THE SYNTHESIS OF HYDROXYMETHYL CONTAINING CYCLITOL DERIVATIVES

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

BY

NİHAL KAYA

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

SEPTEMBER 2009

Approval of the thesis:

THE SYNTHESIS OF HYDROXYMETHYL CONTAINING CYCLITOL DERIVATIVES

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ABSTRACT

THE SYNTHESIS OF HYDROXYMETHYL CONTAINING CYCLITOL DERIVATIVES

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September 2009, 165 pages

Cyclitols have attracted a great deal of attention in recent years because of diverse biological activities exhibited by them and also synthetic usefulness in the synthesis of other natural compounds or pharmaceuticals. The presence of hydroxymethyl groups in many cyclitols units building natural products is also attracting a remarkable attention. In this study, novel synthetic strategies leading to cyclitol derivatives including hydroxymethyl groups were investigated and the syntheses of bis-homoinositol derivative **127** and hydroxymethyl containing conduritol derivative **137** were achieved successfully.

For the synthesis of bishomo-*chiro*-inositol (**127**), lactone derivative **132** was synthesized as key compound. The molecule was functionalized with the use of photooxygenation and epoxidation reactions to get target stereochemistry.

For the synthesis of hydroxymethyl containing conduritol **137**, hydroxymethyl substituted *p*-benzoquinone derivative **136** was synthesized as a key compound.

Bromination of related double bond, reduction of carbonyl groups and the following substitution of bromine atoms form the basis of our strategy.

As a result we enabled to synthesize novel cyclitol derivatives stereoselectively by using commercially available starting compounds and well known reactions.

Keywords: Cyclitols, Conduritols, Inositols, Hydroxymethyl Containing cyclitols, Photooxygenation.

ÖZ

HİDROKSİMETİL GRUBU İÇEREN SİKLİTOL
TÜREVLERİNİN SENTEZİ

Kaya, Nihal

Doktora, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2009, 165 sayfa

Siklitollerin sentezi, çeşitli biyolojik aktiviteleri ve bazı doğal bileşiklerin ve ilaçların sentezinde kullanılabilir olmaları nedeniyle son yıllarda oldukça ilgi konusu olmuştur. Ayrıca doğal ürünleri oluşturan siklitollerin birçoğunda hidroksimetil gruplarının bulunması dikkate değer bir ilgi çekmektedir. Bu çalışmada hidroksimetil grubu içeren siklitol türevlerine ulaşabilmek için yeni sentetik yöntemler denenmiş ve bis-homoinositol türevi **127** ve hidroksimetil sübstitüe konduritol türevi **137** başarıyla sentezlenmiştir.

Bishomo-*chiro*-inositolün (**127**) sentezi için lakton türevi **132,** anahtar bileşik olarak sentezlenmiştir. Molekül, hedef stereokimyayı elde edebilmek için fotooksijenasyon ve epoksitleme reaksiyonlarının kullanılmasıyla fonksiyonelleştirilmiştir.

Hidroksimetil grubu içeren konduritol **137**'nin sentezi için hidroksimetil sübstitüe *p*-benzokinon türevi **136**, anahtar bileşik olarak sentezlenmiştir. İlgili

çift bağın brominasyonu, karbonil gruplarının indirgenmesi ve brom atomlarının müteakip sübstitüsyonu stratejimizin temelini oluşturmuştur.

Sonuç olarak ticari olarak bulunabilen başlangıç maddelerini ve iyi bilinen reaksiyonları kullanarak yeni siklitol türevlerini stereoseçici olarak sentezlemeyi başardık.

Anahtar Kelimeler: Siklitoller, Konduritoller, İnositoller, Hidroksimetil Grubu İçeren Siklitoller, Fotooksijenasyon.

To my dear family

ACKNOWLEDGMENTS

I would like to express my feelings of gratitude to my supervisor Prof. Dr. Metin Balcı for his skillful guidance, endless patience, encouragement and support throughout this study. It was a great pleasure for me to be a student of him.

I owe my thanks to Fatoş Polat Doğanel, Seda Karayılan, Zehra Uzunoğlu for their extraordinary work for my NMR spectra.

I would like to express my thanks to my lab-mates, so called SYNTHOR group. I am grateful to Dilem, Yasemin, Raşit and Benan for their friendship.

I also thank to The Scientific and Technological Research Council of Turkey (TÜBİTAK) for the doctoral scholarship.

My mother and my father… Thank you very much for tolerating and supporting me in anything I want to do. I also thank to Sinan for hardware support.

Lastly but mostly, my thanks are devoted to Deniz and Yağmur Utku for their endless moral support, encouragement and for sharing a life with me.

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LIST OF ABBREVIATIONS

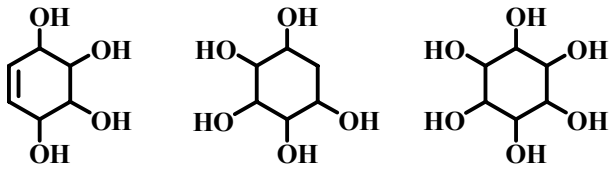
^{o}C	degrees Celsius
CAN	ceric ammonium nitrate
COSY	correlation Spectroscopy
δ	chemical shift in parts per million
DEPT	distortionless enhancement by polarization transfer
d	doublet
dd	doublet of doublets
FT	Fourier transform
HETCOR	heteronuclear correlation spectroscopy
HMBC	heteronuclear multi bond correlation
HMQC	heteronuclear multi quantum correlation
HOMO	highest occupied molecular orbital
Hz	hertz
LUMO	lowest unoccupied molecular orbital
IR	infrared
J	coupling constant
m	multiplet
m-CPBA	m-chloroperoxybenzoic acid
NMR	nuclear magnetic resonance
ppm	parts per million
q	quartet
s	singlet
t	triplet
TMS	Tetramethylsilane
TPP	Tetraphenlyporphyne

CHAPTER 1

INTRODUCTION

1.1 CYCLITOLS

Cyclitols is the general name used for the polyhydroxycycloalkanes. The unsaturated derivatives of these ring systems, as well as compounds related to them by O-substitution, by C-substitution, and in some cases by replacement of hydroxyl groups with other substituents, are also included in this general class [1]. Among these the most common cyclitols are conduritols (**1**), quercitols (**2**), and inositols (**3**).



1 **2** **3**

1.2 CONDURITOLS

Conduritols (**1**), 1,2,3,4-tetrahydroxycyclohexenes, represent a very important class of cyclitols due to their biological properties and synthetic roles as starting materials in the preparation of bioactive molecules, such as glycosidase inhibitors [2]. A number of conduritols and their derivatives have been found to possess antibiotic, antileukemic, and tumor-inhibitory properties [3].

Conduritol was firstly isolated as a new alcohol from the bark of the vine *Marsdenia condurango* by Kübler in 1908. The structure and configuration of this compound were established 30 years later by Dangschat and Fischer. There are six possible diastereomers of conduritol and they have been labelled A, B, C, D, E, and F assigned in the order of their discovery (Fig. 1).

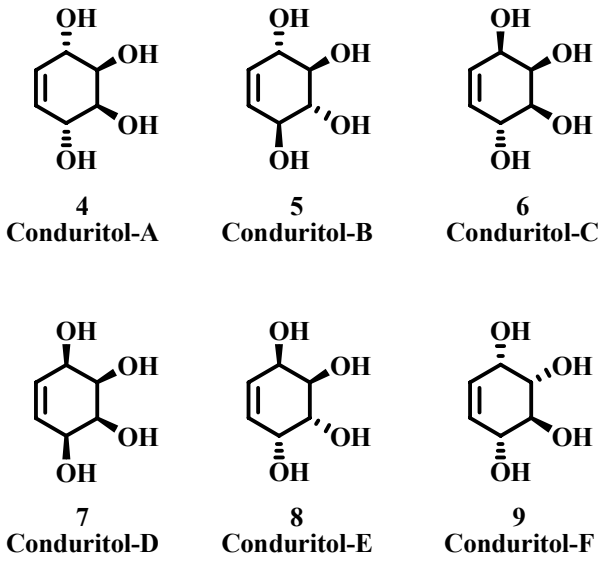


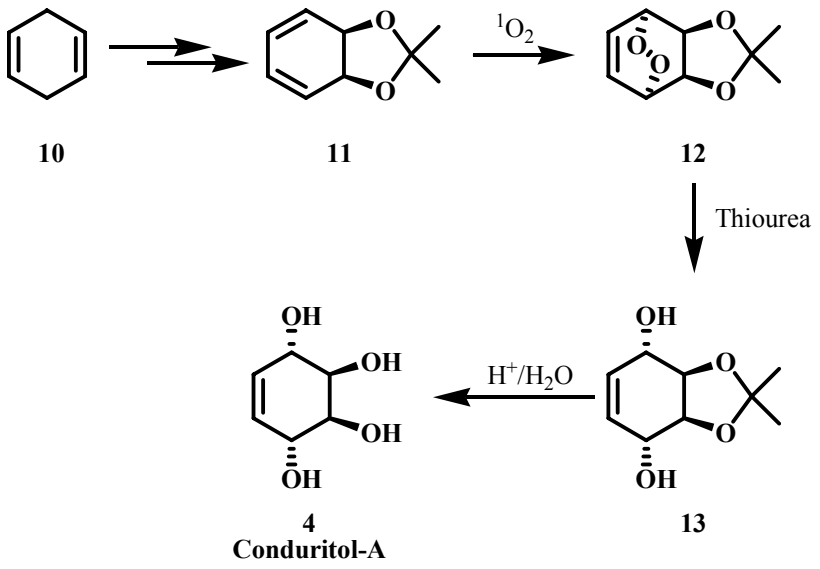
Figure 1. Conduritol diastereomers

Conduritols A and D are symmetrical; the others exist as four enantiomeric pairs. In nature, the occurrence of only conduritols A and F has been established [4a,b]. Because stereoselectivity plays a crucial role in the chemical recognition of molecules participating in the regulation of the biological process, to have access to these cyclitols in enantiopure forms is particularly attractive and of synthetic interest [2].

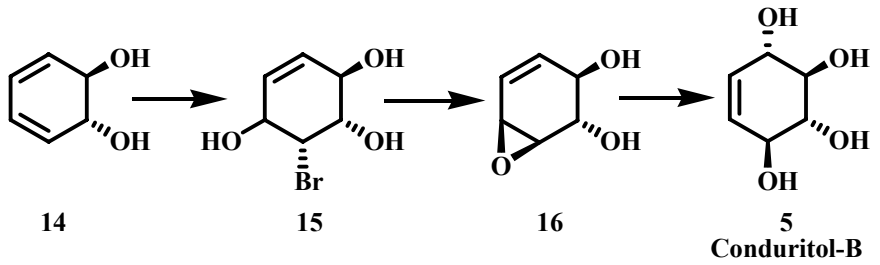
All the possible conduritol isomers have been synthesized and their biological importance has been studied. The first successful and non-stereospecific synthesis of conduritol-A (**4**) was carried out by Nakajima *et al.* starting from

trans-benzenediol [4]. Twenty-five years later Knapp *et al.* described the first stereospecific synthesis of conduritol-A from p-benzoquinone in a multistep sequence [5].

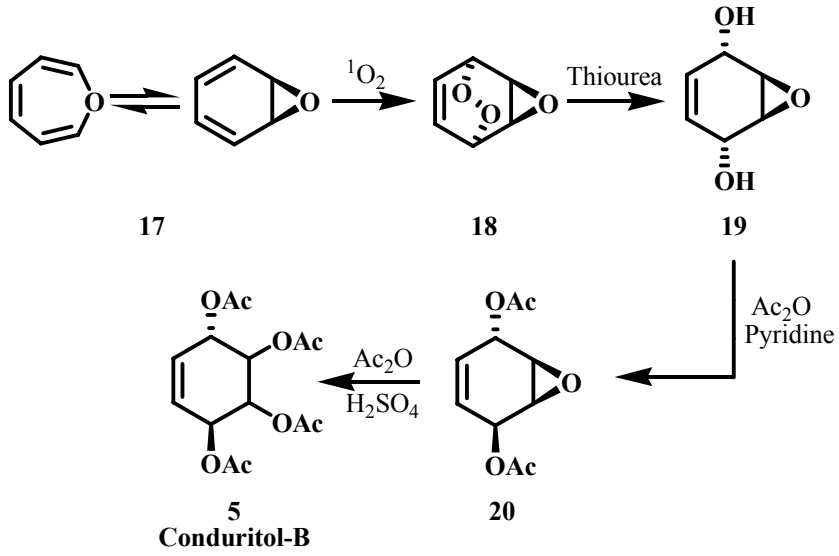
Balcı *et al.* described an efficient and stereospecific synthesis of conduritol-A (**4**) starting from readily available cyclohexa-1,4-diene (**10**). Their synthetic strategy was based on the introduction of two oxygen functionalities at the C_2 and C_3 positions by $KMnO_4$ oxidation and the other two oxygen functionalities at the C_1 and C_4 positions by photooxygenation [6].



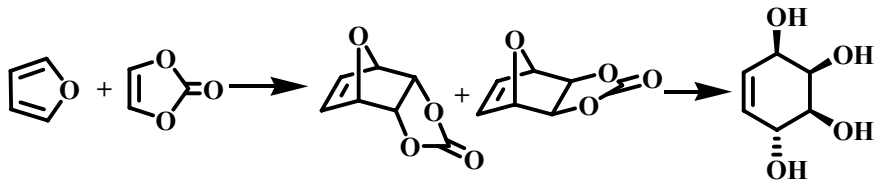
Berchtold [7] developed an efficient synthetic pathway for conduritol-B (**5**) starting from trans-benzenediol (**14**) which gave bromide **15** with NBS in aqueous THF. Dehydrobromination of **15** gave **16**, and solvolysis of it, in water, provided conduritol-B (**5**).



Also Balcı *et al*. provided the formation of conduritol-B (**5**) with the acid-catalyzed epoxide ring-opening reaction in acetic anhydride beside the formation of conduritol-F (**9**) in the ratio of 1:2 starting from oxepine-benzenoxide (**17**) [3,8]. The formation of conduritol-B has an explanation on the basis of involving of the neighboring acetoxy group in the process of the epoxide ring- opening.

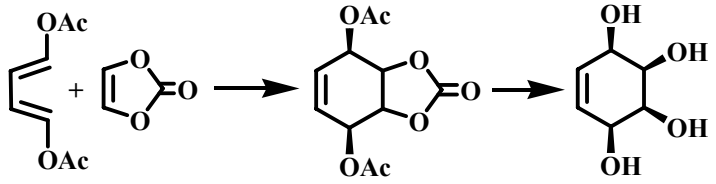


Conduritol-C (**6**) was synthesized starting from trans-benzenediol (**14**) and cis-benzenediol by Nakajima [4a] and Berchtold [7] respectively. Yurev and Zefirov have developed a short and stereospecific synthesis of conduritol-C (**6**). [4+2] cycloaddition of furan (**21**) and ethylene carbonate (**22**) gave *endo*- and *exo*-adduct mixture **23** and **24**. This mixture was hydrolyzed under acidic conditions followed by basic cleavage of carbonate to form conduritol-C (**6**) [4a].



21 **22** **23** **24** **6**
Conduritol-C

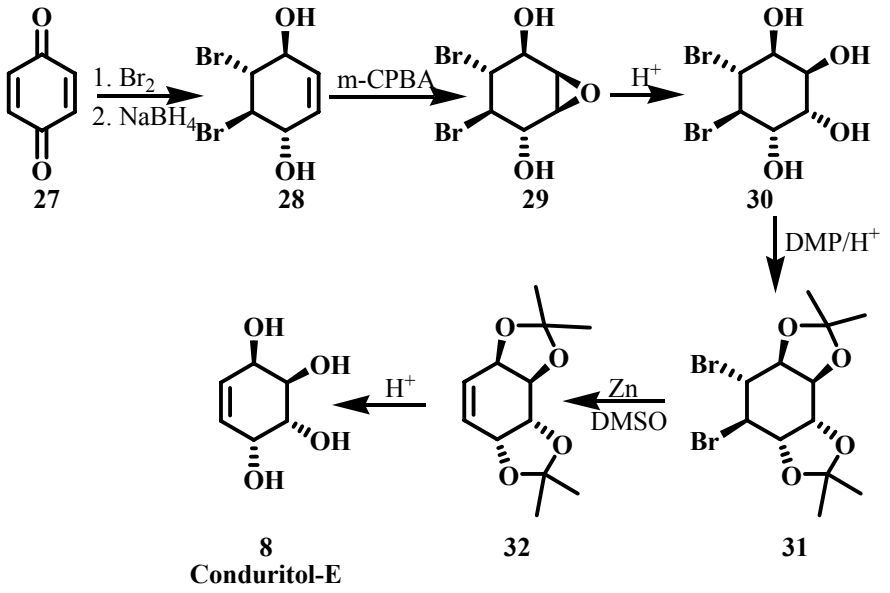
Criegee and Becher developed a short synthetic method for the synthesis of conduritol-D (**7**). The key compound was obtained by Diels-Alder reaction between diacetoxy butadiene **25** and ethylene carbonate (**22**) at high temperature and high pressure. Conduritol-D (**7**) was obtained by saponification of **26** with $Ba(OH)_2$ [4a].



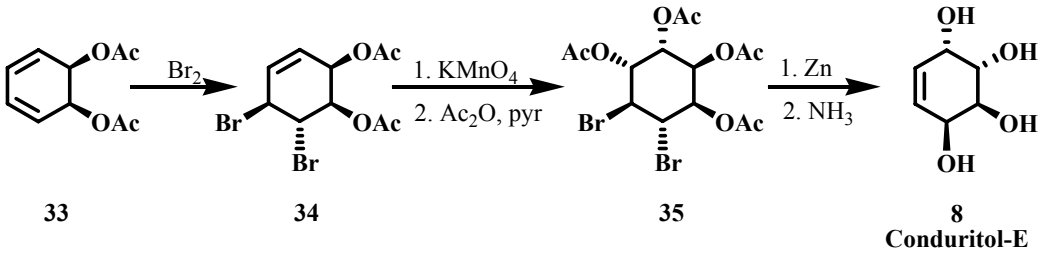
25 **22** **26** **7**
Conduritol-D

Nakajima *et al*. described the first synthesis of conduritol-E (**8**) in a way that the synthetic pathway was not useful and stereospecific [9]. A stereospecific synthesis was developed by Angyal and Gilham [10] and later also again by Nakajima.

A new and stereospecific synthesis of conduritol-E (**8**) was developed by Balcı *et al*. starting from p-benzoquinone (**27**) [9].



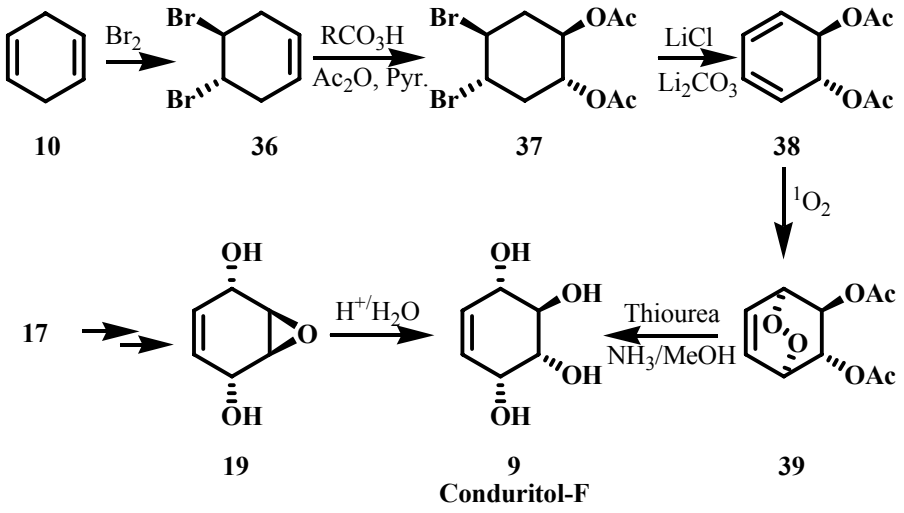
Balcı *et al*. also described a short and convenient method to obtain conduritol-E (**8**) starting from diacetate **33** [11]. Bromination of **33** gave product **34**. After the oxidation of **34** followed by protection of hydroxyl groups with acetoxy groups, **35** was obtained. Conduritol-E (**8**) was obtained by the elimination of vicinal bromides in **35** followed by hydrolysis.



As mentioned before, the occurrence of only two conduritols, namely conduritol-A (**4**) and conduritol-F (**9**) in nature has been established. Conduritol-F (**9**) was discovered by Plouvier in 1962 from *Crysanthemum Leucanthemitol* and called

L-Leucanthemitol firstly. On the other hand, Nakajima *et al*. achieved its first synthesis in 1959 before its discovery [3].

Balcı *et al.* developed a new and stereospecific synthesis by two different approaches. Importance of the first approach is achieving correct configuration of oxygen functionalities successfully just in two steps with photooxygenation and selective reduction of the peroxide linkage by thiourea. In the second approach starting compound was oxepine-benzenoxide (**17**). Epoxide **19** was obtained by identical steps with those reported in the synthesis for conduritol-B as mentioned before [8].



Nowadays *Chung et al*. developed synthetic routes to enantiomeric pairs of all possible stereoisomeric conduritol derivatives by efficient enzymatic resolution of conduritol-B and conduritol-C derivatives, followed by oxidation/reduction and the Mitsunobu reaction in stereo- and regioselective manners [12].

Recently Ogasawara *et al.* reported the first integrated synthesis of conduritols A-F (**4-9**) starting from the single chiral compound **(+)-40** using a methoxymethyl (MOM) ether as the common protecting group [13] (Fig. 2).

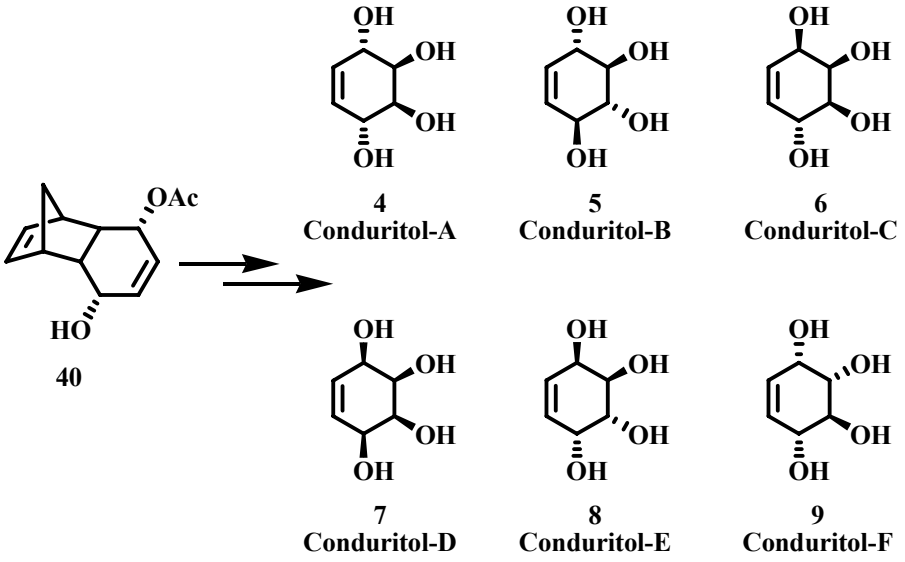


Figure 2. Integrated synthesis of conduritols A-F

1. 3 QUERCITOLS

In 1849, Braconnot isolated from the acorns of an oak tree (genus *Quercus*) a colorless, crystalline compound, $C_6H_{12}O_5$, which was named quercitol (**2**). Although the cyclohexapentanol structure of this compound was established in 1885, and its configuration in 1932, no synthesis had been reported until the 1960s [14].

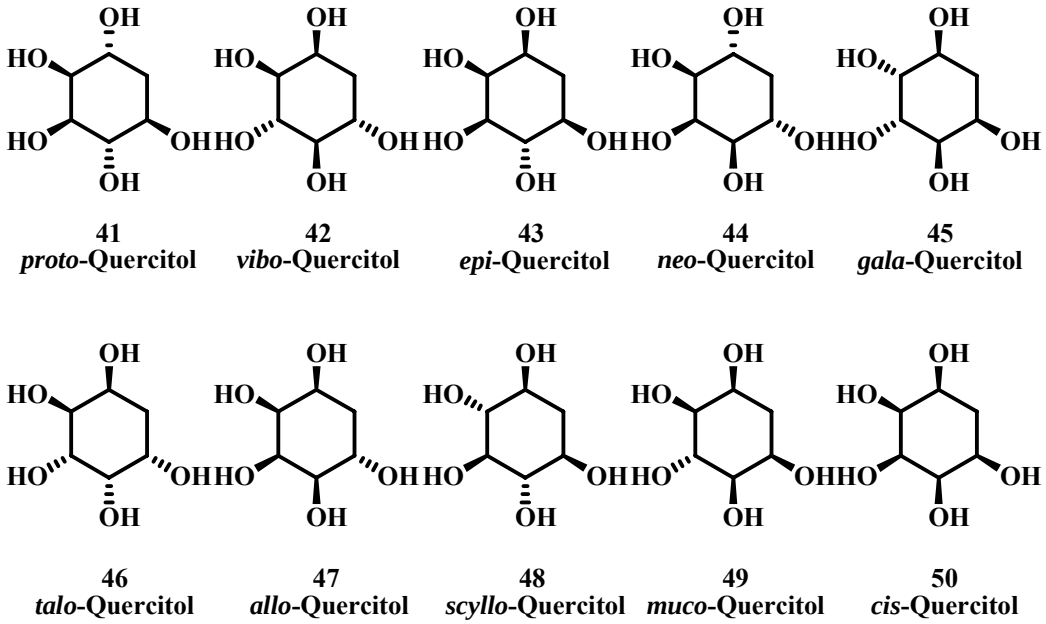
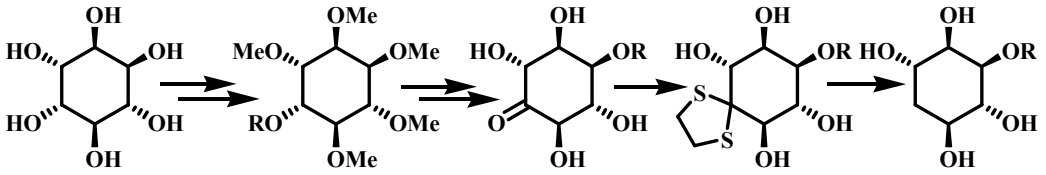


Figure 3. Quercitol stereoisomers

Since the cyclohexapentanols correspond to the open-chain heptitols, in symmetry properties, there are ten possible diastereomeric forms; four meso and six DL-pairs (sixteen stereoisomeric forms) [15]. Not to be confused, quercitols have configurational prefix to designate each diastereomer [16] (Fig. 3). Only three optically active forms have so far been found in nature and they only exist in plants; the two of them are (+)-proto-quercitol (**41**), (-)-proto-quercitol (**41**), and the other one is (-)-vibo-quercitol (**42**) [17]. The availability of (+)-and (-)-quercitol by isolation and the development of syntheses for all the other isomers, some of them in optically active forms, made possible the statement that quercitols constitute the largest all-known family of diastereomers [15].

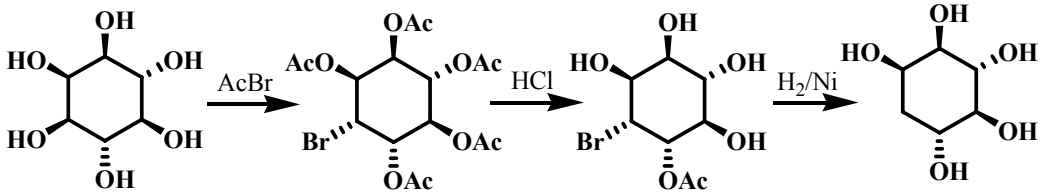
So far ten possible diastereoisomer of quercitols were synthesized by many different methods and in all previously reported syntheses, starting materials were natural products or compounds that required many steps to synthesize [18].

The synthesis of (-)-*proto*-quercitol (**41**) was accomplished by McCasland using (-)-*chiro*-inositol (**80**) in many steps [14].



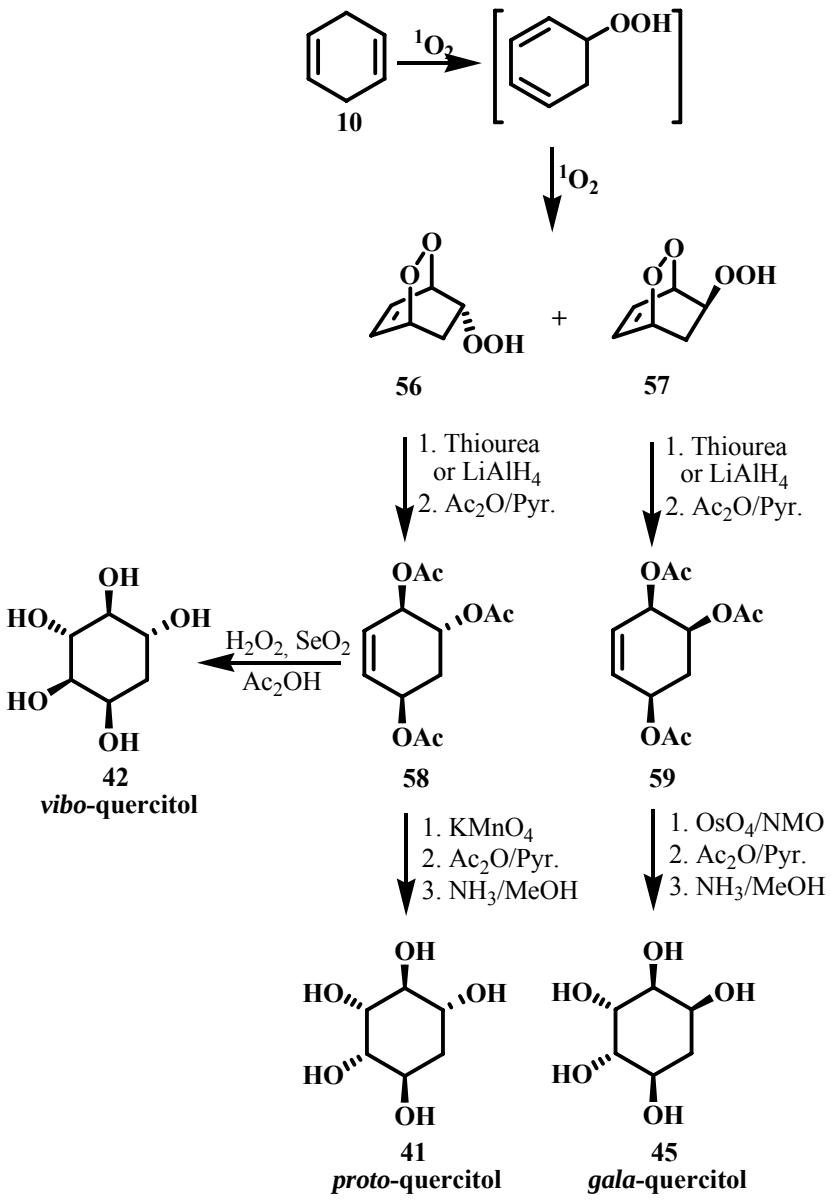
80 **51** **52** **53** **41** ***proto*-quercitol**

vibo-Quercitol (**42**) was synthesized by McCasland and Horswill starting from naturally occurring *myo*-inositol (**76**). In this synthesis, *myo*-inositol was treated with acetyl bromide first and then, related product **54** was hydrolyzed. The hydrogenation of **55** gave *vibo*-Quercitol (**42**) [19].

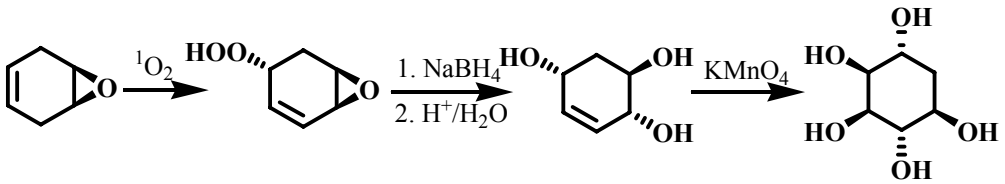


76 **54** **55** **42** ***vibo*-quercitol**

Balcı *et al.* described a short, efficient and stereospecific synthesis for racemic *proto*-quercitol (**41**) starting from commercially available 1,4-cyclohexadiene (**10**). Herewith they applied for the first time a singlet oxygen ene reaction combined with the singlet oxygen [2+4] addition successively [20].

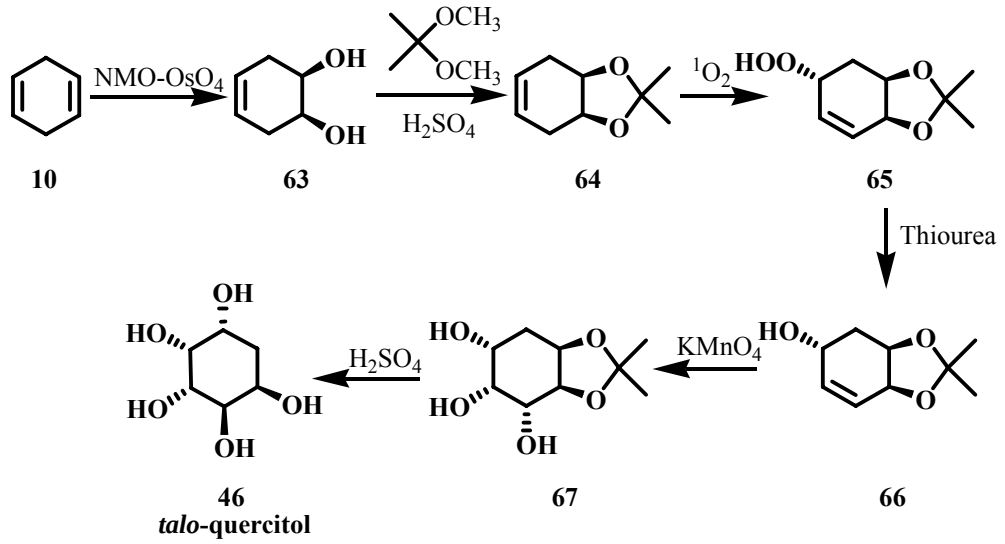


In fact, this novel and efficient synthetic route led to the syntheses of *proto*-quercitol (**41**), *vibo*-quercitol (**42**) and *gala*-quercitol (**45**) starting from same compound, 1,4-cyclohexadiene (**10**) [17,18]. Another *proto*-quercitol (**41**) synthesis by Balcı *et al.* was developed starting with epoxide **60** using photooxygenation.



60 **61** **62** **41**

There are many syntheses described for *talo*-quercitol (**46**) in literature with low yields. However, Balcı *et al.* developed a novel, stereospecific synthesis of *talo*-quercitol (**46**) in high yields [21]. 1,4-Cyclohexadiene (**10**) was used as the starting material and OsO_4-catalyzed NMO oxidation of it afforded diol **63**. The photooxygenation followed by reductive cleavage of peroxide linkage gave the corresponding alcohol **66**. In the next step, the double bond was oxidized in a cis fashion with $KMnO_4$. Introduction of two hydroxyl groups to the double bond in a trans fashion gave *vibo*-quercitol (**42**) with further steps in the same study [21]).



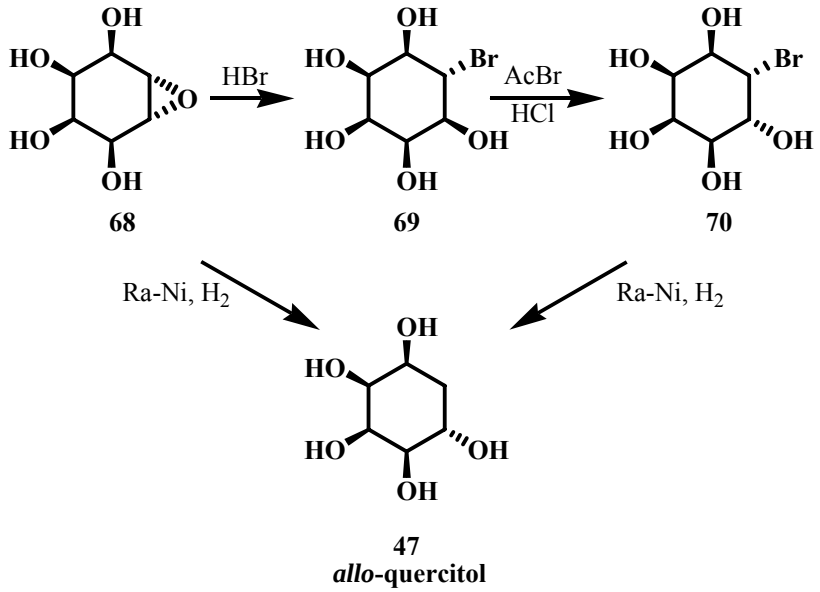
10 **63** **64** **65**

46 **67** **66**

***talo*-quercitol**

McCasland *et al*. described an important synthesis for the *allo*-quercitol (**47**) starting from conduritol-D epoxide (**68**) to obtain same product *allo*-quercitol (**47**) with different reaction pathways.

