DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR AMINOCYCLITOLS

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ZEYNEP EKMEKÇİ

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DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR AMINOCYCLITOLS

submitted by **ZEYNEP EKMEKÇİ** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. İlker Özkan
Head of Department, **Chemistry** _____

Prof. Dr. Metin Balcı
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Cihangir Tanyeli
Chemistry Dept., METU _____

Prof. Dr. Metin Balcı
Chemistry Dept., METU _____

Prof. Dr. Özdemir Doğan
Chemistry Dept., METU _____

Prof. Dr. Aliye Altundaş
Chemistry Dept., Gazi University _____

Prof. Dr. Canan Ünaleroğlu
Chemistry Dept., Hacettepe University _____

Date: 01.12.2011

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last Name: ZEYNEP EKMEKÇİ

Signature :

ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR AMINOCYCLITOLS

Ekmekçi, Zeynep

Ph.D., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

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Aminocyclitols are cyclitols in which at least one of the hydroxyl groups is exchanged with an amino functional group. In turn, they constitute a wide group of natural products with interesting biological properties and are widely distributed throughout. In particular, antibiotics containing an aminocyclitol unit have stimulated the development of synthetic methodologies in the search for analogues with enhanced pharmacological profiles.

In this study, three different methods were applied to synthesize diaminoconduritol derivative **202**. In the first method, 1,2,3,6-tetraphthalic anhydrate (**196**), derived from Diels-Alder reaction between of maleic anhydride and 3-sulfolene, was used as a starting compound. Starting with the opening of anhydride group with trimethyl silylazide, tetrazolinone derivative **205** instead of bisamino cyclohexane derivative **201** was obtained.

In the second method, we started the synthesis of target compound **202** by the Birch reduction of benzene. Lactame **218** was synthesized as a key compound. Functionalization of lactame **218** was started with the cleavage of bond between nitrogen and carbonyl group in **218**. At the end of the method, imidazole derivative **215** was obtained instead of target compound **202**.

Diaminoconduritol **242** was synthesized successfully by bishydrazide method. In this strategy, 1,2,3,6-tetraphthalic anhydrate (**196**) was used as a starting material. After conversion of bisurethane **223** to acylazide derivative **230**, Curtius degradation and phtooxygenation reactions were used to introduce the amine and oxygen functionalities into the cyclohexene ring.

Key words: Aminocyclitols, aminoconduritols, diaminoconduritols, Curtius rearrangement, photooxygenation reaction.

ÖZ

AMİNOSİKLİTOLLERİN SENTEZİ İÇİN YENİ YÖNTEMLERİN GELİŞTİRİLMESİ

Ekmekçi, Zeynep

Doktora, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Aralık 2011, 128 sayfa

Aminosiklitoller hidroksil gruplarından en az birisinin amino grubu ile değiştirilmiş olan siklitollerdir. Bu tür bileşikler doğada yaygın bir şekilde bulunan ve ilginç biyolojik aktivite gösteren bileşiklerin bir parçasıdır. Özellikle bazı antibiyotiklerde aminosiklitol gruplarının bulunması, yeni sentetik yöntemlerin geliştirilmesini ve daha etkin ilaç hammaddesi olabilecek analogların sentezini olumlu yönde etkilemiştir.

Bu çalışmada, diaminoconduritol türevi **202** nin sentezi için üç farklı metot denendi. İlk metotta, maleik anhidrit ve 3-sülfolen in Diels-Alder reaksiyonu ile elde edilen 1,2,3,6-tetrahidrofitalik anhidrit (**196**) başlangıç maddesi olarak kullanıldı. Trimetilsilylazide ile anhidrit grubunun açılması ile başlayan bu metotta molekül **201** yerine tetrazolinone türevi **205** elde edildi.

İkinci metotta, hedef molekül **202** nin sentezine benzen in Birch indirgenmesi ile başlandı. Lactame **218**, anahtar molekül olarak sentezlendi. Bu molekülde

bulunan nitrojen ve karbonil arasındaki bağın kırılması ile lactam **218** in fonksiyonlandırılmasına başlandı. Bu metodun sonunda hedef molekül **202** yerine imidazole türevi **215** elde edildi.

Bishidrazide metodu ile diaminokonduritol **202** başarılı bir şekilde sentezlendi. Bu stratejide, 1,2,3,6-tetrahidrofitalik anhidrit (**196**) başlangıç maddesi olarak kullanıldı. Bisürethan **223** ün asilazide **230** a dönüştürülmesinden sonra Curtius düzenlenmesi ve fotooksijenasyon reaksiyonları amin ve hidroksil gruplarının moleküle takılmasında kullanıldı.

Anahtar Kelimeler: Aminosiklitoller, aminokonduritoller, diaminokonduritoller, Curtius düzenlemesi, fotooksijenasyon reaksiyonu.

To my lovely husband, Evren

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Finally but not lastly, I want to express my thanks to my husband Evren for him support, confidence and encouragement that make this work possible.

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SCHEMES

LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
br	Broad
^{o}C	Degrees Celsius
COSY	Correlation Spectroscopy
δ	Chemical shift in parts per million
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DEPT	Distortionless enhancement by polarization transfer
DEAD	Diethyl azodicarboxylate
d	Doublet
dd	Doublet of doublets
FT	Fourier transforms
HETCOR	Heteronuclear correlation spectroscopy
HMBC	Heteronuclear multi bond correlation
HMQC	Heteronuclear multi quantum correlation
HOMO	Highest occupied molecular orbital
Hz	Hertz
LUMO	Lowest unoccupied molecular orbital
IR	Infrared
J	Coupling constant
m	Multiplet
m-CPBA	*m*-chloroperoxybenzoic acid
NMO	N-methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
MOMCl	Methoxymethyl chloride
ppm	Parts per million
q	Quartet

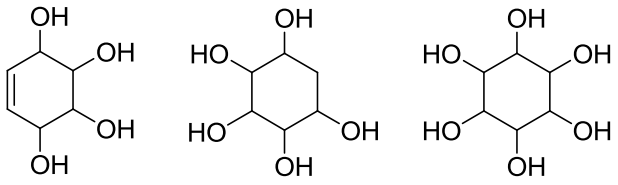
s	Singlet
t	Triplet
TMS	Tetramethylsilane
TMSA	Trimethyl silyl azide
TPP	Tetraphenlyporphyrine

CHAPTER 1

INTRODUCTION

1.1 Cyclitols

Cyclic compounds containing at least three hydroxyl groups in their skeleton and each of hydroxyl groups attaches to different C atoms in the ring system are named as cyclitols [1, 2]. The compounds have been attracting great attention of the synthetic community because of their biological properties and therapeutic potential. Especially, they act as inhibitors of glycosidases enzyme having a potential for treatment of various disorders and diseases such as diabetes, viral or bacterial infection and cancer [3]. Conduritols (**1**), quercitols (**2**) and inositols (**3**) are the most common types of cyclitols. Figure 1.1 depicts their structures.



1 **2** **3**

Figure 1.1 The structures of conduritol, quercitol and inositol, respectively.

1.2 Conduritols

One of the important classes of cyclitols is conduritol (**1**). Its general skeleton consist of cyclohex-5-ene-1,2,3,4-tetrol and it was first isolated from the bark of the vine *Marsdenia condurango* in 1908 by Kubler [4]. After 30 years, Dangschat and Fischer established its constitution and configuration to be conduritol-A (**4**) [5].

Six diastereisomers of conduritols were labeled as A-F to avoid ambiguity [6]. Figure 1.2 shows the structures of them.

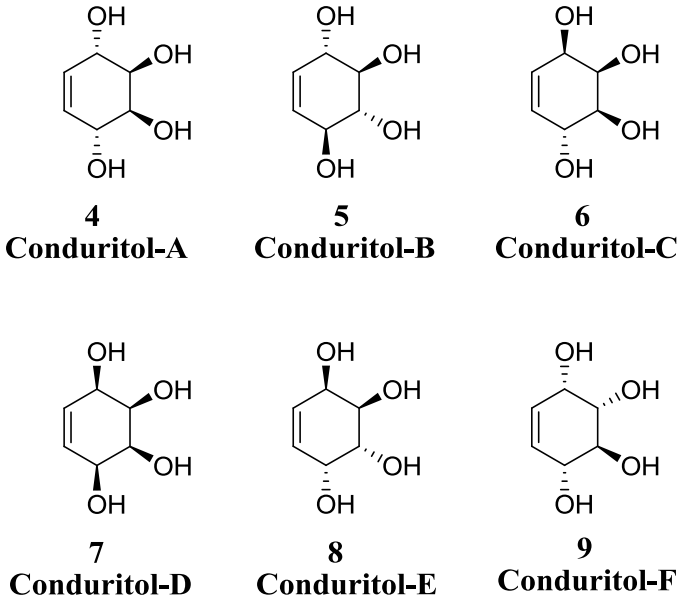


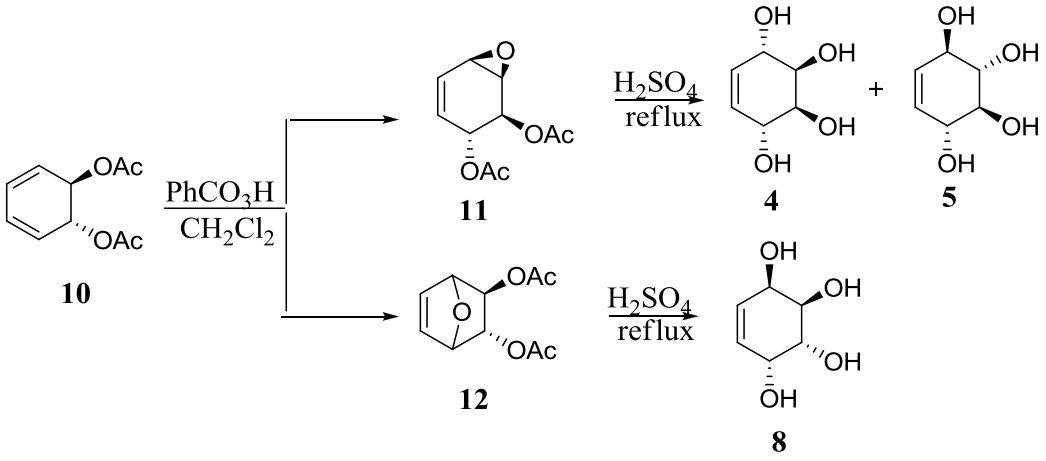
Figure 1.2 The structures of six diastereomers

1.2.1 Synthesis of conduritols

1.2.1.1 Conduritol-A

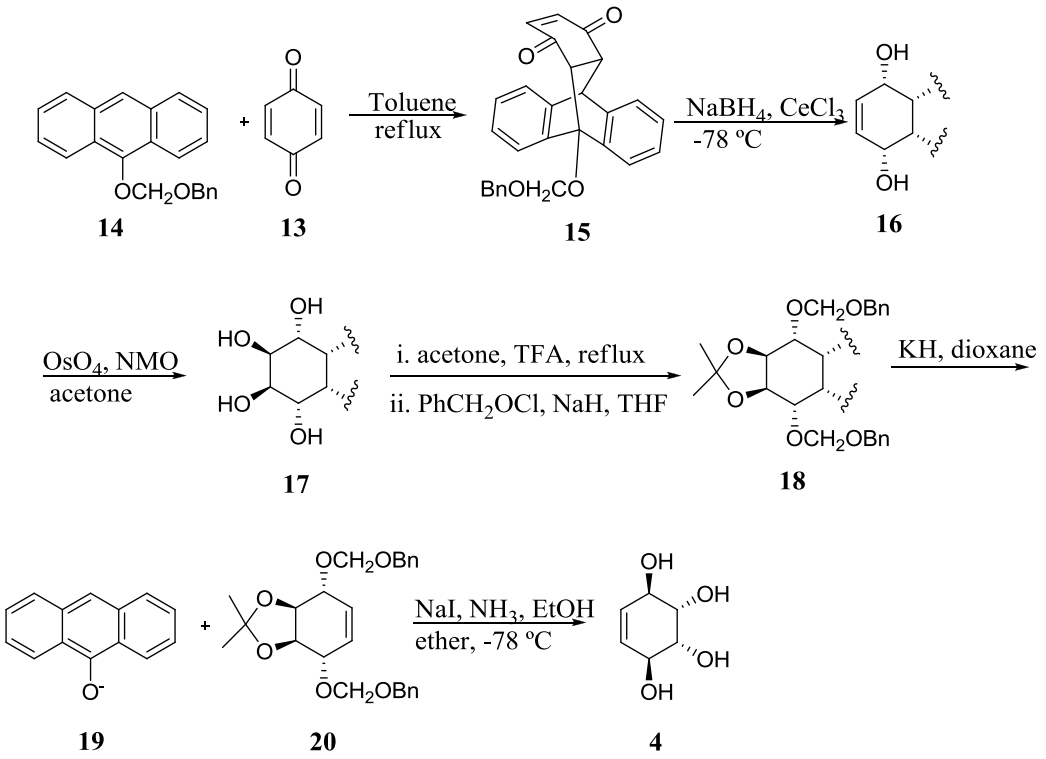
Only conduritol-A and conduritol-F have been found in nature. Many synthetic methodologies have been described in the literature. Some of them are given below in a chronological order.

In 1957, Nakajima *et al*. first succeeded to synthesize conduritol-A (**4**) in non-stereospecific way by starting with oxidation of diacetate **10** with perbenzoic acid. The mixture of **11** and **12** obtained at the end of the reaction was hydrolyzed in acidic medium to give conduritol-A (**4**), conduritol-B (**5**) and conduritol-E (**8**) [7] (Scheme 1).



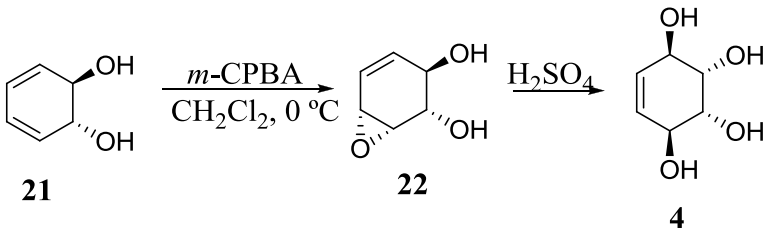
Scheme 1 The synthesis of conduritol-A (**4**), conduritol-B (**5**), conduritol E(**8**)

In 1983, Knapp *et al*. first performed stereospecific synthesis of conduritol-A by starting with protection of *p*-benzoquinone (**13**) with anthracene derivative **14**. After *cis*-reduction of ketone groups followed by *cis*-diol functionalization of double bond, conduritol-A (**4**) was obtained [8] (Scheme 2).



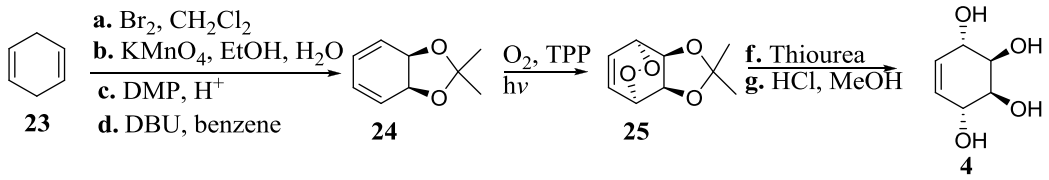
Scheme 2 The synthesis of conduritol-A (**4**), conduritol-B (**5**)

In 1985, Berchold *et al.* epoxidized diene derivative **21** with *m*-CPBA and hydrolysis of epoxide **22** to afforded conduritol-A (**4**) [9] (Scheme 3).



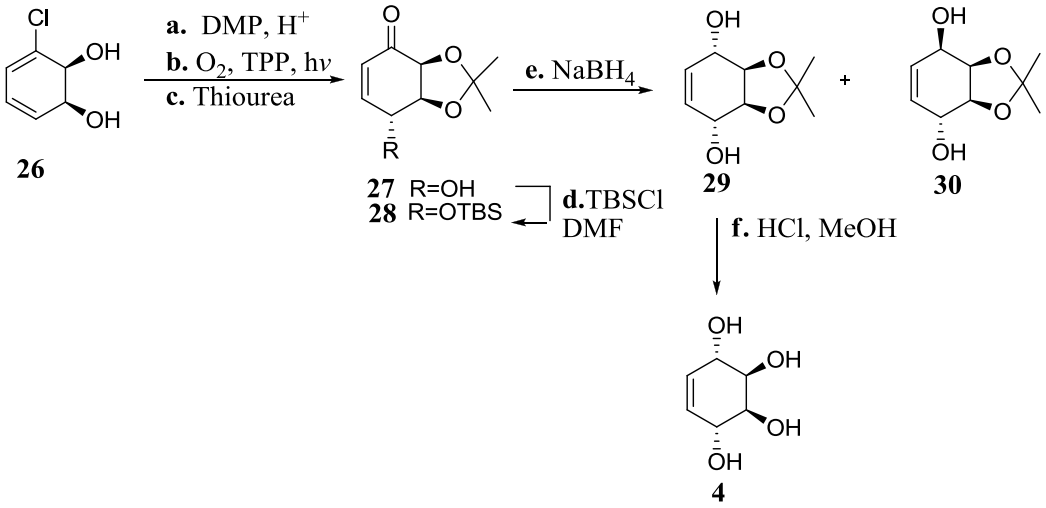
Scheme 3 The synthesis of conduritol-A (**4**)

In 1988, Balci *et al*. developed a new stereospecific synthetic strategy for conduritol-A (**4**) [10]. It was started with oxidation of 1,4-cyclohexadiene (**23**) followed by protection of hydroxyl groups with 2,2-dimethoxypropane to give acetonide **24**. To functionalize C1 and C4 positions with hydroxyl group, the diene moiety in **24** was submitted to photooxgenation reaction followed by cleavage of the peroxide-bond in **25** to give conduritol-A (**4**) (Scheme 4).



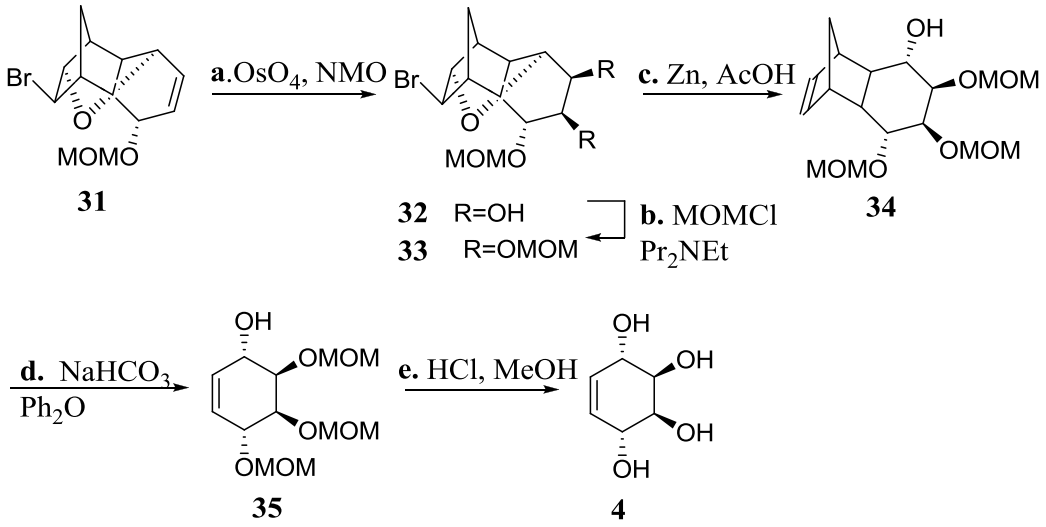
Scheme 4 The synthesis of conduritol-A **(4)**

In 1991, Hudlicky *et al*. performed a chemoenzymatic synthetic method for conduritol-A (**4**) [11]. They started with protection of *cis*-diol **26**. Singlet oxygen addition and cleavage of peroxide linkage were performed to obtain compound **27**, respectively. Hydroxyl group in **27** was protected with *tert*-butyldimethylsilane (TBS). After the protection, reduction of carbonyl group in **28** with sodium borohydrate gave a mixture of alcohols **29** and **30**. To obtain conduritol-A (**4**), isomer **29** was hydrolyzed under acidic condition (Scheme 5).



Scheme 5 The synthesis of conduritol-A (**4**)

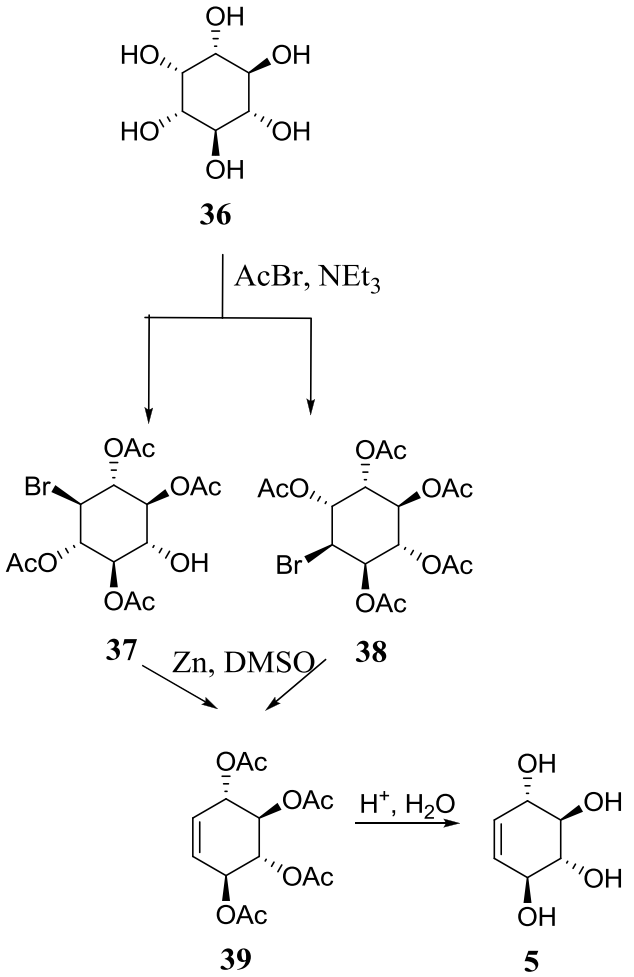
In 1999, Ogasawara *et al*. described the synthesis of all six conduritol isomers by using Diels Alder reaction [12]. After hydroxylation of **31** with OsO_4, hydroxyl groups in **32** were protected as MOM-ethers. To obtain conduritol-A (**4**), reductive cleavage of bridged system in **33** and deprotection of hydroxyl groups in **35** were performed (Scheme 6).



Scheme 6 The synthesis of conduritol-A (**4**)

1.2.1.2. Conduritol-B

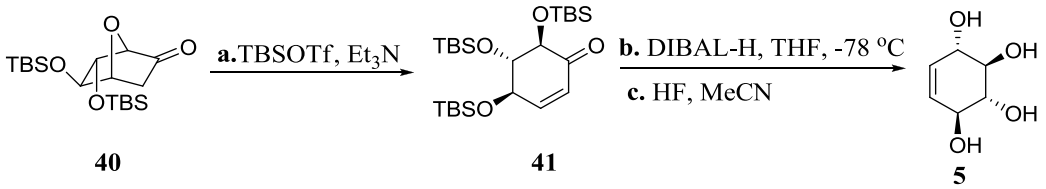
In 1953, McCasland and Horswill developed a synthetic method to obtain conduritol-B (**5**) in three steps starting from *myo*-inositol (**36**) [13]. Two bromoquercitol derivatives **37** and **38**, produced from *myo*-inositol (**36**) were converted to conduritol-B (**5**) by debromination and deacetylation reactions, respectively (Scheme 7).



Scheme 7 The synthesis of conduritol-B (**5**)

In 1957, Nakajima *et al*. synthesized conduritol-B (**5**) in a mixture of conduritol-A (**4**) and conduritol-E (**8**) [7] as shown in Scheme 1.

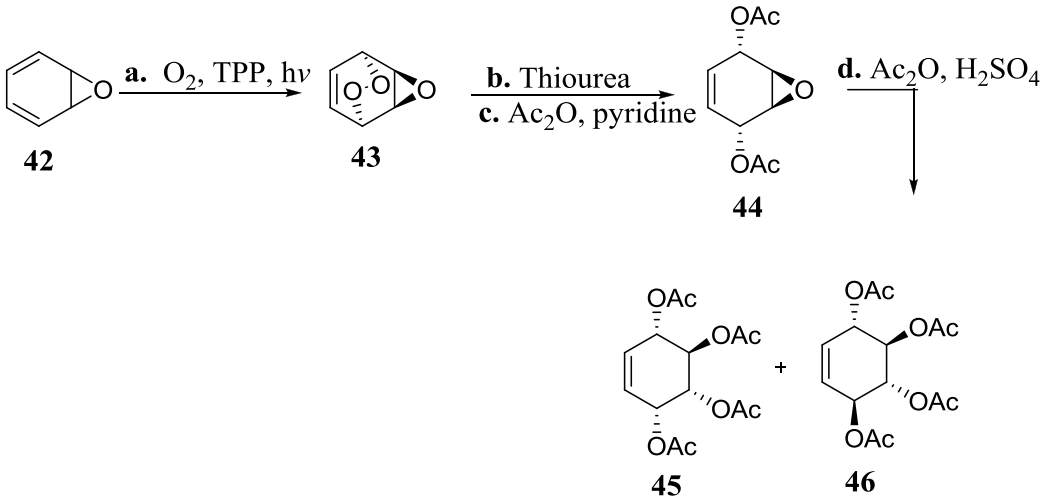
In 1989, Vogel *et al*. reported the enantioselective synthesis of (-)-conduritol-B (**5**) [14]. In the first step, ring opening of oxygen bridge in bicyclic system **40** was performed by *tert*-buthylsilyl triflate. The formed compound **41** was converted to conduritol-B (**5**) by reduction of enone **41** and deprotection of *tert*-butylsilyl groups (Scheme 8).



40 **41** **5**

Scheme 8 The synthesis of conduritol-B (**5**)

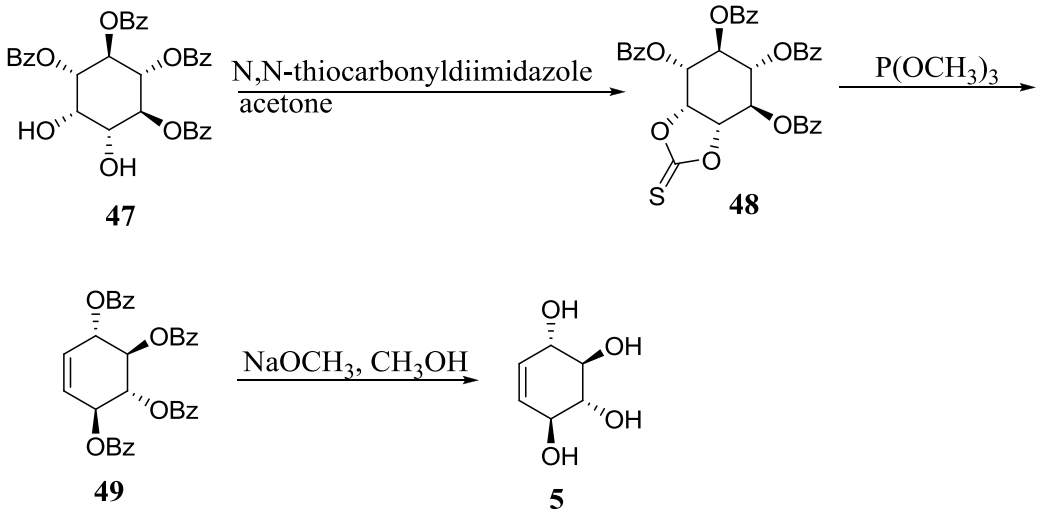
In 1990, Balci *et al.* synthesized protected conduritol-B (**46**) by [4+2] cycloaddition of singlet oxygen to benzene-oxide **42** [15]. It was followed by thiourea reduction of peroxide linkage followed by acylation of the formed diols. The ring opening of epoxide under acidic condition afforded a mixture of tetraacetated conduritol-F (**45**) and conduritol-B (**46**) (Scheme 9).



42 **43** **44** **45** **46**

Scheme 9 The synthesis of conduritol-F **(45)** and conduritol-B **(46)**

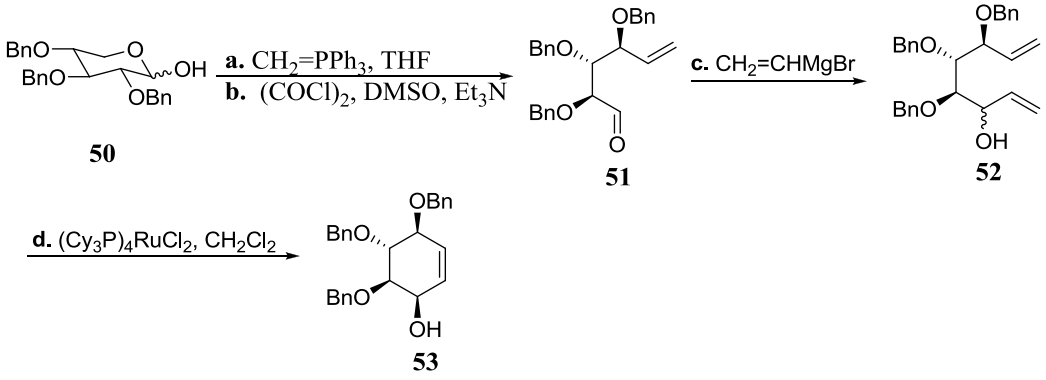
In 1993, Ozaki *et al*. performed the first synthesis of (+)-conduritol-B (**5**) [16]. Starting compound **47**, derived from L-Quebrachitol was transferred to thiocarbonate **48** with N,N-thiocarbonyldiimidazole. After treatment with trimethyl phosphite, protected conduritol **49** was obtained, which was converted to conduritol-B (**5**) by deprotection of benzylic groups (Scheme 10).



Scheme 10 The synthesis of conduritol-B (**5**)

In 1997, Ley *et al*. reported to a new synthesis method for (+)-conduritol-B starting from a *myo*-inositol derivative [17].

In 1999, Kornienko and D`Alarcao described a different approach for the synthesis of protected conduritol-B derivative (**53**) [18]. Treatment of starting material **50** with Wittig reagent followed by subsequent oxidation gave enal **51**. Diasteriomeric alcohols mixture **52** was obtained by Grignard reaction of compound **51**. After successful separation of the alcohols, they were subjected to metathesis reaction to obtain conduritol-B derivative **53** (Scheme 11).



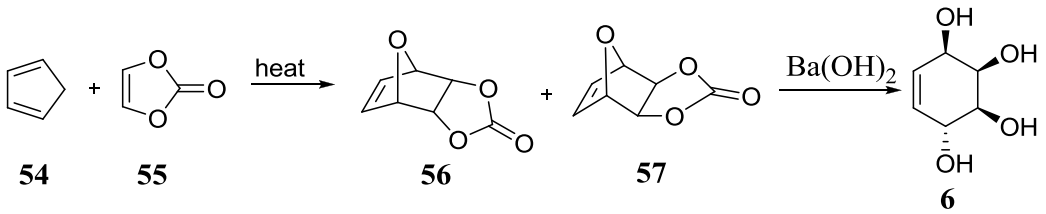
50 **51** **52** **53**

Scheme 11 The synthesis of conduritol-B derivative **53**

1.2.1.3 Conduritol-C

In 1955, McCasland *et al*. first synthesized conduritol-C (**6**) starting from *epi*-inositol in a similar method used in the synthesis of conduritol-B (**5**) [19]. Scheme 7 depicts the pathway.

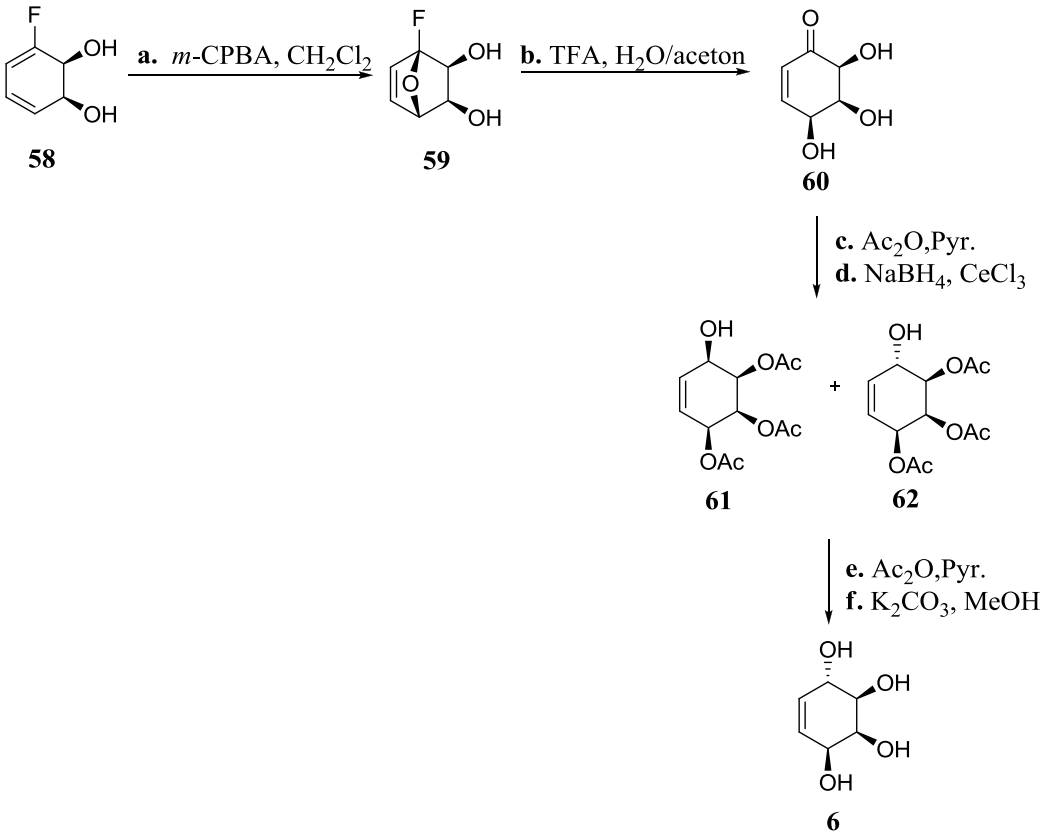
In 1961, Yurey *et al*. developed a stereospecific method for synthesis of conduritol-C (**6**) [20]. They started with a simple Diels-Alder reaction of furan (**54**) and ethylene carbonate (**55**) and obtained a mixture of *endo*-**56** and *exo*-**57**. By means of cleavage of the carbonate in basic condition, conduritol-C (**6**) was obtained (Scheme 12).



54 **55** **56** **57** **6**

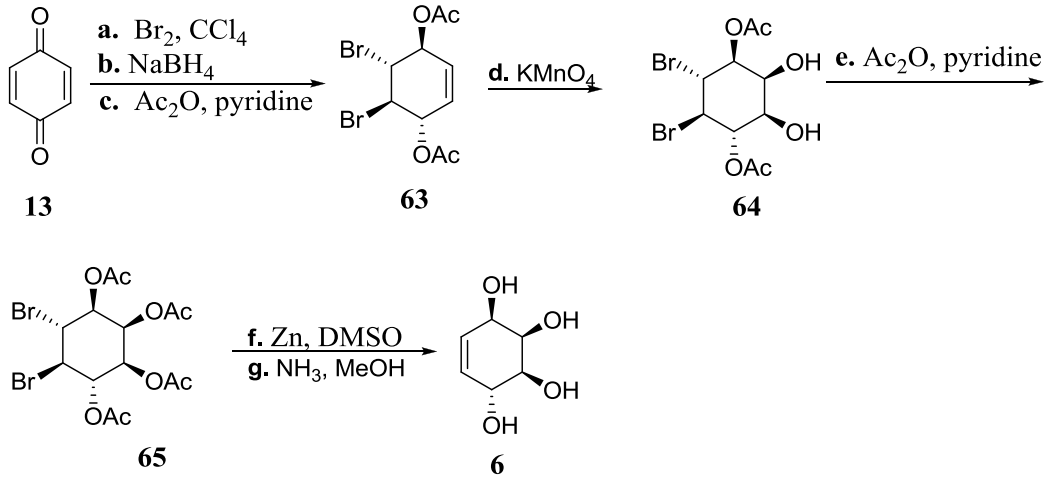
Scheme 12 The synthesis of conduritol-C (**6**)

In 1991, Carless *et al*. first synthesized (+)-conduritol-C (**6**) starting with epoxidation of chiral compound **58** in the presence of buffer solution of Na_2CO_3 to form epoxide **59** [21]. After conversion of epoxide to triol **60**, acetylation followed by Luche reduction resulted in a mixture of conduritol-C **61** and conduritol-D **62** derivatives. Conduritol-C (**6**) was afforded with deprotection of acetyl groups (Scheme 13).



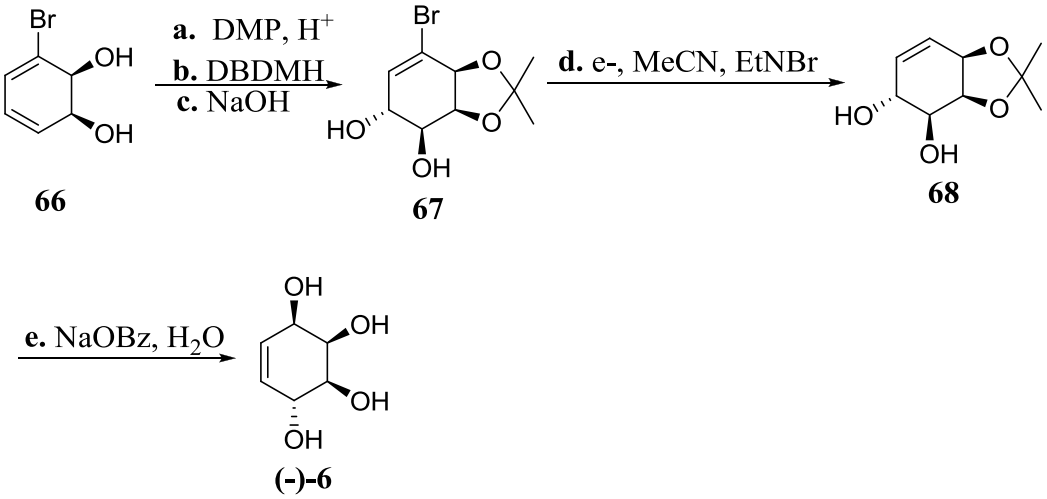
Scheme 13 The synthesis of conduritol-C (**6**)

In 1992, Balci *et al*. described a new method for the conduritol-C (**6**) [22]. Benzoquinone (**13**) was converted to *trans*-hydroxyl compound **63** by reduction of carbonyl groups followed by bromination. Treatment of **63** with $KMnO_4$ resulted in *cis*-diol derivative **64**. After protection of the hydroxyl groups, reductive elimination followed by deprotection of acetyl groups in basic condition, compound **65** was transferred to conduritol-C (**6**) (Scheme 14).



Scheme 14 The synthesis of conduritol-C (**6**)

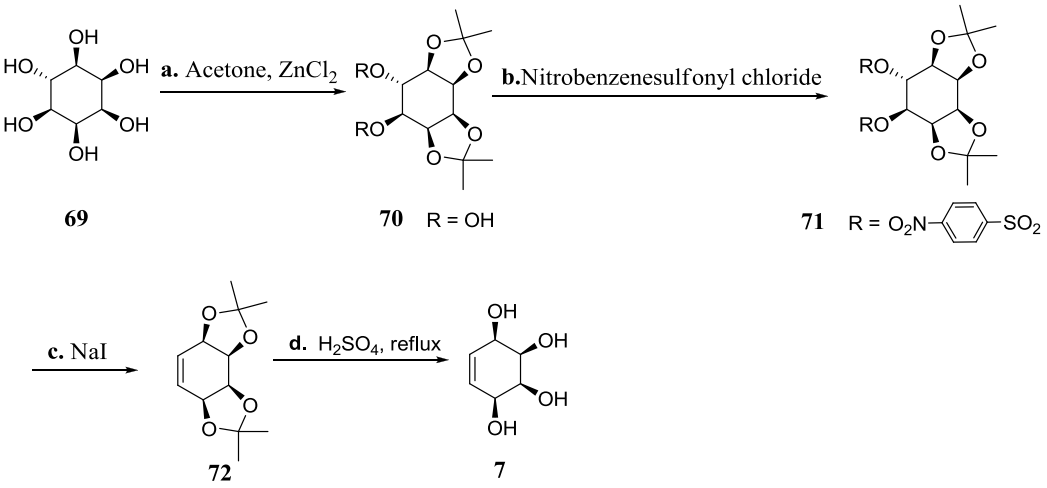
In 1999, Hudlicky *et al*. reported a new approach for conduritol-C (**6**) [23]. *cis*-Diol derivative **66** was protected as its ketal and subsequent hydroxylation of one of the double bonds formed compound **67**. By means of electrochemical reduction followed by deprotection of acetyl groups, compound **67** was converted to conduritol-C (**6**) (Scheme 15).



Scheme 15 The synthesis of conduritol-C (**6**)

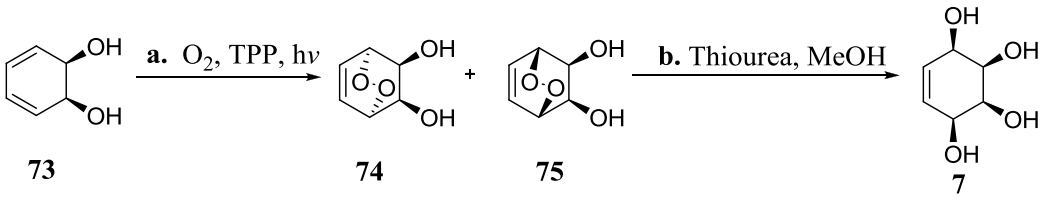
1.2.1.4. Conduritol-D

In 1955, Angyal *et al.* published the first synthesis of conduritol-D (**7**) [24]. They used *epi*-inositol (**69**) as the starting material. The synthesis was started with transforming of four *cis*-diols in **69** to diacetonide **70**. *trans*-Diol groups in **70** were protected with nitrobenzenesulfonyl group. Elimination of sulfoxide groups was performed in the presenceof NaI at the high temperature. Conduritol-D (**7**) was obtained by hydrolysis of protecting groups in **72** (Scheme 16).



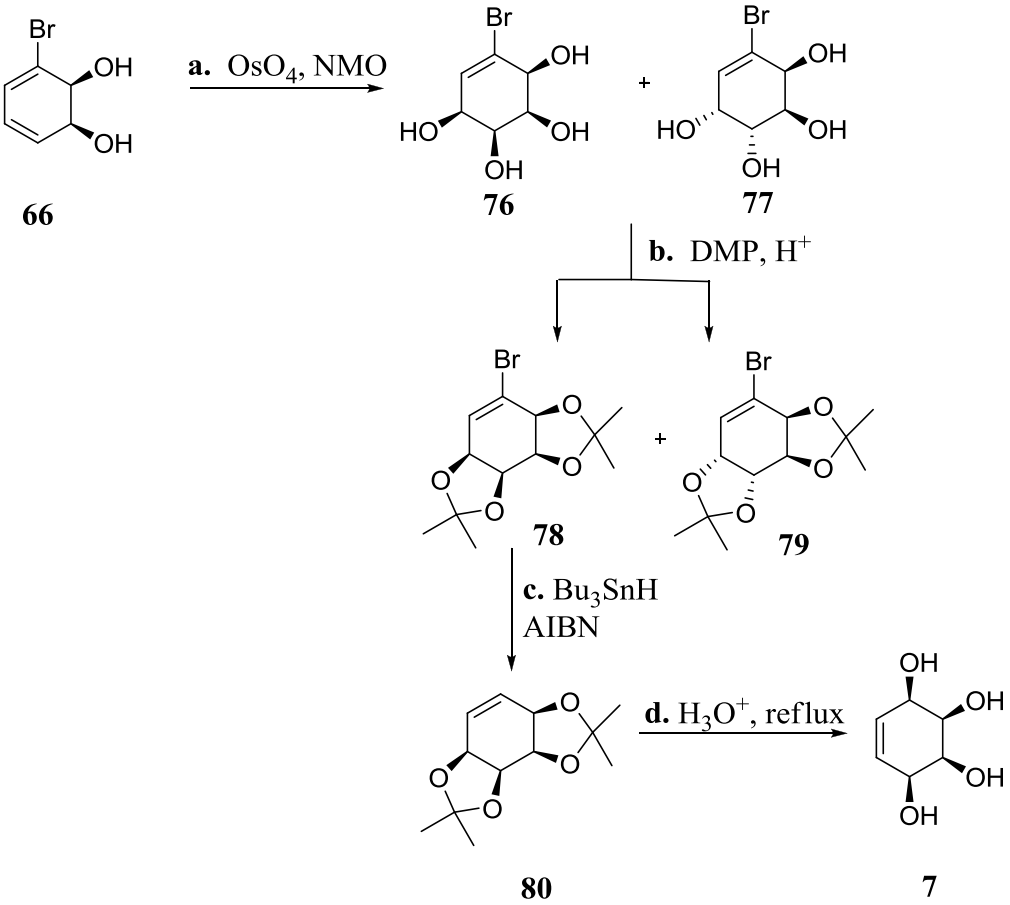
Scheme 16 The synthesis of conduritol-D (**7**)

In 1989, Carless *et al.* described a chemoenzymatic method leading to the synthesis of conduritol-D (**7**) [25]. Singlet-oxygen addition to *syn*-benzene diol (**73**) gave a mixture of bicyclic endoperoxide **74** and **75**. By cleavage of peroxide linkage in **75**, conduritol- D (**7**) was obtained (Scheme 17).



Scheme 17 The synthesis of conduritol-D (**7**)

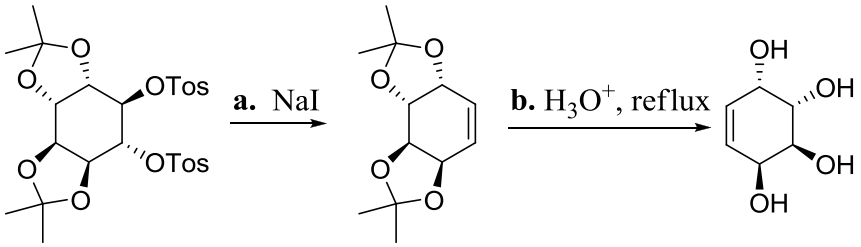
In 1997, Donohoe *et al*. found a simple method for conduritol-D (**7**) [26]. A mixture of acetonides **78** and **79** was synthesized by protection of tetrols **76** and **77** formed by hydroxylation of compound **66**. After separation of these isomers, reductive elimination of bromine atom in **78** with tri-n-butyltin hydride followed by deprotection of acethyl groups provided conduritol-D (**7**) (Scheme 18).



