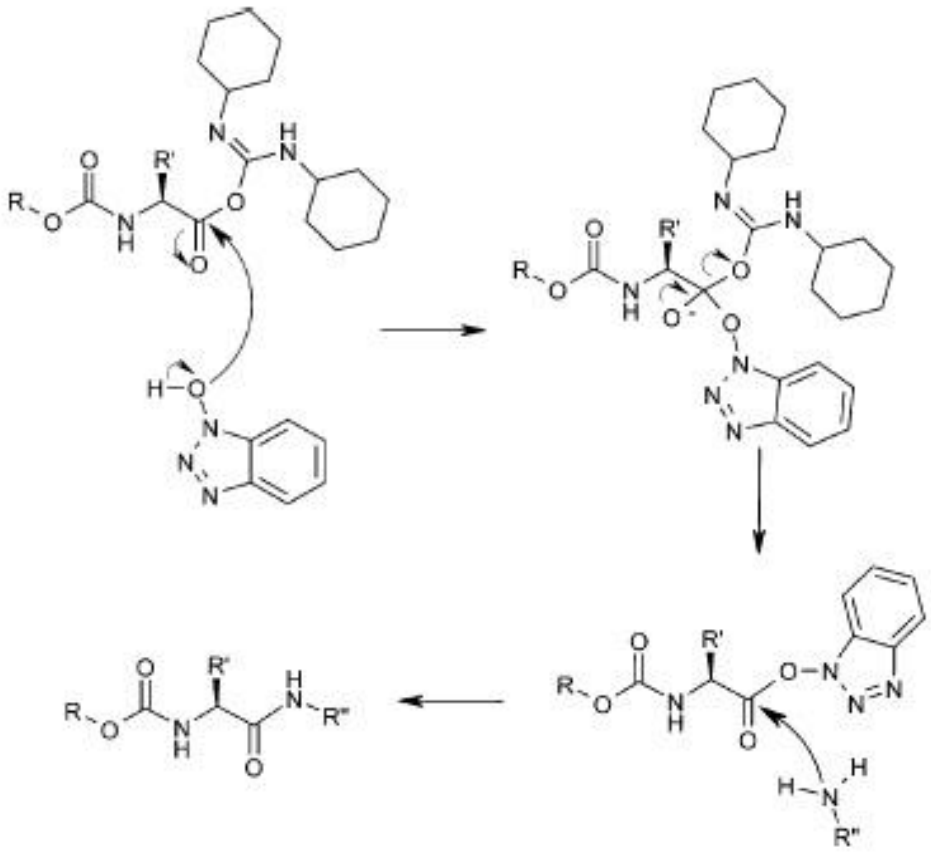


Fig. 1.15 Mechanism of activation by 1-hydroxy-1H-benzotriazole when used as an additive with DCC.

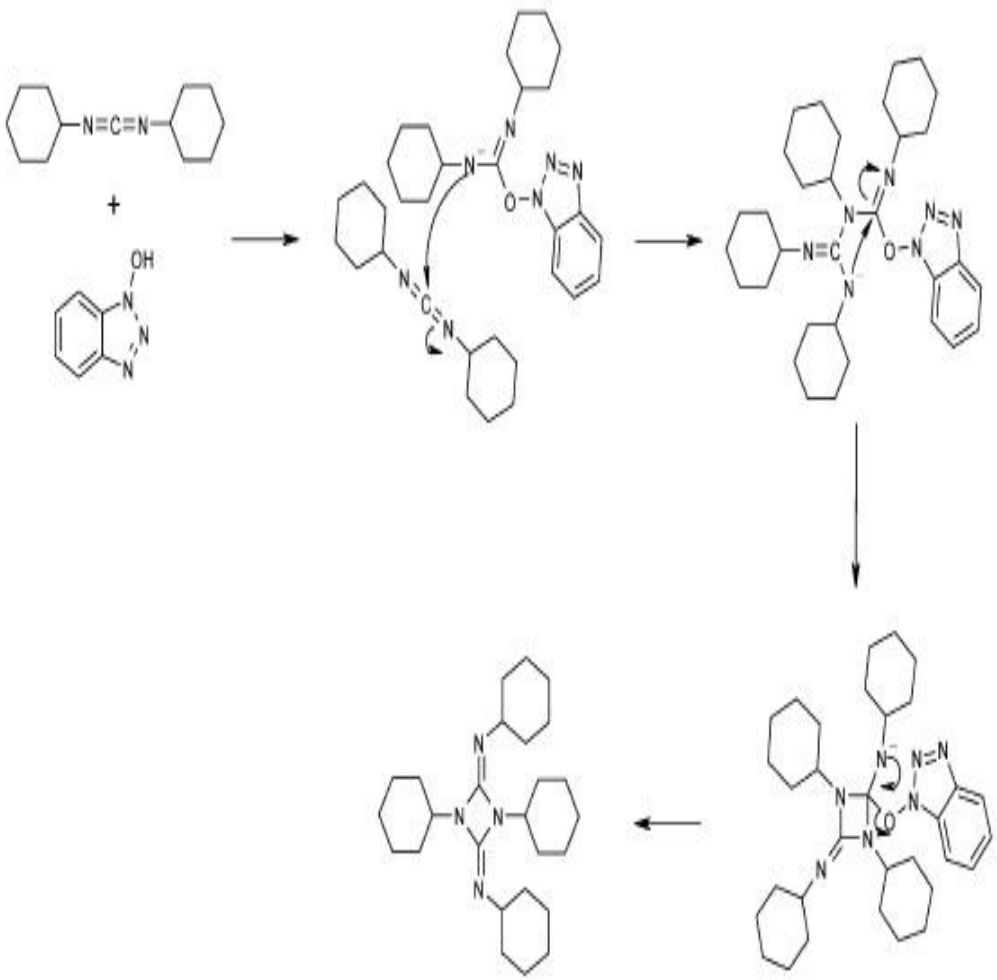


Fig. 1.16 Formation of the diazetidine by-product when using DCC/HOBt.

In 1994, Carpino reported a related additive, 1-hydroxy-7-azabenzotriazole (HOAt) (Fig. 1.17), which was even more efficient than HOBt in terms of yield, kinetics and reduced epimerisation levels. For example epimerisation during coupling of Z-Val-OH and H-Val-OMe using DCC dropped from 41,9% with HOBt to 14,9% with HOAt, while during the coupling of Z-PheVal-OH to H-Ala-OMe using EDC, it dropped from 4,1% with HOBt to under 2% with HOAt.

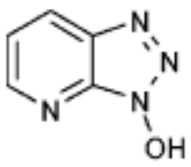


Fig. 1.17 Structure of 1-hydroxy-7-azabenzotriazole.

1.4.1.3 Other carbodiimides

Since the application of DCC to amide bond formation, many carbodiimides, including DIC (diisopropylcarbodiimide), have been reported and this field has been reviewed. In particular, attention has focused on so-called water-soluble carbodiimides, as the ureas formed when using DCC or the popular diisopropylcarbodiimide DIC can sometimes be difficult to remove. (Williams and Ibrahim, 1981)

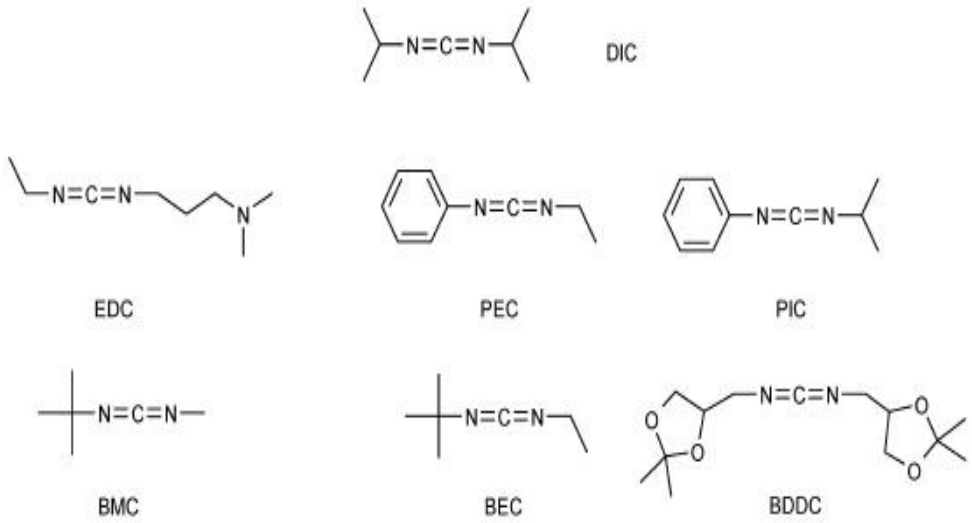


Fig. 1.18 Structure of some common carbodiimides.

1.4.2 Acylimidazoles using CDI

Carbonyl diimidazole (CDI) is a useful coupling reagent that allows one-pot amide formation. Acyl carboxy imidazole and imidazole are initially formed but readily react together to yield the activated species as the acylimidazole (Fig. 1.19). Practically, the acylimidazole is preformed for 1 h and then the amine is added. This reaction, which generates imidazole in situ, does not need an additional base and is even compatible with HCl salts of the amine. This reagent is commonly used on a large scale in peptide chemistry and its use can be extended to the formation of esters and thioesters. (Montalbetti and Falque, 2005)

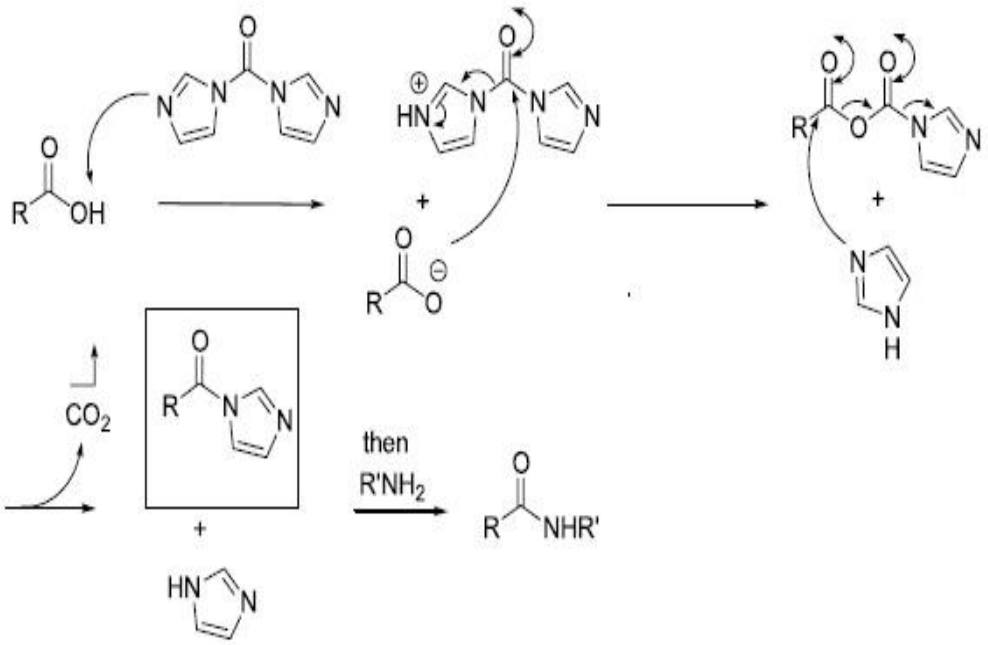


Fig. 1.19 One-pot amide preparation using CDI.

Amidation reactions between different sterically hindered acid aldehydes and amines have been reported to be efficiently catalyzed by CDI. First, compound is activated with CDI, then, addition of *N*,*N*-diethylethylenediamine to the reaction mixture leads to the imine amide product. Remarkable rate enhancement was observed in the reaction due to catalysis by the released carbon dioxide. (Vaidyanathan et al., 2004)

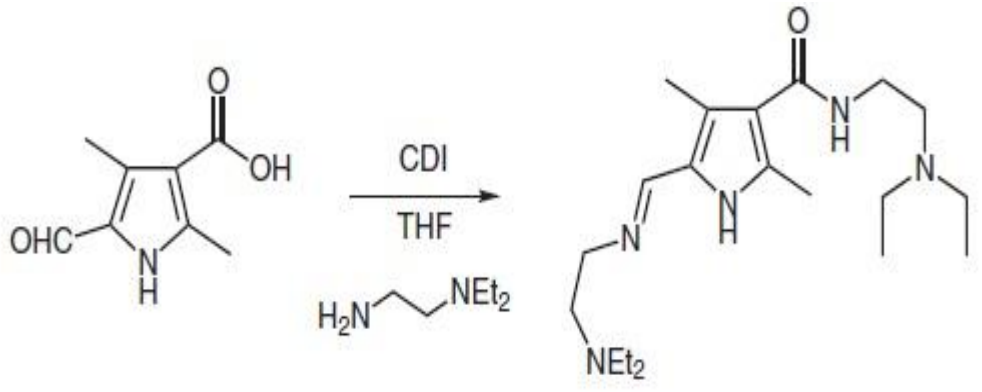


Fig. 1.20 Amidations Using *N*,*N*'-Carbonyldiimidazole.

Recently, the first amidation reaction of unprotected α-amino acids in water under neutral conditions with various aliphatic, aromatic, and heteroaromatic

primary amines in the presence of CDI at ambient temperature was reported. Zwitterionic amino acids first react with CDI leading to the formation of the intermediate mixed anhydride, followed by nucleophilic attack of amines facilitating the formation of amides in moderate yields. (Sharma and Jain, 2007)

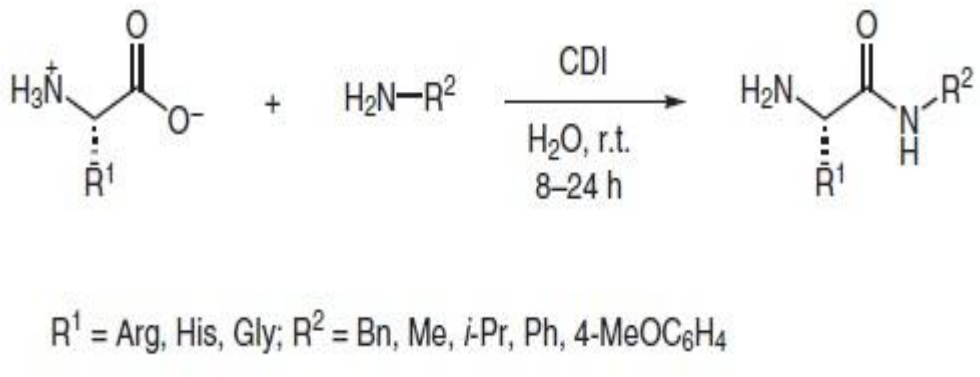


Fig. 1.21 Amidation of unprotected a-amino acids in water.

1.5 The Nitroaldol Reaction

The nitroaldol (Henry) reaction involves the addition of nitronates to aldehydes and ketones to give a β-nitroalcohol. These products are useful synthetic building blocks as the nitro group can be transformed into a range of other functional groups, and this has stimulated some recent research into the development of a catalytic asymmetric variant.

The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992. Since then, interest in this area has been expanded upon considerably and various reports have been continuously appearing in the literature on development of various metal and nonmetal based catalysts for the asymmetric Henry reaction. (Boruwa et al., 2006)

1.5.1 Rare earth-BINOL complexes

Shibasaki et al. observed that rare earth alkoxides are sufficiently basic due to the low ionisation potential (ca. 5.4–6.4 ev) and electronegativity (1.1–1.3) of the rare earth elements. During this study, it was observed that optically active rare earth alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$ promote the nitroaldol reactions with ee

up to 90%. These authors suggested that the first step of the reaction is the ligand exchange between the binaphthol and nitromethane (Figure 1.22).

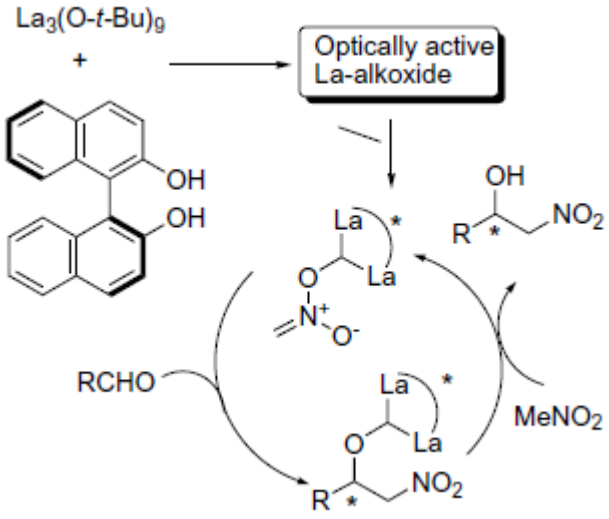
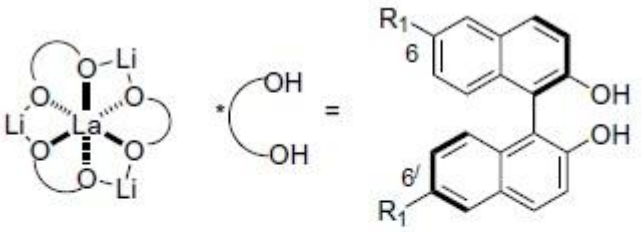


Fig. 1.22 Ligand exchange between binaphthol and nitromethane.

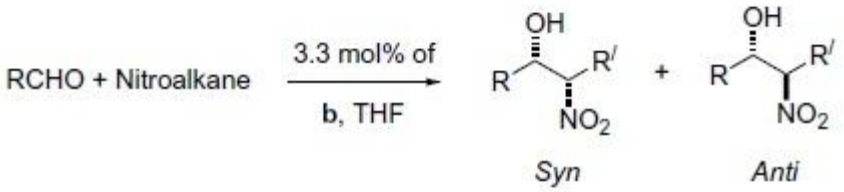
Shibasaki's Rare earth–BINOL catalyst has been shown to have structure (Fig. 1.23) based on 1H, 13C and X-ray crystallographic data. This catalyst afforded nitroalcohols in 79–91% yield and with 86:14–95.5 er from aliphatic aldehydes and nitromethane.

To expand the scope of this reaction, Shibasaki et al. Applied this catalyst system to complex nitroalkanes in which the catalyst is required to control the enantioselectivity as well as its diastereoselective outcome.

The introduction of two TES groups at the 6- and 6'-position of the binapthol turned out to make a good catalyst b, which led to the generation of β-nitroalcohols with better diastereoselectivity with the syn-isomer as the predominant product. (Shibasaki et al., 1995, 1997)



a R_1 = H
b R_1 = OTES



Syn *Anti*

R	nitroalkane	yield	*syn:anti*	ee of *syn*
$PhCH_2H_2$	$CH_3CH_2NO_2$	70	89:11	96
$PhCH_2CH_2$	$CH_3(CH_2)_2NO_2$	85	93:7	98
$PhCH_2CH_2$	$OH(CH_2)_2NO_2$	97	92:8	98
$CH_3(CH_2)_4$	$OH(CH_2)_2NO_2$	95	92:8	98

Fig. 1.23 Catalyst b results.

The catalytic cycle initially proposed by Shibasaki et al. was later modified upon. It is suggested that the lanthanum metal in LLB acts as a Lewis acid to activate the aldehyde, and the lithium binapthoxide moiety functions as a Bronsted base to deprotonate the nitroalkane to form lithium nitronate. This nitronate complex then activates the aldehyde to form complex, which undergoes nucleophilic addition to generate complex. Subsequent release of the nitroalcohol regenerates the catalyst. (Shibasaki and Yoshikawa, 2002)

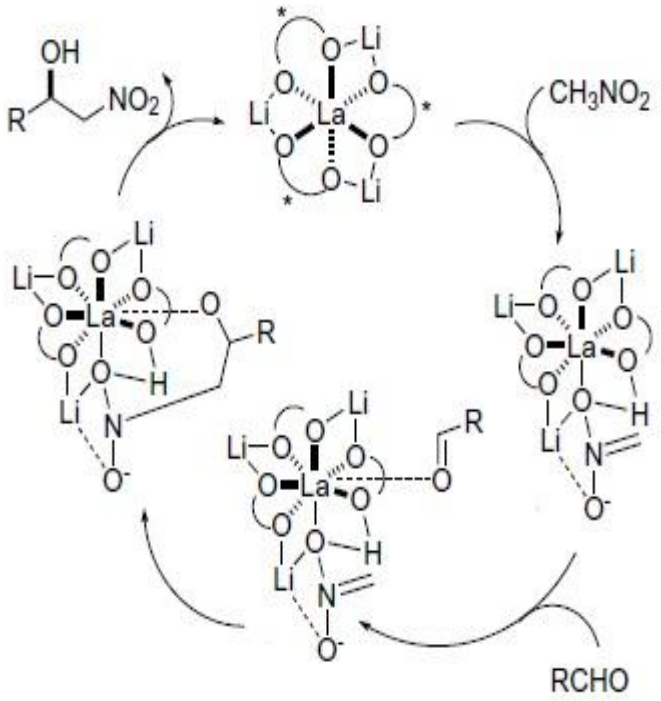


Fig. 1.24 Proposed mechanism for heterobimetallic complexes; (H_2O is omitted for clarity).

1.5.2 Zinc(II)-Based catalysis

Zinc-centred metal complexes of ambifunctional character represent another family of efficient catalysts in the context of the asymmetric nitroaldol reaction.

Trost has designed a very effective catalyst of this group, consisting of a dinuclear zinc complex with a chiral semi-azacrown ligand. High levels of enantioselection are regularly achieved in nitroaldol reactions catalysed by 5 mol-% ligand with a broad range of aliphatic and aromatic aldehydes. This technology has been applied to the synthesis of the β-receptor agonists (–)-arbutamine and (–)-denopamine. (Trost and Yeh, 2002; Trost et al., 2002)

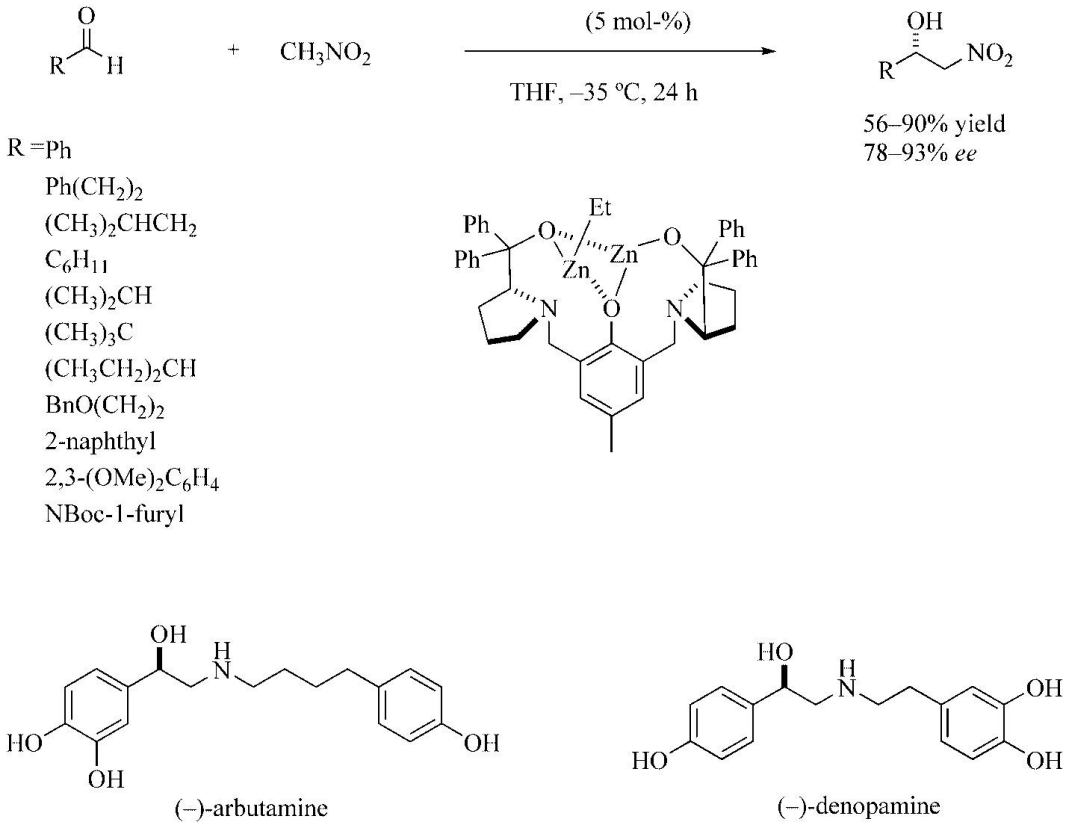


Fig. 1.25 Trost's dinuclear Zn complex's performance in catalytic asymmetric Henry reactions and some synthetic targets approached.

The complex formed upon admixture of Et_2Zn and the dimeric chiral amino alcohol ligand has been reported to produce nitroaldol products with low to moderate enantioselectivities. (Zhong, 2004)

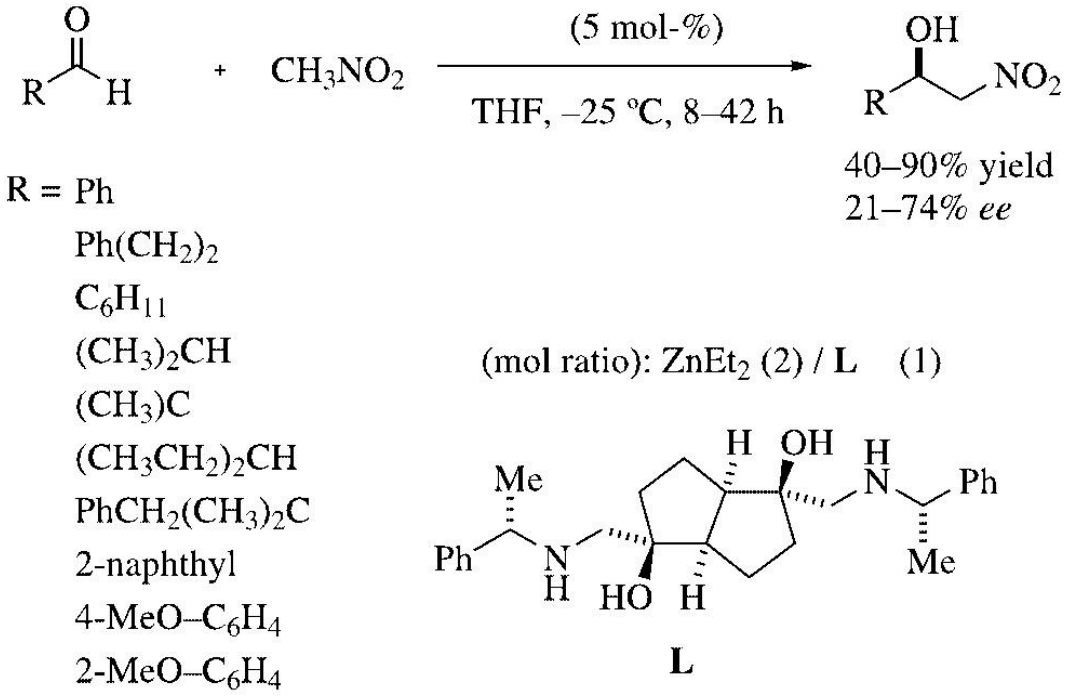


Fig. 1.26 A synthetic amino alcohol dimer as a ligand for the Zn-catalysed Henry reaction.

Palomo and co-workers have described a practical system that combines a simple Zn^{2+} salt, a chiral amino alcohol ligand and an amine base. In this design, the acid and the basic centres, which are presumed concurrently to activate the electrophilic aldehyde and the pronucleophilic nitroalkane, respectively, are not integrated in the same molecular entity. This distinguishing feature facilitates straightforward screening of different combinations of metal salts, amine bases and chiral ligands. Among the chiral amino alcohols tested, *N*-methylephedrine (NME) showed the best results, regularly giving *ee* values above 90% for all aliphatic aldehydes tested and slightly below 90% for aromatic aldehydes. Of practical importance, essentially quantitative recovery of the chiral amino alcohol used is easy to carry out from the crude reaction product by simple acid/basic workup. (Palomo et al., 2005)

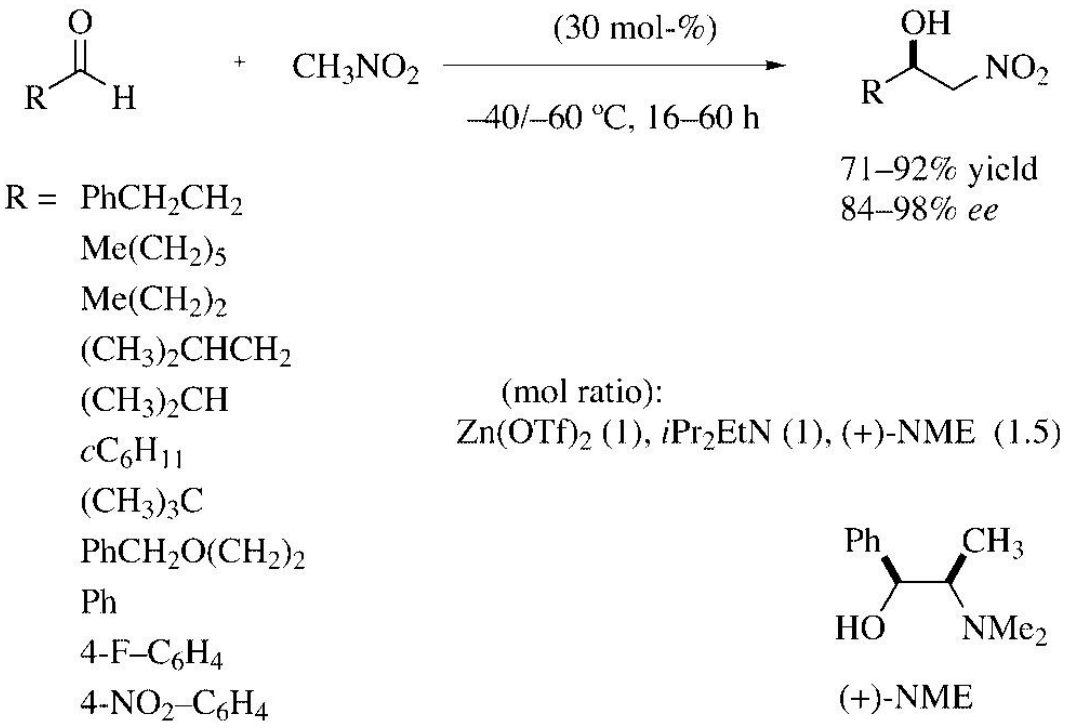


Fig. 1.27 Enantioselective Henry reactions catalysed by the commercially available triad system $Zn(OTf)_2$/*N*-methylephedrine/DIPEA.

