EGE UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

(DOCTOR OF PHILOSOPHY THESIS)

MULTIFUNCTIONAL CHIRAL LIGANDS. SYNTHESIS AND APPLICATIONS FOR ASYMMETRIC CATALYSIS

Leman KARADENİZ

Supervisor: Assoc. Prof. Dr. Stephen T. ASTLEY

Chemistry Department

Department Code: 405.02.01

Presentation Date: 14.04.2011

Bornova-İZMİR

2011

Leman KARADENİZ tarafından doktora tezi olarak sunulan "**Çok Fonksiyonlu Kiral Ligandlar. Asimetrik Kataliz için Sentez ve Uygulamalar**" 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 **14.04.2011** tarihinde yapılan tez savunma sınavında aday oybirliği/oyçokluğu ile başarılı bulunmuştur.

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ÖZET

ÇOK FONKSİYONLU KİRAL LİGANDLAR. ASİMETRİK KATALİZ İÇİN SENTEZ VE UYGULAMALAR

KARADENİZ, Leman

Doktora Tezi, Kimya Bölümü
Tez Yöneticisi: Doç. Dr. Stephen T. Astley
Nisan 2011, 164 Sayfa

Epiklorohidrinin halka açılması, Diels Alder ve Henry (nitroaldol) eliminasyon tepkimesi olmak üzere üç farklı asimetrik sentez tepkimesi üzerinde çalışıldı.

Epiklorohidrinin asimetrik halka açılması, ilk defa bir salisilaldehit türevi nükleofil kullanılarak, kiral Co(III)-salen katalizörleri varlığında % 90 enantiyomerik fazlalık (ef) ile gerçekleştirildi. Bu sayede kiral bir merkez içeren ve aynı zamanda yapısındaki aldehit ve alkil halojenür fonksiyonel grupları sayesinde pek çok tepkime için kullanışlı bir substrat literatüre kazandırıldı. Bu aldehit kullanılarak oksim, benzisoksazol, diol ve Schiff bazı türevleri sentezlendi.

Koruyucu grup olarak Boc ve Cbz içeren yedi tane L-asparagin ve L-glutamin türevi ligand sentezlendi ve enantiyoseçimli Diels Alder tepkimesinde sulu ortamda katalizör olarak kullanıldı. Test tepkimesi olarak, sulu ortamda 3-akriloil-1,3-oksazolidin-2-on ile siklopentadien arasında asimetrik Diels Alder tepkimesi gerçekleştirildi. Tepkime koşulları optimize edildikten sonra ürün, yüksek verim ve *endo/exo* oranları ile elde edildi ancak ef değerlerinin düşük olduğu saptandı.

Sentezlenen L-asparagin ve L-glutamin türevleri ayrıca Henry eliminasyon tepkimesinde de organokatalizör olarak kullanıldı. Tepkime koşulları optimize edildikten sonra farklı aromatik sübstitüe aldehitlere nitrometanın katılması yüksek verimle gerçekleştirildi. Nitroalkenin tek basamakta sentez metodu basit, ucuz ve ılıman koşullarda geliştirildi.

Anahtar Kelimeler: Asimetrik sentez, kiral katalizör, organokatalizör, ariloksi alkol, epiklorohidrin, Diels Alder, norbornene, Henry (nitroaldol) eliminasyon tepkimesi, nitroalken.

ABSTRACT

MULTIFUNCTIONAL CHIRAL LIGANDS. SYNTHESIS AND APPLICATIONS FOR ASYMMETRIC CATALYSIS

KARADENİZ, Leman

Ph.D. in Chemistry
Supervisor: Assoc. Prof. Dr. Stephen T. Astley
April 2011, 164 Pages

Three different types of asymmetric synthesis reactions were investigated. These were the ring-opening of epichlorohydrin, Diels Alder and Henry (nitroaldol) elimination reactions.

The asymmetric ring-opening of epichlorohydrin was performed for the first time using a salicylaldehyde derived nucleofile. This reaction was carried out in the presence of chiral Co(III)-salen catalyst with 90% ee. In this way, a substrate containing a chiral center and thus also useful for many reactions with aldehydes and alkyl halide functional groups in its structure was added to the literature. Oxime, benzisoxazole, diol and Schiff base derivatives of this aldehyde were synthesized.

Seven different L-asparagine and L-glutamine derivative ligands which contain protection groups such as Boc and Cbz were synthesized and applied in the enantioselective Diels Alder reaction in water as a catalyst. The asymmetric Diels Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene was carried out in water as a test reaction. The product was obtained in high yield and with a good *endo/exo* ratio but unfortunately low *ee* values after the reaction conditions were optimized.

The synthesized L-asparagine and L-glutamine derivative ligands were also applied to the Henry (nitroaldol) elimination reaction as an organocatalyst. Addition of nitromethane to a variety of aromatic substituted aldehydes was performed to afford the corresponding nitroalkenes in high yields after the reaction conditions were optimized. Thus, a one-pot synthesis of nitroalkenes via simple, mild and inexpensive methodology was developed.

Key words: Asymmetric synthesis, chiral catalyst, organocatalyst, aryloxy alcohol, epichlorohydrin, Diels Alder, norbornene, Henry (nitroaldol) elimination reaction, nitroalkene.

ACKNOWLEDGEMENT

I would like to give my best thanks to my supervisor, Assoc. Prof. Dr. Stephen T. Astley for his patience and encouragement. He is a great mentor for me, who enriched my knowledge with his exceptional insights into chemistry. I would also like to thank Prof. Dr. Demet Astley for her help and guidance. She is very appreciated for her personal kindness to me.

I would like to express my committee members, Prof. Dr. Serap Alp and Assist. Prof. Dr. Yeşim Salman for their thoughtful comments.

Special thanks also go to the dear Astley group members, Gamze Koz, Kadriye Aydın and Neslihan Korkmaz, for their lasting frienships, suggestions and cooperation.

I want to thank to Research Grand Office of Ege University for supporting the 2007 Fen 044 numbered project. I also thank to TUBITAK for research funds (project number 107T254).

Finally, I am greatful to my family, especially my husband Yusuf Karadeniz for his love, encouragement, understanding and supporting, my son Mete, who gave me so much happy time at home and my parents for their great support of all my life.

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SYMBOLS AND ABBREVIATIONS

Abbreviations

^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
FT-IR	Fourier Transformation Infrared
HPLC	High Pressure Liquid Chromatography
TLC	Thin Layer Chromatography
Boc	*tert*-butyl carbonate
Cbz	Carbobenzoxy
$NaHCO_3$	Sodium Hydrogen Carbonate
Na_2SO_4	Sodium Sulphate
NaOH	Sodium Hydroxide
NaCl	Sodium Chloride
KBr	Potassium Bromide
PPh_3	Triphenyl Phosphine
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DOPA	3,4-dihydroxyphenylalanine
EtOAc	Ethyl Acetate
EtOH	Ethanol
MeOH	Methanol
n-PrOH	n-propanol
n-BuOH	n-Butanol

SYMBOLS AND ABBREVIATIONS (Continue)

Abbreviations

IPA	Isopropylalcohol
THF	Tetrahydrofurane
DCM	Dichloromethane
$CDCl_3$	Chloroform-d
H_2O	Water
HKR	Hydrolytic Kinetic Resolution
ee	Enantiomeric Excess
Hz	Hertz
J	Coupling Constant
ppm	Parts per million
δ	Chemical Shift
s	Singlet
m	Multiplet
d	Dublet
t	Triplet
dd	Double doublet
td	Triple doublet

1. INTRODUCTION

1.1. Chirality

Chirality is a fundamental symmetry property of three-dimensional objects. An object is said to be chiral if it can not be superimposed upon its mirror image. In a chemical context, chirality is applied to the three-dimensional structure of molecules. Many compounds may be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangement of atoms such that they are related as mirror images. In such a case the two possible forms are called *enantiomers* and are said to be *enantiomeric* with each other. To take a simple example, amino acids can be obtained in two forms which are clearly related as mirror images (**Figure 1.1**)

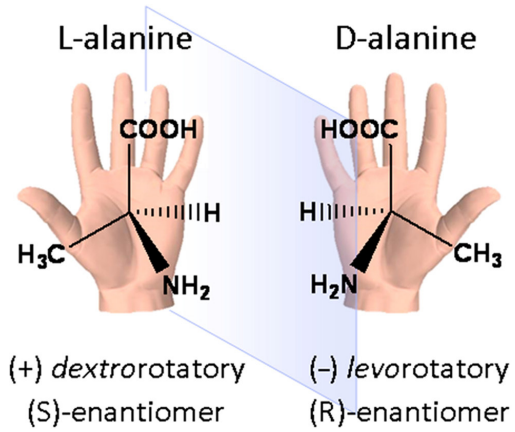
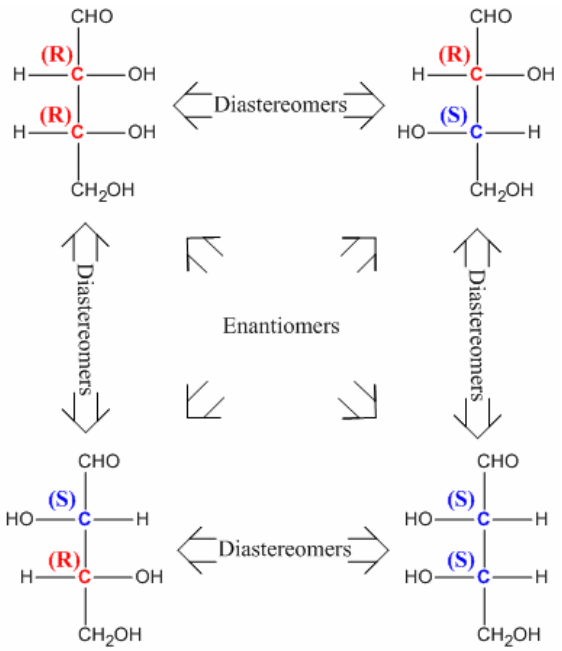


Figure 1.1. Enantiomeric forms of amino acids

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. This means that enantiomers have the same melting point, solubility, chromatographic retention time IR and NMR spectra as each other. If they are mixed, however, the resulting sample will have different physical properties such as melting point and solubility, but the chemical based properties, such as chromatographic and spectroscopic behavior will be unchanged. This has an important consequence if we want to determine the proportion of the two enantiomers in a mixture: the normal chromatographic and spectroscopic methods of analysis must be modified to introduce an external chiral influence. Only then will the enantiomers behave differently from each other and analysis be possible.

Diastereomers are stereoisomers that are not enantiomers or mirror images of each other. Diastereomers can have different physical properties and different reactivity.

If a molecule contains a single asymmetric carbon atom, it is will have two mirror image forms. If a molecule contains two asymmetric carbons, there are 4 possible configurations, and they can not all be mirror images of each other. The possibilities continue to multiply as there are more asymmetric centers in a molecule.



1.2. The Biological Significance of Chirality

The world around us is chiral and most of the important building blocks which make up the biological macromolecules of living systems do so in one enantiomeric form only. When, therefore, a biologically active chiral compound, such as a drug, interacts with its receptor site which is chiral, it should come as no surprise that the two enantiomers of the drug interact differently and may lead to different effects.

A good example is the drug Thalidomide for which both enantiomers have the desired sedative effect but only the (-)-enantiomer (**Figure 1.2**) causes foetal deformities. Unfortunality the drug was used clinically as an equal mixture of the enantiomers but even if the pure (+)-enantiomer had been used problems would have arisen since the two interconvert under physiological conditions.

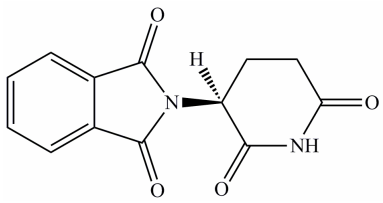


Figure 1.2. (-)-Enantiomer of Thalidomide

A more interesting situation occurs in the case of DOPA (**Figure 1.3**) used in the treatment of Parkinson`s disease. The active drug is the achiral compound dopamine formed from DOPA by decarboxylation but this cannot cross the 'blood-brain barrier' to reach the required site of action. The 'prodrug' DOPA can and is then decarboxylated by the enzyme dopamine decarboxylase. The enzyme, however, is specific and only decarboxylates the (-)-enantiomer of DOPA. It is therefore essential to administer DOPA as the pure (-)-enantiomer otherwise there would be a dangerous build up of (+)-DOPA in the body which could not be metabolized by the ezymes present.

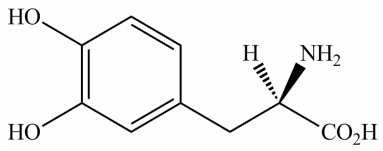


Figure 1.3. (-)-Enantiomer of DOPA

For many chiral compounds the two enantiomers have quite distinct biological activities. (-)-Propranolol (**Figure 1.4**) was introduced in 1960' s as a β-blocker for the treatment of heart disease but the (+)-enantiomer acts as a contraceptive so enantiomeric purity was obviously essential for clinical use.

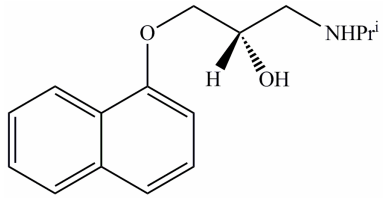


Figure 1.4. (-)-Enantiomer of Propranolol

Even when the other stereoisomers are inert it may still be desirable to synthesize and use the active one in pure form. The first reason for this is economic. The formation of inert isomers represents a waste of starting materials

and resources. Even an expensive asymmetric method may be justified if it gives exclusively the active stereoisomer. The second reason, which is becoming more and more important, might be termed environmental. Although inactive stereoisomers may appear to be inert in short term, unless they are rapidly and safely biodegraded there is a risk of long-term side effects. Thus it is clearly undesirable for an active pharmaceutical product to be administered along with several inactive isomers which do no good and might be harmful.

1.3. Enantiomerically pure components

Pure enantiomers of optically active compounds are often obtained by isolation from biological sources. When we synthesize a chiral compund in the laboratory, however, we obtain a racemic mixture of enantiomers unless an optically active material or reagent is used. The seperation of enantiomers is called resolution, and it is very different process from the usual physical seperations. A chiral probe is necessary for the resolution of enatiomers, and such a chiral compound or apparatus is called resolving agent.

Most of the physical properties of two enantiomeric products are identical, so they cannot be separated by distillation or recrystallization or by other simple physical methods. Their ability to rotate polarized light in different directions allows us to distinguish between the enantiomers, but it does not provide a means for seperation.

1.3.1.Chemical resolution of enantiomers

Unfortunately, few racemic compounds crystallize as seperate enantiomers, and other methods are required. The most common method for resolving a racemic mixture into its enantiomers is to use an enantiomerically pure natural product that bonds with the compound we want to resolve. When the enantiomers of the racemic compouns bond to the pure resolving agent, a pair of diastereomers results, the diastereomers are seperated, and then the resolving agent is cleaved from the seperated enantiomer.

1.3.2.Chromatographic resolution of enantiomers

A more convenient method for resolving enantiomers involves passing the racemic mixture through a column containing particles whose surface is coated

with chiral molecules. Solid optically active compounds such as tartaric acid and sucrose can work. In chromatographic resolution of enantiomers, the enantiomers of the racemic compound form diastereomeric complexes with the chiral material on the column packing. One of the enantiomers binds more tighly than the other, and it movement through the column is slower. The more tighly bound enatiomer leaves the column after the one that is less tightly bound.

1.4. Asymmetric synthesis and General Terms

An asymmetric synthesis may be defined as a synthesis in which an achiral unit in an ensemble of substrate molecules is converted to a chiral unit such that the possible stereoisomers are formed in unequal amounts.

In the simplest case an achiral substrate is converted to an unequal mixture of the two enantiomers of a chiral product containing only one stereogenic unit. The aim is obviously to achieve the highest possible proportion of the desired enantiomer: to maximize the enantioselectivity. If a compound exist as a single enantiomer, it is *enantiomerically pure* or *homochiral.* If a compound exists as a 1:1 mixture of the two possible enantiomers, it is racemic. The process by which the stereogenic unit in a chiral compound is destroyed and then reformed with random stereochemistry leading to a fall in the ee, eventually to zero, is described as *racemization,* while the convertion of one enantiomer to the other is referred to as *enantiomerization*. Mixtures that are not 1:1 are referred to as *scalemic* or *enantiomerically* enriched. The ratio of two enantiomers can be quantified in terms of an *enantiomeric exess* (ee). Enantiomeric exess is popularly used and relates to optical purity as measured by optical rotation:

$$\text{Enantiomeric exess (\%)} = \frac{\text{(Enantiomer 1) - (Enantiomer 2)}}{\text{(Enantiomer 1) + (Enantiomer 2)}} = \text{Optical purity (\%)} = \frac{\text{Optical rotation of mixture}}{\text{Optical rotation of single enantiomer}}$$

Optically active materials cannot be created from inactive starting materials and conditions; hence true asymmetric synthesis is imposible. However, when a new chiral center is created, the two possible configurations need not be formed in equal amounts if anything is present that is not symmetric. Such synthesis, usually called asymmetric or stereoselective syntheses, may be discussed under four headings.

Optical activity cannot be created where there was none before, an optically active material, reagent, or catalyst is necessary to produce an optically active product.

1. Active substrate: If a new chiral center is created in a molecule that is already optically active, the two diastereomers are not formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there.

2. Active reagent: A pair of enantiomers can be seperated by an active reagent that reacts faster with one of them it does with the other . If the absolute configuration of the reagent is known, the configuration of the enantiomers is preferentially formed. Creation of a new chiral center in an inactive molecule can also be accomplished with an active reagent, though it is rare for 100% selectivity to be observed (enantioselective reaction).

3. Reactions in the presence of circulary polarized light: If the light used to initate a photochemical reaction of achiral reagents is circulary polarized, then, in theory a chiral product richer in one enatiomer might be obtained.

4. The use of active catalyst or solvent

1.5. Asymmetric Catalysis

An integral part of asymmetric synthesis is asymmetric catalysis, which is dedicated to the development and applications of enantioenriched catalysts to transform prochiral and racemic substances into valuable enantioenriched synthetic building blocks. Since the first reports appeared in the 1960s, a wide variety of chiral organometallic complexes and organocatalysts (catalysts without a reactive metal component) have been identified as asymmetric catalysts (Aitken, 1992; Koskinen, 1993; Ojima, 1993; Noyori, 1994; Nogradi, 1995; Gawley, 1996; Jacobsen, 1999). These catalysts not only effect useful reactions with high levels of enantioselectivity, but often do so with a broad range of substrates (Yoon, 2003).

2. CHAPTER 1. Co(III) CATALYZED ASYMMETRIC RING-OPENING OF EPICHLOROHYDRIN BY 2,4-DIHYDROXYBENZALDEHYDE

2.1. General Information

An epoxide is a cyclic ether with three ring atoms. The importance of epoxides in organic synthesis arises partly from the occurance of the strained three-membered ring unit in a number of interesting natural products (Tarbell, 1961; Bierl, 1970; Kupchan, 1972) but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agens, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis (Parker, 1959). Further, the stereospecific manner in which epoxides generally react renders these compounds atractive chiral building blocks for asymmetric synthesis.

As an important strategy for the formation of 1,2-bifunctionalized chiral building blocks, the enantioselective ring opening of epoxides with different nucleophiles has attracted much attention from organic chemists. A wide variety of nucleophiles such as alcohols, phenols, carboxylic acids, amines, azide ions, thiols, cyanide ions and halide ions is utilized in this reaction (Pastor, 2005; Hodgson, 1996; Paterson, 1992). Among them, oxygen nucleophiles are the most important ones which lead to α-alkoxy and α-aryloxy alcohols.

2.1.1. Asymmetric ring opening of epoxides

The ring opening reaction affected by nucleophilic compounds is one of the basic transformations of epoxy compounds. It makes it is possible to form new bonds such as C-O (addition of alcohols, phenols, carboxylic acids), C-S (thiols, thiophenols or thioacids), C-N (reactions with amines and their derivatives or azides), C-X (reactions with halogenhydrins or their salts) and C-C (addition of hydrogen cyanide, metalorganic compounds), etc. (Bukowska, 2003). As an important strategy for the formation of 1,2-bifunctionalized chiral building blocks, the enantioselective ring opening of epoxides with oxygen nucleophiles are important ones which lead to α-alkoxy and α-aryloxy alcohols.

Enantiopure α-aryloxy alcohols (**Figure 2.1.**) are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds (Wright, 1997; Baker, 1995; Kirkup, 1996). In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketones (Takahashi, 1990; Gooding, 1993; Yuan, 1997; Kang, 1996; Guanti, 1986) or the ring opening of enantiopure terminal epoxides with phenols. Of these, the latter is probably the most versatile and direct, but available methods for the addition of phenols to epoxides are extremely limited. Forcing conditions are required for the uncatalyzed reaction, such as heating epoxide in the presence of a phenoxide salt to high temperatures in a polar solvent. These thermal methods are generally low-yielding and are particularly unsuitable for sensitive substrates.

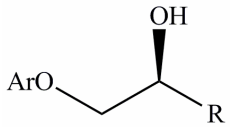
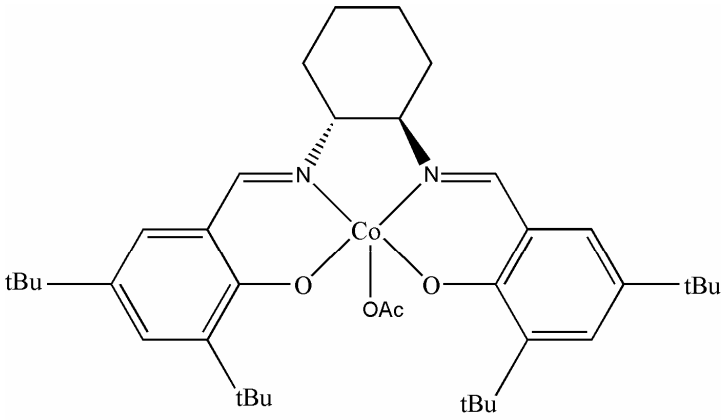


Figure 2.1. α-aryloxy alcohols

The (salen)Co(III)-catalyzed kinetic resolution of terminal epoxides with phenols provides a highly practical route to 1-aryloxy-2-alcohols using an operationally simple procedure and a readily accessible catalyst. In 1999, Jacobsen and Ready reported that the asymmetric (salen)Co(III) complex (**Figure 2.2.**) can be used for the ring-opening reaction of terminal epoxides of variety of monosubstituted phenols in *tert*-butyl methyl ether.



(R,R)-(salen)Co(OAc)

Figure 2.2. Jacobsen' s (salen)Co(III) complexes

Some terminal epoxides were screened in the kinetic resolution with phenol and results are sumarized in **Table 2.1.** Both electron-rich (entries 1 and 4) and electron poor (entries 2, 3, 5 and 6) epoxides as well as epoxides with a range of steric properties reacted with complete regioselectivity.

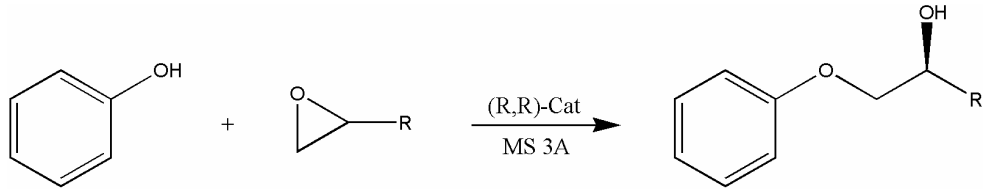


Table 2.1. Kinetic resolution of epoxides with phenol catalyzed by (R,R)-Cat.

Entry	**R**	**Temp(°C)**	**Yield (%)**	**ee (%)**
1	$(CH_2)_3CH_3$	25	97	98
2	CH_2Cl	-15	97	99
3	CH_2O(allyl)	4	93	97
4	c-C_6H_{11}	-15	99	97
5	$C(O)CH_2CH_3$	-20	96	96
6	CO_2CH_3	-20	98	96
7	C_6H_5	-25	-	n.d.

The ring-opening of epoxides with variety of monosubstituted phenols also examined and results are sumarized in **Table 2.2.**

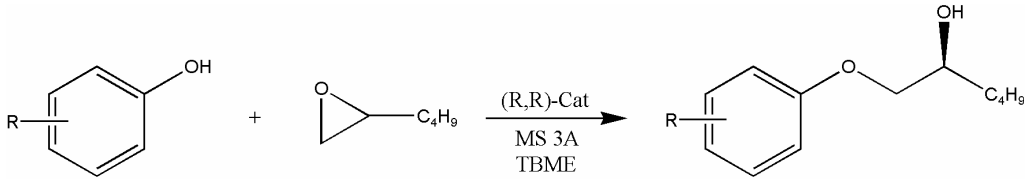


Table 2.2. Kinetic resolution of 1,2-epoxy hexane with phenols catalyzed by (R,R)-Cat.

Entry	R	Temp(°C)	Time	Yield (%)	ee (%)
1	H	25	12	97	98
2	p-CH_3	25	12	95	97
3	m-CH_3	25	16	99	99
4	o-CH_3	25	120	<5	n.d.
5	p-Br	-15	12	92	99
6	o-Br	-30	48	98	92
7	p-OCH_3	4	18	75	99
8	p-NO_2	-20	18	93	91
9	p-$(CH_2)_2$NHBoc	25	12	86	99

The reaction proceeded well when the phenol had meta or para substituents (entries 2 and 3). Regarding ortho substituents, the reaction proceeded when on ortho-bromo substituent (entry 6) was present, but afforded no product when on ortho-methyl group was present (entry 4).

2.1.2. Optically Active (salen)Co(III) Complexes

Studies on asymmetric reactions using optically active metallosalen complexes as catalysts continue to increase. The development of catalysts that are not only enantioselective and high yielding but also useful from a practical standpoint remains a challening goal in asymmetric synthesis. In the ideal case, a catalyst should be readily available or easily synthesized on any scale and should display both high reactivity (turnover frequency) and durability (turnover number). Some chiral salen-metal-based catalysts are given in the **Figure 2.3.** which are used the asymmetric ring-opening of epoxides.

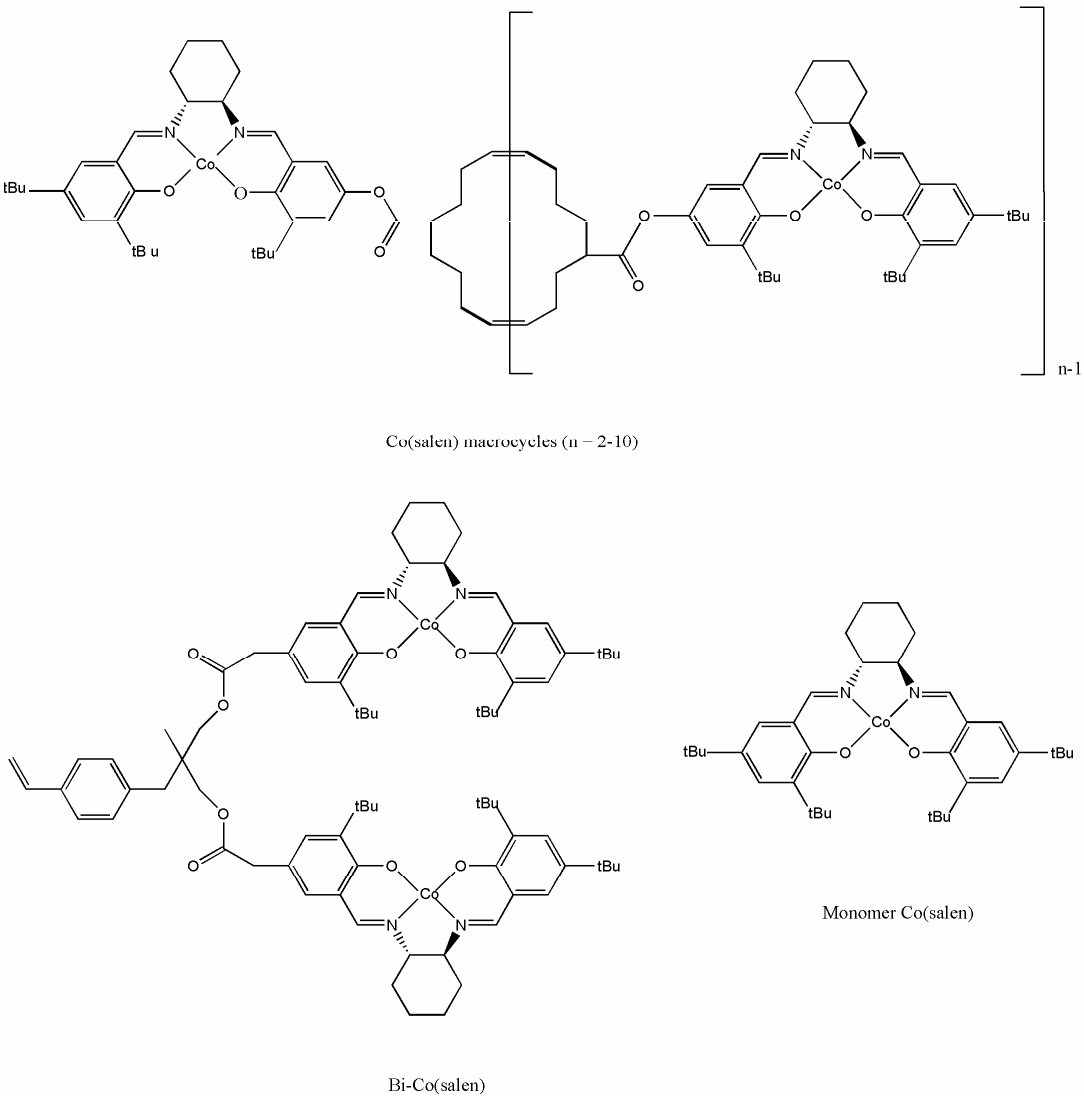


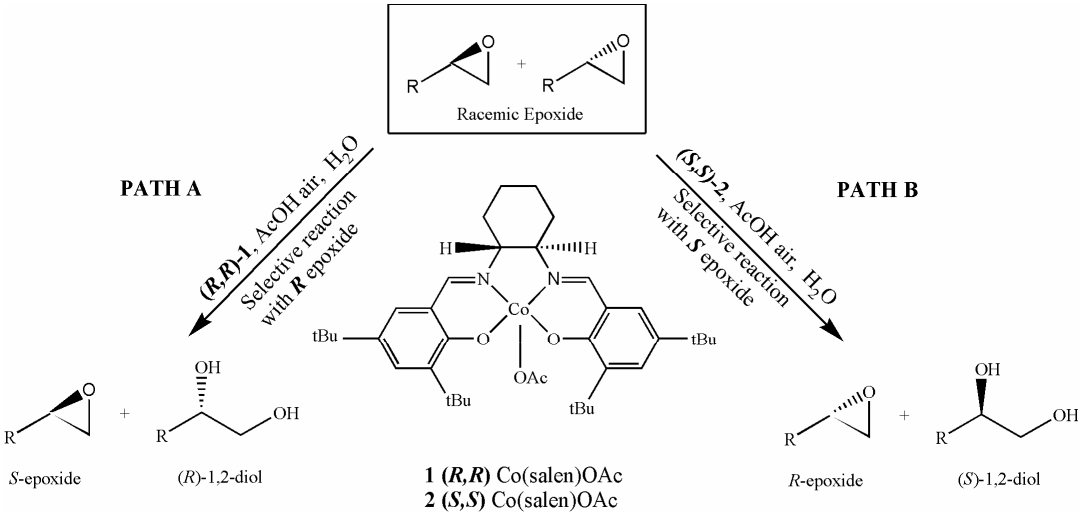
Figure 2.3. Structures of Co(salen)macrocycles, bi-Co(salen), and monomeric Co(salen)

All the catalysts have previously been used in the hydrolytic kinetic resolution of terminal epoxides under differrent conditions (Yoon, 2003; Ready, 2001; Zheng, 2007; Venkatasubbaiah, 2009). The complexes that contain multiple metal centers in appropriate relative proximity and orientation can provide improved reactivity relative to monometallic catalysts.

2.1.3. Hydrolytic Kinetic Resolution (HKR) of Racemic Epoxides

Hydrolytic kinetic resolution of racemic epoxides is an attractive strategy for the synthesis of valuable enantiopure terminal epoxides and corresponding diols in a single step (Schaus, 2002). Easy availability of inexpensive terminal epoxides and the use of water as the sole reagent with a recoverable chiral catalyst makes this solvent free protocol very attractive for its commercial exploitation.

Both terminal epoxides and the respective diols in chirally pure form have wide application in academia and industry (Tokunaga, 1997; Schaus, 2002). For the efficient resolution, the reaction rates of the two enantiomers must be unequal and the reaction must be stopped when only one enantiomer reacts to give a maximum of 50% product leaving behind the other enantiomer unreacted.



Scheme 2.1. HKR of terminal epoxide using Jacobsen complexes

Tokunaga et al. in 1997 pioneered this strategy with the use of (salen)Co(III) complexes **1**, **2** (**Scheme 2.1.**), where (R,R) form of the catalyst selectively allows water to react with the (R)-form of the epoxide to generate (R)-1,2-diol leaving behind the (S)-epoxide in high enantiomeric excess (ee) (PATH A). By simply reversing the chirality of the catalyst from (R,R) to (S,S), epoxides and 1,2-diols in their respective (R) and (S) forms (PATH B) were achieved in high optical purity. This method was found to be highly effective and economical for the low boiling racemic epoxides where catalyst separation was effected by a simple distillation process.

With the use of (salen)Co(III) complex the HKR of racemic epoxides were carried out to achieve corresponding epoxides in high ee with good isolated yields (**Table 2.3.**).

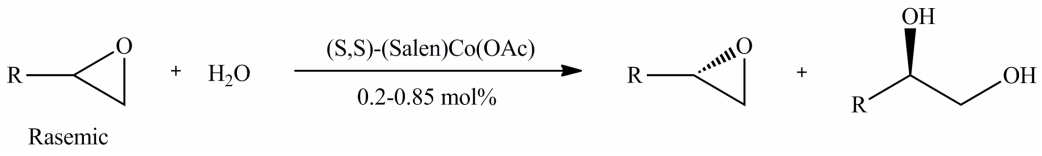
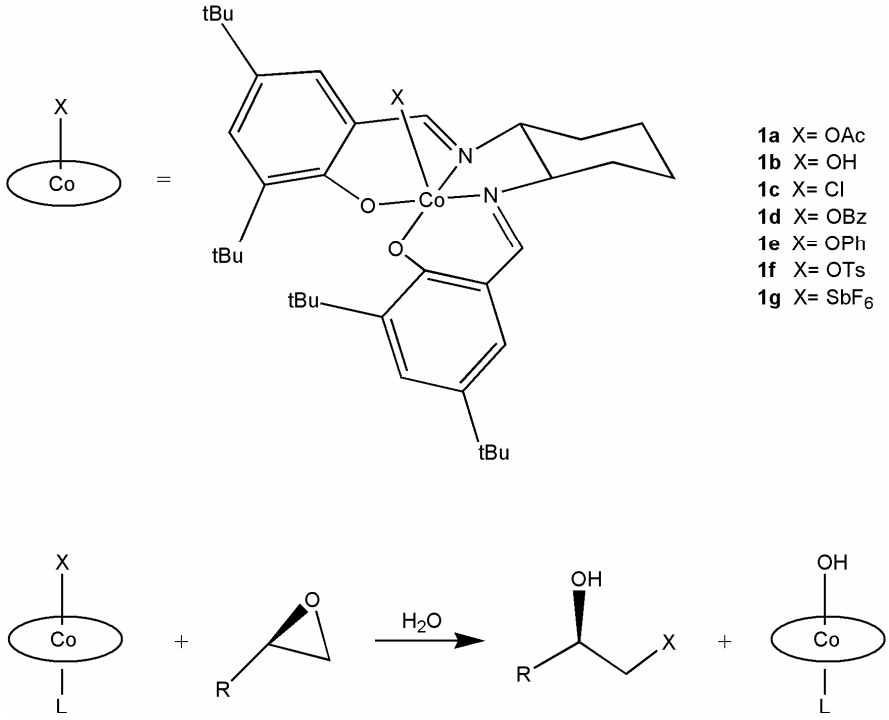


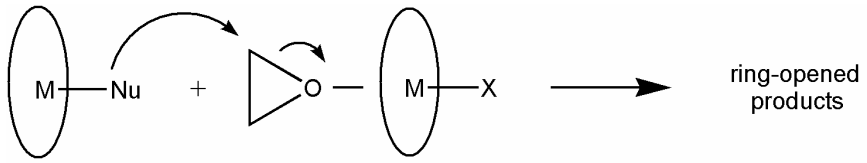
Table 2.3. Kinetic resolution of racemic epoxides

Entry	R	Epoxide	Time (h)	Yield (%)	ee (%)
1	CH_2Cl	Epichlorohydrine	6	97	98
2	CH_3	1,2-Epoxypropane	6	97	99
3	$(CH_2)_3CH_3$	1,2-Epoxyhexane	10	93	97
4	$(CH_2)_5CH_3$	1,2-Epoxyoctane	12	99	97



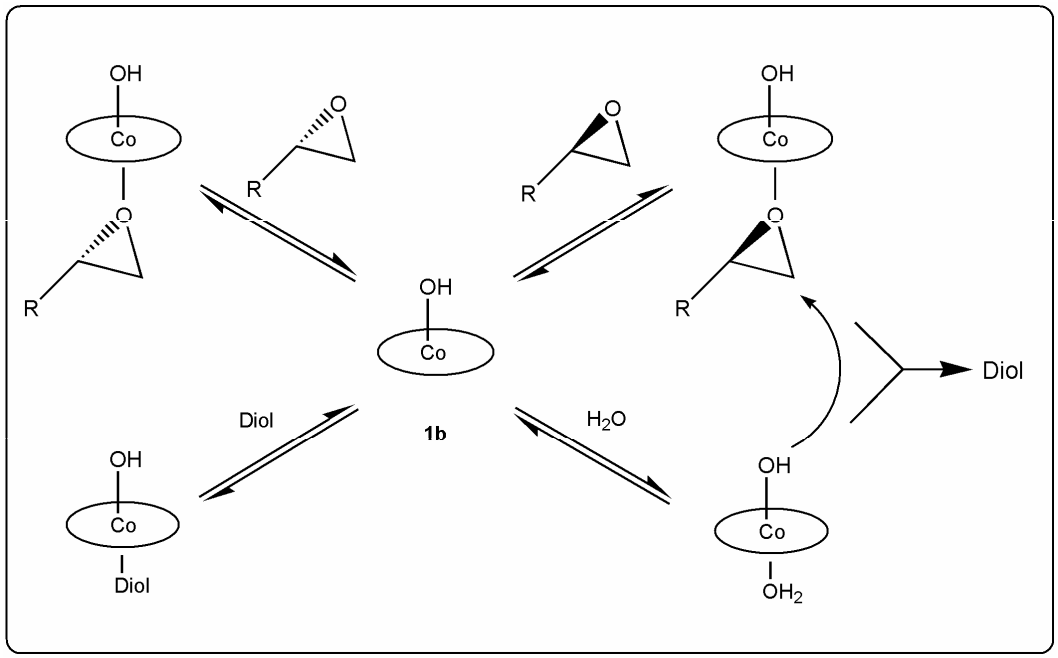
Scheme 2.2. Cobalt-salen catalyzed HKR

The acetate complex has been the most widely used catalyst to date; however, beneficial effects of other counterions on catalyst reactivity have been noted (Schaus, 2002; Kim, 2003). The active form of the catalyst is (salen)Co(OH), which can be generated from either (salen)Co(OAc) or (salen)CoCl by addition of the counterion to the epoxide (**Scheme 2.2.**).



Scheme 2.3. The active form of the catalyst

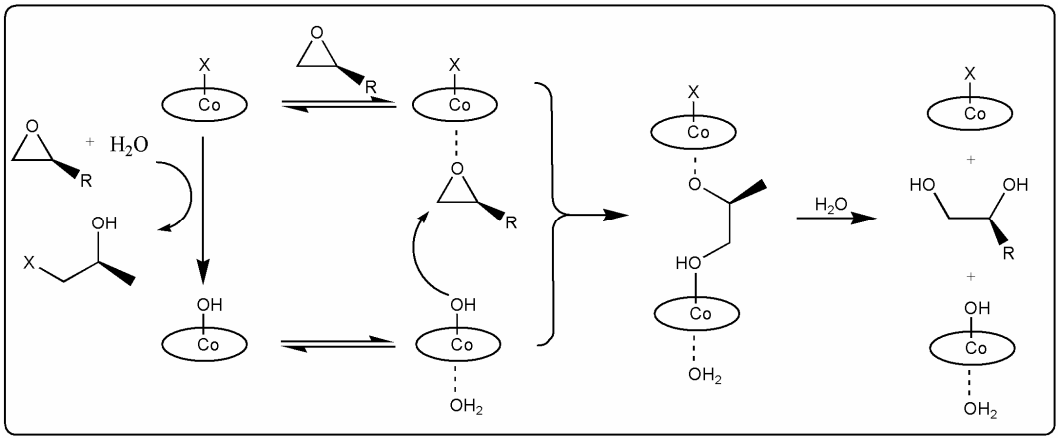
A detailed kinetic study of the HKR has provided insight into the working of this exceptional catalyst system. The HKR has been found to be second order in catalyst (Tokunaga, 1997; Nielsen, 2004), proceeding via a cooperative spelling bimetallic mechanism with simultaneous activation of both the epoxide and nucleophile by different monomeric catalysts, as illustrated in **Scheme 2.4**.



Scheme 2.4. Relevant equilibria in the (salen)Co(OH) catalyzed HKR

It was found that both enantiomers of the epoxide coordinate to the (salen)Co(OH) complex with comparable binding constants. The high selectivity in the ring-opening, therefore, must arise from the preferential reaction of one of the diastereomeric catalyst-epoxide adducts. It was also found that water and epoxide bind with similar affinities to (salen)Co(OH), but the diol product has a much lower affinity. When (salen)Co(X) compounds with less nucleophilic counterions, such as tosylate, were present with (salen)Co(OH), the activity increased by up to 30-fold. Under these conditions, the (salen)Co(X) and

(salen)Co(OH) complexes are believed to play different roles in the catalytic cycle.



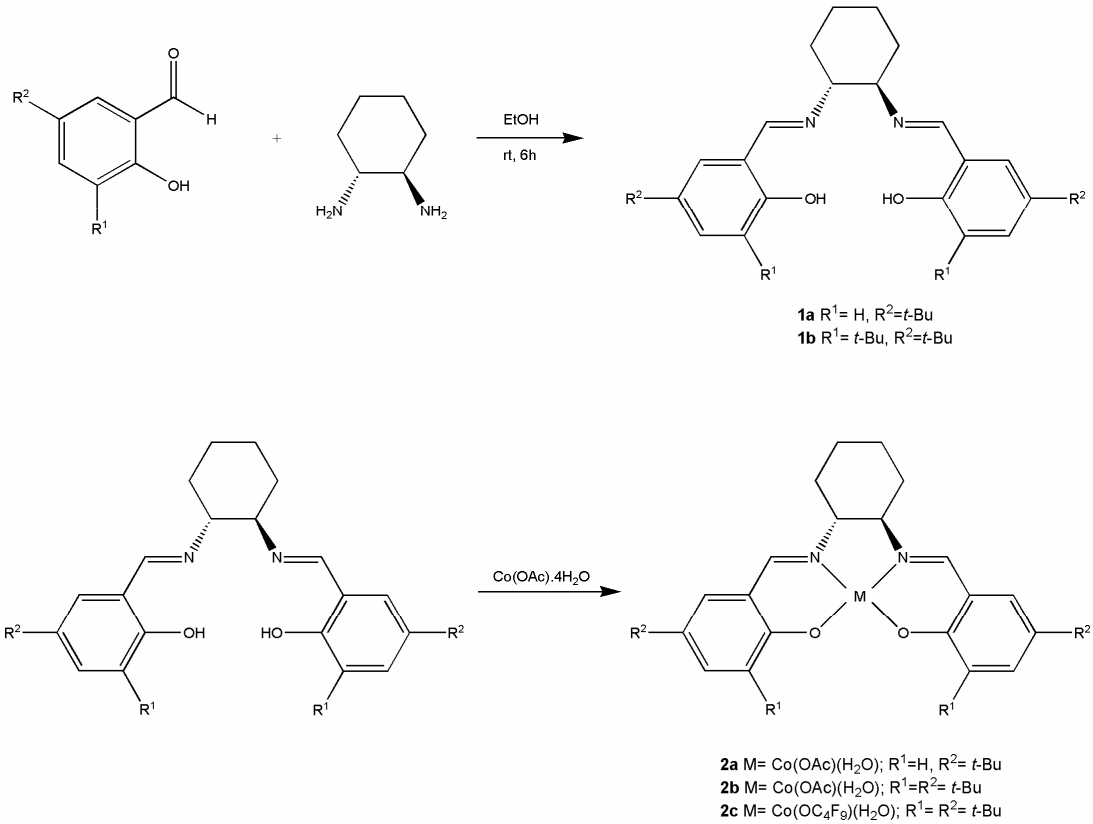
Scheme 2..5. Proposed mechanistic scheme for the dual catalyst role in the HKR

The (salen)Co(X) complex is more Lewis acidic and is expected to bind the epoxide more tightly, better activating it toward nucleophilic attack than the less Lewis acidic (salen)Co(OH). The (salen)Co(X) complex alone, however, does not promote the addition of water to the epoxide (Nielsen, 2004). Rather, the (H_2O)(salen)Co(OH) species, which activates the nucleophile, is also required. The proposed dual catalyst mechanism in **Scheme 2.5.** accounts for the observation that when the (salen)Co(OAc) is employed, the HKR slows considerably in the late stages. As the reaction progresses, the concentration of the more Lewis acidic (salen)Co(OAc) is depleted, because the acetate opens the epoxide to generate (salen)Co(OH). By the time the HKR approaches completion, all the (salen)Co(OAc) has been converted into (salen)Co(OH), which is less Lewis acidic and less active. This example is also unique in that the (salen)Co(X) compound is fulfilling the roles of precatalyst and cocatalyst.

2.2. Results and Discussion

2.2.1. Synthesis of Schiff bases and the (Salen)Co(OAc) catalysts

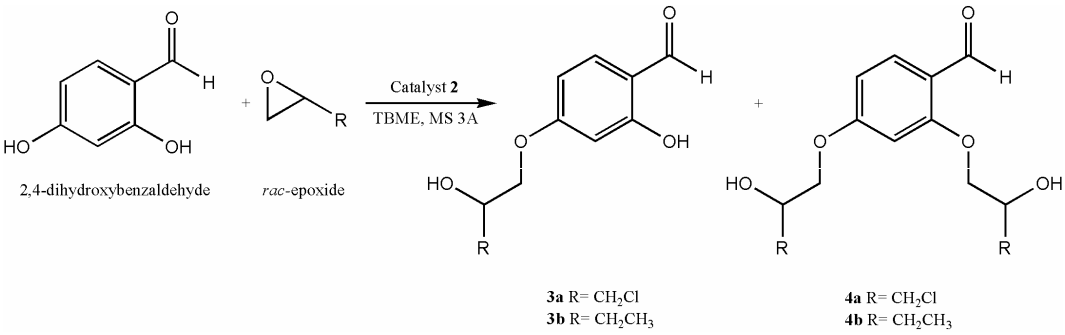
Jacobsen`s chiral (salen)Co(OAc) complexes were used for the asymmetric ring opening of epichlorohydrin with 2,4-dihydroxybenzaldehyde. Chiral salen ligands were synthesized by the condensation of (1R,2R)-1,2-diaminocyclohexane and the salicylaldehyde derivatives (**Scheme 2.6.**).



Scheme 2.6. Synthesis of the salen ligands and Co(III) complexes

2.2.2. Asymmetric ring-opening of epoxides with 2,4-dihydroxybenzaldehyde

In this study, asymmetric ring-opening of epichlorohydrin with 2,4-dihydroxybenzaldehyde were investigated. The products are important since they have significant functional groups on them. The functional groups can be converted to other functional groups. Furthermore, the Schiff bases of the aldehyde can be prepared for ligand synthesis. 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 pharmaceutically compounds. The ring-opening reaction of epoxides with the phenolic oxygens of 2,4-dihydroxybenzaldehyde is illustrated in **Scheme 2.7.**



Scheme 2.7. Asymmetric ring opening of epoxides with 2,4-dihydroxybenzaldehyde in the presence of chiral (salen)Co(III) complexes

The products were isolated with column chromatography. They were characterized by NMR and IR spectroscopy. Compounds **3a**, **3b** and **4a** gave IR, ^{1}H, ^{13}C NMR spectra corresponding to the proposed formulations. The IR spectra of the aldehydes **3a** and **4a** showed the characteristic absorption of a –C=O group at 1631 and 1600 cm^{-1}, respectively. –OH group vibrations gave rise to broad bands in 3416 and 3381 cm^{-1}, respectively. The ^{1}H NMR spectra of **4a** was similar to **3a** but phenolic-OH peak was not observed at 11.36 ppm. In the ^{13}C NMR spectra of **3a** and **4a**, the signals of the –C=O carbon atoms were observed at 194.74 and 188.73 ppm, respectively.

Confirmation that major product (**3a**) had formed cleanly at the 4-OH position was obtained from ^{1}H NMR and conversion of the product to the corresponding benzisoxazole (will be mentioned in section 2.2.4).

In the IR spectra of **3b**, a –C=O stretching absorption band and a –OH group vibration were observed at 1633 and 3428 cm^{-1}, respectively. The ^{1}H NMR spectrum of **3b** showed the characteristic aldehyde proton at 9.72 ppm. Compound **3b** also showed a singlet at 11.44 ppm, which could be ascribed to the phenolic OH group.

The effects of changing the ratios of aldehyde, epoxide and catalyst were investigated (**Table 2.4.**).

Table 2.4. Summarized of the reaction condition and yield of products

Entry	R	Catalyst	Ratio[a]	Time	Yield 3(%)[b]	Yield 4(%)[b]
1	CH_2Cl	2a	50:200:1	2 days	67	5
2		2b	50:200:1	2 days	85	-
3		2c	50:200:1	3 days	88	-
4		2a	50:200:2	12 days	-	61
5		2a	50:55:2.5	24 h	80	14
6		2b	50:55:2.5	22 h	87	6
7		2c	50:55:2.5	24 h	47	-
8	CH_2CH_3	2a	50:55:2.5	2 days	91	n.d.
9		2b	50:55:2.5	3 days	92	-
10		2c	50:55:2.5	5 days	83	-

[a] ratio of aldehyde: epoxide: catalyst

[b] isolated yield after column chromatography

n.d. not determined

It was understood from the TLC while the reaction continued, product **3** was first obtained. As the time progresses, product **3** may undergo partial conversion to product **4,** especially if catalyst **2a** was used (entry 1). By contrast, catalyst **2b** and **2c** afforded only clean conversion to **3a.** When the amount of catalyst **2a** was increased and the reaction time was increased to 12 days, product **3a** was completely consumed and product **4a** was obtained in 61% yield (entry 4). Catalyst **2b** is also good for the synthesis of product **3b**. Although reactions were tried on epichlorohydrin and 1,2-epoxybutane, the best results were obtained for epichlorohydrin. Therefore epichlorohydrin as an epoxide was used in the asymmetric ring opening reaction of epoxide with 2,4-dihydroxybenzaldehyde to search for the optimal conditions.

Some experiments were carried out at different ratio of aldehyde:epichlorohydrin:catalyst (entries 1, 4 and 5). For the ring-opening reactions of epoxides, the best mole equivalent was found to be aldehyde:epichlorohydrin:catalyst = 50:55:2.5 (entry 5). Under these conditions, the reactions were completed within approximately 24 h at room temperature for product **3a** (entries 5, 6 and 7).

More recently, Kim and coworkers reported that a heterobimetallic catalyst prepared from 5-*t*-Bu substituted catalyst **2a** and $AlCl_3$ could afford high enantiomeric excesses of meta substituted phenols and that this type of catalyst was more active than a similar catalyst prepared from **2b**. We thought that it would be interesting to attempt the ring-opening reaction of epichlorohydrin by 2,4-dihydroxybenzaldehyde using catalysts **2a** and **2b** and to observe the effect of added $AlCl_3$ in these reactions (**Table 2.5.**).

Table 2.5. ee and yield of the ring-opening reaction in different conditions

Entry	Catalyst [a] (5 mol%)	$AlCl_3$ (mol%)	Temp. (°C)	Time	Yield(%)[b]	ee[c]
1	2a	-	25	24 h	80	30(S)
2	2a	-	0	11 days	52	38(S)
3	2a	5	25	43 h	66	15(S)
4	2a	5	0	11 days	50	40(S)
5	2b	-	25	22 h	87	5(R)
6	2b	-	0	11 days	33	3(R)
7	2b	5	25	43 h	69	4(R)
8	2b	5	0	11 days	41	4(R)

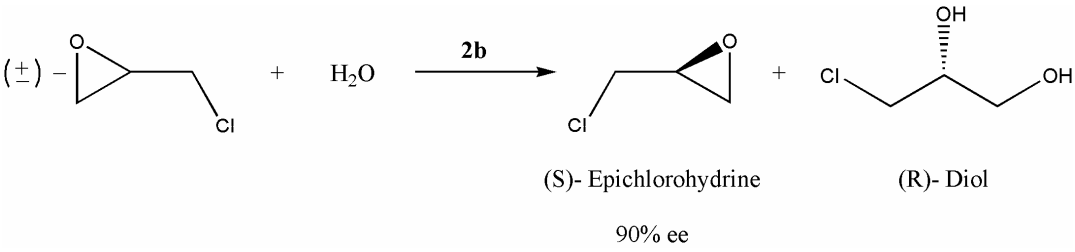
[a] reactions run in TBME
[b] isolated yield after column chromatography based on **3a**
[c] determined by chiral HPLC analysis. major enantiomer in paranthesis

The rates of the reaction for both catalysts **2a** and **2b** were very similar. Thus, the reactions were completed within approximately 22 – 43 h at room temperature (entries 1, 3, 5 and 7). Surprisingly, very poor enantioselectivity was observed for catalyst **2b**. When using catalyst **2a**, enantioselectivity was increased, but in a further surprise, the major enantiomer in this case was the (S)-enantiomer, not the expected (R)-enantiomer. This surprising enantioselectivity clearly suggests that 2,4-dihydroxybenzaldehyde is not activated by catalysts **2a** in the same way that simple phenols are (Larrow, 2004). Decreasing the reaction temperature rapidly decreased rates of reaction but afforded only a small increase in enantiomeric excess (entries 1 and 2). Addition of $AlCl_3$ to the reaction mixture caused no difference in reaction rates (entries 2 and 4). This observation is consistent with the results of Song et al., who have suggested that Lewis acids

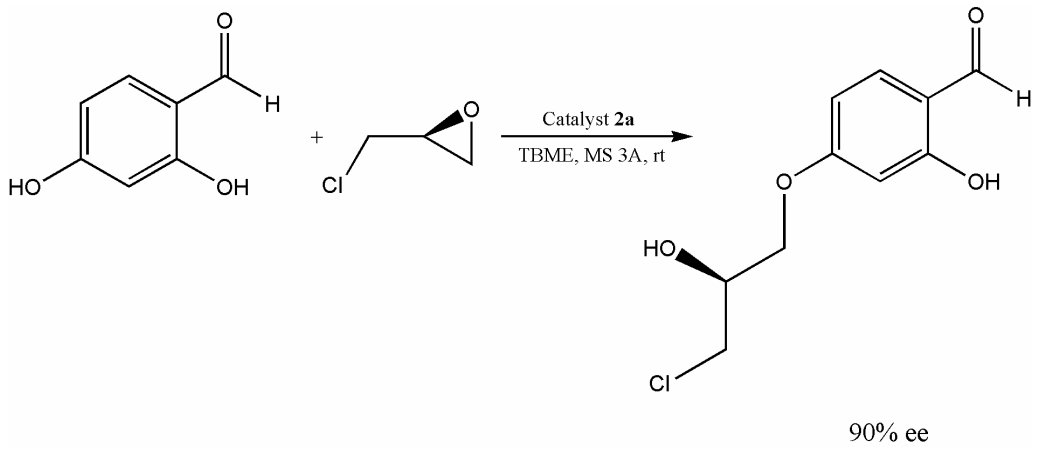
such as $AlCl_3$ do not form bimetallic catalysts with Co(III)salen complexes under these conditions and have no effect on the hydrolytic kinetic resolution of epoxides (Song, 2007).

2.2.3. Preparation of (S)-epichlorohydrin by the Jacobsen`s HKR procedure and using in the ring opening reaction

In section 2.2.2, maximum ee value we could obtain for the asymmetric ring opening of epichlorohydrin with 2,4-dihydroxybenzaldehyde was 40% even at 0 °C. There was one more way to synthesize **3a** with a higher ee, which is to use (S)-epichlorohydrin obtained by the HKR procedure (**Scheme 2.8.** and **2.9.**) and this was also the way to determine the absolute configurations of the product **3a**.



Scheme 2.8. Resolution of epichlorohydrin with HKR procedure

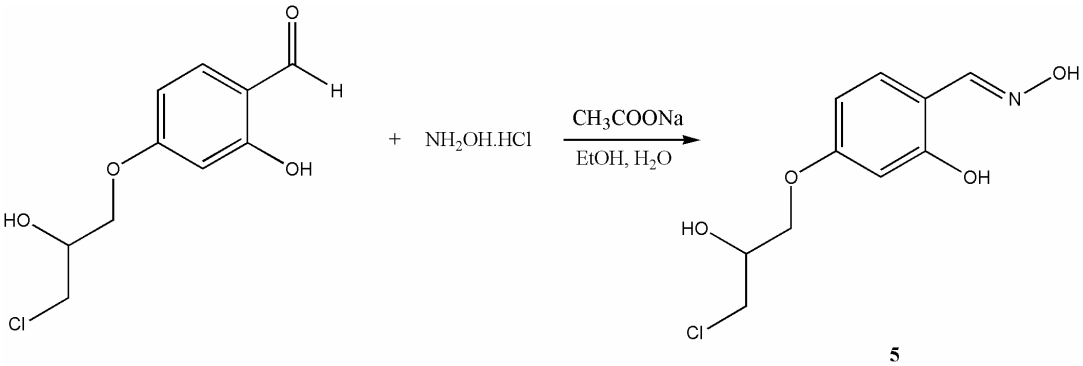


Scheme 2.9. Ring opening of (S)-epichlorohydrin with 2,4-dihydroxybenzaldehyde

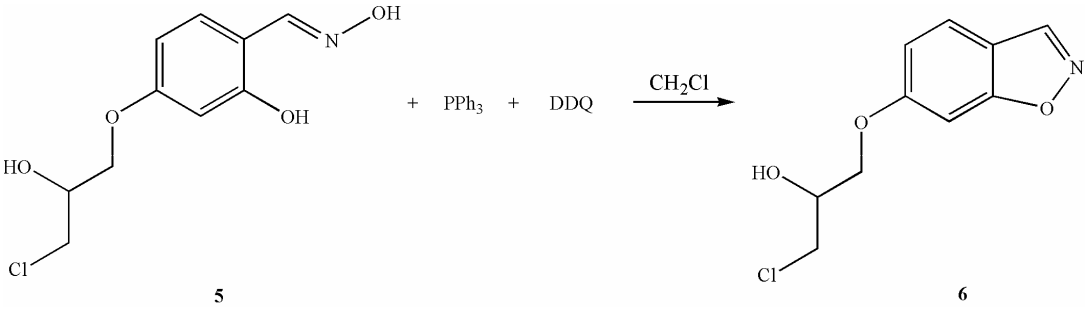
Although the yields of both hydrolytic kinetic resolution and ring-opening of epichlorohydrin reaction were not high enough, we were able to obtain product **3a** with %90 ee and determine the absolute configuration of the product.

2.2.4. Chemical derivatization to confirm the reacting phenolic oxygen

In order to confirm that the major product **3a** of the ring opening reaction had arisen from selective reaction at the 4-OH group, an oxime (Ley, 2001) and a benzisoxazole (Iranpoor, 2006) derivative of product **3a** were synthesized according to the method given in the literature (**Scheme 2.10.** and **2.11.**).



Scheme 2.10. Synthesis of oxime derivative of **3a**

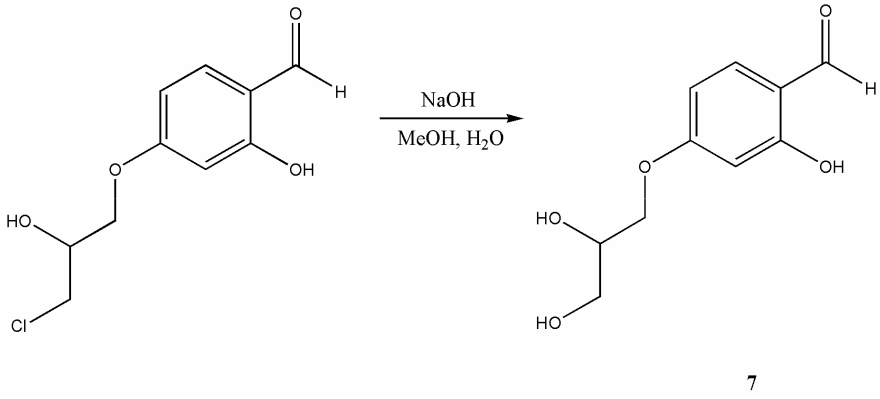


Scheme 2.11. Synthesis of benzisoxazole derivative of **3a**

The IR spectra of **5** showed the characteristic peak of –C=N functional group at 1622 cm^{-1}. The IR spectra of **6** showed some differences from **5**, especially the imine functionality, with shifts towards lower frequency by 4 cm^{-1} as compared to **6**. In the ^{1}H NMR spectra of **5**, a singlet due to the oxime proton was observed at 8.23 ppm. The OH resonance at 10.21 – 11.05 ppm strongly suggests intramolecular hydrogen bonds between the oxime nitrogen and the phenolic hydroxyl groups. In the ^{1}H NMR spectra of **6**, only a singlet proton was observed at 8.59 ppm in 8 – 12 ppm region. In the ^{13}C NMR spectra of **5** and **6**, the signals of the –C=N carbon atoms were observed at 148.61 and 146.03 ppm, respectively.

2.2.5. Diol and Schiff base derivatives of the ring opening product

Diol and Schiff base derivatives of product **3a** were synthesized (**Scheme 2.12.** and **2.13.**). Schiff base derivatives were prepared by condensation of **3a** with primary amines (2-aminophenol and 2-amino-2-metil-1-propanol).



