DEVELOPMENT OF THE METHODOLOGY FOR THE SYNTHESIS OF BIS-AMINOINOSITOLS

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

SEPTEMBER 2011

Approval of the thesis:

DEVELOPMENT OF THE METHODOLOGY FOR THE SYNTHESIS OF BIS-AMINO INOSITOLS

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ABSTRACT

DEVELOPMENT OF METHODOLOGY FOR THE SYNTHESIS OF BIS-AMINOINOSITOLS

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September 2011, 87 pages

Cyclitols are cyclic compounds having hydroxyl groups which attached to different carbons on the ring. Cyclitols have attracted a great deal of attention for having diverse biological activities. Cyclic alcohols play an important role in biological processes such as inhibition of glycosidase, cellular recognition, and signal transduction. In addition to this, these compounds are very important molecules due to being capable of using while synthesizing natural products or pharmaceuticals. In this study, development of new methodology for the synthesis of bis-aminoinositol derivatives was aimed. The starting material, *cis*-diester, was synthesized from the Diels-Alder reaction of furan and maleic anhydride followed by reaction with MeOH. As a second key compound, *trans*-diester was obtained from the Diels-Alder reaction of furan and fumaryl chloride followed by esterification. The diester functionality in these two compounds was planned to be converted into the hydrazide upon treatment with hydrazine monohydrate. Before this reaction, double bond was protected via stereo selective oxidation reaction with *m*-CPBA due to preventing retro Diels-Alder reaction. Then, hydrazide functionality was converted into acyl azide through β-nitroso hydrazide intermediate. Subsequent Curtius rearrangement

reaction resulted in the formation of the isocyanate which was converted to the corresponding bis-urethane by treatment with MeOH. Attempt to cleave the oxa-bridge in urethane with sulfamic acid provided the unexpected tricyclic product **148**. Furthermore, hydrolysis of isocyanate with aqueous HCl formed the diamine **156**. However, *O*-bridge could not be opened with any reagents used for that of urethane derivative as described above. Then, the *cis*-diol **157** was synthesized to prevent the neighboring group participitation during the epoxide-opening reaction. Further ring-opening reactions are under investigation.

Keywords: Aminocyclitols, aminoinositols, retro Diels-Alder, Curtius rearrangement, ring-opening of oxa-bridge.

ÖZ

BİS-AMİNOİNOSİTOL SENTEZİ İÇİN YENİ METOTLARIN GELİŞTİRİLMESİ

Korkmaz Çokol, Nalan

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2011, 87 sayfa

Siklitoller yapısında hidroksil grubu içeren siklik bileşiklerdir ve hidroksil grupları halkadaki farklı karbon atomlarına bağlıdırlar. Siklitoller gösterdikleri biyolojik aktivite çeşitliliği açısından son yıllarda dikkat çekmektedir. Siklik alkoller biyolojik proseslerde, örneğin; glikozidaz enzimini inhibe etmede, hücresel tanımalarda ve sinyal iletiminde önemli bir rol oynamaktadır. Bu çalışmada, furan ve maleik anhidritin Diels-Alder reaksiyonu sonucunda oluşan katılma ürününün methanol ile tepkimesi sonucu kolayca sentezlenebilen *cis*-diester ve ayrıca furan ve fumaril klorürün Diels-Alder reaksiyonu sonucunda oluşan ürünün esterifikasyonu ile *trans*-diester elde edildi. Reaksiyon esnasında gözlenen retro Diels-Alder tepkimesini engellemek için, karbon-karbon çift bağı *m*-CPBA varlığında çift bağın epoksitlenmesi ile korundu. Bu iki moleküldeki diester fonksiyonel grupları hidrazin monohidrat ile reaksiyona sokularak, hidrazite çevrildi. Hidrazit fonksiyonel grubunun β-nitrozo hidrazit ara ürünü oluşturarak açil azite dönüştürülmesi başarıyla gerçekleştirildi. Takip eden Curtius düzenlenmesi ile izosiyanat ve methanol ilavesiyle de üretan elde edildi. Daha sonra, $BF_3.Et_2O$ ve BCl_3 gibi Lewis asitleri ve sülfamik asit kullanılarak, oksijen köprüsünün açılması hedeflendi. Fakat asit

katalizör kullanılarak yapılan halka açılma reaksiyonunda trisiklik yapıda beklenilmeyen bir ürün **148**'in oluştuğu gözlendi. Buna ek olarak, izosiyanatın hidrolizi HCl varlığında gerçekleştirildi ve ilgili diamin **156** elde edildi. Bundan sonraki aşama siklik yapıyı oluşturmak için oksijen köprüsünü açmaktı. Çeşitli reaktiflerle yapılan denemelerde oksijen köprüsünün açılımı gerçekleştirilemedi. Üretandan yola çıkılarak yapılan reaksiyonda gözlenen komşu grup etkisini engellemek için reaksiyona *cis*-diol **157** ile devam edildi. Farklı yöntemler kullanarak halka açma tepkimeleri çalışması devam etmektedir.

Anahtar kelimeler: Aminosiklitol, aminoinositol, retro Diels-Alder, Curtius düzenlenmesi, oksa köprüsünün açılımı.

To my family and lover…

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation and thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, valuable advices, moral support and for enlightening my professional and academic vision throughout my study.

I would like to express my sincere thanks to Serdal Kaya and to Assist. Prof. Dr. Gani Koza for their valuable guidance, discussion and support.

I would like to thank to NMR specialists Zehra Uzunoğlu and Betül Eymur for the NMR experiments.

I would like to thank to Dr. Ebru Mete at Erzurum Atatürk University for the elemental analysis.

I would like to express my great thanks to all the members of SYNTHOR Research Group especially to Zeynep, Dr. Dilem Doğan, Çağatay, Emrah, Selbi, and Yasemin for their friendship and helps.

I wish to express my appreciation to the academic staff of METU Department of Chemistry for their professional support and guidance to the students of Department of Chemistry.

I would like to thank to my friends Sevgi İpekçioğlu, Gamze Karaman, Gönül Hızalan and Merve Kolay for their precious friendship.

I would like to give the biggest thanks to my family especially my sister Hande with their love, affection, support and guidance throughout my whole life. The completion of this study would not have been possible without them.

Finally, I would like to thank to my lover Onur Çokol for his understanding and big love.

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LIST OF ABBREVIATIONS

***m*-CPBA:**	*meta*-Chloroperoxybenzoic acid
DCM:	Dichloromethane
DMP:	2,2-Dimethoxypropane
NMO:	*N*-Methylmorpholine-*N*-oxide
TBAF:	Tetra-*n*-butylammonium fluoride
THF:	Tetrahydrofuran
TPP:	Tetraphenylporphyrin
PTSA:	*p*-Toluenesulfonic acid
NMR:	Nuclear magnetic resonance
IR:	Infrared
J:	Coupling constant
Hz:	Hertz
ppm:	Parts per million
mg:	milligram
mmol:	millimole

CHAPTER 1

INTRODUCTION

1.1 Cyclitols

Glycosidase inhibitors and glycomimics have drawn attention in recent years. They are used in treatment for some diseases such as diabetes, cancer, AIDS, etc. Carbohydrates which like monosaccharides in shape and size have been devised and activities of these compounds were analyzed. It was determined that they show various biological activities [1].

Cyclitols are cyclic compounds having hydroxyl groups which attached to different carbons on the ring. Cyclitols are carbasugars in which *endo*-oxygen is replaced with a carbon atom. They are very important compounds due to having biological activities. Cyclitols play important role in some biological processes such as inhibition of glycosidase, cellular recognition and signal transduction. Furthermore, cyclitols are used for the synthesis of various natural products showing similar activities [1]. Conduritols (**1**), quercitols (**2**), and inositols (**3**) are the most general types of cyclitols (Figure 1).

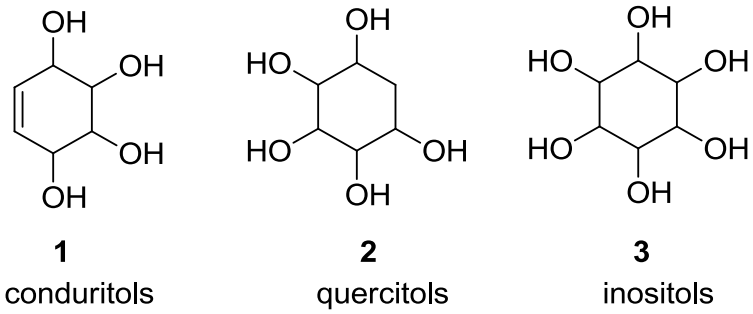


Figure 1 Cyclitol derivatives

1.2 Conduritols

Conduritols (**1**) are cyclohex-5-ene-1,2,3,4-tetrols. There are six stereoisomers (Figure 2) among which two are meso-compounds; conduritol-A (**4**) and conduritol-D (**7**), and four are enantiomeric pairs; conduritol-B (**5**), conduritol-C (**6**), conduritol-E (**8**), and conduritol-F (**9**). Conduritol-A (**4**) and conduritol-F (**9**) are naturally occurring compounds.

Conduritols and their derivatives are very important compounds due to they have biological activities; for instance, they can be used as inhibitors of glycosidase. Conduritol-A (**4**) analogues are used for releasing of insulin from isolated pancreatic islets when glucose concentration is changing. Furthermore, conduritol derivatives are involved in some antibiotics. They show antileukemic growth-regulating activities. Besides, conduritol derivatives are used as key compounds for the synthesis of inositols, quercitols, deoxyinositols, aminoconduritols, conduritol epoxides etc. [2].

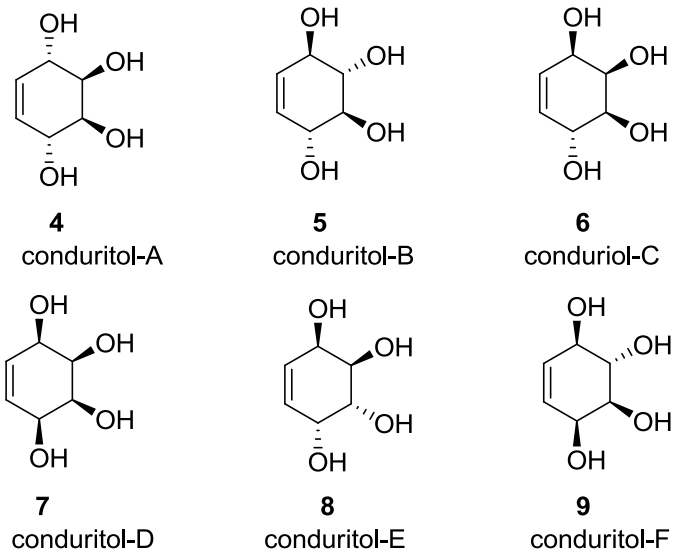
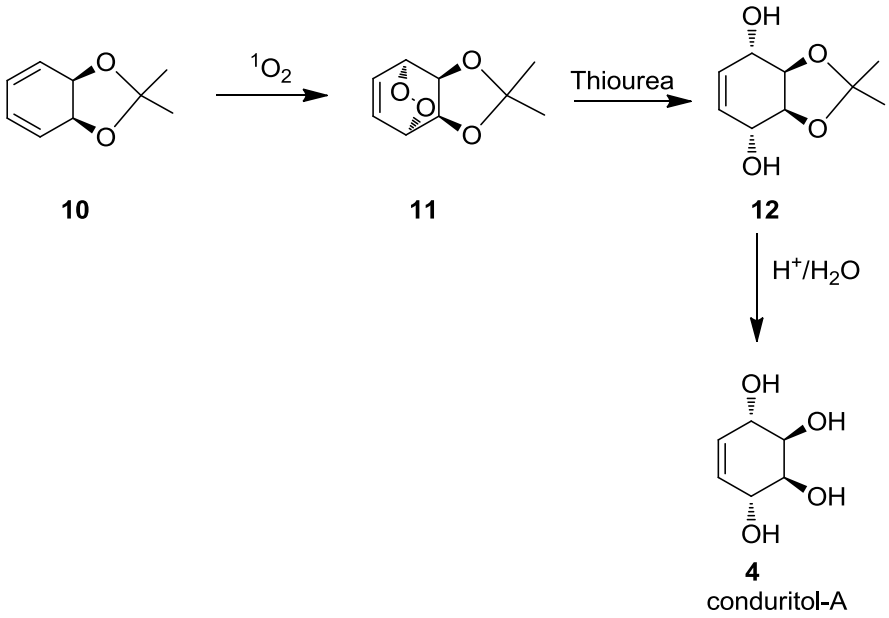


Figure 2 Conduritol diastereomers

Conduritol-A (**4**) was discovered in 1908. Conduritol-A (**4**) was the first compound known as cyclohexenetetrol. Kübler isolated it from the bark of the vine *Mursdeniu Condurungo* [3]. Moreover, Balcı *et al*. developed a new and concise synthetic method for conduritol-A (**4**) [4]. For the synthesis of conduritol-A (**4**), the key compound **10** was submitted to photooxygenation reaction to give compound **11**. To cleave peroxide linkage, thiourea was used for selective reduction to provide compound **12**. After hydrolysis of ketal functionality, conduritol-A (**4**) was obtained (Scheme 1).



Scheme 1 Synthesis of conduritol-A

Also Balcı *et al*. successfully synthesized conduritol-B (**5**) and conduritol-F (**9**) through the acid-catalyzed epoxide ring-opening reaction in acetic anhydride by using oxepine-benzenoxide system (**13**) as starting agent (Scheme 2) [5]. The formation of conduritol-B (**5**) has an explanation on the basis of involving of the neighboring acetoxy group in the process of the epoxide ring-opening.

For the synthesis of conduritol-E (**8**)**,** compound **17** was reacted with *m*-CPBA to give epoxy compound **18**. It is well known that epoxide ring-opening reaction is trans and forms a single product. In the case of ring-opening of compound **18**, due to the unsymmetrical structure, two ring-opening products are expected. However,

treatment of compound **18** with water in presence of acid provided compound **19** as the sole product, which is precursor of conduritol-E (**8**). By using DMP and Zn/DMSO, di-*O*-isopropylidene derivative **20** was obtained. After addition acid, ketal functionality was removed and conduritol-E (**8**) was produced (Scheme 2) [6].

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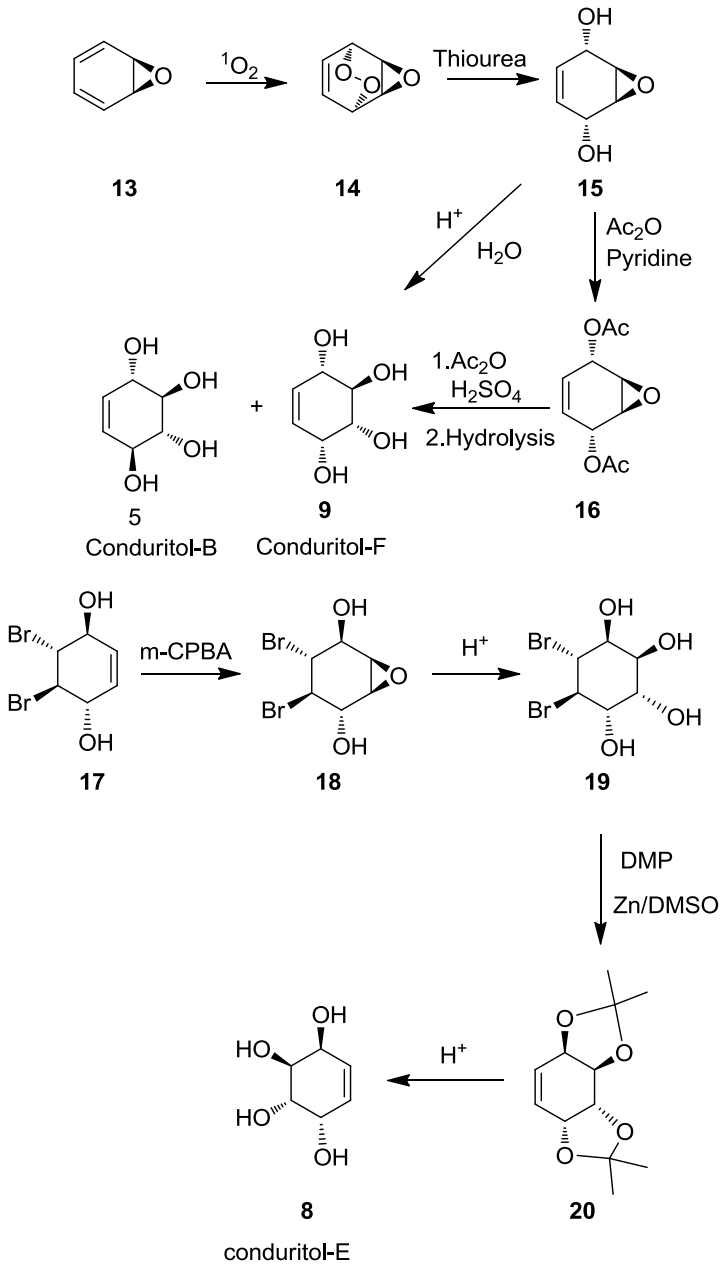


Scheme 2 Synthesis of conduritol-F, conduritol-B and conduritol-E

1.3 Quercitols

Quercitols are cyclic compounds which have six carbon atoms. Except one carbon atom, each has one hydroxyl group. So, they are considered as cyclohexanepentols. There are sixteen stereo isomeric forms of quercitols and four of them are symmetric (Figure 3). Other 12 forms are grouped as 6 pairs of enantiomers. Only three of them, which are optically active namely (+)-*proto*-quercitol, (-)-*proto*-quercitol, and (-)-*vibo*-quercitol are found in plants [7]. There are many ways for the synthesis of quercitols such as reduction (hydrogenation) of inososes and inosos oximes or deoxyino-soses, hydrogenation of bromoquercitols, reduction of anhydroinositols and transformation of conduritols.

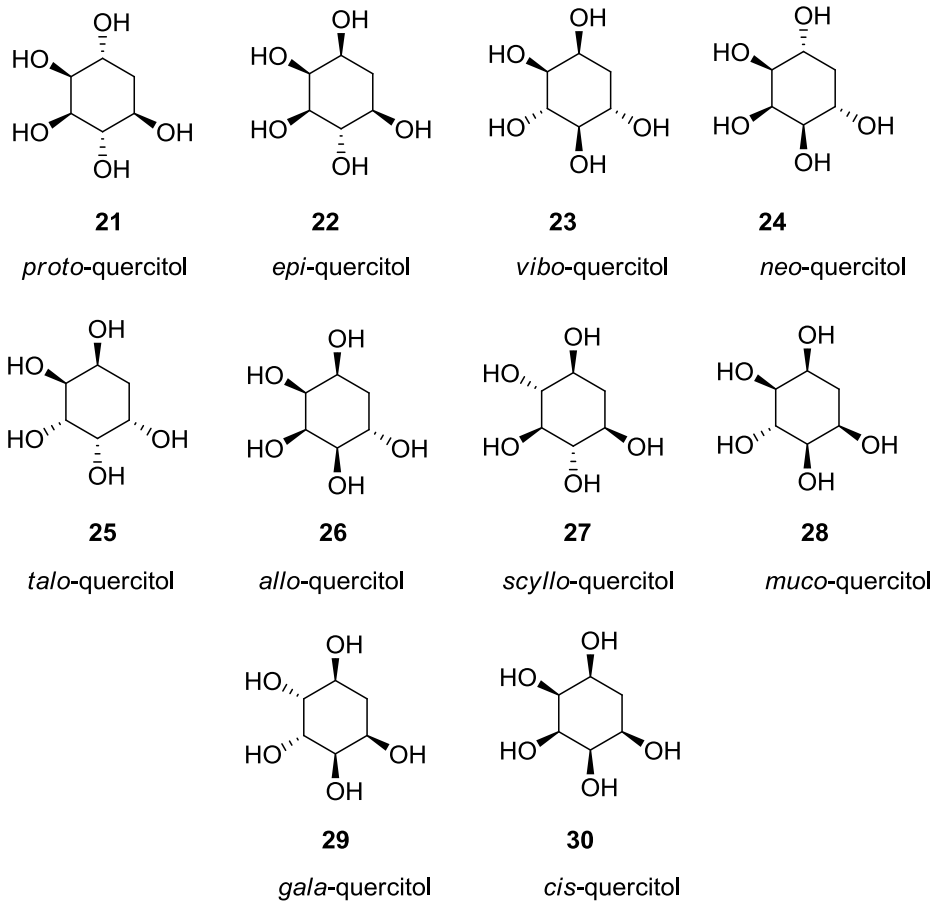
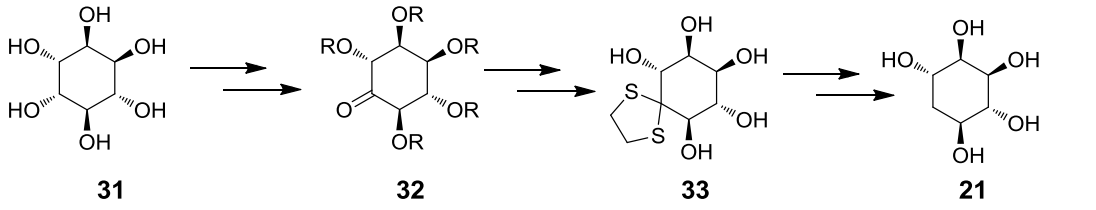


Figure 3 Quercitol stereoisomers

Synthesis of ten stereoisomers among sixteen molecules was accomplished with different ways. Natural products or commercially available compounds can be used as starting materials to synthesize quercitol stereoisomers in many steps [8].

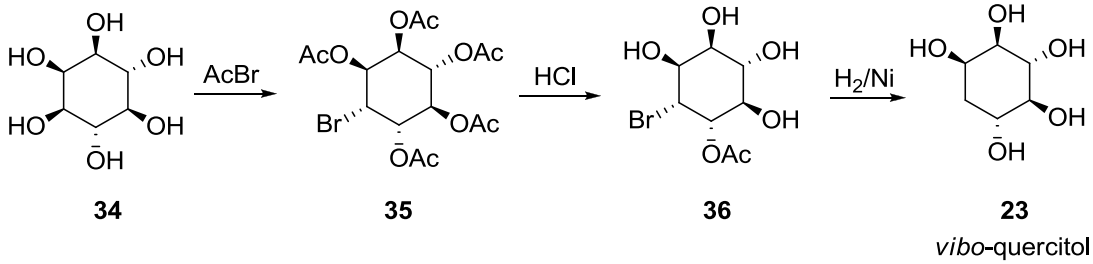
(+)-*proto*-quercitol (**21**) was discovered in 1849 by Braconnot who isolated it from the acorns of an oak tree (genus *Quercus*) as a colorless, crystalline compound, $C_6H_{12}O_5$ [9]. Its cyclohexapentol structure was detected in 1885, and its configuration in 1932. However, there had been no synthesis which was pronounced until the 1960s. In 1961, Plouvierl discovered (-)-*proto*-quercitol in leaves of the tree Eucalyptus populnea F. Muell. The other quercitol derivative, which is a natural compound, (-)-*vibo*-quercitol (**23**) was found in many plants such as *gymnema sylvestre*, *stephania hernandifolia menispennum canadanse* and *vibumurn tinus* [8].

Proto-quercitol (**21**) was synthesized by removal of the hydroxyl group at the position C-2 of (-)-*chiro*-inositol (Scheme 3) [9].



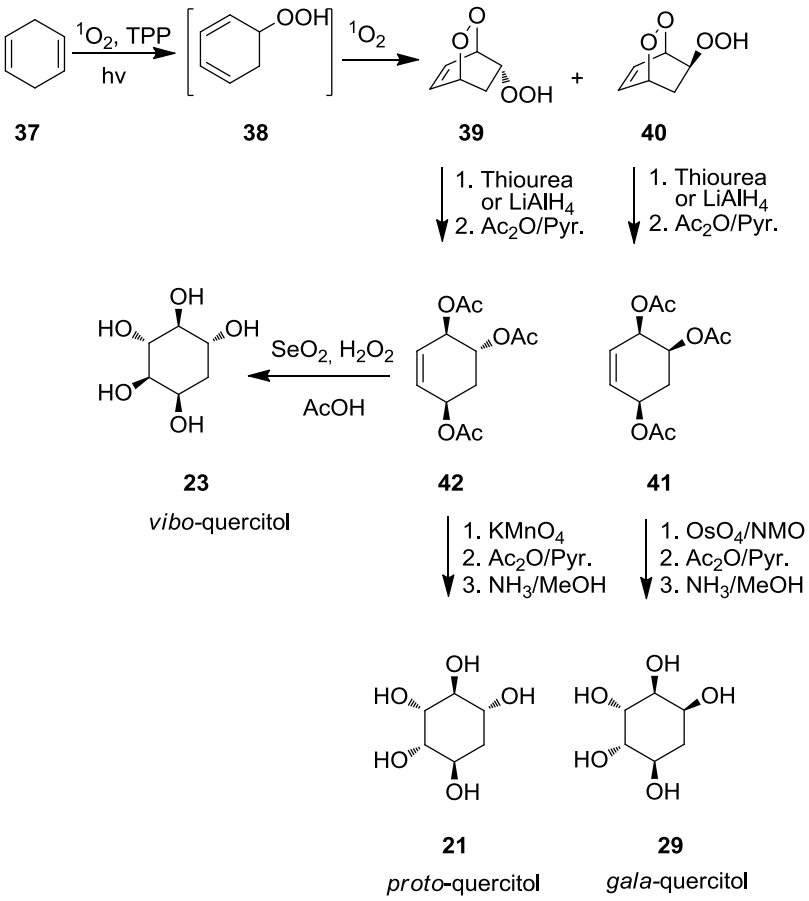
Scheme 3 Synthesis of *proto*-quercitol

McCasland and Horswill started with naturally occurring *myo*-inositol (**34**) to synthesize *vibo*-quercitol (**23**). In this pathway, firstly acetyl bromide was added and then the resulting molecule **35** was treated with HCl for hydrolysis. After hydrogenation of compound **36**, *vibo*-quercitol (**23**) was obtained (Scheme 4) [10].



Scheme 4 Synthesis of *vibo*-quercitol

Balcı *et al.* synthesized *vibo*-, *proto*- and *gala*-quercitols from 1,4- cyclohexadiene (**37**) in three steps. In addition to this, the synthesis of *vibo*- (**23**), *proto*- (**21**) and *gala*- (**29**) quercitols by using singlet oxygen ene reaction combined with the singlet oxygen [2+4] cycloaddition was the first reported by Balcı and his coworkers (Scheme 5) [11].



Scheme 5 Synthesis of *proto*- (**4**) and *gala*- (**12**) quercitols

1.4 Inositols

Inositols are cyclic compounds which have hydroxyl groups. They are cyclohexanols and resemble sugar as a basis of skeleton. The difference between inositol and sugar is that one oxygen in cyclohexane skeleton of sugar is replaced with a carbon atom. So, they are also called as carbasugars. In nature, there are nine stereoisomers (Figure 4) [12]. All of these isomers are known and three of them are commercially available. The most important and naturally occurring one is *myo*-inositol (**34**). This was the first cyclohexanehexol discovered by Schere in 1850 [13]. Schere isolated *myo*-inositol (**34**) from meat. Then, all cyclohexanehexols were started to be called as inositol. *Myo*-inositol (**34**) plays an important role in some cellular processes. *Scyllo*- (**49**), *chiro*- (**31** and **48**), *muco*- (**46**) and *neo*- (**47**) inositol are other naturally occurring stereoisomers of inositols. Besides, these isomers are considered to be formed from *myo*-inositol by inversion of configuration [12]. The others are *cis*- (**43**), *epi*-(**44**), *allo*- (**45**) are unnatural synthetic isomers [14].

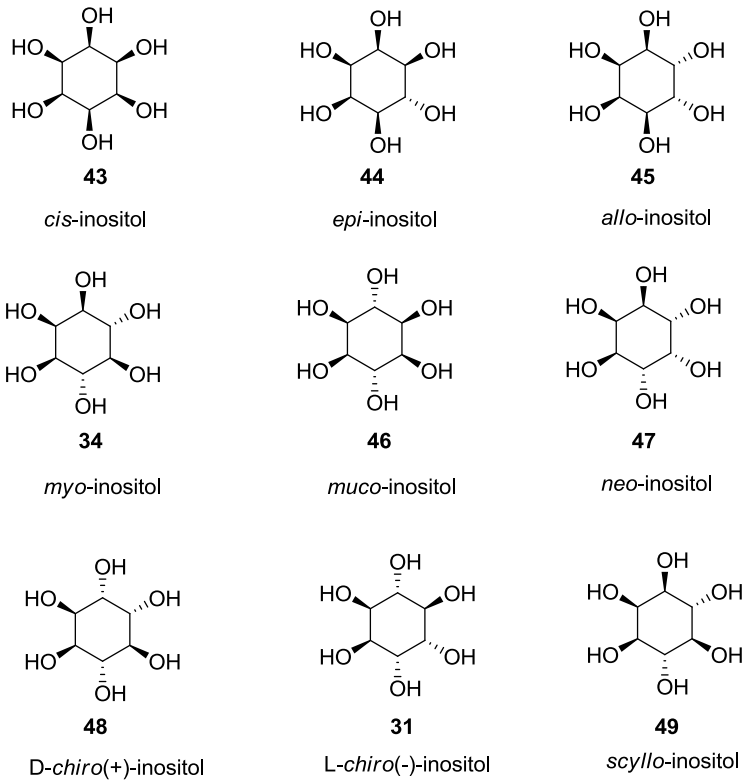
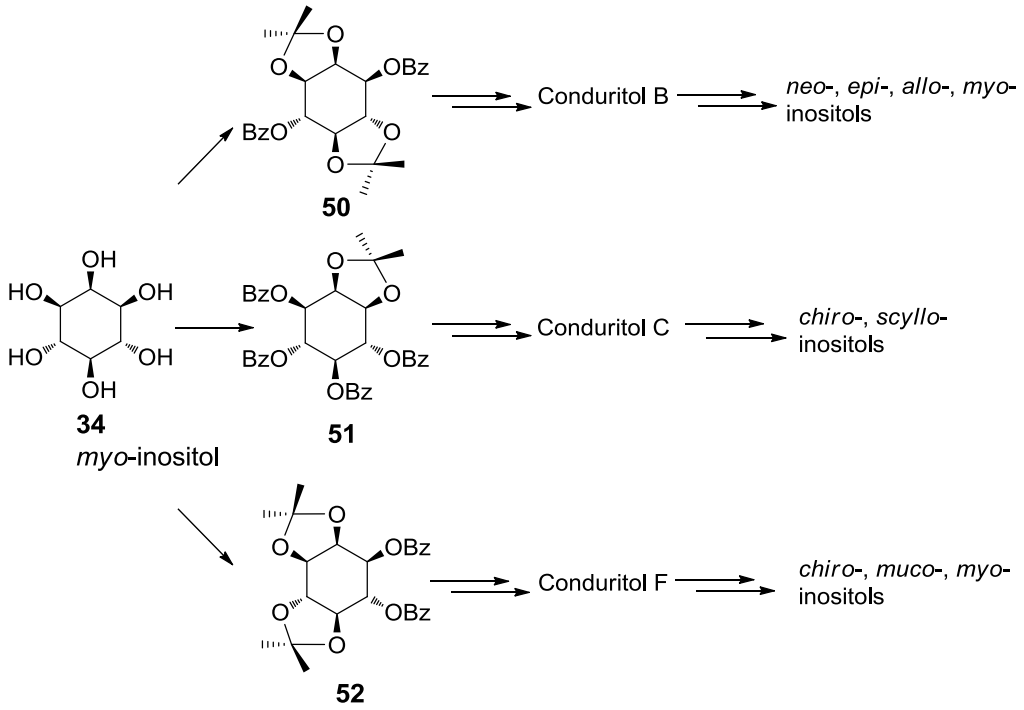


Figure 4 Inositol stereoisomers

In the literature, there are many ways for the synthesis of the inositols and their derivatives. They have been evaluated for their biological properties [13]. Chung *et al.* synthesized six inositol stereoisomers from conduritol intermediates (Scheme 6) [15].



Scheme 6 Synthesis of six inositol stereoisomers from conduritol intermediates

D-(+) - and L-(-)-*chiro*-inositol are the most abundant in nature. They exist in plants as the methyl esters of D-(+)-pinitol (**53**) and L-(-)-quebrachitol (**54**) (Figure 5) [16]. L-quebrachitol is an inositol which is used as an intermediate for the synthesis of polyhydroxylated natural products.

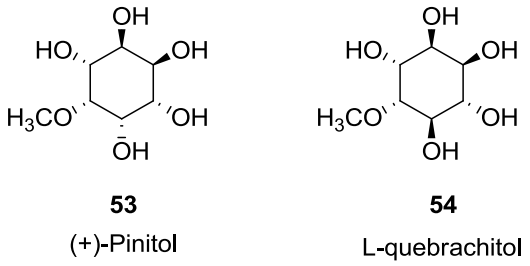


Figure 5 D-(+)-pinitol and L-(-)-quebrachitol

Scyllo-inositol exists in animals and plants and it was isolated. It was explored that some insects and mammalian urines has *scyllo*-inositol [17].

1.4.1 Bis-Homoinositol

Bis-homoinositols are hydroxymethylated inositols. There is a methylene group attached to hydroxyl group in the structure (Figure 6).