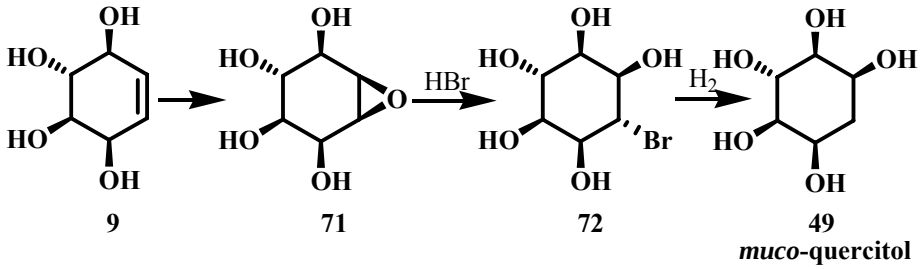
In the same study, hydrogenation of product **69**, led to synthesis of *cis*-quercitol (**50**) [16].



68 **69** **70**

47
***allo*-quercitol**

Nakajima et al. used a similar reaction pathway in order to synthesize *muco*-quercitol (**49**) starting from conduritol-F (**9**).



9 **71** **72** **49**
***muco*-quercitol**

Because of their biological activities, for example, *myo*-inositol analog quercitols like *neo, epi, vibo,* and *scyllo* and their azido derivatives show tumour-inhibitory effect [19], the interest for the synthesis of quercitols has increased. Thus, the examples given here for the syntheses of quercitols can be multiplied.

1.4 INOSITOLS

Over 100 years ago, Scherer isolated an optically inactive isomer of cyclohexanol and named the compound *inosit*. The name was applied to the other isomers as these were discovered or synthesized, so that it is now a generic term. The original isomer came to be called *meso*- or *i*-inositol, and more recently *myo*-inositol (**76**).

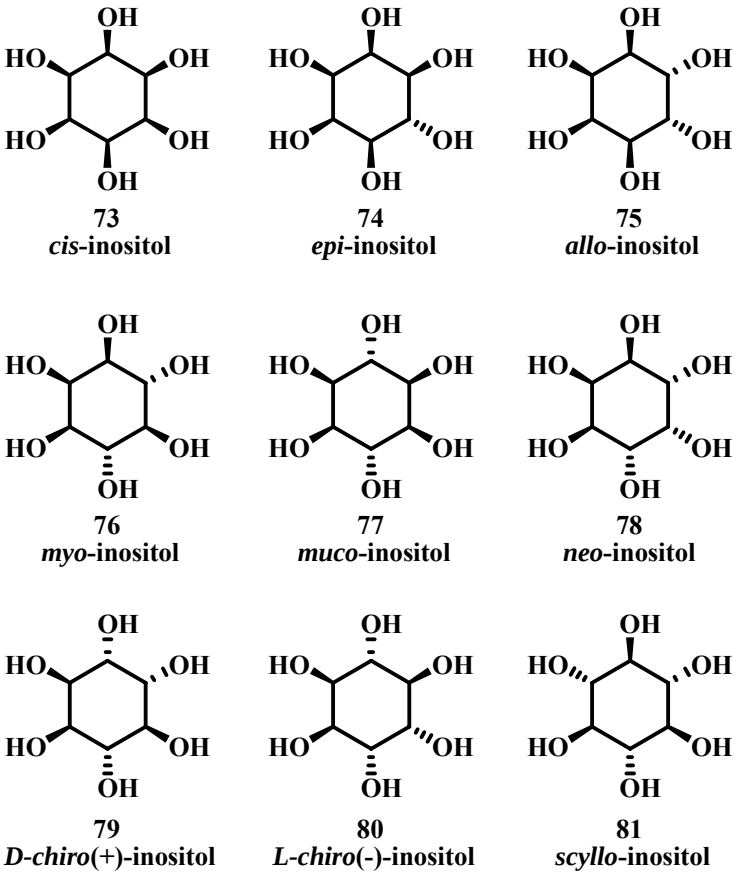


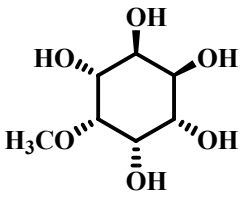
Figure 4. Inositol stereoisomers

As shown theoretically by Bouveault in 1894, there are nine inositols in all-seven meso forms and one DL pair. These have stereo formulas **73-81** and are distinguished from each other by the configurational prefixes shown with formulas (Fig. 4) [15].

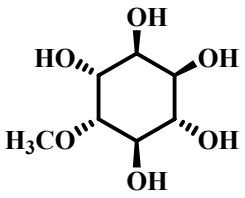
The inositols are beautifully crystalline, high-melting substances, markedly stable to heat, acids, and alkalis. *neo*-Inositol (**78**) and *scyllo*-inositol (**81**) have surprisingly low solubility in water.

The most widely distributed isomer is *myo*-inositol (**76**). It appears to be present; both free and combined, in the tissues of nearly all living species. In animals and microorganisms the combined *myo*-inositol (**76**) is mostly in the form of phospholipids. *myo*-Inositol (**76**) is available commercially as a by-product of the corn wet-milling industry. It is prepared from phytate salts isolated from steep liquor.

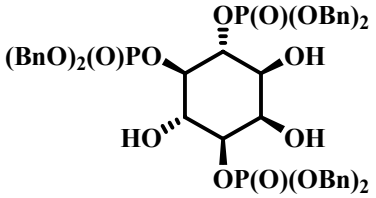
The next most abundant inositols are the optically active isomers D-(+)- and L-(-)-*chiro*-inositol (**79** and **80**). These occur in higher plants, predominantly as the methyl esters D-(+)-pinitol (**82**) and L-(-)-quebrachitol (1-L-(-)-2-*O*-methyl-*chiro*-inositol) (**83**), respectively. L-quebrachitol offers an alternative molecular architecture for the construction of polyhydroxylated natural products [22].



82
(+)-Pinitol



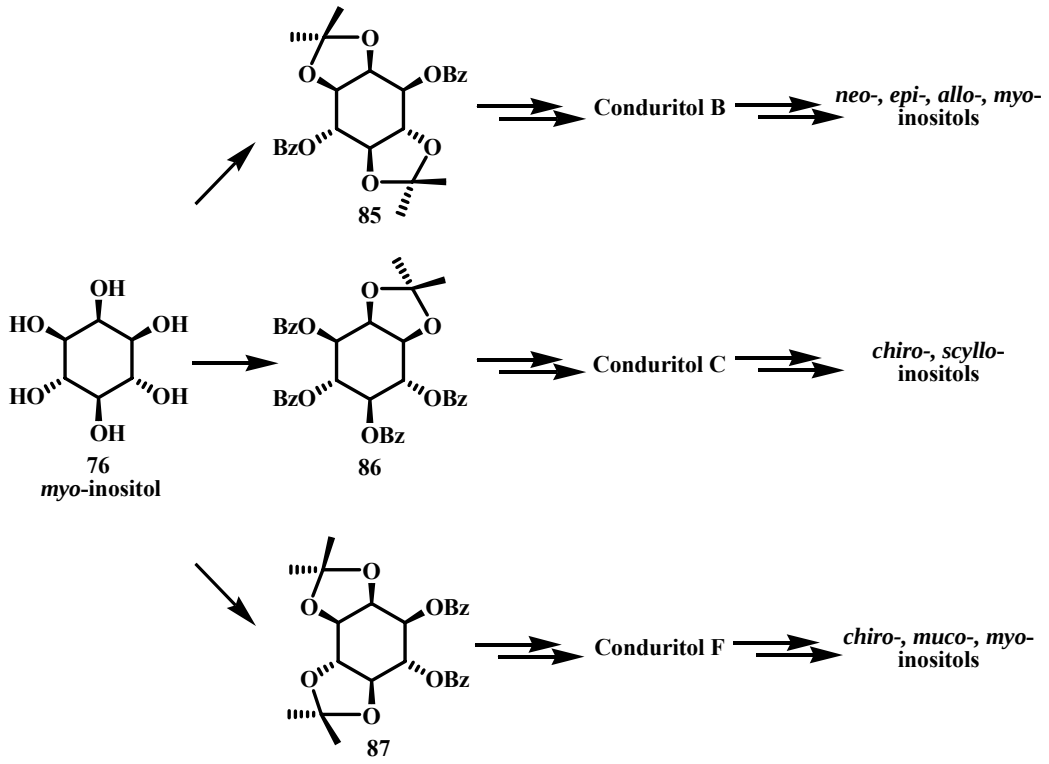
83
L-quebrachitol



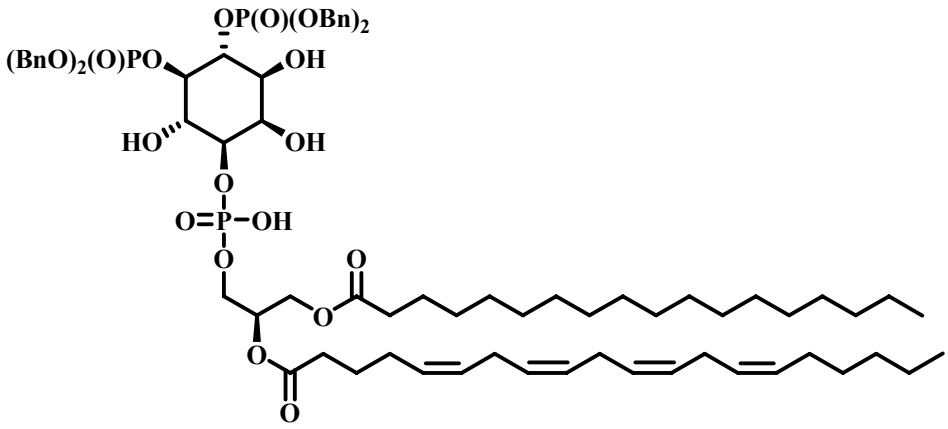
84
1,4,5-IP$_3$

scyllo-Inositol (**81**), also called scyllitol, has been isolated from plants and animals. It has been detected in several species of insects and in mammalian urines. The natural cyclitols that are available in quantity are important as starting materials for the synthesis of other compounds of the group [15].

The inositols had previously been synthesized in varying efficiencies from halobenzenes, benzene, hexahydroxybenzene, tetrahydroxyquinone, sugars, inositols, and others. The first general synthesis of six inositol stereoisomers was carried out *via* conduritol intermediates prepared from *myo*-inositol (**76**) by Chung *et al*. [23].



Due to their biological roles the synthesis of the inositol phosphates became a major research theme in organic chemistry. After the observation by Berridge in 1984 that inositol 1,4,5-triphosphate (IP_3) (**84**) was the missing second messenger, a fundamental cell-signal transduction mechanism was elucidated. This led to a dramatic increase in interest in the inositol phosphates [24].



88 PIP_2

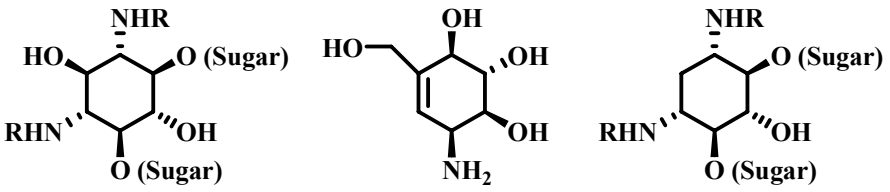
In particular IP_3 which acts as a second messenger by binding to specific receptors on the endoplasmic reticulum thus it stimulates the release of calcium ions from intracellular stores. The second messengers generated in the phosphatidylinositol (PI) cycle, by receptor controlled hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) (**88**) [24].

1.5 CONDURITOL AND INOSITOL DERIVATIVES

Aminocyclitols, haloconduritols, double bond substituted conduritols, and other analogues of conduritols and inositols like bishomo-conduritols and bishomo-inositols have also gained importance in recent years because of diverse biological activities exhibited by them. Many bioactive natural products contain these conduritol and inositol derivatives as their building block.

1.5.1 AMINOCYCLITOLS

Aminocyclitols are subclasses of cyclitols in which one or more hydroxyl groups have been replaced for amino groups. Aminocyclitols represent a continuing and growing class of important compounds. The interest attaching to these substances at present is mainly due to their presence as components of certain antibiotics, namely streptomycin (containing streptamine moiety), validamycin (containing valienamine moiety), neomycin, paramycin, kanamycin (containing 2-deoxy-streptamine moiety), hydroxymycin, etc [25].



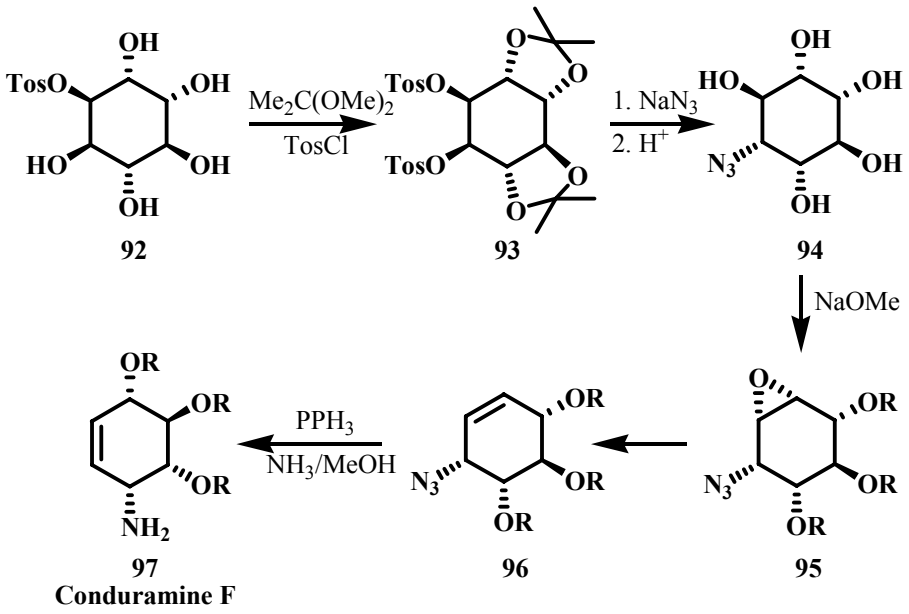
89
Streptamine

90
Valienamine

91
2-deoxy-streptamine

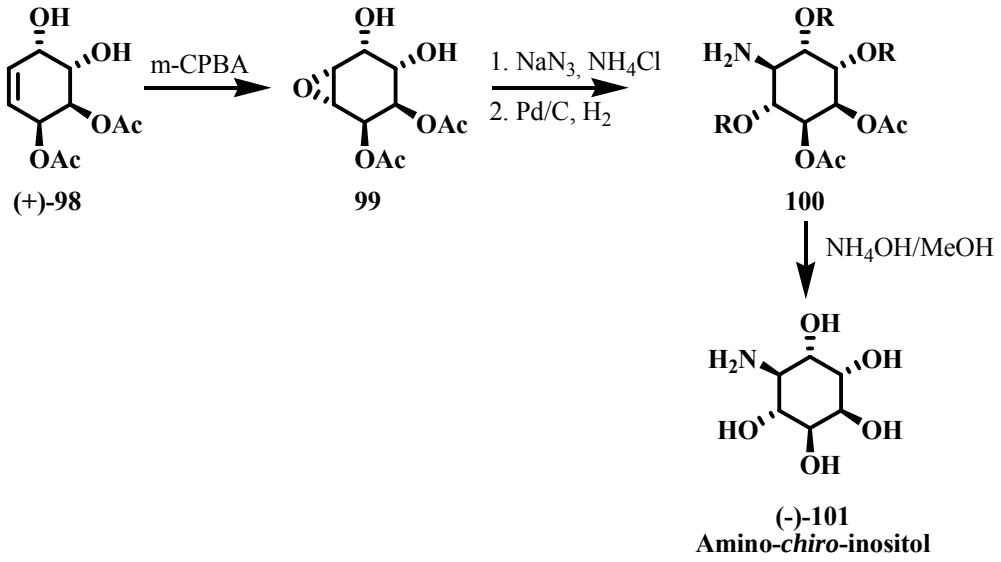
Aminoconduritols (conduramines) are prominent compounds, because they are useful intermediates in the synthesis of amino- and diaminocyclitols, the aglycon parts of numerous aminoglycosidase antibiotics. Moreover, some derivatives inhibit certain glycosidases [26].

The early examples of synthesis of optically pure aminoconduritols were presented in 1981 by Paulsen and coworkers who synthesized conduramines F_1 and conduramines F_4 (**97**) from natural quebrachitol derivative **92** [4a].



Azido and amino derivatives of inositols have great potential as bioactive molecules. The enzyme inhibitory activity of glycosidases reported for free and conjugated aminoinositols. They also play a central role in antibiotic action. The presence in the framework of these cyclitols of six stereogenic carbons makes their synthesis in enantiopure form very demanding and only a few examples were reported as yet.

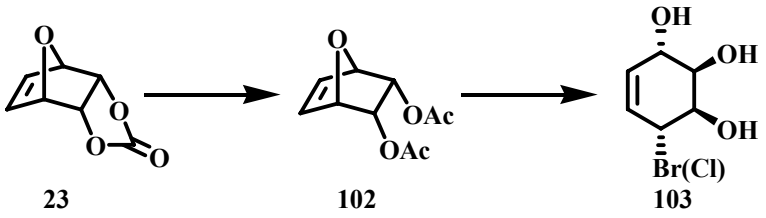
Recently Nicolosi *et al.* reported a new chemoenzymatic synthesis of aminoinositol (inosamine) [27].



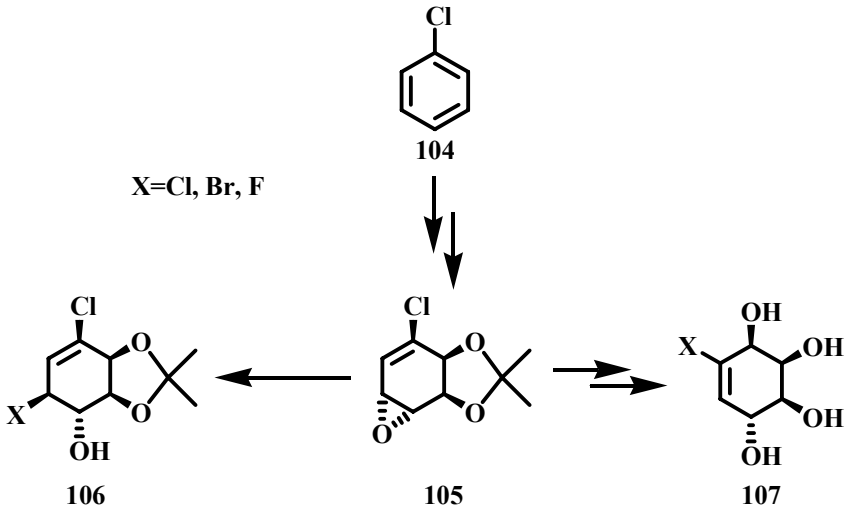
1.5.2 HALOCONDURITOLS

Haloconduritols are also important derivatives of cyclitols in connection with conduritols. It has been reported that bromoconduritols is an active site directed, covalent inhibitor of α-glucosides. Because of this they are interest of AIDS research [28]. Haloconduritols are also key compounds for the synthesis of other important cyclitol derivatives.

Recently haloconduritols having conduritol-A skeleton were reported [29]. Furan-vinylene carbonate adduct **23** was the key compound and it was converted to cis-diacetate **102**. Then ring opening reaction provided the corresponding haloconduritols **103** in high yields.



Hudlicky *et al*. and Carless reported the synthesis of double bond substituted conduritols starting from halobenzenes [30,31]. In this study acid-catalyzed ring opening reaction of epoxide **105** gave double bond substituted conduritol **107** where X can be chlorine, fluorine, and bromine atoms. Moreover, nucleophilic attack at the allylic epoxide carbon atom of **105** resulted in the formation of **106**.



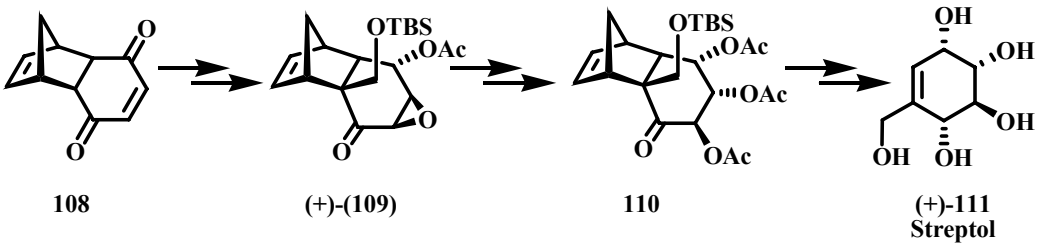
1.5.3 HYDROXYMETHYL SUBSTITUTED CYCLITOLS

Some of hydroxymethyl substituted conduritol and inositol derivatives also exhibit biological activities. Some of them are given below.

(+)-Streptol (**111**) (also known as valienol) was isolated from culture of unidentified *Streptomyces* sp. by Sakuda *et al.* and shown to inhibit the growth of lettuce seedlings at a concentration above 13 ppm.

Mehta *et al.* have reported simple and enantioselective synthesis of the natural product (+)-Streptol (**111**) recently [32]. Firstly chiral precursor (+)-(**109**) was accomplished. The regioselective cleavage of epoxide ring was followed by retro

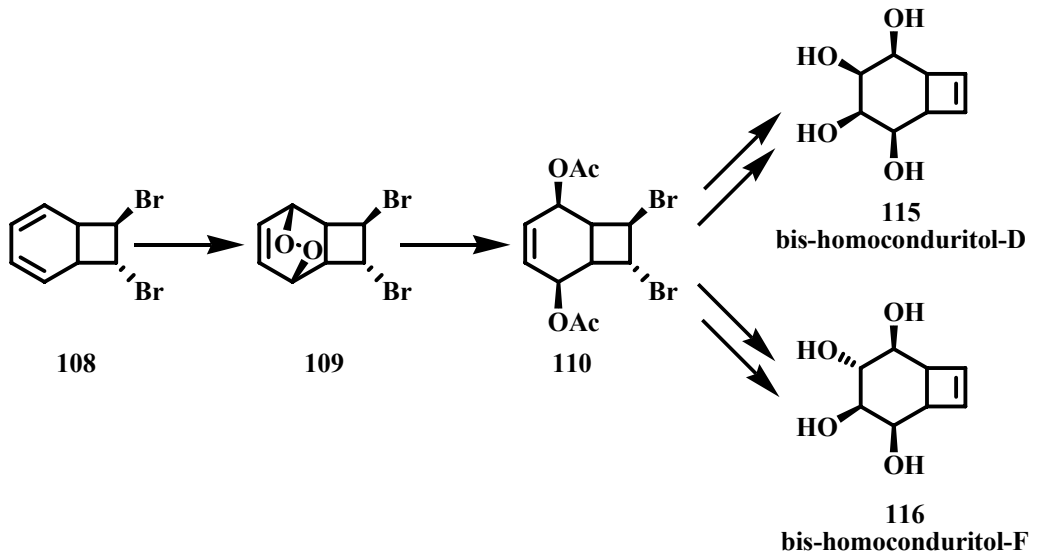
Diels-Alder reaction to eliminate cyclopentadiene. After the reduction, deprotection and hydrolysis steps provided (+)-Streptol (**111**).



108 **(+)-(109)** **110** **(+)-111 Streptol**

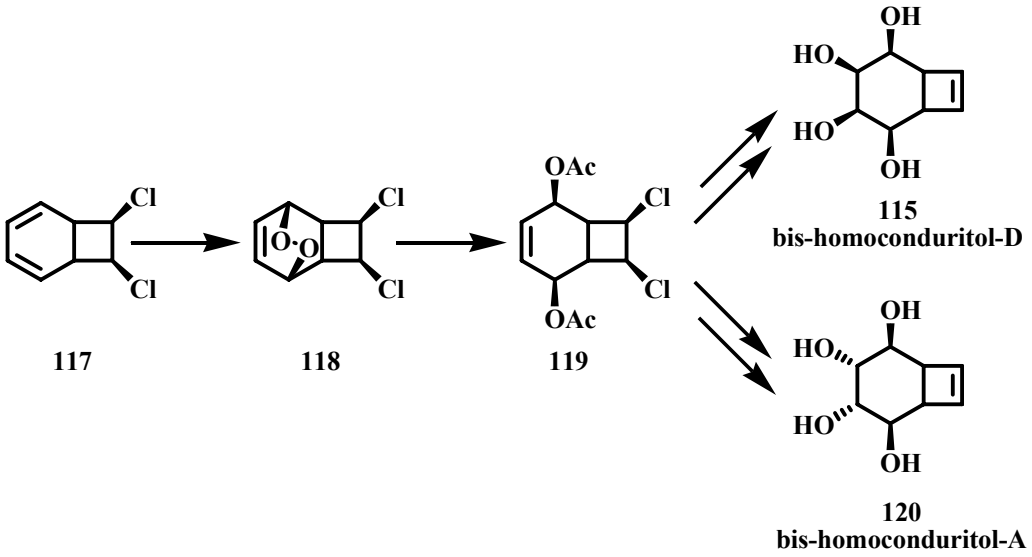
The other hydroxymethyl substituted cyclitol derivatives are bis-homoconduritols and bis-homoinositols. Because these cyclitol derivatives are new generation of possible glycosidase inhibitors their syntheses have gained importance nowadays.

Balcı *et al.* succeeded in the synthesis of this new class of compounds, bis-homoconduritols-A, -D, and -F and bis-homoinositols [33,34,35,36].

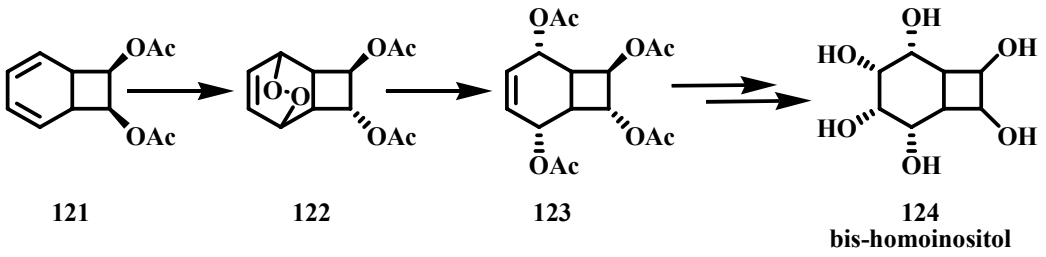


108 **109** **110** **115 bis-homoconduritol-D** **116 bis-homoconduritol-F**

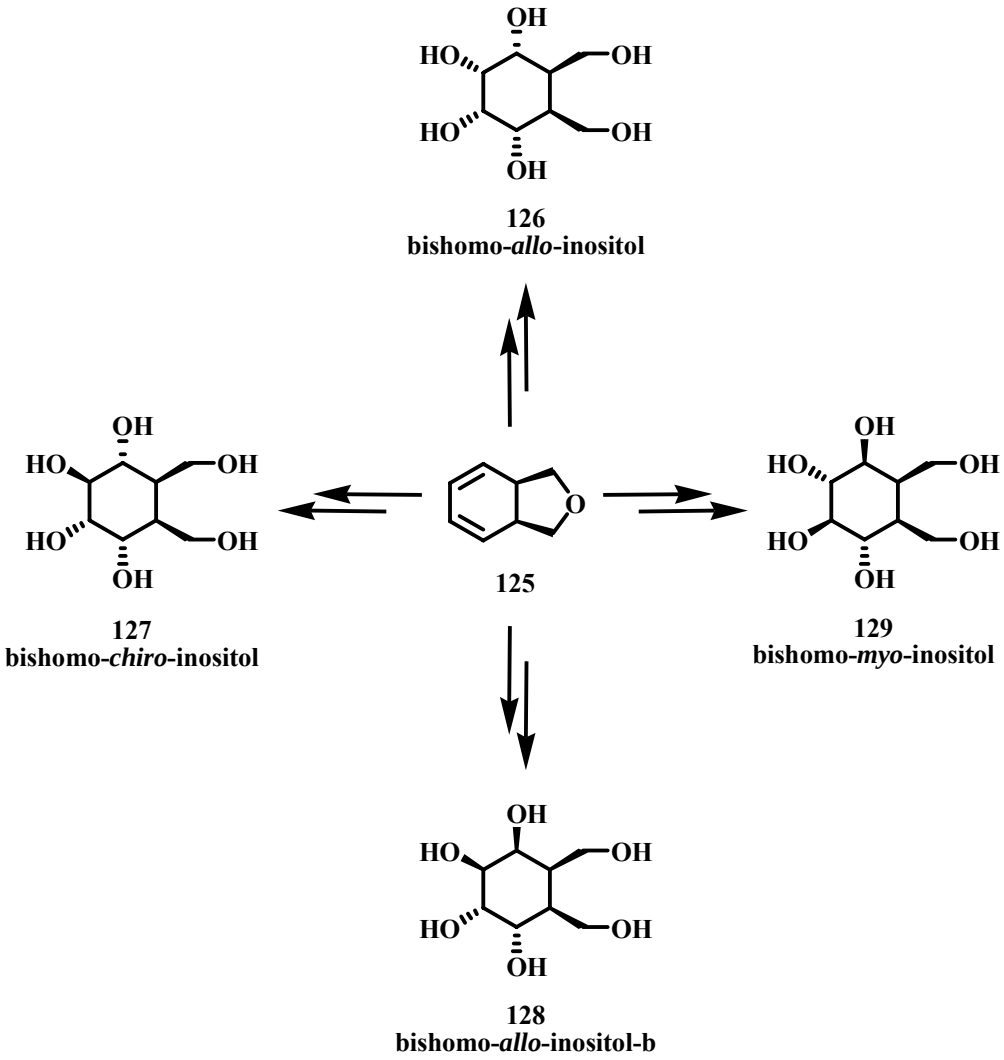
In these studies, a short stereocontrolled approach to bis-homoconduritols-A, -D, and -F has been accomplished starting from commercially available, simple molecules [33,34].



Balcı *et al.* reported the first synthesis and characterization of a new inositol analogue, bis-homoinositol (**124**) [35].



In present days, Balcı *et al.* designed a synthesis of an analogue of bis-homoinositols using simple starting materials [36]. In this study, tetrahydro benzofuran derivative used as the key compound **125**.



1.6 BIOLOGICAL SIGNIFICANCE OF CYCLITOLS

Molecular entities having polyhydroxylated cyclohexanoids or aminocyclitol core structures have attracted a great deal of attention in recent years because of diverse biological activities exhibited by them, ranging from herbicidal and anti-microbial on the hand to glycosidase inhibition and mediation of cellular communication on the other. While several of the known cyclitols have been encountered in nature, many more have been accessed through syntheses to evaluate their biological potential.

The syntheses of cyclitols remains an active area of current research and new approaches continue to be explored to achieve greater preparative efficiency and higher levels of stereo- and regiocontrol [37].

As mentioned before an increasing interest in the synthesis of glycosidase inhibitors has been observed due to their biological properties. Glycosidase inhibitors can be classified in two distinct classes: reversible inhibitors (glycals, glyconolactones, glycosylamines, aminocyclitols, etc), and irreversible inhibitors (conduritol epoxides, 5,6-anhydro-1-deoxynojirimycine) [38].

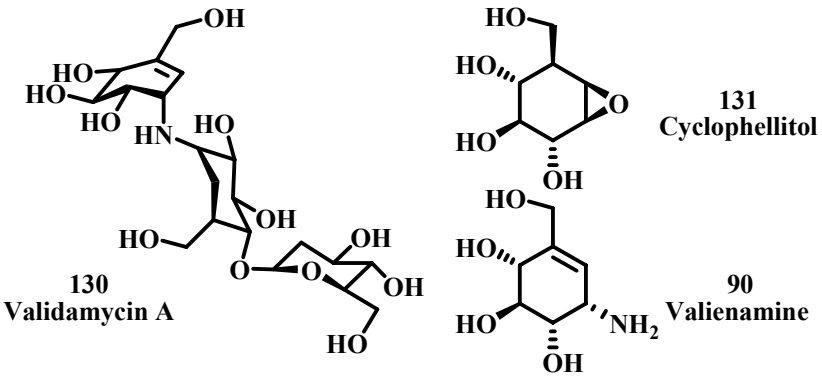
Inhibitors of glycosidase enzymes have potential for the treatment of various disorders and diseases such as diabetes, cancer and AIDS; for example acarbose, a pseudotetrasaccharide, is an inhibitor of α-D-glucosidase and is in clinical use for the treatment of diabetes. Glycosidase inhibitors have also proved useful in the investigation of metabolic disorders such as Gaucher's disease [39].

Conduramine and conduritol derivatives have shown promising features such as inhibitory activity for glycosidases. In addition, a number of conduritol derivatives have been found to possess antifeedant, antibiotic, anti-leukemic, and growth regulating activity. For example conduritol A is present with numerous other complex natural products in the leaves of *Gymnema sylvestre*, a shrub which as been used as a folk remedy for diabetes. It has also been shown to suppress blood glucose level, which can reduce the need for insulin [4b].

Among the naturally occurring glycosidase inhibitors, cyclitol epoxides and aminocyclitols have been extensively studied due to their antibiotic properties [38]. Cyclophellitol (**131**) and valienamine (**90**) are good examples for this type

of cyclitols. Valienamine is a branched-chain unsaturated aminocyclitol which is a common building block of validamycin A (**130**).

Validamycin A (**130**) is the major and the most active component of the antibiotic validamycins and widely used to control sheath blight in rice plants [40].



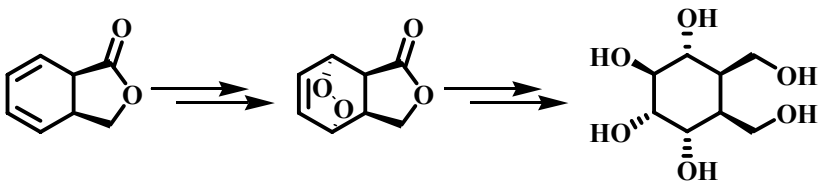
Very recently, the valienamine moiety linked to D-glucose *via* an imino linkage has been found as an essential unit in a homologous series of pseudo-oligosaccharides such as acarboses, trestatins, and adiposins, all of which show a marked inhibitory effect against α-glucosidases in mammals. Furthermore, valienamine (**90**) itself has been found to show both the α-glucosidase inhibition and the antibiotic activity against Bacillus species [40].

1.7 AIM OF THE STUDY

The syntheses of cyclitol derivatives have attracted a great deal of attention due to their biological activities, their role in intracellular communication and their versatilities as synthetic intermediates. Consequently, to find short, efficient and stereospecific methodology for the syntheses of them has an importance.

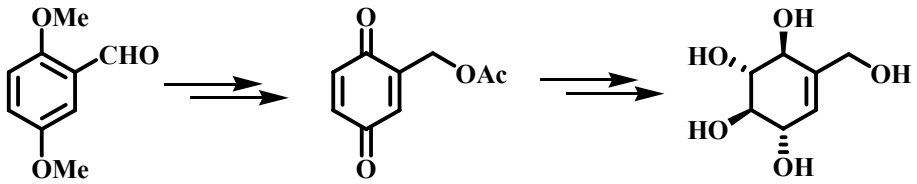
In a great number of natural products having a cyclitol unit the presence of hydroxymethyl group has attracted a remarkable attention. It is known that these groups have important and diverse roles in biological activities. Owing to the importance of these groups, the aim of our study is to develop new and efficient strategies for the synthesis of conduritol and inositol derivatives containing hydroxymethyl groups.

In the first part of our study, hydroxymethyl groups are coming from lactone moiety of intermediates. The key reaction step features the application of singlet oxygen ene reaction to provide an introduction of oxygen functionality to the key compounds.



132 **133** **127**

In the second part of our study, hydroxymethyl group is coming from aldehyde unit of starting material. The key reaction step is the formation of *p*-benzoquinone derivative.



135 **136** **137**

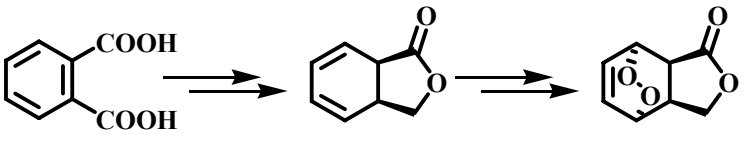
Since these highly oxygenated cyclohexane and cyclohexene compounds are considered a mimetic of biologically active cyclitol derivatives like valienamine, streptol and *etc*. we also aimed to investigate their biological activities.