1.5.3 Copper-Based catalysis

Chiral complexes of copper, particularly Cu^{II}–bis(oxazoline) complexes, have found wide application in the general context of catalytic asymmetric transformations. The first application of these type of organometallics to the asymmetric nitroaldol reaction was reported by Jørgensen (2001) and involves reactions between nitromethane and α-keto esters in the presence of chiral Cu^{II}–BOX complexes and triethylamine as the co-catalyst, working at room temperature. The newly formed quaternary stereocentre is obtained with selectivities generally above 90% for aliphatic and electron-poor aromatic aldehydes, but significantly lower *ee* values are attained with neutral or electron-rich aromatic congeners.

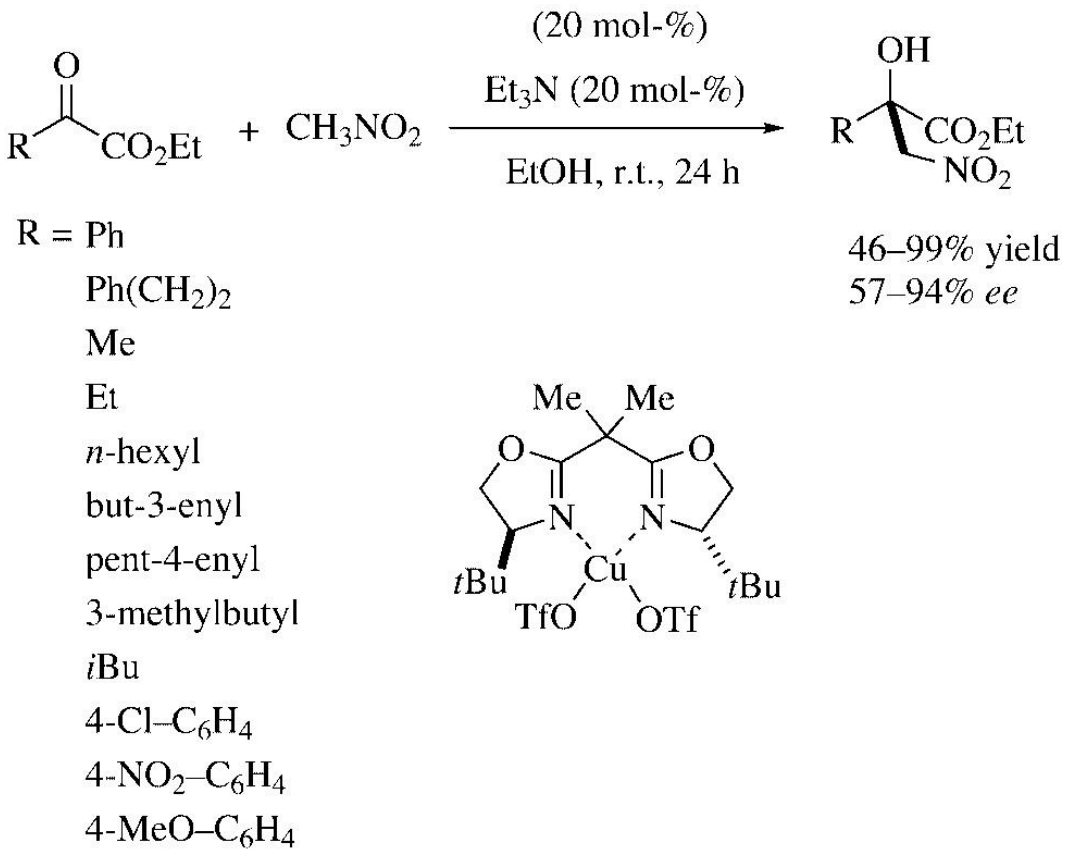


Fig. 1.28 Henry reactions between α-keto esters and nitromethane catalysed by Cu^{II}–BOX complex and triethylamine base, affording tertiary alcohols.

In this method, the optimum loading of the two catalytic components – Cu^{II} complex and triethylamine – is 20 mol-% each (1:1 ratio); ratios above this value give lower selectivity, ratios below show lower yields. Bases other than triethylamine also gave detrimental yields and/or selectivity. A reaction model that considers both racemic and asymmetric pathways, with triethylamine as an active participant, has been proposed. (Jørgensen et al., 2001, 2002)

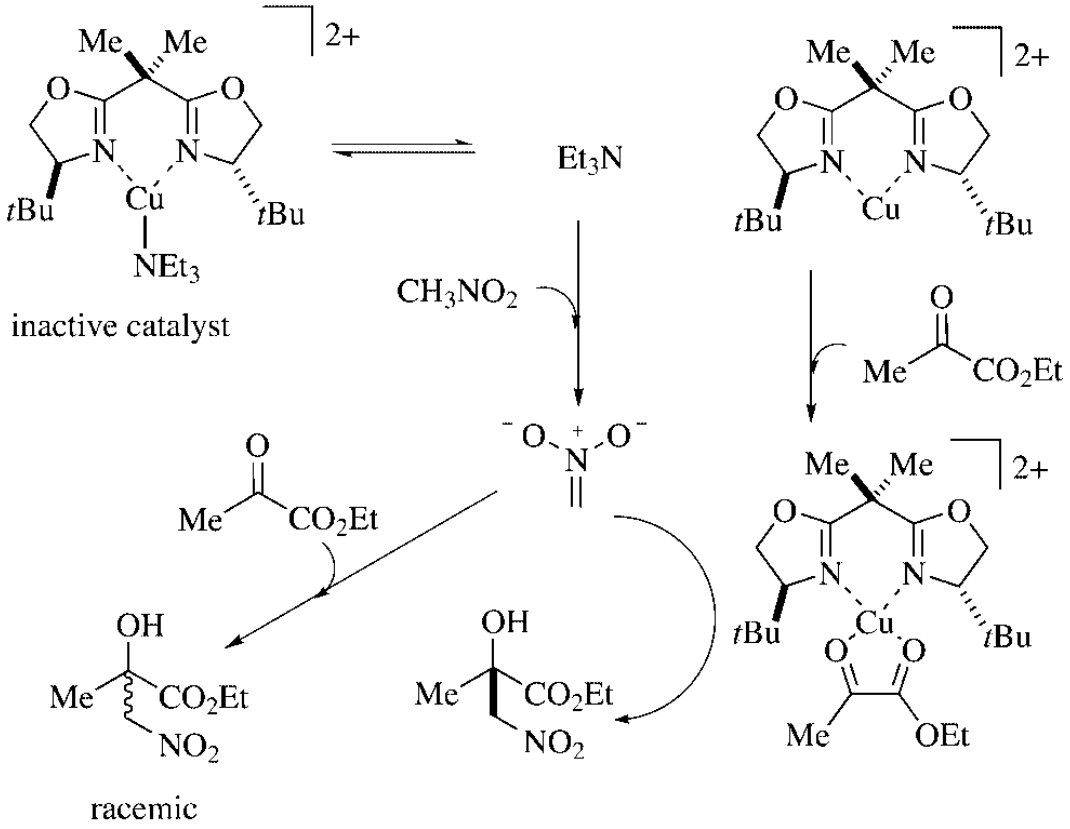


Fig. 1.29 Double role played by triethylamine co-catalyst as the reaction promoter and deactivator of the Lewis acid catalyst.

A more efficient Cu^{II} catalyst, which is active at loading levels of 5 mol-%, has been described by Evans (2003) for nitroaldol reactions between nitromethane and aldehydes. The method is quite general for a range of both aliphatic and aromatic aldehydes and works under very mild reaction conditions (EtOH, room temperature). The catalyst design required a weakly acidic metal complex bearing moderately basic charged ligands that would facilitate deprotonation of nitroalkanes, and the $Cu(OAc)_2$–BOX complex was found to fulfil the requirements best. A transition state model involving a Jahn–Teller effect on copper coordination and positioning of reactants in the most favourable orientations according to steric and electronic considerations has been proposed. Copper is thus coordinated both to the nitronate and to the aldehyde carbonyl, producing a preferential boat conformation that correctly predicts the observed stereochemistry.

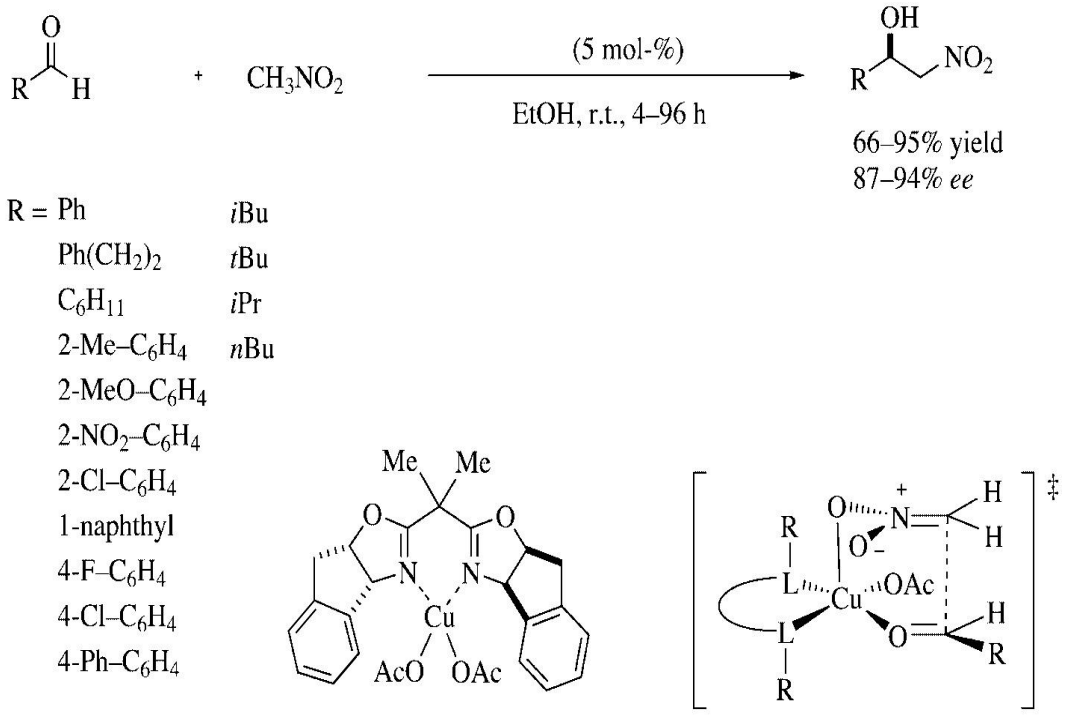


Fig. 1.30 Bifunctional $Cu(OAc)_2$–BOX catalyst for broad-scope enantioselective Henry reactions developed by Evans, together with the proposed TS model.

Chiral Cu^{II}–diamine complexes have also very recently been shown to act as useful catalysts in Henry reactions. In view of the well known stereochemical biases of Cu^{II}–sparteine complexes, and their conformational rigidity, complexes of both $CuCl_2$ and $Cu(OAc)_2$ with (–)-sparteine were screened against Henry reactions between nitromethane and a range of representative aromatic and aliphatic aldehydes. Interestingly, while the $Cu(OAc)_2$–(–)-sparteine complex was able to catalyse the reaction without any need for external base, essentially racemic products were obtained. On the other hand, the $CuCl_2$–(–)-sparteine complex alone was inefficient in promoting the reaction, but a smooth reaction took place in the presence of a small quantity of triethylamine, with *ee* values in the 80's. The authors found the quantity of triethylamine added to be very influential: an increase in the amount of triethylamine base beyond the 3 mol-% level lowered the enantioselectivity. Also noteworthy is the requirement for methanol as solvent, since other solvents such as dichloromethane or THF gave poor results. The experimentally observed differences between the complexes derived from $Cu(OAc)_2$ and from $CuCl_2$ were explained on the basis of the significant differences in the bond angles and torsion angles around the copper(II) site as determined in the solid state. (Maheswaran et al., 2006)

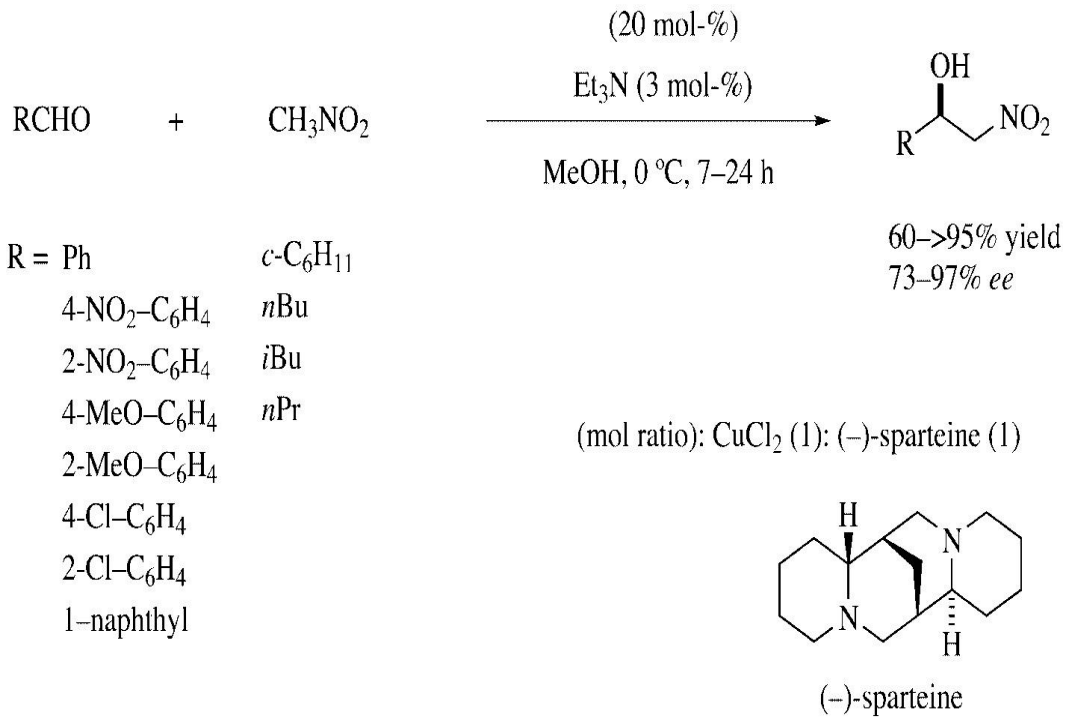


Fig. 1.31 A combined Cu^{II}–(–)-sparteine/Et_3N catalytic system for Henry reactions of nitromethane.

1.6 Separation of Enantiomers by Chromatography on Chiral Columns

Chromatography is an important means of separating enantiomers on both an analytical and preparative scale. These separations are based on use of a chiral stationary phase (CSP). Chromatographic separations result from differential interactions of the enantiomers with the solid column packing material. The differential adsorption arises from the diastereomeric nature of the interaction between the enantiomers and the CSP. Hydrogen bonding and aromatic π-π interactions often contribute to the binding.

One important type of chiral packing material is derivatized polysaccharides, which provide a chiral lattice, but separation is improved by the addition of structural features that enhance selectivity. One group of compounds includes aroyl esters and carbamates, which are called Chiralcels (also spelled Chiracel); two of the most important examples are the 4-methylbenzoyl ester, called Chiralcel OJ, and the 3,5-dimethylphenyl carbamate, called Chiralcel OD. There is a related series of materials derived from amylose rather than cellulose, which have the trade name Chiralpak.

Related materials can be prepared in which the polysaccharides are linked to a silica support by covalently bound tether groups. For example, silica derivatized by 3-aminopropyl groups can be linked to polysaccharides using diisocyanates. These materials seem to adopt organized structural patterns on the surface, and this factor is believed to contribute to their resolving power. The precise structural basis of the chiral recognition and discrimination of derivatized polysaccharides has not been elucidated, but it appears that in addition to polar interactions, π-π stacking is important for aromatic compounds.

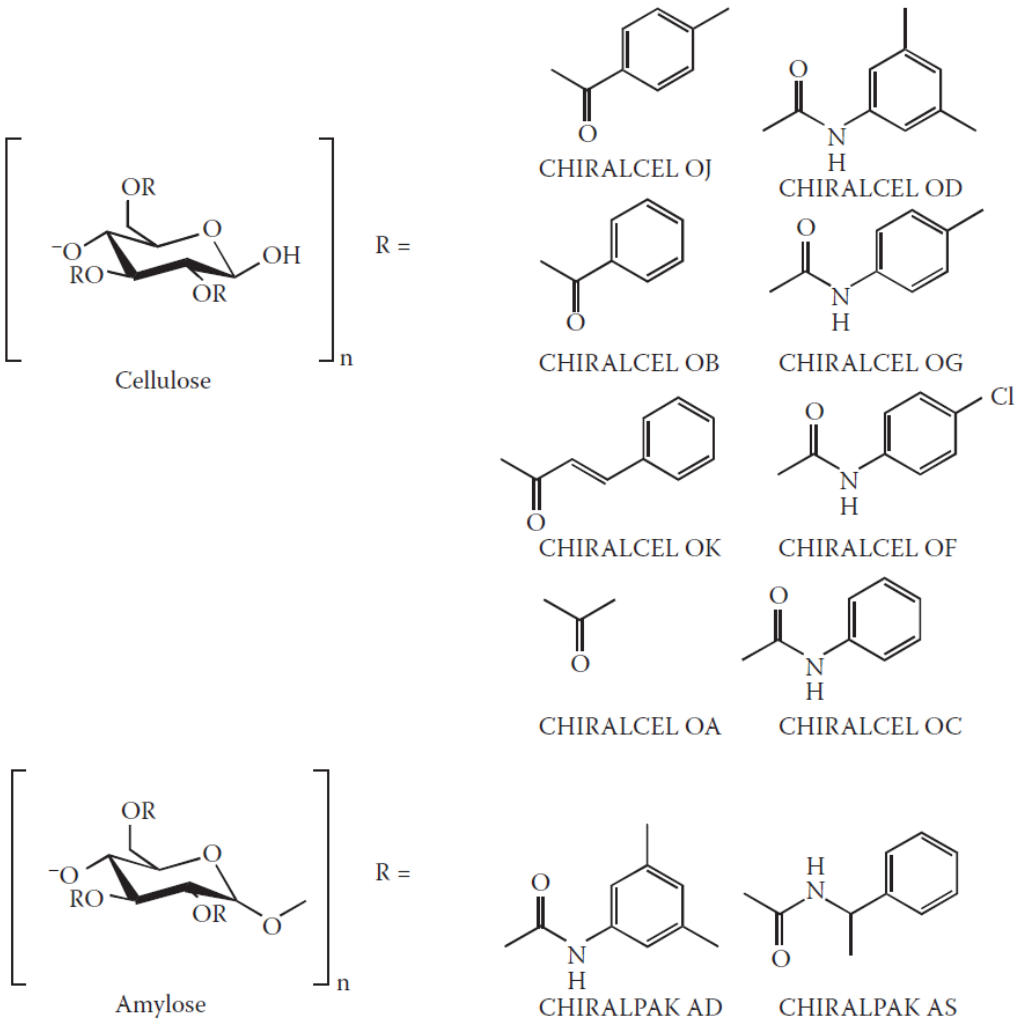


Fig. 1.32 Structures of commercially available polysaccharide CSPs.

Other types of CSPs, known as brush type, have been constructed synthetically. A chiral structure, usually an amide, is linked to silica by a tether molecule. This approach has the potential for design of the chiral recognition elements. The ability to synthetically manipulate the structures also permits

investigation of the role of specific structural elements in chiral selectivity. Several synthetic CSPs were developed by W. H. Pirkle and co-workers at the University of Illinois. An important example is the 3,5-dinitrobenzoyl (3,5-DNB) derivative of *R*-phenylglycine, which is attached to silica by aminopropyl tethers. The 3,5-DNB derivatives of several other amino acids and diamines have also been explored.

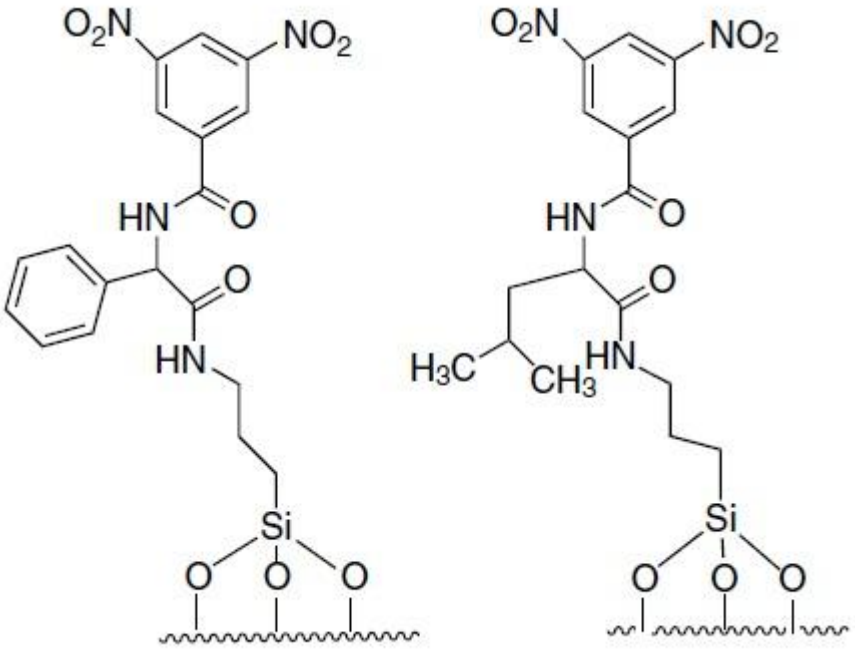


Fig. 1.33 Dinitrobenzoyl derivatives of amino acids as chiral stationary phases.

Cetirizine·2HCl is an antihistamine marketed as Zyrtec. It has a 'low grade' chiral centre. The molecule is chiral only because one of the benzene rings has a *para*-chloro substituent. It is very difficult to resolve cetirizine or to synthesise it asymmetrically. One company, Sepracor Inc., whose business is making single enantiomers, found that the related amide could be separated by chiral HPLC on Chiral Technologies 'Chiralpak AD' columns: the two enantiomers having very different retention times (4.8 and 8.8 minutes). They could separate nearly 40 g of racemic material with one injection and, by repeated injections, could easily separate 1.6 kg of (-)-(*R*)-amide with 99.8% ee. The separate enantiomers were converted to cetirizine in two steps and the (+)-(*R*)-enantiomer found to be biologically active. (Pflum et al., 2001)

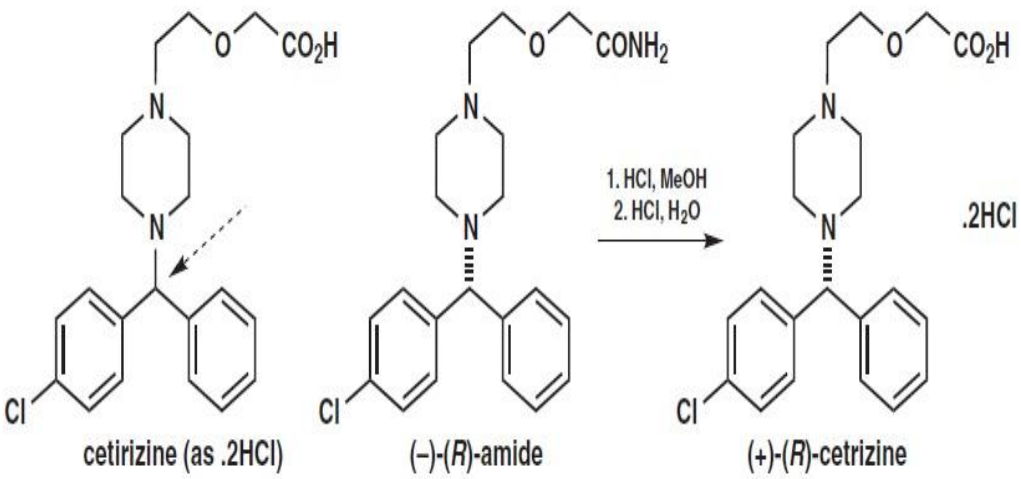


Fig. 1.34 Separate enantiomers were converted to cetirizine in two steps.

Chiral HPLC is the method of choice for analysing enantiomers and determining % ee. It can be used preparatively. In either application it is best to consult an expert when choosing columns and solvents.

2. MATERIALS AND METHODS

2.1 General Techniques and Materials

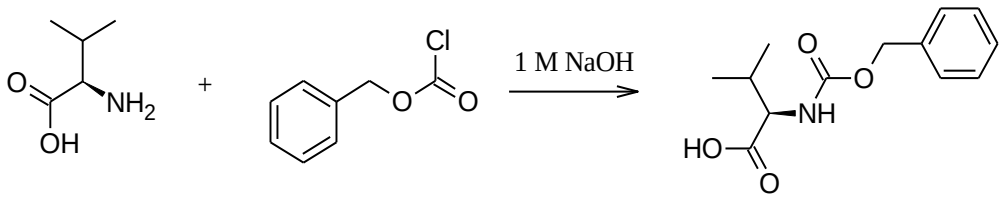
In spectroscopic studies IR spectra were recorded using a Mattson FTIR 1000. ^{1}H-NMR and ^{13}C-NMR spectra were carried out using a 400 MHz Varian NMR spectrometer. Melting points were recorded with an electro thermal digital melting points apparatus. All solvents distilled before use.

For TLC (thin layer chromatography) silica gel F_{254} (Merck 5554) precoated plates were used and for column chromatography (CC) Silica gel 60 (Merck 7743) was used. For UV active components, the spots were observed under the UV lamp for TLC.

L-tert-leucine (Alfa Aesar), L-isoleucine (Alfa Aesar), L-valine (Alfa Aesar), Benzyl chloroformate (Aldrich), 2-aminophenol (Merck), DCC (Aldrich), Di-tert-butyl dicarbonate (Aldrich), Sodium bicarbonate (Carlo-Erba), $Cu(OAc)_2.nH_2O$ (Carlo-Erba), Nitromethane (Aldrich), 2-bromobenzaldehyde (Aldrich), Borane-THF complex (Aldrich), 1,1'-Carbonyldiimidazole (Aldrich), Triethylamine (Merck), 85% Phosphoric acid (Carlo-Erba) were used as received.

2.2 Experiments

2.2.1 Synthesis of N-benzyloxycarbonyl-L-Valine



L-Valine Benzylchloroformate N-Benzyloxycarbonyl L-Valine

A solution containing 351.45 mg (3 mmol) of L-Valine in 3 ml of 1 M NaOH was cooled in an ice bath and treated with 0.47 ml (563 mg, 3.3 mmol) of benzylchloroformate, followed by slow addition of 3 ml of 1 M NaOH. The resulting mixture was allowed to warm up to ambient temperature and stirred overnight. The crude product was extracted with three 15 mL portions of diethyl ether, and the aqueous phase was acidified with 6 N HCl to pH < 4.0. The

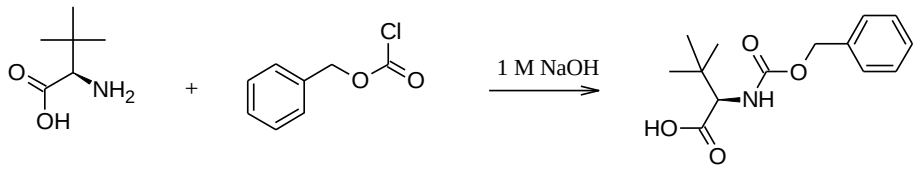
precipitate that developed was dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated in the rotary evaporator.

The reaction was monitored by TLC. The eluting solvent of TLC is 1:1 ethyl acetate/methanol.

N-Benzyloxycarbonyl-L-Valine was obtained in 41.2% yield.

The IR spectrum (fig. 3.1), ^{1}H-NMR (fig. 3.12) and ^{13}C-NMR (fig. 3.24) spectrums of N-benzyloxycarbonyl-L-Valine (compound 1) are shown in figures.

2.2.2 Synthesis of N-benzyloxycarbonyl-L-tert-leucine



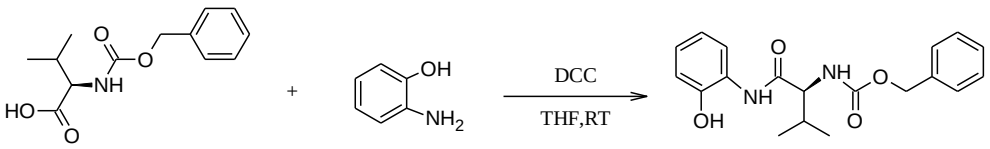
L-tert leucine Benzylchloroformate N-Benzyloxycarbonyl L-tert leucine

N-benzyloxycarbonyl-L-tert-leucine was synthesised according to the same procedure as described above.

L-tert-leucine (524.68 mg, 4mmol), benzylchloroformate (0.63 ml, 4.4 mmol), 8 ml 1 M NaOH were used. N-benzyloxycarbonyl-L-tert-leucine was obtained in 46% yield.

The IR spectrum (fig. 3.2), ^{1}H-NMR (fig. 3.13) and ^{13}C-NMR (fig. 3.25) spectrums of N-benzyloxycarbonyl-L-tert-leucine (compound 2) are shown in figures.

2.2.3 Synthesis of benzyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate



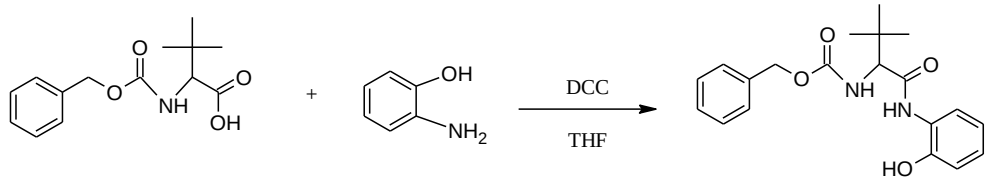
N-Benzyloxycarbonyl L-Valine | 2-aminophenol | benzyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of N-benzyloxycarbonyl-L-Valine (310.6 mg, 1.24 mmol) in THF (5 ml) were added 2-aminophenol (135.32 mg, 1.24 mmol) and a slight excess of N,N'-dicyclohexylcarbodiimide (274.42 mg, 1.33 mmol). This mixture was stirred at room temperature for 6 h. The insoluble N,N'-dicyclohexylurea was removed by filtration and the solvent was evaporated. Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate was obtained in 38.4% yield.

The IR spectrum (fig. 3.3), ^{1}H-NMR (fig. 3.14) and ^{13}C-NMR (fig. 3.26) spectrums of {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (compound 3) are shown in figures.