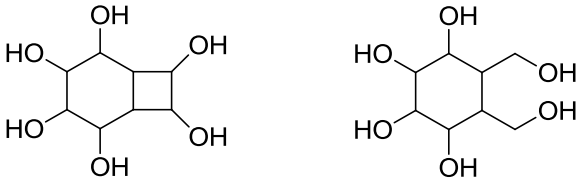
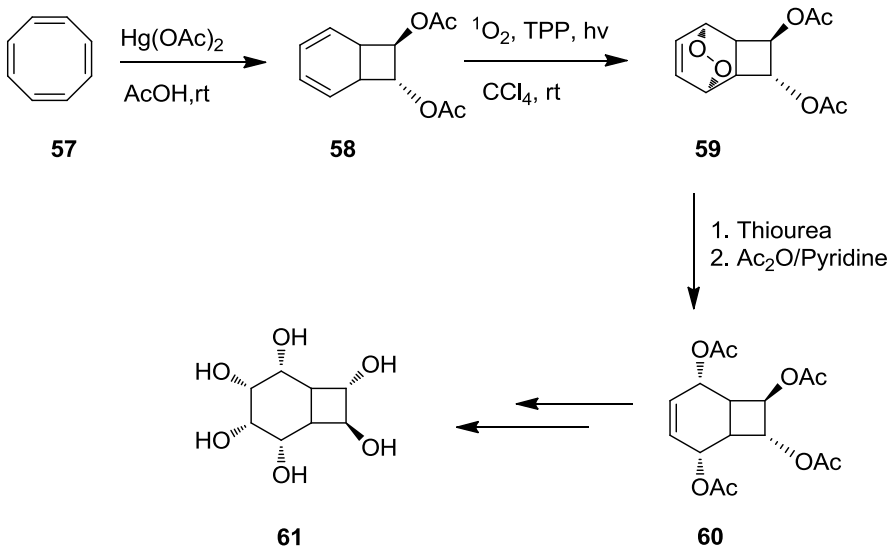


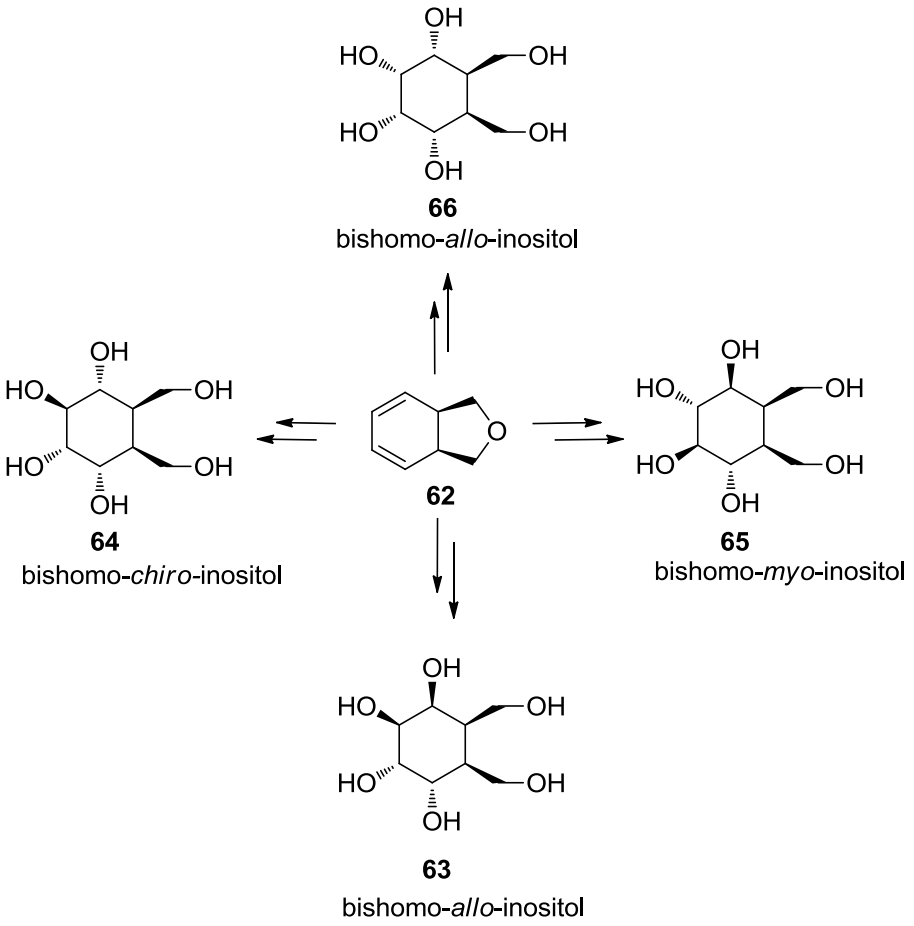
Figure 6 Bishomoinositols

In 2003, *Balcı and Kara* developed a new and short synthetic method for the synthesis of bis-homoinositol **61** starting from cyclooctatetrane (**57**) **(**Scheme 7) [13].



Scheme 7 Synthesis and characterization of a new inositol analogue, bishomoinositol from commercially available cyclooctatetrane

In 2008, Balcı and Baran established a new synthetic method for the synthesis of bis-homoinositol derivatives. 1,3,3a,7a-tetrahydro-2-benzofuran (**62**) was used as starting compound. In this methodology, photooxgenation, epoxidation and *cis*-hydroxylation was applied to compound **62** in order to synthesize various bis-homoinositol derivatives (**63-66**) (Scheme 8) [12].

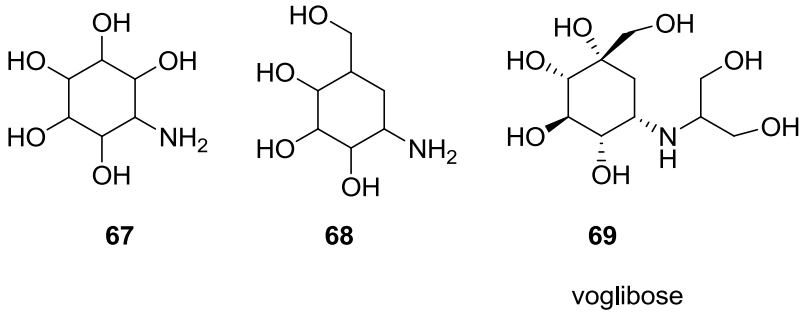


Scheme 8 Synthesis of bishomo-inositol derivatives (**63-66**)

1.5 Aminocyclitol

Aminocyclitols, N-linked inositols, are types of inositols in which one or more hydroxyl groups are substituted by amine functionality [18].

Amino substituted molecules have drawn attention for they are promising in drug discovery such as compound **67** and **68**, especially voglibose (**69**) (Figure 7) which employs as 2 type diabetes therapy [19].



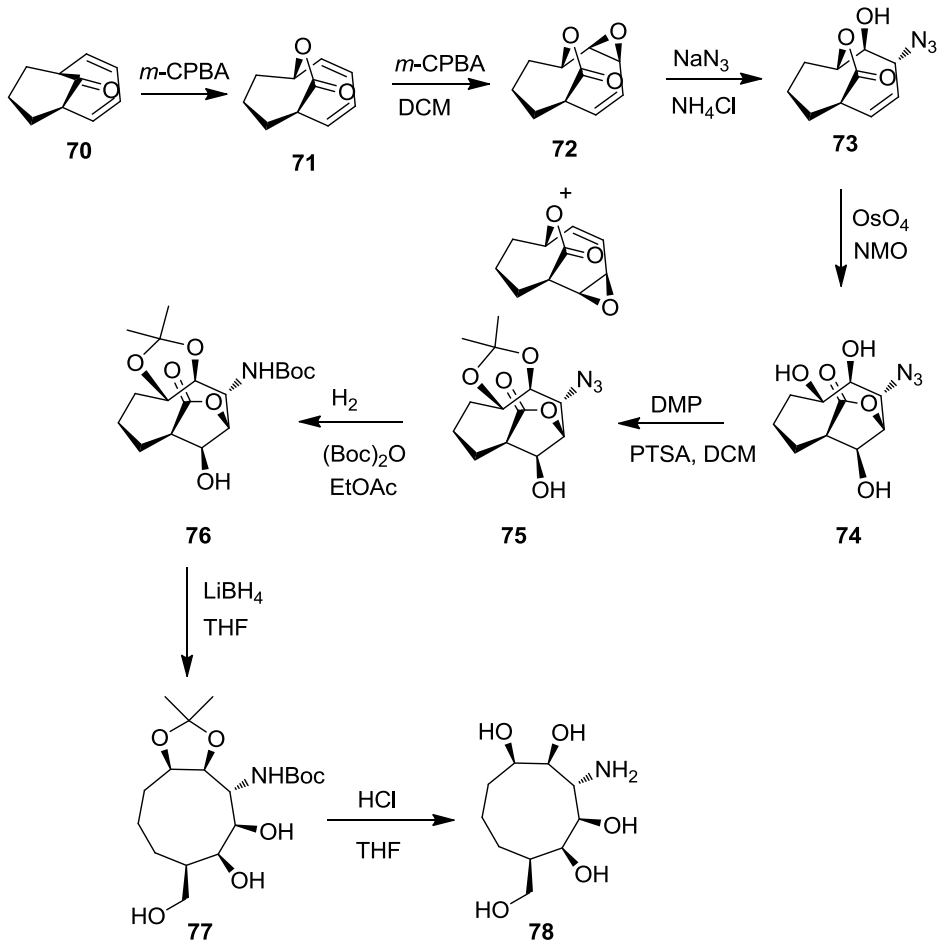
67 **68** **69**

voglibose

Figure 7 Aminocyclitol derivatives

Because aminocyclitols have important biological properties, synthesis of its mimics which have different ring sizes such as seven, eight and nine-membered ring system has attracted attention [18].

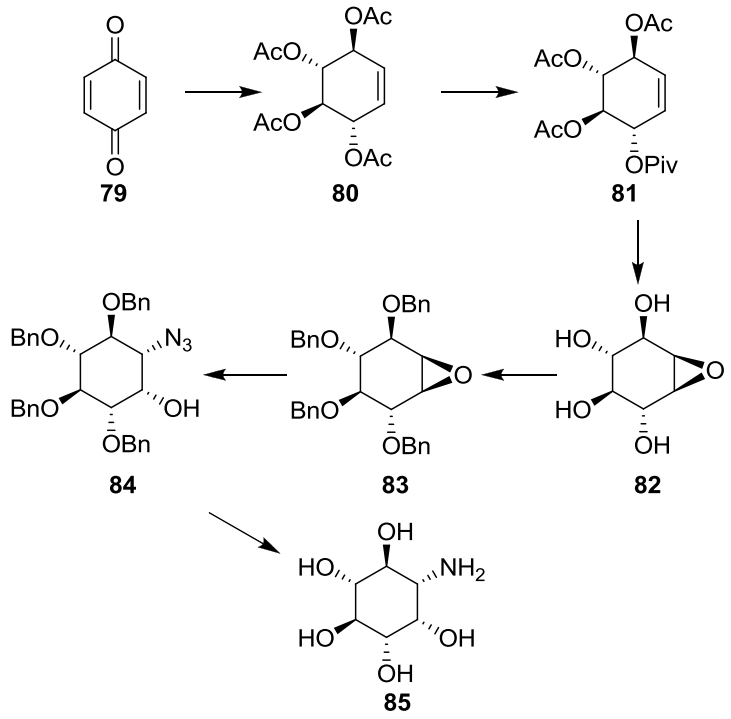
Recently, Mehta *et al*. reported the synthesis of nine-membered ring aminocyclitol (**78**) starting from commercially available bicyclo[4.3.1]deca-2,4-dien-10-one. The detailed reaction steps for this conversion are given in Scheme 9 [19].



Scheme 9 Formation of regioisomeric amino-cyclononanose

Research into aminoglycoside antibiotics has attracted attention. Recently, synthesis of compounds derived from inositols has been widely studied. A great number of inositols has become interesting compounds for this field of research.

In 2007, Amadeu L'ebaria *et al.* worked on synthesis of aminocyclitols as glycolipid mimetic which are used for glucocerebrosidase enzyme inhibitors. In the light of this, starting from *p*-benzoquinone, enantiomerically pure 1-amino-1-deoxy-*myo*-inositol (**85**) was synthesized (Scheme 10) [20].



Scheme 10 Synthetic analysis of 1-amino-1-deoxy-*myo*-inositol

Aminocyclitols play an important role in biological events. They constitute comprehensive group of natural products. Aminocyclitols are found extensively in nature in different areas. They are used for inhibition of some enzymes such as glycosidases. Recently, carbohydrate mimetics, like compound **86** and **87** have drawn attention (Figure 8). Lately, seven- and eight-membered ring systems and decane derivatives which contain polyhdroxy and amino groups have risen to notice in the domain of science [18].

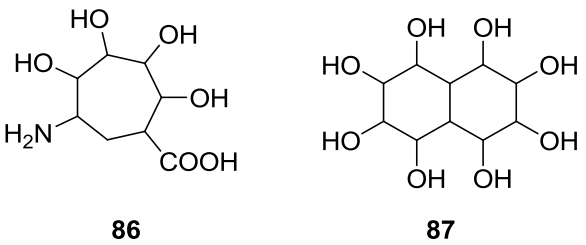
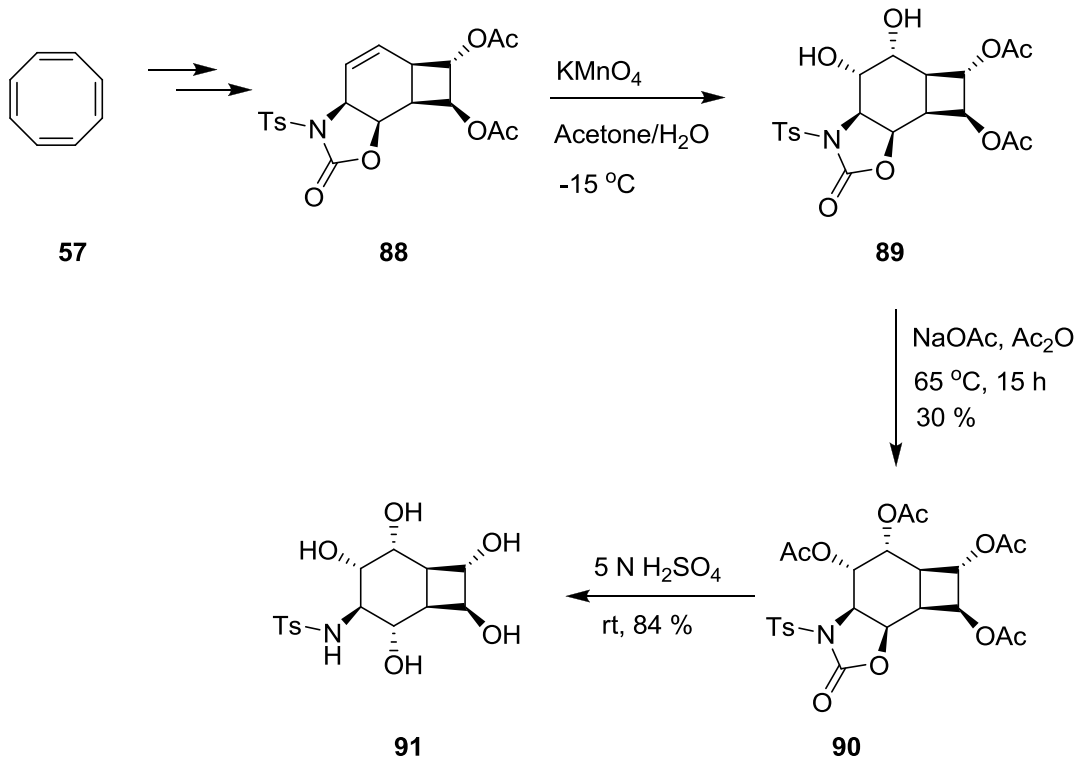


Figure 8 Carbohydrates mimetic

Significantly, attention has been directed towards to compounds containing amino-cyclic unit due to their biological activities.

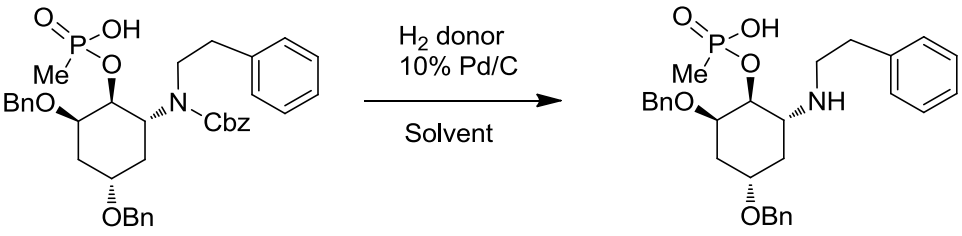
In 2006, Balcı *et al.* reported a synthetic pathway for the synthesis of new aminocyclitol derivative **91** starting from cyclooctatetrane (**57**) (Scheme 11) [18].



Scheme 11 Synthesis of new aminocyclitol derived from cyclooctatetrane

Aminocyclitols are very important compounds for being capable of using as amines/bases in some catalytic reactions.

Rudolf K. Alleman *et al.* worked on the effect of 6-aminocyclitols (**92**) on Pd/C catalyzed hydrogenolysis reaction (Scheme 12). Cyclitol amines are used as amines and bases. They are poisonous to Pd/C catalysts and reactivity of them can be changed against *O*-benzyl protecting group [21].



Scheme 12 Chemoselective deprotection of the Cbz group during hydrogenolysis of methylphosphonate

Aminocyclitol antibiotics are used in some pharmaceuticals which are capable of using for treatment of some diseases such as cancer. This encourages scienists to search into aminosugar chemistry. KA-3093 antibiotic, 5-*O*-methyl-*myo*-inosamine (**94**), has *myo*-inositol configuration and this unit is the first pointed cyclitol moiety regarding with hygronycin A which exists an inosamine unit (**95**) in the structure (Figure 9) [22].

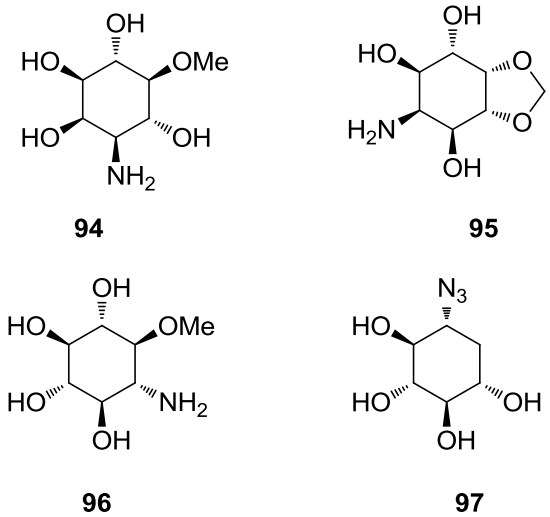
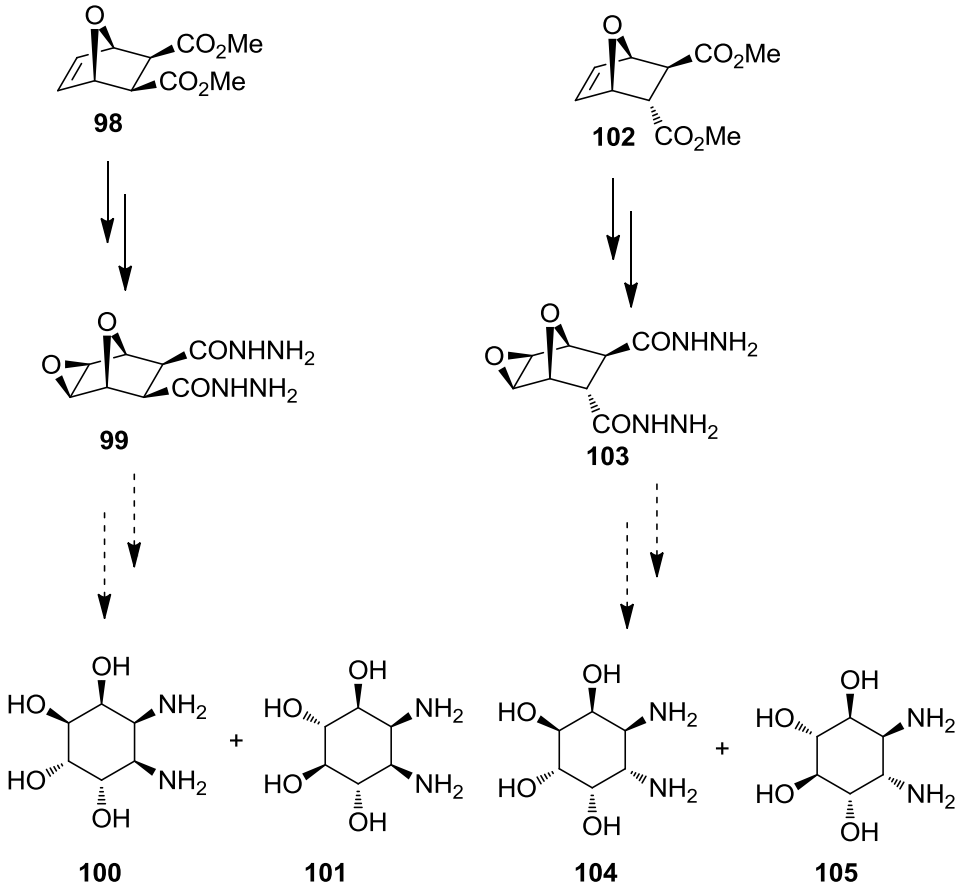


Figure 9 Aminocyclitol derivatives found in some antibiotics

1.6 Aim of the study

Cyclitols and especially aminocyclitols have recently attracted the scientists. It was proven that those compounds and their derivatives have shown a various biological activities in many biologically important processes. Therefore, our aim was to develop a new methodology for the synthesis of bis-aminoinositols. Starting with *cis*- and *trans*-diester of bicyclic systems **98** and **102**, our purpose was to convert diester groups to amino groups and cleave *O*-bridge to obtain cyclohexane skeleton. We planned to transform diester groups to $-NH_2$ through Curtius rearrangement and then cleave *O*-bridge whereby way of acidic epoxide ring-opening reaction to obtain bis-aminoinositols (Scheme 13).

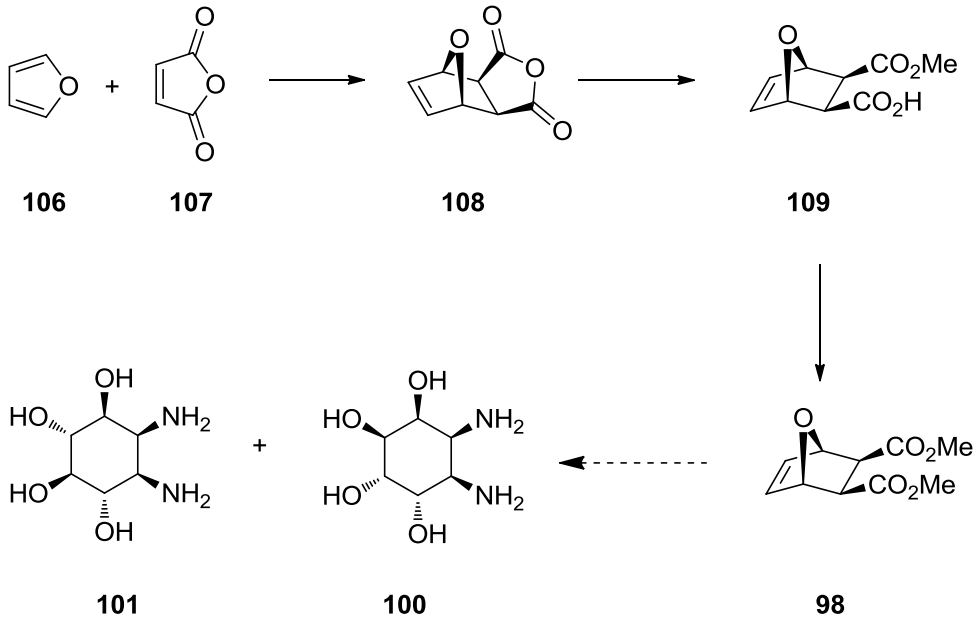


Scheme 13 Synthetic plan for the synthesis of bis-aminoinositols

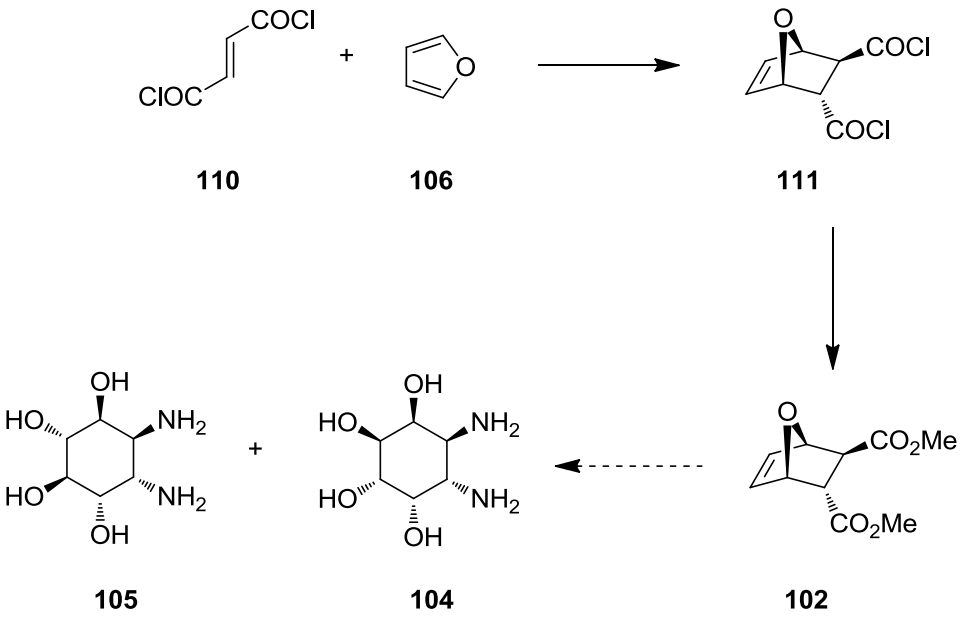
CHAPTER 2

RESULTS AND DISCUSSION

To synthesize aminocyclitol derivatives; furan, maleic anhydride and fumaryl chloride were used as starting materials. The reason why we used these compounds as starting materials is that they are commercially available and cheap. Our aim was to synthesize *cis*- and *trans*-diesters of bicyclic system **98** and **102** as key compounds through Diels-Alder reaction (Scheme 14, Scheme 15).



Scheme 14 Reaction pathway for formation of **98**



110 **106** **111** **105** **104** **102**

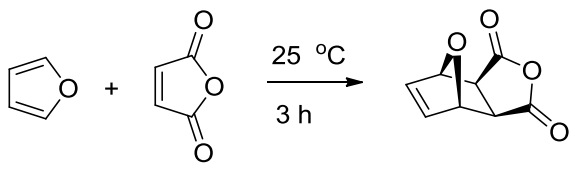
Scheme 15 Reaction pathway for formation of **102**

2.1 Synthesis of key compound 98

2.1.1 Synthesis of *exo*-adduct 108

First, we started with the synthesis of oxanorbornane skeleton **108**. In 2008, Chola *et al.* obtained this compound from the Diels-Alder reaction of furan and maleic anhydride. According to the literature, a mixture of furane and maleic anhydride was sitrred at room temperature for 16 h and *exo*-adduct was obtained in 98% yield [23].

To carry out this reaction, maleic anhydride was dissolved in furan and the resulting mixture was stirred for 3 h at room temperature. This reaction gave thermodynamically more stable *exo*-adduct **108** in a yield of 95% (Scheme 16).



106 **107** **108**

Scheme 16 Formation of *exo*-adduct **108**

Exclusive formation of *exo*-adduct **108** was observed at the end of the reaction. The stereochemistry of *exo*-adduct **108** was determined by ^{1}H NMR spectrum. The olefinic protons resonate at 6.58 ppm as triplet. Double bond and bridgehead protons resonate as quasi-triplet (AA´BB´). On the other hand, the protons adjacent to carbonyl groups resonate as singlet due to the dihedral angle between the relevant protons. We know from Karplus equation that when dihedral angle between two protons approaches to 90°, coupling constant decreases. We assume dihedral angle between those protons is close to 90°, which clearly indicates the formation of *exo*-product. According to the literature, for *endo*-adduct of reaction of furan and *N*-phenyl-maleimide, dihedral angle is approximately 30° and coupling constant between two protons is J = 5.2 Hz [24]. Actually, *endo*-isomer is initially formed in reaction media two times faster than *exo*-isomer but it goes back to its reactants because rate of reverse reaction is greater than that of forward reaction. Then, *exo*-adduct **108** is formed. At this time, reaction does not reverse due to thermodynamical stability of this product [25].

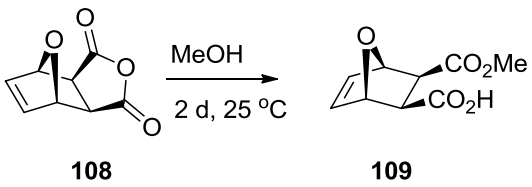
In ^{1}H NMR spectrum, olefinic protons resonate at 6.58 ppm as quasi-triplet. Bridgehead protons and other two protons on the ring resonate as triplet and singlet at 5.46 and 3.18 ppm.

In ^{13}C NMR spectrum, there are four signals at 169.9, 137.0, 82.3, 48.7 ppm.

IR spectrum also confirmed the formation of the product with carbonyl signal at 1789 cm^{-1}.

2.1.2 Synthesis of half ester of bicyclic system 109

According to the literature, when *exo*-adduct **108** was dissolved in MeOH at room temperature, half ester of this bicyclic system **109** was obtained in 87% yield [23].



108 **109**

Scheme 17 Synthesis of compound **109**

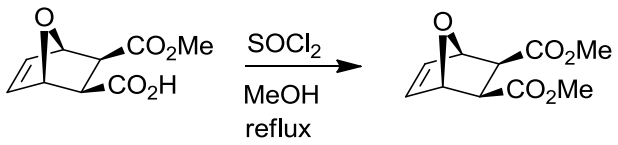
This reaction was carried out for 2 d and the desired compound **109** was obtained in 97% yield (Scheme 17).

The structure of the compound **109** was proven by ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum, olefinic protons resonate as an AB system between 6.43-6.39 ppm with coupling constants of J = 5.7 Hz (AB coupling) and J = 1.6 Hz (coupling with bridgehead protons). Bridgehead protons couple with only olefinic protons. They do not give any coupling with other protons which attached to carbons neighboring carboxylic acid and ester group on account of dihedral angle does not permit to eventuate any coupling. They resonate at 5.25 and 5.21 ppm. The other protons on the bicyclic ring resonate at 2.81 and 2.78 ppm as an AB system. The coupling constant between those protons is J = 9.0 Hz. In ^{13}C NMR spectrum, there are nine signals which are compatible with the structure. They appear at 177.0, 171.7, 136.8, 136.5, 80.6, 80.3, 52.3, 47.3, 46.8 ppm.

In IR spectrum, peaks at 3023, 1736 cm^{-1} indicate existence of carboxylic acid.

2.1.3 Synthesis of *cis*-diester 98

To synthesize *cis*-diester **98**, carboxylic acid functionality must be converted to ester group. For this reason, $SOCl_2$ was added to a solution of **109** in MeOH gently [26]. The mixture was stirred at reflux temperature for 3.5 h. Compound **98** was obtained at the end of the reaction in 70% yield (Scheme 18).



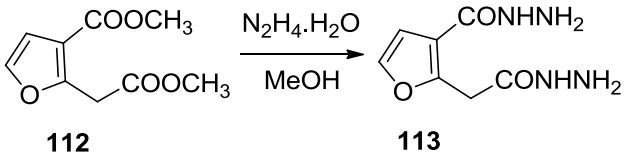
109 **98**

Scheme 18 Synthesis of key compound **98**

^{1}H and ^{13}C NMR are compatible with the structure. In ^{1}H NMR spectrum, double bond protons resonate as quasi-triplet with coupling constant of J = 0.9 Hz. Bridgehead protons give also quasi-triplet at 5.20 ppm and protons attached to

carbon adjacent ester group resonate as singlet at 2.76 ppm. In ^{13}C NMR spectrum, there are five signals resonating at 171.9, 136.6, 80.4, 52.3, 46.9 ppm.
In IR spectrum, disappearance of carboxylic acid peak proves the conversion to ester.

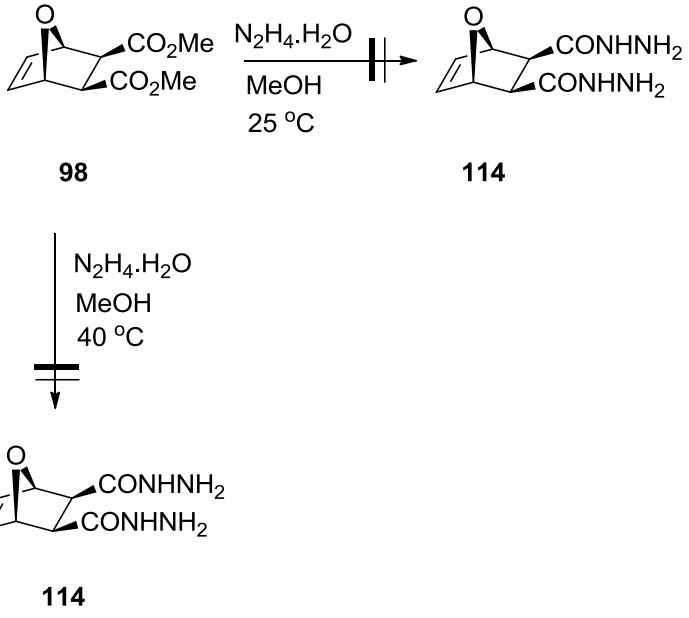
After synthesizing the key compound **98**, our plan was to convert ester functionalities into hydrazides. In 2009, Balcı *et al.* succeded this conversion by treatment of furan diester **112** with hydrazine monohydrate in MeOH (Scheme 19) [27].



112 **113**

Scheme 19 Reaction of furan diester **112** with hydrazine monohydrate

To apply this reaction to our system, hydrazine monohydrate was added to a solution of compound **98** in MeOH at room temperature. However, after completion of the reaction, NMR spectral studies did not reveal the formation of the expected product **114**, instead a retro Diels-Alder reaction occurred.