CHAPTER 2

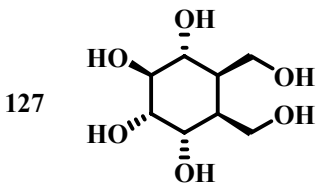
RESULTS AND DISSCUSSION

2.1 THE REACTION PATH FOR THE SYNTHESIS OF REL-(1R,2S,3S,4S,5S,6R)-5,6-BIS(HYDROXYMETHYL)CYCLOHEXANE-1,2,3,4-TETROL (127)

In order to be able to synthesize hydroxymethyl containing inositol derivative, we should have synthesized such a key compound that it included double bonds and a unit providing hydroxymethyl groups on target molecule. The lactone moiety fused with cyclohexadiene was thought to be the most convenient one for this purpose. In this study we preferred to use singlet oxygen reaction due to its widespread use and great utility in organic syntheses nowadays. As a result of this the following synthetic route was developed.



138 132 133



127

2.1.1 SINGLET OXYGEN

Although the existence of singlet molecular oxygen has been recognized since 1924, its chemistry has developed dramatically. Not only have chemists contributed to the exponentially growing chemistry of singlet oxygen, but other scientists such as biologists and biochemists have also shown substantial interest in this field. This interest has grown considerably since the recognition of the biochemical roles of the excited state of oxygen in certain blood diseases, in cancer-inducing mechanisms, in a possible free-radical-like aging mechanism, in the role of bacterial activities of phagocytes, and in metabolic hydroxylation. In addition to investigations into the role of singlet oxygen in these phenomena and the mechanism of its reactions, its synthetic applications have also been explored and their utility has been demonstrated [41].

The reactivity of a molecule is closely related to its electronic structure so the scientists concern with the Molecular Orbital Theory to describe the various electronic configuration of molecular oxygen (Fig 5) [42]. Thus the molecular oxygen in its ground state has two unpaired electron with parallel spin and in the degenerated π^*2_p orbitals so oxygen can be shown $^3O_2$ in the ground state.

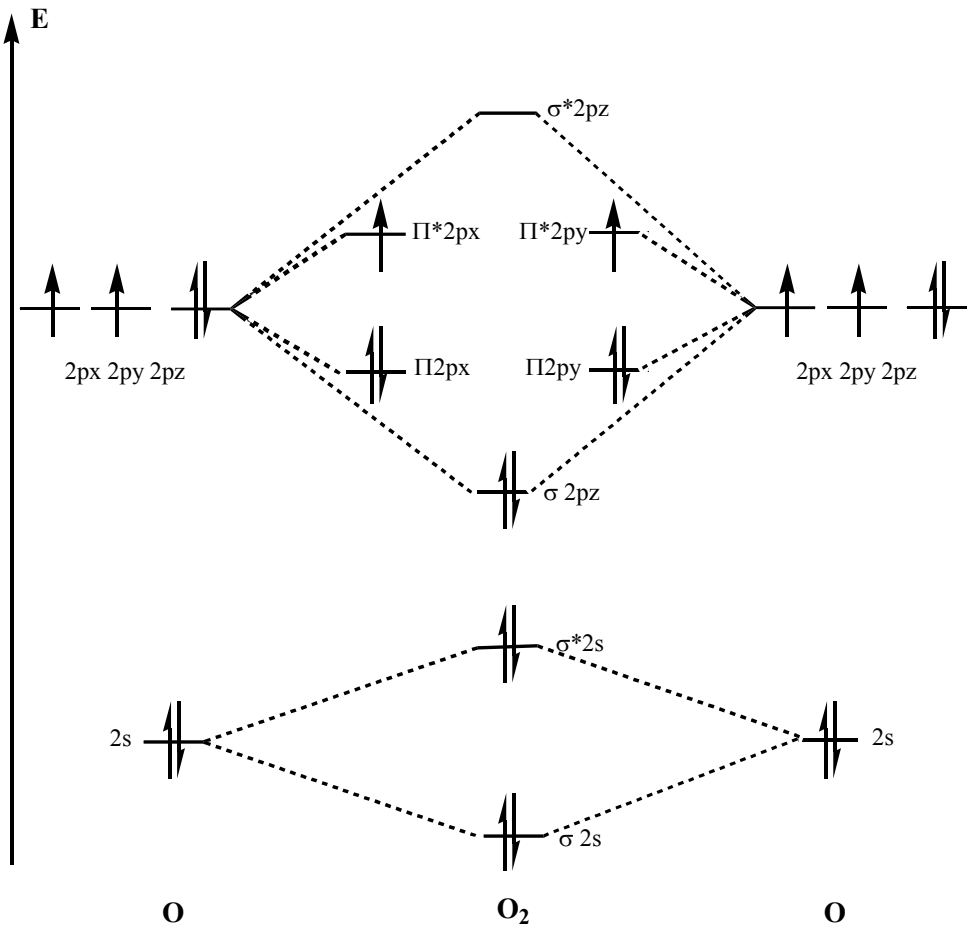


Figure 5. The Molecular Orbital of Diatomic Oxygen Molecule

The unpaired electrons in parallel spins in the ground state of the oxygen impart the paramagnetism, which so facilitates the measurement of gaseous oxygen. More importantly, these parallel electron spins forbid the direct entry of paired electrons and allow the reaction include one-electron step. As a result, while the reaction of oxygen is exothermic, the barrier of spin allows the reaction between triplet oxygen and molecule ground state singlet. The other two lowest electronic states of molecular oxygen known as *singlet oxygen* have electrons with antiparallel spins and can be generated by an input of energy.

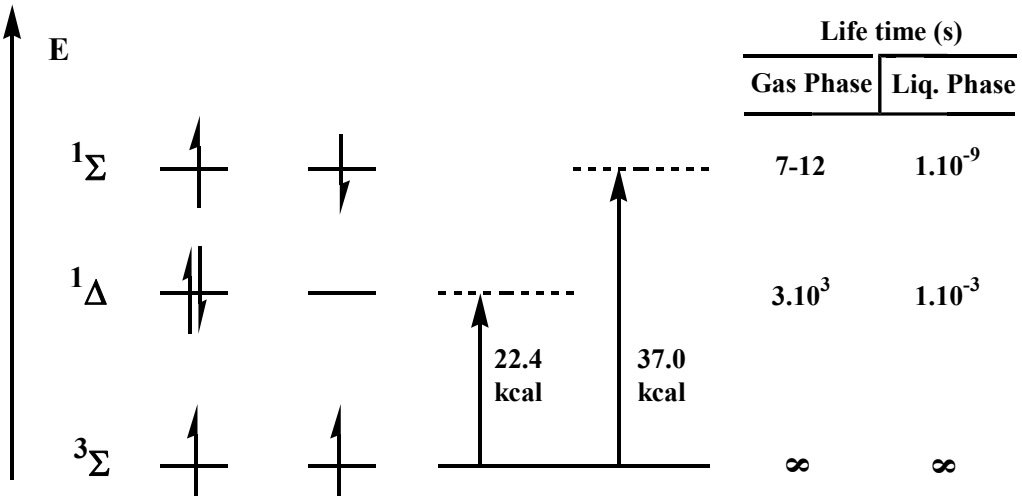


Figure 6. Energy Diagrams and Life Time of Singlet and Triplet Oxygen States

The $^1\Delta_g$ state has energy 22.4 kcal above the ground state. It is not a radical; there are no unpaired electrons. The $^1\Sigma_g$ state is even more reactive, 37.5 kcal above the ground state and electrons are in π^*2_p orbitals in antiparallel spins (Fig 6). In both forms of singlet oxygen the spin restriction is removed and so the oxidizing ability is greatly increased [43].

The life times estimated by integrated absorption measurements are 45 minute for the $^1\Delta_g$ state, and 7.1 second for the $^1\Sigma^+_g$ state at a zero pressure, but even at 1 atm pressure intermolecular collisions change the transition mechanism to electric dipole, with much shortened life times. The lifetimes in solution for the singlet molecular oxygen states becomes drastically shortened, with estimates of 10^{-3} sec for the $^1\Delta_g$ state and 10^{-9} sec for the $^1\Sigma^+_g$ state in water [44] due to deactivation of molecule with increasing intermolecular collisions. Generally, the reactions made in solvent are concerned, the $^1\Delta_g$ state is in more intense as active singlet oxygen due to long lifetime considering to Σ^+_g state.

There are two excited states of singlet oxygen, $^1\Sigma_g^+$ and $^1\Delta_g$. The lower energy state, $^1\Delta_g$ is much longer lived and is now believed to be the only singlet oxygen species, which leads to reaction in solution.

Singlet oxygen is most often generated in laboratory by *photosensitization reactions*. If certain molecules are illuminated with light of a given wavelength they absorb it and the energy raises the molecule into an excited state. The excitation energy can then be transferred onto an adjacent oxygen molecule, converting it to the singlet state whilst the photosensitizer molecule returns to the ground state (Fig. 7).

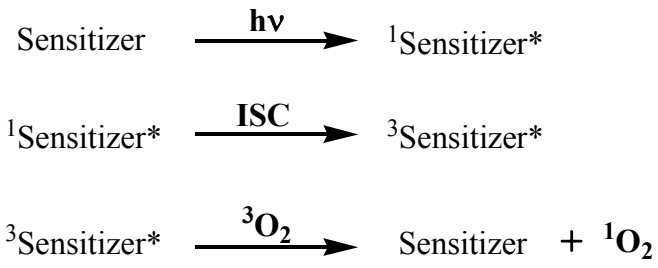


Figure 7. Formation of Singlet Oxygen with Sensitizer

Popular sensitizers of singlet oxygen formation include the dyes *acridine orange, methylene blue, rose bengal, meso-tetraphenlyporphyne* and *toluidine blue*; but any compounds found *in vivo* are also effective, such as the water-soluble vitamin riboflavin and its derivatives, chlorophylls a and b, the bile pigment bilirubin, retinal and various porphyrins, both free and bound to proteins. The polycyclic aromatic hydrocarbons can also be used as sensitizer. The most important step in the formation of singlet oxygen by energy transfer is annihilation of triplet oxygen with triplet sensitizer and it is called as *triplet-triplet annihilation*. The sensitizers must have lower ability to the oxidation with

themselves and its triplet energies (30-70 kcal) must be bigger than the energies of the two states of singlet oxygen.

There are some other chemical methods for generating singlet oxygen in solution including the reaction of hydrogen peroxide with sodium hypochlorite, the thermolysis of triaryl phosphite ozonides, and the decomposition of 9,10-diphenylanthracene peroxide [45].

2.1.1.1 REACTIONS OF SINGLET OXYGEN

The three most common modes of reaction of singlet oxygen with olefins are the ene reaction leading to a hydroperoxide, the Diels-Alder type of cycloaddition forming an endoperoxide, and the direct addition of $^1O_2$ to an activated double bond resulting in the formation of a 1,2-dioxetane (Fig 8). All three types of singlet oxygen reactions have been utilized in organic synthesis for the regiospecific and stereospecific oxidation of olefins [45].

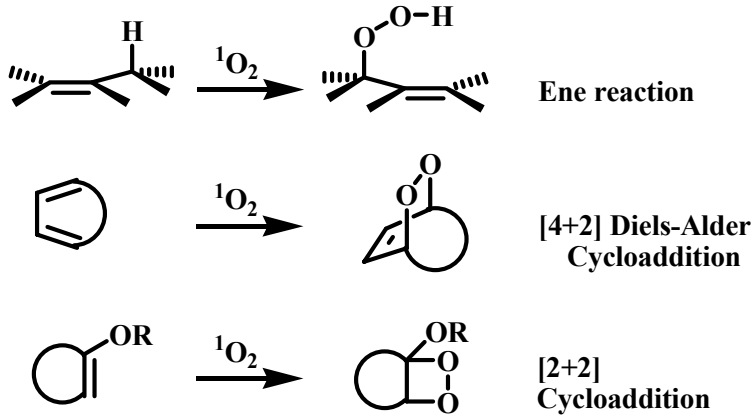
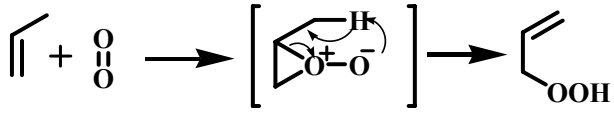


Figure 8. The Types of Singlet Oxygen Reactions

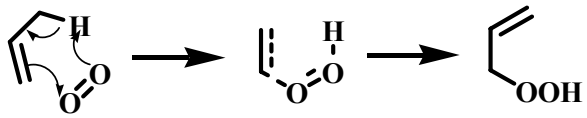
1. Ene Reaction:

The ene reaction, by far the most widely investigated singlet oxygen reaction, involves the formation of an allylic hydroperoxide from an olefin by a process involving abstraction of an allylic proton along with migration of the carbon-carbon double bond. Ene-product formation is strongly dependent on the stereoelectronic and steric effects exerted by the olefin on the attacking electrophilic singlet oxygen. Unlike the Diels-Alder reaction, the mechanism for ene-reaction remains controversial. There are some possible mechanisms for ene-reactions but two of them are considered to be more important.

a) Perepoxide mechanism



b) Concerted Mechanism



2. [4+2] Diels-Alder Cycloaddition Reaction:

[4+2] Cycloaddition reaction of singlet oxygen is observed with conjugated dienes and yields endoperoxides [41].

The rate constant for these reactions of $^1O_2$ are very much higher than those for the corresponding normal Diels-Alder reactions [46], principally because of the

much lower activation energies for the singlet oxygen reactions. The effect of substituents on the diene in these reactions is very similar to that reported for the same reactions in solution and for the normal Diels-Alder reaction. It has therefore been assumed by most workers that a "product like" 6-center cyclic transition state occurs in all such reactions and these reactions go through concerted mechanism like Diels-Alder reactions.

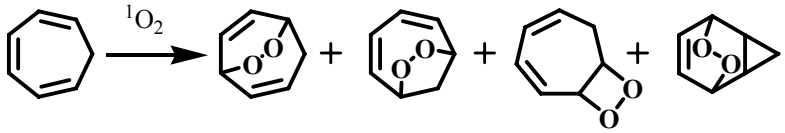
The lowering the activation energy for the reaction when electron donating groups are placed on the diene can then be accounted for by considering the interactions between the highest occupied molecular orbital (HOMO) on the diene and the lowest unoccupied molecular orbital (LUMO) on oxygen [47]. Such an interaction can give rise to a polar transition state and hence account for the big difference between the gap phase and solution reaction rates. However, in Diels-Alder reaction, this big difference is not observed between two phases. Also, the endo selectivity is lost in singlet oxygen reaction. These results remove the similarities between normal Diels-Alder and [4+2] cycloaddition reaction of singlet oxygen.

3. [2+2] Cycloaddition Reaction:

The formation of 1,2-dioxetanes by singlet oxygen [2+2] cycloaddition to double bonds is usually limited to highly strained or electron-rich olefins such as vinyl sulfides, enol ethers, enamines or alkyl substituted alkenes which do not take part in an "ene" reaction.

These unstable peroxides normally decompose on warming to form carbonyl products resulting from the oxidative cleavage of the original carbon-carbon double bond. Because of the restriction of this type of oxygenation to specific types of olefinic systems, applications of the dioxetane-singlet oxygen reaction in synthesis have been limited [45].

The photooxygenation of cycloheptatriene, **138** performed by Balcı and Adam is a good example including all addition reactions of singlet oxygen at the same time [48].

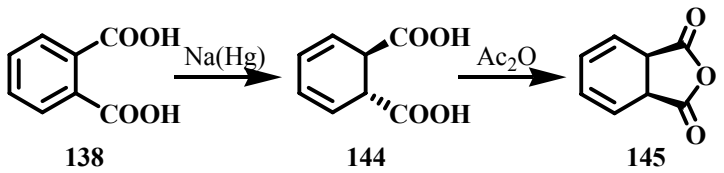


139 **140** **141** **142** **143**

2.1.2 THE SYNTHESIS OF REL-(3aR,7aS)-3a,7a-DIHYDRO-2-BENZOFURAN-1,3-DIONE (145)

The compounds including 1,3 diene units are very useful precursors for the synthesis of cyclitol derivatives. Moreover, to possess this unit in the molecule has a great importance since we aimed to use [4+2] cycloaddition reaction of singlet oxygen basically. For this reason we tried to synthesize a key compound having both this diene and anhydride unit which leads to get hydroxymethyl groups on target molecule as mentioned before.

To synthesize dihydrophthalic anhydride **145**, we used phthalic acid (**138**) as starting material and we applied method developed by McDonald and Reineke [49]. Since the acidity of α hydrogens of the molecule is too high due to carbonyl groups and their allylic positions, the resulting compound became very sensitive against reaction media. As a result, this study required extra care not to decompose the following products.



138 **144** **145**

Here we firstly reduced phthalic acid by using freshly prepared 3% sodium amalgam. This was followed by the formation of cyclic anhydride unit with acetic anhydride. In this way dihydrophthalic anhydride **145** was synthesized in a yield of 85 % successfully.

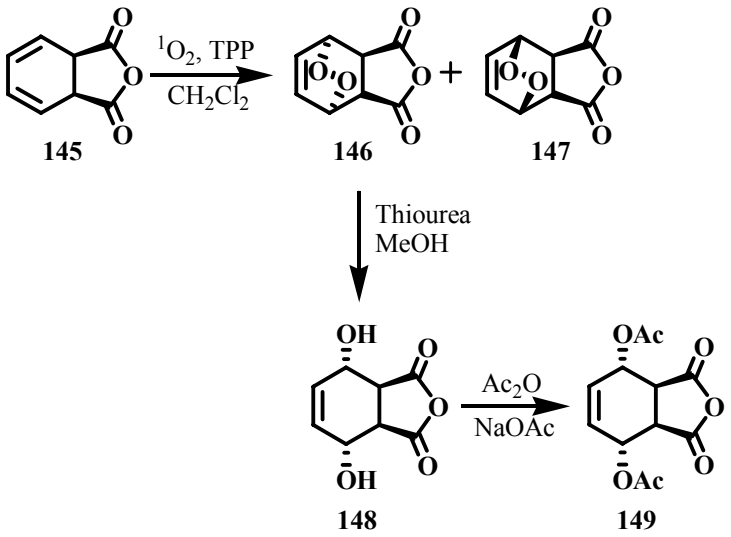
Melting point of it is consistent with the literature value. The further identification was done on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum olefinic protons resonate as AA′BB′-system between 5.83 and 6.11 ppm. Other protons resonate at 3.94 ppm as singlet.

In ^{13}C-NMR spectrum carbonyl carbon resonates at 172.2 ppm and olefinic carbons give signal at 124.9 and 118.4 ppm. Saturated carbons give signal at 41.2 ppm.

2.1.3 THE SYNTHESIS OF REL-(3aS,7aR)-3a,7a-DIHYDRO-2-BENZOFURAN-1(3H)-ONE (132)

In our previous work, we focused on the synthesis of inositol derivatives by the use of dihydrophthalic anhydride **145** as key compound instead of using lactone derivative **132**. In that study the photooxygenation was carried out in order to add oxygen functionalities to the compound, and than endoperoxide bridge was cleavaged with thiourea. We tried to acetylate the resulting diol **148** for purification and better characterization. Unfortunately, at this point we encountered an unexpected situation. Although we tried various acetylation

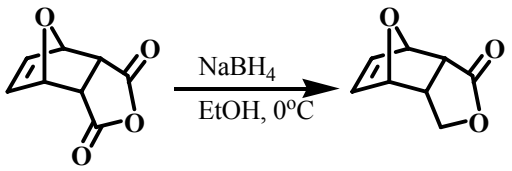
reactions, none of which gave the expected acetylated product **149**. Since all products aromatized, we finally tried acetylation reaction in buffered media. However, yield was too low since aromatic compounds formed beside the target molecule in spite of buffered medium [50].



145 **146** **147** **148** **149**

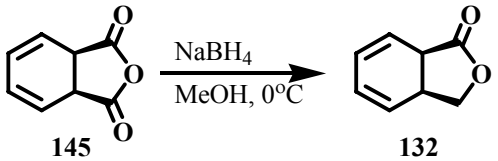
Many problems appeared during thiourea reduction of endoperoxide **146** and acetylation of resulting diol **148** because of quite acidic α-hydrogens being next to carbonyl groups and on allylic position of dienes. In order to overcome this problem we decided to reduce the reactivity of these α-hydrogens. As a result of this, we attempted to reduce anhydride unit to lactone without touching the diene system.

For this purpose we tried different reducing agents but most of them resulted in the opening of anhydride unit. So we decided to use the method of Takano and Ogasawara although the yield of product is low [51]. They used this method to reduce tricyclic anhydride **150** into tricyclic lactone **151**.



150 **151**

In our work $NaBH_4$ in methanol was used for the reduction of anhydride unit and the expected lactone **132** [52,53] was obtained as a viscous liquid in a yield of 25 %.



145 **132**

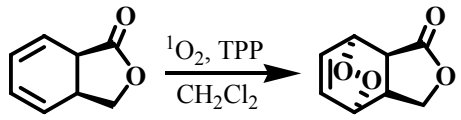
To confirm the structure of compound **132** ^{1}H-NMR and ^{13}C-NMR spectra were used. In ^{1}H-NMR spectrum we observed two sets of signals for olefinic protons. Two olefinic protons resonate between 6.02 and 5.95 ppm as multiplet due to carbonyl group and the other ones resonate between 5.67 and 5.61 ppm as multiplet. Methylene protons give signal as multiplet between 4.49 and 4.43 ppm due to inductive effect of oxygen atom. Tertiary protons give overlapped signals between 3.35 and 3.25 ppm due to carbonyl group and secondary effect of oxygen atom.

^{13}C-NMR spectrum is also consistent with the structure. Carbonyl carbon resonates at 178.4 ppm and olefinic carbons give signals at 124.9, 124.8, 124.4 and 119.5 ppm. Carbon next to oxygen atom resonates at 73.7 ppm whereas tertiary ones resonate at 40.4 and 35.2 ppm.

2.1.4 THE SYNTHESIS OF REL-(1S,2S,6S,7R)-4,8,9-TRIOXATRICYCLO [5.2.2.0^{2,6}]UNDEC-10-EN-3-ONE (133)

Being synthesized a key compound including 1,3 diene moiety enabled us to perform [4+2] cycloaddition reaction of singlet oxygen. Knowing that this reaction has performed for the similar molecules by Balcı *et al*. [6] we decided to apply same methodology to lactone derivative **132**.

As mentioned before the application of the photooxygenation reaction has a great importance since the corresponding molecule can gain two oxygen functionalities in just one step in a very effective way. The photooxygenation was carried out in methylene chloride with TPP in catalytical amounts for eight hours. At the end of the reaction we obtained corresponding endoperoxide **133** as expected.



132 **133**

Since starting compound does not have a planar structure there are two possibilities for the sides, from which oxygen molecule can approach the molecule. ^{1}H-NMR and ^{13}C-NMR spectra reveal the formation of only one isomer. The product was presumed to have an anti relationship between endoperoxide bridge and the lactone unit due to repulsive interaction between nonbonded electron pairs on the heteroatoms present in the lactone unit and on the singlet oxygen molecule.

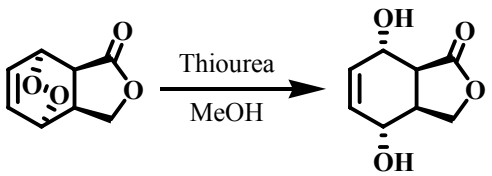
In ^{1}H-NMR spectrum olefinic protons resonate between 6.73 and 6.66 ppm as multiplet. One of the bridgehead protons (next to oxygen atoms) resonates as

multiplet between 5.00 and 4.97 (one is closer to carbonyl group) and the other one resonates as multiplet between 4.78 and 4.73. Methylene protons give rise to an AB-system. A part of the system resonates at 4.35 ppm as triplet and B part of it appears at 3.81 ppm as doublet of doublets. Tertiary protons also resonate as AB-system. A part of the system gives signal at 3.42 ppm as doublet of doublets and B part of it gives signal between 3.33 and 3.24 ppm as multiplet.

In ^{13}C-NMR spectrum, we observe carbonyl signal at 178.2 ppm. Olefinic carbons resonate at 136.4 and 134.7 ppm and carbons next to oxygen atoms give signal at 74.3, 73.1 and 72.1 ppm. Tertiary carbon next to carbonyl group resonates at 43.5 ppm whereas the other tertiary one resonates at 36.8 ppm.

2.1.5 THE SYNTHESIS OF REL-(3aS,4R,7S,7aS)-4,7-DIHYDROXY-3a,4,7,7a-TETRAHYDRO-2-BENZOFURAN-1(3H)-ONE (152)

Bicyclic endoperoxides can be readily reduced by $LiAlH_4$ or thiourea to give 2-ene-1,4-diols. Therefore the combination of photooxygenation of 1,3-dienes followed by reduction provides convenient and efficient access to the 2-ene-diols with the syn configuration. Thiourea reduction has some advantages over both catalytic hydrogenation and $LiAlH_4$ reduction. It reduces only the oxygen-oxygen bond and thus preserves most other functional groups in the molecule [41].

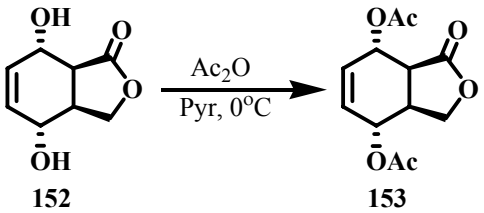


133 **152**

For this reason we applied thiourea reduction to endoperoxide **133** in methanol/acetone mixture in order to get 2-ene-1,4-diols derivative **152**. The reaction was performed at 0 ^{o}C to prevent aromatization due to sensitivity of this compound against basic medium. We obtained the expected diol derivative **152** in a yield of 79 %. Since only the oxygen-oxygen bond breaks in this reaction, it preserves the configuration at all carbon atoms. The identification of the resulting product was done on the basis of ^{1}H-NMR and IR spectra moreover the product was acetylated without further purification in order to confirm structure.

2.1.6 THE SYSTHESIS OF REL-(3aS,4R,7S,7aS)-7-(ACETYLOXY)-1-OXO-1,3,3a,4,7,7a-HEXAHYDRO-2-BENZOFURAN-4-YL ACETATE (153)

Acetylation of 1,4-diol derivative was performed for the purification and better characterization. The reaction was carried out by using acetic anhydride in pyridine at 0 ^{o}C to prevent aromatization and diacetate **153** was formed.



152 **153**

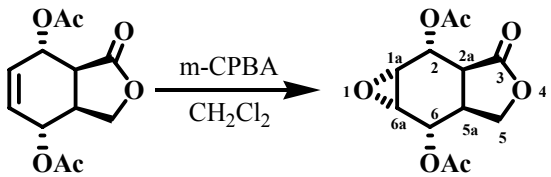
The structure of compound **153** was elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. In ^{1}H-NMR spectrum olefinic protons resonate as AB-system between 5.94 and 5.87 ppm. One of the protons attached to the carbon bearing acetoxy group resonates at 5.53 ppm as broad singlet. The other one resonates at 5.18 ppm as doublet of doublets with coupling constants J = 7.9 and 1.6 Hz. Methylene protons resonate as doublet at 4.32 ppm with a coupling constant J =

2.9 Hz. Tertiary protons resonate as AB-system in which A part resonate at 3.02 ppm as doublet of doublets with coupling constants J = 7.9 and 1.6 Hz and B part resonate at 2.77 ppm as triplet of triplets with coupling constants J = 7.9 and 2.9 Hz.

In ^{13}C-NMR spectrum there are three carbonyl carbon signals as expected. Two olefinic carbons resonate at 130.2 and 126.9 ppm. Carbons bearing acetoxy groups resonate at 70.2 and 67.6 ppm. Other signals are also consistent with the structure.

2.1.7 THE SYNTHESIS OF REL-(1aR,2R,2aS,5aS,6S,6aS)-6-(ACETYLOXY)-3-OXOOCTAHYDROOXIRENO[*f*][2]BENZOFURAN-2-YL ACETATE (154)

For further functionalization of double bond of diacetate **153** we tried hydroxylation reactions. In the first attempt, diacetate **153** was submitted to a *cis*-hydroxylation reaction with OsO_4-NMO however yield was very low. As a result of this, our attention was directed to epoxidation reaction. The diacetate **153** was reacted with *m*-CPBA to give epoxy diacetate **154** as sole isomer.



153 **154**

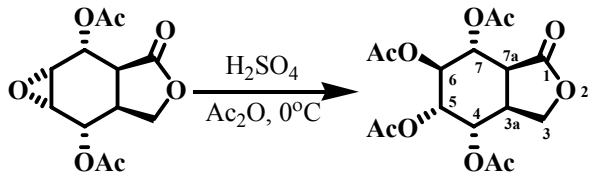
The exact configuration of the epoxide was confirmed by NMR spectral measurements and comparison with similar structures studied by Balcı *et al*. [36] showing that epoxide ring have *anti* relation with lactone ring. In ^{1}H-NMR spectrum one of the protons attached to the carbon bearing acetoxy group

resonates between 5.60 and 5.58 ppm as multiplet. The other one resonates at 5.07 ppm as doublet being splitted by one of the tertiary protons with a coupling constant J = 9.5 Hz. Methylene protons have AB-system between 4.27 and 4.18 ppm and both parts resonate as doublet of doublets. Epoxide protons also resonate as AB-system in which A part resonate at 3.59 ppm as doublet of doublets with coupling constants J = 4.6 and 1.8 Hz and B part resonate at 3.49 ppm as doublet with a coupling constant J = 4.6 Hz. Tertiary protons H_{2a} and H_{5a} also resonate as AB-system in which A part resonate between 3.03 and 2.89 ppm as multiplet and B part resonate at 2.89 ppm as doublet of doublets with coupling constants J = 9.5 and 3.9 Hz respectively. A coupling constant of J = 9.5 Hz support the *trans* relation between the related tertiary proton H_{5a} and its neighboring proton (H_6) attached to the carbon bearing acetoxy group.

In ^{13}C-NMR spectrum disappearance of signals belonging to olefinic carbons and appearance of two signals at 53.9 and 53.6 support the formation of epoxide ring. Other signals are also consistent with the structure.

2.1.8 THE SYNTHESIS OF REL-(3aS,4S,5S,6S,7R,7aS)-4,6,7-TRIS (ACETYLOXY)-1-OXOOCTAHYDRO-2-BENZOFURAN-5-YL ACETATE (155)

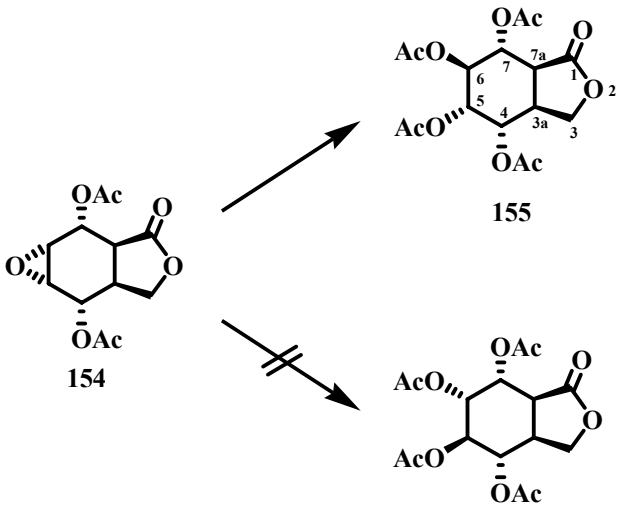
Epoxy diacetate **154** was subjected to an acid-catalyzed ring opening reaction in the presence of acetic anhydride.



154 **155**

Epoxy diacetate **154** was treated with sulfuric acid for 30 minutes followed by acetylation to give tetraacetate **155** in a yield of 75 %.

Actually, two possible products might be formed when we performed acid-catalyzed ring opening reaction. NMR spectral studies confirmed the formation of compound **155** as the sole product.



The structure of compound **155** was elucidated on the basis of ^{1}H-, ^{13}C- and 2D-NMR spectra. Full assignments for the protons attached to carbon bearing acetoxy groups are made by the help of the COSY spectrum. On the other hand full configurational assignments were able to be made by the spectral analysis of the compound **156** obtained in the next step since some of the coupling constants did not clearly show *trans* relations (High coupling constant values of axial-axial positions clearly show *trans* relation).

In ^{1}H-NMR spectrum we observe three signal groups for four protons attached to carbon bearing acetoxy groups since two of them (H_5 and H_6) are overlapped resonating as multiplet between 5.26 and 5.21 ppm. H_7 resonates at 5.37 ppm as

triplet with a coupling constant J = 2.9 Hz. H_4 resonates at 5.16 ppm as doublet of doublets with coupling constants J = 9.8 and 2.6 Hz. Methylene protons have AB-system between 4.27 and 4.19 ppm. H_{7a} resonates at 3.08 ppm as doublet of doublets with coupling constants J = 7.7 and 2.9 Hz. H_{3a} resonates between 3.03 and 2.97 ppm as multiplet.

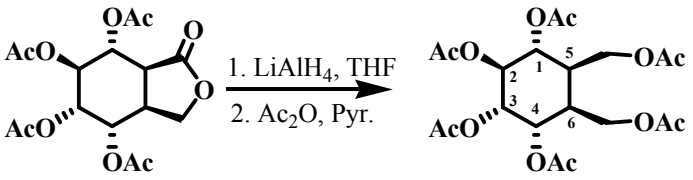
In ^{13}C-NMR spectrum there are five signals for carbonyl carbons at 173.9, 171.0, 170.4, 169.9 and 169.7 ppm as expected. Four signals are observed for carbon atoms neighboring with oxygen atoms although there should be five signals. The fifth signal can be easily seen in DEPT-135 spectrum since it belongs to methylene carbon. Other signals are also consistent with the structure.

The configuration of tetraacetate **155** is actually confirmed by the spectral analysis of the compound **156** obtained in the next step as mentined above. Since the following reactions do not affect the relevant stereogenic centers, there is no change in the configurations of acetoxy groups. As a result of this, the complete configurational assignment of compound **156** confirms the structure of tetraacetate **155** as well. The configurational assignments show that the epoxide ring in **154** undergoes a normal *trans* ring-opening reaction. The neighboring acetoxy groups are not involved anchimericly in the ring-opening reaction. This can be attributed to the *cis* configuration of the acetoxy groups with respect to the epoxide ring [36].

2.1.9 THE SYNTHESIS OF REL-(1R,2S,3S,4S,5S,6R)-2,3,4-(ACETYLOXY)-5,6-BIS[(ACETYLOXY)METHYL]CYCLOHEXYL ACETATE (156)

The next step was the reduction of lactone ring to the corresponding hydroxymethyl groups. For the synthesis of the hexaacetate **156**, tetraacetate **155**

was reacted with $LiAlH_4$ in dry THF under nitrogen. After the reaction was completed, THF was removed and the residue was dissolved in pyridine without any purification. Than, acetic anhydride was added in order to obtain hexaacetate **156** in a yield of 74 %.



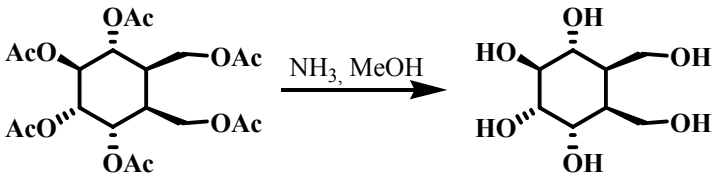
155 **156**

The structure of compound **156** was elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. In ^{1}H-NMR spectrum H_4 resonates at 5.41 ppm as triplet with a coupling constant J = 2.7 Hz. H_1 resonates at 5.32 ppm as triplet with a coupling constant J = 10.6 Hz, clearly indicating that the neighboring protons H_2 and H_5 are in *trans* positions. The appearance of H_2 at 5.24 ppm as doublet of doublets with coupling constants J = 10.6 and 10.1 Hz also support the *trans* relation of the protons H_2 and H_3. H_3 resonates at 5.13 ppm as doublet of doublets with coupling constants J = 10.1 and 3.0 Hz, clearly supports the *cis* relation of the protons H_3 and H_4. As a result of these, we assigned a *trans-trans-cis* relation to the acetoxy groups in the compound **156**. These configurational assignments also support the configuration of the former compound **155**.

In ^{13}C-NMR spectrum there are six signals for carbonyl carbons at 170.3, 170.2, 170.0, 169.9, 169.8 and 169.6 ppm as expected. Other signals are also consistent with the structure.