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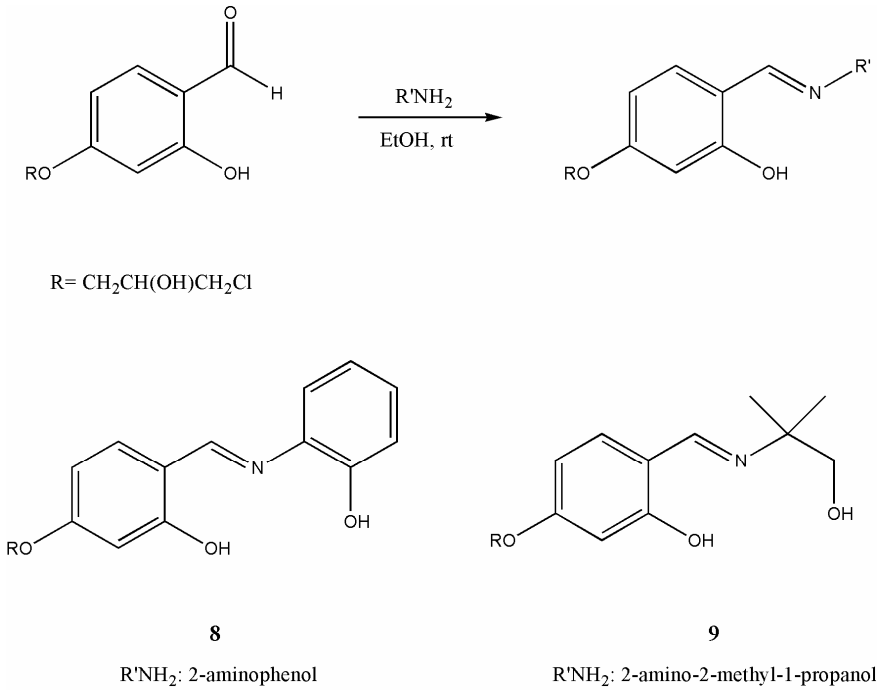
Scheme 2.12. Synthesis of diol derivative of **3a**



8

$R'NH_2$: 2-aminophenol

9

$R'NH_2$: 2-amino-2-methyl-1-propanol

Scheme 2.13. Synthesis of Schiff base derivatives of **3a**

Schiff base derivatives of product **3a** are tridentate ligands which contain a stereogenic center and may have interesting catalytic properties in asymmetric reactions.

The products were isolated with column chromatography. They were characterized by NMR and IR spectroscopy. All compounds gave IR, ^{1}H, ^{13}C NMR spectra corresponding to the proposed formulations. In the IR spectra of **7**, a –C=O stretching absorption band and a –OH group vibration were observed at 1634 and 3420 cm^{-1}, respectively. The ^{1}H NMR spectrum of **7** showed the characteristic aldehyde proton at 9.72 ppm. Compound **7** also showed a singlet at 11.44 ppm, which could be ascribed to the phenolic OH group. In the ^{13}C NMR spectra of **7**, the signals of the –C=O carbon atom was observed at 194.65 ppm.

The Schiff base structure of the salicylidene moiety of the obtained compounds is confirmed by the presence of strong imine (–C=N) vibration bands occurring in the range 1615 – 1618 cm^{-1} of the IR spectra. In addition, the ^{1}H NMR spectra of **8** and **9** showed the characteristic imine proton at 8.32 and 8.83 ppm, respectively and in the ^{13}C NMR spectra of **8** and **9**, the signals of the –C=N carbon atoms were observed at 163.52 and 163.95 ppm, respectively.

2.3. Conclusion

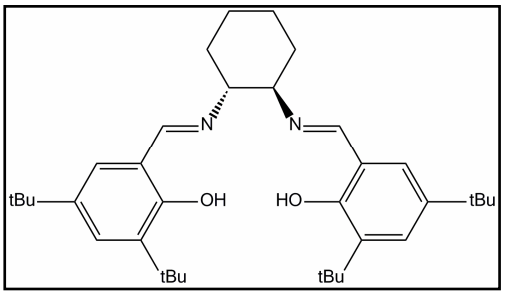
In summary, asymmetric ring-opening of epichlorohydrin has been performed for the first time using a salicylaldehyde derived nucleofile (2,4-dihydroxybenzaldehyde) in the presence of chiral Co-salen catalysts. Suprisingly, two products were obtained under different conditions. The major product was synthesized with max 40% ee. The ring-opened product was also synthesized with 90% ee using (S)-epichlorohydrin obtained by hydrolytic kinetic resolution procedure. The absolute configuration of the product was also determined by HKR. A diol and two novel Schiff base derivatives of the ring-opened product were product which can behave as polydentate chiral ligands in asymmetric synthesis. This procedure therefore opens a route for the preparation of certain α-aryloxy alcohols which may be difficult to synthesis using alternative methods.

2.4. Material and Methods

All reactions were performed under nitrogen atmosphere. Chemicals were purchased from Merck, Sigma-Aldrich, Alfa Aesar or Fluka and used without any purification. Solvents were used as received from commercial suppliers.

Molecular sieve 3A was powdered and activated in an oven at 130°C. IR spectra were recorded using a Perkin Elmer 100. ^{1}H NMR and ^{13}C NMR spectra were carried out using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. Melting points were recorded with an electro thermal digital melting points apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. For column chromatography silica gel 60 (Merck 7743) was used. HPLC analyses were performed using Chiralcel OD-H column and ethylacetate:hexane solvent systems.

2.4.1. N,N'-Bis(3,5-di-tert-butylsalicylidene)-(1R,2R)-1,2-cyclohexane diamine (1b)

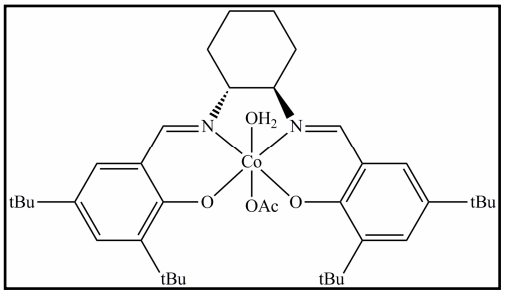


A solution of (1R,2R)-1,2-diaminocyclohexane (0.074 g, 0.64 mmol) in ethanol (10 mL) was added to a solution of 3,5-di-tert-butyl-2-hydroxy benzaldehyde (0.300 g, 1.28 mmol) in 10 mL ethanol and stirred at room temperature for 6 hours. The resulting yellow solid was filtered, washed with cold ethanol and air dried (87% yield). mp. 179-180 ºC.

2.4.2. [N,N'-Bis(3,5-di-tert-butylsalicylidene)-(1R,2R)-1,2-cyclohexane diaminato]cobalt(II)

To a stirring solution of $Co(OAc)_2.4H_2O$ (0.032 g, 0.128 mmol) in methanol (5 mL) was added dropwise to the solution of **1b** (0.070 g, 0.128 mmol) in dichloromethane (5 mL) under nitrogen. The resulting orange-red solution was stirred at room temperature for 15 minutes.

2.4.3. Oxidation of Co(II) complex to Co(III) complex (2b)

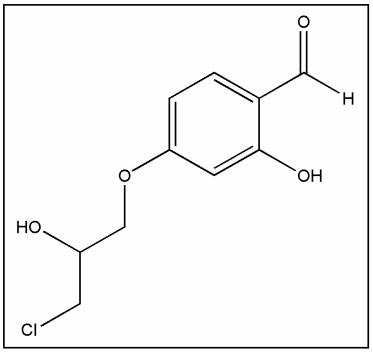


Acetic acid (with 1:2 mol ratio) was added to the Co(II) solution prepared in 2.4.2. The solution was allowed to stirr at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution

was concentrated in *vacuo* to leave a crude brown solid. The resulting catalyst residue was used for ring-opening reactions without any purification and structure determination (78% yield).

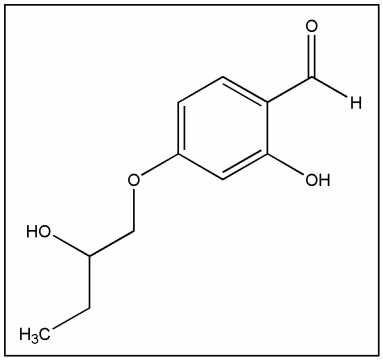
1a, 2a and **2c** were prepared using the same procedures.

2.4.4. 4-(3-Chloro-2-hydroxypropoxy)-2-hydroxybenzaldehyde (3a)



A solution of the appropriate catalyst, MS (100 mg), epichlorohydrin and 2,4-dihydroxybenzaldehyde in 0.15 mL *tert*-butylmethyl ether (TBME) was stirred. The reaction was monitored by TLC until completion. The solution was concentrated in *vacuo* and the resulting crude product was purified by column chromatography (1:2 ethyl acetate: hexane) to afford the title compound as a white solid. mp 93.1-94.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.36 (s, 1H), 9.66 (s, 1H), 7.38 (d, 1H, J = 8.8 Hz), 6.49 (dd, 1H, J = 8.4, 2.4 Hz), 6.38 (d, 1H, J = 2.4 Hz), 4.18 – 4.10 (m, 1H), 4.07 (d, 2H, J = 5.6 Hz), 3.80 – 3.71 (m, 2H), 2.52 (brs, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 194.74, 165.50, 164.58, 135.67, 115.87, 108.58, 101.80, 69.75, 69.14, 46.01 ppm. Anal. Calcd. for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 51.75; H, 4.80 %. IR (KBr): 3416, 1631, 1507 cm^{-1}. HPLC, Chiralcel OD-H column, 80:20 ethyl acetate : hexane, 313 nm, 1mL/min flow rate, (R), t= 16 min., (S), t= 22 min.

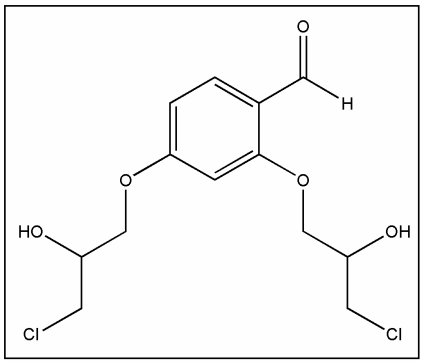
2.4.5. 2-hydroxy-4-(2-hydroxybutoxy)benzaldehyde (3b)



A solution of the appropriate catalyst, MS (100 mg), 1,2-epoxybutane and 2,4-dihydroxybenzaldehyde in 0.15 mL *tert*-butylmethyl ether (TBME) was stirred. The reaction was monitored by TLC until completion. The solution was concentrated in *vacuo* and the resulting crude product was purified by column chromatography (1:2 ethyl acetate: hexane) to afford the title compound as a yellow oil (91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.44 (s, 1H), 9.72 (s, 1H), 7.43 (d, 1H, J = 8.4 Hz), 6.56 (dd, 1H, J = 8.8, 2.4 Hz), 6.43 (d, 1H, J = 2.4 Hz), 4.04 – 4.01 (m, 1H), 3.96 – 3.88 (m,

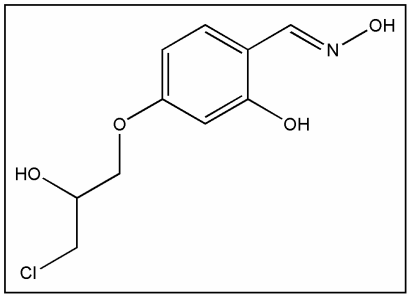
2H), 2.16 (brs, 1H), 1.65 – 1.60 (m, 2H), 1.04 (t, 3H, J = 7.2 Hz). Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 61.65; H, 6.47 %. IR (NaCl): 3428, 1633, 1506 cm^{-1}.

2.4.6. 2,4-bis(3-chloro-2-hydroxypropoxy)benzaldehyde (4a)



A solution of the appropriate catalyst, MS (100 mg), epichlorohydrin and 2,4-dihydroxybenzaldehyde in 0.15 mL *tert*-butylmethyl ether (TBME) was stirred. The reaction was monitored by TLC until completion. The solution was concentrated in *vacuo* and the resulting crude product was purified by column chromatography (1:2 ethyl acetate: hexane) to afford the title compound as a white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.19 (s, 1H), 7.76 (d, 1H, J = 8.4 Hz), 6.61 (dd, 1H, J = 8.4, 2 Hz), 6.51 (d, 1H, J = 2.4 Hz), 4.27 – 4.21 (m, 2H), 4.20 – 4.16 (m, 4H), 3.81 – 3.72 (m, 4H), 3.20 (brs, 1H), 2.74 (brs, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 188.73, 165.02, 162.28, 132.72, 119.81, 107.38, 100.17, 69.84, 69.80, 69.25, 45.94, 45.74. Anal. Calcd. for $C_{13}H_{16}Cl_2O_5$: C, 48.32; H, 4.99. Found: C, 51.56; H, 5.69 %. IR (NaCl): 3381, 1672, 1602 cm^{-1}.

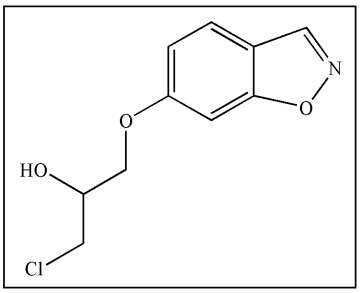
2.4.7. 4-(3-chloro-2-hydroxypropoxy)-2-hydroxybenzaldoxime (5)



A solution of $NH_2OH.HCl$ (23.47 mg, 0.34 mmol) and CH_3COONa (27.7 mg, 0.34 mmol) in 5 mL water was added dropwise to the solution of **3a** (75.3 mg, 0.33 mmol) in 2 mL ethanol and stirred at rt for 3 hours. Ethanol was evaporated and crude product was extracted with TBME – water. Organic phase was separated, dried with Na_2SO_4 and filtered. TBME was evaporated in *vacuo* and product was crystallized from dichloromethane – hexane to give the title compound as white crystals (79% yield). mp. 100-103 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 8.23 (s, 1H), 7.35 (d, 1H, J = 8.8 Hz), 6.47 (dd, 1H, J = 8.8, 2.8 Hz), 6.43 (d, 1H, J= 2.4 Hz), 4.02 – 3.98 (m, 1H), 3.95 – 3.92 (m, 2H), 3.73 – 3.61 (m, 2H). ^{13}C NMR (400 MHz, DMSO) δ (ppm) 161.03, 158.26, 148.61, 130.06, 112.20, 107.20, 69.75, 69.23, 47.31. Anal. Calcd. for $C_{10}H_{12}ClNO_4$:

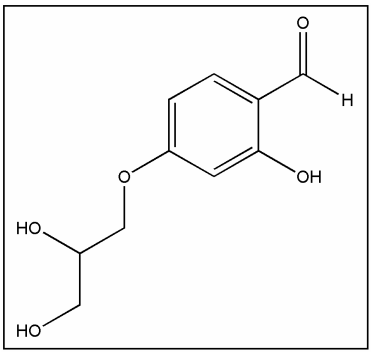
C, 48.89; H, 4.92; N, 5.70. Found: C, 48.46; H, 4.82; N, 5.76%. IR (KBr): 3379, 1621, 1577, 1514 cm^{-1}.

2.4.8. 6-(3-Chloro-2-hydroxypropoxy)-1,2-benzisoxazole (6)



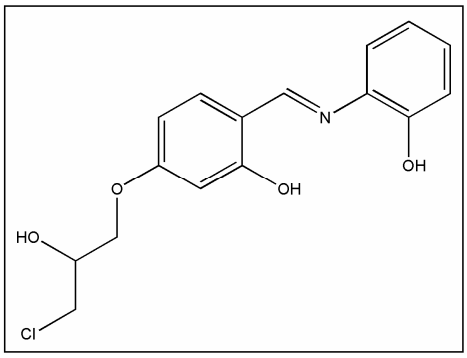
Oxime **5** (0.080 g, 0.33 mmol) was added to the suspension of triphenylphosphine (0.128 g, 0.49 mmol) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (0.111 g, 0.49 mmol) in dichloromethane and stirred at rt for 3 hours. At the end of 3 hours suspension was filtered and the filtrate was concentrated in *vacuo*. Product was purified by column chromatography (1:3 ethyl acetate: hexane) to give white crystalline compound (86% yield). mp. 79.4-82 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 8.59 (s, 1H), 7.59 (d, J= 8 Hz, 1H), 7.08 (s, 1H), 6.97 (dd, J= 8.8, 2.4 Hz, 1H), 4.31 – 4.27 (m, 1H), 4.19 – 4.17 (m, 2H), 3.84 – 3.74 (m, 2H). ^{13}C NMR (400 MHz, DMSO) δ (ppm) 164.12, 161.04, 146.03, 122.58, 115.51, 114.88, 93.76, 69.89, 69.36, 46.10. Anal. Calcd. for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.39; H, 4.41; N, 6.22%. IR (KBr): 3371, 1618, 1492 cm^{-1}.

2.4.9. 4-(2,3-Dihydroxypropoxy)-2-hydroxybenzaldehyde (7)



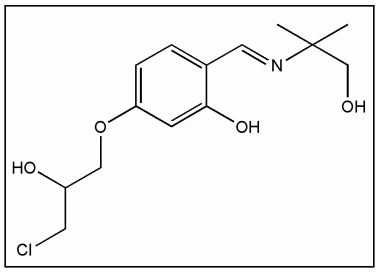
Aqueous solution of NaOH (0.86 M, 4.3 mmol) was added to solution **3a** (0.100 mg, 0.43 mmol) in 5 mL MeOH and the mixture was refluxed for 2 hours. After removal of solvent, the mixture was extracted with CH_2Cl_2. The combined organic extract was washed with water, brine and finally dried over Na_2SO_4. The organic phase was filtered and concentrated. The product was obtained yellow oil (56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.43 (s, 1H), 9.72 (s, 1H), 7.43 (d, J= 8.4 Hz, 1H), 6.56 (dd, J= 8.8, 2.0 Hz, 1H), 6.45 (d, J= 2.4 Hz, 1H), 4.17 – 4.10 (m, 1H), 4.07 – 4.05 (m, 2H), 3.59 – 3.52 (m, 2H), 2.53 (brs, 1H), 1.6 (brs, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 194.65, 165.97, 164.59, 135.56, 115.66, 108.7, 101.7, 69.67, 68.94, 59.51. Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 58.18; H, 5.97%. IR (NaCl) 3410, 1634, 1575, 1506 cm^{-1}.

2.4.10. 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxyphenyl)imino]methyl}phenol (8)



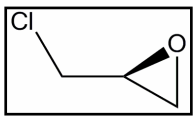
A solution of aldehyde **3a** (46 mg, 0.19 mmol) and 2-aminophenol (22 mg, 0.19 mmol) in 10 mL ethanol was stirred at rt for 2 hours. The product was crystallized from ethanol to give the title compound as yellow crystals (82% yield). mp. 164-165.7 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 14.33 (s, 1H), 9.69 (s, 1H), 8.83 (s, 1H), 7.45 (d, J= 8.4 Hz, 1H), 7.33 (dd, J= 8.0, 1.6 Hz, 1H), 7.07 (t, J= 7.2, 1.6 Hz, 1H), 6.93 (dd, J= 8.0, 1.2 Hz, 1H), 6.85 (t, J= 7.4, 1.2 Hz, 1H), 6.48 (dd, J= 8.8, 2.4 Hz, 1H), 6.39 (d, J= 2.4 Hz, 1H), 5.55 (s, 1H), 4.04 – 3.99 (m, 3H), 3.75 – 3.63 (m, 2H). ^{13}C NMR (400 MHz, DMSO) δ (ppm) 166.03, 163.52, 160.63, 151.16, 134.71, 134.58, 128.03, 120.30, 119.74, 117.08, 113.93, 107.45, 102.38, 69.87, 69.25, 47.24. Anal. Calcd. for: $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.39. Found: C, 59.73; H, 5.01; N, 4.35%. IR (KBr): 3319, 1615, 1598, 1524, 1465 cm^{-1}.

2.4.11. 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxy-1,1-dimethylethyl)imino]methyl}phenol (9)



The product was prepared with the same method used in 2.4.10 using aldehyde **3a** (43 mg, 0.19 mmol) and 2-amino-2-methyl-1-propanol (16,5 mg, 0.19 mmol). The product was crystallized from ethanol to give the title compound as yellow crystals (80% yield). mp. 140-142 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 14.55 (s, 1H), 8.32 (s, 1H), 7.23 (d, J= 8.8 Hz, 1H), 6.23 (dd, J= 8.4, 2.4 Hz, 1H), 6.13 (d, J= 2.4 Hz, 1H), 5.51 (d, J= 4.8 Hz, 1H), 5.01 (s, 1H), 4.00 – 3.92 (m, 2H), 3.67 (ddd, J= 10.8, 4.8, 4.4 Hz, 2H), 3.41 (d, J= 4 Hz, 2H), 1.22 (s, 6H). ^{13}C NMR (400 MHz, DMSO) δ (ppm) 171.31, 163.95, 161.44, 134.67, 112.20, 106.01, 102.85, 69.54, 69.21, 59.69, 47.24, 24.47, 22.93. Anal. Calcd. for: $C_{14}H_{20}ClNO_4$: C, 55.72; H, 6.68; N, 4.64. Found: C, 55.45; H, 6.61; N, 4.72%. IR (KBr): 3281, 1633, 1613, 1529 cm^{-1}.

2.4.12. Hydrolytic kinetic resolution of epichlorohydrin



A mixture of catalyst **2b** (242 mg), epichlorohydrin (6.26 ml) and THF (0.8 ml) was cooled to 0 °C, water (0.8 ml) was added and stirred at 0 °C for 16 hours. (S)-Epichlorohydrin was obtained by vacuum distillation. The purity of the product was controlled using refractive index of standard epichlorohydrin and the HKR product (Standard epichlorohydrin : 1.43862, HKR product : 1.43858).

2.5. Appendix A. Spectra and Chromatograms

A.1. IR spectra

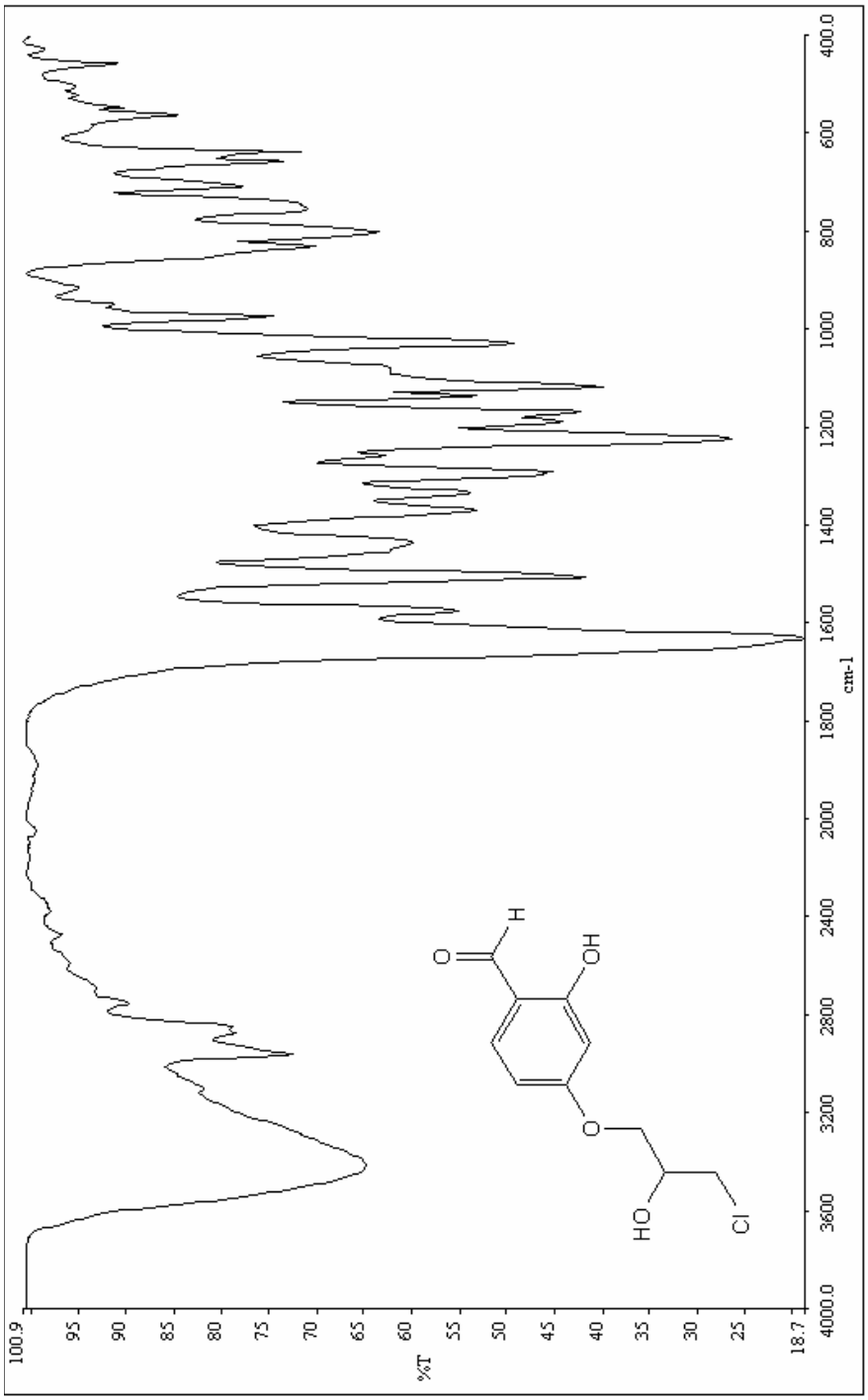


Figure A.1.1. IR spectrum of 4-(3-Chloro-2-hydroxypropoxy)-2-hydroxybenzaldehyde (**3a**)

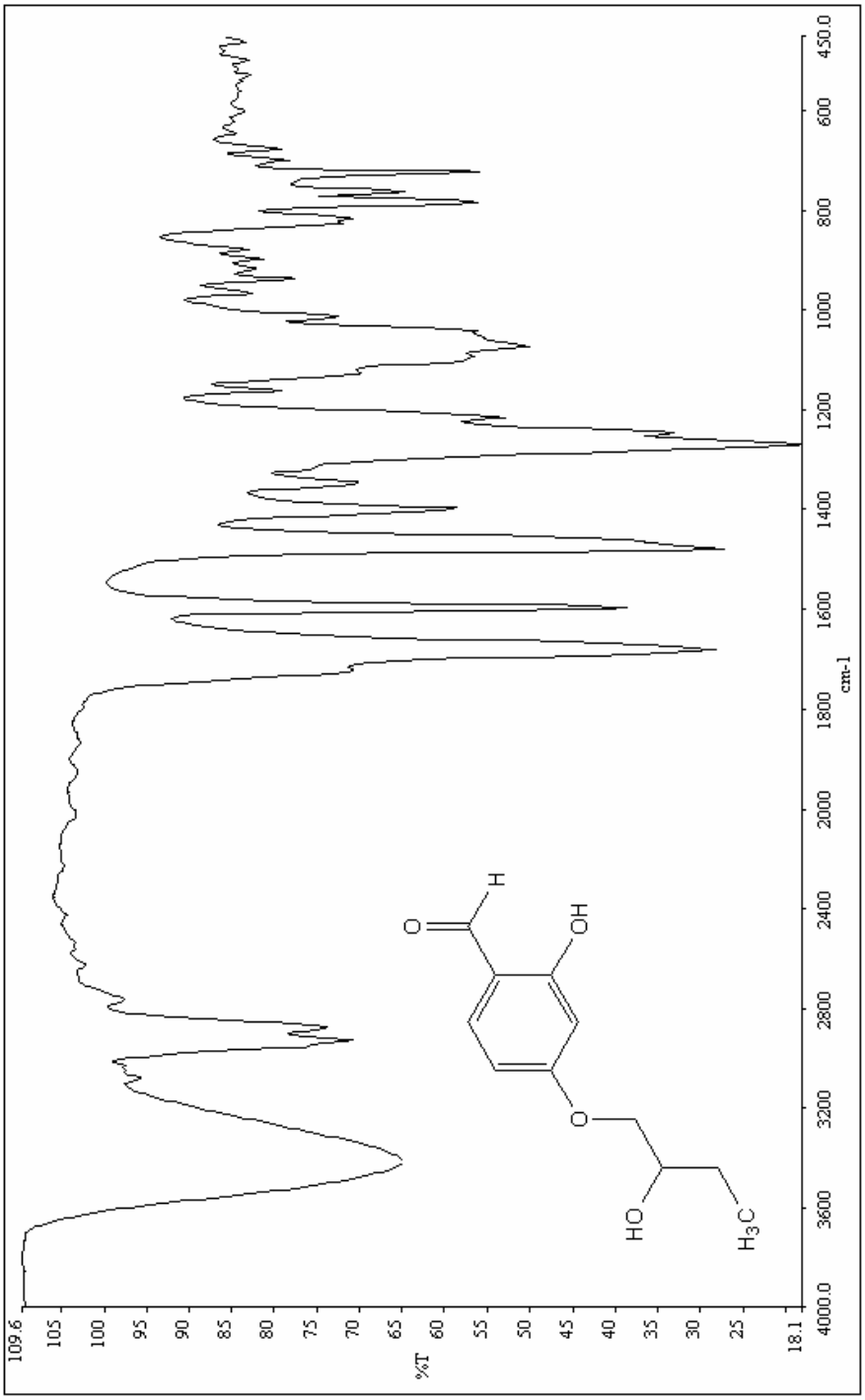


Figure A.1.2. IR spectrum of 2-hydroxy-4-(2-hydroxybutoxy)benzaldehyde (**3b**)

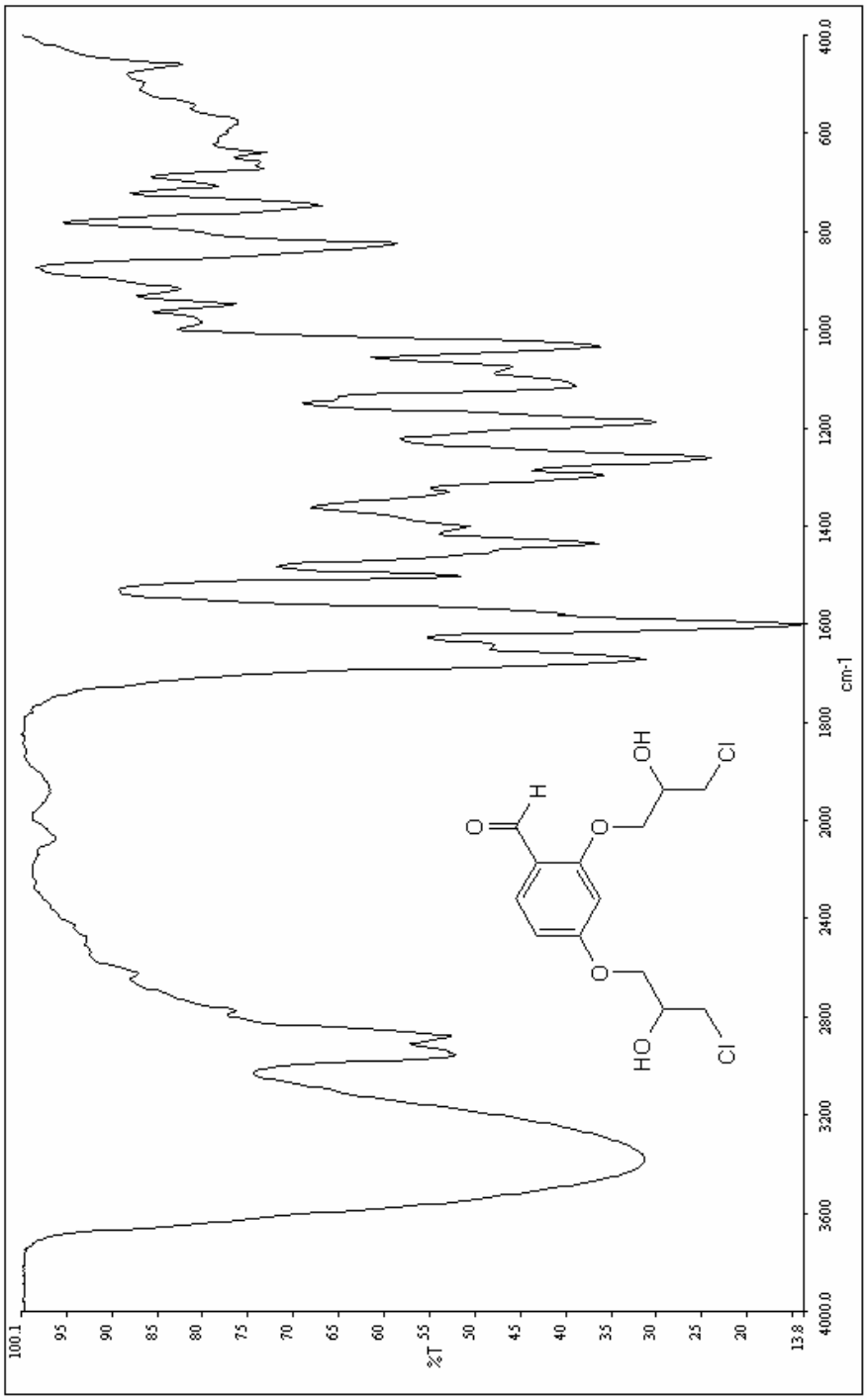


Figure A.1.3. IR spectrum of 2,4-bis(3-chloro-2-hydroxypropoxy)benzaldehyde (**4a**)

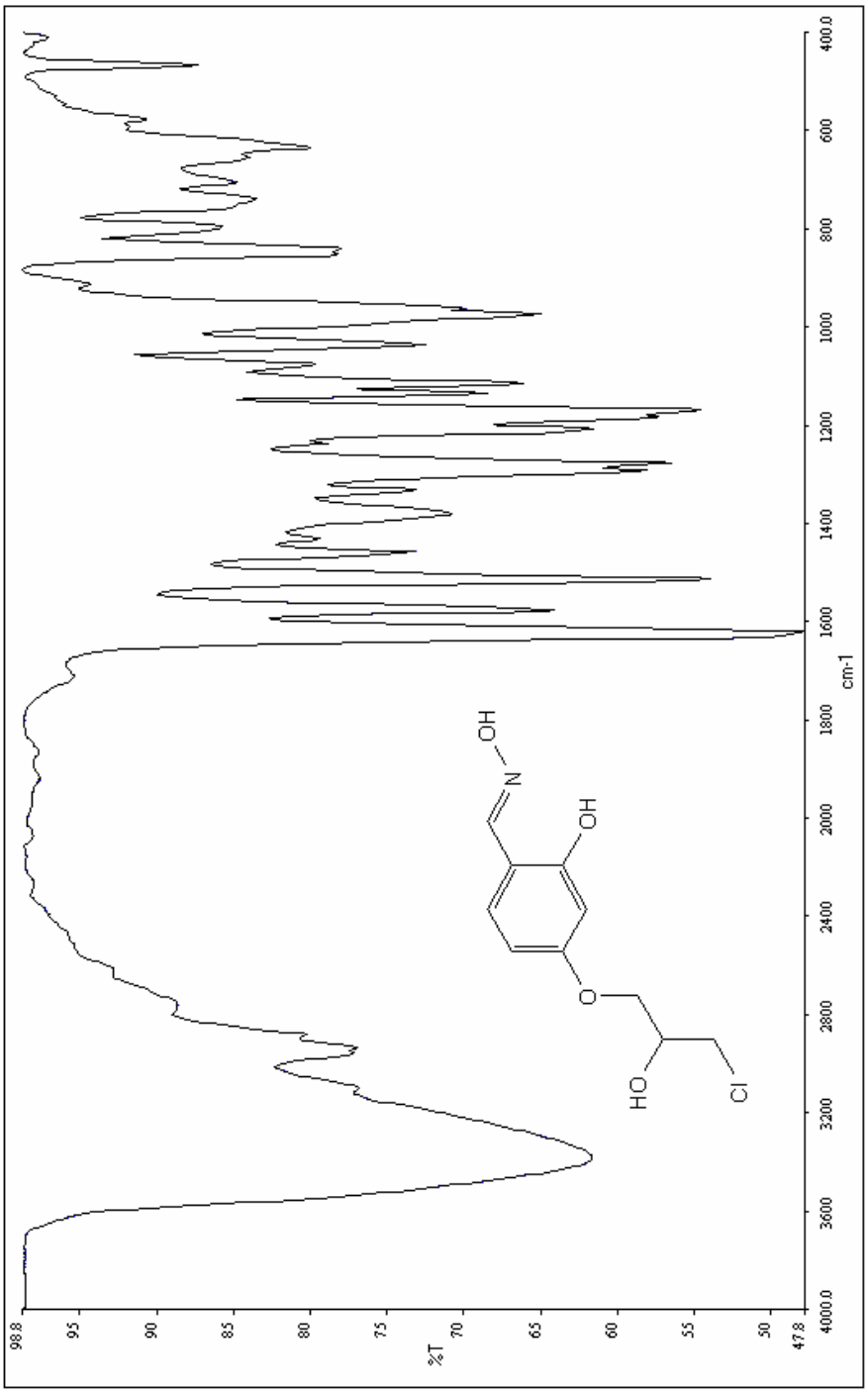


Figure A.1.4. IR spectrum of 4-(3-chloro-2-hydroxypropoxy)-2-hydroxybenzaldoxime (**5**)

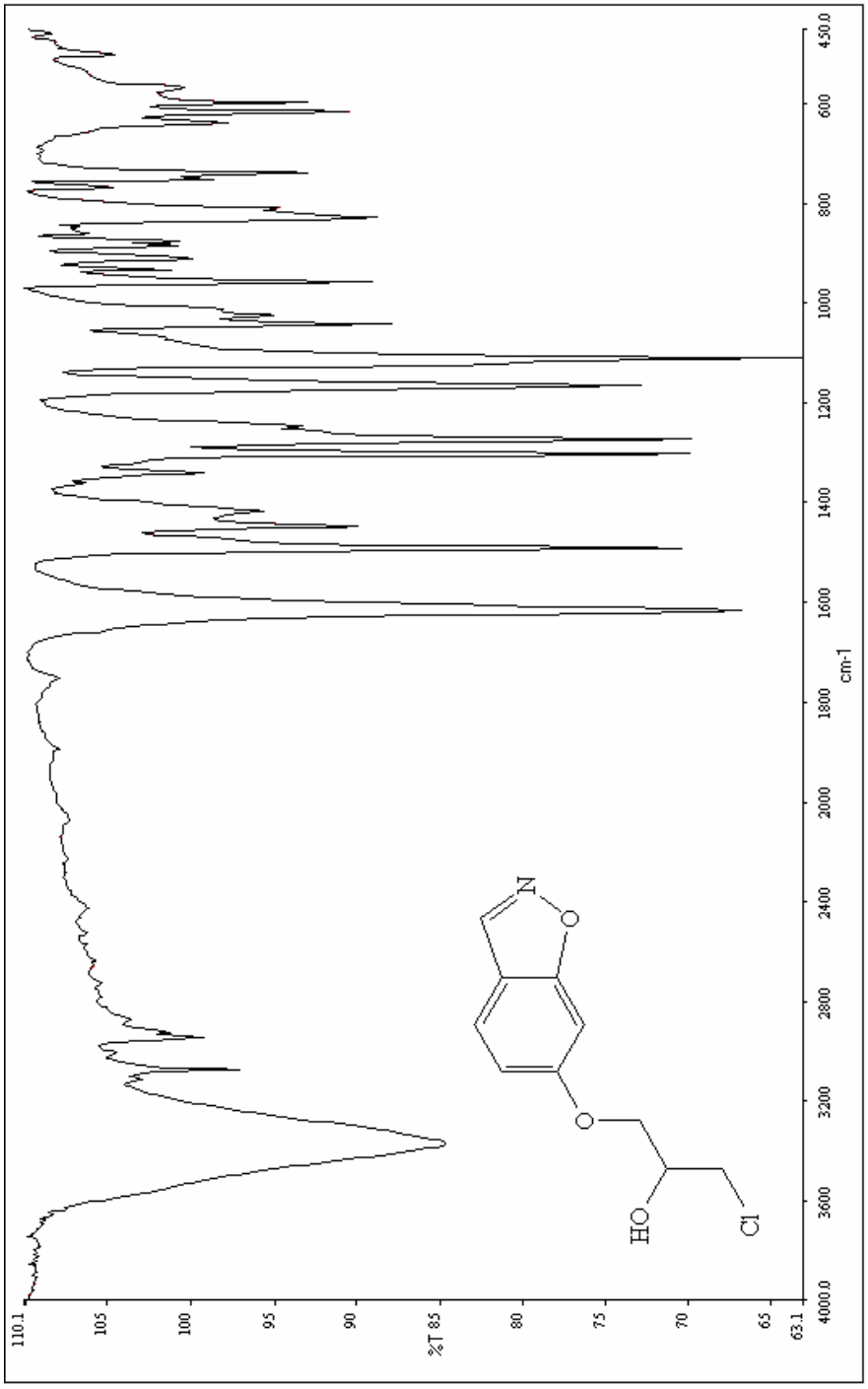


Figure A.1.5. IR spectrum of 6-(3-Chloro-2-hydroxypropoxy)-1,2-benzisoxazole (**6**)

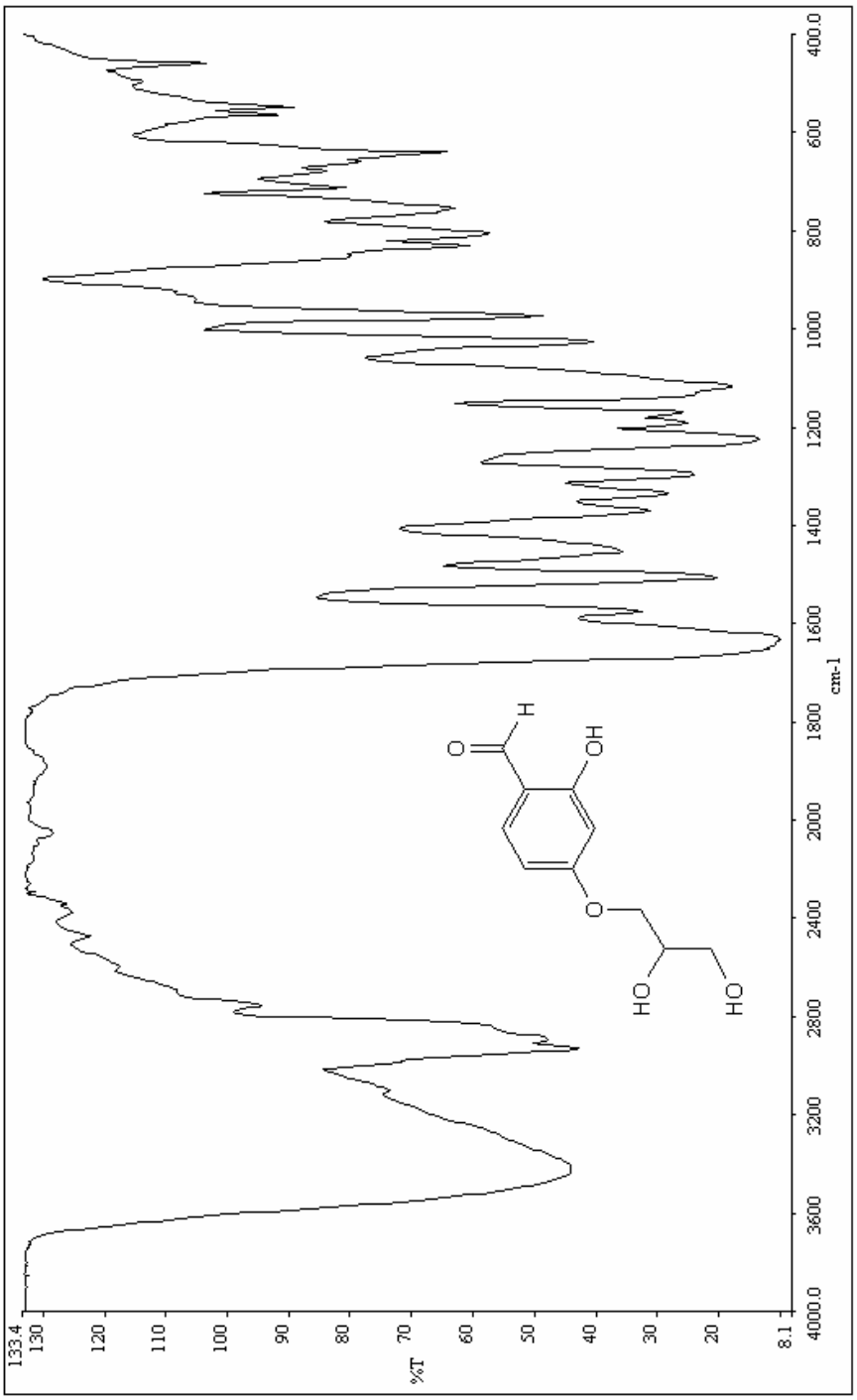


Figure A.1.6. IR spectrum of 4-(2,3-Dihydroxypropoxy)-2-hydroxybenzaldehyde (**7**)

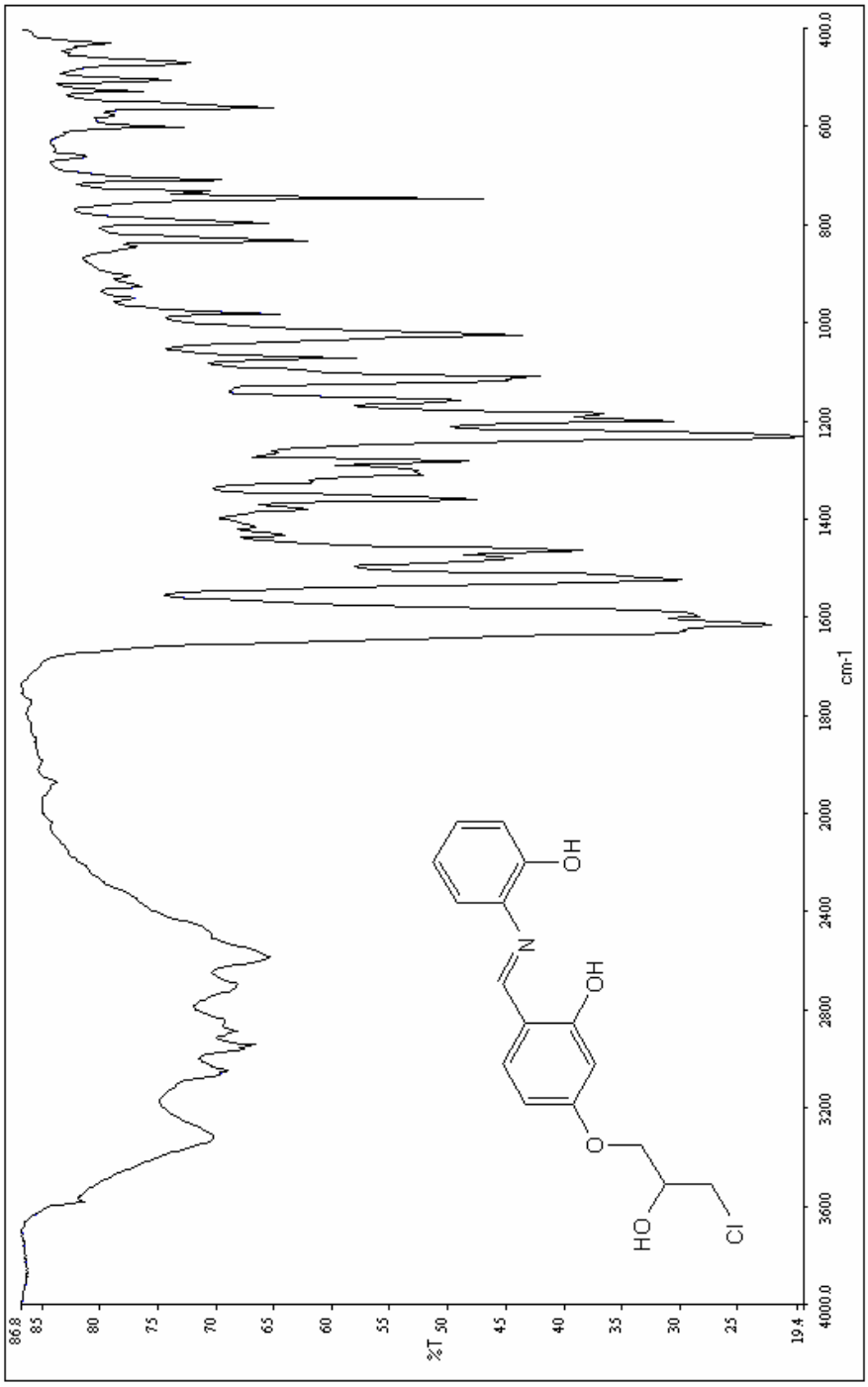


Figure A.1.7. IR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxyphenyl)imino]methyl}phenol (**8**)

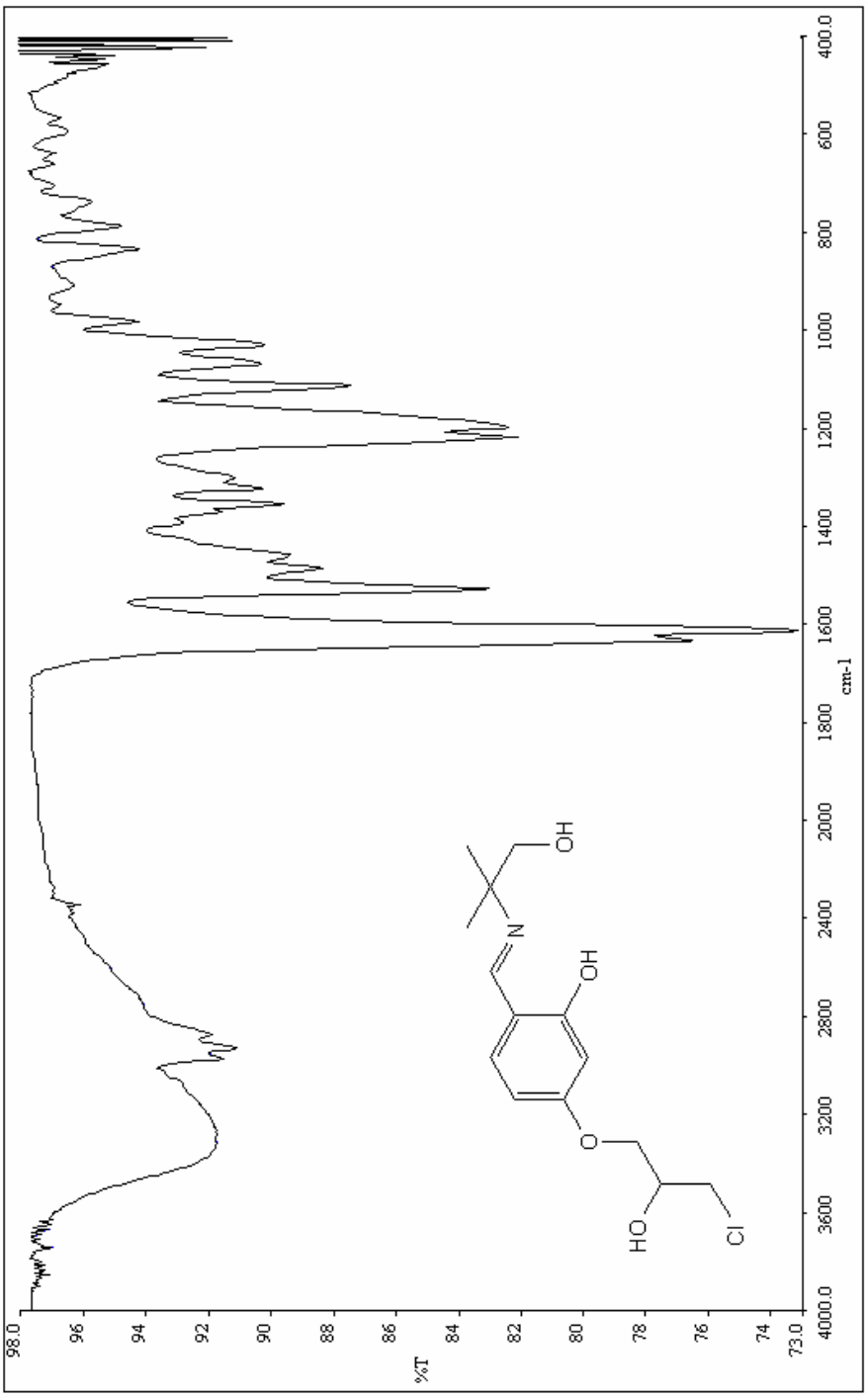


Figure A.1.8. IR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxy-1,1-dimethylethyl)imino]methyl}phenol (**9**)

A.2. ^{1}H NMR spectra

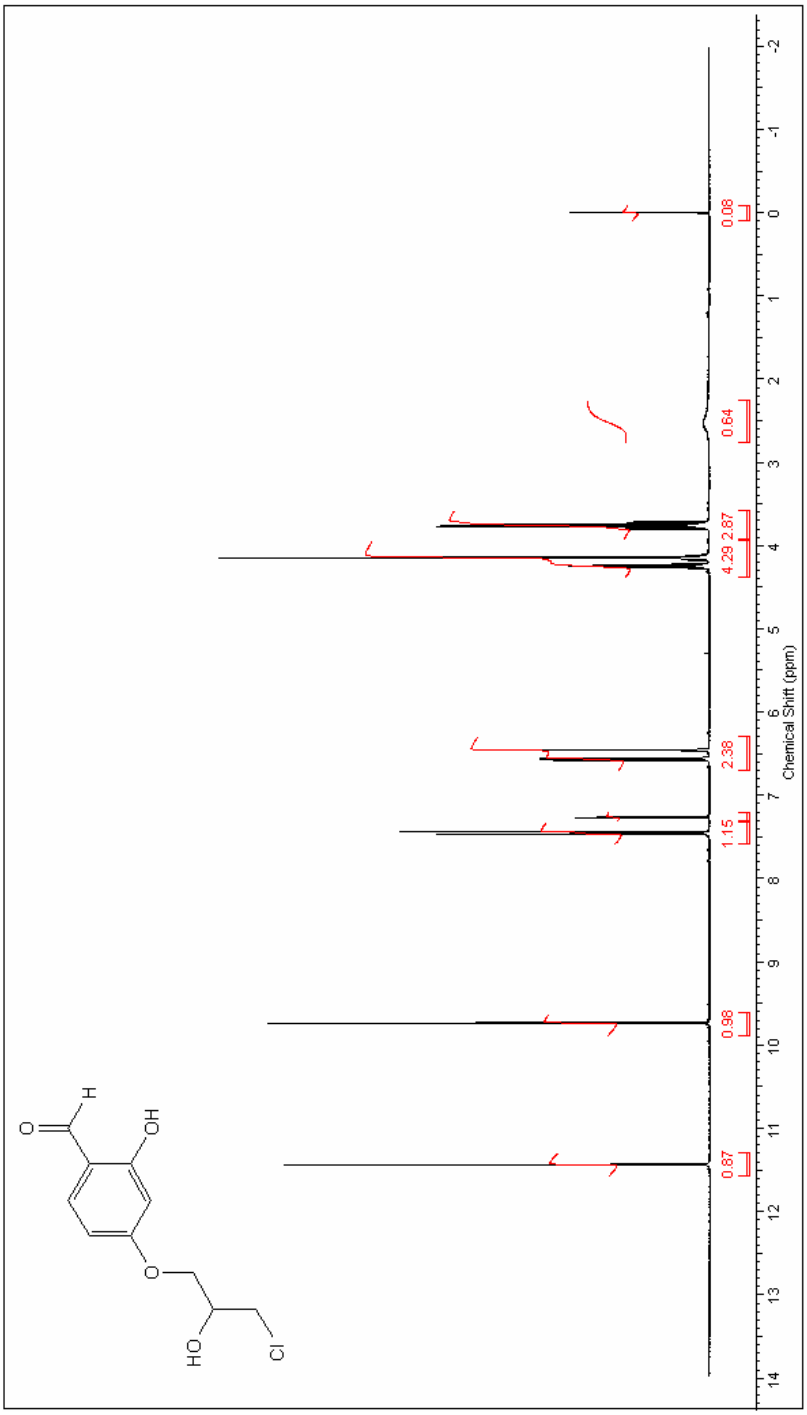


Figure A.2.1. ^{1}H NMR spectrum of 4-(3-Chloro-2-hydroxypropoxy)-2-hydroxybenzaldehyde (**3a**)

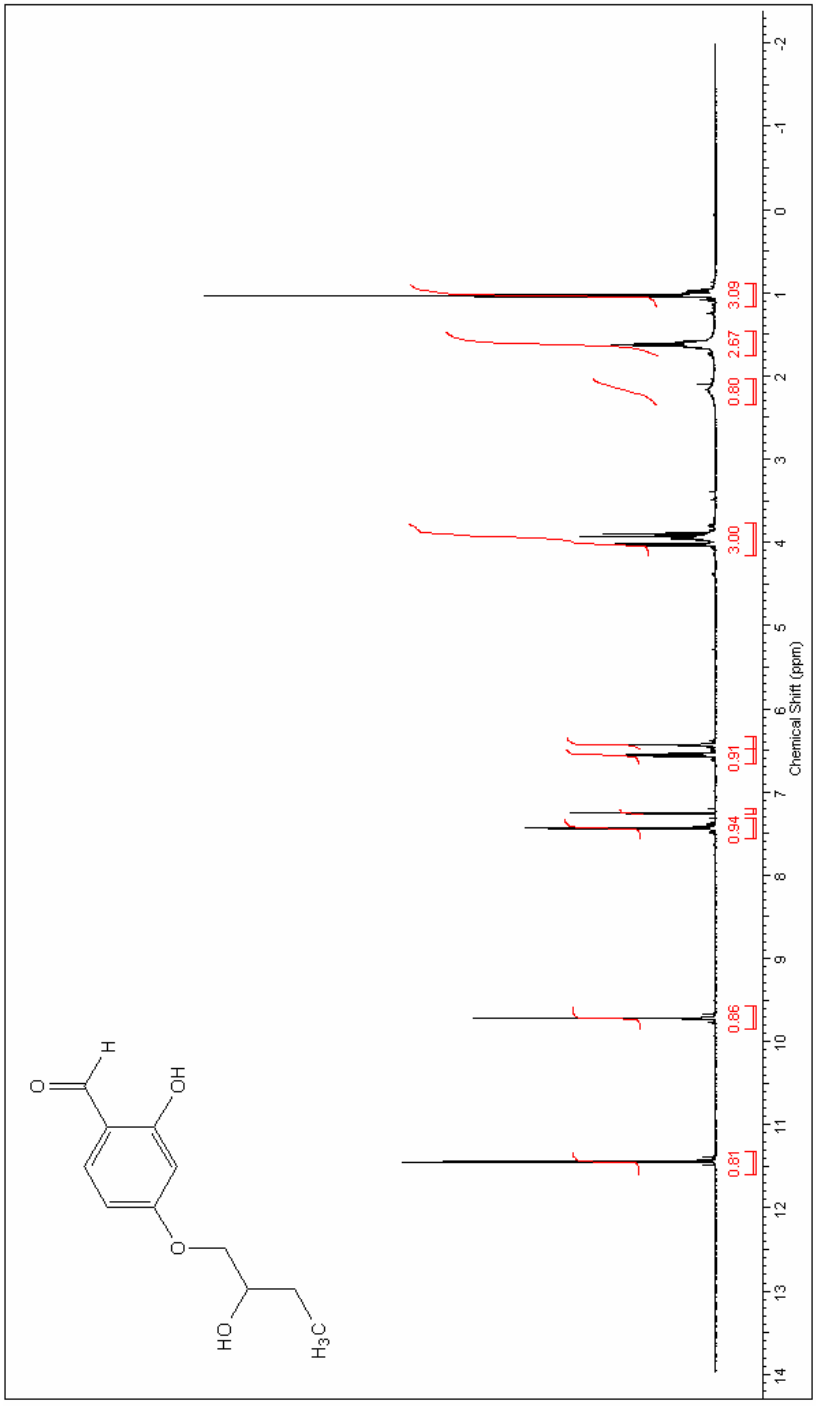


Figure A.2.2. ^{1}H NMR spectrum of 2-hydroxy-4-(2-hydroxybutoxy)benzaldehyde (**3b**)

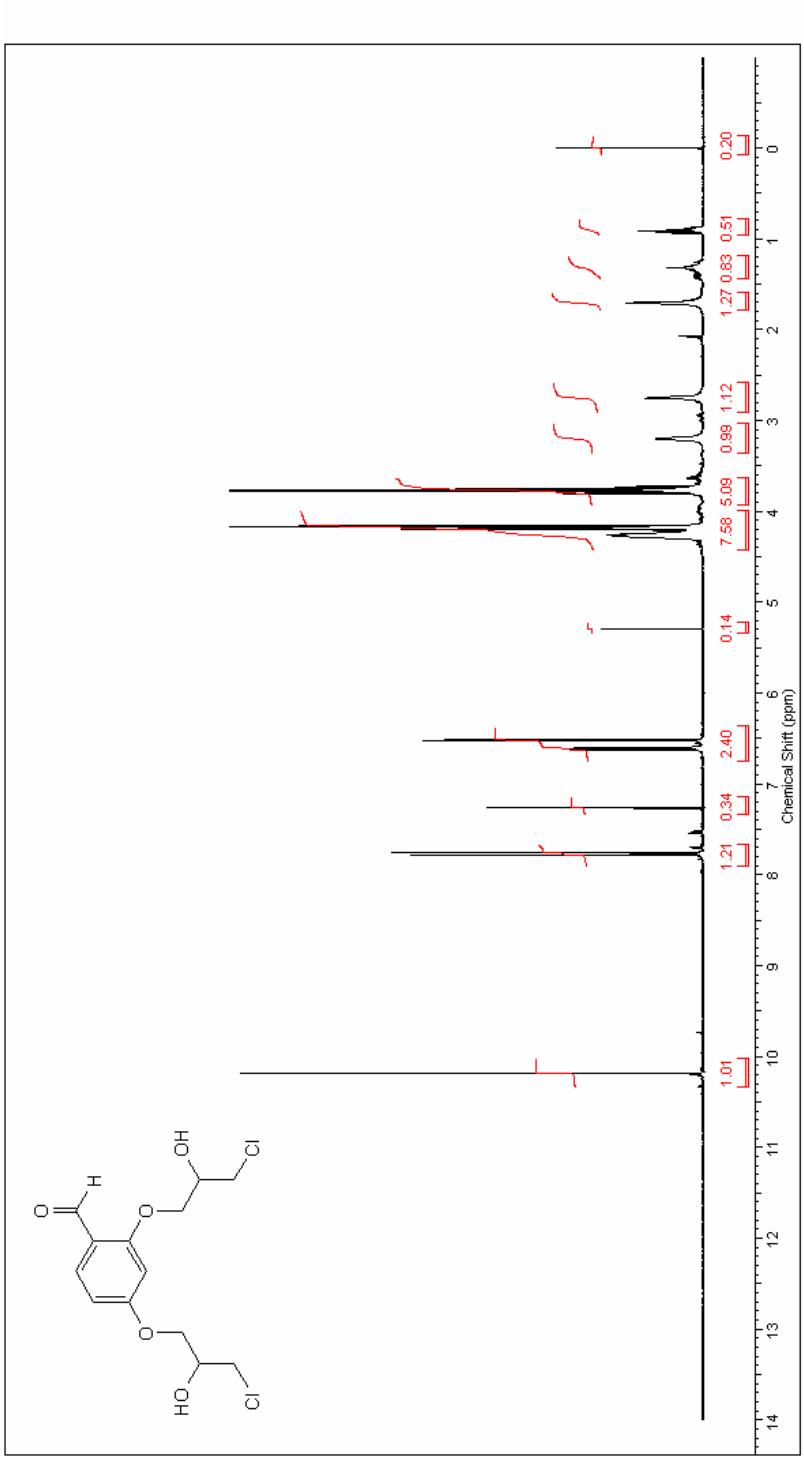


Figure A.2.3. ^{1}H NMR spectrum of 2,4-bis(3-chloro-2-hydroxypropoxy)benzaldehyde (**4a**)