98 **114**

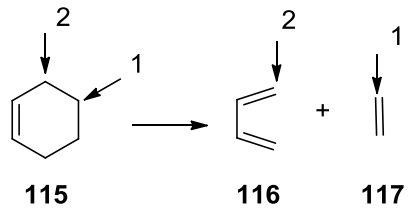
114

Scheme 20 Reaction of compound **98** with hydrazine monohydrat

2.1.3.1 Retro Diels-Alder reaction

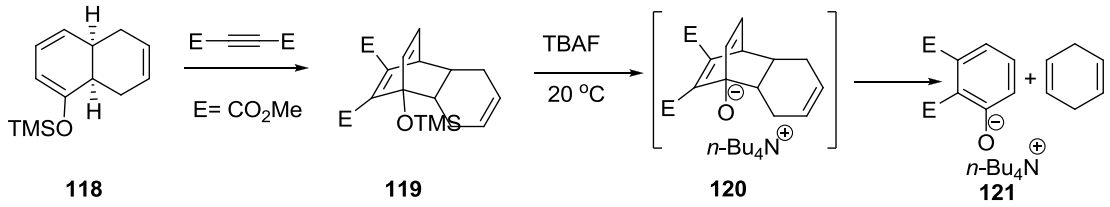
Diels-Alder reaction may be reversible reaction. If diene or dienophile or both are much more stable molecules than cycloaddition product, then reverse reaction can take place.

High temperature is necessary for retro Diels-Alder reaction to overcome activation barrier. However, in some cases, retro Diels-Alder reaction is observed even at very low temperatures. In following example, when an oxide anion is attached to position **1** or **2** in cyclohexadiene ring (**115**) (Scheme 21), the rate of retro Diels-Alder reaction increases.



Scheme 21 Retro Diels-Alder reaction of **115**

There is an example which expresses the role of oxide anion for retro Diels-Alder reaction at low temperature. Cyclo compound **118** gives Diels-Alder reaction with dimethyl but-2-ynedioate. Compound **119** has oxide anion at position **2**, it gives retro Diels-Alder reaction by treatment with TBAF at 20 °C (Scheme 22) [28].

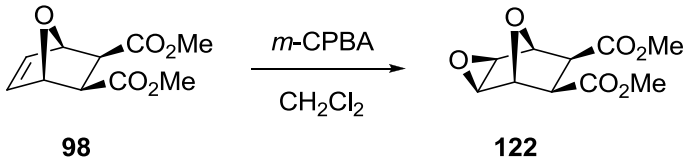


Scheme 22 Function of an oxide anion in retro Diels-Alder reaction

Therefore, we assume that the presence of oxygen-bridge plays in this case an important role and decreases the energy barrier for retro Diels-Alder reaction.

2.2 Synthesis of *cis*-epoxide 122

To prevent retro Diels-Alder reaction, double bond protection was required. To do this, double bond was thought to be epoxidized. In our system, to a stirred solution of *cis*-diester **98** in CH_2Cl_2, *m*-CPBA was added at 0 ^oC and the resulting mixture was stirred at room temperature for 24 h [29]. After completion of reaction, epoxidation of double bond was successfully achieved and compound **122** was obtained in a yield of 98% (Scheme 23).



98 **122**

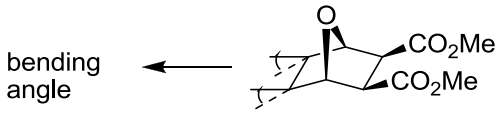
Scheme 23 Epoxidation of compound **98**

^1H and ^{13}C NMR supported the formation of epoxide. In ^1H NMR spectrum, singlets at 4.78 and 3.63 ppm were assigned to bridgehead and ester methyl protons. Epoxide protons resonate at 3.31 ppm as singlet and protons attached to carbon next to ester group also give singlet at 2.92 ppm. In ^{13}C NMR spectrum, dissappearance of olefinic carbon resonances proved the formation of product; there are five signals at 170.3, 76.4, 52.4, 49.2, and 49.1 showing the presence of symmetrical structure.
The NMR spectral studies confirmed that the epoxidation reaction was stereo-selective and only *exo*-epoxide-isomer **122** was formed.

The exclusive formation of the *exo*-isomer can be explained by the pyramidalization of the double bond as well as the directing effect of bridge oxygen atom.

2.2.1 Double bond pyramidilization

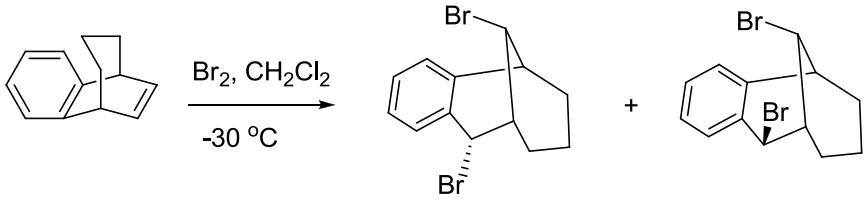
Double bond pyramidilization means that there is a deviation of angle between double bond and olefinic protons. Electrophile approaches from one face of bicyclic system. For our molecule **98**, *m*-CPBA would attack from *exo* face of the double bond (Figure 10).



98

Figure 10 Double bond pyramidilization of **98**

Balcı *et al.* reported that the bromination of 6,7,8,9-tetrahydro-5H-5,9-ethenobenzo[a][7]annulene (**123**) occurs exclusively from *endo* face of double bond due to double bond pyramidilization (Scheme 24) [30].

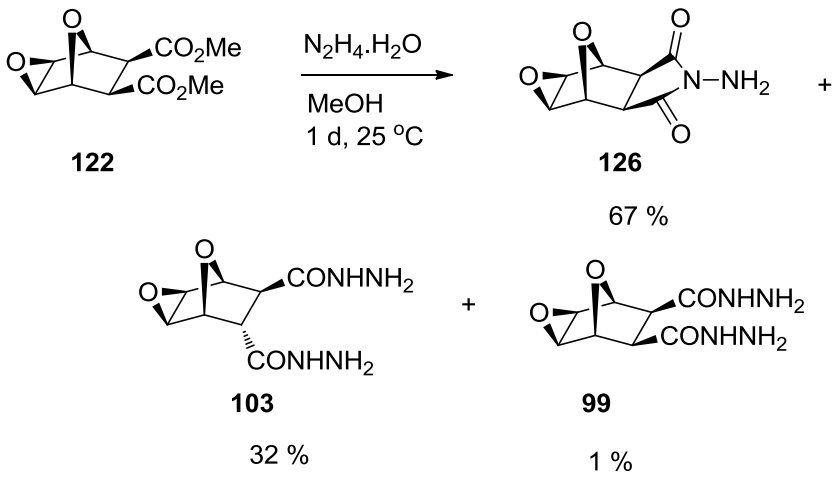


123 **124** **125**

Scheme 24 Bromination of 6,7,8,9-tetrahydro-5H-5,9- et henobenzo[a][7]annulenereaction

2.3 Reaction of epoxide 122 with hydrazine monohydrate

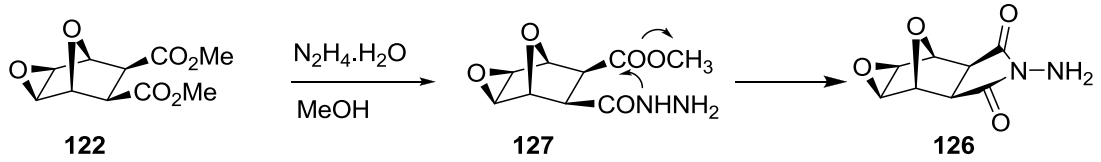
After protection of the double bond in **98**, the formed bicyclic epoxide **122** was treated with hydrazine monohydrate at room temperature in presence of MeOH (Scheme 25). NMR spectral studies of the reaction mixture indicated the presence of three products.



Scheme 25 Reaction of compound **122** with hydrazine monohydrate for 1 d

The major product **126** was isolated by dissolving of the resulting mixture in chloroform at 60 °C. Amino-imide **126** was soluble in chloroform.

For the formation of **126**, we propose the following mechanism. We assume one of the ester groups in **122** reacts first with one mole of hydrazine to give monohydrazide **127**, which undergoes cyclization reaction to give **126** (Scheme 26).



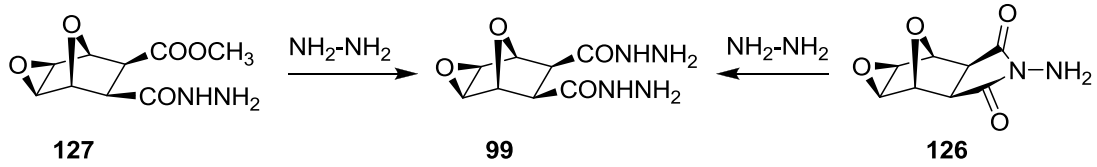
Scheme 26 Proposed mechanism of formation of **126** from **122**

The structure **126** is consistent with ^{1}H and ^{13}C NMR spectral data. In ^{1}H NMR spectrum, epoxide protons resonate at 3.12 ppm as singlet. Bridgehead protons and other two protons on the ring also resonate as singlets at 4.63 and 3.68 ppm. $-NH_2$ protons appear also as singlet at 5.05 ppm. In ^{13}C NMR spectrum, there are four

carbon resonances. Carbonyl carbon resonates at 173.7 ppm and other saturated carbon atoms on the ring give signals at 75.7, 49.1, 45.8 ppm.

With the formation of cyclization product **126**, the expected *cis*-dihydrazide **99** was also observed in the reaction media. *Cis*-dihydrazide **99** may be formed by two different routes. By the first route, one of the carbonyl group in **126** can be attacked by hydrazine (Scheme 27). The ring-opening reaction of amino-imide can form *cis*-dihydrazide **99** as shown in Scheme 27. Due to solubility problem, all attempted purification methods failed, therefore, we could not isolate *cis*-dihydrazide.

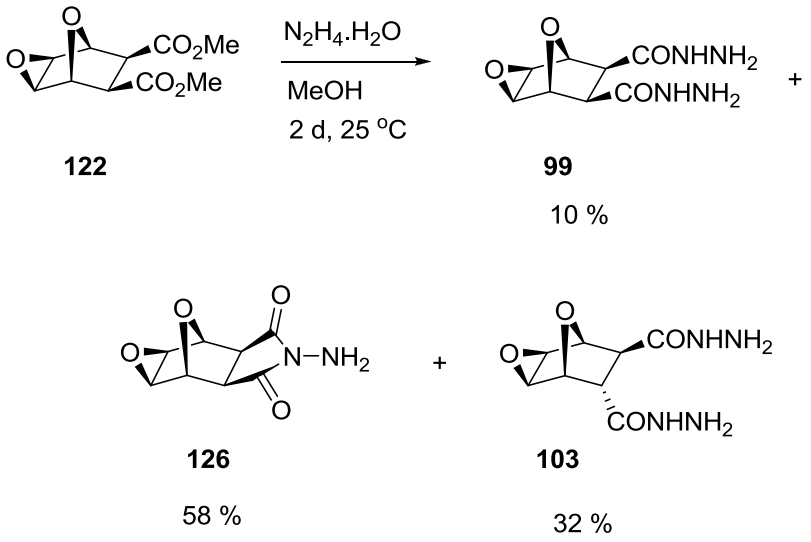
By the second route, the initially formed **127** can undergo further substitution reaction with an additional mole hydrazine to give **99** (Scheme 27).



127 **99** **126**

Scheme 27 Formation of *cis*-dihydrazide **99**

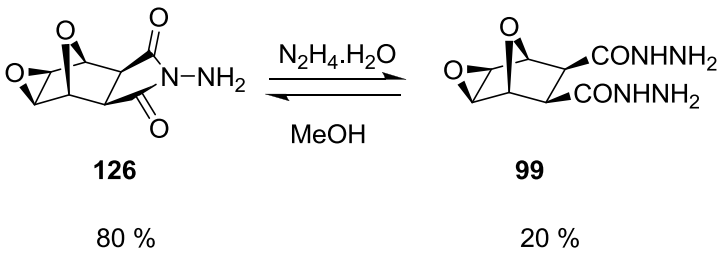
In order to distinguish these two different ways, the time of the reaction was increased from 1 d to 2 d. The spectral analysis of the reaction mixture after 2 d showed that there was an increase in the proportion of *cis*-dihydrazide **99** (Scheme 28). Then, it was considered that there was a conversion of cyclization product **126** to bicyclic *cis*-dihydrazide **99**.



Scheme 28 Reaction of compound **122** with hydrazine monohydrate for 2 d

In ^{1}H NMR spectrum of **99**, -NH and –NH_2 protons resonate at 8.40 and 4.10 ppm as singlet. Bridgehead and epoxide protons give also singlets at 4.52 and 3.40 ppm and other protons attached to carbon neighbouring hydrazide functionality resonate at 2.80 ppm as singlet.

To prove the formation of *cis*-dihydrazide, an additional reaction was performed. To a solution of cyclization product **126** in MeOH, $N_2H_4.H_2O$ was added to see whether there was a conversion or not. One day after, 20% conversion to bicyclic *cis*-dihydrazide **99** was observed (Scheme 29).

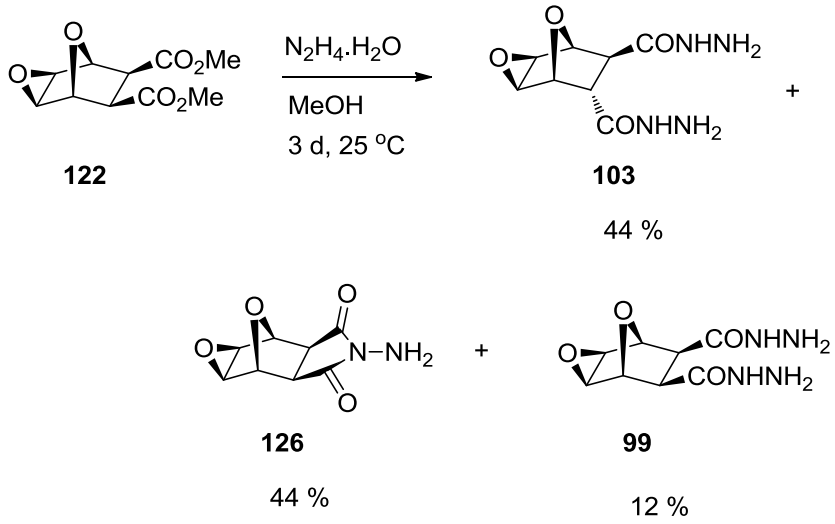


Scheme 29 Equilibrium between **126** and **99**

Prolonged reaction time did not change the ratio. Therefore, we assume that equilibrium between **126** and **99** was established at the reaction temperature. *trans*-dihydrazide **103** was also formed as the third product.

The ratio of this product was not affected by prolonged reaction time as much as the ratio of **99**. There was an inversion of configuration. How this epimeric form could be formed is that there was an enolate formation after *cis*-dihydrazide (**99**) was formed.

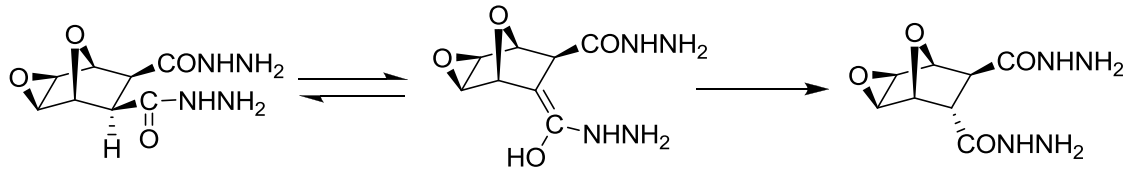
We carried out an additional reaction lasting for three days and observed that the ratio of **103** was increased from 32% up to 44% at the expence of *cis*-hydrazide **99** (Scheme 30).



Scheme 30 Reaction of compound **122** with hydrazine monohydrate for 3 d

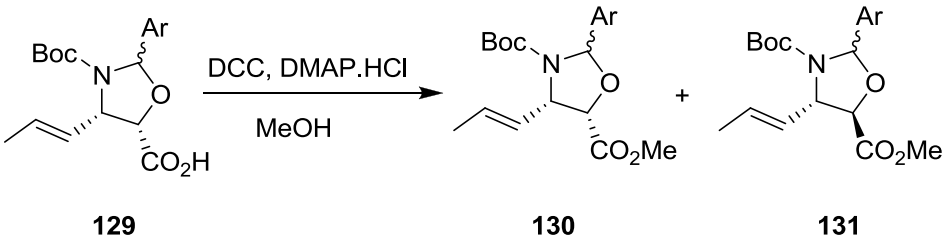
Furthermore, we treated *trans*-dihydrazide in MeOH with hydrazine monohydrate under the same reaction conditions to see whether **103** would undergo a configurational isomerization or not. We noticed that the *trans*-dihydrazide **103** was stable.

Enol form of compound **99** was formed and then converted into *trans*-product through C-α epimerization. Because *trans*-product is thermodynamically more stable form, reaction did not reverse (Scheme 31).



Scheme 31 Formation of **103** from *cis*-dihydrazide **99**

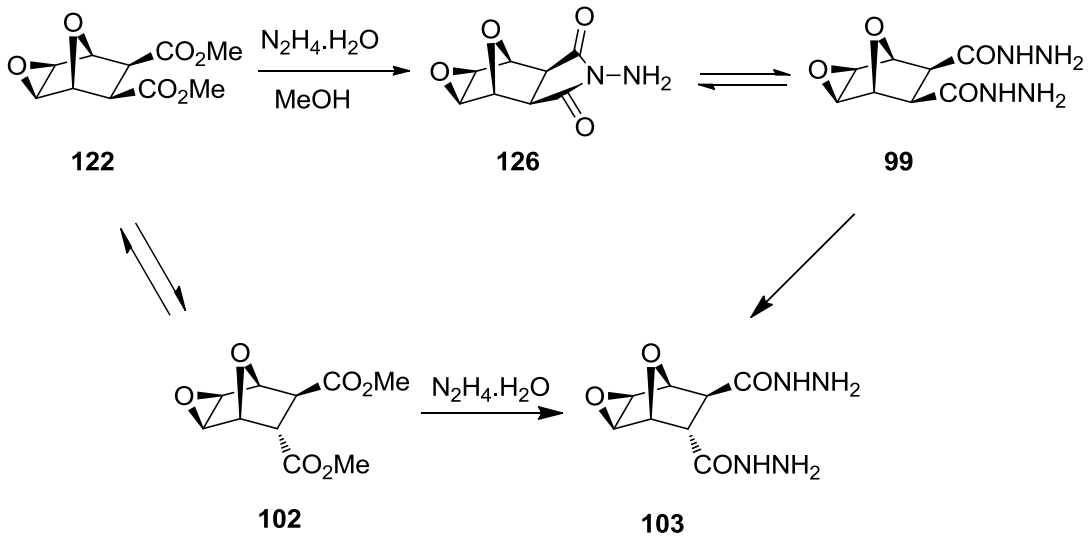
It is established that during esterification of compound **129**, there occurs a C-α epimerization when treatment of compound **129** with DCC/DMAP.HCl (Scheme 32) [31].



Scheme 32 C-α epimerization

The isomerized product **103** is formed by isomerization of the *cis*-dihydrazide **99**. However, the starting material, diester **122** can also undergo partly configurational isomerization followed by substitution of the ester groups with hydrazine monohydrate.

As a conclusion, following scheme can be shown for the summary of this reaction pathway (Scheme 33).



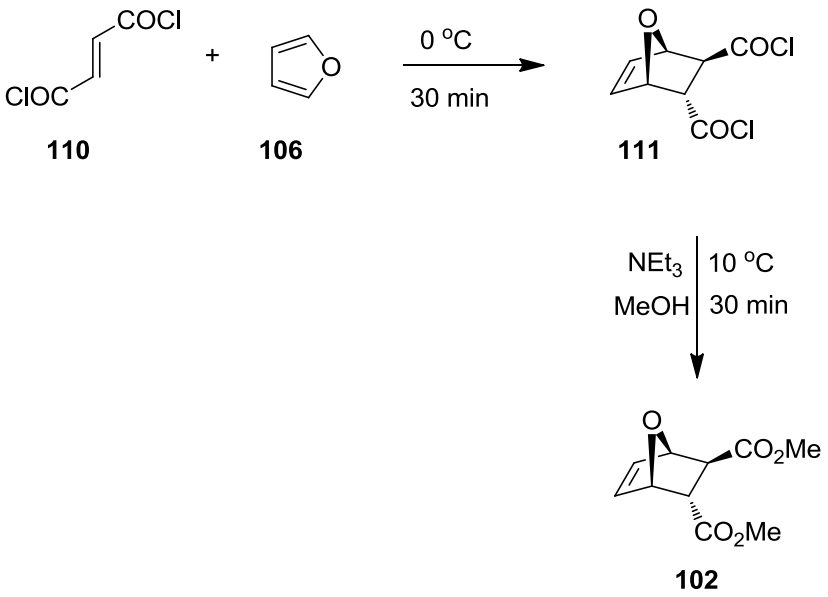
Scheme 33 Summary of reaction of **122** with hydrazine monohydrate

We assume that these two ways are responsible for configurational isomerization. After getting all these results, all attention was directed towards to use of *trans*-diester **122** of the bicyclic system **102** as a key compound.

2.4 Synthesis of key compound 102

To synthesize key compound **102**, fumaryl chloride (**110**) was added to furan at 0 ^{o}C. Then, at 10 ^{o}C, triethylamine was added in presence of MeOH to obtain *trans*-diester of the bicyclic system **102**. At the end of the reaction, compound **102** was synthesized in a yield of 72% (Scheme 34).

^{1}H and ^{13}C NMR spectra supported the formation of compound **102**. In ^{1}H NMR spectrum, olefinic protons resonate at 6.29 and 6.45 as doublet of doublets. Large coupling between these two olefinic protons is 5.7 Hz and small coupling caused by bridgehead protons is 1.7 Hz. The bridgehead protons give doublet at 5.18 ppm. The proton with *cis*-configuration to *O*-bridge resonates as triplet at 3.55 ppm with a coupling constant of J = 4.3 Hz. The other proton attached to carbon neighboring ester group resonates at 2.78 ppm as doublet with coupling constant of J = 4.3 Hz. Finally, methoxy methyl protons resonate at 3.60 and 3.69 ppm as singlets.



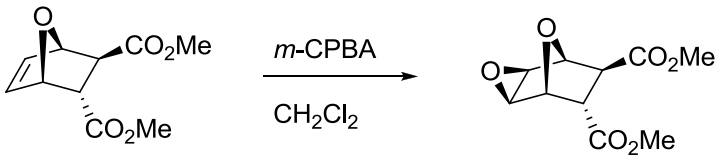
Scheme 34 Synthesis of compound **102**

To avoid retro Diels-Alder reaction, oxidation of double bond was the further step before the dihydrazide formation reaction.

2.5 Synthesis of *trans*-epoxide 132

Our reaction pathway was followed by epoxidation of double bond for preventing retro Diels-Alder reaction. The bicyclic alkene **102** was dissolved in CH_2Cl_2 and cooled to 0 °C. To this solution, *m*-CPBA was added gently. The resulting solution was stirred at room temperature for 2 days. The compound **132** was obtained in 72% yield as a white solid (Scheme 35).

In ^{1}H NMR spectrum, disappearance of double bond proton resonances proved formation of epoxide **132**. One of the bridgehead protons resonates at 4.68 ppm and gives doublet with the coupling constant of J = 5.3 Hz.



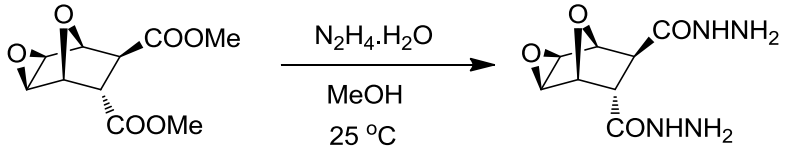
102 **132**

Scheme 35 Epoxidation of compound **102**

The other bridgehead proton gives a singlet at 4.75 ppm. Epoxide ring protons resonate at 3.39 and 3.33 ppm as individually doublet and form AB system with chemical shift difference of 21.7 Hz and coupling constant is J = 3.3 Hz . On the other hand, one proton which is neighboring with ester group with *cis*-configuration to *O*-bridge resonates at 3.58 ppm and gives triplet with coupling constant of J = 5.0 Hz. -OCH_3 protons give characteristic singlets at 3.68 and 3.69 ppm respectively.
In ^{13}C NMR spectrum, there are 10 signals. Carbonyl carbons resonate at 171.3 and 170.0 ppm, bridgehead carbons appear at 77.9 and 74.9 ppm and the other carbons resonate at 52.7, 52.5, 50.5, 49.1, 48.3, 48.1 ppm.

2.6 Synthesis of *trans*-dihydrazide 103

To a solution of compound **132** in MeOH, $N_2H_4.H_2O$ was added at room temperature and stirred for 24 h. After completion of reaction, as expected, only one product **103** was observed in 91% yield (Scheme 36).



132 **103**

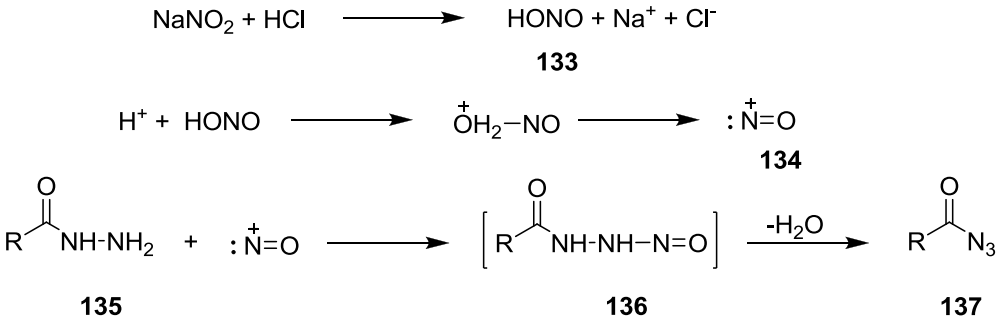
Scheme 36 Reaction of **132** with hydrazine monohydrate

^1H and ^{13}C NMR are consistent with the structure. In ^1H NMR spectrum, there are two signals at 9.08 and 9.19 ppm arising from –NH protons. $-NH_2$ protons are split into doublet separately at 4.18 and 4.20 ppm with coupling constant of J = 3.9 Hz.

One of the epoxide protons gives doublet at 3.42 ppm with a coupling of J = 3.5 Hz whereas the other epoxide proton resonance is overlapped by $-OCH_3$ signal. One of bridgehead protons is not coupled with neighboring protons due to the dihedral angle of approximately 90°. Other bridgehead proton gives doublet with a coupling constant of J = 5.1 Hz. One of the protons which is near hydrazide group and has *trans*-configuration with *O*-bridge resonates at 2.90 ppm and split into doublet, whereas the other proton resonance is again overlapped by methyl proton resonance. In ^{13}C NMR spectrum, there are eight resonances. There are two characteristic carbonyl carbon peaks at 170.4 and 167.8 ppm. Bridgehead carbons resonate at 78.5 and 74.7 ppm. Epoxide carbons and other two carbons on bicyclic ring give signals at 49.2, 48.9, 48.2, 45.7 ppm.

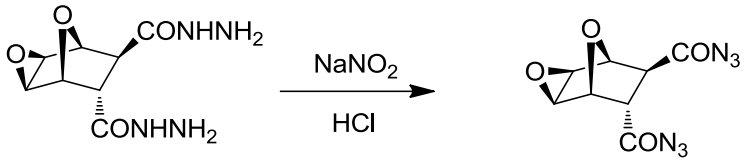
2.7 Synthesis of acyl azide 138

To convert compound **135** to corresponding acyl azide **137** through β-nitroso hydrazide intermediate **136**, modified Sandmeyer reaction was used in 1986 by Kim *et al* [32]. During the reaction, firstly, $NaNO_2$ was protonated. After departure of water molecule, nitrosonium ion **134** was formed. Then, nonbonding electrons on nitrogen of $-NH_2$ part of hydrazide attack to positively charged nitrosonium ion to form β-nitroso hydrazide intermediate **136**. After removal of water molecule, corresponding acyl azide **137** is formed as depicted in Scheme 37.



Scheme 37 Modified Sandmeyer reaction: Acyl azide through β-nitroso Hydrazide intermediate

According to our synthetic plan, hydrazide **103** should be converted into acyl azide **138** to follow the reaction pathway. For this reason, to a solution of compound **103** in 1 N HCl, $NaNO_2$ was added gently at 0 ^oC and reaction mixture was stirred for 0.5 h (Scheme 38).



103 **138**

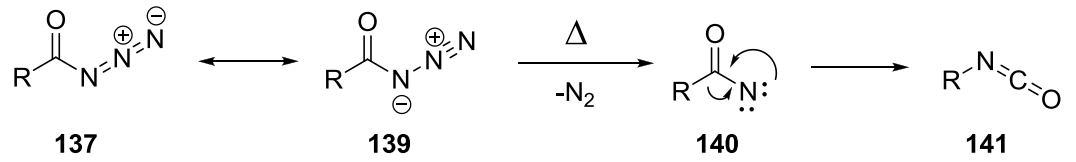
Scheme 38 Acyl azide formation from compound **103**

The resulting product **138** was confirmed by IR spectrum. IR spectrum gave a sharp characteristics signal at 2165 cm^{-1} which indicates azide moiety.

In addition to this, ^1H and ^{13}C NMR spectra supported the formation of corresponding acyl azide. In ^1H NMR spectrum, epoxide protons resonate at 3.42 ppm as an AB system. Because two doublet peaks are close to each other, it is seen as quartet and coupling constant is 3.2 Hz. Chemical shift difference is 6.1 Hz and $\Delta\delta/J$ is equal to 1.8. Due to this reason, roof effect is dominant and it is split into doublets of doublet via AB system. One of the bridgehead protons resonates at 4.69 ppm and is split into doublet due to the coupling with proton attached to adjacent carbon of azide functionality with a coupling constant of J = 5.2 Hz. Other bridgehead proton gives singlet at 4.75 ppm. In ^{13}C NMR spectrum, there are eight resonances at 177.5, 176.4, 78.1, 75.2, 52.6, 50.0, 48.9, 48.2 ppm.

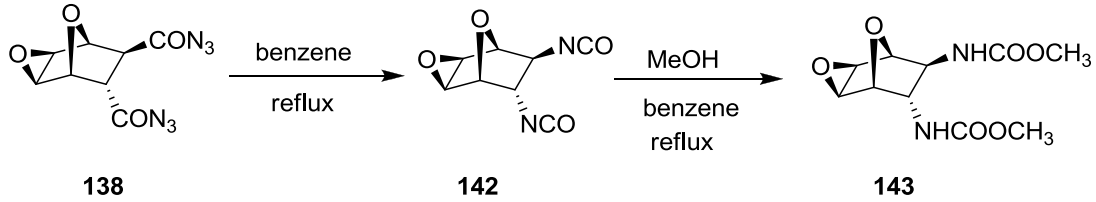
2.8 Synthesis of *trans*-urethane 131 through Curtius Rearrangement

Generally, acyl azides **137** can be converted into corresponding isocyanate **139** through Curtius rearrangement. This reaction was discovered by Theodor Curtius in 1894 (Scheme 39) [33].



Scheme 39 Curtius Rerrangement

During this reaction, after departure of N_2 gas, nitrene **140** is formed as intermediate. Nitrene has six valence electrons. It has empty π orbital. To fill out it, while electrons on nitrogen atom makes double bond, -R group migrates. This is called Curtius rearrangement.



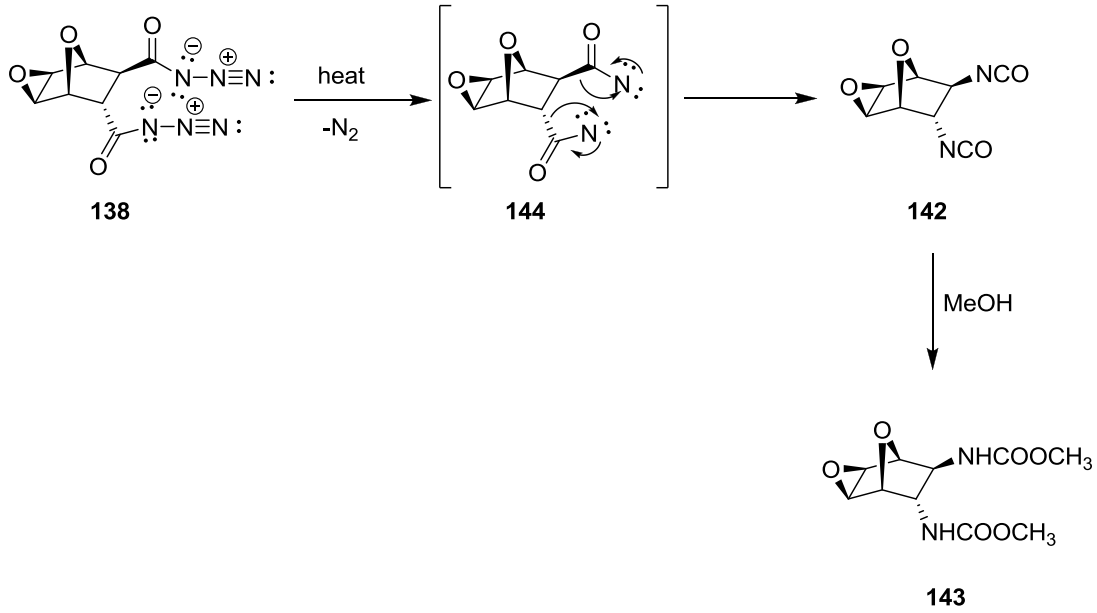
Scheme 40 Formation of urethane **143**

In our system, bicyclic acyl azide **138** was heated in dry benzene at reflux temperature for 1 hour. Before adding MeOH to form corresponding urethane **143**, it was cooled to 40 ^{o}C and treated with MeOH. After completion of reaction, final product **143** was obtained in 98% yield (Scheme 40).

^{1}H and ^{13}C NMR spectra are compatible with the structure. In ^{1}H NMR spectrum, broad –NH protons and methoxy protons confirmed the formation of bis-urethane **143**. –NH protons resonate at 5.25 and 5.15 ppm as broad singlets. Epoxide protons again give doublets individiually at 3.51 and 3.38 ppm with coupling constant of 3.2 Hz. One of the bridgehead protons gives sharp and highly intense singlet at 4.25 ppm. On the other hand, other bridgehead proton gives broad singlet at 4.73 ppm. Actually, it must appear as doublet because; it should have coupled with the proton which is adjacent urethane functionality. However, this bridgehead proton has *cis*-configuration with urethane group, and nitrogen decreases the relaxation time of

bridgehead proton and causes broad singlet. Therefore, any coupling could not be seen. Protons which are attached to carbon next to urethane group resonate at 3.69 and 3.54 ppm. -OCH_3 protons give individually singlets at 3.62 and 3.63 ppm.