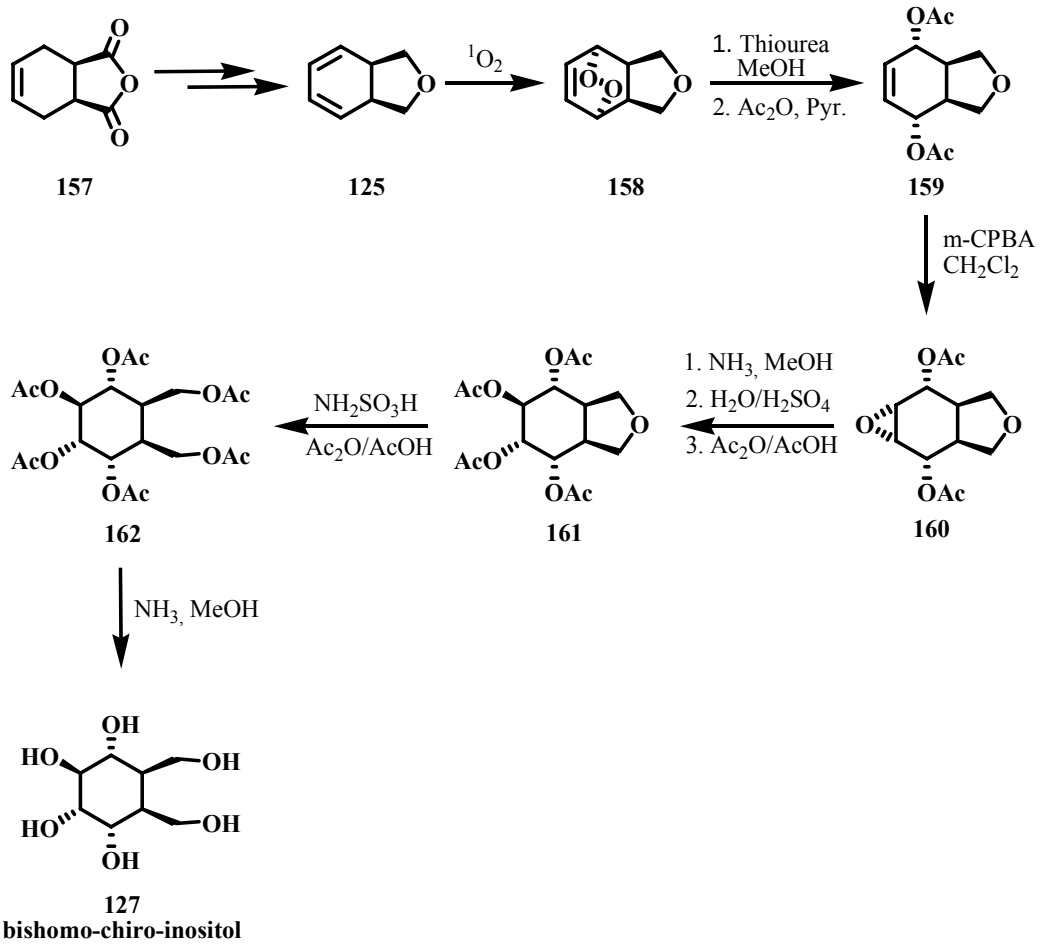
2.1.10 THE SYNTHESIS OF REL-(1R,2S,3S,4S,5S,6R)-5,6-BIS(HYDROXYMETHYL)CYCLOHEXANE-1,2,3,4-TETROL (127)

In order to synthesize the target inositol derivative deacetylation reaction was carried out. The acetate groups were removed by treatment of hexaacetate **156** with ammonia in methanol to give hexol, bishomo-*chiro*-inositol (**127**) in high yield (94 %).



156 **127**
bishomo-*chiro*-inositol

At same time our group achieved to synthesize bishomo-*chiro*-inositol (**127**) with another synthetic pathway using simple starting materials [36]. In this study, tetrahydro benzofuran derivative was used as the key compound **125**. All spectroscopic data obtained from the ^{1}H- and ^{13}C-NMR spectra were completely in agreement with the proposed structures [36].

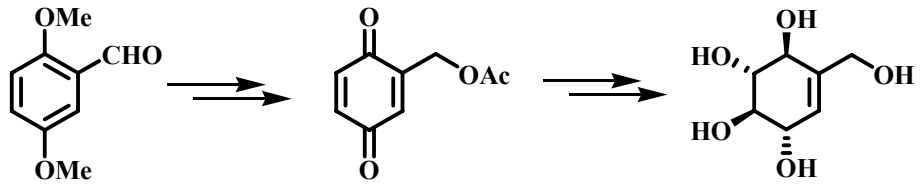


2.2 THE REACTION PATH FOR THE SYNTHESIS OF REL-(1S,2R,3R,4S)-5-(HYDROXYMETHYL)CYCLOHEX-5-ENE-1,2,3,4-TETROL (137)

When we formulated our strategy for the synthesis of hydroxymethyl substituted conduritol derivative **137** we are motivated by the presence of various simple conduritol syntheses starting from *p*-benzoquinone derivatives up to now [9,54]. Since our aim was to introduce the hydroxymethyl substituent on one of sp^2 carbon atoms in conduritols we decided to synthesize aldehyde substituted *p*-benzoquinone derivative as key compound.

At the beginning of our study we formulated and tested couple of reaction pathways attempted to synthesize aldehyde or hydroxymethyl substituted *p*-benzoquinone derivatives. Among them the most effective one was the preparation of substituted *p*-benzoquinone derivative **136** from dimethyl ethers of hydroquinone. This is because methyl ethers of phenol derivatives are stable under various reaction conditions and can be converted to the desired quinones in the latter stages of a synthetic scheme [55].

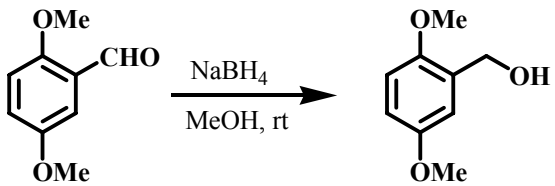
In the light of this information, we chose 2,5-dimethoxybenzaldehyde as starting material bearing aldehyde group that can be easily reduced to hydroxymethyl group. As a result the following synthetic route was developed.



135 **136** **137**

2.2.1 THE SYNTHESIS OF (2,5-DIMETHOXYPHENYL)METHANOL (163)

In the first step, 2,5-dimethoxybenzaldehyde (**135**) was reacted with $NaBH_4$ in methanol to reduce aldehyde group into hydroxymethyl group yielding dimethoxybenzyl alcohol **163** in high yield (85 %) .

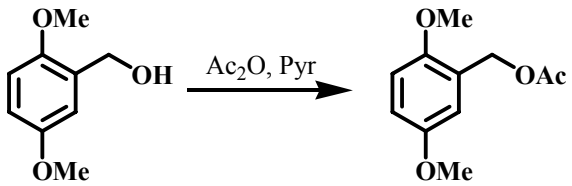


135 **163**

NMR data was in good agreement with the structure of **163** and data was also consistent with the literature data [61]. Absence of signal for an aldehyde proton indicated that reduction was succeeded. The signals belonging to methylene protons next to oxygen atom at 4.64 ppm and broad signal for hydroxyl proton at 2.58 ppm are evidences for the existence of the compound **163**. The other signals are the characteristic aromatic and methoxy group signals.

2.2.2 THE SYNTHESIS OF 2,5-DIMETHOXYBENZYL ACETATE (164)

In order to protect hydroxyl group of dimethoxybenzyl alcohol **163,** acetylation reaction was carried in the presence of acetic anhydride and pyridine at room temperature in four hours. After the work-up, the residue was recrystallized from EtOAc-hexane to get white crystals of **164** in a yield of 88 %.



163 **164**

The structure of compound **164** was elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. The sharp singlet arising from protons of acetyl group at 2.1 ppm reveals the formation of compound **164**. Methylene protons next to acetoxy group resonate at 5.14 ppm as singlet.

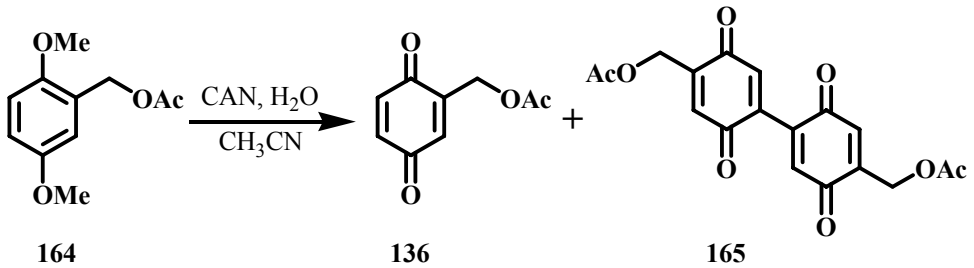
In the ^{13}C-NMR spectrum, carbonyl and methyl carbons of acetyl group resonate at 170.9 and 20.9 ppm respectively as expected. The other signals are the characteristic aromatic and methoxy group signals.

2.2.3 THE SYNTHESIS OF (3,6-DIOXOCYCLOHEXA-1,4-DIEN-1-YL)METHYL ACETATE (136)

The next step was the synthesis of *p*-benzoquinone derivative **136** as a key compound via oxidative demethylation. So far, oxidative demethylation has been achieved by using cerium(IV) ammonium nitrate (CAN), hypervalent iodine reagents (PIFA; phenyliodine(III) bis(trifluoroacetate), PIDA; phenyliodine(III) diacetate.), nitric acid, silver(II) oxide (AgO)-mineral acid, manganese dioxide (MnO_2)-nitric acid, cobalt(II) fluoride (CoF_3), and NBS-H_2SO_4 [55].

Among them we performed oxidative demethylation by using CAN and PIFA. PIFA oxidation gave same product that was formed with the use of CAN in similar yields. Since PIFA is much more expensive we preferred to study with CAN instead of PIFA. CAN oxidative demethylation caused formation of dimeric side product however we reduced yield of side product by performing reaction at low temperatures.

So hydroquinone dimethylether derivative **164** was oxidized to *p*-benzoquinone derivative **136** via oxidative demethylation in 30 minutes by using aqueous solution of CAN with a yield of 67 %. The dimeric side product **165** was separated from the major product **164** by the filtration of reaction mixture in which yellow crystals of dimeric product **165** was precipitated at -5 ^{o}C during the reaction in a yield of 16 %.

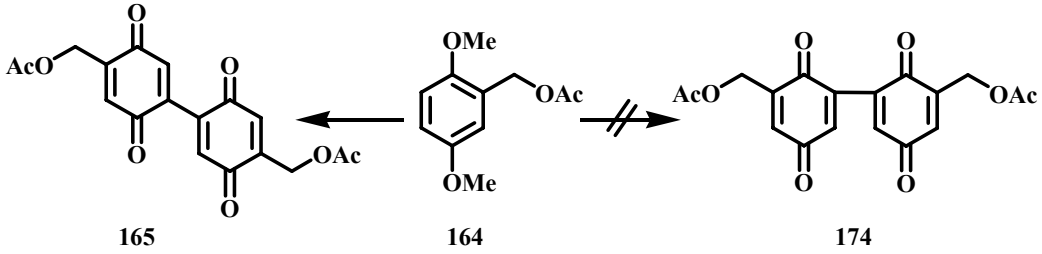


164 **136** **165**

The structures of compounds **136** and **165** were elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, dissappearance of methoxy groups clearly indicates that oxidative demethylation is succeeded. The olefinic protons resonate as multiplet between 6.81-6.75 ppm. The other olefinic proton resonates as quartet due to methylene protons in the allylic position and olefinic proton like *meta* positioned protons of aromatic compounds. Since the couplings are quite similar coincidentally it resonates as quartet. Methylene protons resonate as doublet at 4.99 ppm due to olefinic proton.

In the ^{13}C-NMR spectrum, the apperance of carbonyl carbons at 185.8 and 184.9 ppm also reveals the formation of *p*-benzoquinone derivative **136**.

The characterization of the dimer **165**, as a side product, was done on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum we observe the proton signals having nearly the same chemical shifts with that for the monomer **136**. In this case the area under each peak is different which supports the dimeric structure rather than the monomer.



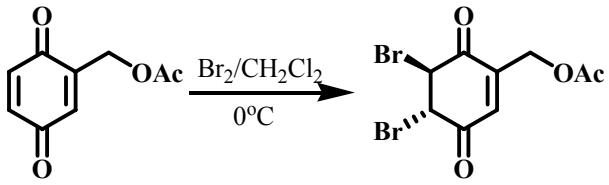
165 **164** **174**

Because the olefinic protons resonate as triplet due to allylic positioned methylene protons we understand that spectrum belongs to dimeric compound **165** rather than the other possible dimeric compound **174**. If the structure belonged to dimer **174**, olefinic protons should give further splitting with the other olefinic protons.

In the ^{13}C-NMR spectrum of compound **165**, we observe nine carbon signals and each of them belongs to two identical carbon atoms due to its dimeric structure.

2.2.4 THE SYNTHESIS OF [REL-(4S,5S)-4,5-DIBROMO-3,6-DIOXOCYCLOHEX-1-EN-1-YL]METHYL ACETATE (166)

In this step we aimed to brominate only one double bond of key compound **136** having two double bonds in unequal reactivities actually. Whereas one of the double bond is substituted with hydroxymethyl group, the other one is unsubstituted. The quinone derivative **136** was brominated at low temperature to give only the *trans*-dibromo compound **166** in high yield. The regiospecific addition of Br_2 to the unsubstituted double bond can be attributed to the steric effect caused by hydroxymethyl group. Furthermore the reaction was carried out at low temperature in order to increase selectivity of bromine atoms [56]. Since bromination reactions occur via bromonium cation formation, bromine atoms on the product **166** are in *trans* position [57]. Addition of equimolar bromine to *p*-benzoquinone **136** provided dibromo compound **166** in a yield of 90 %.



136 **166**

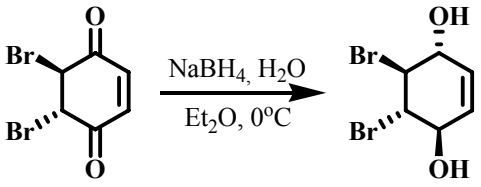
The structure of compound **166** was elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, olefinic proton resonates as quasi-quartet due to the coupling with allylic protons and α-proton. Methylene protons have an AB system and each part of the system splits into doublet of doublets due to geminal and allylic couplings between methylene protons themselves and olefinic proton

respectively. Methylene protons have a geminal coupling constant of 17.4 which is a high value caused by neighboring π-bond directly attached to the methylene carbon atom. Protons attached to the carbon atoms bearing bromine atoms have also AB-system and each part of the system splits into doublet due to vicinal coupling.

In the ^{13}C-NMR spectrum of compound **166**, we observe nine carbon signals with the expected chemical shifts. The disappearance of two olefinic carbons and appearance of two new signals at 45.2 and 45.0 belonging carbon atoms bearing bromine atoms clearly reveal the structure of dibromo compound **166**.

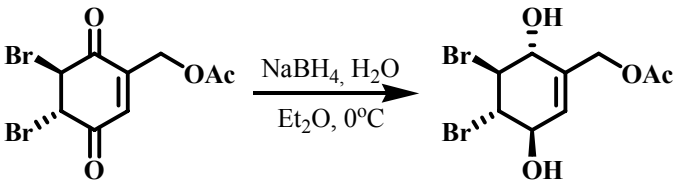
2.2.5 THE SYNTHESIS OF [REL-(3R,4S,5S,6R)-4,5-DIBROMO-3,6-DIHYDROXYCYCLOHEX-1-EN-1-YL]METHYL ACETATE (169)

Carbonyl groups can be reduced in the presence of metal hydrides like sodium or lithium borohydrides. However, if a molecule has an α,β-unsaturated system, reduction should be performed in certain conditions to prevent the reduction of double bond together with the carbonyl groups. Vogel *et al*. reported that double bonds were not reduced upon treatment of dibromo compound **167** with sodium borohydride in the presence of water and diethyl ether at 0 ^{o}C. The resulting diol **168** was formed as the sole product [56].



167 **168**

By using same method, dibromo compound **166** was reduced to produce diol **169** in a yield of 70 % without purification. Here only one isomer was obtained since bromine atoms have *trans* configuration. Hydride ions can only attack to carbonyl groups from the same side with the bromine atoms.

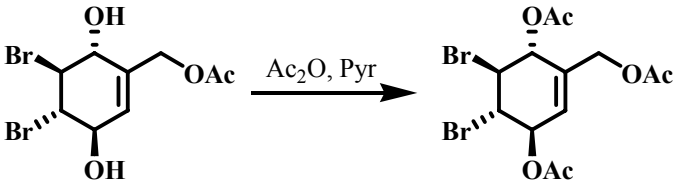


166 **169**

In order to make more accurate characterization of diol **169**, the crude product was acetylated.

2.2.6 THE SYNTHESIS OF REL-(1R,4R,5S,6S)-4-(ACETYLOXY)-2-[(ACETYLOXY)METHYL]-5,6-DIBROMOCYCLOHEX-2-EN-1-YL ACETATE (170)

We performed acetylation of diol derivative for the purification and better characterization. The reaction was carried out by using acetic anhydride in pyridine at 0 ^{o}C and triacetate **170** was formed. The reaction was performed at low temperatures since we observed the formation of aromatic by products when it was proceeded at room temperature.



169 **170**

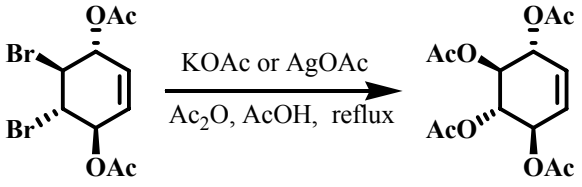
The crude product was purified via column chromatography and further purification was done by crystallization from ether-hexane solution in a yield of 74 %.

The structure of compound **170** was determined on the basis of ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, olefinic proton resonates at 5.82 ppm as singlet. One of the protons attached to the carbon bearing acetoxy group resonates at 5.91 ppm as doublet and the other one resonates between 5.72 and 5.70 ppm as multiplet. Methylene protons resonate as AB-system and both parts of the system resonate as doublet with a coupling constant J = 13.4 Hz at 4.66 and 4.39 ppm respectively. Protons attached to carbons bearing bromine atoms also have AB-system. A part of the system resonate at 4.33 ppm as doublet of doublets with coupling constants J = 12.3 and 11.4 Hz. B part of the system resonate at 4.29 ppm as doublet of doublets with coupling constants J = 12.3 and 10.9 Hz. It means that coupling constant between these protons is 12.3 Hz and this value is consistent with a typical axial/axial coupling constant in cyclohexene ring, indicating *trans* configuration and equatorial/equatorial position of the bromine atoms. Other coupling constants (11.4 and 10.9 Hz) also confirm *trans* configuration of the neighboring acetoxy groups and bromine atoms.

In the ^{13}C-NMR spectrum of compound **170**, we observe three carbonyl carbon signals resonating at 170.2, 169.8 and 169.6 ppm as expected. There are three signals belonging to carbons bearing acetoxy group resonating at 72.9, 71.7 and 62.6 ppm and the last one belongs to methylenic carbon atom. Other signals are also consistent with the structure.

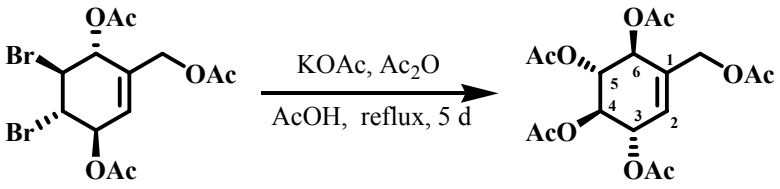
2.2.7 THE SYNTHESIS OF [REL-(3S,4R,5R,6S)-3,4,5,6-TETRAKIS(ACETYLOXY)CYCLOHEX-1-EN-1-YL]METHYL ACETATE (173)

The next step was the substitution of bromine atoms and for this purpose the method reported by Taylor *et al.* [54] was used. In their study triacetate **171** was treated with silver or potassium acetate and acetic anhydride in acetic acid in order to substitute the bromine atoms with acetoxy groups.



171 **172**

In our study we used potassium acetate and acetic anhydride by refluxing in acetic acid to substitute bromine atoms providing pentaacetate **173**. After the work-up process, the crude product was recrystallized from EtOAc-hexane mixture in a yield of 77 %.



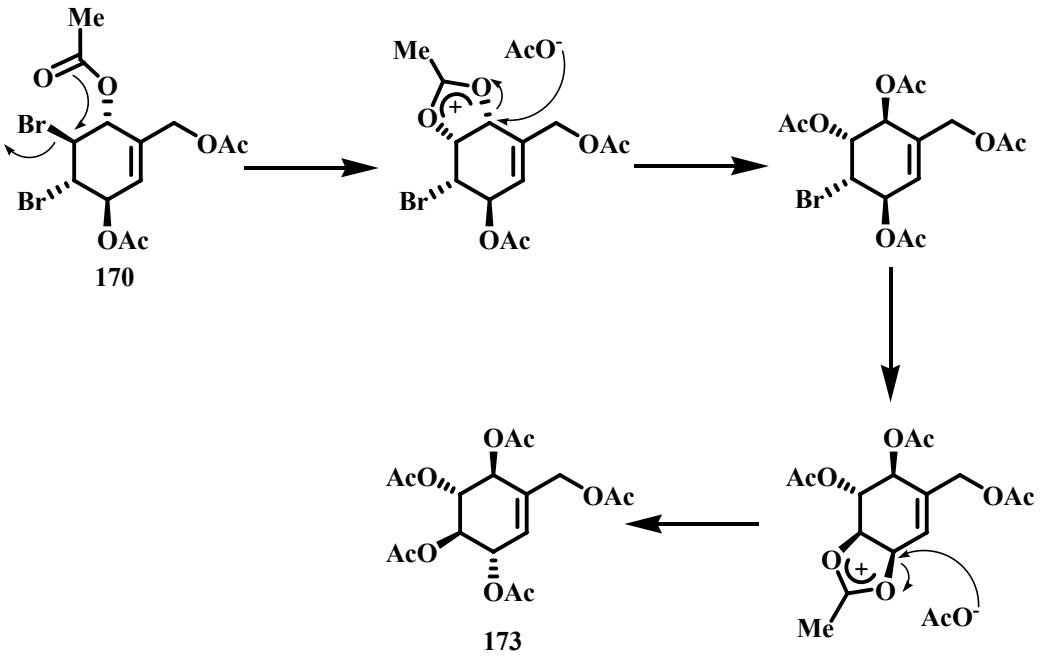
170 **173**

The structure of compound **173** was elucidated on the basis of ^{1}H-,^{13}C- and 2D-NMR spectra. In the ^{1}H-NMR spectrum, H_1 resonates at 5.79 ppm as broad doublet with a coupling constant J = 7.0 Hz, indicating H_2 is in *trans* position. H_5 resonates at 5.76 ppm as broad singlet and this signal is belongs to olefinic

proton which is also confirmed by HMQC spectrum. H_4 resonates at 5.59 ppm as broad doublet with a coupling constant J = 7.1 Hz, indicating H_3 is in *trans* position. H_2 and H_3 resonate as AB-system in which A part resonates at 5.37 ppm as doublet of doublets with coupling constants J = 10.9 and 7.8 Hz. B part of the system resonates at 5.32 ppm as doublet of doublets with coupling constants J = 10.9 and 7.1 Hz, clearly indicating H_2 and H_3 are in *trans* position and their neighboring protons are also in *trans* position.

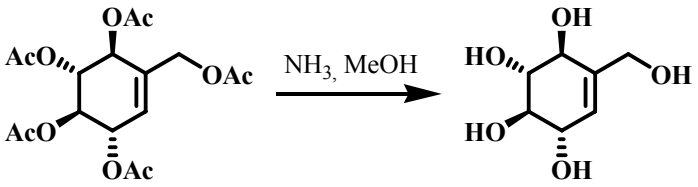
These results show that the relative configuration of the acetoxy groups is *trans/trans/trans*. The stereoselective formation of **173** can be explained by the neighboring group participation [59,60].

In the ^{13}C-NMR spectrum of compound **173**, we observe five carbonyl carbon signals resonating at 170.2, 170.1, 170.0, 169.9 and 169.7 ppm as expected. Other signals are also consistent with the structure.



2.2.8 THE SYNTHESIS OF REL-(1S,2R,3R,4S)-5-(HYDROXYMETHYL) CYCLOHEX-5-ENE-1,2,3,4-TETROL (137)

The final step was the conversion of acetoxy groups into hydroxy groups by deacetylation reaction. The acetate groups were removed by treatment of pentaacetate **173** with ammonia in methanol to give hydroxymethyl containing conduritol **137** quantitatively in two hours.

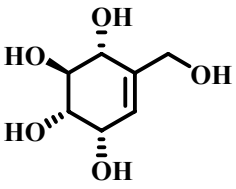


173 **137**

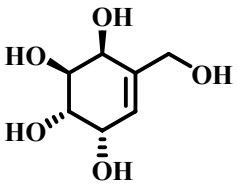
The structure of compound **137** was determined on the basis of ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, olefinic proton resonates at 5.6 ppm as singlet. –OH protons resonate at 4.7 ppm as broad singlet. Tertiary protons next to hydroxyl groups resonate between 4.22 and 4.15 ppm as multiplet and at 4.05 ppm as doublet. Methylene protons have AB-system and each part resonates as doublet of doublets.

In the ^{13}C-NMR spectrum of compound **137**, disappearance of carbonyl carbon signals support the structure. Other signals are also consistent with the structure.

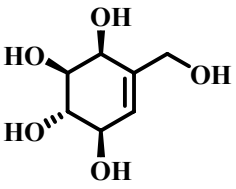
The synthesis of compound **137** [40] and some other configurational isomers of the compound **137** [32,37,62] were reported related to biologically interesting valienamine (**90**).



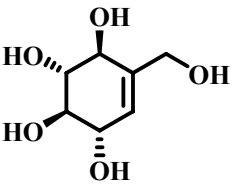
111
(+)-Streptol



174
(+)-MK7607



175
1-*epi*-(+)-MK7607



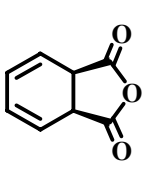
137

CHAPTER 3

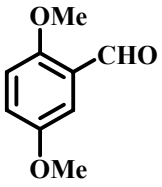
CONCLUSION

The cyclitol derivatives as natural products have attracted a great deal of attention due to their biological activities and their synthetic roles as starting material in the preparation other bioactive molecules. For this reason, the synthesis of cyclitol derivatives remains an active area of current research and new approaches continue to be explored to achieve greater preparative efficiency and higher levels of stereo- and regiocontrol. Consequently, as a researcher to find short, efficient and stereospecific methodology for the syntheses of them has an importance.

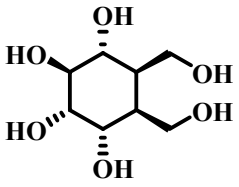
Since we know that many biologically active cyclitol derivatives like valienamine, streptol and *etc*. contain hydroxymethyl groups we aimed to investigate a novel and efficient routes leading to syntheses of hydroxymethyl containing inositol and conduritol derivatives.



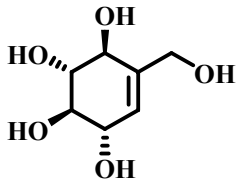
145



135



127



137

The stereoselective synthesis of hydroxymethyl containing inositol and conduritol derivatives **127** and **137** were achieved successfully. In the synthesis

of bishomo-*chiro*-inositol (**127**) we used dihydrophthalic anhydride **145** as starting material and introduced a complex stereochemistry in a very simple way by the use of photooxygenation and epoxidation reactions. The synthesis of hydroxymethyl containing conduritol **137** was achieved with well known reactions in an efficient way, starting from commercially available 2,5-dimethoxybenzaldehyde (**135**).

The inhibitory activity of bishomo-*chiro*-inositol (**127**) was screened against α-glycosidase but it showed no inhibition [36]. The inhibitory activity of hydroxymethyl containing conduritol **137** is under investigation.

As a conclusion, stereoselective synthesis of bishomo-*chiro*-inositol (**127**) and hydroxymethyl containing conduritol **137** were accomplished with a very efficient way and we believe that these molecules and synthetic methodologies can also be used for the synthesis of other cyclitol derivatives in the future.

CHAPTER 4

EXPERIMENTAL

4.1 GENERAL CONSIDERATIONS

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

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

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

All the solvent purifications were done as stated in the literature [58].

4.2 THE REACTION PATH FOR THE SYNTHESIS OF REL-(1R,2S,3S,4S,5S,6R)-5,6-BIS(HYDROXYMETHYL)CYCLOHEXANE-1,2,3,4-TETROL (127)

4.2.1 The Synthesis of 3 % Sodium amalgam

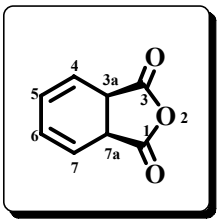
Clean sodium (22.8 g) is placed in a 500 mL three necked round bottomed flask, provided with a dropping funnel containing 750 g of mercury. The air inside the flask was replaced by dry nitrogen with a continuous flow (by passing from inlet to outlet sockets). About 10 mL of mercury were added to commence exothermic reaction then reaction was maintained by the slow addition of the mercury. When about half the mercury was introduced, the amalgam started to solidify. After the addition of all mercury, the cold amalgam was taken into mortar and powdered in it under the stream of nitrogen gas. Sodium amalgam was stored in a tightly stoppered bottle [58].

4.2.2 The Synthesis of rel-(1R,2R)-cyclohexa-3,5-diene-1,2-dicarboxylic acid (144)

A vigorously stirred, particle-free solution of 15 g (0.09 moles) of phthalic acid (**138**) and 26 g of sodium acetate in 150 mL of water was cooled in an ice bath while a total of 385 g of 3% sodium amalgam was added with small portions. With each portion of added amalgam there was also added 3-4 mL (54 mL total) of 50% acetic acid. After the addition completed, the solution was filtered through a filter paper by decanting it from the mercury. The cold filtrate was treated with 150mL of cold 20% sulfuric acid; the acid began to crystallize immediately. After standing for a night at 20–22 ^{o}C, the acid was collected by suction filtration, washed well with ice-cold water, removing excess sulfuric

acid, and dried in the air [49] giving 12 g (80%) of crystalline product, m.p. 209-211°C.

4.2.3 The Synthesis of rel-(3aR,7aS)-3a,7a-dihydro-2-benzofuran-1,3-dione (145)



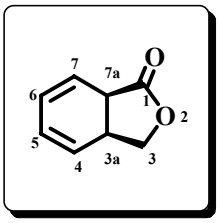
To 90 mL of acetic anhydride, which was magnetically stirred under a nitrogen atmosphere and heated to 98-100 ^{o}C, was added 12 g (0.07 moles) of trans-1,2-dihydrophthalic acid **144**. After solution of diacid became completely clear (30 min), yellow solution was cooled to room temperature and acetic anhydride was carefully removed (at 50-60 ^{o}C) in vacuo using an oil pump and liquid nitrogen cooled trap to collect distillate. After removing acetic anhydride, the residue was cooled to form crystals. It was washed with hexane and dried in the air [49] giving 9.5 g (85%) of crystalline product, m.p. 105-107 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.11 (d, A part of the AA′BB′-system, J=9.1 Hz, H_4 and H_7), 5.83 (d, B part of the AA′BB′-system, J=9.1 Hz, H_5 and H_6), 3.94(s, H_{3a} and H_{7a}).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 172.2 (2C), 124.9 (2C), 118.4 (2C), 41.2 (2C).

IR (cm^{-1}): 1690, 1410, 1230, 900, 770, 690.

4.2.4 The Synthesis of rel-(3aS,7aR)-3a,7a-dihydro-2-benzofuran-1(3H)-one (132)



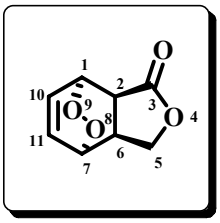
To a solution of 3 g of anhydride **145** (0.02 moles) in 75 mL of methanol was added in small portions 1 g of sodium borohydride (0.026 moles) with stirring and cooling in an ice bath. The reaction mixture was allowed to come slowly to 20 ^{o}C by permitting the ice in the cooling bath to melt (about 2 hours). Then, the reaction mixture was cooled to 0 ^{o}C again and acidified with 10 % hydrochloric acid to pH 2. After removal of nearly whole methanol, the residue was extracted with CH_2Cl_2 and the extract washed successively with water, saturated $NaHCO_3$ solution and water. It was dried over anhydrous magnesium sulfate and filtered [51]. The solvent was evaporated and 0.63 g of lactone as a colorless liquid (25 %) was obtained.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.02-5.95 (m, H_4 and H_7), 5.67-5.61 (m, H_5 and H_6), 4.49-4.43 (m, H_3), 4.03-3.96 (m, $H_{3'}$), 3.35-3.25 (m, H_{3a} and H_{7a}).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 178.4, 124.9, 124.8, 124.4, 119.5, 73.7, 40.3, 35.2.

IR (cm^{-1}): 1750, 1380, 1150, 1000, 690.

4.2.5 The Synthesis of rel-(1S,2S,6S,7R)-4,8,9-trioxatricyclo[5.2.2.$0^{2,6}$]undec-10-en-3-one (133)



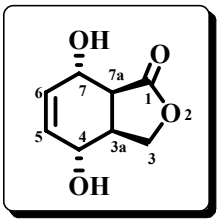
2 g of lactone **132** (0.015 moles) and a catalytic amount of mesa-tetraphenylporphin (TPP) were dissolved in 250 mL of CH_2Cl_2 in the flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (500W) for eight hours while the dry oxygen gas was bubbled through with a constant rate at room temperature. The solvent was removed by a rotary evaporator. The yield of endoperoxide **133** was 90 % as yellow crystals, m.p. 110-113 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.73-6.66 (m, H_{10} and H_{11}), 5.0-4.97 (m, H_1), 4.78-4.73 (m, H_7), 4.35 (t, A part of the AB-system, J=9.8 Hz, H_5), 3.81 (dd, B part of the AB-system, J=9.8 and 4.0 Hz, $H_{5'}$), 3.42 (dd, A part of the AB-system, J=9.8 and 5.0 Hz, H_2), 3.33-3.24 (m, B part of the AB-system, H_6).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 178.2, 136.4, 134.7, 74.3, 73.1, 72.1, 43.5, 36.8.

IR (KBr, cm^{-1}): 2980, 1900, 1695, 1500, 1306, 1039, 991.

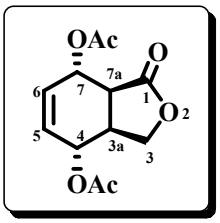
4.2.6 The Synthesis of rel-(3aS,4R,7S,7aS)-4,7-dihydroxy-3a,4,7,7a-tetrahydro-2-benzofuran-1(3H)-one (152)



To a magnetically stirred solution of 1.15 g of thiourea (0.015 mmol) in 20 mL of methanol was added slowly a solution of endoperoxide **133** (2.1 g, 0.012 moles) in 15 mL of acetone. After the reaction mixture was stirred for an additional two hours at 0 ^{o}C, it was filtered and the solvents were removed. 1.7 g of diol **152** was obtained in the yield of 79 %. Without purification it was acetylated.

IR (cm^{-1}): 3360, 3270, 1750, 1600, 1400, 1090, 700.

4.2.7 The Synthesis of rel-(3aS,4R,7S,7aS)-7-(acetyloxy)-1-oxo-1,3,3a,4,7,7a-hexahydro-2-benzofuran-4-yl acetate (153)



To a magnetically stirred solution of **152** (2 g, 0.012 moles) in 10 mL of pyridine was added acetic anhydride (4.8 g, 0.047 moles) dropwise at 0 ^{o}C. The reaction mixture was stirred for an additional 8 hours at 0 ^{o}C. The mixture was poured into 50 mL of HCl solution in ice and extracted with ether (3 x 50 mL). The

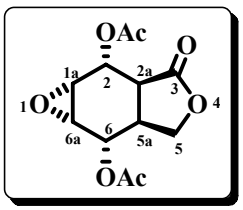
combined organic extracts were washed with $NaHCO_3$ solution and water and then dried over $MgSO_4$. The removal of solvent under reduced pressure and crystallization of the residue from CH_2Cl_2/hexane (2:1) gave 2.4 g (80%) of diacetate **(153)** as white crystals, m.p. 125-127 ^oC.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.94 (dt, A part of the AB-system, J=10.4 and 2.6 Hz, H_6), 5.87 (d, B part of the AB-system, J=10.4 Hz, H_5), 5.53 (bs, H_7), 5.18 (dd, J=7.9 and 1.6 Hz, H_4), 4.32 (d, J=2.9 Hz, H_3 and $H_{3'}$), 3.02 (dd, A part of the AB-system, J=7.9 and 1.6 Hz, H_{7a}), 2.77 (tt, B part of the AB-system, J=7.9 and 2.9 Hz, H_{3a}), 2.12 (s, 3H), 2.09 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 173.9, 170.5, 169.8, 130.2, 126.9, 118.5, 70.2, 67.6, 64.0, 42.6, 36.7, 20.9 (2C).