Scheme 18 The synthesis of conduritol-D (**7**)

1.2.1.5 Conduritol-E

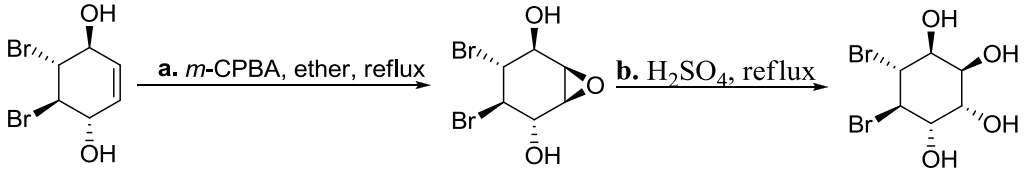
In 1955, Angyal *et al.* described the first stereospecific synthesis of conduritol-E (**8**). The route was similar to the synthesis of conduritol-D (**7**) [24]. Compound **81** was converted to conduritol-E (**8**) by treatment of **81** with sodium iodide followed by hydrolysis (Scheme 19).



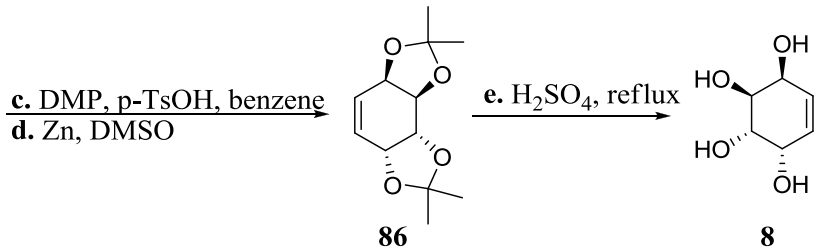
81 **82** **8**

Scheme 19 The synthesis of conduritol-E (**8**)

In 1992, Balci *et al*. developed a new synthetic method for conduritol-E (**8**) starting from epoxidation of compound **83** [27]. Treatment of tetrol derivative **85** with 2,2-Dimethoxypropane in acidic medium followed by reductive elimination of bromine atoms and removal of protecting groups in acidic medium formed conduritol-E (**8**) (Scheme 20).



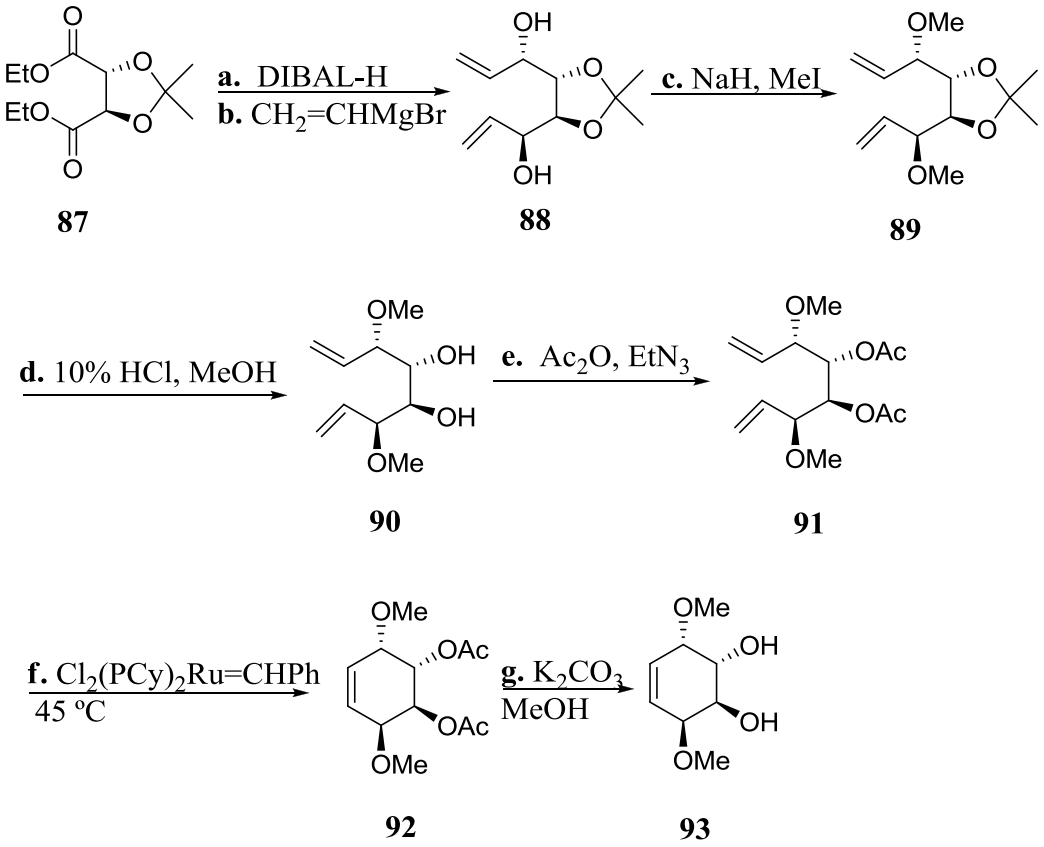
83 **84** **85**



86 **8**

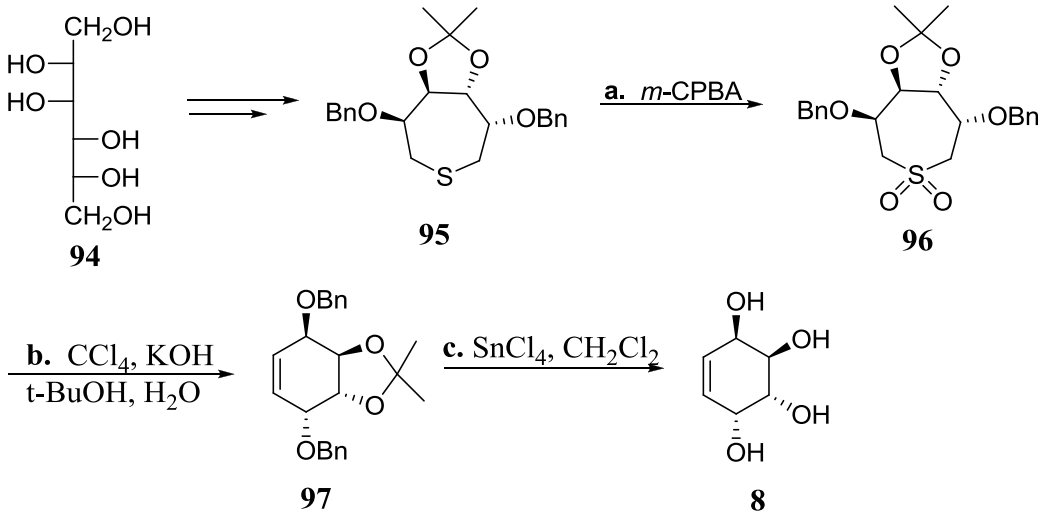
Scheme 20 The synthesis of conduritol-E (**8**)

In 1999, Chang *et al*. produced (+)-conduritol-E derivative **93** by using diethyl-L-tartrate (**87**) as a starting material [28]. The first reaction was the conversion of ester groups in **87** to aldehyde groups with DIBAL. After reaction of aldehyde functionalities with vinylmagnesiumbromide, hydroxyl groups in **88** were converted to methoxy group by using sodiumhydride and methyl iodide. The key step in their method was ring-closing metathesis of the diene compound **91**. Conduritol-E derivative **93** was obtained by removal of protecting groups in **92** (Scheme 21).



Scheme 21 The synthesis of conduritol-E derivative **93**

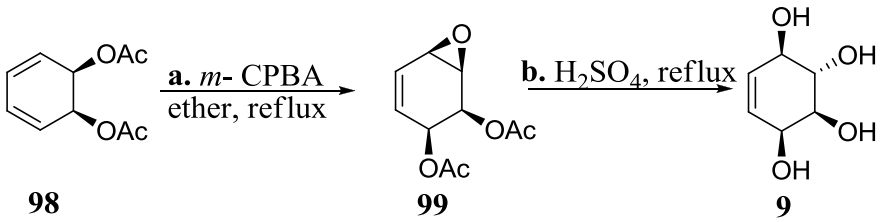
In 2000, Cere *et al.* devised a new method for (-)-conduritol-E (**8**) starting with oxidation of thioether **95** formed from D-mannitol (**94**) [29]. Conduritol-E (**8**) was synthesized from Ramberg-Backlund reaction of compound **96** followed by deprotection (Scheme 22).



Scheme 22 The synthesis of conduritol-E (**8**)

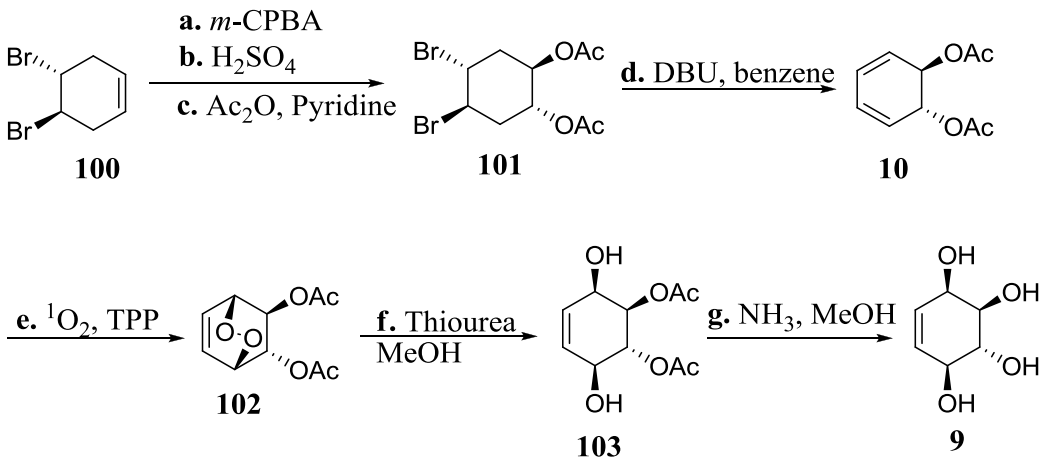
1.2.1.6 Conduritol-F

Coduritol-F has been found in almost all green plants. In 1957, Nakajima *et al*. reported the first synthesis of conduritol-F (**9**) **[**7]. They achieved to obtain conduritol-F (**9**) by epoxidation of protected benzene diol **98** followed by hydrolysis in acidic medium (Scheme 23).



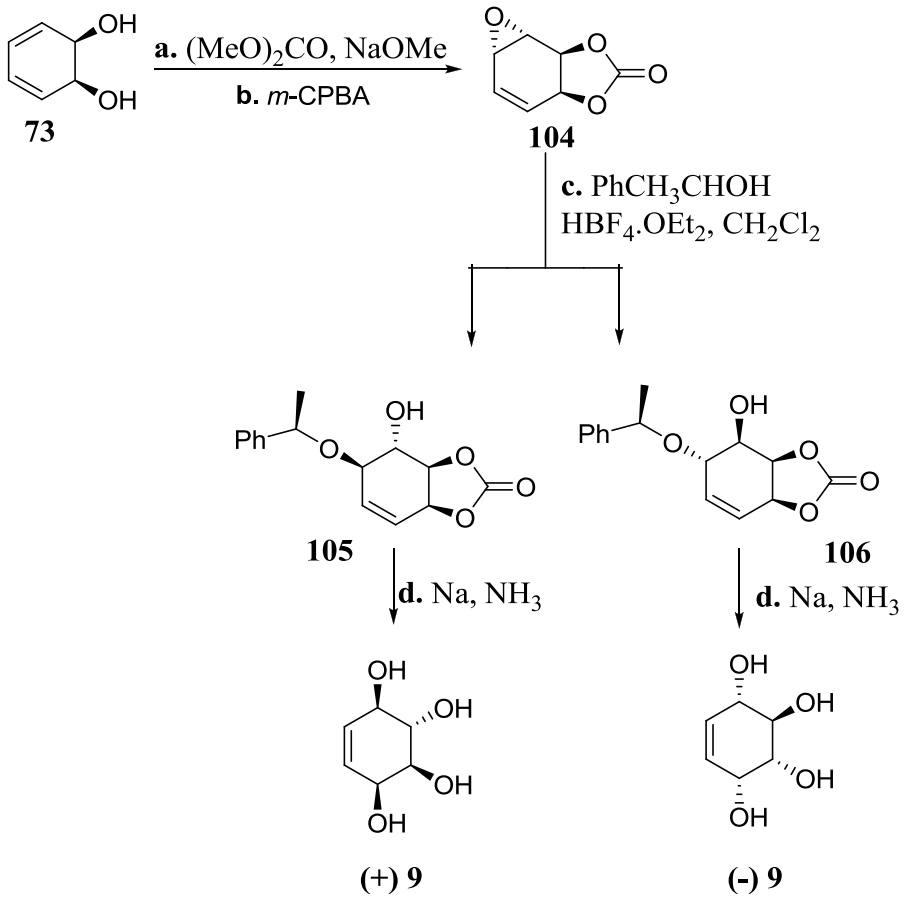
Scheme 23 The synthesis of conduritol-F (**9**)

In 1990, Balci *et al.* reported a stereospecific method for conduritol-F (**9**) starting with epoxidation of dibromocyclohexene (**100**) [15]. Bicyclic endoperoxide **102** was formed from photooxygenation reaction of 1,3-diene **10** obtained from two moles of hydrogen bromide elimination of compound **101**. By cleavage of peroxide linkage and deprotection of acetyl group in **103**, conduritol-F (**9**) was formed (Scheme 24).



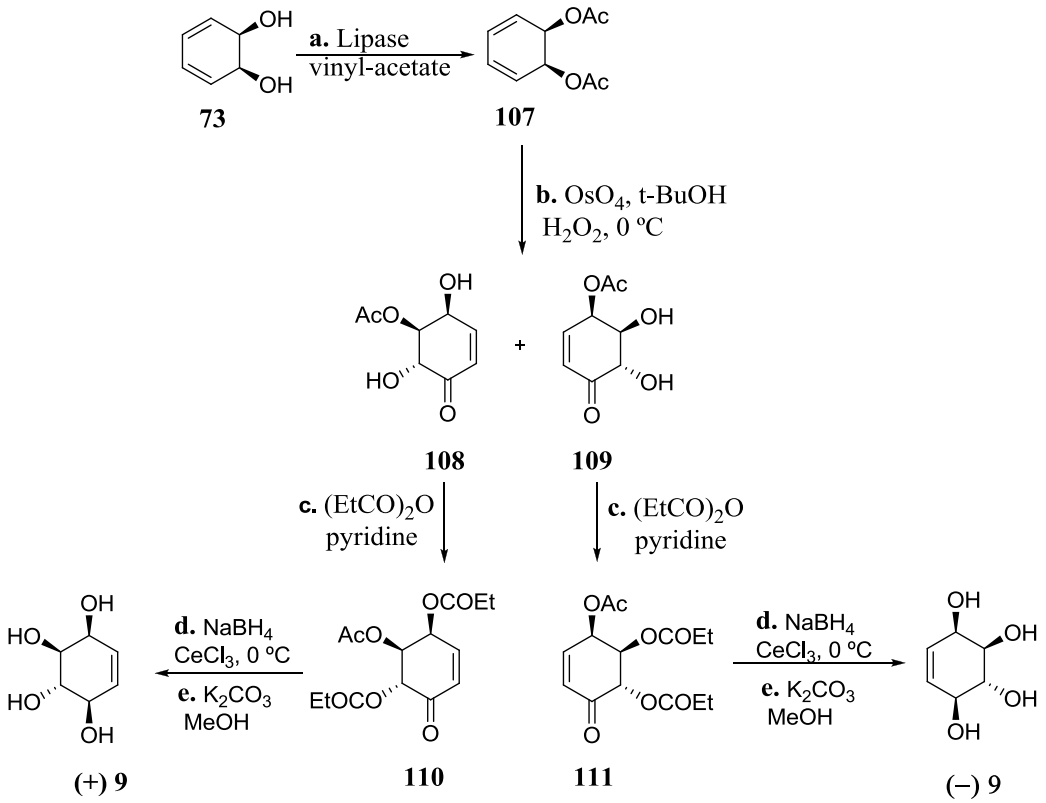
Scheme 24 The synthesis of conduritol-F (**9**)

In 1990, Ley *et al*. published enantiomer pairs of conduritol-F (**9**) [30]. *syn*-Benzene diol (**73**) was first converted to its carbonate. After its stereoselective epoxidation with *m*-CPBA, diastreomer diols **105** and **106** were obtained by opening of oxirane ring in **104**. Racemic mixture of conduritol-F was synthesized successfully by reaction of carbonates with Na in NH_3 (Scheme 25).



Scheme 25 The synthesis of enantiomer pairs of conduritol-F (**9**)

In 1996, Nicolosi *et al*. synthesized conduritol-F (**9**) starting from meso-diol **73** [31]. To produce chiral alcohol **107**, enzymatic acetylation was applied to meso-diol **73**. By means of hydroxylation under Milsa conditions [32], diastereomeric mixture of **108** and **109** were obtained. To separate them, hydroxyl groups were converted to acetates. Conduritol-F (**9**) was obtained with Luch-reduction, followed by deprotection of the acetyl groups (Scheme 26).



73 **107** **108** **109** **110** **111** (+) **9** (–) **9**

Scheme 26 The synthesis of enantiomer pairs of conduritol-F (**9**)

1.3 Aminoconduritols (Conduramines)

Conduramines are obtained by replacing one of the OH groups in conduritols with amine functional group (Figure 1.3).

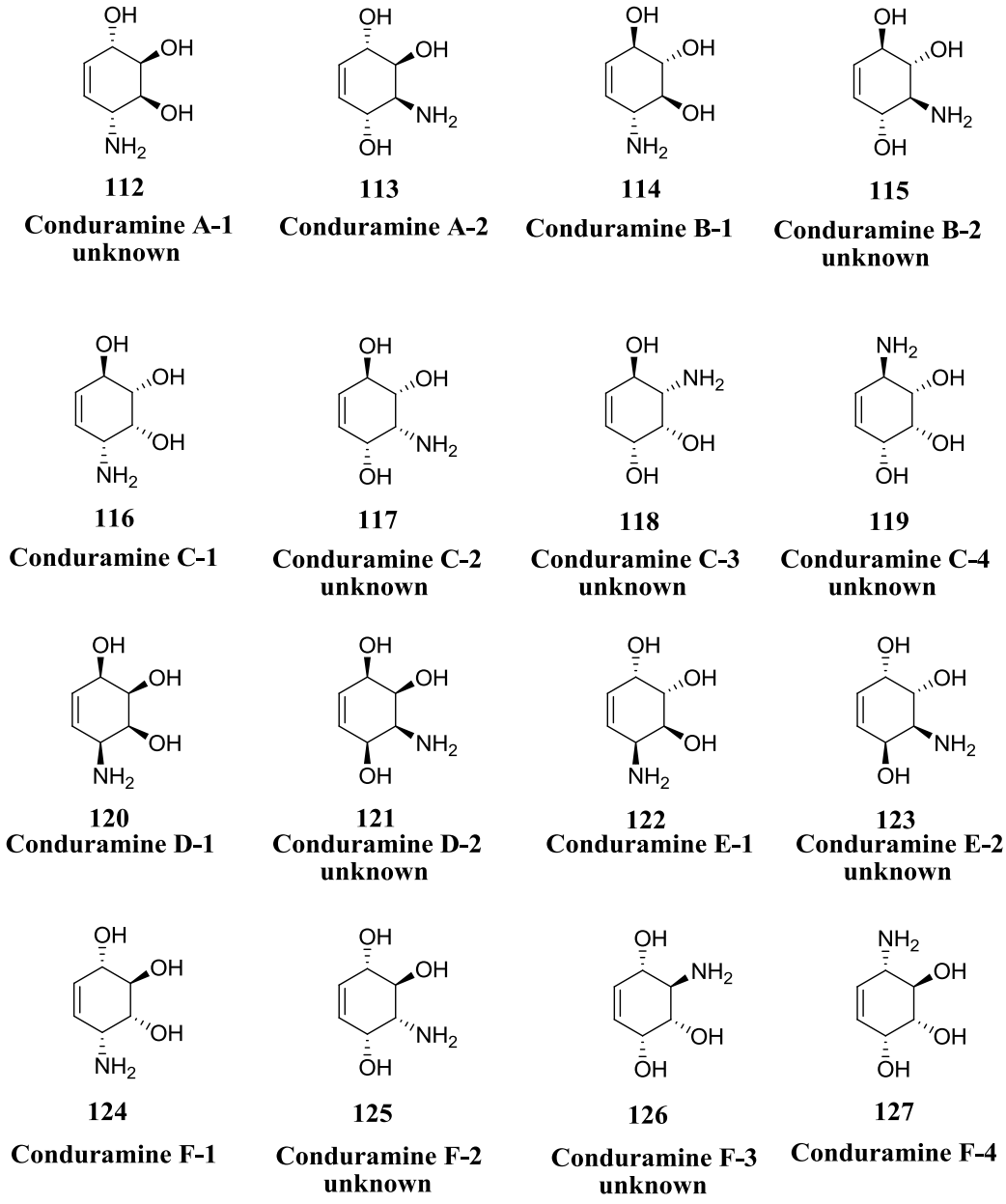
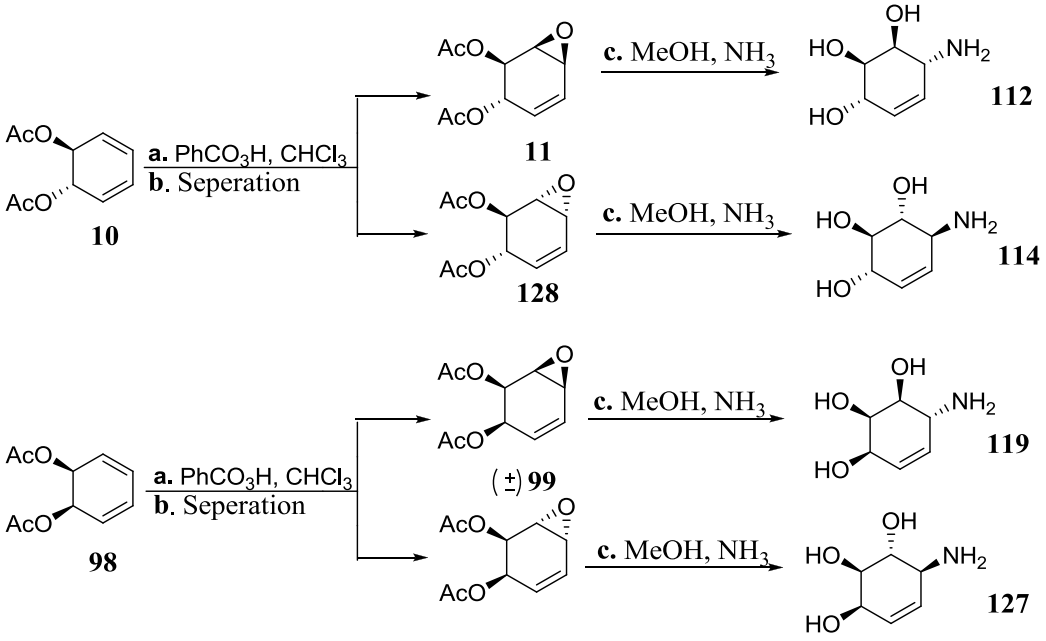


Figure 1.3 Structures of conduramines

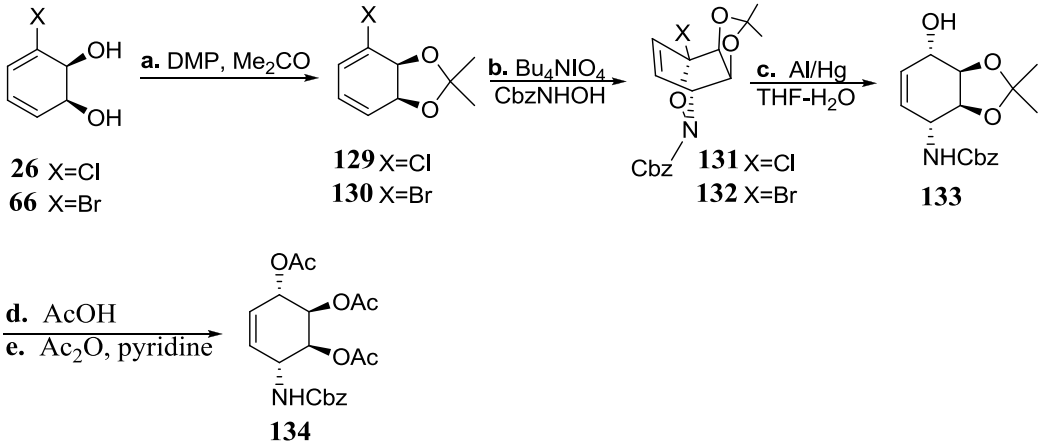
1.3.1 Synthesis of Aminoconduritols

In 1962, Nakajima *et al.* first reported the synthesis of racemic conduramines A-1 (**112**) , B-1 (**114**), C-4 (**119**) and F-4 (**127**) [33]. *trans*-Diacetate **10** was used as a starting compound for the synthesis of conduramine A-1 (**112**) and conduramine B-1 (**114**). On the other hand, *cis*-diacetate **98** was handled for conduramine C-4 (**119**) and conduramine F-4 (**127**) synthesis. First reaction was epoxidation of starting compounds **10** and **98**. While epoxidation of compound **10** gave an isomeric mixture of **11** and **128**, (±) **99** was obtained from epoxidation of compound **98**. After separation of isomers, to obtain desired aminoconduritols, anti-opening of epoxide was eventuated in NH_3/MeOH (Scheme 27).



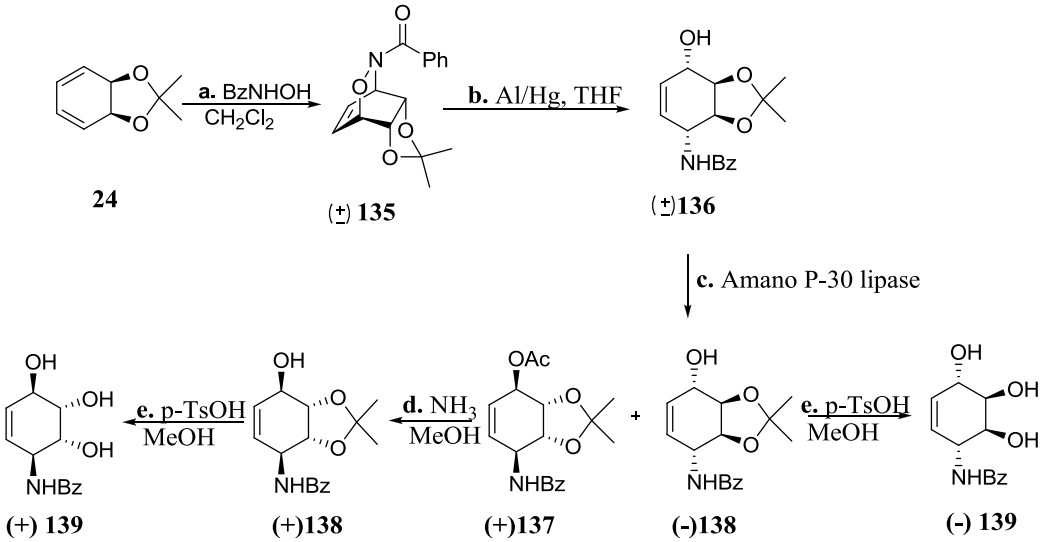
Scheme 27 The synthesis of racemic conduramines A-1 (**112**), B-1 (**114**), C-4 (**119**) and F-4 (**127**)

In 1991 and 1992, Hudlicky *et al.* developed an effective method for conduramine A-1 derivative **134** starting with protection of chlorodiol **26** and bromodiol **66** [34, 35]. Subsequent hetero-Diels-Alder reaction of **129** and **130** with Cbz-N=O resulted in corresponding oxazolidine derivatives **131** and **132**. Al/Hg cleavage of N-O bond as well as removal of halide was achieved with Al/Hg in THF. Conduramine A-1derivative **134** was formed after deprotection of ketal group followed by acetylation (Scheme 28).



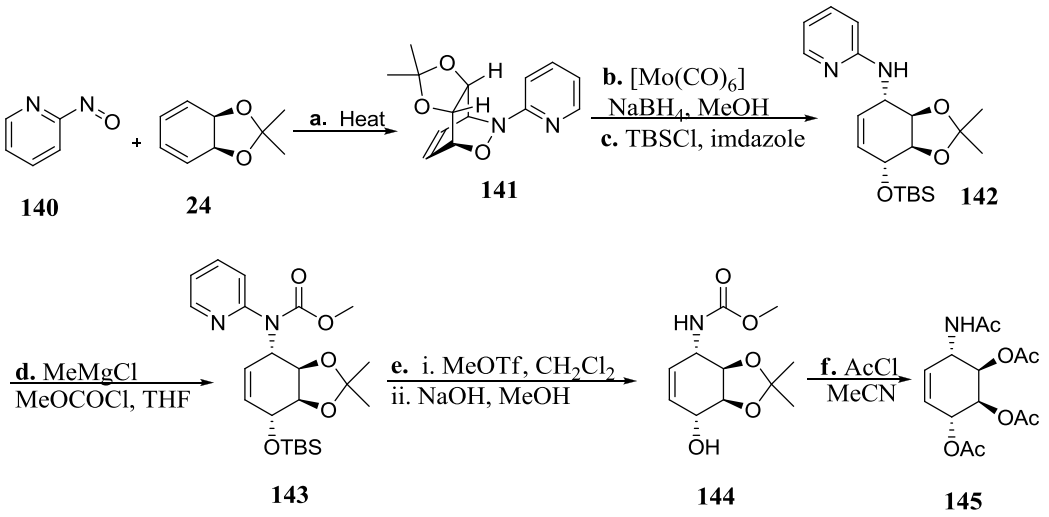
Scheme 28 The synthesis of conduramine A-1 derivative **134**

In 1992, Johnson *et al*. produced protected enantiomeric pure aminoconduritol A-1 (**139**) [36]. The key step was the Diels-Alder reaction of diene **24** with PhCON=O. After cleavage of N-O bond in **135**, the formed amino alcohol **136** was treated with Amano P-30 for enantiomeric separation to give (+) **137** and (-) **138** (Scheme 29). Both enantiomer of conduramine A-1 derivate **139** were obtained.



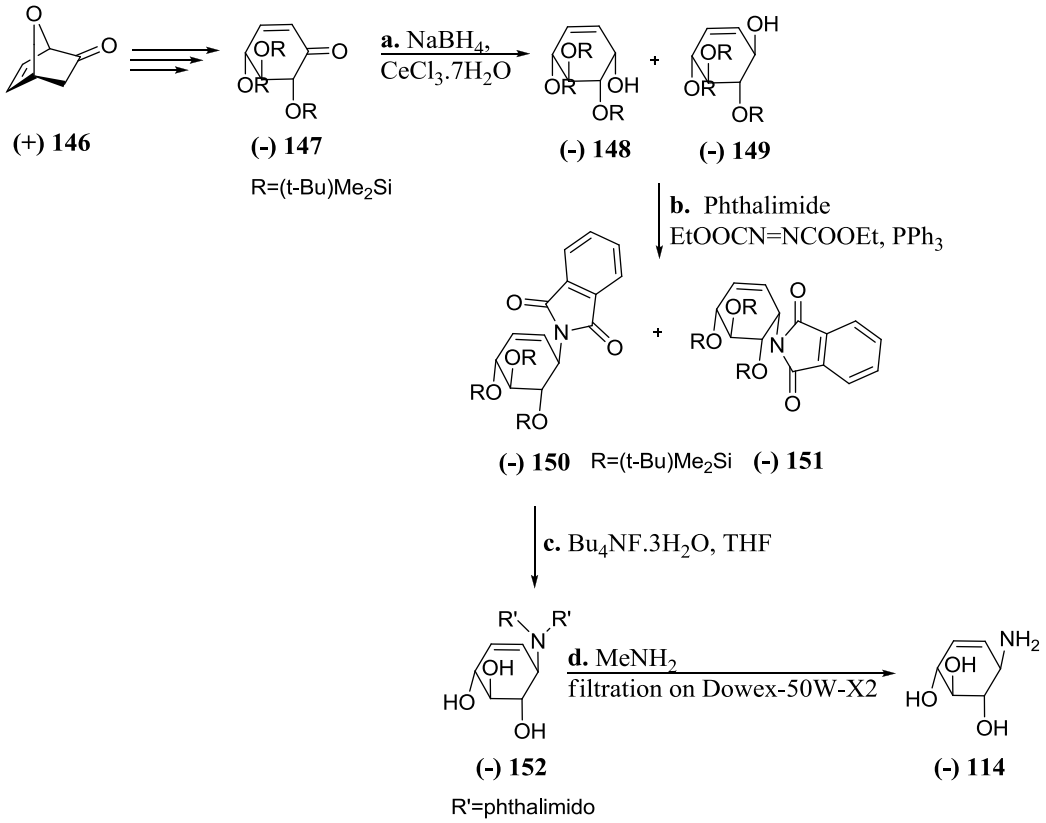
Scheme 29 The synthesis of enantiomeric pure aminoconduritol A-1 **139**

In 2009, Studer *et al*. presented a highly efficient catalyst for enantioselective nitroso-Diels-Alder (NDA) reaction for synthesis of the protected (-) conduramine A-1 **145** [37]. Compound **142** was obtained by reduction of N-O linkage and protection of hydroxyl group. The treatment of magnesium amide with methyl chloroformate led to carbamoylation of the amino group in **143**. After cleavage of pyridine group and hydrolysis of the pyridinium salt, protected conduramine A-1 **145** was obtained (Scheme 30).



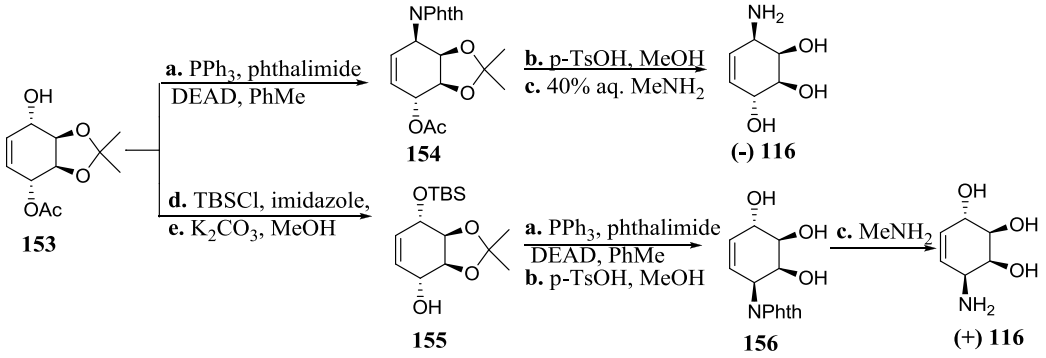
Scheme 30 The synthesis of the protected (-) conduramine A-1 **145**

In 2005, Vogel *et al*. published a new method for (-) conduramine B-1 (**114**) starting with the conversion of oxabicyclo[2.2.1]hept-5-en-2-one (+)-**146** to cyclohexenone derivative (-)-**147** by using their "naked sugar" methodology [38, 39]. By means of reduction of ketone group in **147**, a mixture of alcohols (-)-**148** and (-)-**149** was obtained. They were converted to N-substituted phthalimides (-)-**150** and (-)-**151** by the treatment with phthalimide, diethyl azodicarboxylate and PPh_3. After separation of compound (-)-**150**, it was desilated under acidic medium and reacted with methylamine, respectively. Thus, desired (-)-conduramine B-1 (**114**) was gained (Scheme 31).



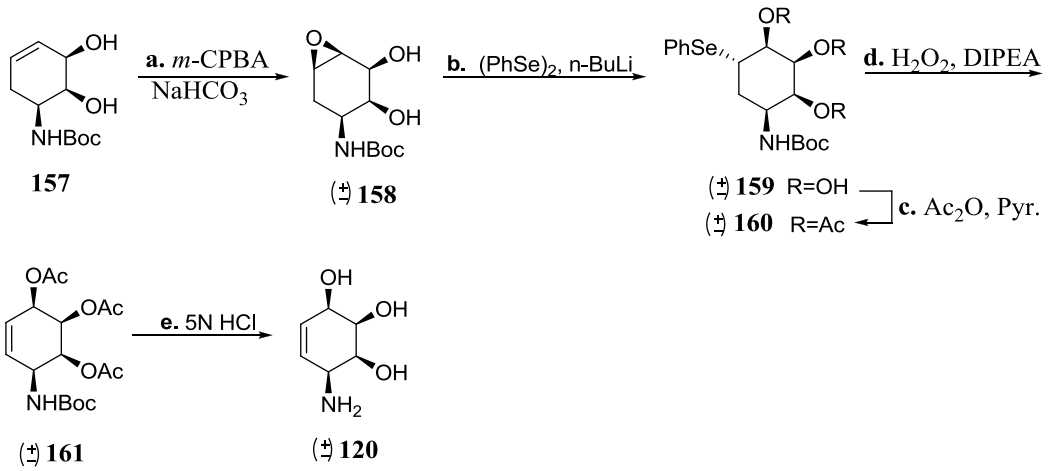
Scheme 31 The synthesis of conduramine B-1 (**114**)

In 1992, Johnson *et al*. first published the synthesis of (+) and (-)-conduramine C-1 (**116**) [40]. The reaction of phthalimide with compound **153** converted it to fully protected conduramine C-1 (**154**). (-)-**116** was obtained after deprotection of **154**. On the other hand, when compound **153** was treated with *tert*-butyldimethylsilyl chloride followed by deacetylation, alcohol derivative (-)-**155** was formed. (+)-Conduramine C-1 (**116**) was synthesized by aminolysis of **155** followed by deprotection of **156** (Scheme 32).



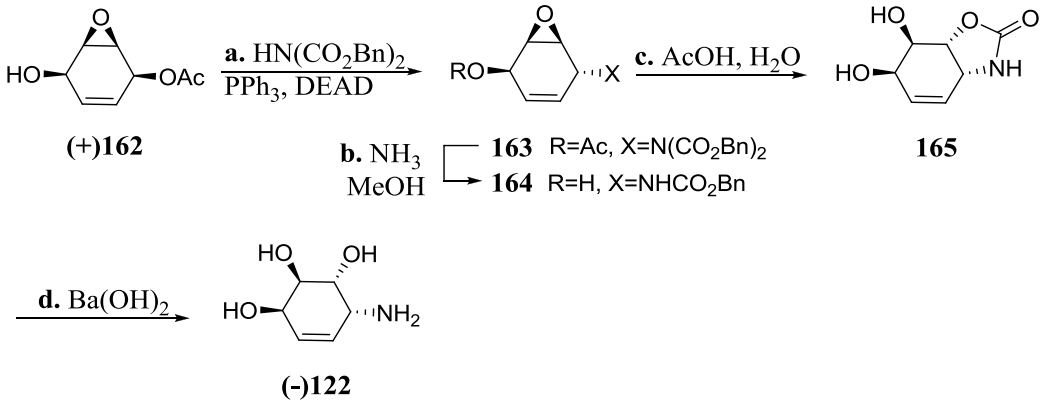
Scheme 32 The synthesis of (+) and (-)-conduramine C-1 (**116**)

In 1982, Muchowski *et al*. first devised a method for racemic conduramine D-1 (**120**) starting with epoxidation of starting material **157** [41]. After regioselective opening of oxirane ring in **158** and acetylation of hydroxyl groups in **159**, aminoconduritol D-1 (**120**) was formed by oxidative selenide elimination followed by deprotection (Scheme 33).



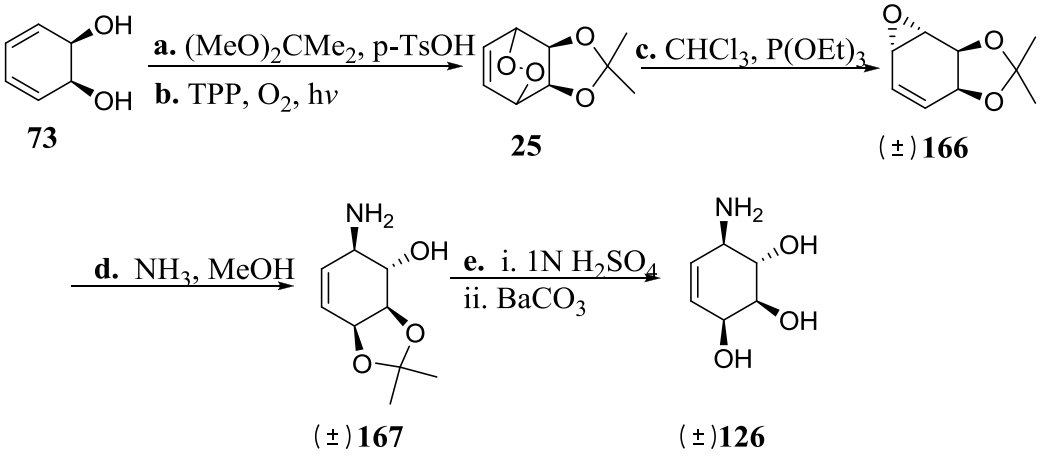
Scheme 33 The synthesis of racemic conduramine D-1 (**120**)

In 2000, Prinzbach *et al*. described a synthetic pathway for (-)-conduramine E-1 (**122**) [42]. Synthesis was started with Mitsunobu substitution of allylic alcohol derivative (+)-**162** with $HN(CO_2Bn)_2$. Besides, selective removal of benzyl carbamate led to compound **164**. By means of the neighbouring group participation of carbamate, regioselective ring opening was occurred and it resulted in isoxazolone **165**. (-)-Conduramine E-1 (**122**) was obtained by the hydrolysis of **165** under basic condition (Scheme 34).



Scheme 34 The synthesis of conduramine E-1 (**122**)

In 1994, Balci *et al.* described a stereospecific synthesis of conduramine F-4 (**127**) [43]. *syn*-Benzene diol (**73**) was firstly converted to acetonide then reacted with singlet oxygen to give endoperoxide **25**. Besides, treatment of **25** with $P(OEt)_3$ gave the allylic epoxide **166**. After reaction of allylic epoxide with ammonia in methanol, amine group was incorporated to aminoconduritol skeleton. (±)-Aminoconduritol F-4 (**127**) was afforded by acid hydrolysis of acetonide group in **167** (Scheme 35).



73 **25** (±)**166**

(±)**167** (±)**126**

Scheme 35 The synthesis of conduramine F-4 (**127**)

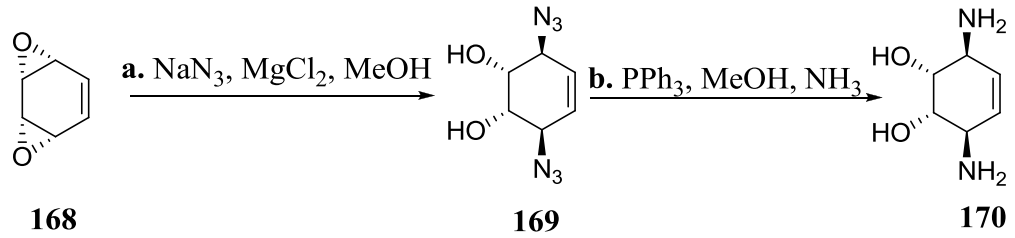
In 2006, Lysek *et al* synthesized the enantiomers of conduramine F-1 by using same method applied to synthesis of conduramine B-1 (**114**) [44]. The difference in the synthesis was the using of N-substituted (-) phthalimide (**151**). When they used (-)-N-substituted phthalimide (**150**), conduramine B-1 (**114**) was formed as shown in Scheme 31.

1.4 Diaminoconduritols

Diaminoconduritols are conduritols in which two of the hydroxyl groups are replaced with the amino functional groups.

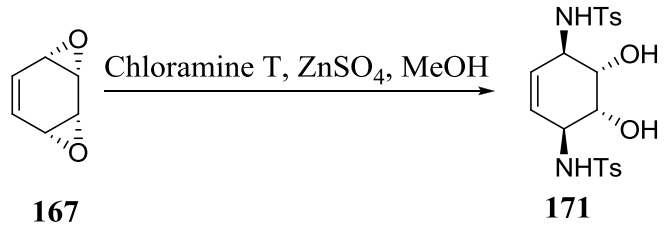
1.4.1 Synthesis of diaminoconduritols

In 1979, Vogel *et al*. reported the synthesis of *meso*-diaminoconduritol (**170**) [45]. The first reaction was the regioselective ring opening of the epoxide rings to form the diazide derivative **169**. Diaminoconduritol **170** was obtained by reduction of azide groups in **169** to amine functional groups (Scheme 36).



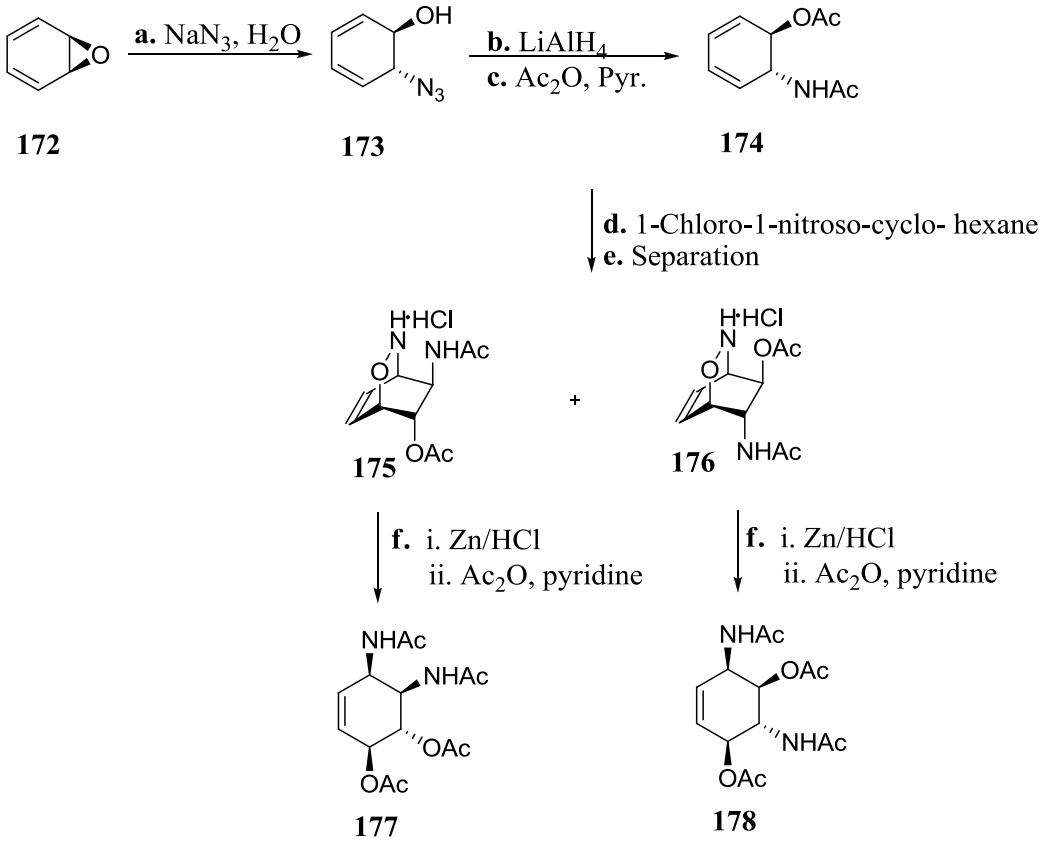
Scheme 36 The synthesis of meso-diaminoconduritol (**170**)

In 1988, Prinzbach *et al.* used a similar approach to synthesize the diaminoconduritol derivative **171** [46] (Scheme 37).