2.2.4 Synthesis of benzyl {1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate



N-Benzyloxycarbonyl L-tert leucine | 2-aminophenol | benzyl {1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

Benzyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutanyl}carbamate was synthesised according to the same procedure as described above.

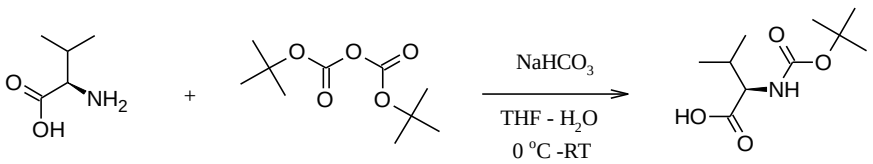
N-benzyloxycarbonyl-L-tert-leucine (132.64 mg, 0.5 mmol), 2-aminophenol (60.02 mg, 0.55 mmol), N,N'-dicyclohexylcarbodiimide (113.48 mg, 0.55 mmol), 10 ml THF were used.

Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

Benzyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutanyl}carbamate was obtained in 35.7% yield.

The IR spectrum (fig. 3.4), ^{1}H-NMR (fig. 3.15) and ^{13}C-NMR (fig. 3.27) spectrums of benzyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutanyl}carbamate (compound 4) are shown in figures.

2.2.5 Synthesis of N-tert-butyloxycarbonyl-L-Valine



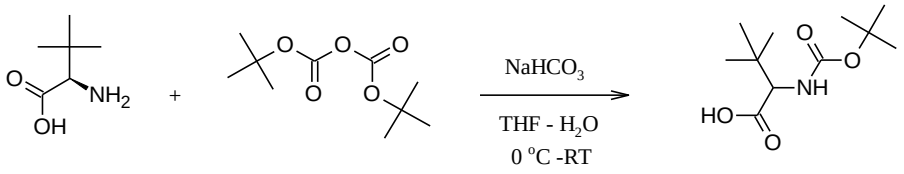
L-Valine di-tert-butyl dicarbonate N-tert-butyloxycarbonyl L-Valine

A mixture of L-Valine (468.6 mg, 4mmol) in 50 ml of a 1:1 mixture of THF/H_2O was added first $NaHCO_3$ (1344 mg, 16 mmol) and then di-tert-butyldicarbonate (1043.2 mg, 4.78 mmol). The reaction mixture was stirred at room temperature overnight and then the THF was removed in vacuo. The residue was adjusted to pH 2 by the addition of 6 M HCl. The acidic solution was extracted several times with ethyl acetate. The combined organic extracts were washed with H_2O and brine and then dried over anhydrous Na_2SO_4. Evaporation of solvent in vacuo gave the product by 91% yield.

The reaction was monitored by TLC. The eluting solvent of TLC is 1:1 ethyl acetate:methanol.

The IR spectrum (fig. 3.5), ^{1}H-NMR (fig. 3.16) and ^{13}C-NMR (fig. 3.28) spectrums of N-tert-butyloxycarbonyl-L-Valine (compound 5) are shown in figures.

2.2.6 Synthesis of N-tert-butyloxycarbonyl-L-tert-leucine



L-tert leucine di-tert-butyl dicarbonate N-tert-butyloxycarbonyl L-tert leucine

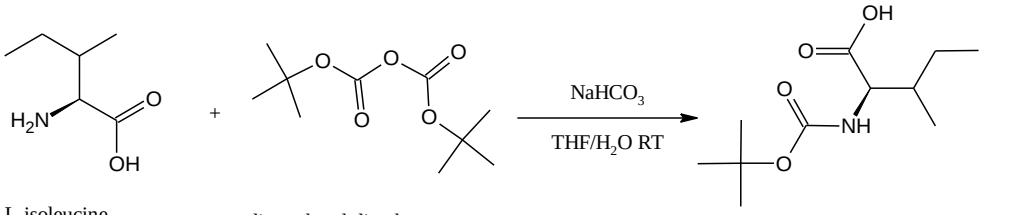
N-tert-butyloxycarbonyl-L-tert-leucine was synthesised according to the same procedure as described above.

L-tert-leucine (524.68 mg, 4 mmol), $NaHCO_3$ (1344 mg, 16 mmol), di-tert-butyldicarbonate (1043.23 mg, 4.78 mmol) were used.

N-tert-butyloxycarbonyl-L-tert-leucine was obtained in 96% yield.

The IR spectrum (fig. 3.6), ^{1}H-NMR (fig. 3.17) and ^{13}C-NMR (fig. 3.29) spectrums of N-tert-butyloxycarbonyl-L-tert-leucine (compound 6) are shown in figures.

2.2.7 Synthesis of N-tert-butyloxycarbonyl-L-isoleucine



L-isoleucine di-tert-butyl dicarbonate N-tert-butyloxycarbonyl-L-isoleucine

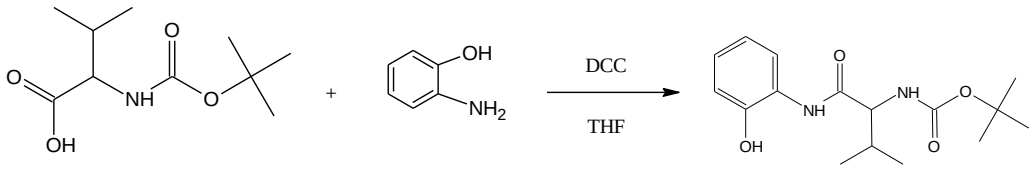
N-tert-butyloxycarbonyl-L-isoleucine was synthesized according to the same procedure as described above.

L-isoleucine (655.85 mg, 5 mmol), $NaHCO_3$ (1680 mg, 20 mmol), di-tert-butyldicarbonate (1305.1 mg, 5.98 mmol) were used.

N-tert-butyloxycarbonyl-L-isoleucine was obtained in 93% yield.

The IR spectrum (fig. 3.7) and ^{1}H-NMR (fig. 3.18) spectrum of N-tert-butyloxycarbonyl-L-isoleucine (compound 7) are shown in figures.

2.2.8 Synthesis of tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate



N-tert-butyloxycarbonyl L-Valine

2-aminophenol

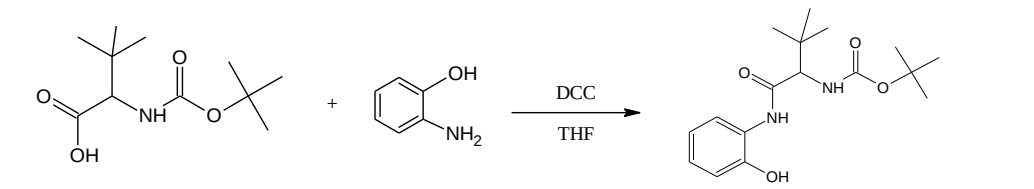
tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate

To a stirred solution of N-tert-butyloxycarbonyl-L-Valine (702.6 mg, 3.23 mmol) and 2-aminophenol (352.5 mg, 3.23 mmol) in THF (10 mL) was added dicyclohexylcarbodiimide (DCC, 732.5 mg, 3.55 mmol) at 0°C. The resulting mixture was allowed to warm up to ambient temperature and stirred overnight. Then the mixture was filtered. The filtrate was concentrated. Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-yl}carbamate was obtained in 57.3% yield.

The IR spectrum (fig. 3.8), ^{1}H-NMR (fig. 3.19) and ^{13}C-NMR (fig. 3.30) spectrums of tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-yl}carbamate (compound 8) are shown in figures.

2.2.9 Synthesis of tert-butyl {1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate



N-tert-butyloxycarbonyl-L-tert-leucine

2-aminophenol

tert-butyl {1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate was synthesized according to the same procedure as described above.

N-tert-butyloxycarbonyl-L-tert-leucine (231.3 mg, 1 mmol), 2-aminophenol (109.13 mg, 1 mmol), DCC (226.8 mg, 1.1 mmol) were used. Reaction carried out at room temperature for 6 h.

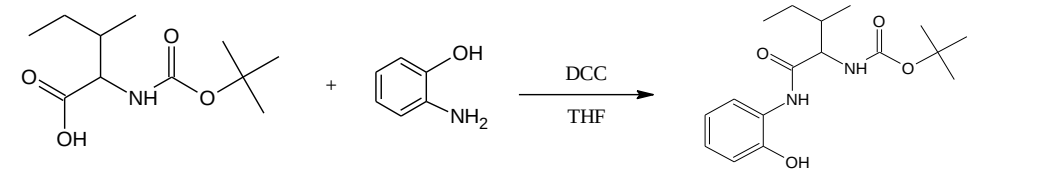
Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate was obtained in 21% yield.

The IR spectrum (fig. 3.9), ^{1}H-NMR (fig. 3.20) and ^{13}C-NMR (fig. 3.31) spectrums of tert-butyl{1-[(2-hydroxyphenyl)amino]-3,3-dimethyl-1-oxobutan-2-yl}carbamate (compound 9) are shown in figures.

2.2.10 Synthesis of *tert*-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate

2.2.10.1 First method



N-tert-butyloxycarbonyl-L-ısoleucine 2-aminophenol *tert*-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl -1-oxopentan-2-yl}carbamate

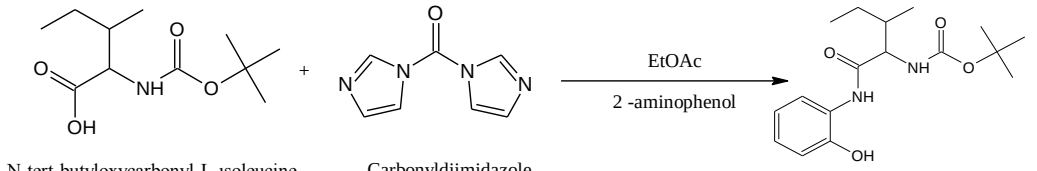
Tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate was synthesized according to the same procedure as described above.

N-tert-butyloxycarbonyl-L-isoleucine (151 mg, 0.65 mmol), 2-aminophenol (70.9 mg, 0.65 mmol), DCC (149 mg, 0.72 mmol), catalytic amount of triethylamine (0.72 mmol) were used.

Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate was obtained in 11% yield.

2.2.10.2 Second method



N-tert-butyloxycarbonyl-L-ısoleucine Carbonyldiimidazole *tert*-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl -1-oxopentan-2-yl}carbamate

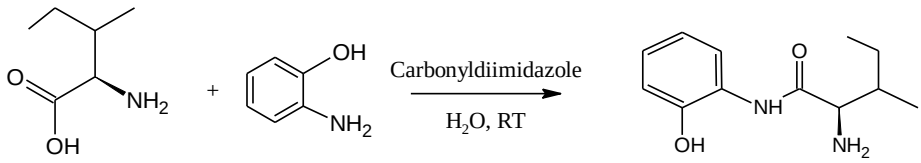
A mixture of N-tert-butyloxycarbonyl-L-isoleucine (219 mg, 0.95 mmol) and CDI (170.3 mg, 1.05 mmol) in EtOAc (10 ml) was stirred at reflux for 2 h. After that 2-aminophenol (103.7 mg, 0.95 mmol) was added and the mixture stirred at room temperature overnight. The reaction was monitored by TLC. The eluting solvent of TLC is 2:1 hegzan/ethyl acetate.

Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:2 ethyl acetate/hexane.

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate was obtained in 20% yield.

The ^{1}H-NMR (fig. 3.21) spectrum of tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate (compound 10) is shown in figures.

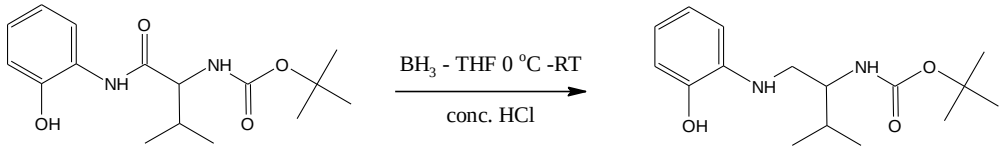
2.2.11 Synthesis of (2*R*)-2-amino-*N*-(2-hydroxyphenyl)-3-methylpentanamide



L-isoleucine 2-aminophenol (2*R*)-2-amino-*N*-(2-hydroxyphenyl)-3-methyl pentanamide

To solution of L-isoleucine (131.17 mg, 1 mmol) in H_2O (5 ml), CDI (194.58 mg, 1.2 mmol) was added at ambient temperature and the reaction mixture was stirred for 30 min. 2-aminophenol (130.95 mg, 1.2 mmol) was then added and the stirring continued for another 24 h at ambient temperature. The solvent was evaporated under reduced pressure to afford crude product. The product could not be isolated.

2.2.12 Synthesis of tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methylbutan-2-yl}carbamate



tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate

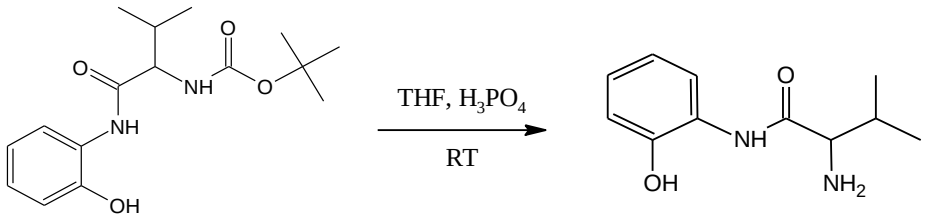
tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl butan-2-yl}carbamate

Tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (97 mg, 0.31 mmol) was dissolved in anhydrous THF (5 ml) under a slowly flowing argon gas. 1 M BH_3-THF solution (0.93 mmol, ~1 ml) was added dropwise to the stirred reaction at 0°C. The resulting mixture was allowed to warm up to ambient temperature and stirred for 16 h. Aqueous 6 M HCl solution (3 ml) was added dropwise and the reaction mixture was basified with aqueous saturated $NaHCO_3$ solution to pH=8 before being extracted with dichloromethane (3×15 ml). The organic phases collected were dried and filtered and the solvent was removed under reduced pressure. Column chromotography was carried out using silica gel with 1:4 ethyl acetate/hexane solvent system. TLC was carried out using 1:4 ethyl acetate/hexane.

Tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methylbutan-2-yl}carbamate was obtained in 56% yield.

The IR spectrum (fig. 3.10), ^{1}H-NMR (fig. 3.22) and ^{13}C-NMR (fig. 3.32) spectrums of tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methylbutan-2-yl}carbamate (compound 11) are shown in figures.

2.2.13 Synthesis of 2-amino-*N*-(2-hydroxyphenyl)-3-methylbutanamide



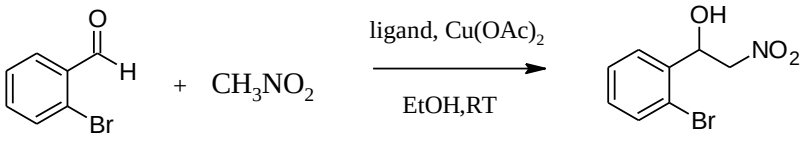
tert-butyl {1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate

2-amino-*N*-(2-hydroxyphenyl)-3-methyl butanamide

To a solution of tert-butyl{1-[(2-hydroxyphenyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (344.4 mg, 1.12 mmol) in THF (1 ml) at room temperature was added aqueous phosphoric acid (85 wt%, 3 ml) dropwise. The mixture was stirred for 4 h. Then 5 mL of water was added and the mixture was basified with aqueous saturated $NaHCO_3$ solution to pH=8. The mixture was then extracted with ethyl acetate (2×20 mL). The combined ethyl acetate phase was dried over sodium sulfate, concentrated in vacuo to give the product by 85% yield.

The IR spectrum (fig. 3.11), ^{1}H-NMR (fig. 3.23) and ^{13}C-NMR (fig. 3.33) spectrums of 2-amino-*N*-(2-hydroxyphenyl)-3-methylbutanamide (compound 12) are shown in figures.

2.2.14 General procedure for Henry reactions



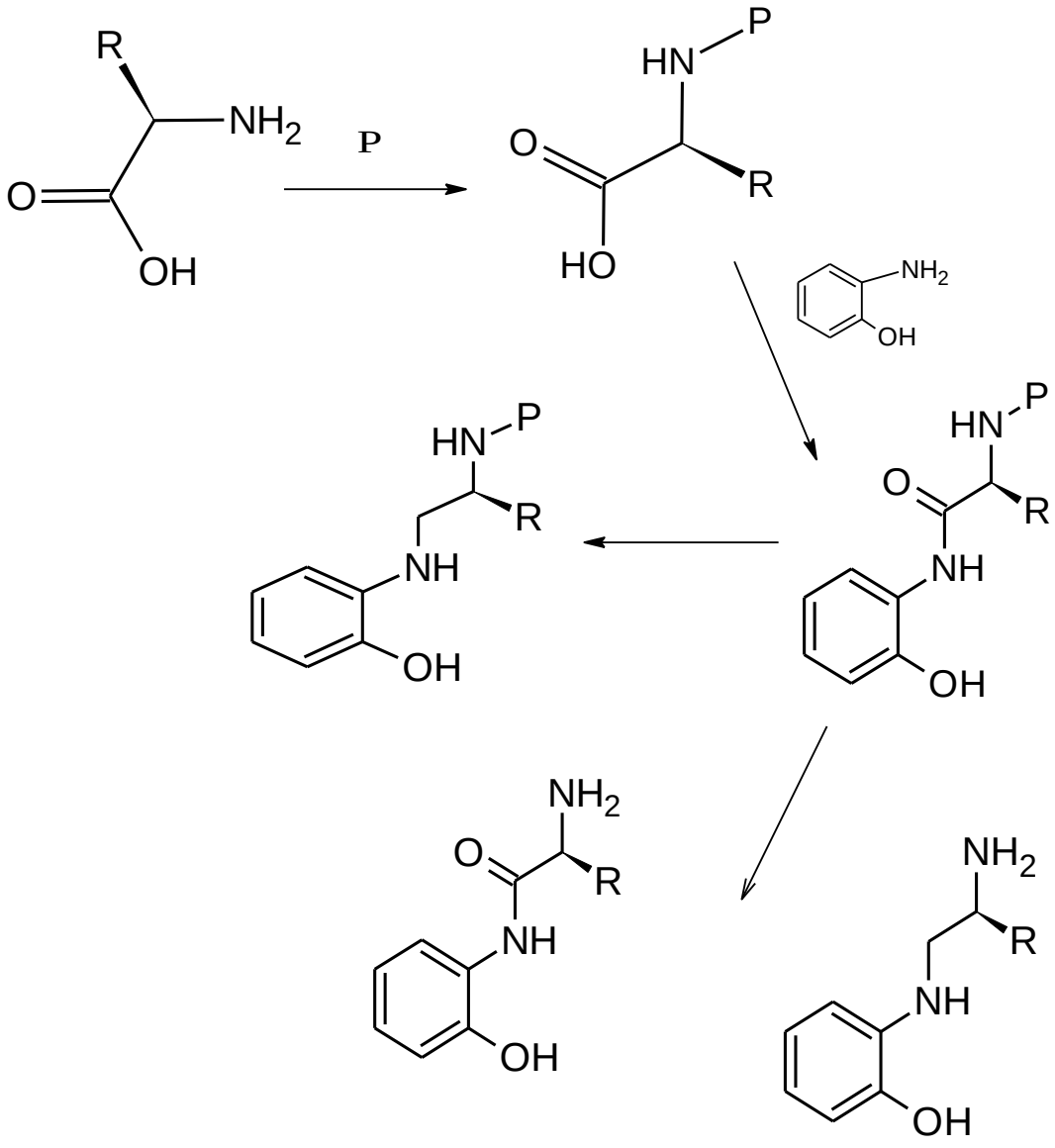
2-Bromobenzaldehyde nitromethane 1-(2-bromophenyl)-2-nitroethanol

Ligand (0.05 mmol) and $Cu(OAc)_2$ monohydrate (10 mg, 0.05 mmol) were placed in a round-bottomed flask. Ethanol (1.5 mL) was added and the mixture was stirred for 1 h. After that, nitromethane (0.27 mL, 5 mmol) and 2-bromobenzaldehyde (0.5 mmol) were added. After stirring for 48 h the volatile components were evaporated and the crude product was purified by column chromatography (5:1 hexane/ethyl acetate).

Results are shown in table 3.2.

3. RESULTS AND DISCUSSION

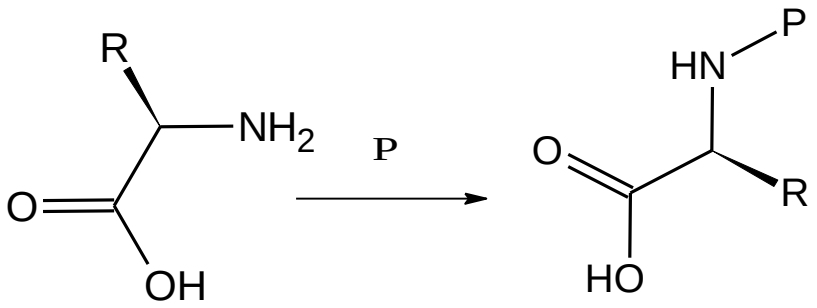
In this study we have been interested in preparing novel chiral tridentate ligands from simple amino acids. These are useful because tridentate ligands sometimes have good catalytic abilities. As can be seen below, our strategy involved initial protection of the NH_2 group of the amino acid followed by a coupling reaction with 2-aminophenol:



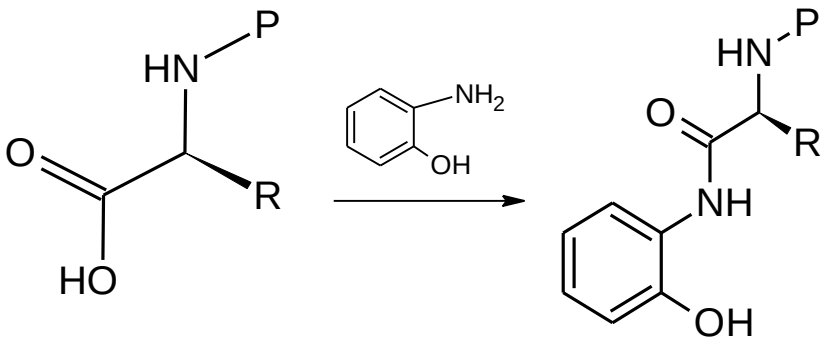
The products are important since they have significant functional groups on them. $–NH_2$ and –OH groups can be converted to other functional groups and it can be reached to give other polydentate ligands. Furthermore, the Schiff bases of the amines can be prepared. The most important feature of the products is that they contain a chiral centre. The chirality of the compounds give them a potential

role as key synthetic intermediates for a variety of a pharmaceutacally important compounds.

In the ligand synthesis, first we compared protecting groups benzyloxycarbonyl (Cbz) and tert-butyloxycarbonyl (Boc). We obtained better results and yields with Boc protecting group.



For 2-aminophenol addition to protected amino acids we tried to use CDI and DCC coupling agents:

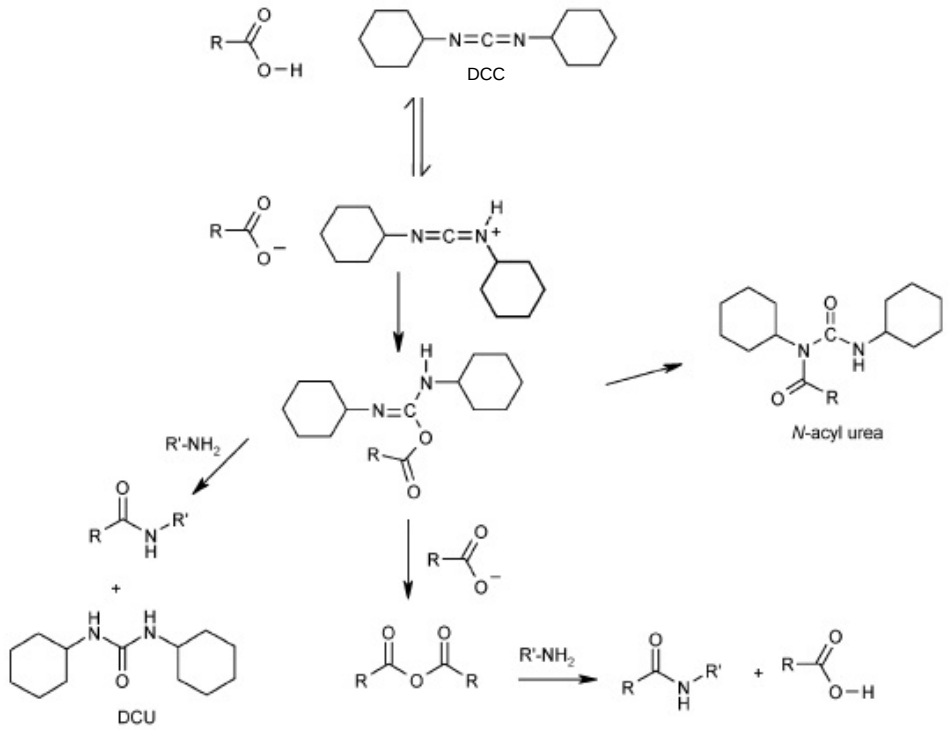


We did amide coupling reactions with CDI but the reactions gave side products and low yields. For this reason, we used DCC as a coupling agent for amide coupling. Conditions for DCC mediated reactions are given in Table 3.1 and the mechanism of the coupling reaction is given in the following scheme.

Table 3.1 Conditions for DCC mediated reactions.

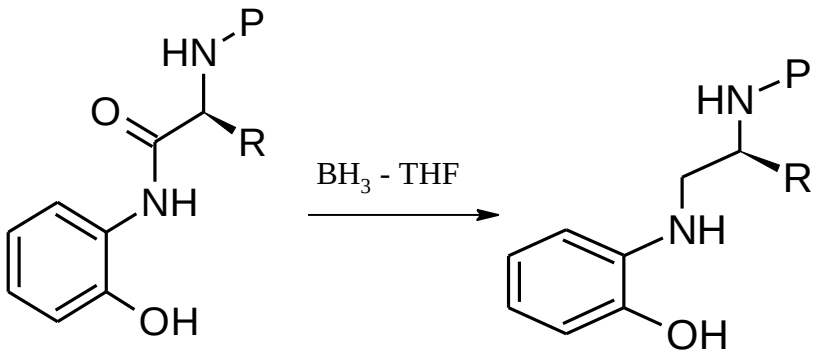
Protected amino acid	**Solvent**	**Temperature**	**Additive**	**Time**	**Yield**
N-Cbz-L-Valine	THF	RT	-	24 h	38%
N-Cbz-L-tertleucine	Dichloromethane	RT	-	24 h	35.7%
N-Boc-L-tertleucine	THF	RT	-	24 h	20%
N-Boc-L-isoleucine	THF	0°C-RT	triethylamine	24 h	10%
N-Boc-L-Valine	THF	RT	-	24 h	36%
N-Boc-L-Valine	THF	0°C-RT	DMAP	24 h	26%
N-Boc-L-Valine	THF	0°C-RT	-	24 h	57.3%

The best result in DCC coupling is 57.3% yield. Formation of unreactive N-acylurea can be considerably diminished by reacting the protected amino acid and DCC at 0°C. Thus the reaction yield is increased.

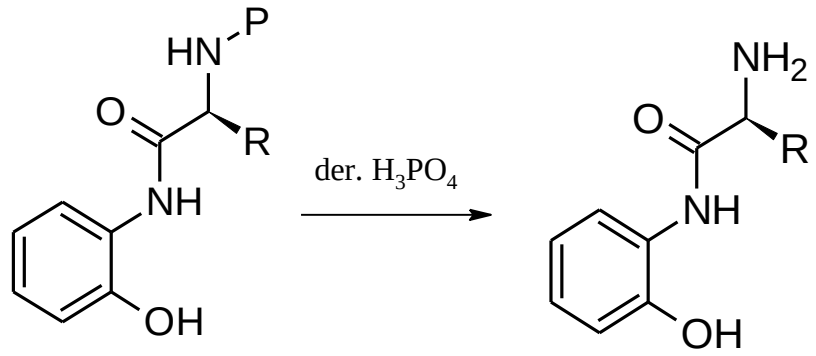


In a recent publication (Sharma and Jain, 2007), coupling reactions using CDI in water under neutral conditions were reported. Therefore we attempted the amidation reaction of 2-aminophenol in water under similar conditions with unprotected amino acids using CDI. However, we could not isolate the product and the reaction gave side products.

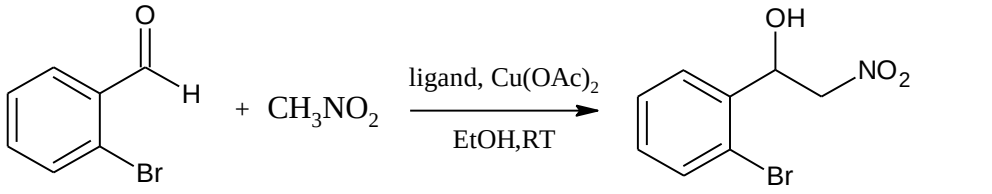
We were interested to find ways to modify the ligands, and first we looked for a way for reducing the amide without affecting the carbamate side. For this we used borane-tetrahydrofuran complex:



We were also interested in finding a method to remove the protection group, and for this purpose we used concentrated phosphoric acid:



Subsequently, we investigated the catalytic abilities of our ligands in the Henry Reaction with 2-bromobenzaldehyde in the presence of Cu(II) ions.

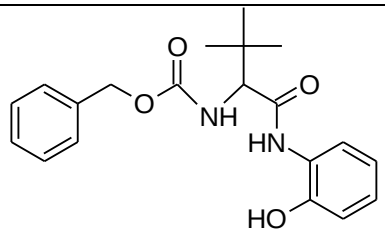
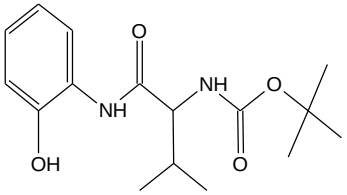
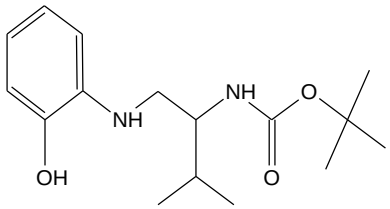
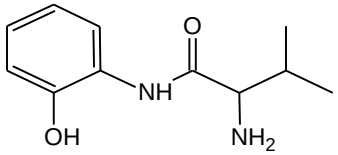


2-Bromobenzaldehyde

1-(2-bromophenyl)-2-nitroethanol

Although the desired product was obtained, the observed enantiomeric excess and yields were disappointing. The results of Henry reactions are given in Table 3.2

Table 3.2 Results of Henry Reactions.