Mechanism of this reaction is shown following in Scheme 41.

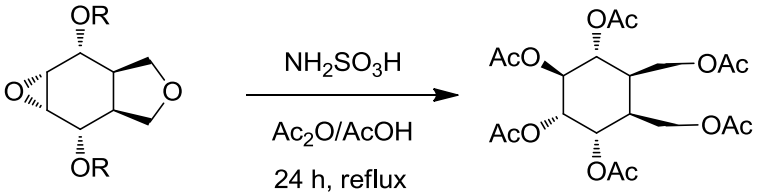


138 **144** **142** **143**

Scheme 41 Mechanism of formation of bicyclic urethane

2.9 Ring-opening reaction of 143

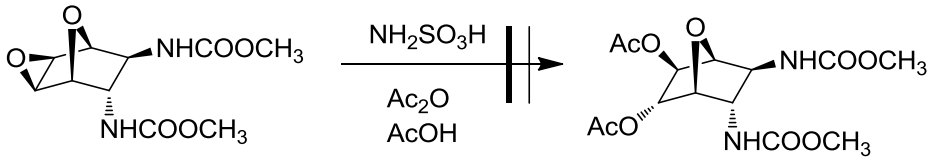
To generate cyclohexane skeleton, further step was the epoxide ring-opening reaction as well as the cleavage *O*-bridge. Recently, Balcı *et al.* succesfully achieved to open epoxide ring and tetrahydrofuran ring of compound **145** through acid-catalyzed ring-opening reaction and synthesized compound **146** with 89% yield (Scheme 42) [12].



145 **146**

Scheme 42 Acid-catalyzed epoxide and tetrahydrofurane ring-opening reaction of **145**

This ring-opening procedure was applied to our system. To a solution of compound **143** in Ac_2O/AcOH, catalytic amount of sulfamic acid was added and reaction mixture was stirred for 24 hour at reflux temperature. Our expectation was that epoxide ring would be opened through stereoselective S_N2 reaction. Since the structure **147** looks like a tetrahydofuran ring, we would also expect cleavage of *O*-bridge. But at the end of the reaction, ^1H and ^{13}C NMR measurements indicated that the compound **147** was not formed (Scheme 43).



143 **147**

Scheme 43 Expected product from acid-catalyzed reaction of **143**

Exact structure could not be determined by ^1H and ^{13}C NMR as well as 2D-NMR (DEPT-90, DEPT-135, COSY, HMQC and HMBC) experiments. Single crystal X-ray analysis proved the formation of tricyclic compound **148** (Figure 11).

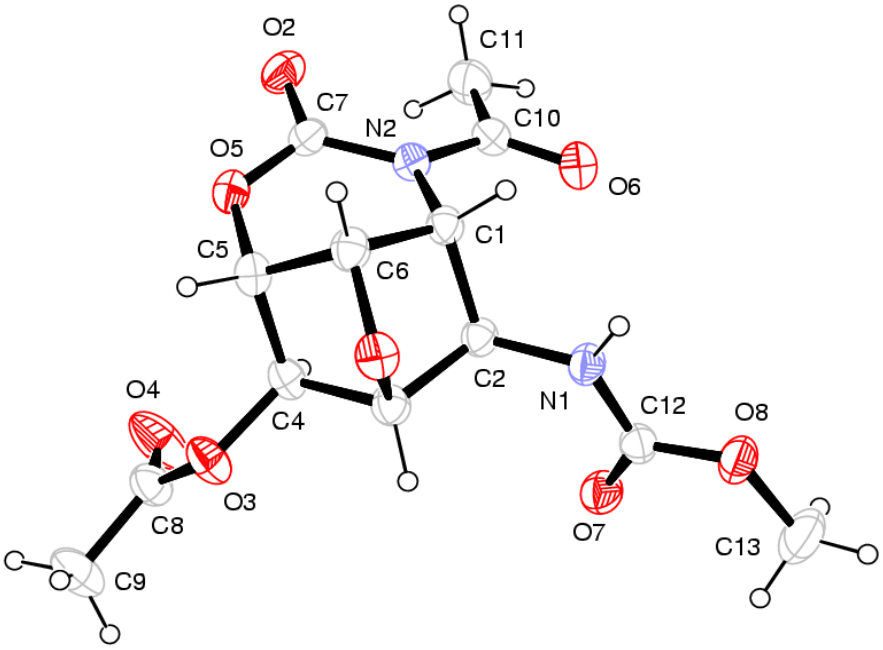
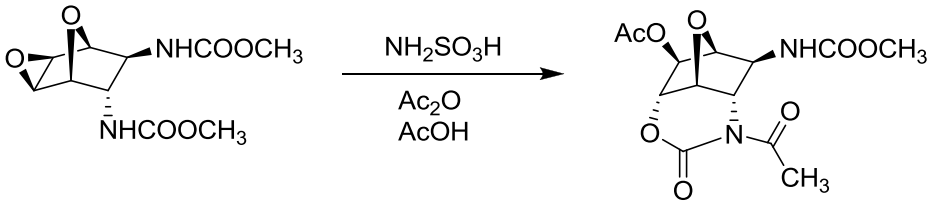


Figure 11 The molecular structure of compound **148** determined by single crystal X-ray analysis



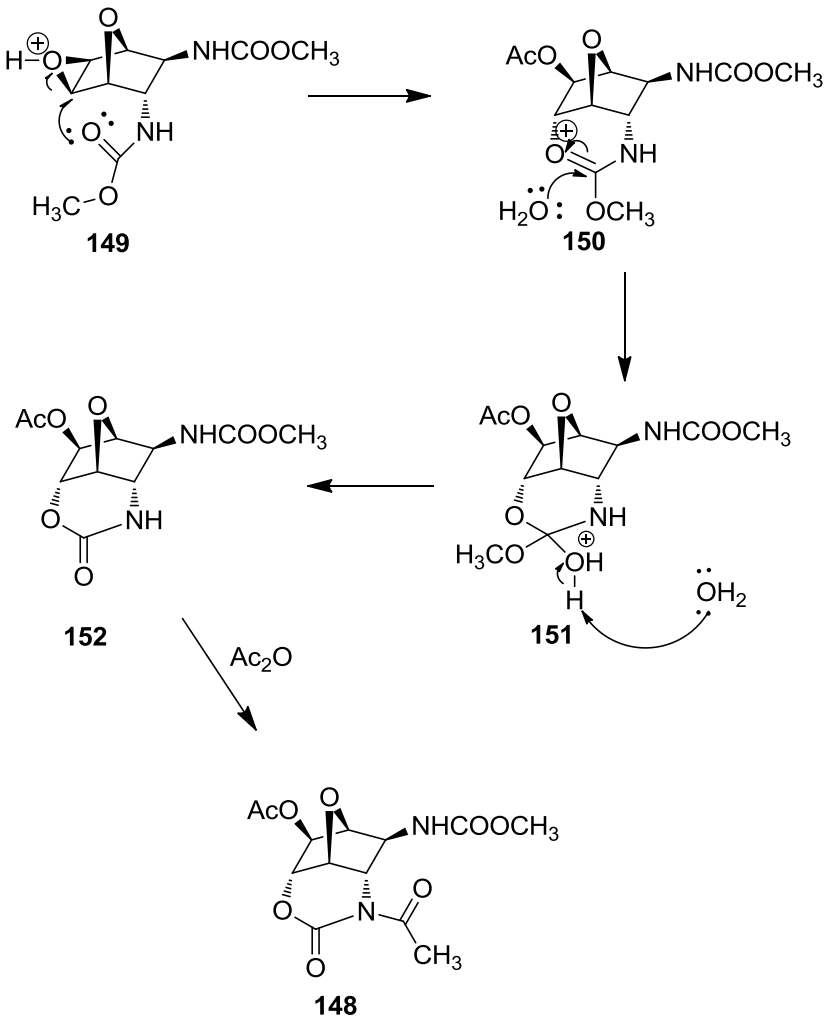
143 **148**

Scheme 44 Formation of compound **148**

For the formation of **148**, we suggest the following mechanism. After protonation of epoxide oxygen atom, oxygen atom of carbonyl group of *endo*-configurated urethane moiety attacks the epoxide carbon in **149** through S_N2 reaction and epoxide ring-opening and cyclization take place. Acetylation of hydroxyl group is carried out through attack of oxygen of hydroxyl group to acetic anhydride in presence of acetic

acid. After that, water has nucleophilic character and attacks the carbon atom in **150**. Removal of CH_3OH forms cyclic amide **152**. Further acetylation of –NH group results in the formation of final product **148** (Scheme 44).

Suggested mechanism of this reaction is shown in Scheme 45;



Scheme 45 Suggested mechanism of formation of tricyclic compound **148**

The ^{13}C spectrum of **148** showed the presence of 13 carbon resonances. Four of them appear in the sp^2-region at 172.9, 169.7, 155.8 and 147.2. We assigned these signals to carbonyl carbon resonances.

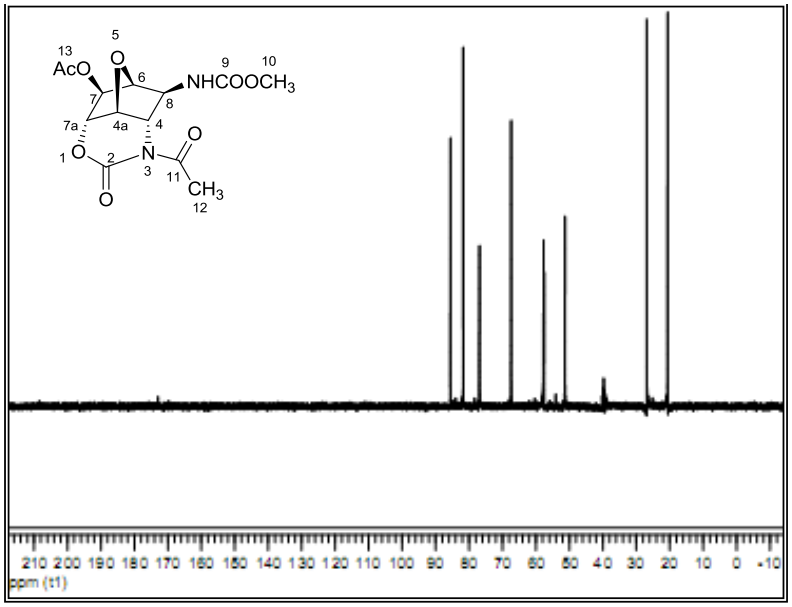


Figure 12 DEPT-135 of compound **148**

DEPT-135 spectrum showed nine distinct signals arising from –CH and $–CH_3$ groups (Figure 12). The fact that there was no negative signal clearly indicated the absence of any $–CH_2$ group.

DEPT-90 exhibits only –CH carbons. So, -CH and CH_3 carbons could be easily assigned. In this spectrum, C_4, C_{4a}, C_8, C_6, C_7, C_{7a} carbons were observed.

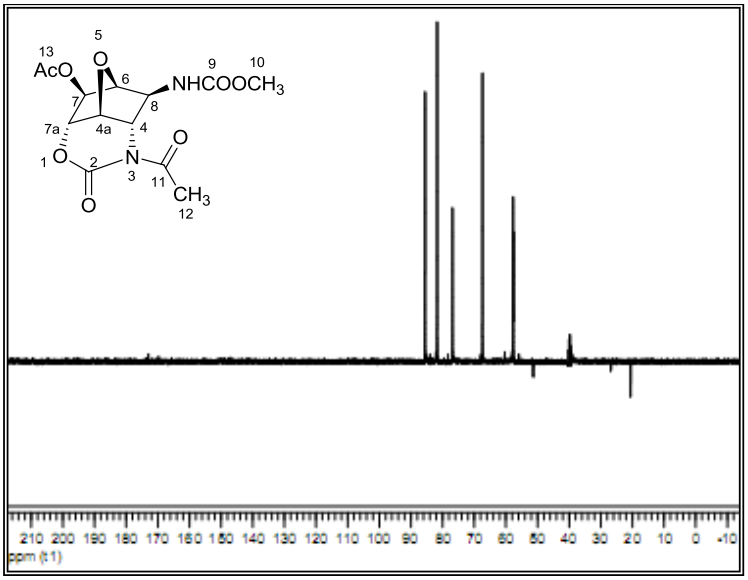


Figure 13 DEPT-90 spectrum of compound **136**

The presence of only six carbon resonances in the DEPT-90 spectrum showed the presence of three CH_3 resonances. From the chemical shift of $-CH_3$ resonances, it was easy to distinguish between $-OCH_3$ and acetyl group (Figure 13).

In COSY spectra (Figure 14), all couplings between protons can be observed in one spectrum. Therefore, we could determine the neighboring protons. From COSY spectra, H_8 was assigned through coupling with –NH proton with coupling constant of J = 6.4 Hz and it resonates as doublet at 3.80 ppm in ^{1}H NMR and at 57.7 ppm in ^{13}C NMR. H_{4a} appears as triplet at 4.76 ppm in ^{1}H NMR due to the *endo*-configuration of the neighboring substituents H_4 and H_{7a}. The C_{4a} carbon atom resonates at 67.4 ppm in ^{13}C NMR.

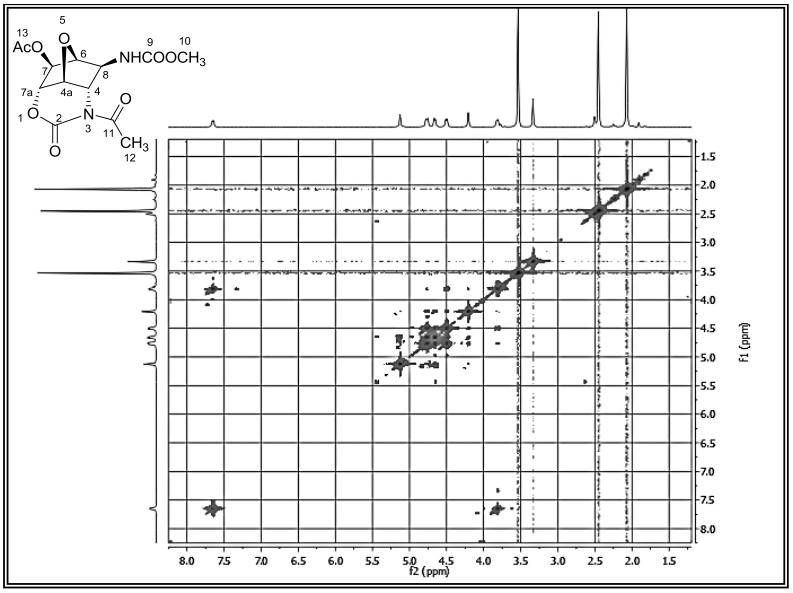


Figure 14 COSY spectrum of compound **148**

In HMBC spectrum (Figure 15), correlation through 2 or 3 bonds between ^{1}H and ^{13}C peaks are seen. The determined correlations are in agreement with the determined structure.

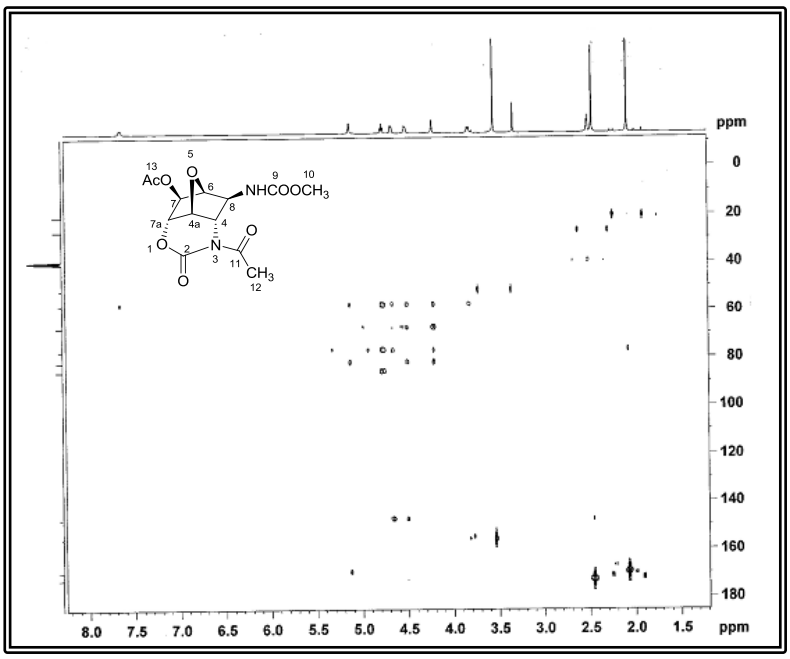


Figure 15 HMBC spectrum of compound **148**

For example, acetyl carbonyl carbon (C_{11}) attached to nitrogen resonates at 172.9 ppm and correlates with $-CH_3$ proton resonance at 2.45 ppm. Acetate carbonyl carbon (C_{13}) shows a correlation through 2 bonds with $-CH_3$ peak at 2.07 ppm and this methyl carbon resonates at 20.1 ppm.

C_2 can be determined only from HMBC spectrum. Because, there is no adjacent proton which gives direct correlation. C_2 correlates with H_{7a} and H_4 through 3 bonds and it resonates at 147.2 ppm.
Other carbonyl carbon involved in urethane group can be localized by using the information of correlation with methoxy proton. This carbonyl group resonates at 155.8 ppm. However, from ^{1}H NMR spectrum, it can be easily assigned due to there is an only one methoxy methyl proton and it gives singlet at 3.54 ppm in ^{1}H NMR spectrum and 51.3 ppm in ^{13}C NMR spectrum.

Carbonyl carbon C_{13} signal intersects two cross peaks. One of them is methyl protons adjacent to C_{13} which was defined before and other one is H_7. On the basis of these correlations, H_7 resonance (5.12 ppm) as well as C_7 resonance (76.9 ppm) were assigned correctly.

C_{7a} correlates with protons H_7, H_6 and H_4 resonating at 5.12, 4.20 and 4.50 ppm. Resonance signal of C_6 and C_4 appear at 85.5 and 57.6 ppm. So, H_{7a} could be easily defined and it gives doublet at 4.65 ppm in ^{1}H NMR and the corresponding C_{7a} atom resonates at 81.7 ppm in ^{13}C NMR spectrum.

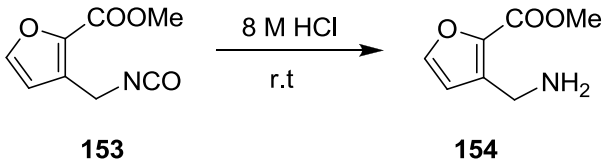
The location of C_4 was proven on the basis of the correlation between C_2 and, H_{7a} and H_4.

After determination of the correct structure of compound **148**, it was easily realized that a carbonyl group having *endo*-configuration in **143** will always involve in the ring-opening process of the epoxide ring. At this stage, we decided to change our strategy and continue our synthetic process with a compound without epoxide ring or

without carbonyl group having *endo*-configuration. Therefore, compound **138** should be converted into corresponding amine or the double bond in **98** should be protected as diol.

2.10 Synthesis of corresponding amine 156

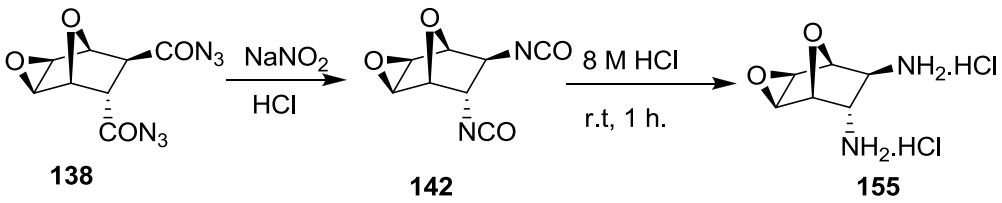
We again turned our attention to isocyanate of bicyclic system. Isocyanate functionalities were decided to be converted into amine. In 2010, Balcı *et al.* synthesized *methyl 2-(aminomethyl)furan-3-carboxylate* (**154**) through hydrolysis reaction of isocyanate **153** (Scheme 46) [34].



153 **154**

Scheme 46 Amine formation through hydrolysis of isocyanate

We aimed to perform this reaction in 2 parts. First part was formation of ammonium salt of this system. To apply this reaction in our system, acyl azide **138** was converted into isocyanate **142** in dry benzene. Then, to this solution, 8M HCl was added and this mixture was stirred at room temperature for 1 h. After completion of reaction, compound **155** was obtained in 95 % yield (Scheme 47).



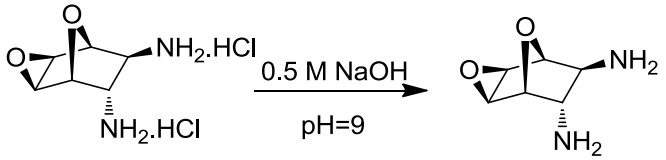
138 **142** **155**

Scheme 47 Formation of diamminium salt 155 from compound **142**

^{1}H and ^{13}C NMR confirmed the formation of the product. In ^{1}H NMR, one of the bridgehead protons resonates as singlet at 4.65 ppm and other one is split into doublet with J = 4.6 Hz and gives signal at 4.71 ppm. Epoxide protons resonate as AX system because chemical shift difference is much larger than coupling constant. Coupling between epoxide protons is J = 3.2 Hz and they resonate at 3.63 and 3.74 ppm. One of the protons neighboring -$^{+}NH_3$ resonates at 3.55 ppm as doublet. Other proton could not be seen due to the overlapping with solvent peak. -$^{+}NH_3$ protons resonate at 8.82 and 8.65 ppm.

In ^{13}C NMR spectrum, epoxide carbons, carbons neighboring ammonium salt functional group and bridgehead carbons resonate at 47.2, 47.7, 54.6, 56.8, 74.1, 77.9 ppm.

The second part of the reaction was conversion of isocyanate functionality into amine. To do this, ammonium salt was dissolved in water and it was cooled to 0 ^{o}C (ice-bath). 0.5 M NaOH solution was added to adjust pH of the aqueous phase to 9 at 0 ^{o}C. Then, ethyl acetate was added and the mixture was stirred at the same temperature for 1 h. After completion of reaction, amine **156** was obtained as yellow oil (Scheme 48).



155 **156**

Scheme 48 Diamine **156** formation

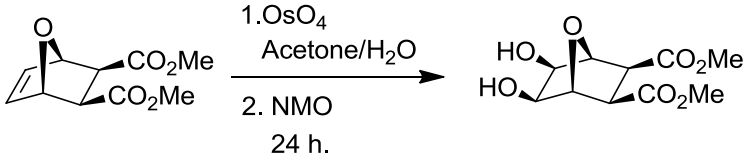
^{1}H and ^{13}C NMR are consistent with the structure. Epoxide protons resonate at 3.62 and 3.34 ppm as doublets with the coupling constant of J = 3.4 Hz. One of the bridgehead protons appear at singlet at 4.07 ppm and other one gives doublet with a coupling constant of J = 4.7 Hz at 4.25 ppm. Proton which is adjacent to amino group and has *trans*-configuration to *O*-bridge resonates at 2.55 ppm as doublet with

the coupling constant of J = 2.7 Hz. Other proton adjacent to amino group resonates as doublet of doublets at 3.14 ppm. In ^{13}C NMR spectrum, there are six resonances at 87.3, 77.1, 75.4, 68.4, 67.3, 57.1 ppm.

IR spectrum gave characteristics signal of amine functionality at 3446 cm^{-1}.

2.11 Synthesis of compound 157 through *cis*-dihydroxylation of compound 98

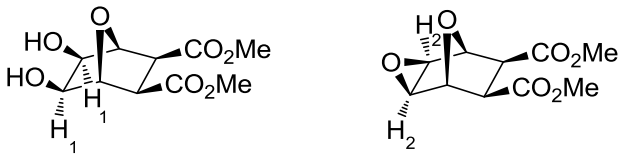
Van Rheenen *et al*. succesfully achieved *cis*-dihydroxylation of double bond with OsO_4 (cat) in presence of NMO [35]. To apply this reaction to our starting material, *cis*-diester of bicyclic alkene **98**, firstly OsO_4 solution was prepared in acetone/H_2O (1:1). To a solution of *cis*-diester in this solution, NMO was added at 0 ^oC under nitrogen atmosphere and reaction mixture was stirred at room temperature for 24 h then, bicyclic *cis*-diol **157** was obtained in 78% yield (Scheme 49).



98 **157**

Scheme 49 *Cis*-dihydroxylation of compound **98**

^1H and ^{13}C NMR results are compatible with the structure. Similarity was observed between NMR spectra of **157** and **122**. A remarkable difference was observed between the resonances of H_1 and H_2 in **157** and **122** (Figure 16).



157 **122**

Figure 16 H_1 and H_2 in **157** and **122**

While H_2 protons resonate at 3.31 ppm, H_1 protons give singlet at 3.85 ppm. Epoxide proton resonances were shifted to higher field compared to the resonances of alkoxy protons in **157**.

IR spectrum also proved the formation of diol **157** with the signal of hydroxyl group at 3357 cm^{-1}.

In ^{13}C NMR spectrum, there are five lines which give signal at 171.0, 83.3, 72.1, 51.5, 46.3 ppm.

Ring-opening reactions with diol **157** as well as with amino-epoxide **156** will continue in the future.

CHAPTER 3

EXPERIMENTAL

3.1 General

Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$_{d6}$ and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quasi-triplet (quasi t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm^{-1}).

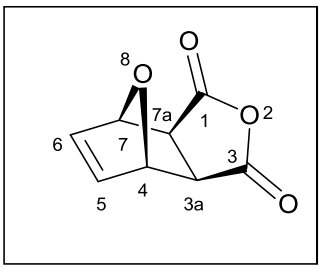
Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ACD/NMR.

Solvents were purified as reported in the literature [36].

3.2 Synthesis of rel-(3a*R*,4*R*,7*R*,7a*S*)-3a,4,7,7a-tetrahydro-4,7-epoxy-2-benzo furan-1,3-dione (**108**)

Maleic anhydride **107** (13.43 g, 136.9 mmol) was dissolved in 50 ml furane **106** at room temperature. This reaction was stirred at the same temperature for 3 h. A pure sample of *exo*-isomer **108** was obtained as a white solid after evaporating excess furane (21.6 g, 95%) (m.p.= 112-113 °C).



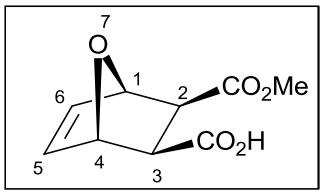
^{1}H-NMR (400 MHz, $CDCl_3$) 6.58 (quasi t, J = 0.9 Hz), 5.46 (quasi t, J = 0.9 Hz), 3.18 (s, 2H, H-3a, H-7a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 169.9, 137.0, 82.3, 48.7

IR (ATR) 1789, 1282, 1230, 1087, 1021, 904, 881

3.3 Synthesis of rel-(1*R*,2*S*,3*R*,4*R*)-3-(methoxycarbonyl)-7-oxabicyclo[2.2.1] hept-5-ene-2-carboxylicacid (**109**)

Methanol (203 µL) was added to *exo*-adduct **108** (3.25 g, 16 mmol) at room temperature. The reaction mixture was stirred until the anhydride was consumed (TLC). The solvent was evaporated in vacuo and the residue was dissolved in ethylacetate. After evaporating ethylacetate, white solid hemiester **109** was obtained (3.07 g, 97%) (m.p. = 106-107°C).



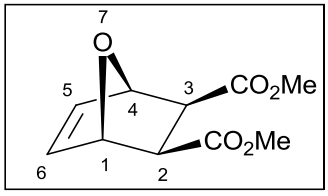
^{1}H-NMR (400 MHz, $CDCl_3$) 9.77 (br s, OH, 1H), 6.40 (dd, $J_{5,6}$ = 5.7 Hz, $J_{5,4}$ = 1.6 Hz, 1H, H-5), 6.41 (dd, $J_{6,5}$ = 5.7 Hz, $J_{6,1}$ = 1.6 Hz, 1H, H-6) 5.25 (br s, 1H, H-4), 5.21 (br s, 1H, H-1), 3.64 (s, OCH_3, 3H), 2.81 (d, $J_{2,3}$= $J_{B,A}$ = 9.0 Hz, 1H, H-2), 2.78 (d, $J_{3,2}$ = $J_{A,B}$ = 9.0 Hz, 1H, H-3)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 177.0, 171.7, 136.8, 136.3, 80.6, 80.3, 52.3, 47.3, 46.9

IR (ATR) 3023, 2955, 1736, 1437, 1354, 1244, 1197, 909, 819

3.4 Synthesis of rel-(1*R*,2*R*,3*S*,4*R*)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**98**)

Hemiester **109** (3.76 g, 19 mmol) was dissolved in MeOH (40 ml). To this solution was added thionyl chloride (2.73 ml) and the mixture was heated at reflux for 4 h. After completion of reaction, solvent and excess thionyl chloride was evaporated. rel-(1*R*,2*S*,3*R*,4*S*)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxy late (**98**) was crystallized in ethyl acetate (25 ml). Then the crystals were removed by filtration (2.82 g, 70%) (m.p. = 117–118°C).



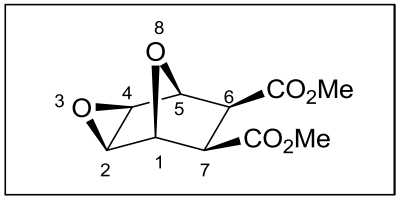
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 6.39 (quasi t, *J* = 0.9 Hz), 5.20 (quasi t, *J* = 0.9 Hz), 3.64 (s, 3H, -OCH_3), 2.76 (s, 2H, H-2, H-3)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 171.9, 136.6, 80.4, 52.2, 46.9

IR (ATR) 2988, 2948, 1746, 1733, 1434, 1344, 1196, 1008, 905

3.5 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*R*)-dimethyl-3,8-dioxatricyclo[3.2.1.0^{2,4}] octane -6,7-dicarboxylate (**122**)

Diester **98** (1.0 g, 4.7 mmol) was dissolved in CH_2Cl_2 (45 ml) and cooled to 0 ^{o}C. To this solution was added *m*-CPBA (1.76 g, 9.4 mmol) and the reaction mixture was strirred for 1 day. Excess *m*-CPBA was removed by filtration and to the filtrate was added saturated sodiumthiosulfate solution (100 ml) and the mixture was stirred for 10 min. After the organic layer was extracted, it was cooled to 0 ^{o}C. 0.5 M NaOH (100 ml) was added to cooled organic phase and extracted with CH_2Cl_2 (2x50 ml), dried over $MgSO_4$. After evaporation of solvent, epoxide **122** was obtained as a white solid. (1.05 g, 98%) (m.p. = 143-144°C)



^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 4.78 (s, 2H, H-1, H-5), 3.63 (s, 6H, -OCH_3), 3.31 (s, 2H, H-2, H-4), 2.92 (s, 2H, H-6, H-7)

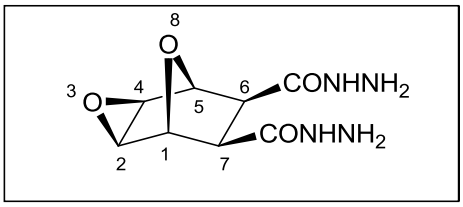
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 170.3, 76.4, 52.4, 49.2, 49.1

IR (ATR) 2953, 2253, 1740, 1437, 1280, 1215, 1168, 904, 725

3.6 Synthesis of compound 99, 103 and 126

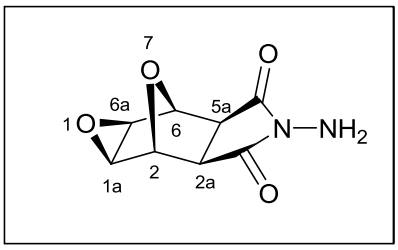
To a solution of epoxide **122** (2.71 g, 11.8 mmol) in MeOH (50 ml) at 25 ^{o}C hydrazine monohydrate (4.04 ml, 83 mmol) was added and the resulting mixture was stirred at room temperature. After 24 h, solvent was evaporated in vacuo and excess hydrazine monohydrate was removed by washing cold MeOH (15 ml) to give compound **99** (1%), compound **103** (32%), compound **126** (67%). This mixture in chloroform was heated to 60 ^{o}C and stirred for 1 day. After filtration, filtrate was evaporated in vacuo and compound **126** (67%) (m.p. = 239-240°C) was obtained as a white solid. When this reaction mixture was stirred under the same conditions for 2 d, compound **99**, compound **103**, compound **126** was obtained in the yield of 10%, 32%, 58%. When the reaction was carried out for 3 d under the same conditions, compound **99**, compound **103** compound **126** was observed in reaction media in the yield of 12%, 44%, 44%.