Scheme 37 The synthesis of diaminoconduritol derivative **171**

In 1984, Krezse *et al.* synthesized the protected diaminoconduritol derivatives **177** and **178** in five steps starting from benzene oxide **172** [47]. The key step was the hetero-Diels-Alder reaction of racemic cyclohexadiene derivative **174** with 1-chloro-1-nitrosocyclohexane to give a mixture of **175** and **176**. After separation of isomers, each of them was treated with Zn in acidic medium to reduce N-O linkage. Protection of hydroxyl and amino groups gave rise to afford desired products **177** and **178**, respectively (Scheme 38).

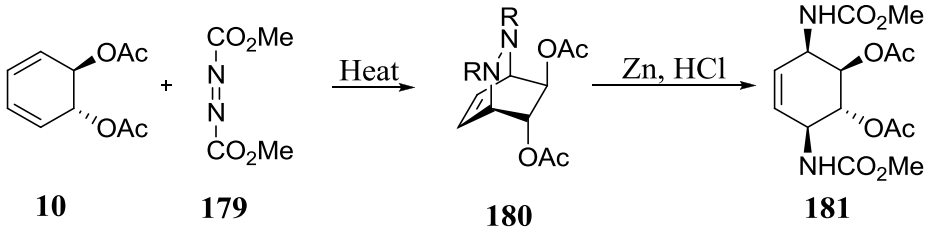


172 **173** **174** **175** **176** **177** **178**

Scheme 38 The synthesis of diaminoconduritol derivatives **177** and **178**

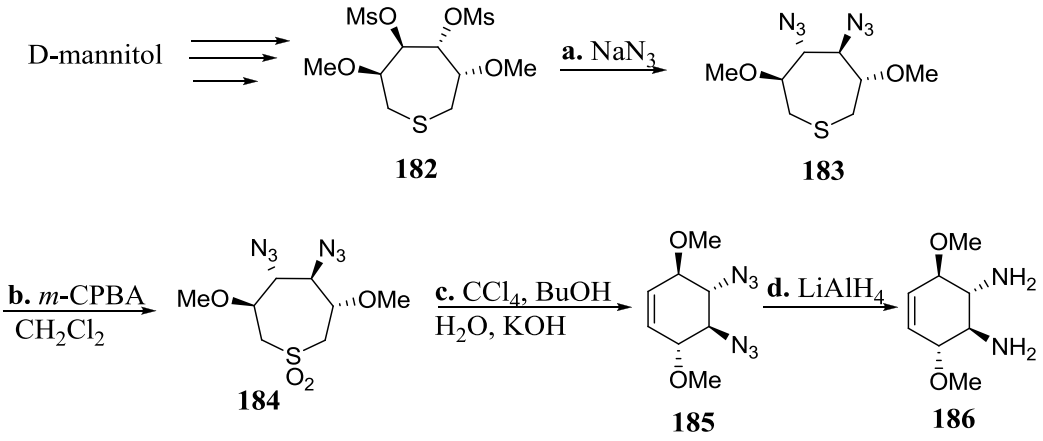
In 1984, Kuo *et al.* described the synthesis of racemic 1,4-diaminoconduramine **181** [48]. Kuo and co-workers started also with hetero-Diels-Alder reaction, too. The reaction was eventuated between dimethyl azodicarboxylate with *trans*-

diacetate **10** to afford compound **180**. Reductive cleavage of N-N linkage led to obtain diaminoconduritol **181** (Scheme 39).



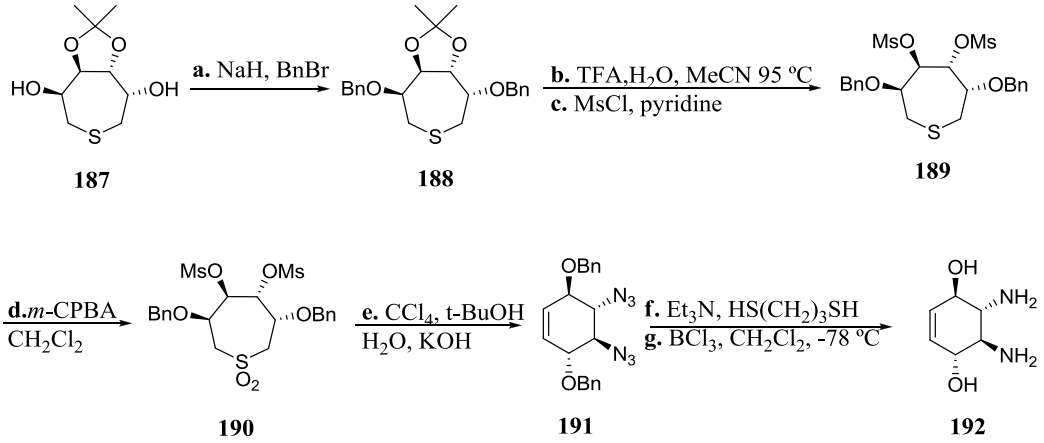
Scheme 39 The synthesis of diaminoconduritol **181**

In 1998, Cere`*et al*. published the first example of 2,3-diaminoconduritol derivative **186** starting with the thiepane (-)-**182**, derived from D-mannitol [49]. Sulfone **183** was synthesized by treatment of **182** with NaN_3 followed by oxidation of **183**. The double bond was formed by application of Ramberg-Böcklund rearrangement. Reduction of the azido group with lithium aluminium hydride caused to the formation of diaminoconduritol **186** (Scheme 40).



Scheme 40 The synthesis of 2,3-diaminoconduritol derivative **186**

In 2001, Cere`*et al*. have published the synthesis of enantiomerically pure deprotected diaminoconduritol **192** using a similar methodology [50] (Scheme 41).

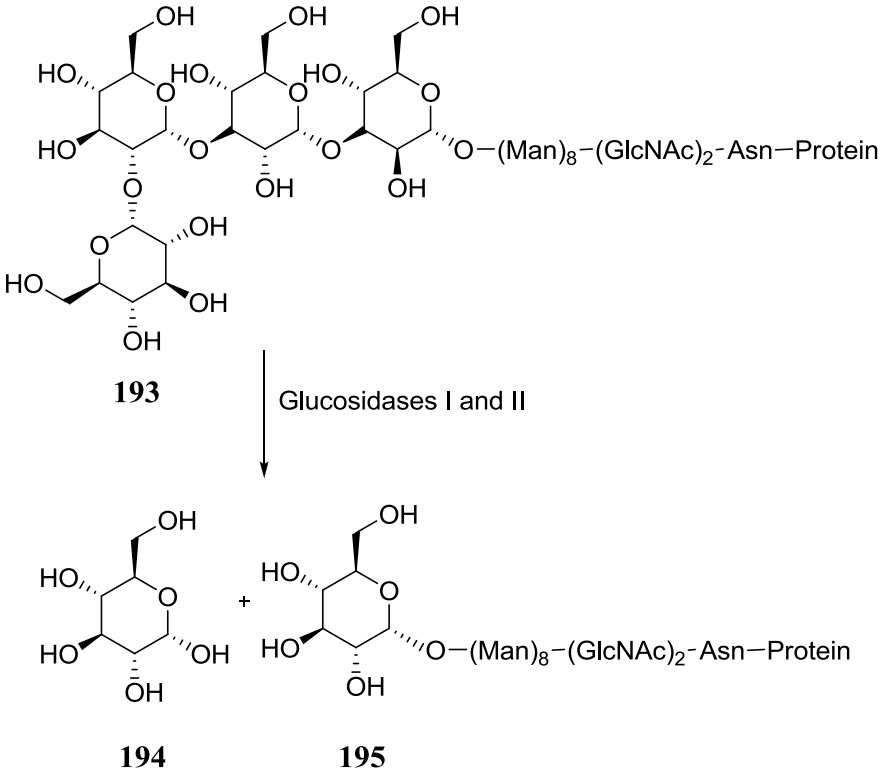


Scheme 41 The synthesis of deprotected diaminoconduritol **192**

1.5 Biological importance of conduritols, conduramines and diaminoconduritols

Glucosidases are enzymes catalyzing the cleavage of glycosidic bonds in oligosaccharides or glycoconjugates. They have a crucial role in the several bio-chemical processes such as degradation of polysaccharides to corresponding monosaccharide, biosynthesis of oligosaccharide units in glycoproteins or glycolipids [51]. The enzymes glucosidases I and II are used in the degradation of *N*-linked oligosaccharide **193**. While Glucosidase I cleaves Glc(1-2)Glc linkages, whereas Glucosidase II cleaves Glc(1-3)Glc linkage. After the cleavage, the immature glycoprotein **195** is processes by the concomitant action of glycosidases and transferases to give specific glycoconjugates. These glycoconjugates are important in biological processes, such as immune response, intercellular recognition, cellular differentiation, the stability and solubility of

proteins, and in pathological processes, such as inflammation and cancer [52] (Scheme 42).



Scheme 42 Degradation of N-linked oligosaccharide **193**

Glucosidase inhibitors attracted as potential therapeutic agents for the treatment of diabetes [53], obesity [54], HIV infections [55], cancer [56] and genetic disorders [57].

Unsaturated cyclitols, the conduritols are found to have a potential in the treatment of diabetes, viral infection, cancer, and other diseases. Several conduritol derivatives exhibited antifeedant, antibiotic, antileukemic, and growth-modulation activity [58]. So, they have attracted great attention of scientist.

While only conduritol F (**9**) is found in small quantities in green plants, conduritol-A (**4**) is coincided to specific tropical plants. Especially, it can be isolated from *Gymnena sylvestre*, a shrub, which is a building structure of a medicine used in India and Asia against diabetes for 2000 years [59].

Besides of these significances, conduritols are also synthetic precursors for the preparation of cyclitols such as quercitols, cyclophellitol, pseudosugars, aminoglycosidic antibiotics, etc [58].

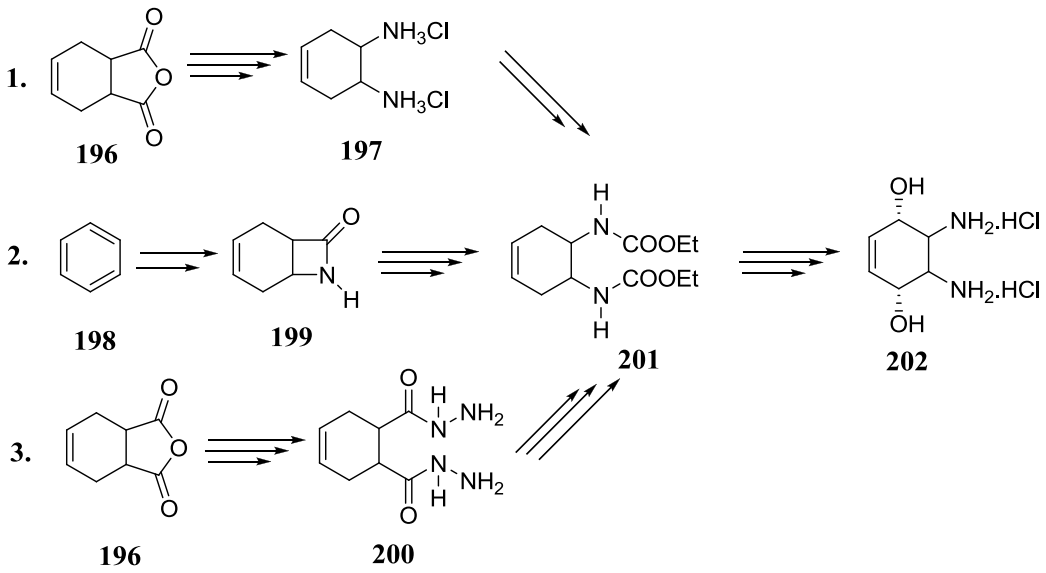
Conduritol-A (**4**) is found to have the most ability to treat obesity and diabetes, especially to hamper intestinal glucose absorbtion. Miyatake *et al.* depicted impact of the condurito-A in diabetic rats. It causes cataracts shown as a result of the inhibition of lens aldose reductase [60]. It was found that conduritol-B (**5**) showed the same activity like conduritol-A (**4**). It was also able to modulate insulin release from isolated pancreatic islets [61].

Aminoconduritols, diaminoconduritols and their analogues comprise parts of aminoglycoside antibiotics such as kanamycin B, tobramycin B. They are two of the best known antibiotics [62, 63]. The antibiotics react with a number of RNA sequences including two important HIV regulatory domains, RRE92 and TAR.93 The hydroxyl and neighboring amine groups take a part in the binding between RNA and aminoglycosides [64]. Acarbose is a kind of aminoconduritol derivative and effective against bacterial, fungal, and plant glucosidases [65, 66]. Kanfer *et al*. [67] and Das *et al.* [68] depicted the potential of the aminoconduritol B-1 (**113**) for Gaucher's disease, which is the most prevalent of the lysosomal storage disorders [69]. Patients with Gaucher's disease exhibit hepatosplenomegaly, anemia, bone lesions and neurological disorders [70].

As a consequence, the compounds containing of hydroxyl and amino groups have been candidates for drug discovery and taken great attention of scientist [71, 72].

1.6 Aim of the work

To synthesize the target molecule **202**, 3 different methods were performed. While 1,2,3,6-tetraphthalic anhydrate (**196**) was used as a starting compound in two methods, 1,4-cyclohexadiene was used in the other one. The compound **201** was thought to be the common product through these syntheses. Scheme 43 summarizes the all synthetic methods.



Scheme 43 The summary of the all synthetic methods

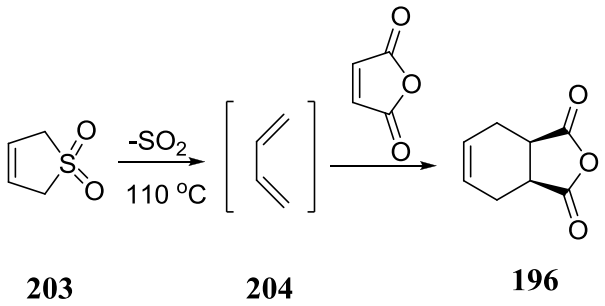
CHAPTER 2

RESULTS AND DISCUSSION

2.1 The synthesis of aminoconduritol derivative (202)

2.1.1. Synthesis of 1,2,3,6-tetrahydrophthalic anhydride (196)

As shown in Scheme 44, the Diels-Alder reaction of maleic anhydride and 3-sulfolene (**203**) was used to obtain the starting material 1,2,3,6-tetraphthalic anhydrate. 3-Sulfolene (**203**) was transferred to 1,3-butadiene (**204**) by heating up to 110 ºC. Formed diene was reacted with maleic anhydride to from unsaturated six membered ring. This is a [4+2] cycloaddition reaction and has a great important in the synthetic methods. It was discovered by Otto Diels and Kurt Alder, who received the Nobel Prize in 1950. The reaction is also classified as a subgroup of pericyclic reactions because its mechanism involves a cyclic transition state [73].



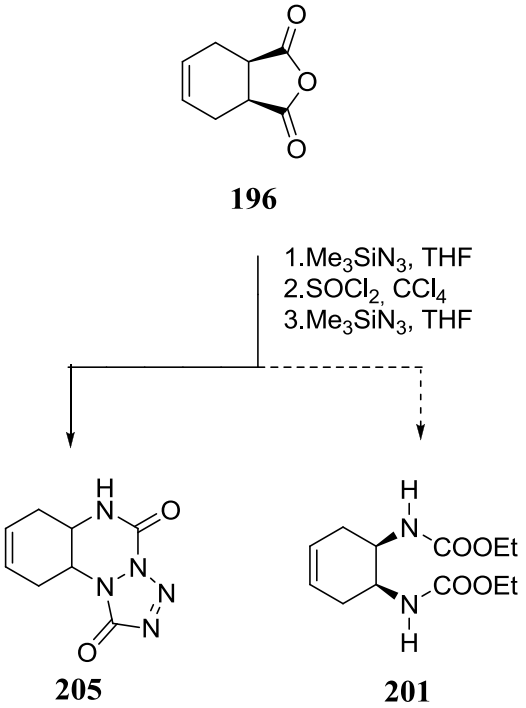
203 **204** **196**

Scheme 44 The synthesis of compound **196**

The identification of compound **196** was made by ^{1}H and ^{13}C NMR spectra, which were taken in $CDCl_3$. Its ^{1}H and ^{13}C NMR spectra are consistent with the literature [74].

2.1.2 Synthesis of 6a,7,10,10a-tetrahydro-1*H*-tetraazolo[1,2*a*][1,2,4]benzotriazine-1,5(6*H*)-dione (205)

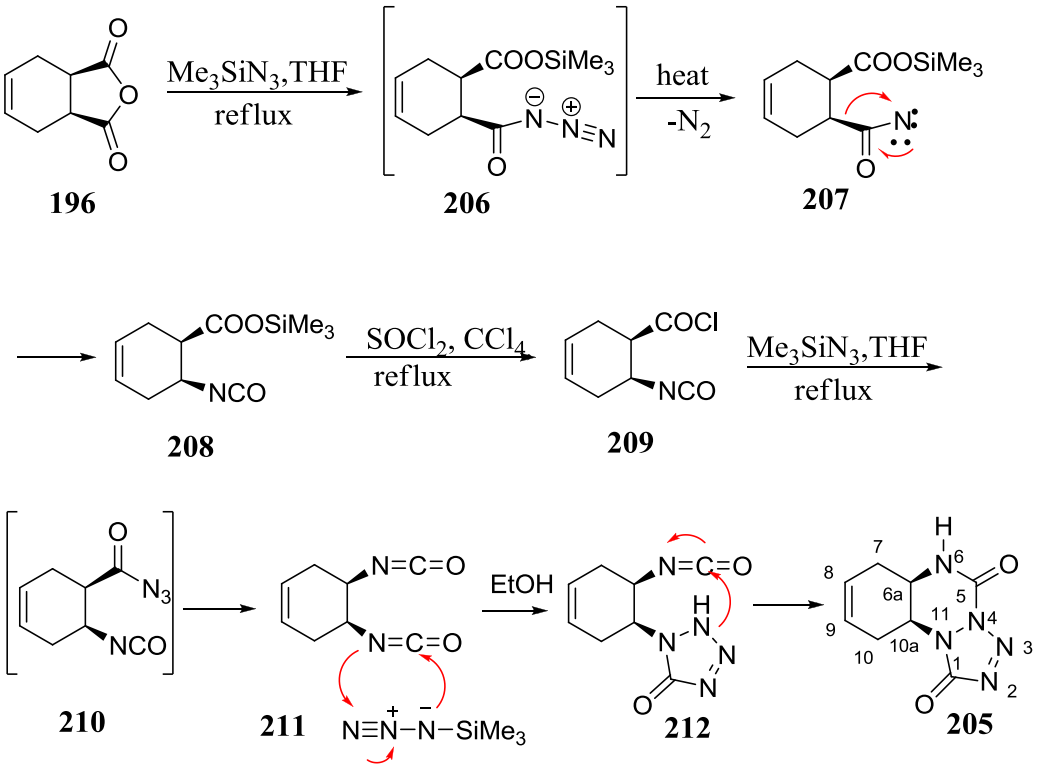
After obtaining the starting material, our first goal was the synthesis of the common product **201**. For this reason, compound **196** was reacted with trimethyl silyl azide (TMSA), thionyl chloride ($SOCl_2$), followed by TMSA and ethanol at reflux temperature of THF as shown in Scheme 45. Tetrazolinone **205**, unexpected product was obtained instead of the expected product **201**. Tetrazolinones are the five-membered, unsaturated heterocyclic ketones containing four nitrogen atoms and one double bond. They have many biological acvities such as herbitical activity [75].



Scheme 45 The summary of first method

We assume that anhydride function in compound **196** was first opened with TMSA to give protected acylazide **206** as an intermediate. Because of the reflux temperature of the solvent, acylazide group was converted to isocyanate **207** by Curtius rearrangement (Scheme 46). This rearrangement was found in 1894 by Theodor Curtius [76].

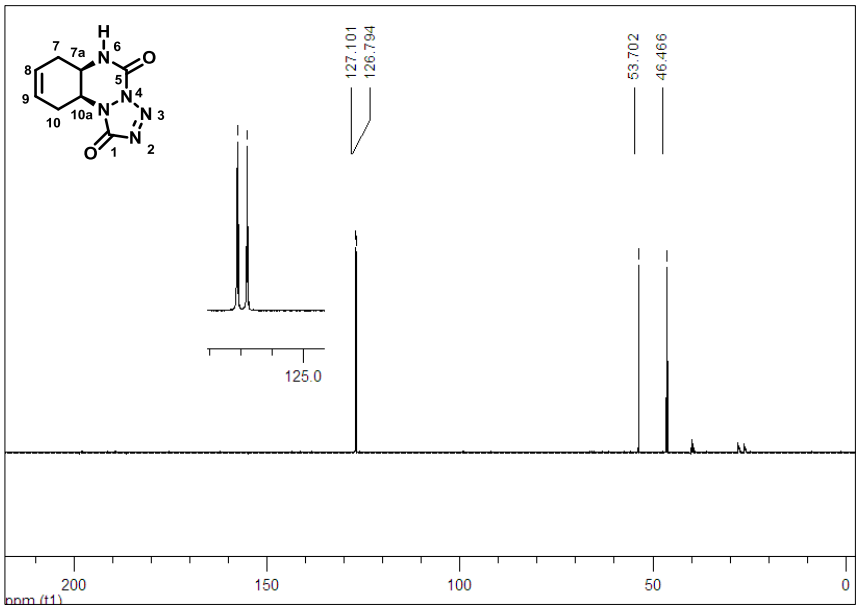
The treatment of isocyanate with $SOCl_2$ followed by TMSA resulted in the formation of labil intermediate **210**. Acyl azide group in **210** was converted upon heating to compound **211**, having two diisocyanate functionalities. The formation was followed by IR. The characteristic frequency values of the azide apperared around 2270 and 2140 cm^{-1}. Since excess TMSA was used, a 1,3 dipolar cycloaddition occurred between trimethylsilyl azide and one of the isocyanate groups in **211** to give **212**.



Scheme 46 The synthesis of compound **205**

Tetrazolinone derivative **205** was formed by intramolecular attacking of lone pair electrons on nitrogen atom in adduct **212** to the carbonyl group of remaining isocyanate function (Scheme 46). The product was characterized by spectral methods. Number of the nitrogen atoms was determined by elemental analysis. HRMS, ^{1}H, ^{13}C NMR and 2D NMR were used to assign the exact structure. According to the results of HRMS and elemental analysis, it was found that compound **205** contains five nitrogen atoms. In the ^{1}H NMR, nine different proton atoms were found. NH proton was observed at 7.63 ppm as singlet. While the double bond protons resonate at 5.84 ppm as quasi-triplet, two CH_2 protons neighboring to double bond resonate at 2.31 and 2.14 ppm as AB systems. Two AB systems are observed. Remaining two CH protons resonate at 4.37 and 3.97 as quintet with coupling constant of 4.6 and 4.1 Hz, respectively. According to ^{13}C NMR, there are eight different C atoms. Two carbonyl carbons resonate at 153.9, 153.5 ppm, while two olefinic carbon atoms appear at 127.6, 127.3 ppm. The saturated carbon atoms resonate at 54.2, 46.9, 28.1, 26.5 ppm. DEPT 90 exhibit only CH carbons in positive region. On the basis of these results it can be seen easily that compound **205** contains four CH carbon atoms. DEPT 135 shows CH and CH_3 carbons in positive phase and CH_2 carbons in negative phase. When positive area is compared with the one in the DEPT 90, peaks are same. It means that compound **205** doesn't have any CH_3 carbon. In the negative region of DEPT 135, there are 2 peaks belonging to CH_2 groups (Figure 2.1). The expanded spectra of **205** can be seen in Figure 4.7 and Figure 4.8 in Appendix.

a)



b)

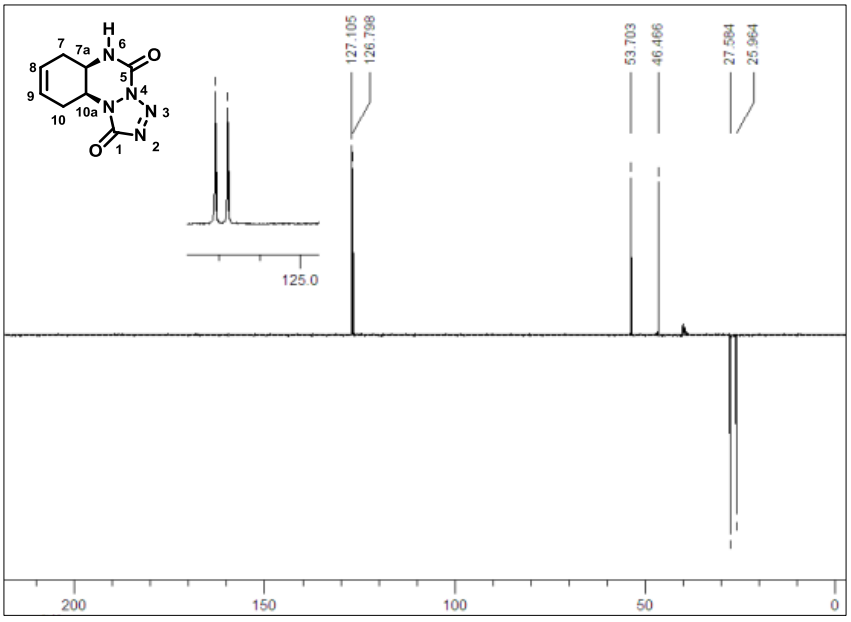


Figure 2.1 a) DEPT 90 b) DEPT 135 spectra of compound **205.**

When these C atoms are emitted from ^{13}C NMR spectrum, two quaternary C atoms are remaining. COSY spectrum is useful for determining the neighboring protons. HMQC is used to find which ^{1}H of a molecule is bonded to which ^{13}C nuclei. By using COSY and HMQC spectra, it was supported that all protons belong to cyclohexene skeleton. HMBC spectrum is suitable for determining long-range ^{1}H and ^{13}C connectivity through three bonds. In the HMBC spectrum, there are correlations between carbonyl carbons and the protons of NH and CH group (Figure 2.2). By using these informations, the structure was determined. The expanded spectrum HMBC can be seen in Figure 4.10.

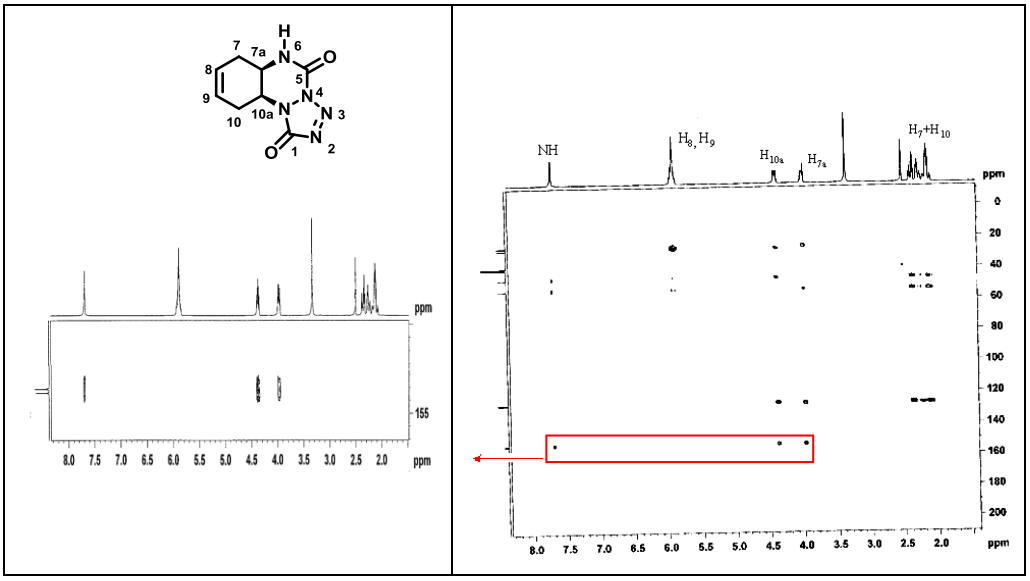


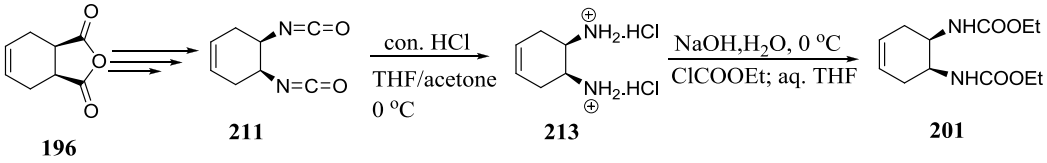
Figure 2.2 HMBC Spectrum of compound **205**

According to HMBC spectrum (Figure 2.2), carbonyl carbons labeled as 1 and 5 show only interactions with protons labeled as 7a and 10a. There are not any interactions with protons 7 and 10. Proton of NH group shows an interaction with carbonyl carbon. There are not any further interactions. All these

information shows the exact position of the carbonyl groups and supports the suggested structure.

2.1.3 Synthesis of diethyl *rel*-(1*R*,2*S*)-cyclohex-4-ene-1,2-diyldi- carbamate (201)

During the formation of **211**, 1.3 equivalents of TMSA was used. Because of the addition excess TMSA to isocyanate group, unexpected tetrazolinone **205** was obtained. To eliminate the formation of **205**, one equivalent TMSA was used in required steps.



196 **211** **213** **201**

Scheme 47 The synthesis of compound **201**

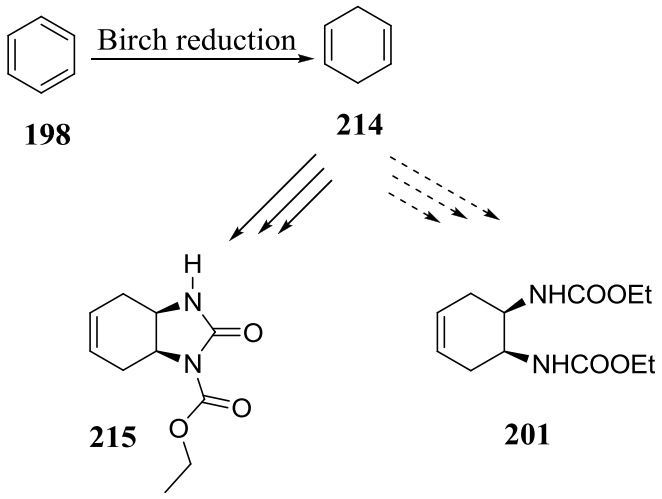
To prove the formation of diisocyanate **211**, it was converted to diamine salts **213** by adding conc. HCl. According to ^{1}H NMR spectrum, six protons of two NH_3Cl groups resonate 8.76 ppm as singlet. Olefinic protons appear as quasi triplet at 5.64 ppm. In the ^{13}C NMR spectrum, three different carbon resonances are observed at 123.7, 47.6, 27.1 ppm. (Figure 4.11 and Figure 4.12)

To synthesize carbamate derivative **201**, diamine salt **213** was firstly neutralized with NaOH and reacted with ethyl chloroformate (Scheme 47). ^{1}H NMR spectrum of carbamate **201** shows olefinic protons at 5.55 ppm, while NH protons are observed at 5.27 ppm. CH_2 protons of cyclohexane skeleton give rise to an AB-system. A part of AB-system resonates at 2.48 ppm as broad doublet (J = 16.4 Hz). B part appears at 1.96 ppm as doublet of doublets with coupling

constant of 16.6 and 4.8 Hz. The large splitting originates from the geminal coupling. While CH_2 protons of ester group split into quartet at 4.05 ppm, methyl protons of ester group resonate as triplet at 1.18 ppm.

2.2 Attempted synthesis of aminoconduritol derivative 202 via lactam 199

The second method was started with the synthesis of 1,4-cyclohexadiene (**214**). While planning the synthesis of common product **201**, again unexpected product **215** was detected. It's formation has been searched (Scheme 48).

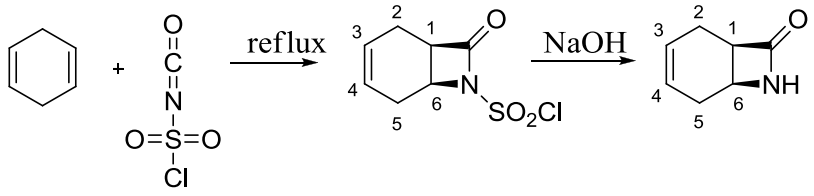


Scheme 48 The summary of second method

Starting material 1,4 diene (**214**) for the second method was synthesized by the Birch reduction of benzene. The reaction was reported in 1944 by Arthur Birch [77]. According to ^{1}H NMR and ^{13}C NMR spectra, it has 2 different protons and carbons. Protons resonate at 5.72 and 2.7 ppm whereas carbons at 124.4 and 25.8 ppm.

2.2.1 Synthesis of *rel*-(1*R*,6*S*)-7-azabicyclo[4.2.0]oct-3-en-8-one (218)

As mentioned before, our first goal was the synthesis of the compound **201**. For this aim, the second methodology was started with the well-known 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to diene **214** (Scheme 49). Pure compound **217** was obtained. Hydrolysis of the sulfonyl chloride group of the cycloadduct **217** was made in the presence of NaOH to give lactam derivative **217** [78].



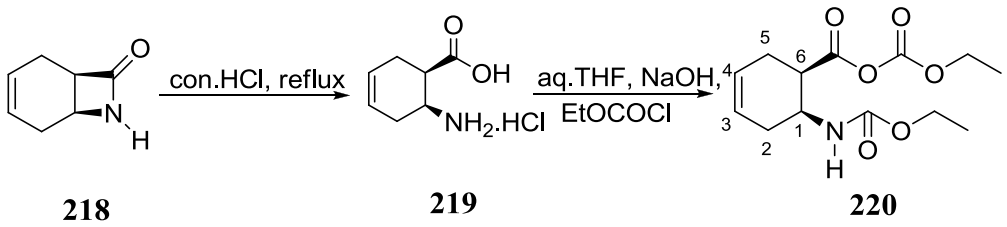
214 **216** **217** **218**

Scheme 49 The synthesis of compound **218**

When the ^{1}H and ^{13}C NMR spectra of compound **217** and **218** are compared, two important differences are observed. One of them is the frequency of H_6 proton. While H_6 in **217** resonates at 4.63 ppm, H_6 in **218** is observed at 3.91 ppm. Another striking difference is the resonance of C_6 carbon atom. The C_6 carbon in **217** resonates at 57.3 pm and the resonance of C_6 in **218** appears at 47.9 ppm. SO_2Cl group is an electron withdrawing group, so it decreases the electron density around proton and carbon nuclei. Therefore, the resonance of H_6 as well as C_6 in **217** appears at lower field. The structure of **218** was assigned by the ^{1}H and ^{13}C NMR spectra and they are consistent with literature [78].

2.2.2 Synthesis of {rel-(1R,6S)-6-[(ethoxycarbonyl)amino]cyclohex-3-en-1-yl}carbonyl ethyl carbonate (220)

After obtaining compound **218**, it was converted to monoacid derivative **219** by hydrolysis. To protect amine group and change the hydroxyl group to a good leaving group, compound **219** was reacted with ethyl chloroformate (Scheme 50). The compound **220** was obtained in 69% of yield.

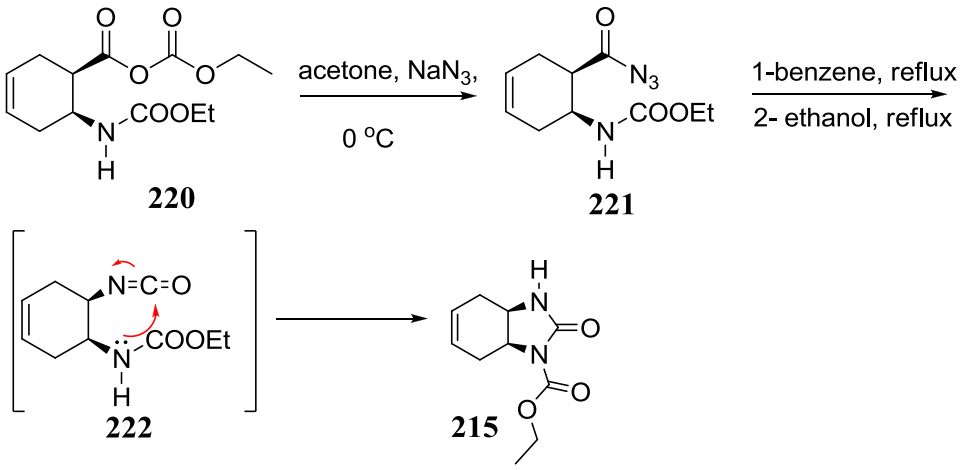


Scheme 50 The synthesis of compound **220**

According to ^{1}H NMR spectrum of **220**, olefinic protons resonate between 5.8-5.4 ppm as multiplet. Two different CH_2 protons of ester groups resonate at 4.05 ppm as triplet. Six protons of methyl groups resonate at 1.18 ppm as quartet. While H_6 proton neighboring to carbonyl group resonates between 2.9-2.7 ppm as multiplet, H_1 resonance appears between 4.3-4.1 ppm as multiplet. Both CH_2 groups ($2H_2$ and $2H_5$) give AB systems. Since, chemical environment of them are so similar, parts of AB systems collide with each other. Thus, the signals of them appear between 2.65- 2.1 ppm as multiplet. NH group is easily seen at 10.8 ppm as broad singlet. In the ^{13}C NMR spectra, while three carbonyl carbons resonate at 178.4, 171.3 and 156.4 ppm, two olefinic carbon resonances are collapsed and seen at 124.9 ppm. The remaining eight carbon signals are observed with the expected chemical shift.

2.2.3 Synthesis of ethyl *rel*-(3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-benzimidazole-1carboxylate (215)

After successful synthesis of the compound **220**, the next step was conversion of the other ester functionality into the amine group. Amine group was thought to be gained by the reaction of sodium azide (NaN_3) with compound **220** followed by Curtius rearrangement and addition of ethanol. In the azidination reaction of **220**, one equivalent of NaN_3 was used. Compound **220** has three different carbonyl carbons. Because of the differences between carbonyl carbons, azide interacted with the more reactive one and then acyl azide adduct **221** was formed. Upon heating of acyl azide **221** at the reflux temperature of benzene, isocyanate **222** was formed as an intermediate. However, we were not able to isolate isocyanate **222**. Only imidazole derivative **215** was formed by intramolecular attacking of lone pair electrons on nitrogen atom to carbonyl carbon of isocyanate (Scheme 51).



Scheme 51 The synthesis of compound **215**

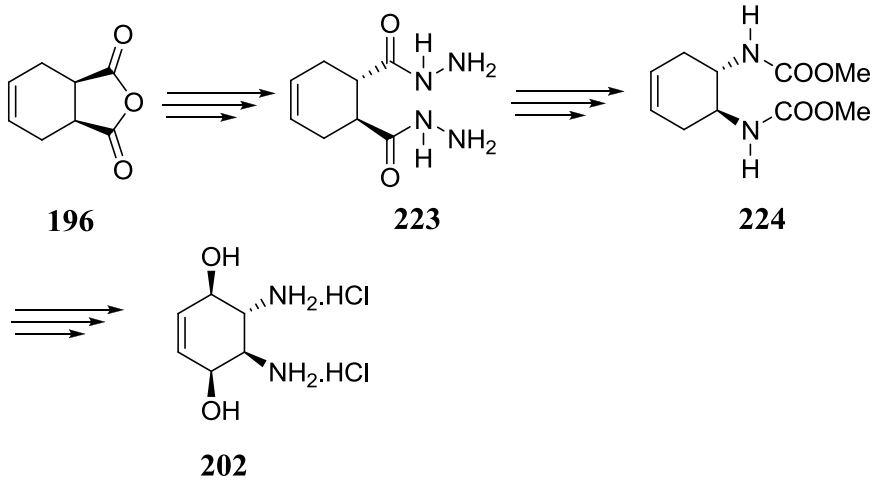
The structure of **215** was established by combination of data obtained from the ^{1}H, ^{13}C NMR spectra, GC-MASS and elemental analysis results. Proton of NH group resonates at 6.85 ppm. Olefinic protons are seen as quasi-triplet at 5.83

ppm. The CH_2 protons of ethoxy group and H_{7a} resonate between 4.30-4.14 as a multiplet while the protons methyl protons of ethoxy group appear at 1.27 ppm as a triplet having a coupling constant of 7.1 Hz. H_{3a} proton resonance is split into doublet of triplets with a coupling at constant of 10.9 and 5.0 Hz. Compound **215** has two different CH_2 groups. Their chemical environments are similar, therefore, their chemical shifts very close to each other. For this reason, these four protons are seen as multiplet in the expected region. According to ^{13}C NMR spectrum, two carbonyl carbons resonate at 156.4 and 151.9 ppm. Olefinic carbons appear at 127.0 and 126.7 ppm. Saturated carbons are seen at 62.2, 54.1, 47.5, 28.5, 26.9 and 14.4 ppm. These results are consistent with the proposed structure.

We were not able to reach our aim with this method, therefore we had to change out synthetic strategy and continue with bishydrazides method.

2.3 The synthesis of bisurethane derivative 224 via bishydrazides 223

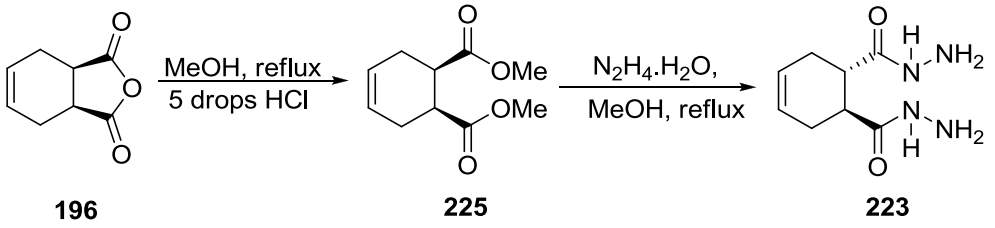
By application of third method, bishydrazides method, the aim was successfully achieved. Scheme 52 simply depicts the pathway. The starting material is same with one used in the first method. The anhydride **196** was again synthesized by [4+2] Diels-Alder reaction.



Scheme 52 The summary of third method

2.3.1 Synthesis of *rel*-(1*S*,2*S*)-cyclohex-4-ene-1,2-dicarbohydrazide (223)

The synthesized anhydride was reacted with methanol in the presence of catalytic amount of conc. HCl. This outcome was determined as a diester **225** through spectral analysis. To rich target compound diaminoconduritol **202**, neighboring two amine groups should be attached to the skeleton via isocyanate groups. Although there are many pathways to perform isocyanates in the literature, isocyanate was planned to be obtained through the compound **223**, which can be obtained upon the reaction of ester with hydrazine. The diester **225** was reacted with hydrazine at the reflux temperature of methanol to give the desired compound **223**.

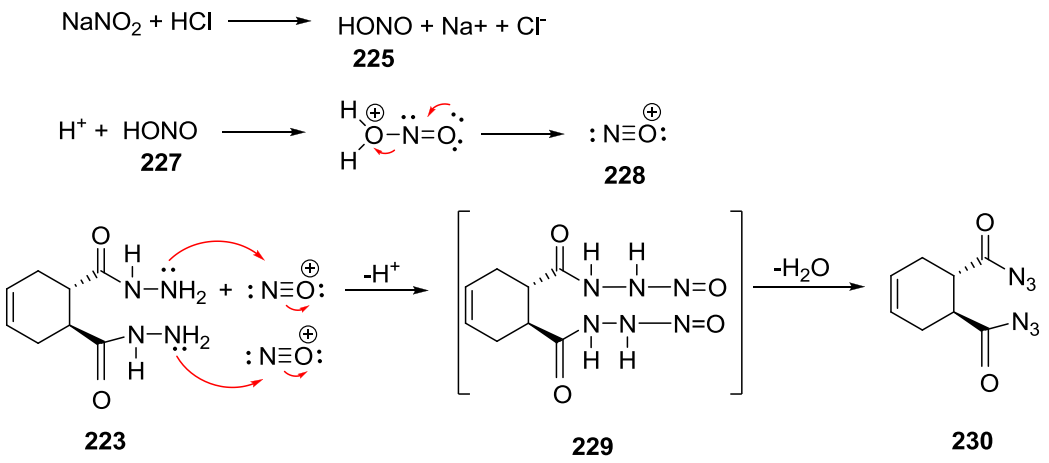


Scheme 53 The synthesis of compound **223**

According to ^{1}H and ^{13}C NMR spectral analyses, two NH protons resonate at 8.95 ppm and four NH_2 protons resonate at 4.08 ppm. While carbonyl carbons resonate at 173.3 ppm, olefinic ones appear at 125.4 ppm. The remaining carbon atoms are seen at 39.9 and 28.9 ppm. The spectral data were in agreement with the expected constitution in **223**. However, we were not able to determine the exact configuration of hydrazide groups in **223**. It is well-known that carbonyl groups having α-proton can easily undergo epimerization reaction in the presence of bases. Since diester **225** is reacted with a base such as hydrazine, it is likely that one of the carbonyl groups can undergo isomerization reaction during reaction with hydrazine. In order to address this question, whether an epimerization took place or not, we decided to change the symmetry in **223** by epoxidation of the double bond. In case of a *trans*-configuration of hydrazide groups, epoxidation of the double bond would distinguish between two substituents. In the epoxidation reaction, reagent should be dissolved in dichloromethane (DCM). However, dihydrazide derivative was not able to dissolve in DCM. So, epoxidation reaction was applied to urethane derivative **230,** which has symmetry and was soluble in DCM. We determined that the configuration in **224** was completely changed during hydrazination reaction. It will be explained in the corresponding section.