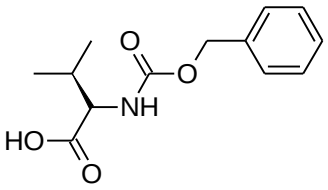
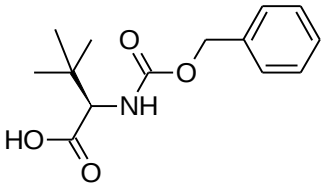
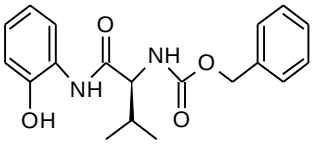
Ligand	Time	Yield	Ee%
	48 h	22%	racemic
	48 h	32%	racemic
	48 h	36%	3%
	48 h	40%	8%

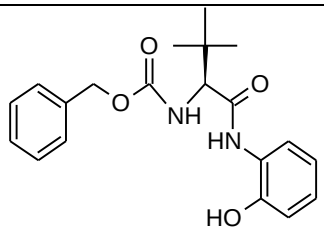
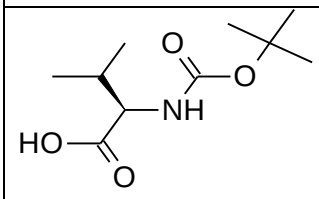
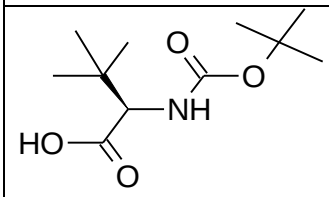
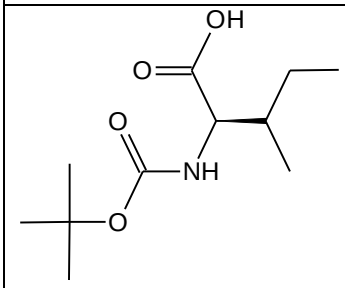
The products were characterized by IR, ^{1}H-NMR and ^{13}C-NMR.

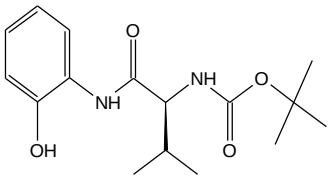
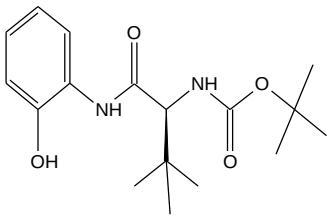
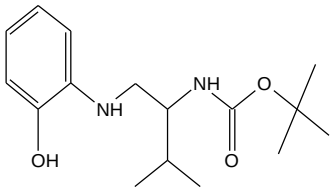
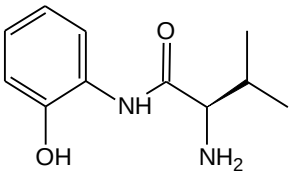
3.1 IR Spectra and Mode of Bonding

The IR spectra of all solid compounds were carried out as KBr pellets whereas liquid products were run by dissolving the compound in dichloromethane solution and applying the solution to a NaCl disc. The expected and observed data are recorded in Table 3.3 Data in the table indicate that the compound are the expected compounds.

Table 3.3 IR results of the products.

Compound	Substituent	Expected peak(cm^{-1})	Observed peak(cm^{-1})
	Carbonyl C=O	1800-1650	1716,1713
	Aromatic C=C	1600-1500	1530
	Aromatic =C-H	3080-3040	3067
	Amide N-H	3460-3050	3324
	C-O	1330-1050	1260,1215
	-OH	3600-2500	3000-2500
	Aliphatic $–CH_3$	2960-2850	2966
	Carbonyl C=O	1800-1650	1812,1711
	Aromatic C=C	1600-1500	1524
	Aromatic =C-H	3080-3040	3067
	Amide N-H	3460-3050	3402
	C-O	1330-1050	1238
	-OH	3600-2500	3200-2500
	Aliphatic $–CH_3$	2960-2850	2873,2967,2981
	Carbonyl C=O	1800-1650	1682,1637
	Aromatic C=C	1600-1500	1599
	Aromatic =C-H	3080-3040	3065
	Amide N-H	3460-3050	3296
	C-O	1330-1050	1247
	-OH	3600-2500	3200-2500
	Aliphatic $–CH_3$	2960-2850	2958,2924

	Carbonyl C=O Aromatic C=C Aromatic =C-H Amide N-H C-O -OH Aliphatic –CH_3	1800-1650 1600-1500 3080-3040 3460-3050 1330-1050 3600-2500 2960-2850	1703,1657 1500 3066 3296 1240 3500-3040 2964
	Carbonyl C=O Amide N-H C-O -OH Aliphatic –CH_3	1800-1650 3460-3050 1330-1050 3600-2500 2960-2850	1692 3392 1173 3200-2500 2970,2868
	Carbonyl C=O Amide N-H C-O -OH Aliphatic –CH_3	1800-1650 3460-3050 1330-1050 3600-2500 2960-2850	1749,1724 3373 1159 3200-2500 2981
	Carbonyl C=O Amide N-H C-O -OH Aliphatic –CH_3	1800-1650 3460-3050 1330-1050 3600-2500 2960-2850	1715 3324 1166 3200-2500 2969,2935,2879

	Carbonyl C=O	1800-1650	1689,1654
	Aromatic C=C	1600-1500	1599
	Aromatic =C-H	3080-3040	-
	Amide N-H	3460-3050	3293
	C-O	1330-1050	1168
	-OH	3600-2500	3200-2500
	Aliphatic $-CH_3$	2960-2850	2970,2932
	Carbonyl C=O	1800-1650	1690,1657
	Aromatic C=C	1600-1500	1500
	Aromatic =C-H	3080-3040	3065
	Amide N-H	3460-3050	3293
	C-O	1330-1050	1168
	-OH	3600-2500	3200-2500
	Aliphatic $-CH_3$	2960-2850	2969,2923,2868
	Carbonyl C=O	1800-1650	1682
	Aromatic C=C	1600-1500	1609
	Aromatic =C-H	3080-3040	3054
	Amide N-H	3460-3050	3340
	C-O	1330-1050	1171
	-OH	3600-2500	3200-2500
	Aliphatic $-CH_3$	2960-2850	2964,2925,2873
	Carbonyl C=O	1800-1650	1672
	Aromatic C=C	1600-1500	1596
	Aromatic =C-H	3080-3040	-
	Amide N-H	3460-3050	3276
	$-NH_2$	3500-3300	2963
	-OH	3600-2500	3200-2500
	Aliphatic $-CH_3$	2960-2850	2873,2725

3.2 ^{1}H-NMR Spectroscopic Studies

3.2.1 Compound 1

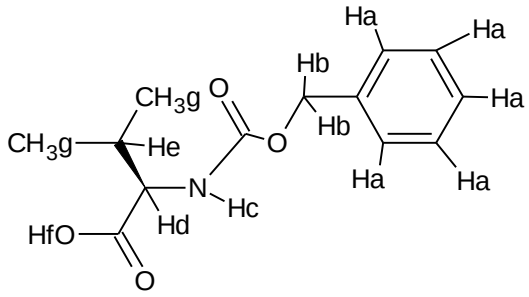


Table 3.4 ^{1}H NMR spectral data of compound 1

H	δ (ppm)	J (Hz)
H_a	7,32	s
H_b	5,12	s
H_c	5,24	8.8 d
H_d	4,33	4.8;8.8(dd)
H_e	2,22	m
H_f	-	-
H_g	1,01;0.94	6.4(d)

3.2.2 Compound 2

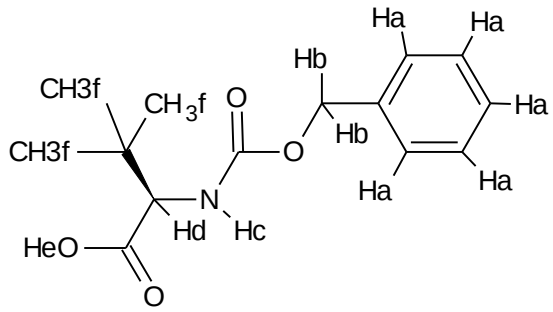


Table 3.5 ^{1}H NMR spectral data of compound 2

H	**δ (ppm)**	**J (Hz)**
H_a	7,31	s
H_b	5,09;5,03	11.5 d
H_c	5,29	8.8 d
H_d	4,16	8.8 d
H_e	-	-
H_f	1,05	s

3.2.3 Compound 3

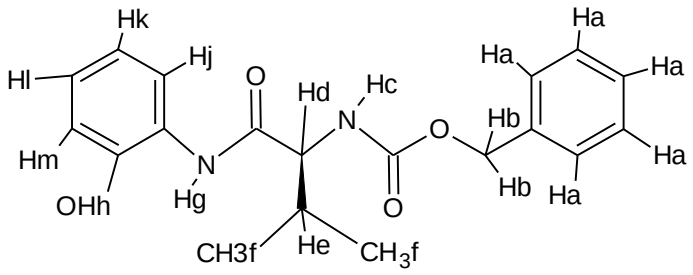


Table 3.6 ^{1}H NMR spectral data of compound 3

H	δ (ppm)	J (Hz)
H_a	7,25	s
H_b	5,09;5,01	12 d
H_c	5,80	9.2 d
H_d	4,29	-
H_e	2,13	m
H_f	1,01;0,99	4.4(d)
H_g	8,56	s
H_h	8,91	s
H_j	7,02	m
H_k	6,69	m
H_l	7,04	m
H_m	6,92	7.2 d

3.2.4 Compound 4

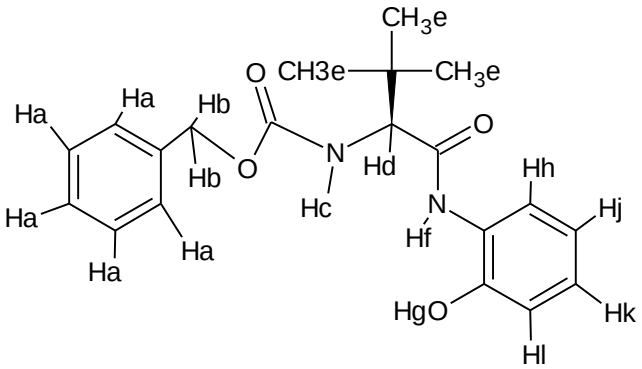


Table 3.7 ^{1}H NMR spectral data of compound 4

H	δ (ppm)	J (Hz)
H_a	7,25	s
H_b	5,09;4,98	12 d
H_c	5,80	9.6 d
H_d	4,37	9.6 d
H_e	1,04	s
H_f	8,42	s
H_g	8,85	s
H_h	7,01	m
H_j	6,69	m
H_k	7,04	m
H_l	6,94	7.2 d

3.2.5 Compound 5

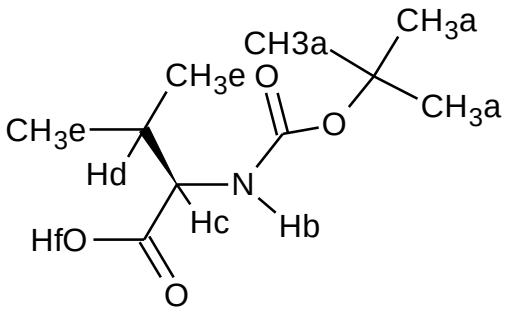


Table 3.8 ^{1}H NMR spectral data of compound 5

H	δ (ppm)	J (Hz)
H_a	1,42	s
H_b	-	-
H_c	3,83	4.8 d
H_d	2,06	m
H_e	0,92;0,85	6.4 d
H_f	8,53	s

3.2.6 Compound 6

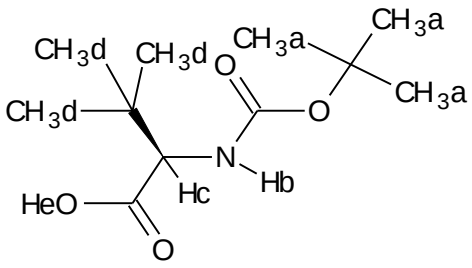


Table 3.9 ^{1}H NMR spectral data of compound 6

H	δ (ppm)	J (Hz)
H_a	1,44	s
H_b	-	-
H_c	3,94	s
H_d	1,07	s
H_e	-	-

3.2.7 Compound 7

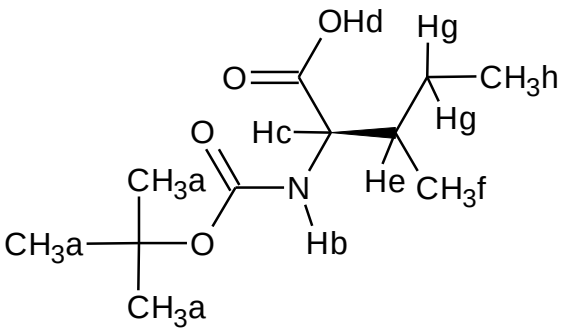


Table 3.10 ^{1}H NMR spectral data of compound 7

H	δ (ppm)	J (Hz)
H_a	1,43	s
H_b	6,46	s
H_c	4,08	7.2 d
H_d	6,49	s
H_e	1,83	m
H_f	0,92	6.8 d
H_g	1,48;1,35;1,22	m
H_h	0,89	8 t

3.2.8 Compound 8

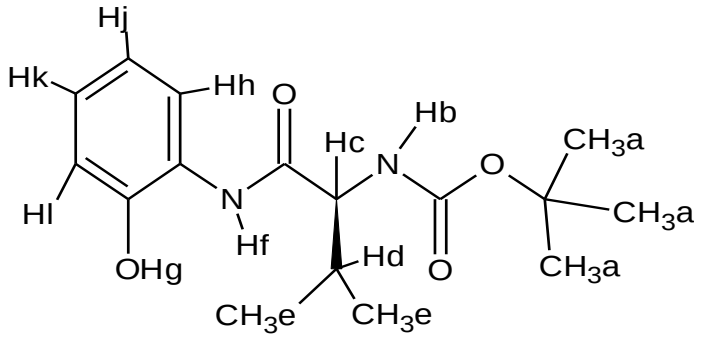


Table 3.11 ^{1}H NMR spectral data of compound 8

H	**δ (ppm)**	**J (Hz)**
H_a	1,43	s
H_b	4,18	s
H_c	5,39	8.8 d
H_d	2,19	m
H_e	1,03;1,00	6.8 d
H_f	8,78	s
H_g	8,85	s
H_h	7,12	1.2;8 dd
H_j	6,77	m
H_k	7,05	m
H_l	6,95	m

3.2.9 Compound 9

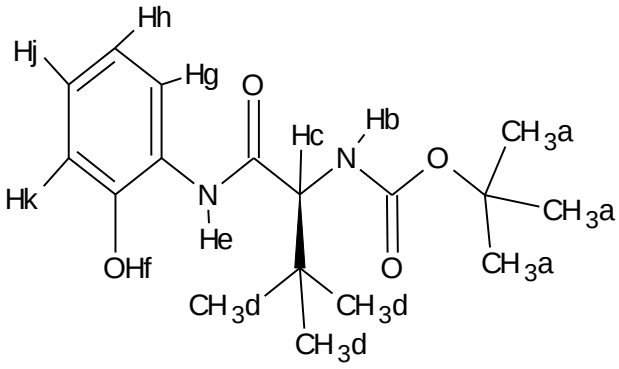


Table 3.12 ^{1}H NMR spectral data of compound 9

H	δ (ppm)	J (Hz)
H_a	1,42	s
H_b	5,44	s
H_c	4,19	s
H_d	1,08	s
H_e	8,60	s
H_f	8,67	s
H_g	7,15	7.6 d
H_h	6,96	7.2 d
H_j	7,05	8 t
H_k	6,77	7.2 t

3.2.10 Compound 10

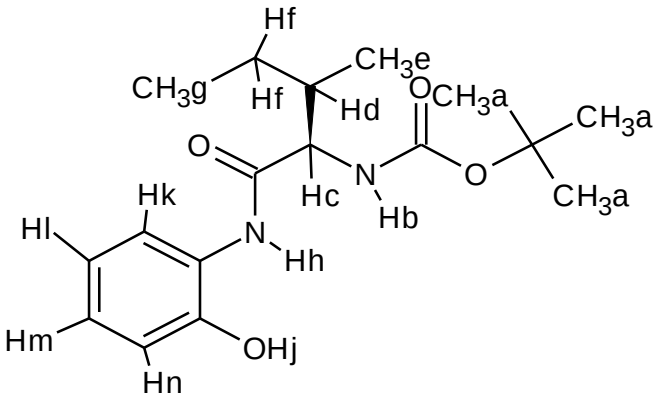


Table 3.13 ^{1}H NMR spectral data of compound 10

H	**δ (ppm)**	**J (Hz)**
H_a	1,44	s
H_b	5,30	s
H_c	4,21	-
H_d	1,80	m
H_e	1,00	6.8 d
H_f	1,22	m
H_g	0,93	7.6 t
H_h	7,93	s
H_j	8,78	s
H_k	7,09	8 d
H_l	6,94	7.6 d
H_m	7,05	6.8 t
H_n	6,77	7.6 t

3.2.11 Compound 11

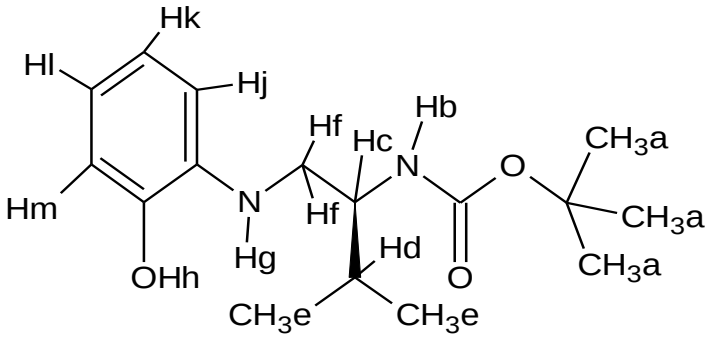


Table 3.14 ^{1}H NMR spectral data of compound 11

H	δ (ppm)	J (Hz)
H_a	1,43	s
H_b	4,61	s
H_c	3.04	m
H_d	1,84	m
H_e	0,94;0,91	6.8 d
H_f	3,19;3,61	-
H_g	-	-
H_h	7.24	s
H_j	6,58	m
H_k	6,54	m
H_l	6,80	m
H_m	6,74	m

3.2.12 Compound 12

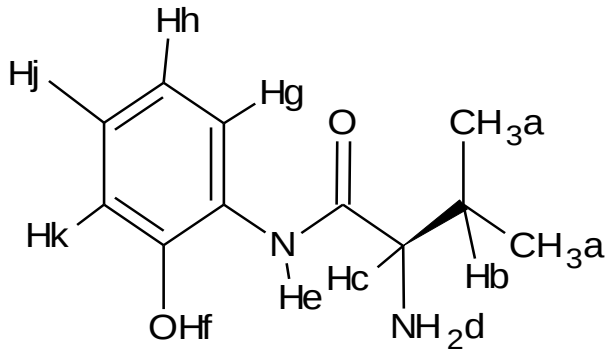


Table 3.15 ^{1}H NMR spectral data of compound 12

H	**δ (ppm)**	**J (Hz)**
H_a	1,05;0,88	7.2 d
H_b	2,45	m
H_c	3,46	3.6 d
H_d	-	-
H_e	-	-
H_f	9,80	s
H_g	7,09	m
H_h	6,84	m
H_j	7,00	m
H_k	6,93	m

3.3 ^{13}C-NMR Spectroscopic Studies

3.3.1 Compound 1

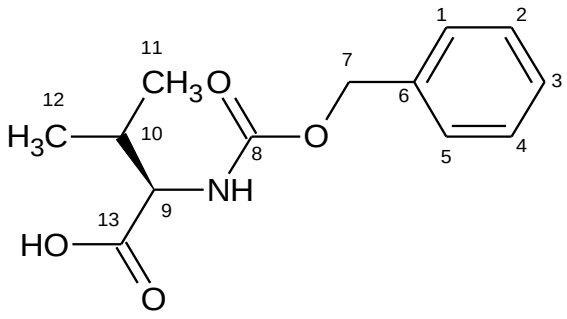


Table 3.16 ^{13}C-NMR spectral data of the compound 1

C	Compound-1
$C_{1,2,3,4,5,6}$	128,35-128,46-128.77-128,46-128,35-136,37
C_7	67,44
C_8	156,63
C_9	59,12
C_{10}	31,24
$C_{11,12}$	17,59-19,20
C_{13}	176

3.3.2 Compound 2

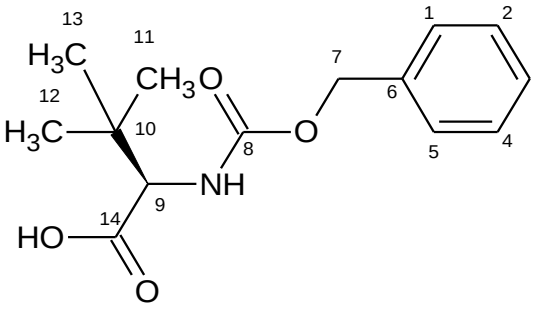


Table 3.17 ^{13}C-NMR spectral data of the compound 2

C	Compound-2
$C_{1,2,3,4,5,6}$	128,65-128,80-128,53-128,80-128,65-136,23
C_7	67,58
C_8	156,31
C_9	63,23
C_{10}	35,16
$C_{11,12,13}$	26,65
C_{14}	167,31

3.3.3 Compound 3

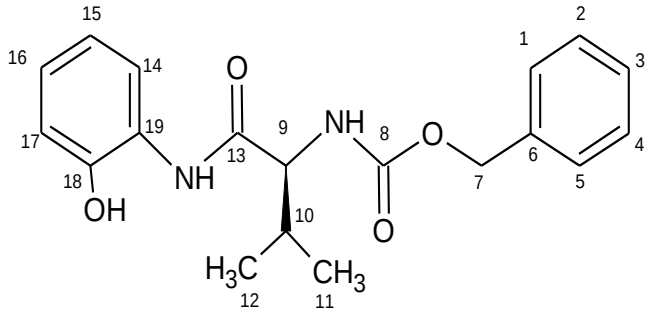


Table 3.18 ^{13}C-NMR spectral data of the compound 3

C	Compound-3
$C_{1,2,3,4,5,6}$	128,58-128,83-128,26-128,83-128,58-136,01
C_7	67,79
C_8	156,99
C_9	41,02
$C_{10,11,12}$	31,12-19,47-18,27
C_{13}	171,53
$C_{14,15,16,17,18,19}$	122,72-120,69-127,42-119,58-148,86-125,35

3.3.4 Compound 4

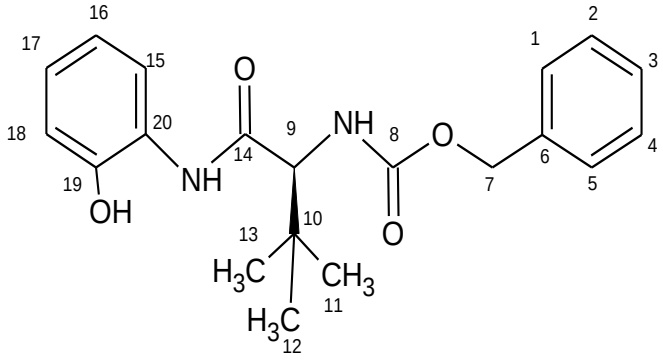


Table 3.19 ^{13}C-NMR spectral data of the compound 4

C	Compound-4
$C_{1,2,3,4,5,6}$	128,10-128,76-128,50-128,76-128,10-135,90
C_7	67,75
C_8	157,28
C_9	63,31
C_{10}	35,06
$C_{11,12,13}$	26,78
C_{14}	170,98
$C_{15,16,17,18,19,20}$	120,64-122,78-127,38-119,62-148,99-125,42

3.3.5 Compound 5

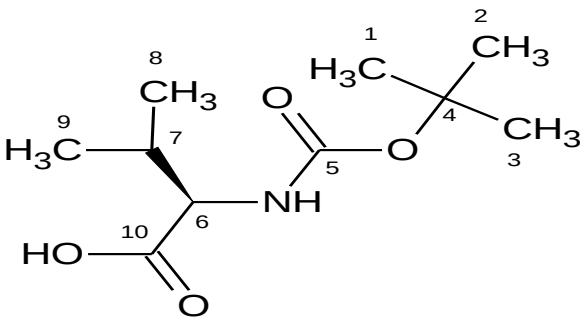


Table 3.20 ^{13}C-NMR spectral data of the compound 5

C	Compound-5
$C_{1,2,3}$	27,90
C_4	79,42
C_5	156,84
C_6	59,17
$C_{7,8,9}$	30,82-17,33-18,74
C_{10}	174,56

3.3.6 Compound 6

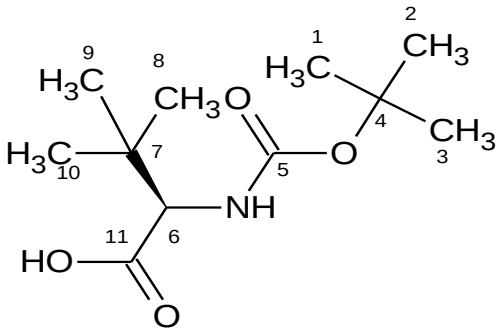


Table 3.21 ^{13}C-NMR spectral data of the compound 6

C	Compound-6
$C_{1,2,3}$	27,61
C_4	79,46
C_5	156,79
C_6	62,30
C_7	33,75
$C_{8,9,10}$	25,98
C_{11}	173,78

3.3.7 Compound 8

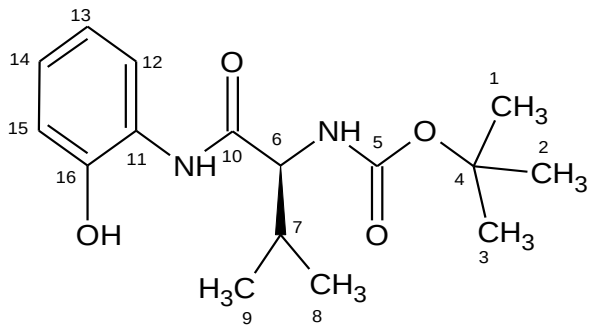


Table 3.22 ^{13}C-NMR spectral data of the compound 8

C	Compound-8
$C_{1,2,3}$	28,52
C_4	81,03
C_5	156,73
C_6	60,97
$C_{7,8,9}$	31,12-19,52-18,49
C_{10}	172,12
$C_{11,12,13,14,15,16}$	125,51-122,66-120,56-127,12-119,12-148,73

3.3.8 Compound 9

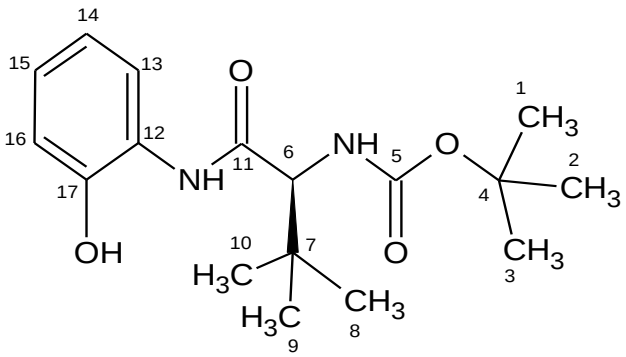


Table 3.23 ^{13}C-NMR spectral data of the compound 9

C	Compound-9
$C_{1,2,3}$	28,56
C_4	77,55
C_5	156,76
C_6	63,07
C_7	34,77
$C_{8,9,10}$	26,83
C_{11}	171,22
$C_{12,13,14,15,16,17}$	125,51-120,56-122,60-126,98-118,89-148,60

3.3.9 Compound 11

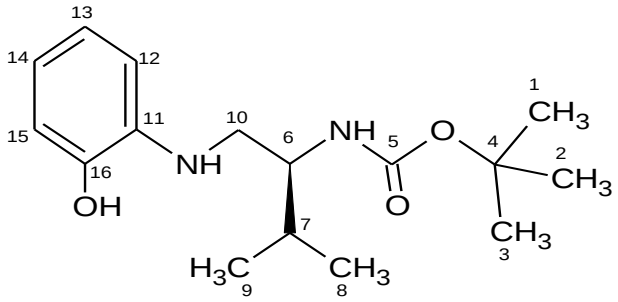


Table 3.24 ^{13}C-NMR spectral data of the compound 11

C	Compound-11
$C_{1,2,3}$	28,63
C_4	80,00
C_5	157,11
C_6	56,07
C_7	30,63
$C_{8,9}$	18,05-19,81
C_{10}	47,36
$C_{11,12,13,14,15,16}$	121,19-110,00-117,83-114,77-111,96-144,33

3.3.10 Compound 12

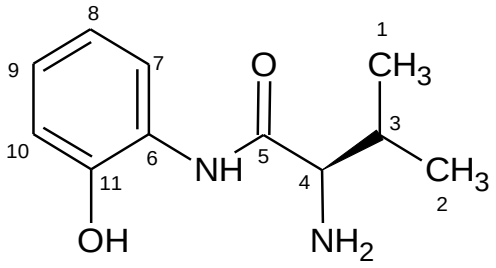


Table 3.25 ^{13}C-NMR spectral data of the compound 12

C	Compound-12
$C_{1,2}$	18,67-16,08
C_3	31,94
C_4	60,86
C_5	174,63
$C_{6,7,8,9,10,11}$	125,84-121,49-119,37-125,10-115,55-148,16