3.6.1 rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*R*)-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane-6,7-dicarbohydrazide (**99**)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 8.40 (s, 2H, -NH), 4.10 (s, 4H, NH_2), 4.52 (s, 2H, H-1, H-5), 3.40 (s, 2H, H-2, H-4), 2.80 (s, 2H, H-6, H-7)

3.6.2 rel-(1a*R*,2*S*,2a*R*,5a*S*,6*S*,6a*S*)-4-aminopentahydro-1a*H*-2,6-epoxyoxireno[f]isoindole-3,5-dione (**126**)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 5.05 (s, 2H, -NH_2), 4.63 (s, 2H, H-2, H-6), 3.68 (s, 2H, H-2a, H-5a), 3.12 (s, 2H, H-1a, H-6a)

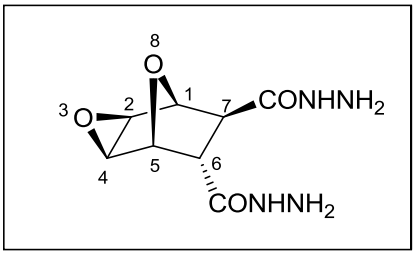
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ ppm 173.7, 75.7, 49.1, 45.8

IR (ATR) 3331, 3246, 1693, 1592, 1186, 1170, 1018, 854, 704

Anal. Calcd. for $C_8H_8N_2O_4$ (196,05): C 48.98, H 4.11, N 14.28, O 32.63; ; Found: C 48.72, H 4.134, N 14.09

3.7 Synthesis of rel-(1*S*,2*S*,4*R*,5*S*,6S,7S)-3,8-dioxatricyclo[3.2.1.$0^{2,4}$]octane-6,7-dicarbohydrazide (**103**)

To a solution of *trans*-epoxide **132** (2.71 g, 11.8 mmol) in MeOH (50 ml) at 25 °C was added hydrazine monohydrate (4.04 ml, 83 mmol) and stirred for 1 d. After completion of reaction, the solvent was evaporated in vacuo and excess hydrazine monohydrate was removed by washing with MeOH (10 ml) to give dicarbohydrazide **103** as a white solid. (2.44 g, 91%) (m.p. > 300 °C)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (s, 1H, -NH), 9.08 (s, 1H, -NH), 4.52 (d, J = 5.1 Hz, 1H, H-5), 4.43 (s, 1H, H-1), 4.20 (d, J = 3.9 Hz, 2H, -NH_2), 4.18 (d, J = 3.9 Hz, 2H, -NH_2), 3.42 (d, $J_{4,2}$ = $J_{2,4}$ = 3.5 Hz, 1H, H-4), 2.90 (d, J = 5.1 Hz, 1H, H-7)

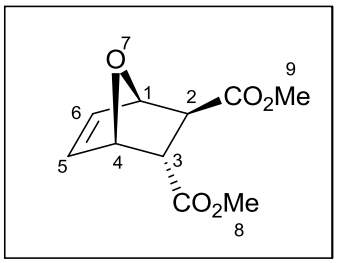
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ ppm 170.4, 167.8, 78.5, 74.7, 49.2, 48.8, 48.2, 45.7

IR (ATR) 3390, 3372, 3304, 1664, 1637, 1599, 1510, 1356, 1247, 1039, 928

Anal. Calcd. for $C_8H_{12}N_4O_4$ (228,21): C 42.10, H 5.30, N,24.55, O, 28.04; Found: C 43.61, H 5.258, N 24.07

3.8 Synthesis of rel-(1*R*,2S,3S,4*R*)-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**102**)

Fumaryl chloride **110** (1.5 ml, 13 mmol) was added to furan **106** (1ml, 13 mmol) which was pre-cooled to 0 °C (ice-salt bath). The reaction mixture was stirred for 0.5 h without removing the ice bath. After completion of reaction, light green solid was obtained. Anhydrous methanol (5 ml, 0.1mol) and triethylamine (4.2 ml, 30 mmol) were added to ether (50 ml) at 10 °C. Then, light green solid was added with small portions to this solution at 10 °C and reaction mixture was stirred for 0.5 h. After that, cold water (40 ml) was added to solution. Then the mixture was extracted with ether (2 x 20 ml). The combined organic extracts were washed with water (40 ml) and brine (20 ml), dried over $MgSO_4$ and the solvent was evaporated to give pale yellow solid **102**. (1.98 g, 72%) (m.p. = 78–79 °C). The product was crystallized in ether.



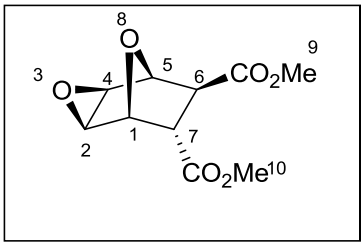
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 6.45 (dd, $J_{5,6}$ = 5.74, $J_{5,4}$ = 1.7 Hz, 1H, H-5), 6.29 (dd, $J_{6,5}$ = 5.79, $J_{6,1}$ = 1.50 Hz, 1H, H-6), 5.19-5.16 (m, 2H, H-4, H-1), 3.69 (s, 3H, -OCH_3), 3.60 (s, 3H, -OCH_3), 3.55 (t, $J_{3,4}$ = $J_{3,2}$ = 4.3 Hz, 1H, H-3), 2.78 (d, $J_{2,3}$ = 3.9 Hz, 1H, H-2)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 171.3, 170.0, 77.9, 74.9, 52.7, 52.5, 50.5, 49.1, 48.3, 48.1

IR (ATR) 2955, 1727, 1434, 1377, 1196, 1178, 1163, 1023, 915, 870

3.9 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*S*)-dimethyl-3,8-dioxatricyclo[3.2.1.0^{2,4}] octane-6,7-dicarboxylate (132)

Diester **102** (1.0 g, 4.7 mmol) was dissolved in CH_2Cl_2 (45 ml) and cooled to 0 ^oC. To this solution was added *m*-CPBA (1.76 g, 9.4 mmol) and the reaction mixture was strirred for 2 days. Excess *m*-CPBA was removed by filtration and to the filtrate was added saturated sodiumthiosulfate solution (100 ml) and the mixture was stirred for 10 min. After the organic layer was extracted, it was cooled to 0 ^oC. 0.5 M NaOH (100 ml) was added to cooled organic phase and extracted with CH_2Cl_2 (2x50 ml), dried over $MgSO_4$. After evaporation of solvent, epoxide **132** was obtained as a white solid. (0.7 g, 72%) (m.p. = 108-109 °C)



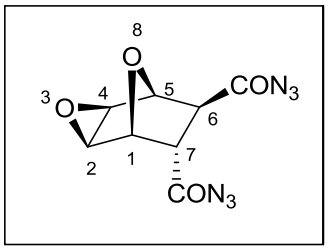
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 4.74 (s, 1H, H-5) 4.68 (d, $J_{1,7}$ = 5.3 Hz, 1H, H-1), 3.69 (s, 3H, -OCH_3) 3.68 (s, 3H, -OCH_3) , 3.58 (t, $J_{7,1}$ = $J_{7,6}$ =5.0 Hz, , 1H, H-7), 3.39 (d, $J_{2,4}$ = $J_{A,B}$ = 3.3 Hz, 1H, H-2), 3.33 (d, $J_{4,2}$ = $J_{B,A}$ = 3.3 Hz, 1H, H-4), 3.01 (d, $J_{6,7}$ = 4.9 Hz, 1H, H-6)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 171.4, 170, 78.0, 74.9, 52.7, 52.5, 50.5, 49.1, 48.4, 48.1

IR (ATR) 2959, 1720, 1434, 1372, 1344, 1307, 1250, 1215, 998, 970, 887, 857

3.10 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*S*)-3,8-dioxatricyclo[3.2.1.$0^{2,4}$]octane-6,7-dicarbonyl azide (**138**)

The dihydrazide **103** (2.46 g, 10.8 mmol) was dissolved in aq. HCl (35 ml, 1M) at 0 ^{o}C. To a stirred solution, sodium nitrite (0.78 g, 11.38 mmol) in water (9 ml) was added dropwise and reaction mixture was stirred at 0-5 ^{o}C for 0.5 h. (2x60 ml) EtOAc was used for extraction. After organic phases were combined, aq Na_2CO_3 solution (40 ml) was used to wash organic phase. Then, it was washed with brine (30 ml), dried over $MgSO_4$. After evaporation of solvent, acyl azide **138** was obtained as a white solid. (1.3 g, 63%)



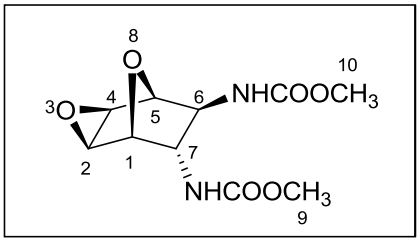
^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm), 4.75 (s, 1H , H-5) 4.69 (d, $J_{1,7}$ = 5.1 Hz, 1H, H-1), 3.42 (d, $J_{2,4}$= $J_{A,B}$ = $J_{4,2}$ = $J_{B,A}$ = 3.2 Hz, 2H, H-2, H-4), 3.59 (t, $J_{7,1}$ = $J_{7,6}$ = 5.0 Hz, 1H, H-7), 3.00 (d, $J_{6,7}$ = 4.9 Hz, 1H, H-6)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 177.5, 176.4, 78.1, 75.2, 52.6, 50.0, 48.9, 48.2

IR (ATR) 2165, 1696, 1324, 1285, 1209, 1176, 985, 860

3.11 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*S*)-dimethyl-3,8-dioxatricyclo[3.2.1.$0^{2,4}$] octane-6,7-diyldicarbamate (**143**)

(0.89 g, 4.6 mmol) Acyl azide **138** is added to dry benzene (40 ml) and is heated to reflux temperature. The solution is stirred at this temperature for 1 h. At this stage, acyl azide **138** is converted into isocyanate **142**. Then, this solution of isocyanate **142** is coolled to 40 ^{o}C and distilled methanol (1.2 ml, 29.4 mmol) was added to this solution. It is allowed to stir at reflux temperature for 1 h. After completion of reaction, solvent was evaporated in vacuo to give urethane **143** as a white solid. (1.16 g, 98%) (m.p. = 191-192 °C)



^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 5.25 (br s, 1H, -NH) 5.15 (s, 1H, -NH) 4.73 (br s, 1H, H-1), 4.25 (s, 1H, H-5), 3.69 (m, 1H, H-7), 3.63 (s,3H, -OCH_3), 3.62 (s, 3H, -OCH_3) 3.54 (m, 1H H-4) 3.51 (d, $J_{2,4}$ = 3.2 Hz, 1H, H-2), 3.38 (d, $J_{4,2}$ = 3.2 Hz, 1H, H-4)

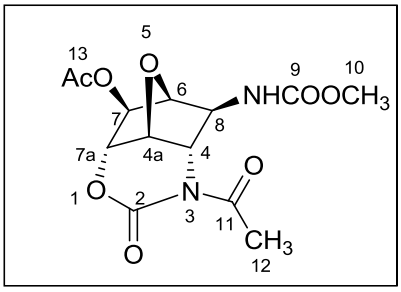
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 156.34, 156.3, 79.1, 73.1, 61.1, 61.0, 56.9, 51.5, 51.3, 47.7

IR (ATR) 1682, 1541, 1311, 1281, 1238, 1196, 1022, 890, 820

Anal. Calcd. for $C_{10}H_{14}N_2O_6$ (258,23): C 46.51, H 5.46, N 10.85, O 37.18; Found: C 48.07, H 5.23, N 10.88

3.12 Synthesis of rel-(4a*S*,4*R*,6S,7a*R*,7*R*,8*S*)-3-acetyl-2-oxohexahydro-2*H*-4,6-methanofuro[2,3-e][1,3]oxazin-7-yl acetate-8-yl carbamate (148)

Sulfamic acid (0.08 g, 0.82 mmol) was added to a stirred solution of urethane **143** (0.85 g, 3.29 mmol) in AcOH/Ac_2O (15 ml 1:1). The mixture was stirred at reflux temperature for 24 h. 50 ml water was poured into this mixture and 2-3 drop of HCl was added to acidify the solution. For extraction of organic phase, dichloromethane was used. (2x50 ml) Water and (2x25 ml) $NaHCO_3$ were used for washing organic phase which was then dried over $MgSO_4$. After evaporation, white solid **148** which was then crystallized in $CHCl_3$ over hexane atmosphere was obtained. (27 %, 0.29 g) (m.p. = 201-202 °C)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 7.63 (d, 1H, -NH), 5.12 (s, 1H, H-7), 4.76 (t, $J_{4a,7a}$ = $J_{4a,4}$ = 5.4 Hz, 1H, H-4a) 4.65 (d, $J_{7a,4a}$= 5.3 Hz, 1H, H-7a), 4.50 (d, $J_{4,4a}$ = 5.3 Hz, 1H, H-4), 4.20 (s, 1H, H-6), 3.81 (d, $J_{8,\text{-NH}}$ = 6.2 Hz), 3.54 (s, 3H, -OCH_3), 2.45 (s, 3H, H-12), 2.07 (s, 3H, H-13)

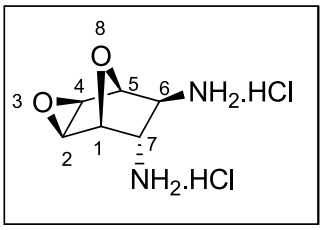
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ ppm 172.9, 169.7, 155.8, 147.2, 85.5, 81.7, 76.9, 67.4, 57.7, 57.6, 51.3, 26.8, 20.6

IR (ATR) 1682, 1541, 1311, 1281, 1238, 1196, 1022, 890, 820

Anal. Calcd. for $C_{13}H_{16}N_2O_8$ (328,27): C 47.56, H 4.91, N 8.53, O 38.99; Found: C 47.17, H 4.98, N 8.39

3.13 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*S*)-3,8-dioxatricyclo[3.2.1.$0^{2,4}$]octane-6,7-diaminiumchloride (155)

(0.89 g, 4.6 mmol) Acyl azide **138** is dissolved in dry benzene (40 ml) and is heated to reflux temperature. The solution is stirred at this temperature for 1 h. At this stage, acyl azide **138** is converted into isocyanate **142**. Then, to this solution, 8M HCl (10 ml) was added and this mixture was stirred at room temperature for 1 h. after completion of reaction, water phase which includes diaminium salt is separated from organic phase (dry benzene phase). Solvent was evaporated in vacuo and light brown salt **155** is obtained. (0.93 g, 95%)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (br s, 1H, H-9), 8.65 (br s, 1H, H-10), 4.71 (d, $J_{1,7}$ = 4.6 Hz, 1H,H-1), 4.65 (s, 1H, H-5), 3.74 (d, $J_{2,4}$= 3.2 Hz,1H, H-2), 3.63 (d, $J_{4,2}$ = 3.2 Hz), 3.55 (m, 2H, H-7, H-6)

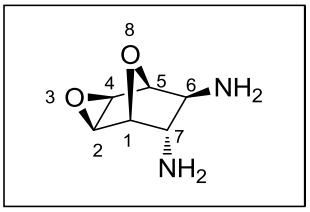
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ ppm 77.9, 74.1, 56.8, 54.6, 47.7, 47.2

IR (ATR) 3174, 3089, 2983, 2895, 2809, 1599, 1506, 1479, 1231, 1087, 1071, 956, 927

HRMS Spectrum: Found: 143.08181; Calculated $[M+H]^+$: 144.0815

3.14 Synthesis of rel-(1*S*,2*R*,4*S*,5*S*,6*S*,7*S*)-3,8-dioxatricyclo[3.2.1.$0^{2,4}$]octane-6,7-diamine (156)

After dissolving compound **155** (0.8 g, 3.7 mmol) in water (15 ml), ethyl acetate (15 ml) was added and this mixture was cooled 0 ^{o}C. The pH value of the aqueous phase was adjusted to 10 by the addition of 0.5 M NaOH solution at the same temperature. The mixture was extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was evaporated to give yellow oily amine **156** (0.11 g, 23%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 4.25 (d, $J_{1,7}$ = 4.7 Hz, 1H, H-1), 4.07 (s, 1H, H-5), 3.62, (d, $J_{2,4}$ = 3.4 Hz, 1H, H-2,), 3.34 (d, $J_{4,2}$ = 3.4 Hz, 1H, H-4), 3.14 (dd, $J_{7,1}$ = 4.7 Hz and $J_{7,6}$ = 2.7 Hz, 1H, H-7), 2.55 (d, $J_{6,7}$ = 2.7 Hz, 1H, H-6)

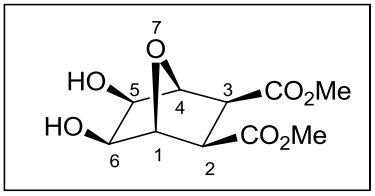
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ ppm 87.3, 77.1, 75.4, 68.4, 67.3, 57.1.

IR (ATR) 3523,9, 3502.7, 3446.8, 1737.7, 1372.7, 1232.6,1044.06

HRMS Spectrum: Found: 143.07978; Calculated $[M+H]^+$: 143.0815

3.15 Synthesis of rel-(1*S*,2*R*,3*S*,4*S*,5*R*,6*S*)-dimethyl-5,6-dihydroxy-7-oxabicyclo [2.2.1]heptane-2,3-dicarboxylate (157)

Cis-diester of bicyclic system **98** (0.4 g, 2 mmol) was dissolved in canned OsO_4 solution which contains 12 mg (0.048 mmol) OsO_4 in 10 ml of acetone/H_2O (1:1) and (0.5 g, 4.35 mmol) NMO was added to this solution at 0 ^oC. The resulting mixture was stirred at room temperature for 24 h. under nitrogen atmosphere. After evaporation of solvent under vacuo, pale yellow solid **157** was obtained. (0.35 g, 78 %) (m.p. =200-201 °C)



^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 4.83 (d, $J_{1,6}$ = $J_{4,5}$ = 4.4 Hz, 2H, H-1,H-4), 4.32 (s, 2H, -OH), 3.77 (d, $J_{6,1}$ = $J_{5,4}$ = 4.4 Hz, 2H, H-6, H-5), 3.53 (s, 6H, -OCH_3), 3.03 (s, 2H, H-3, H-2)

^{13}C-NMR (100.6 MHz, DMSO-d_6) 171.0, 83.3, 72.1, 51.5, 46.3

IR (ATR) 3357, 2951, 1732, 1717, 1435, 1356, 1247, 1196, 1169, 1037, 983, 920

HRMS Spectrum: Found: 245.07395; Calculated $[M-H]^-$: 245.06668

CHAPTER 4

CONCLUSION

Cylitols concerning a large group of natural products have attracted a great deal of attention from the synthetic community due to their glycosidase inhibition activities and their versatility as synthetic intermediates. Aminocyclitols also play an important role in biological events. They compose of comprehensive group of natural products. Aminocyclitols are found extensively in nature in different areas. They have a character of inhibition of some enzymes such as glycosidases. So, bis-aminoinositol synthesis is the interest of this study.

In this work, we tried to develop a new synthetic methodology for the synthesis of bis-aminoinositol derivatives, such as compound **100, 101, 105** and **104**. For this synthesis, compound **98** and **102** were considered to be our key compounds. To convert the diester functionality in compound **98** and **102** into hydrazide group, hydrazine monohydrate was used. In this step, retro Diels-Alder reaction was observed. Then, double bond in bicyclic system was oxidized with *m*-CPBA to prevent reverse Diels-Alder reaction. For the reaction of *cis*-diester of epoxide **122** with hydrazine monohydrate, we observed three different products which are **99**, **103** and **126**. Formation of compound **103** was thought due to α-epimerization. Then, we turned our attention to only *trans endo*-diester of bicyclic epoxide **132**. Treatment of compound **132** with hydrazine monohydrate gave only one product, compound **103** due to thermodynamic stability. Then compound **103** was converted into acyl azide through modified Sandmeyer. This acyl azide **138** was converted to isocyanate followed by methanol addition to give urethane **143**. Further step was the cleavage of oxa-bridge with the help of acid-catalyzed ring-opening reaction. However, highly stable tricyclic product **148** was formed. Furthermore, Lewis acids such as $BF_3.Et_2O$

and BCl_3 and sulfuric acid as well were used to open oxa-bridge, but we could not achieve. After Curtius rearrangement reaction, hydrolysis of the isocyanate functionality in presence of HCl resulted in corresponding amine **156**. Further step was to cleave oxa-bridge to get cyclic structure. However, O-bridge could not be opened with any reagents used for urethane derivative as described above. Then, we turned our attention to follow reaction pathway with diol of bicyclic system **157** due to preventing neighboring group participation like that in formation of compound **148**. So, we submitted compound **98** to OsO_4 – NMO oxidation reaction and we obtained compound **157**. We planned to apply hydrazine monohydrate addition reaction. Further reactions to complete this project are planned.

This developed methodology opens up a new entry to the synthesis of isomeric 1,2-aminoinositol derivatives.