IR (cm^{-1}): 1780, 1720, 1700, 1240, 1200, 1020, 950.

4.2.8 The Synthesis of rel-(1aR,2R,2aS,5aS,6S,6aS)-6-(acetyloxy)-3-oxooctahydrooxireno[f][2]benzofuran-2-yl acetate (154)



To 0.55 g (2.16 mmol) of diacetate **153** in 20 mL of CH_2Cl_2 was added 0.411 g (1.67 mmol, 70 %) of *m*-chloroperbenzoic acid. The resulting mixture was refluxed for 8 days, and then it was extracted with 50 % $NaHSO_3$ solution. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (50 mL) and dried ($MgSO_4$). Then, the solvent was removed under reduced pressure to

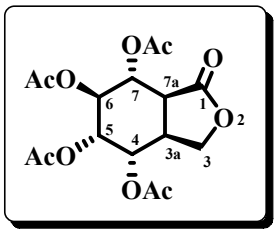
give 0.46 g (79 %) of epoxide **154**, which was crystallized from EtOAc, m.p. 152-153 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.60-5.58 (m, H_2), 5.07 (d, J=9.5 Hz, H_6), 4.27 (dd, A part of the AB-system, J=9.7 and 5.7 Hz, H_5), 4.18 (dd, B part of the AB-system, J=9.7 and 1.3 Hz, $H_{5'}$), 3.59 (dd, A part of the AB-system, J=4.6 and 1.8 Hz, H_{1a}), 3.49 (d, B part of the AB-system, J=4.6 Hz, H_{6a}), 3.03-2.97 (m, A part of the AB-system, H_{2a}), 2.89 (dd, B part of the AB-system, J=9.5 and 3.9 Hz, H_{5a}), 2.16 (s, 3H), 2.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 175.9, 171.7, 171.0, 69.6, 68.9, 67.4, 53.9, 53.6, 42.1, 35.9, 20.9 (2C).

IR (cm^{-1}): 1770, 1720, 1370, 1220, 1160, 1050, 600.

4.2.9 The Synthesis of rel-(3aS,4S,5S,6S,7R,7aS)-4,6,7-tris(acetyloxy)-1-oxooctahydro-2-benzofuran-5-yl acetate (155)



To a magnetically stirred solution of epoxide **154** (0.4 g, 1.5 mmol) in 10 mL of CH_2Cl_2 and 2 mL of acetic anhydride was added 7 drops of concentrated H_2SO_4 at -5 ^{o}C. The reaction mixture was stirred for 30 minutes. Afterwards, 10 mL of water was added and it was stirred for a while. After the removing of CH_2Cl_2 the reaction mixture was extracted with ether (3x50 mL). The combined organic

extracts were washed with $NaHCO_3$ solution and water and then dried over $MgSO_4$. The removal of solvent under reduced pressure and crystallization of the residue from EtOAc/hexane (2:1) gave 0.41 g (75 %) of tetraacetate **155**, m.p. 150-155 ^oC.

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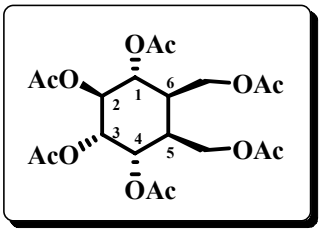
^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.37 (t, J=2.9 Hz, H_7), 5.26-5.21 (m, H_5 and H_6), 5.16 (dd, J=9.8 and 2.6 Hz, H_4), 4.27 (dd, A part of the AB-system J=9.6 and 5.2 Hz, H_3), 4.19 (dd, B part of the AB-system, J=9.6 and 2.0 Hz, $H_{3'}$), 3.08 (dd, J=7.7 and 2.9 Hz, H_{7a}), 3.03-2.97 (m, H_{3a}), 2.11 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 173.9, 171.0, 170.4, 169.9, 169.7, 68.6 (2C), 67.9, 67.3, 66.5, 42.9, 35.4, 20.9, 20.8, 20.8, 20.7.

IR (cm^{-1}): 1730, 1710, 1360, 1200, 1020.

4.2.10 The Synthesis of rel-(1R,2S,3S,4S,5S,6R)-2,3,4-(acetyloxy)-5,6-bis[(acetyloxy)methyl]cyclohexyl acetate (156)



0.5 g (1.34 mmol) of tetracetate **155** was dissolved in 15 mL of dry THF under nitrogen. 130 mg (3.35 mmol) of $LiAlH_4$ in 15 mL dry THF was added in small portions to this mixture at 0 ^oC. After the mixture came to room temperature it was magnetically stirred for additional six hours. Then, it was hydrolyzed with

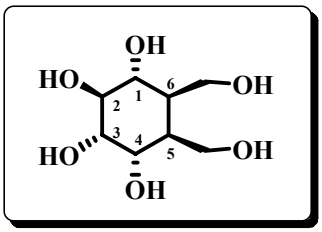
water until the gas evolution completed. After evaporation of solvent, pyridine (10 mL) and acetic anhydride (2 mL) were added to the residue, followed by stirring for eight hours at room temperature. The resulting mixture was poured into 50 mL of HCl solution in ice and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ solution and water and then dried ($MgSO_4$). After solvent was removed, 0.45 g of hexaacetate **156** was obtained as colorless liquid with a yield of 74 %.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.41 (t, J=2.7 Hz, H_1), 5.32 (t, J=10.6 Hz, H_2), 5.24 (dd, J=10.6 and 10.1 Hz, H_3), 5.13 (dd, J=10.1 and 3.0 Hz, H_4), 4.27-4.17 (m, 3H), 3.93 (dd, J=11.7 and 3.8 Hz, 1H), 2.58-2.51 (m, H_5 or H_6), 2.40-2.36 (m, H_6 or H_5), 2.08 (s, 6H), 1.96 (s, 6H), 1.94 (s, 3H), 1.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 170.3, 170.2, 170.0, 169.9, 169.8,169.6, 71.6, 70.1, 69.8, 69.6, 61.5, 61.1, 39.3, 36.8, 20.9, 20.8, 20.6, 20.6, 20.5 (2C).

IR (KBr, cm^{-1}): 2964, 1746, 1433, 1369, 1230, 1040, 952.

4.2.11 The Synthesis of rel-(1R,2S,3S,4S,5S,6R)-5,6-bis(hydroxymethyl) cyclohexane-1,2,3,4-tetrol (127)



0.5 g (1.08 mmol) of hexaacetate **156** was dissolved in methanol (25 mL), NH_3(g) was passed through the solution for five hours, and the solvent was

concentrated in vacuo to give 214 mg of **127** (94 %) as a white solid from EtOH, mp 175-177 ^{o}C

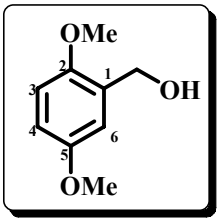
^{1}H-NMR (400 MHz, DMSO, δ:ppm): 4.55 (bs, 1H), 4.43 (bs, 2H), 4.34 (bs, 1H), 4.27 (bs, 2H), 3.88 (bs, 1H), 3.70-3.67 (m, 1H), 3.53-3.50 (m, 1H), 3.46-3.43(m, 1H), 3.37 (bs, 1H), 3.3 (bd, J=7.9 Hz, 1H), 3.27-3.17 (m, 2H), 2.01-1.94 (m, 2H).

^{13}C-NMR (100 MHz, DMSO, δ:ppm): 75.4, 71.9, 71.4, 70.2, 60.9, 58.6, 43.3, 40.1.

IR (KBr, cm^{-1}): 3400, 2931, 2904, 1447, 1382, 1343, 1324, 1256, 1239, 1214, 1196.

4.3 THE REACTION PATH FOR THE SYNTHESIS OF REL-(1S,2R,3R,4S)-5-(HYDROXYMETHYL)CYCLOHEX-5-ENE-1,2,3,4-TETROL (137)

4.3.1 The Synthesis of (2,5-dimethoxyphenyl)methanol (163)



$NaBH_4$ (546 mg, 14.4 mmol) was slowly added to magnetically stirred solution of 2,5-dimethoxybenzaldehyde **135** (2 g, 12 mmol) in 60 mL of methanol. The resulting mixture was stirred for 30 minutes and concentrated under reduced

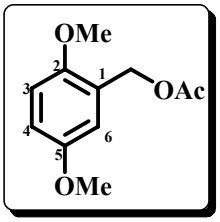
pressure and residue was partitioned between CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield 1.7 g (85 %) of **163** as yellow-oily product.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.89 (bs, H_6), 6.80-6.75 (m, H_3 and H_4), 4.64 (bs, -CH_2-), 3.79 (s, -OCH_3), 3.75 (s, -OCH_3), 2.58 (bs, -OH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 153.7, 151.5, 130.3, 114.7, 112.9, 111.2, 61.7, 55.8, 55.7.

IR (cm^{-1}): 3300, 1500, 1210, 1040, 800, 710.

4.3.2 The Synthesis of 2,5-dimethoxybenzyl acetate (164)



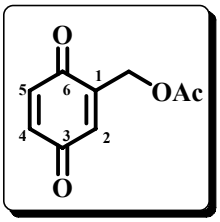
To a stirred solution of **163** (2 g, 11.9 mmol) in 20 mL of pyridine was added 4.5 mL of acetic anhydride (47.6 mmol). The mixture was stirred for four hours and partitioned between CH_2Cl_2 and water. The organic extracts were washed with $NaHCO_3$ solution and water and then dried ($MgSO_4$). After the solvent was removed and residue was recrystallized from EtOAc/hexane to give 2.2 g of acetylated compound **164** as white crystals with a yield of 88 %, m.p. 65-67 ^oC.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.91 (bs, H_6), 6.81 (bs, H_3 and H_4), 5.14 (s, -CH_2-), 3.79 (s, -OCH_3), 3.76 (s, -OCH_3), 2.10 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 170.9, 153.5, 151.7, 125.4, 115.7, 113.7, 111.6, 61.6, 56.1, 55.7, 20.9.

IR (cm^{-1}): 1720, 1470, 1230, 1020, 880, 830, 700.

4.3.3 The Synthesis of (3,6-dioxocyclohexa-1,4-dien-1-yl)methyl acetate (136)



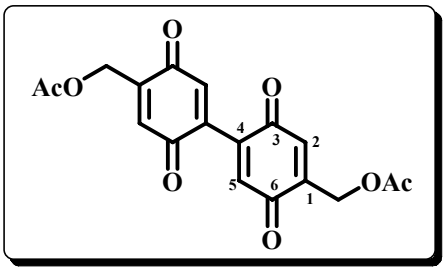
To a stirred solution of **164** (1 g, 4.76 mmol) in 25 mL of CH_3CN at -5 ^oC was added dropwise a solution of CAN (7.82 g, 14.3 mmol) in 25 mL water. The mixture was stirred for an additional 30 minutes. The resulting mixture was filtered to separate dimeric product, then the filtrate was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield 0.57 g (67 %) of yellow crystals of 1,4-benzoquinone derivative **136** m.p. 124-126 ^oC.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.81-6.75 (m, H_4 and H_5), 6.69 (q, J=1.7 Hz, H_2), 4.99 (d, J=1.7 Hz, 2H), 2.18 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 185.8, 184.9, 168.8, 141.9, 135.5, 135.4, 130.4, 58.3, 58.1, 19.5.

IR (cm^{-1}): 1740, 1630, 1230, 1030, 920, 800.

Spectral Data for Dimeric Benzoquinone Derivative (165)



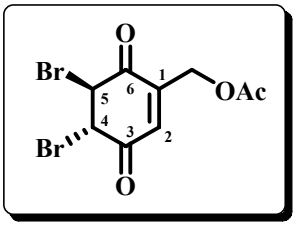
Yellow crystalline compound, m.p. 150-153 ^{o}C

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.85 (s, $2H_5$), 6.78 (t, J=1.7 Hz, $2H_2$), 5.02 (d, J=1.7 Hz, 4H), 2.17 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 185.2 (2C), 184.1 (2C), 169.9 (2C), 143.5 (2C), 139.4 (2C), 136.0 (2C), 131.9 (2C), 59.2 (2C), 20.6 (2C).

IR (cm^{-1}): 1730, 1650, 1640, 1380, 1200, 1050, 920.

4.3.4 The Synthesis of [rel-(4S,5S)-4,5-dibromo-3,6-dioxocyclohex-1-en-1-yl]methyl acetate (166)



To a stirred solution of **136** (1 g, 5.55 mmol) in 30 mL of CH_2Cl_2 at 0 ^{o}C was added dropwise a solution of Br_2 (0.90 g, 5.60 mmol) in 25 mL CH_2Cl_2. The

mixture was stirred for an additional 2 hours at 0 ^{o}C and then allowed to warm to room temperature. The solvent was removed under reduced pressure to afford 1.7 g of dibromo compound **166** in a yield of 90 % m.p. 105-112 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 6.63 (quasi q, J=1.8 Hz, H_2), 5.0 (dd, A part of the AB-system, J=17.4 and 1.8 Hz, 1H), 4.93 (dd, B part of the AB-system, J=17.4 and 1.8 Hz, 1H), 4.80 (d, A part of the AB-system, J=2.8 Hz, H_5), 4.77 (d, B part of the AB-system, J=2.8 Hz, H_4).

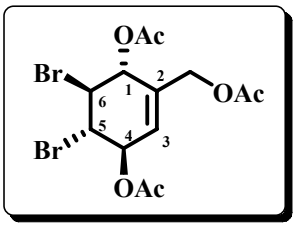
^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 186.7, 186.4, 169.6, 143.6, 131.2, 59.6, 45.2, 45.0, 20.5.

IR (cm^{-1}): 1750, 1685, 1620, 1240, 1000, 900.

4.3.5 The Synthesis of [rel-(3R,4S,5S,6R)-4,5-dibromo-3,6-dihydroxycyclohex-1-en-1-yl]methyl acetate (169)

To a stirred solution of **166** (8 g, 23.5 mmol) in 200 mL of ether at -5 ^{o}C was added dropwise a solution of $NaBH_4$ (2.22 g, 58.6 mmol) in 50 mL of iced-water. The mixture was stirred for an additional 2.5 hours in ice bath. The organic phase was separated and aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$ to yield 5.7 g (70 %) of diol **169**. For further characterization the crude product was acetylated without purification.

4.3.6 The Synthesis of rel-(1R,4R,5S,6S)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5,6-dibromocyclohex-2-en-1-yl acetate (170)



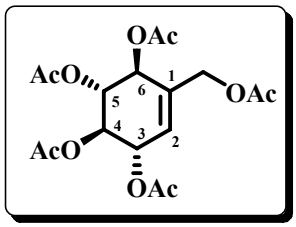
To a magnetically stirred solution of **169** (6.5 g, 18.9 mmol) in 20 mL of pyridine was added acetic anhydride (5.8 g, 56.8 mmol) dropwise at 0 ^{o}C. The reaction mixture was stirred for an additional 10 hours at 0 ^{o}C. The mixture was poured into 50 mL of HCl solution in ice and extracted with $CHCl_2$ (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ solution and water and then dried over $MgSO_4$. The removal of solvent under reduced pressure was followed by separation via column chromatography with ether/hexane (1:4). The crystallization of the residue from ether/hexane (2:1) afforded 6.0 g (74%) of triacetate **170** as white crystals, m.p. 142-146 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.91 (d, J=5.6 Hz, H_1), 5.82 (s, H_3), 5.72-5.70 (m, H_4), 4.66 (d, A part of the AB-system, J=13,4 Hz, 1H of –CH_2-), 4.39 (d, B part of the AB-system, J=13.4 Hz, 1H of –CH_2-), 4.33 (dd, A part of the AB-system, J=12.3 and 11.4 Hz, H_1), 4.29 (dd, B part of the AB-system, J=12.3 and 10.9 Hz, H_2), 2.15 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 170.2, 169.8, 169.6, 134.7, 126.5, 72.9, 71.7, 62.6, 52.8, 51.6, 20.8, 20.7, 20.6.

IR (cm^{-1}): 1750, 1710, 1350, 1205, 1020, 700, 650.

4.3.7 The Synthesis of [rel-(3S,4R,5R,6S)-3,4,5,6-tetrakis(acetyloxy) cyclohex-1-en-1-yl]methyl acetate (173)



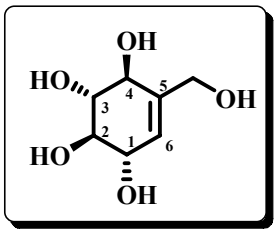
A vigorously stirred mixture of **170** (2 g, 4.67 mmol), 30 mL of glacial acetic acid, 7 mL of Ac_2O and anhydrous KOAc (2.3 g, 23.4 mmol) was refluxed for 6 days under N_2. The solvent was removed under reduced pressure. Methanol was added to the residue and stirred for 10 minutes. The solution was concentrated and the residue was partitioned between ether and water. The organic layer was washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was recrystallized from ether/hexane (2:1) to give 1.4 g (77 %) of pentaacetate **173**, m.p. 88-90 ^oC.

^{1}H-NMR (400 MHz, $CDCl_3$, δ:ppm): 5.79 (bd, J=7.0 Hz, H_6), 5.76 (bs, H_2), 5.59 (bd, J=7.1 Hz, H_3), 5.37 (dd, A part of the AB-system, J=10.9 and 7,8 Hz, H_4 or H_5), 5.32 (dd, B part of the AB-system, J=10.9 and 7.1 Hz, H_4 or H_5), 4.68 (d, A part of the AB-system, J=13.3 Hz, 1H), 4.40 (d, B part of the AB-system, J=13.3 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ:ppm): 170.2, 170.1, 170.0, 169.9, 169.7, 133.7, 126.2, 71.9, 70.8, 70.7, 62.4, 20.8, 20.7, 20.6, 20.5 (2C).

IR (cm^{-1}): 1710, 1360, 1210, 1020, 950, 900.

4.3.8 The Synthesis of rel-(1S,2R,3R,4S)-5-(hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (137)



1 g (2.6 mmol) of pentaacetate **173** was dissolved in methanol (25 mL), NH_3(g) was passed through the solution for 2 hours, and the solvent was concentrated in vacuo to give 0.4 g of **137** (90 %) as a white solid, m.p. 150-151 ^oC.

^{1}H-NMR (400 MHz, D_2O, δ:ppm): 5.6 (s, 1H), 4.7 (bs -OH), 4.22-4.15 (m, 3H), 4.05 (d, J=14.0, 1H), 3.51 (dd, A part of the AB-system, J=10.5 and 7,8 Hz, 1H), 3.44 (dd, B part of the AB-system, J=10.5 and 7.6 Hz, 1H).

^{13}C-NMR (100 MHz, D_2O, δ:ppm): 138.4, 125.0, 75.6, 75.2, 71.9, 71.4, 61.1.

IR (cm^{-1}): 3200, 1690, 1050, 970, 700.