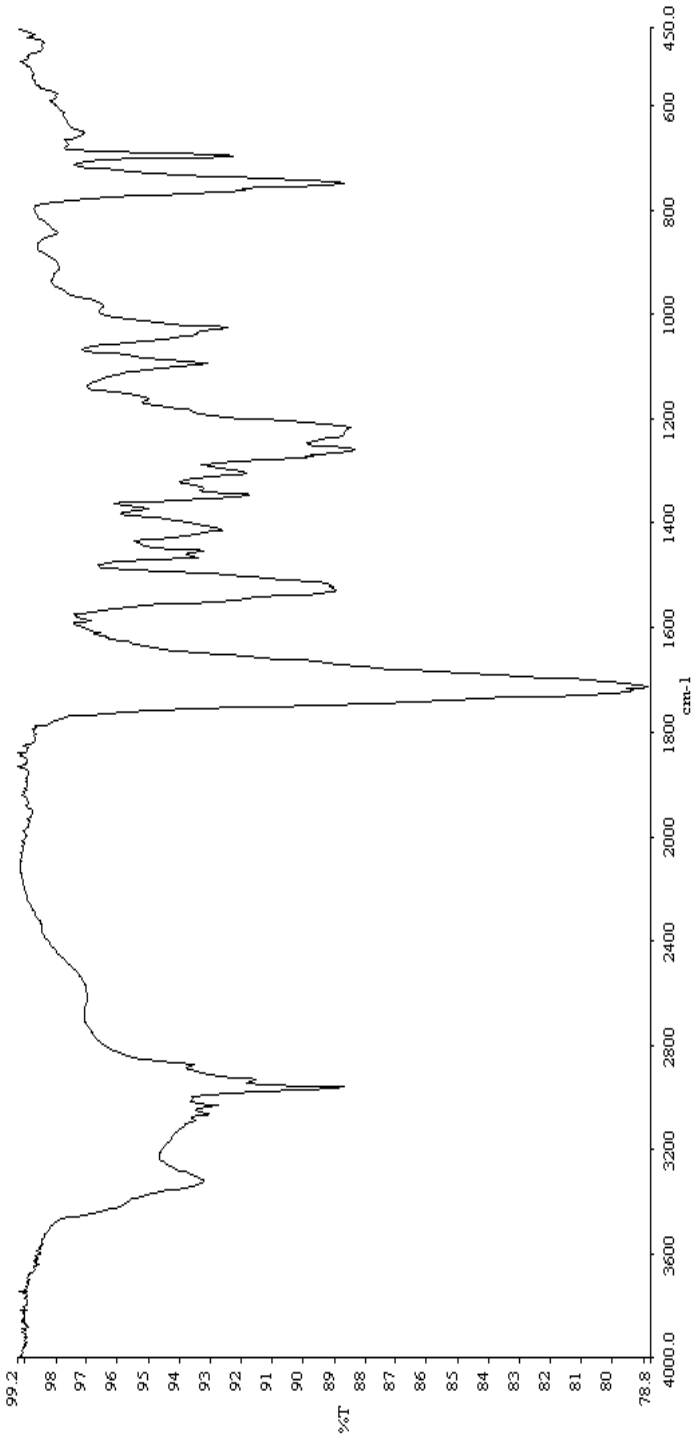


Fig. 3.1 The IR spectrum of Compound 1

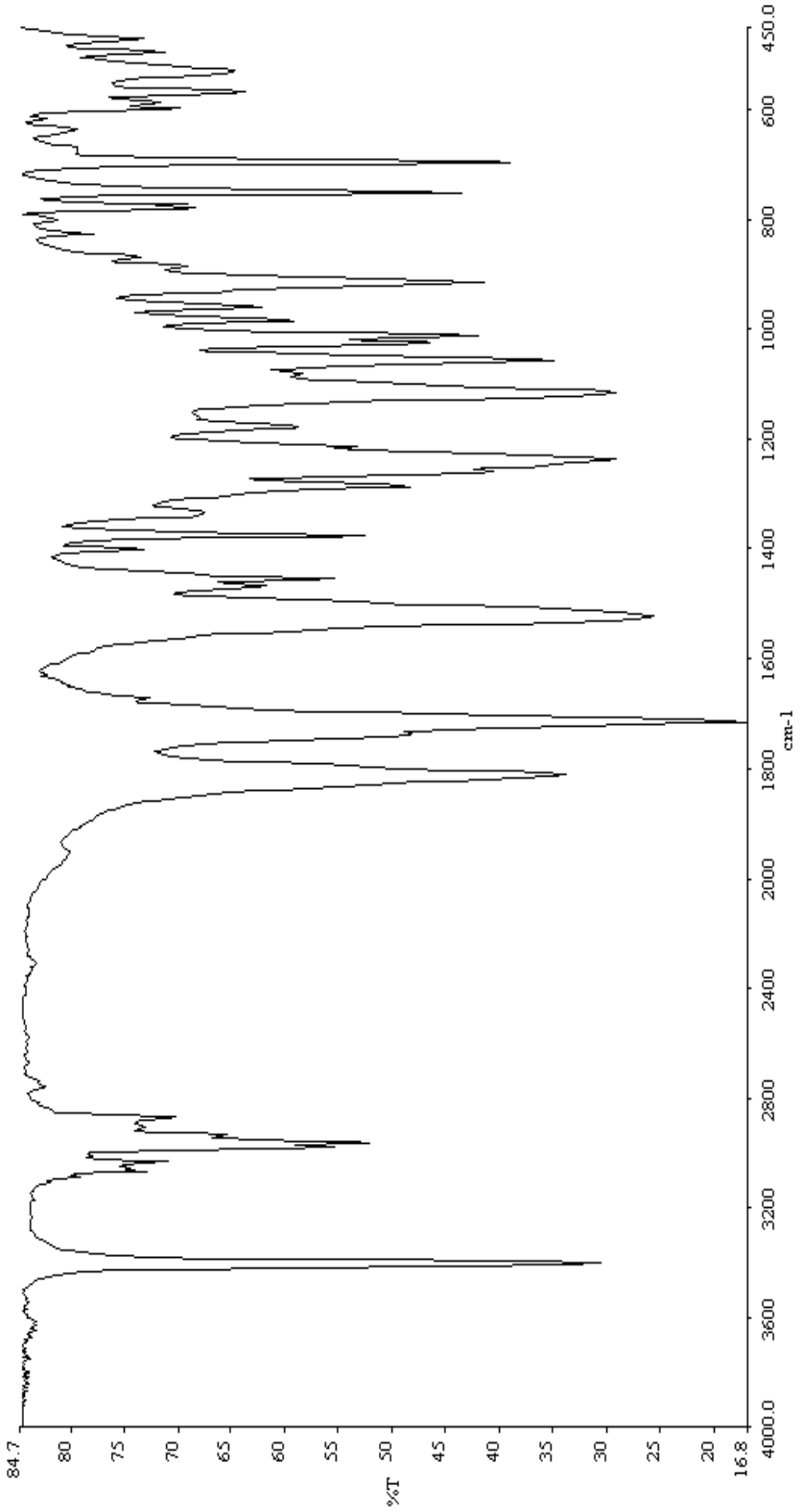


Fig. 3.2 The IR spectrum of Compound 2

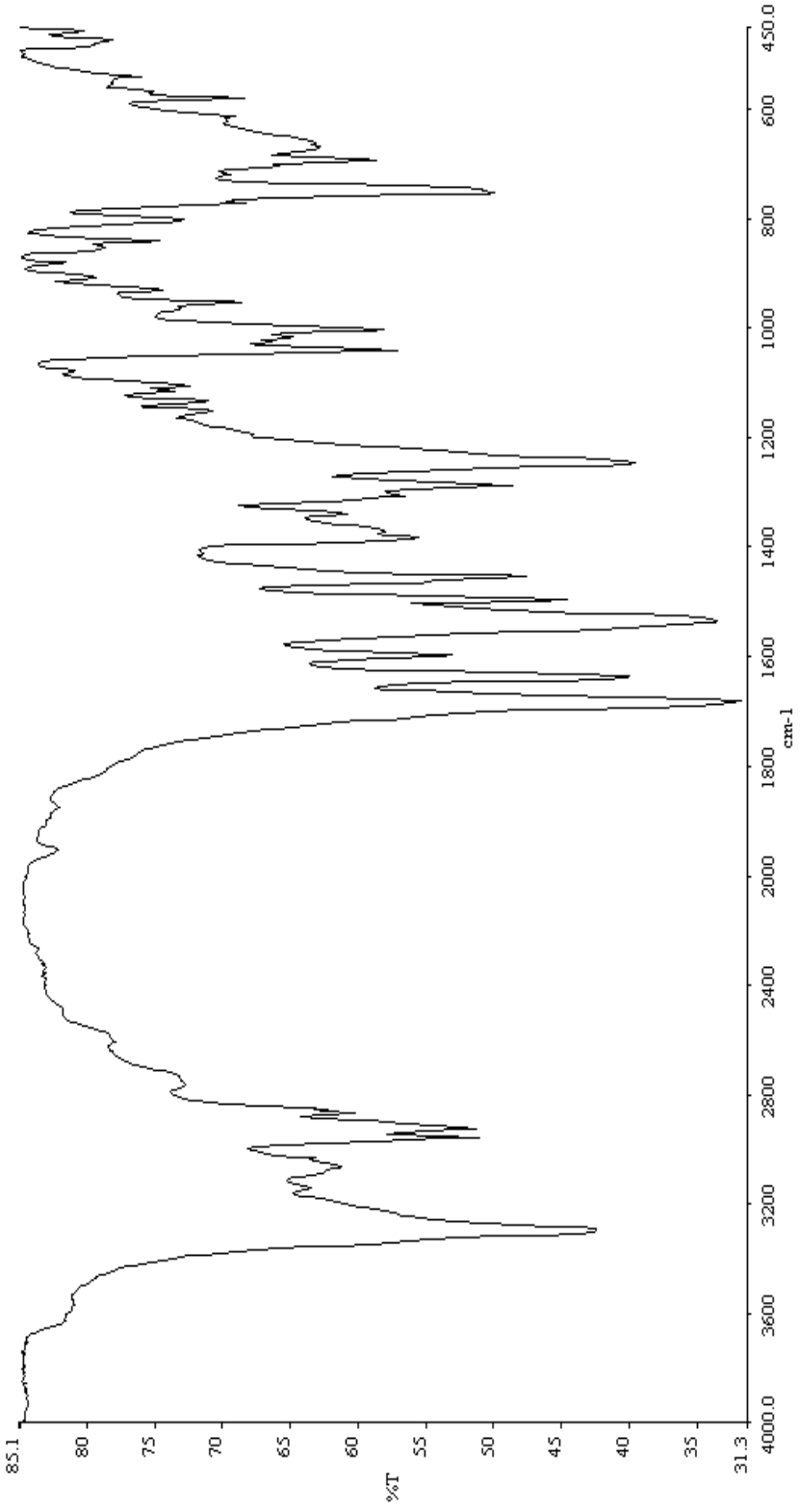


Fig. 3.3 The IR spectrum of Compound 3

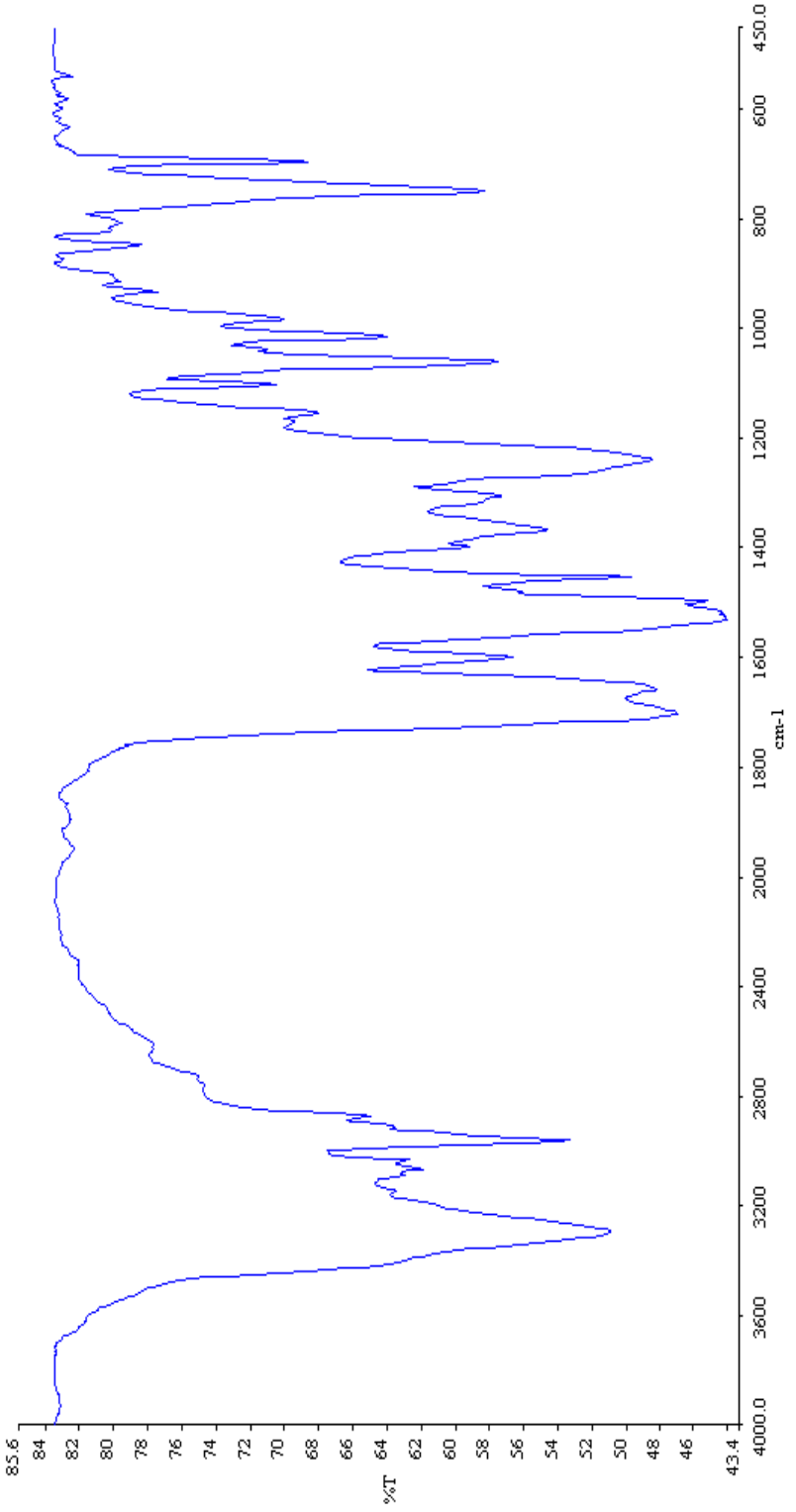


Fig. 3.4 The IR spectrum of Compound 4

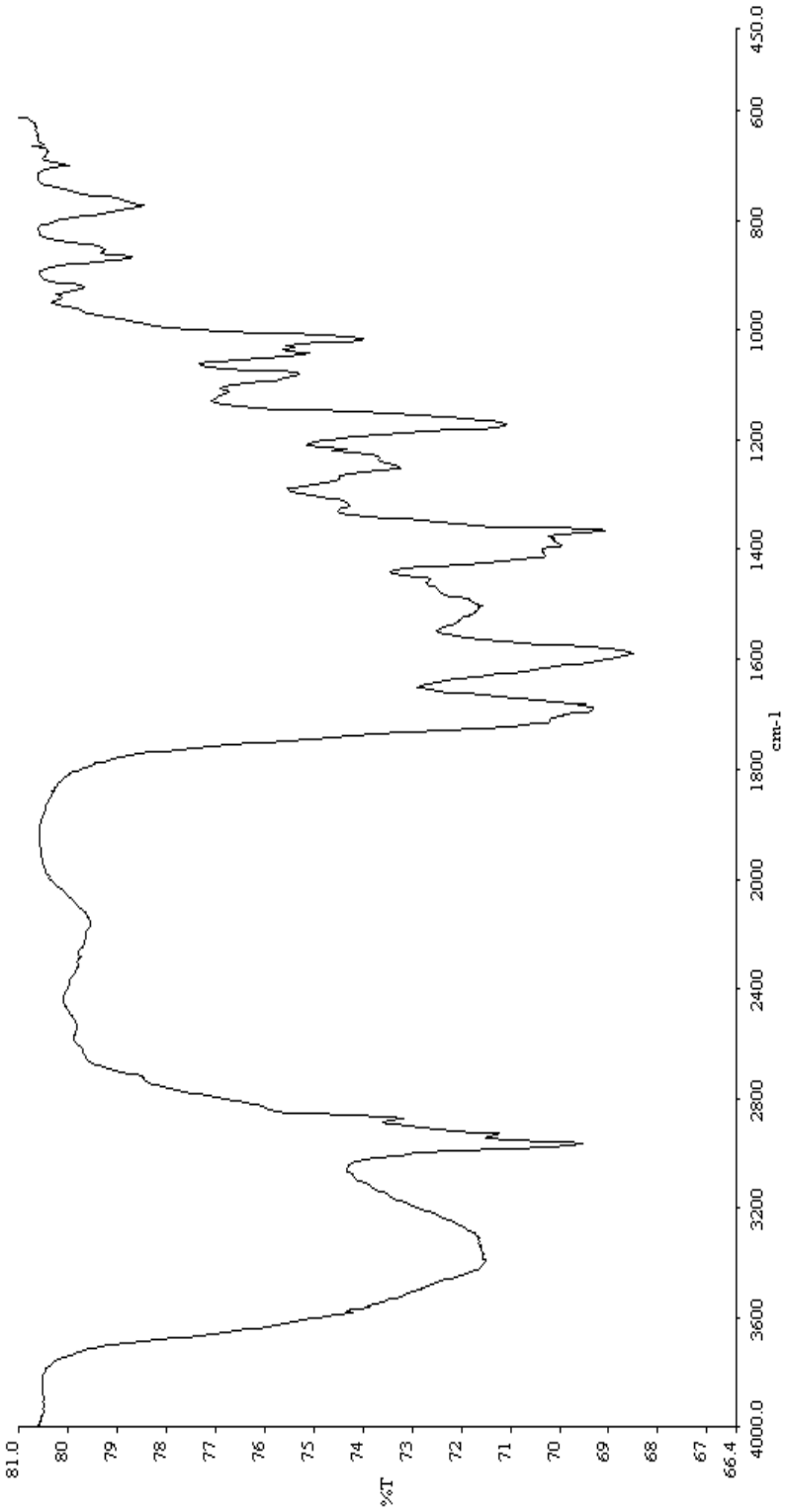


Fig. 3.5 The IR spectrum of Compound 5

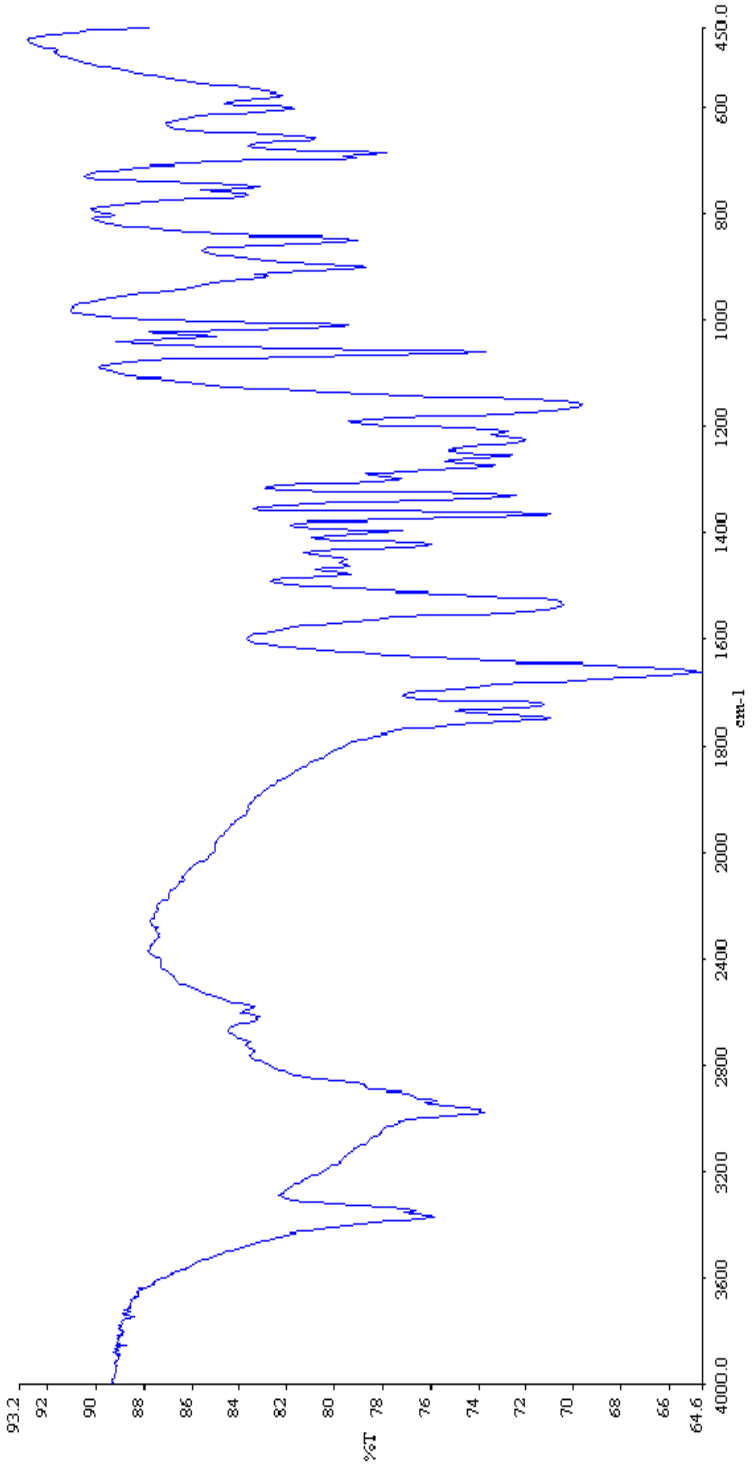


Fig. 3.6 The IR spectrum of Compound 6

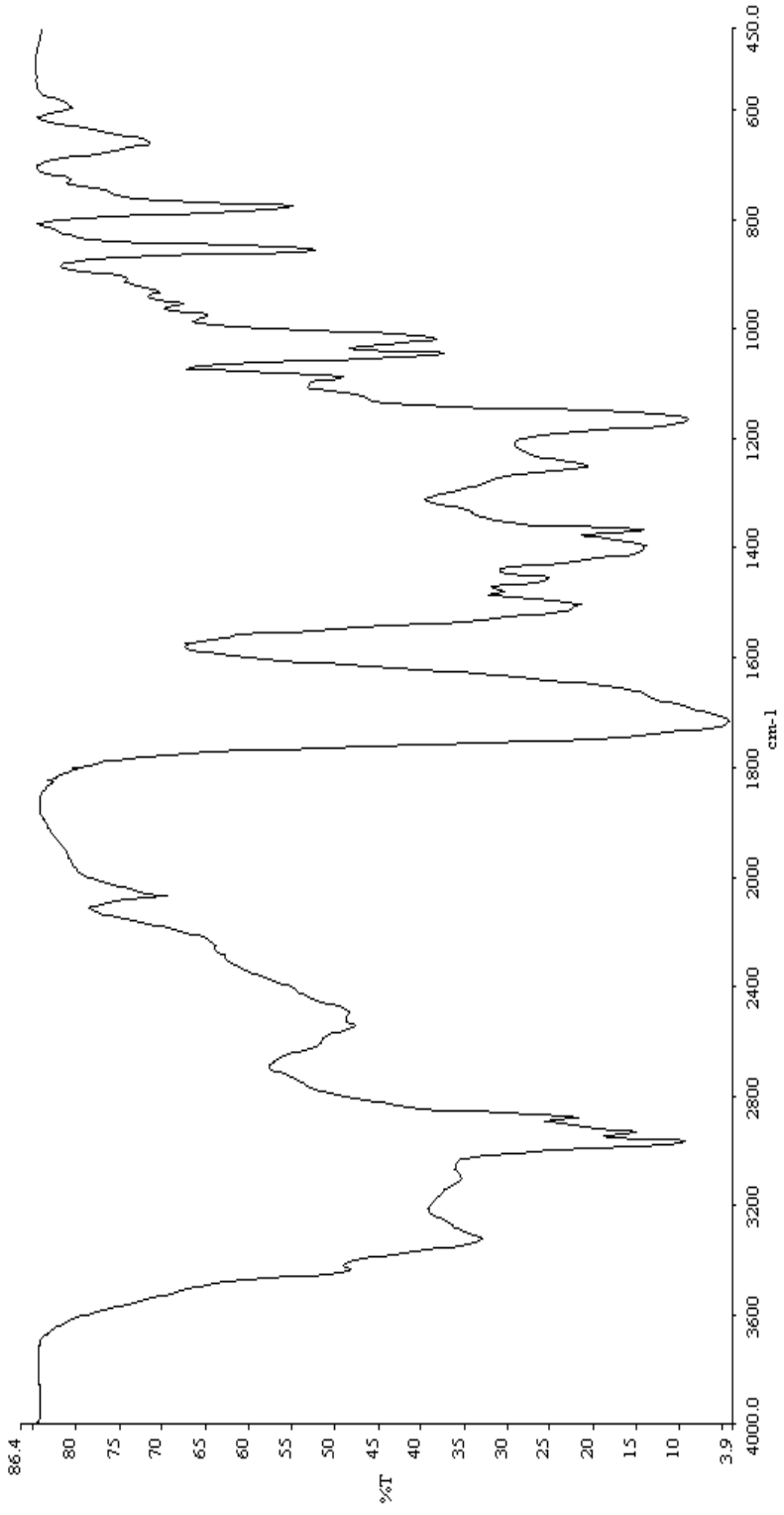


Fig. 3.7 The IR spectrum of Compound 7

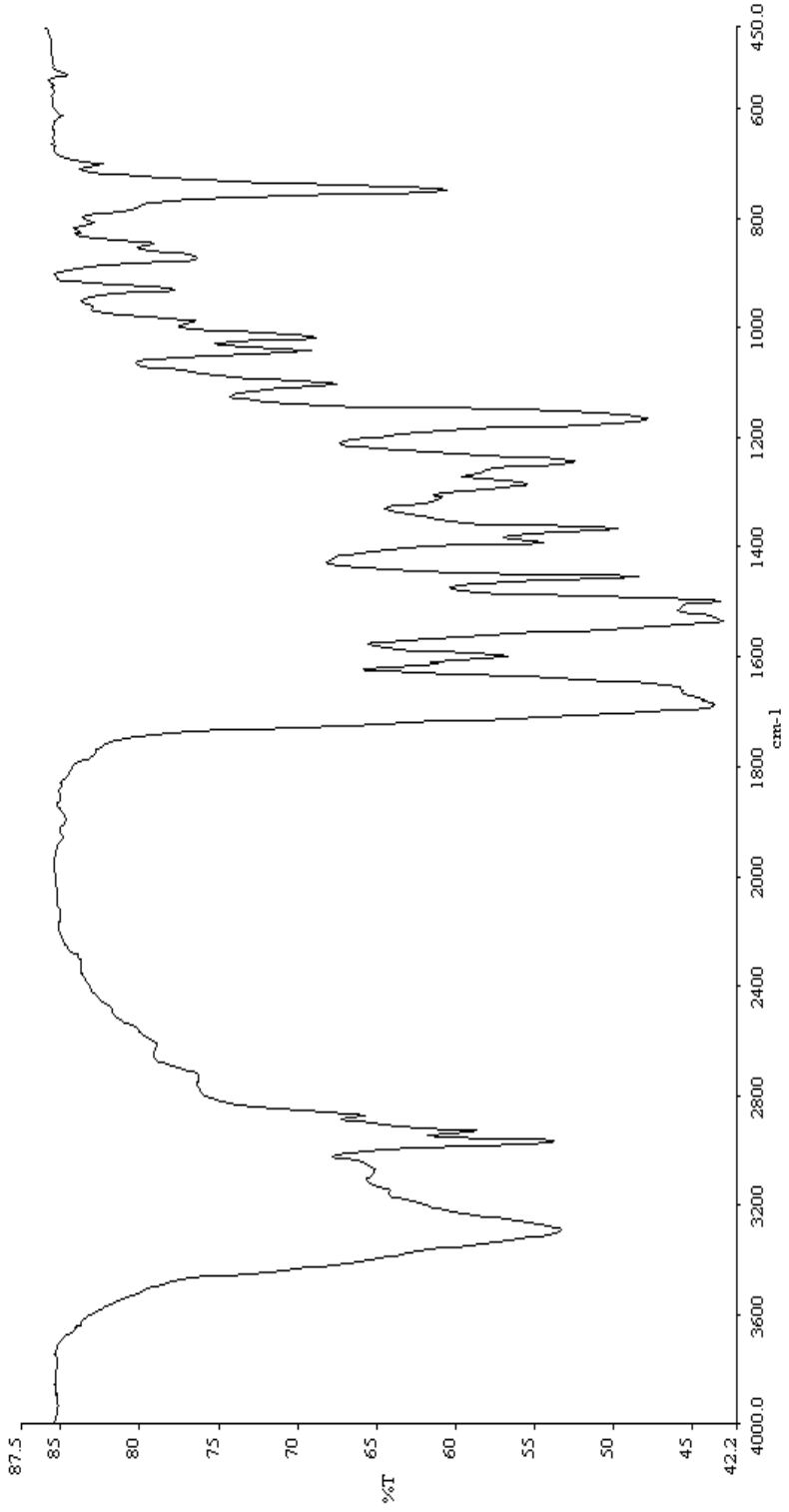


Fig. 3.8 The IR spectrum of Compound 8

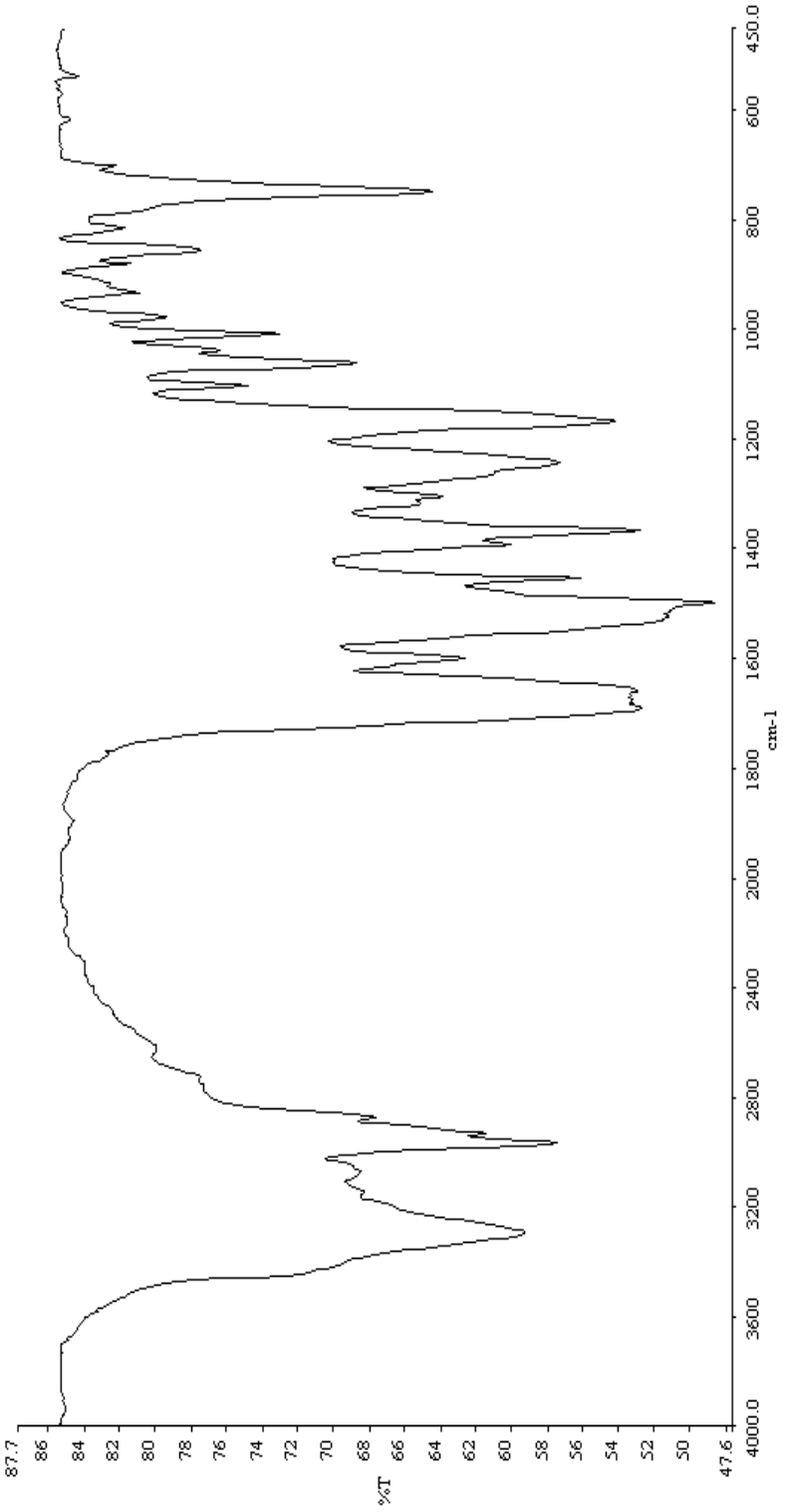


Fig. 3.9 The IR spectrum of Compound 9

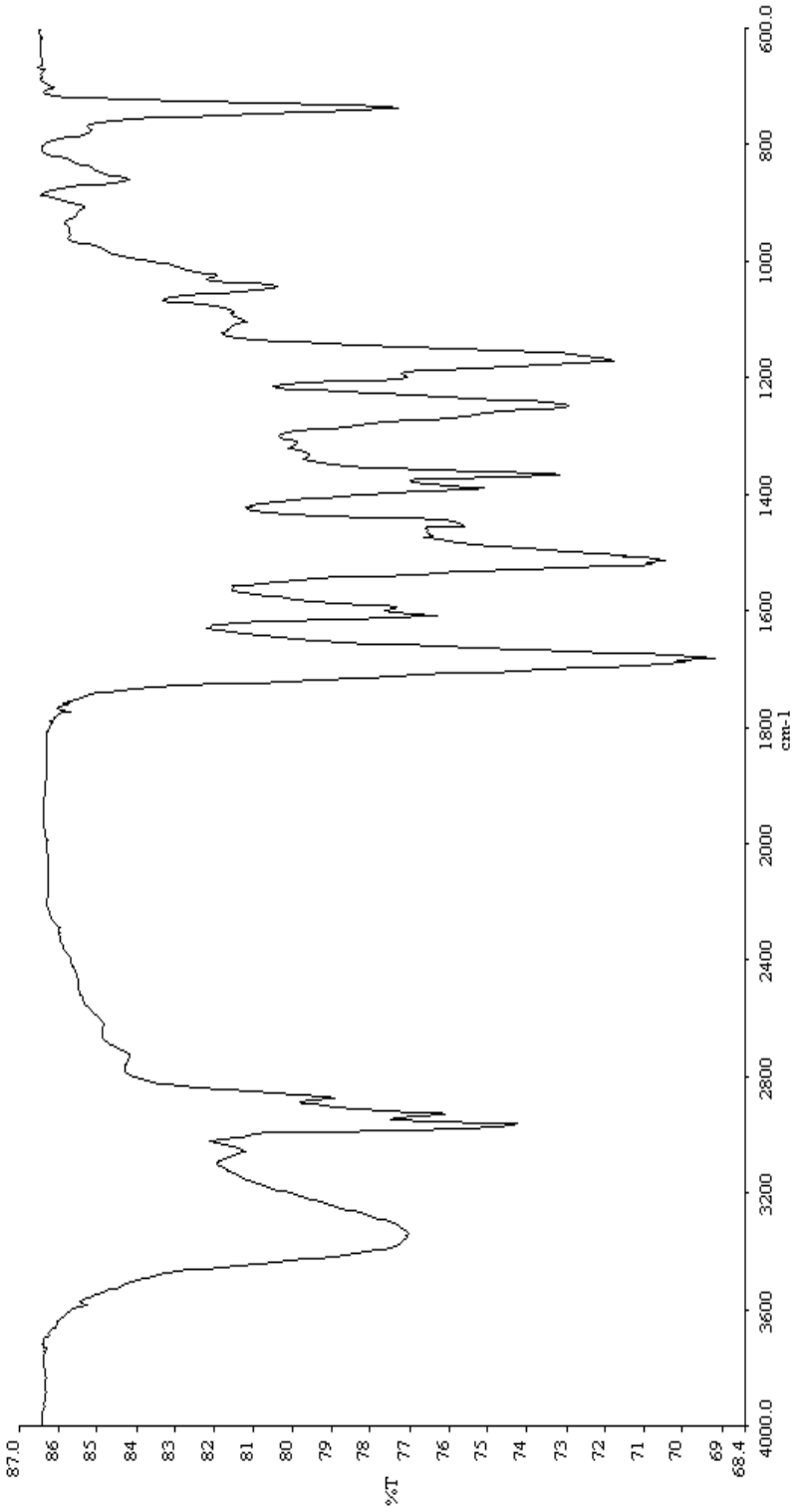