2.3.2 Synthesis of *rel*-(1*S*,2*S*)-cyclohex-4-ene-1,2-dicarbonyl diazide (230)

For obtaining acylazide derivative **230**, modified Sandmeyer reaction [79] was used. Diazide **230** was synthesized by conversion of dihydrazide derivative **223** in the medium containing sodium nitrite and acid at 0 ºC (Scheme 54).



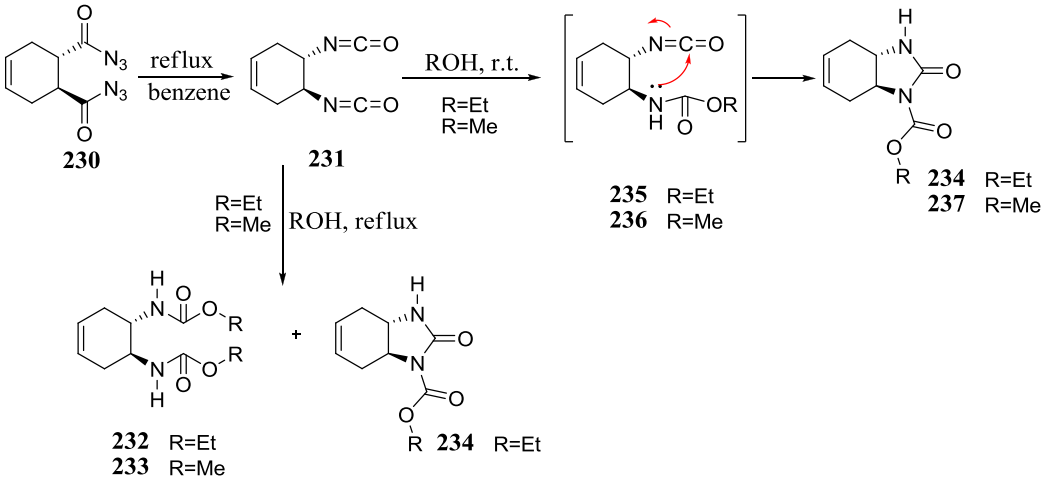
Scheme 54 The synthesis of compound **230**

The reaction was started by the formation of the nitrous acid **226** in acidic medium. Subsequently, nitrosonium ion **228** was formed by dehydration. Nucleophilic attack of NH_2 group in compound **223** to nitrosonium ion eventuated the corresponding β-nitroso hydrazide intermediate **229** and then it was converted to diazide derivative **230**.

2.3.3 Synthesis of dicarbamate (232 and 233) and imidazole (234 and 237) derivatives

As mentioned before, diacylazide **230** was converted to diisocyanate **231** by Curtius rearrangement. To obtain **201**, ethanol was added to diisocyanate **231** and then the mixture heated at reflux temperature for 6 h. After removing of solvent, the residue was purified by column chromatography and two products were isolated (Scheme 55). According to ^{1}H and ^{13}C NMR spectra, first spot was found to be carbamate derivative **232**. Protons of double bond resonate between 5.59-5.51 ppm as multiplet. Two NH protons are observed at 5.20 ppm as a broad singlet. Methylene and methyl protons of ester group resonate at 4.04 ppm

as a quartet and at 1.17 ppm as a triplet with coupling constant of 6.7 Hz, respectively. While CH_2 protons in cyclohexane skeleton give AB system, CH protons are seen at 3.92 ppm as quartet having coupling constant 5.8 Hz. In the ^{13}C NMR spectra, six different carbon atoms are seen as expected. Carbonyl carbon resonates at 157.1 ppm. Olefinic carbons are present at 124.9 ppm and other four carbon atoms resonate at 60.9, 51.7, 32.6 and 14.6 ppm.



Scheme 55 The synthesis of compounds **232**, **233**, **234** and **237**

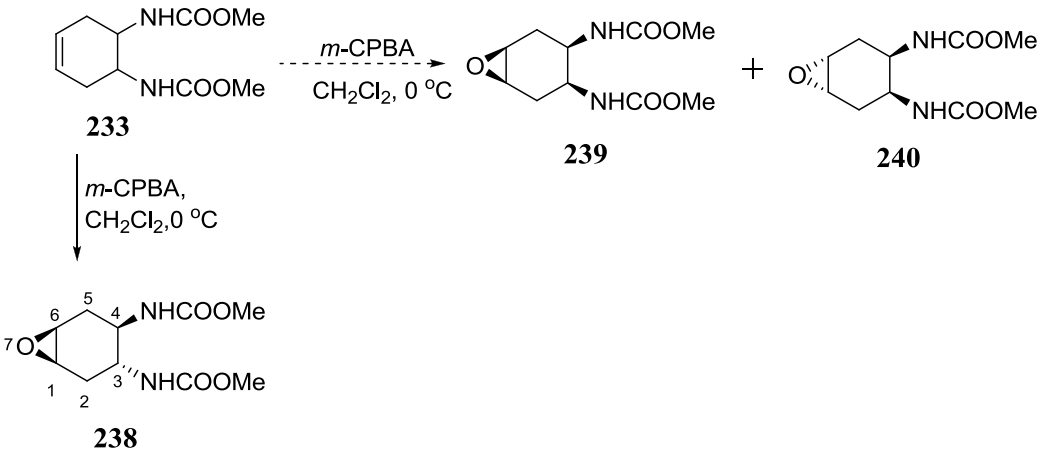
After analysis of the ^{1}H and ^{13}C NMR spectra and the HRMS results of the second compound, it was found to be imidazole derivative **234**. To check the effect of temperature on product distribution, the reaction was carried out with EtOH at room temperature. Only imidazole derivative **234** was formed. It means that when ethanol reacts with one isocyanate group at room temperature, the formed urethane **235** group blocks the attacking of ethanol to other isocyanate moiety. Consequently, an intramolecular addition between **235** and ethanol takes place as shown in Scheme 55. We assume that the reactivity of EtOH at higher temperature is increased and attack on isocyanate group can complete the intramolecular cyclization reaction. When the reaction was carried out with MeOH at room temperature, again cyclization product **237** was formed as the

sole product as in the case of reaction with EtOH. However, when bisisocyanate **231** was treated with MeOH at reflux temperature, contrary to the reaction with EtOH, only intermolecular addition product **233** was formed.

The reason of this outcome may be explained by bulkiness of **235**, which hinders, in some way the addition of second EtOH to **235**. It is well known that the rate of addition of alcohols to isocyanate decreases by the increased bulkiness of groups [80].

2.3.4 Determination of the configuration of urethane groups in 232: Reaction of 232 with *m*-chloroperbenzoic acid

As mentioned in section 2.3.3, dimethylcarbamate **233** was synthesized from dihydrazide **223**. To determine the configuration of carbamate moieties, symmetry of compound **233** was changed by epoxidation reaction. If the compound **233** has *trans*-configuration, only one epoxide **238** will be formed, since the both faces of the double bond are equal. However, in case of *cis*-conjugation of the substituents, *m*-chloroperbenzoic acid will differentiate between two faces and form an isomeric mixture consisting of **239** and **240** (Sheme 56). The ^{1}H NMR spectrum of the product formed after epoxidation of **233** consists of two different epoxide proton resonances in equal intensities. These resonances may arise either from the epoxide protons in **238** or from the epoxide protons in **239** and **240**, formed in a ratio of 1:1. To distinguish between those, COSY spectrum was taken. If the epoxide proton resonances would arise from **238**, then there must be a correlation between the epoxide protons. In case of **239** and **240**, there should be no correlation.



Scheme 56 Determination of the configuration of urethane groups in **233**

According to COSY spectrum, an interaction between H_1 and H_6 protons was observed (Figure 2.3). It means that these protons belong to one compound, which is **239**, and carbamate moieties are in *trans*-position. Finally, we assigned the *trans*- configuration to the molecule **238**. The expended spectrum of **238** can be seen in Figure 4.70.

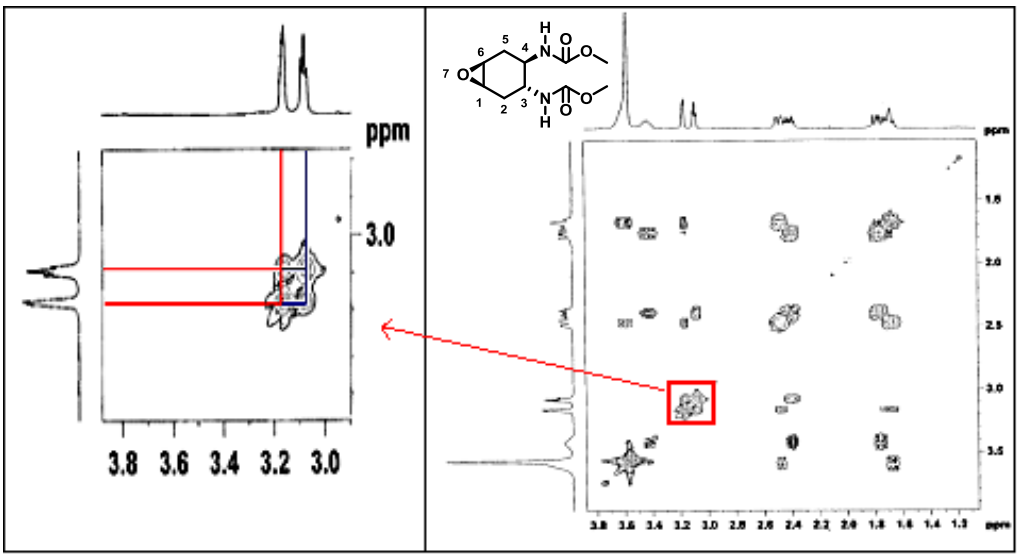
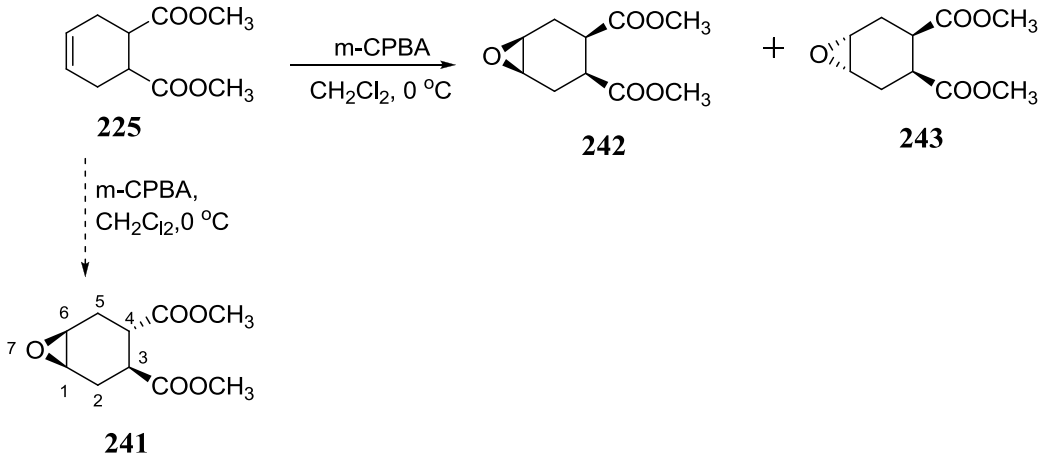


Figure 2.3 COSY Spectrum of compound **238**

After correct assignment of the configuration of urethane functionalities in **239**, we were interested in determining the configuration of ester groups in **225** to determine at which stage isomerization took place. *trans*-Dihydrazine **223** was synthesized from *cis*-dicarboxylate **225**. The diester **225** was submitted to epoxidation reaction with *m*-chloroperbenzoic acid. Spectral analysis of the mixture revealed the formation of two epoxides **242** and **243** with *anti*- and *syn*-configuration.



Scheme 57 Determination of the configuration of ester groups in **225**

COSY spectrum of the mixture did not indicate any correlation between epoxide protons (Figure 2.4). This clearly shows the formation of two isomers and the *cis*-configuration of ester groups in **225**. The expanded spectrum can be seen in Figure 4.66.

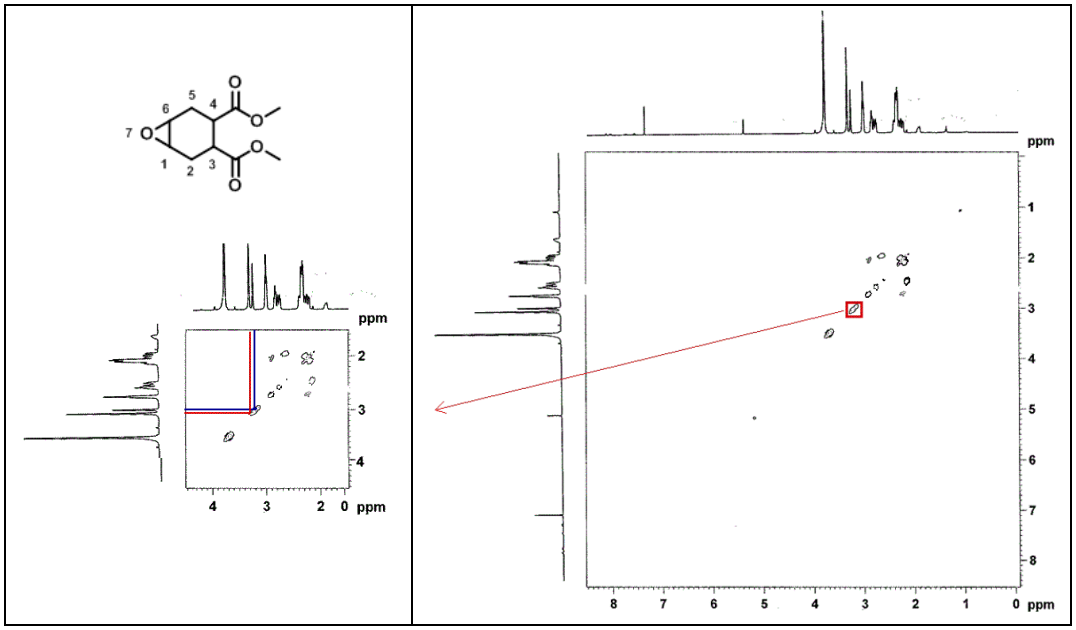


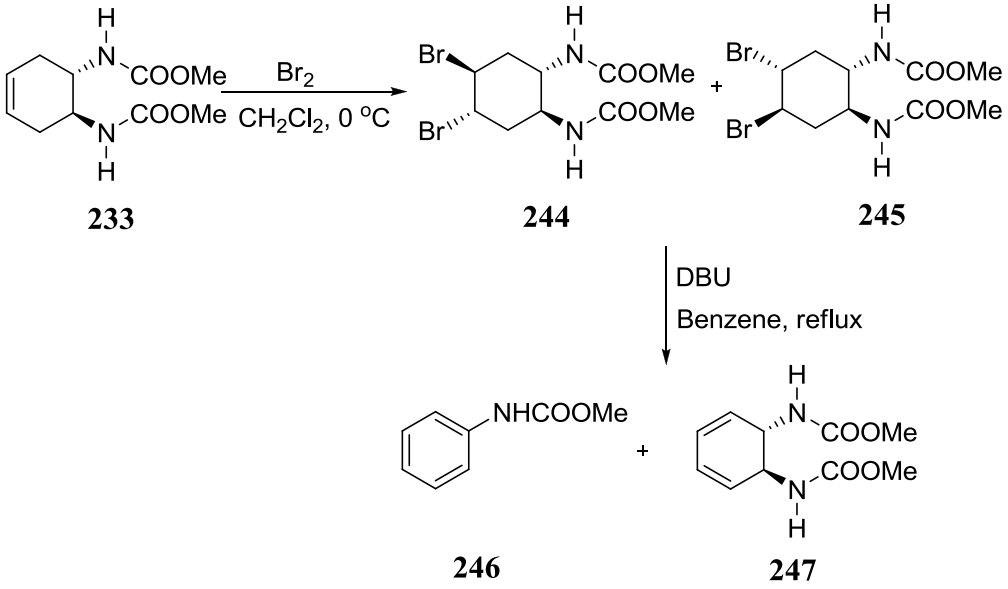
Figure 2.4 COSY spectrum of mixture **242** and **243**

2.3.5 Synthesis of dimethyl rel-(1*S*,6*R*)-cyclohexa-2,4-diene-1,6 diyldi-carbamate (247)

After successful synthesis of bis-carbamate **232**, the next step was the introduction of hydroxyl groups to C-2 and C-5 positions. One of the best methods to introduce oxygen to C-2 and C-5 positions is the photooxygenation reaction of a diene moiety. Therefore, we decided to convert the double bond in **233** into a diene system by addition of bromine followed by elimination reactions (Scheme 58).

Bromine atom can approach the double bond from top or bottom. There is no differentiation between those approaches. However, the formed bromonium ion can be opened in two ways. Bromide ion can attack C_1 as well as C_6 atoms to give an isomeric mixture consisting of **244** and **245**. We assume that bromide ion

attack the bromonium ion formed as intermediate, from the less hindered side and form **244** as the sole product.



233 **244** **245**

246 **247**

Scheme 58 The synthesis of compound **247**

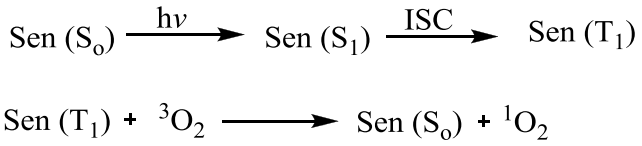
Reaction of double bond in compound **233** with the bromine provided *trans*-vicinal dibromide. According to ^{13}C NMR spectrum, carbonyl carbon of urethane moiety resonates at 155.8 ppm. When compared to aldehydes and ketons, it resonates at high field because of the mesomeric effect of the oxygen and nitrogen atoms next to the carbonyl carbon. While tertiary carbon next to nitrogen atom is observed at 50.6 ppm, another tertiary carbon and methoxy carbon resonate at 49.6 and 49.3 ppm, respectively. The remaining peak at 33.2 ppm belongs to methylene carbon. In the ^{1}H NMR spectrum, NH protons resonate at 4.56 ppm as broad singlet. Two types of CH protons are observed between 3.80-3.68 ppm. The other peaks are consistent with the structure.

After addition of bromine, dehydrobromination reaction was carried out by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. DBU was used because of its non-nucleophilic property. So, side products, which were resulted from

nucleophilic property were not obtained. At the end of reaction, two products were detected. While one of them was the desired product **247**, the other one was the aromatic compound **246**. NMR spectra of **246** are consistent with those reported in the literature [81]. For the compound **247**, protons of diene system give an AA'BB' system. A part of AA'BB' system resonates at 5.90 ppm as a quasi-doublet, whereas B part of AA'BB' system are observed also as a quasi-doublet at 5.71 ppm. Two NH protons resonate at 5.00 ppm as a broad singlet. The ^{13}C NMR data are completely in agreement with diene system. Especially, the presence of two double bond carbon resonances shows the formation of a symmetrical diene structure.

2.3.6 Photooxygenation of diene 247

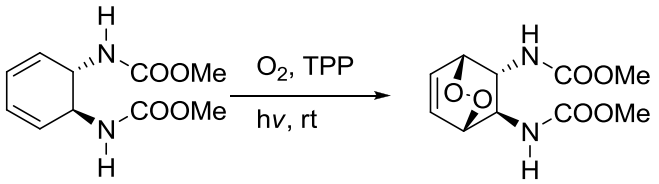
Photooxygenation reaction is very common method for the synthesis of cyclic and bicylic endoperoxides. These endoperoxides are also key compounds for the synthesis of corresponding diols. Singlet oxygen is generally prepared in the reaction medium by using photosensitizers [82]. The mechanism for the generation of singlet oxygen was proposed by Kautsky.



Scheme 59 The mechanism for the generation of singlet oxygen

In this mechanism, sensitizer is excited with light to form corresponding excited singlet state. In this step, inter system crossing (ISC) occures. It is an energy transfer from singlet state to triplet state of the sensitizer. After that, electronic excitation energy is transferred from the triplet of the sensitizer to triplet dioxygen, to form the sensitizer in its ground state and singlet oxygen.

The diene **247** was reacted with singlet oxygen in the presence of tetraphenylporphyrin (TPP) as the sensitizer and bicyclic endoperoxide **248** was fomed as the sole product (Scheme 60).



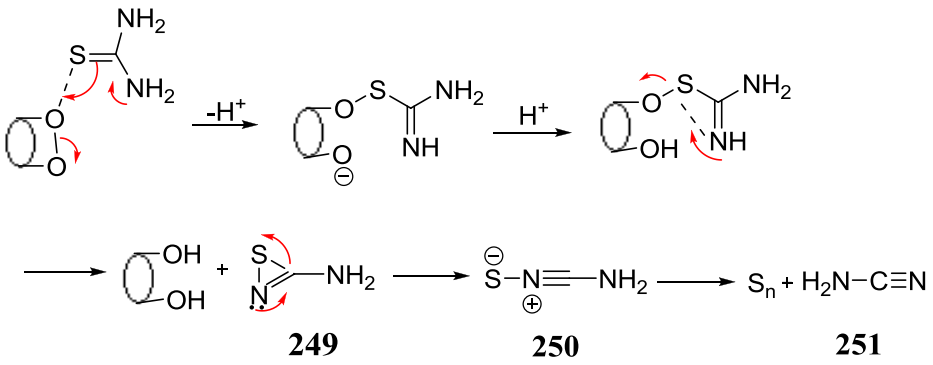
247 **248**

Scheme 60 The synthesis of compound **248**

In the ^{1}H NMR spectrum, two NH protons resonate as doublets at 7.93 and 7.40 ppm with coupling constants 6.8 and 6.6 Hz, respectively. Olefinic protons resonate at 6.82 and 6.64 ppm as triplets with coupling constants 6.9 and 6.4 Hz. The bridge-head protons are observed between 4.73-4.61 ppm as a multiplet. As expected, methoxy protons appear at 3.61 and 3.59 ppm. According to ^{13}C NMR spectrum, carbonyl carbons resonate at 156.6 and 156.1 ppm, whereas olefinic carbons appear at 132.4 and 130.7 ppm. Bridgehead carbons resonate at 74.7 and 71.2 ppm and methoxy carbons at 52.7 ppm. Carbon atoms attached to nitrogen atom resonate at 51.4 and 49.0 ppm.

2.3.7 Synthesis of *rel*- (1*R*,4*S*,5*R*,6*S*)-5,6 bis(methoxycarbonylamino) cyclo-hex -2-ene- 1,4-diyldiacetate (253)

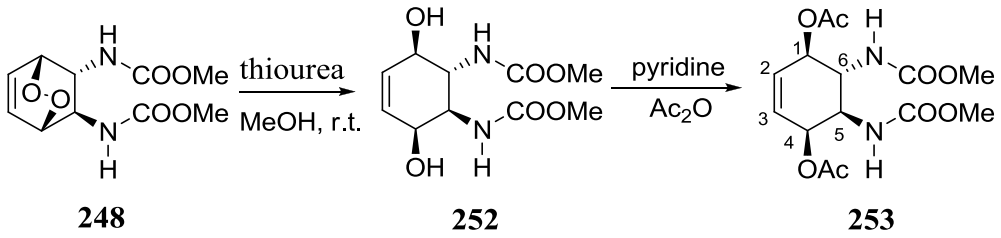
After photooxygenation reaction, endoperoxide group was transferred to hydroxyl group by using thiourea. The hydrogenolysis of endoperoxides using thiourea was first described by Schenck and Dunlap in 1956 [83]. Additionally, Balci reported that elemental sulfur can precipitate in these reactions [84]. The mechanism of the reaction is given in Scheme 61.



Scheme 61 The mechanism of the hydrogenolysis of endoperoxides

The reaction starts by attacking of the sulfur to an oxygen atom of endoperoxide. The attacking led to formation of sulfenate intermediate and it results in diol derivative and thiazirine **249**. With the ring opening in the compound **249**, it is converted to compound **250** and then it easily decomposes to cyanamide **251** and elemental sulfur.

The purification of the hydroxylated adduct **250** was hard. Therefore, hydroxyl groups were acetylated in the presence of acetic anhydride and pyridine as a base (Scheme 62).



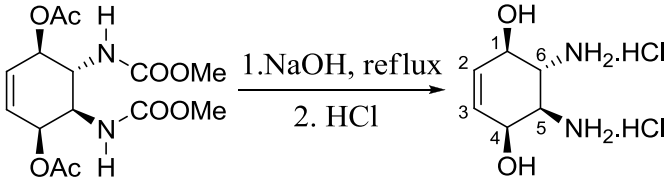
Scheme 62 The synthesis of compound **253**

According to ^{13}C NMR spectrum, carbonyl carbons of acetate groups resonate at 170.9 and 170.0 ppm. Because of mesomeric effect of nitrogen atoms, carbonyl carbons of carbamate moieties are present at 158.6 and 157.2 ppm. Methyl

carbon atoms of acetate groups are overlapped at 20.9 ppm. While olefinic carbon atoms are seen at 131 and 126 ppm as expected, four secondary carbon atoms resonate at 52.5, 52.4, 52.3, 52.2 ppm. In the ^{1}H NMR spectrum, olefinic protons give AB system. A part of AB system is seen at 6.08 ppm as doublet of doublets of doublets with coupling constant 9.8 Hz, 5.0 and 1.7 Hz. There is a long range coupling between olefinic H_3 and H_5 protons. B part of AB system is observed at 5.82 ppm as a doublet of doublets with coupling constant J =10.1 Hz and J = 2.0 Hz. Two NH protons are present at 5.27 and 5.07 ppm as broad singlets. While methyl protons of acetyl groups resonate at 2.12 and 2.13 ppm as a singlet, the methoxy protons are observed as a singlet at 3.69 ppm, shifted to low field due to the inductive effect of oxygen. H_1, H_4, H_5 and H_6 resonate at 5.43, 5.29, 4.17 and 3.99 ppm. All these data are in agreement with the proposed structure.

2.3.8 Synthesis of *rel*-(1*R*,4*S*,5*R*,6*R*)-5,6-diaminocyclohex-2-ene-1,4-diol dihydro-chloride (202)

With the help of acetylation of diol derivative **252**, characterization of **253** was performed. After that, to obtain target diaminoconduritol **202**, deprotection was applied in basic medium (Scheme 63).



253 **202**

Scheme 63 The synthesis of compound **202**

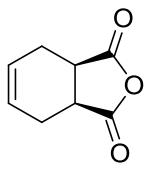
For this aim, compound **253** was dissolved in MeOH and NaOH was added. The mixture was heated at reflux temperature. At the end of the reaction, water was

added and then extracted with DCM. Water phase was separated and acidified with 4M HCl. After acidification, water was removed and salt of the diaminoconduritol **202** was obtained. In the ^{13}C NMR spectrum, 6 different C atoms were observed. Two of them at 131.5 and 126.5 ppm belong to olefinic carbons. While peaks at 67.6 and 62.9 ppm are related with the tertiary carbons attached to hydroxyl groups, tertiary carbon atoms neighboring nitrogen atoms resonate at 52.3 and 50.9 ppm. According to ^{1}H NMR spectrum, olefinic two protons resonate between 6.04 and 5.94 as a multiplet. H_5 and H_6 protons resonate as an AB-system at 3.87 and 3.59 ppm, respectively. The coupling J_{56} = 11.6 Hz, extracted from AB-system, clearly shows the *trans*-configuration of amine groups. Both parts of AB-system are further spit into doublet of doublets by the adjacent alkoxy protons. The resonance signal of H_5 is split by 4.2 Hz indicating the *cis*-configuration with the adjacent proton H_4, whereas the resonance by J = 8.7 Hz. This value supports the *trans*-configuration of H_1 and H_6 protons. These two large coupling constants show the *trans*-configuration of H_6 proton with the neighboring protons.

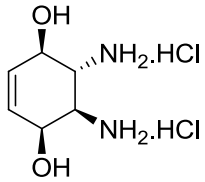
CHAPTER 3

CONCLUSION

In this study, three different methods were designed for the synthesis of target diaminoconduritol derivative **202**.

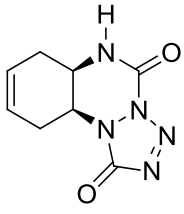


196

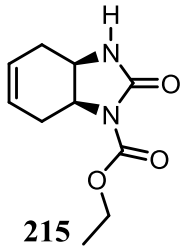


202

While 1,2,3,6-tetraphthalic anhydrate (**196**) derived from Diels-Alder reaction between of maleic anhydride and 3-sulfolene was used as a starting compound in two methods, 1,4-cyclohexadiene was used in the other one. In the first two methods, unexpected products **205** and **215** were obtained.



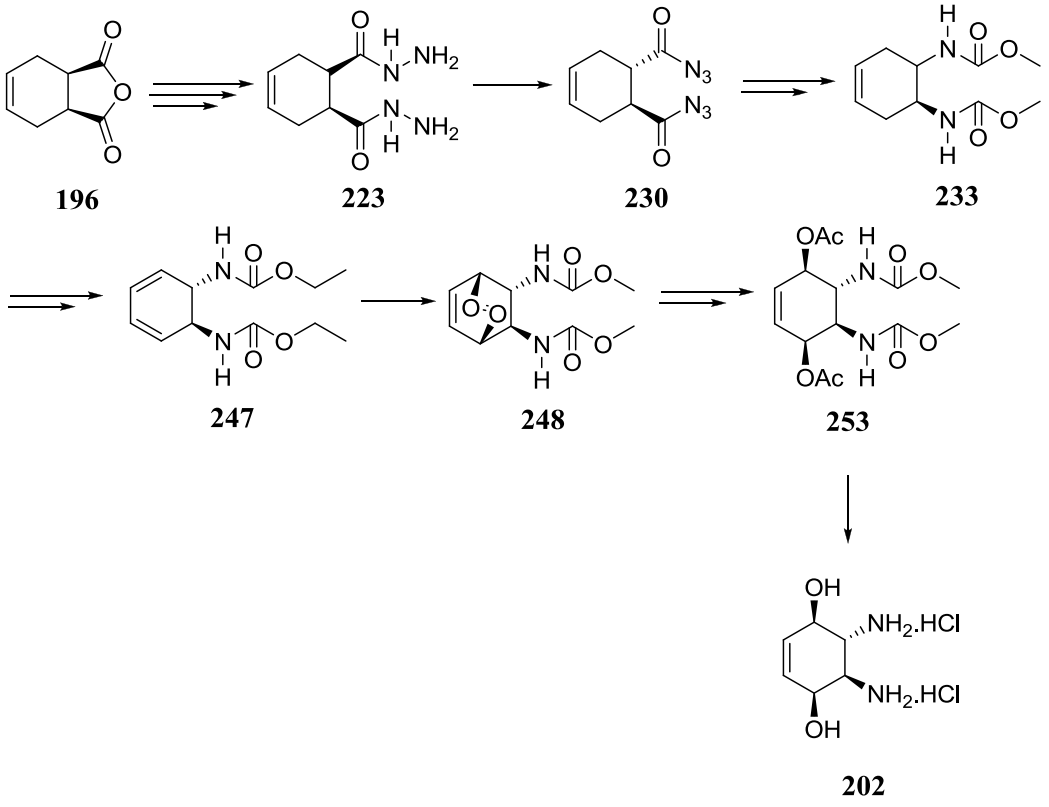
205



215

In the third method, compound **247** was synthesized successfully by starting from 1,2,3,6-tetraphthalic anhydride (**196**) in high yield. First aim was to obtain

carbamate derivative **201**. For that reason, the anhydride group was transferred to methyl ester moieties. The ester groups were converted to dihydrazide group. After obtaining acyl azide derivative **230** from dihydrazide derivative **223**, the compound **201** was obtained by Curtius degradation followed by addition of the corresponding alcohol. The second goal was the synthesis of the compound **202**. To attach two hydroxyl groups, diene derivative **247** was synthesized from carbamate derivative **201** by bromination and elimination reaction, respectively. Photooxygenation reaction gave rise to endoperoxide **248**. Hyroxyl groups were formed by cleavage of the O-O bond of endoperoxide **248**. Subsequently, acetylation was applied for analysis of protected diaminoconduritol **253**. Finally, the salt of target diaminoconduritol **202** was obtained by deprotection of compound **253** in basic medium (Scheme 64).



Scheme 64 The summary of third method

CHAPTER 4

EXPERIMENTAL

4.1 General considerations

Nuclear Magnetic Resonance (^{1}H, ^{13}C, and 2D) spectra were recorded on a Bruker Instruments Avance Series-Spectrospin DPX-400, Ultra Shield (400 MHz), High Performance digital FT-NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (TMS) reference and deuterochloroform ($CDCl_3$), deuteroacetone and deuterowater as the solvents. Coupling constants (*J* values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols; s: singlet, d: doublet, t: triplet, q: quartet and m: multiplet.

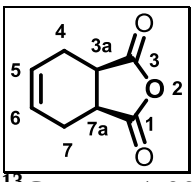
Infrared spectra were recorded on a Nicolet 8700 FT-IR Spectrometer with ATR (Attenuated Total Reflection) attachment. Band positions are reported in reciprocal centimeters (cm^{-1}).

Column chromatographic separations were performed by using Fluka Silicagel 60 with 0.063-0.170 mm particle size. The relative proportions of solvents refer to volume:volume ratio. Thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Fluka.

All the solvent purifications were done as stated in the literature [85].

4.2 Synthesis of *rel*-(3a*R*,7a*S*)-3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione 196)

The compound was synthesized as described in the literature [74].

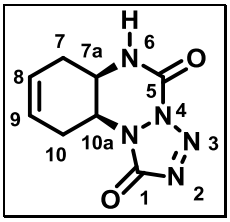


^{1}H NMR (400 MHz, d-MeOH, ppm) δ: 5.60-5.51 (m, 2H, H_5 and H_6), 3.01-2.89 (m, 2H, H_{4a} andH_{7a}), 2.49-2.21 (m, 4H, $2H_4$ and $2H_7$).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 176.7, 129.0, 40.9, 24.4.

4.3 Synthesis of 6a,7,10,10a-tetrahydro-1*H*-tetraazolo[1,2-*a*][1,2,4]benzotri-azine-1,5(6*H*)-dione (205)

1,2,3,6-Tetrahydrophthalic anhydride (**196**) (1 g, 6.6 mmol) was dissolved in 40 mL of dry THF. Me_3SiN_3 (TMSA) (1.06 g, 9.2 mmol) was added to the stirred solution [86]. The solution was heated to reflux temperature. N_2 evolution was over after 30-45 min. The solution was cooled and concentrated in vacuum. The residue was dissolved in 20 mL of $CC1_4$. DMF (3 drops) was added followed by $SOC1_2$ (0.347 g, 2.92 mmol). The reaction mixture was heated to 40-50 ºC. When the infrared absorption at 1720 cm^{-1} (ester) disappeared (30-45 min), the solution was cooled to room temperature and concentrated in vacuum (bath temperature should be below 35 ^{o}C). The remaining residue was dissolved in 25 mL of dry THF. TMSA (1.06 g, 9.02 mmol) was added at r.t. to the stirred solution, which was subsequently heated to 80-85 ºC. Reflux was done throughout 90 min. After reaction was complete, the solution was cooled to room temperature and concentrated in vacuum. Brown precipitate was filtered from gauche and washed with CH_2Cl_2 to give unexpected product **205** (1.15g, 5.55 mmol, 61%, and brown solid) Mp: 143-144 ºC.



^{1}H NMR (400 MHz, DMSO, ppm) δ: 7.62 ppm (s, 1H, -NH-), 5.84 (qt, *J* = 4.1 Hz, 2H, $H_8$and H_9), 4.37 (p, *J* = 4.6 Hz, 1H, H_{10a}), 3.97 (p, *J* = 4.1 Hz, 1H, H_{7a}), 2.36 (dd, A-part of AB system, *J* = 15.6 Hz, *J* = 4.4 Hz, 1H), 2.24 (md B- part of AB system, *J* = 15.5 Hz, 1H), 2.20- 2.06 (m, AB system, 2H)

^{13}C NMR (400 MHz, DMSO, ppm) δ: 153.9, 153.5, 127.6, 127.3, 54.2, 46.9, 28.1, 26.5.

IR (KBr, cm^{-1}):3344, 3316, 3043, 2970, 2171, 2152, 1751,176, 1340, 1179, 627.

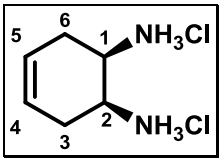
Anal.: Calculated for $C_8H_9N_5O_2$: C: 46.38; H: 4.38; N: 33.80. found: C: 45.50; H: 4.79; N:31.25.

HRMS: Calculated for $C_8H_9N_5O_2$ $[M+Na]^+$: 208.0829 found $[M+Na]^+$: 208.0879.

4.4 Synthesis of *rel*-(1*R*,2*S*)-cyclohex-4-ene-1,2-diamine dihydrochloride (213)

1,2,3,6-Tetrahydrophthalic anhydride (**196**) (3 g, 19.8 mmol) was dissolved in 40 mL of dry THF. Me_3SiN_3 (TMSA) (2.28 g, 19.8 mmol) was added to the stirred solution. The solution was heated to reflux temperature. N_2 evolution was over after 30-45 min. The solution was cooled and concentrated in vacuum. The residue was dissolved in 20 mL of $CC1_4$. DMF (3 drops) was added followed by $SOC1_2$ (1.041 g, 8.76 mmol). The reaction mixture was heated to 40-50 ºC. After 1hour, the solution was cooled to room temperature and concentrated in vacuum (bath temperature should be below 35 ^{o}C). The remaining residue was dissolved in 25 mL of dry THF. TMSA (2.28 g, 19.8 mmol) was added at r.t. to the stirred solution, which was subsequently heated to 80-85 ºC. Reflux was done throughout 90 min. After reaction was complete, half of the solvent was removed and same amount of acetone was added. When the solution was cooled to 0 ^{o}C, concentrated HCl was added. Stirring was continued until CO_2 formation

finished. White precipitate was filtered and washed with Me_2CO and Et_2O to obtain product **213** (0.64 g, 5.7 mmol, 30% white solid) [86].

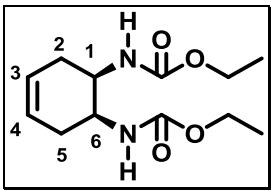


^{1}H NMR (400 MHz, DMSO, ppm) δ: 8.76 (s, 6H, $2NH_3Cl$), 5.64 (quasi-t, 2H, H_4 and H_5), 3.82 (br s, 2H, H_1 and H_2), 2.56 (br d, A-part of AB system, *J* = 16.9 Hz, 2H), 2.28 (dd, B part of AB-system, *J* = 16.9 Hz, J = 5.9 Hz, 2H).

^{13}C NMR (400 MHz, DMSO, ppm) δ: 123.7, 47.6, 27.1.

4.5 Synthesis of diethyl rel-(1*S*,6*R*)-cyclohex-4-ene-1,6-diyldicarbamate (201)

To a suspention of compoud **213** (4.95 g, 44mmol) in dry DCM was added Et_3N (8.90 g, 88 mmol) at 0 ºC and this solution was stirred for half hour. It was followed by adding ClCOOEt (10.54 g, 97 mmol) in dry DCM. The reaction mixture was stirred 16 h at r.t. The solution was acidified with 2 M $HCl_{(aq)}$ and extracted with DCM (40 mL) two times. The combined organic phases were combined and dried over $MgSO_4$, filtered and evaporated in vacuum. The residue was purified by column chromatography (CH_2Cl_2) to obtain product **201**. Mp: 132-133 ºC.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.55 (qt, 2H, 2H, H_3 and H_4), 5.27 (br s, 2H, 2-NH-), 4.05 (q, *J* = 6.98 Hz, 4H, 2-COO*C*$H_2$$CH_3$), 3.92 (q, *J* = 3.95 Hz, 2H, H_1 and H_6), 2.48 (br d, A part of AB-system, *J* = 16.41 Hz, 2H), 1.96 (dd, B-part of AB-system *J* = 16.63 Hz, *J* = 4.83 Hz,2H), 1.18 (t, *J* = 7.07 Hz, 6H, 2-$COOCH_2$*C*H_3).

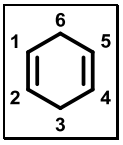
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 157.1, 124.9, 60.9, 51.7, 32.64, 14.6.

IR (ATR): 3302, 2982, 2912, 1677, 1536, 1303, 1278, 1055, 1038, 664.

HRMS: Calculated for $C_{12}H_{20}N_2O_4$ $[M+H]^+$: 257.1495 found $[M+H]^+$: 257.1487.

4.6 Synthesis of cyclohexa-1,4-diene (214)

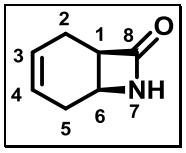
In 500 mL, two necked flask, dry benzene (27.3 g, 0.35 mol), *tert*-buthanol (72 g, 0.96 mol) and dry THF (120 ml) were mixed and the medium was saturated with NH_3 gas at 0 ^oC. Lithium (7.35 g) was added to the reaction mixture with small portions in 5 minutes. The reaction temperature was allowed to increase gradually to r.t. and it was stirred for 5 h. After the mixture was cooled in ice bath, small portions of ice wad added until there was no more lithium left. The mixture was acidified with 2N cold HCl solution. Organic layer was separated and washed with cold water (100 mL), $NaHCO_3$ (5%, 50 ml) and water (75 mL) respectively. Reduction product was dried over $CaCl_2$ and filtered to obtain diene **213** (22 g, 0.27 mol, 77%) [77].



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.72 (s, 4H, H_1, H_2, H_4 and H_5), 2.7 (s, 4H, H_3 and H_6).
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 124.4, 25.8.

4.7 Synthesis of *rel*-(1*R*,6*S*)-7-azabicyclo[4.2.0]oct-3-en-8-one (218)

It was synthesized as described in the literature [78].

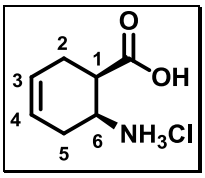


^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 6.44 (s, 1H, NH), 5.82-5.75(m, 1H, H_4), 5.70-5.61 (m, 1H, H_3), 3.91 (t, *J*= 4.76 Hz, 1H, H_6), 3.29 (t, *J* = 4.78 Hz, 1H, H_1), 2.42-2.22 (m, 2H, H_5), 2.15-2.01 (m, 2H, H_2).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 170.9, 126.0, 124.3, 47.95, 46.9, 27.1, 21.2.

4.8 Synthesis of *rel*-(1*R*,6*S*)-6-aminocyclohex-3-ene-1-carboxylic acid (219)

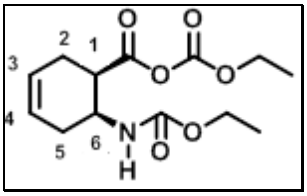
It was synthesized as described in the literature [78].



^{1}H NMR (400 MHz, DMSO, ppm) δ: 8.17 (br s, 3H, NH_3Cl), 5.70-5.50 (m, 2H, H_3 and H_4), 3.58-3.48 (m, 1H, H_6), 3.06-2.97 (m, 1H, H_1), 2.44-2.22 (m, 4H, H_2 and H_5).
^{13}C NMR (400 MHz, DMSO, ppm) δ: 173.6, 125.4, 123.0, 45.9, 27.5, 24.9.

4.9 Synthesis of {*rel*-(1*R*,6*S*)-6-[(ethoxycarbonyl)amino]cyclohex-3-en-1-yl}carbonyl ethyl carbonate (220)

Compound **219** (1.16 g, 6.53 mmol) was dissolved in 40 mL THF and 2 ml distilled water and cooled in an ice bath. NaOH (1.04 g, 26.00 mmol) was dissolved in minimum amount of water. The solution of NaOH was added drop by drop. After 30 min., a cold (0 ºC) solution of ethyl chloroformate (4.24 g, 39.07 mmol) in 10 ml of THF was added dropwise over 10 min. The reaction mixture was stirred for 4 hours in ice bath. Reaction mixture was diluted with EtOAc (50 ml) and washed with 10% HCl solution (3x30ml). The organic layer was washed with brine (2 × 20 mL), dried with $MgSO_4$ and concentrated in vacuum. The residue was purified by colon chromatography (CH_2Cl_2) to afford product **219** (1.28 g, 4.48 mmol, 69%, white solid) Mp: 132-133 ºC.



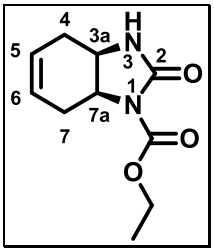
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.63 (quasi-t, 2H, H_3 and H_4), 5.16 (d, *J* = 6.3 Hz, 1H, NH), 4.40-4.14 (m, 4H, 2-COO*CH*$_2$CH$_3$), 3.01-2.89 (m, 1H, H_1), 2.62-2.13 (m, AB-system, 2 H_2 and 2 H_5), 1.32 (t, *J* = 7.2 Hz, 3H, -COOCH$_2$*CH*$_3$), 1.86 (t, *J* = 6.5 Hz, 3H, -COOCH$_2$*CH*$_3$).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 166.2, 154.9, 147.7, 124.0, 123.2, 64.7, 59.9, 45.2, 41.6, 29.3, 24.3, 13.5, 12.9.

IR (ATR): 3401, 3325, 2982, 2934, 1815, 1716, 1514, 1239, 1084, 986.

4.10 Synthesis of ethyl *rel*-(3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-benzimidazole-1carboxylate (215)

Compound **220** was dissolved in 30 mL of acetone. Sodium azide in 10 mL of water was added to the solution and it was kept at 0 ºC for 1h. After 1h, ethyl acetate (30 mL) was added and organic phase was separated. It was washed with water (2 × 30 mL). Organic phase was dried over $MgSO_4$. After solvent was remover, 30 mL of dry benzene was added and heated to reflux temperature. After the rearrangement was finished, solvent was evaporated to obtain product **215** (157 mg, 67%, white solid) Mp: 135-136 ºC.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 6.83 (s, 1H, -NH-), 5.83 (qt, *J*= 4.5 Hz, H_5 and H_6), 4.30-4.14 (m, 2H, H_{7a} and –COO*CH*$_2$CH$_3$), 3.93 (p, *J* = 4.8 Hz, 1H, H_{3a}), 2.36 (dt, A part of AB system, *J* = 15.6 Hz, *J*=5.2 Hz, 1H, H_7), 2.28 (dt, B part of AB system, *J*=15.6 Hz, *J*=5.1 Hz, 1H, H_7), 2.24 (dt, A part of AB-system, *J*= 15.3 Hz, *J*=5.0 Hz, 1H, H_4), 2.14 (dt, B part of AB-system, *J*=15.9 Hz, *J*=4.4 Hz, 1H, H_4), 1.38 (t, *J* = 7.0 Hz, 3H, -COOCH$_2$*CH*$_3$).

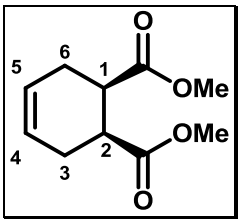
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 156.4, 151.9, 127.0, 126.7, 62.2, 54.1, 47.5, 28.5, 26.9, 14.4.