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APPENDIX A

NMR AND FT-IR SPECTRA OF COMPOUNDS

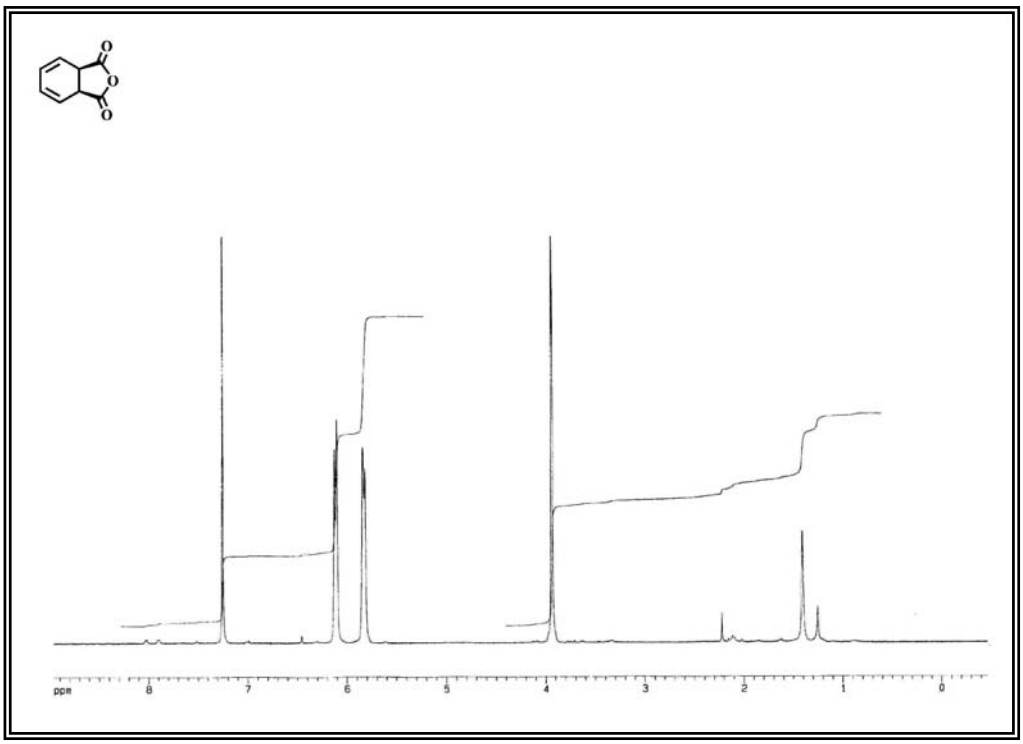

Figure 9. ^{1}H-NMR of spectrum of compound **145**

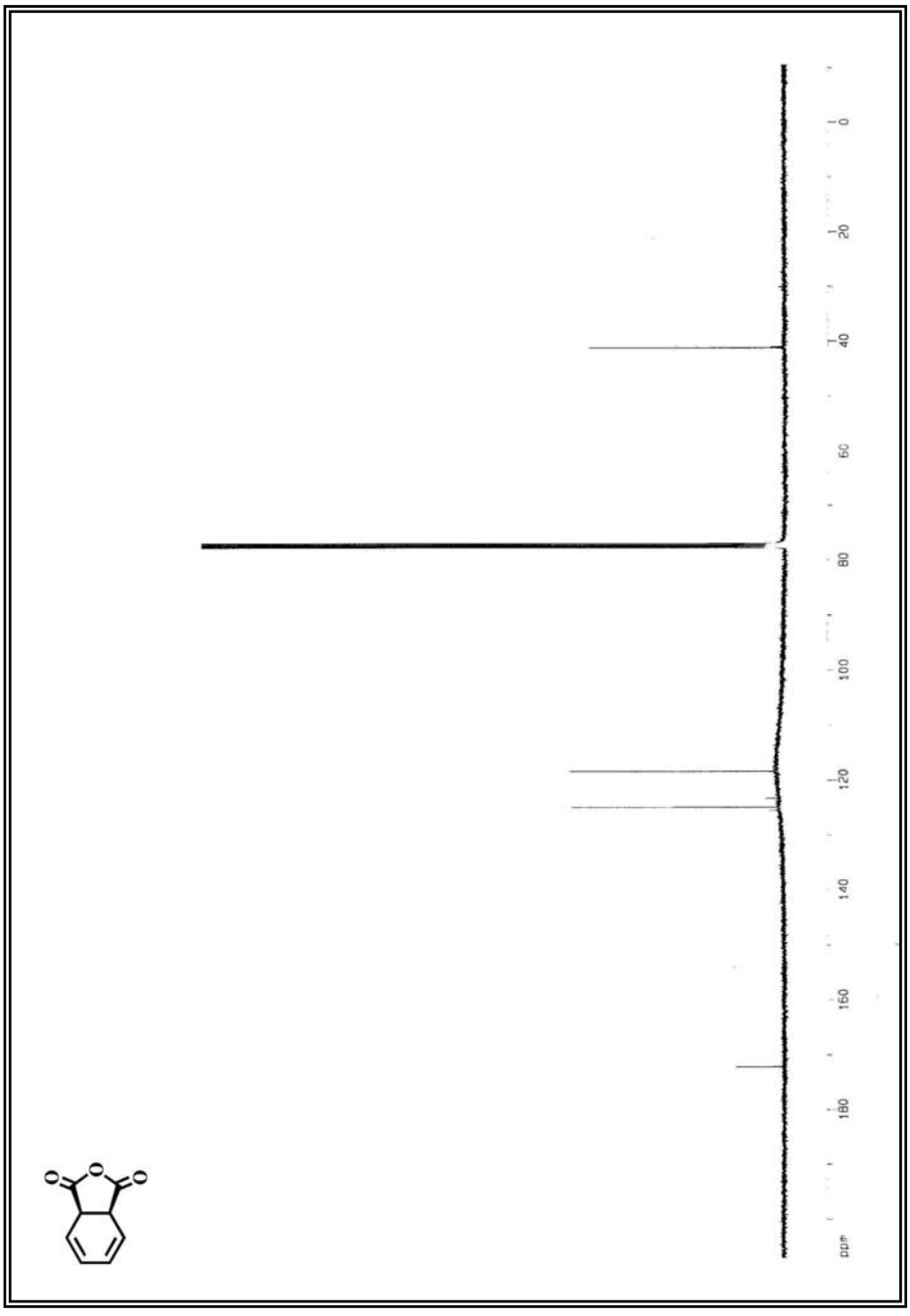

Figure 10. ^{13}C-NMR spectrum of compound **145**

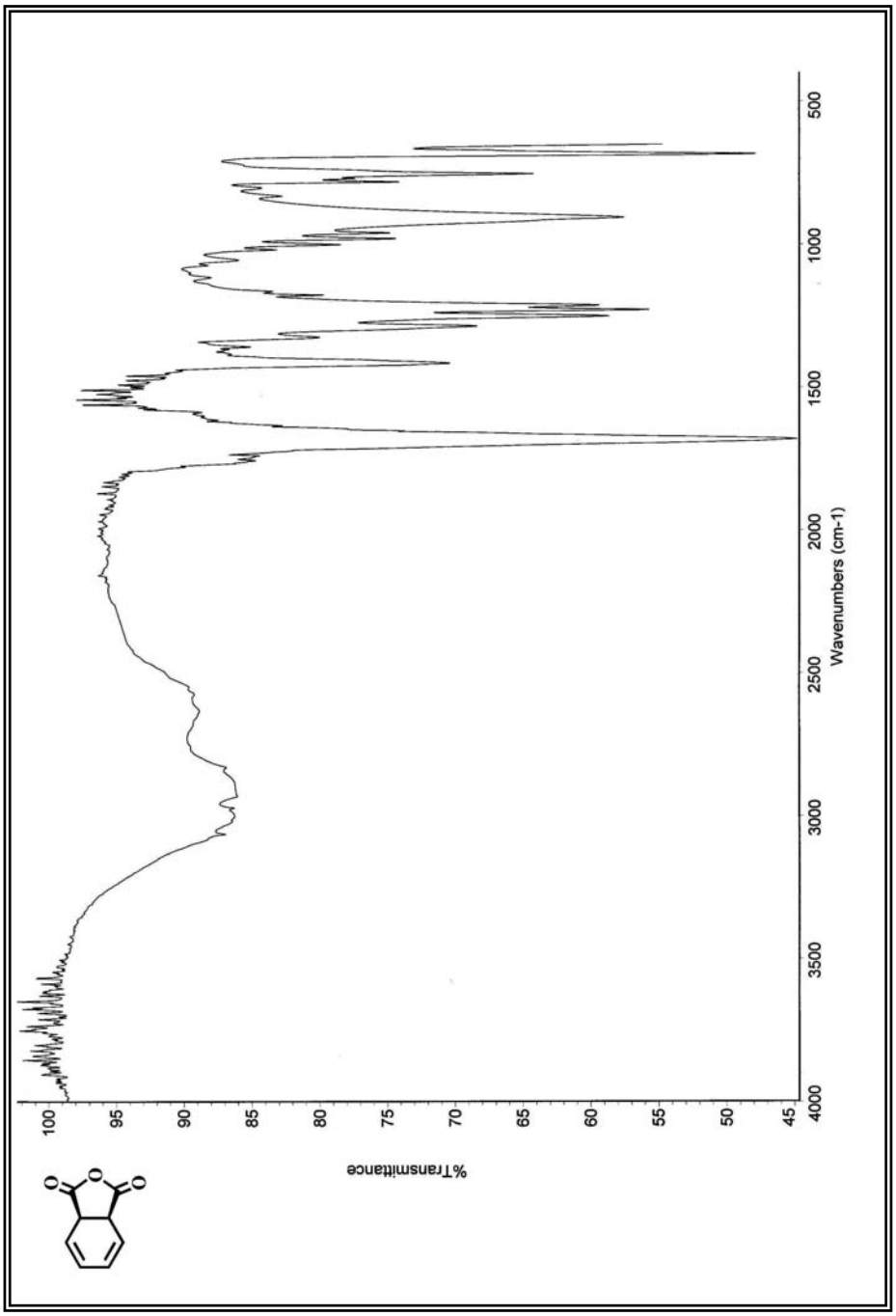

Figure 11. IR spectrum of compound **145**

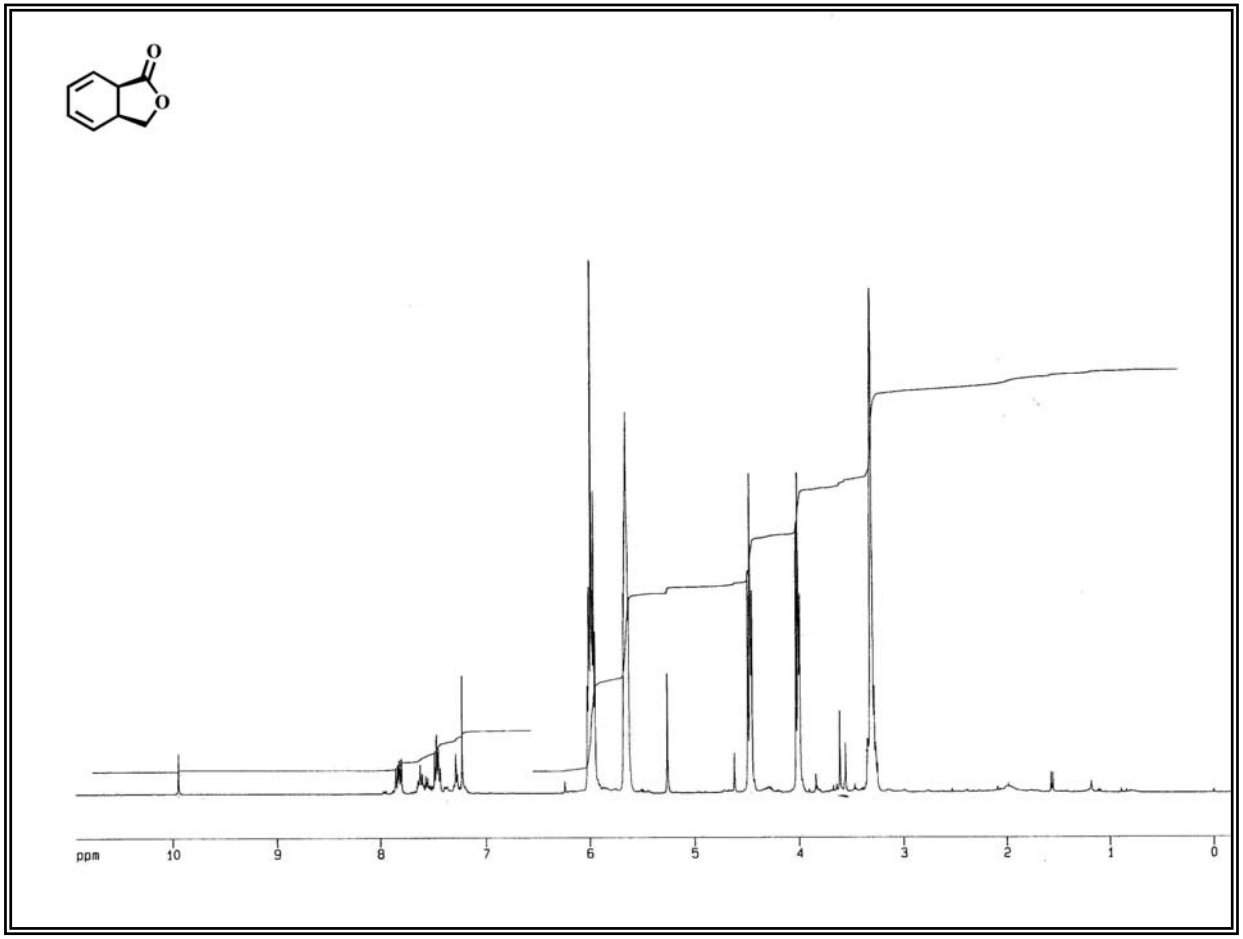

Figure 12. ^{1}H-NMR of spectrum of compound **132**

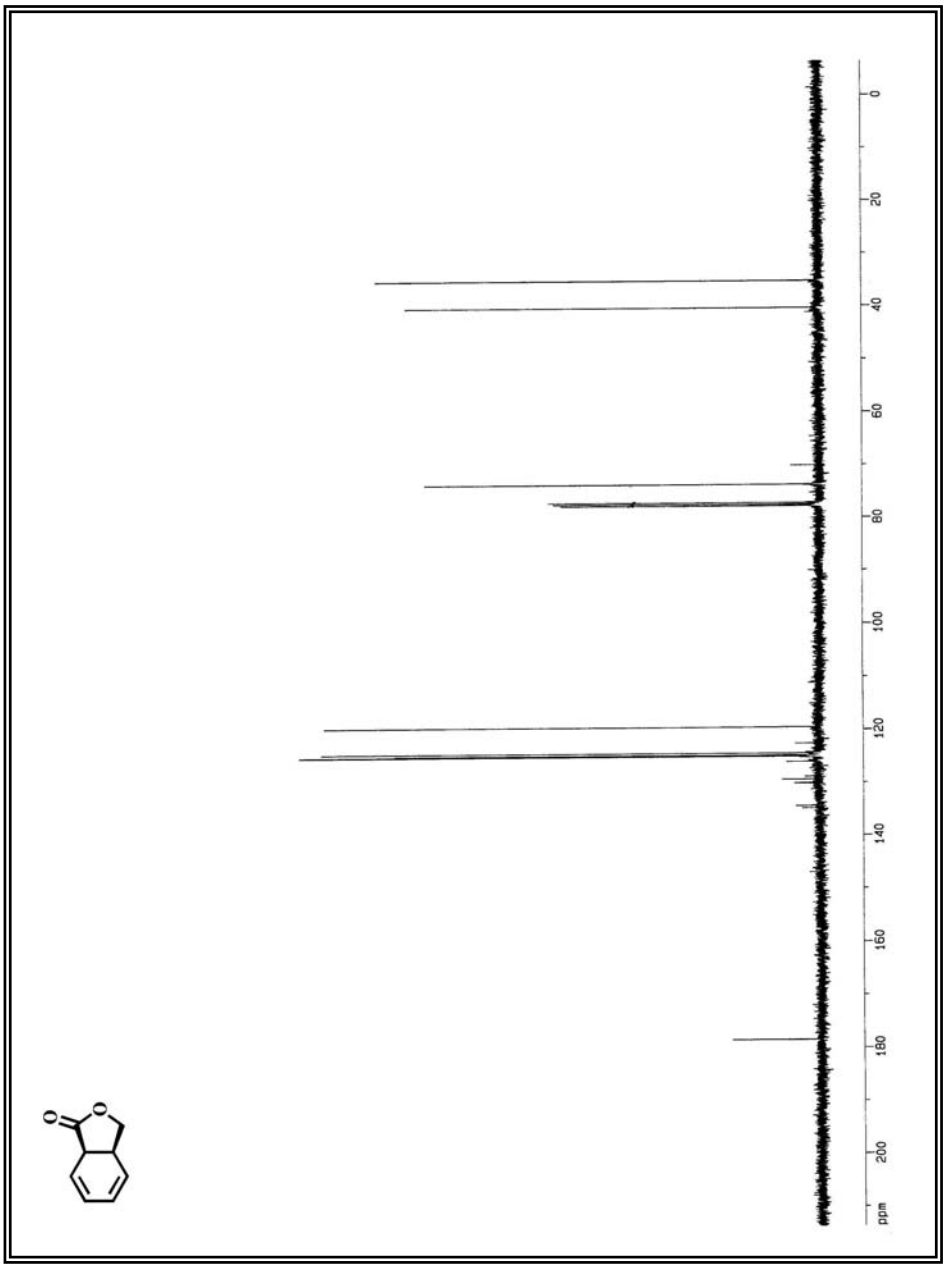

Figure 13. ^{13}C-NMR spectrum of compound **132**

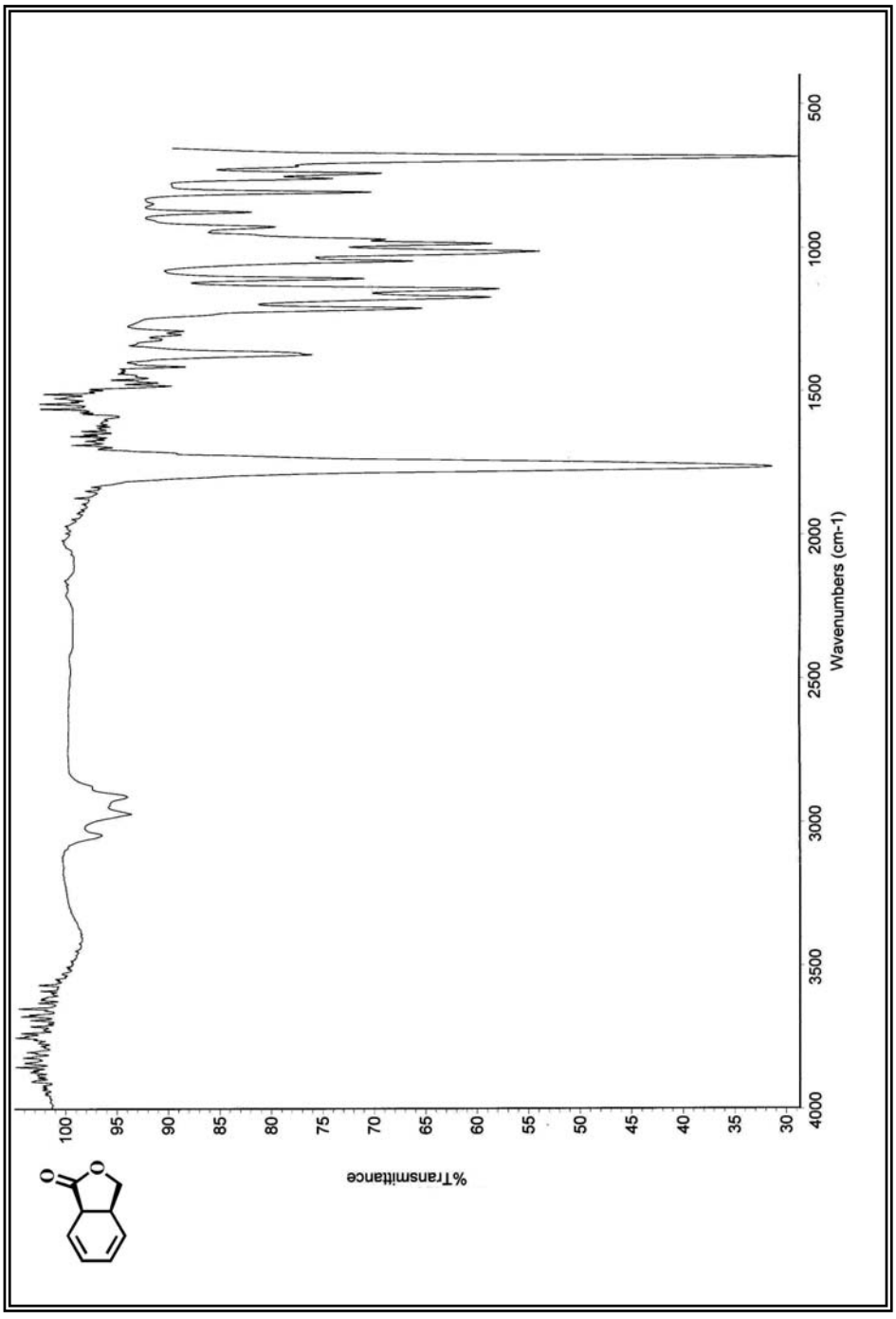

Figure 14. IR spectrum of compound **132**

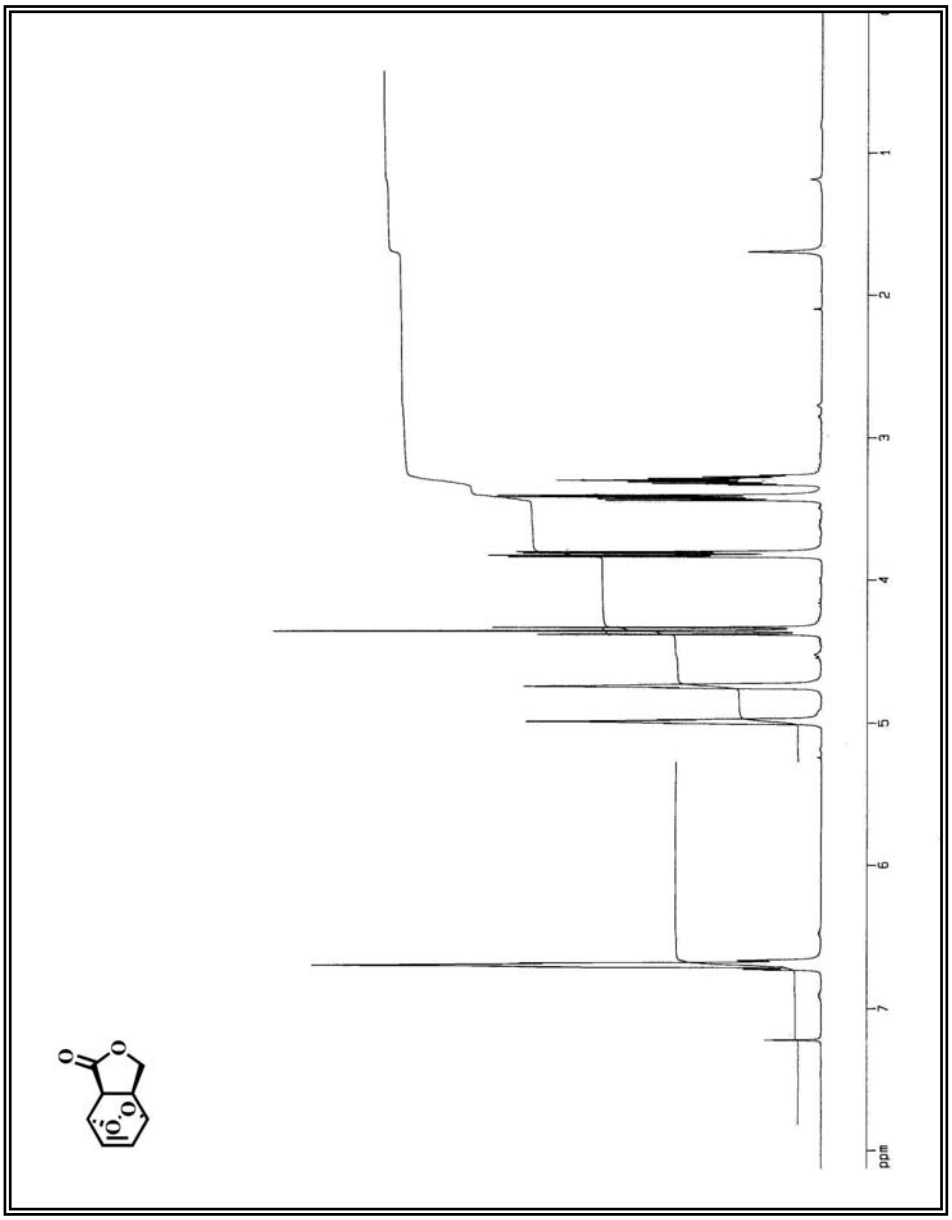

Figure 15. ^{1}H-NMR of spectrum of compound **133**

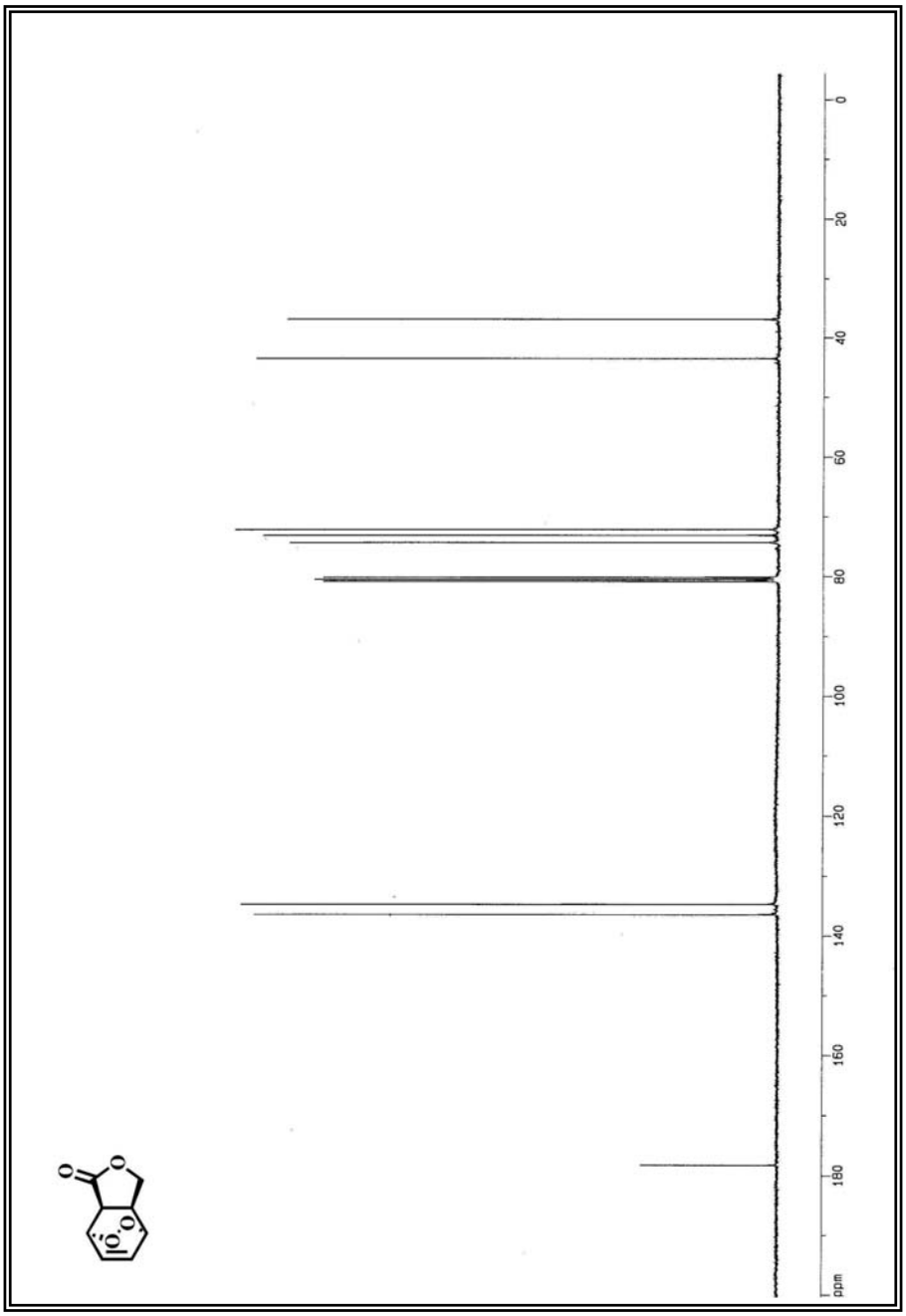

Figure 16. ^{13}C-NMR of spectrum of compound **133**

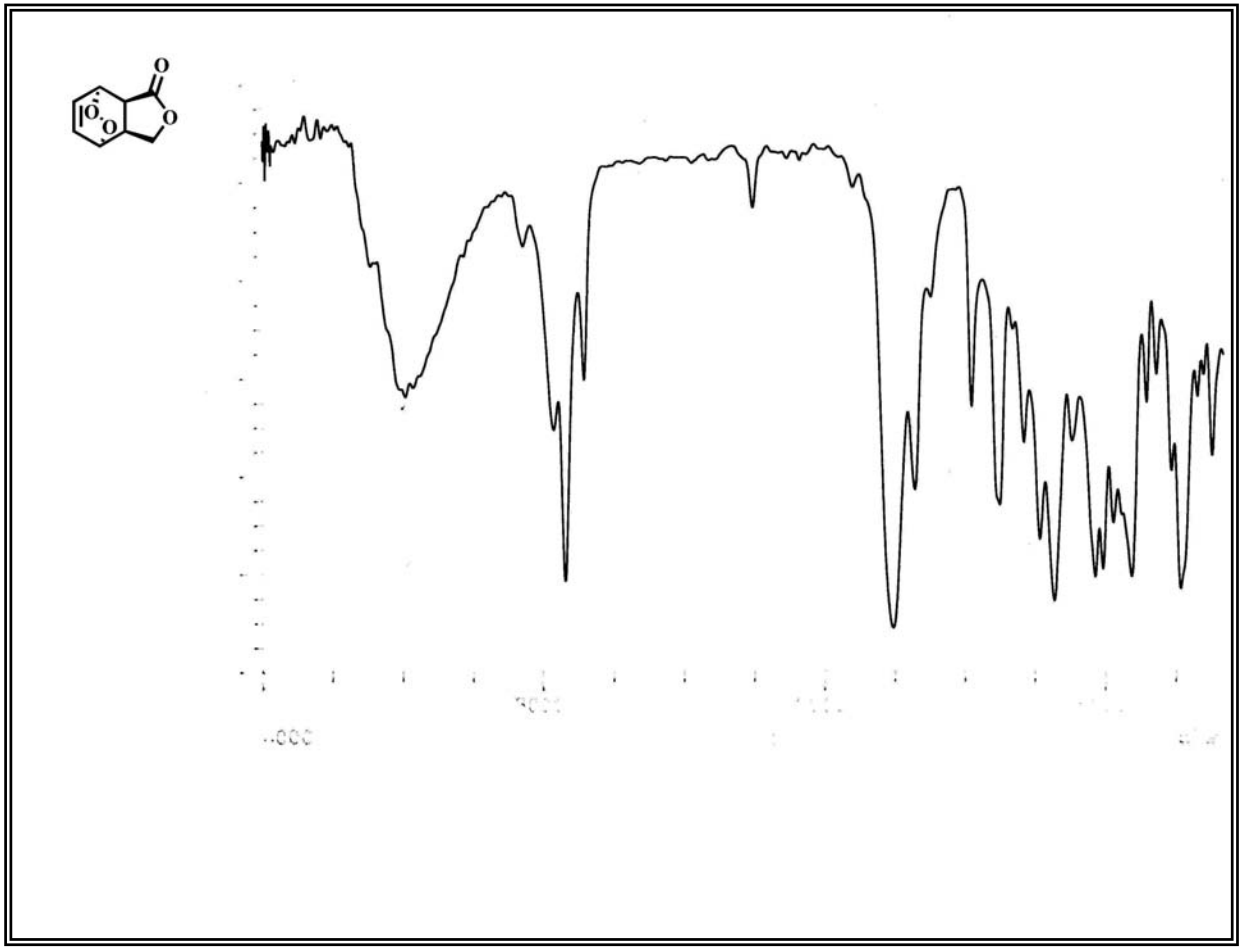

Figure 17. IR spectrum of compound **133**

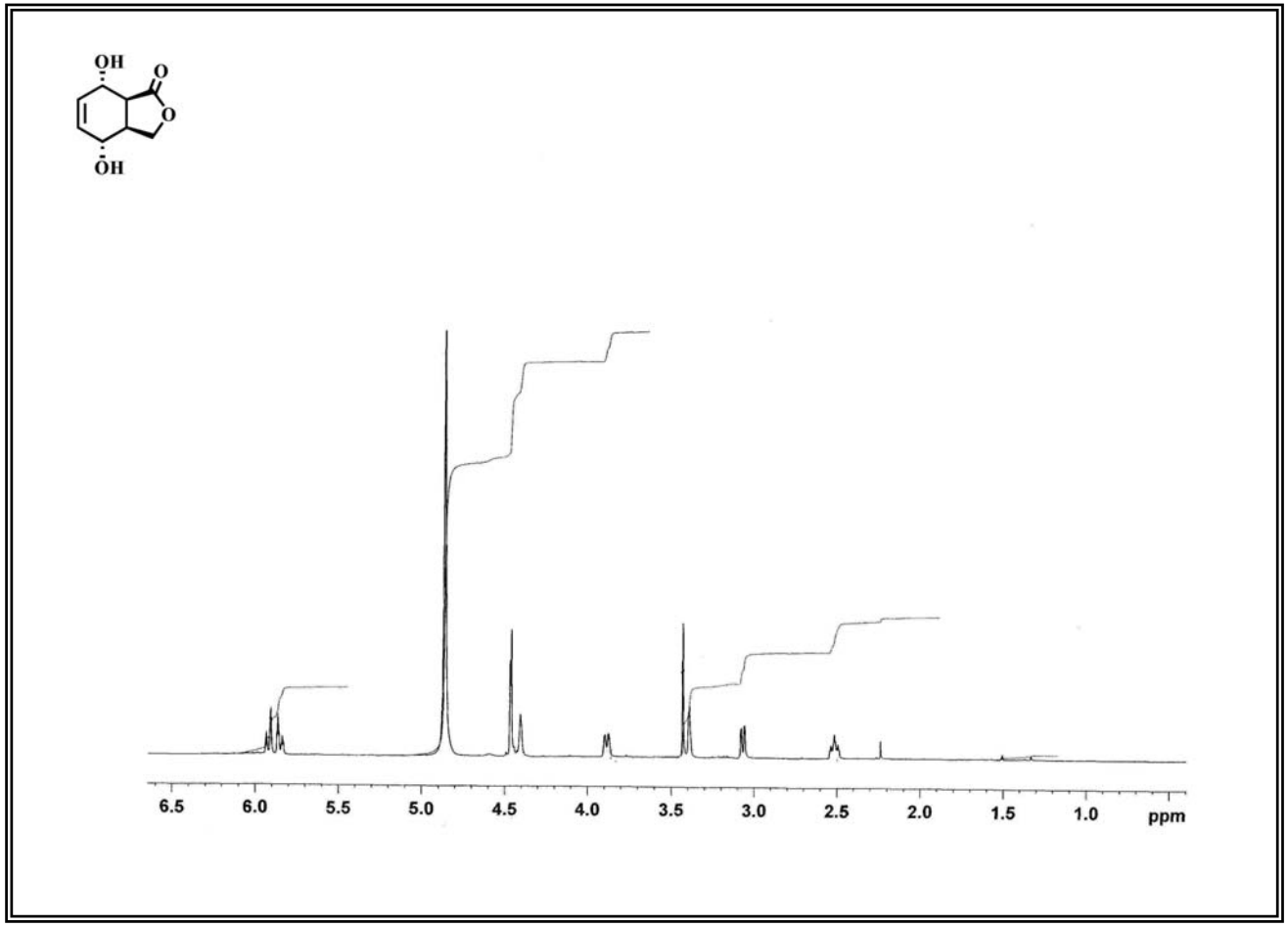

Figure 18. ^{1}H-NMR of spectrum of compound **152**

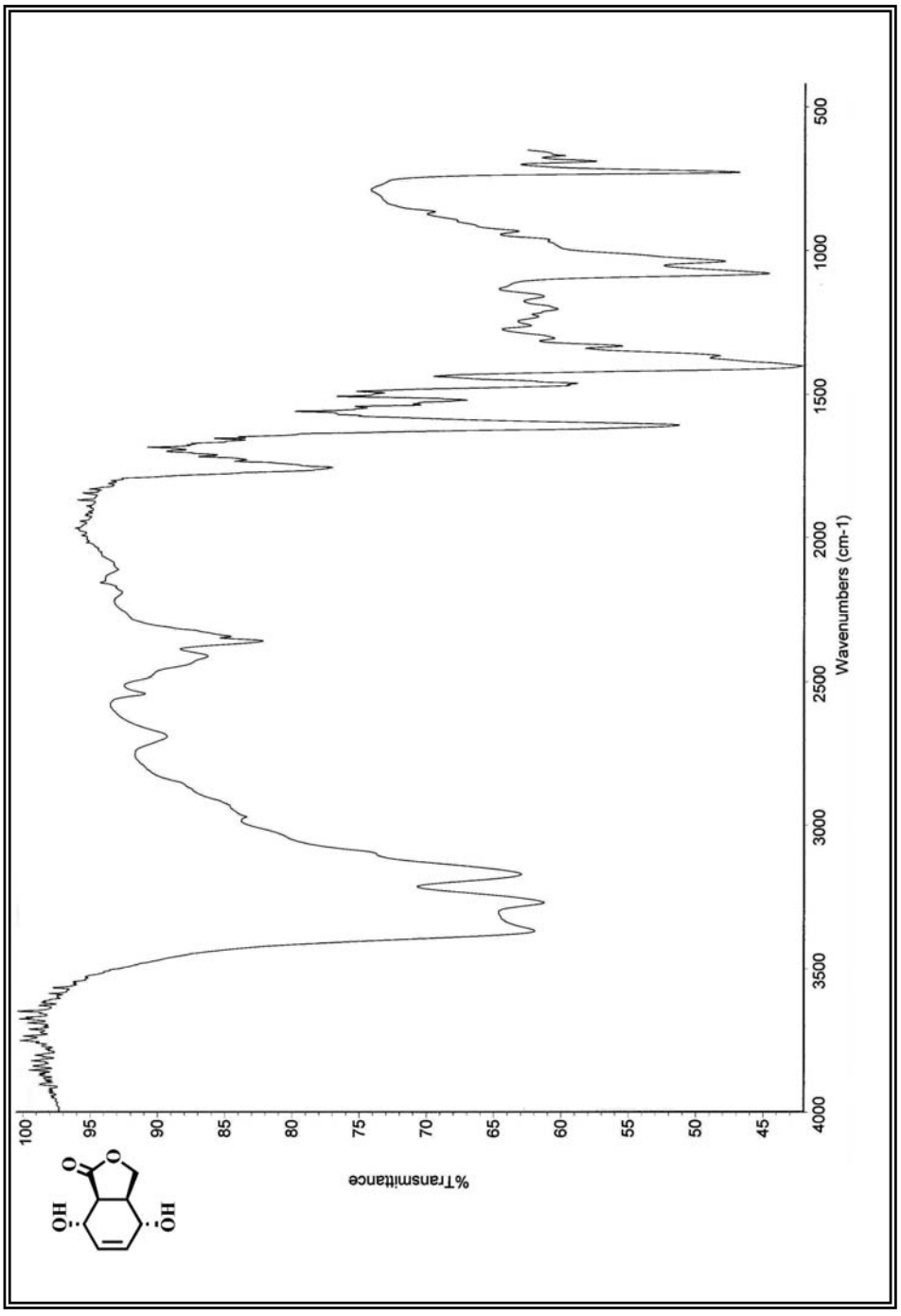

Figure 19. IR spectrum of compound **152**