Fig. 3.10 The IR spectrum of Compound 11

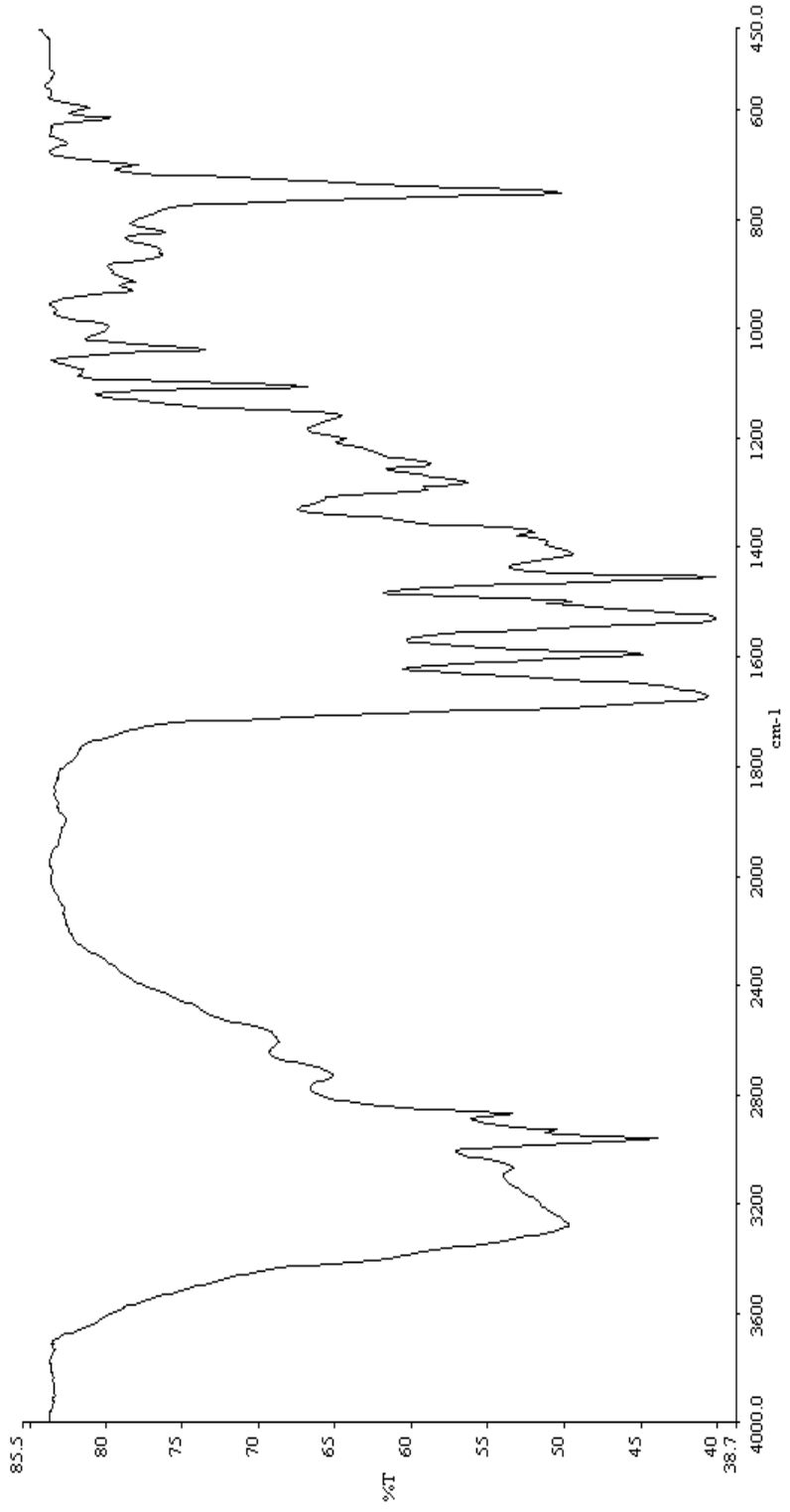


Fig. 3.11 The IR spectrum of Compound 12

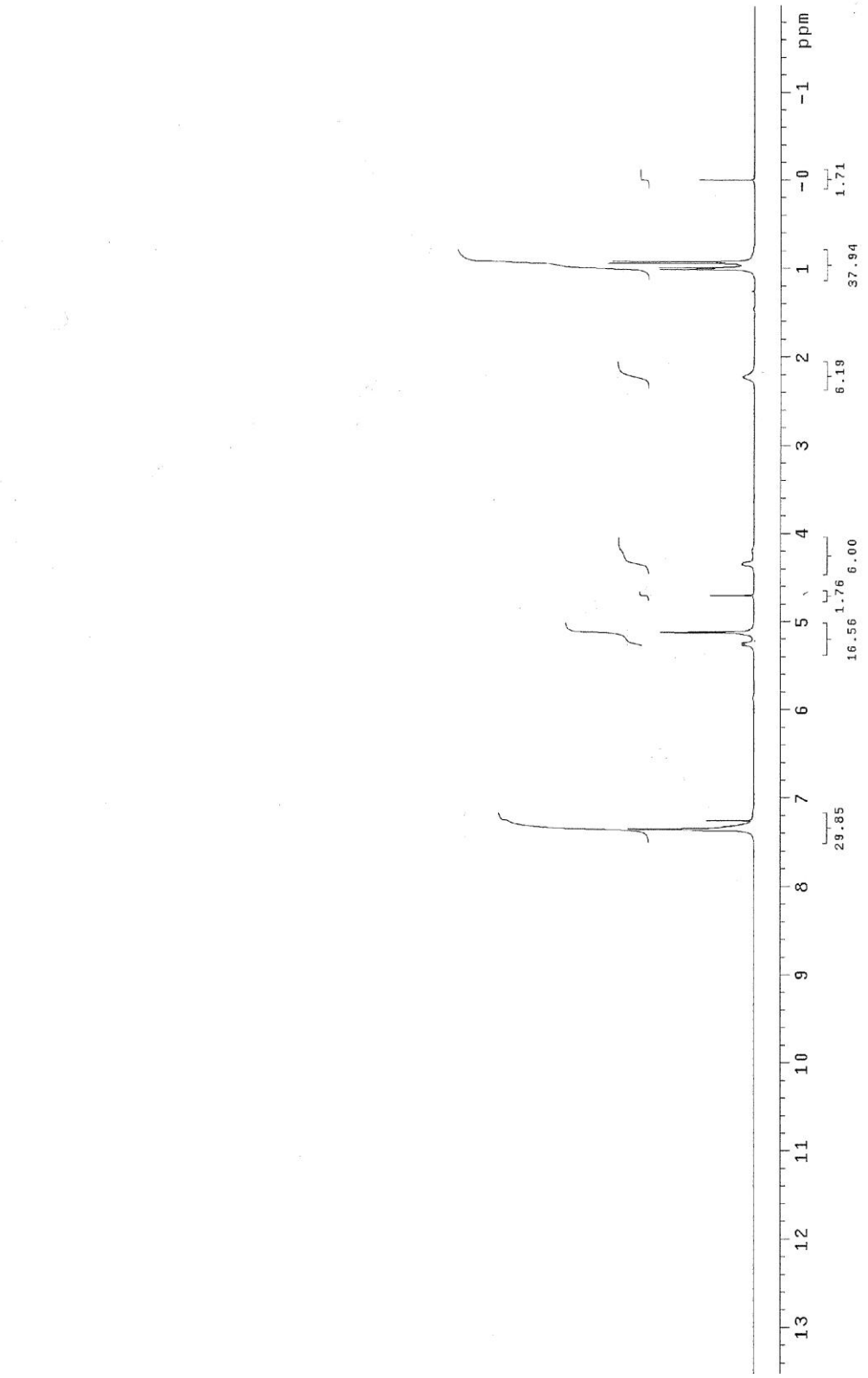


Fig. 3.12 The ^{1}H-NMR spectrum of Compound 1

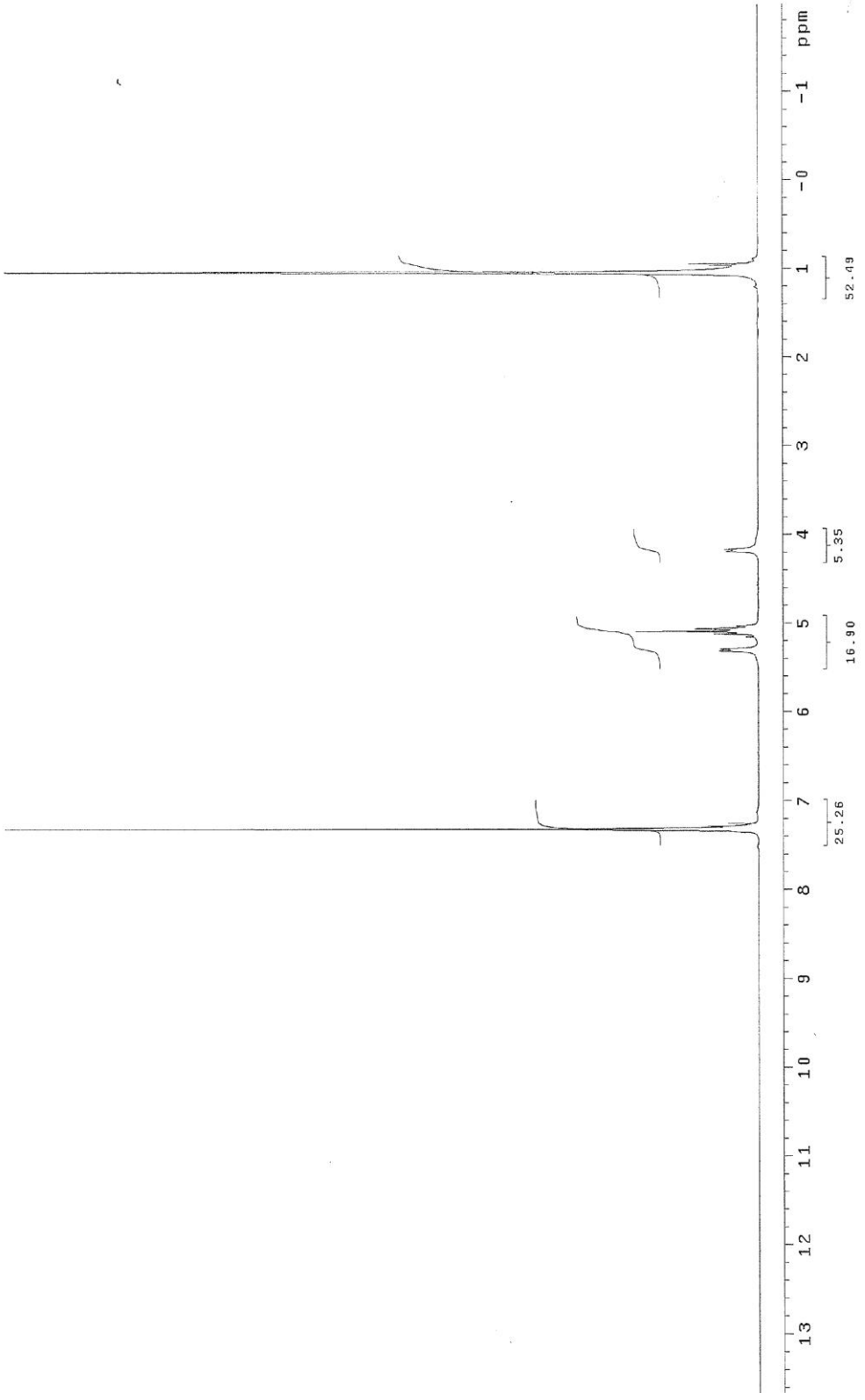


Fig. 3.13 The ^{1}H-NMR spectrum of Compound 2

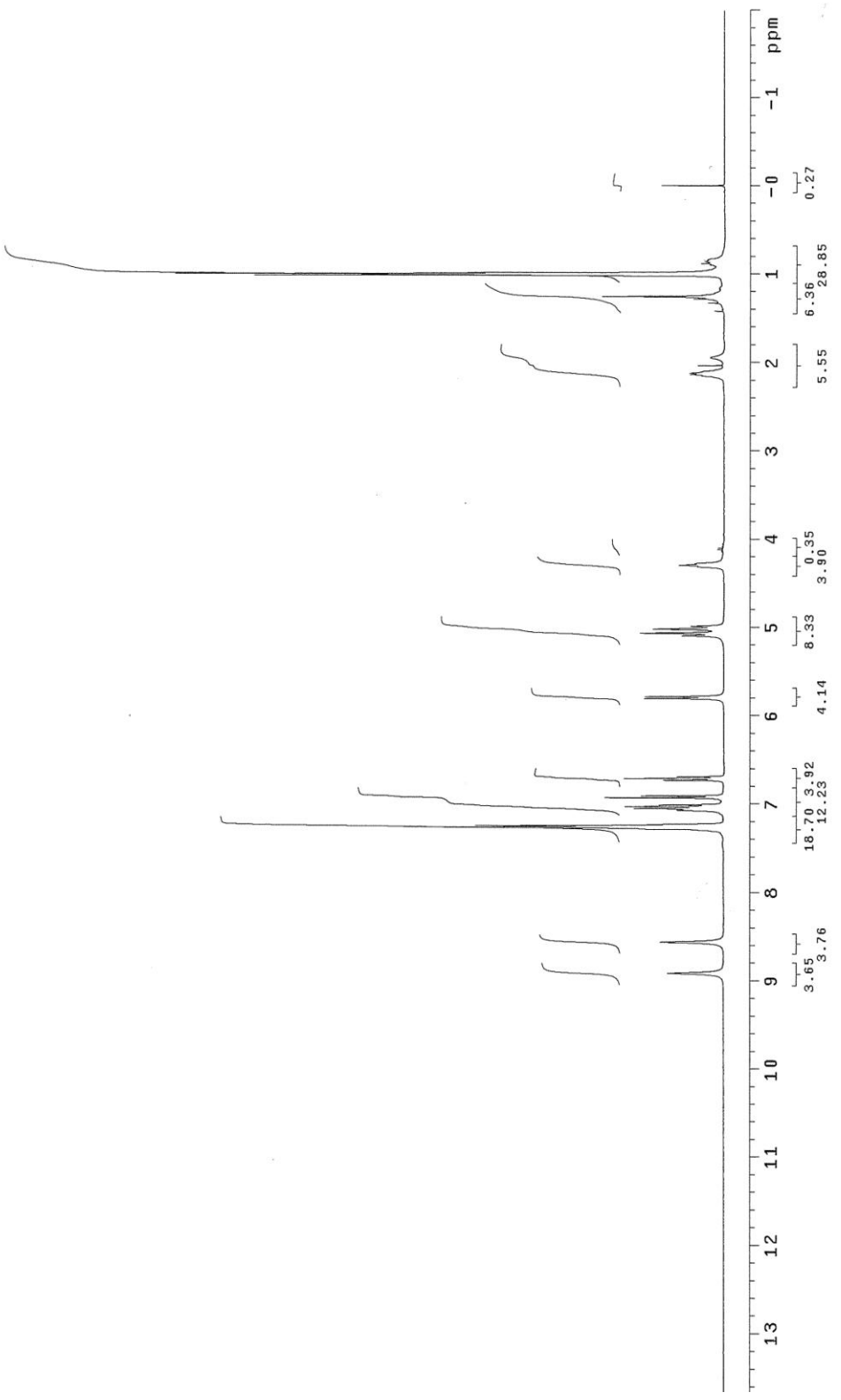


Fig. 3.14 The ^{1}H-NMR spectrum of Compound 3

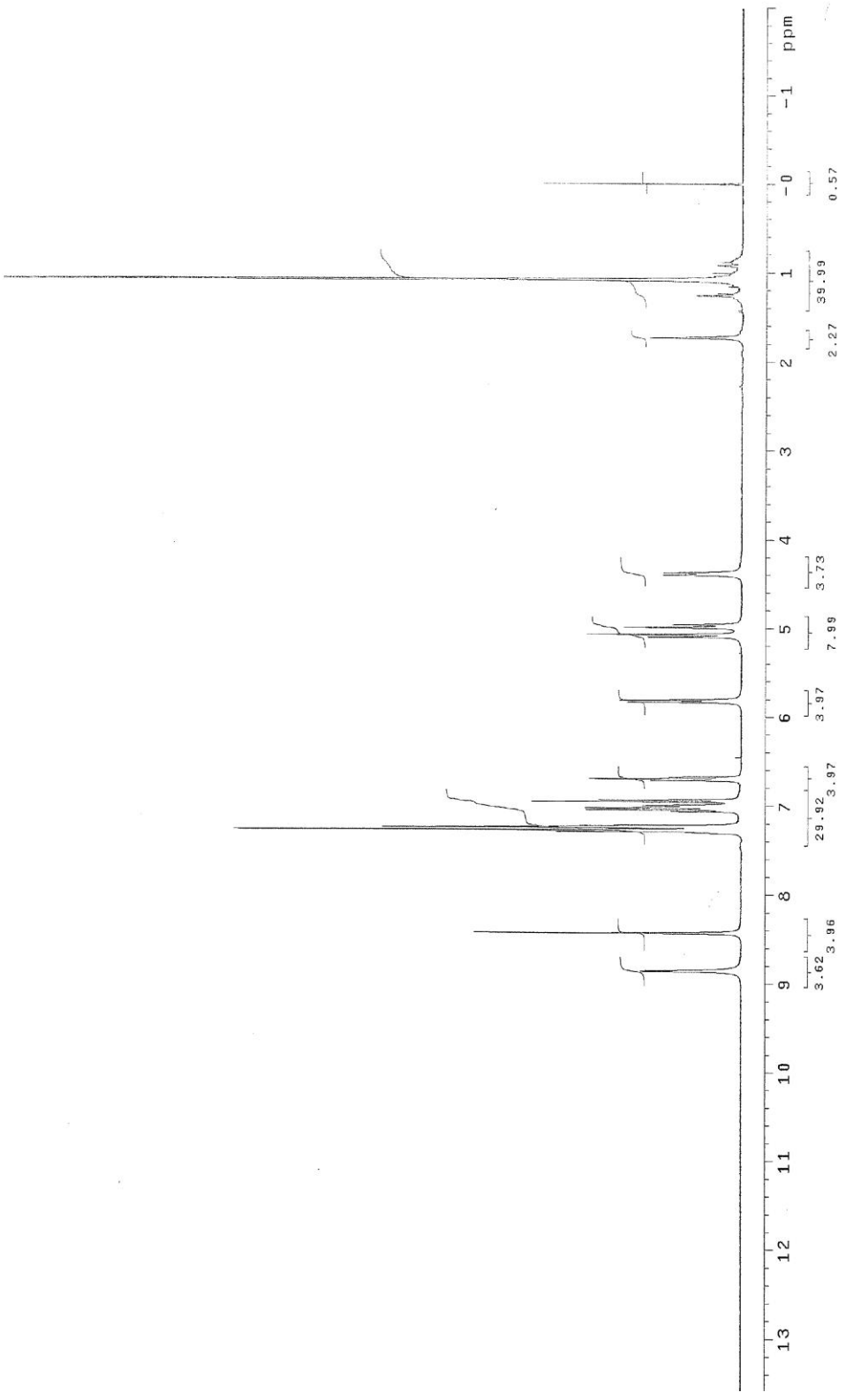


Fig. 3.15 The ^{1}H-NMR spectrum of Compound 4

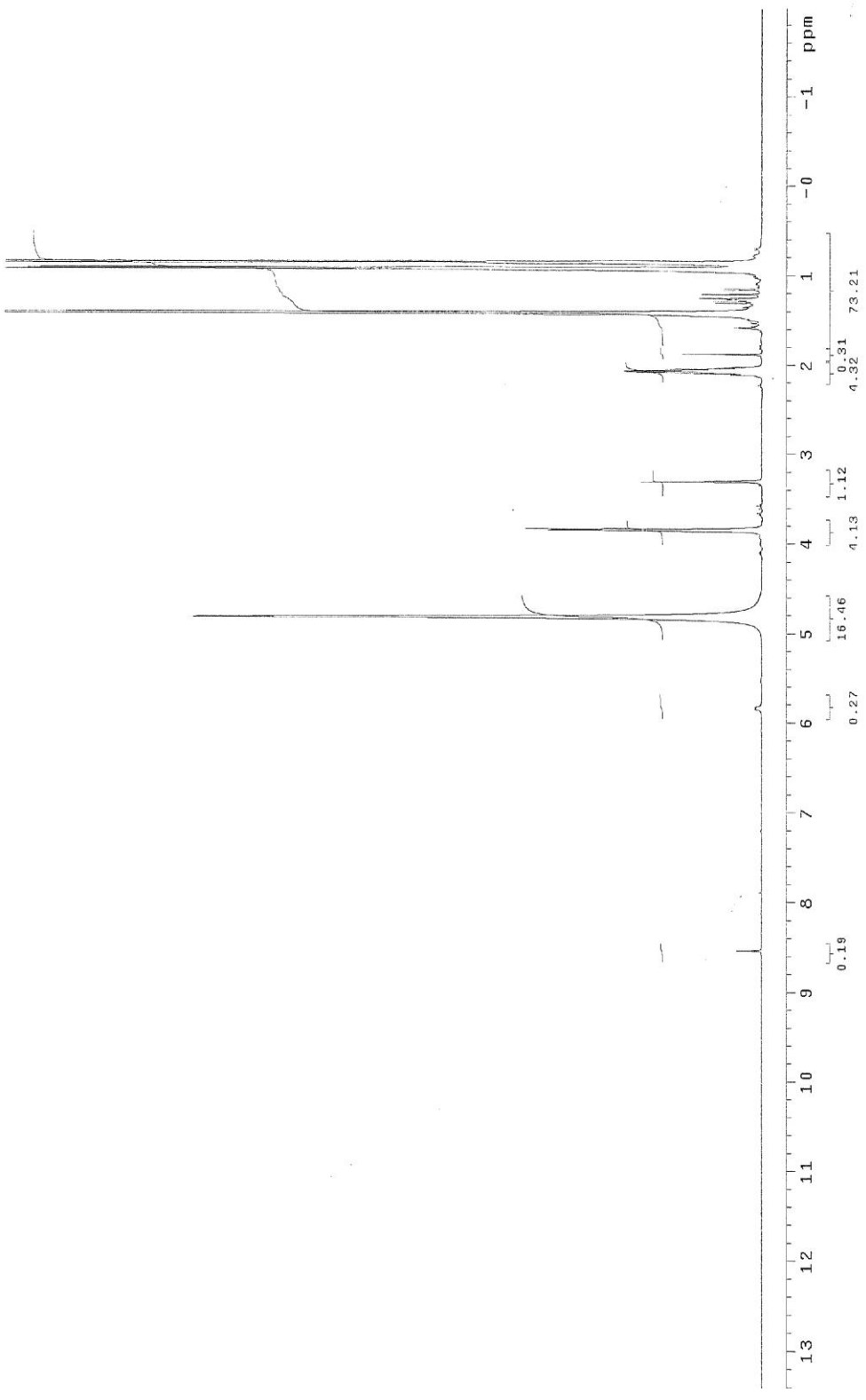


Fig. 3.16 The ^{1}H-NMR spectrum of Compound 5

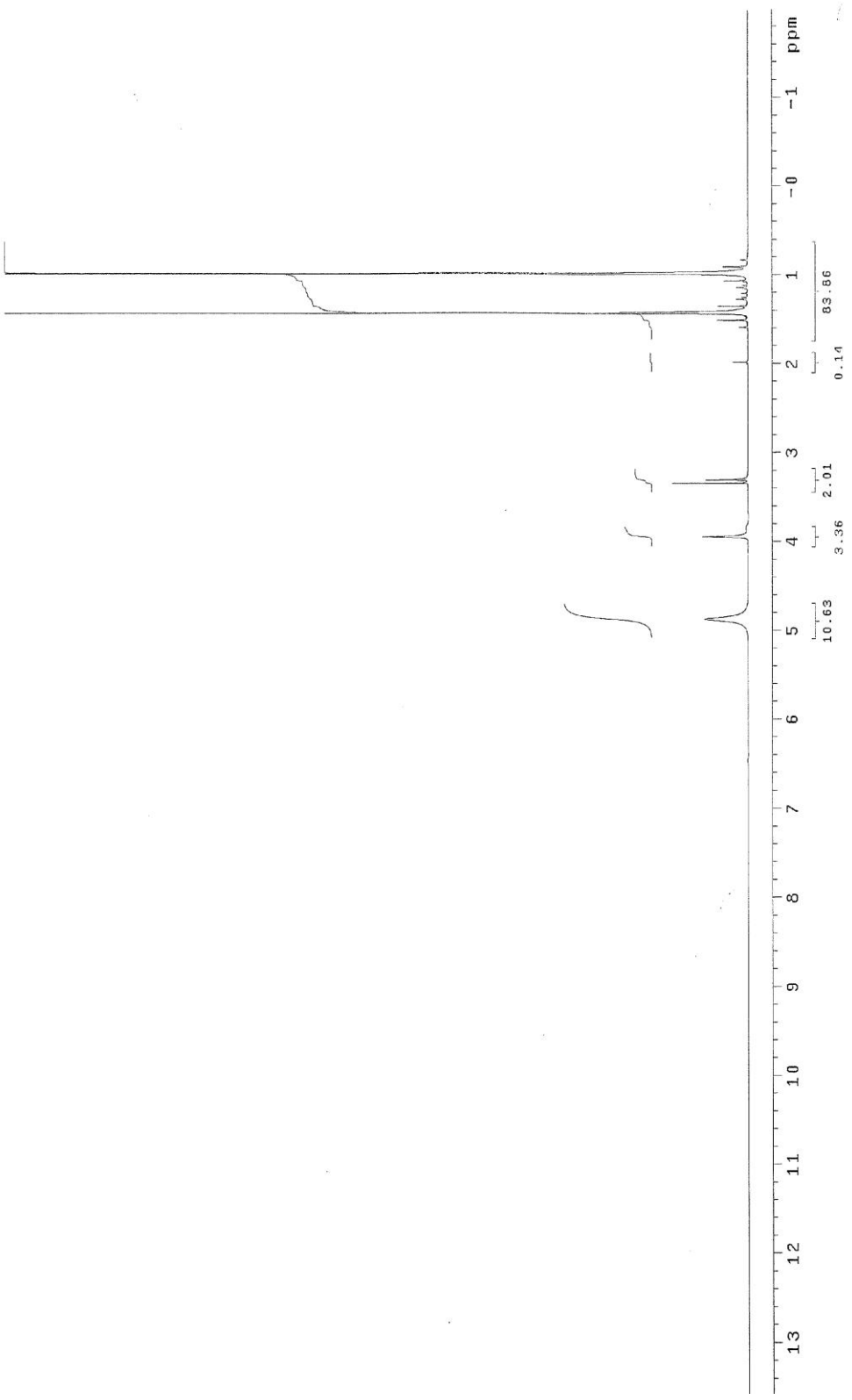


Fig. 3.17 The ^{1}H-NMR spectrum of Compound 6

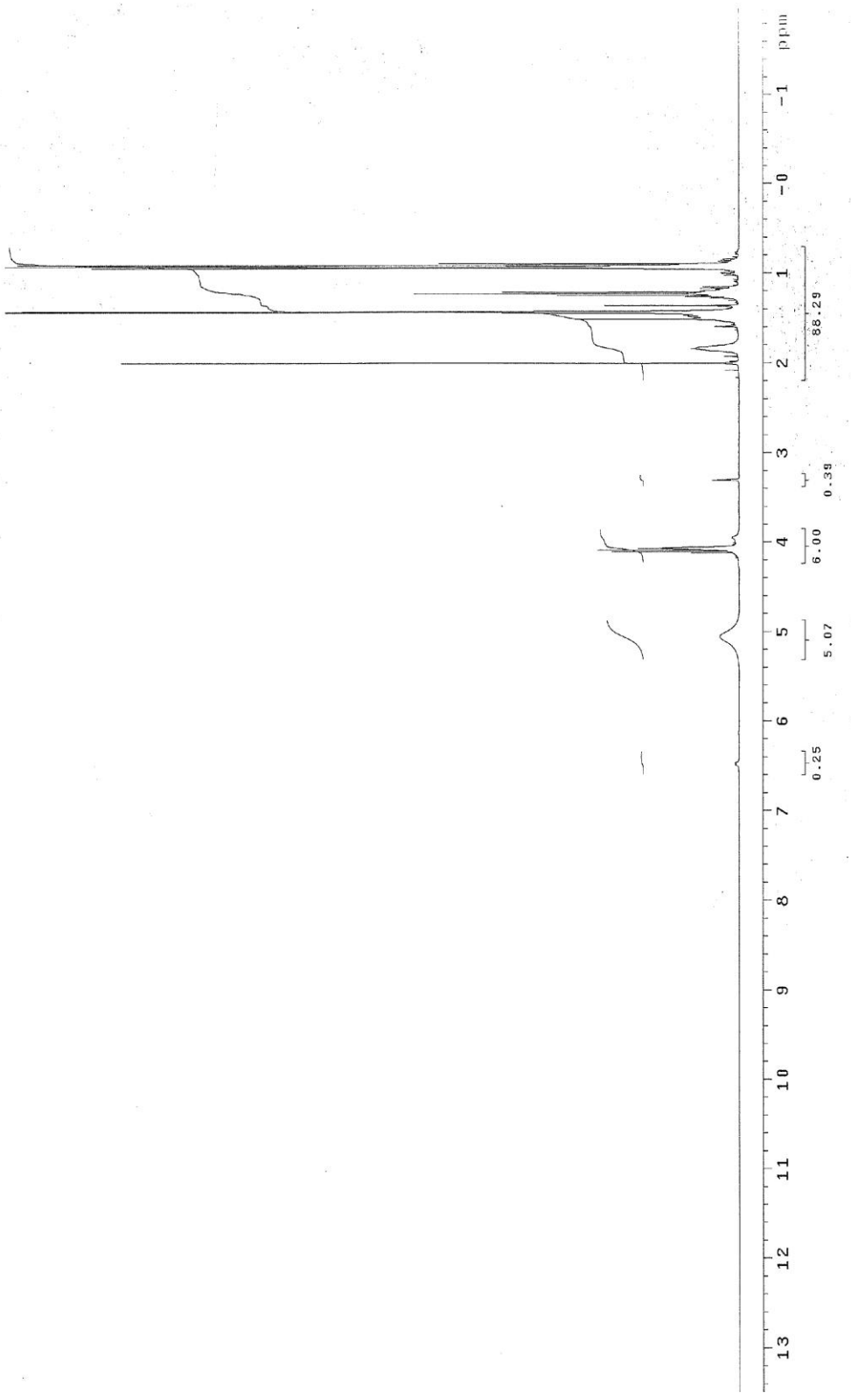


Fig. 3.18 The ^{1}H-NMR spectrum of Compound 7