IR (ATR): 3307, 3029, 2980, 2909, 1778, 1714, 1318, 1285, 1138, 1099, 778.

Anal.: Calculated for $C_{10}H_{14}N_2O_3$: C: 57.12; H: 6.22; N: 13.38. Found: C: 57.13; H: 6.71; N: 13.38.

4.11 Synthesis of *rel*-(1*R*,2*S*)-dimethyl cyclohex-4-ene-1,2-dicarboxylate (225)

1,2,3,6-Tetrahydrophthalic anhydride (**196**) was (65 g, 0.427 mol) was dissolved in 200 ml of MeOH. 5 drops HCl was added as a catalyst. The solution was refluxed overnight. After the reaction was evaporated in vacuum and purified by colon chromatography (CH_2Cl_2) to afford product **225** (61.33 g, 0.31mol, 72.5%, colorless liquid)



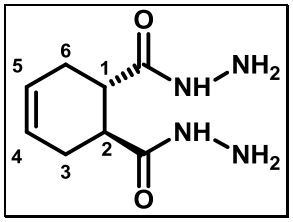
^{1}H NMR (400 MHz, $CDCl_3$,ppm) δ: 5.63 (m, 2H, $H_4$and H_5), 3.63 (s, 6H, 2-COOCH_3), 2.91-2.84 (m, 2H, $H_1$and H_2), 2.51 (dd, A-part of AB system, *J*=15.6 Hz, *J*=4.4 Hz, 2H), 2.34 (dd, B-part of AB-system, *J*=15.6 Hz, *J*=4.8 Hz, 2H).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 173.5, 124.9, 51.6, 39.6, 25.6.

4.12 Synthesis of *rel*-(1*S*,2*S*)-cyclohex-4-ene-1,2-dicarbohydrazide (223)

Rel-(1*R*,2*S*)-dimethyl cyclohex-4-ene-1,2-dicarboxylate **225** (43.22gr, 0.22 mol) was dissolved in 75 ml of MeOH. Hydrazinemonohydrate (38.22 g, 37 ml, 0.76 mol) was added to the solution in room temperature and then the mixture was refluxed overnight. The solution was concentrated in vacuum. The residue was

filtered by gauche and washed with DCM to purify the product **223**. (26 g, 0.13 mol, 59%, white solid) [87].

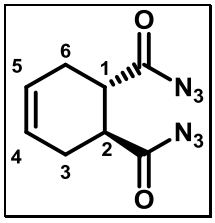


^{1}H NMR (400 MHz, DMSO, ppm) δ: 8.98 (s, 2H, 2-NH-), 5.65 (br s, 2H, H_5 and H_6), 3.64 (br s, 8H, 2-NH_2 and H_2O in DMSO), 2.60-2.44 (m, 2H, H_1 and H_2), 2.20-1.95 (m, 4H, 2 H_6 and 2 H_3)

^{13}C NMR (400 MHz, DMSO, ppm) δ: 174.4, 126.3, 45.5, 29.9.

4.13 Synthesis of (1S,2S)-cyclohex-4-ene-1,2-dicarbonyl diazide (230)

Compound **223** (6.2 g, 31 mmol) was dissolved in 100 ml of 1M HCl and cooled to 0 ºC. $NaNO_3$ (15g, 62 mol), dissolved in min. amount of water was added dropwise, keeping the temperature below 5 ºC. The mixture was stirred in ice bath for 1 h, and then extracted with ether (3 × 75 mL). The combined ether layer washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and solvent was evaporated under 30 ºC to give product **230** (5.2 g, 24 mmol, 77 %, light yellow liquid) [87].

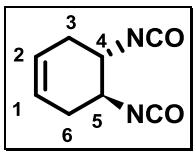


^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.72-5.64 (m, 2H, H_4 and H_5), 2.88-2.78 (m, 2H, H_1 and H_2), 2.50- 2.38 (m, A-part of AB system, 2H), 2.20- 2.06 (m, B-part of AB system, 2H).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 181.7, 124.6, 42.9, 27.7.

4.14 Synthesis of *rel*-(4*S*,5*S*)-4,5-diisocyanatocyclohexene (231)

Compound **230 (**5.2 g, 24 mmol) was dissolved in 75 mL of dry benzene and heated to reflux temperature for 90 min. After the rearrengement was completed, benzen was evaporated [87].



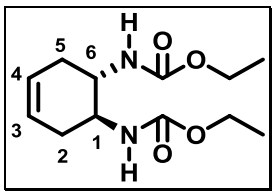
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.64 (m, 2H, H_1 and H_2), 3.73-3.66 (m, 2H, H_4 and H_5), 2.63-2.52 (m, A-part of AB system, 2H), 2.28-2.17 (m, B-part of AB system, 2H).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 123.7, 55.29, 32.62.

4.15 Synthesis of diethyl *rel*-(1S,6S)-cyclohex-3-ene-1,6-diyldicarbamate (232) and ethyl *rel*-(3a*S*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-benzimidazole-1-carboxylate (234)

Compound **229** obtained by refluxing of compound **230** (5.2 g, 24 mmol) was dissolved in 75 mL of EtOH and heated to reflux temperature. After six hours, solvent was evaporated. The residue gave a crude mixture consisting of **230** and **234** which was separated by silica gel chromatography eluting with CH_2Cl_2. While the first fraction was compound **232** [81] (3.43 g, 13.4 mmol, 56%) Mp: 126-127 ºC, the second fraction was identified as **234** (1.99g, 9.45 mmol, 39%) Mp: 136-138 ºC.

For compound **232**

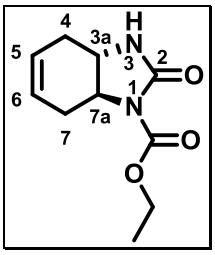


^{1}H NMR (400 MHz, $CDCl_3$,ppm) δ: 5.59-5.51 (m, 2H, H_3 and H_4), 5.20 (br s, 2H, 2-NH-), 4.04 (q, *J*=6.7 Hz, 4H, 2-COO$CH_2$$CH_3$), 3.92 (q, *J*=5.8 Hz, 2H, H_1 and H_6), 2.47 (br d, A-part of AB system *J*=

16.2 Hz, 2H), 1.96 (dd, B- part of AB system, J = 16.3 Hz, J = 5.6 Hz, 2H), 1.17 (t, J=7.0 Hz, 6H, 2-COOCH$_2$*CH$_3$*).

^{13}C NMR (400 MHz, CDCl$_3$, ppm) δ: 157.1, 124.9, 60.9, 51.7, 32.6, 14.6.

For compound **234**



^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.74 (br s, 1H, H$_3$), 5.68-5.58 (m, 2H, H$_5$and H$_6$), 4.23 (q, J = 7.2 Hz, 2H, H$_1$), 3.56 (dt, J = 10.8 Hz, J = 4.72 Hz, H$_{7a}$)3.31 (dt, J = 10.9 Hz, J = 5.0 Hz, 1H, H$_{3a}$), 2.94-2.82 (m, 1H), 2.44-2.34 (m, 1H), 2.22-2.02 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H, -COOCH$_2$*CH$_3$*).

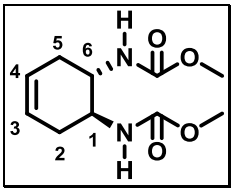
^{13}C NMR (400 MHz, CDCl$_3$, ppm) δ: 158.2, 152.9, 125.9, 124.7, 62.7, 59.7, 53.8, 31.3, 30.9, 14.6.

IR (KBr, cm^{-1}): 3298, 3022, 2860, 1771, 1687, 1351, 1321, 1289, 1142, 1152, 1013, 680.

HRMS: Calculated for $C_{10}H_{14}N_2O_5$ $[M+H]^+$: 211.1077 found $[M+H]^+$: 211.1085.

4.16 Synthesis of dimethyl *rel*-(1*S*,6*S*)-cyclohex-3-ene-1,6-diyldicarbamate (233)

Compound **231** obtained by refluxing of compound **230** (17.8 g, 81 mmol) was dissolved in 150 mL of MeOH and heated to reflux temperature for 6 hours and then the solvent was evaporated. The residue was purified by colon chromatography CH_2Cl_2 to give compound **233** (17.4 g, 87%, white solid) Mp: 175-176 ºC.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.53 (br d, *J* = 2.5 Hz, 2H, H_3 and H_4), 4.92 (br s, 2H, 2-NH-), 3.74-3.56 (m, 8H, H_1 H_6, and 2-COO*C*H_3), 2.52-2.40 (m, A part of AB-system, 2H), 2.03-1.88 (m, B part of AB-system, 2H).

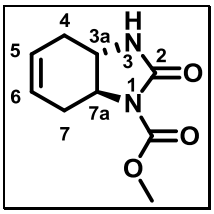
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 157.5, 124.9, 52.2, 51.8, 32.6.

IR (ATR): 3305, 2951, 2921, 2843, 1679, 1540, 1281, 1249, 1085, 1059, 669.

HRMS: Calculated for $C_{10}H_{16}N_2O_4$ $[M+H]^+$: 229.1183 found $[M+H]^+$: 229.1185.

4.17 Synthesis of methyl *rel*-(3a*S*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-benzimidazole-1-carboxylate (237)

Compound **231** obtained by refluxing of compound **230** (2.04 g, 9.3 mmol) was dissolved in 50 mL of MeOH and stirred at rt. for 6 hours. When the time finished, the solvent was evaporated. The residue was purified by column chromatography using CH_2Cl_2 to give compound **237** (1.7 g, 8.6 mmol, 93%, white solid) Mp: 172-174 ºC.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.70-5.58 (m, 2H, H_5 and H_6), 5.49 (br s, 1H, -NH-), 3.79 (s, 3H, COO*C*H_3), 3.57 (dt, (*J* = 10.9 Hz, *J* = 4.9 Hz, 1H, H_{7a}), 3.32 (dt, *J* = 10.9 Hz, *J* = 4.9 Hz, 1H, H_{3a}), 2.96- 2.86 (m, 1H, H_7), 2.43-2.33 (m, 1H, H_7), 2.22-2.05 (m, 2H, H_4).

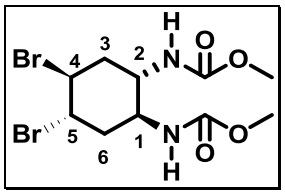
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 157.9, 153.4, 125.7, 124.4, 59.6, 53.6, 53.4, 30.9, 30.6.

IR (ATR): 3329, 3232, 3029, 2913, 2854, 2246, 1740, 1682, 1318, 1289, 1142, 723

HRMS: Calculated for $C_9H_{12}N_2O_3$ $[M+Na]^+$: 219.07401 found $[M+Na]^+$: 219.0769.

4.18 Synthesis of dimethyl *rel*-(1*S*,2*R*,4*S*,5*S*)-4,5-dibromocyclohexane-1,2-diyldicarbamate (244)

To a magnetically stirred solution of **233** (19.5 g, 85.5 mmol) in 150 mL of CH_2Cl_2 at 0 ^oC was added drop wise a solution of bromine (27.4 g, 171 mmol) in 25 mL of CH_2Cl_2 over a period of 1 h. The reaction mixture was stirred for an additional 2 hours at room temperature. Because of low solubility of product **244** in DCM, homogenous mixture was observed. After the consuming of bromine solution, saturated sodium metabisulfite solution was slowly added to homogenous mixture at 0 ^oC to take excess bromine. Solvent was evaporated and residue was washed with EtOAc by using gouch to purified product **244** (27.3 g, 81 mmol, 95% white solid) Mp: 197-198 ºC.



^{1}H NMR (400 MHz, DMSO, ppm) δ: 4.56 (br s, 2H, 2-NH-), 3.80-3.68 (br s, 4H, H_1, H_2, H_4 and H_5), 3.20 (s, 6H, 2-COO*C*H_3), 1.64 (br s, 4H, $2H_3$ and $2H_6$).

^{13}C NMR (400 MHz, DMSO, ppm) δ: 155.8, 50.6, 49.6, 49.3, 33.2.

IR (ATR): 3333, 2943, 1694, 1533, 1288, 1244, 1049, 777.

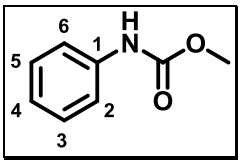
HRMS: Calculated for $C_9H_{12}Br_2N_2O_3$ $[M+Na]^+$: 408.9369 found $[M+Na]^+$: 408.9335.

4.19 Synthesis of dimethyl *rel*-(1*S*,6*S*)-cyclohexa-2,4-diene-1,6 diyldicarbamate (247) and methyl phenylcarbamate (246)

To a solution of dibromide **244** (3.0 g, 7.77 mmol) in 100 mL of dry benzene was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (4.73 g, 31.08 mmol) at r.t. The reaction mixture was refluxed for 6 h and then cooled to r.t. The solid was filtered off. Solvent was evaporated. Residue was dissolved in100

mL of EtOAc and extracted with aqueous sodium bicarbonate (2 × 50 mL). The organic phase was dried over $MgSO_4$, and evaporated in vacuum. Elimination of the residue gave a crude mixture consisting of **246** and **247** (820 mg), which was separated by silica gel chromatography eluting with EtOAc/CH_2Cl_2/ hexane (1:2:0.5). The first fraction was compound **246 (**106 mg, 0.70 mmol, 9%).The second fraction was identified as **247** (299 mg, 1.32 mmol, 17%) Mp: 162-163 ºC.

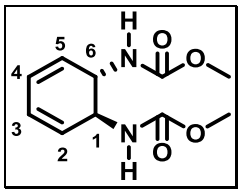
For compound 246



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.49 (br s, 1H, -NH-), 7.46-7.41 (m, 2H, H_1 and H_6), 7.26 (tt, J = 7.5 Hz, J = 1.8 Hz, 2H, H_3 and H_5), 7.05 (tt, J = 7.4 Hz, J= 1.04Hz, 1H, H_4), 3.77 (s, 3H, -COOCH_3).

^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 153.1, 136.9, 128.0, 122.5, 117.8, 51.3.

For compound 247



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 5.90 (quasi-d, A part of AA'BB'-system, J = 8.4 Hz, 2H, H_3 and H_4), 5.71 (quasi-d, B part of AA'BB -system, J = 8.7 Hz, 2H, H_2 and H_5), 5.00 (br s, 2H, 2-NH-), 4.40 (br s, 2H, H_1 and H_6), 3.61 (s, 6H, 2-COOCH_3).

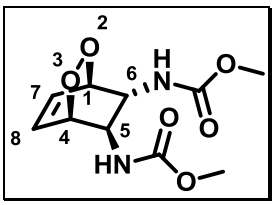
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 157.2, 128.7, 125.1, 53.0, 52.3.

IR (ATR): 3291, 2991, 1688, 1537, 1263, 1026, 685.

HRMS: Calculated for $C_{10}H_{14}N_2O_4$ $[M+Na]^+$: 249.0846 found $[M+Na]^+$: 249.0828.

4.20 Synthesis of dimethyl *rel*-(1*R*,4*R*,5*R*,6*S*)-2,3-dioxabicyclo[2.2.2]oct-7-ene-5,6-diyldicarbamate (248)

To a stirred solution of **247** (390 mg, 1.72 mmol) in 30 mL of CH_2Cl_2 was added 20 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a lamp (500 W) while oxygen was passed through solution, in which the mixture was stirred for 24 h at room temperature. After 24 hours, solvent was evaporated (30 °C, 20 mmHg). Because of the low solubility of product **248**, the residue was washed with CH_2Cl_2 to obtain endoperoxide **248 (**364 mg, 1.41 mmol, 82%) Mp: 153-155 ºC.



^{1}H NMR (400 MHz, DMSO, ppm) δ: 7.93 (d, *J* = 6.8Hz, 1H, -NH-), 7.40 (d, *J* = 6.6 Hz, 1H, -NH-), 6.82 (t, *J* = 6.9 Hz, 1H, H_7), 6.64 (t, *J* = 6.4 Hz,1H, H_8), 4.73-4.61 (m, 2H, H_1 and H_4), 3.96-3.88 (m, 1H, H_5), 3.61 (s, 3H, -COO*CH*$_3$), 3.59 (s, 3H, -COO*CH*$_3$), 3.56-3.48 (m, 1H, H_6).

^{13}C NMR (400 MHz, DMSO, ppm) δ: 156.6, 156.1, 132.4, 130.7, 74.7, 71.2, 52.7, 51.4, 49.0.

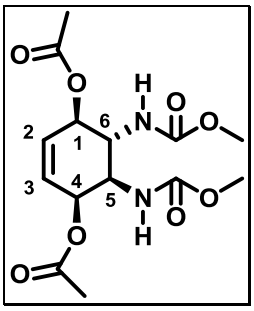
IR (ATR): 3328, 2955, 1682, 1526, 1291, 1229, 1033, 941.

HRMS: Calculated for $C_{10}H_{214}N_2O_6$ $[M+Na]^+$: 281.0741 found $[M+Na]^+$: 281.0803.

4.21 Synthesis of *rel*-(1*R*,4*S*,5*R*,6*R*)-5,6-bis(methoxycarbonylamino) cyclohex-2-ene-1,4-diyldiacetate (253)

To a magnetically stirred solution of endoperoxide **248** (364 mg, 1.41 mmol) in 50 mL MeOH was added to thiourea (215 mg, 2.82 mmol) at room temperature. The mixture was stirred for 3 h at room temperature. The solids were removed by filtration. Pyridine (10 mL) and Ac_2O (3 mL) were added to the formed viscose liquid residue followed by stirring for 12 h at room temperature. Then

the residue was quenched with 30 mL of ice-cold HCl, after stirring for 5 min, and the mixture was extracted with ether (3 × 50 mL). The combined organic phase was washed with $NaHCO_3$ solution and water and then dried over $MgSO_4$. After evaporation of solvent, the residue was separated by silica gel chromatography eluting with EtOAc / *n*-hexane to obtain compound **253** (305 mg, 0.89 mmol, 63%) Mp: 180-182 °C.



^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 6.08 (ddd, A part of AB-system, *J* = 9.8 Hz, *J* = 5.0 Hz and *J* = 1.7 Hz, 1H, H_2), 5.82 (dd, B part of AB-system, *J* = 10.1 Hz, *J* = 2.04 Hz, 1H, H_3), 5.43 (br d, *J* = 9.2 Hz, 1H, H_4), 5.29 (q, *J* = 4.1 Hz, 1H, H_1), 5.27 (bs, 1H, –NH), 5.07 (1H, -NH-), 4.17 (q, *J* = 9.5 Hz, 1H, H_5), 3.99 (dt, *J* = 11.0 Hz, *J* = 3.7 Hz, 1H, H_6), 3.69 (s, 6H, 2-NHCOO*CH*$_3$), 2.13 (s, 3H, -$OCOCH_3$), 2.12 (s, 3H, - OCO*CH*$_3$).

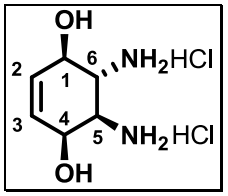
^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 170.1, 170.0, 158.0, 157.2, 131.6, 126.1, 71.7, 68.4, 52.5, 52.4, 52.3, 52.2, 20.9.

IR (ATR): 3327, 2950, 1732, 1694, 1532, 1234, 1040, 920.

HRMS: Calculated for $C_{14}H_{20}N_2O_8$ $[M+Na]^+$: 367.11119 found $[M+Na]^+$: 367.1177.

4.22 Synthesis of *rel*-(1*R*,4*S*,5*R*,6*R*)-5,6-diaminocyclohex-2-ene-1,4-diol dihydro- chloride (201)

To a magnetically stirred solution of compound **250** (148 mg, 0.43mmol) in 10 mL of MeOH was added to 2 mL of 2M NaOH at r.t. The mixture was stirred overnight. The solid was removed by filtration and pH of the solution was adjusted to 1 by adding 1M HCl and then it was extracted with EtOAc (3 × 20 mL). Water phase was evaporated to give compound **201** (30 mg, 0.14 mmol, 33%, white solid)



^{1}H NMR (400 MHz, D_2O, ppm) δ: 6.04-5.94 (m, 2H, H_2 and H_3), 4.52 (t, *J* = 4.2 Hz, 1H, H_4), 4.45-4.39 (dd, *J* = 8.6 Hz, *J* = 4.0 Hz, 1H, H_1), 3.87 (dd, *J* = 11.6 Hz, 1H, H_5), 3.59 (dd, *J* = 11.6 Hz, *J* = 8.7 Hz, 1H, H_6).

^{13}C NMR (400 MHz, D_2O, ppm) δ: 131.5, 126.6, 67.6, 62.9, 52.3, 50.9.

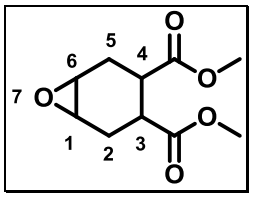
IR (ATR): 3339, 2845, 1620, 1556, 1514, 1004, 927.

HRMS: Calculated for $C_6H_{13}N_2O_2$ $[M^*]^+$: 145.0972 found $[M^*]^+$: 145.1010.

4.23 Synthesis of dimethyl 7-oxabicyclo[4.1.0]heptane-3,4-dicarboxylate (238) and dimethyl-7-oxabicyclo[4.1.0]hept-3,4-diyldicarbamate (231).

To a stirred solutions of **224** (500 mg, 2.52 mmol) and **230** (500 mg, 2.19 mmol) in 30 mL of CH_2CI_2 were added *m*-CPBA 60% (941 mg, 5.04 mmol, 818 mg, 4.38 mmol respectively). The reaction mixtures were stirred overnight. The solid matters were removed by filtration, and the filtrates were washed with saturated $NaHCO_3$ (2 × 50 mL), and water (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave epoxides **238** (328 mg, 70%, white solid) Mp: 175-176 ºC and **231** (374 mg, 70%, white solid) Mp: 192-193 ºC.

For compound 238:



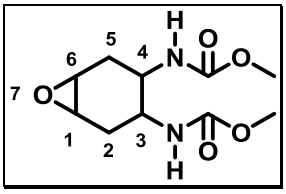
^{1}H NMR (400 MHz, CCl_3, ppm) δ: 3.70-5.56 (br s, 9H), 3.20-3.13 (m, 2H), 3.11-3.07 (m, 1H), 2.88-2.80 (m, 2H) 2.72-2.54 (m, 2H).

^{13}C NMR (400 MHz, CCl_3, ppm) δ: 173.3, 172.8, 51.8, 51.7, 51.4, 50.8, 37.5, 37.4, 24.7.

IR (ATR): 36.13, 2998, 2953, 1727, 1435, 1204, 1031, 809.

HRMS: Calculated for $C_{10}H_{14}O_5$ $[M+H]^+$: 245.1132 found $[M+H]^+$: 245.1162.

For compound 231:



^{1}H NMR (400 MHz, CCl_3, ppm) δ: 3.73-3.51 (m, 7H, -2COO*C*H_3+H_4), 3.43 (p, *J* = 9.0 Hz, H_3), 3.22-3.13 (m, 1H, H_6), 3.07 (t, *J* = 4.3 Hz, 1H, H_1), 2.54-2.33 (m, 2H, $2H_5$), 1.88-1.61 (m, 2H, $2H_2$).

^{13}C NMR (400 MHz, CCl_3, ppm) δ: 157.3, 52.7, 52.2, 50.9, 50.7, 48.4, 48.3, 31.5, 30.9.

IR (ATR): 3301, 2990, 2951, 1681, 1543, 1465, 1312, 1285, 1248, 1090, 652.

HRMS: Calculated for $C_{10}H_{16}N_2O_5$ $[M+H]^+$: 215.0914 found $[M+H]^+$: 215.0950