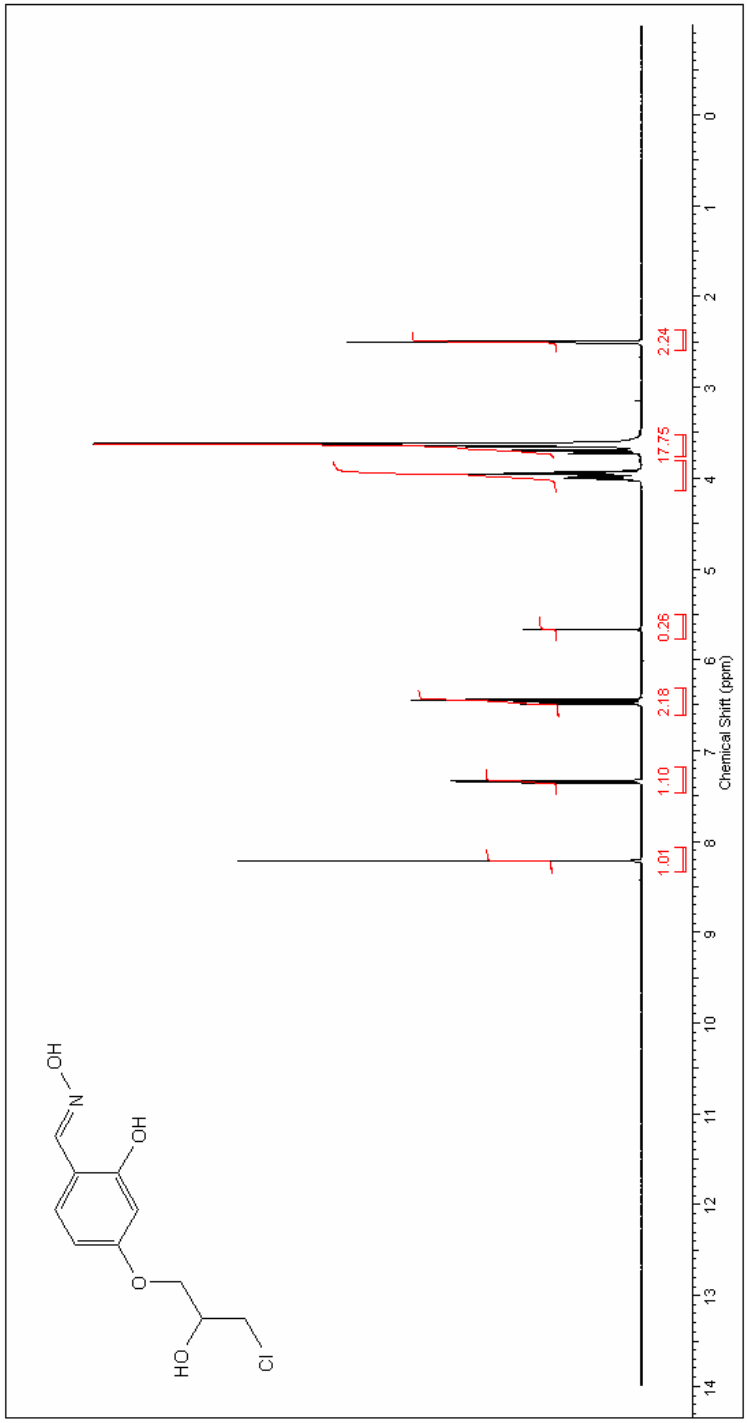


Figure A.2.4. ^{1}H NMR spectrum of 4-(3-chloro-2-hydroxypropoxy)-2-hydroxybenzaldoxime (**5**)

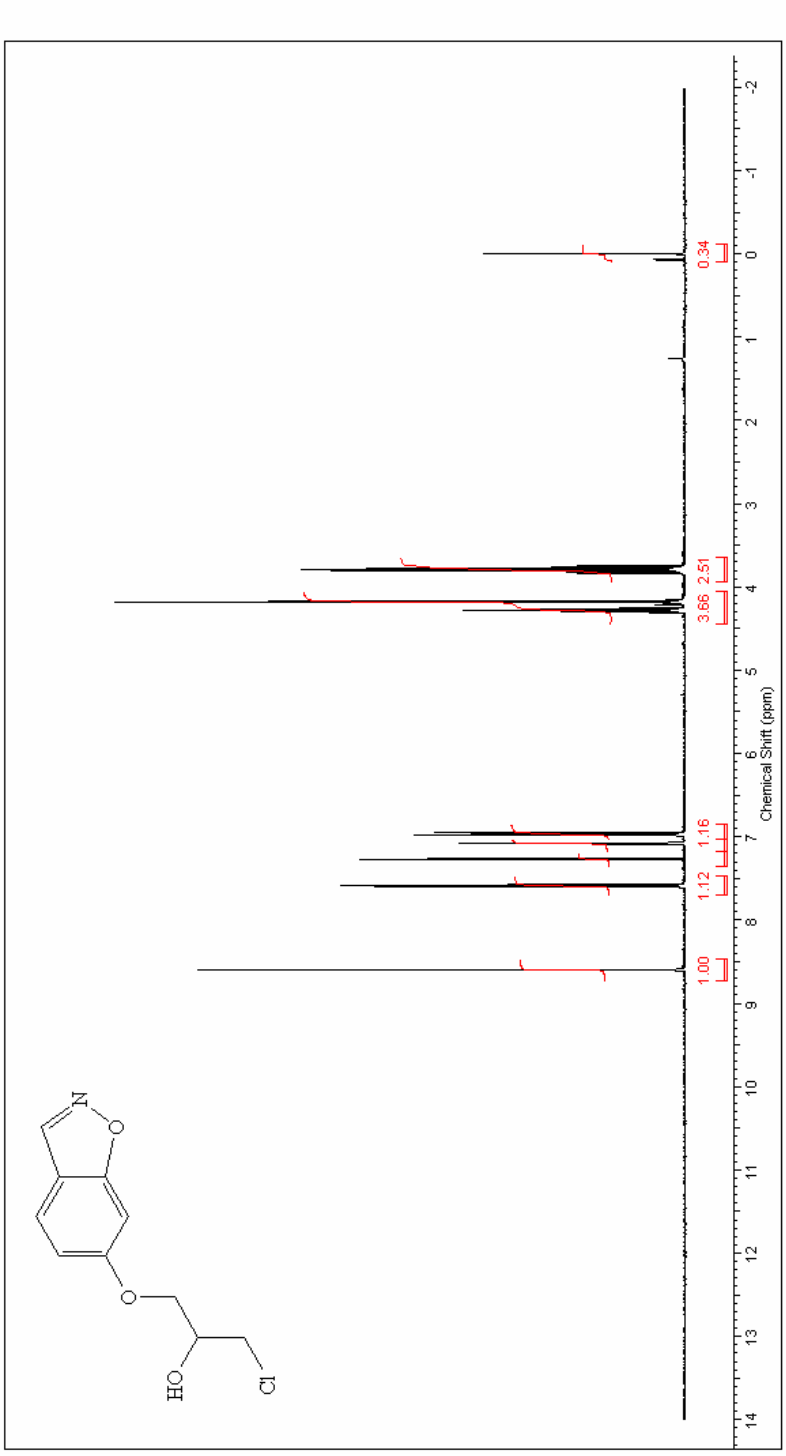


Figure A.2.5. ^{1}H NMR spectrum of 6-(3-Chloro-2-hydroxypropoxy)-1,2-benzisoxazole (**6**)

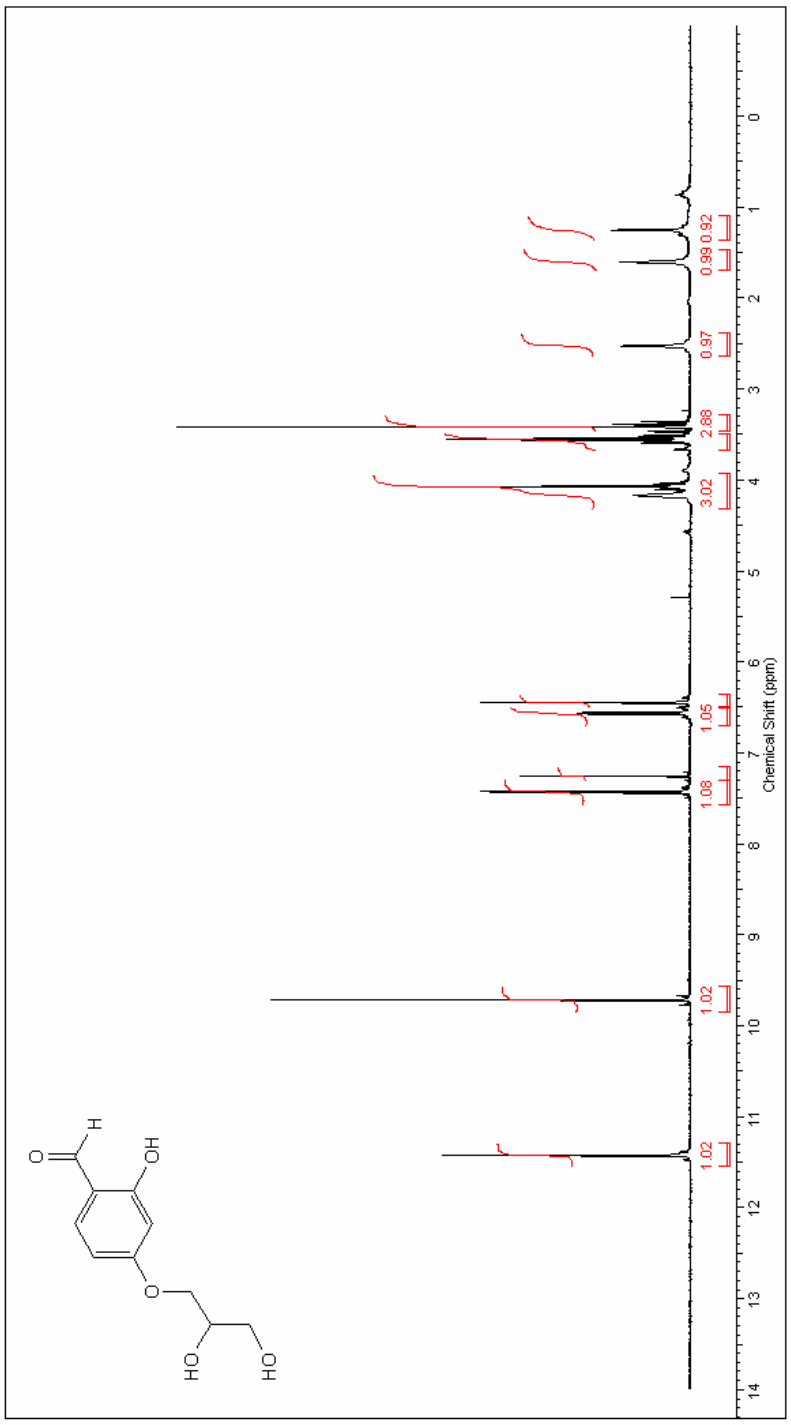


Figure A.2.6. ^{1}H NMR spectrum of 4-(2,3-Dihydroxypropoxy)-2-hydroxybenzaldehyde (**7**)

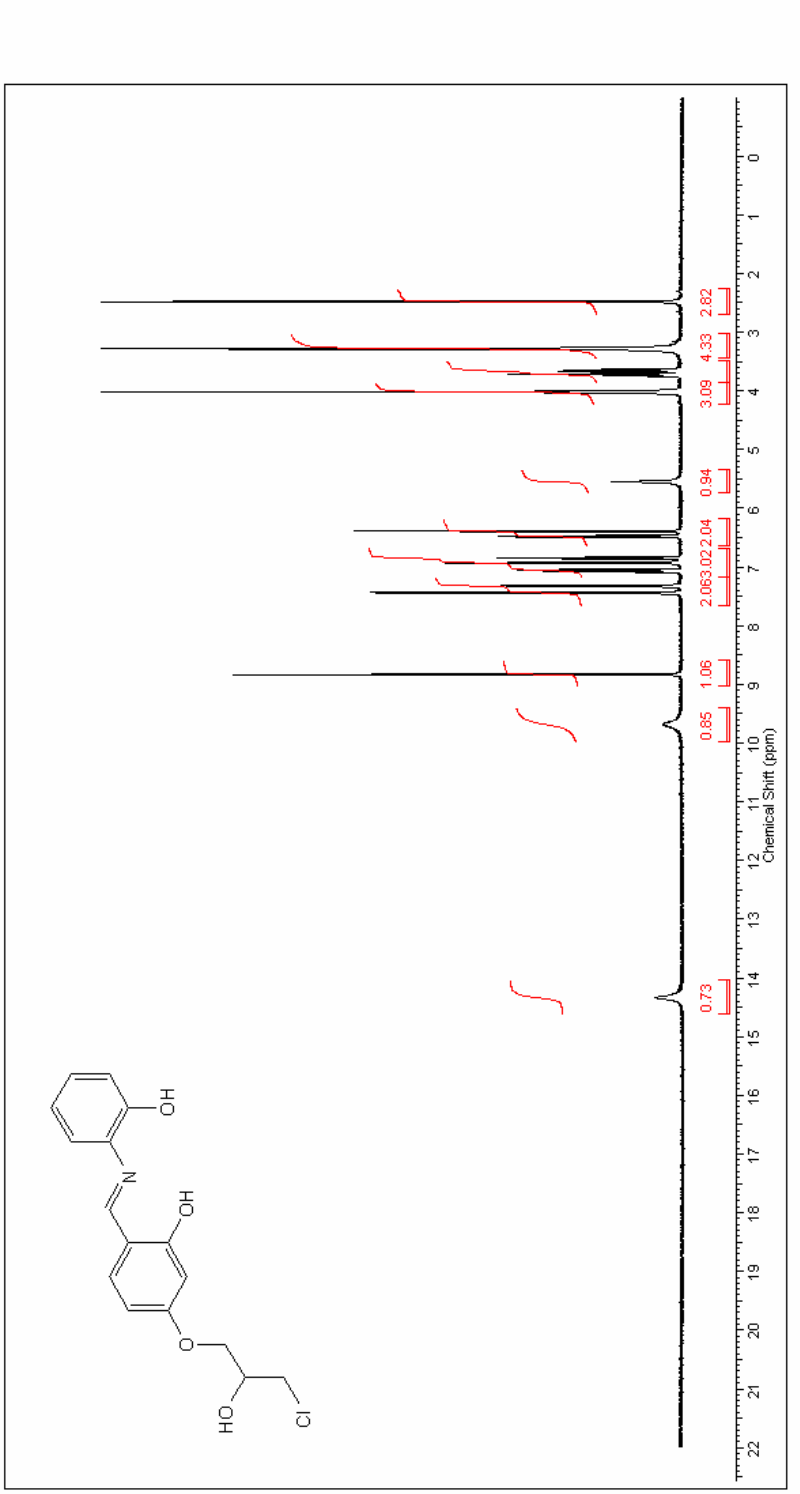


Figure A.2.7. ^{1}H NMR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxyphenyl)imino]methyl}phenol (**8**)

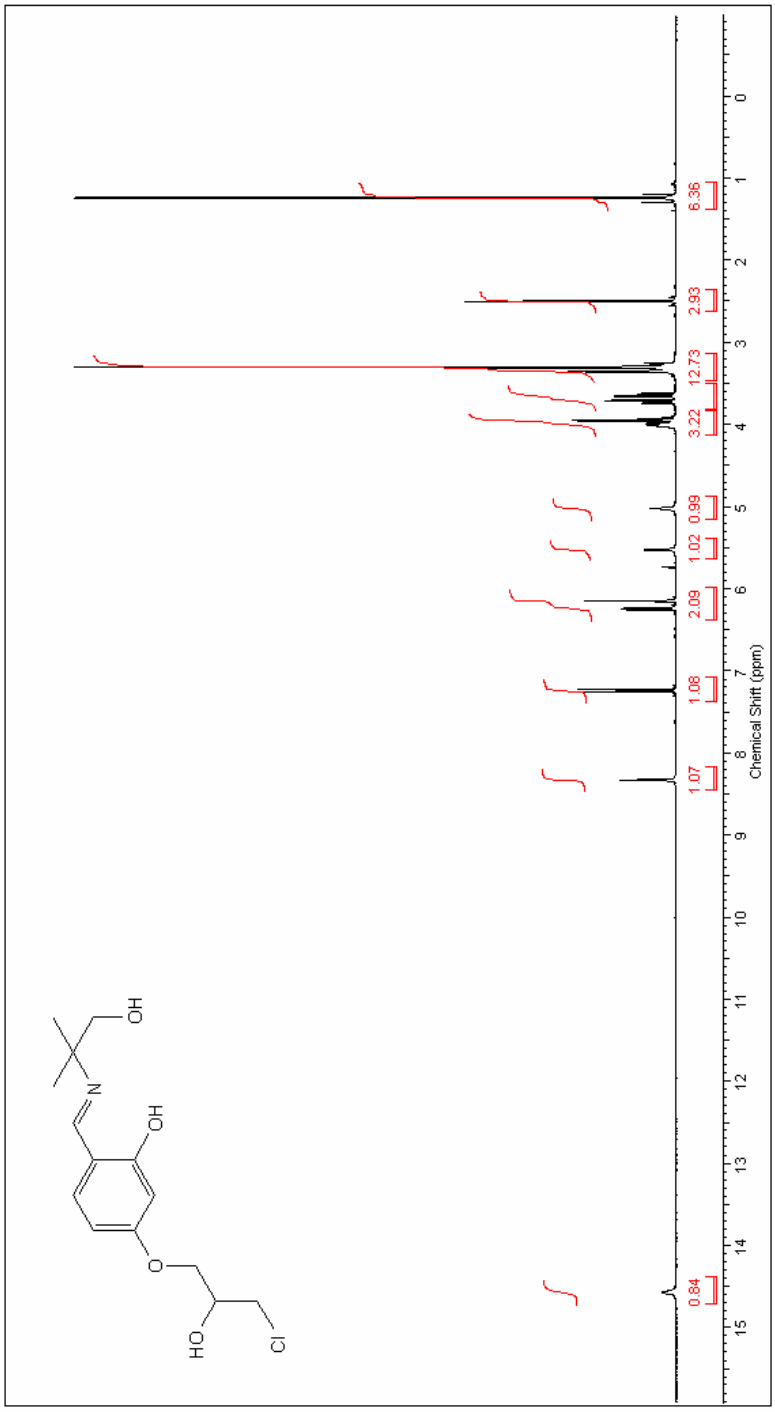


Figure A.2.8. ^{1}H NMR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxy-1,1-dimethylethyl)imino]methyl}phenol (**9**)

A.3. ^{13}C NMR spectra

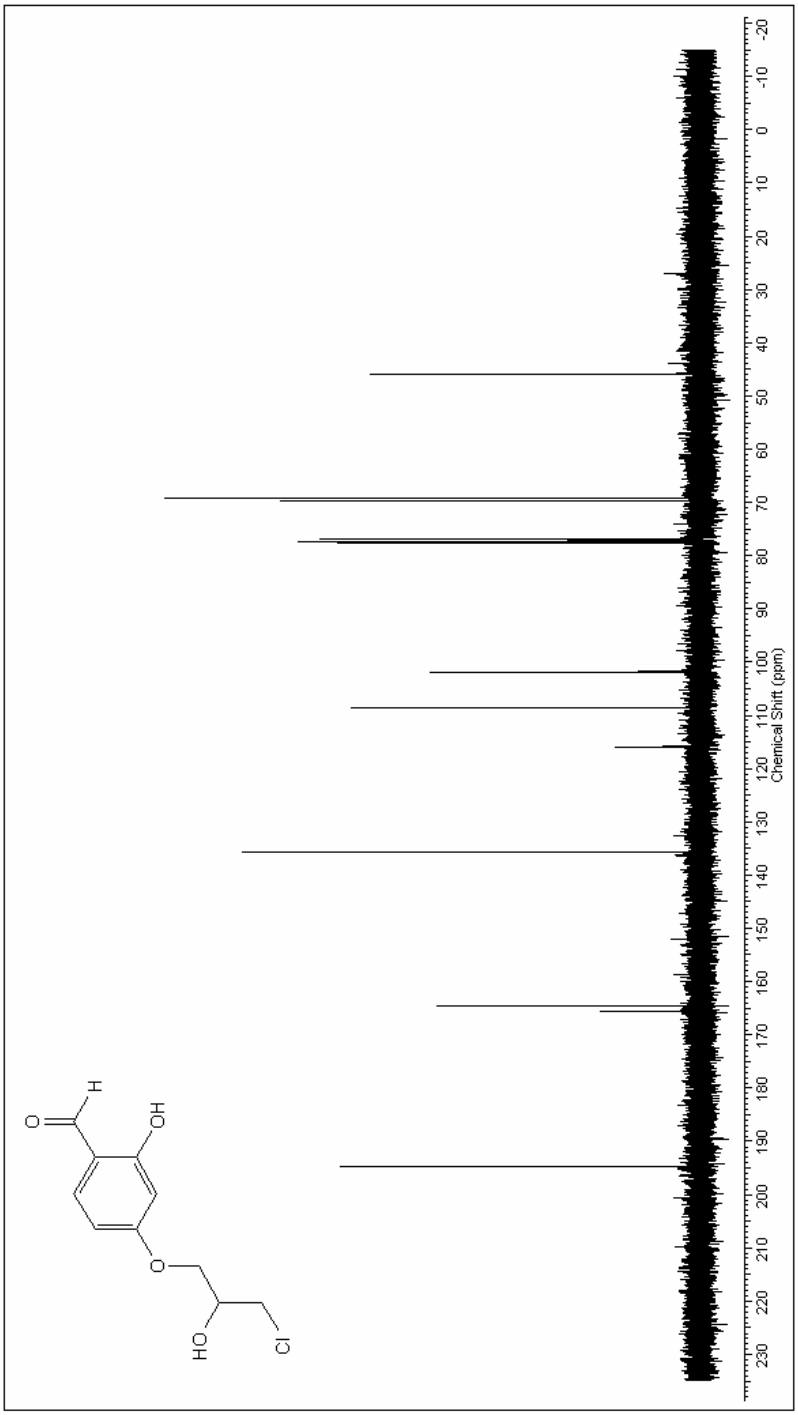


Figure A.3.1. ^{13}C NMR spectrum of 4-(3-Chloro-2-hydroxypropoxy)-2-hydroxybenzaldehyde (**3a**)

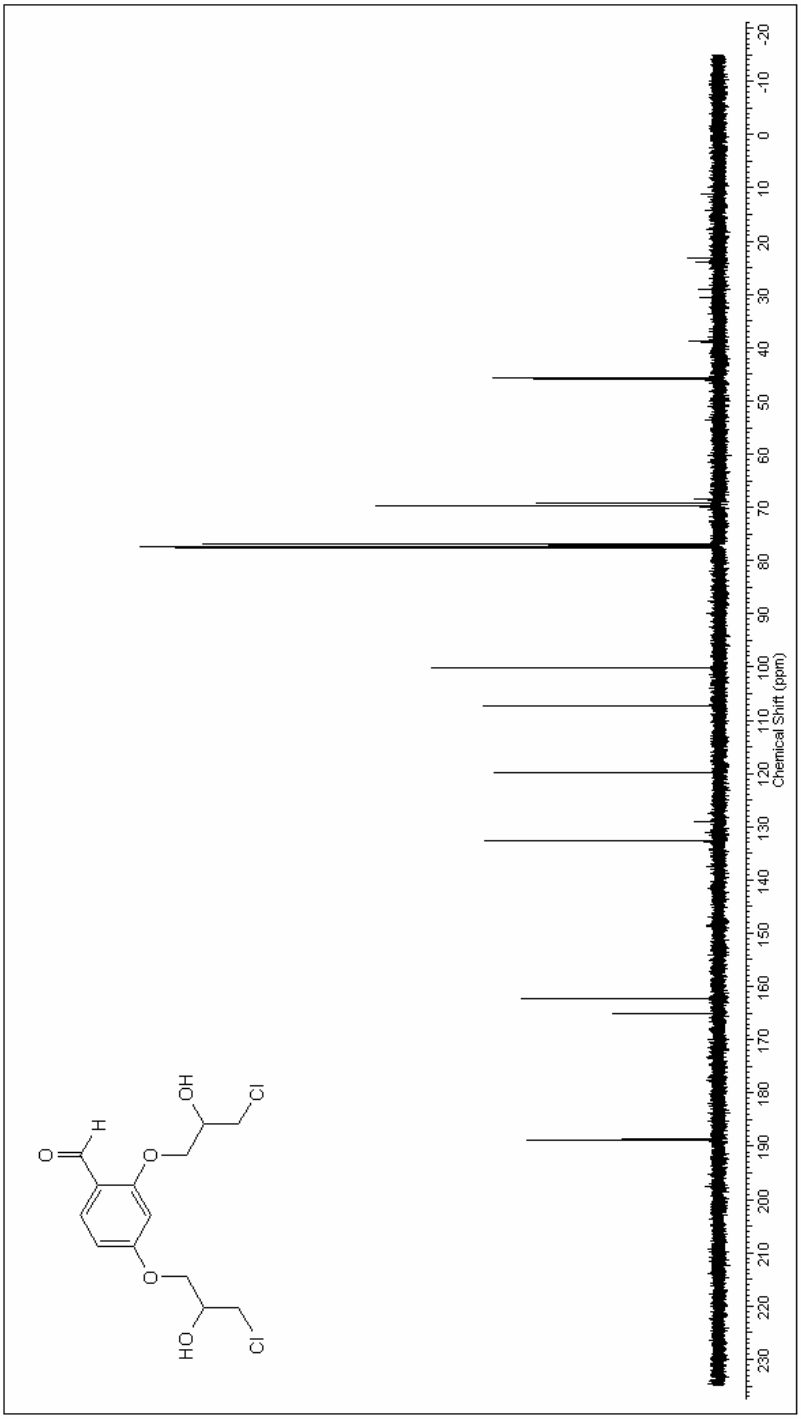


Figure A.3.2. ^{13}C NMR spectrum of 2,4-bis(3-chloro-2-hydroxypropoxy)benzaldehyde (**4a**)

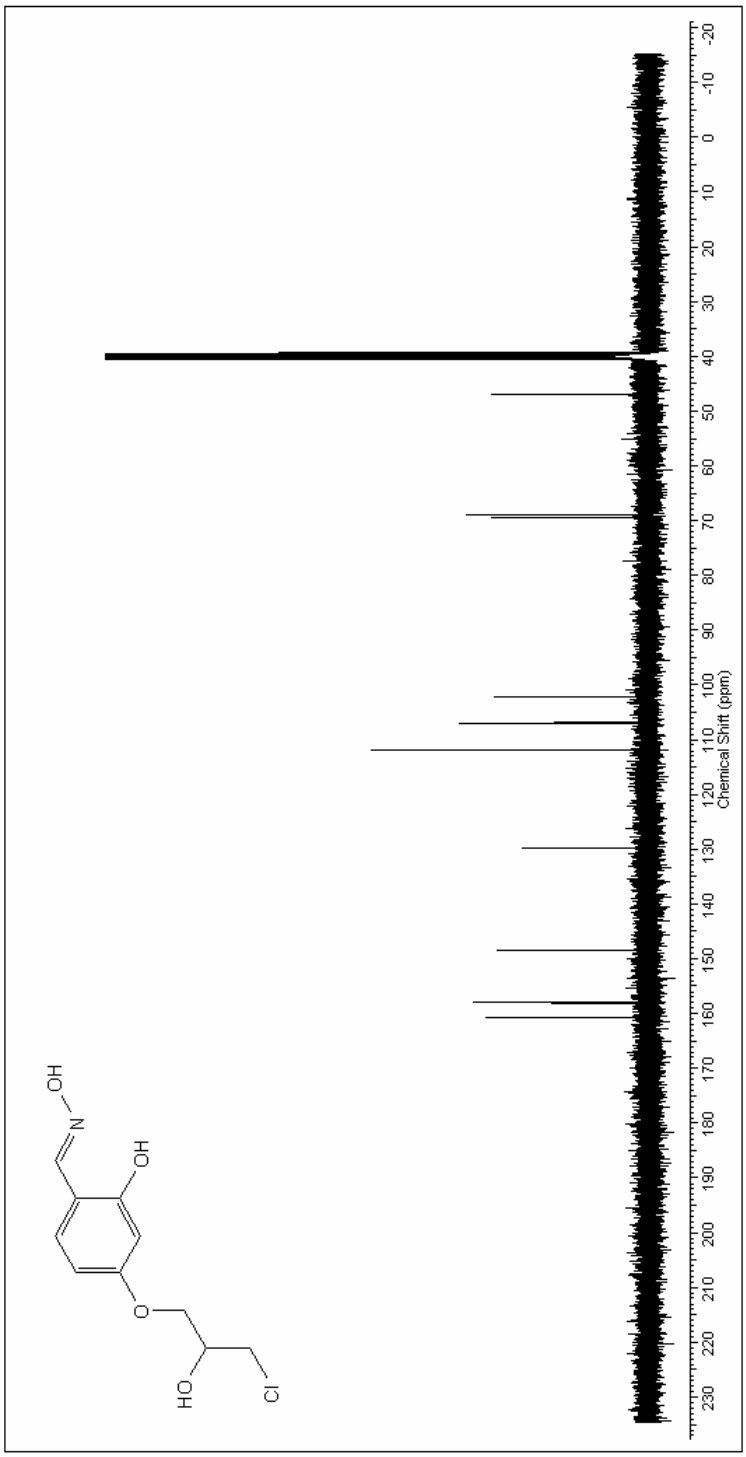


Figure A.3.3. ^{13}C NMR spectrum of 4-(3-chloro-2-hydroxypropoxy)-2-hydroxybenzaldoxime (**5**)

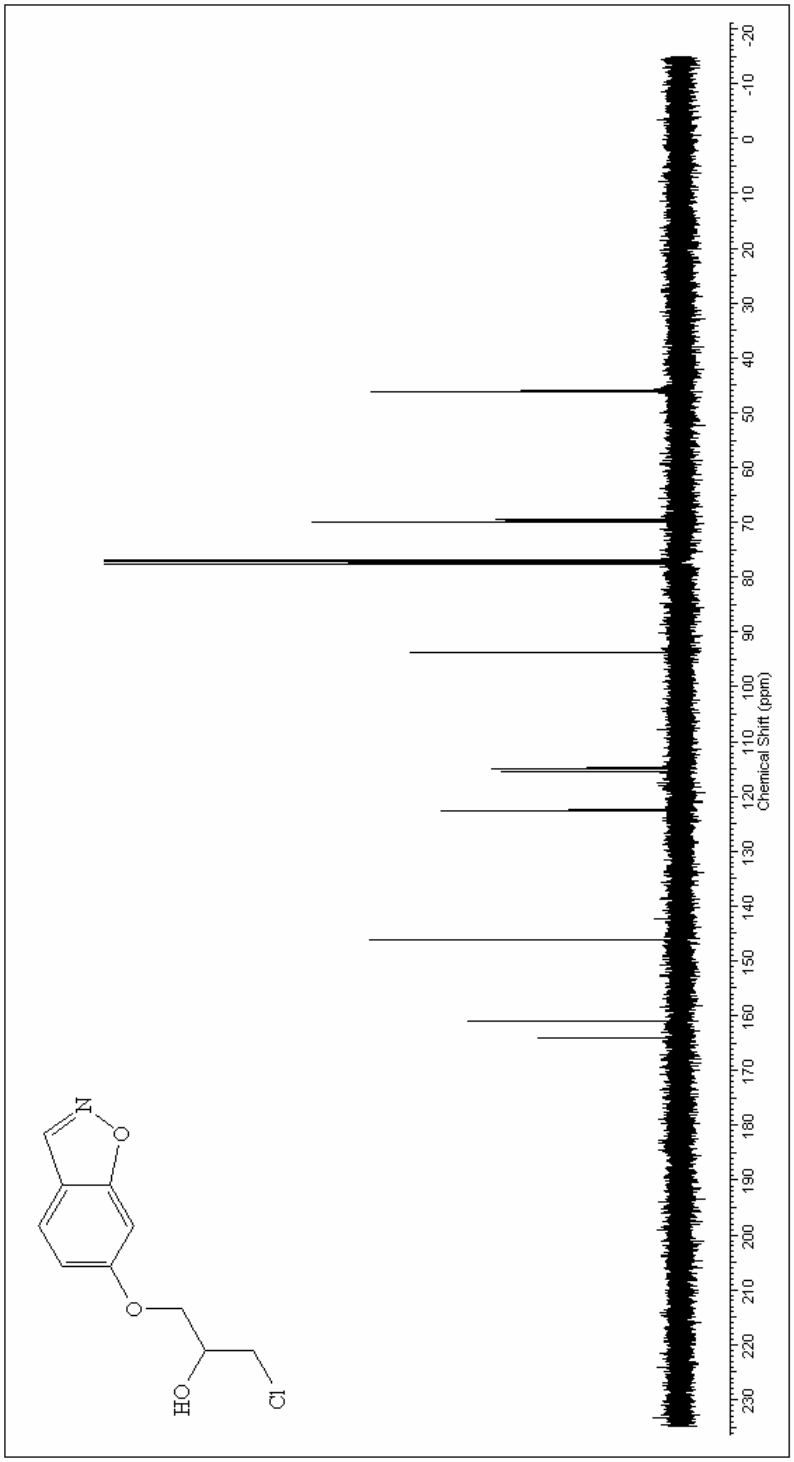


Figure A.3.4. ^{13}C NMR spectrum of 6-(3-Chloro-2-hydroxypropoxy)-1,2-benzisoxazole (**6**)

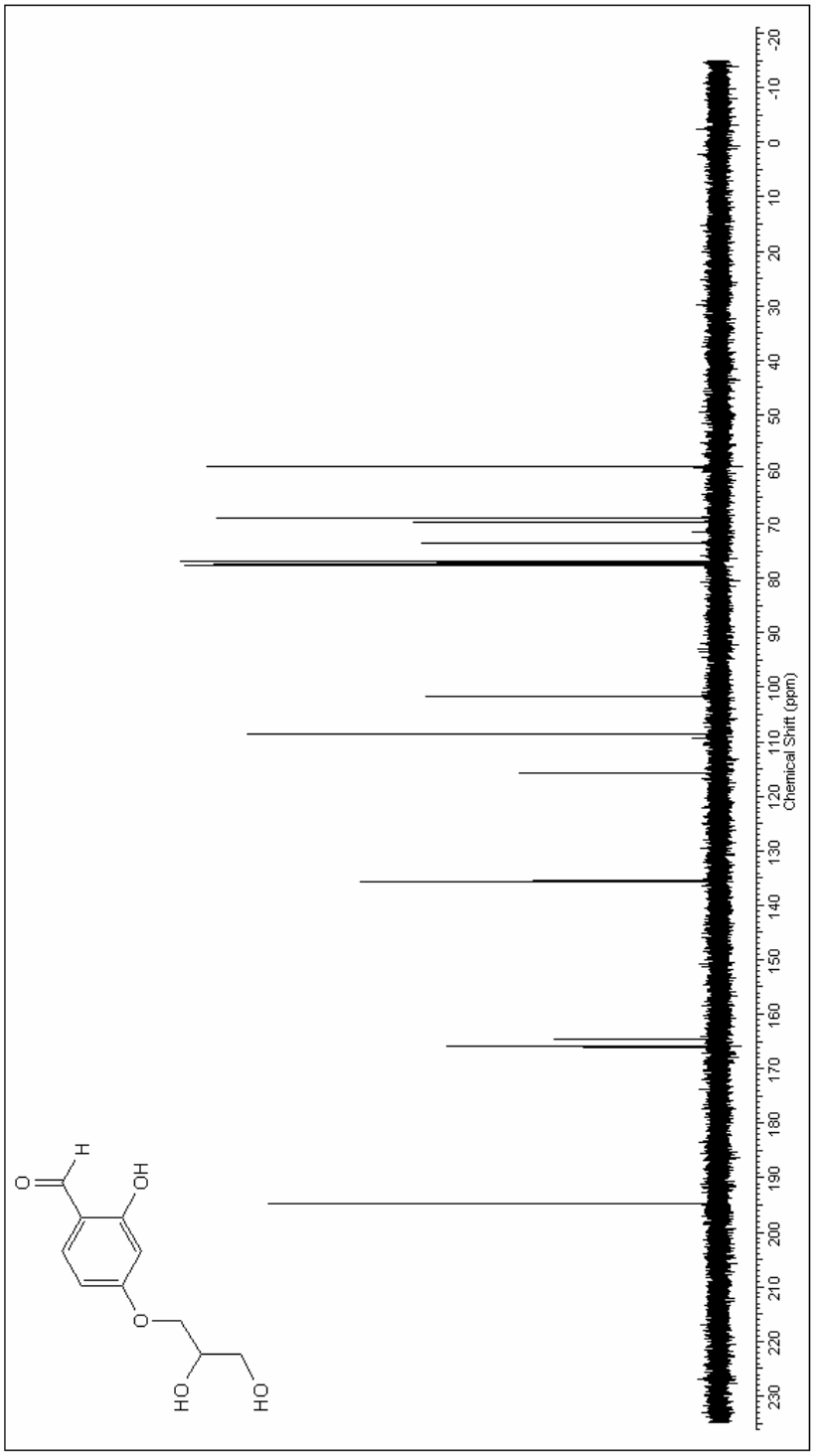


Figure A.3.5. ^{13}C NMR spectrum of 4-(2,3-Dihydroxypropoxy)-2-hydroxybenzaldehyde (**7**)

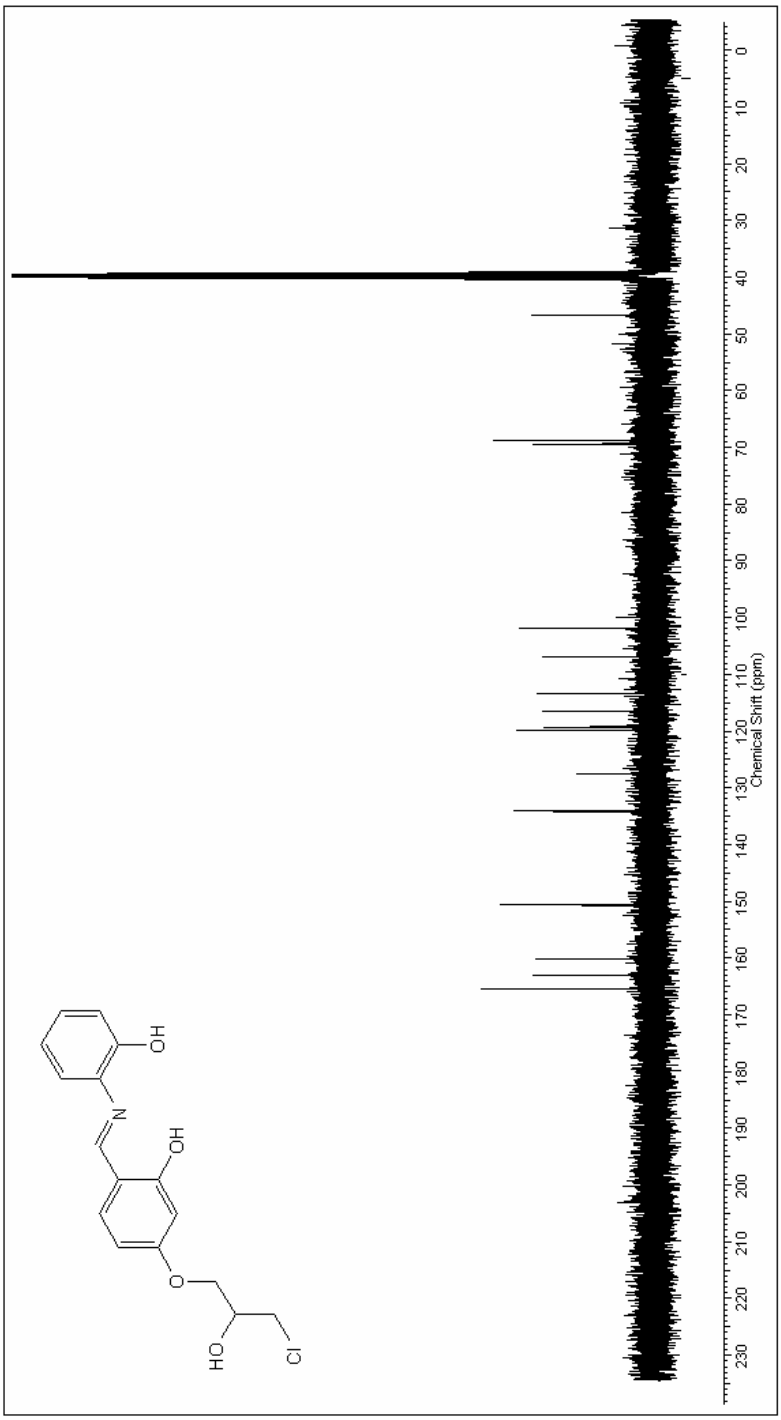


Figure A.3.6. ^{13}C NMR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxyphenyl)imino]methyl}phenol (**8**)

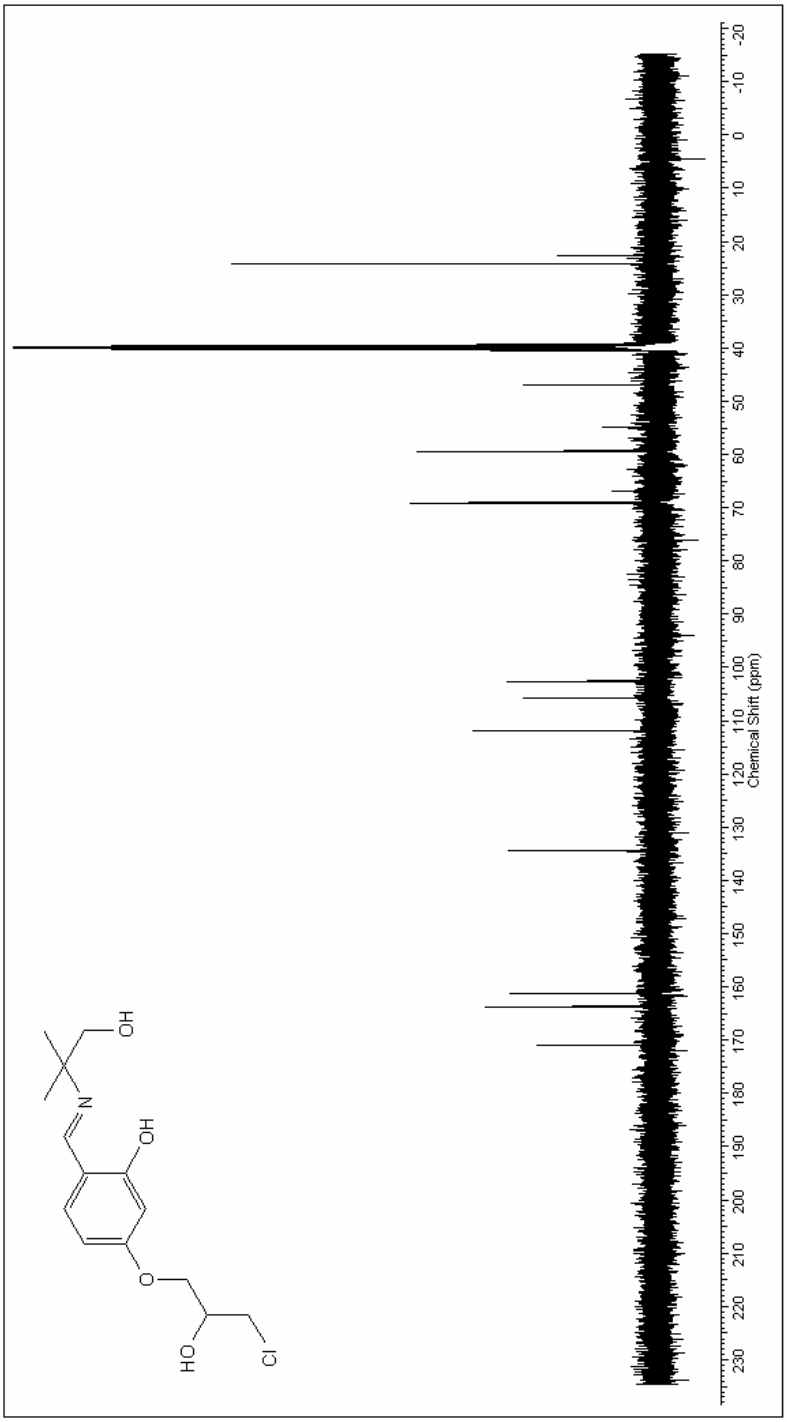
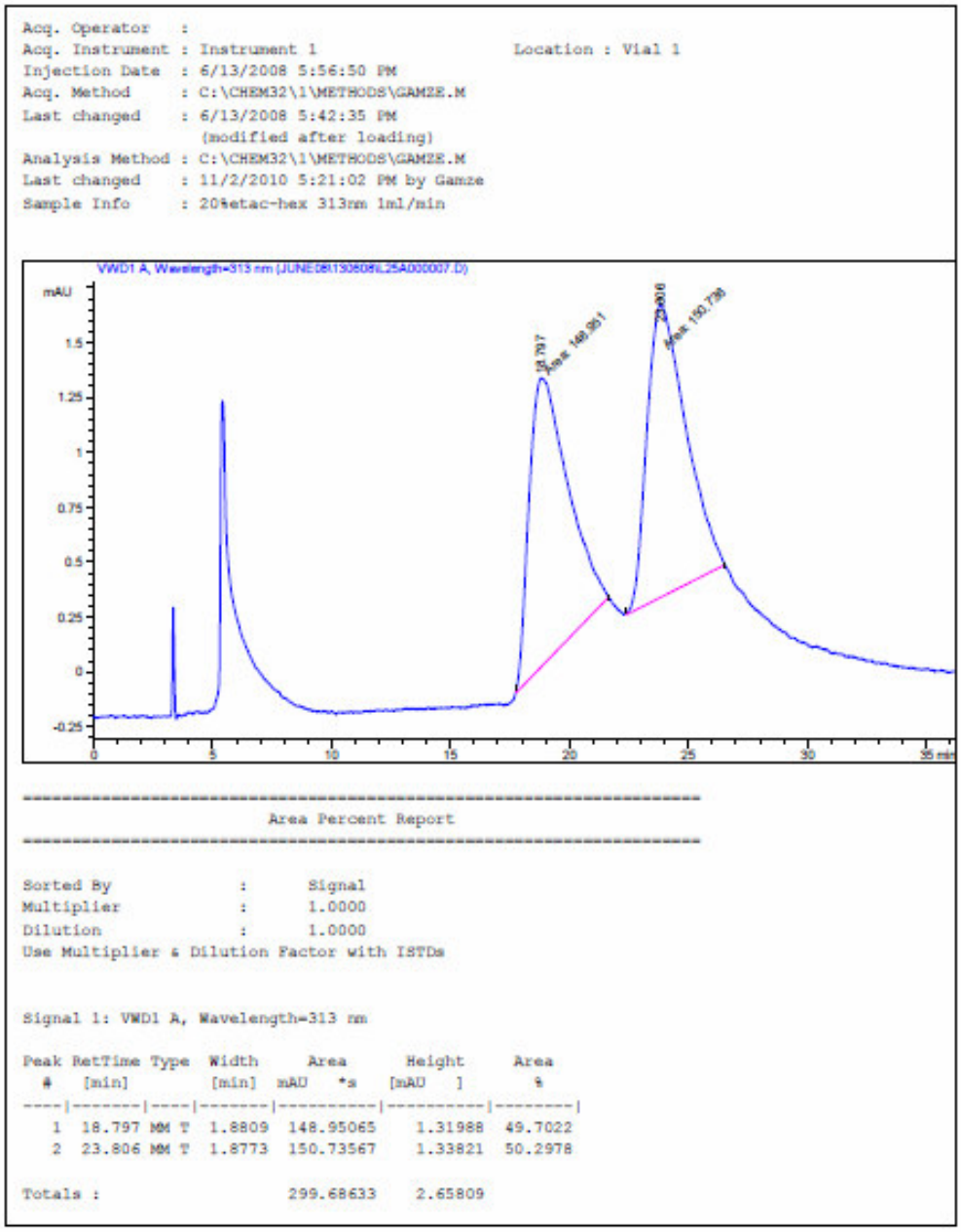


Figure A.3.7. ^{13}C NMR spectrum of 5-(3-chloro-2-hydroxypropoxy)-2-{(*E*)-[(2-hydroxy-1,1-dimethylethyl)imino]methyl}phenol (**9**)

A.4. Chromatograms



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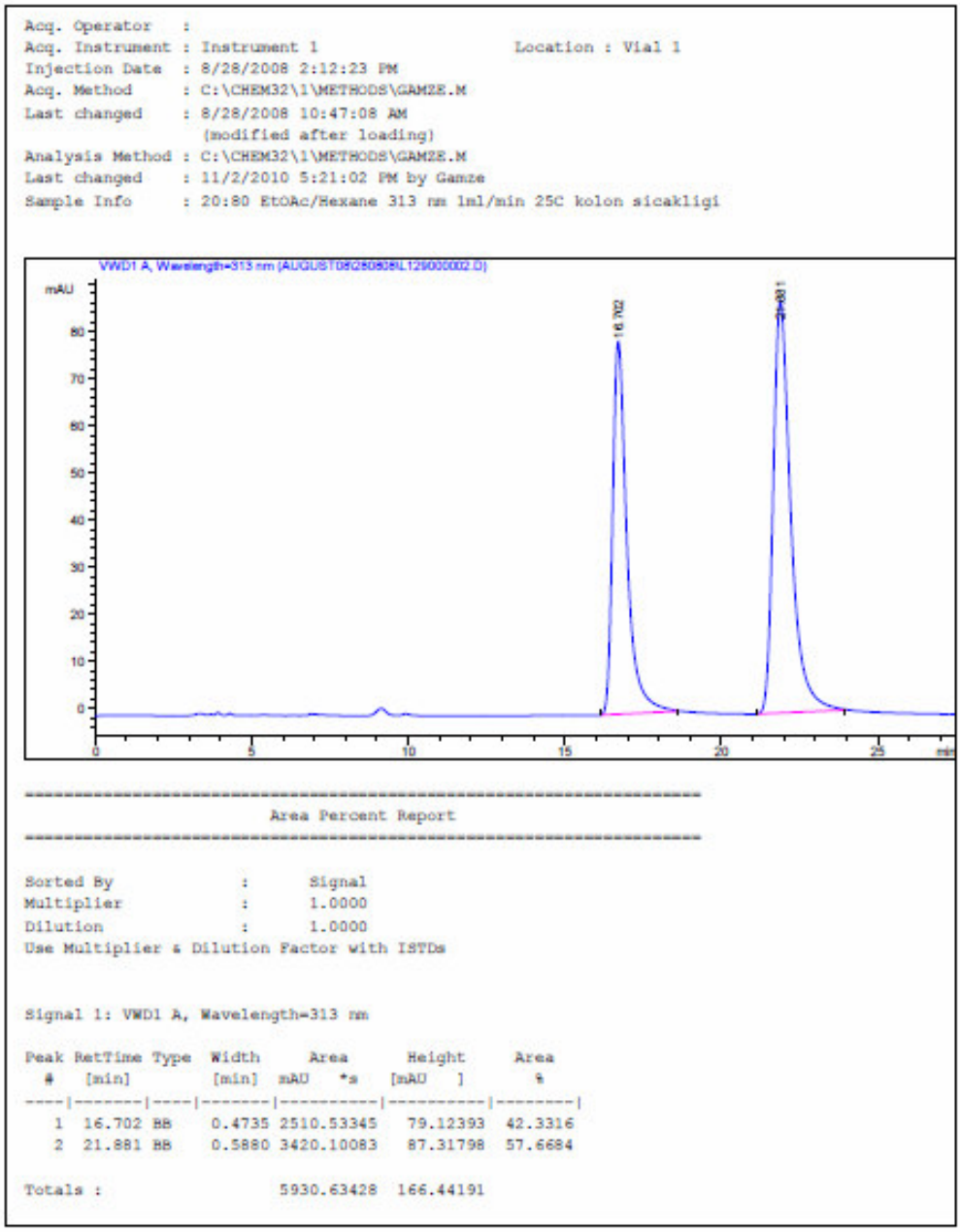
2	23.806	MM T	1.8773	150.73567	1.33821	50.2978
Totals :				299.68633	2.65809	

Figure A.4.1. HPLC chromatogram of racemic **3a**



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   2  21.881 BB    0.5880 3420.10083   87.31798  57.6684

Totals :                 5930.63428  166.44191
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Figure A.4.2. HPLC chromatogram of **3a** synthesized using **2a** and $AlCl_3$ at rt

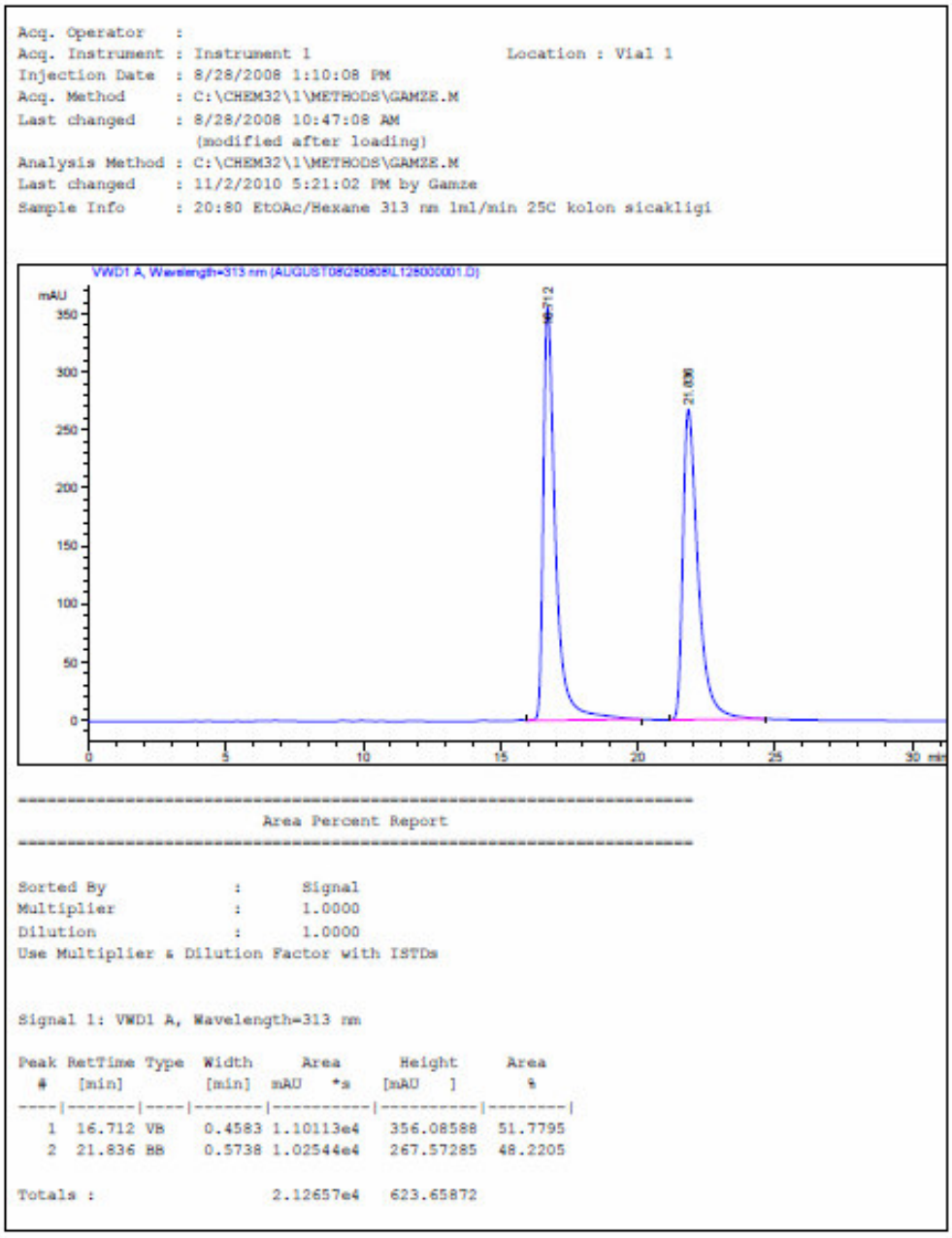

Figure A.4.3. HPLC chromatogram of **3a** synthesized using **2b** and $AlCl_3$ at rt