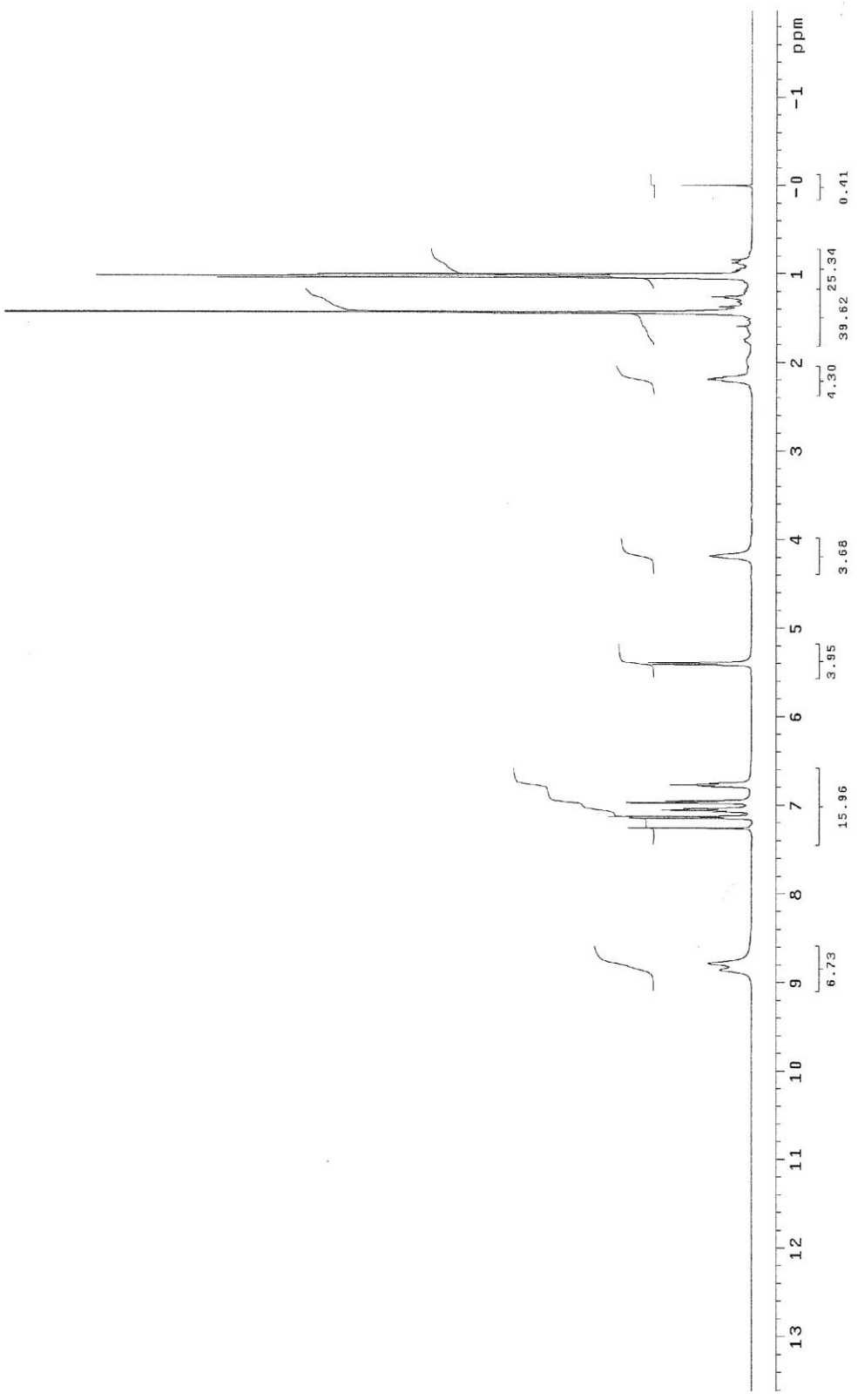


Fig. 3.19 The ^{1}H-NMR spectrum of Compound 8

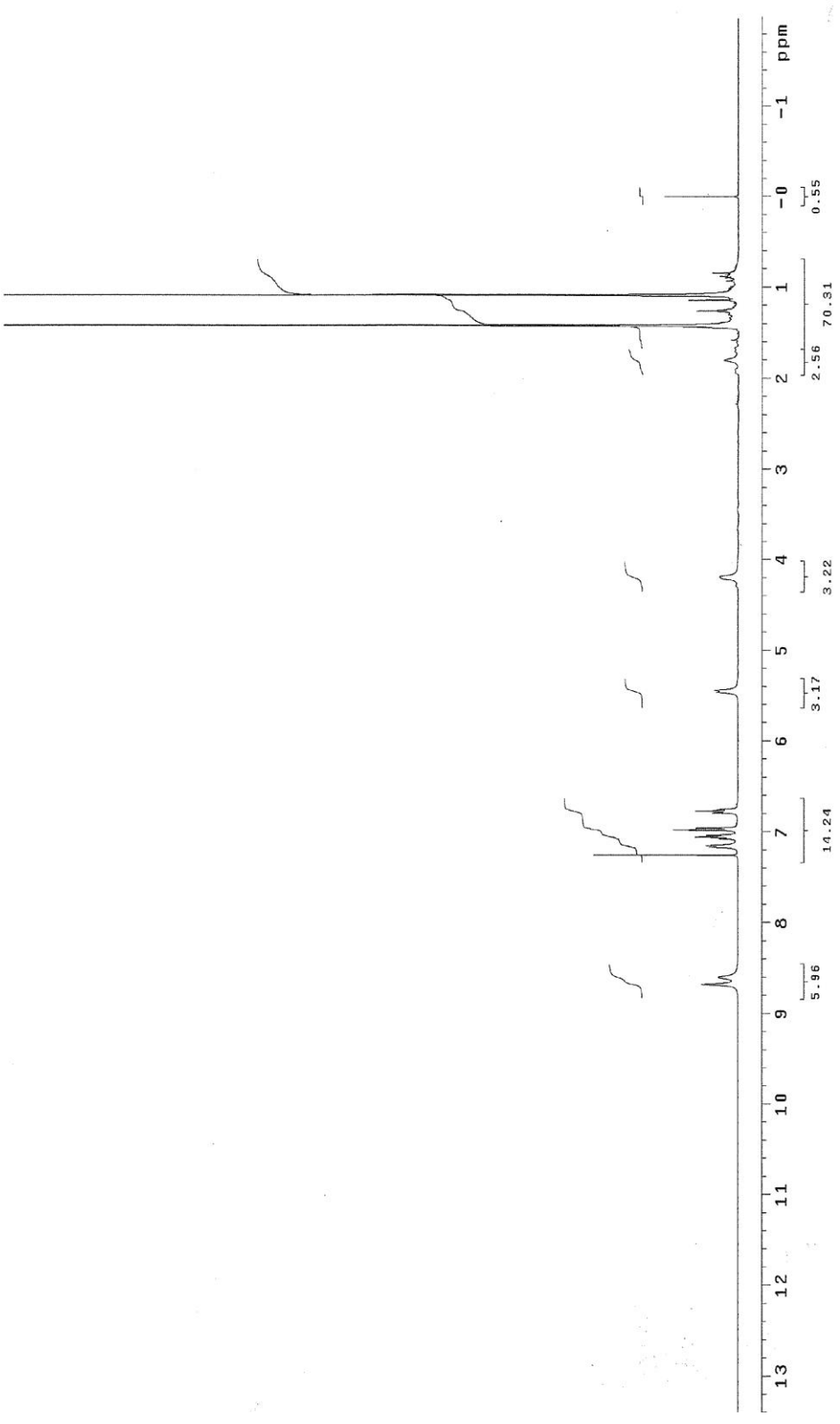


Fig. 3.20 The ^{1}H-NMR spectrum of Compound 9

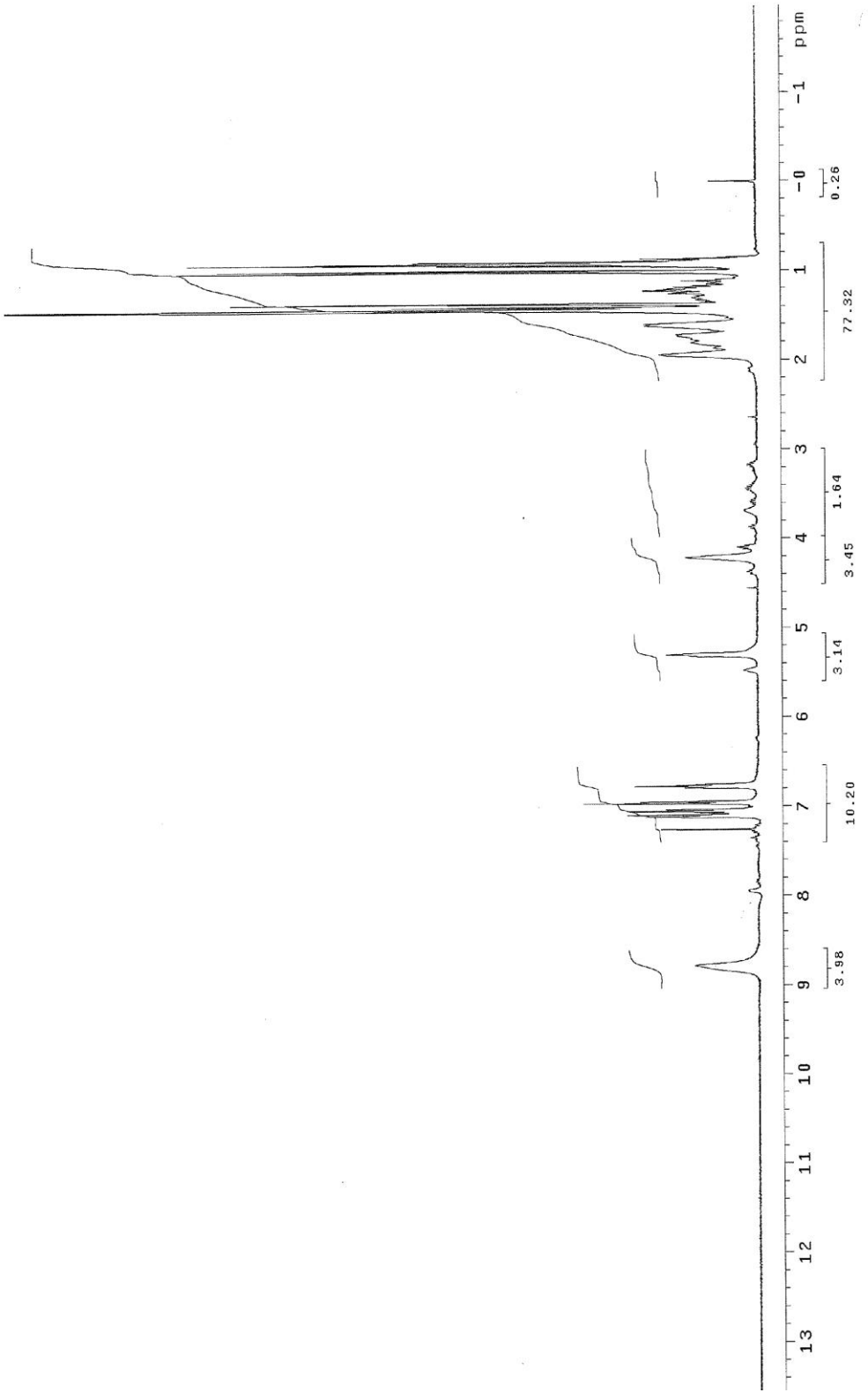


Fig. 3.21 The ^{1}H-NMR spectrum of Compound 10

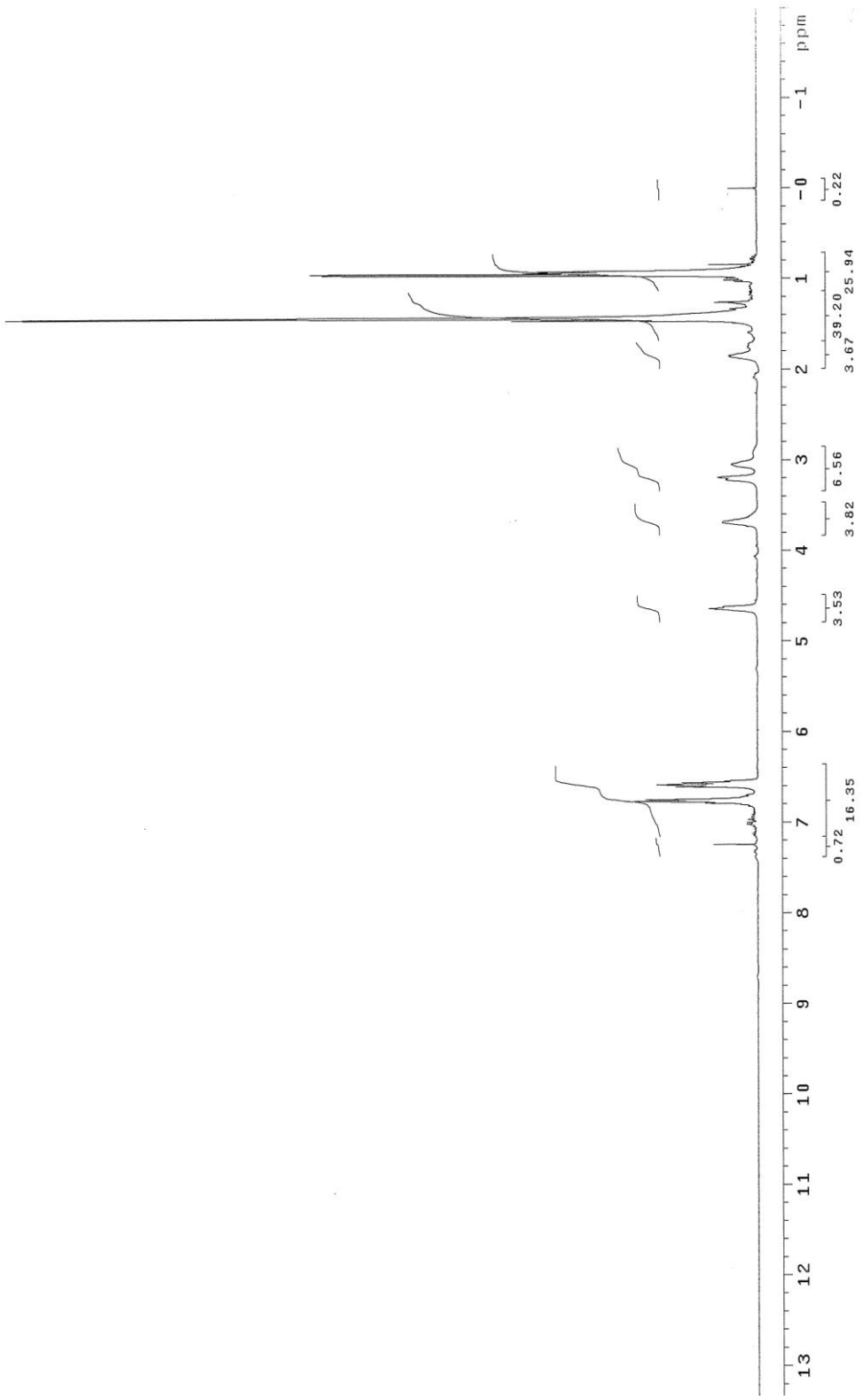


Fig. 3.22 The ^{1}H-NMR spectrum of Compound 11

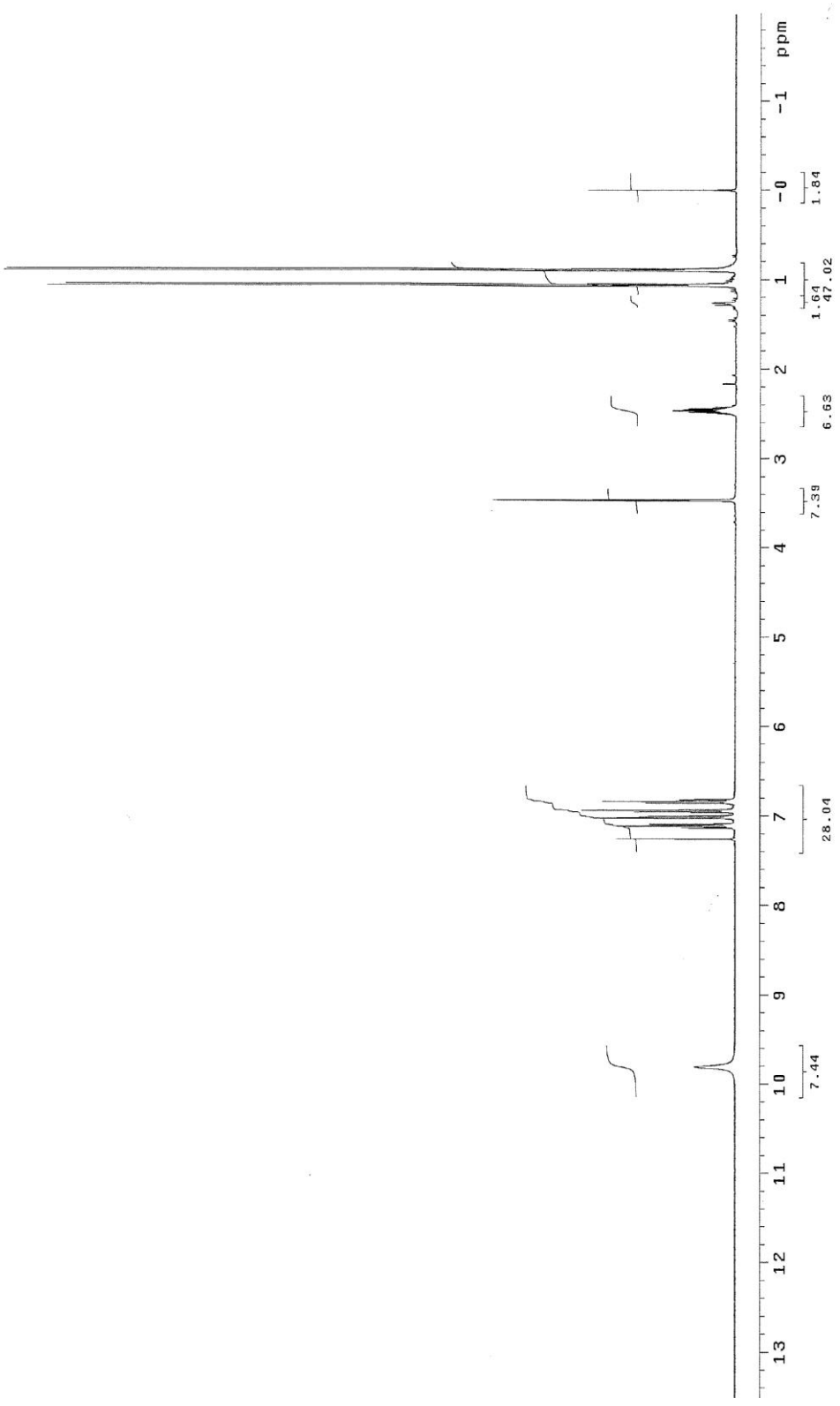


Fig. 3.23 The ^{1}H-NMR spectrum of Compound 12

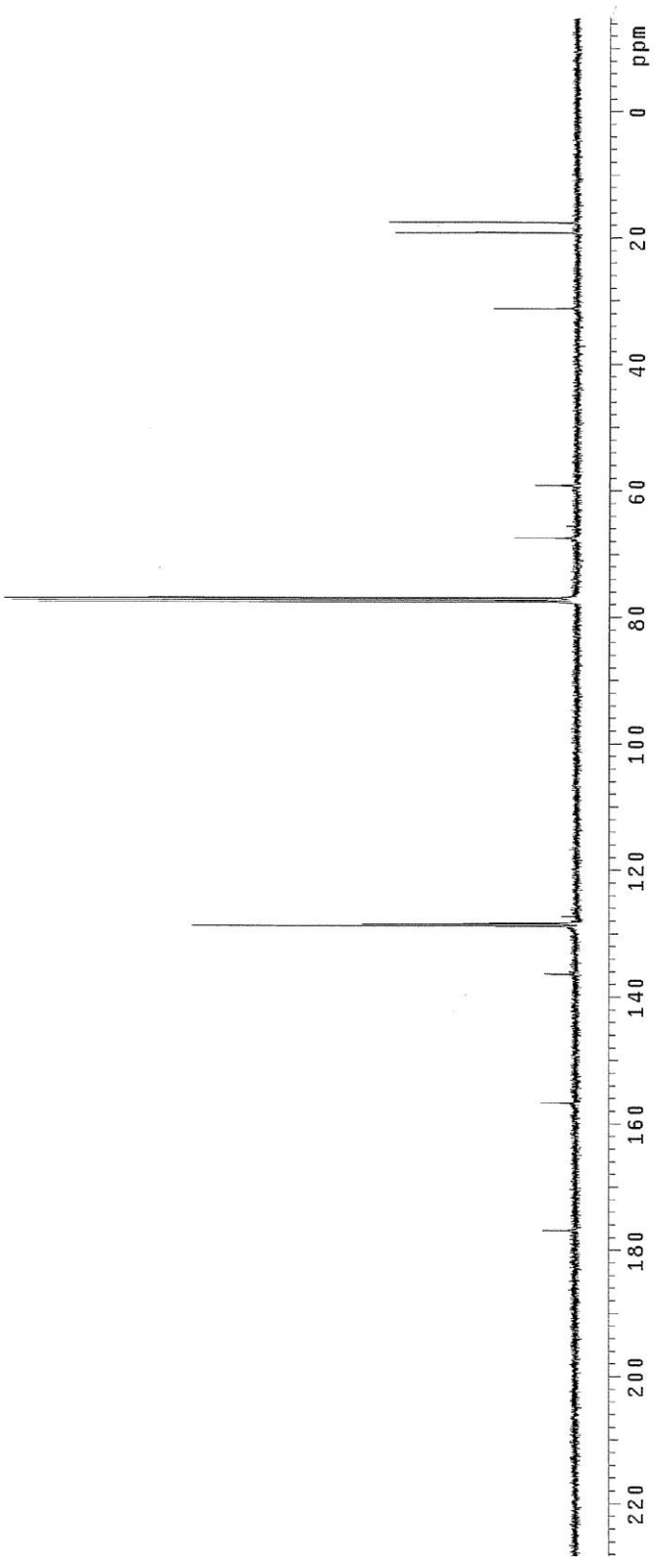


Fig. 3.24 The ^{13}C-NMR spectrum of Compound 1

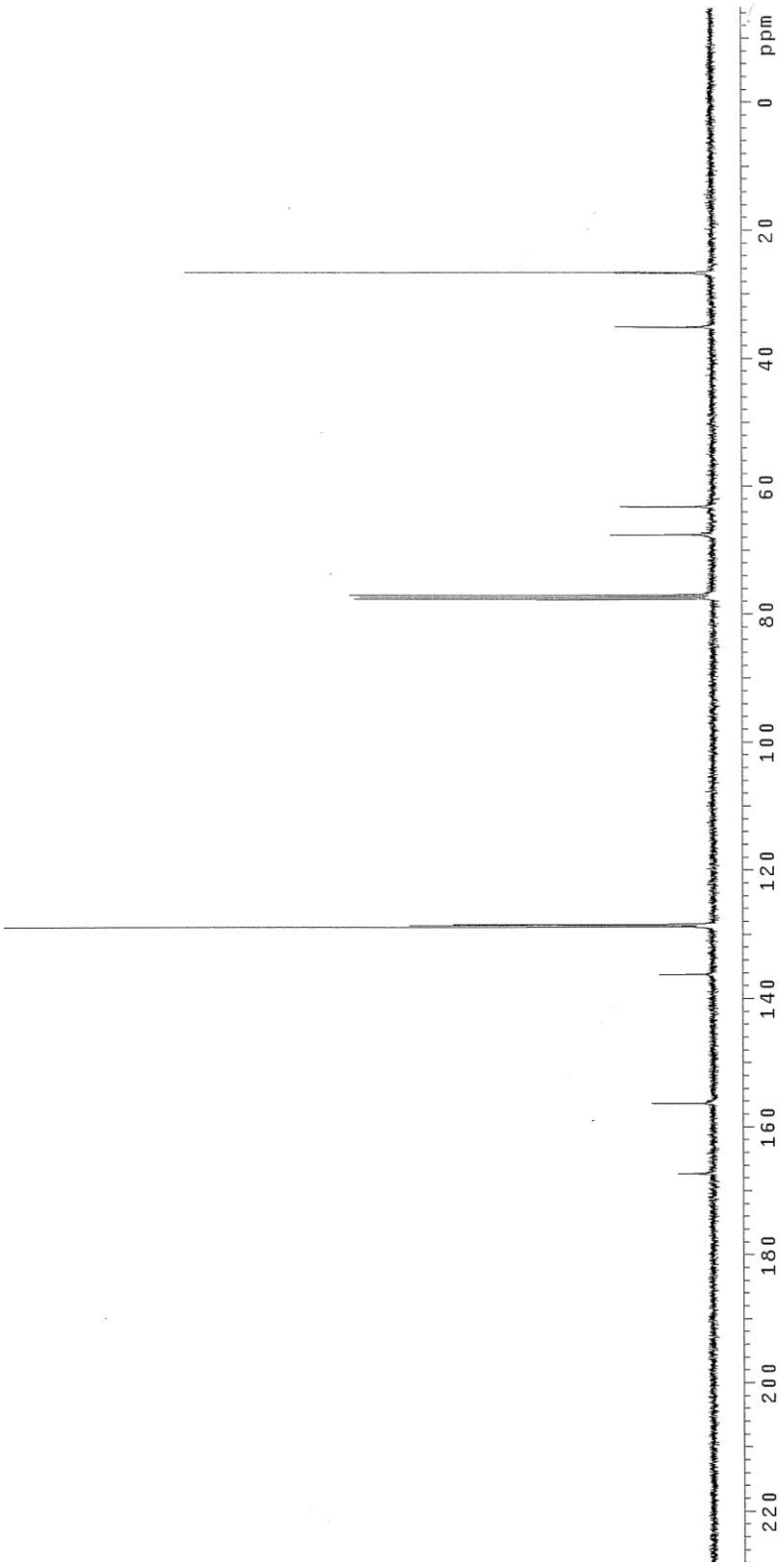


Fig. 3.25 The ^{13}C-NMR spectrum of Compound 2

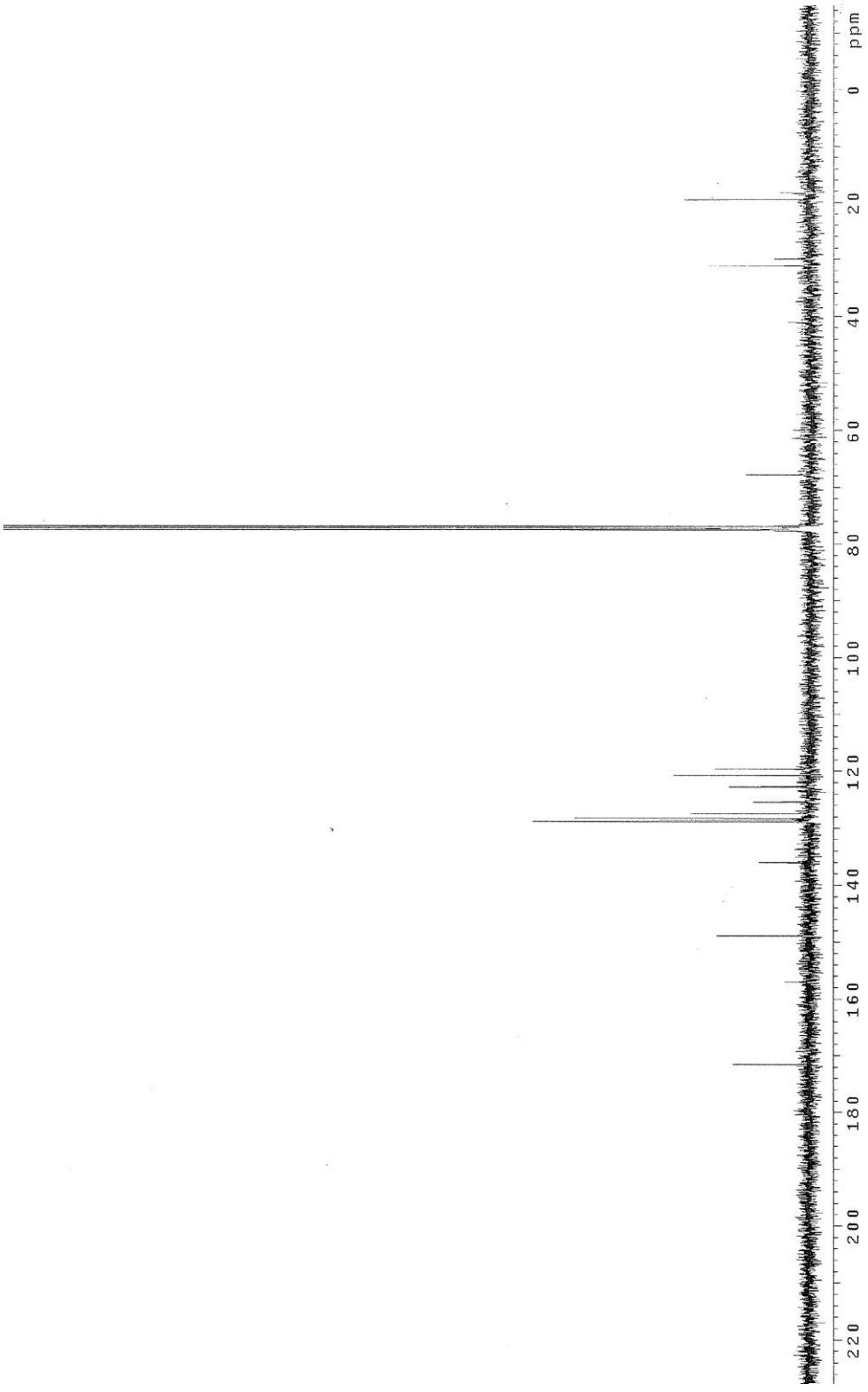


Fig. 3.26 The ^{13}C-NMR spectrum of Compound 3

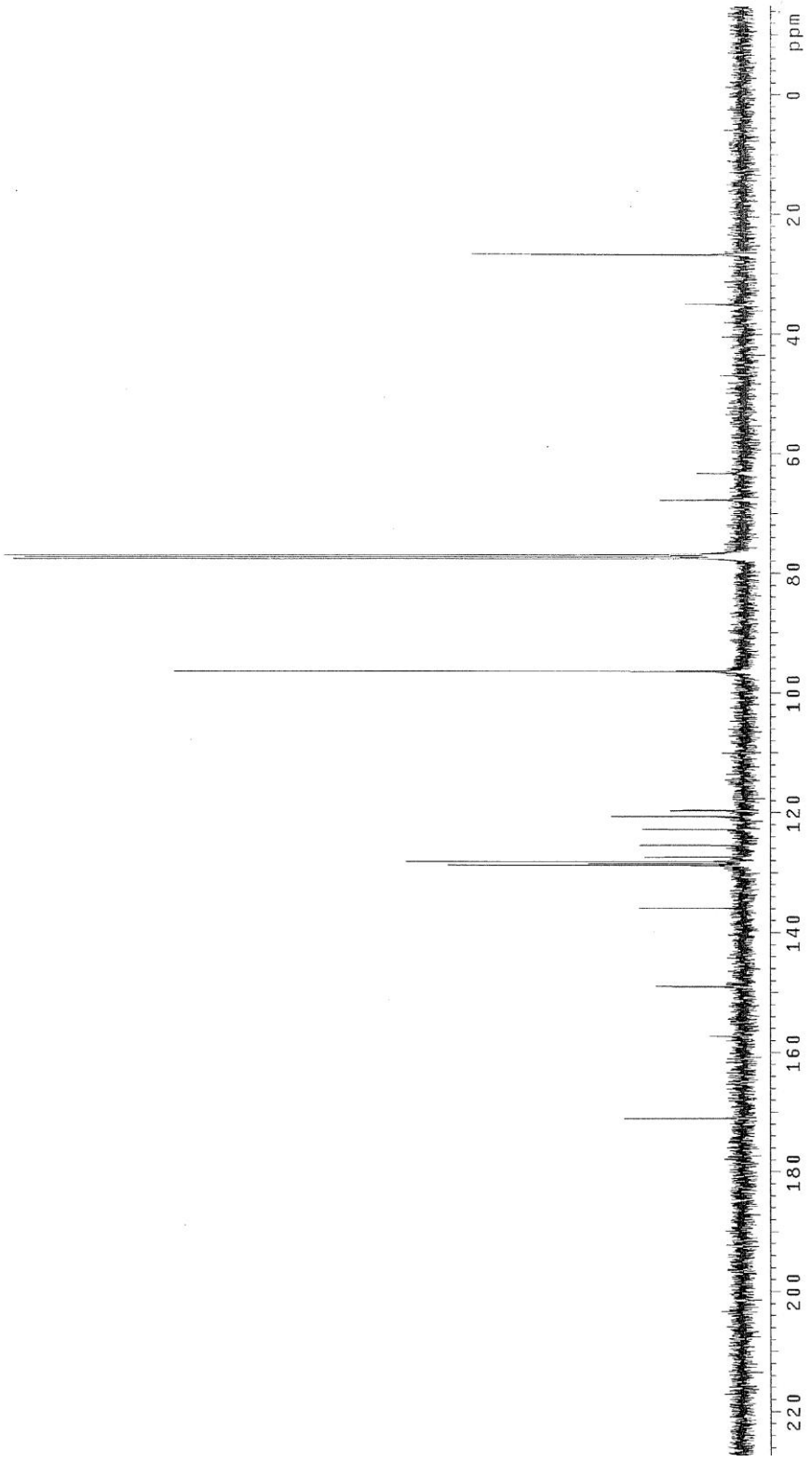