APPENDIX A

SPECTRAL DATA

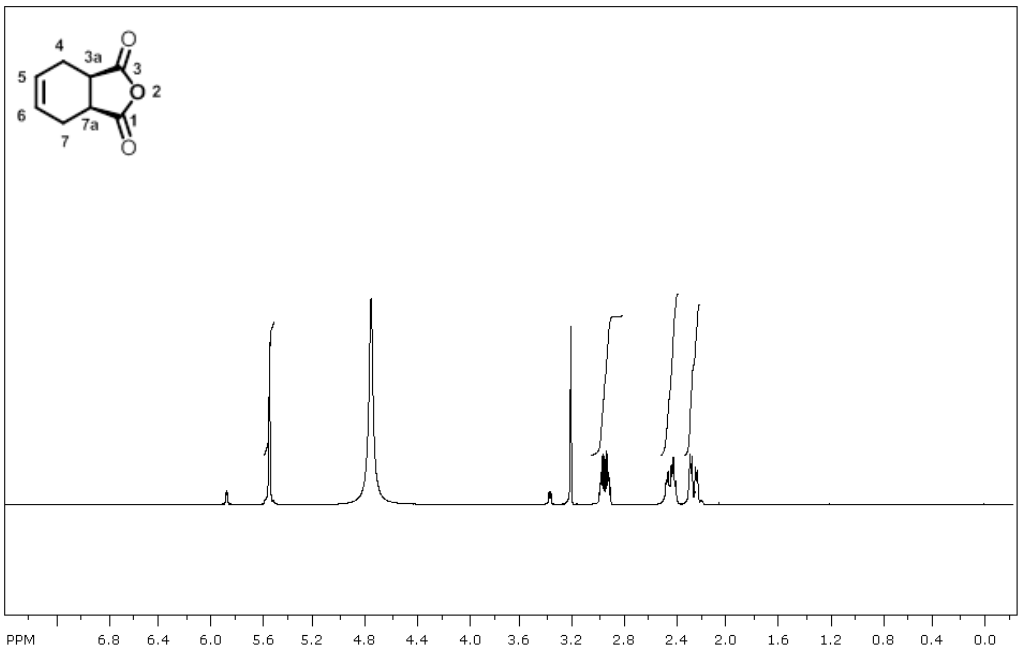


Figure 4.1 ^{1}H-NMR spectrum of compound **196**

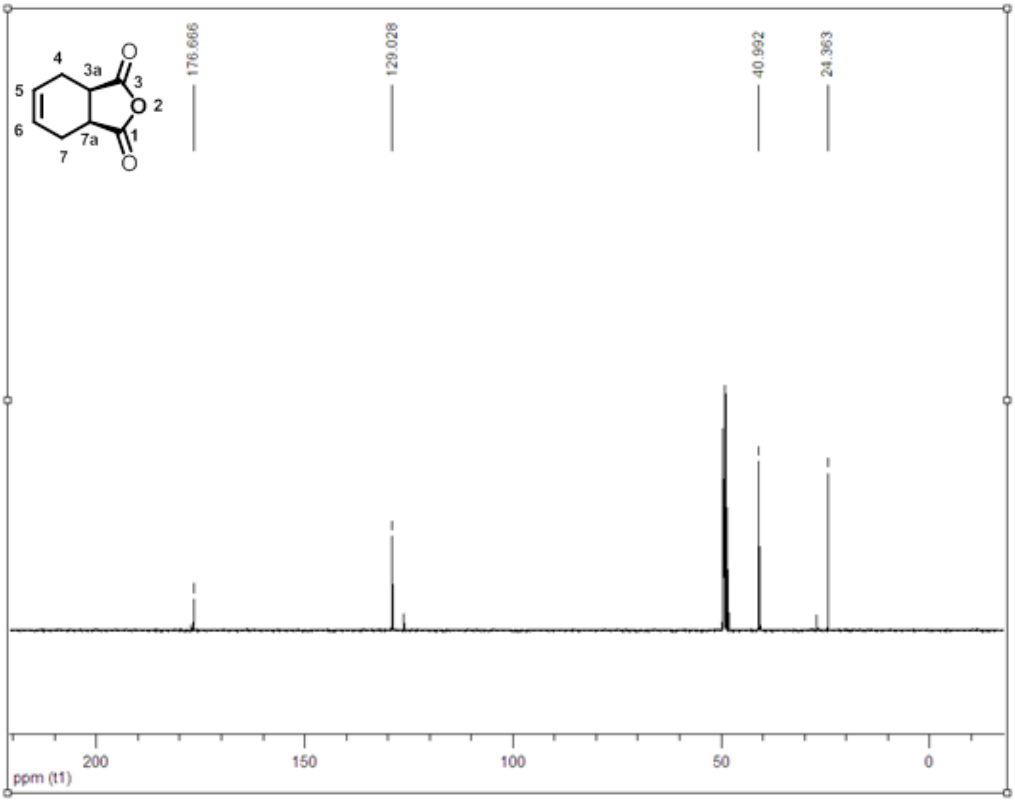


Figure 4.2 ^{13}C-NMR spectrum of compound **196**

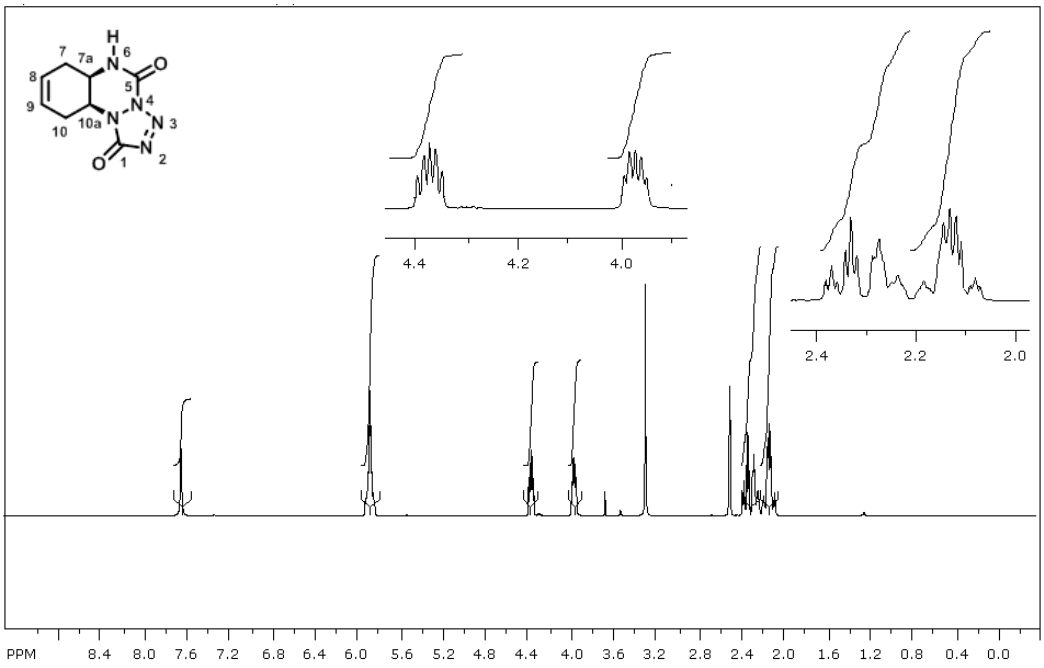


Figure 4.3 ^{1}H-NMR spectrum of compound **205**

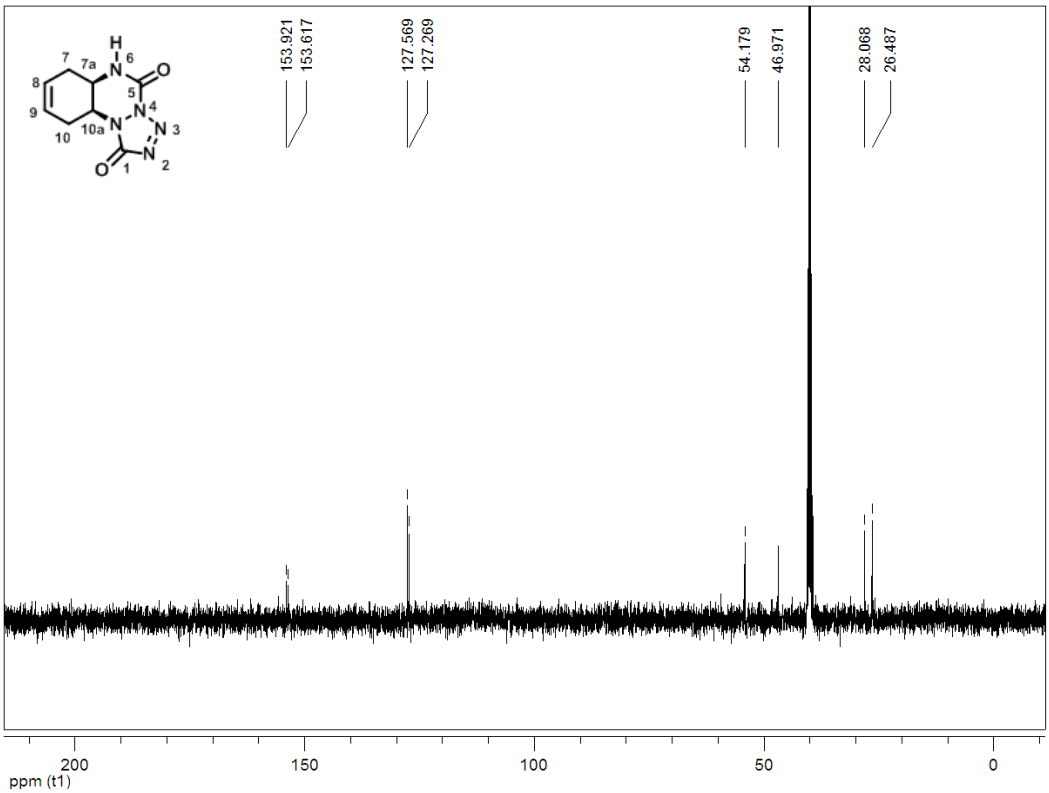


Figure 4.4 ^{13}C-NMR spectrum of compound **205**

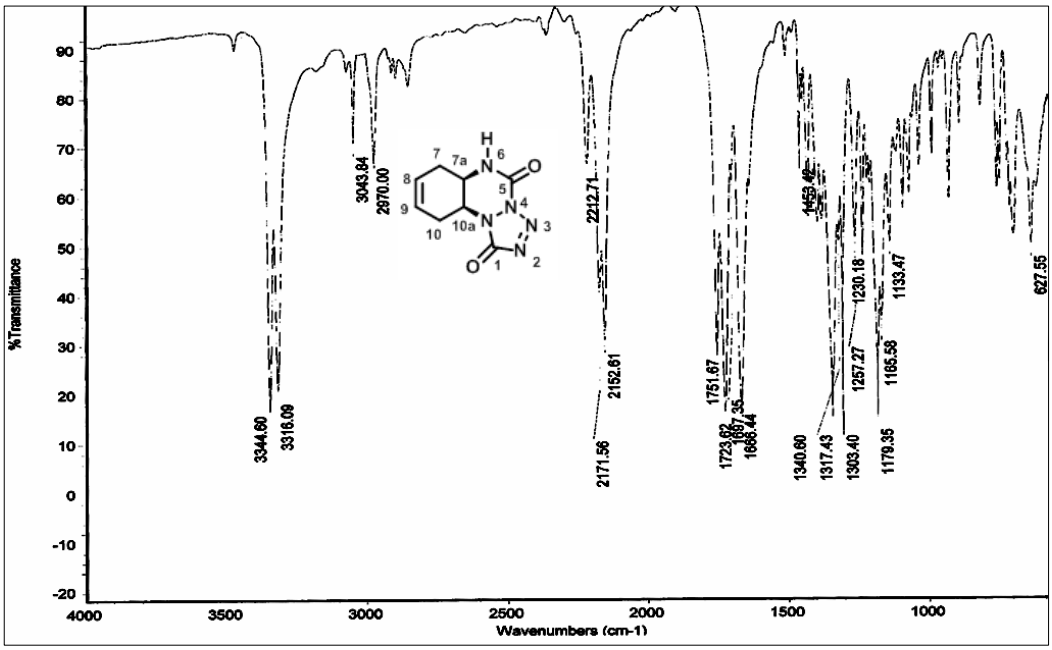


Figure 4.5 IR spectrum of compound **205**

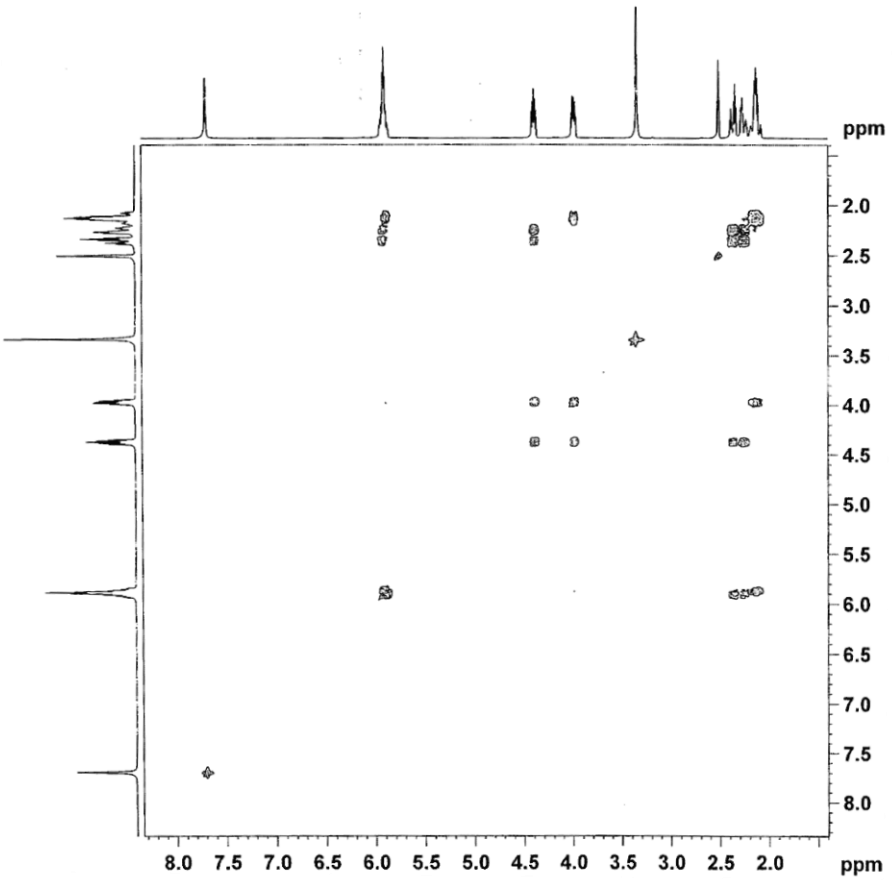


Figure 4.6 COSY spectrum of compound **205**

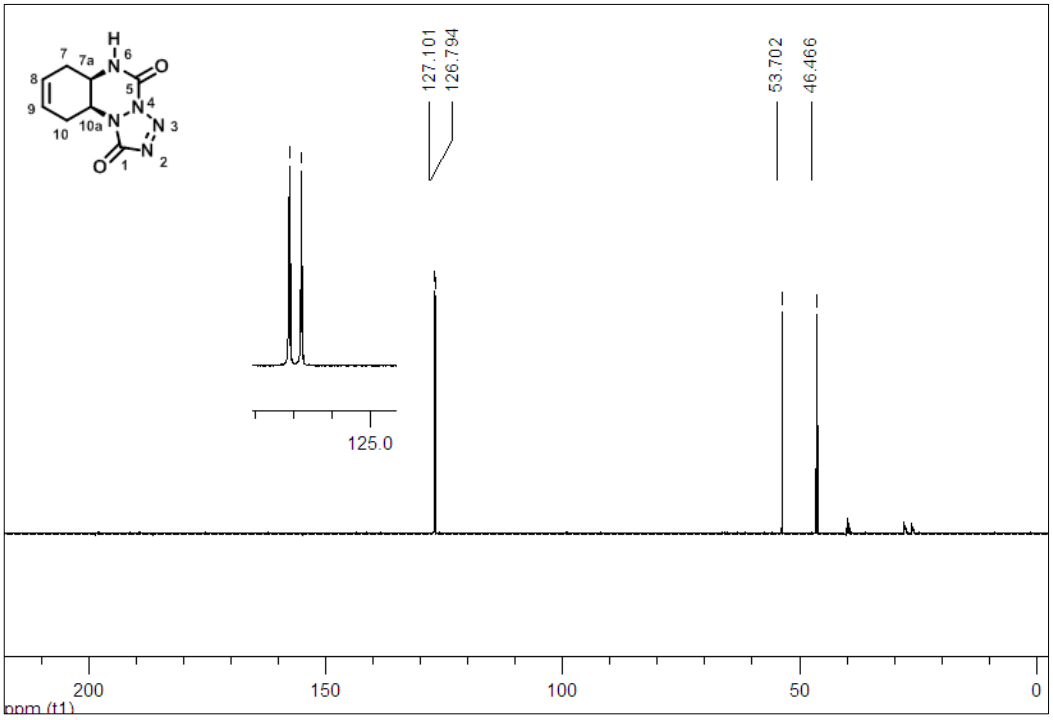


Figure 4.7 DEPT 90 spectrum of compound **205**

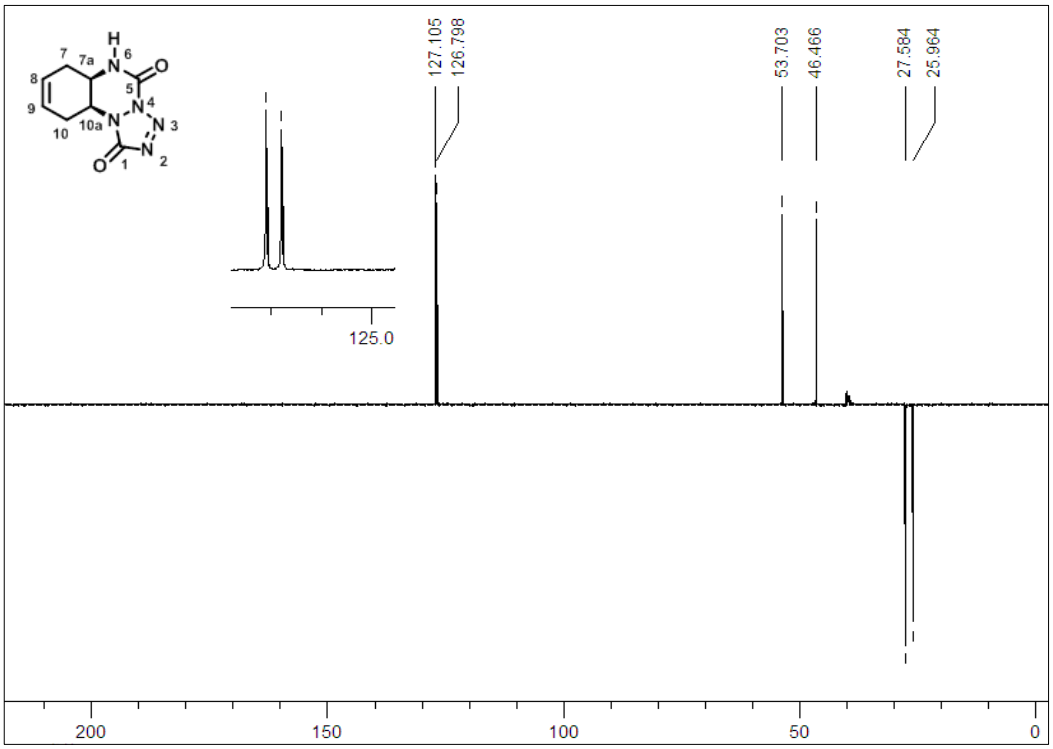


Figure 4.8 DEPT 135 spectrum of compound **205**

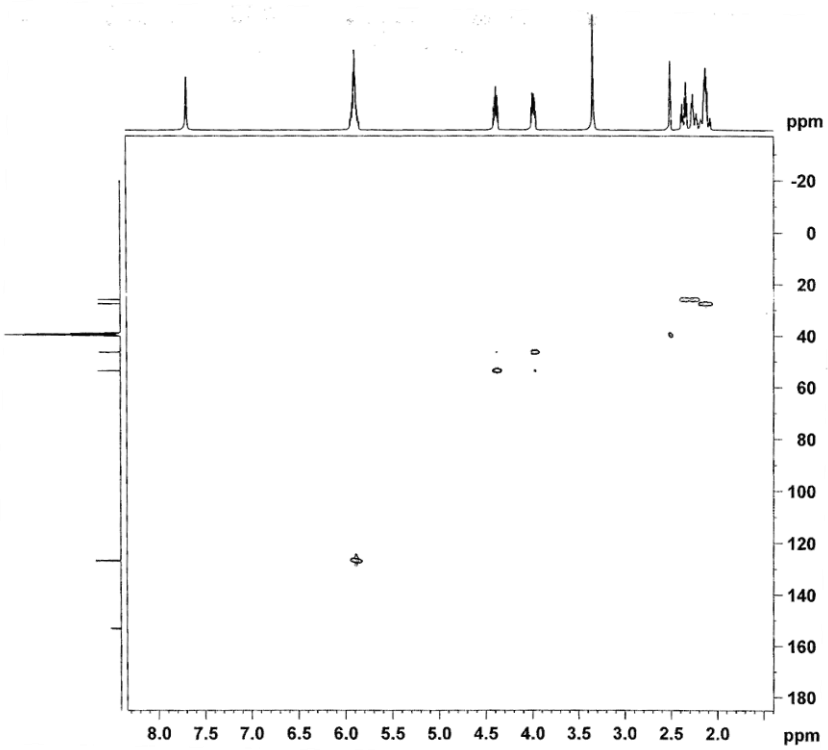


Figure 4.9 HMQC spectrum of compound **205**

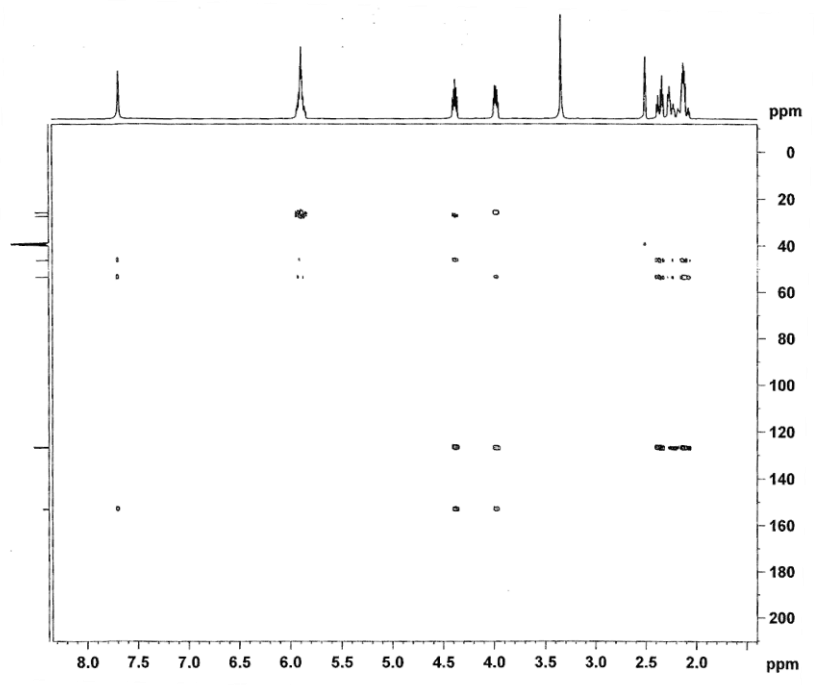


Figure 4.10 HMBC spectrum of compound **205**

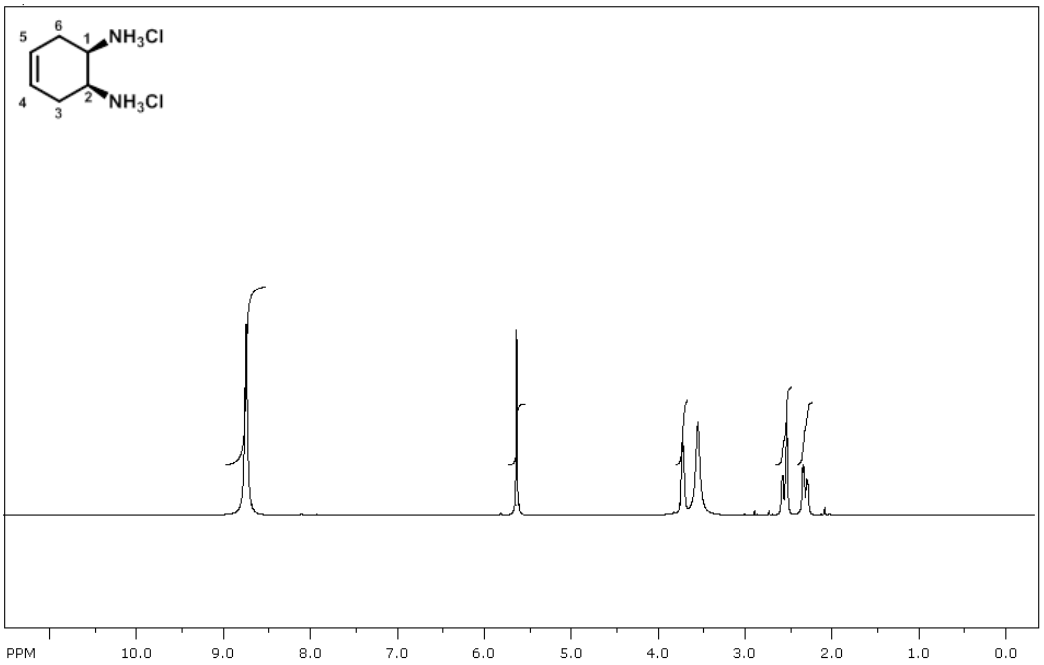


Figure 4.11 ^{1}H-NMR spectrum of compound **213**

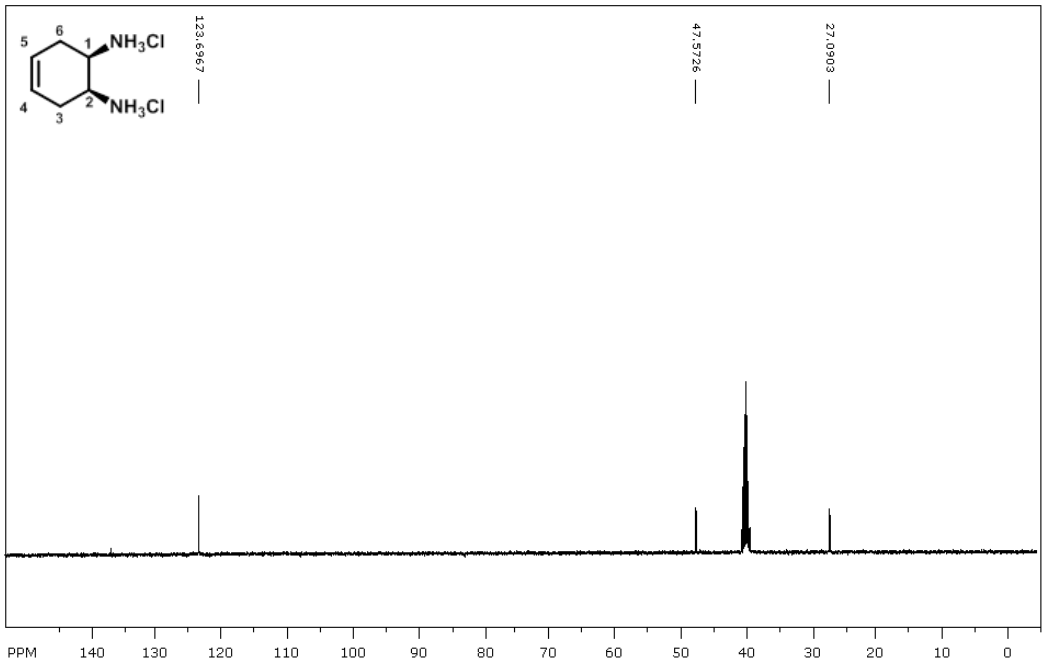


Figure 4.12 ^{13}C-NMR spectrum of compound **213**

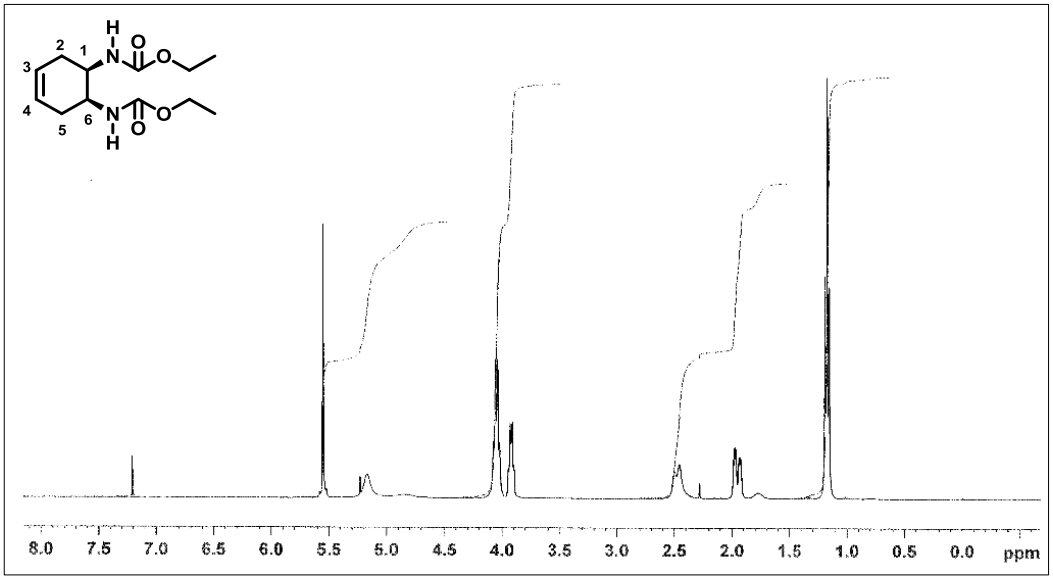


Figure 4.13 ^{1}H-NMR spectrum of compound **201**

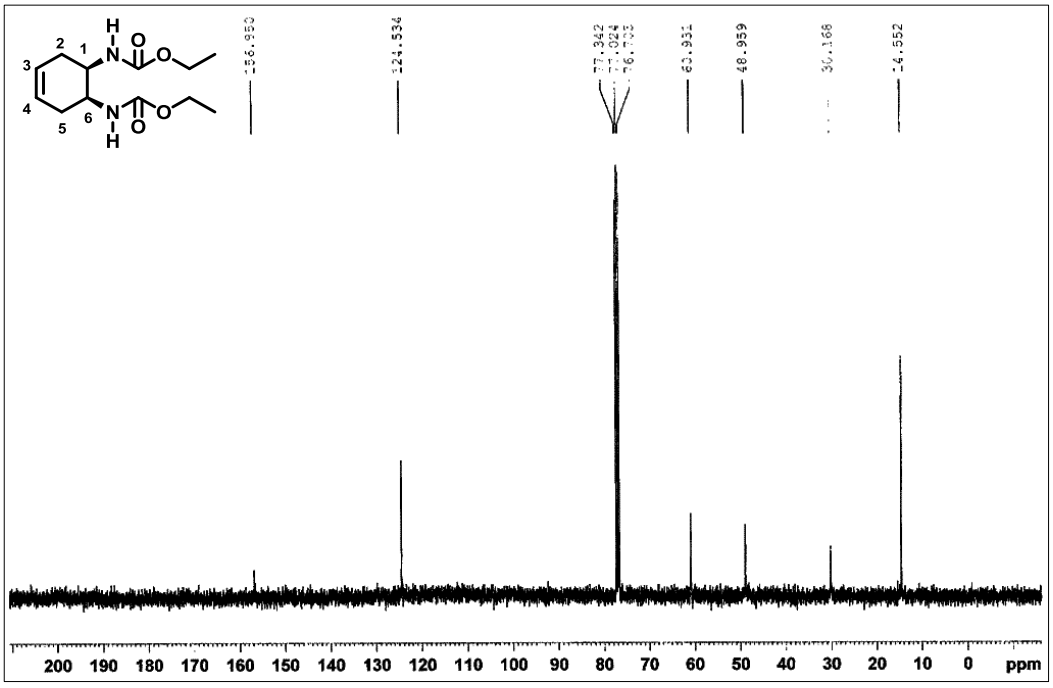


Figure 4.14 ^{13}C-NMR spectrum of compound **201**

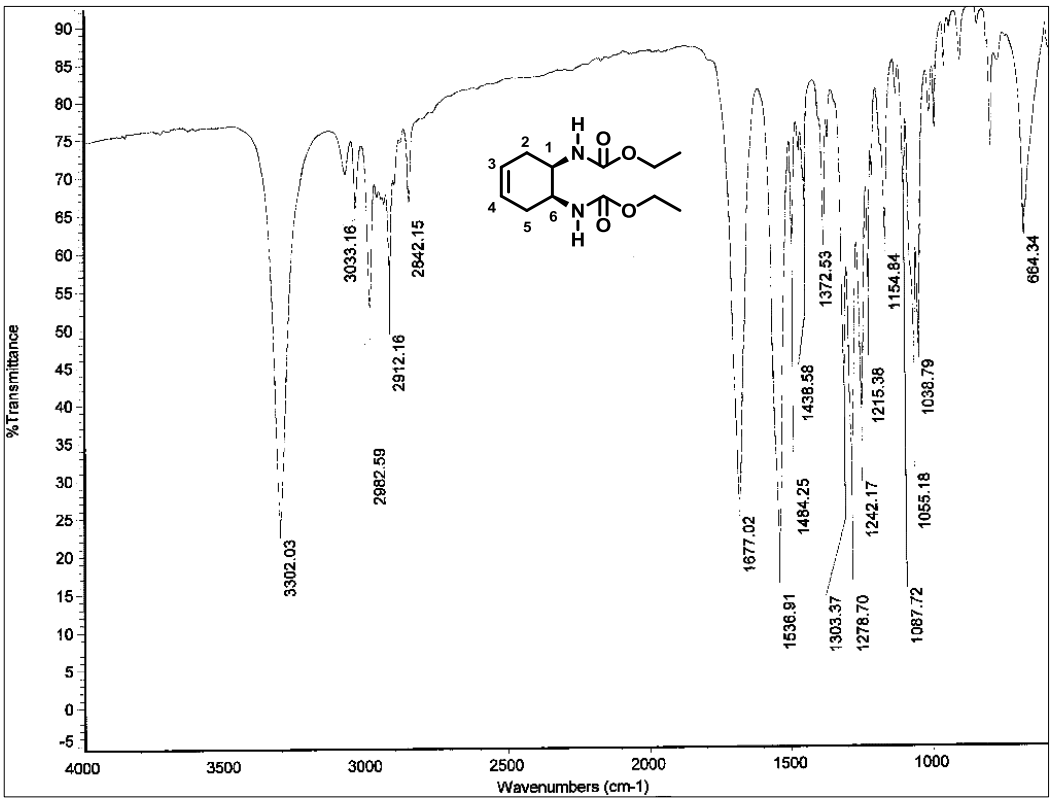


Figure 4.15 IR spectrum of compound **201**

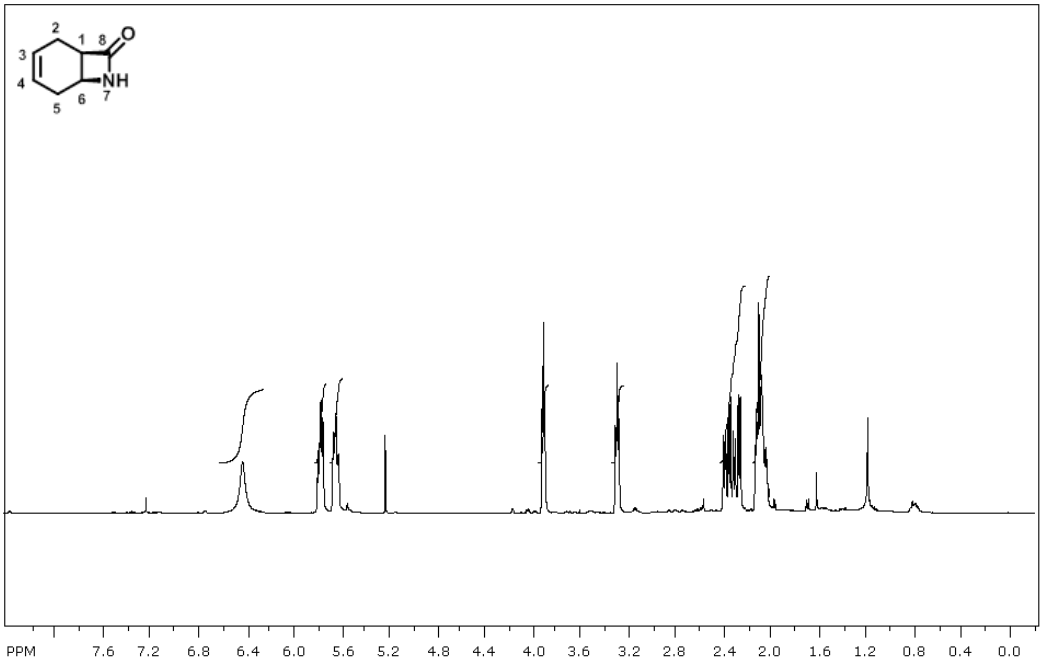


Figure 4.16 ^{1}H-NMR spectrum of compound **218**

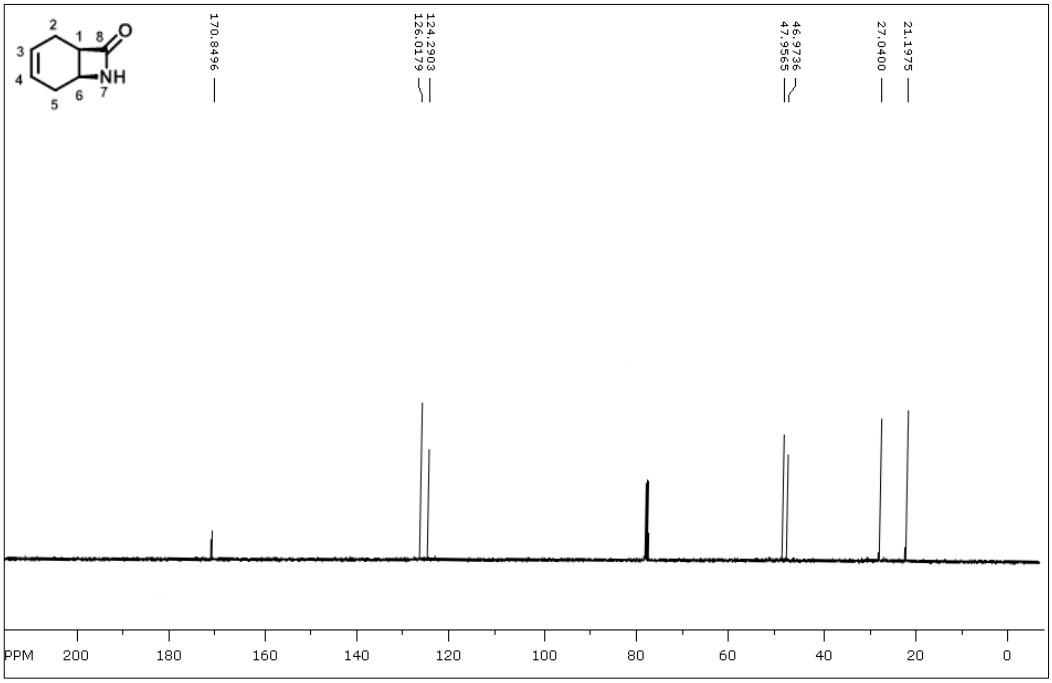


Figure 4.17 ^{13}C-NMR spectrum of compound **218**

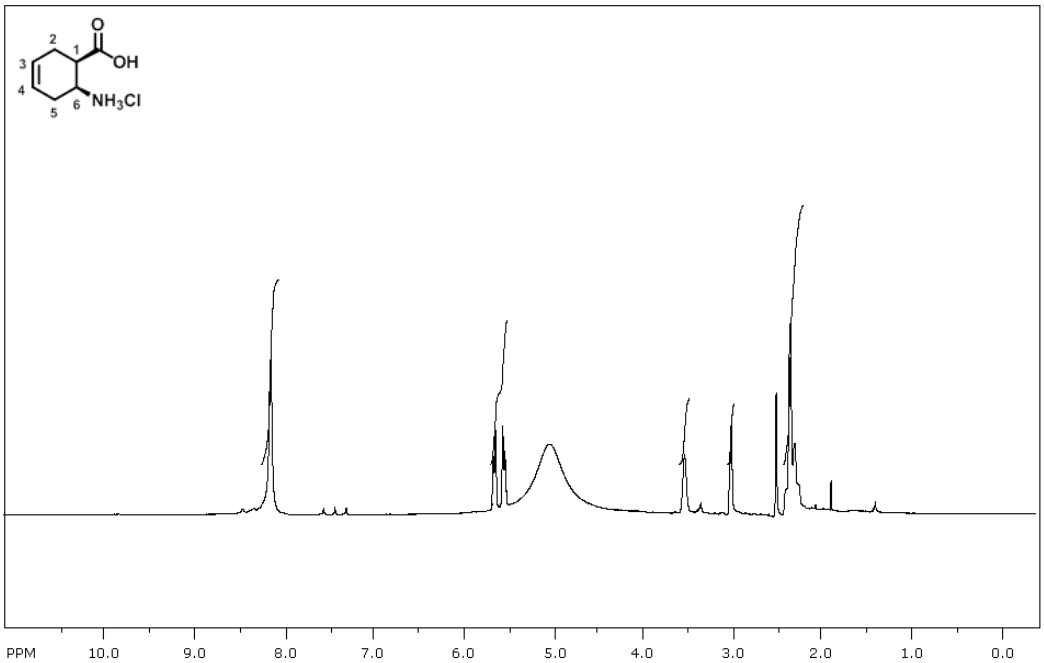


Figure 4.18 ^{1}H-NMR spectrum of compound **219**

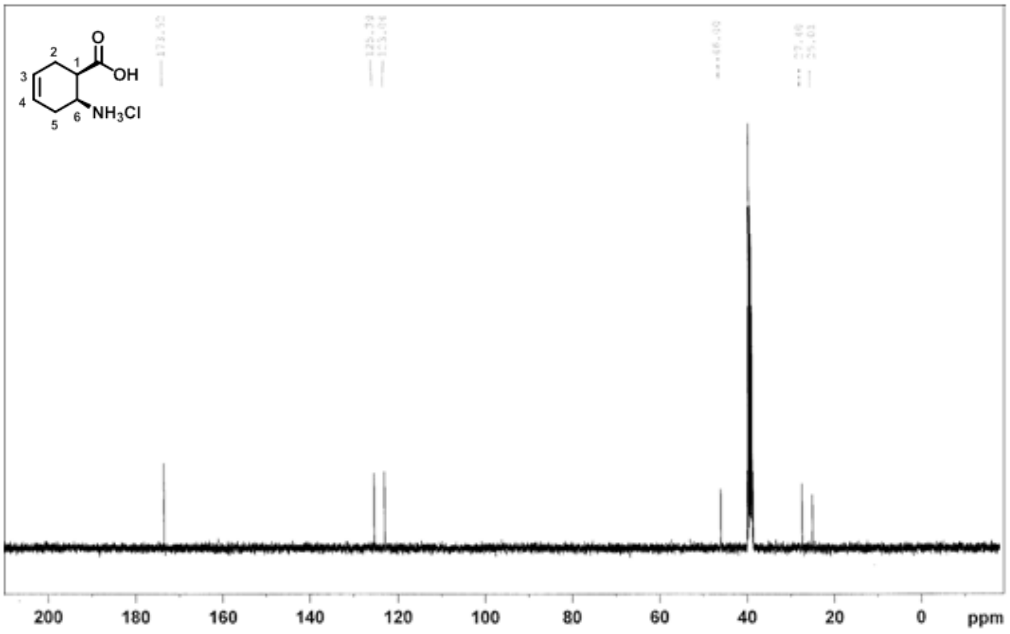


Figure 4.19 ^{13}C-NMR spectrum of compound **219**

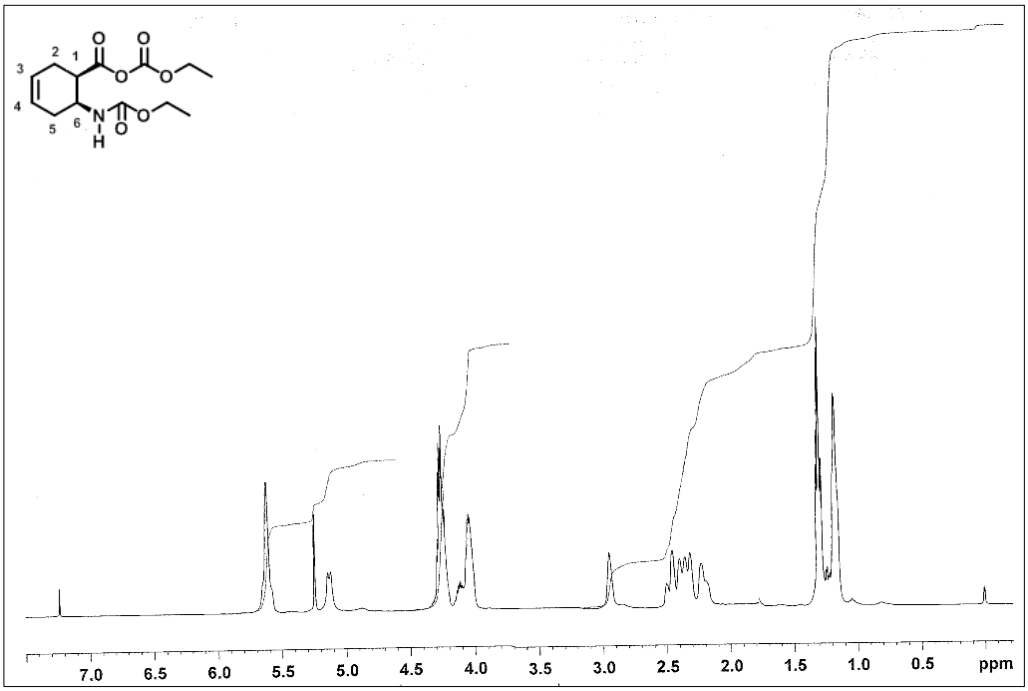


Figure 4.20 ^{1}H-NMR spectrum of compound **220**

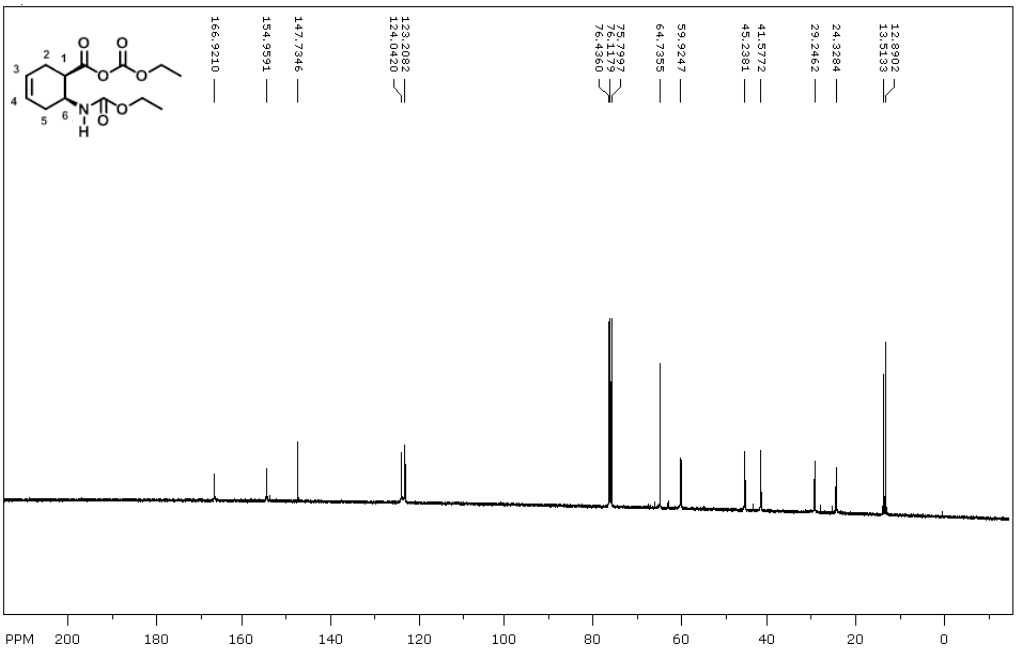


Figure 4.21 ^{13}C-NMR spectrum of compound **220**

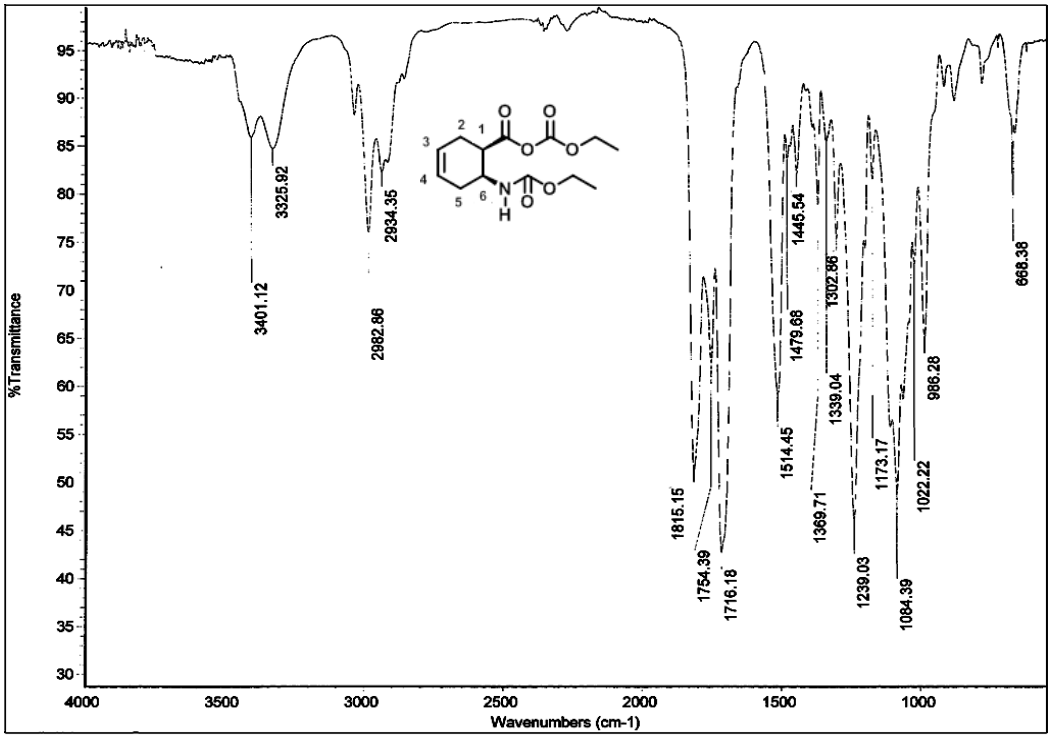


Figure 4.22 IR spectrum of compound **220**

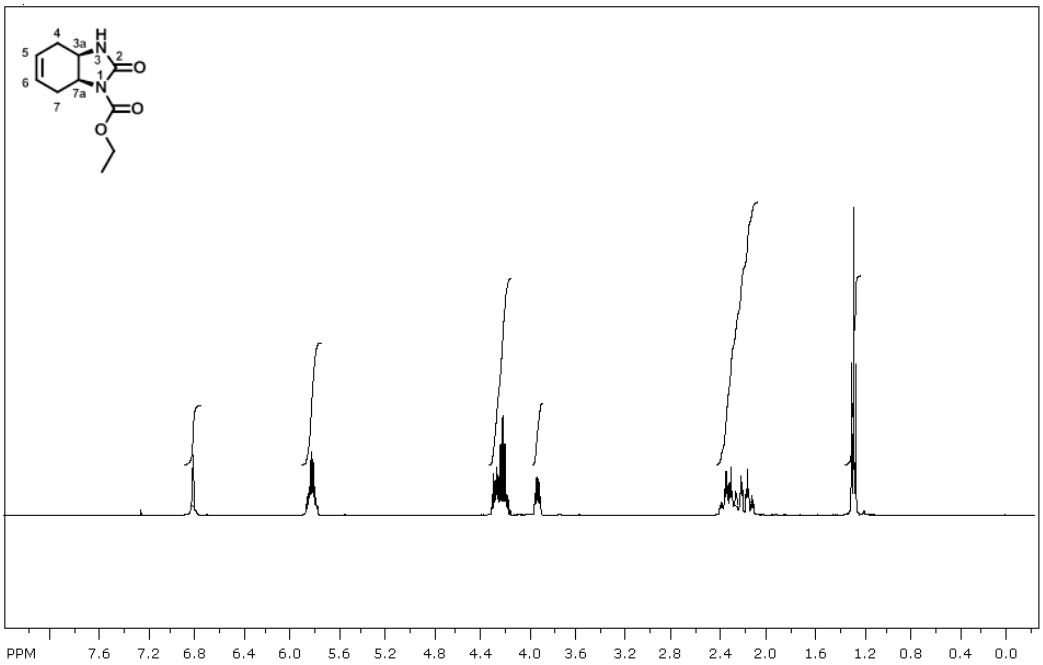


Figure 4.23 ^{1}H-NMR spectrum of compound **215**

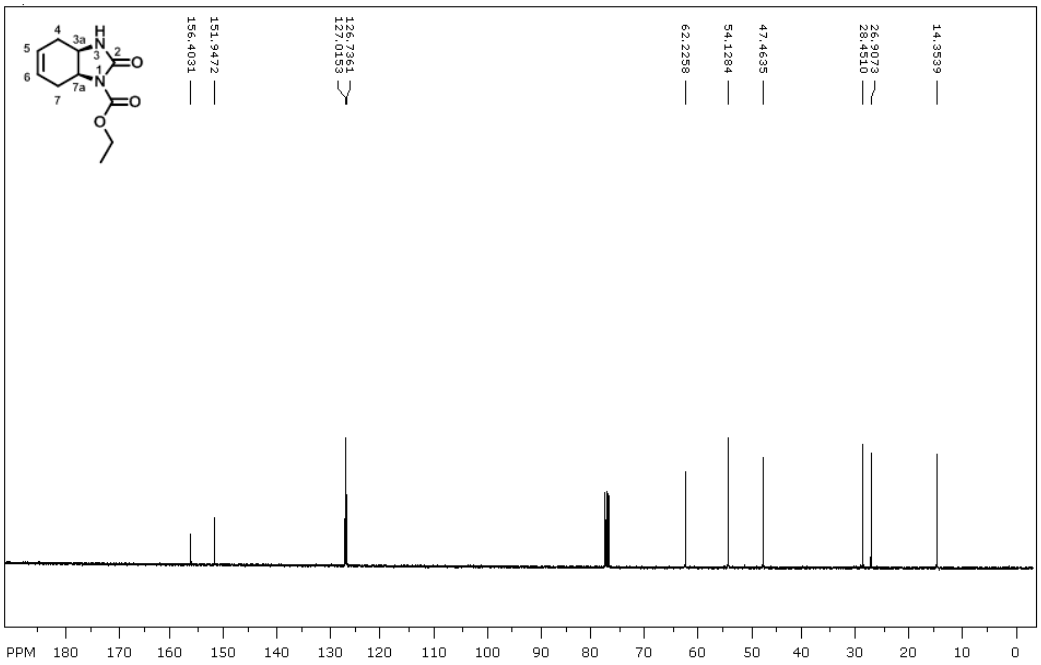


Figure 4.24 ^{13}C-NMR spectrum of compound **215**

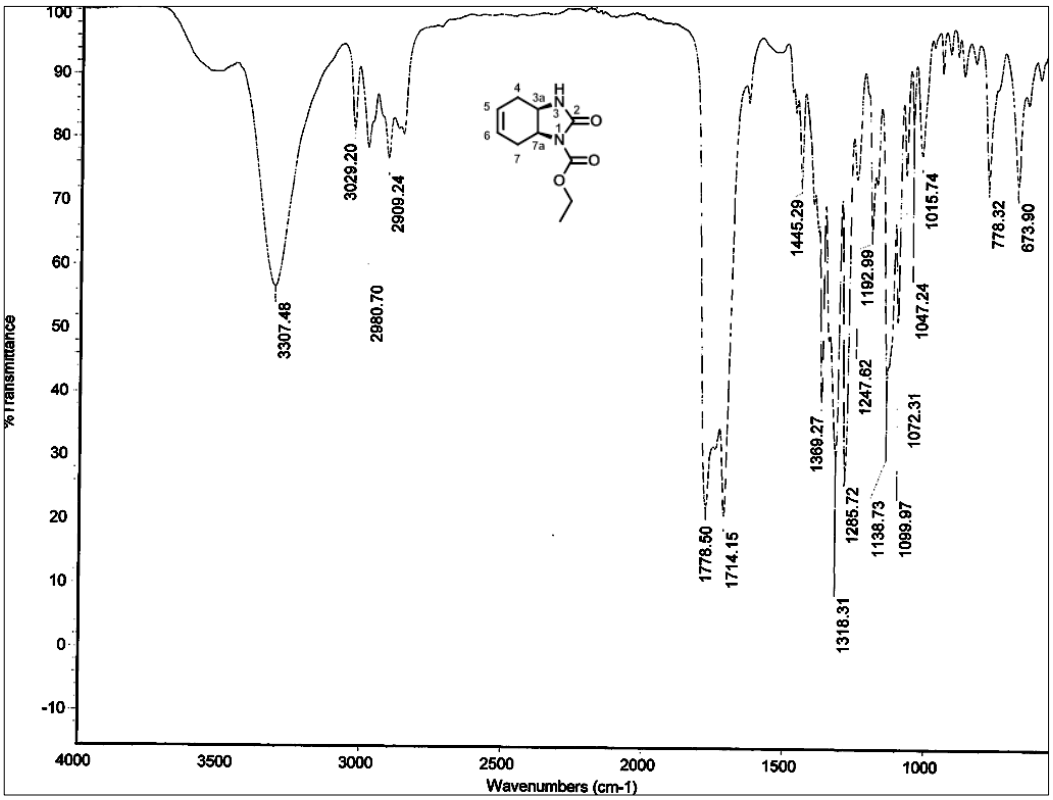


Figure 4.25 IR spectrum of compound **215**

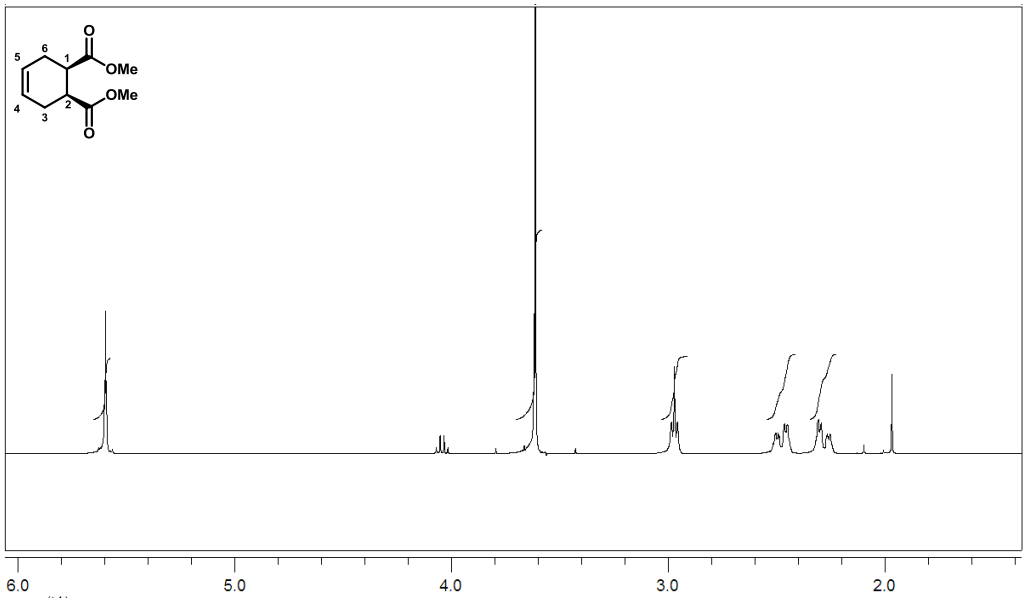


Figure 4.26 ^{1}H-NMR spectrum of compound **225**

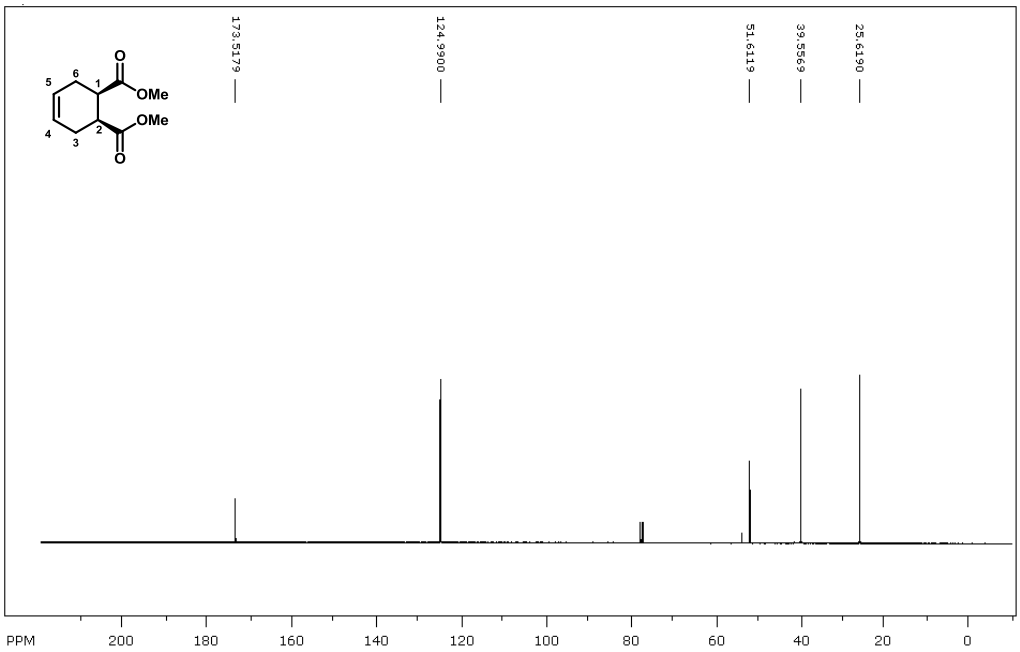


Figure 4.27 ^{13}C-NMR spectrum of compound **225**

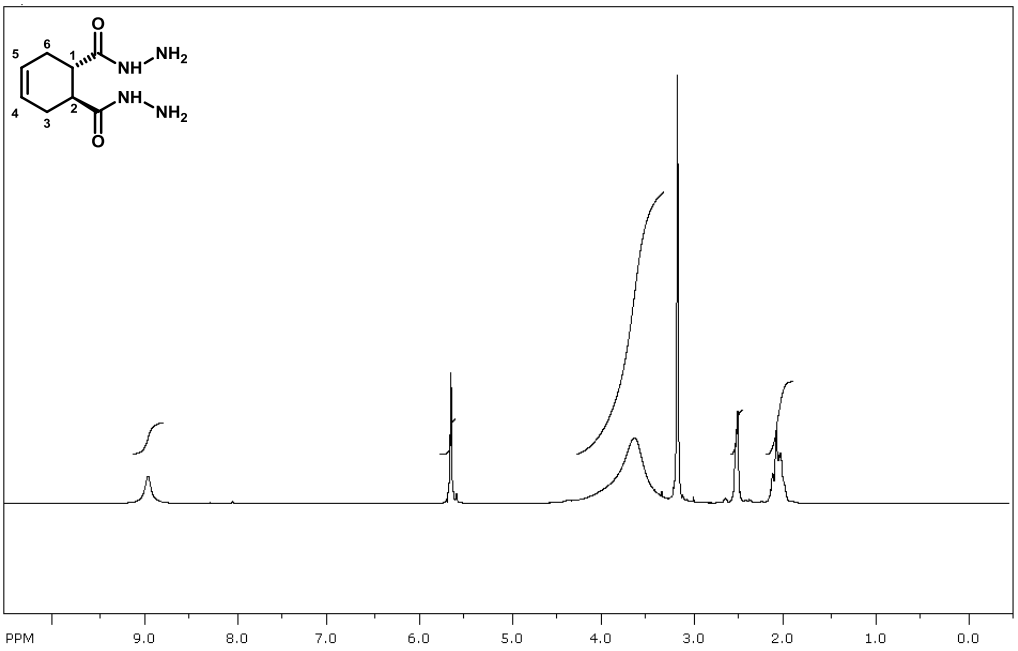


Figure 4.28 ^{1}H-NMR spectrum of compound **223**