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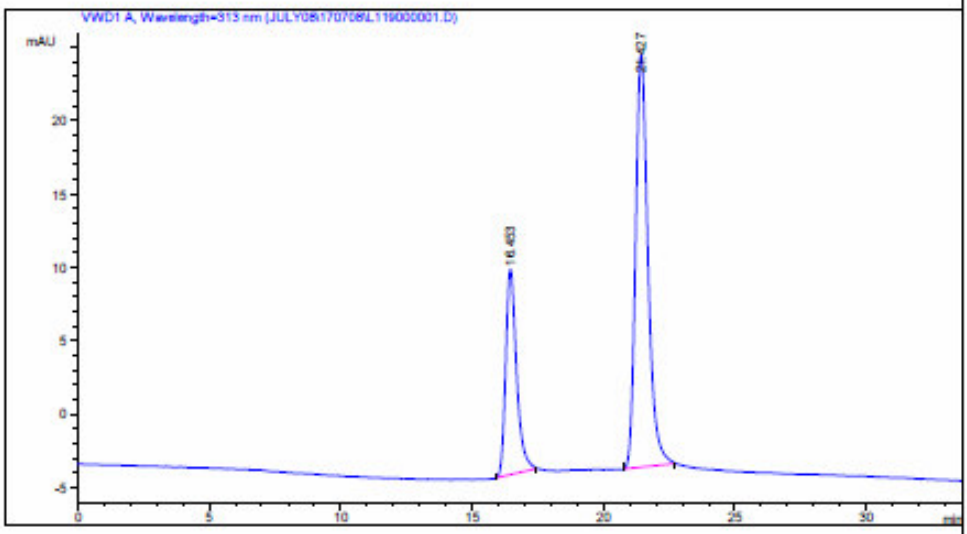
                  gi
```

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=313 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
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   1  16.453 BB    0.4336  401.42685   13.99667  30.2786
   2  21.427 BB    0.4999  924.34863   28.12694  69.7214

Totals :                  1325.77548   42.12361
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Figure A.4.4. HPLC chromatogram of **3a** synthesized using **2a** and $AlCl_3$ at 0°C

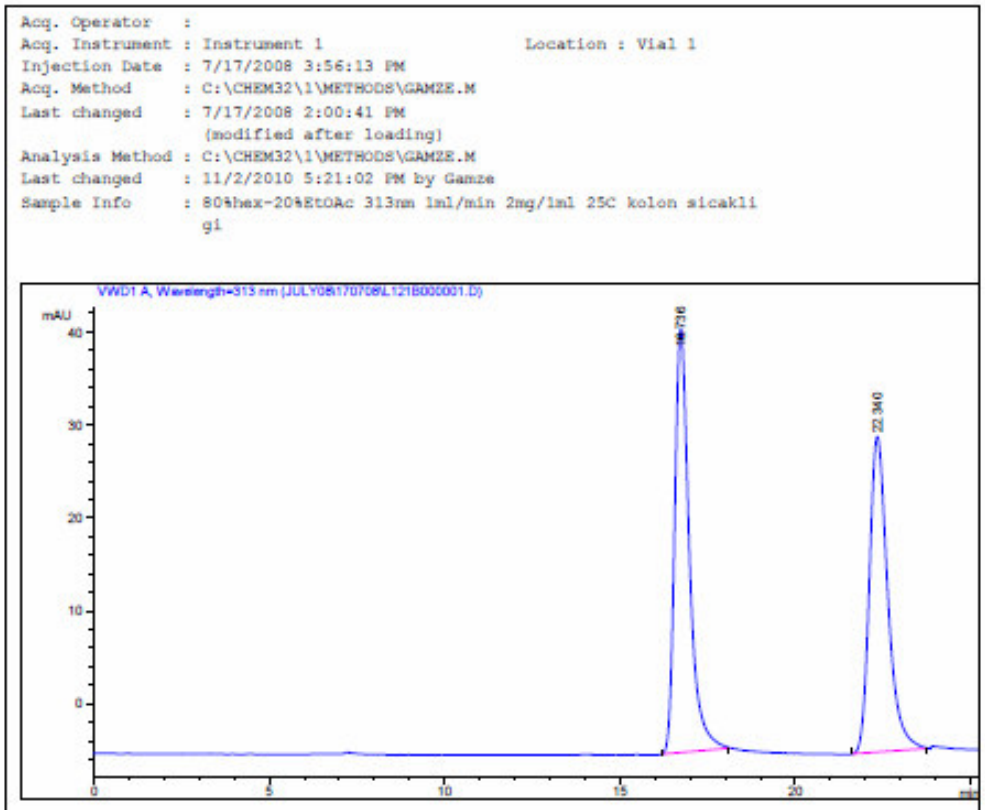
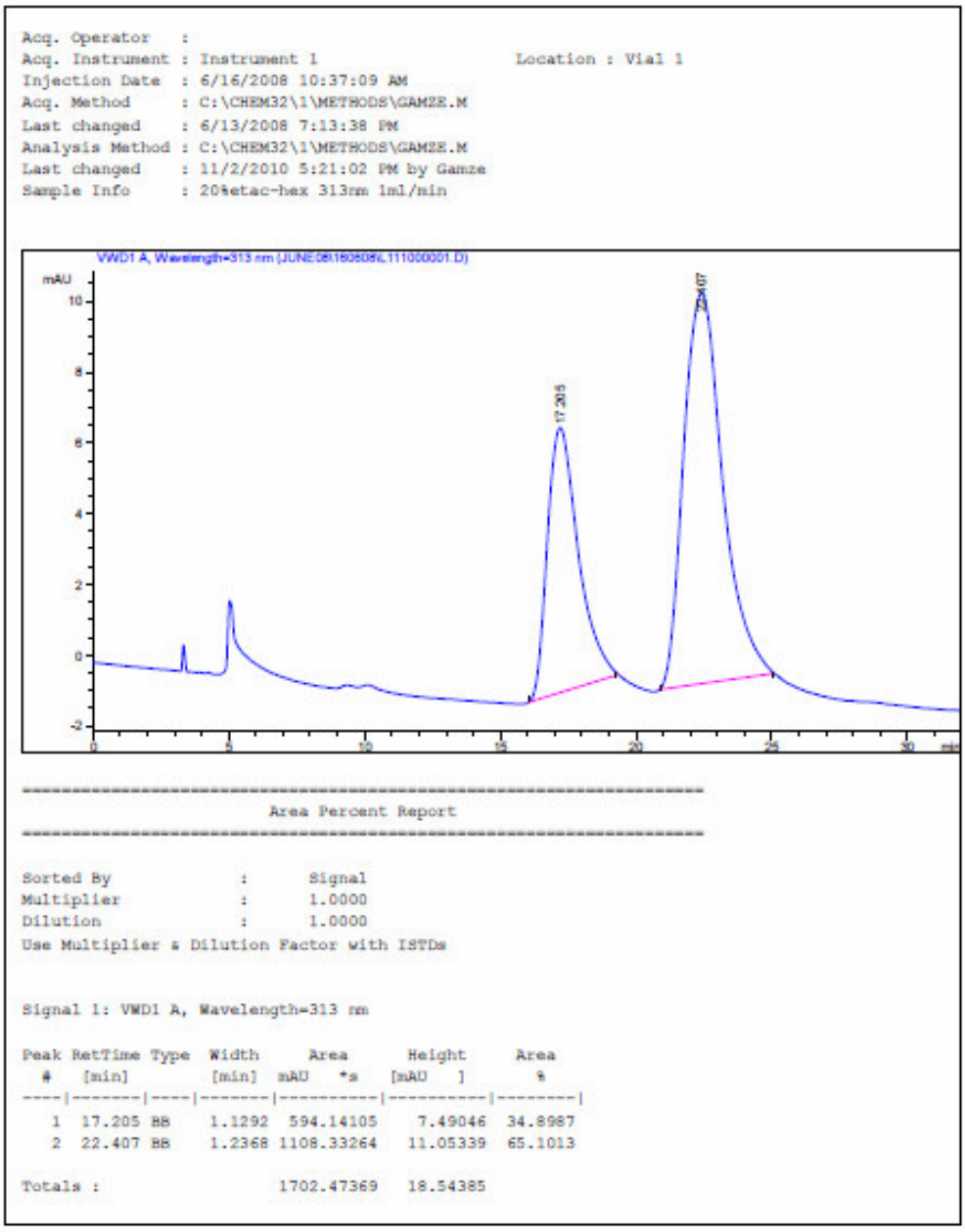


Figure A.4.5. HPLC chromatogram of **3a** synthesized using **2b** and $AlCl_3$ at 0°C



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Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=313 nm

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   1  17.205 BB    1.1292  594.14105    7.49046  34.8987
   2  22.407 BB    1.2368 1108.33264   11.05339  65.1013

Totals :                  1702.47369   18.54385
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Figure A.4.6. HPLC chromatogram of **3a** synthesized using **2a** at rt

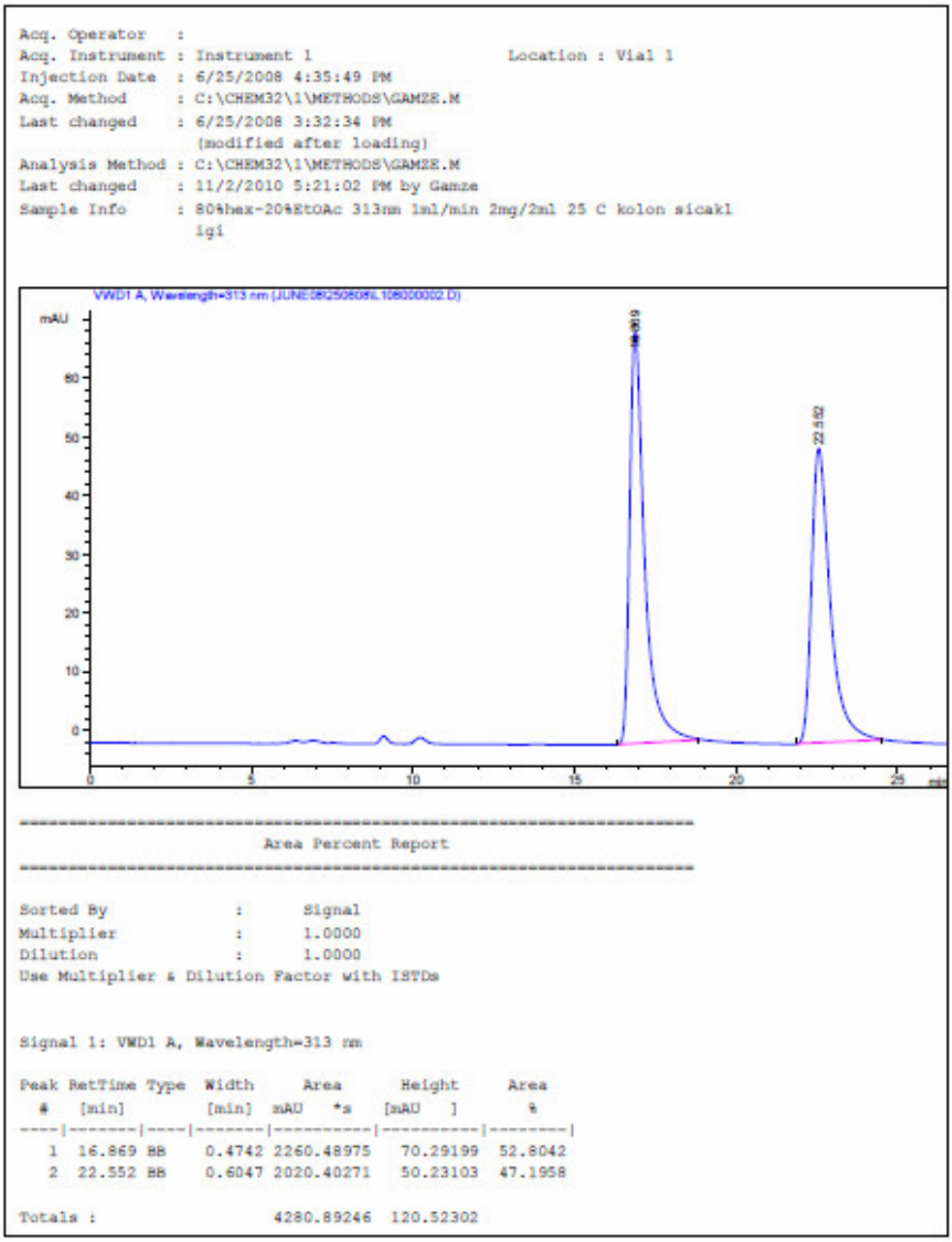
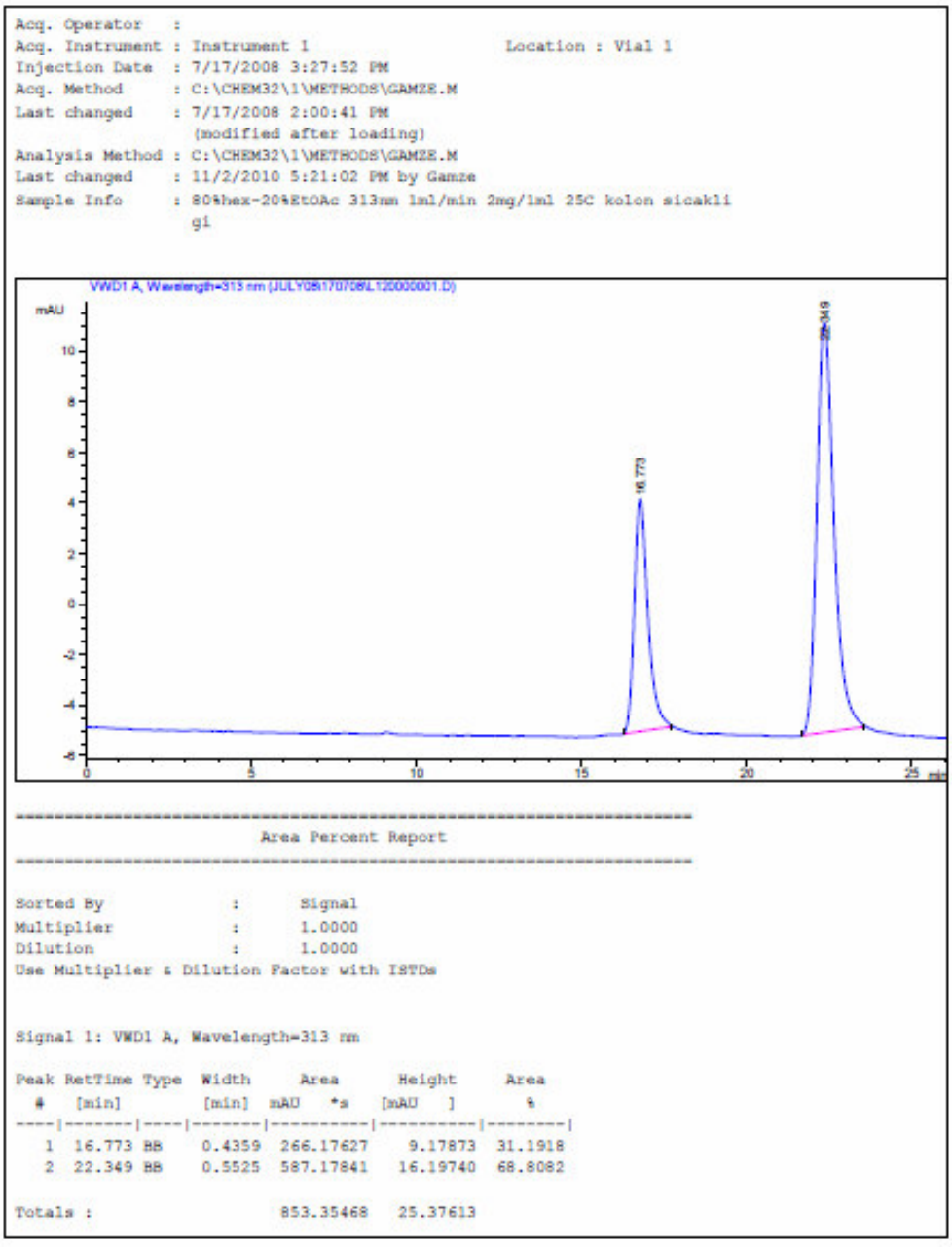


Figure A.4.7. HPLC chromatogram of **3a** synthesized using **2b** at rt



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                  gi
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Signal 1: VWD1 A, Wavelength=313 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1  16.773 BB    0.4359  266.17627    9.17873  31.1918
   2  22.349 BB    0.5525  587.17841   16.19740  68.8082

Totals :                  853.35468   25.37613
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Figure A.4.8. HPLC chromatogram of **3a** synthesized using **2a** at 0°C

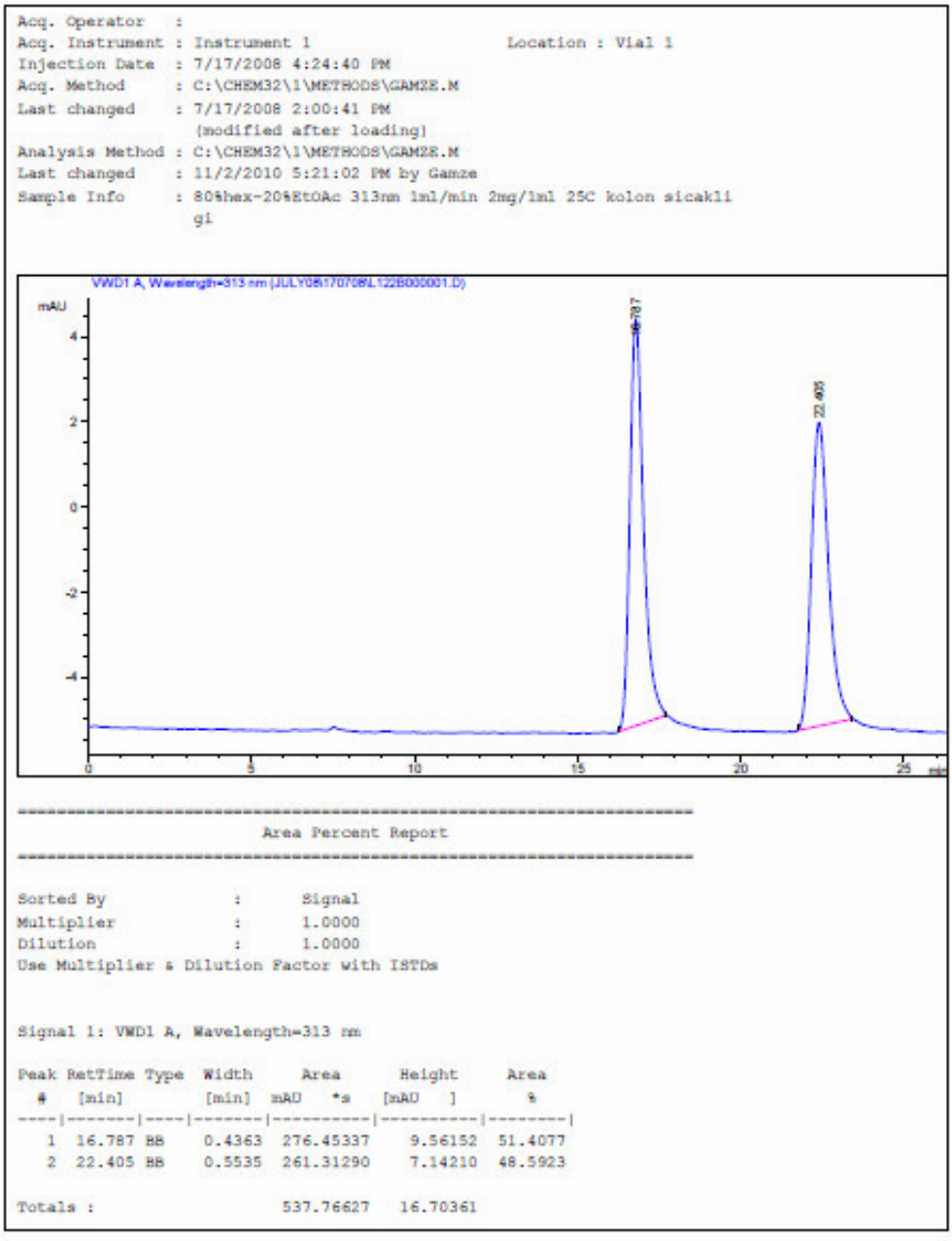
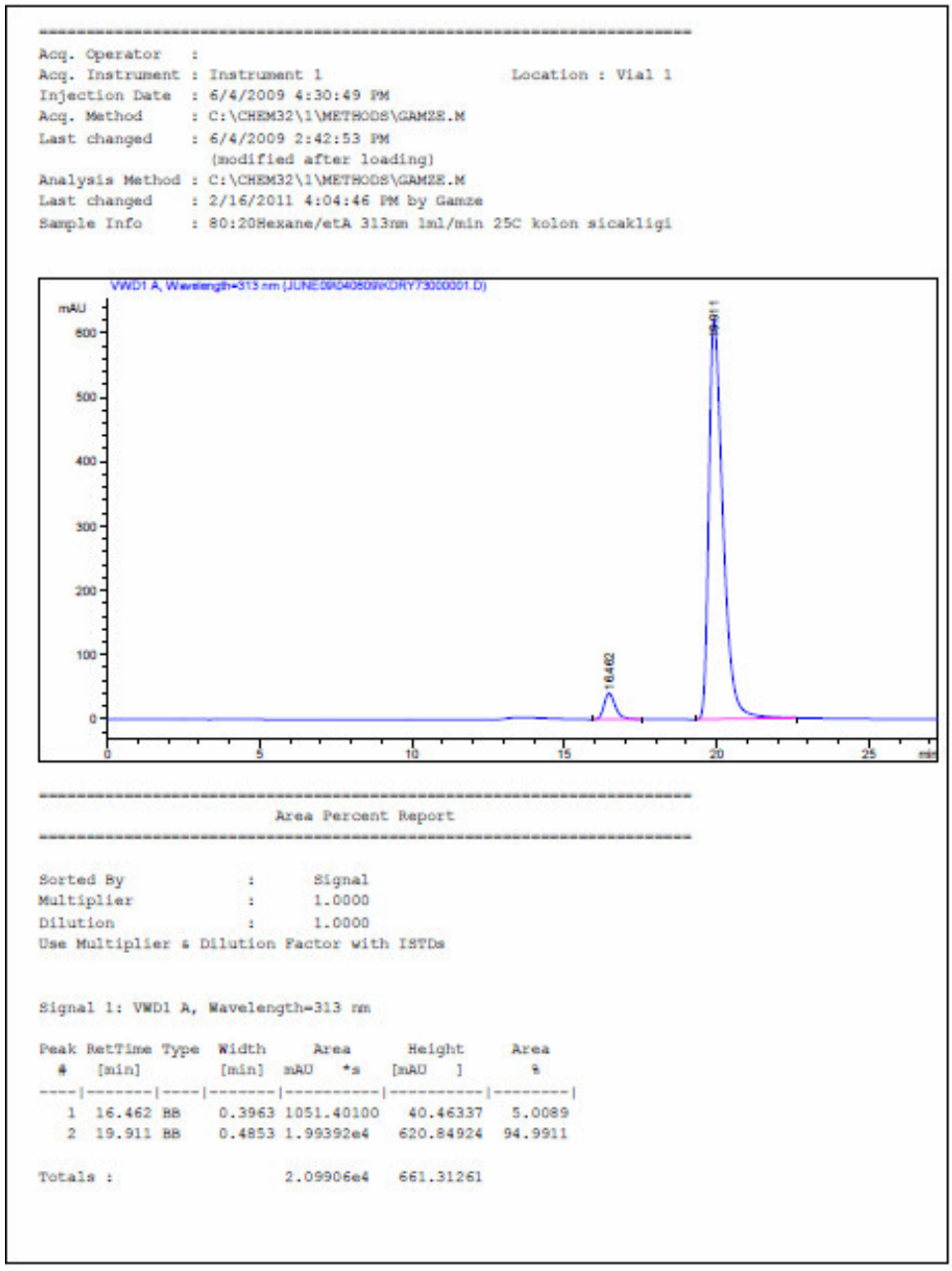


Figure A.4.9. HPLC chromatogram of **3a** synthesized using **2b** at 0°C



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Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=313 nm

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   1  16.462 BB     0.3963 1051.40100   40.46337   5.0089
   2  19.911 BB     0.4853 1.99392e4   620.84924  94.9911

Totals :                  2.09906e4   661.31261
```

Figure A.4.10. HPLC chromatogram of **3a** synthesized using (S)-epichlorohydrine

3. CHAPTER 2. A CHIRAL LEWIS-ACID-CATALYZED DIELS ALDER REACTION IN WATER

3.1. General Information

Nowadays increasing number of medicines, fragrance substances, and agricultural chemicals are produced in their optically active forms. The use of optically active compounds in practical pharmaceutical chemistry has become more and more important.

Various methods for the preparation of optically active compounds are known; these include kinetic resolution, enzymatic and microbiological reactions, asymmetric synthesis and asymmetric catalysis; the latter seems to be the most promising. The bicyclo[2.2.1]heptane (or norbornane) skeleton constitutes a structural base of numerous biologically important natural compounds, such as borneol, camphor, etc. Many amines used as a drugs are derivatives of norbornene, norbornane and adamantane (Kasyan, 2002). Cage-like amines having a norbornene fragment typically display antiviral activity. For example, 2-(1-Aminoethyl)bicyclo[2.2.1]heptane hydrochloride is known as viral inhibitor and is readily obtained from norbornane as a mixture of two stereoisomers, *endo* and *exo* (Kasyan, 1998).

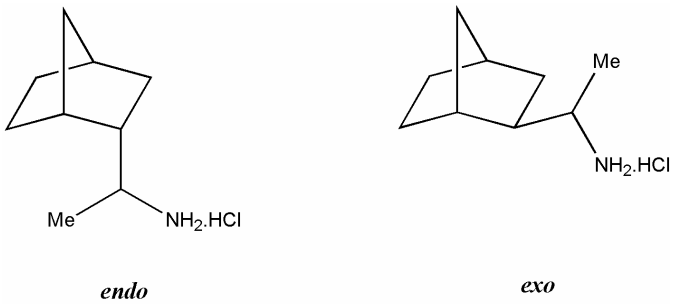


Figure 3.1. Stereoisomers of 2-(1-aminoethyl)bicyclo[2.2.1]heptane

Interest in norbornene derivatives is rising as a result of their increased accessibility due to improvement of procedures for the Diels Alder reactions. In most cases, Diels Alder reactions are highly selective; therefore, it becomes possible to reveal factor responsible for the reaction rate, reaction direction and equilibrium in the absence and in the presence of catalysts. Asymmetric Diels Alder reactions involving cyclopentadiene underlie one of the most promising and convenient methods for the synthesis of optically active norbornene derivatives.

In addition, norbornene is used as a model for studying mechanisms of some organic reactions (Kasyan, 2000).

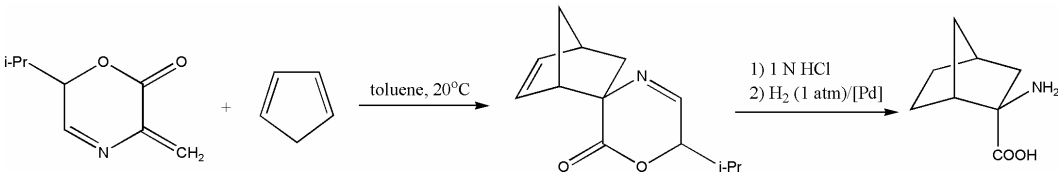
3.1.1. Asymmetric Diels Alder reactions with chiral addens

3.1.1.1. Noncatalytic asymmetric Diels Alder reactions

The asymmetric Diels Alder reaction was described for the first time in 1948 by Korolev and Mur who studied reactions of substituted 1,3-butadienes with di-(–)-menthyl fumarate or maleic anhydride. Auxiliary chiral substituent was introduced into both dienophile and diene molecule. The noncatalytic reactions were carried out in xylene at 140 ˚C; after removal of the chiral fragment, the products were isolated with an optical yield (*enantiomeric excess, ee*) of 0.6-6.8% (Korolev, 1948).

The asymmetric Diels Alder reaction of di-(–)-menthyl fumarate with buta-1,3-diene was found to be strongly affected by ultrahigh pressure. The reaction at 70 ˚C under atmospheric pressure takes 24 h and gives 98% of optically inactive product, while increased pressure favored formation of the positively rotating enantiomer. At 2500 MPa, the *ee* value was 2.9% and at 5000 MPa, 4.7%

First studies in the series of uncatalyzed asymmetric Diels Alder reactions showed relatively low stereo- and enantioselectivity. Therefore, asymmetric Diels Alder reactions at fairly high temperatures without a catalyst have attracted little interest. During the past decade, only a few publications were concerned with uncatalyzed asymmetric Diels Alder reactions, 2-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid was synthesized by reaction of cyclopentadiene with chiral dienophiles in toluene at room temperature (**Scheme 3.1.**) (Chinehilla, 1999).



Scheme 3.1. Synthesis of 2-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid

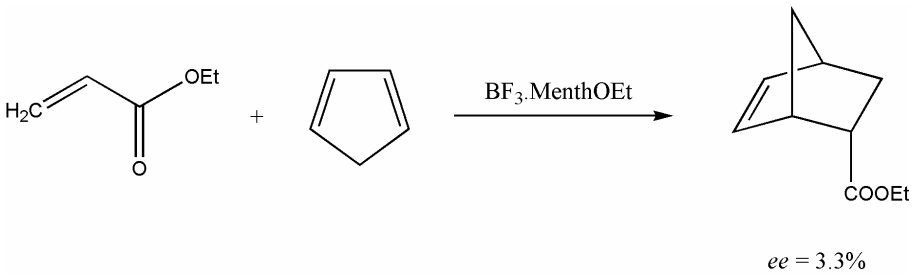
3.1.1.2. Asymmetric Diels Alder reactions in the presence of achiral catalysts

The first example of catalytic asymmetric Diels Alder reaction, the reaction of buta-1,3-diene with di-(–)-menthyl fumarate, showed that its enantioselectivity increases in the presence of Lewis acids (Walborsky, 1963). The best results were obtained in toluene in the presence of $TiCl_4$: the corresponding (*R,R*)-stereoisomer was formed with an *ee* value of 78%. The reaction occured at an appreciable rate at room temperature and even at -70 ˚C.

In the past decade, asymmetric Diels Alder reactions of cyclopentadiene in the presence of achiral catalysts have attracted many scientists attention and chiral compounds have been synthesized with a high optical purity. Cycloaddition of chiral acrylates to cyclopentadiene has become a common model for studying asymmetric induction in Diels Alder reactions, though incomplete *endo*-selectivity hinders analysis of the results. The selectivity is usually estimated by analyzing mixtures of alcohols obtained after removal of auxiliary chiral fragment via reduction with $LiAlH_4$. A high enantioselectivity (*ee* = 80%) was attained with the use of 3,3-dimethylbutan-2-ol as chiral alcohol. (–)-8-phenylmenthol ensured even higher efficiency (*ee* = 99%) (Sauer, 1966).

3.1.2. Asymmetric Diels Alder reactions in the presence of chiral catalysts

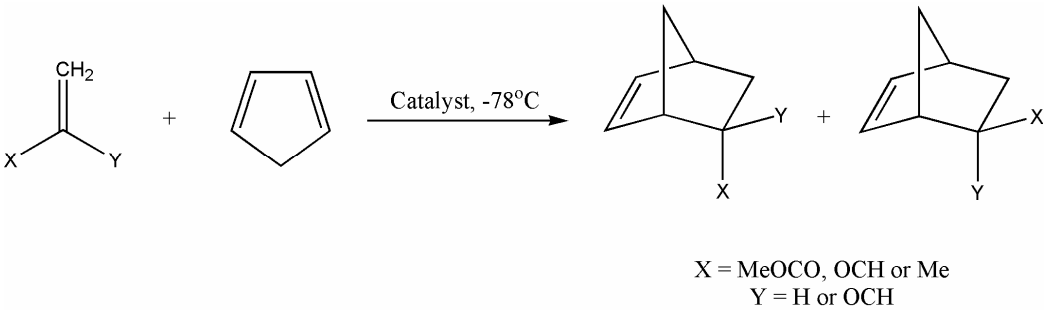
The first example of asymmetric Diels Alder reaction with the use of a chiral catalysts was reported in 1976: the reaction of cyclopentadiene with ethyl acrylate was performed in methylene chloride at 30 ˚C (**Scheme 3.2.**) (Guseinov, 1976).



Scheme 3.2. Asymmetric Diels Alder reaction of cyclopentadiene with ethyl acrylate

Although its enantioselectivity was poor (*ee* = 3.3%), this new approach was successfully developed (Hashimoto, 1979). Chiral metal complex catalysts (Lewis

acids) were synthesized by reaction of $EtAlCl_2$ with optically active alcohols, such as (–)-menthol and (+)-borneol and reactions of cyclopentadiene with dienophiles in presence of these catalysts gave the corresponding adduct with a chemical yield of up to 84% and *ee* of up to 72% (**Scheme 3.3.**).

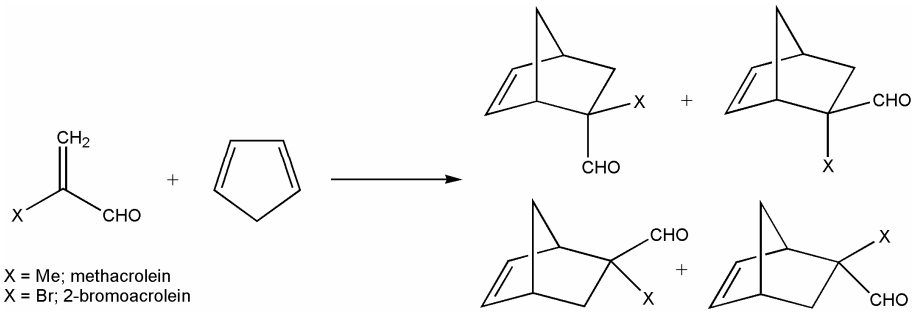


Scheme 3.3. Enantioselective Diels Alder reactions catalysed by chiral metal complexes

The main requirement imposed on chiral catalysts for asymmetric Diels Alder reactions is that they should contain fragments of optically active natural compounds, such as menthol, derivatives of camphor, amino acids and various diols and polyols capable of forming complexes with various metals.

3.1.2.1. Chiral Aluminum-Containing Catalysts

Hashimoto et al. were the first to use aluminum-containing chiral catalysts in asymmetric Diels Alder reactions on the basis of cyclopentadiene (Hashimoto, 1979). A number of norbornene derivatives were synthesized in high chemical and optical yields. Asymmetric Diels Alder reactions of cyclopentadiene with methacrolein and 2-bromoacrolein in the presence of Al-containing chiral catalysts were given in **Scheme 3.4.** (Fraile, 1996).



Scheme 3.4. Asymmetric Diels Alder reactions in the presence of Al-containing chiral catalysts

The catalysts were synthesized by treatment of (*S*)-tyrosine, (*S*)-proline or (–)-menthol applied onto silica gel with a solution of $EtAlCl_2$. The effect of the reaction conditions on the chemical and optical yields and isomeric composition of compouds which were given in the **Figure 3.2**.

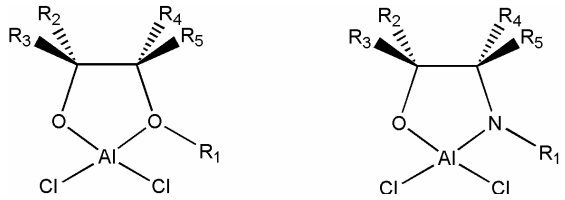
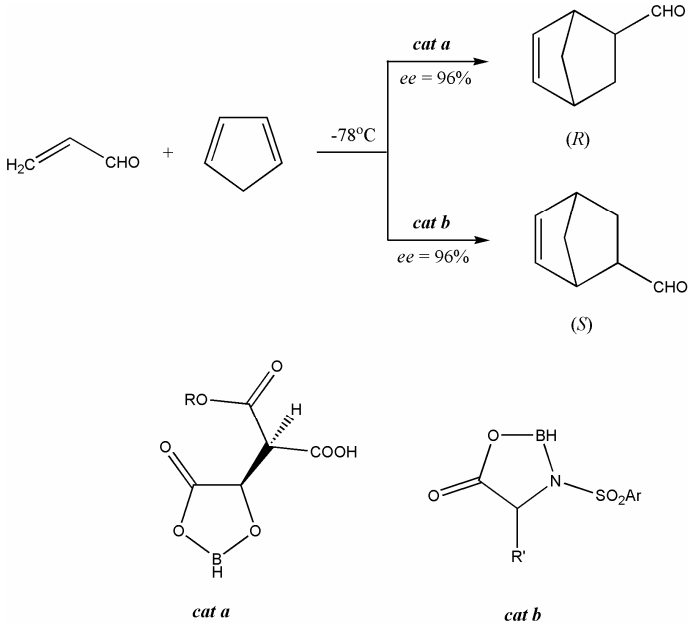


Figure 3.2. Structure of Al-containing chiral catalysts

3.1.2.2. Chiral Boron-Containing Catalysts

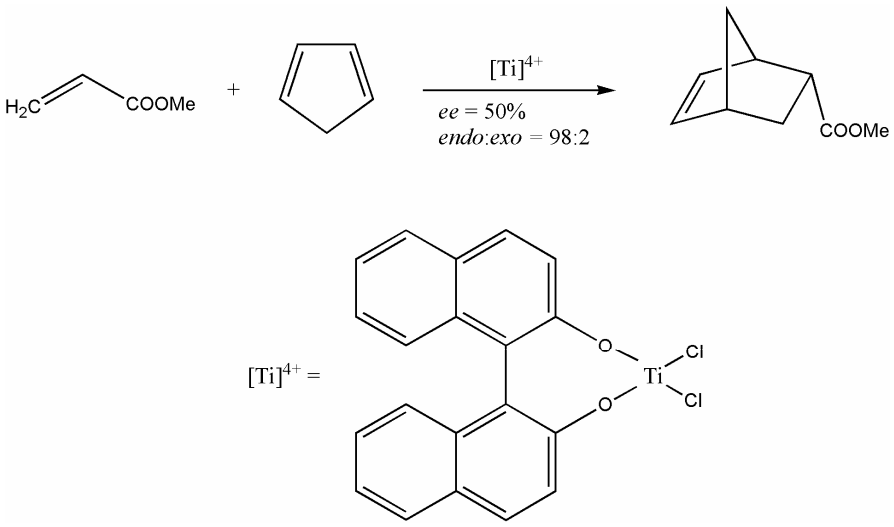
The first asymmetric Diels Alder reaction in the presence of a chiral catalyst was performed using boron-containing compound (Guseinov, 1976). Later on, numerous studies were concerned with asymmetric Diels Alder reactions catalyzed by chiral boron compounds. Various boron-containing catalysts with chiral ligands were successfully used in the recent years. It was found that the catalytic efficiency depends on the structure and electronic properties of the ligand. New boron compounds were used to catalyze asymmetric Diels Alder reactions of cyclopentadiene with acrolein to obtain unsaturated aldehydes (**Scheme 3.5.**) (Lohray, 1992).



Scheme 3.5. Lohray' s boron catalysts for Diels Alder reaction

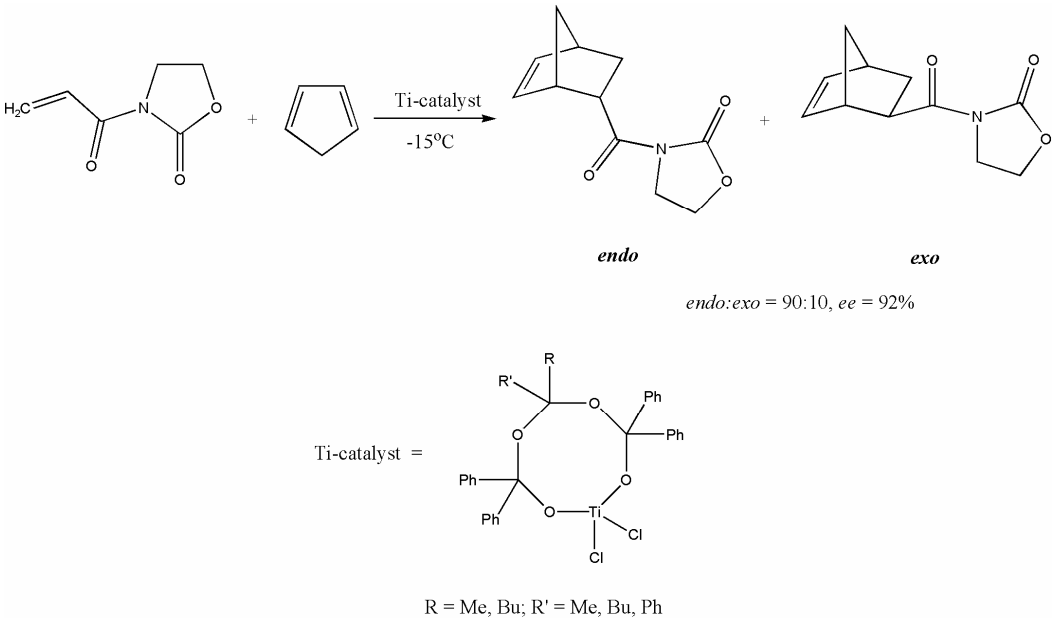
3.1.2.3. Chiral Titanium-Containing Catalysts

Titanium complexes as chiral catalysts for asymmetric Diels Alder reaction were prepared for the first time on the basis of optically active diols (Kagan, 1992). A number of titanium-containing coordination compounds were synthesized from various optically active compounds and were used to catalyze asymmetric [4+2]-cycloadditions. For example, Carpius and Jureza studied the addition of cyclopentadiene to acrylamide and crotonamide in the presence of a chiral catalyst prepared from optically active 1,1'-binaphthalene-2,2'-diol and $TiCl_4$. Asymmetric Diels Alder reaction of cyclopentadiene with methyl acrylate in the presence of chiral titanium complex gave adduct compound with a high stereoselectivity (*endo/exo*-isomer ratio 98:2; *ee* = 50%) (**Scheme 3.6.**) (Seebach, 1987).



Scheme 3.6. Diels Alder reaction between methyl acrylate and cyclopentadiene catalysed by chiral titanium complex

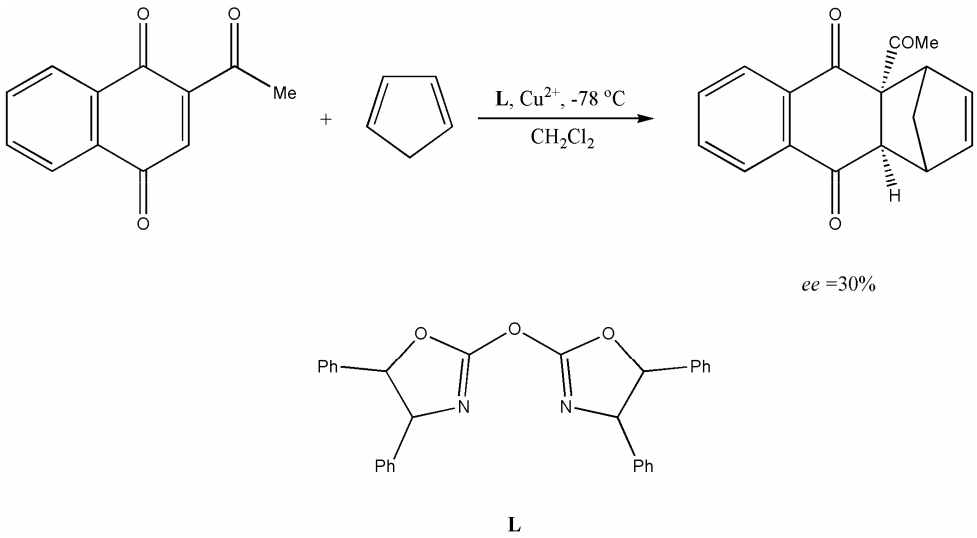
Narasaka et al. synthesized chiral complexes from dichlorodiisopropoxytitanium and used them in asymmetric Diels Alder reactions (**Scheme 3.7.**) (Narasaka, 1989).



Scheme 3.7. Enantioselective Diels Alder reaction catalysed by Ti^{4+} catalyst

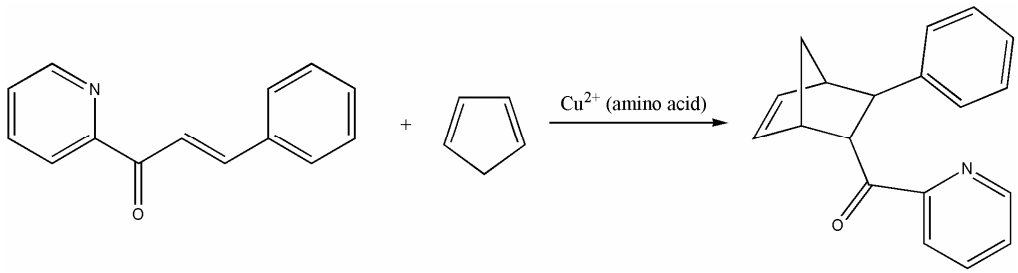
3.1.2.4. Chiral Copper(II)-Containing Catalysts

Chiral copper(II) complexes have been used in asymmetric Diels Alder reactions relatively recently. Ghosh et al. studied reactions of substituted aliphatic esters derived from glyoxylic acid in the presence of chiral Cu(II) complexes with bis(dihydrooxazoles) (Ghosh, 1996). The yield of the product was 76% (*ee* = 70%). Brimble and McEwan reported on the asymmetric Diels Alder reactions of substituted 1,4-naphtho-quinones with cyclopentadiene in the presence of chiral Cu(II) complexes based on **L** (**Scheme 3.8.**) (Brimble, 1997).



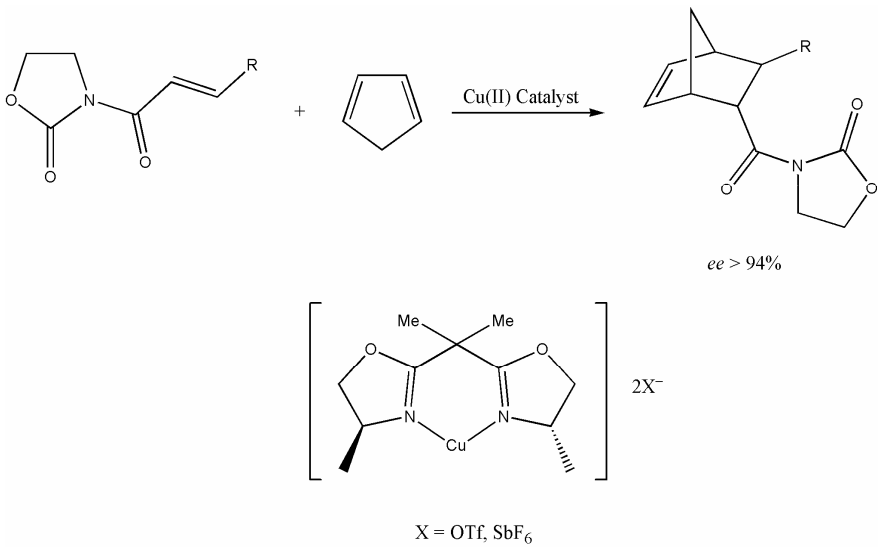
Scheme 3.8. Bifunctional Cu^{2+} catalyst for enantioselective Diels Alder reaction

In the recent time, much attention is given to organic reactions occurring in aqueous medium. The first examples of asymmetric Diels Alder reactions in the presence of chiral Cu(II) complexes in aqueous medium were described in 1998 and 1999 (Otto, 1998; Otto, 1999). Here, copper(II) complexes were prepared using natural amino acids as chiral ligands (L-valine, L-leucine, L-phenylalanine, L-tyrosine, L-tryptophane and L-abrine). The complexes were found to be effective catalysts in the reaction of 3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one with cyclopentadiene (**Scheme 3.9.**). The best results were obtained using aromatic amino acids as ligands in the chiral copper(II) complexes. The product with *ee* = 74% was isolated in the reaction performed in the presence of 10% of the catalyst at room temperature (48 h).



Scheme 3.9. Asymmetric Diels Alder reaction in aqueous solution

New chiral bis(dihydrooxazole) copper(II) complexes successfully catalyzed the asymmetric Diels Alder reactions of cyclopentaidene with 1-(oxazolidin-3-yl)prop-2-en-1-ones to give adduct with high stereo- and enantioselectivity (**Scheme 3.10.**) (Evans, 1999; Evans, 2000).

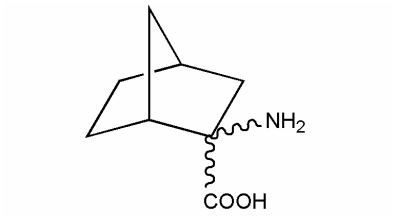


Scheme 3.10. Evans's Cu complex's performance in catalytic asymmetric Diels Alder reactions

3.1.3. Biological Activity

A specific feature of living matter is that almost all its chemical components having one or more asymmetric carbon atoms exist exclusively in a single stereochemical configuration possessing optical activity. Biochemical processes occurring in human organism are also stereospecific. As noted above, enantiomers having identical chemical properties often exhibit strongly different physiological activities.

Substituted bicyclo[2.2.1]heptenes are convenient synthons for the preparation of various physiologically active compounds and they can be readily obtained as enantiomerically pure substances via asymmetric Diels Alder reactions of cyclopentadiene. Amino derivatives of bicyclo[2.2.1]heptene system are good starting materials for the synthesis of effective biologically active compounds. As early as 1972, Tager and Christense noted that aminonorbornanecarboxylic acid is a physiologically active substance and that it could exhibit antiviral activity (Tager, 1972).



2-aminonorbornane-2-carboxylic acid

Figure 3.3. Structure of 2-aminonorbornane-2-carboxylic acid

A widely used procedure is based on the Diels Alder reaction of cyclopentadiene with derivatives of α,β-unsaturated α-amino acids (Clerici, 2001). β-substituted dienphiles can also be involved in this reaction. Diastereoselective and enantioselective versions have also been tested.

Biological activity of unsubstituted 2-aminonorbornane-2-carboxylic acid was studied in many aspects. It was shown that acid is selectively transported by sodium-independent systems destined to transport hydrophobic amino acids to almost all cells. The transport system is selective for one diastereoisomer of 2-aminonorbornane-2-carboxylic acid (*endo* or *exo*). Another kind of activity

(glutaminase-activating) was revealed by incubation of 2-aminonorbornane-2-carboxylic acid with a simple of rat mitochondria (Zaleski, 1986).

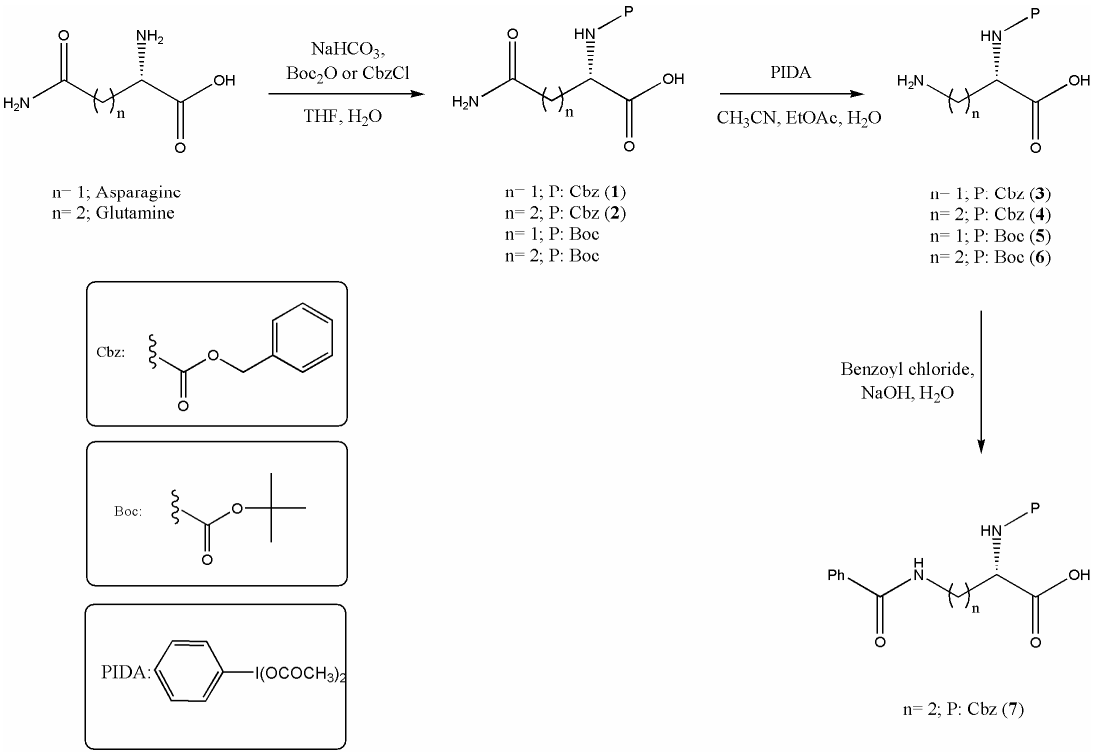
3.2. Results and Discussion

Water is becoming increasingly popular as a medium for organic reactions. Apart from the obvious economic and environmental benefits, the aqueous medium can have favorable effects on many organic transformations. In the field of Lewis-acid catalysis, the use of water is still in its infancy (Engbberts, 1996). Accordingly, reports on Lewis-acid catalysis of Diels Alder reactions in water or mixture of organic solvents with small amounts of water are scarce (Otto, 1995; Otto, 1996). Examples of enantioselective Lewis-acid catalyzed Diels Alder reactions in water have been lacking to date.

Here we present L-asparagine and L-glutamine derivatives which contain protection groups such as Boc (*tert*-butyl carbonate) and Cbz (carbobenzoxy) and applications in the asymmetric Diels Alder reactions in water.

3.2.1. Synthesis of L-asparagine and L-glutamine derivatives

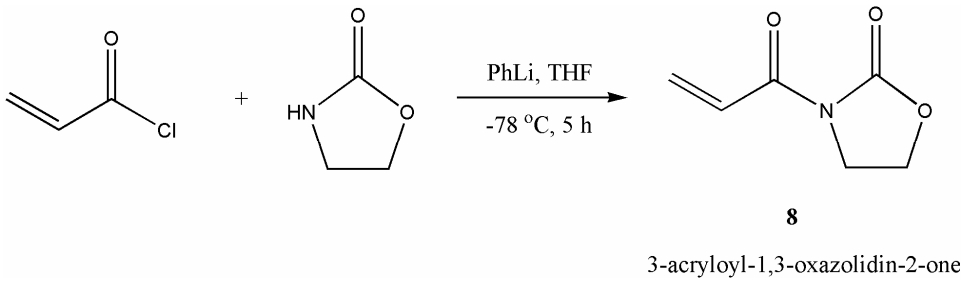
In order to obtain amino acid derived chiral ligands, we prepared Boc and Cbz protected L-asparagine (**1**) and L-glutamine (**2**). Then we transformed the amide group in **1** and **2** to the amino group using Hoffman rearrangement (**3**-**6**) and finally we prepared an amide derivative of Cbz protected L-glutamine with benzoyl acid (**7**) (**Scheme 3.11.**) (Kraml, 2005; Zhang, 1997; Andruszkiewicz, 2004).



Scheme 3.11. Synthesis of amino acid derivatives as chiral ligands

3.2.2. Synthesis of dienophile

The Diels Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene was carried out in water as a test reaction. Therefore 3-acryloyl-1,3-oxazolidin-2-one was synthesized as a dienophile according to the literature method (Evans, 1981).



Scheme 3.12. Synthesis of 3-acryloyl-1,3-oxazolidin-2-one

3.2.3. Enantioselective Diels Alder reaction catalyzed by L-asparagine and L-glutamine derivatives

L-asparagine and L-glutamine derivatives (**1**-**7**) were used in the Diels Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene in the presence of $Cu(NO_3)_2.3H_2O$. The primary aim of this work was to find out the best catalyst and then search for the optimal conditions for the asymmetric Diels Alder reaction.

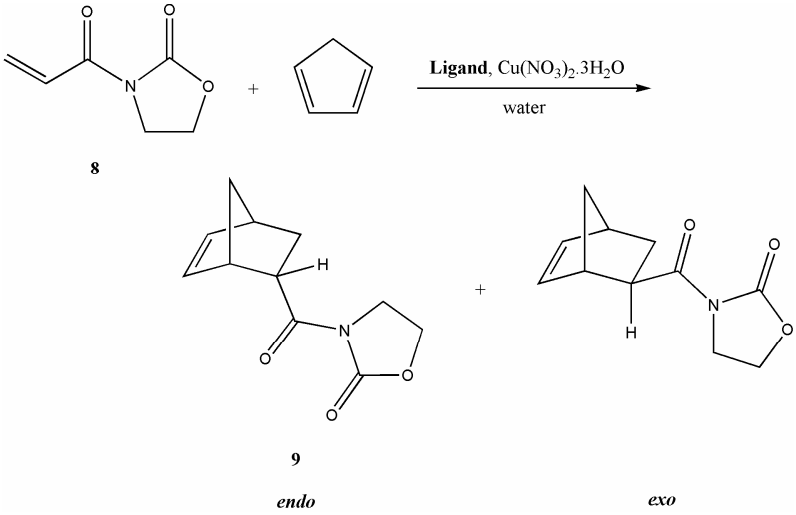


Table 3.1. Catalyst and temperature effect on the asymmetric Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene in the presence of $Cu(NO_3)_2.3H_2O$

Entry	Ligand	Temp. (°C)	Time[a]	Yield (%)	*endo*/*exo*[b]	*ee*% *endo*(*exo*)[b]
1	**1**	0	4 h	76	94:6	2(6)
2	**2**	0	4 h	83	91:9	3(4)
3	**3**	0	4 h	85	96:4	rac(2)
4	**4**	0	4 h	95	95:5	6(7)
5	**5**	0	4 h	93	94:6	5(rac)
6	**6**	0	4 h	79	94:6	6(7)
7	**7**	0	4 h	93	96:4	rac(rac)
8	**4**	-5	7 h	83	96:4	rac(rac)
9	**4**	-10	12 h	90	96:4	3(rac)
10	**4**	-15	24 h	80	95:5	3(2)

[a]detected by TLC

[b]determined by chiral HPLC analysis

All reactions were run in the presence of water and the *endo*/*exo* ratio, the *ee* values and the yields were reported in **Table 3.1.** Each reaction was performed with the amino acid derivatives as a chiral ligand and copper(II)nitrate trihydrate as a Lewis acid. From the data in **Table 3.1.** some features can be pointed out: (*i*) All catalysts are *endo*-selective (entries 1 – 7). (*ii*) For L-asparagine and L-glutamine derivatives **1** – **7**, the best catalyst is **4** (entry 4) in terms of both the *endo*/*exo* ratio and the enantioselectivity. (*iii*) When the temperature is decreased, the reaction takes a longer time and the *ee* value decreases (entries 8, 9 and 10). Synthetically, 0 °C should be the optimized temperature for this reaction.

The reaction of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene over the proposed ligand (**4**) was used as a model to optimize some operating conditions.

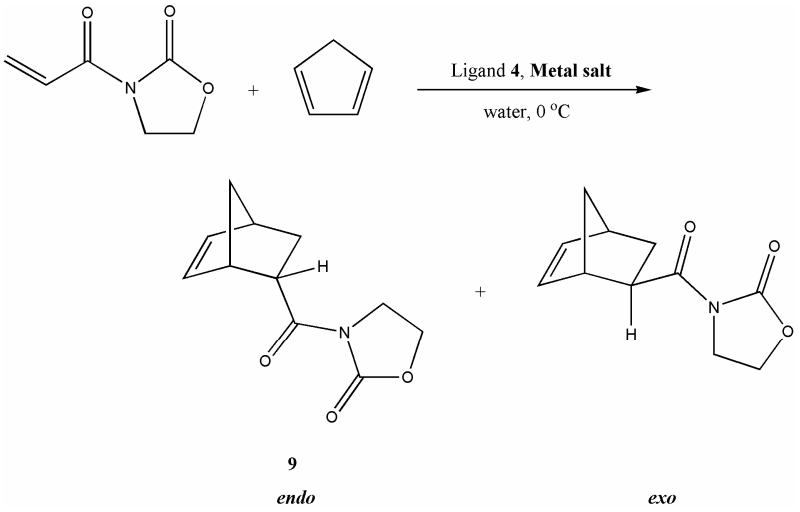


Table 3.2. Effect of the transition metal salts on the asymmetric Diels Alder cycloaddition reaction

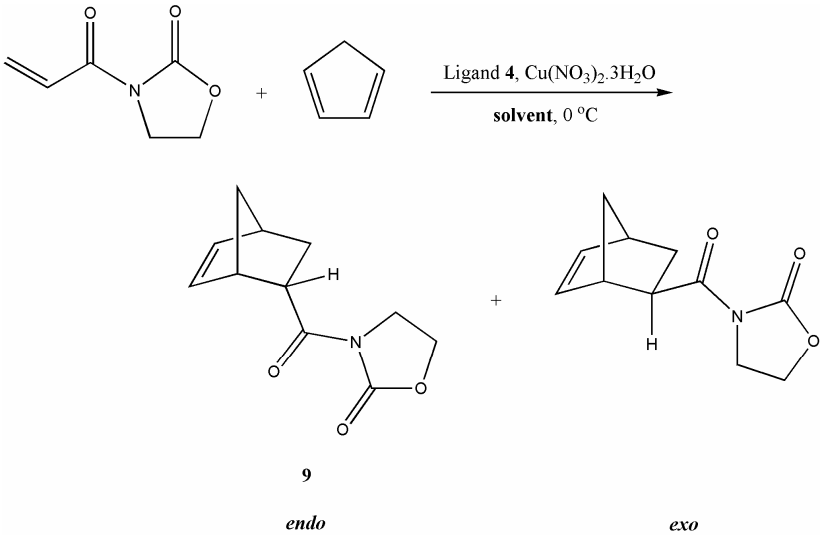
Entry	Metal salts	Time[a]	Yield (%)	*endo*/*exo*[b]	*ee*% *endo*(*exo*)[b]
1	$Ni(OAc)_2{\cdot}4H_2O$	4 h	92	95:5	5(2)
2	$Zn(OAc)_2{\cdot}2H_2O$	4 h	97	93:7	5(10)
3	$Co(OAc)_2{\cdot}4H_2O$	4 h	96	94:6	6(2)
4	$Mn(OAc)_2{\cdot}4H_2O$	4 h	88	89:11	rac(7)
5	$Cu(OAc)_2{\cdot}H_2O$	4 h	86	95:5	5(rac)

[a]detected by TLC

[b]determined by chiral HPLC analysis

Another parameter examined was the transition metal salts effect on the asymmetric Diels Alder cycloaddition reaction in water (**Table 3.2.**). According to the data prensented, the effectiveness of the metals in activating this Diels Alder cycloaddition follows the order: $Mn^{2+} < Zn^{2+} < Co^{2+} < Ni^{2+} \approx Cu^{2+}$, in good agreement with the empirical order given by Irving and Williams (Mn < Co < Ni < Cu > Zn) for the bivalent ion complexation (Irving, 1953).

Finally, we compared the *endo*/*exo* ratio and enantioselectivity results obtained in water and organic solvents (**Table 3.3.**).



9

endo ***exo***

Table 3.3. Solvent effect on the asymmetric Diels Alder of 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene

Entry	Solvent	Time[b]	Yield (%)	*endo*/*exo*[c]	*ee*% *endo*(*exo*)[c]
1	CH_3CN[a]	6 days	43	85:15	6(rac)
2	THF[a]	5 days	54	87:13	rac(2)
3	EtOH[a]	3 days	94	88:12	6(rac)
4	$CHCl_3$[a]	3 days	91	90:10	4(rac)
5	water	4 h	95	95:5	6(7)

[a] $[Cu(NO_3)_2 \cdot 3H_2O]$ = 1.00 mM; [Ligand 4] = $[Et_3N]$ = 1.75 mM; dienophile = 10 mM; cyclopentadiene = 80 mM

[b] detected by TLC

[c] determined by chiral HPLC analysis

Table 3.3. clearly demonstrates that the stereoselectivity benefits considerably from the use of water as the solvent. This is in line with literature

observations that arene – arene intractions are less efficient in organic solvents than in water (Otto, 1999).

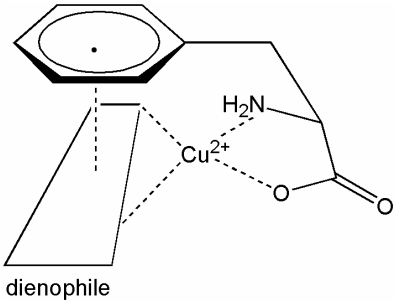


Figure 3. 4. Transition-state assembly suggested for the aqueous Lewis-acid-catalyzed Diels Alder reaction

The arene – arene interaction is a specific interaction between the aromatic system of the α-amino acid ligand and the coordinated dienophile which is responsible for the enhanced stability of the ternary complex (**Figure 3.4.**).

3.3. Conclusion

The influence of a series of α-amino acid derivative ligands on the yield and the stereoselectivity of the Diels Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene in water has been investigated. The L-glutamine ligand which contains an aromatic system was found to be the best catalyst in water as a result of arene – arene interaction. This system exhibited greater reactivity, shorter reaction time, better yield and higher *endo/exo* ratio but unfortunately lower *ee* values.

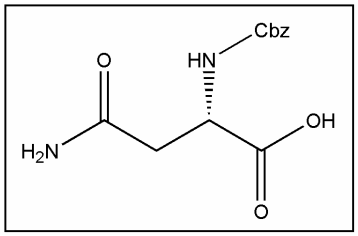
The L-glutamine derivative ligand is an advantageous catalyst for an asymmetric catalytic reaction being cheap and easily accessable starting materials with an easy two step procedure for its preparation. On the other hand, the catalyst is very stable in air and water, so it does have potential in other asymmetric applications.

3.4. Material and Method

Chemicals were purchased from Merck, Sigma-Aldrich, Alfa Aesar or Fluka and used without any purification. Solvents were used as received from commercial suppliers. IR spectra were recorded using a Perkin Elmer 100. ^{1}H

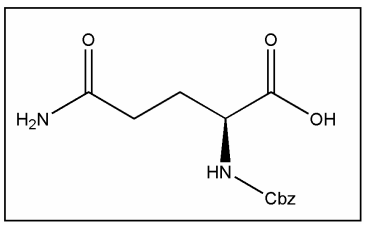
NMR and ^{13}C NMR spectra were carried out using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. Melting points were recorded with an electro thermal digital melting points apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. For column chromatography silica gel 60 (Merck 7743) was used. HPLC analyses were performed using Chiralcel OD-H column. Ligands 1-6 and 3-acryloyl-1,3-oxazolidin-2-one were prepared according to the literature method (Kraml, 2005; Zhang, 1997; Andruszkiewicz, 2004; Evans, 1981).