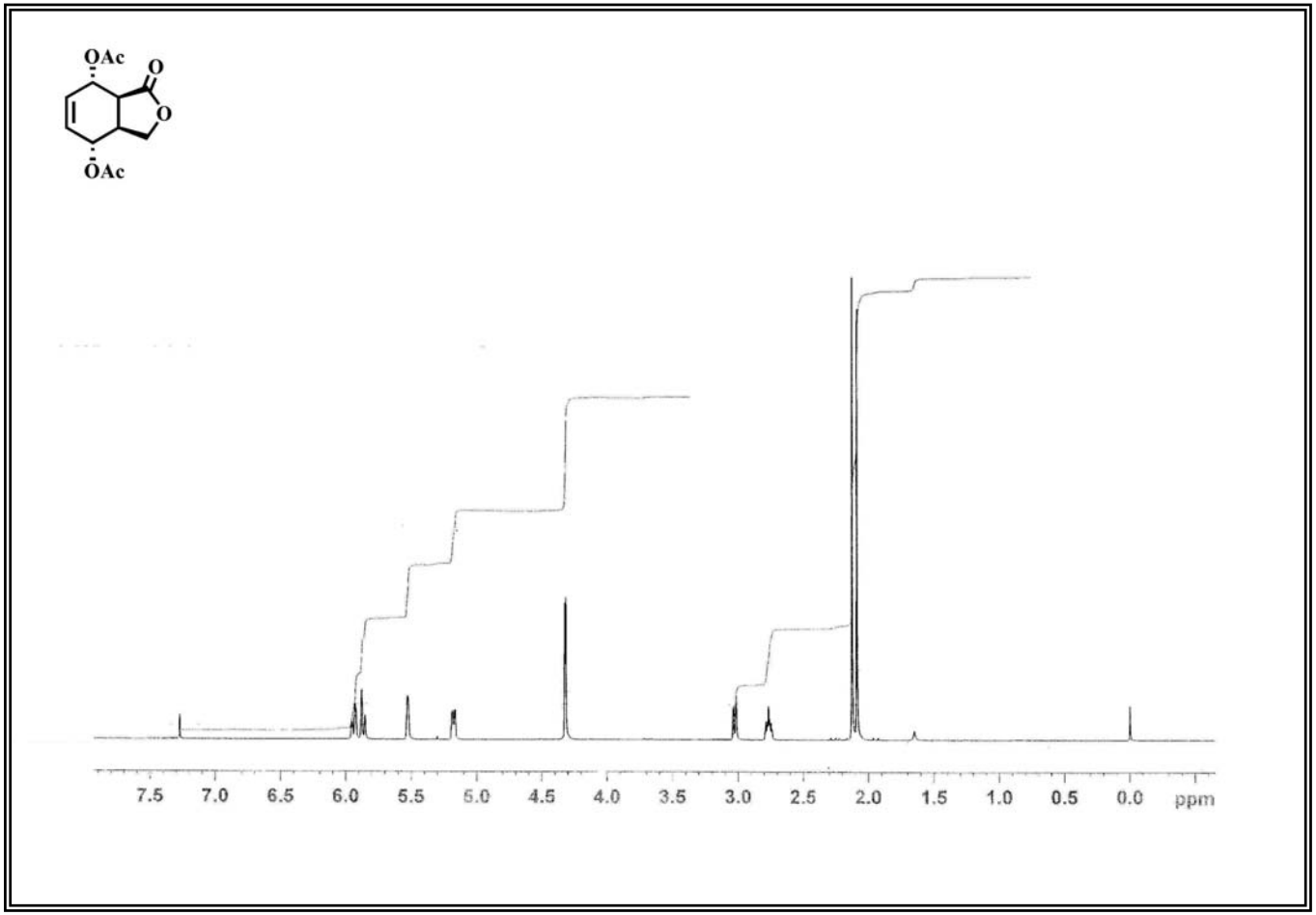

Figure 20. ^{1}H-NMR of spectrum of compound **153**

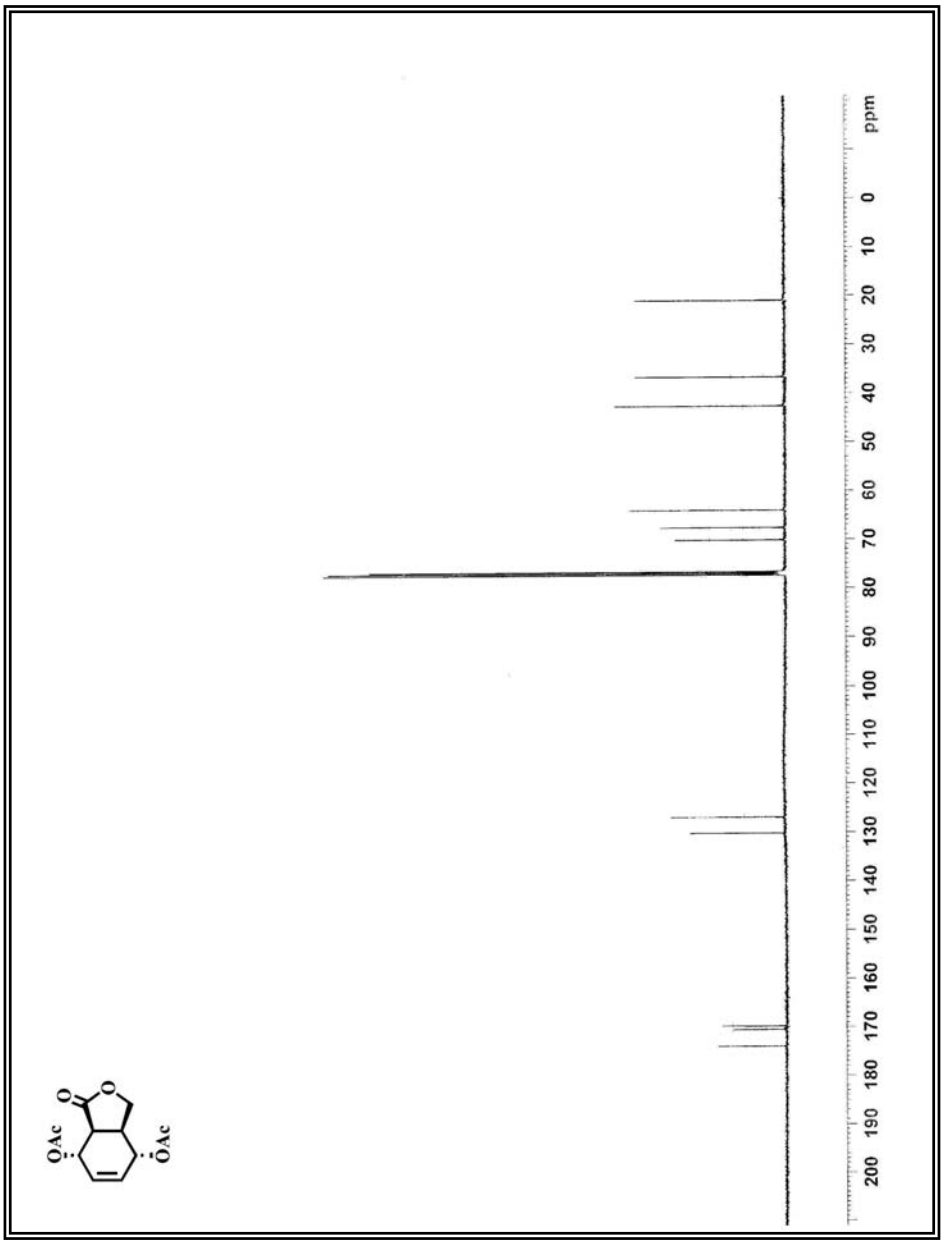

Figure 21. ^{13}C-NMR spectrum of compound **153**

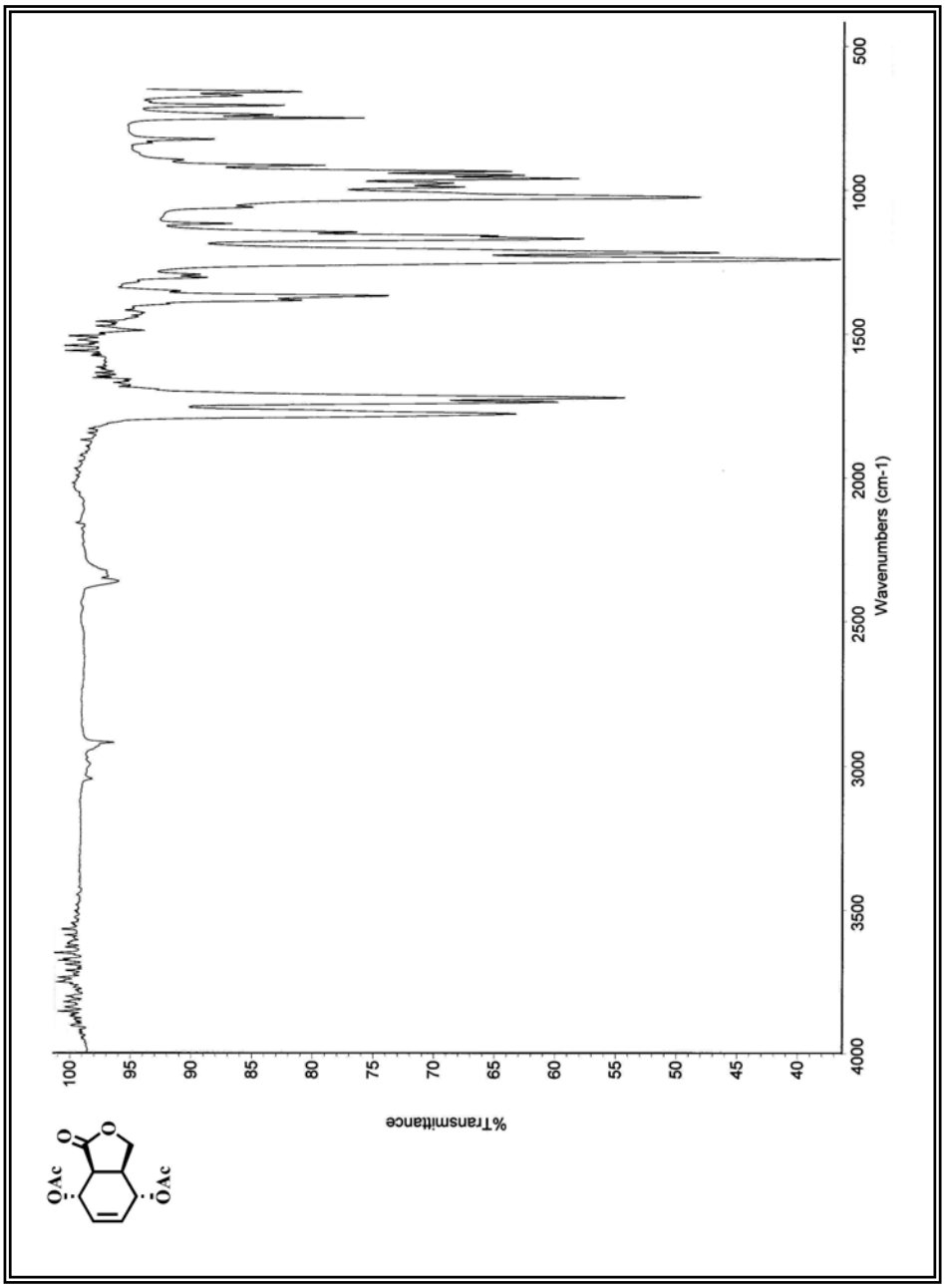

Figure 22. IR spectrum of compound **153**

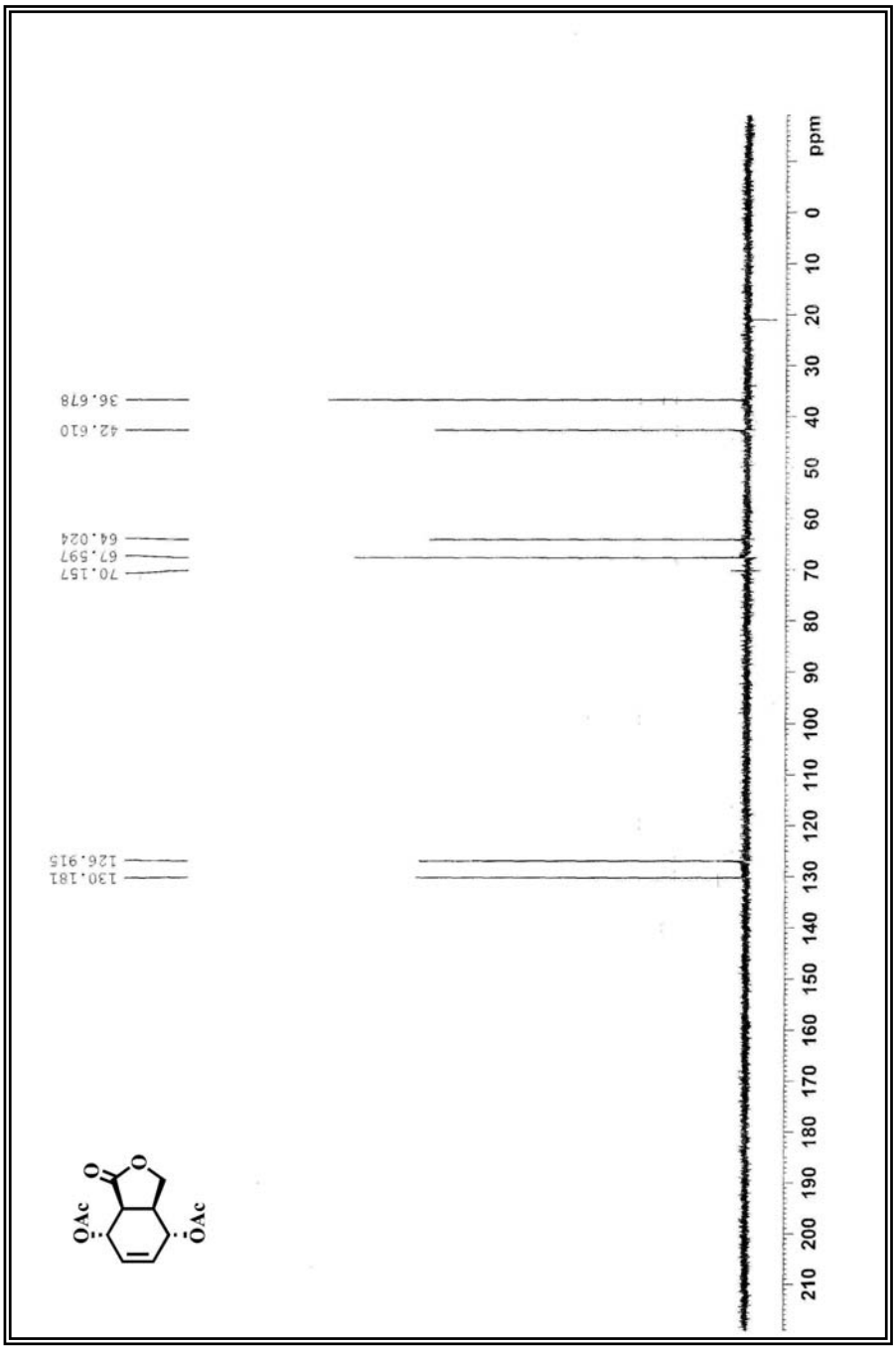

Figure 23. DEPT-90 spectrum of compound **153**

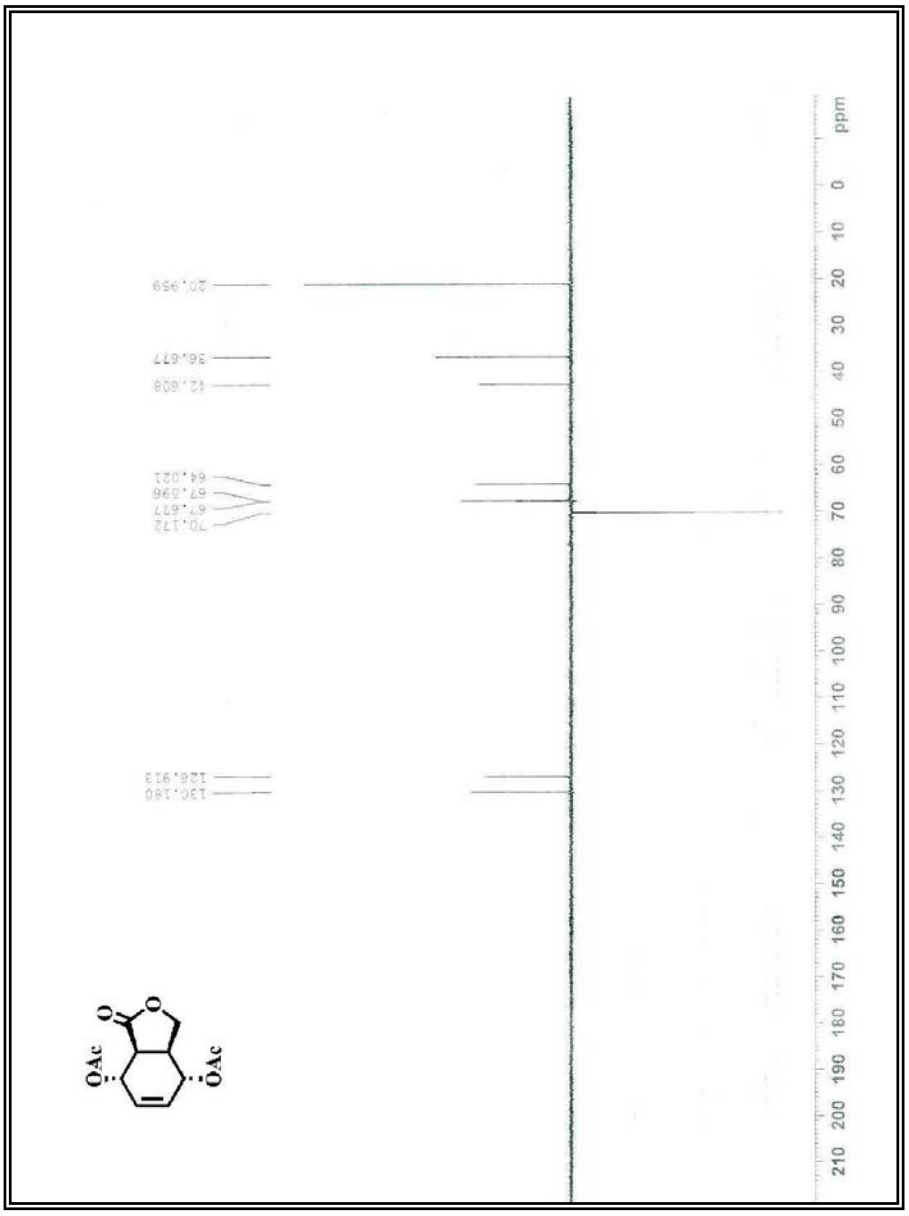

Figure 24. DEPT-135 spectrum of compound **153**

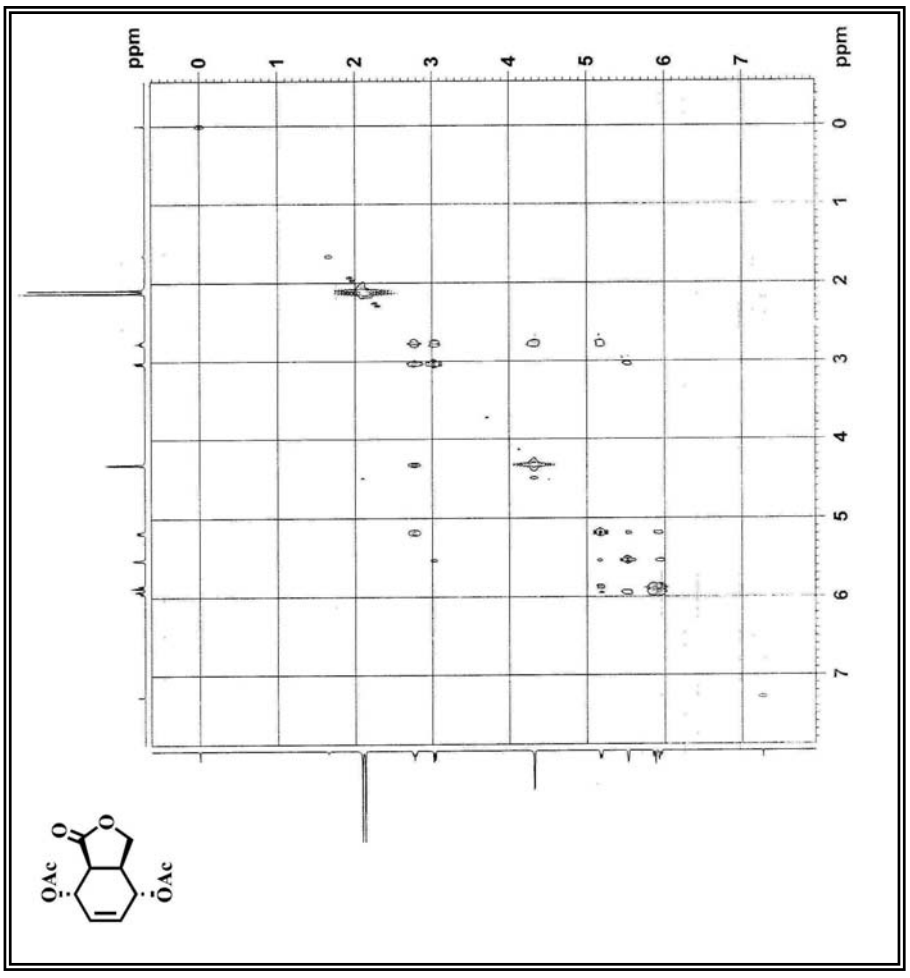

Figure 25. COSY spectrum of compound **153**

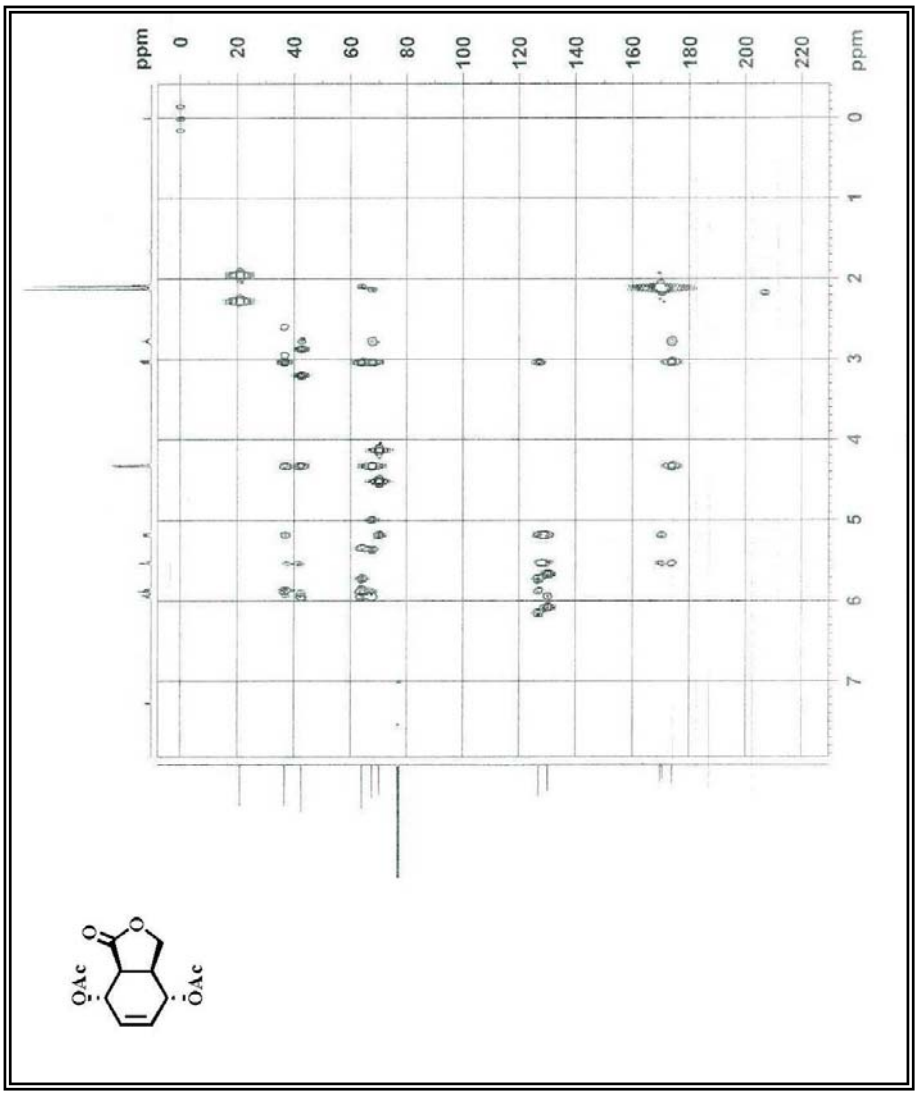

Figure 26. HMBC spectrum of compound **153**

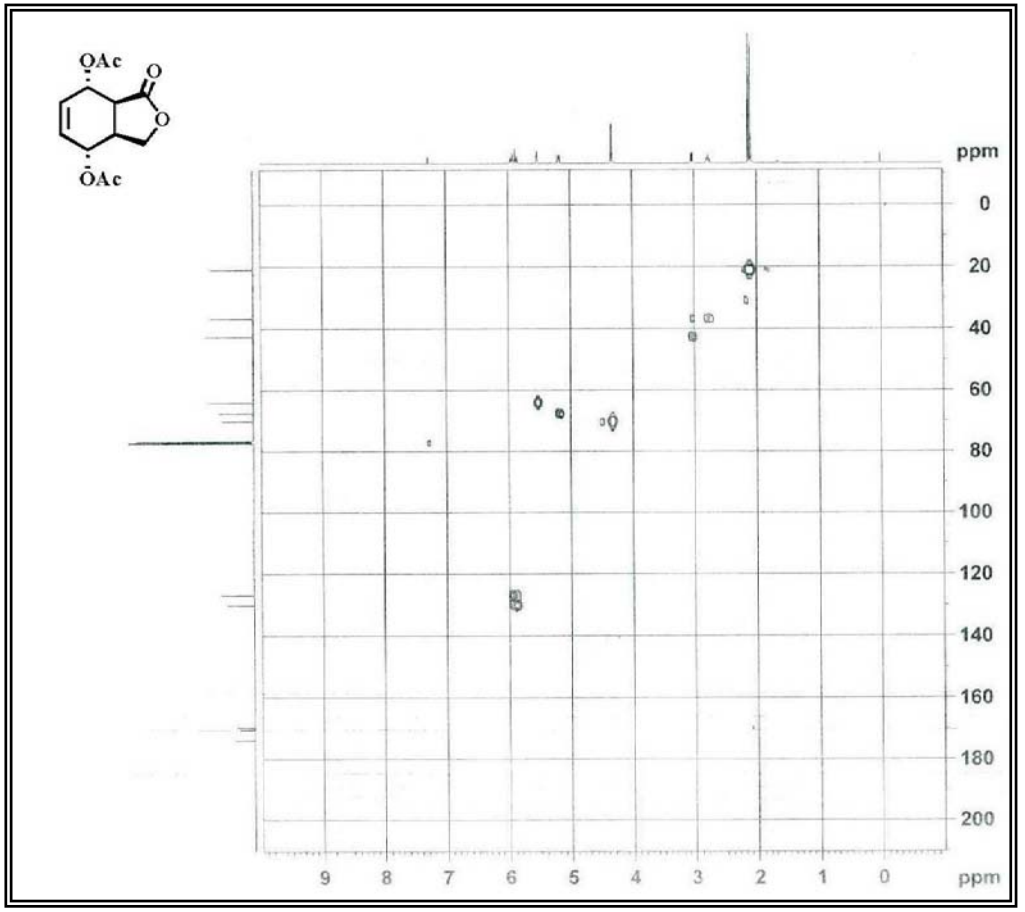

Figure 27. HMQC spectrum of compound **153**

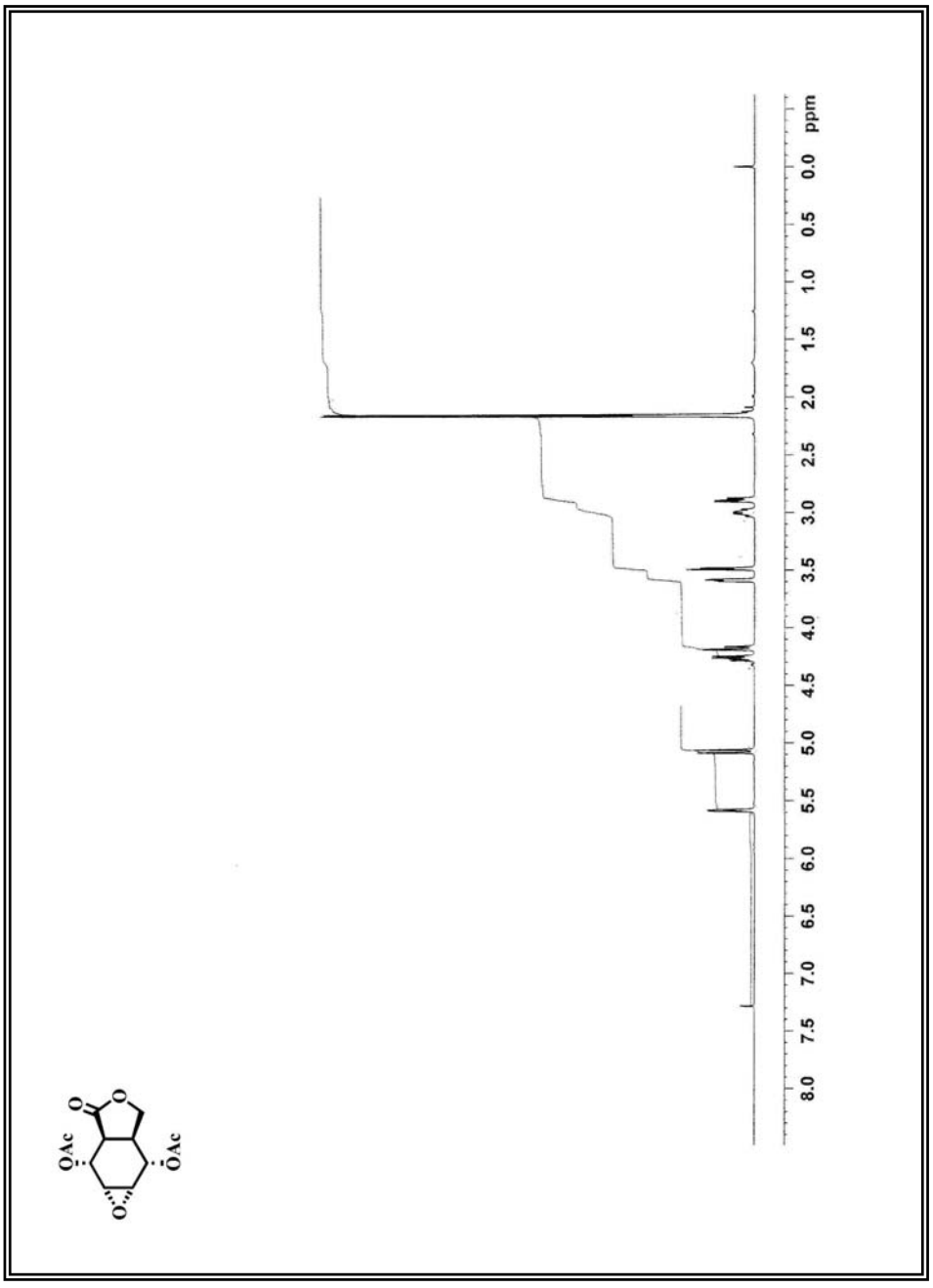

Figure 28. ^{1}H-NMR of spectrum of compound **154**

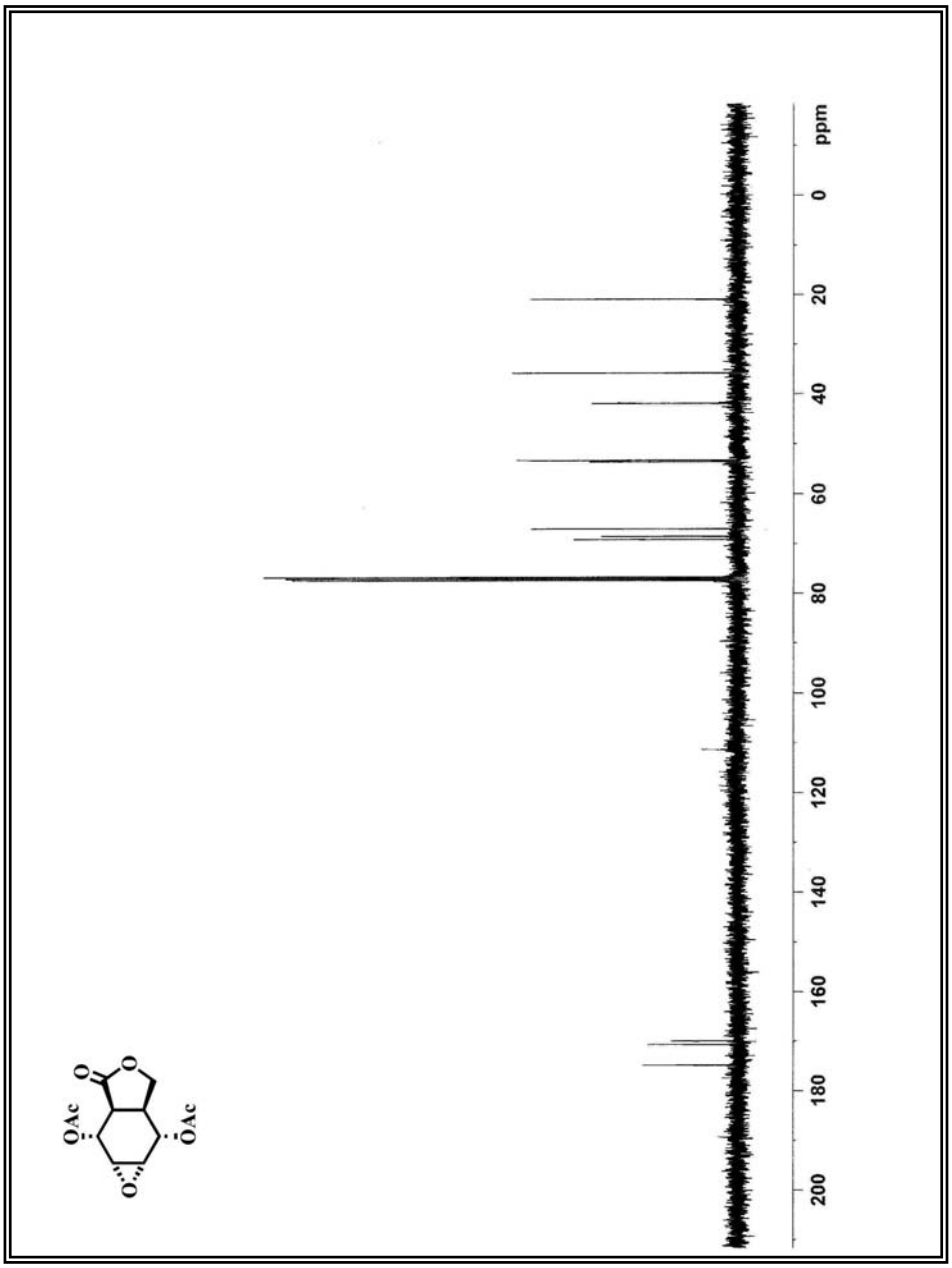

Figure 29. ^{13}C-NMR of spectrum of compound **154**

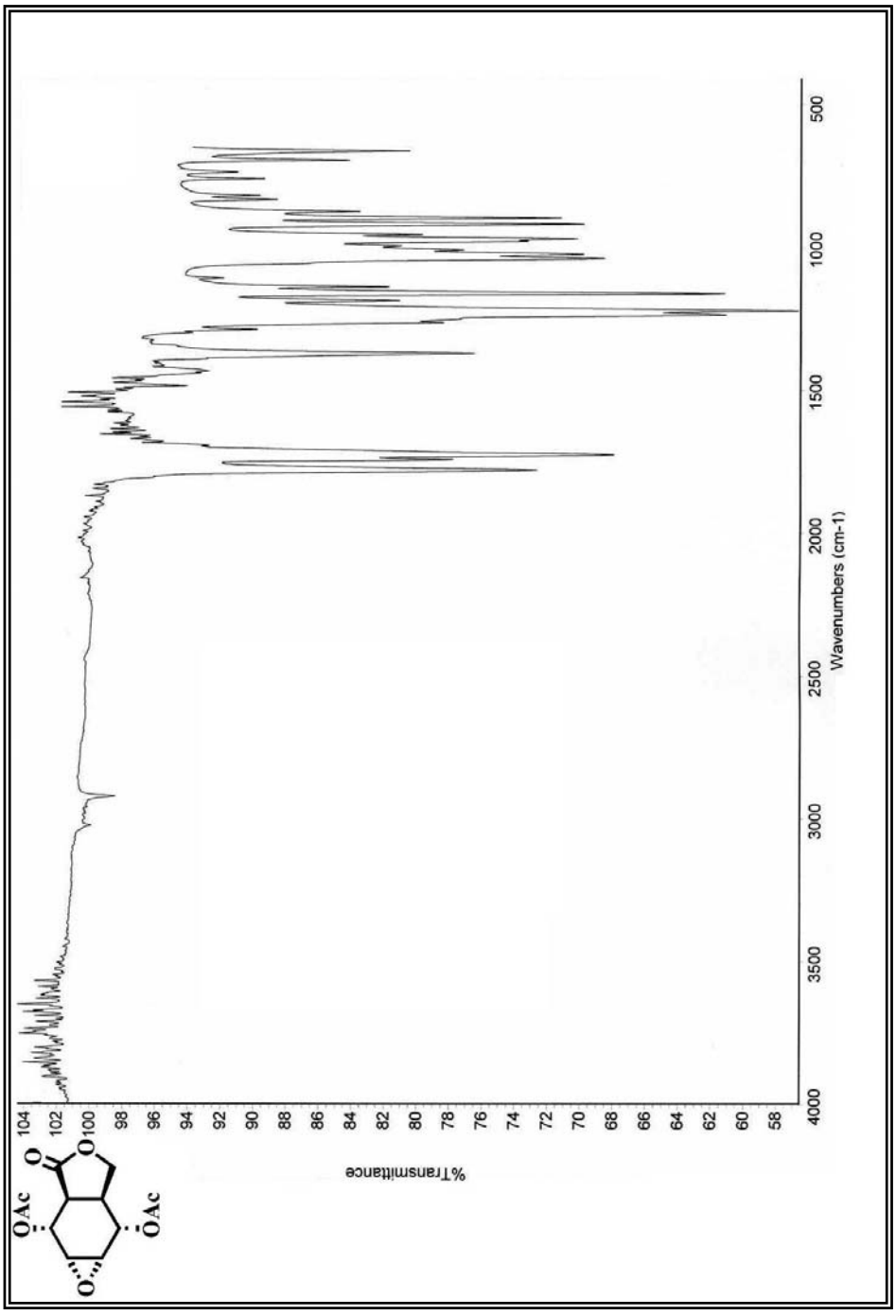

Figure 30. IR spectrum of compound **154**

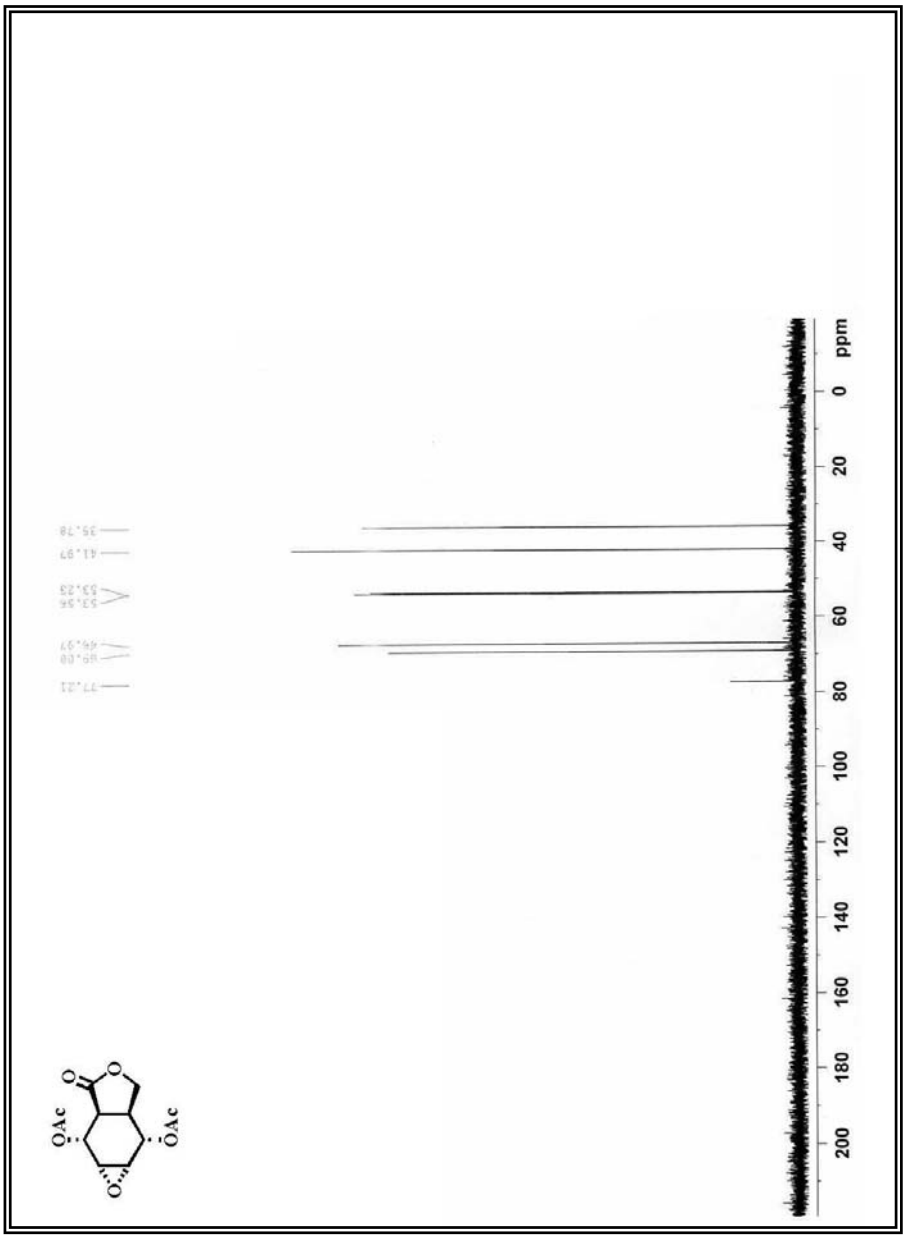

Figure 31. DEPT-90 spectrum of compound **154**

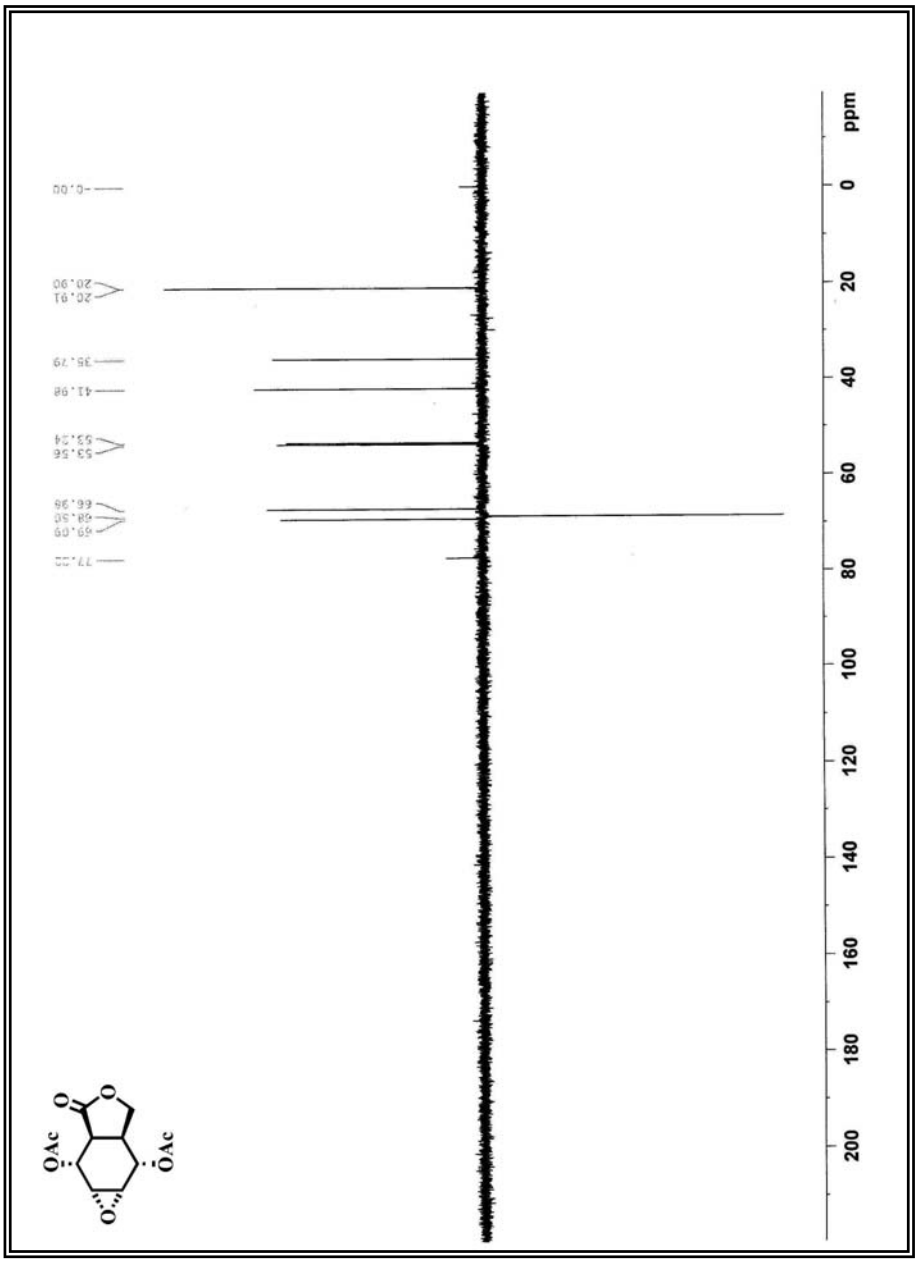