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APPENDIX A

SPECTRAL DATA

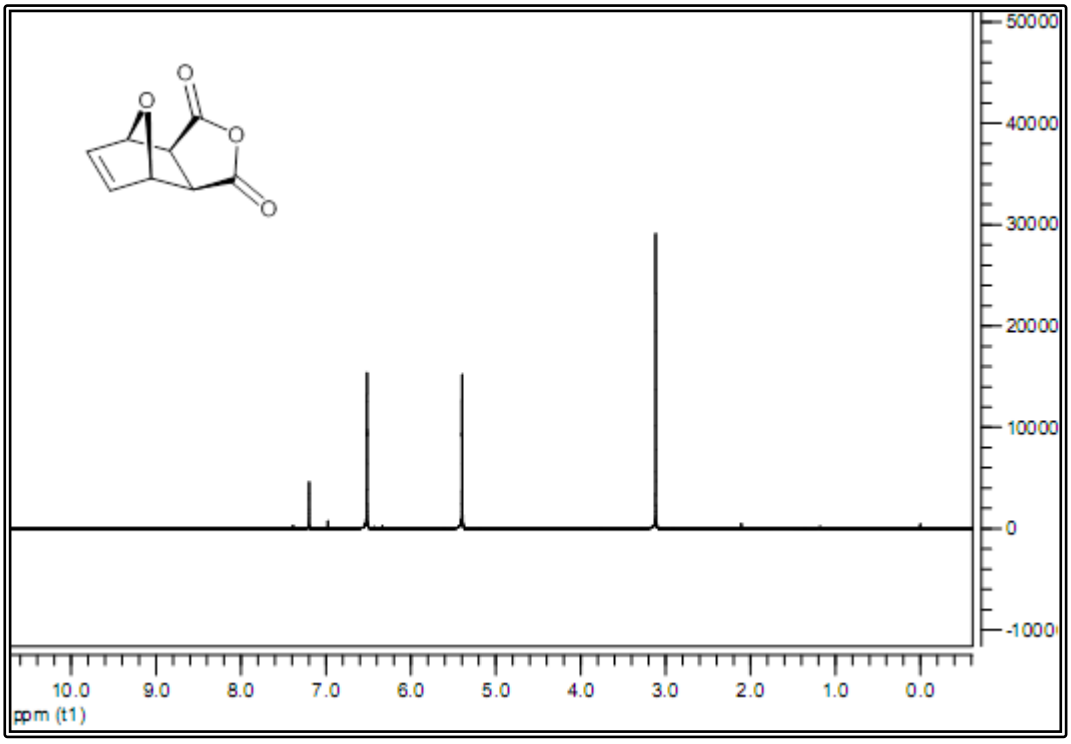

Figure 17 ^{1}H-NMR Spectrum of Compound **108**

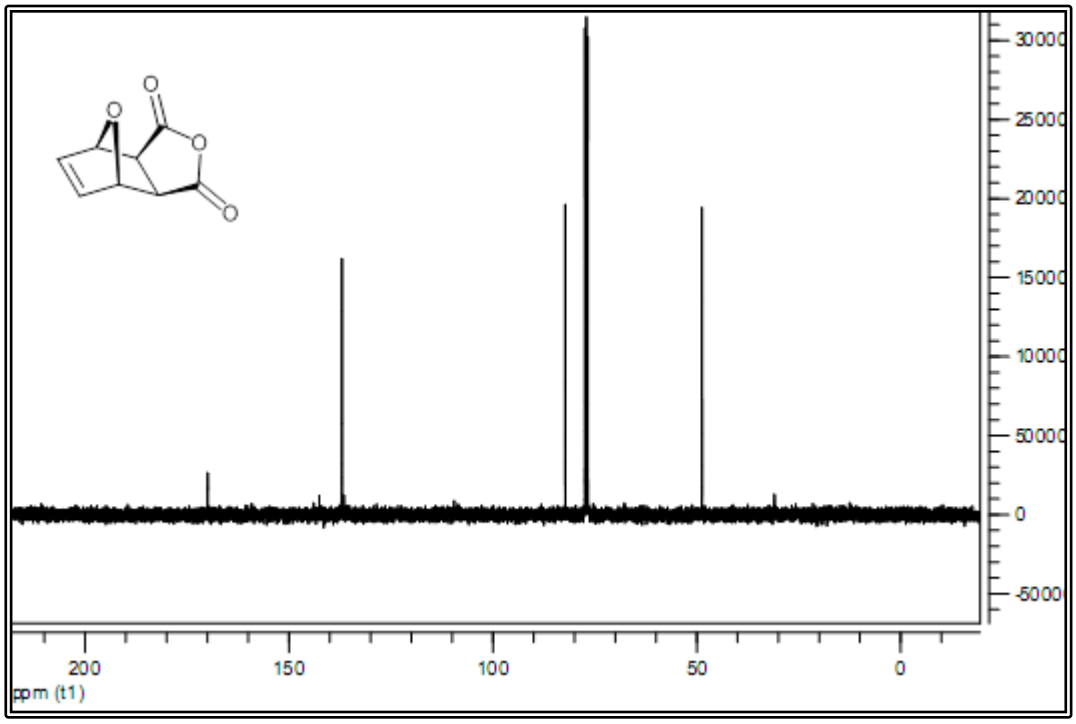

Figure 18 ^{13}C-NMR Spectrum of Compound **108**

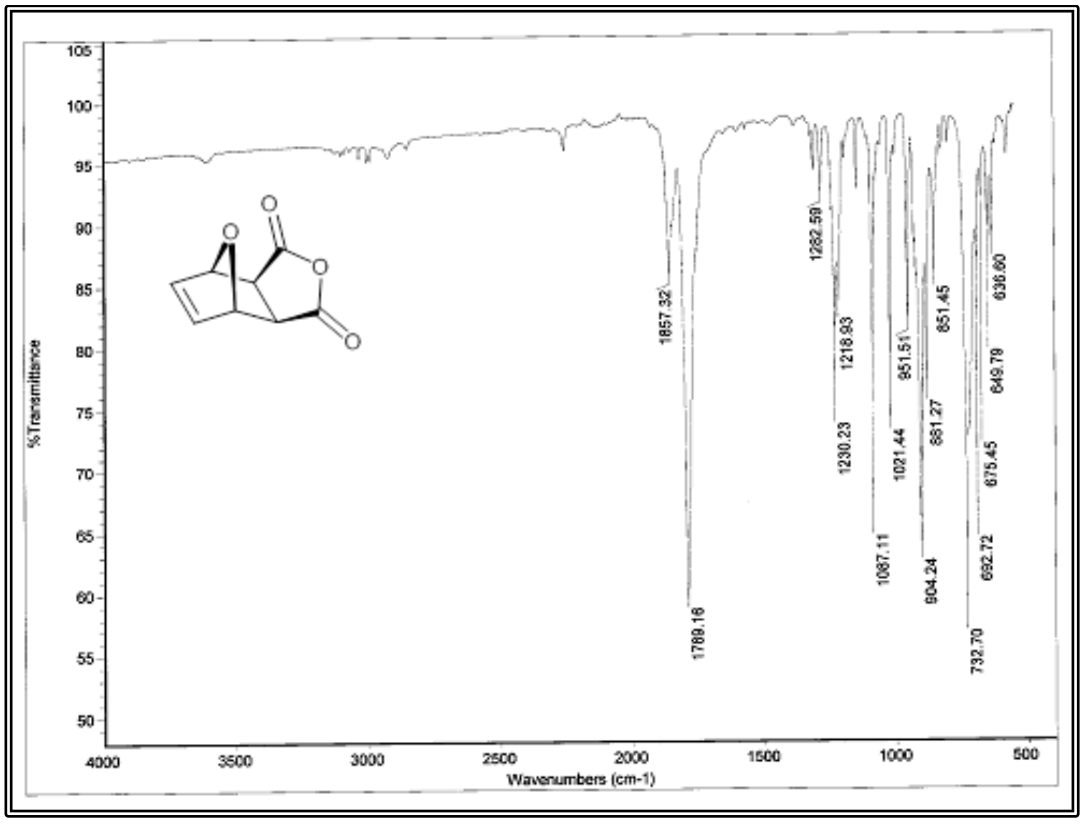

Figure 19 IR Spectrum of Compound **108**

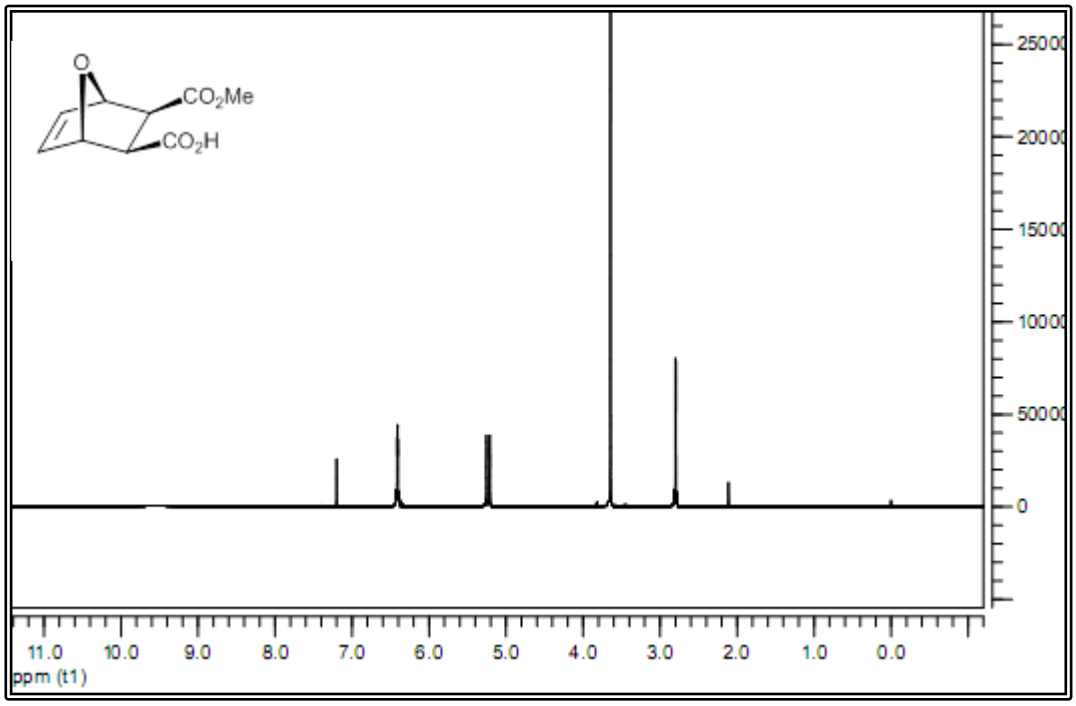

Figure 20 ^{1}H-NMR Spectrum of Compound **109**

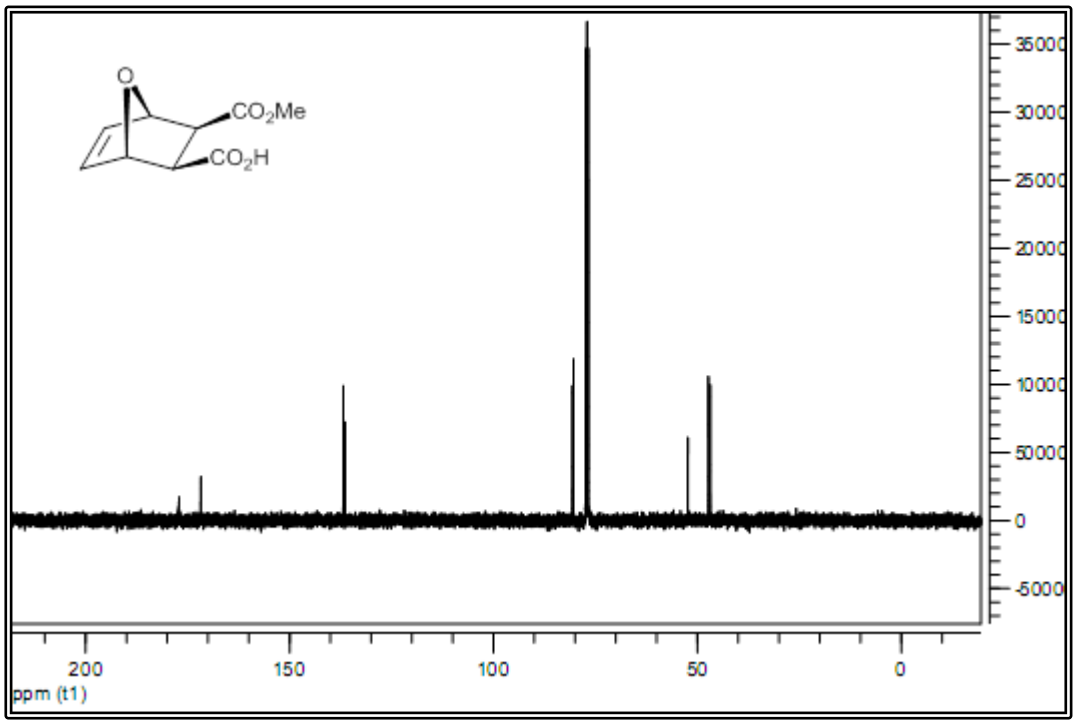

Figure 21 ^{13}C -NMR Spectrum of Compound **109**

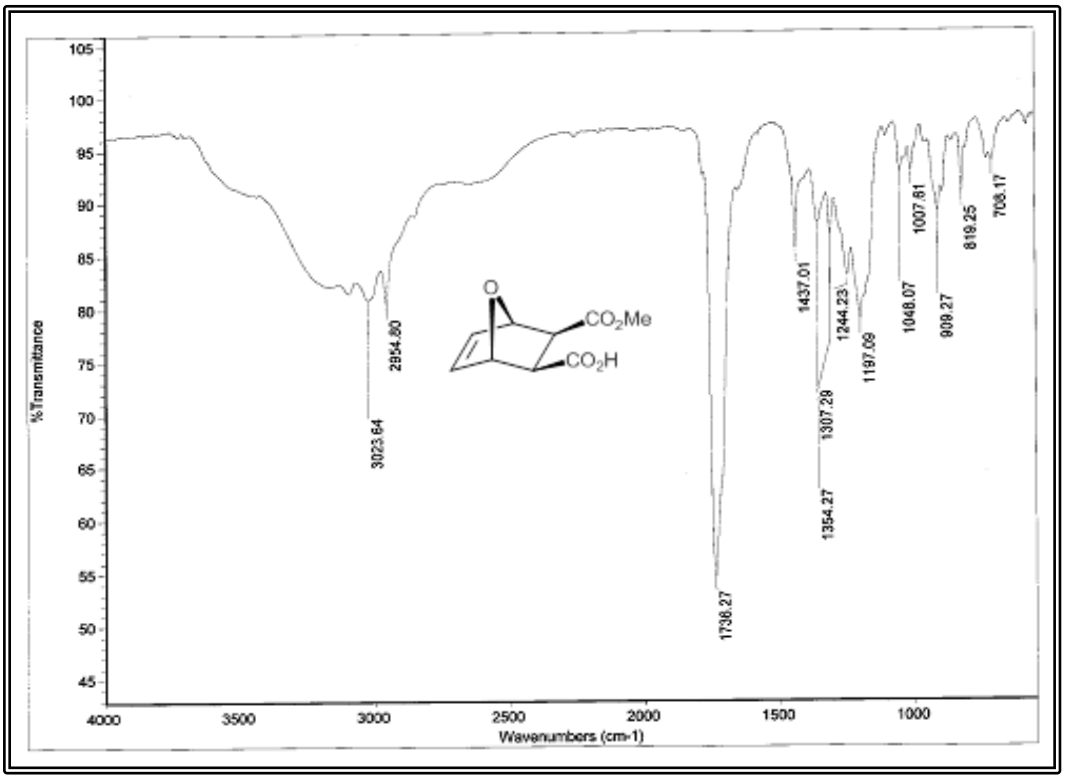

Figure 22 IR Spectrum of Compound **109**

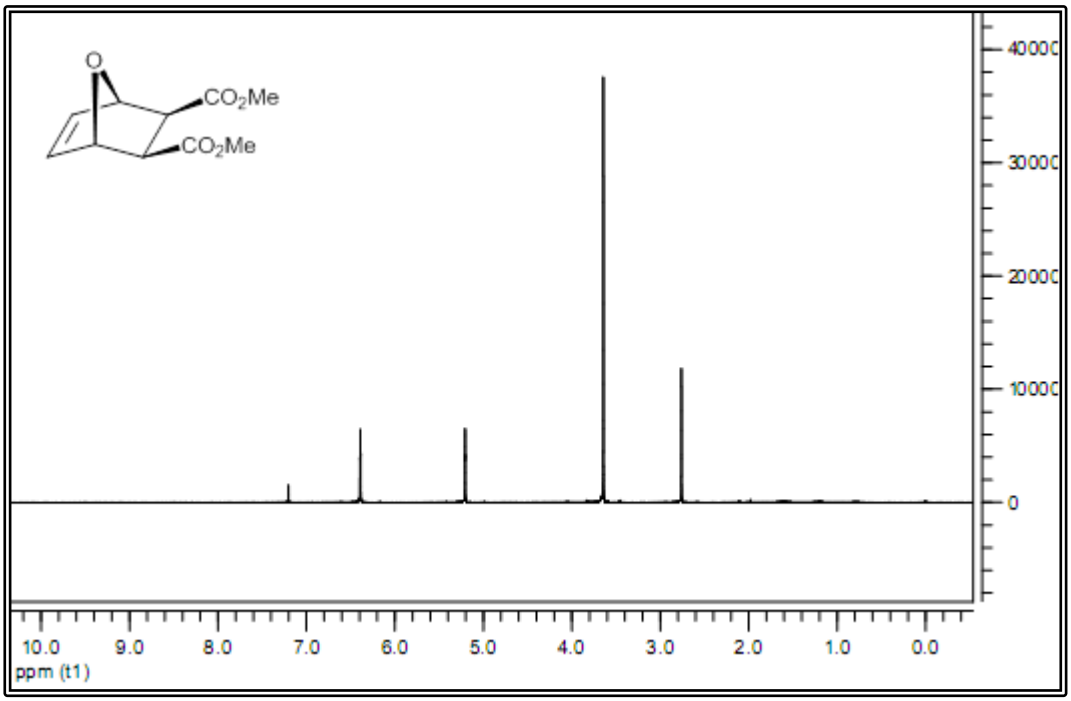

Figure 23 ^{1}H-NMR Spectrum of Compound **98**

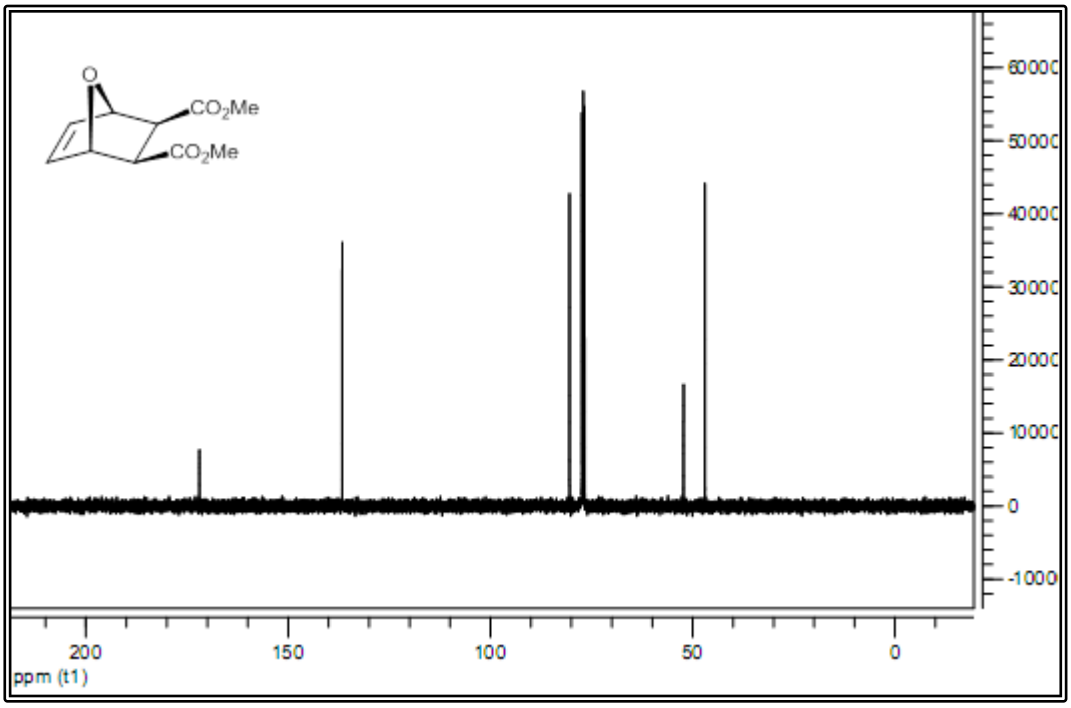

Figure 24 ^{13}C -NMR Spectrum of Compound **98**

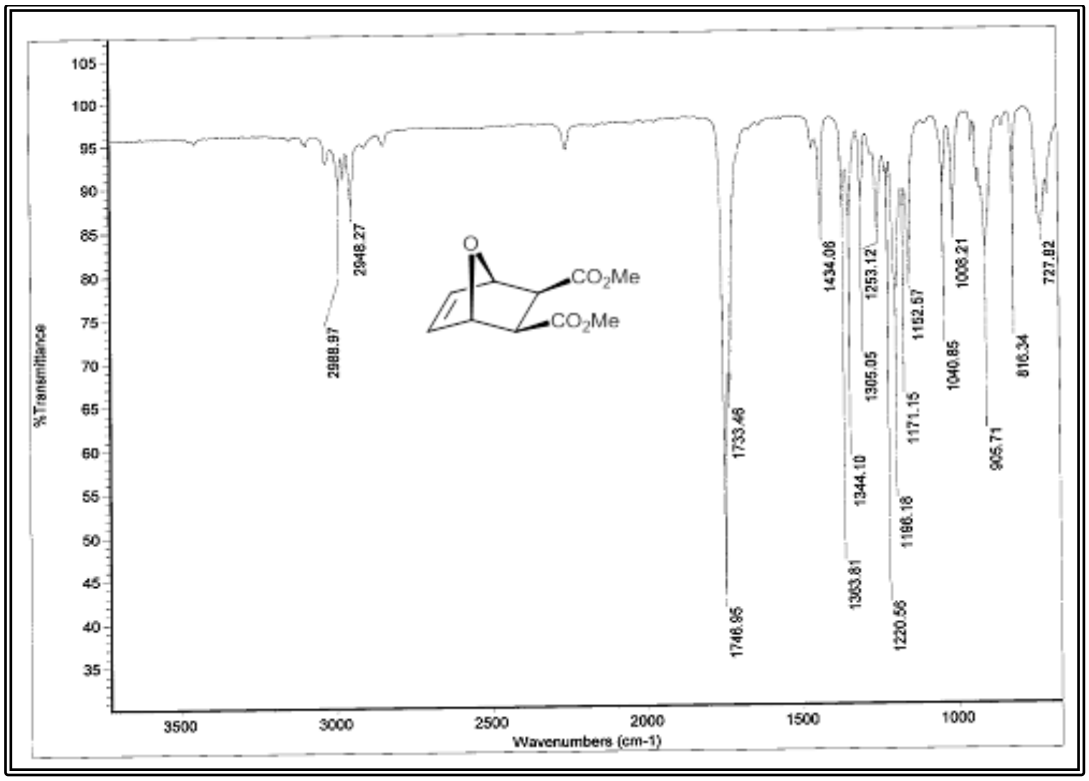

Figure 25 IR Spectrum of Compound **98**

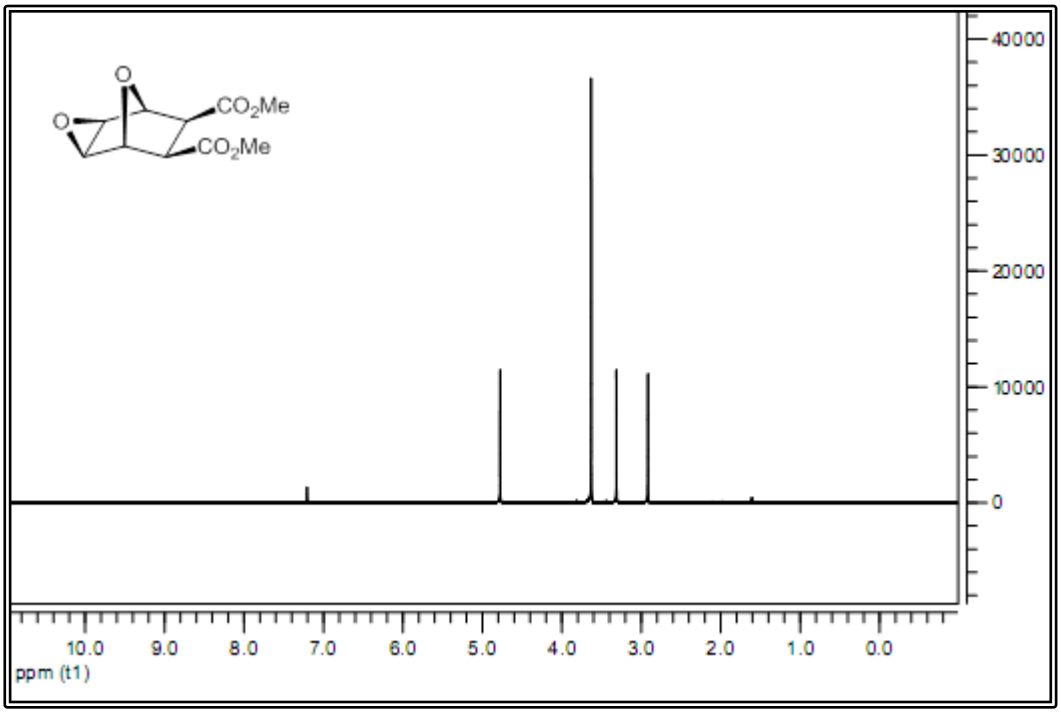

Figure 26 ^{1}H-NMR Spectrum of Compound **122**

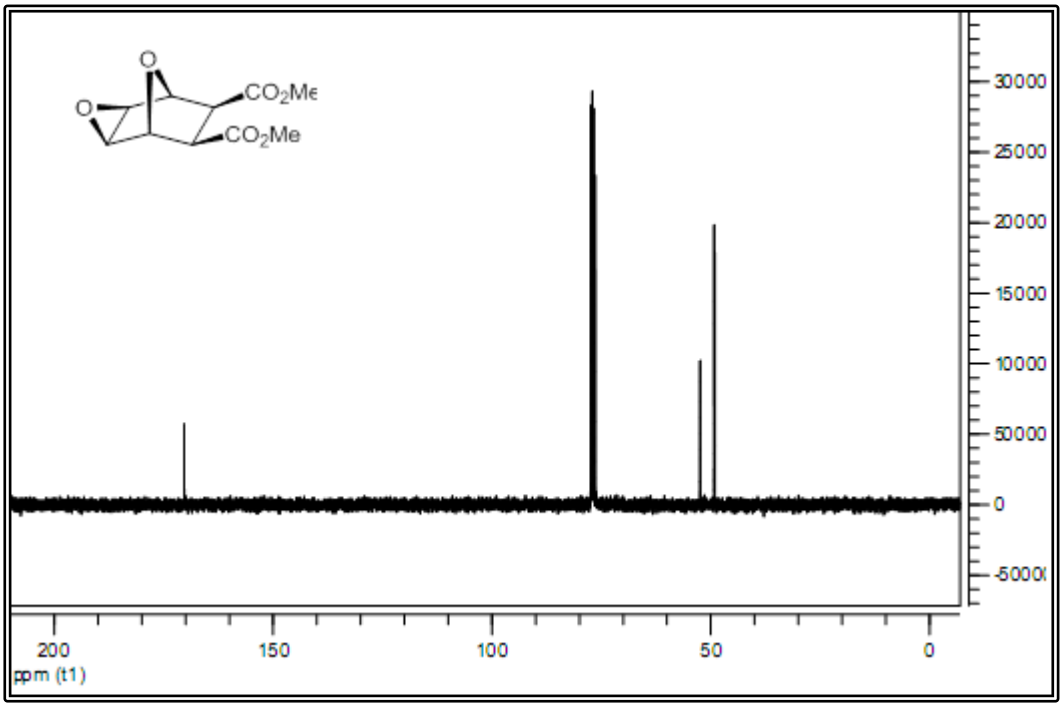

Figure 27 ^{13}C -NMR Spectrum of Compound **122**

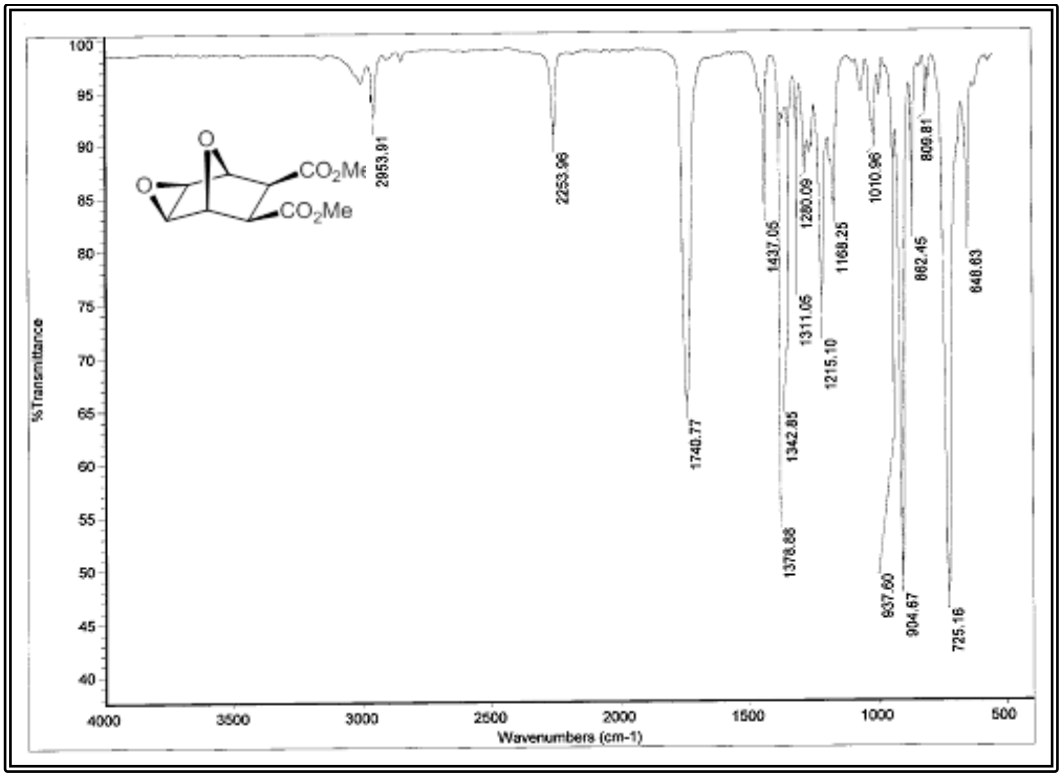

Figure 28 IR Spectrum of Compound **122**

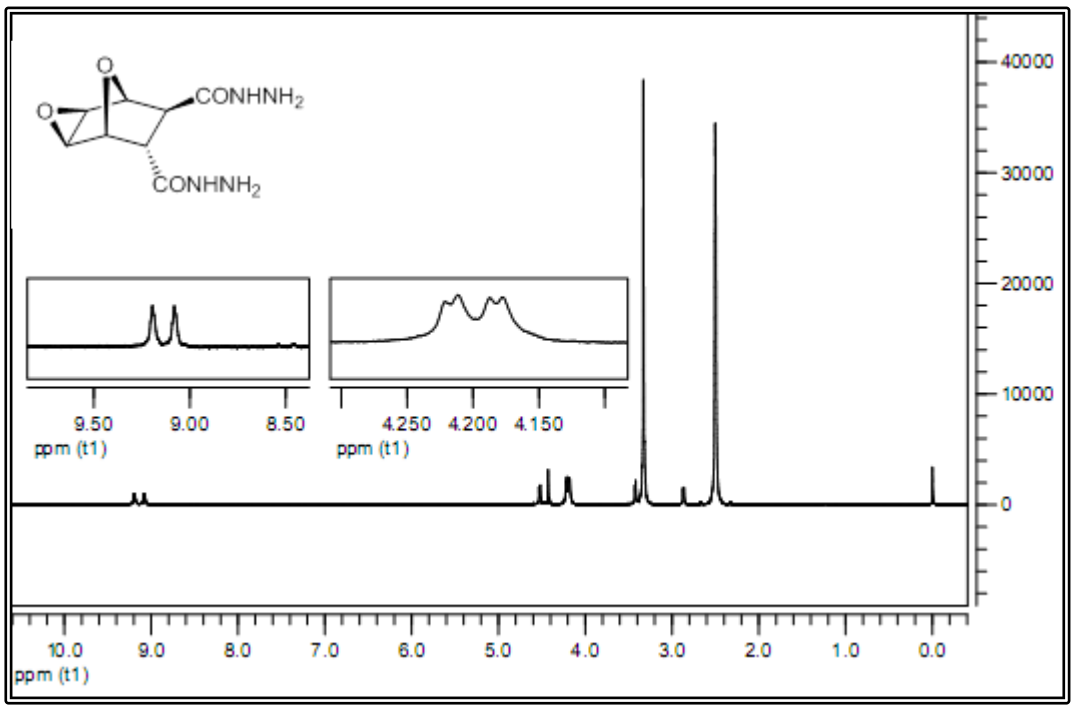

Figure 29 ^{1}H-NMR Spectrum of Compound **103**

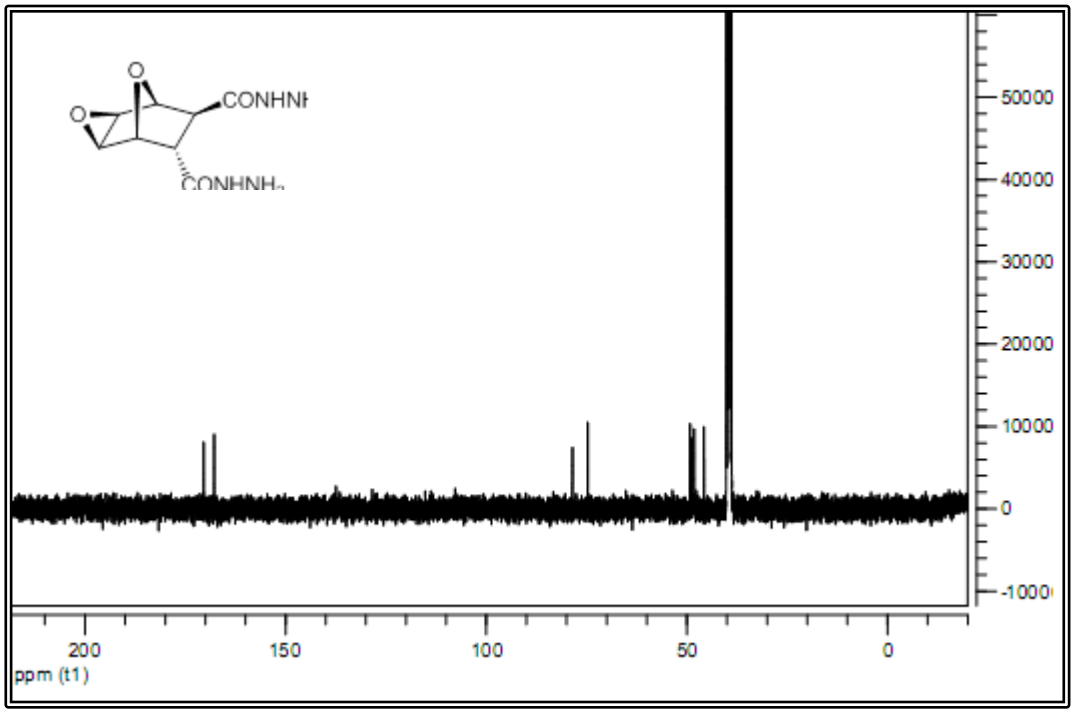

Figure 30 ^{13}C -NMR Spectrum of Compound **103**

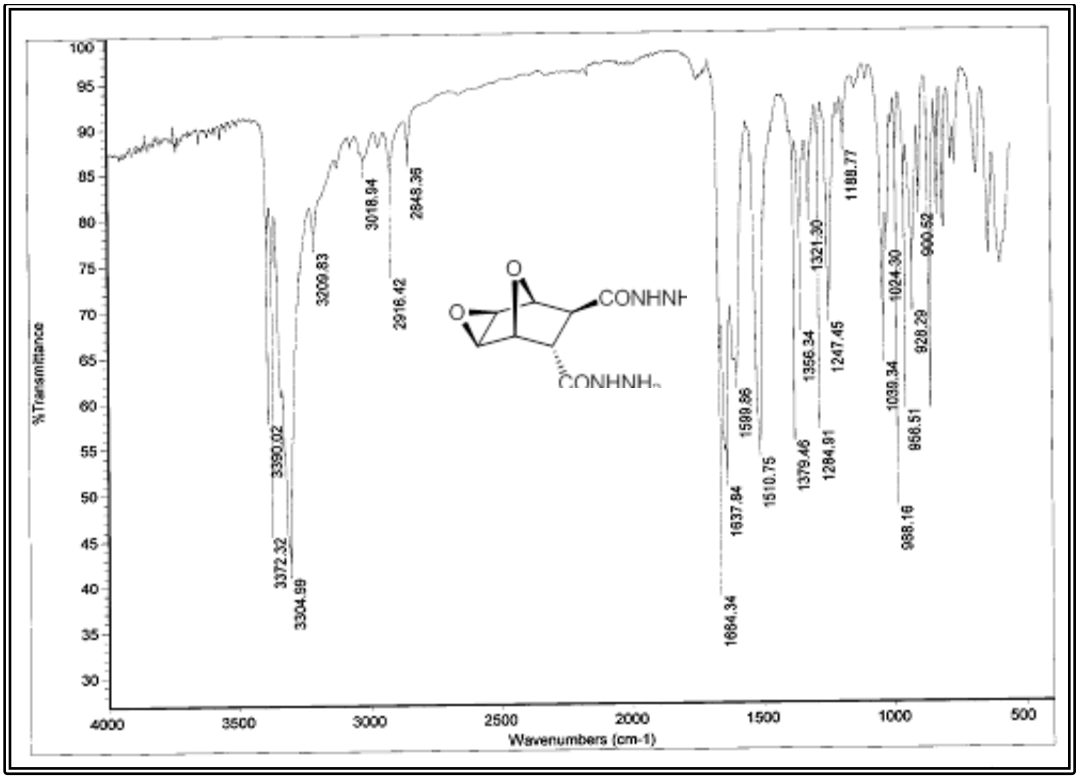