3.4.1. Carbobenzyloxy-L-asparagine (1)



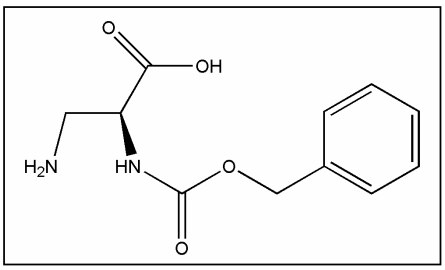
To a solution of L-asparagine (346 mg, 2.3 mmol) and $NaHCO_3$ (395 mg, 4.6 mmol) in water (10 mL) was added solution of benzyl chloroformate (600 mg, 3.5 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture was stirred at rt for a few hours until there was no starting material left. THF was evaporated in *vacuo* and 0.2 M NaOH was added dropwise (pH=5) and extracted with diethylether. The water phase was evaporated in *vacuo* to give the title compound as a white solid (68% yield). mp. 163 – 165 °C; ^1H NMR (DMSO) δ (ppm) 7.40 – 7.31 (m, 5H), 6.87 (s, 1H), 5.01 (s, 2H), 4.35 – 4.29 (m, 1H), 2.56 – 2.40 (m, 2H). IR (KBr) 3413, 3339, 1701, 1645 cm^{-1}.

3.4.2. Carbobenzyloxy-L-glutamine (2)



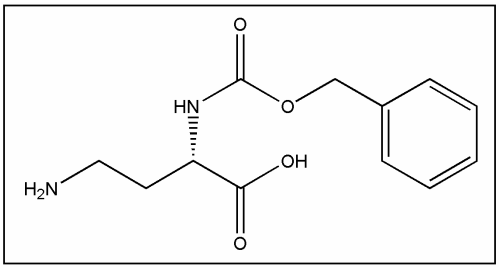
To a solution of L-glutamine (336 mg, 2.3 mmol) and $NaHCO_3$ (395 mg, 4.6 mmol) in water (10 mL) was added solution of benzyl chloroformate (600 mg, 3.5 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture was stirred at rt for a few hours until there was no starting material left. THF was evaporated in *vacuo* and 0.2 M NaOH was added dropwise (pH=5) and extracted with diethylether. The water phase was evaporated in *vacuo* to give the title compound as a white solid (74% yield). mp. 134 – 138 °C; ^1H NMR (DMSO) δ (ppm) 7.54 – 7.24 (m, 5H), 6.72 (s, 1H), 5.01 (s, 2H), 3.96 – 3.89 (m, 1H), 2.48 (s, 1H), 2.13 (t, 2H, J = 8 Hz), 1.98 – 1.68 (m, 2H). IR (KBr) 3439, 3321, 1702, 1654 cm^{-1}.

3.4.3. (2S)-3-amino-2-{[(benzyloxy)carbonyl]amino}propanoic acid (3)



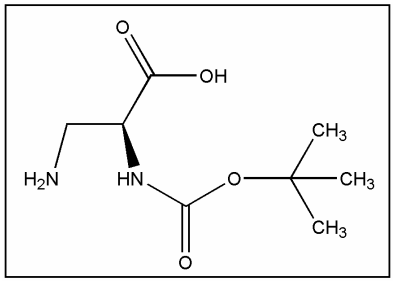
A slurry of **1** (500 mg, 1.88 mmol), ethyl acetate (2.4 mL), acetonitrile (2.4 mL), water (1.2 mL) and PIDA (iodobenzenediacetate) (726 mg, 2.25 mmol) was cooled and stirred at 16 °C for 30 min. The temperature was allowed to reach 20 °C, and the reaction was stirreed until completion (4 h). The mixture was cooled to 5 °C and the product was filtered, washed with ethyl acetate (1.0 mL) and dried in *vacuo* at 50 °C to give **3** as a white solid (80% yield). mp. 210 °C (dec); ^{1}H NMR (DMSO/TFA) δ (ppm) 7.94 (bs, 3H), 7.67 (d, 1H), 7.36- 7.28 (m, 5H), 5.05 (s, 2H), 4.32 – 4.26 (m, 1H), 3.25 – 2.98 (m, 2H). IR (KBr) 3304, 1694, 1591 cm^{-1}.

3.4.4. (2S)-4-amino-2-{[(benzyloxy)carbonyl]amino}butanoic acid (4)



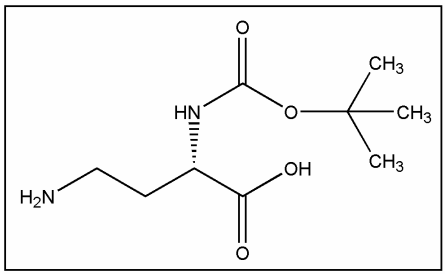
A solution of **2** (280 mg, 1.0 mmol) in THF (2.4 ml) and water (0.6 mL) was treated with PIDA (380 mg, 1.2 mmol) and stirred magnetically at 4 °C for 8 hr. After evaporation of the solvents the resulting foamy solid was dissolved in water (2.0 mL) and extracted with ethyl acetate (3 × 5 mL). The aqueous layer was evaporated to dryness to yield a crude product which was washed with a mixture of ethyl acetate – CH_2Cl_2 (1:1, v:v, 2.0 mL) to afford **4** as a white solid (85% yield). mp. 190 – 192 °C; ^{1}H NMR (D_2O) δ (ppm) 7.36 (bs, 5H), 5.06 (s, 2H), 3.98 – 3.95 (m, 1H), 2.97 (t, 2H, J = 8 Hz), 2.12 – 1.86 (m, 2H). IR (KBr) 3344, 3281, 1714, 1688 cm^{-1}.

3.4.5. (2S)-3-amino-2-[(*tert*-butoxycarbonyl)amino]propanoic acid (5)



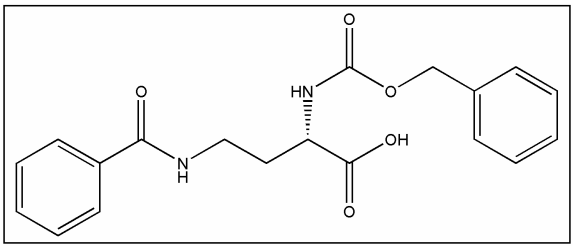
A solution of *N*-*tert*-butoxycarbonyl-(*S*)-asparagine (265 mg, 1.14 mmol), ethyl acetate(1.2 mL), acetonitrile (1.2 mL), water (0.6 mL) and PIDA (440 mg, 1.37 mmol) was coold and stirred at 10 °C for 30 min. The temperature was allowed to reach 20 °C and the reaction was stirred until until completion (3 – 4 h). The mixture was heated to 70 °C until completely dissolved and then slowly cooled to ambient temperature over a 3 h period. The solid was filtered, washed with ethyl acetate (0.2 mL) and dried in *vacuo* at 50 °C to give **5** as a white solid (75% yield). mp. 215 °C (dec); ^{1}H NMR (D_2O) δ (ppm) 4.10 (bs, 1H), 3.34 – 3.10 (m, 2H), 1.38 (s, 9H). IR (KBr) 3345, 1685, 1532 cm^{-1}.

3.4.6. (2S)-4-amino-2-[(*tert*-butoxycarbonyl)amino]butanoic acid (6)



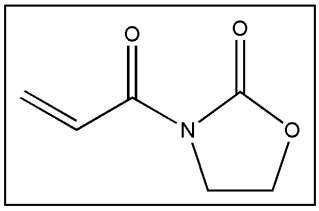
N-*tert*-butoxycarbonyl-(*S*)-glutamine (369 mg, 1.5 mmol) in THF (3.6 mL) and water (0.9 mL), PIDA (579 mg, 1.8 mmol) was added at 4 °C. After stirring for 6 hr the reaction mixture was evaporated to dryness, the residue was dissolved in water (2.0 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was discarded and the aqueous layer was evaporated to dryness and the crude solid was washed several times with cold CH_2Cl_2 and dried in *vacuo* to afford **6** as a white solid (85% yield). mp. 206 – 207 °C; ^{1}H NMR (D_2O) δ (ppm) 3.90 (bs, 1H), 3.00 (t, 2H, J = 8 Hz), 2.05 – 1.85 (m, 2H), 1.37 (s, 9H). IR (KBr) 3416, 1698, 1531 cm^{-1}.

3.4.7. (2S)-4-(benzoylamino)-2-{[(benzyloxy)carbonyl]amino}butanoic acid (7)



To a solution of **4** (70 mg, 0.28 mmol) and NaOH (11.2 mg, 0.28 mmol) in water (10 mL) at 0 °C was added benzoyl chloride (43.3 mg, 36 μL, 0.31 mmol). The cooling bath was removed and the resulting reaction mixture was stirred at rt for a few hours until there was no starting material left. The white solid was filtered, washed with cold water (41% yield). mp. 112 -114 °C; ^{1}H NMR (DMSO) δ (ppm) 8.47 (s, 1H), 7.83 (d, 2H, J = 8 Hz), 7.63 – 7.29 (m, 8H), 5.04 (s, 2H), 4.07 (m, 1H), 2.50 (bs, 2H), 2.07 – 1.83 (m, 2H). ^{13}C NMR (DMSO) δ (ppm) 174.37, 166.98, 156.82, 137.68, 135.22, 131.72, 129.02, 128.88, 128.36, 127.86, 66.12, 52.60, 37.09, 31.28. IR (KBr) 3352, 3328, 1687, 1642 cm^{-1}.

3.4.8. 3-acryloyl-1,3-oxazolidin-2-one (8)



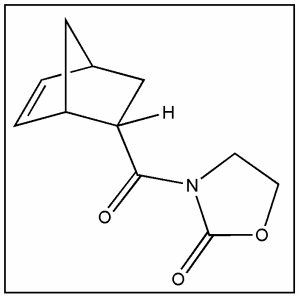
To the solution of 2-oxazolidinone (100 mg, 1.15 mmol) in dry THF, phenyl lithium (1.15 mmol) was slowly added at -78 ˚C. After stirring for 3 h, acryloyl chloride (147 mg, 1.63 mmol) was slowly added. After 2h, the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and dried in *vacuo*. The residue was purified by silica gel column chromatography to afford **8** (78% yield). mp. 85.4-87 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.49 (dd, 1H, J = 16.8, 10 Hz), 6.55 (dd, 1H, J = 17.2, 2 Hz), 5.90 (dd, 1H, J = 10.4, 2 Hz), 4.44 (t, 2H, J = 7.6 Hz), 4.08 (t, 2H, J = 6.8 Hz). IR (NaCl) 1784, 1693, 1678, 1615 cm^{-1}.

3.4.9. General procedure for Diels Alder reaction

A solution of ligand (0.2 mmol) and NaOH (0.2 mmol) in 5 mL water was added to solution of $Cu(NO_3)_2{\cdot}3H_2O$ (0.2 mmol) in 10 mL water. The catalyst solution was cooled to 0 °C, and solution of 3-acryloyl-1,3-oxazolidin-2-one (**8**) (1 mmol) in a minimal amount of ethanol and freshly distilled cyclopentadiene (2 mmol) were added in this order. The reaction was performed at 0 °C and

monitored by TLC. After the completion of reaction, the mixture was extracted with diethyl ether. The combined extracts were dried over Na_2SO_4 and evaporated in *vacuo*. The *endo:exo* ratios and enantiomeric excess were determined through HPLC analysis on a Chiralcel OD-H column.

3.4.9.1. 3-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-1,3-oxazolidin-2-one (9)



^{1}H NMR ($CDCl_3$) δ (ppm) 6.22 (dd, 1H, J = 5.2, 3.2 Hz), 5.85 (dd, 1H, J = 6, 3.2 Hz), 4.41 – 4.37 (m, 2H), 3.98 – 3.92 (m, 3H), 3.29 (bs, 1H), 2.94 (bs, 1H), 1.96 – 1.38 (m, 4H). IR (NaCl) 1778, 1695, 1386 cm^{-1}. HPLC conditions: 90:10 hexane/*i*-PrOH, 1 ml/min flow rate, 210 nm. The average retention times 17 and 18 min for exo; 19 and 21 min for endo.

3.5. Appendix B. Spectra and Chromatograms

B.1. IR spectra

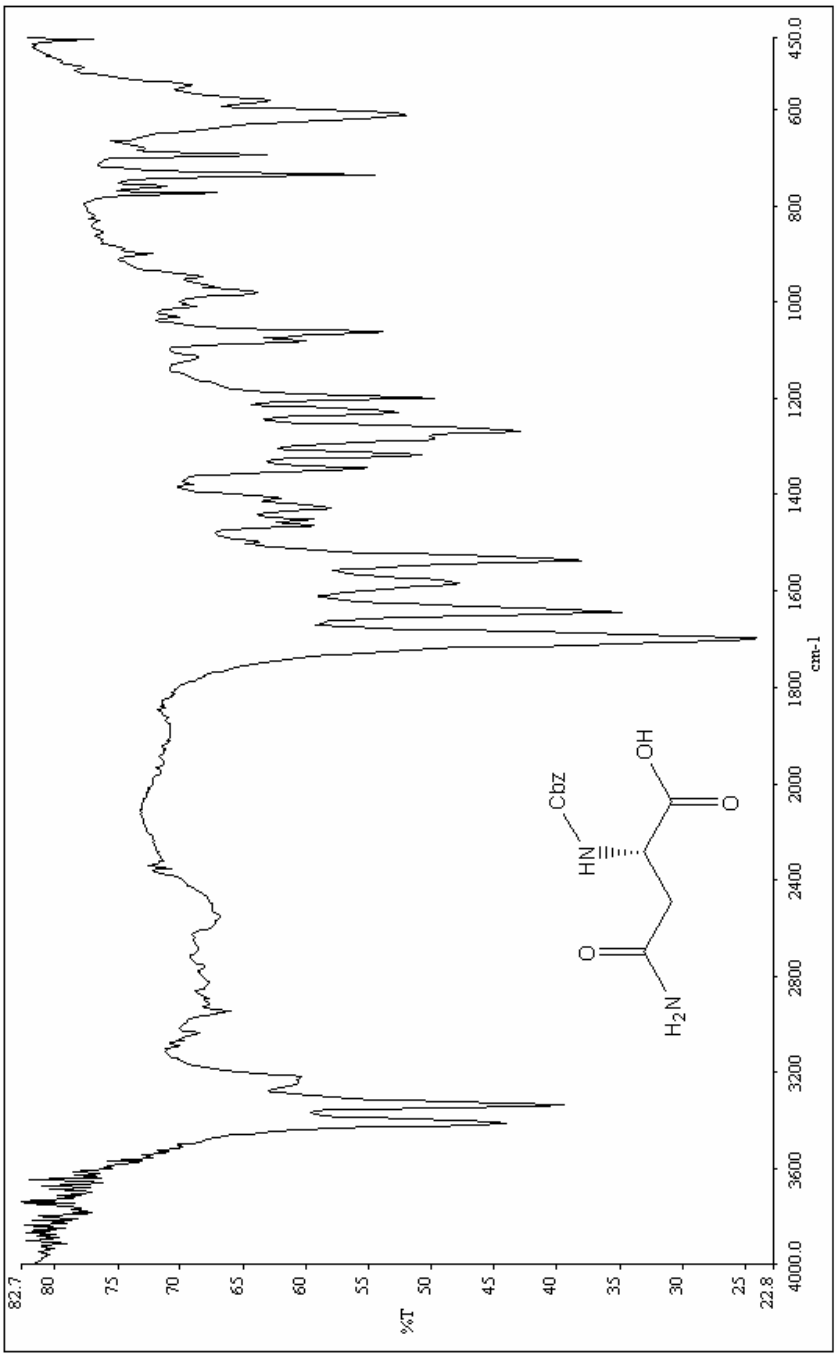


Figure B.1.1. IR spectrum of Carbobenzyloxy-L-asparagine (**1**)

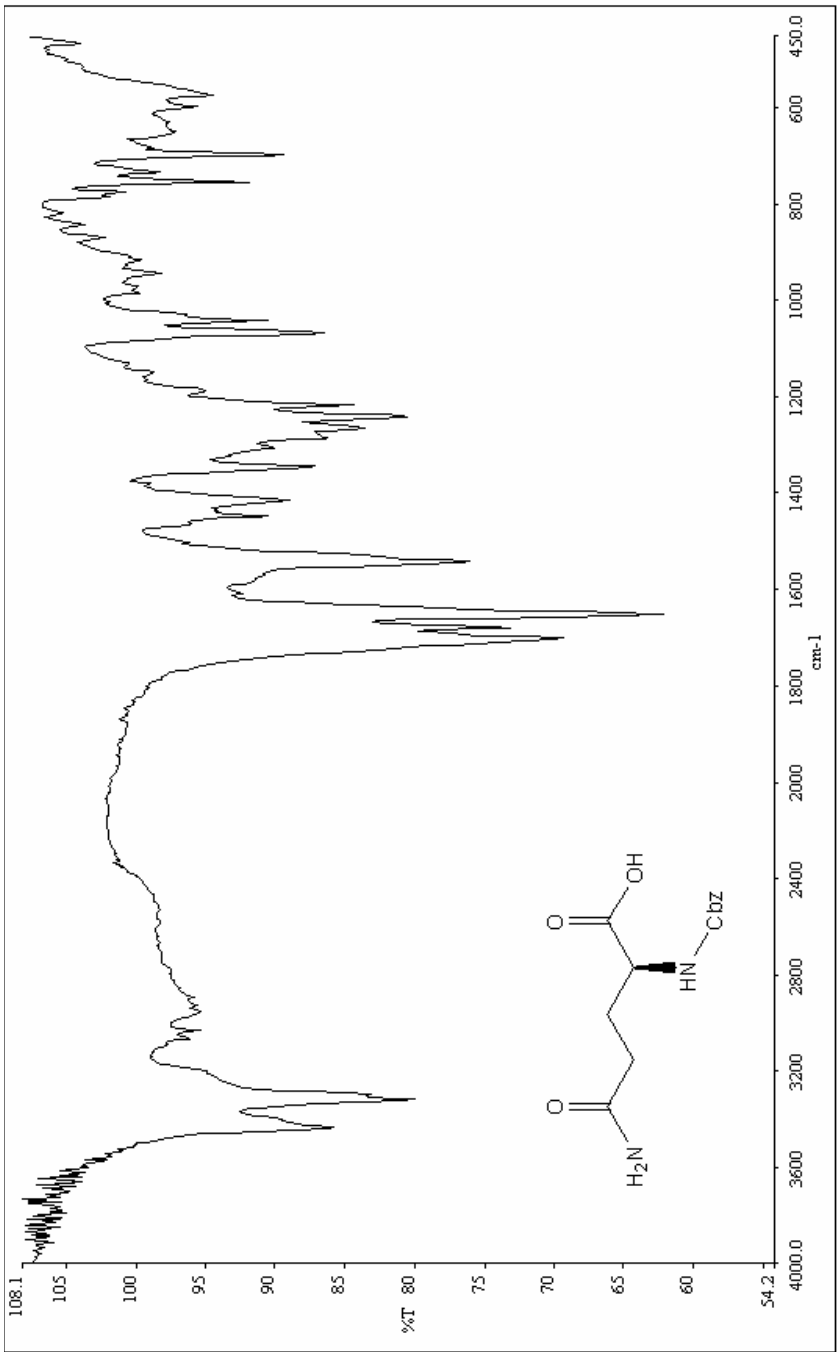


Figure B.1.2. IR spectrum of Carbobenzyloxy-L-glutamine (**2**)

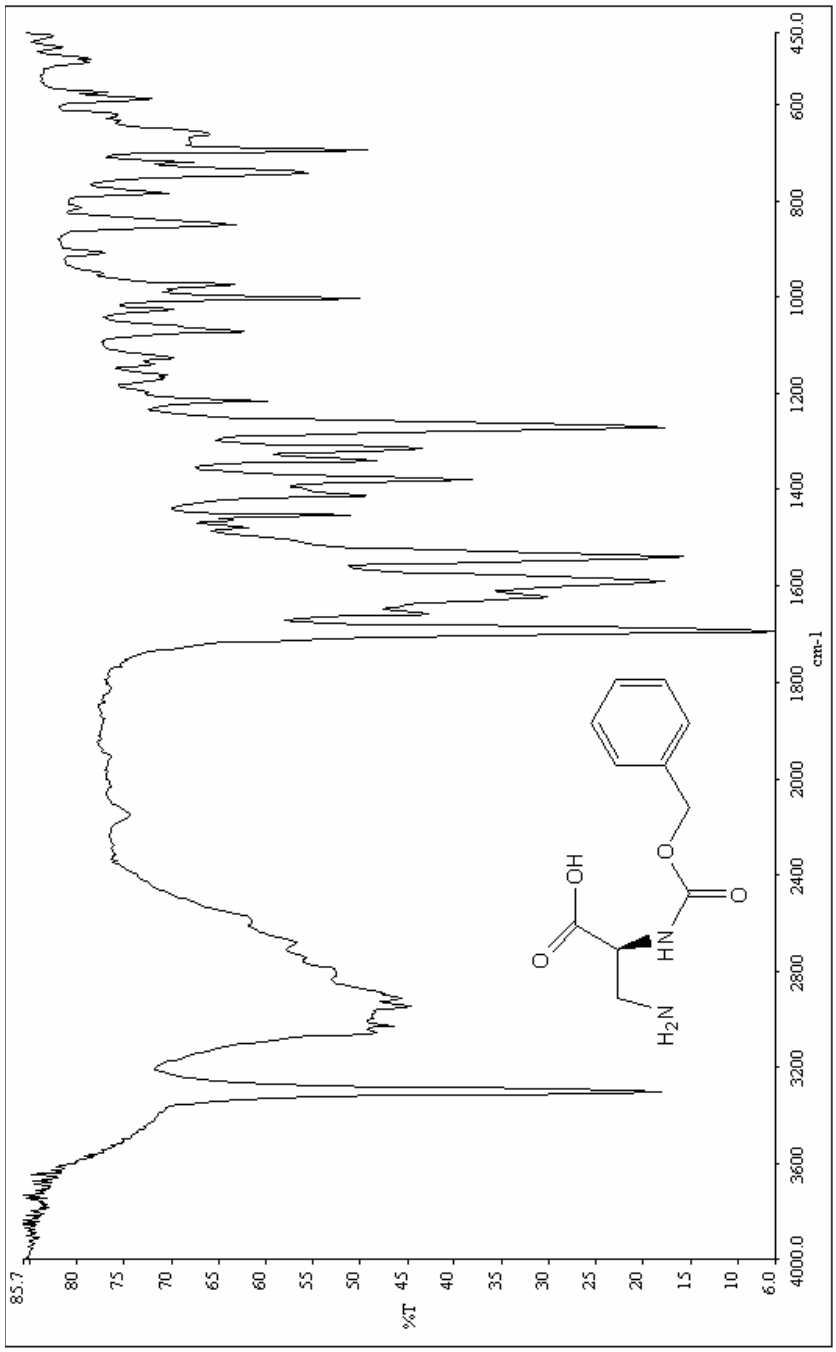


Figure B.1.3. IR spectrum of (2S)-3-amino-2-{[(benzyloxy)carbonyl]amino}propanoic acid (**3**)

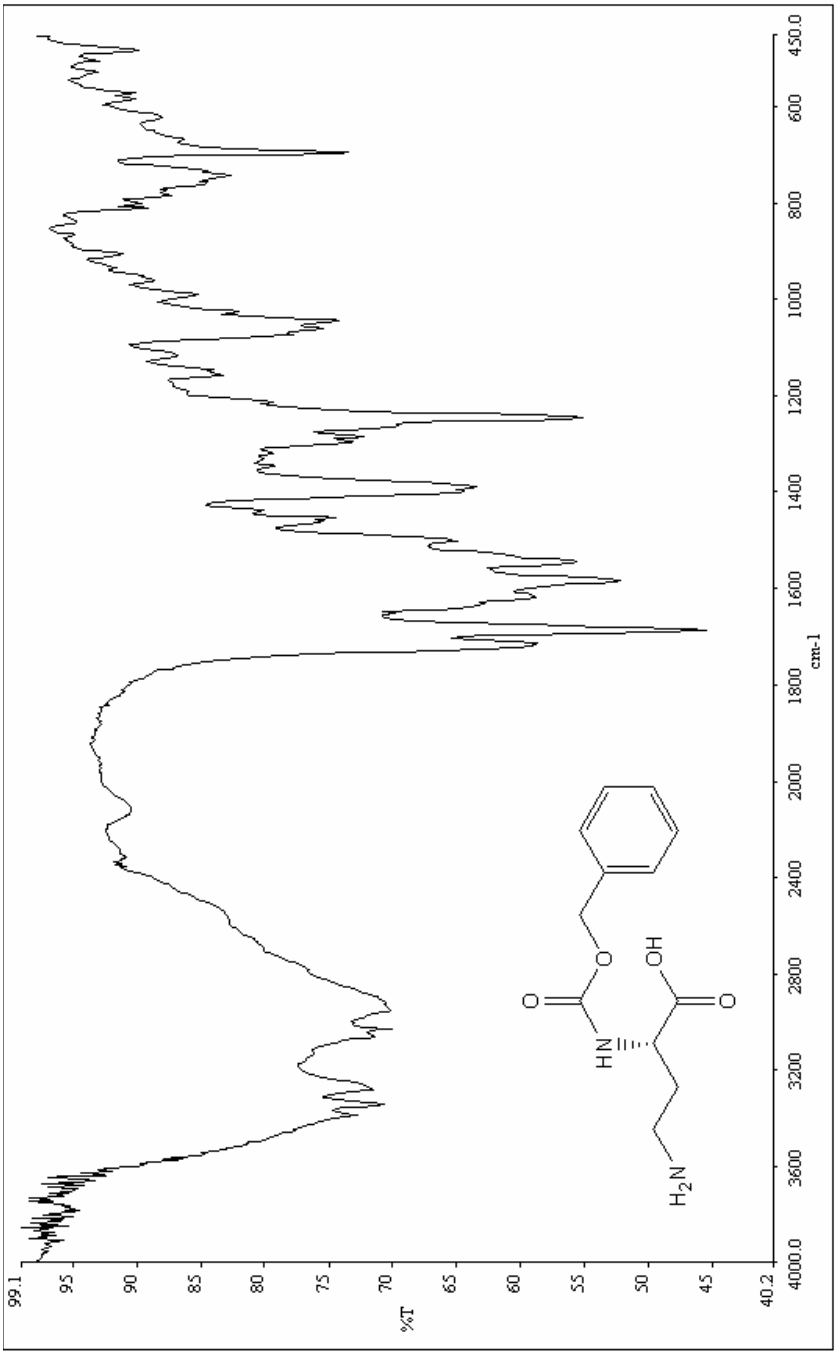


Figure B.1.4. IR spectrum of (2S)-4-amino-2-{[(benzyloxy)carbonyl]amino}butanoic acid (**4**)

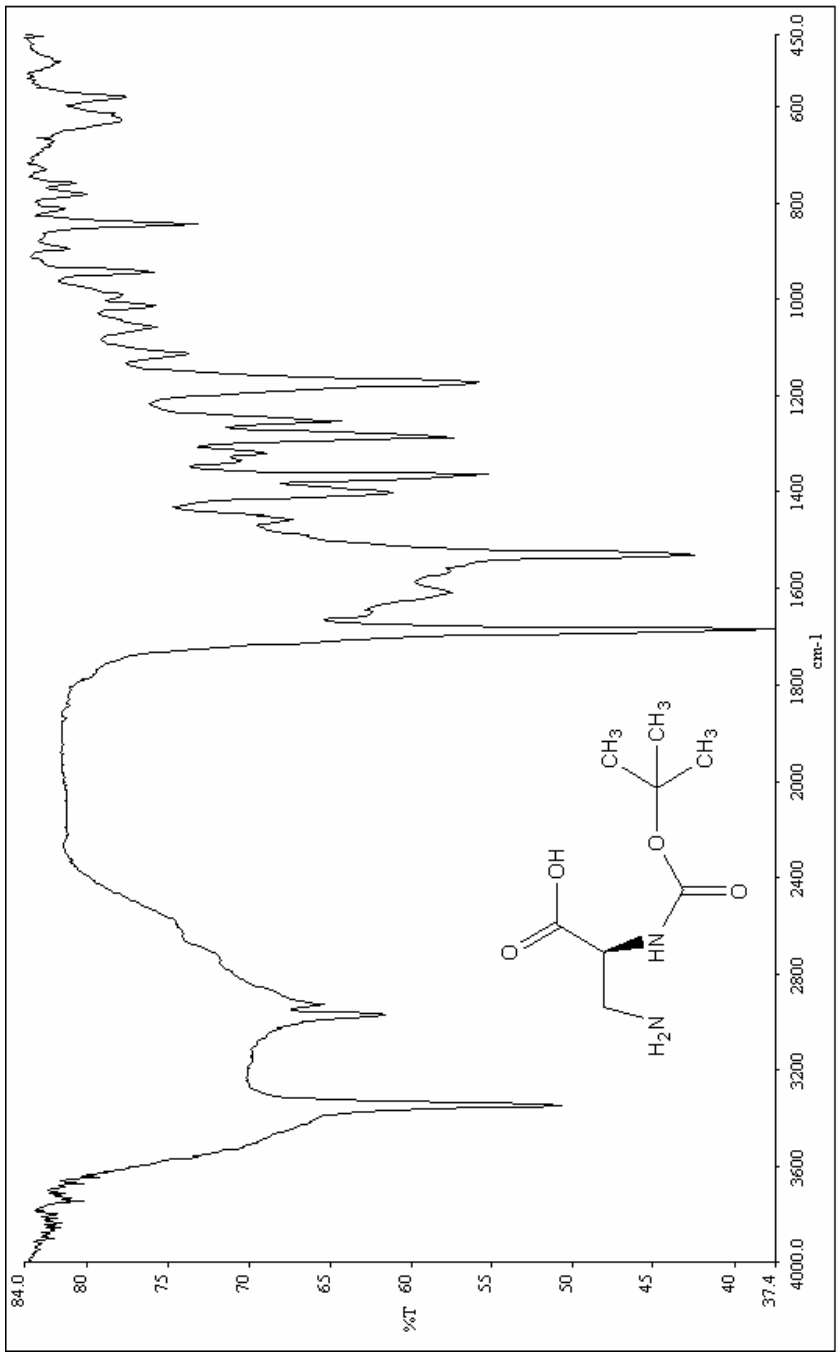


Figure B.1.5. IR spectrum of (2S)-3-amino-2-[(*tert*-butoxycarbonyl)amino]propanoic acid (**5**)

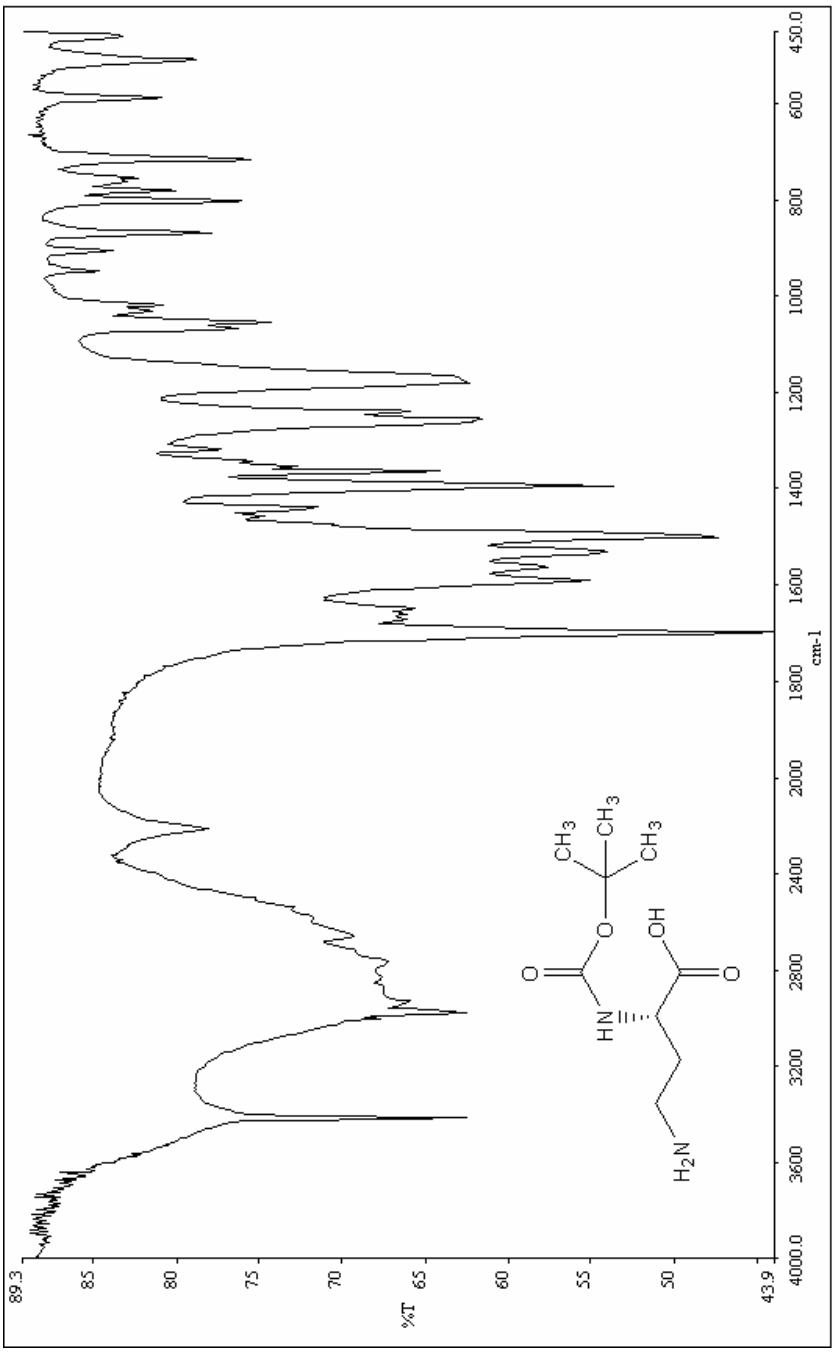


Figure B.1.6. IR spectrum of (2S)-4-amino-2-[(*tert*-butoxycarbonyl)amino]butanoic acid (**6**)

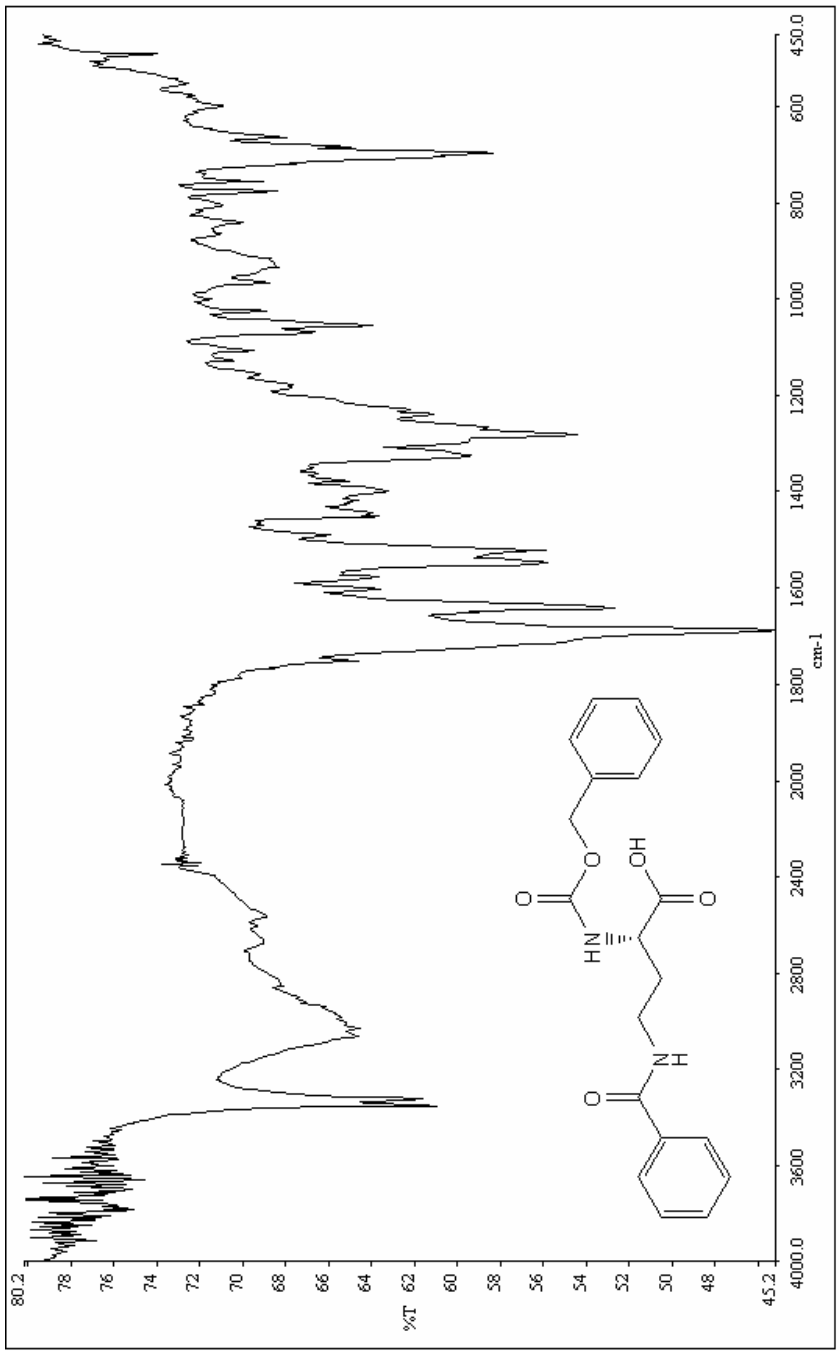


Figure B.1.7. IR spectrum of (2S)-4-(benzoylamino)-2-{[(benzyloxy)carbonyl]amino}butanoic acid (**7**)

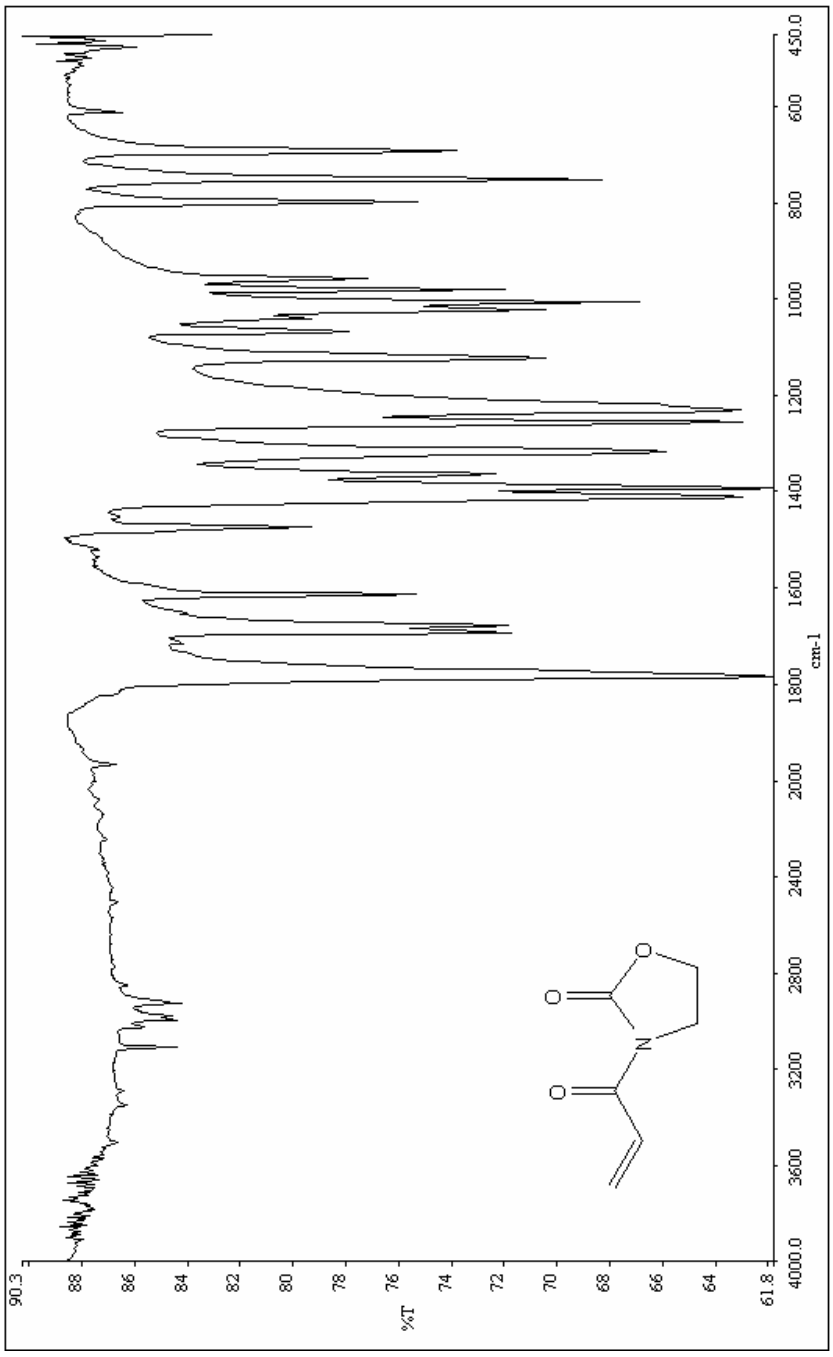


Figure B.1.8. IR spectrum of 3-acryloyl-1,3-oxazolidin-2-one (**8**)

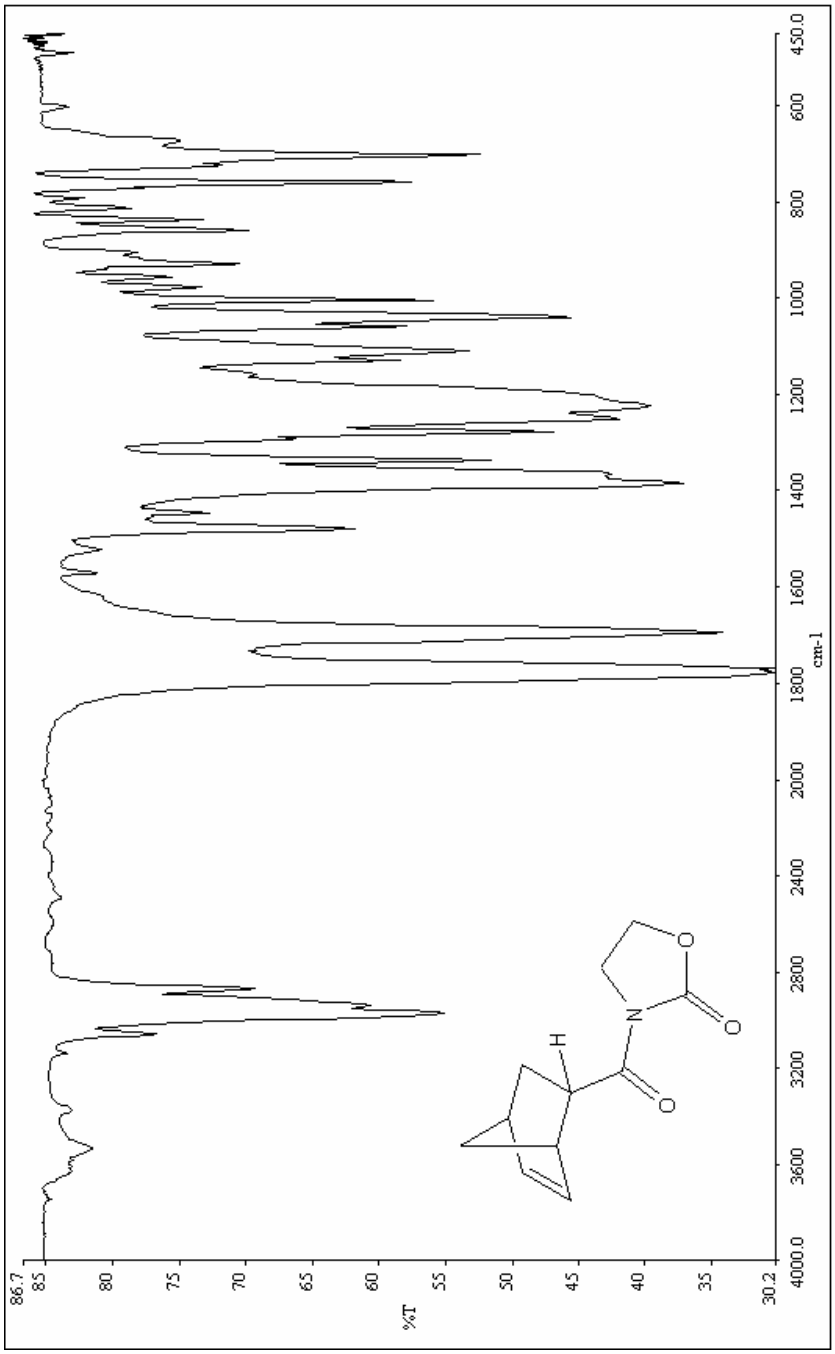


Figure B.1.9. IR spectrum of 3-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-1,3-oxazolidin-2-one (**9**)

B.2. ^{1}H NMR spectra

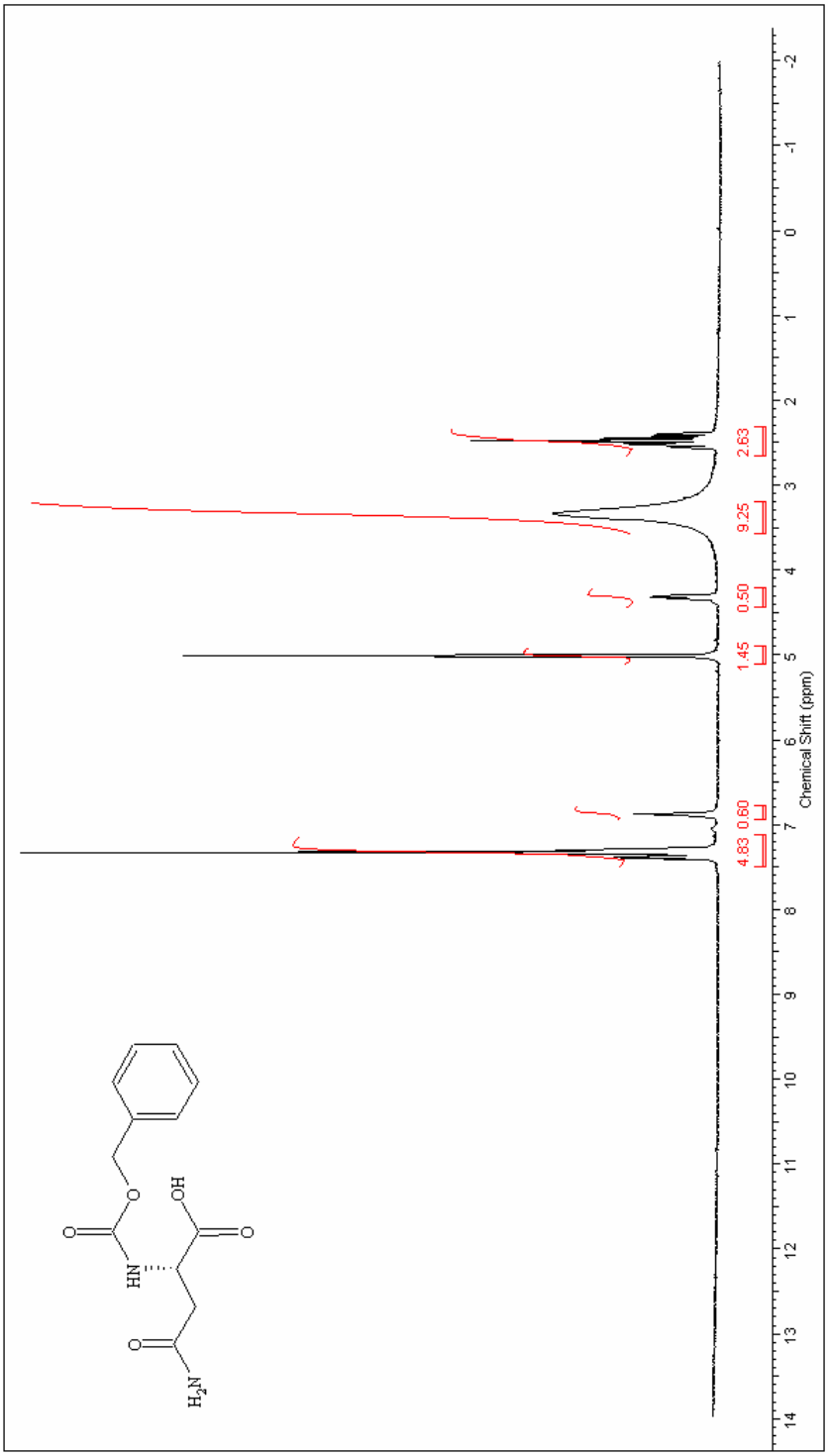


Figure B.2.1. ^{1}H NMR spectrum of Carbobenzyloxy-L-asparagine (**1**)

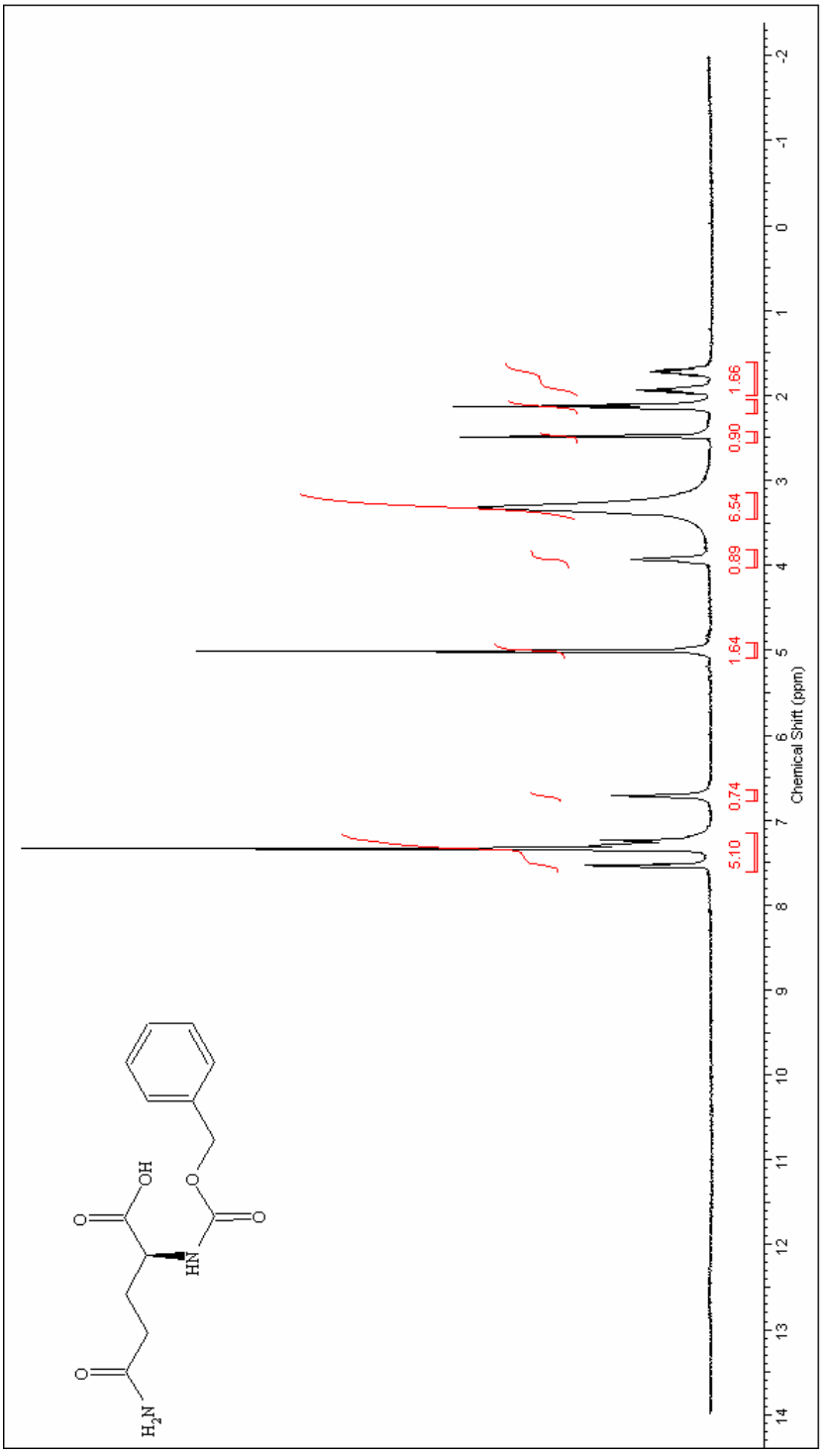


Figure B.2.2. ^{1}H NMR spectrum of Carbobenzyloxy-L-glutamine (**2**)

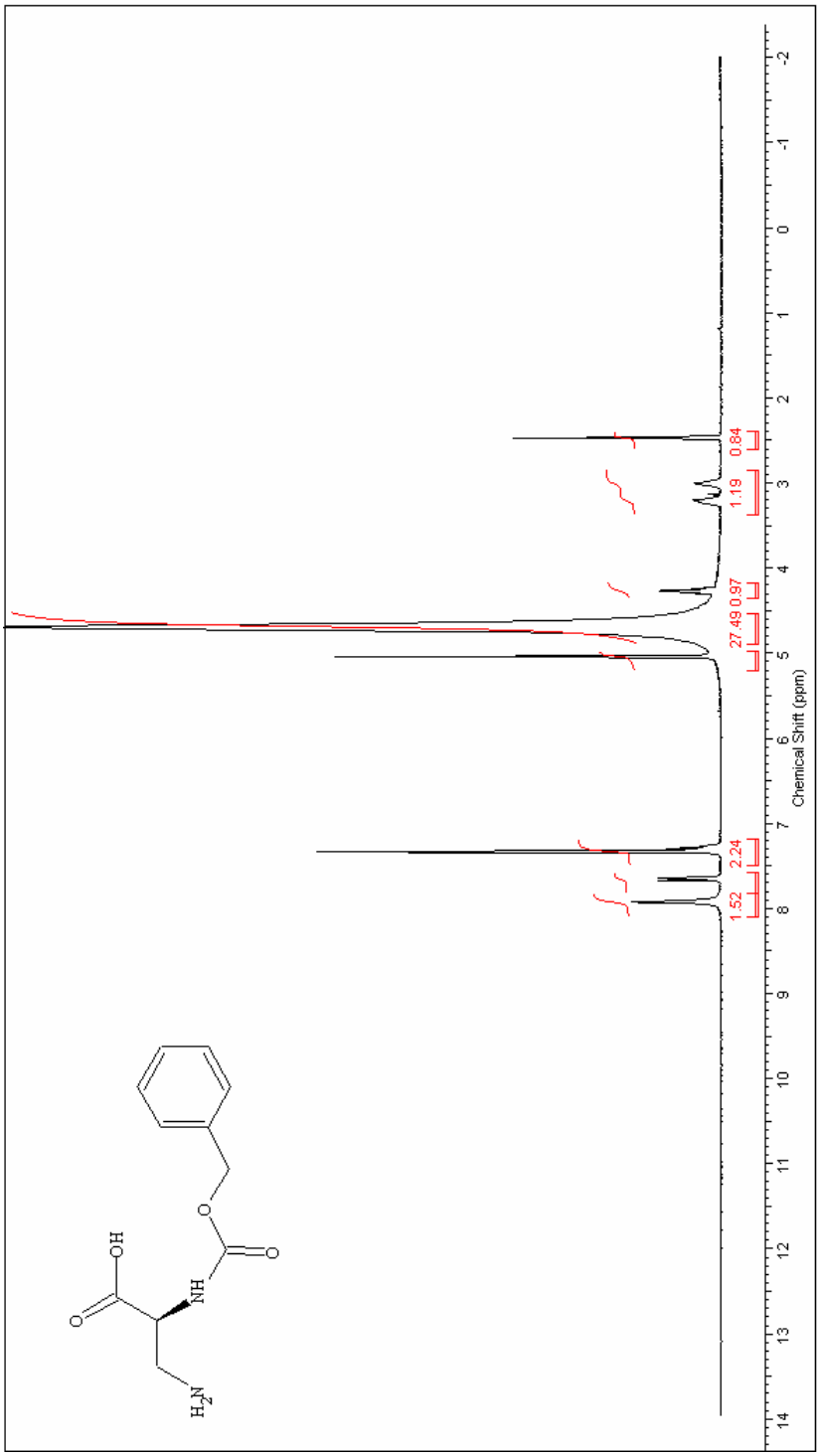


Figure B.2.3. ^{1}H NMR spectrum of (2S)-3-amino-2-{[(benzyloxy)carbonyl]amino}propanoic acid (**3**)

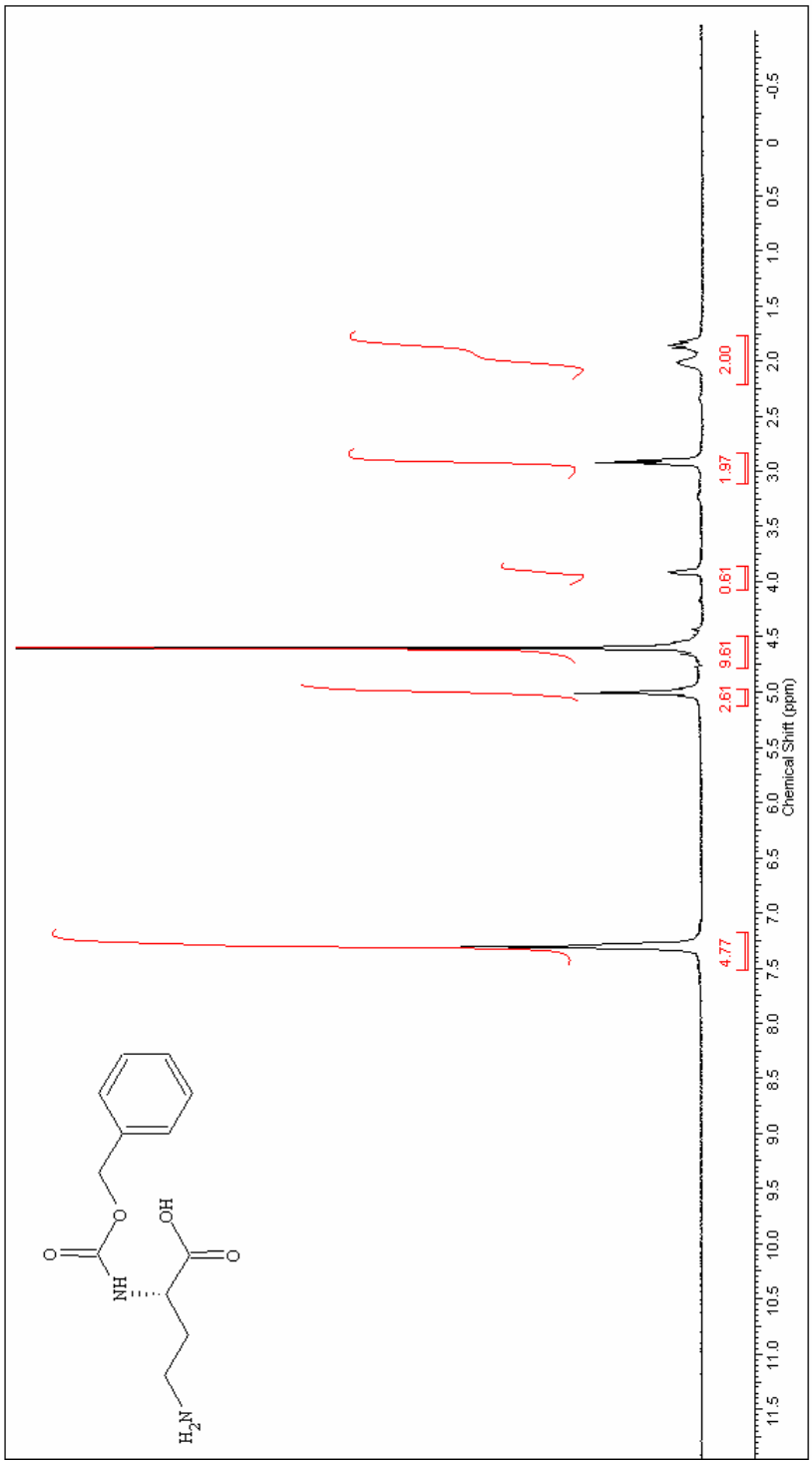


Figure B.2.4. ^{1}H NMR spectrum of (2S)-4-amino-2-{[(benzyloxy)carbonyl]amino}butanoic acid (**4**)

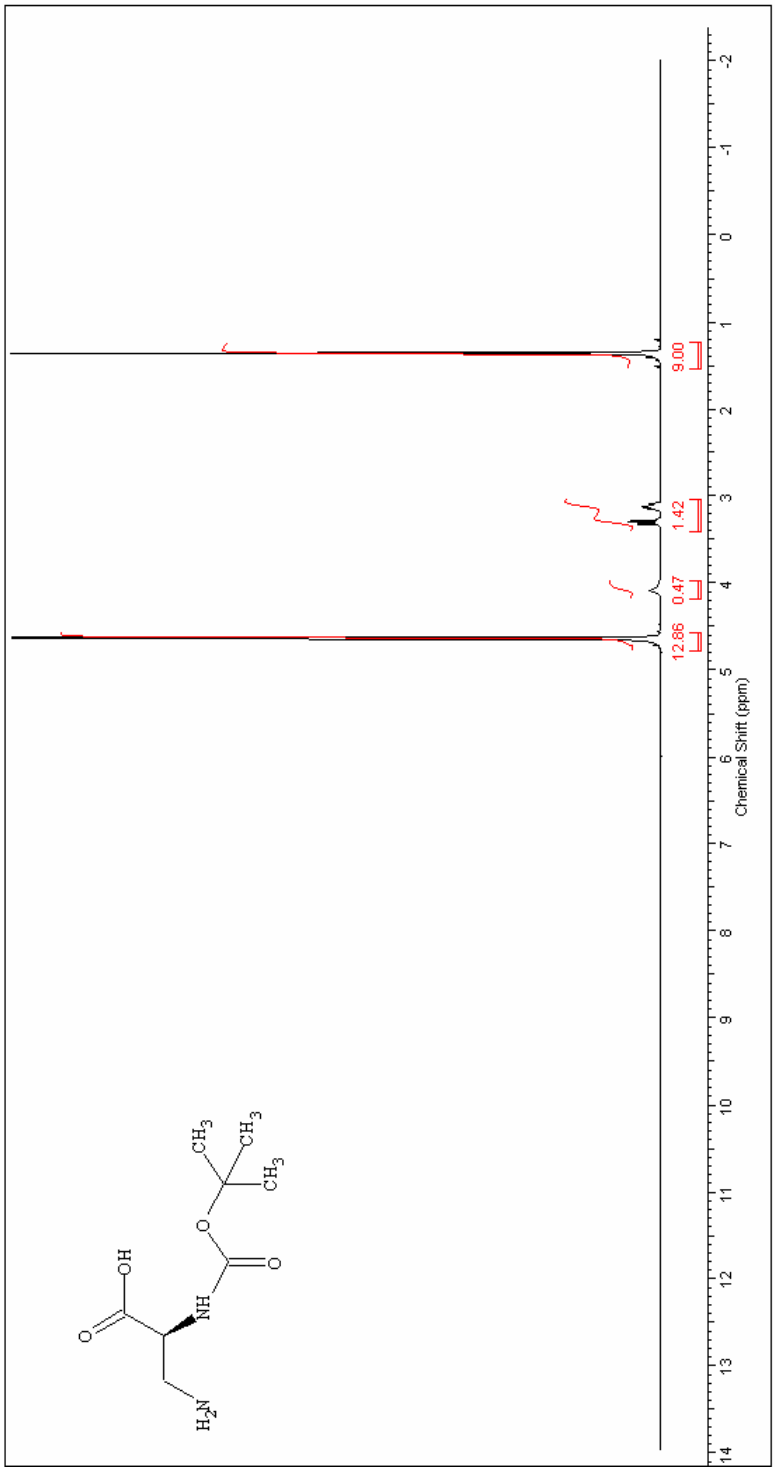


Figure B.2.5. ^{1}H NMR spectrum of (2S)-3-amino-2-[(*tert*-butoxycarbonyl)amino]propanoic acid (**5**)