Fig. 3.27 The ^{13}C-NMR spectrum of Compound 4

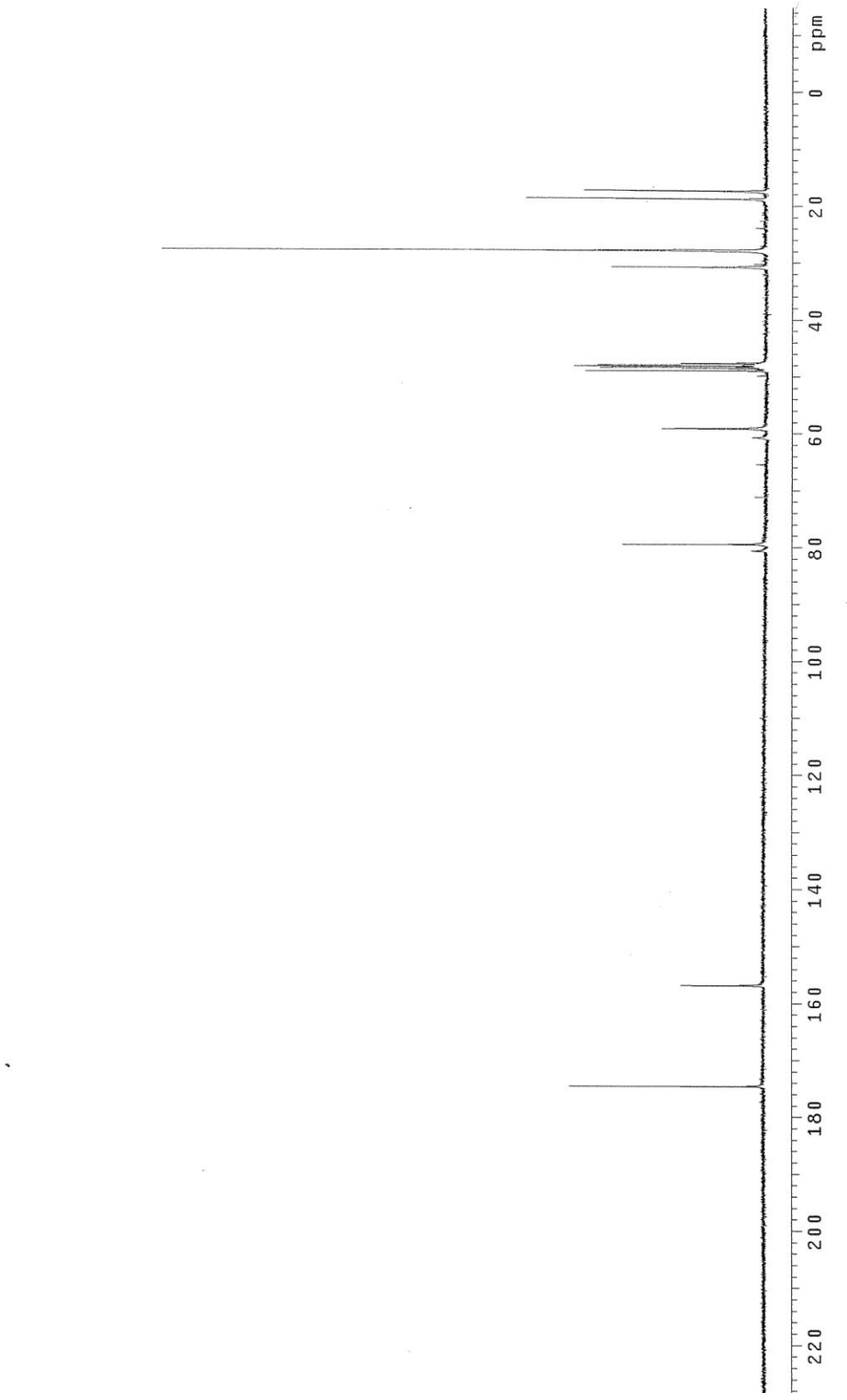


Fig. 3.28 The ^{13}C-NMR spectrum of Compound 5

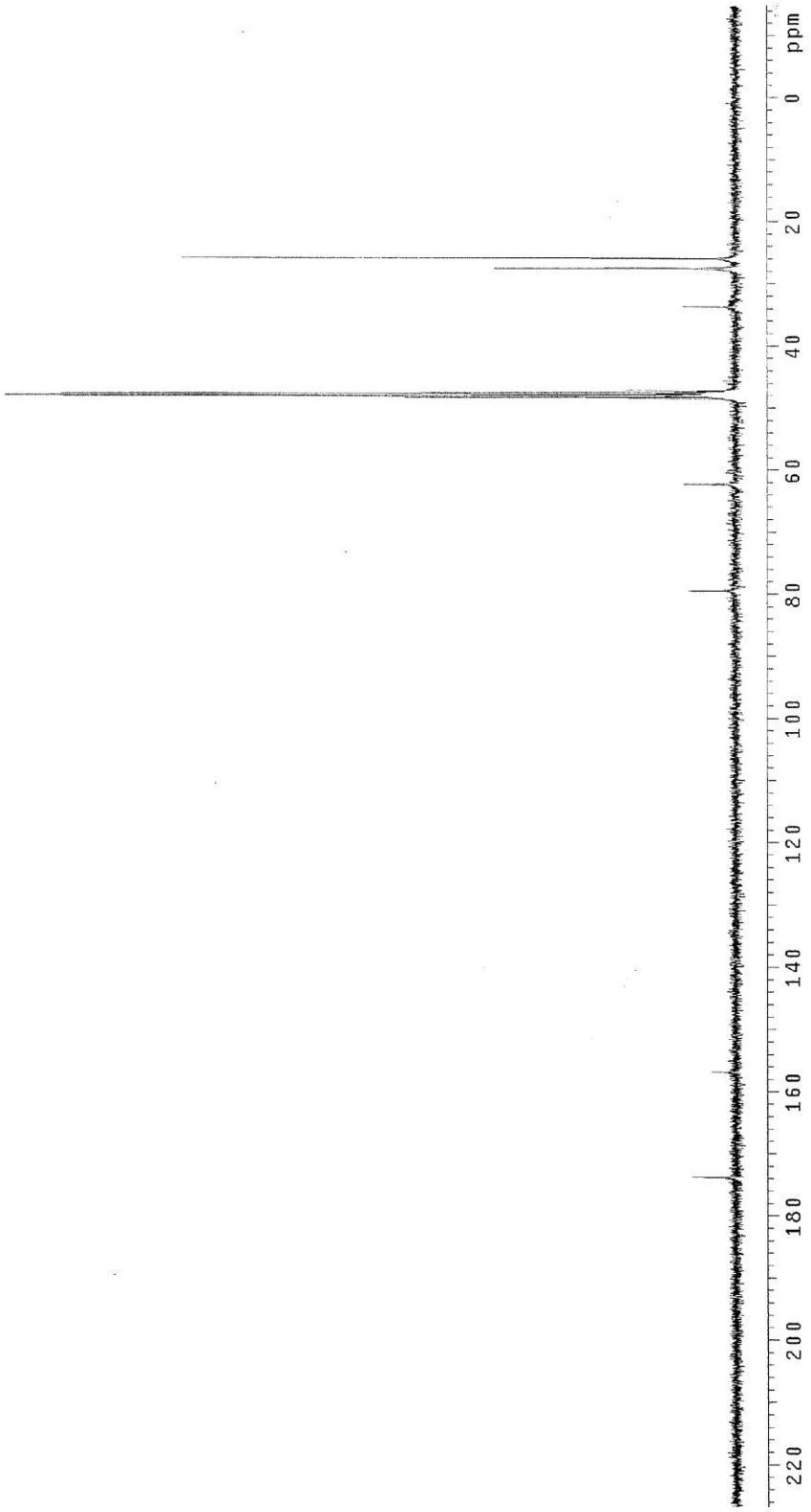


Fig. 3.29 The ^{13}C-NMR spectrum of Compound 6

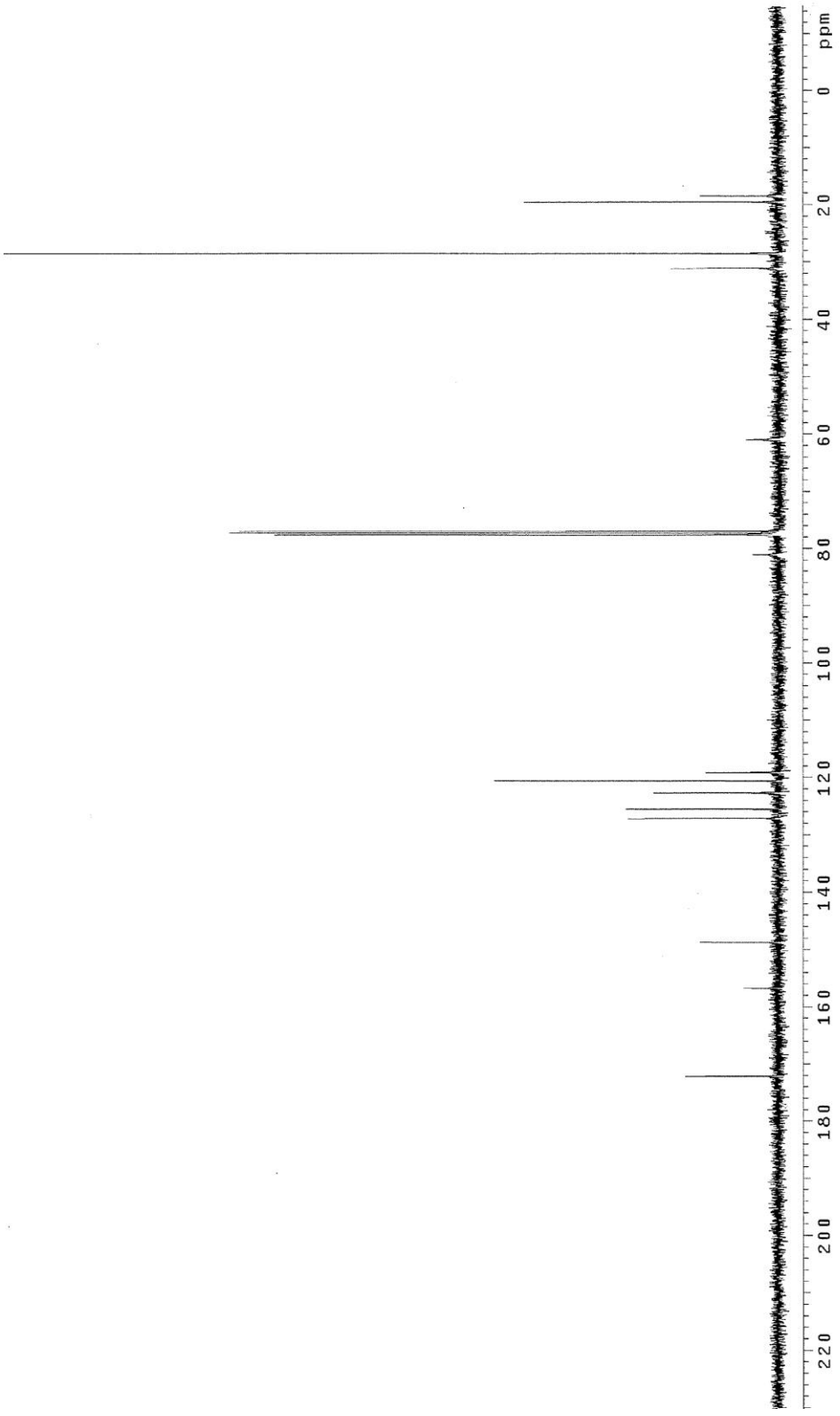


Fig. 3.30 The ^{13}C-NMR spectrum of Compound 8

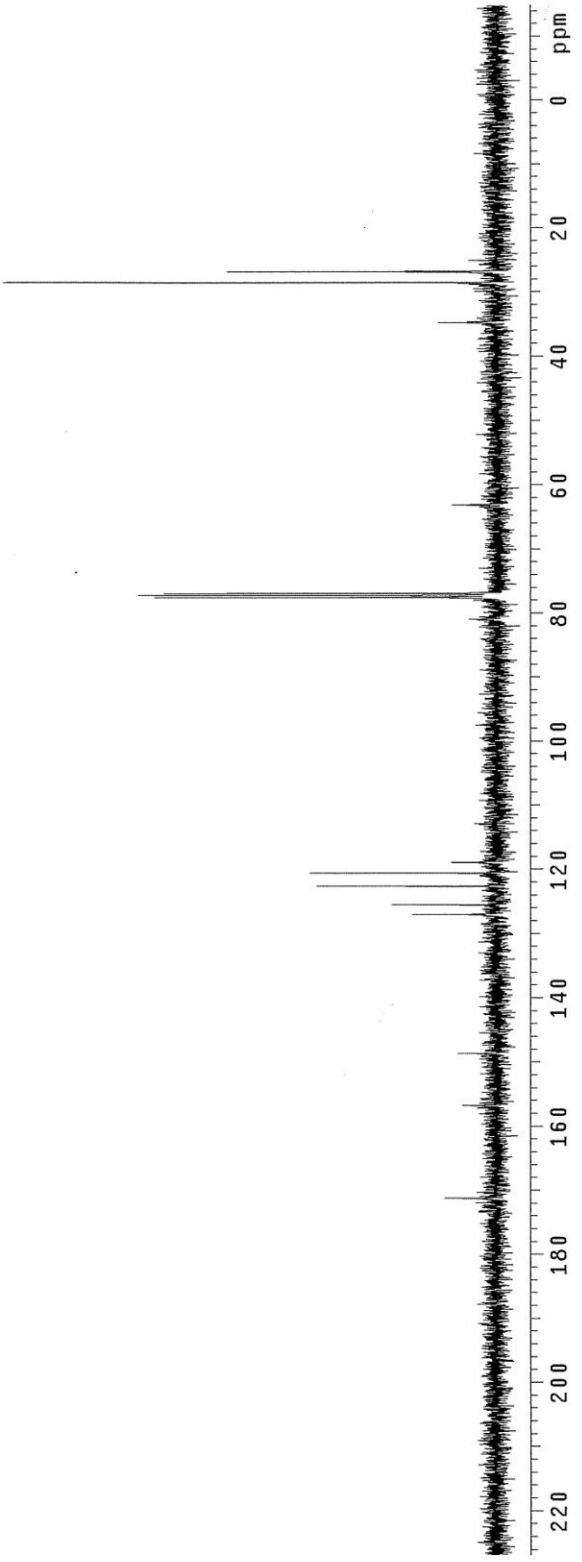


Fig. 3.31 The ^{13}C-NMR spectrum of Compound 9

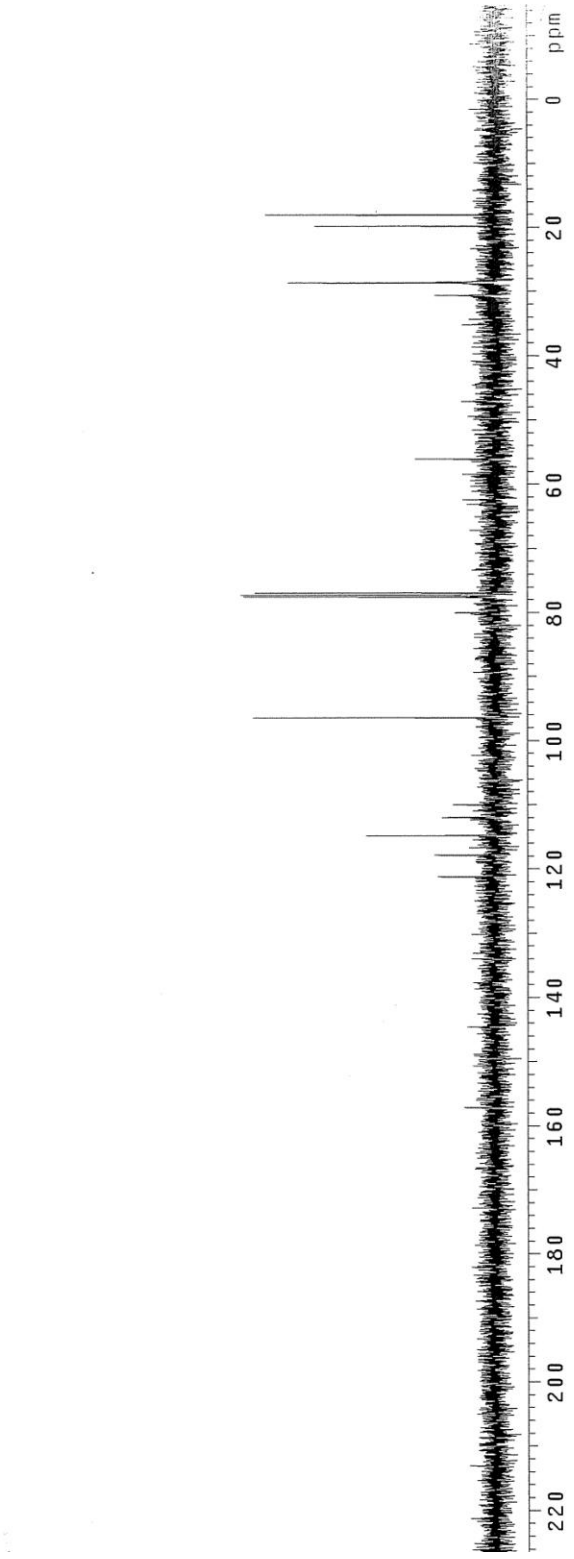


Fig. 3.32 The ^{13}C-NMR spectrum of Compound 11

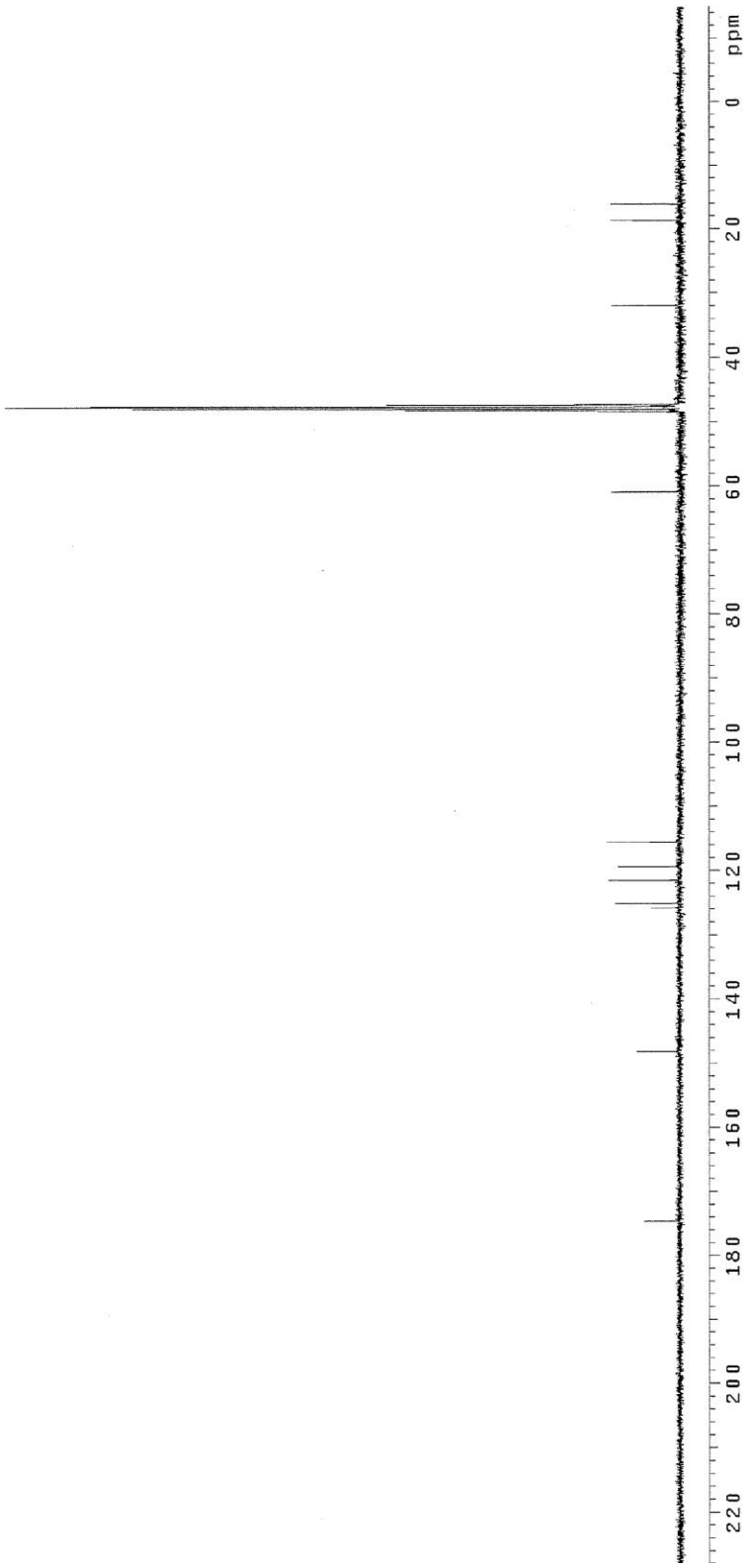


Fig. 3.33 The ^{13}C-NMR spectrum of Compound 12

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EDUCATIONAL BACKROUND

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WORK EXPERIENCES

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