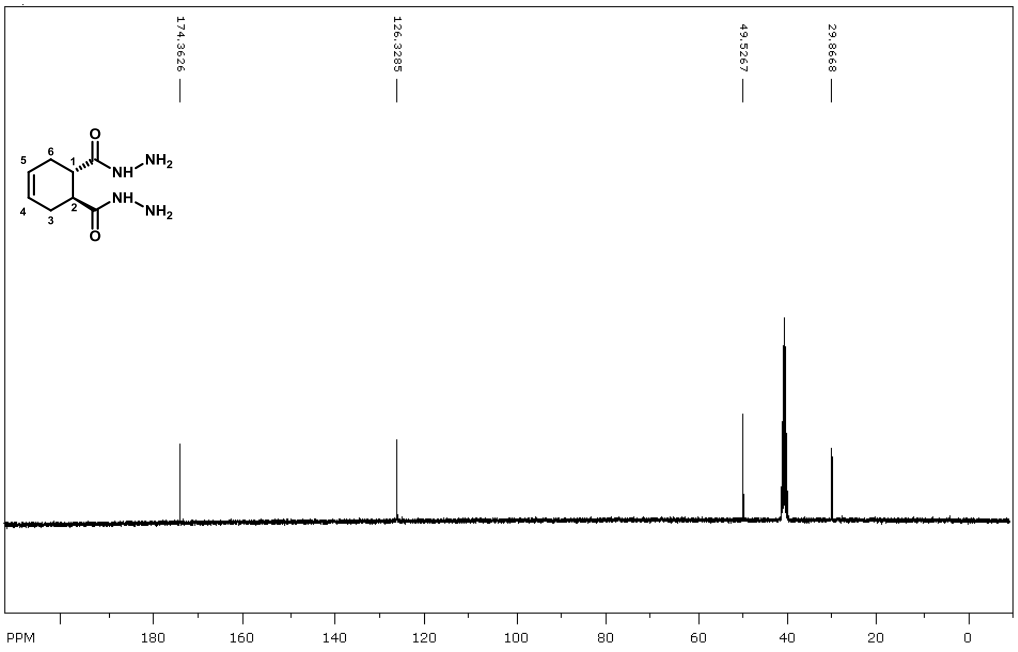


Figure 4.29 ^{13}C-NMR spectrum of compound **223**

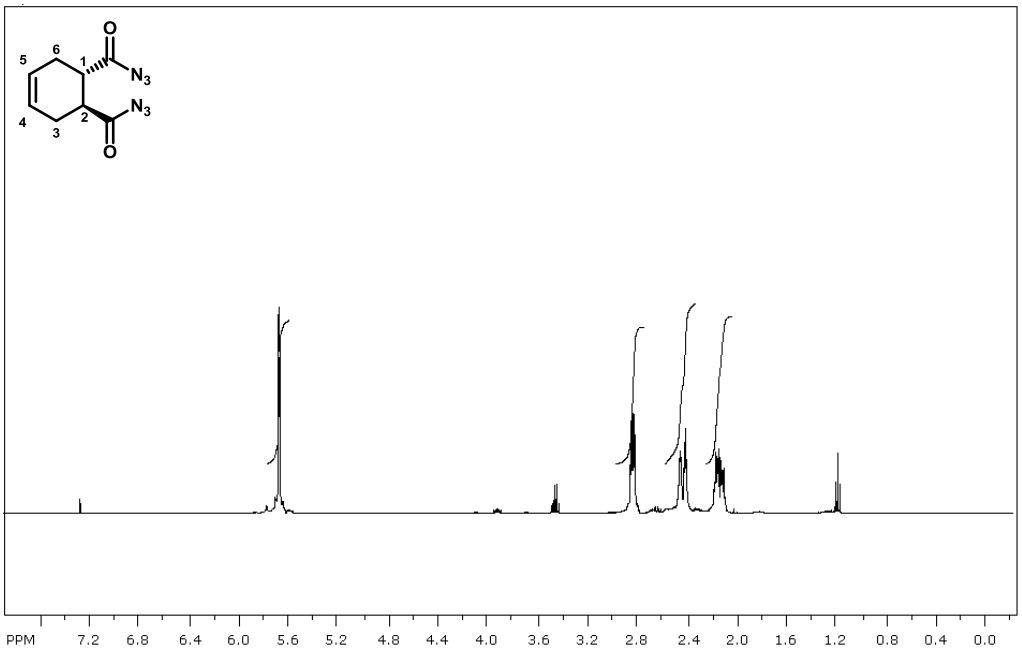


Figure 4.30 ^{1}H-NMR spectrum of compound **230**

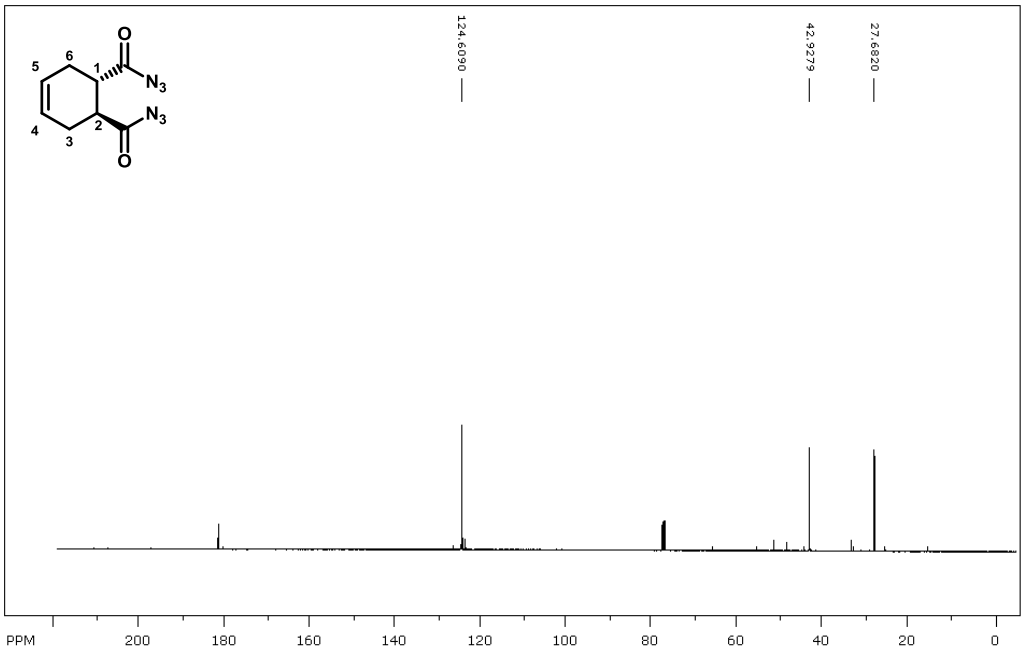


Figure 4.31 ^{13}C-NMR spectrum of compound **230**

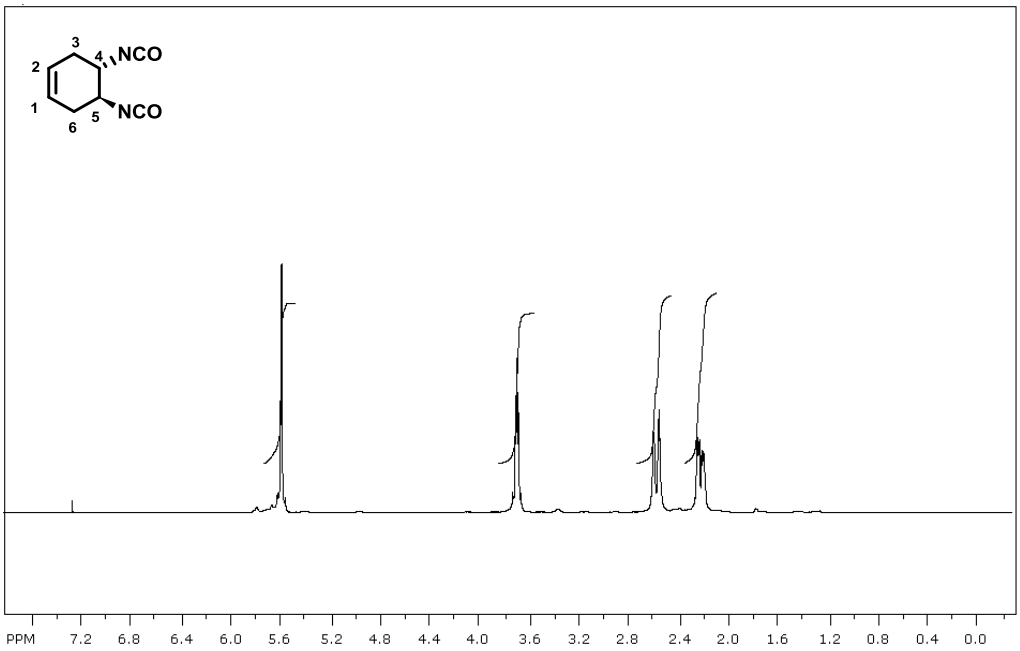


Figure 4.32 ^{1}H-NMR spectrum of compound **231**

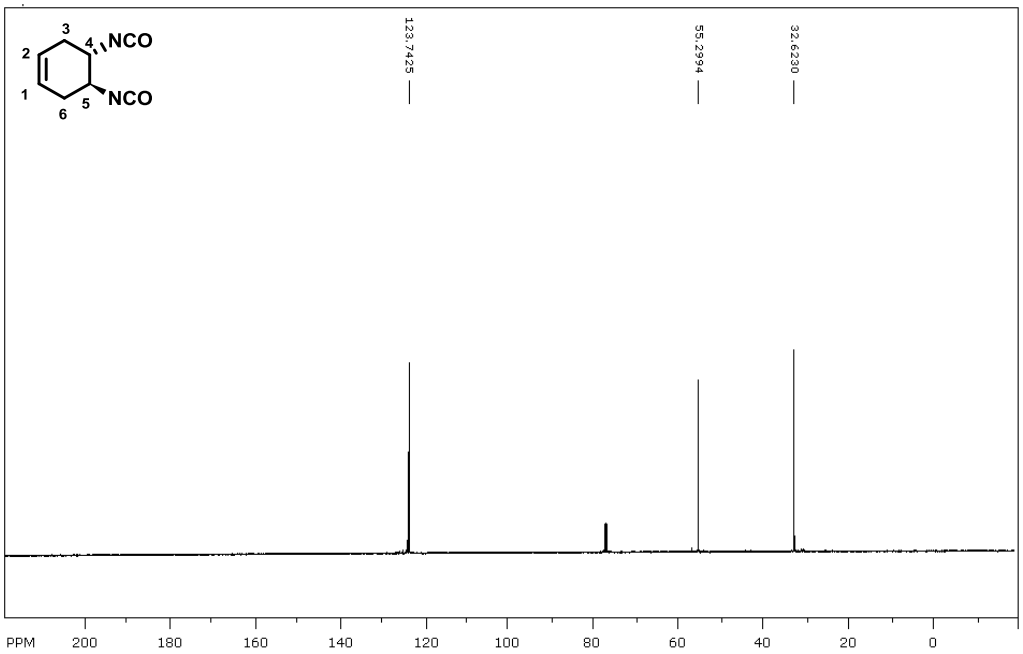


Figure 4.33 ^{13}C-NMR spectrum of compound **231**

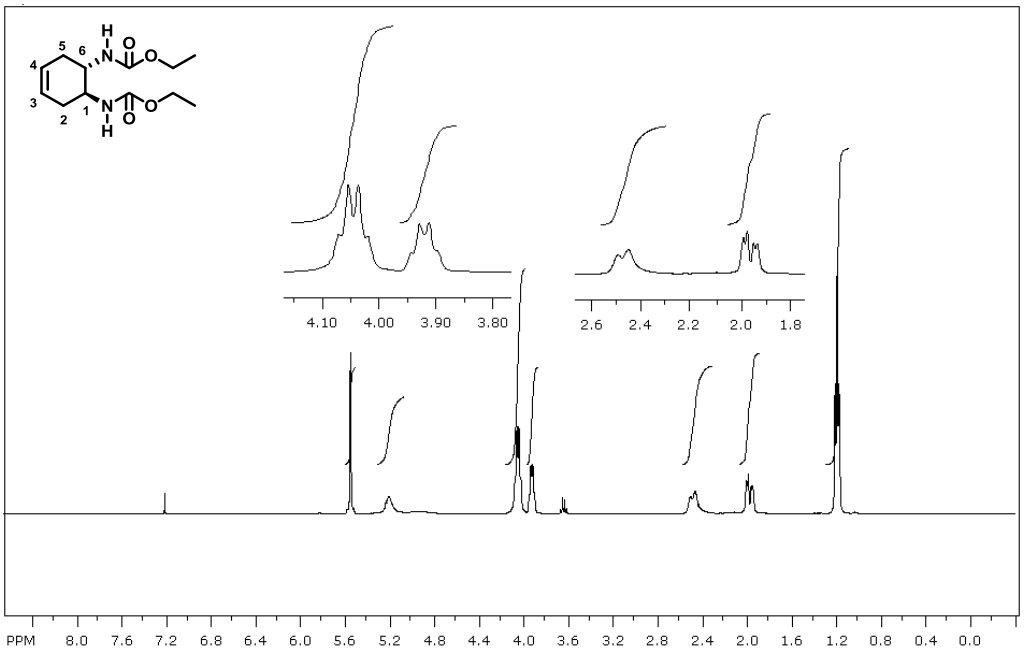


Figure 4.34 ^{1}H-NMR spectrum of compound **232**

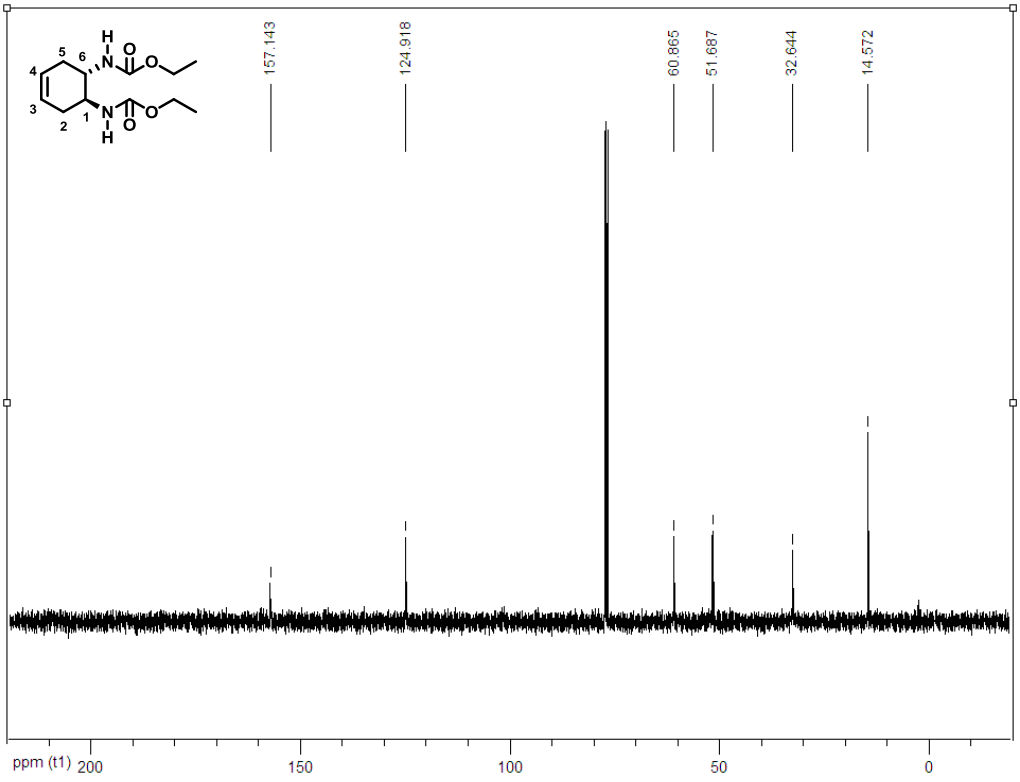


Figure 4.35 ^{13}C-NMR spectrum of compound **232**

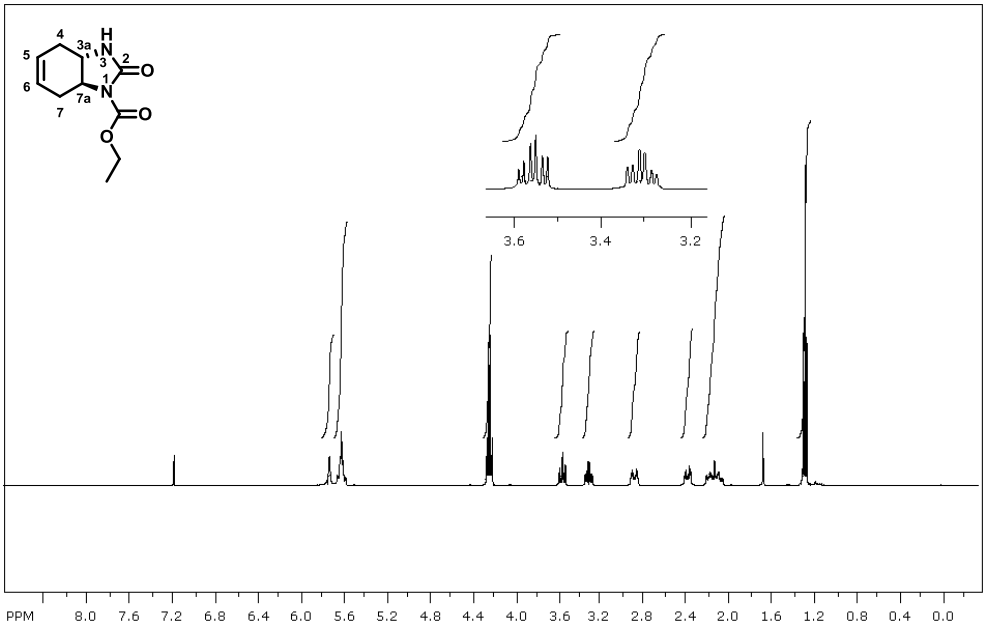


Figure 4.36 ^{1}H-NMR spectrum of compound **234**

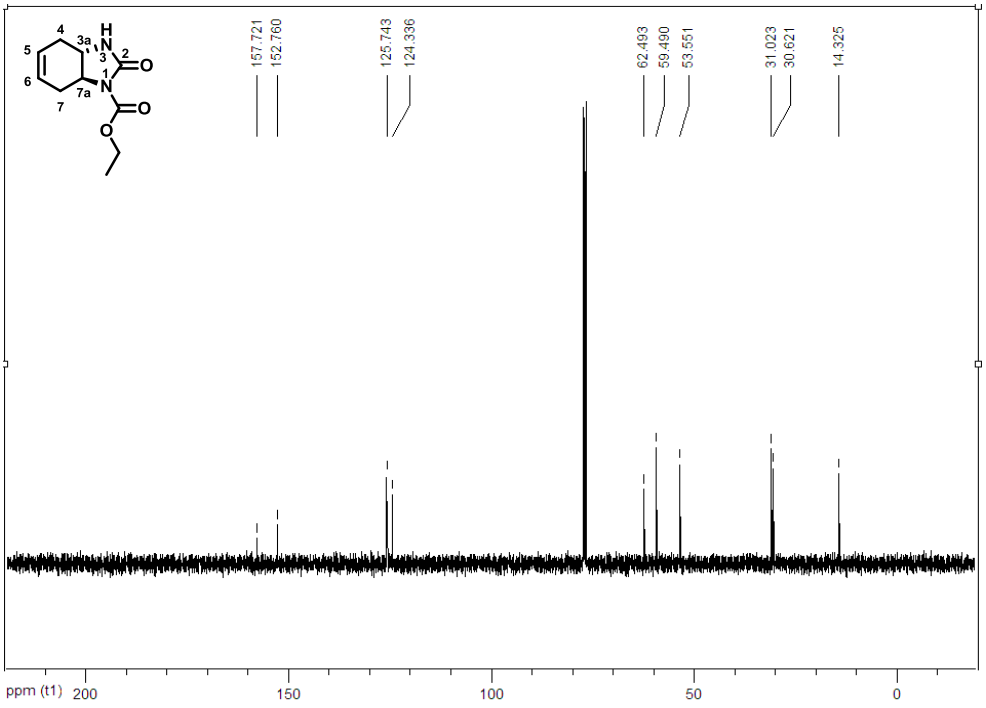


Figure 4.37 ^{13}C-NMR spectrum of compound **234**

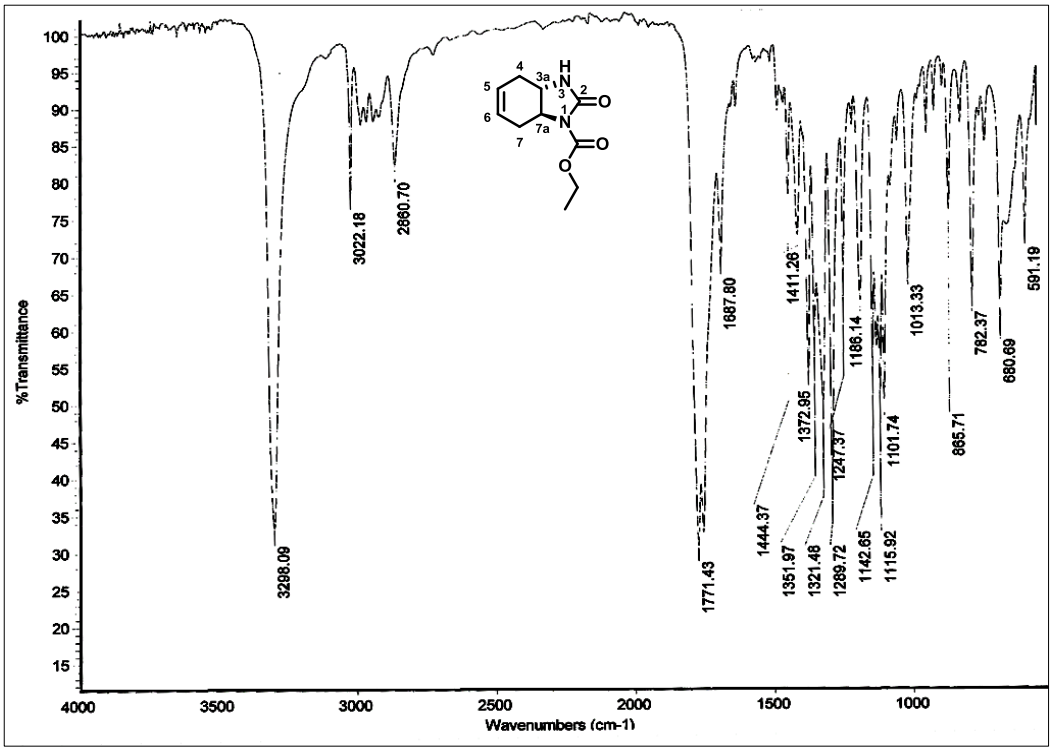


Figure 4.38 IR spectrum of compound **234**

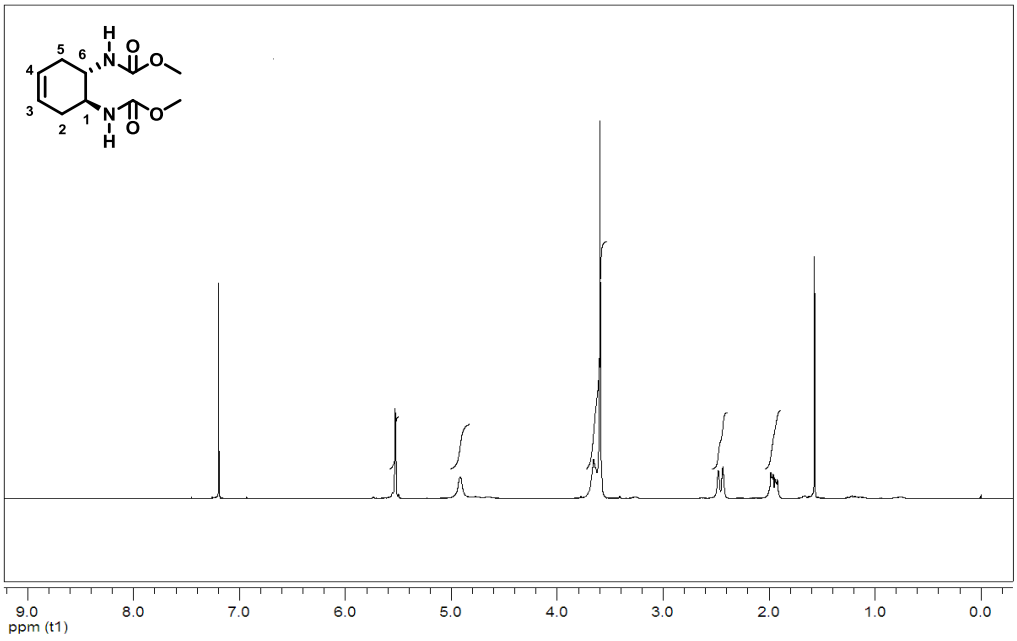


Figure 4.39 ^{1}H-NMR spectrum of compound **233**

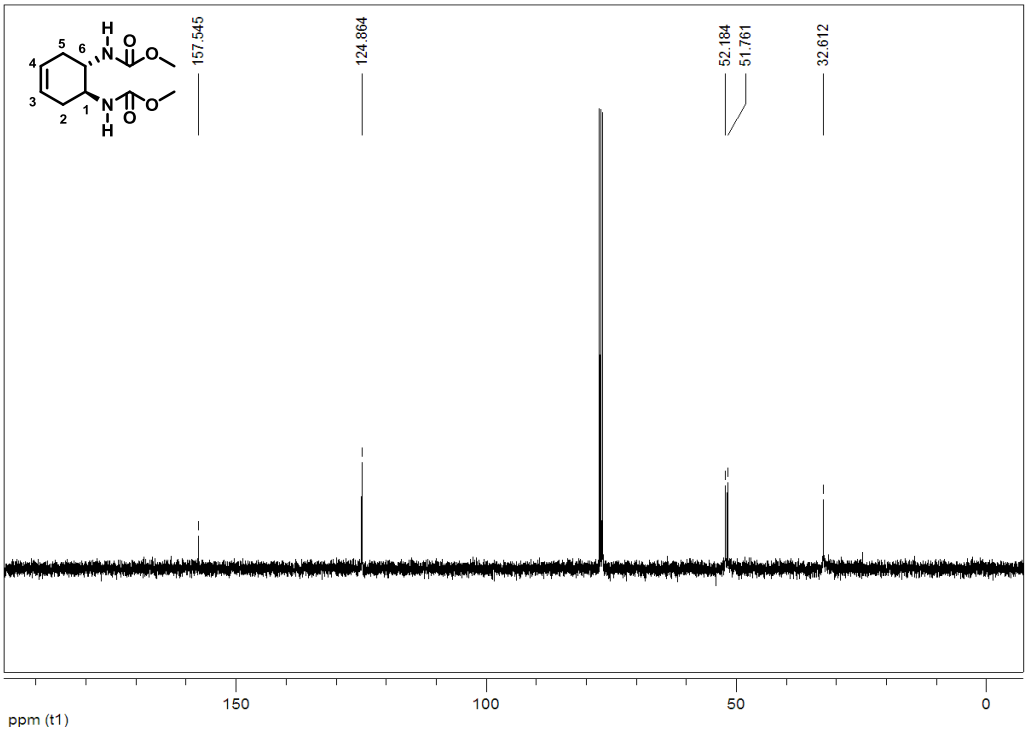


Figure 4.40 ^{13}C-NMR spectrum of compound **233**

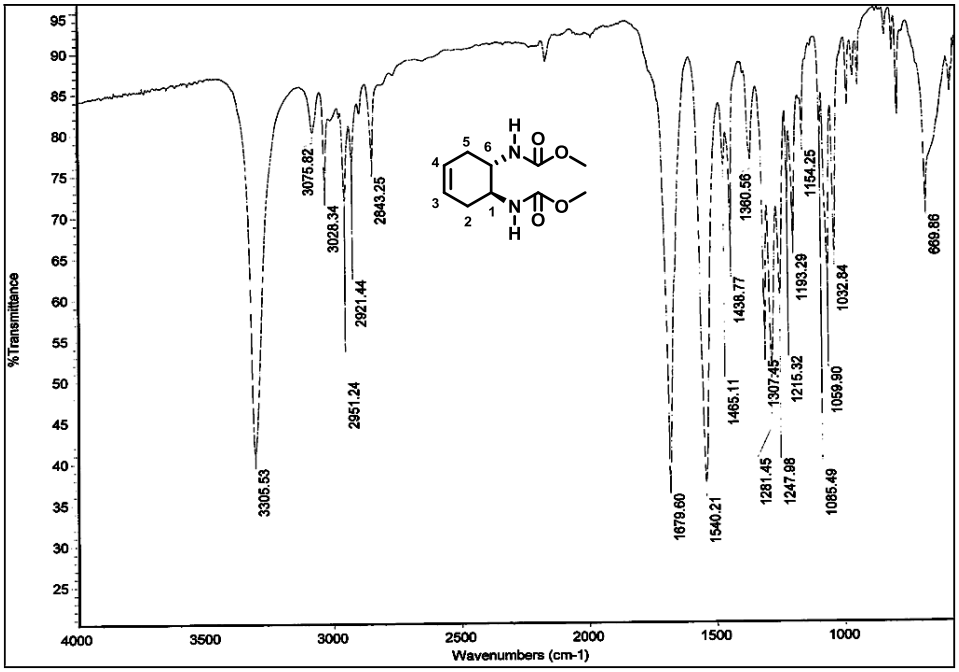


Figure 4.41 IR spectrum of compound **233**

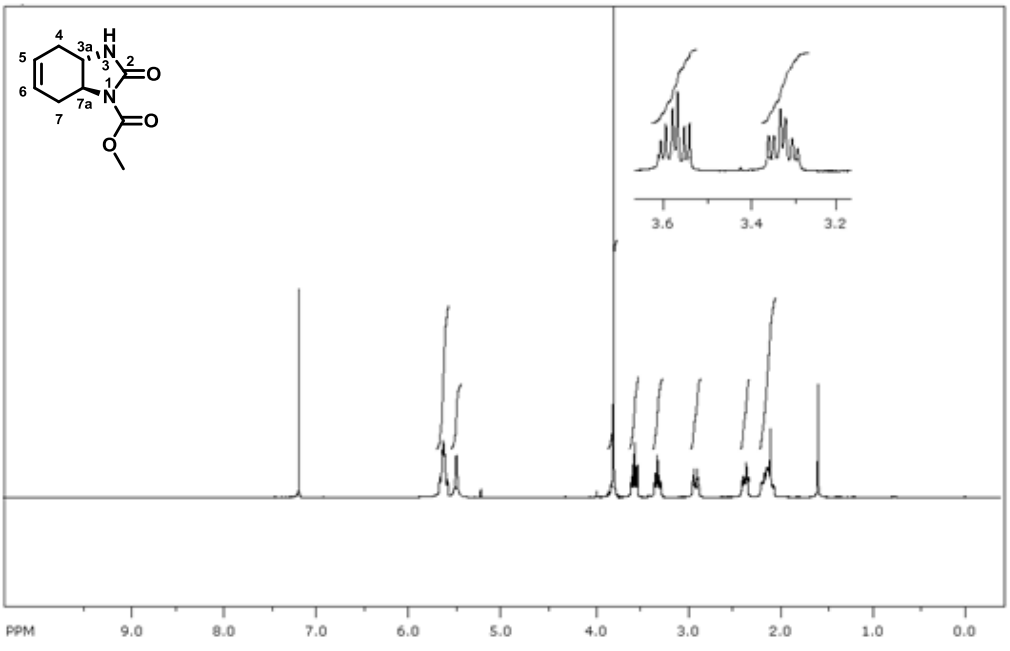


Figure 4.42 ^{1}H-NMR spectrum of compound **237**

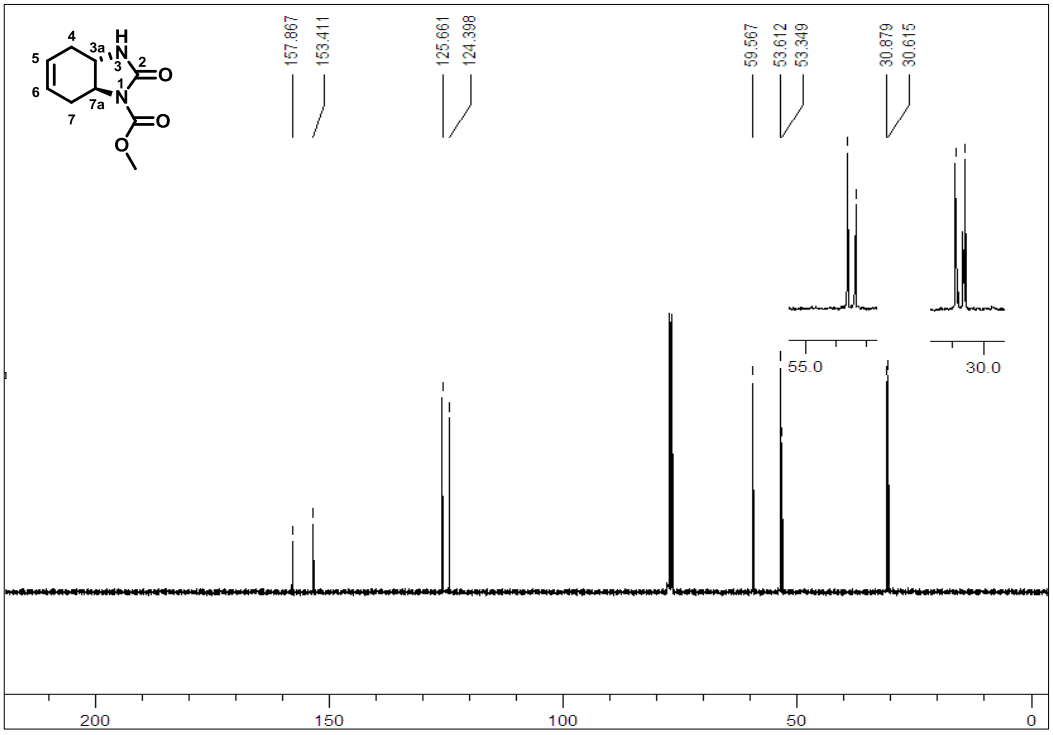


Figure 4.43 ^{13}C-NMR spectrum of compound **237**

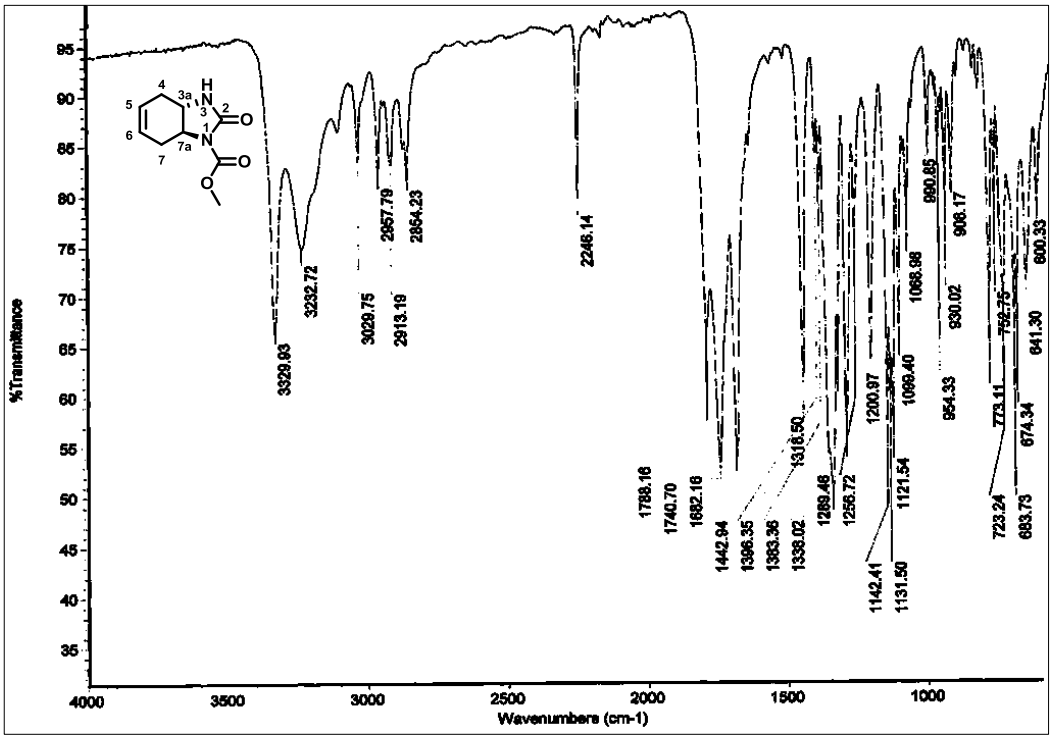


Figure 4.44 IR spectrum of compound **237**

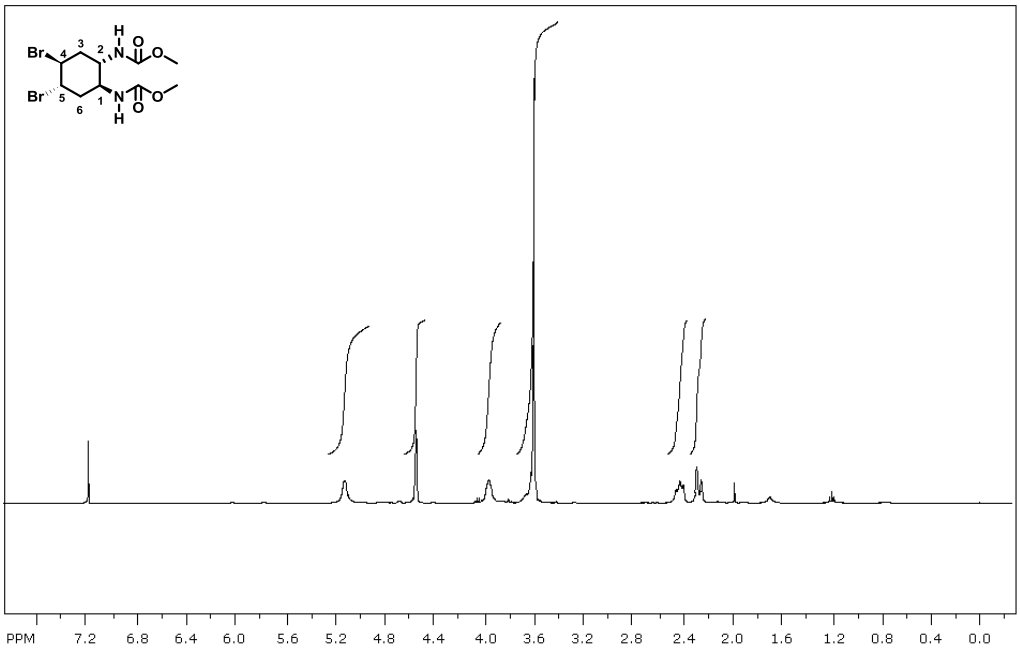


Figure 4.45 ^{1}H-NMR spectrum of compound **244**

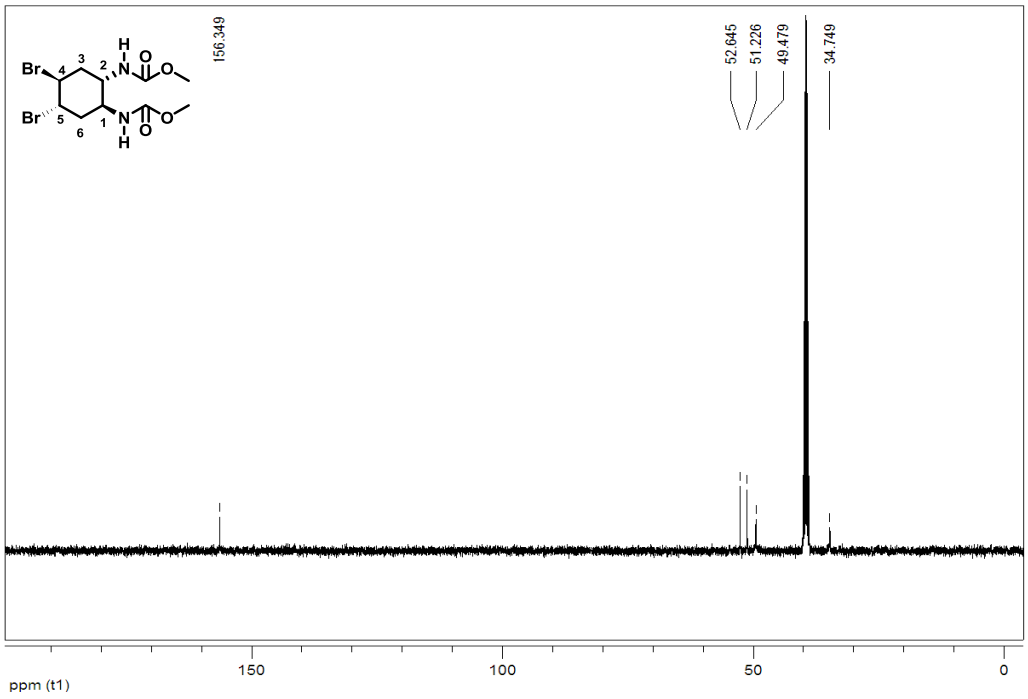


Figure 4.46 ^{13}C-NMR spectrum of compound **244**

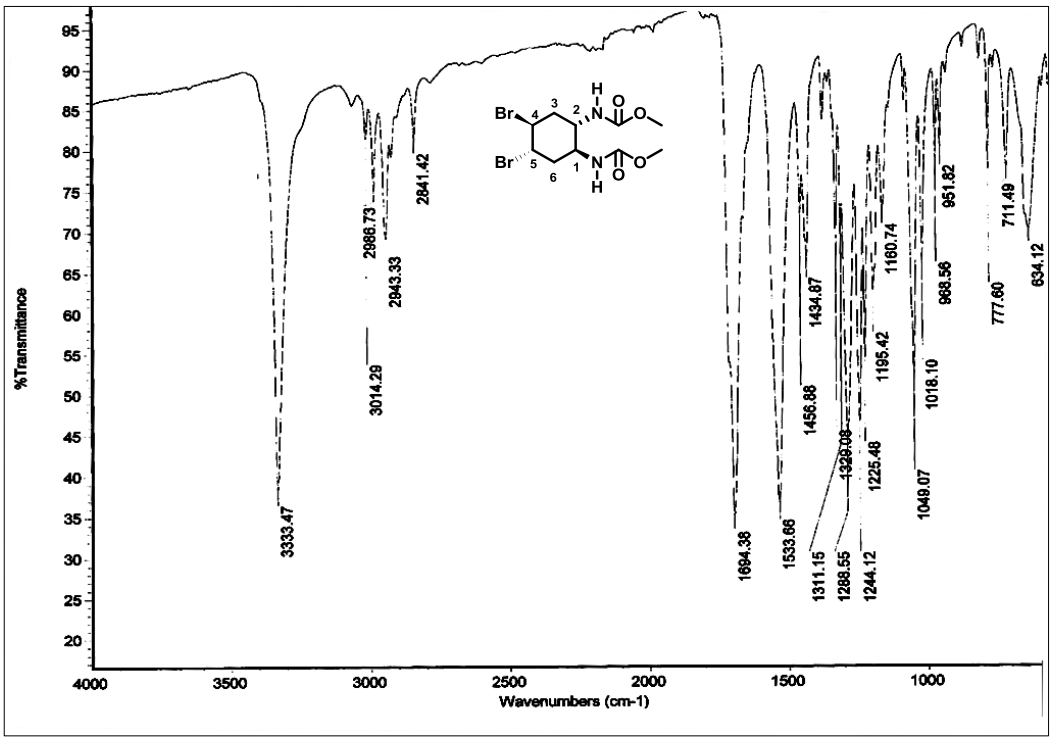


Figure 4.47 IR spectrum of compound **244**

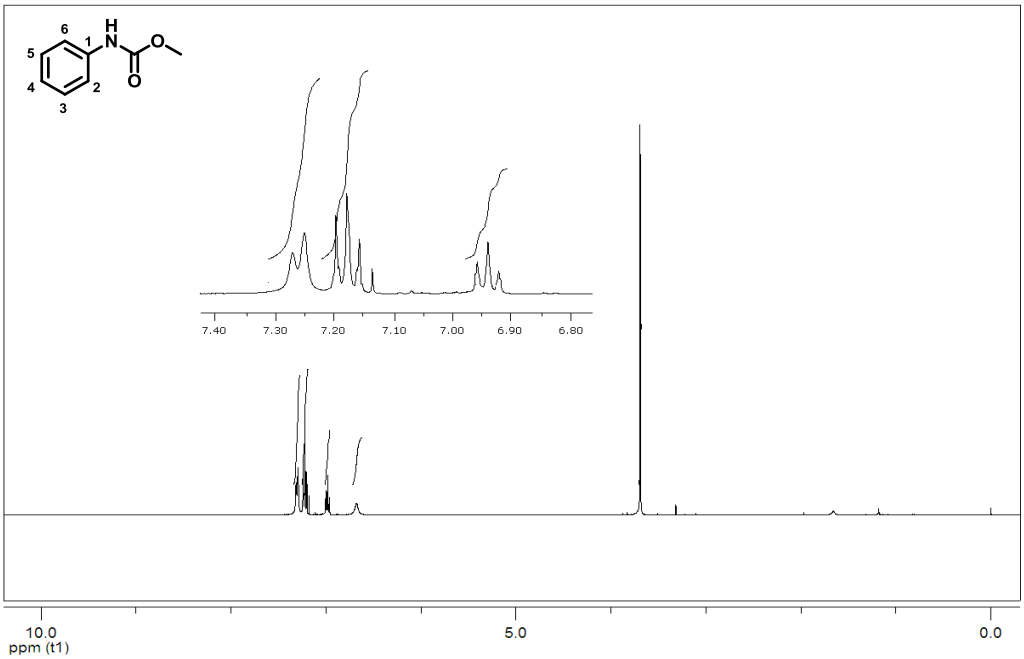


Figure 4.48 ^{1}H-NMR spectrum of compound **246**

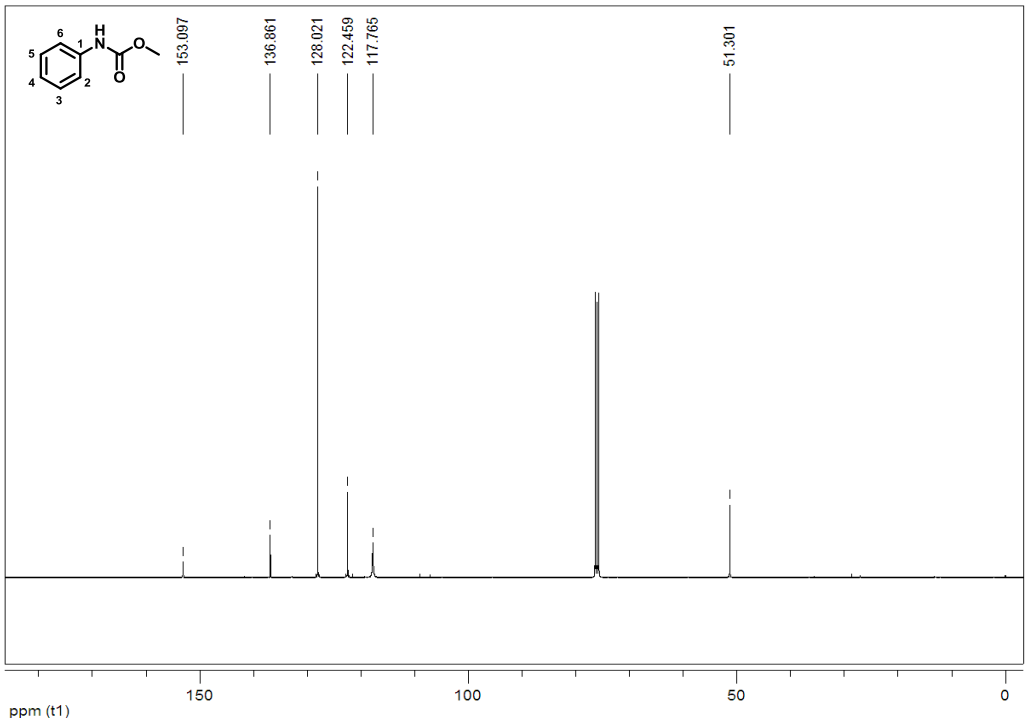


Figure 4.49 ^{13}C-NMR spectrum of compound **246**

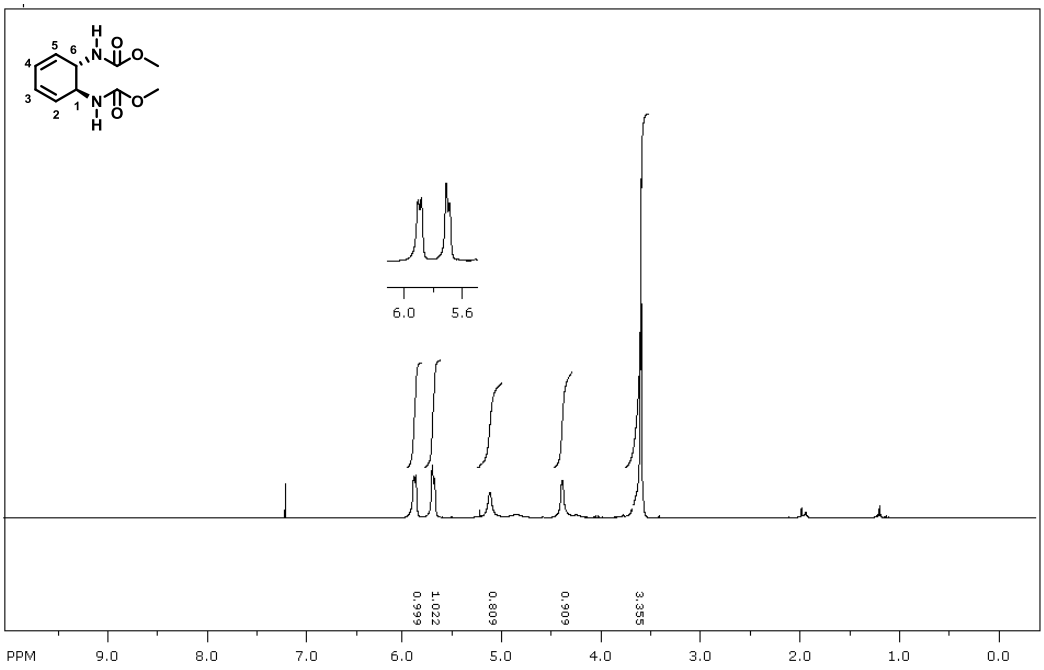


Figure 4.50 ^{1}H-NMR spectrum of compound **247**

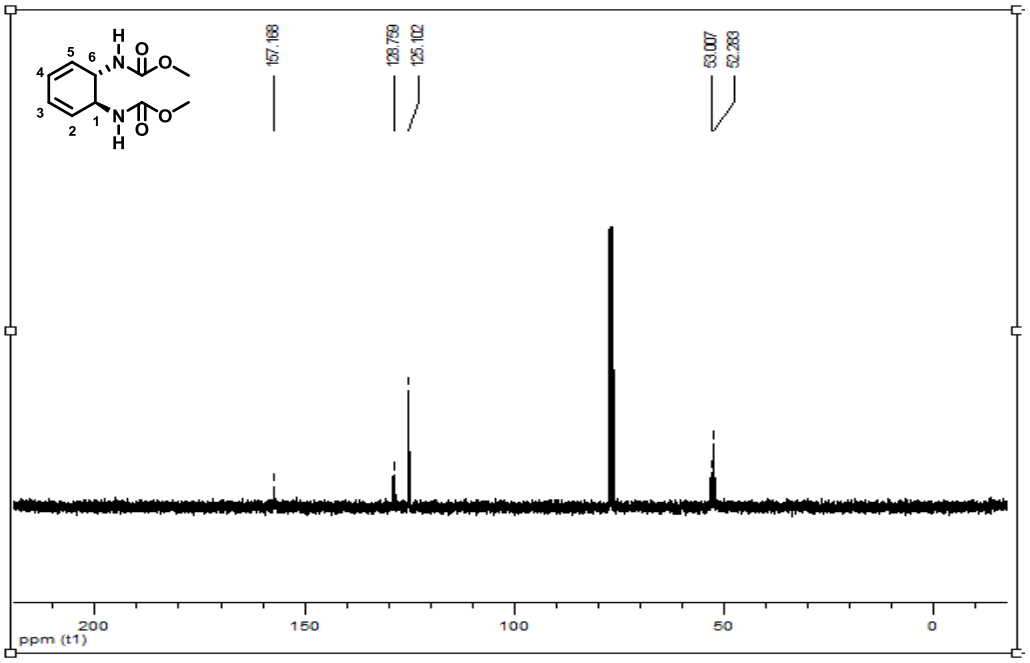


Figure 4.51 ^{13}C-NMR spectrum of compound **247**

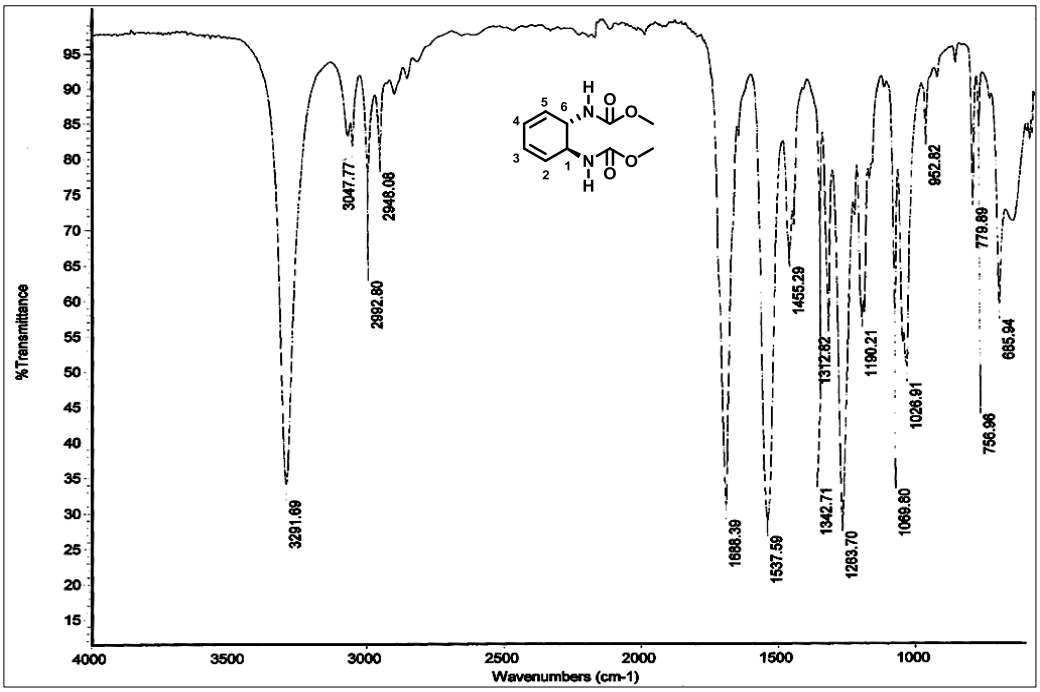


Figure 4.52 IR spectrum of compound **247**

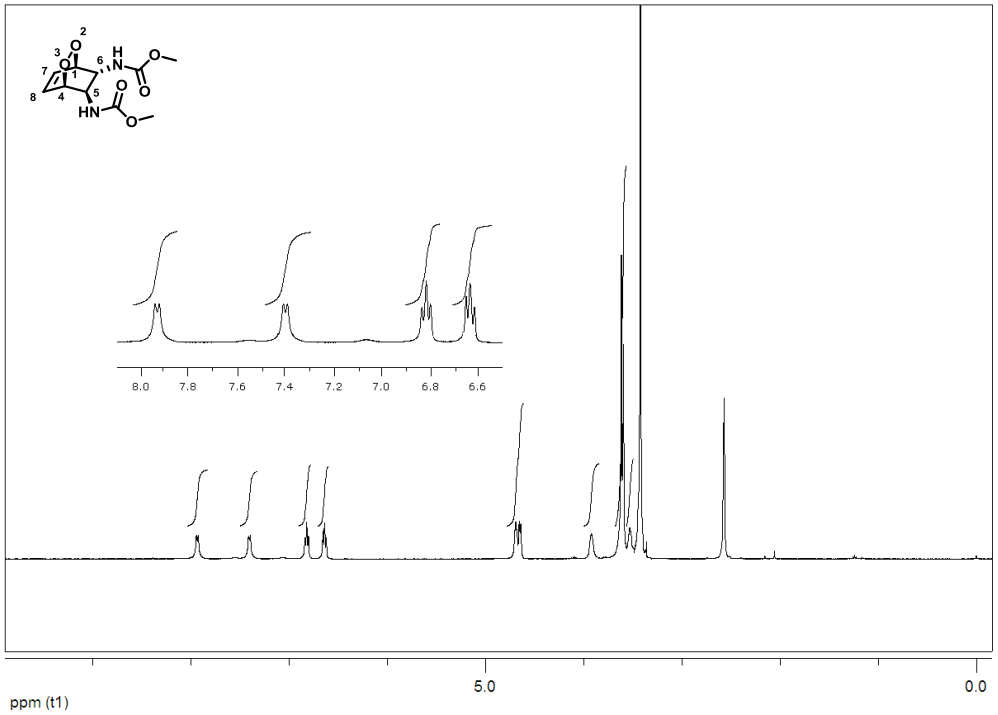


Figure 4.53 ^{1}H-NMR spectrum of compound **248**

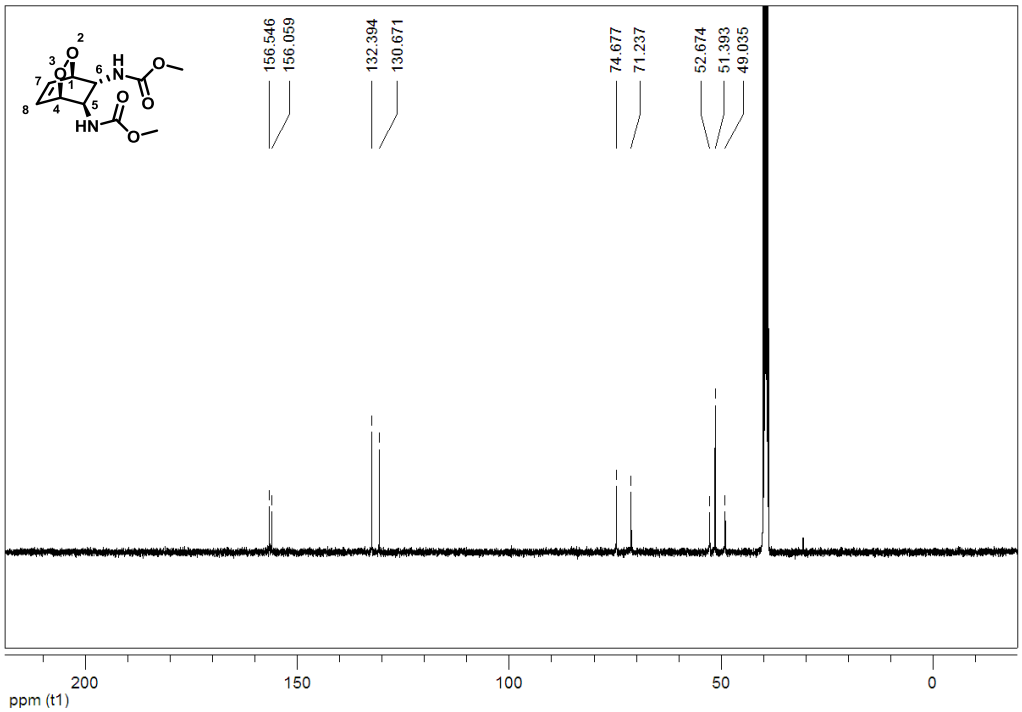


Figure 4.54 ^{13}C-NMR spectrum of compound **248**

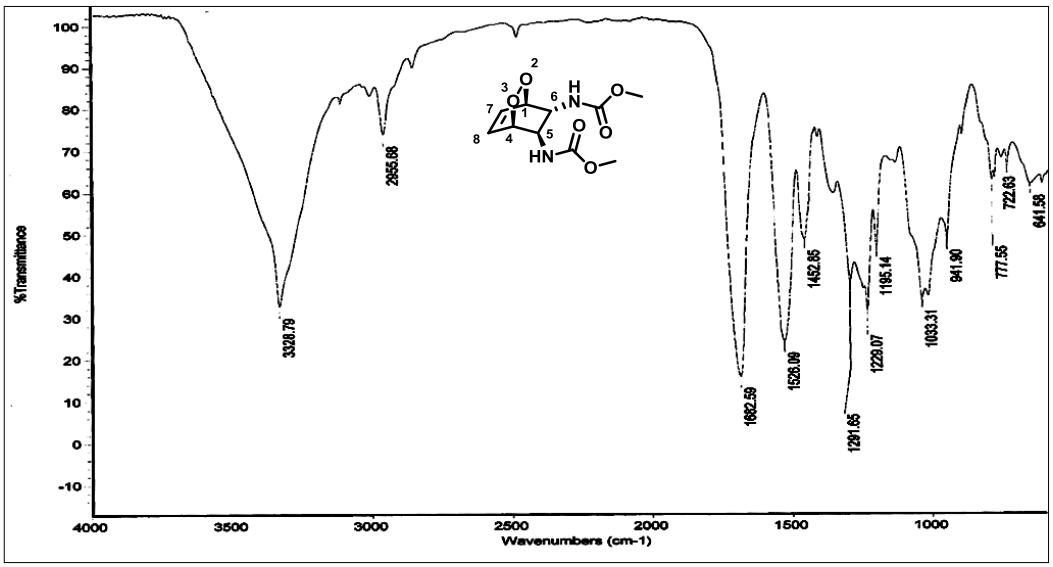


Figure 4.55 IR spectrum of compound **248**

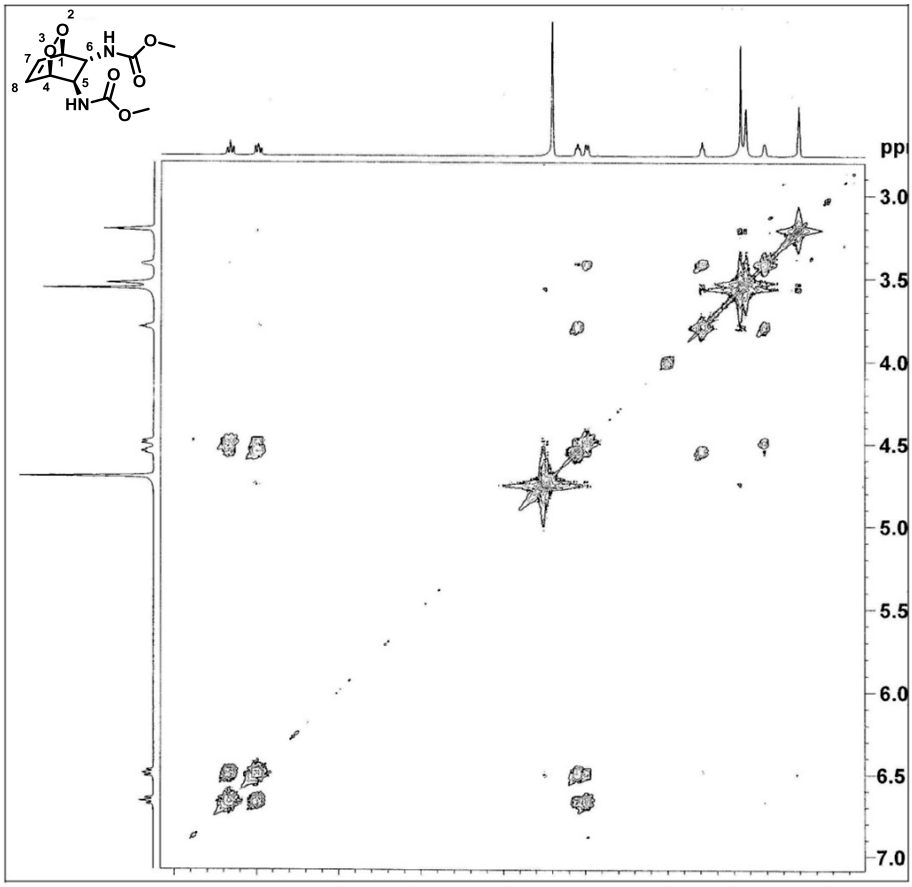


Figure 4.56 COSY spectrum of compound **248**

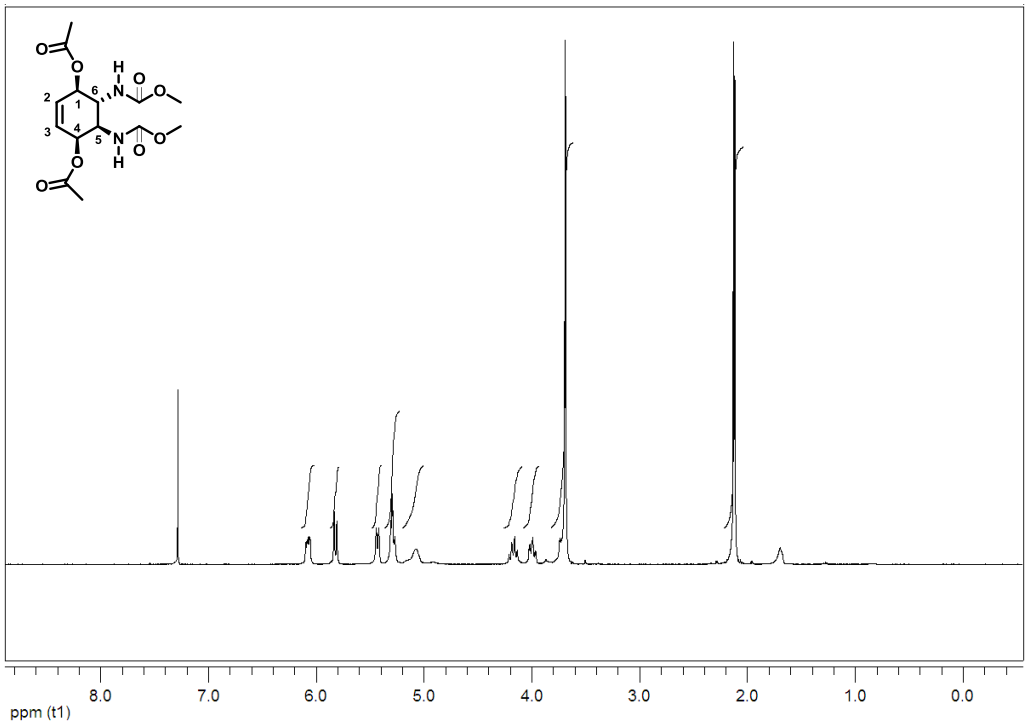