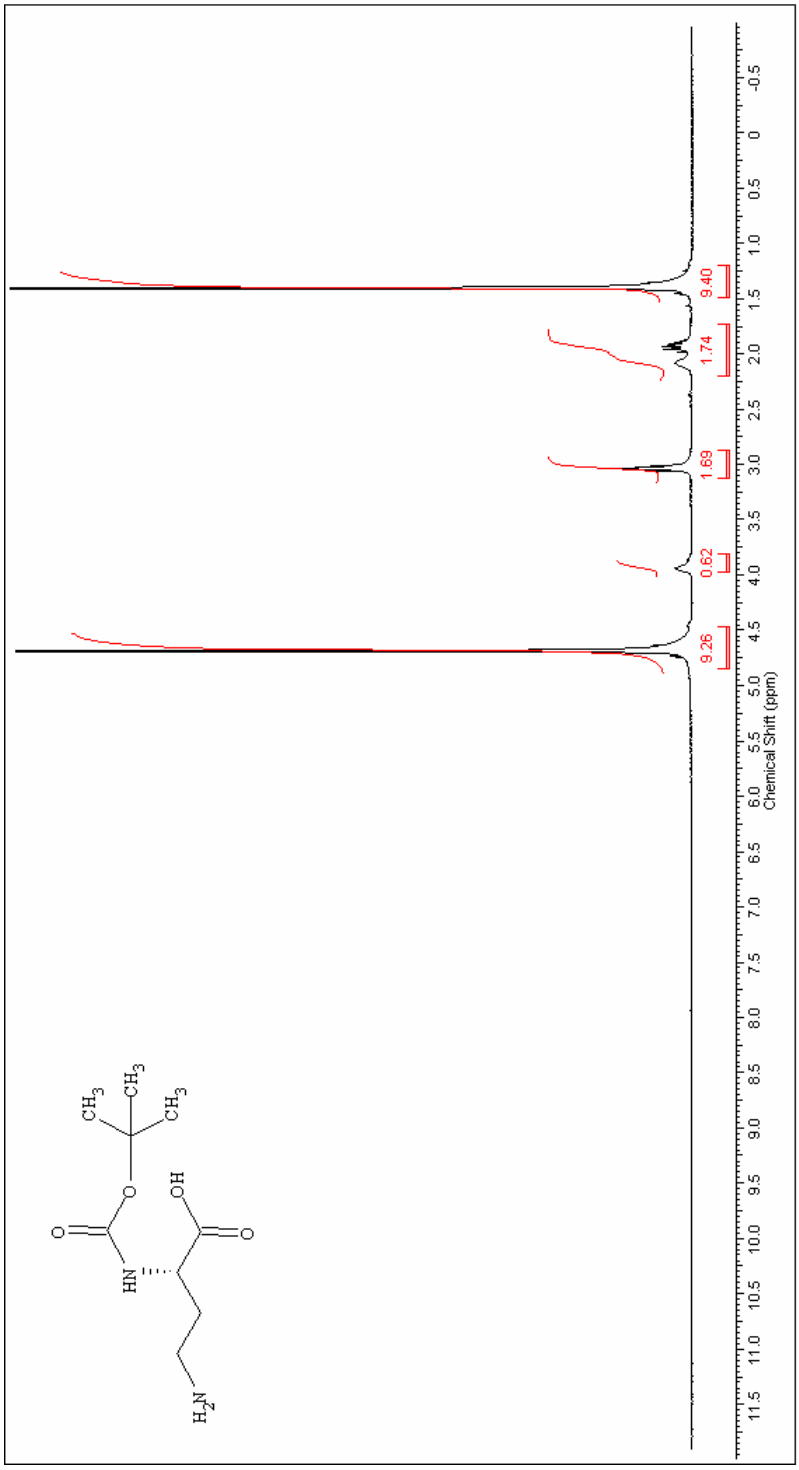


Figure B.2.6. ^{1}H NMR spectrum of (2S)-4-amino-2-[(*tert*-butoxycarbonyl)amino]butanoic acid (**6**)

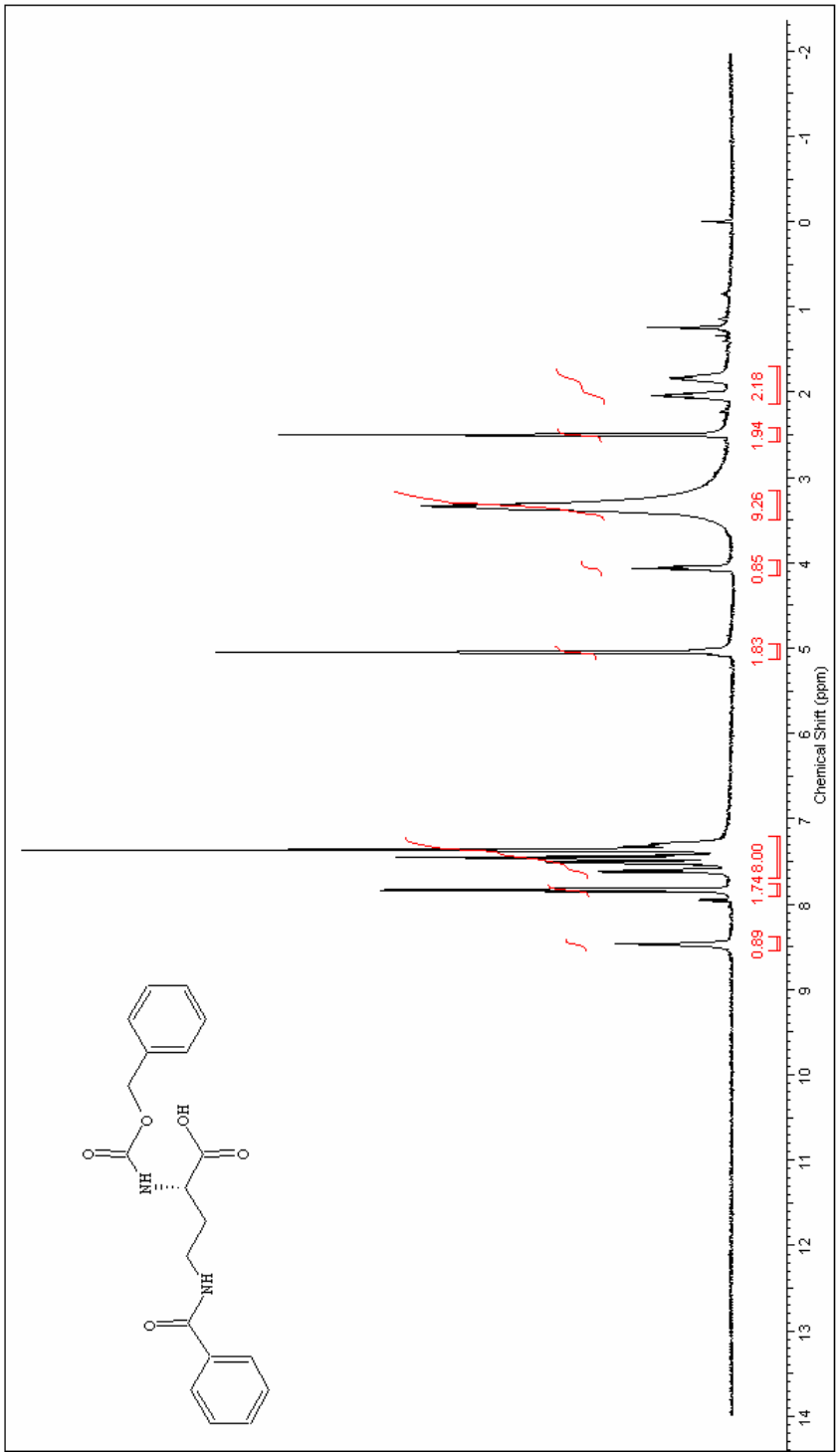


Figure B.2.7. ^{1}H NMR spectrum of (2S)-4-(benzoylamino)-2-{[(benzyloxy)carbonyl]amino}butanoic acid (**7**)

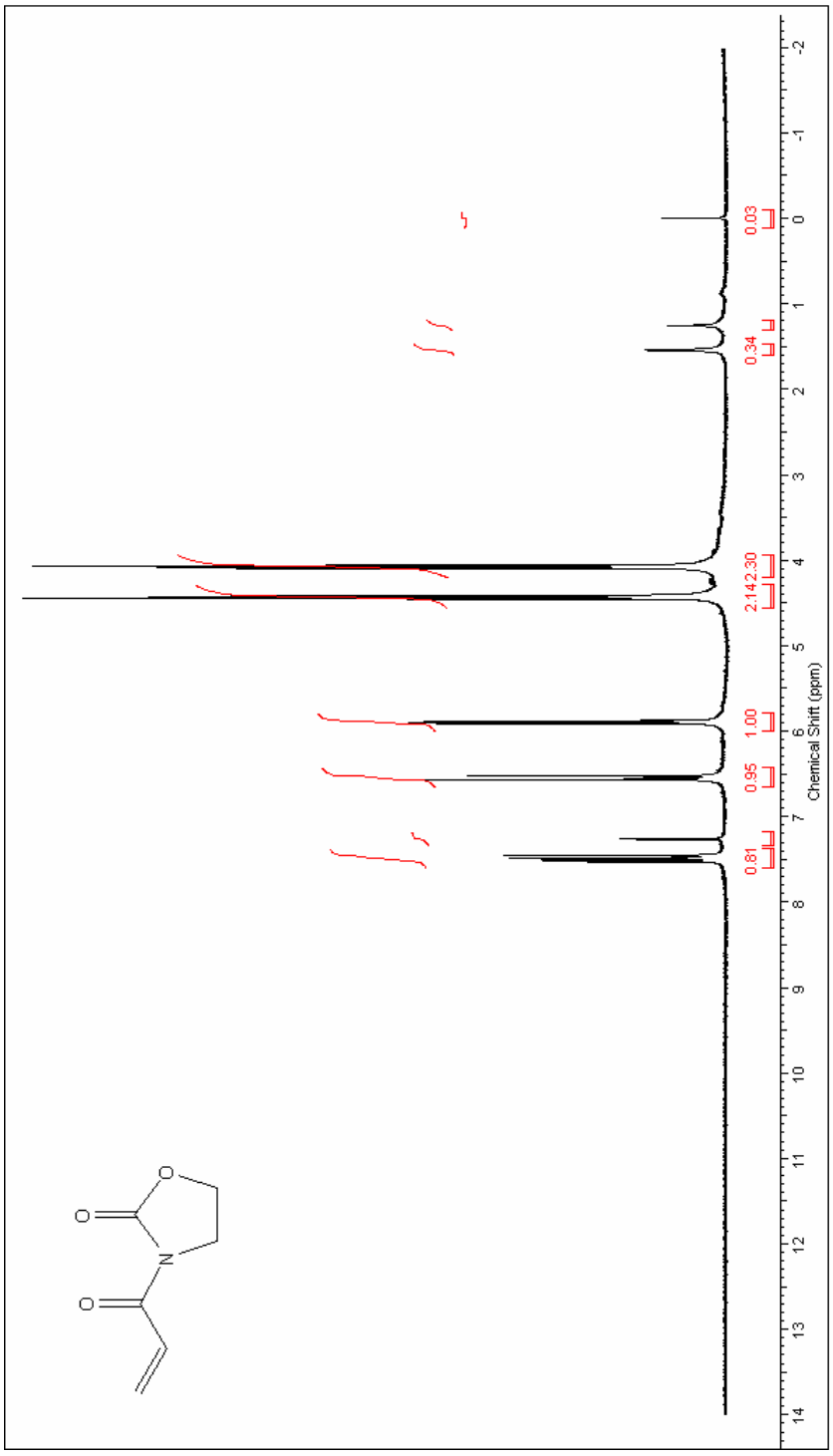


Figure B.2.8. ^{1}H NMR spectrum of 3-acryloyl-1,3-oxazolidin-2-one (**8**)

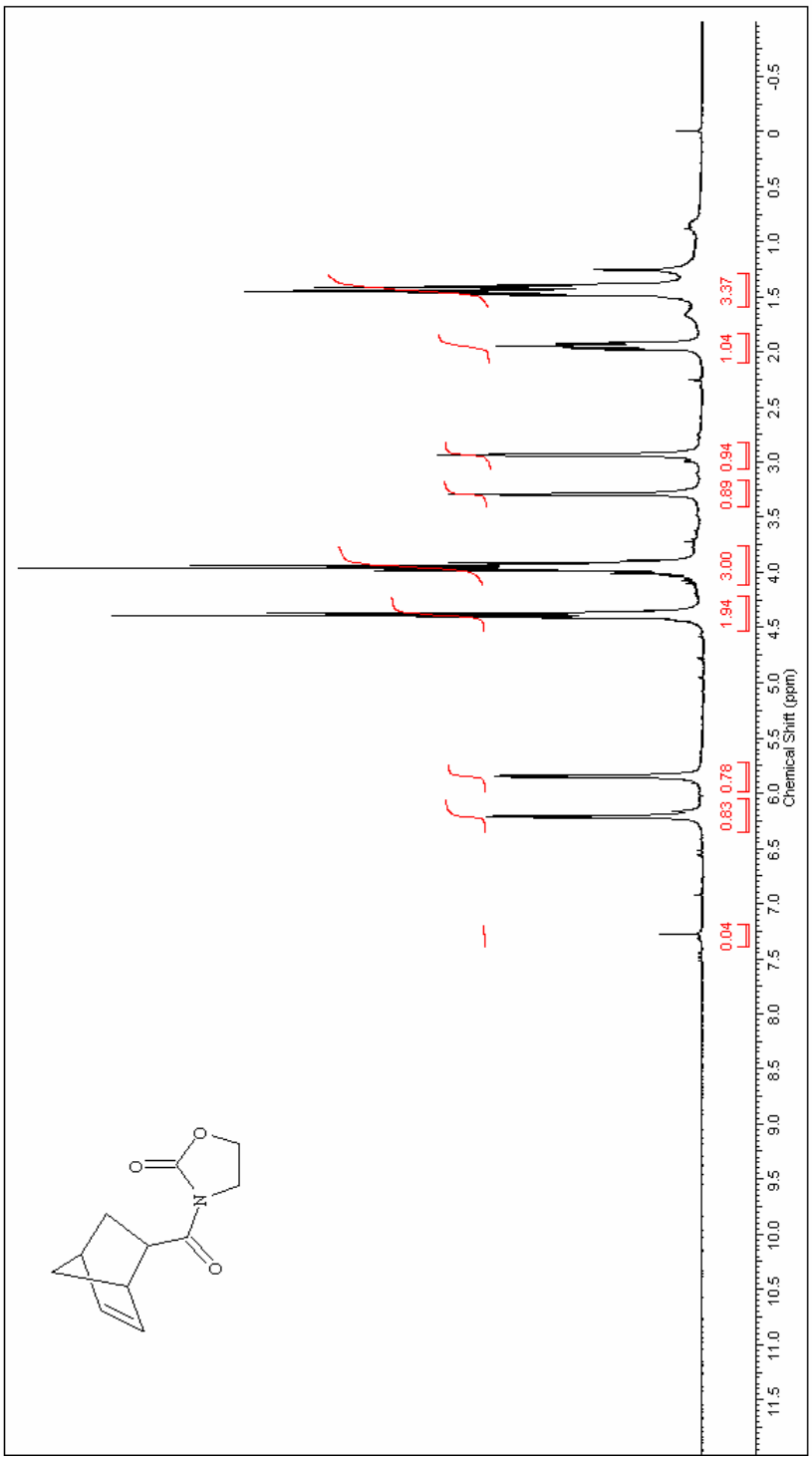


Figure B.2.9. ^{1}H NMR spectrum of 3-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-1,3-oxazolidin-2-one (**9**)

B.3. ^{13}C NMR spectra

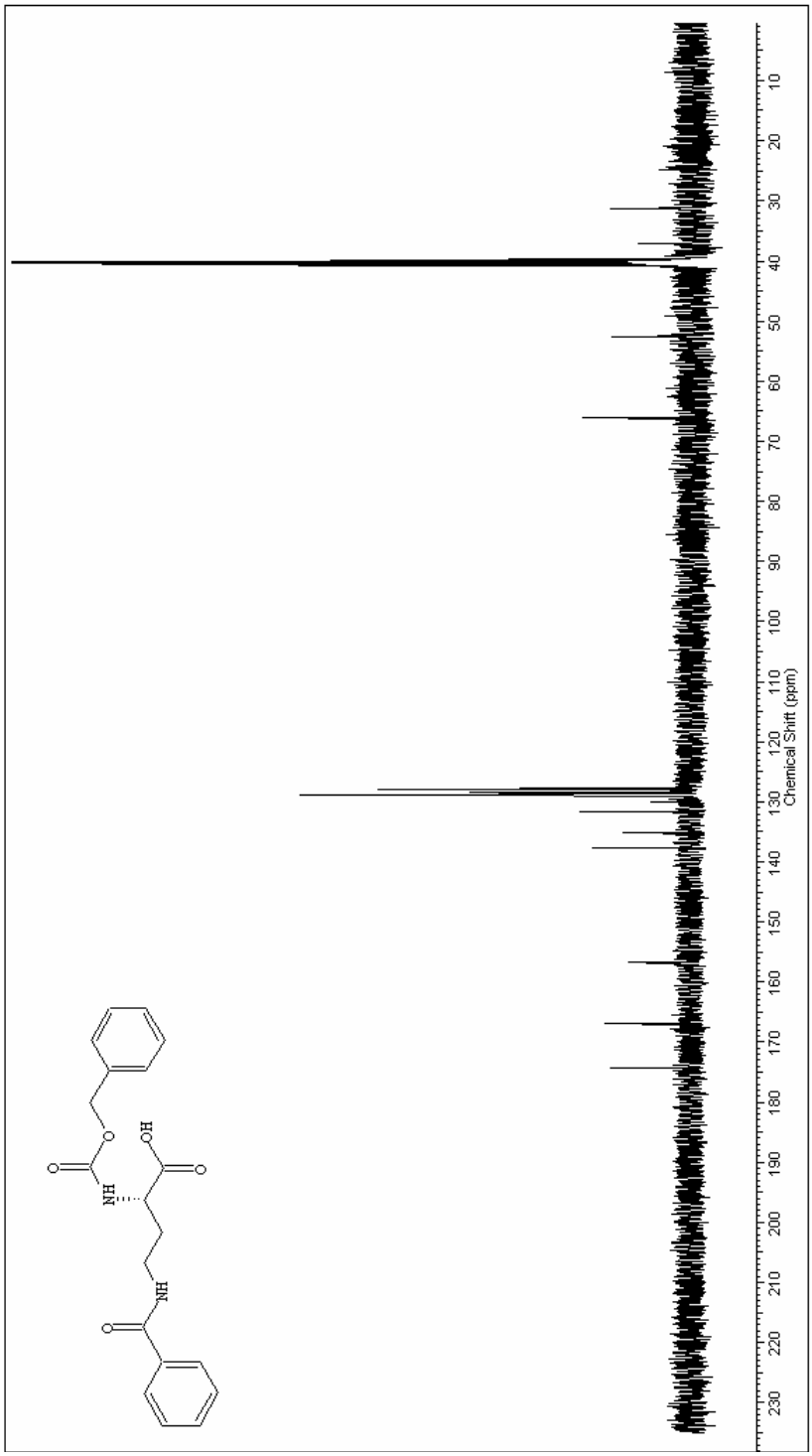


Figure B.3.1. ^{13}C NMR spectrum of (2S)-4-(benzoylamino)-2-{[(benzyloxy)carbonyl]amino}butanoic acid (**7**)

B.4. Chromatograms

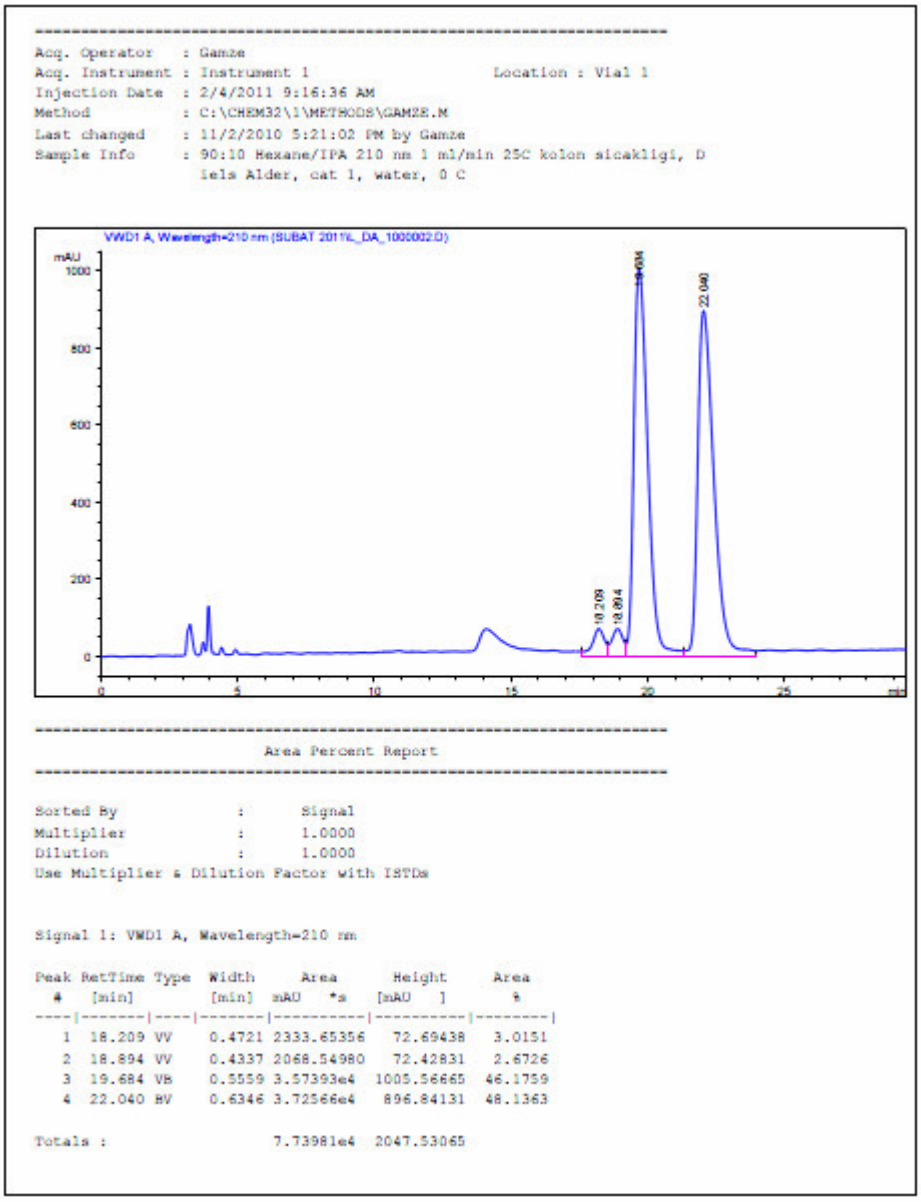


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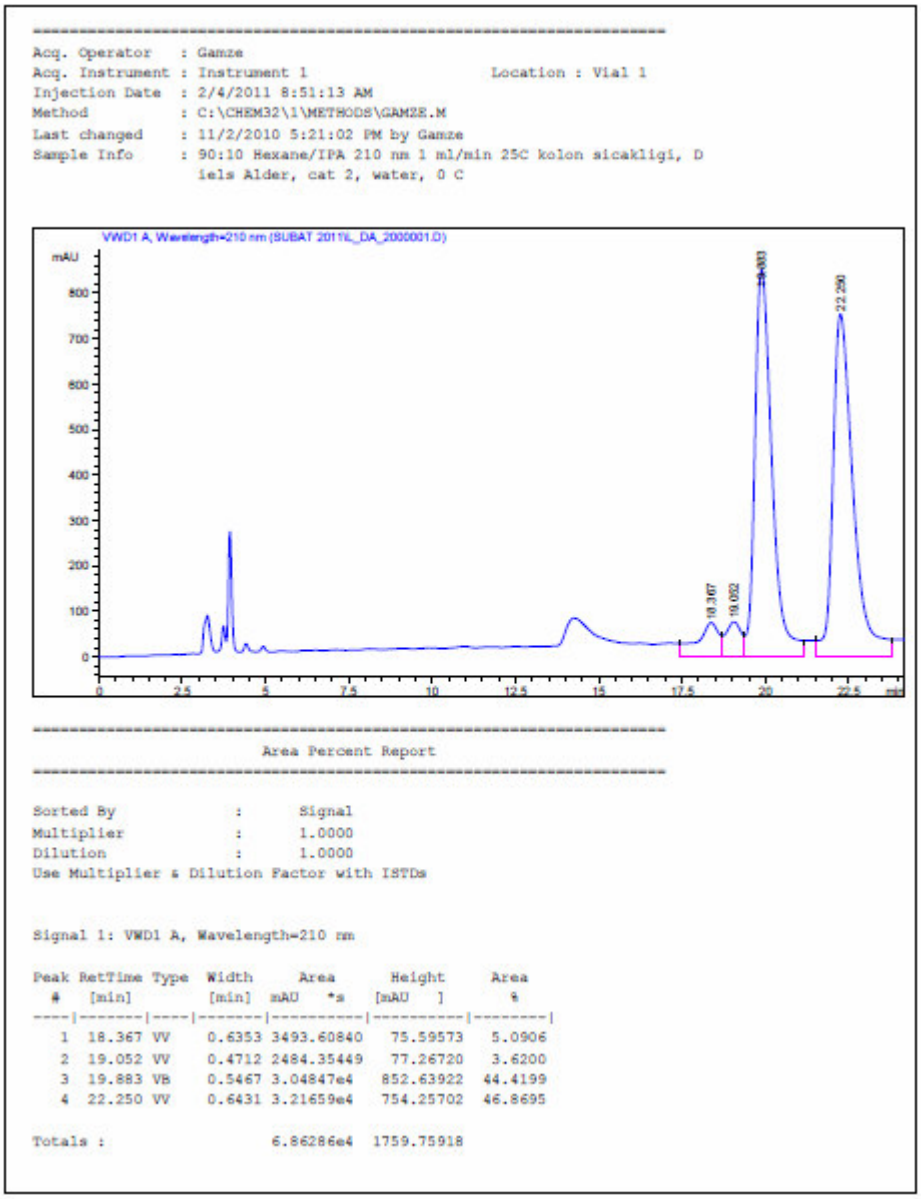
Figure B.4.1. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **1**



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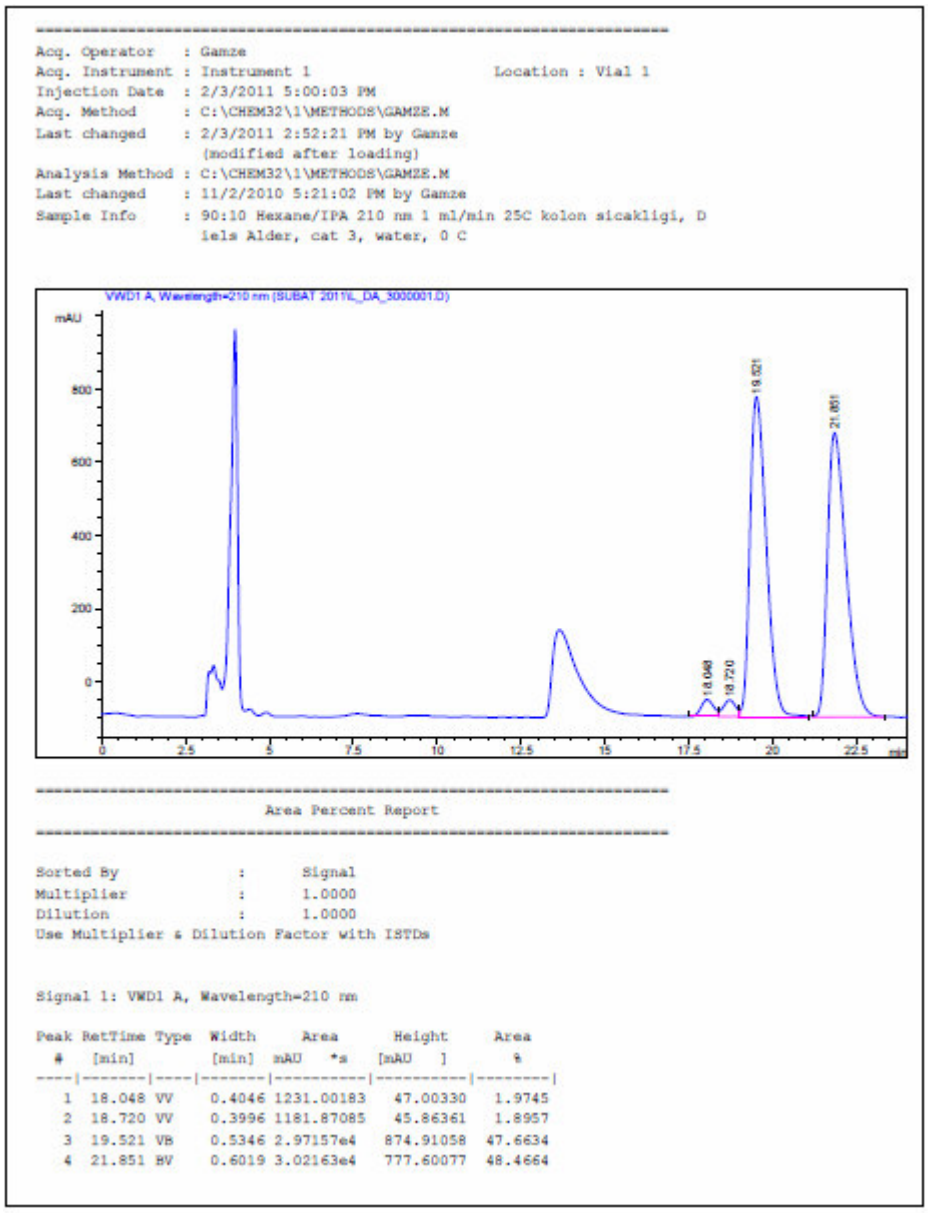
2	19.052	VV	0.4712	2484.35449	77.26720	3.6200
3	19.883	VB	0.5467	3.04847e4	852.63922	44.4199
4	22.250	VV	0.6431	3.21659e4	754.25702	46.8695
Totals :				6.86286e4	1759.75918	

Figure B.4.2. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **2**



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Use Multiplier & Dilution Factor with ISTDs


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   4  21.851 BV    0.6019 3.02163e4   777.60077  48.4664
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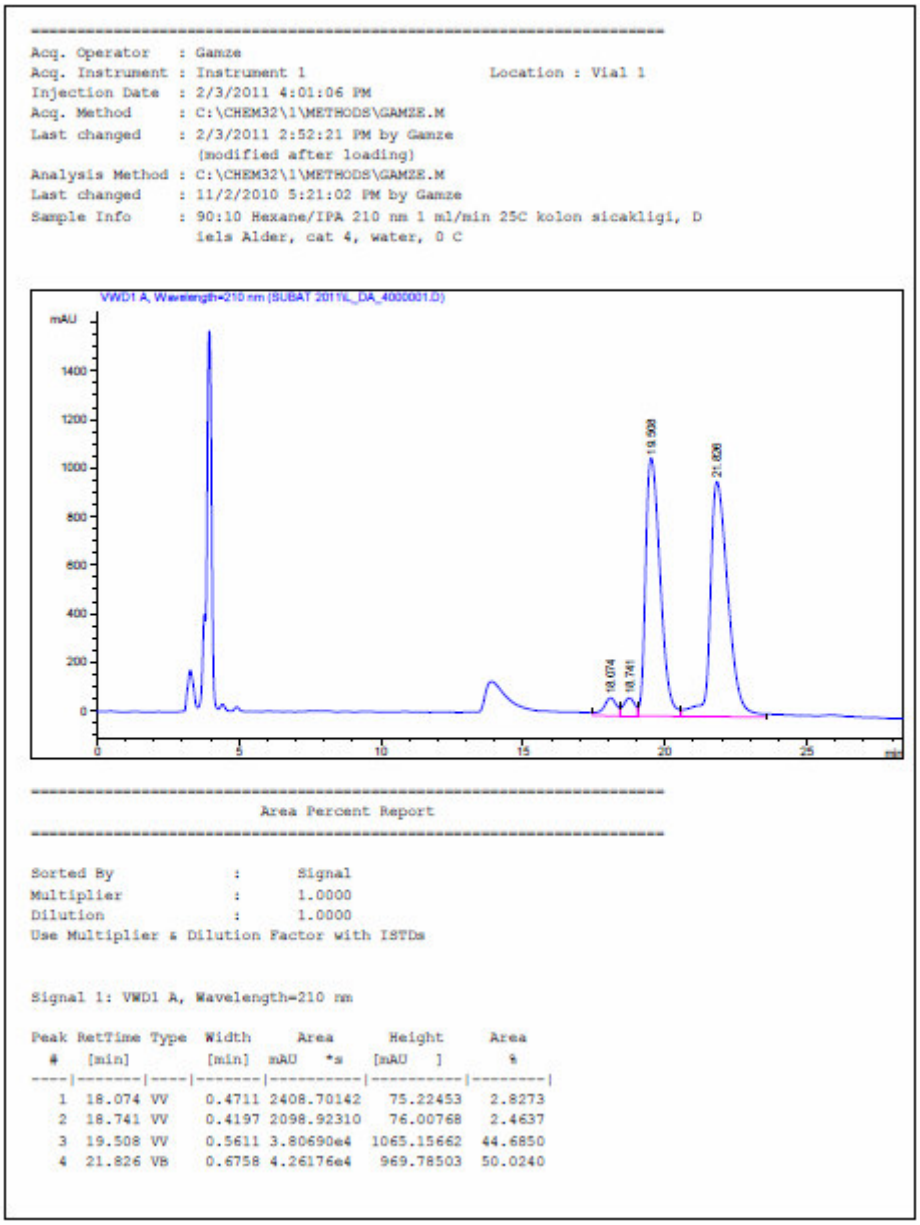
Figure B.4.3. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **3**



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Use Multiplier & Dilution Factor with ISTDs


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   2  18.741 VV    0.4197 2098.92310   76.00768   2.4637
   3  19.508 VV    0.5611 3.80690e4  1065.15662  44.6850
   4  21.826 VB    0.6758 4.26176e4   969.78503  50.0240
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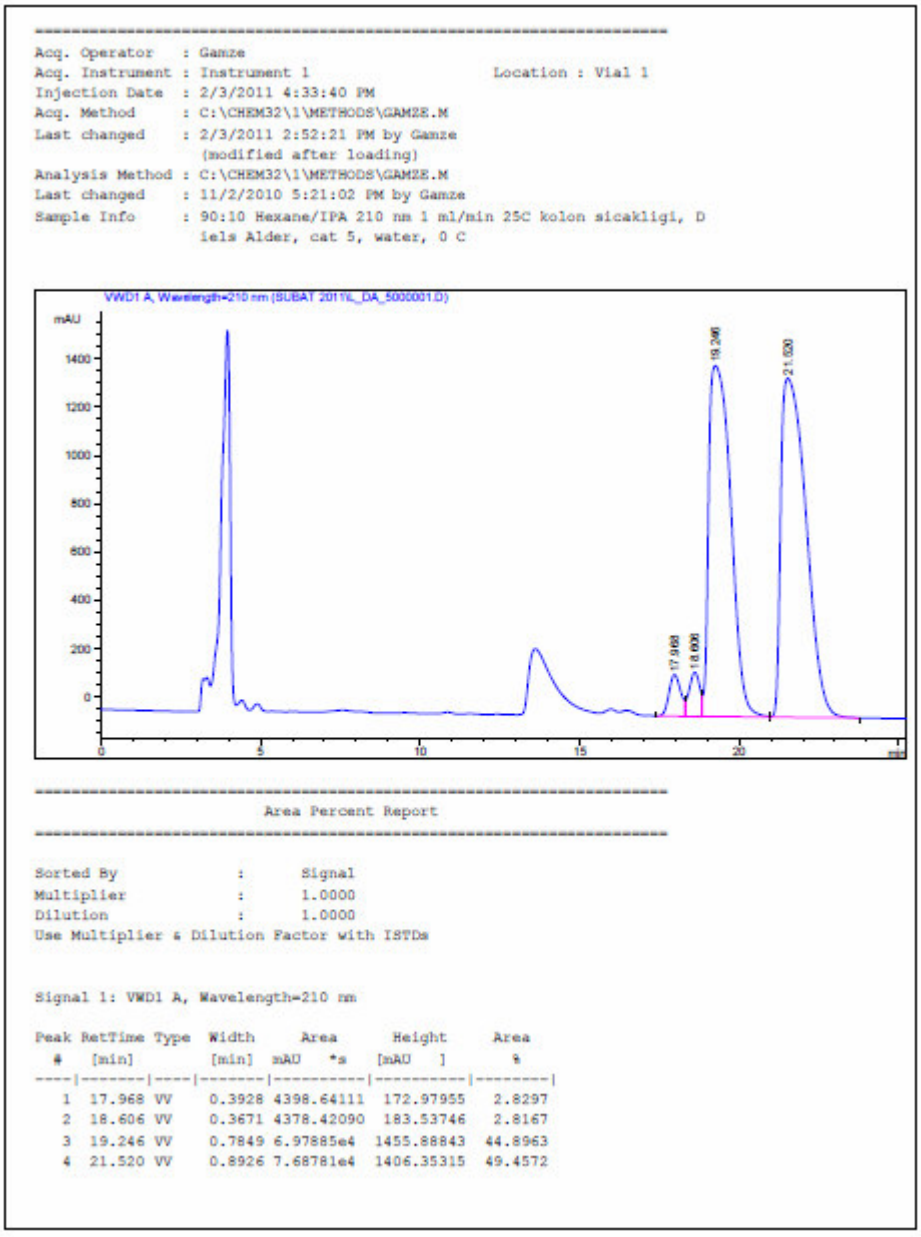
Figure B.4.4. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **4**



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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

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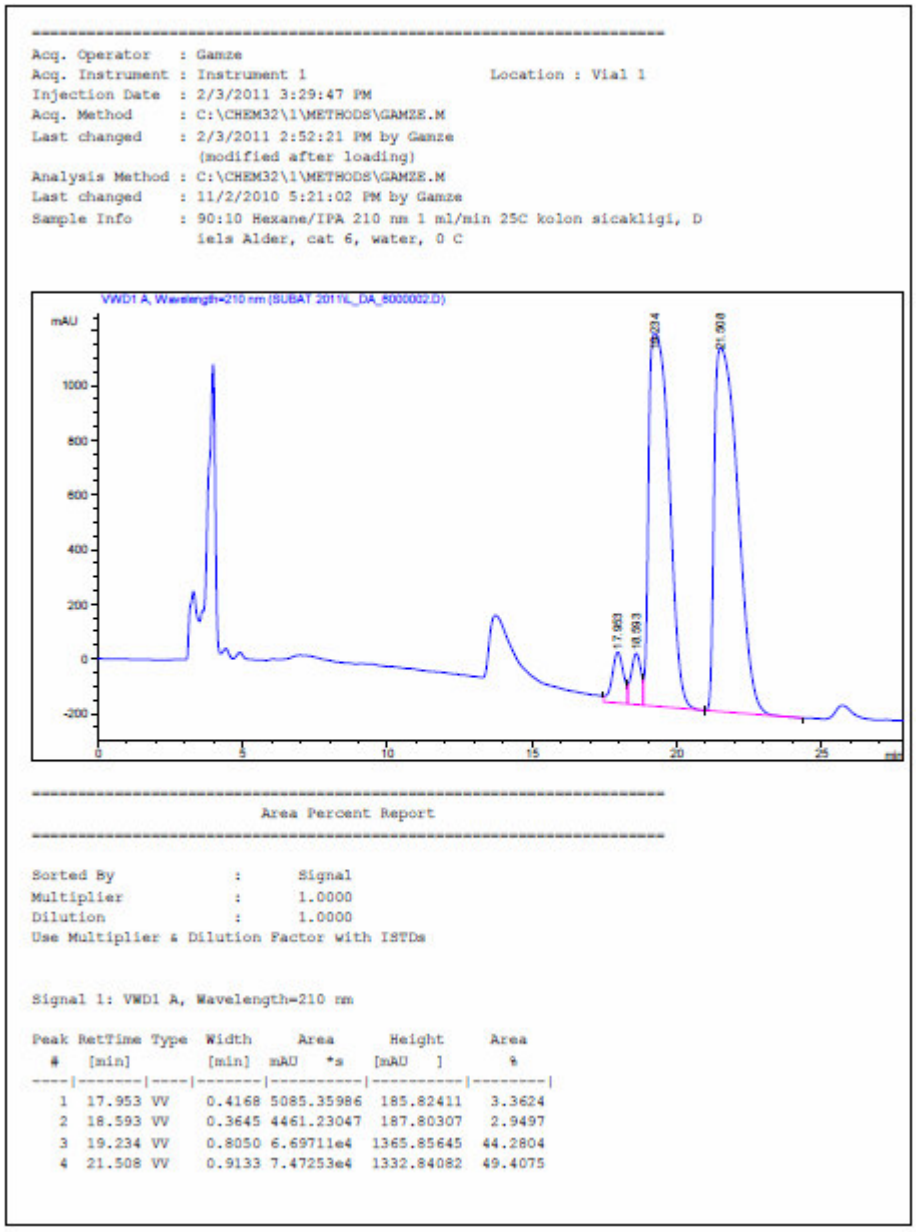
   2  18.606 VV    0.3671 4378.42090  183.53746   2.8167
   3  19.246 VV    0.7849 6.97885e4  1455.88843  44.8963
   4  21.520 VV    0.8926 7.68781e4  1406.35315  49.4572
```

Figure B.4.5. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **5**



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Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/3/2011 3:29:47 PM
Acq. Method     : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/3/2011 2:52:21 PM by Gamze
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 6, water, 0 C
```



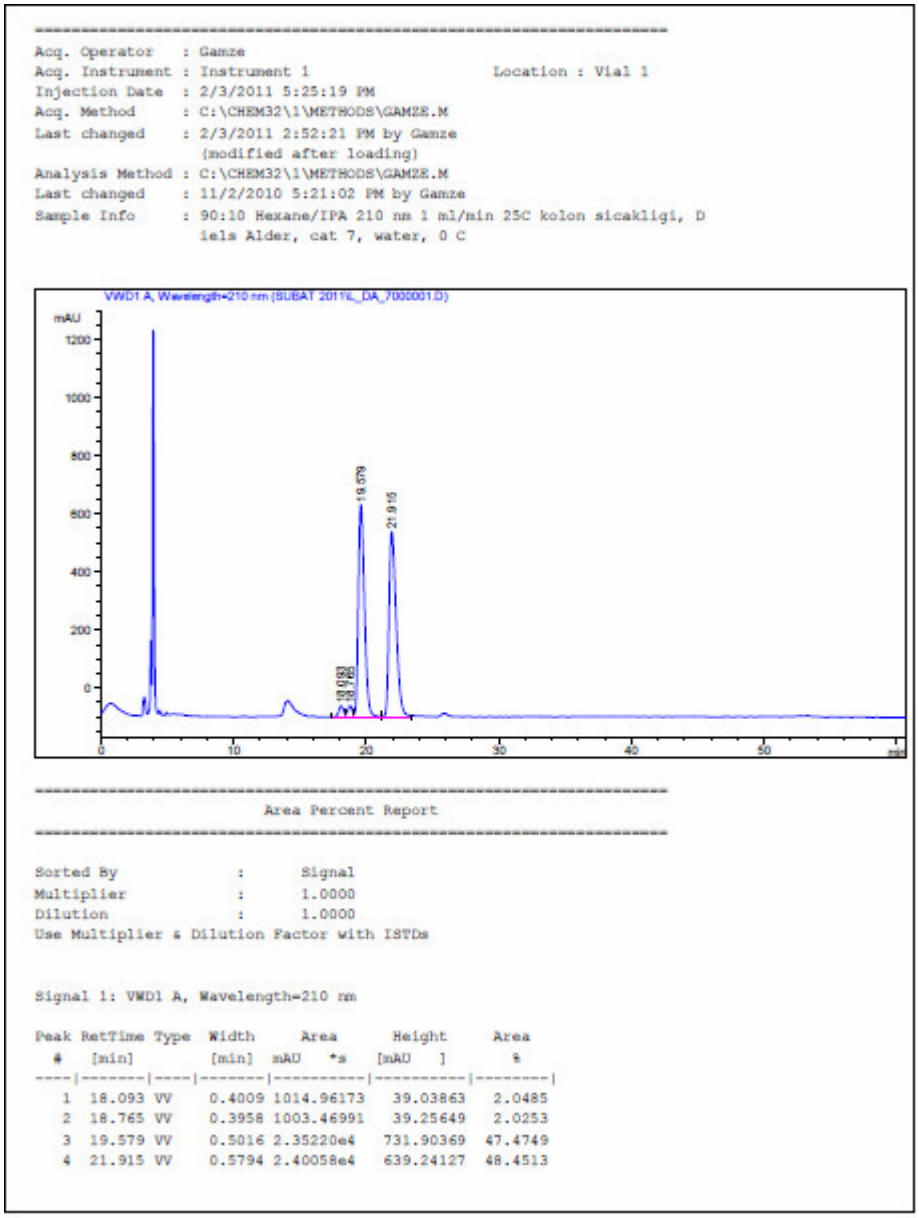
```
                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.953 VV    0.4168 5085.35986  185.82411   3.3624
   2  18.593 VV    0.3645 4461.23047  187.80307   2.9497
   3  19.234 VV    0.8050 6.69711e4  1365.85645  44.2804
   4  21.508 VV    0.9133 7.47253e4  1332.84082  49.4075
```

Figure B.4.6. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **6**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/3/2011 5:25:19 PM
Acq. Method     : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/3/2011 2:52:21 PM by Gamze
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 7, water, 0 C
```



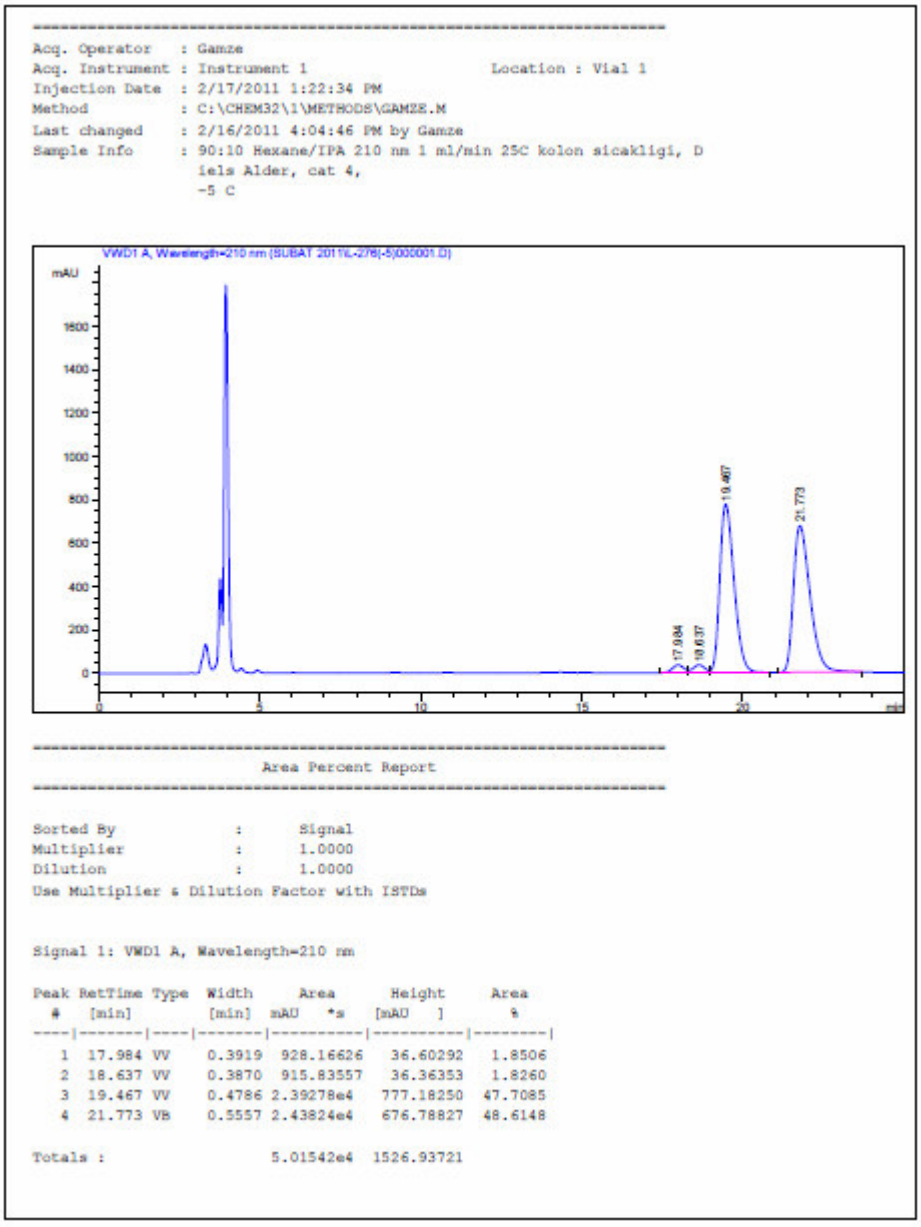
```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  18.093 VV     0.4009 1014.96173   39.03863   2.0485
   2  18.765 VV     0.3958 1003.46991   39.25649   2.0253
   3  19.579 VV     0.5016 2.35220e4   731.90369  47.4749
   4  21.915 VV     0.5794 2.40058e4   639.24127  48.4513
```

Figure B.4.7. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at 0 ˚C with catalyst **7**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/17/2011 1:22:34 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/16/2011 4:04:46 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4,
                  -5 C
```


Area Percent Report

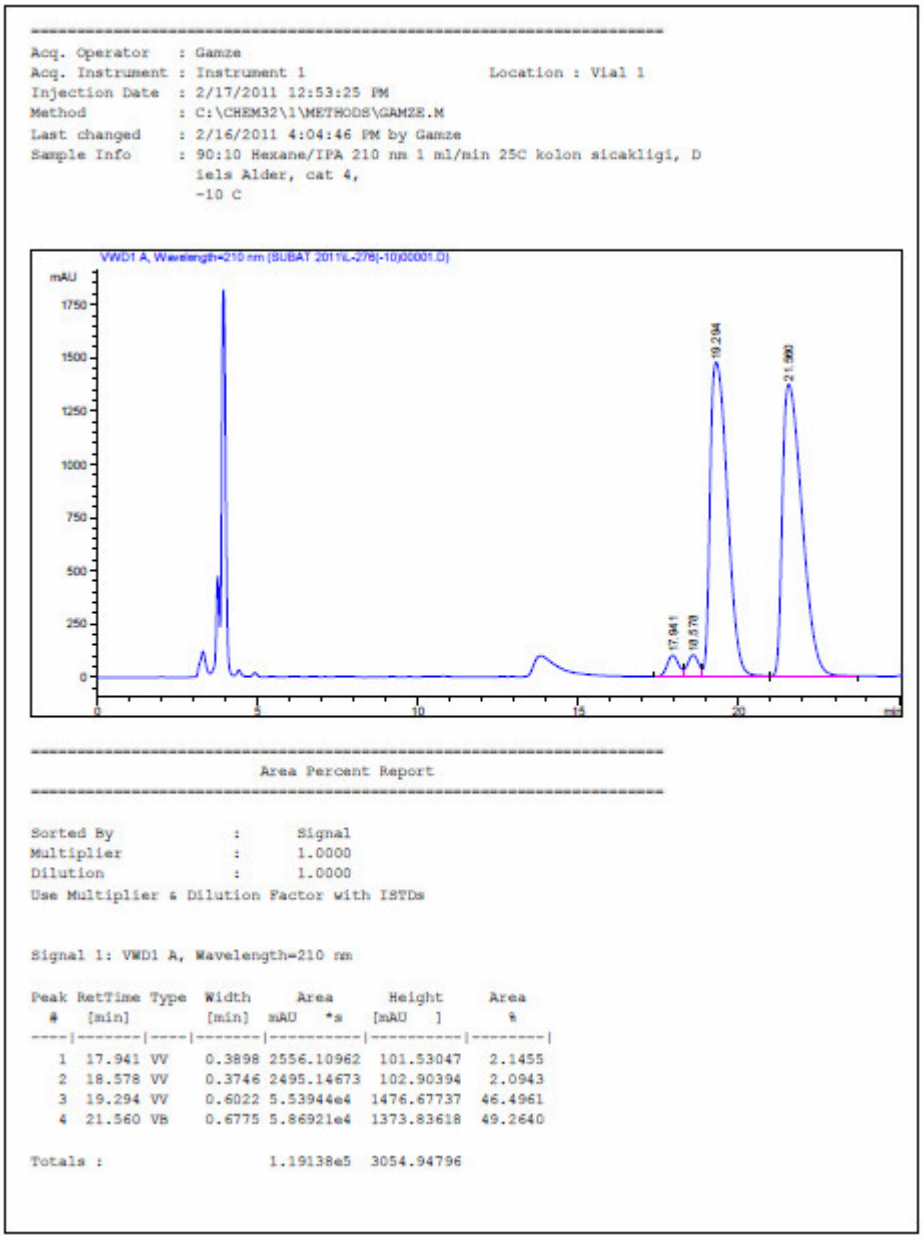
```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.984 VV    0.3919  928.16626   36.60292   1.8506
   2  18.637 VV    0.3870  915.83557   36.36353   1.8260
   3  19.467 VV    0.4786 2.39278e4   777.18250  47.7085
   4  21.773 VB    0.5557 2.43824e4   676.78827  48.6148

Totals :                  5.01542e4  1526.93721
```

Figure B.4.8. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at -5 ˚C with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/17/2011 12:53:25 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/16/2011 4:04:46 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4,
                  -10 C
```



```
                          Area Percent Report

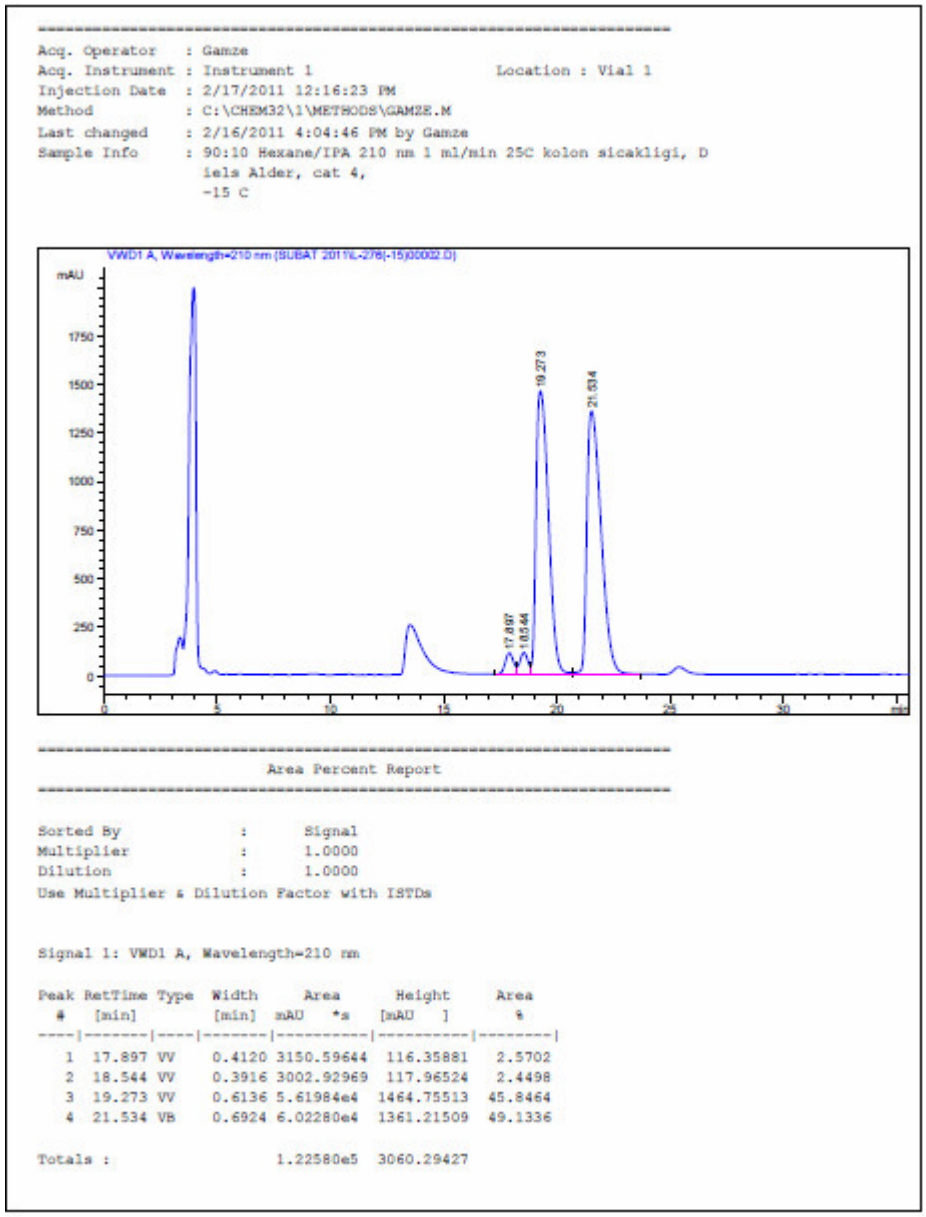
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.941 VV     0.3898 2556.10962  101.53047   2.1455
   2  18.578 VV     0.3746 2495.14673  102.90394   2.0943
   3  19.294 VV     0.6022 5.53944e4  1476.67737  46.4961
   4  21.560 VB     0.6775 5.86921e4  1373.83618  49.2640

Totals :                  1.19138e5  3054.94796
```

Figure B.4.9. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at -10 ˚C with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/17/2011 12:16:23 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/16/2011 4:04:46 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4,
                  -15 C
```


Area Percent Report

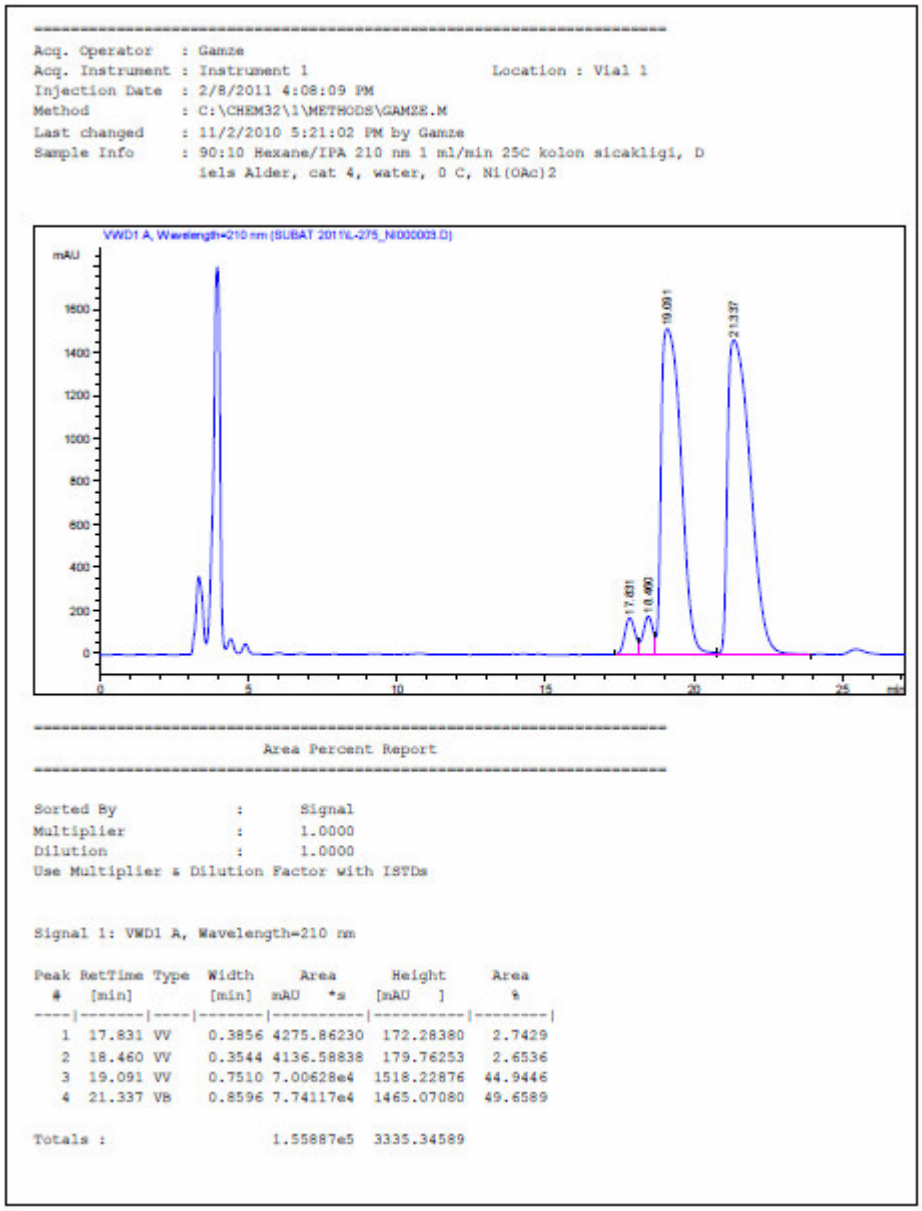
```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.897 VV    0.4120 3150.59644  116.35881   2.5702
   2  18.544 VV    0.3916 3002.92969  117.96524   2.4498
   3  19.273 VV    0.6136 5.61984e4  1464.75513  45.8464
   4  21.534 VB    0.6924 6.02280e4  1361.21509  49.1336

Totals :                 1.22580e5  3060.29427
```