Figure 31 IR Spectrum of Compound **103**

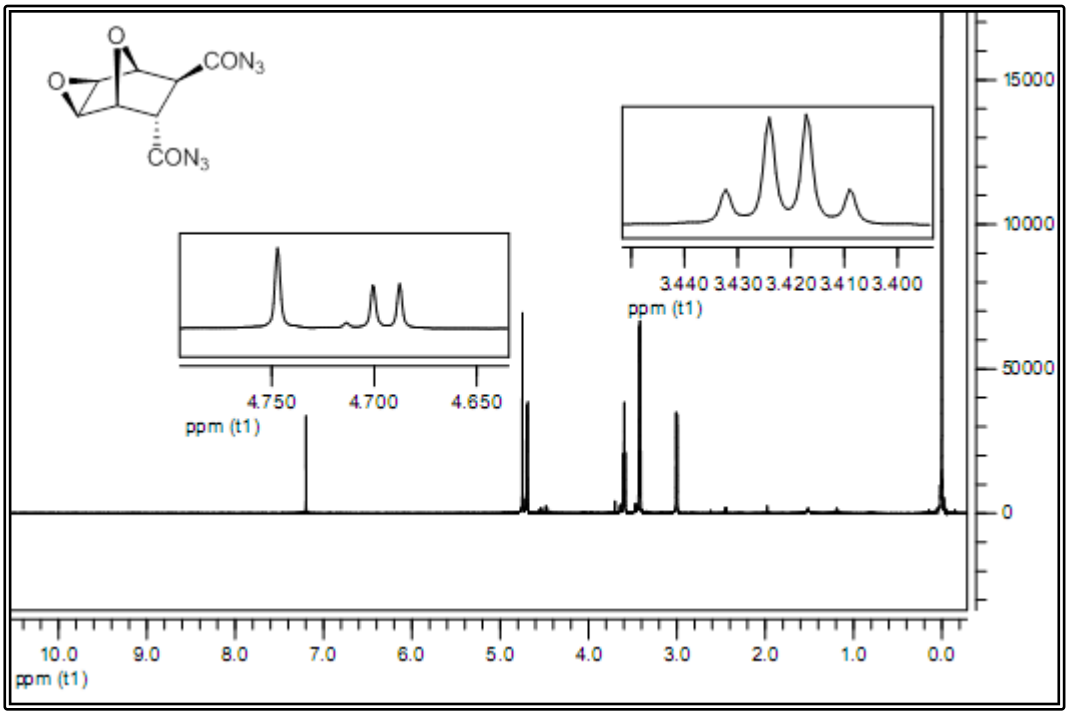

Figure 32 ^{1}H-NMR Spectrum of Compound **138**

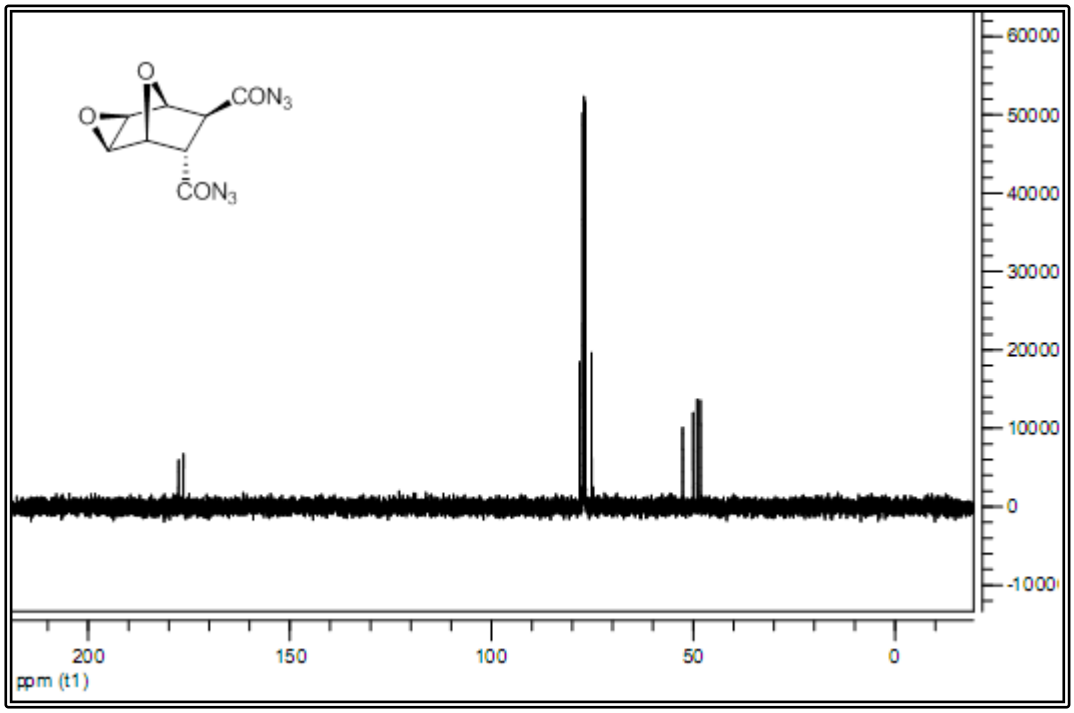

Figure 33 ^{13}C -NMR Spectrum of Compound **138**

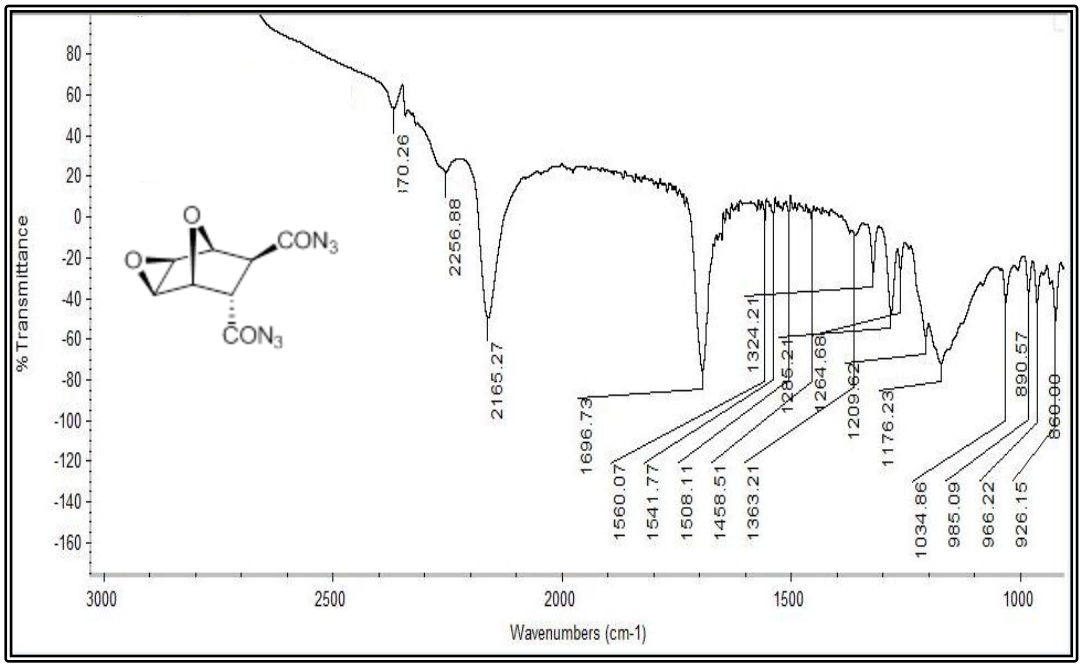

Figure 34 IR Spectrum of Compound **138**

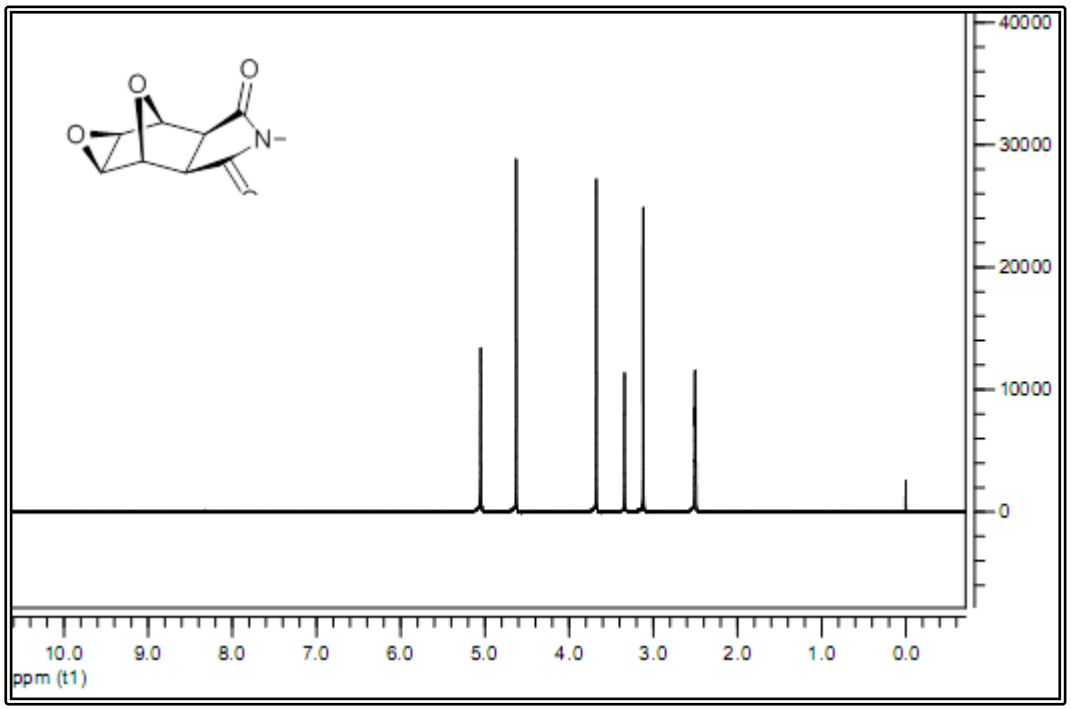

Figure 35 ^{1}H-NMR Spectrum of Compound **126**

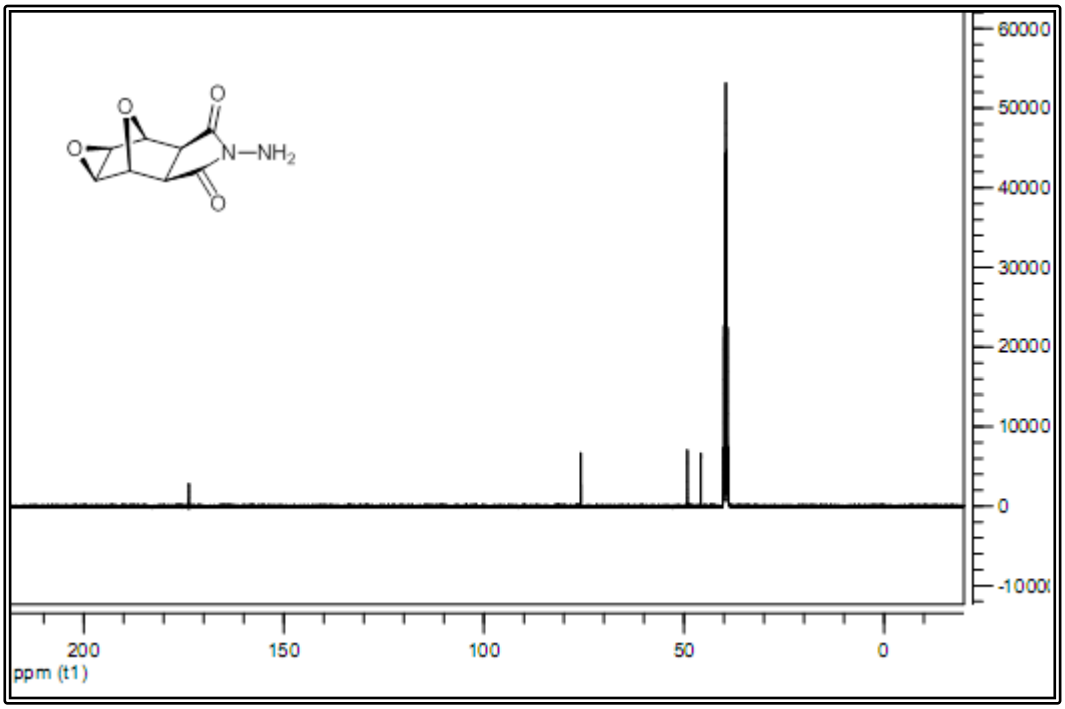

Figure 36 ^{13}C -NMR Spectrum of Compound **126**

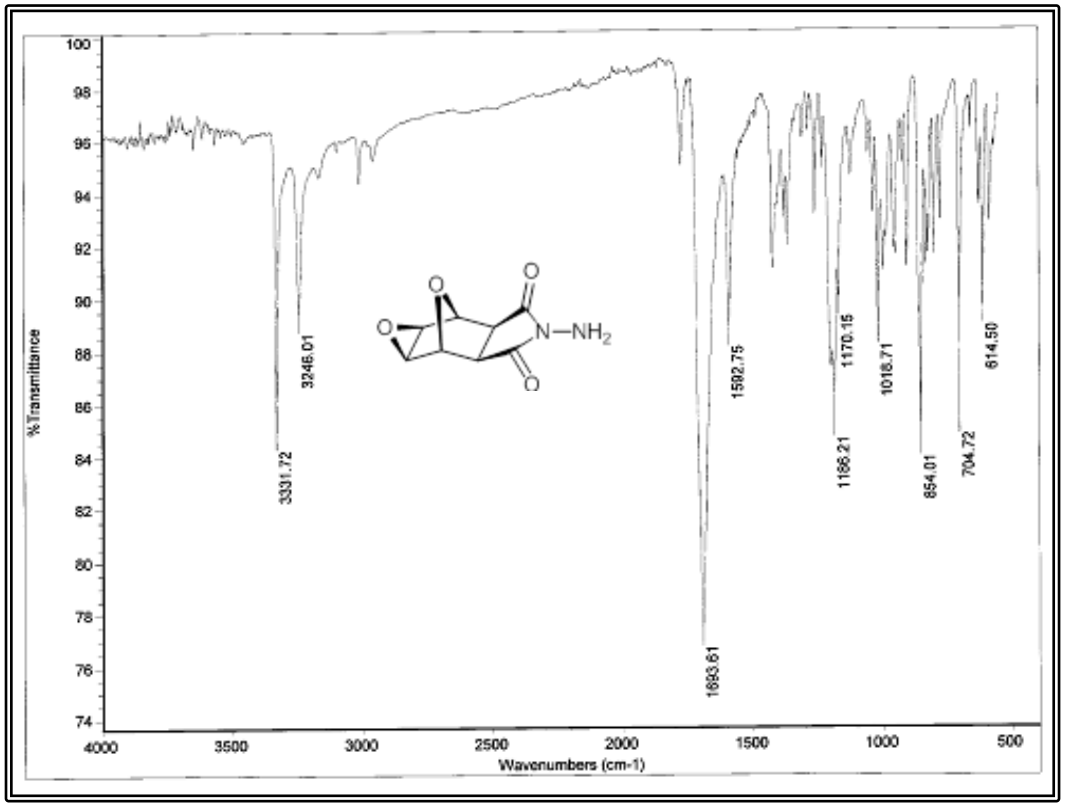

Figure 37 IR Spectrum of Compound **126**

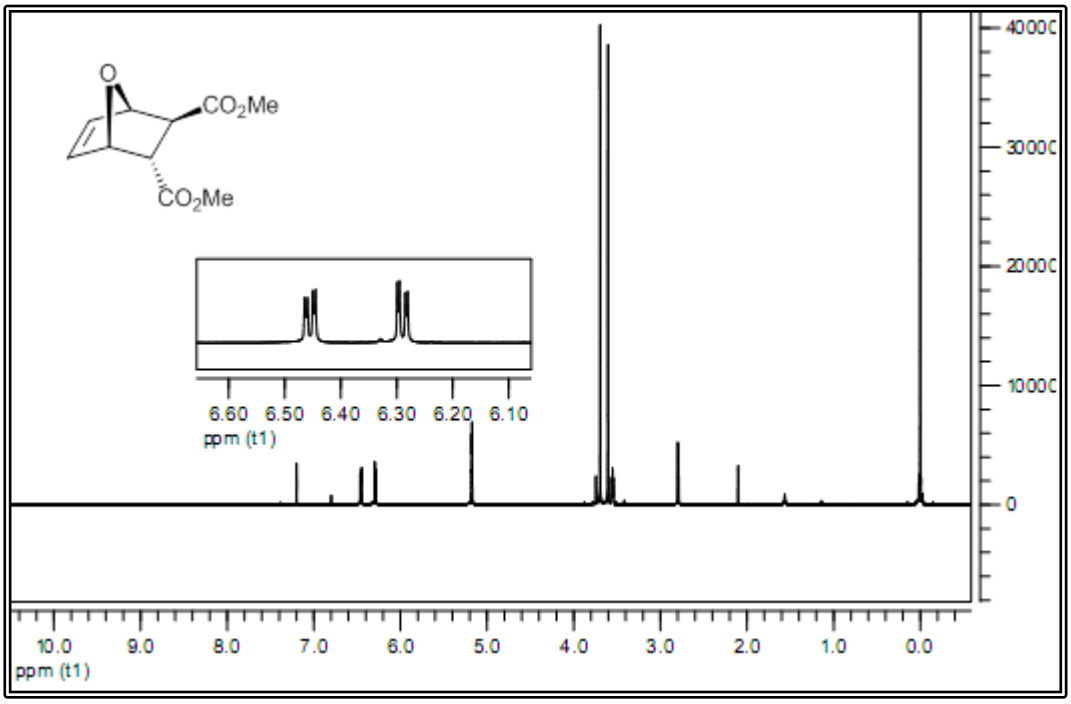

Figure 38 ^{1}H-NMR Spectrum of Compound **102**

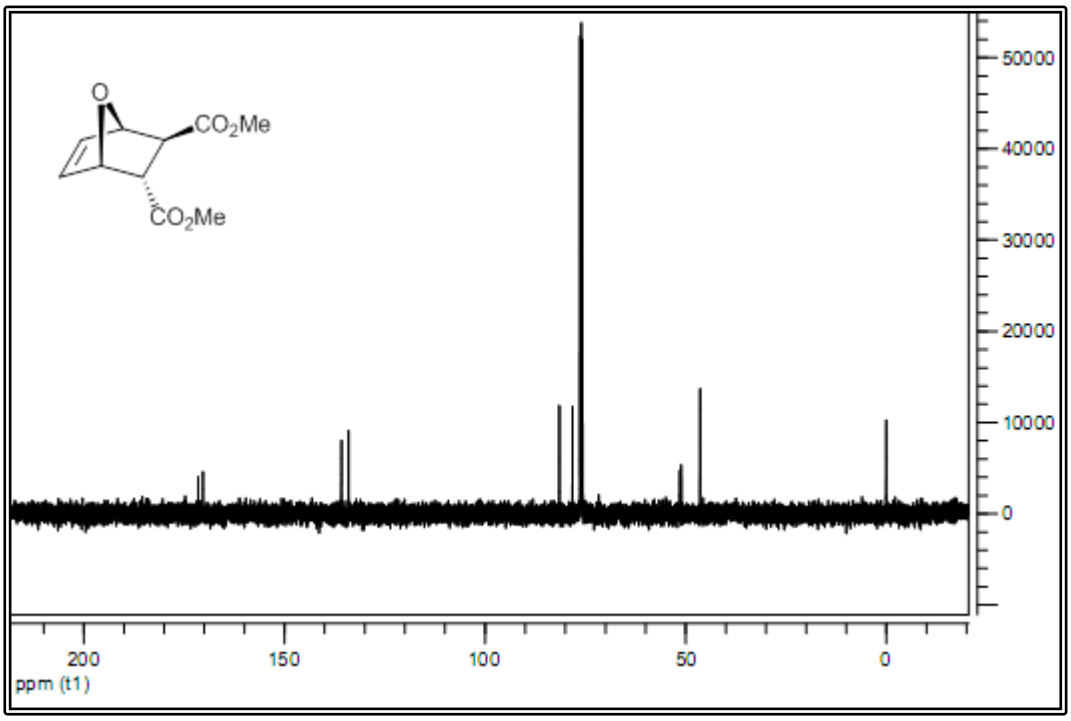

Figure 39 ^{13}C -NMR Spectrum of Compound **102**

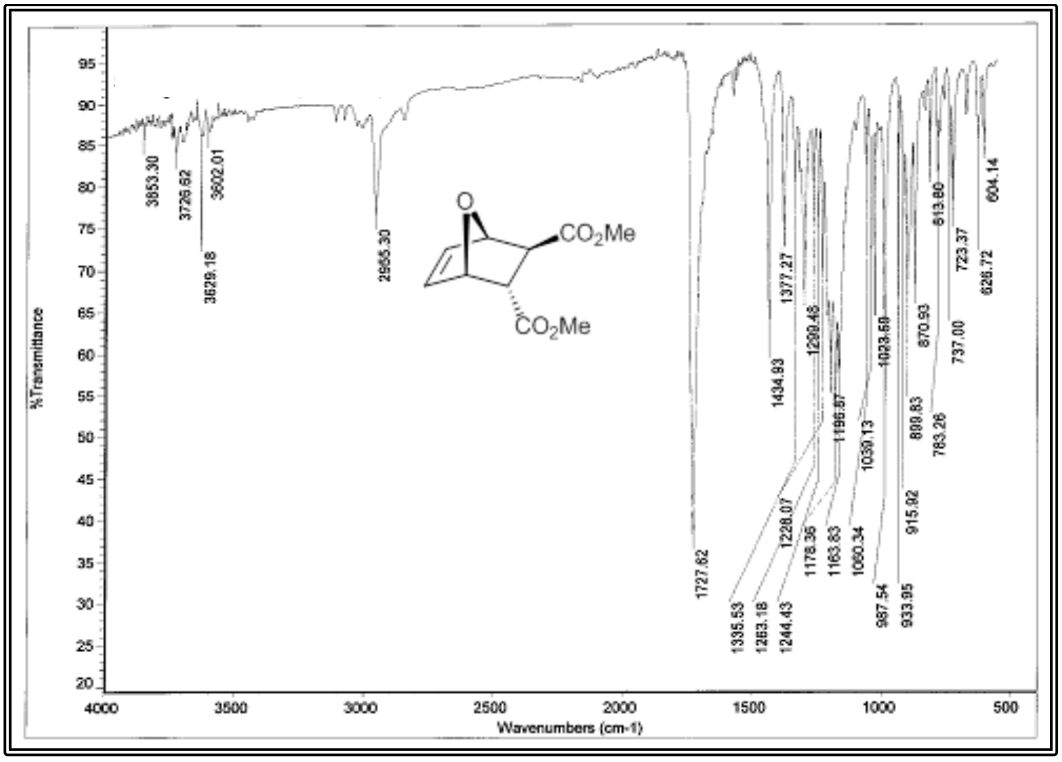

Figure 40 IR Spectrum of Compound **102**

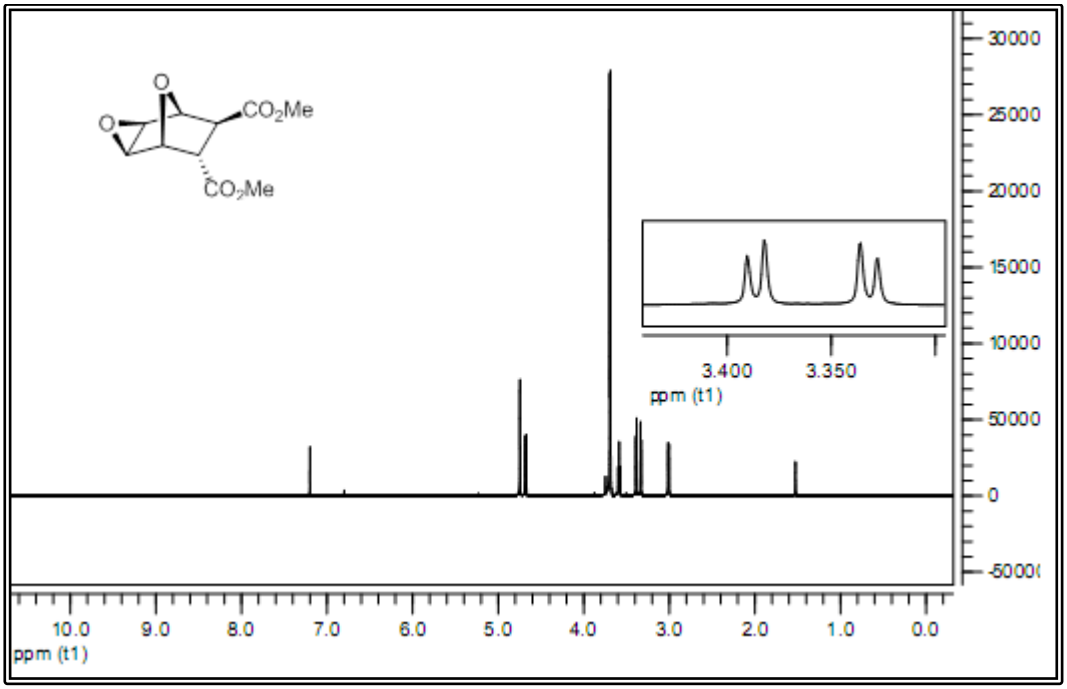

Figure 41 ^{1}H-NMR Spectrum of Compound **132**

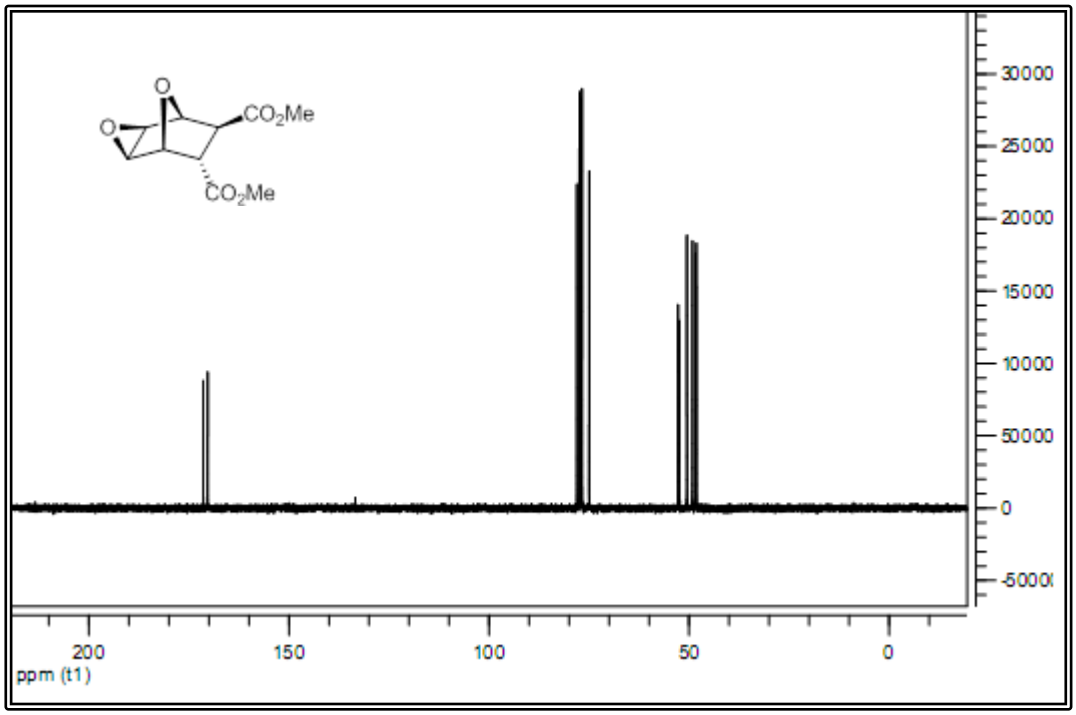

Figure 42 ^{13}C -NMR Spectrum of Compound **132**

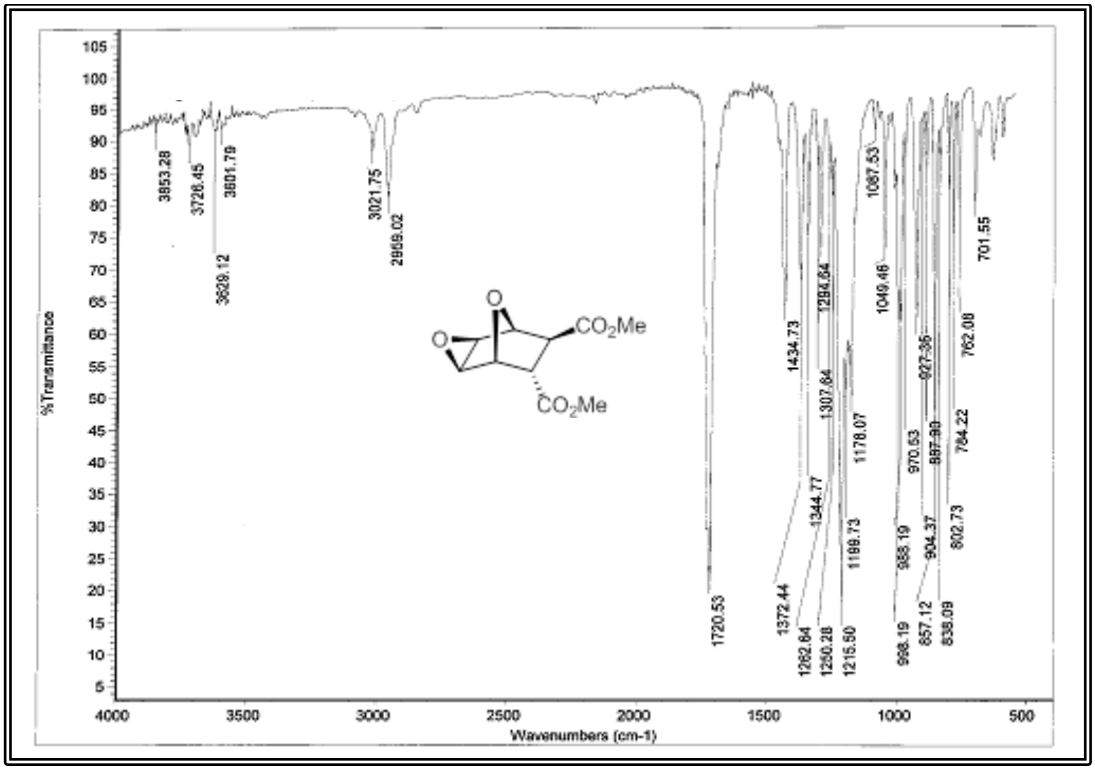

Figure 43 IR Spectrum of Compound **132**

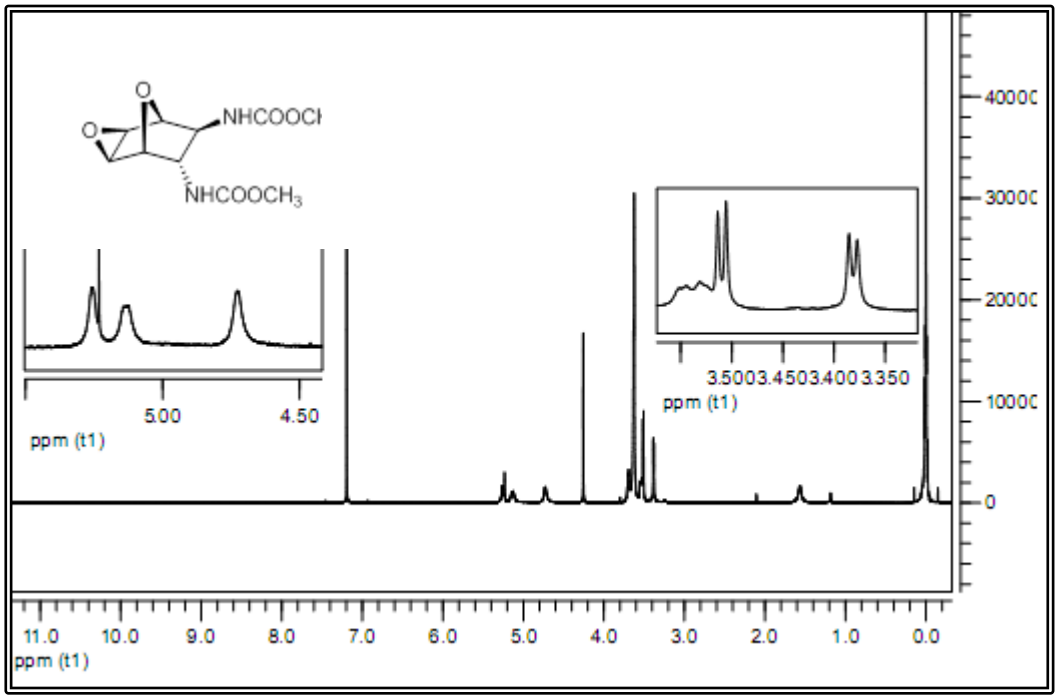

Figure 44 ^{1}H-NMR Spectrum of Compound **143**

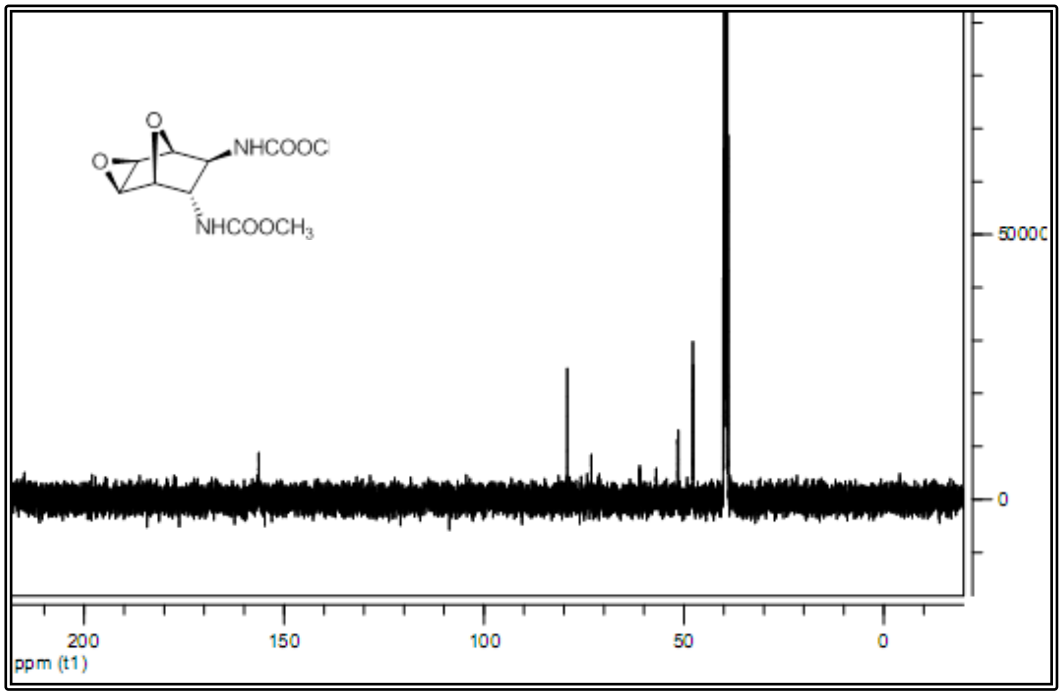

Figure 45 ^{13}C -NMR Spectrum of Compound **143**

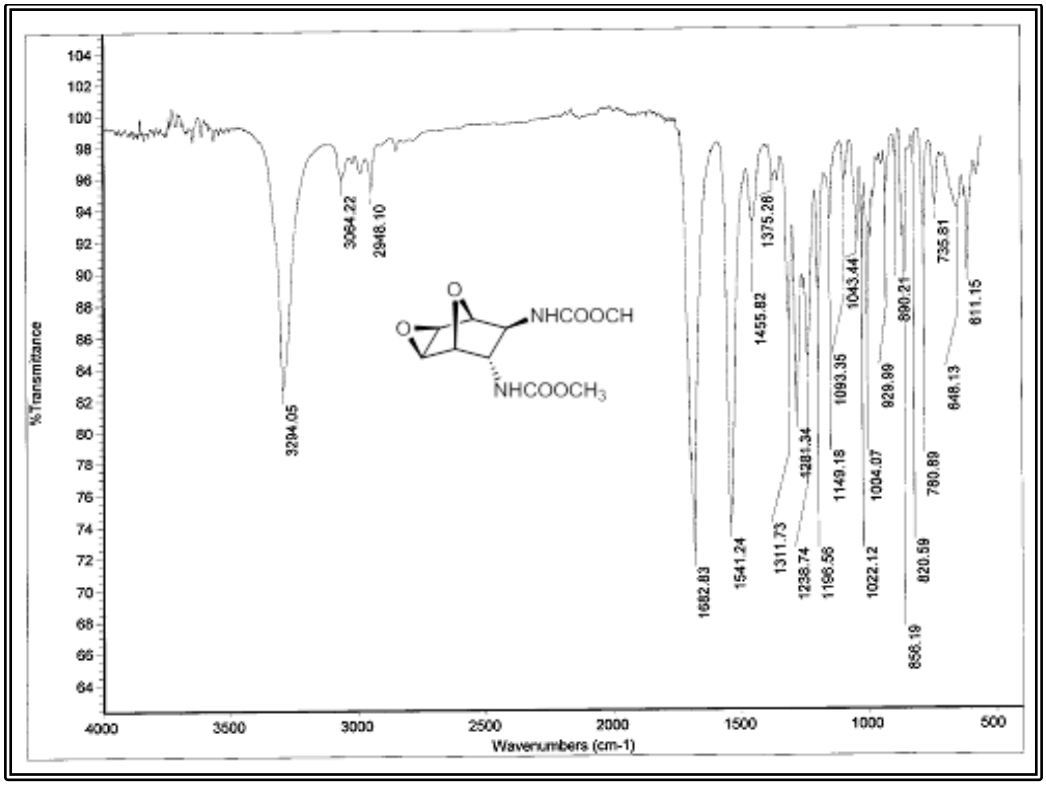

Figure 46 IR Spectrum of Compound **143**

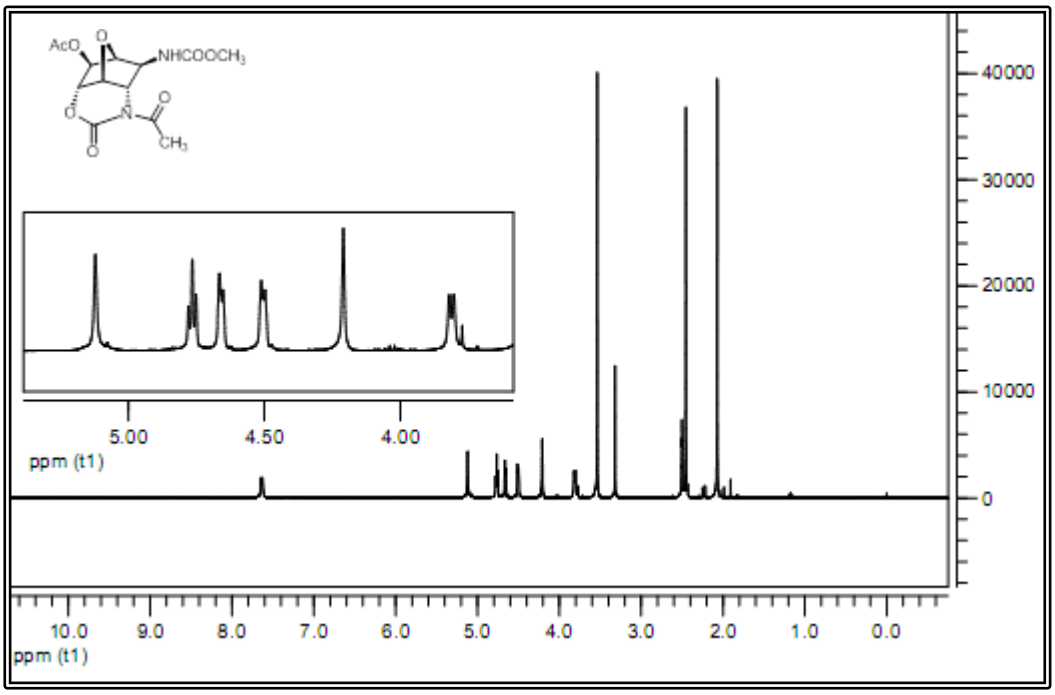