Figure 4.57 ^{1}H-NMR spectrum of compound **253**

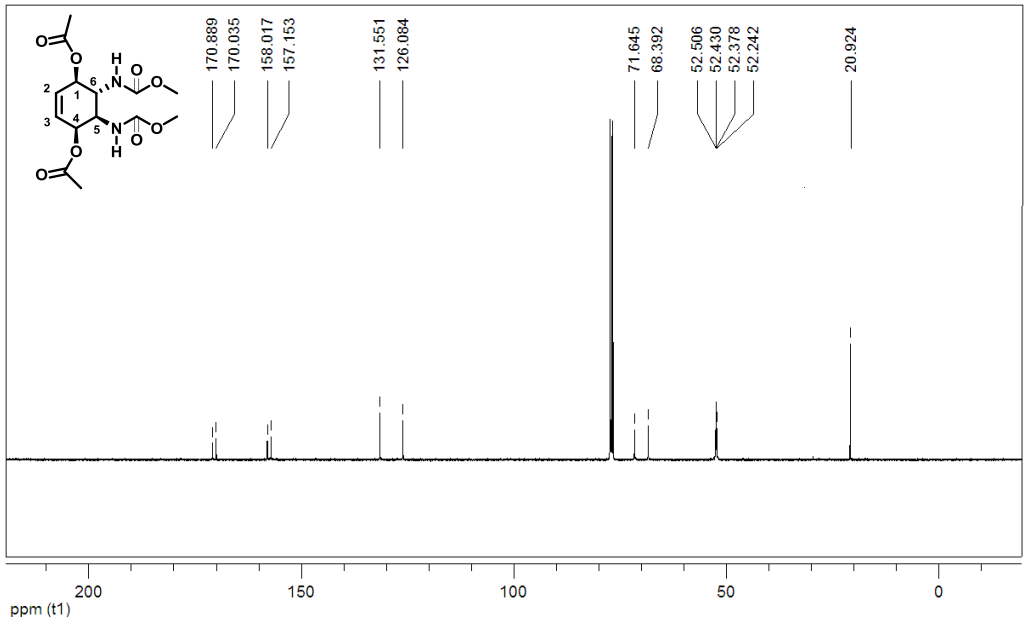


Figure 4.58 ^{13}C-NMR spectrum of compound **253**

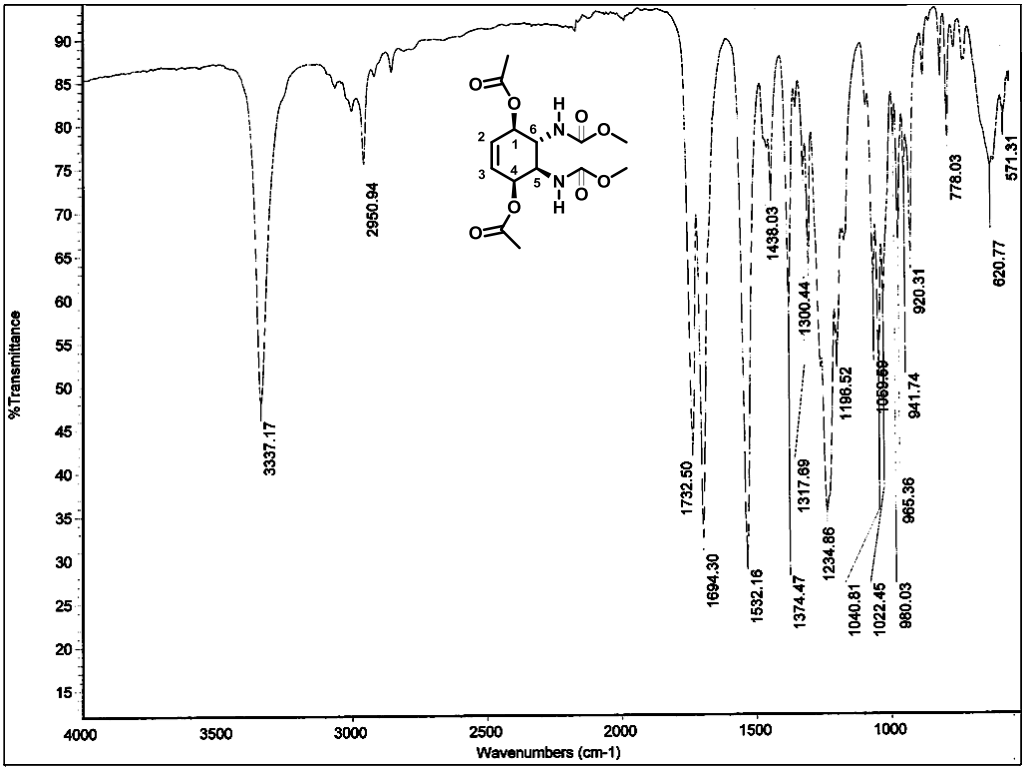


Figure 4.59 IR spectrum of compound **253**

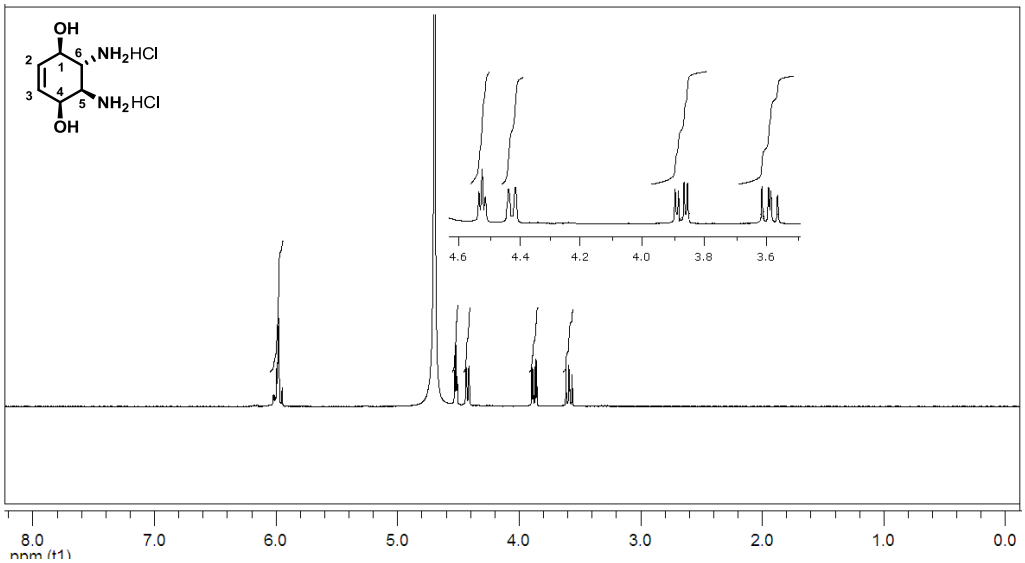


Figure 4.60 ^{1}H-NMR spectrum of compound **202**

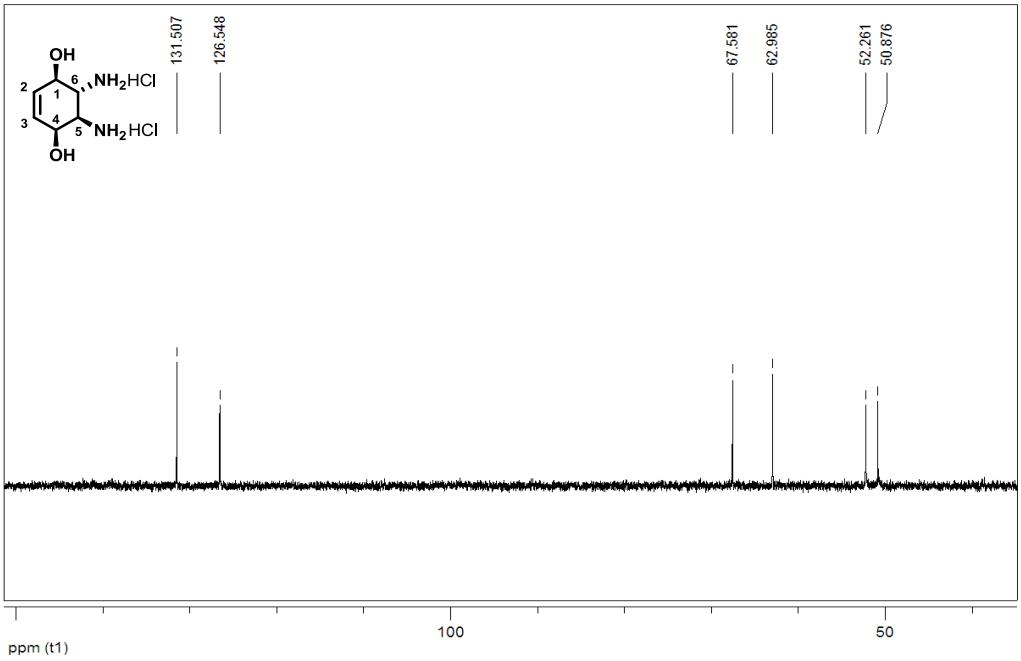


Figure 4.61 ^{13}C-NMR spectrum of compound **202**

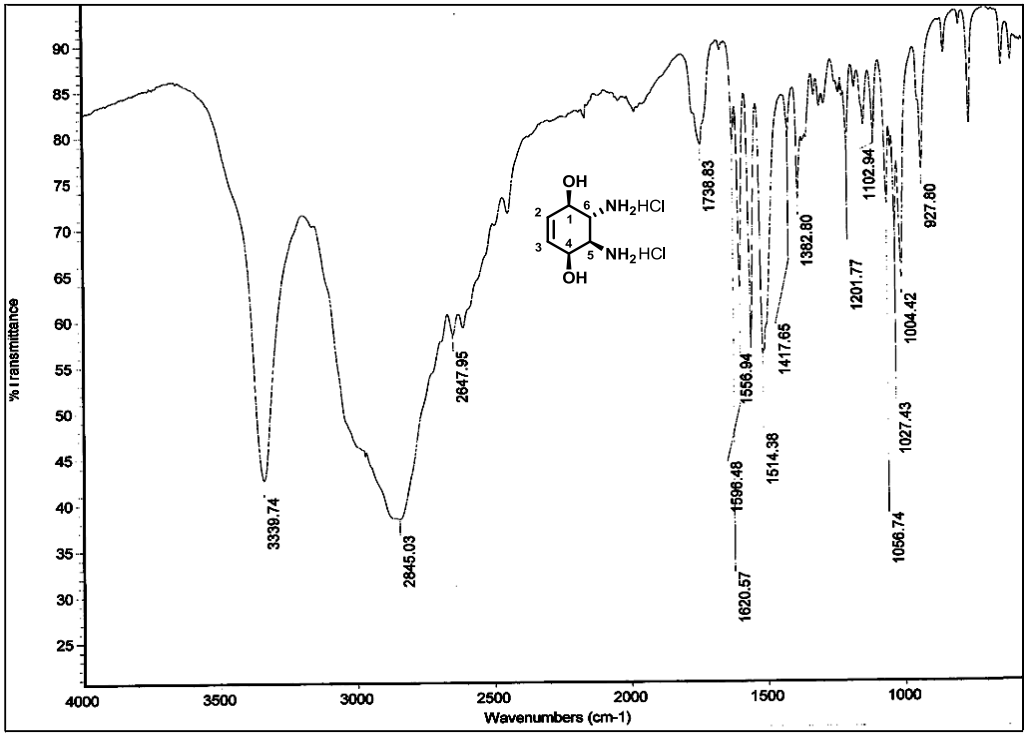


Figure 4.62 IR spectrum of compound **202**

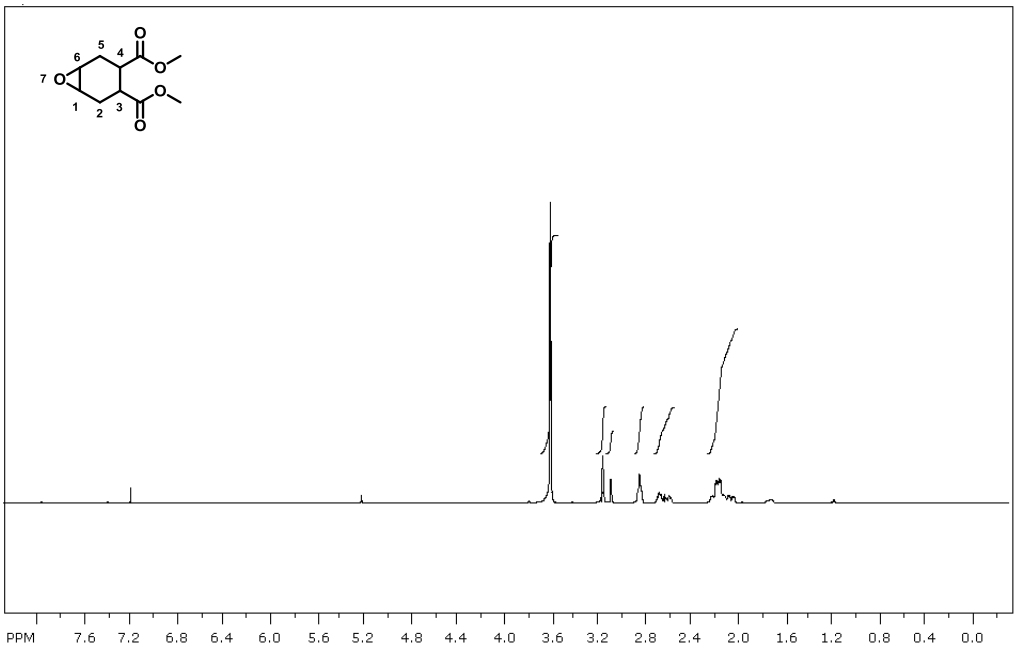


Figure 4.63 ^{1}H-NMR spectrum of mixture of **242** and **243**

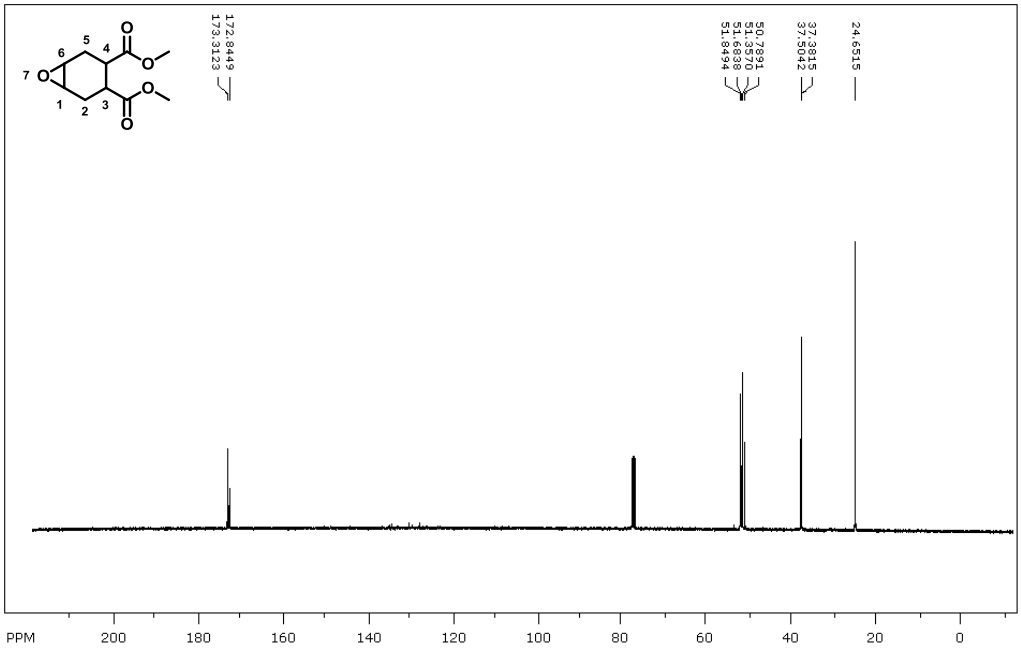


Figure 4.64 ^{13}C-NMR spectrum of mixture of **242** and **243**

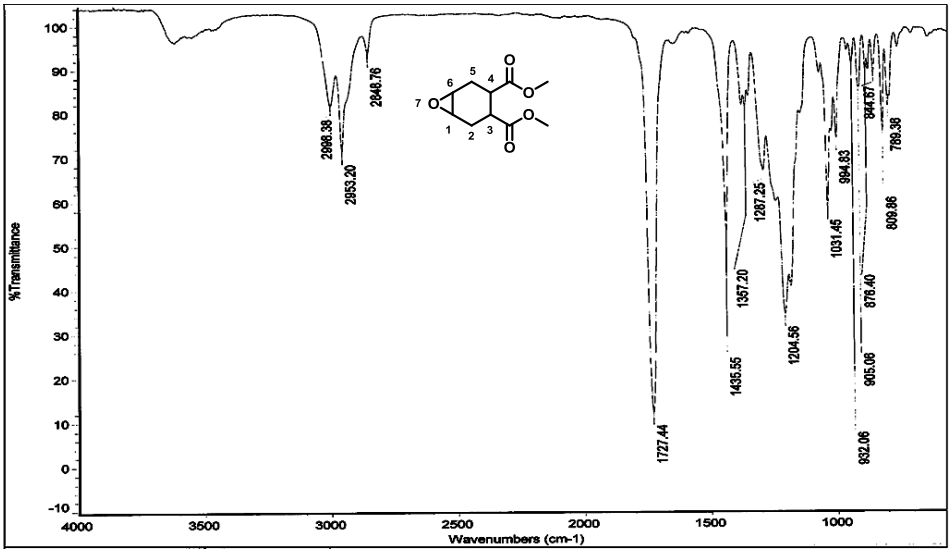


Figure 4.65 IR spectrum of mixture of **242** and **243**

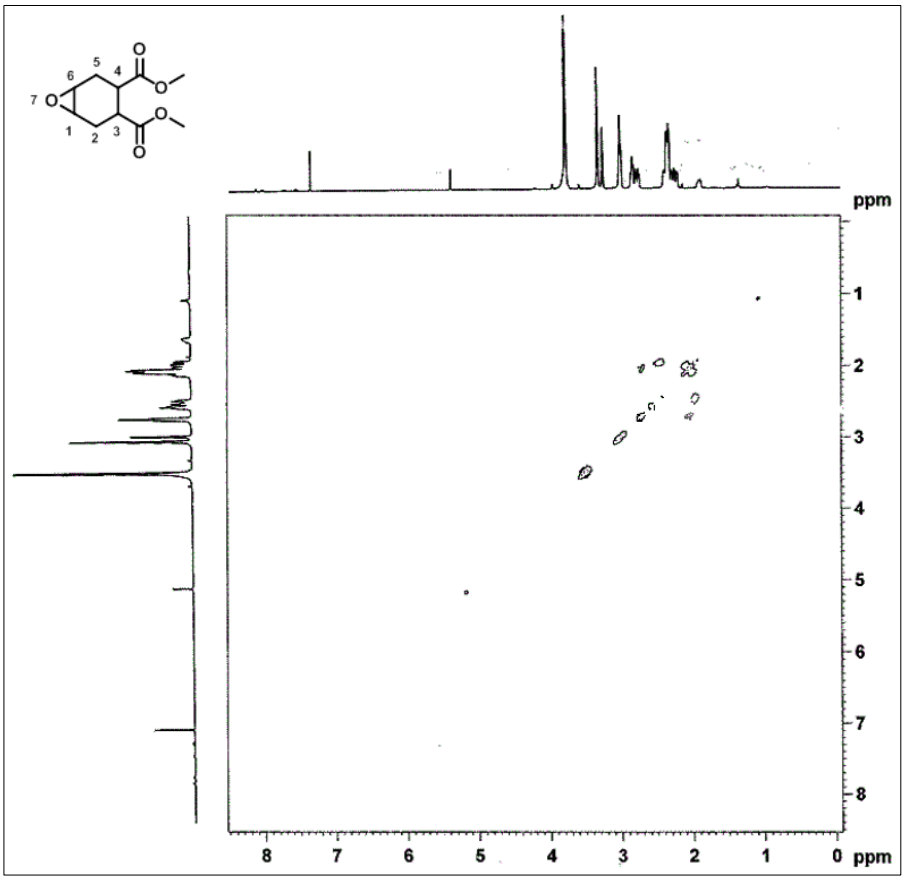


Figure 4.66 COSY spectrum of mixture of **242** and **243**

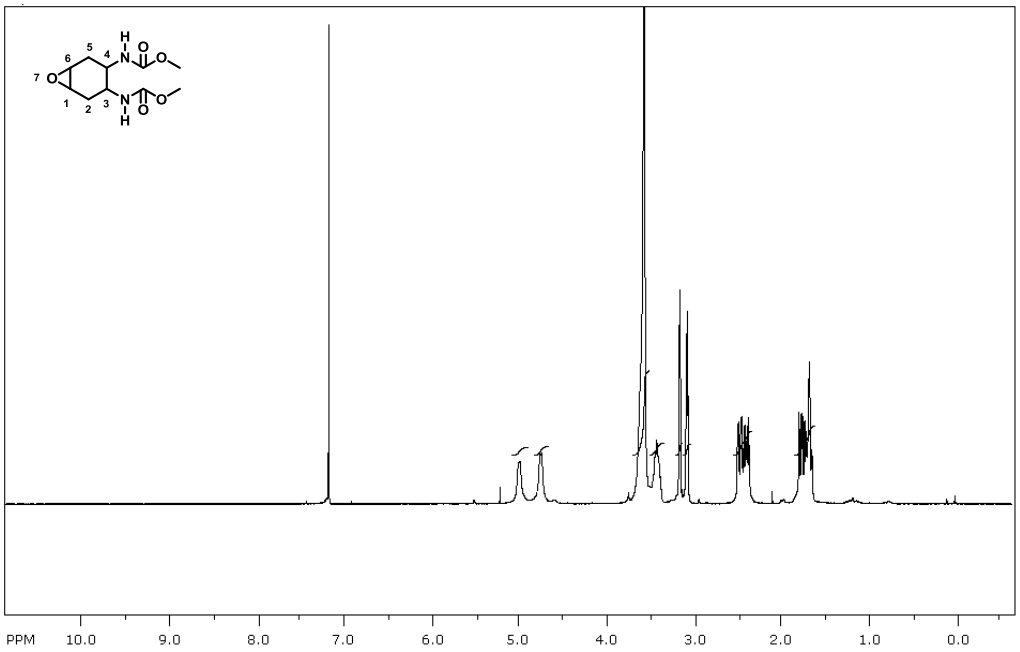


Figure 4.67 ^{1}H-NMR spectrum of compound **238**

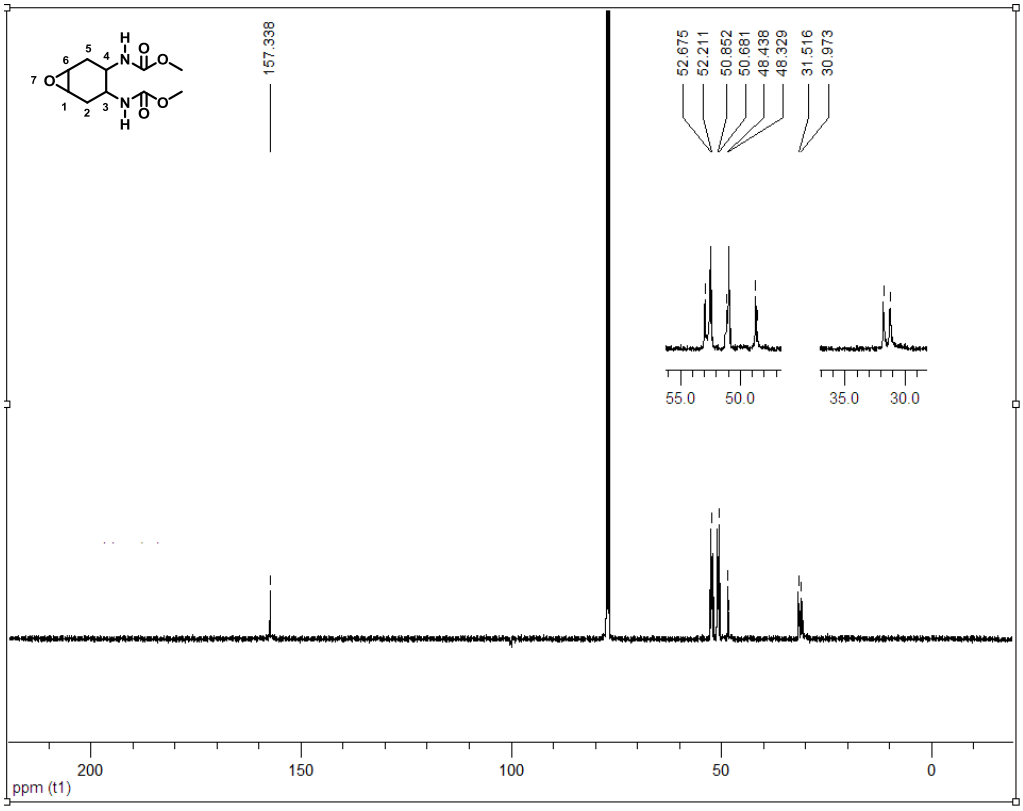


Figure 4.68 ^{13}C-NMR spectrum of compound **238**

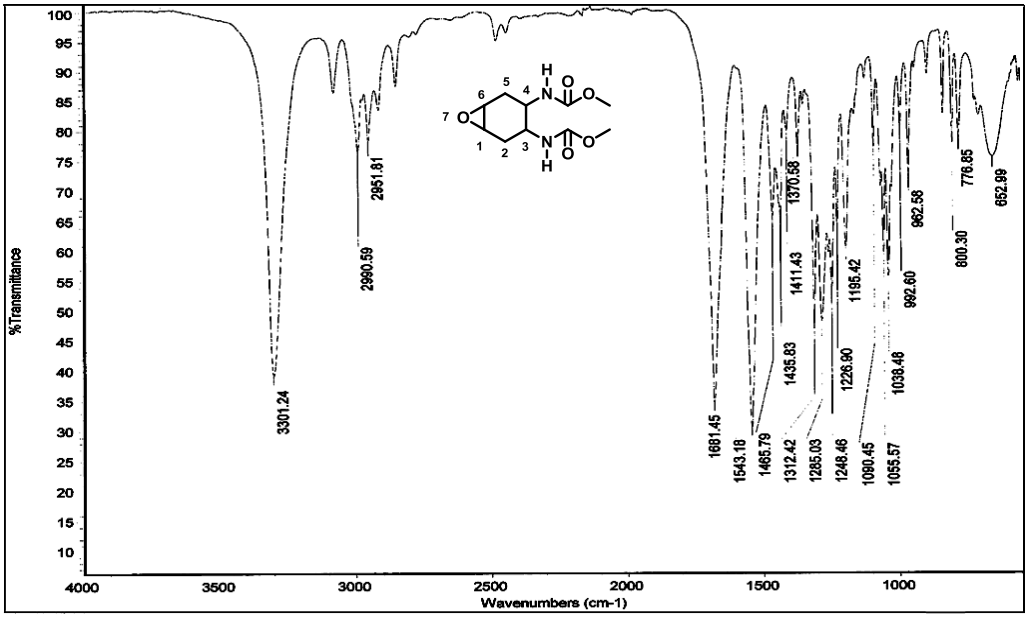


Figure 4.69 IR spectrum of compound **238**

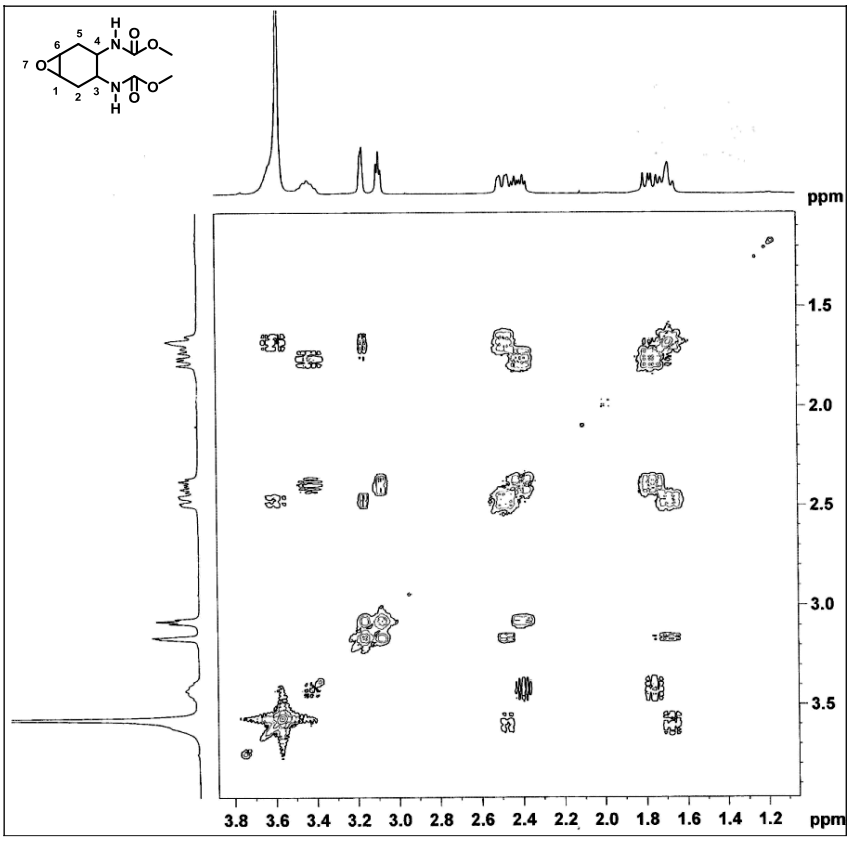


Figure 4.70 COSY spectrum of compound **238**

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CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name:	Zeynep (DOST) EKMEKÇİ
Nationality:	Turkish (T.C.)
Date and Place of Birth:	18 October 1981, Samsun
Marital Status:	Married
e-mail:	zdost@metu.edu.tr, ekmekcizeynep@gmail.com

EDUCATION

Degree	Institution	Year of Graduation
MS	METU-Chemistry	2006
BS	GAZI UNIV. Chemistry Education	2003
High Scool	Namık Kemal Lisesi, Samsun	1998

WORK EXPERIENCE

Year	Place	Enrollment
2003-present	METU- Chemistry	Research Asistant
2009-2010	UMASS-Amherst-Chemistry	Visiting Researcher

PUBLICATIONS

International Refereed Journal Papers

1. **Ekmekci, Z**.; Yilmaz, M. D.; Akkaya, E. U., A Monostyryl-boradiazaindacene (BODIPY) Derivative as Colorimetric and Fluorescent Probe for Cyanide Ions, *Organic Letters*, **2008**, *10,* 461-464. DOI: 10.1021/ol702823u
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4. **Ekmekci, Z.**; Balci, M., Diaminokonduritoller İçin Yeni Sentetik Metot, 22. Ulusal Kimya Kongresi, Ekim **2008**, Magusa.
5. **Ekmekci, Z.**; Yilmaz, M. D.; Akkaya, E. U., Siyanür İyonu İçin Monostyryl Boradiazaindacene Türevi, 15. Yıl Mühendislik-Mimarlık Kongresi, Kasım **2007**, Isparta.
6. **Ekmekci, Z.**; Balci, M., Aminosiklitoller İçin Yeni Sentetik Metotların Geliştirilmesi, 21. Ulusal Kimya Kongresi, Ağustos **2007**, Malatya.