Figure B.4.10. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in water at -15 ˚C with catalyst **4**



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Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/8/2011 4:08:09 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4, water, 0 C, Ni(OAc)2
```


Area Percent Report

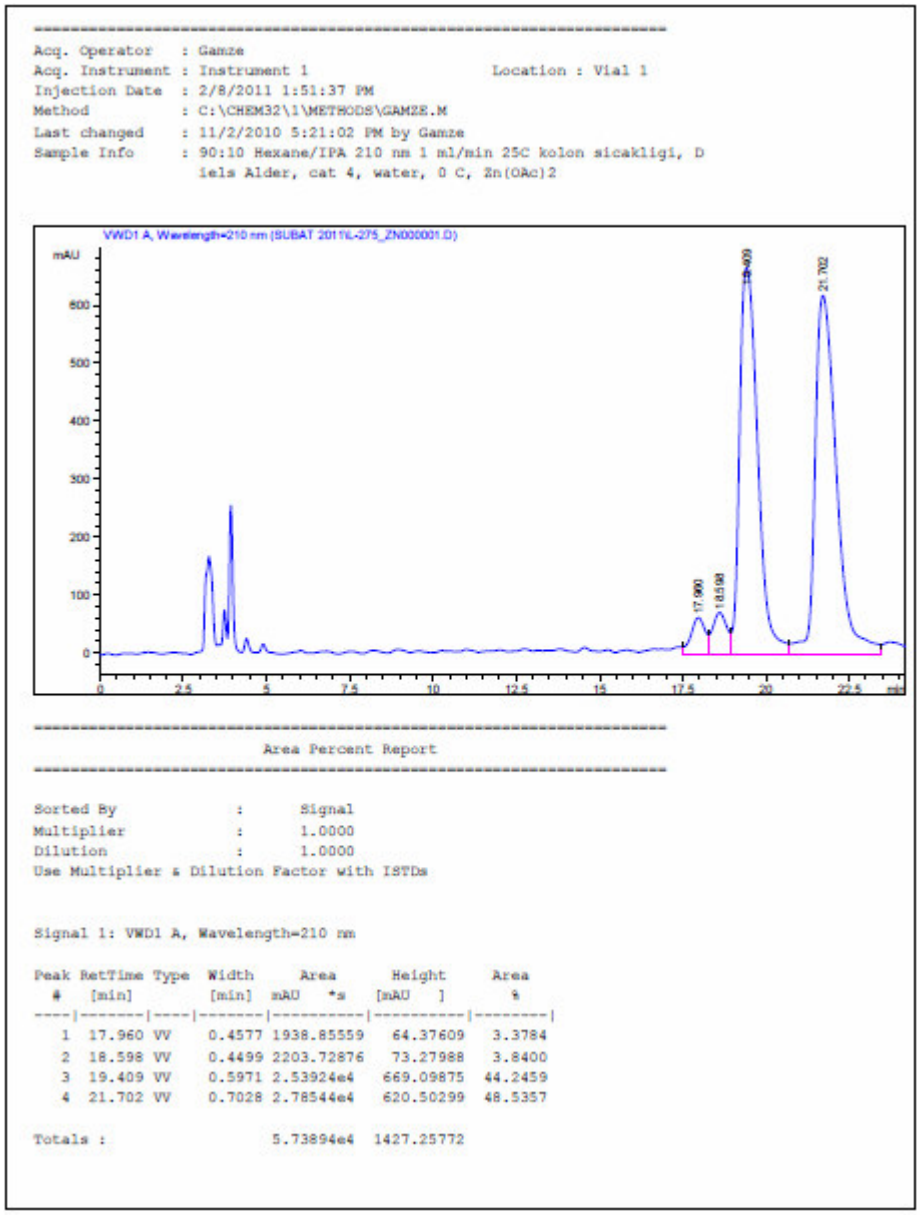
```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  17.831 VV     0.3856 4275.86230  172.28380   2.7429
   2  18.460 VV     0.3544 4136.58838  179.76253   2.6536
   3  19.091 VV     0.7510 7.00628e4  1518.22876  44.9446
   4  21.337 VB     0.8596 7.74117e4  1465.07080  49.6589

Totals :                  1.55887e5  3335.34589
```

Figure B.4.11. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in the presence of $Ni(OAc)_2 \cdot 4H_2O$ with catalyst **4**



```
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Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/8/2011 1:51:37 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4, water, 0 C, Zn(OAc)2
```



```
                        Area Percent Report

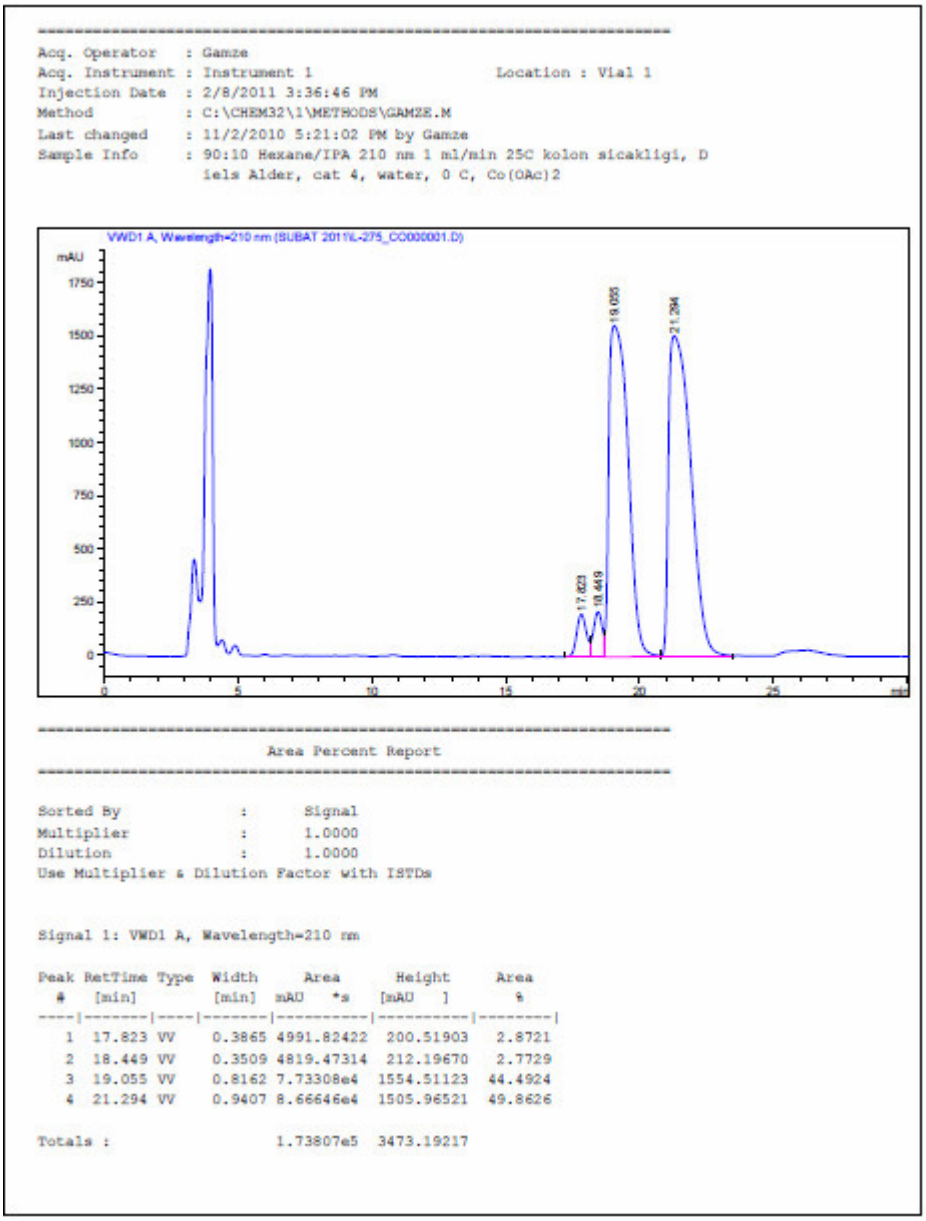
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.960 VV    0.4577 1938.85559   64.37609   3.3784
   2  18.598 VV    0.4499 2203.72876   73.27988   3.8400
   3  19.409 VV    0.5971 2.53924e4   669.09875  44.2459
   4  21.702 VV    0.7028 2.78544e4   620.50299  48.5357

Totals :                 5.73894e4  1427.25772
```

Figure B.4.12. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in the presence of $Zn(OAc)_2 \cdot 2H_2O$ with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/8/2011 3:36:46 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4, water, 0 C, Co(OAc)2
```


Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.823 VV     0.3865 4991.82422  200.51903   2.8721
   2  18.449 VV     0.3509 4819.47314  212.19670   2.7729
   3  19.055 VV     0.8162 7.73308e4  1554.51123  44.4924
   4  21.294 VV     0.9407 8.66646e4  1505.96521  49.8626

Totals :                  1.73807e5  3473.19217
```

Figure B.4.13. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in the presence of $Co(OAc)_2 \cdot 4H_2O$ with catalyst **4**

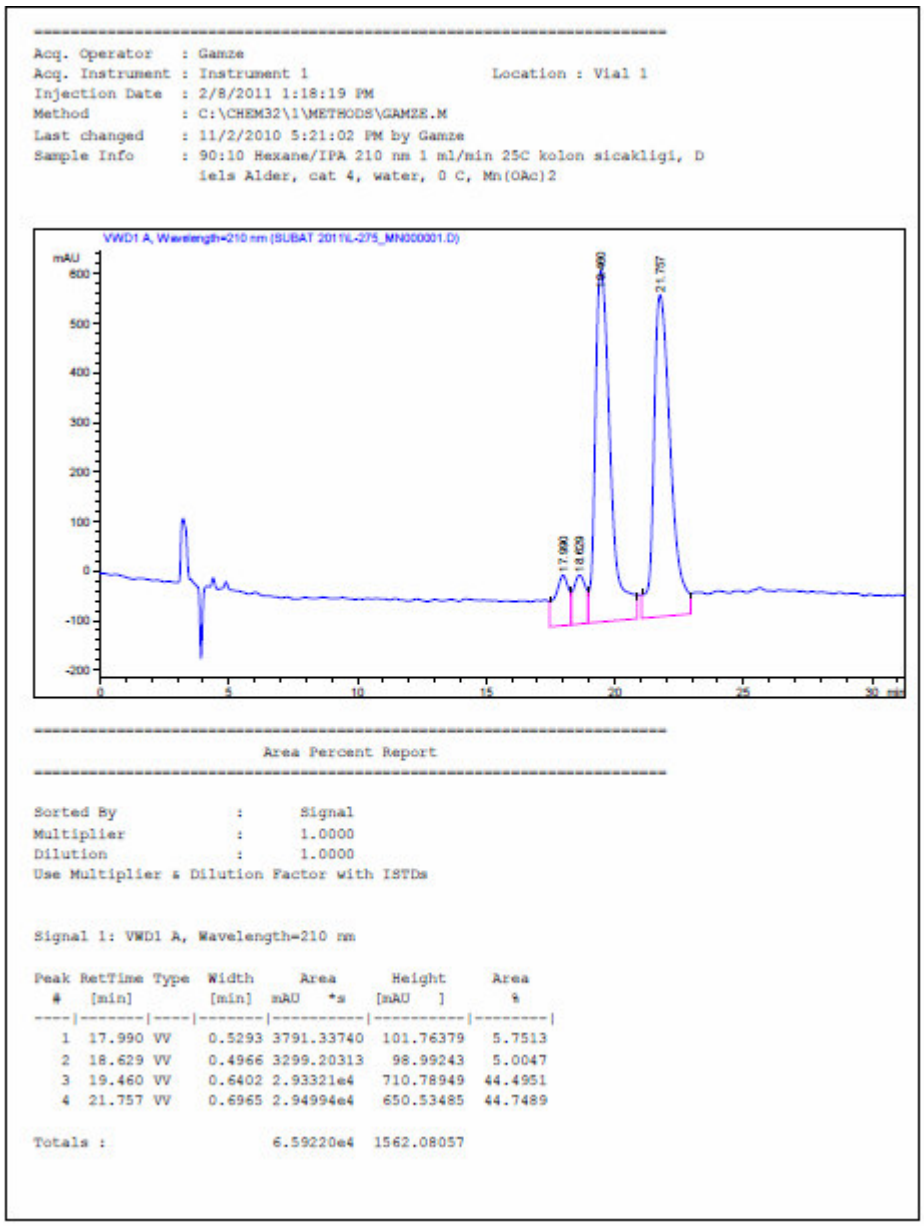
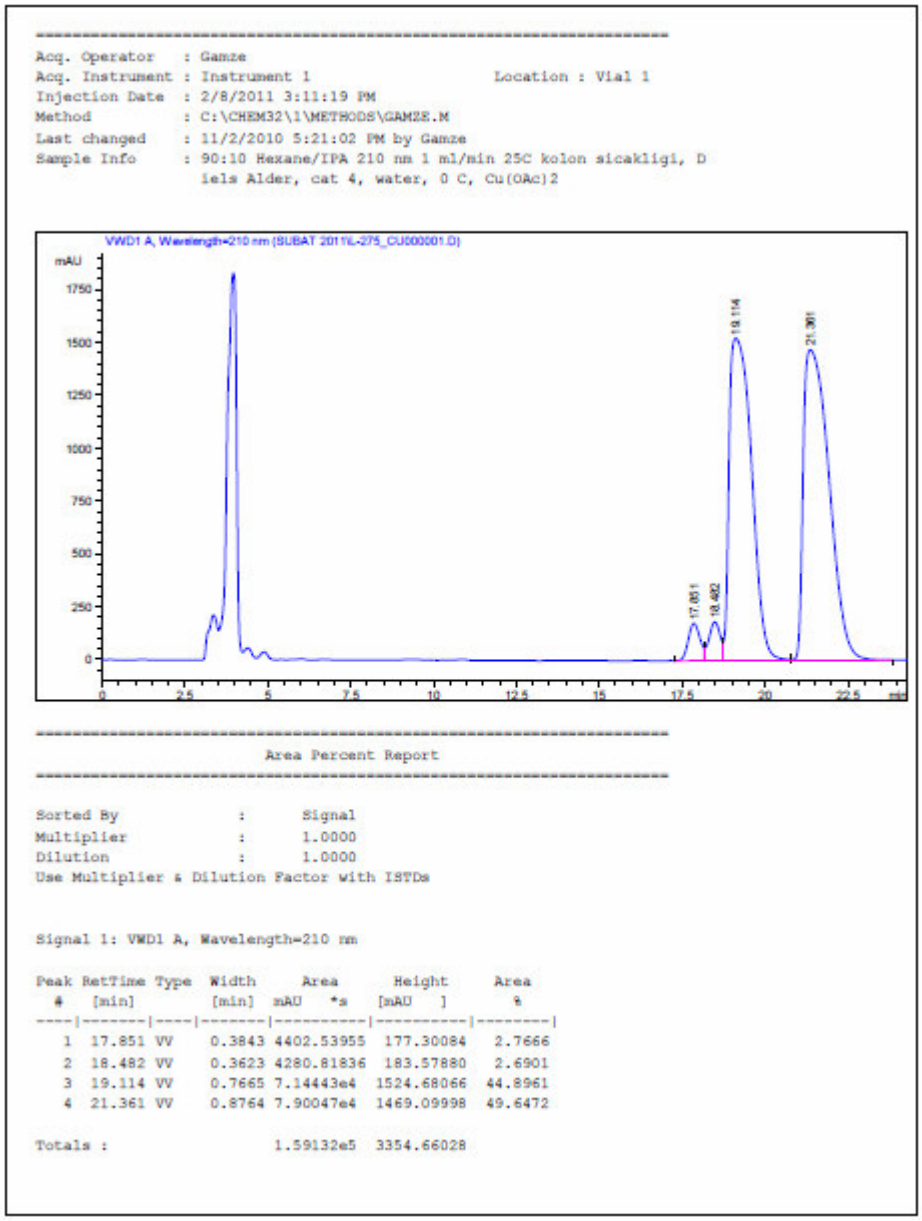


Figure B.4.14. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in the presence of $Mn(OAc)_2 \cdot 4H_2O$ with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/8/2011 3:11:19 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 11/2/2010 5:21:02 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4, water, 0 C, Cu(OAc)2
```

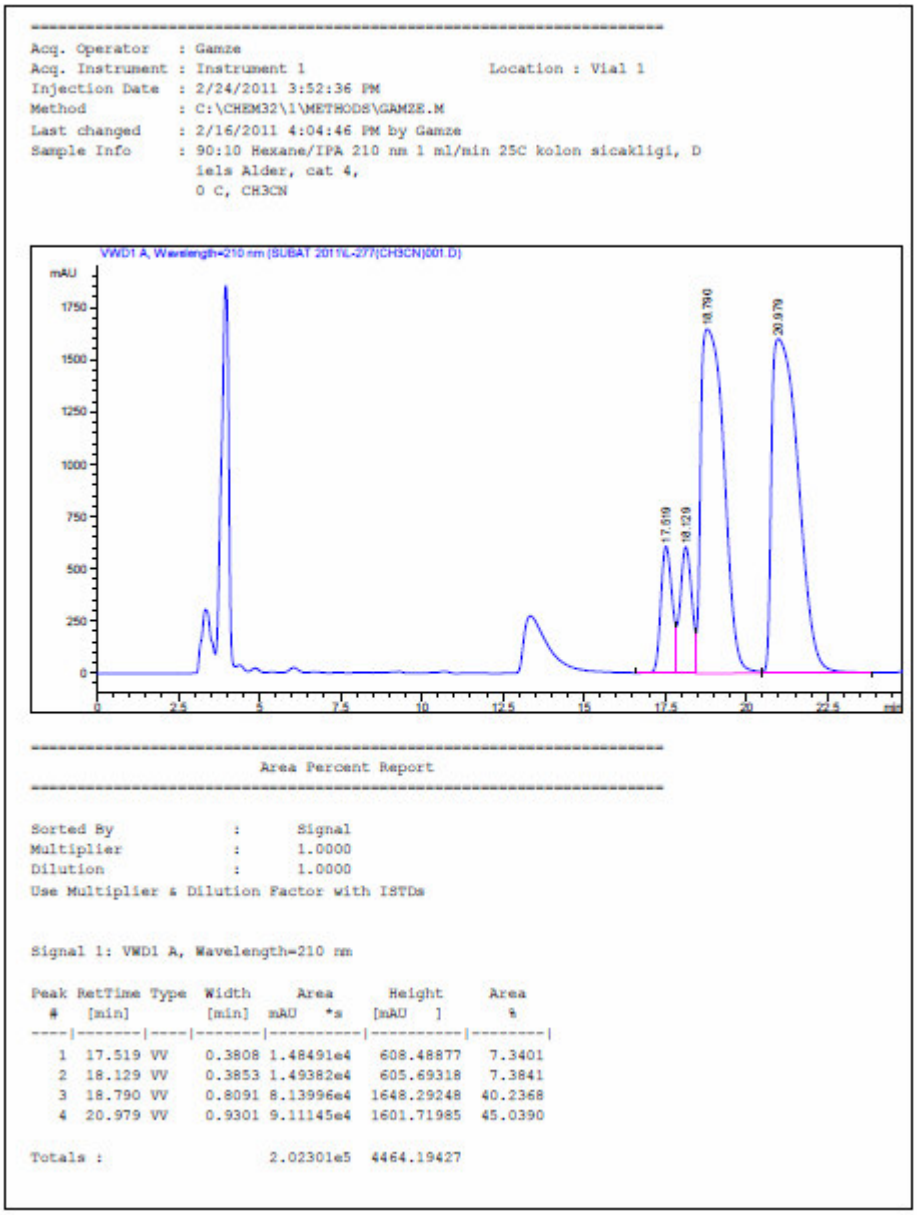

Area Percent Report

```
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm
```

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.851	VV	0.3843	4402.53955	177.30084	2.7666
2	18.482	VV	0.3623	4280.81836	183.57880	2.6901
3	19.114	VV	0.7665	7.14443e4	1524.68066	44.8961
4	21.361	VV	0.8764	7.90047e4	1469.09998	49.6472
Totals :				1.59132e5	3354.66028	

Figure B.4.15. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in the presence of $Cu(OAc)_2 \cdot H_2O$ with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/24/2011 3:52:36 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/16/2011 4:04:46 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4,
                  0 C, CH3CN
```



```
                        Area Percent Report

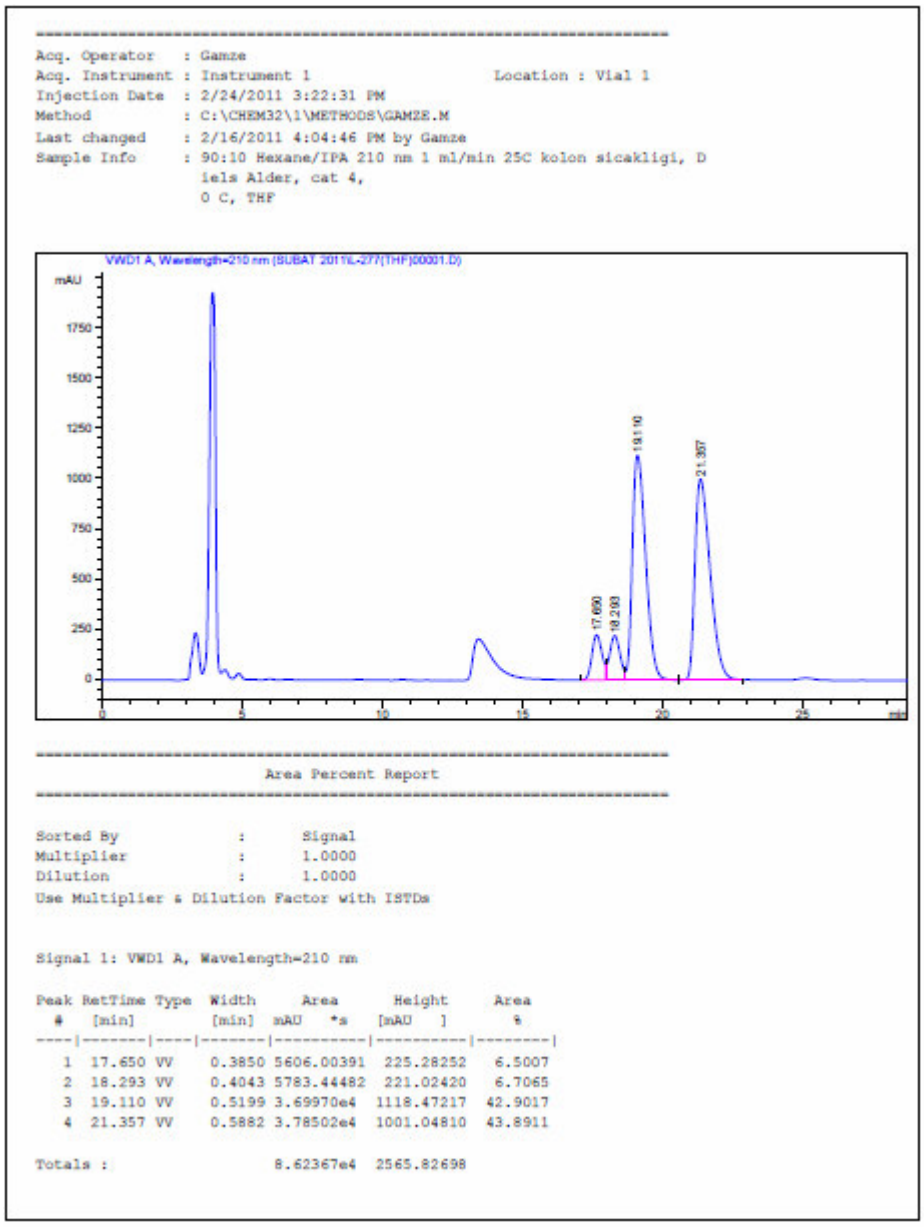
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.519 VV    0.3808 1.48491e4   608.48877   7.3401
   2  18.129 VV    0.3853 1.49382e4   605.69318   7.3841
   3  18.790 VV    0.8091 8.13996e4  1648.29248  40.2368
   4  20.979 VV    0.9301 9.11145e4  1601.71985  45.0390

Totals :                 2.02301e5  4464.19427
```

Figure B.4.16. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in CH_3CN at 0 ˚C with catalyst **4**



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Acq. Operator    : Gamze
Acq. Instrument  : Instrument 1                    Location : Vial 1
Injection Date   : 2/24/2011 3:22:31 PM
Method           : C:\CHEM32\1\METHODS\GAMZE.M
Last changed     : 2/16/2011 4:04:46 PM by Gamze
Sample Info      : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                   iels Alder, cat 4,
                   0 C, THF
```



```
                          Area Percent Report

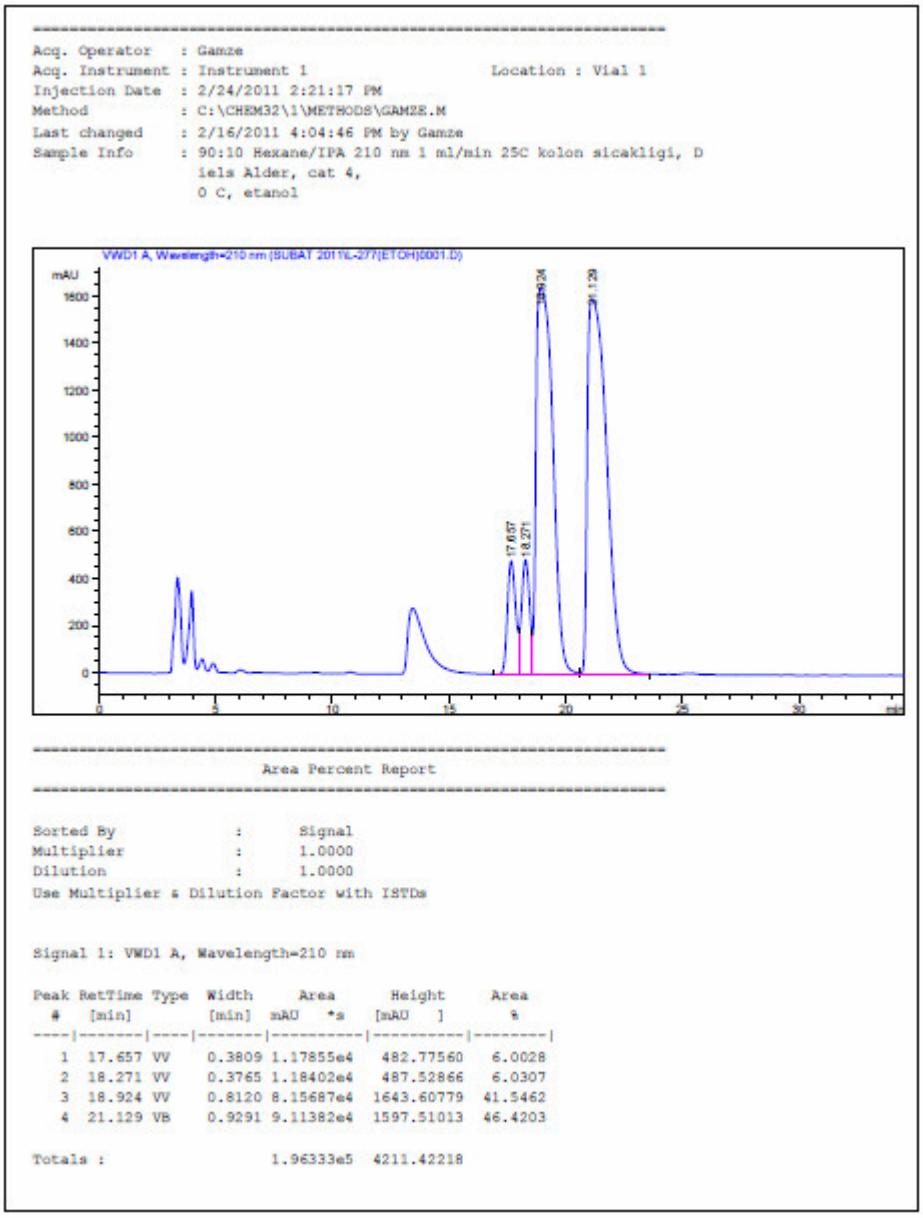
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.650 VV    0.3850 5606.00391  225.28252   6.5007
   2  18.293 VV    0.4043 5783.44482  221.02420   6.7065
   3  19.110 VV    0.5199 3.69970e4  1118.47217  42.9017
   4  21.357 VV    0.5882 3.78502e4  1001.04810  43.8911

Totals :                 8.62367e4  2565.82698
```

Figure B.4.17. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in THF at 0 ˚C with catalyst **4**



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Acq. Operator    : Gamze
Acq. Instrument  : Instrument 1                    Location : Vial 1
Injection Date   : 2/24/2011 2:21:17 PM
Method           : C:\CHEM32\1\METHODS\GAM2E.M
Last changed     : 2/16/2011 4:04:46 PM by Gamze
Sample Info      : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                   iels Alder, cat 4,
                   0 C, etanol
```



```
                          Area Percent Report

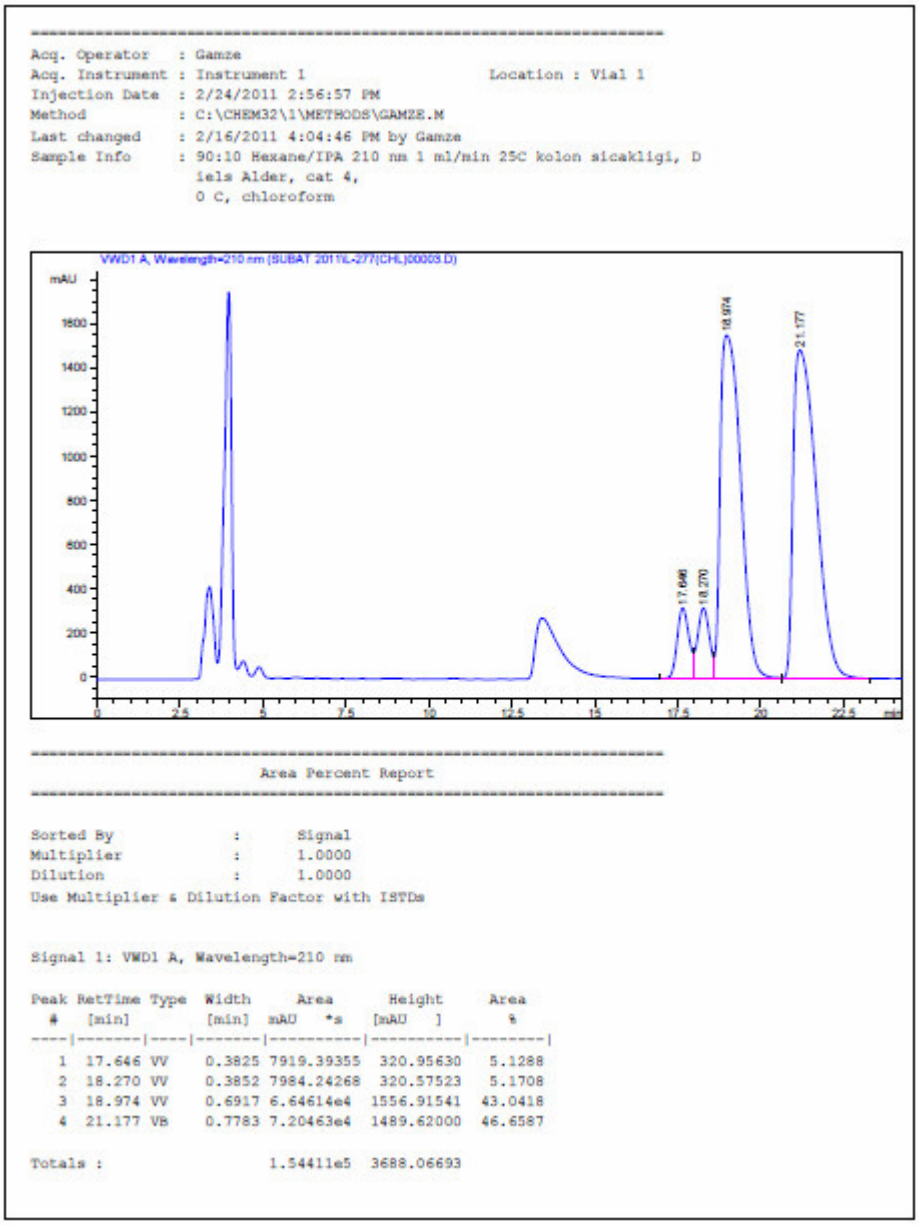
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.657 VV     0.3809 1.17855e4   482.77560   6.0028
   2  18.271 VV     0.3765 1.18402e4   487.52866   6.0307
   3  18.924 VV     0.8120 8.15687e4  1643.60779  41.5462
   4  21.129 VB     0.9291 9.11382e4  1597.51013  46.4203

Totals :                  1.96333e5  4211.42218
```

Figure B.4.18. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in EtOH at 0 ˚C with catalyst **4**



```
Acq. Operator   : Gamze
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 2/24/2011 2:56:57 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 2/16/2011 4:04:46 PM by Gamze
Sample Info     : 90:10 Hexane/IPA 210 nm 1 ml/min 25C kolon sicakligi, D
                  iels Alder, cat 4,
                  0 C, chloroform
```



```
                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.646 VV    0.3825 7919.39355  320.95630   5.1288
   2  18.270 VV    0.3852 7984.24268  320.57523   5.1708
   3  18.974 VV    0.6917 6.64614e4  1556.91541  43.0418
   4  21.177 VB    0.7783 7.20463e4  1489.62000  46.6587