Figure 47 ^{1}H-NMR Spectrum of Compound **148**

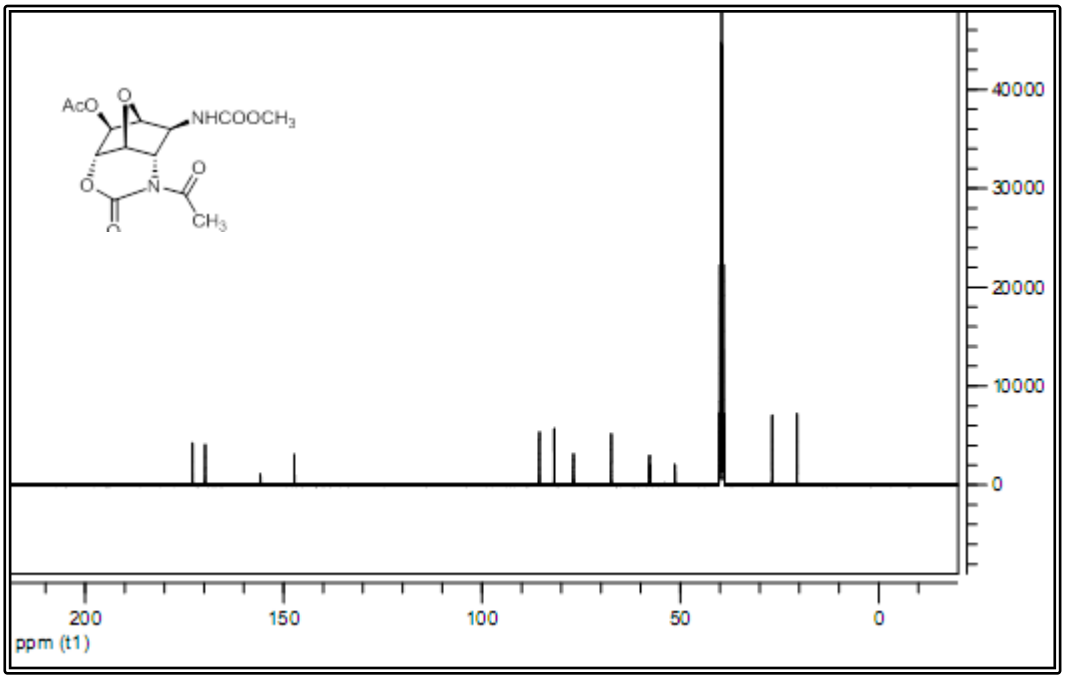

Figure 48 ^{13}C -NMR Spectrum of Compound **148**

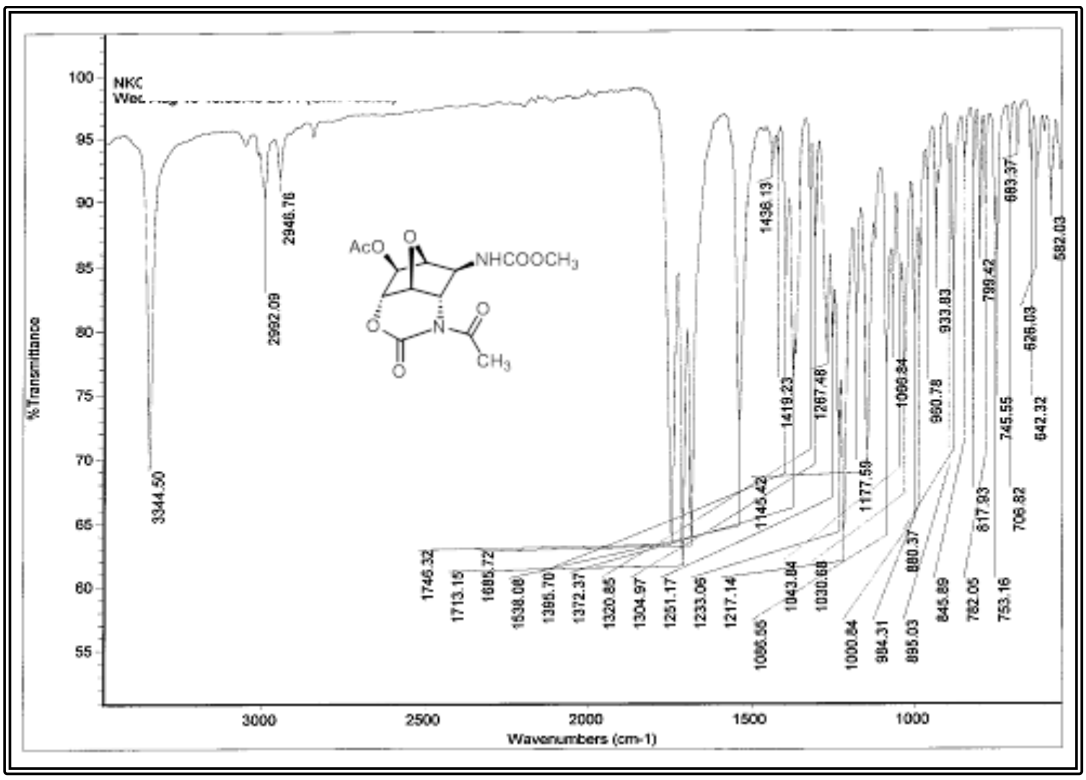

Figure 49 IR Spectrum of Compound **148**

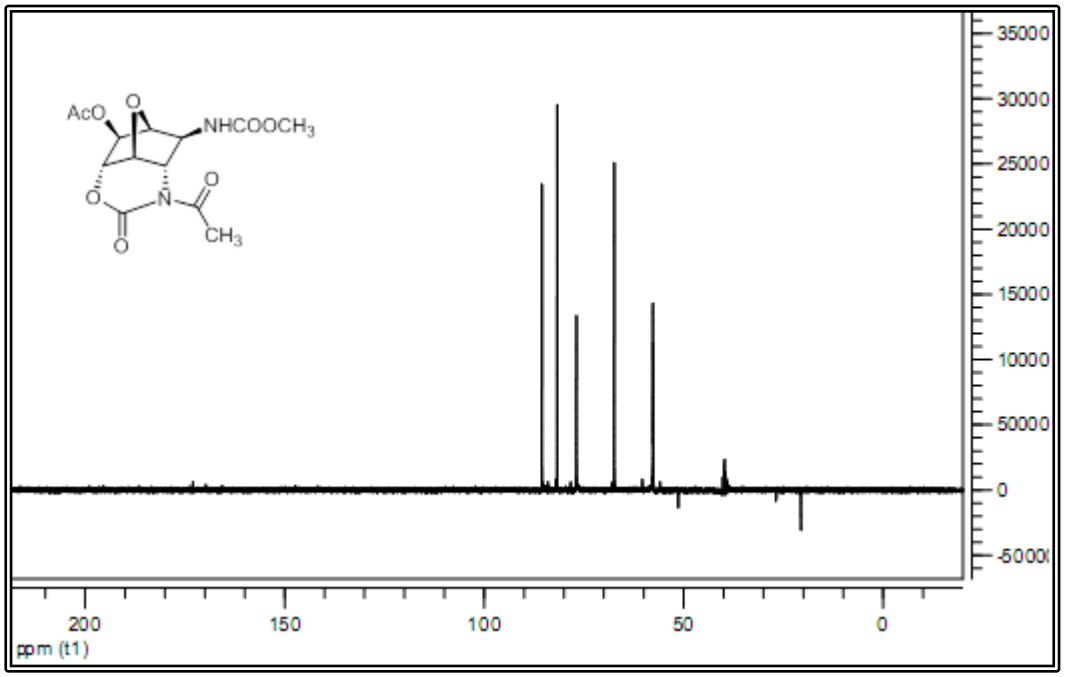

Figure 50 DEPT 90 spectrum of compound **148**

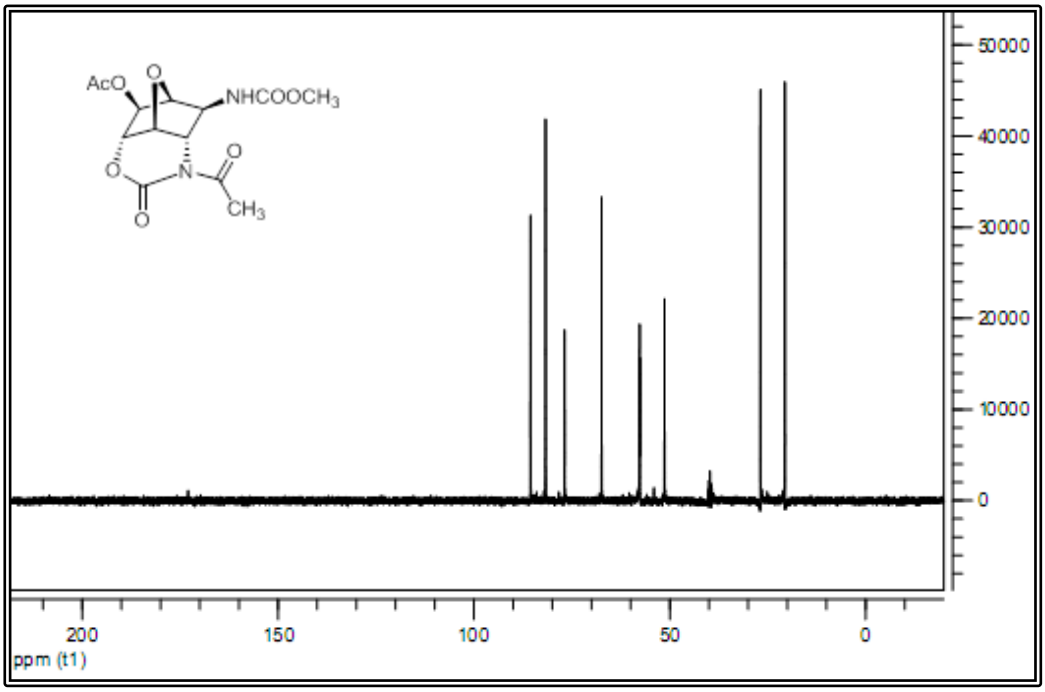

Figure 51 DEPT 135 of compound **148**

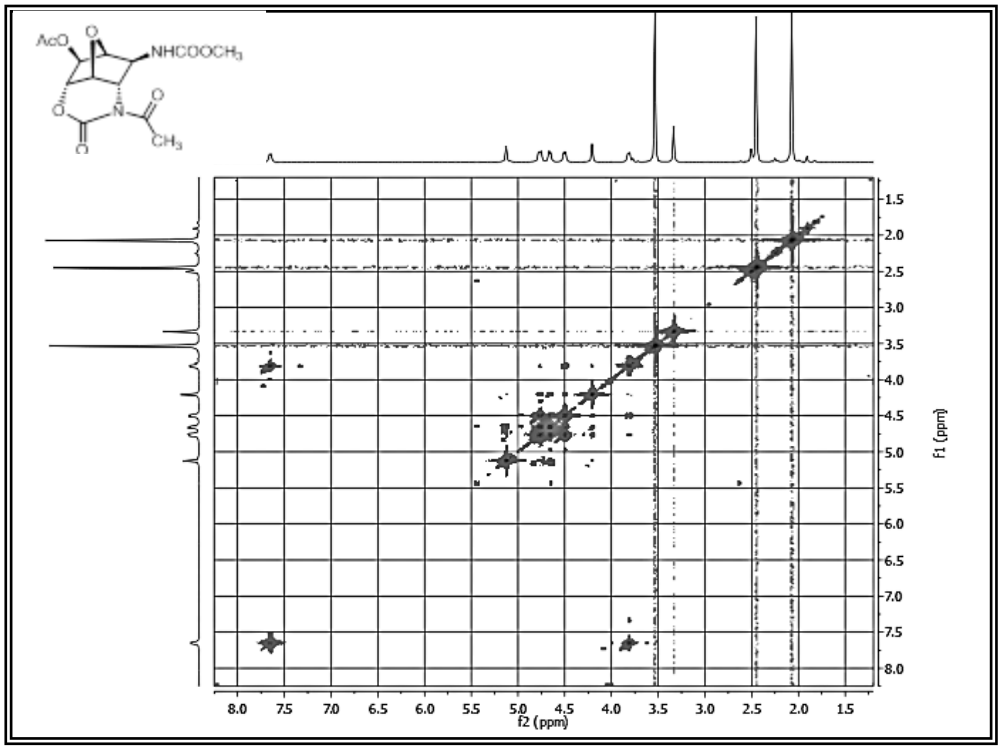

Figure 52 COSY spectrum of compound **148**

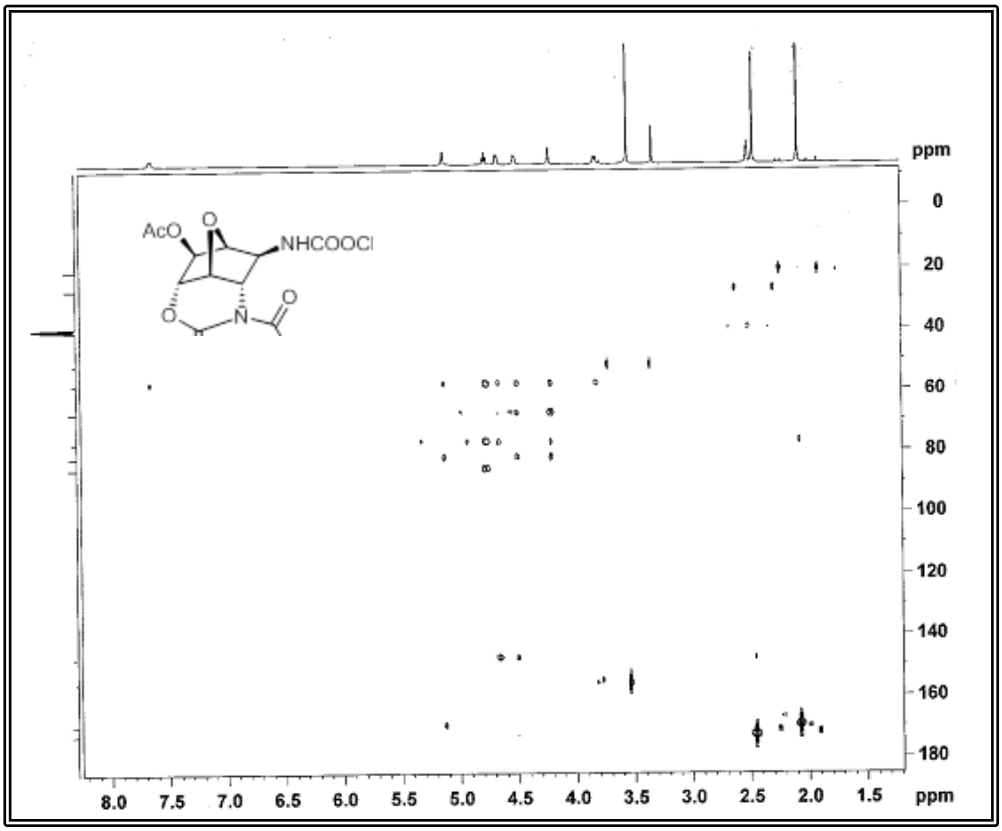

Figure 53 HMBC spectrum of compound **148**

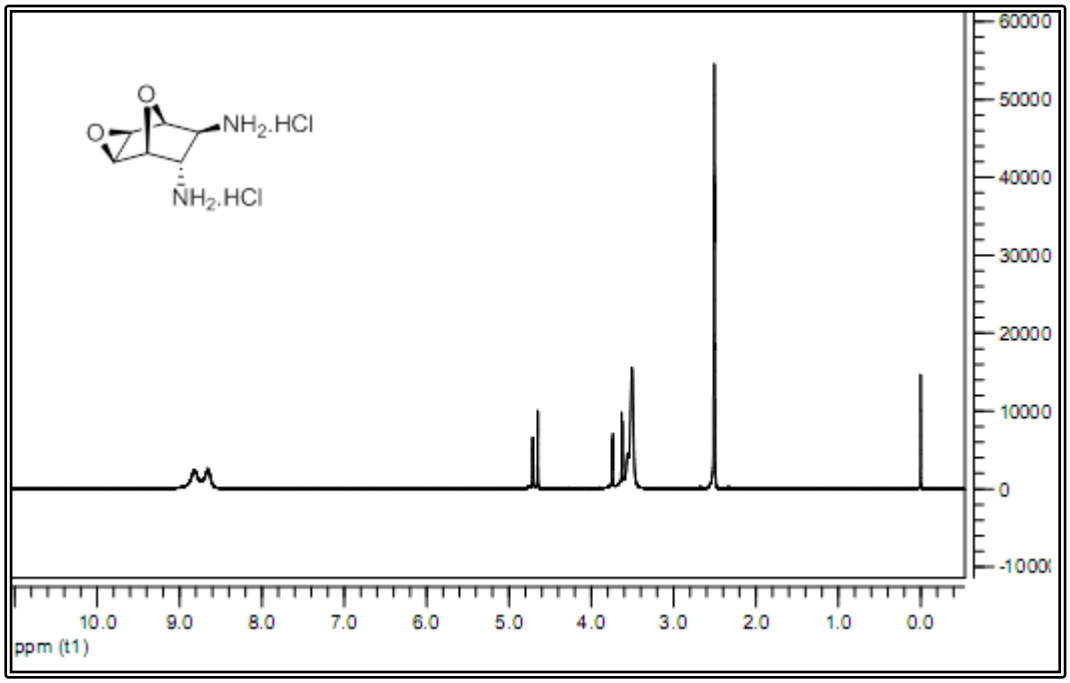

Figure 54 ^{1}H-NMR Spectrum of Compound **155**

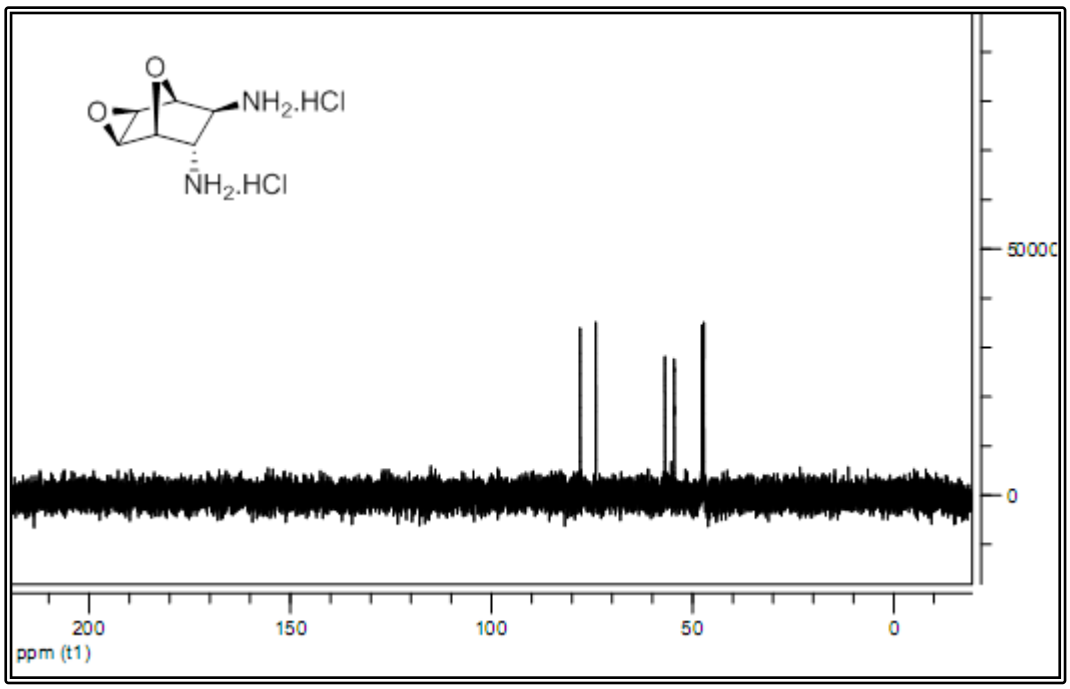

Figure 55 ^{13}C NMR Spectrum of Compound **155**

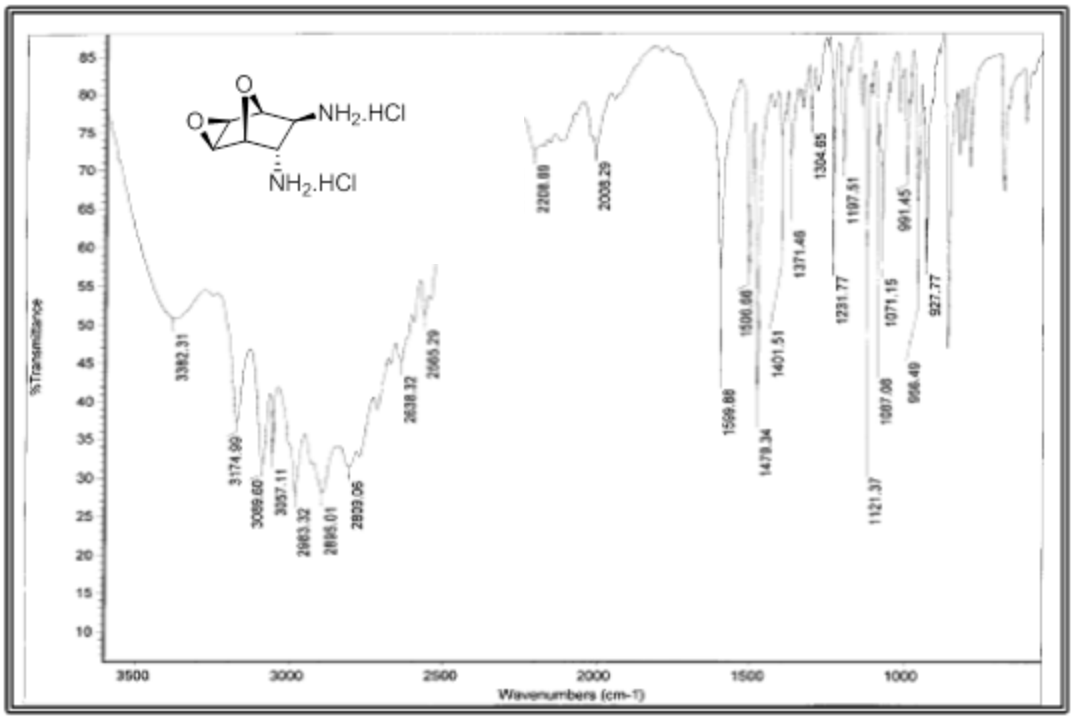

Figure 56 IR Spectrum of Compound **155**

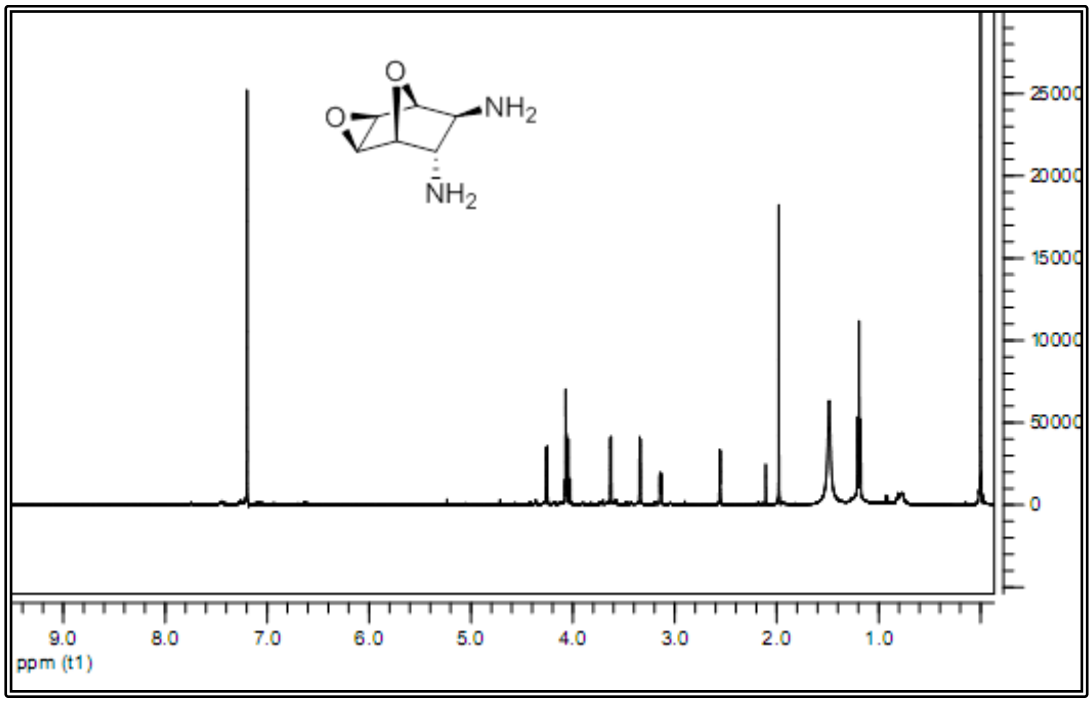

Figure 57 ^{1}H-NMR Spectrum of Compound **156**

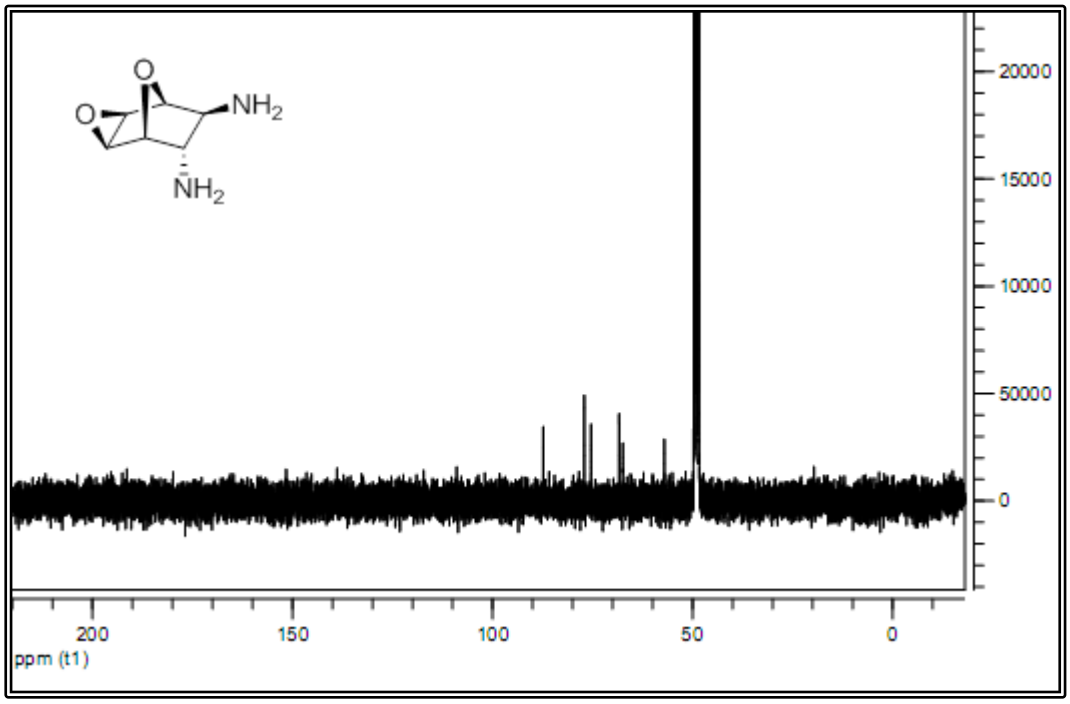

Figure 58 ^{13}C -NMR Spectrum of Compound **156**

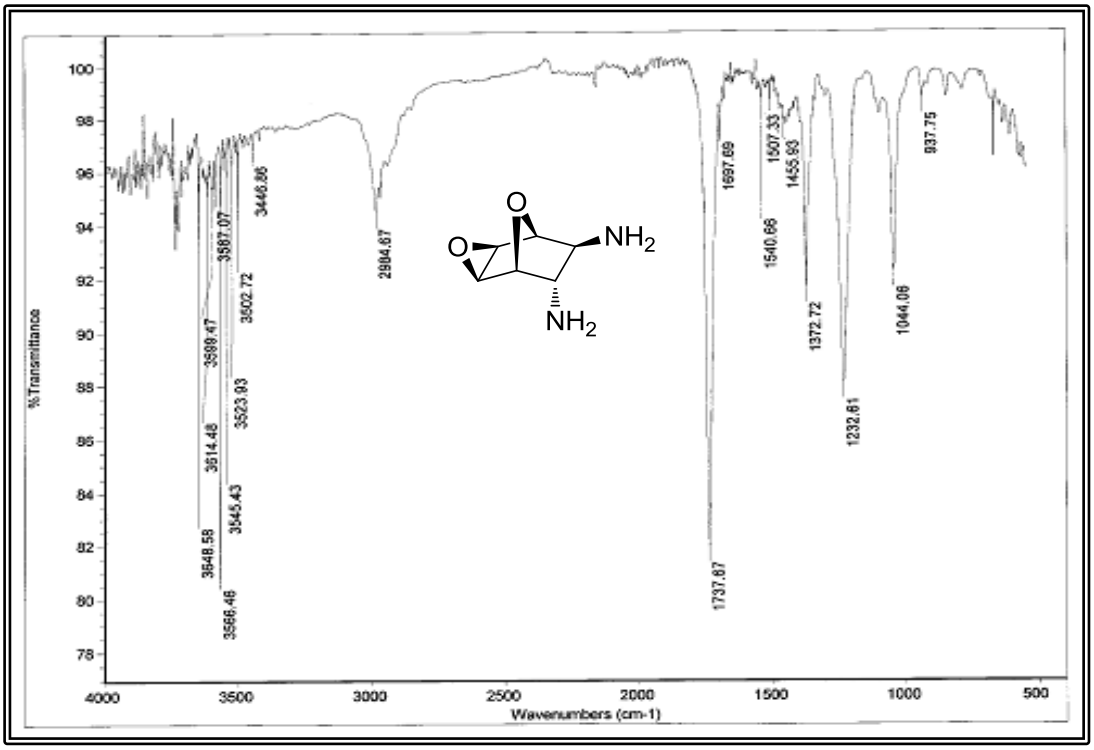

Figure 59 IR Spectrum of Compound **156**

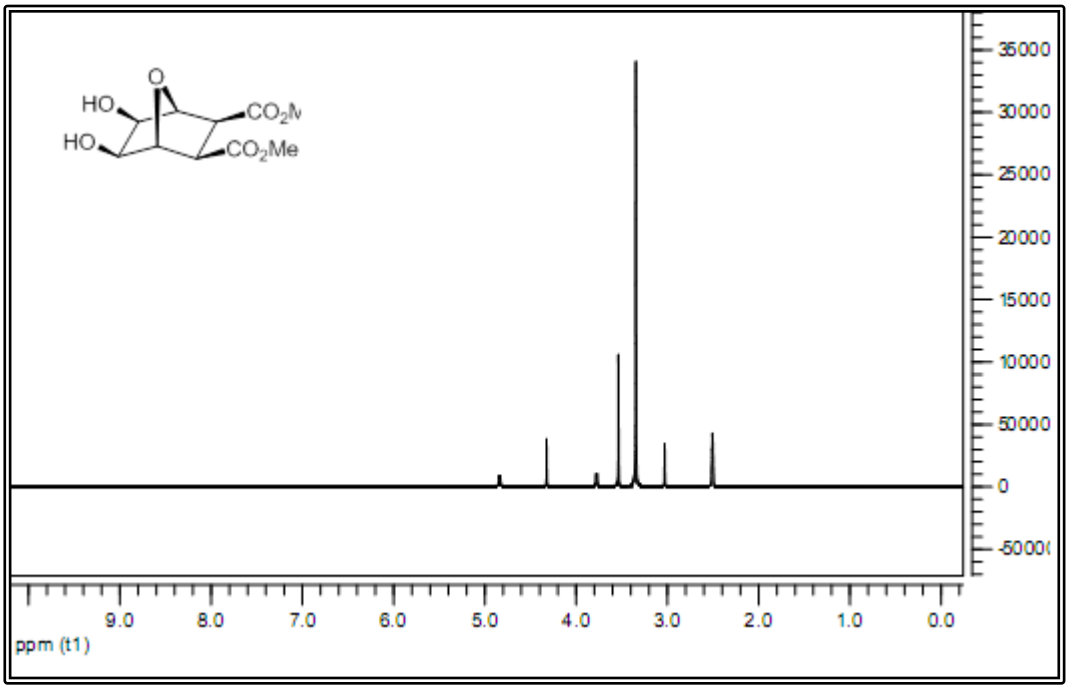

Figure 60 ^{1}H-NMR Spectrum of Compound **157**

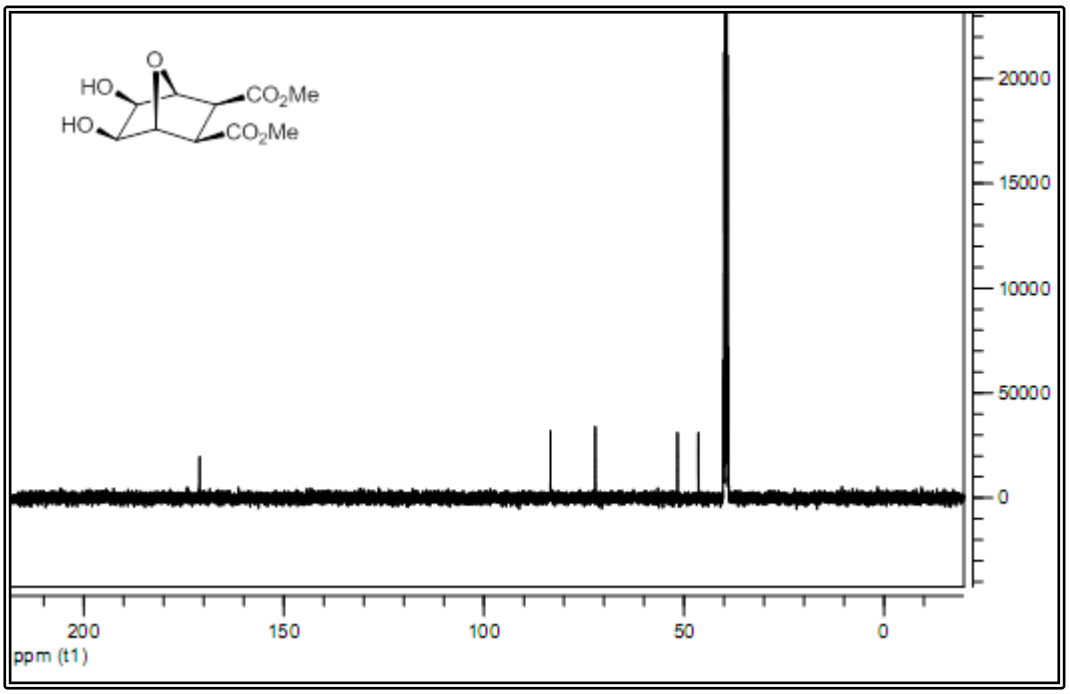

Figure 61 ^{13}C -NMR Spectrum of Compound **157**

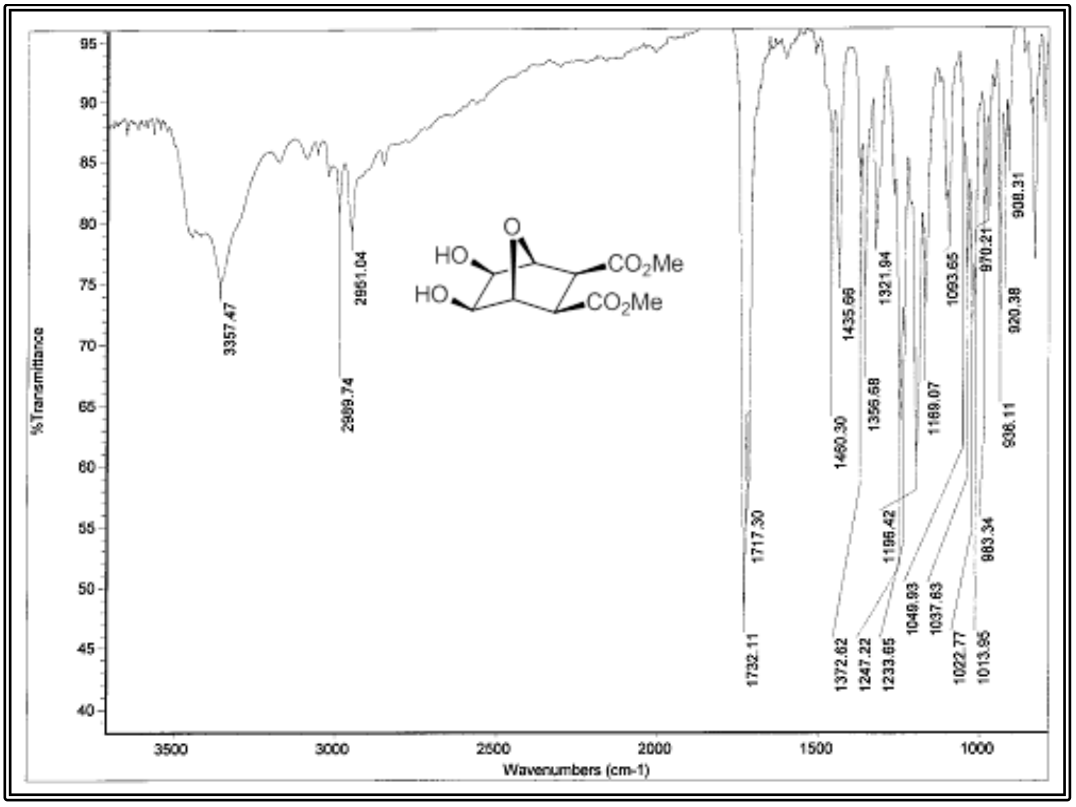

Figure 62 IR Spectrum of Compound **157**