Totals :                  1.54411e5  3688.06693
```

Figure B.4.19. HPLC chromatogram of Diels Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one in $CHCl_3$ at 0 ˚C with catalyst **4**

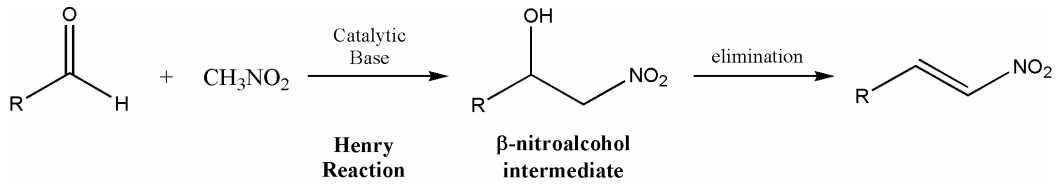
4. CHAPTER 3. ONE-POT SYNTHESIS OF CONJUGATED NITROALKENES BY L-ASPARAGINE AND L-GLUTAMINE DERIVATIVES

4.1. General Information

Among the various C–C bond forming reactions, the nitroaldol or Henry reaction is one of the classical named reactions in organic synthesis. Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile is a widely used transformation, since its discovery in 1895 (Henry, 1895). The resulting product of this reaction is a β-nitroalcohol, which are synthetic precursors of bioactive compounds (Luzzio, 2001; Trost, 2002; Dodda, 2008). Moreover, the nitro group opens the way for further modifications by reduction, Nef reaction, as well as displacement by the carbon, sulfur, and azide nucleophiles. Thus, the Henry reaction provides access to a large set of useful bifunctional compounds, particularly unusual amino alcohols with the stereogenic carbinol center not accessible by reduction of amino acids. When imine is applied, sequential aza-Henry reaction and reduction afford chiral diamines (Westerman, 2003). This powerful tool for creating at least one stereogenic center is therefore applicable to the synthesis of chiral ligands, pharmaceuticals, and natural compounds. However, the wide applicability of this transformation, until recently, was impaired due to the nonavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centres.

4.1.1. Henry reaction and subsequent elimination

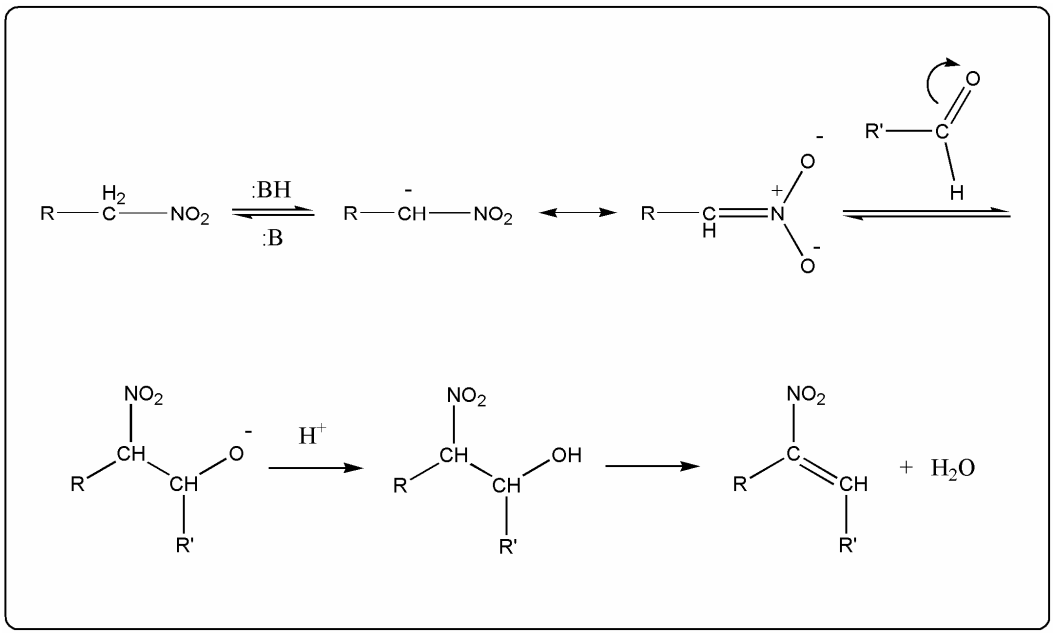
Nitroalkenes can generally be prepared from the dehydration of β-nitroalcohol, which in turn can be synthesized from the Henry reaction (**Scheme 4.1**.).



Scheme 4.1. Standart Henry reaction followed by dehydration

The Henry reaction is a base-catalyzed C-C bond-forming reaction between nitroalkanes and aldehydes or ketones. It is similar to the aldol addition,

and also referred to as the nitroaldol reaction. If acidic protons are available, the products tend to eliminate water to give nitroalkenes. Proposed mechanism of the Henry-elimination reaction given in **Scheme 4.2**.



Scheme 4.2. Proposed mechanistic scheme for general Henry reaction

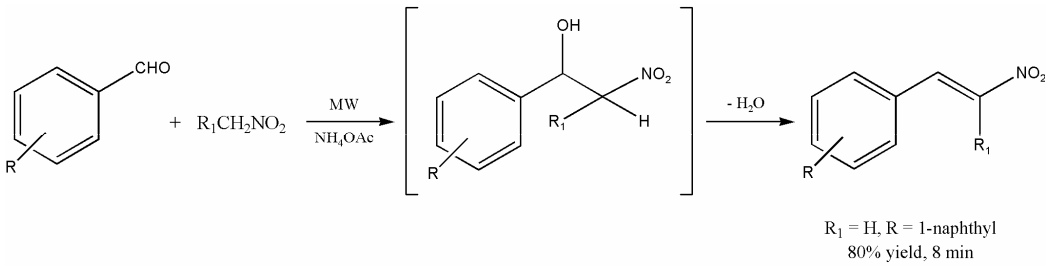
The classical methods for dehydration of nitroalkanols to nitroalkenes effected by several reagent such as methane sulfonylchloride (Melton, 1975), phthalic anhydride (Buckley, 1947; Ranganathan, 1980), dicyclohexyl carbodiimide (DCC) (Knochel, 1982a), pivaloyl chloride (Knochel, 1982b) organic bases, etc. requires high temperatures and longer reaction times.

Recently, Henry reaction (condensation of carbonyl compounds with nitroalkanes followed by β-elimination of the resulting 2-nitro alcohols) to afford nitroalkenes has been attempted using microwave techniques (900 W) in ammonium acetate (Varma, 1997), ultrasound (US)/NH_4OAc/HOAc (McNulty, 1998), direct nitration of alkenes with copper(II) tetrafluoroborate and $NaNO_2$ in acetonitrile (Campos, 2000), MW irradiation (100-110 ˚C) (Varma, 1998), and ceric ammonium nitrate (CAN) (Rao, 2005). In addition, various heterogeneous catalysts such as zeolite (Ballini, 2000), aminopropyl-functionalized silicas (APS) (Sartori, 2004), FDU-ED (diamino-functionalized mesostructured polymers) (Wu, 2008), and MCM-41silica (Sartori, 2001) have been employed for the synthesis of nitroalkenes starting from aromatic aldehydes and nitroalkanes. However, most of the reported methods have one or more of the following drawbacks: for example,

use of expensive reagents and volatile organic solvents, long reaction times, low yields of products, complicated reaction assembly, and tedious workup, etc. In view of the disadvantages, there is a need to develop a mild and efficient base catalyst for the synthesis of nitroalkenes.

4.1.1.1. Microwave Techniques

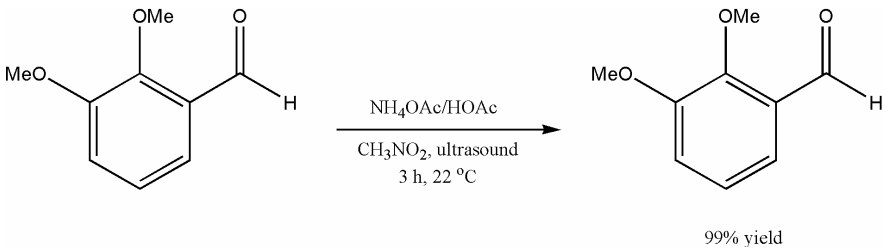
The condensation of aldehydes with nitroalkenes using a catalytic amount of ammonium acetate coupled with the pulsed microwave irradition is found to be an ideal condition that affords high yields of the conjugated nitroalkenes directly without the isolation of the intermediary β-nitroalcohols (Varma, 1997). That the effect is not purely thermal is supported by the fact that using an alternate heating mode (oil bath) at the same temperature of 90 ˚C, the reaction (α-naphthaldehyde) could be completed in 18 hours (**Scheme 4.3.**).



Scheme 4.3. Microwave-assisted synthesis of conjugated nitroalkenes

4.1.1.2. Ultrasound-promoted elimination

McNulty and co-workers have described concerning the ultrasound promoted elimination of H_2O from nitroalkanes to yield nitroalkenes and ultrasound promoted carbonyl addition reactions (McNulty, 1998) (**Scheme 4.4.**).



Scheme 4.4. The ultrasound promoted Henry condensation of 2,3-dimethoxybenzaldehyde

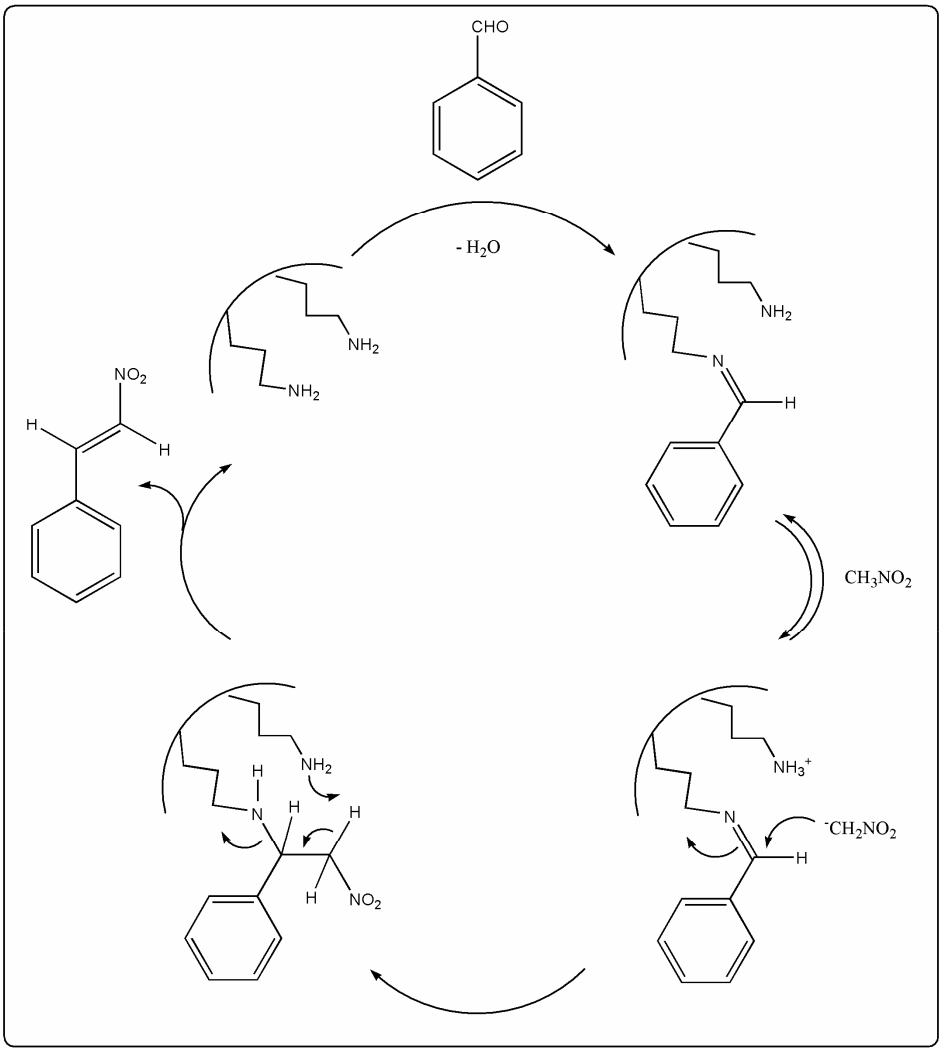
The reaction 2,3-dimethoxybenzaldehyde with ammonium acetate and acetic acid at room temperature and application of ultrasound led to a rapid, clean condensation (complete in 3 h) and subsequent isolation of the nitroalkene product in 99% yield, with no resinous side products being produced. No reaction occurs under these conditions at room temperature until ultrasound is applied. In addition, attempts to conduct the ultrasound promoted reaction at room temperature without acetic acid, or without ammonium acetate, failed.

4.1.1.3. Heterogeneous catalysts

The Henry reaction is catalysed by a variety of substances including organic bases (alkoxides mainly) and inorganic bases (aqueous or alcoholic solution of an alkaline hydroxide). These are all strong bases and can therefore affect other functional groups present in the reactant molecules. Also, they can only act in a homogeneous medium, so they require isolation and purification of the end products, and may even be rendered uselees for recycling.

Presently, the use of eco-friendly heterogeneous catalysts has become an important research target for clean processes in fine chemical industries. Use of heterogeneous base catalysts, which are more stable and easier to be recycled, can offer a process solving the problems in classical methods. Several articles have reported the use of heterogeneous catalysts for one or two steps. The catalysts used were alumina (Rosini, 1983), alumina-KF (Melot, 1986), Amberlyst A-21 (Ballini, 1996), Mg–Al hydrotalcites (Cwik, 2005), Envirocat EPZG (Bandgar, 1996), zeolite (Ballini, 2000), and amines supported on siliceous materials (Sharma, 2007). In order to achieve the maximum yield, high selectivity, and better process efficiency, there is still much work for researchers to accomplish and novel solid base materials with superior performance in catalytic activity and selectivity are expected.

Sartori and co-workers have described that the anchoring of functional aminopropyl groups on MCM-41 silica by the post modification method using 3-aminopropyltriethoxysilane, *N*-methyl-3-aminopropyltrimethoxysilane and *N*,*N*-diethyl-3-aminopropyltrimethoxysilane to give solid basic catalysts called MCM-41-NH_2, MCM-41-NHMe and MCM-41-NEt_2, respectively (Sartori, 2001). All supported catalysts were tested in the model reaction of benzaldehyde with nitromethane as the solvent reagent at 90 ˚C . The mechanistic hypothesis given in **Scheme 4.5**.



Scheme 4.5. A hypothesised catalytic cycle of the MCM-41-NH_2-promoted nitroaldol condensation

4.1.2. Biological activity of nitroalkenes

Over the last few years, compounds comprising a moiety nitroalkenes have been recognized to have a series of relevant biological activities. In fact, some β-nitrostyrene derivatives have recently been tested as pro-apoptotic anticancer agents and the β-nitrostyrene moiety was identified as the pharmacophore for this activity (Kaap, 2003). These compounds have also been described as highly potent and selective human telomerase inhibitors as well as cytotoxic for human cancer cell lines (Kim, 2003; Carter, 2002). Moreover, it was shown that they are able to downregulate the production of some interleukins, thus affecting the immune response in humans. The nitrovinyl side chain attached to the aromatic ring was recognized to be an essential chemical feature in this type of compounds and a critical conformational pattern for their biological activity (Dore, 1975).

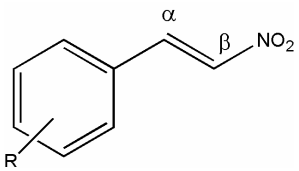


Figure 4.1. β−nitrostyrene

Although the antifungic and antibacterial properties of this type of compounds have been studied since the 1940s, the work in this area during the last decade is rather scarce. In general, the nitrostyrene derivatives were found to be more effective against Gram-positive than Gram-negative bacteria (Brian, 1946).

Drug discovery studies have been significantly intensified in recent years, as part of the search for more effective antibacterial agents displaying activity against Gram-positive and Gram-negative bacteria resistant to the antimicrobials currently used (Nielsen, 2004). The search for novel chemotherapeutic agents, as well as the attempt to modify and improve the currently available ones, has been a priority mainly as a consequence of the rapid spread of multidrug-resistant bacterial pathogens. The development of new antibacterial drugs is presently based on structure – activity relationship (SAR), structure – property – activity relationship (SPAR) and quantitative structure – activity relationship (QSAR) studies (Narasimhan, 2004).

4.1.3. Derivatives of nitroalkene: The synthesis of fine chemicals

Aliphatic nitro compounds have proven to be valuable precursors to a wide variety of building blocks and intermediates in organic synthesis. Because the nitro group can be easily transformed into a variety of groups with different functionalities.

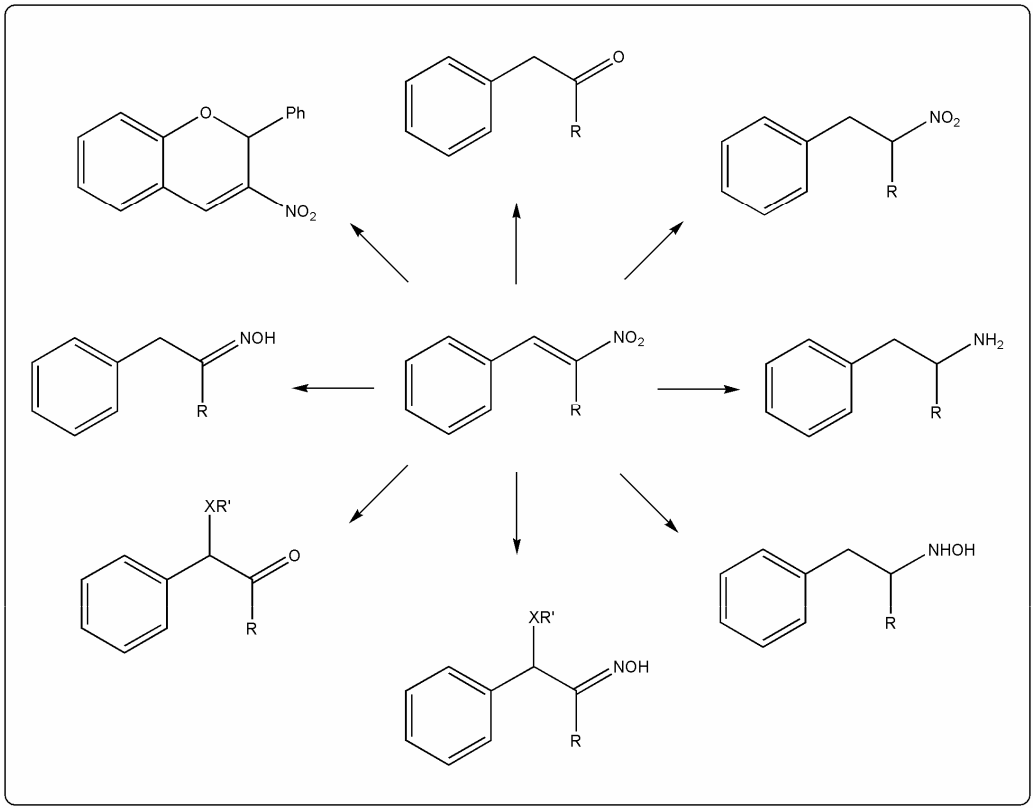


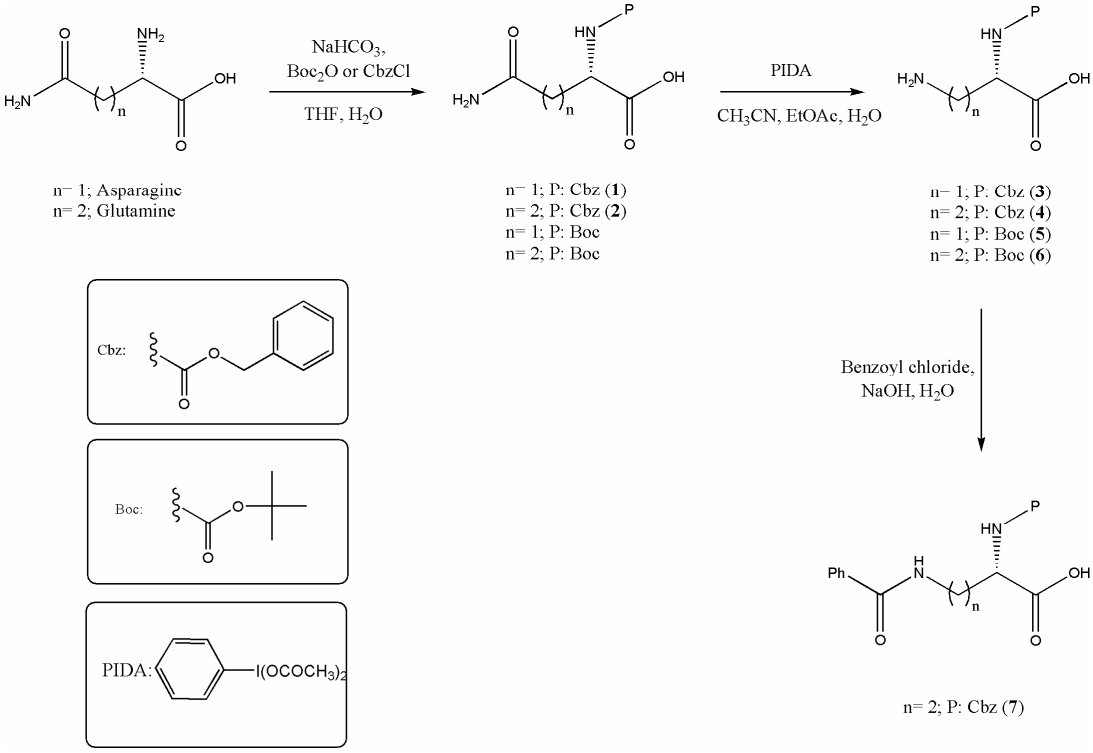
Figure 4.2. β–nitrostyrene reaction starburst and building block application

The reduction of conjugated nitroalkenes provides easy access to a vast array of functionalities including nitroalkanes, N-substituted hydroxylamines, amines, ketons, oximes, α-substituted oximes and ketones (**Figure 4.2.**).

4.2. Results and Discussion

4.2.1. Synthesis of the catalysts

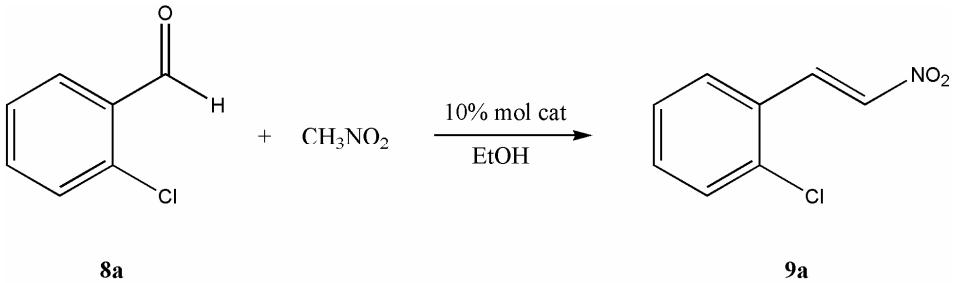
L-asparagine and L-glutamine derivatives were used as a catalyst in the Henry elimination reaction between aromatic substituted aldehydes and nitromethane. The chiral organocatalysts were synthesized by protection of the amino acids and a subsequent Hoffman rearrangement reaction (**Scheme 4.6.**) (Kraml, 2005; Zhang, 1997; Andruszkiewicz, 2004).



Scheme 4.6. Synthesis of the catalysts

4.2.2. Henry-elimination reaction catalyzed by L-asparagine and L-glutamine derivatives

The primary aim of this work was to investigate the best catalyst for the nitroalkene reaction between 2-chlorobenzaldehyde and nitromethane (**Table 4.1.**).



8a **9a**

Table 4.1. Catalyst and temperature effect in the nitroalkene reaction of 2-chlorobenzaldehyde and nitromethane

Entry	Catalyst	Temperature (°C)	Time[a]	Yield[b] (%)
1	**1**	30	20 d	-
2	**2**	30	20 d	-
3	**3**	30	20 d	-
4	**4**	30	48 h	93
5	**5**	30	10 d	56
6	**6**	30	20 d	95
7	**7**	30	20 d	-
8	**4**	35	48 h	87
9	**4**	40	48 h	84
10	**4**	45	42 h	90
11	**4**	50	38 h	93

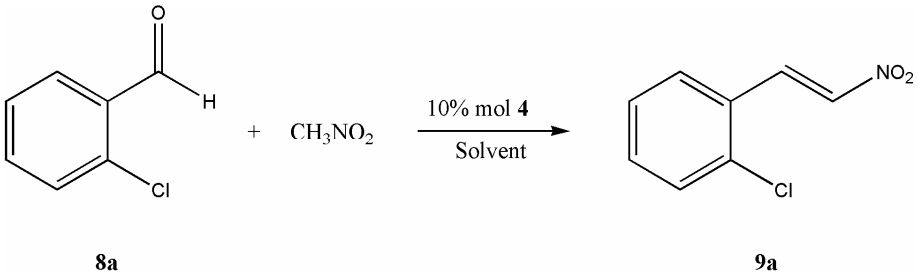
Reaction conditions: 2-chlorobenzaldehyde (1 mmol), nitromethane (5 mmol), catalyst (10% mol)

[a]detected by TLC

[b]isolated yield after column chromatography

No product was obtained in the absence of the catalysts **1**, **2**, **3** and **7** (**Table 4.1**, entries 1, 2, 3 and 7). On the other hand, a low yield was observed for the catalyst **5** (entry 5); meanwhile, 95% yield was attained using catalyst **6** at the end of a long reaction time (entry 6). A very high yield value (93%) was achieved when the reaction was performed using the catalyst **4** (entry 4).

The reaction of 2-chlorobenzaldehyde with nitromethane over the proposed catalyst (**4**) was used as a model to optimize some operating conditions. **Table 4.2.** illustrates the influence of the reaction solvent on the 1-chloro-2-[(*E*)-2-nitrovinyl]benzene yield.



8a **9a**

Table 4.2. Influence of the reaction solvent on 1-chloro-2-[(*E*)-2-nitrovinyl]benzene yield in the reaction of 2-chlorobenzaldehyde with nitromethane

Entry	Solvent	Time[a]	Yield[b] (%)
1	EtOH	48 h	93
2	n-BuOH	5 d	67
3	IPA	5 d	52
4	EtOH : H_2O (10:1)	5 d	58
5	MeOH	5 d	52
6	THF	-	-
7	Toluene	-	-
8	Ethyl acetate	-	-
9	Acetone	5 d	24
10	DMF	-	-
11	Acetonitrile	-	-
12	Dichlorometane	7 d	14
13	n-PrOH	5 d	78

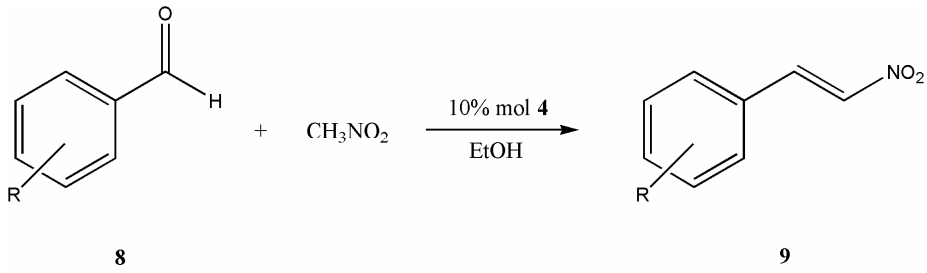
Reaction conditions: 2-chlorobenzaldehyde (1 mmol), nitromethane (5 mmol), catalyst (10% mol), 30 °C

[a]detected by TLC

[b]isolated yield after column chromatography

The reaction solvent has a great influence on the reaction. When the reaction solvent was changed from ethanol to n-BuOH, IPA, EtOH : H_2O (10:1), MeOH, acetone, dichlorometane and n-PrOH the reaction yield decreased while the reaction took a longer time (**Table 4.2**, entries 1-5, 9, 12 and 13). No product was obtained in THF, toluene, ethyl acetate, DMF and acetonitrile (entries 6-8, 10 and 11).

Under the optimized reaction conditions, different aldehydes were tested in order to extend the substrate scope, as shown in **Table 4.3**.



8 **9**

Table 4.3. Nitroalkene reaction of nitromethane with various aldehydes

Entry	R	Time[a] (h)	Product	Yield[b] (%)
1	**8b:** 4-Me	72	**9b**	98
2	**8c:** 4-Et	72	**9c**	77
3	**8d:** 4-MeO	72	**9d**	93
4	**8e:** 2-NO_2	96	**9e**	50
5	**8f:** 3-NO_2	96	**9f**	54
6	**8g:** 4-NO_2	72	**9g**	60

Reaction conditions: aldehyde (1 mmol), nitromethane (5 mmol), catalyst (10 mol), 30°C.

[a]detected by TLC

[b]isolated yield

L-asparagine and L-glutamine derived catalysts generally worked well for various aromatic aldehydes, regardless of the substituents on the aromatic ring, either electron-withdrawing or donating groups.

4.2.3. Re-usability of Catalyst 4

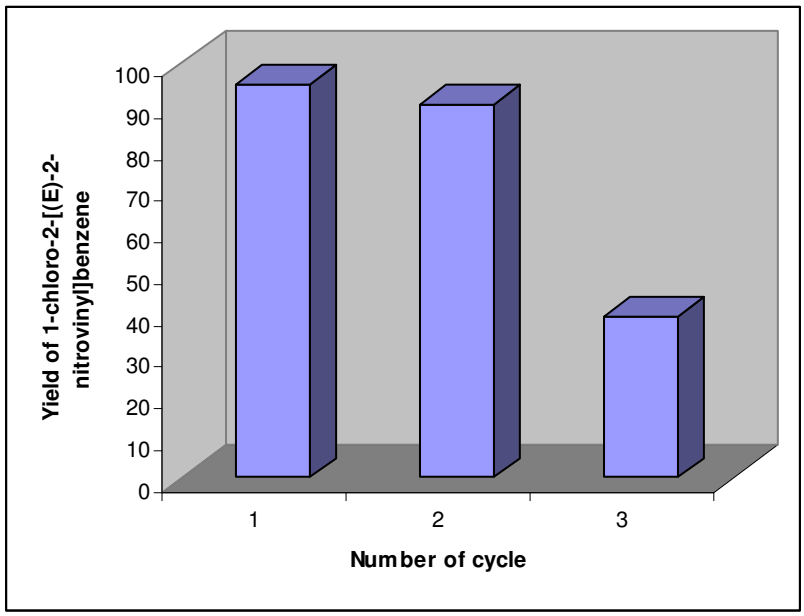


Figure 4.3. Yield of 1-chloro-2-[(*E*)-2-nitrovinyl]benzene after approximately 48 h in the reaction of 2-chlorobenzaldehyde with nitromethane in the presence of re-used catalyst **4**

The re-usability of the catalyst **4** was assessed in the reaction of 2-chlorobenzaldehyde with nitromethane. **Figure 4.3.** shows the results obtained after three re-use cycles. As can be seen, the catalyst retained virtually its whole activity for two cycles.

4.3. Conclusion

In summary, we have developed a simple, mild and inexpensive methodology for the one-pot synthesis of nitroalkenes that are useful intermediates in organic synthesis. The L-glutamine derivative catalyst (**4**) is an advantageous organocatalyst for the reaction which can be easily prepared from cheap starting materials. Only (E)-nitroalkenes are obtained in moderate to high yields in the reaction of nitromethane with aromatic aldehydes. Finally, the catalyst can be re-used at least two times with no appreciable loss of reactivity or selectivity after easy removal from the reaction.

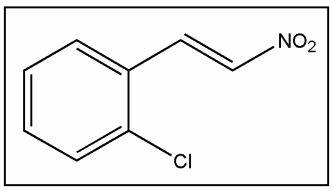
4.4. Material and Method

Chemicals were purchased from Merck, Sigma-Aldrich, Alfa Aesar or Fluka and used without any purification. Solvents were used as received from commercial suppliers. IR spectra were recorded using a Perkin Elmer 100. ^{1}H NMR and ^{13}C NMR spectra were carried out using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. Melting points were recorded with an electro thermal digital melting points apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. For column chromatography silica gel 60 (Merck 7743) was used. Catalyst **1–7** were prepared according to the method given in section 3.4.

4.4.1. General procedure for Henry elimination reaction

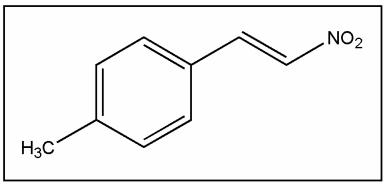
In a typical procedure, aldehyde (1 mmol), nitromethane (5 mmol) and the catalyst (10% mol) were taken in 2 mL solvent and stirred at 30 °C. The reaction was monitored by TLC. After completion of the reaction, solvent was evaporated in *vacuo* and the crude product was purified with column chromatography on silica gel (hexane:EtOAc). The E geometry was readily assigned on the basis of ^{1}H NMR spectra. The structures of the known products were characterized by comparison with data shown in literature.

4.4.1.1. 1-chloro-2-[(*E*)-2-nitrovinyl]benzene (9a)



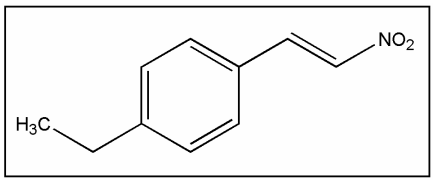
Yellow oil, 93% yield; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.40 (d, 1H, J = 12 Hz), 7.59 (d, 1H, J = 12 Hz), 7.57 (d, 1H, J = 8 Hz), 7.50 (d, 1H, J = 8 Hz), 7.42 (t, 1H, J= 8 Hz), 7.33 (t, 1H, J = 8 Hz). IR (NaCl) 1634, 1520, 1339 cm^{-1}.

4.4.1.2. 1-methyl-4-[(*E*)-2-nitrovinyl]benzene (9b)



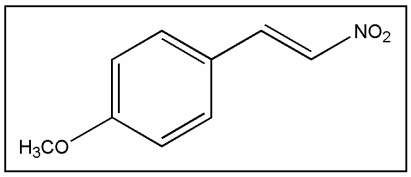
Yellow solid, 98% yield; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.99 (d, 1H, J = 12 Hz), 7.56 (d, 1H, J = 12 Hz), 7.44 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz), 2.41 (s, 3H). IR (KBr) 1633, 1497, 1341 cm^{-1}.

4.4.1.3. 1-ethyl-4-[(*E*)-2-nitrovinyl]benzene (9c)



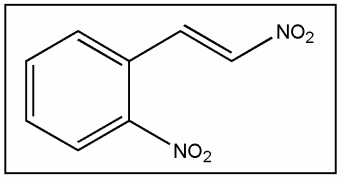
Yellow solid, 77% yield; ^{1}H NMR ($CDCI_3$) δ (ppm) 7.99 (d, 1H, J = 12 Hz), 7.57 (d, 1H, J = 12 Hz), 7.47 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 2.70 (q, 2H, J = 8, 16 Hz) 1.26 (t, 3H, J = 8 Hz). IR (KBr) 1634,1519, 1505, 1342 cm^{-1}.

4.4.1.4. 1-methoxy-4-[(*E*)-2-nitrovinyl]benzene (9d)



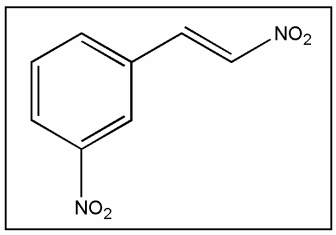
Yellow solid, 93% yield; ^{1}H NMR ($CDCI_3$) δ (ppm) 7.98 (d, 1H, J = 12 Hz), 7.52 (d, 1H, J = 12 Hz), 7.50 (d, 2H, J = 8 Hz), 6.96 (d, 2H, J = 8 Hz), 3.87(s, 3H). IR (KBr) 1604, 1517, 1497 cm^{-1}.

4.4.1.5. 1-nitro-2-[(*E*)-2-nitrovinyl]benzene (9e)



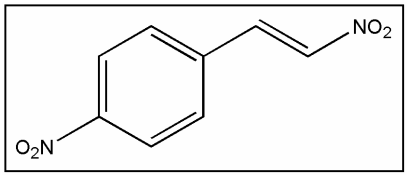
Yellow solid, 50% yield; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.54 (d, 1H, J = 12 Hz), 8.21 (d, 1H, J = 8 Hz), 7.75 (td, 1H, J = 8, 4 Hz), 7.69 (t, 1H, J = 8 Hz), 7.60 (dd, 1H, J = 8, 4 Hz), 7.43 (d, 1H, J = 12 Hz). IR (KBr) 1544, 1520, 1347 cm^{-1}.

4.4.1.6. 1-nitro-3-[(*E*)-2-nitrovinyl]benzene (9f)



Yellow solid, 54% yield; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.42 (bs, 1H), 8.35 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 12 Hz), 7.88 (d, 1H, J = 8 Hz), 7.75 – 7.60 (m, 2H). IR (KBr) 1639, 1556, 1509, 1347 cm^{-1}.

4.4.1.7. 1-nitro-4-[(*E*)-2-nitrovinyl]benzene (9g)



Yellow solid, 60% yield; ^{1}H NMR ($CDCl_3$) δ (ppm) 8.32 (d, 2H, J = 8 Hz), 8.04 (d, 1H, J = 12 Hz), 7.73 (d, 2H, J = 8 Hz), 7.64 (d, 1H, J = 12 Hz). IR (KBr) 1637, 1601, 1519, 1340 cm^{-1}.

4.4.2. The Reusability of the Catalyst 4

After completion of the reaction, solvent was evaporated in *vacuo* and the crude product solved in CH_2Cl_2. The catalyst removed by filtration and washed with CH_2Cl_2 several times and dried. **Figure 4.3** shows the results obtained after three re-use cycles.

4.5. Appendix C. Spectra and Chromatograms

C.1. IR spectra

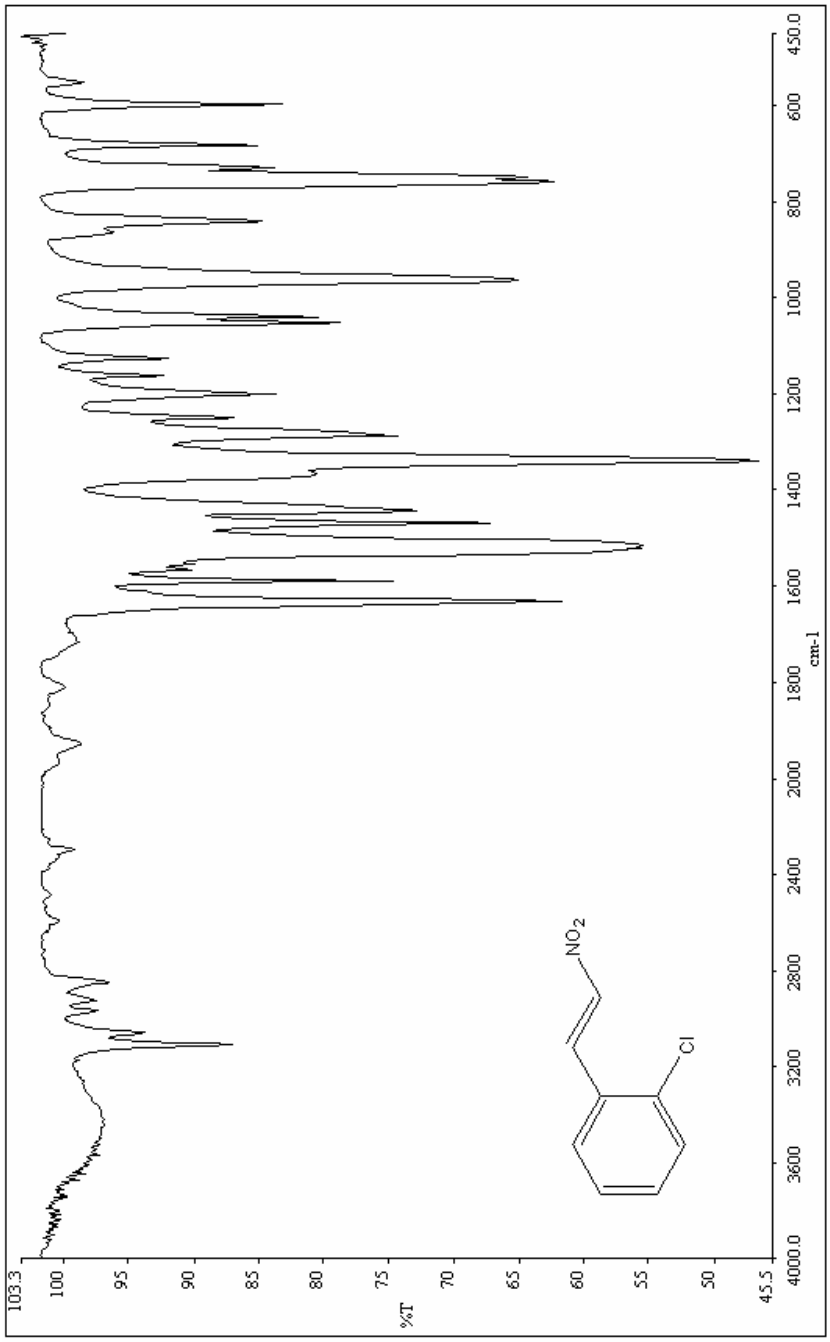


Figure C.1.1. IR spectrum of 1-chloro-2-[(*E*)-2-nitrovinyl]benzene (**9a**)

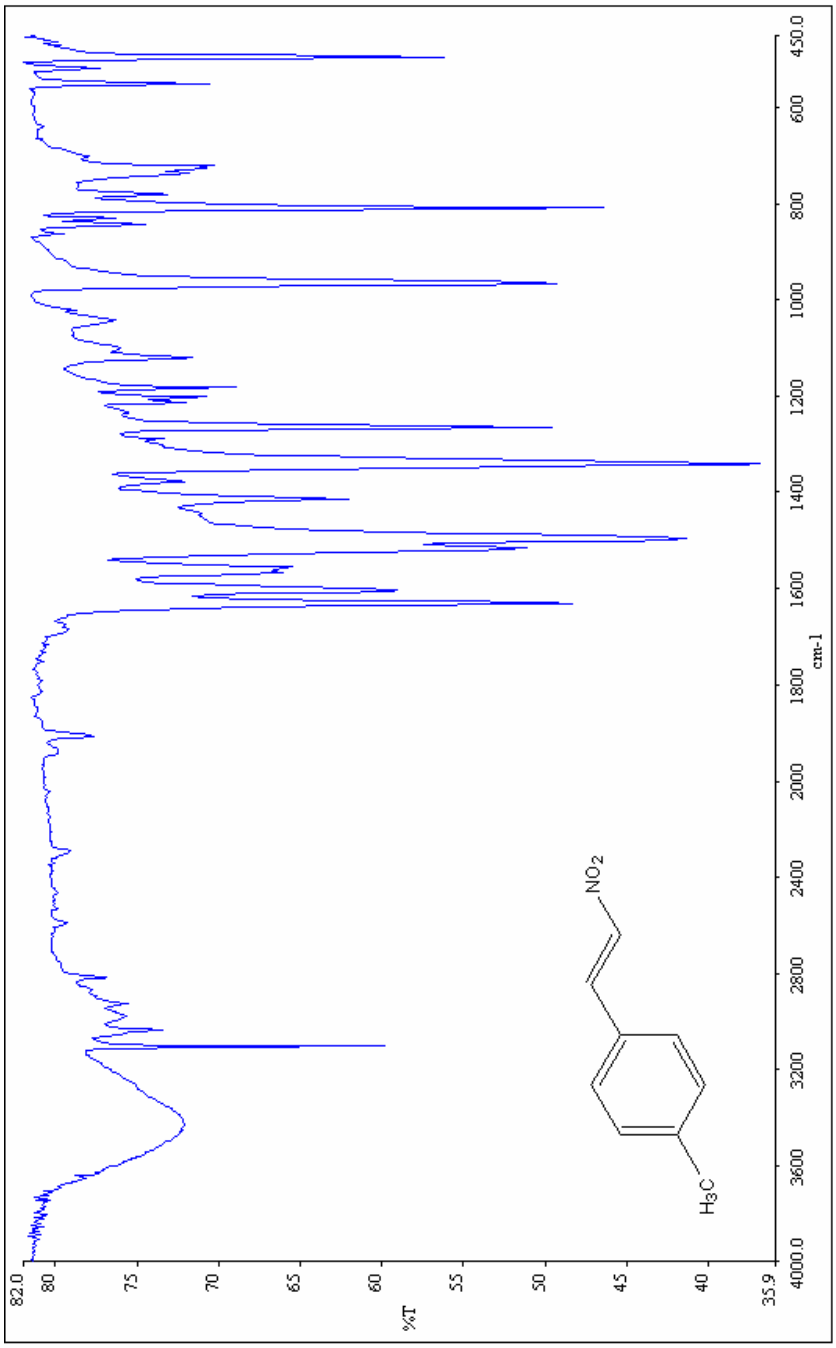


Figure C.1.2. IR spectrum of 1-methyl-4-[(*E*)-2-nitrovinyl]benzene (**9b**)

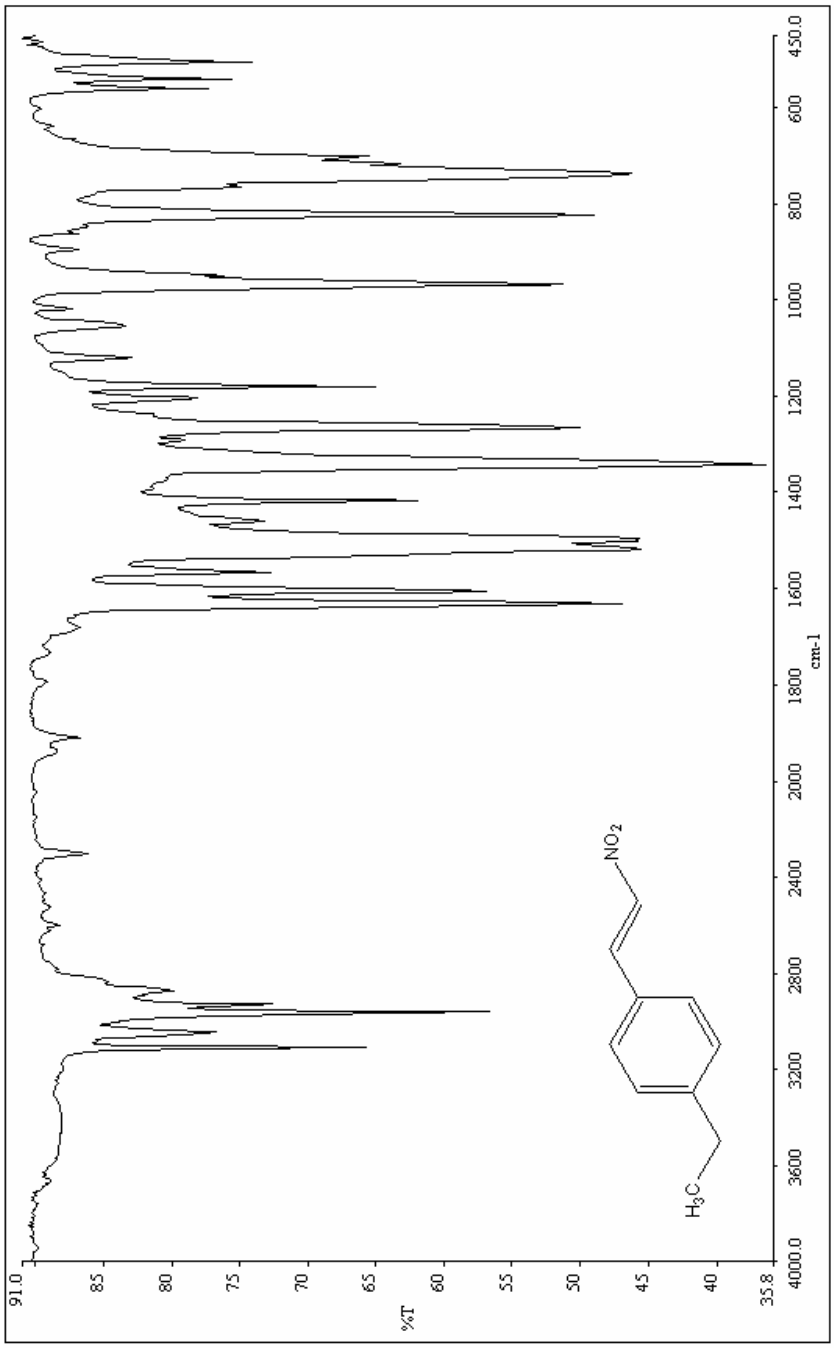


Figure C.1.3. IR spectrum of 1-ethyl-4-[(*E*)-2-nitrovinyl]benzene (**9c**)

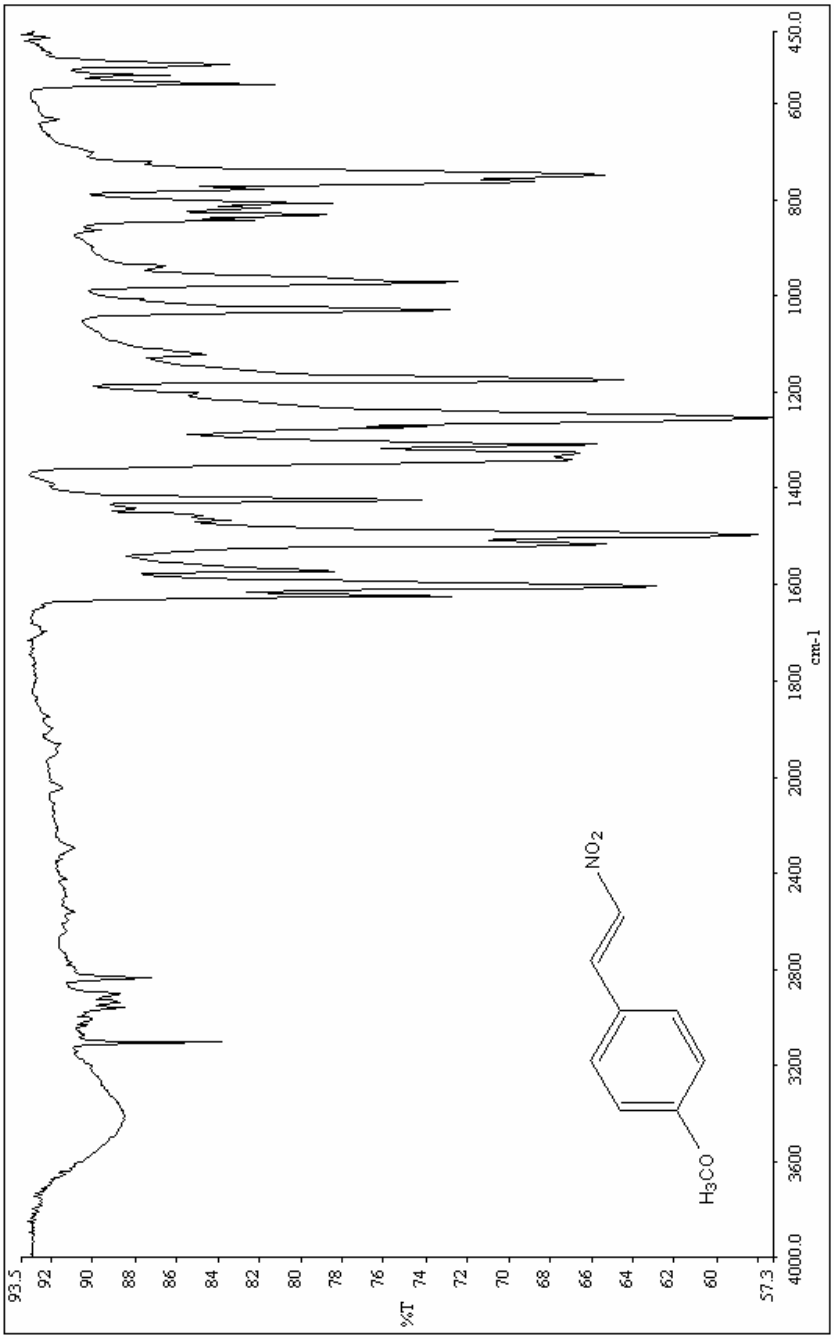


Figure C.1.4. IR spectrum of 1-methoxy-4-[(*E*)-2-nitrovinyl]benzene (**9d**)

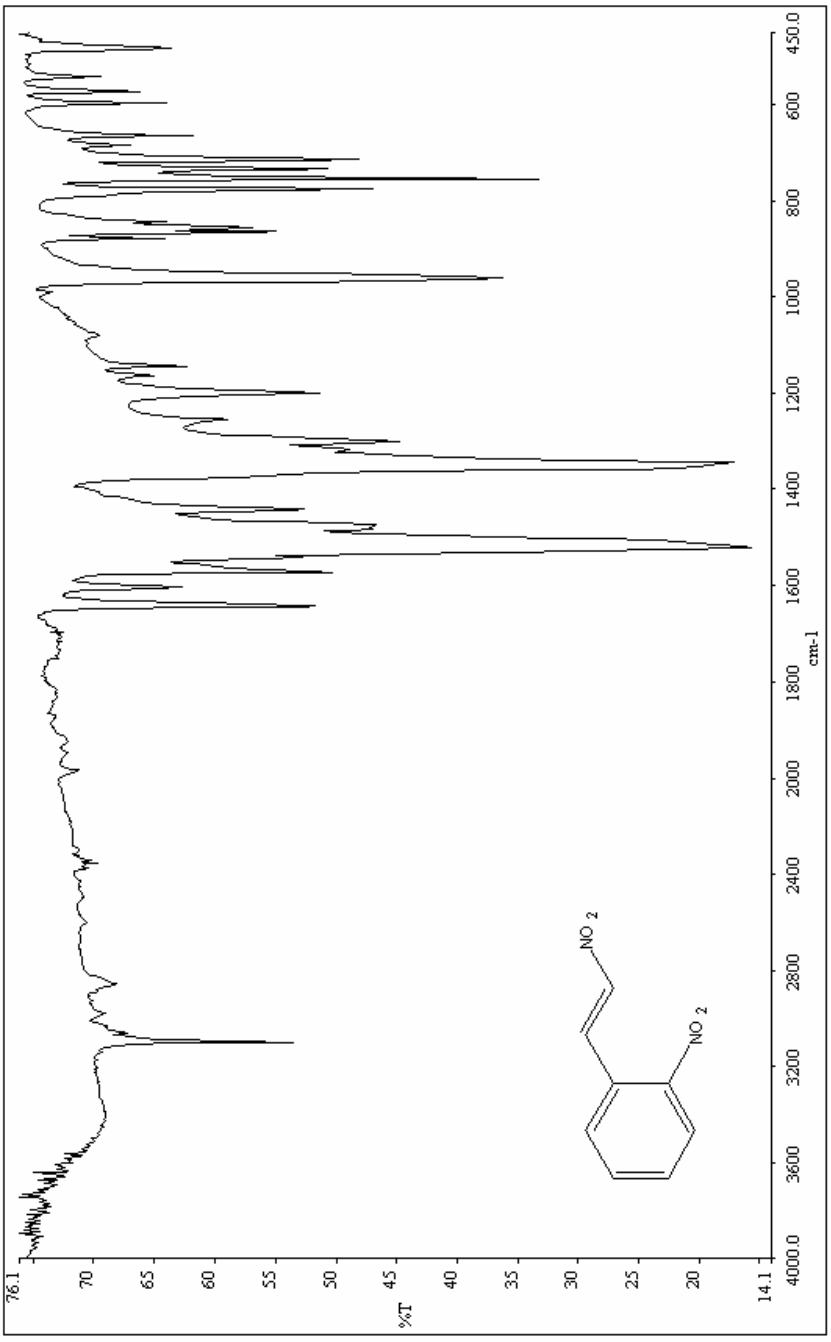


Figure C.1.5. IR spectrum of 1-nitro-2-[(*E*)-2-nitrovinyl]benzene (**9e**)

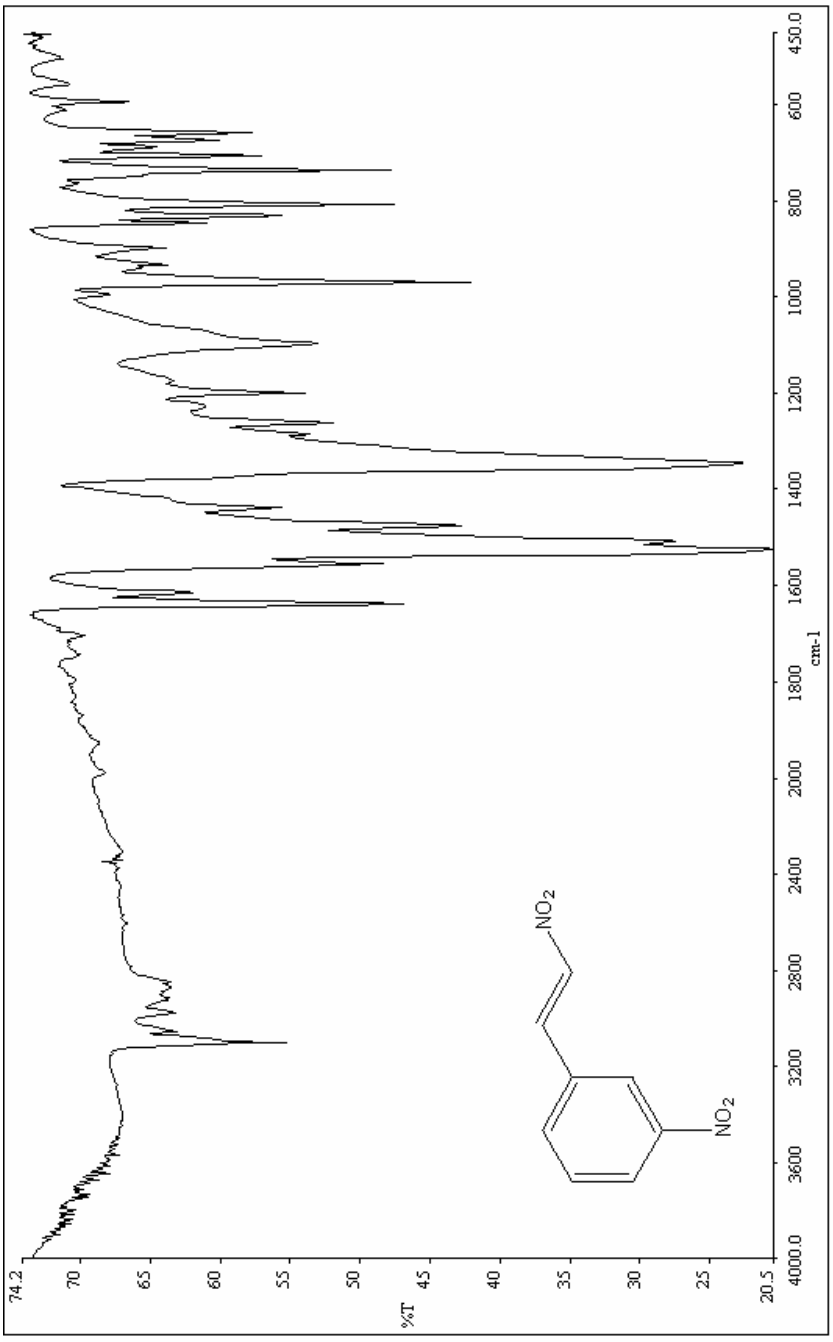


Figure C.1.6. IR spectrum of 1-nitro-3-[(*E*)-2-nitrovinyl]benzene (**9f**)

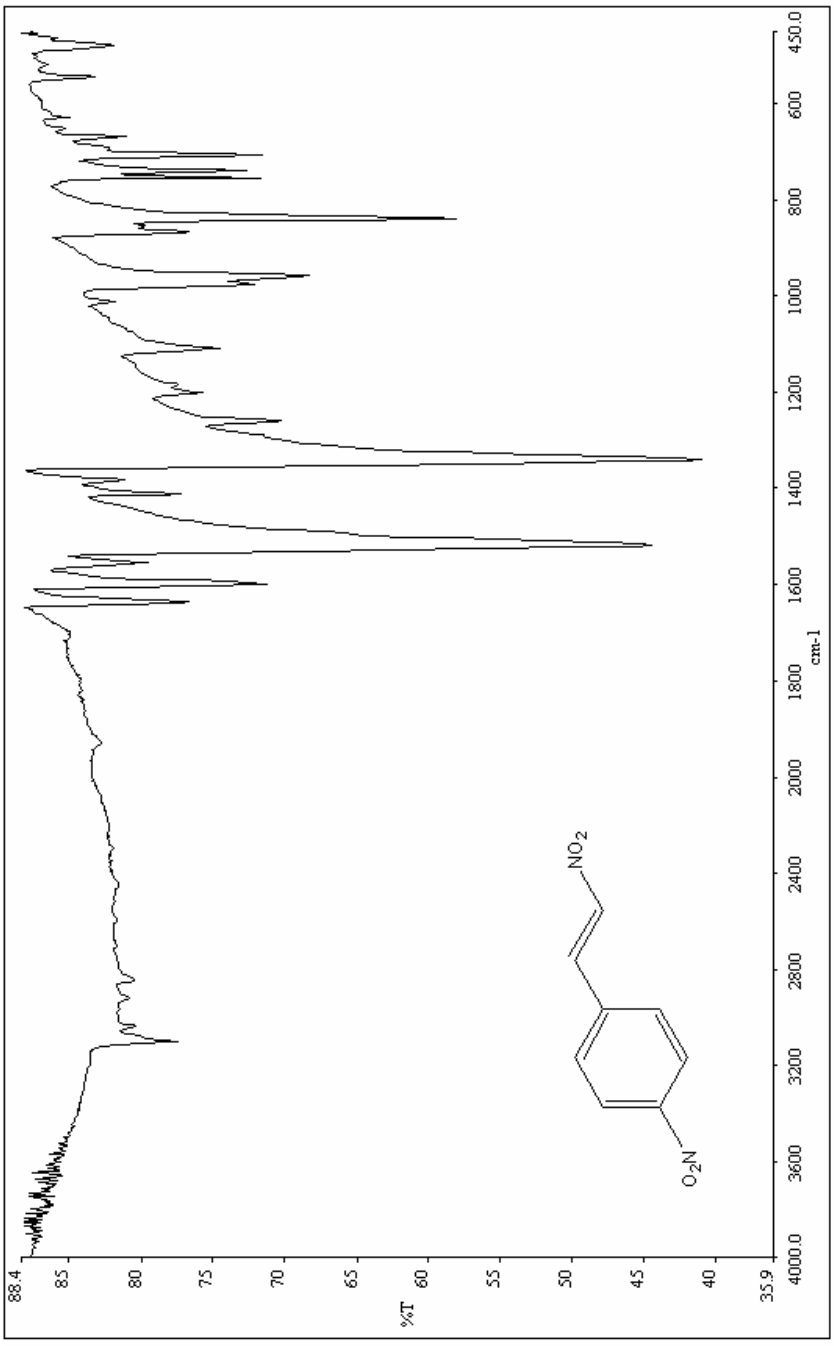


Figure C.1.7. IR spectrum of 1-nitro-4-[(*E*)-2-nitrovinyl]benzene (**9g**)

C.2. ^{1}H NMR spectra

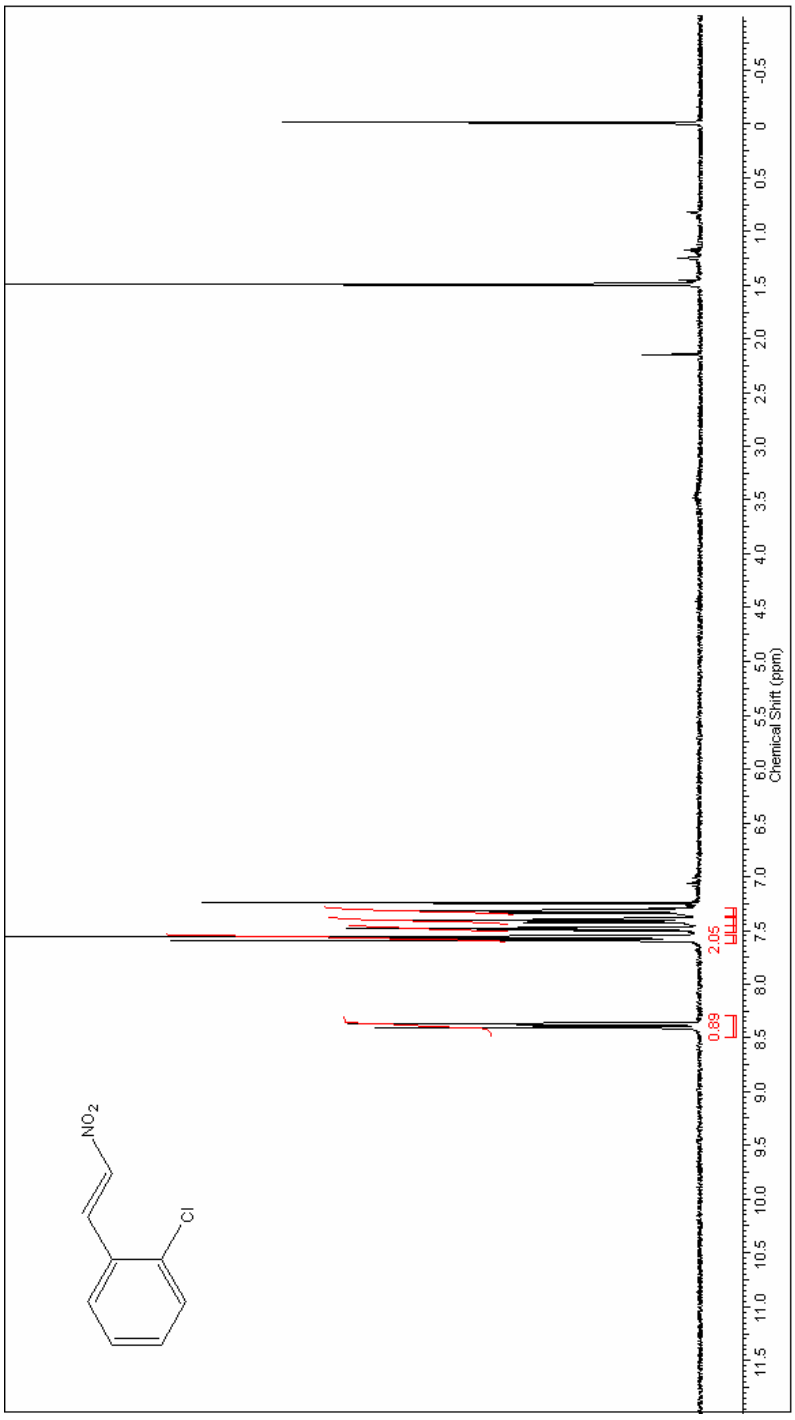


Figure C.2.1. ^{1}H NMR spectrum of 1-chloro-2-[(*E*)-2-nitrovinyl]benzene (**9a**)

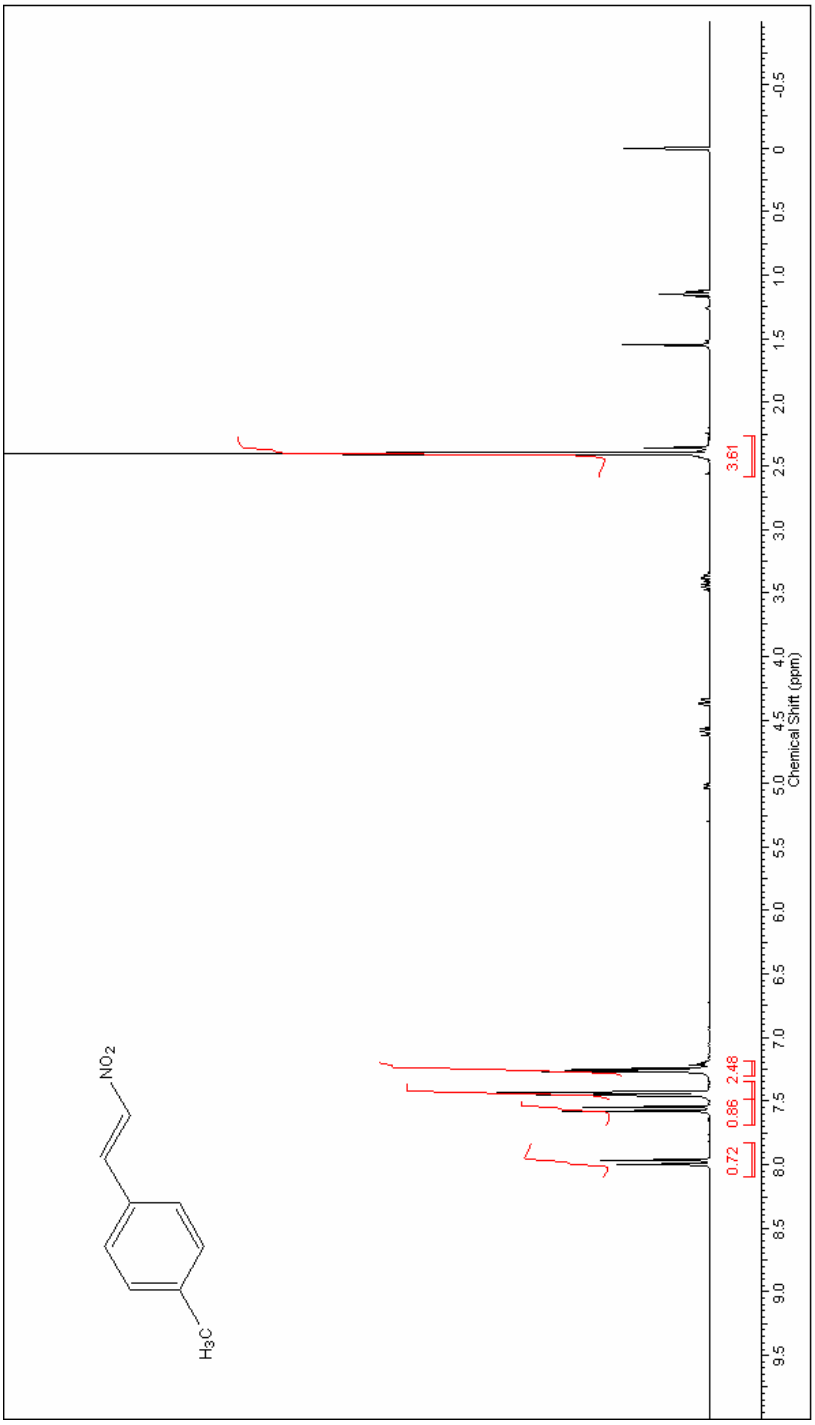


Figure C.2.2. ^{1}H NMR spectrum of 1-methyl-4-[(*E*)-2-nitrovinyl]benzene (**9b**)

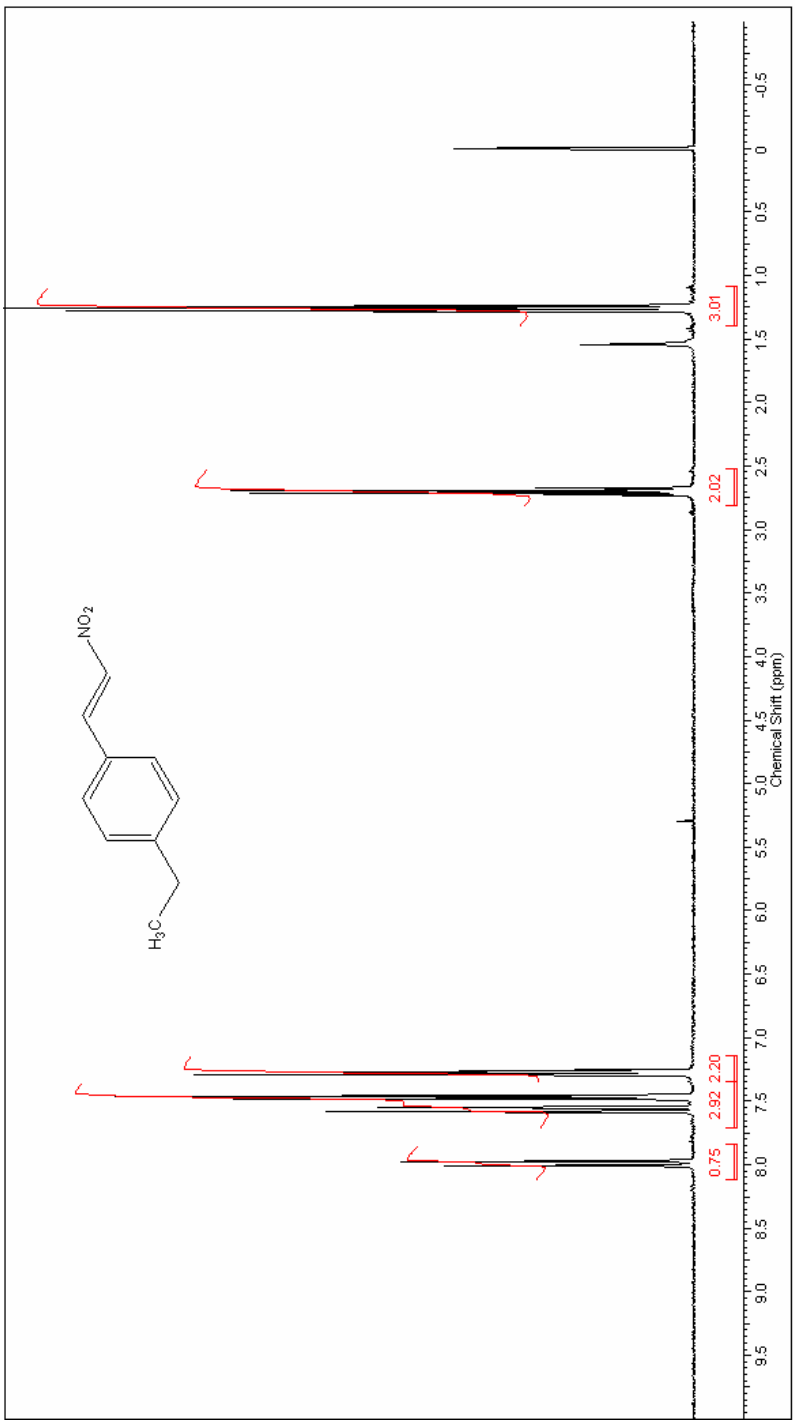


Figure C.2.3. ^{1}H NMR spectrum of 1-ethyl-4-[(*E*)-2-nitrovinyl]benzene (**9c**)

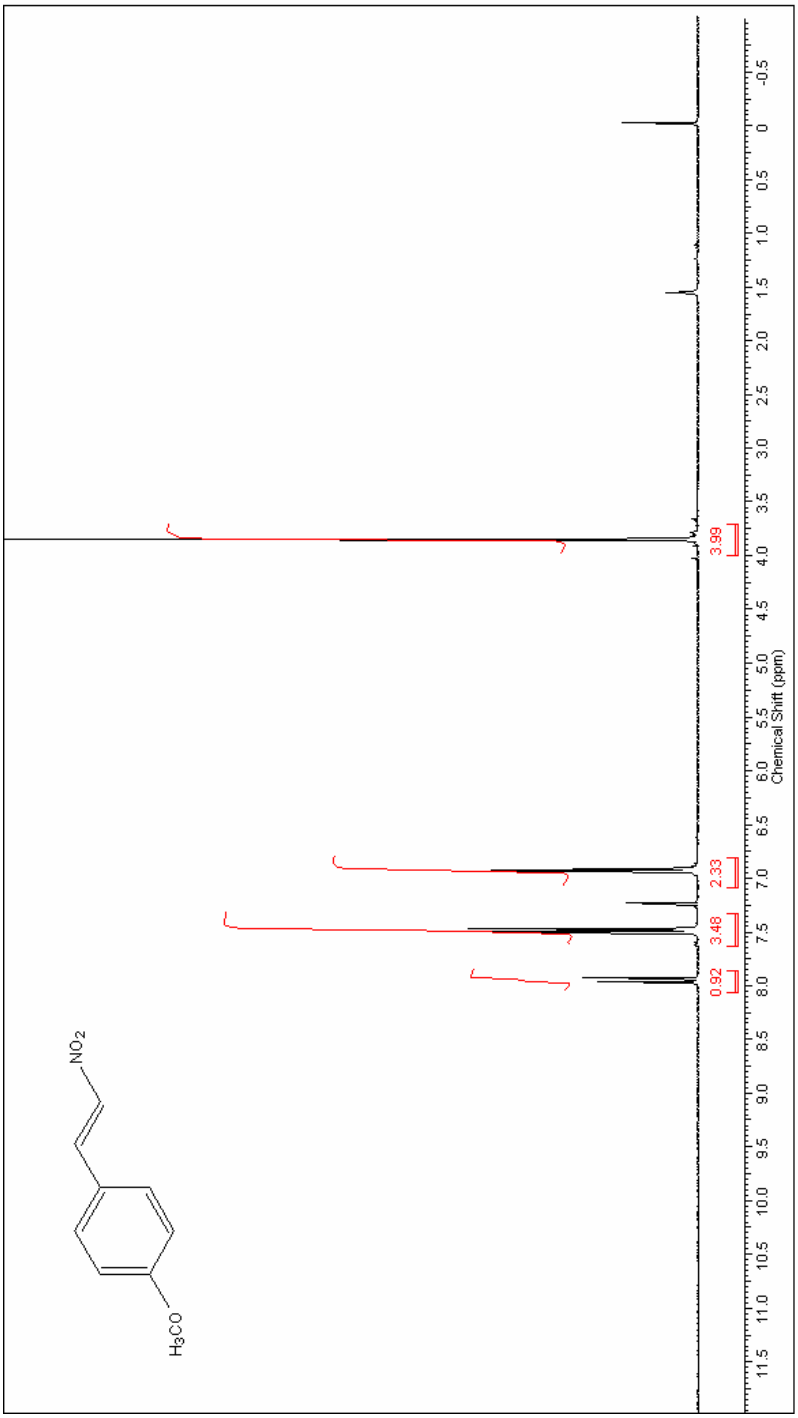


Figure C.2.4. ^{1}H NMR spectrum of 1-methoxy-4-[(*E*)-2-nitrovinyl]benzene (**9d**)

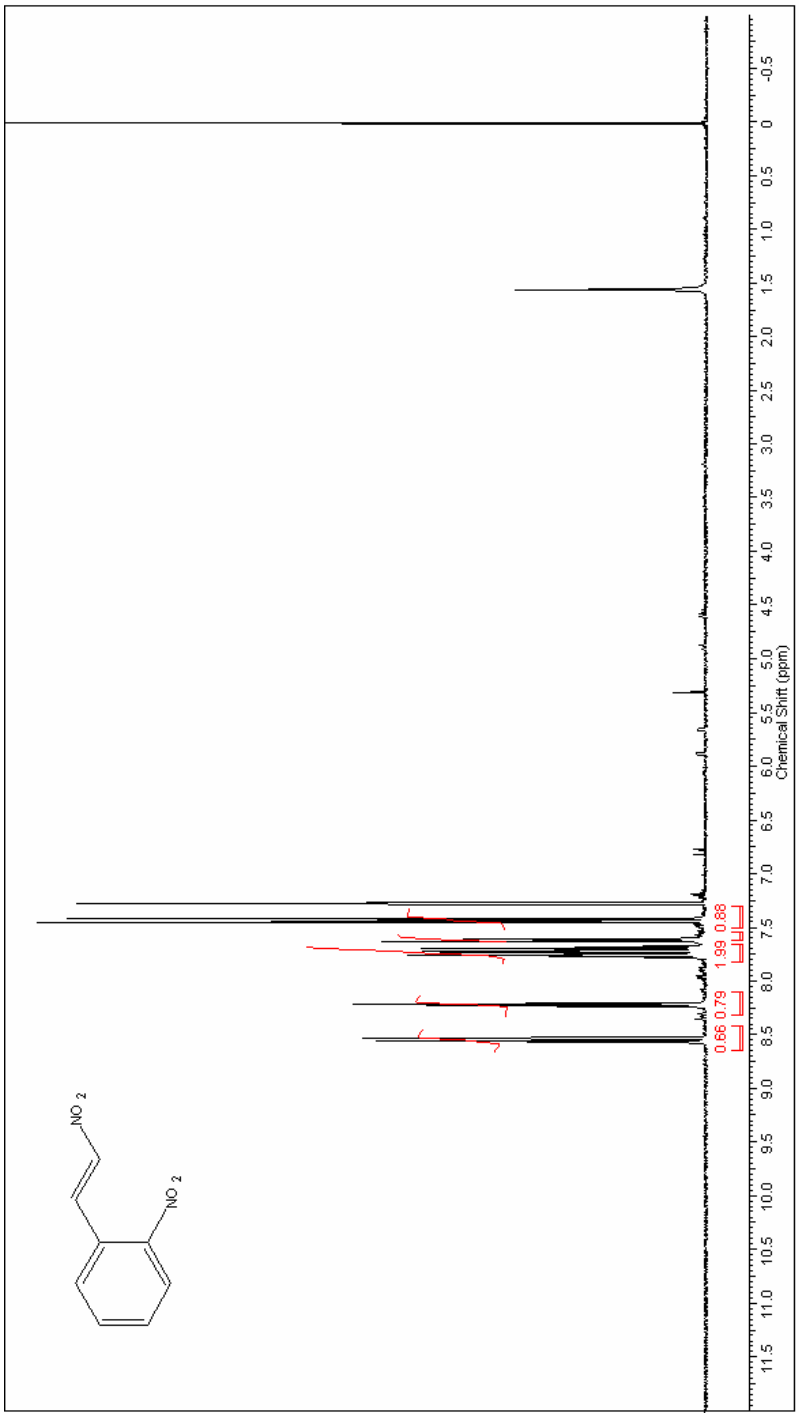


Figure C.2.5. ^{1}H NMR spectrum of 1-nitro-2-[(*E*)-2-nitrovinyl]benzene (**9e**)

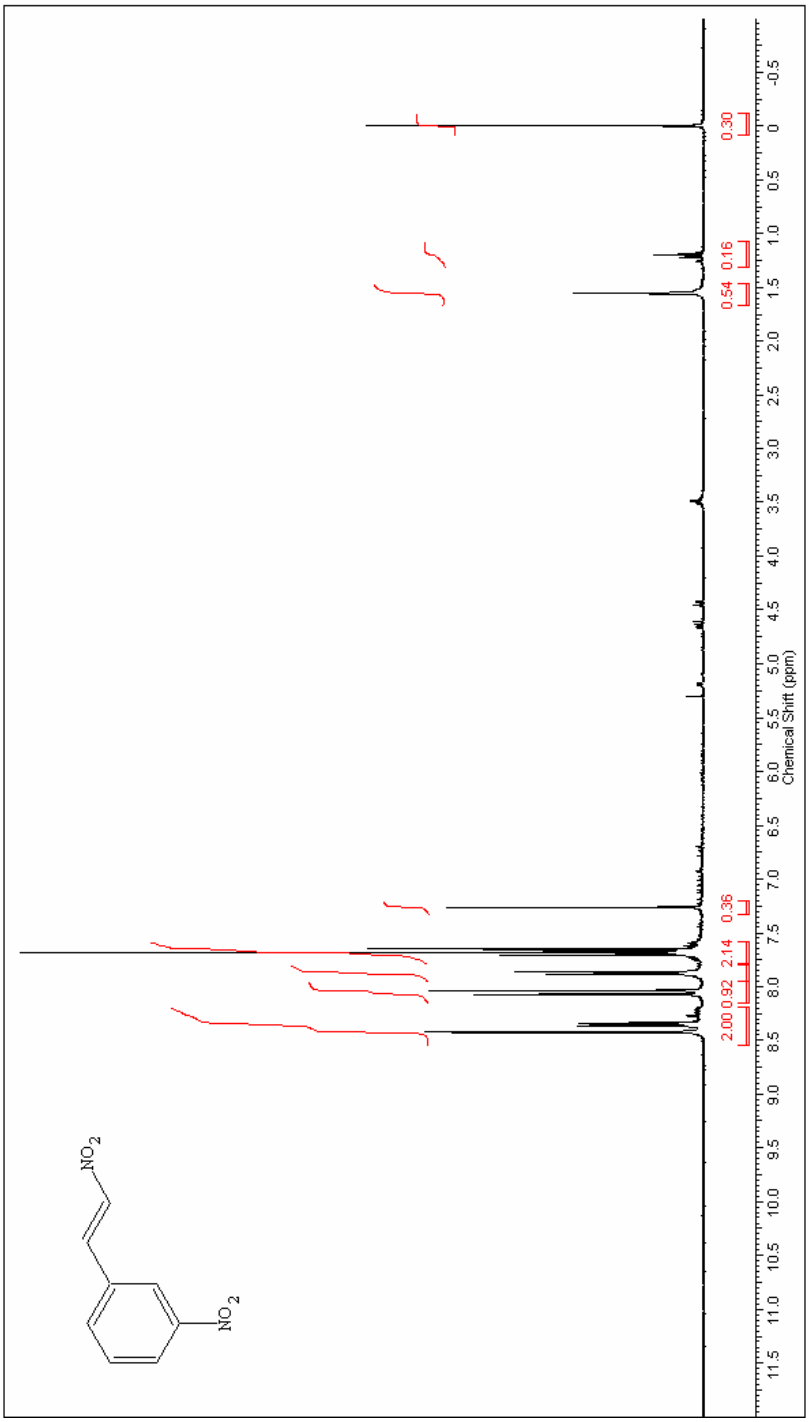


Figure C.2.6. ^{1}H NMR spectrum of 1-nitro-3-[(*E*)-2-nitrovinyl]benzene (**9f**)

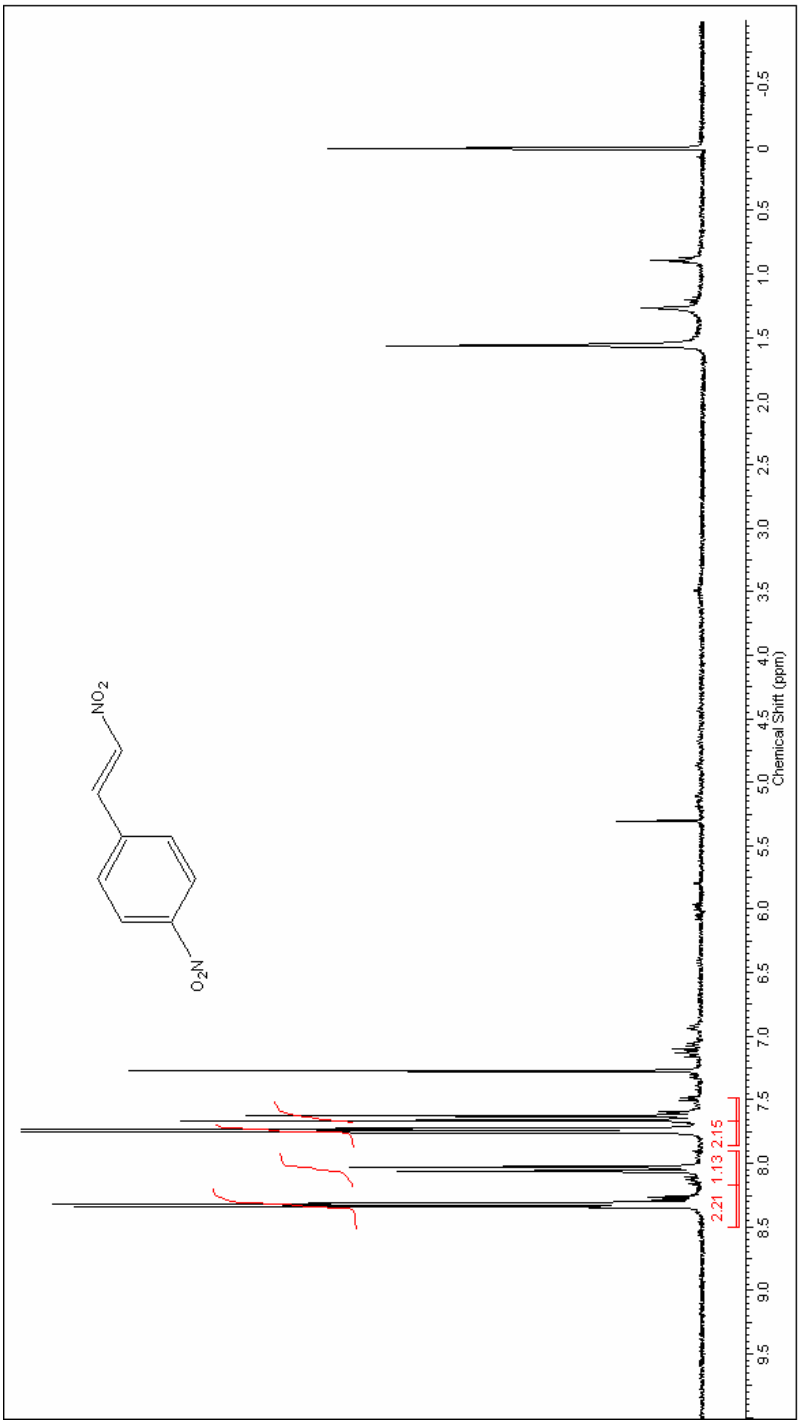


Figure C.2.7. ^{1}H NMR spectrum of 1-nitro-4-[(*E*)-2-nitrovinyl]benzene (**9g**)

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CURRICULUM VITAE

Leman KARADENİZ

Personal Information

1. Date / Place of Birth : 31.07.1979 - Eskişehir, TURKEY
2. Sex : Female
3. Nationality : Turkish

Education

2004 -	E.U. Institute of Natural and Applied Science, Izmir, TURKEY **Ph.D. in Organic Chemistry,** The subject of PhD. Thesis "Multifunctional Chiral Ligands. Synthesis and Applications for Asymmetric Synthesis"
2001-2004	E.U. Institute of Natural and Applied Science, Izmir, TURKEY **MSc. in Inorganic Chemistry,** The subject of MSc. Thesis "Ionic Pt(II) Complexes Containing The Bis(diphenylthiophosphinyl)methane"
1996 - 2000	E.U. Faculty of Science Chemistry Dept. Izmir, TURKEY **BSc. in Chemistry**

Publications

KARADENIZ, L.; KOZ, G.; AYDIN, K.; ASTLEY, S.T., "Co(III) Catalysed Asymmetric Ring Opening of Epichlorohydrin by Salicylaldehyde Derivatives: Reversal of Enantioselectivity and Rate Acceleration on Addition of $AlCl_3$", *Turkish Journal of Chemistry,* 34 (**2010**) 711 – 718.

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Projects

2007 –	**Ege University, Research Fund Accountancy**, 2007 / FEN / 044
2007 - 2008	**TUBITAK-TBAG** (107T254)
2003 - 2004	**TUBITAK-TBAG** (103T193)
2002 - 2004	**Ege University, Research Fund Accountancy**, 2002 / FEN / 010

Courses, Congress and Conferences

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XVII. National Congress on Chemistry, Alkan L., İrişli S., "Organofosfin Sülfür Ligandlı Pt(II) Kompleksleri", **2003**, İstanbul, TURKEY.

Interests Inorganic Chemistry, Organic Synthesis, Asymmetric Synthesis, Catalyst Design