Figure 32. DEPT-135 spectrum of compound **154**

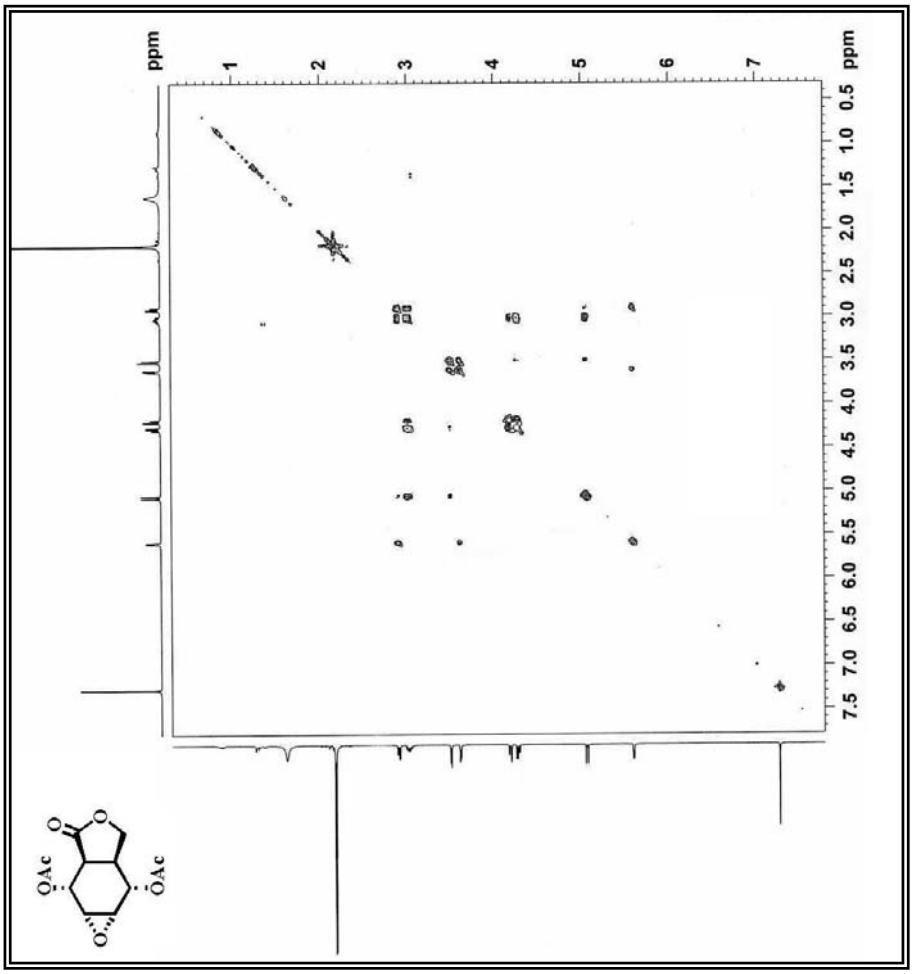

Figure 33. COSY spectrum of compound **154**

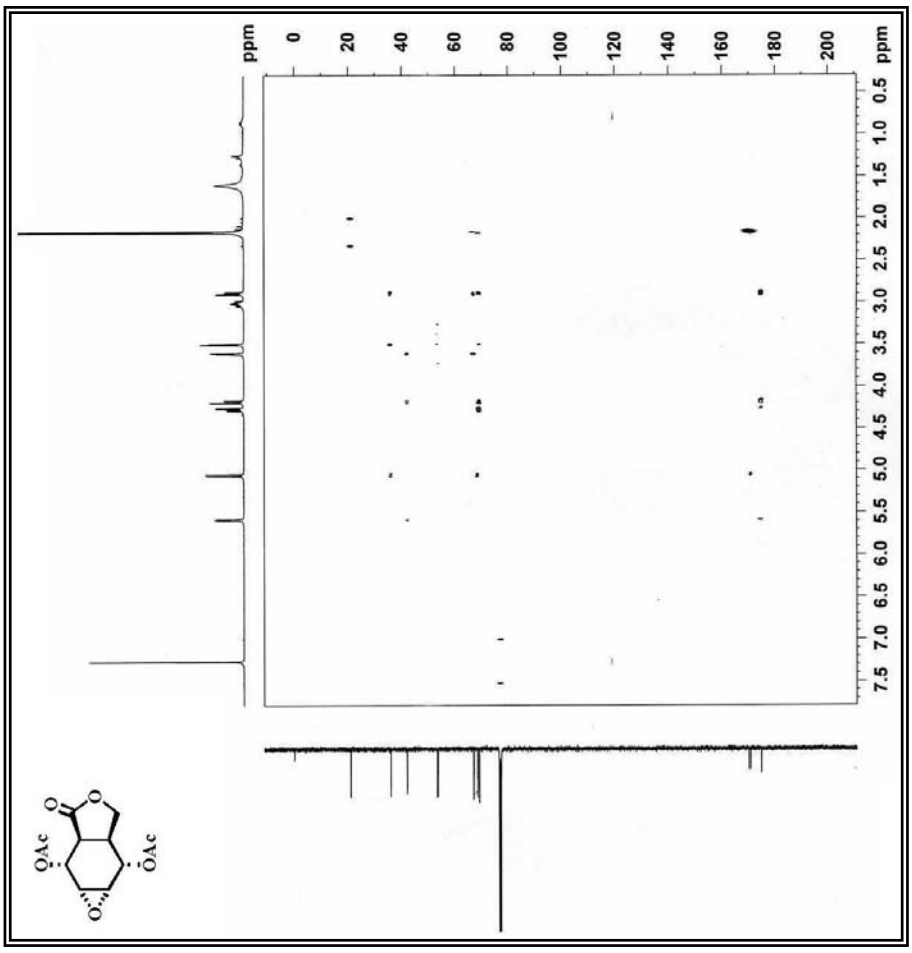

Figure 34. HMBC spectrum of compound **154**

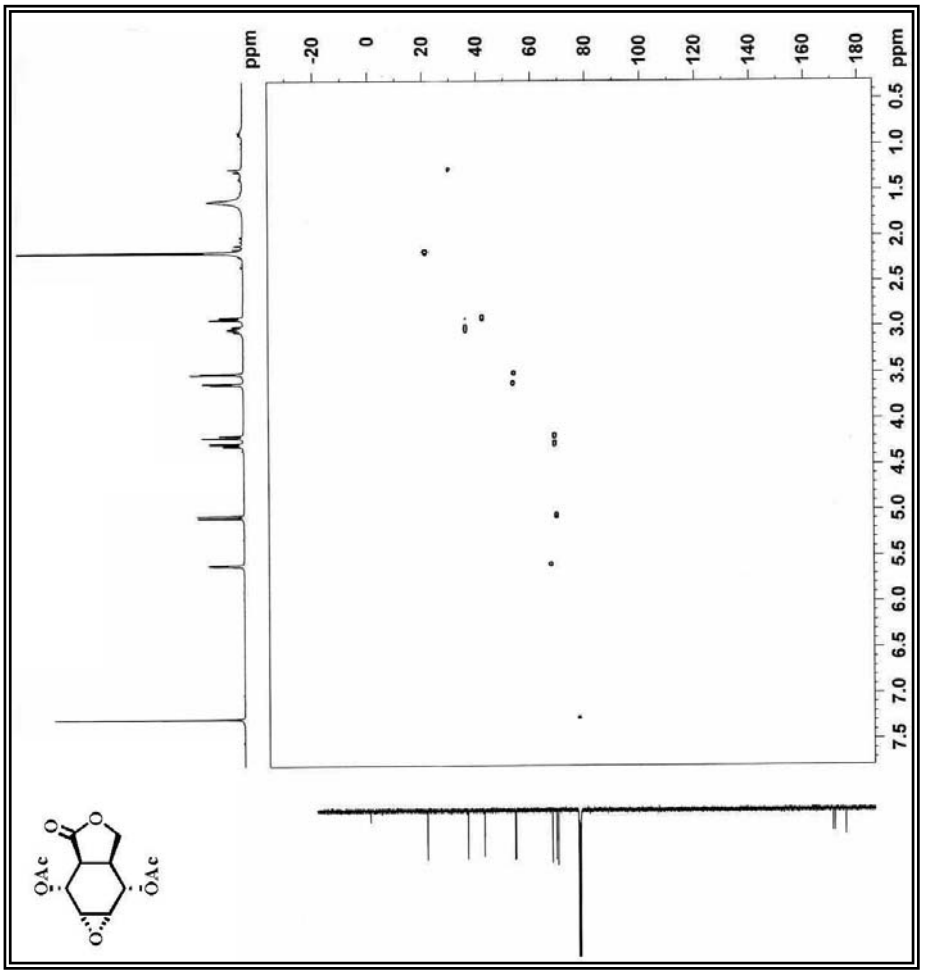

Figure 35. HMQC spectrum of compound **154**

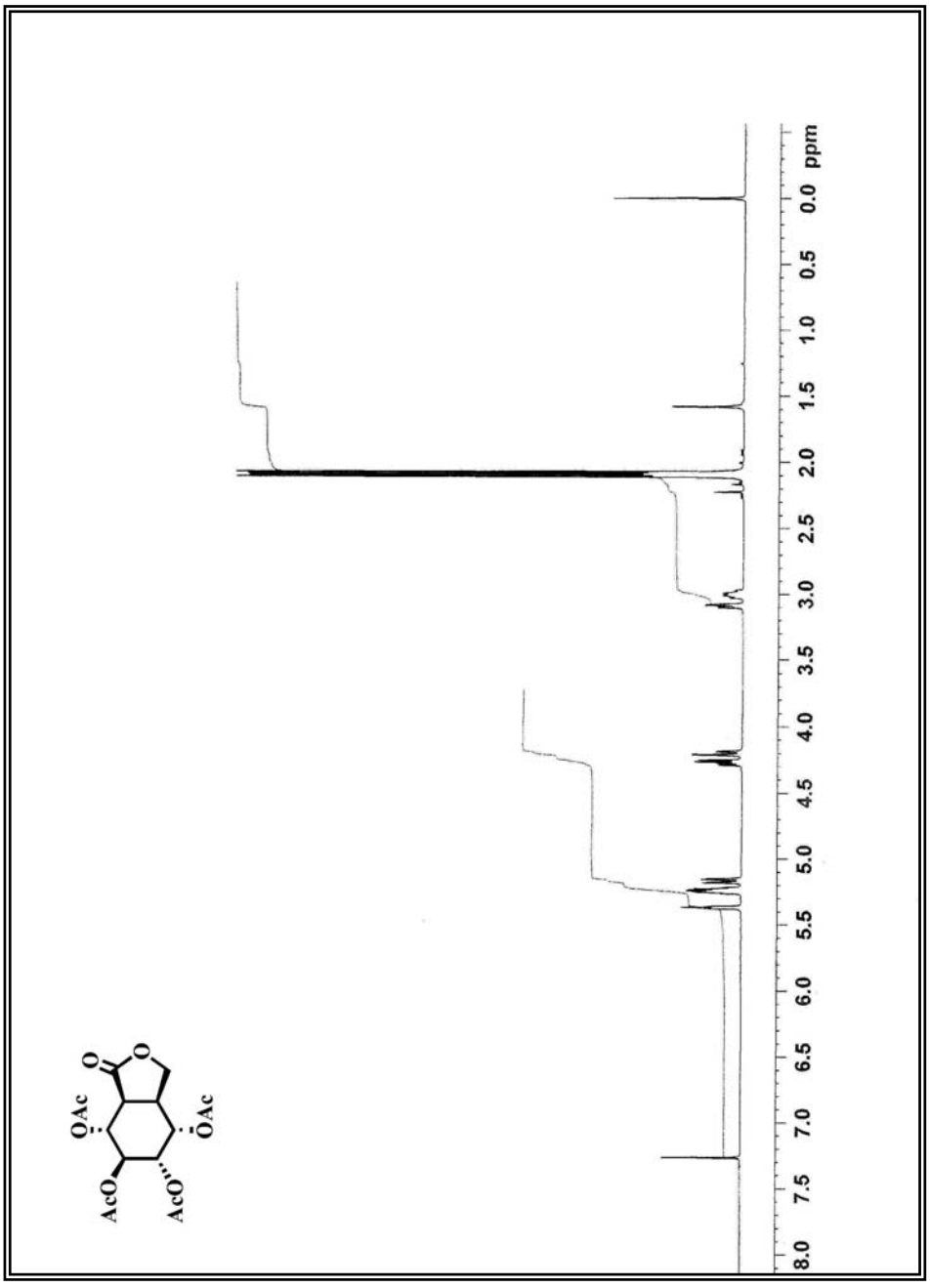

Figure 36. ^{1}H-NMR of spectrum of compound **155**

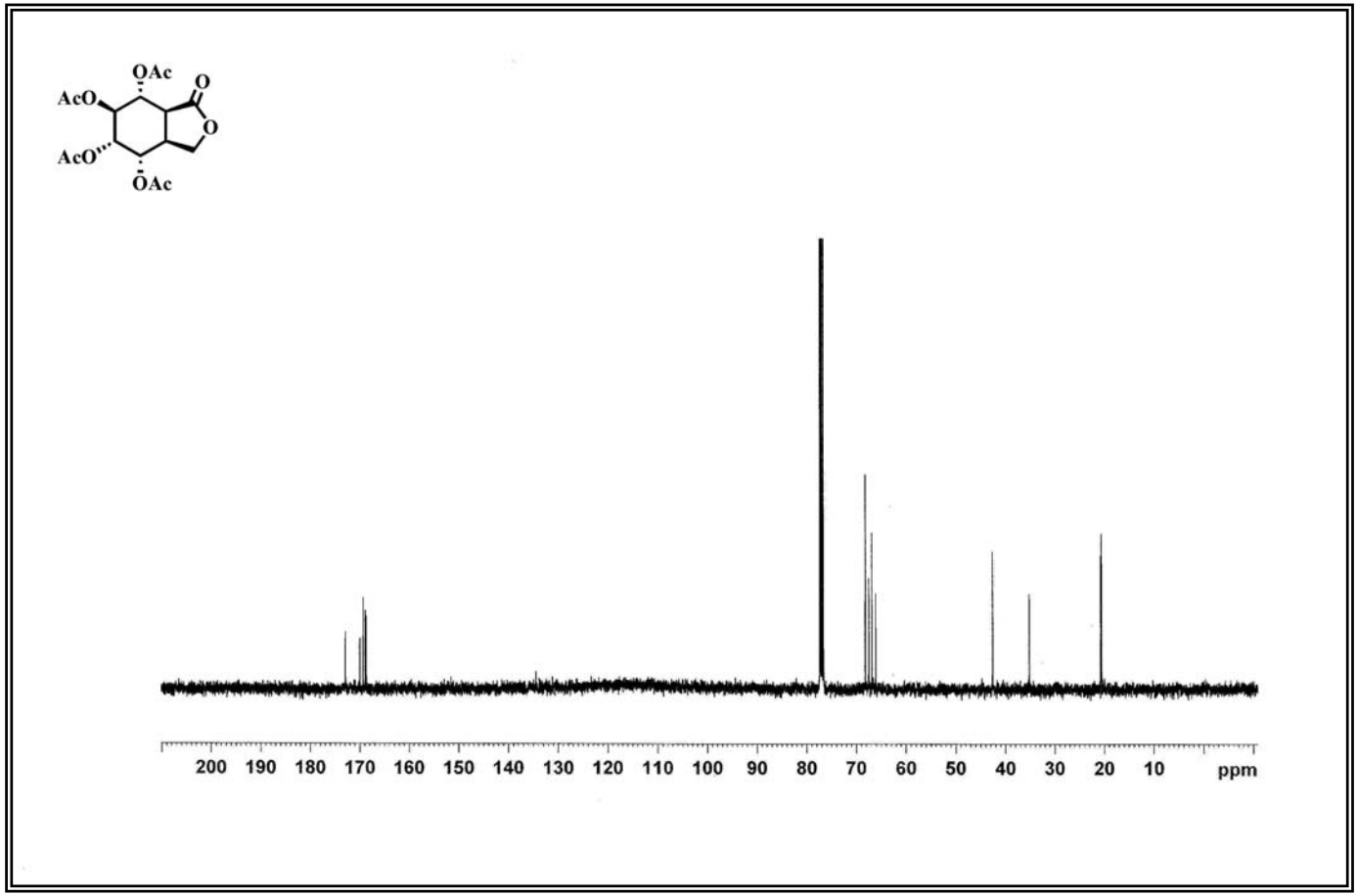

Figure 37. ^{13}C-NMR spectrum of compound **155**

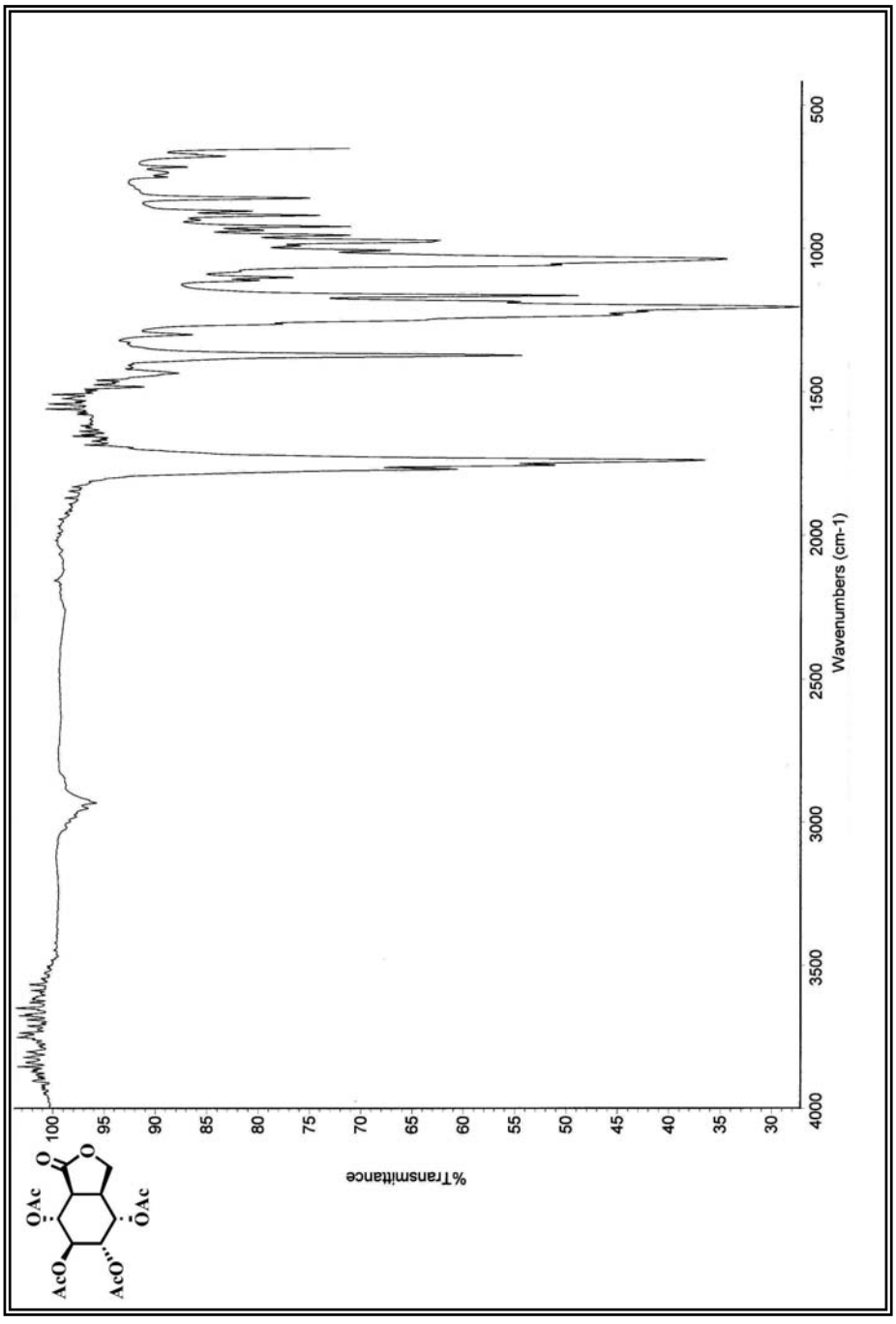

Figure 38. IR spectrum of compound **155**

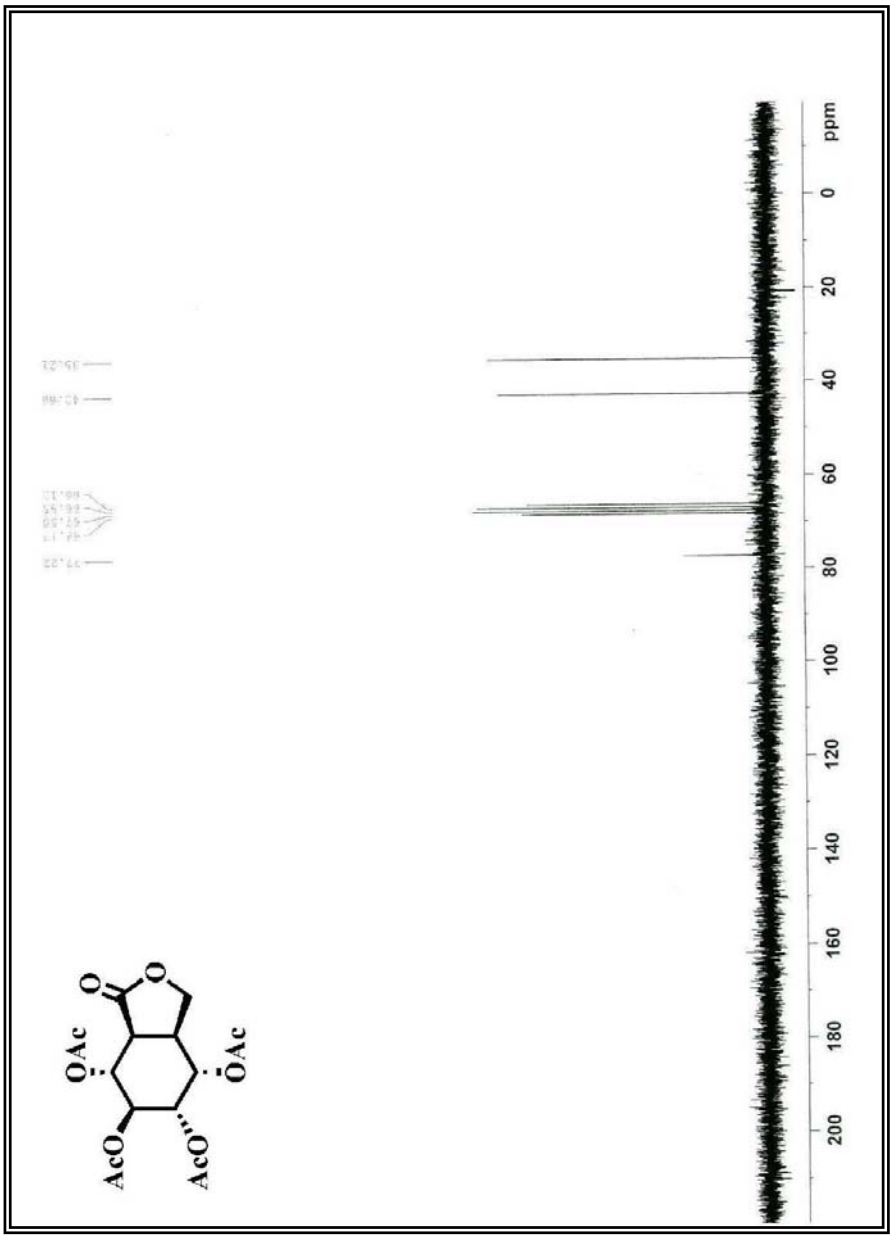

Figure 39. DEPT-90 spectrum of compound **155**

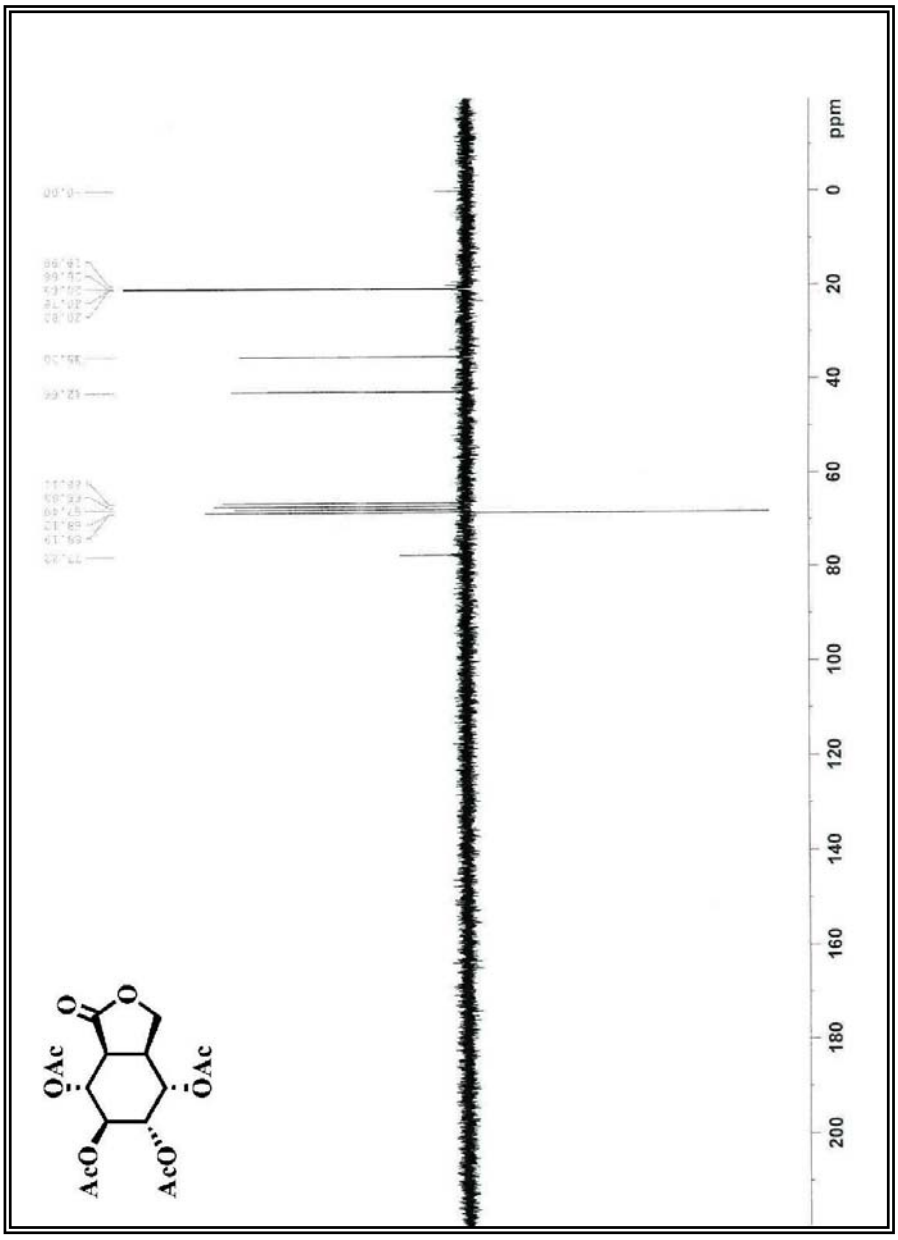

Figure 40. DEPT-135 spectrum of compound **155**

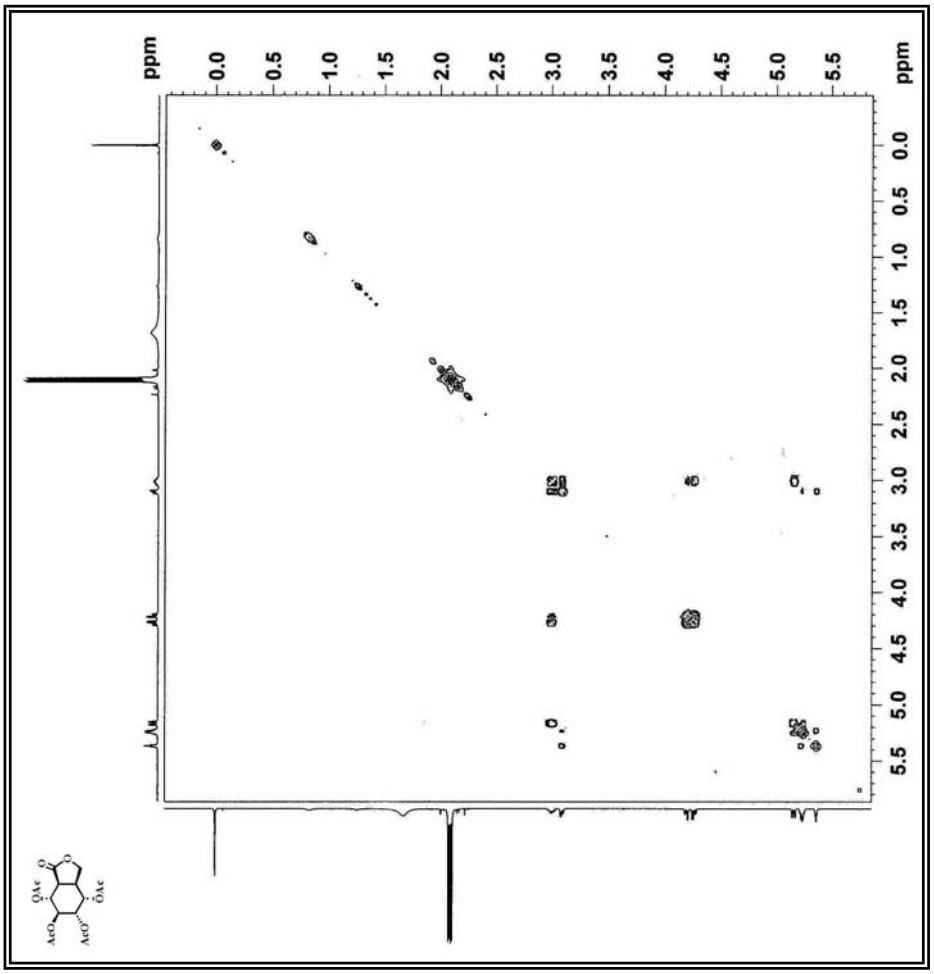

Figure 41. COSY spectrum of compound **155**

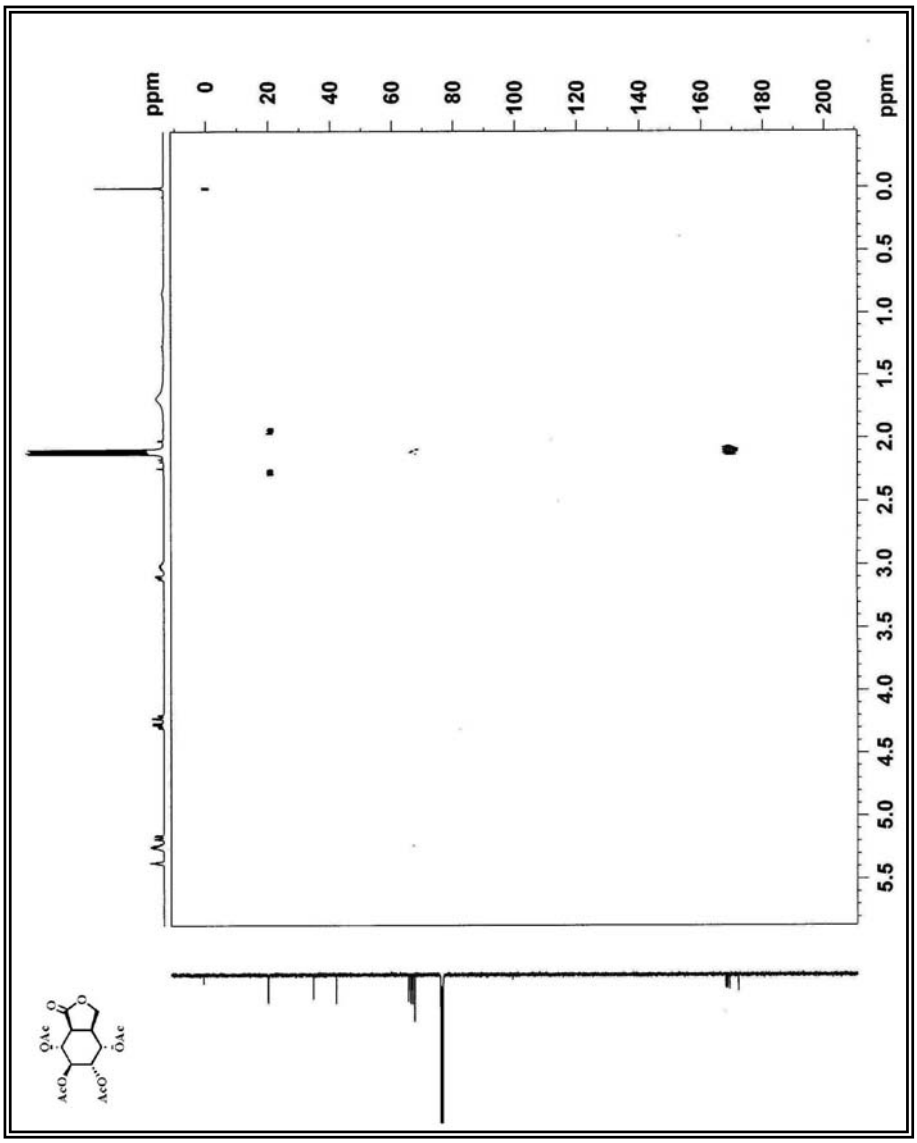

Figure 42. HMBC spectrum of compound **155**

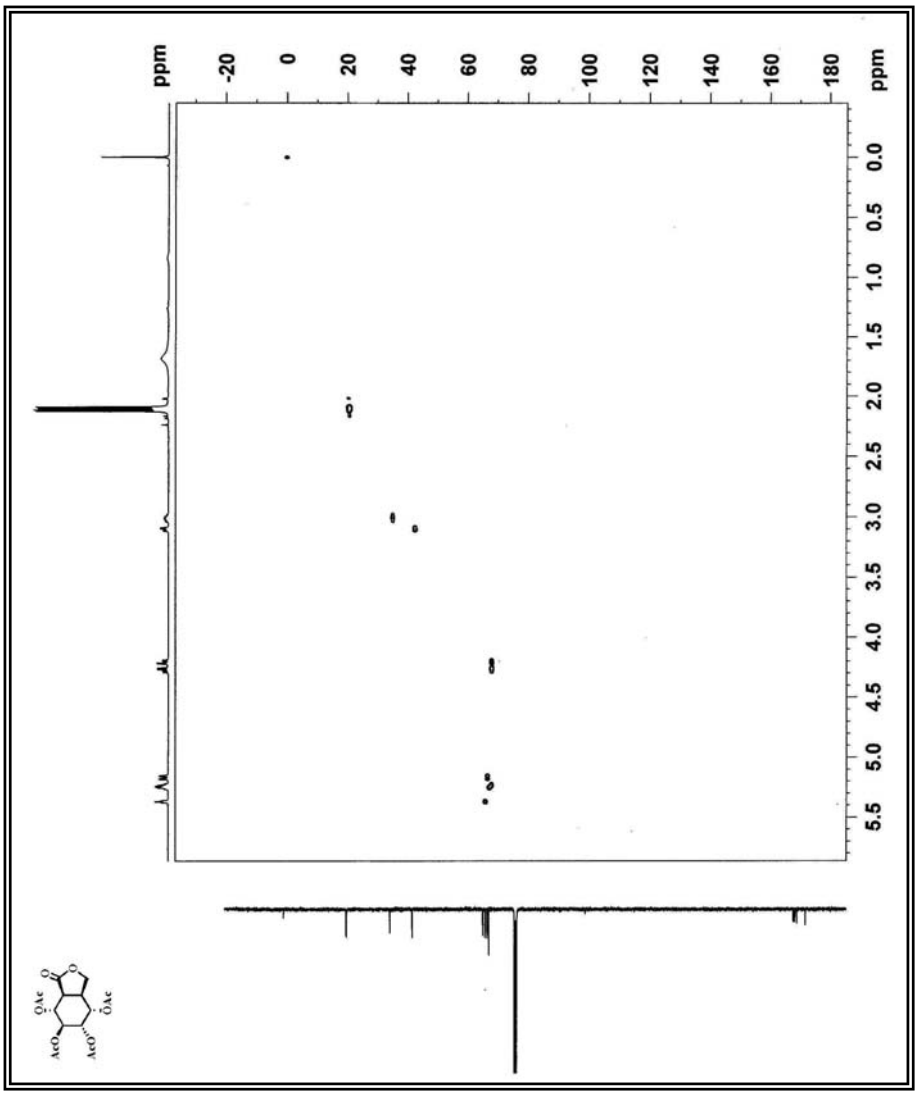

Figure 43. HSQC spectrum of compound **155**

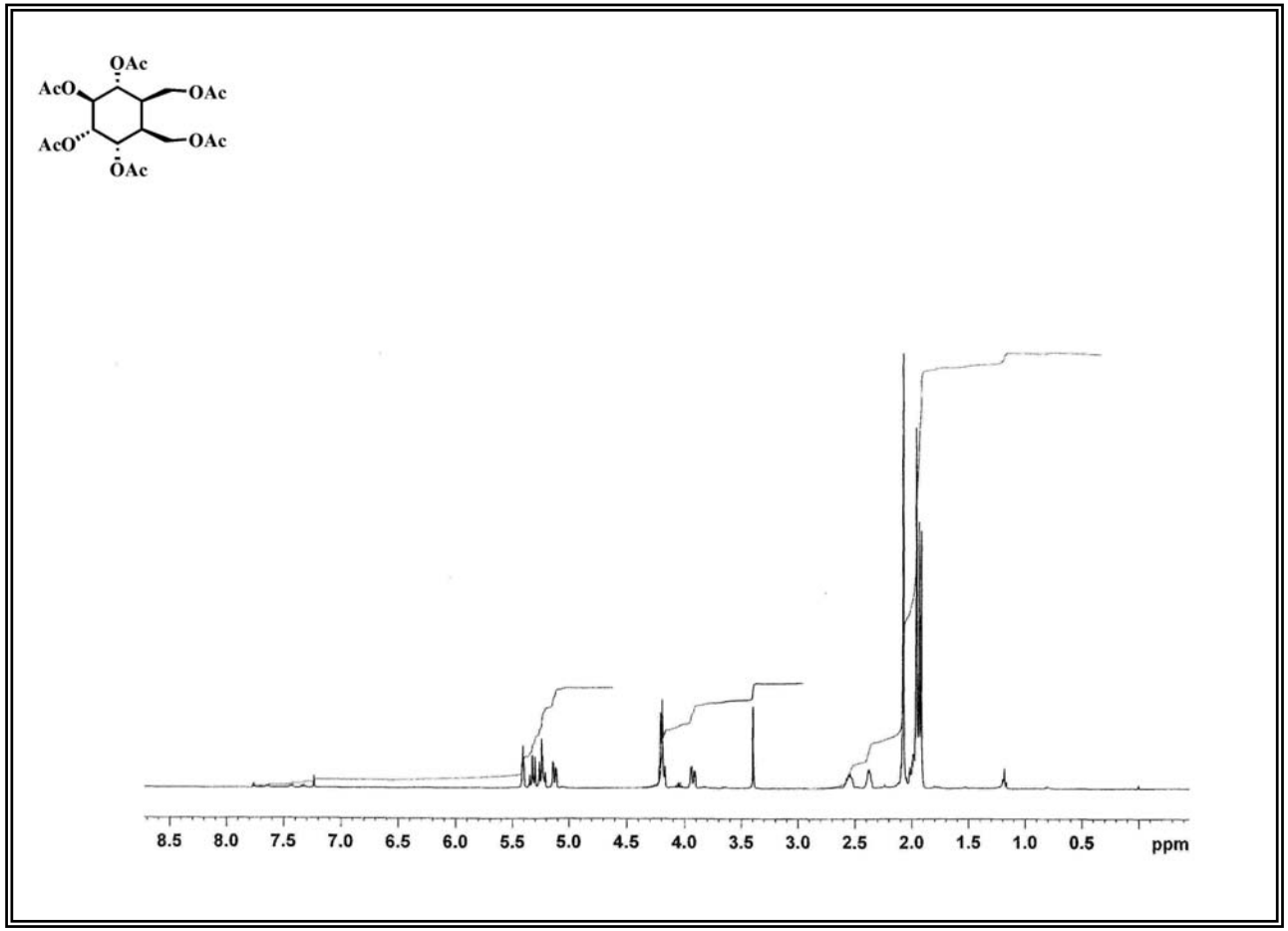

Figure 44. ^{1}H-NMR of spectrum of compound **156**

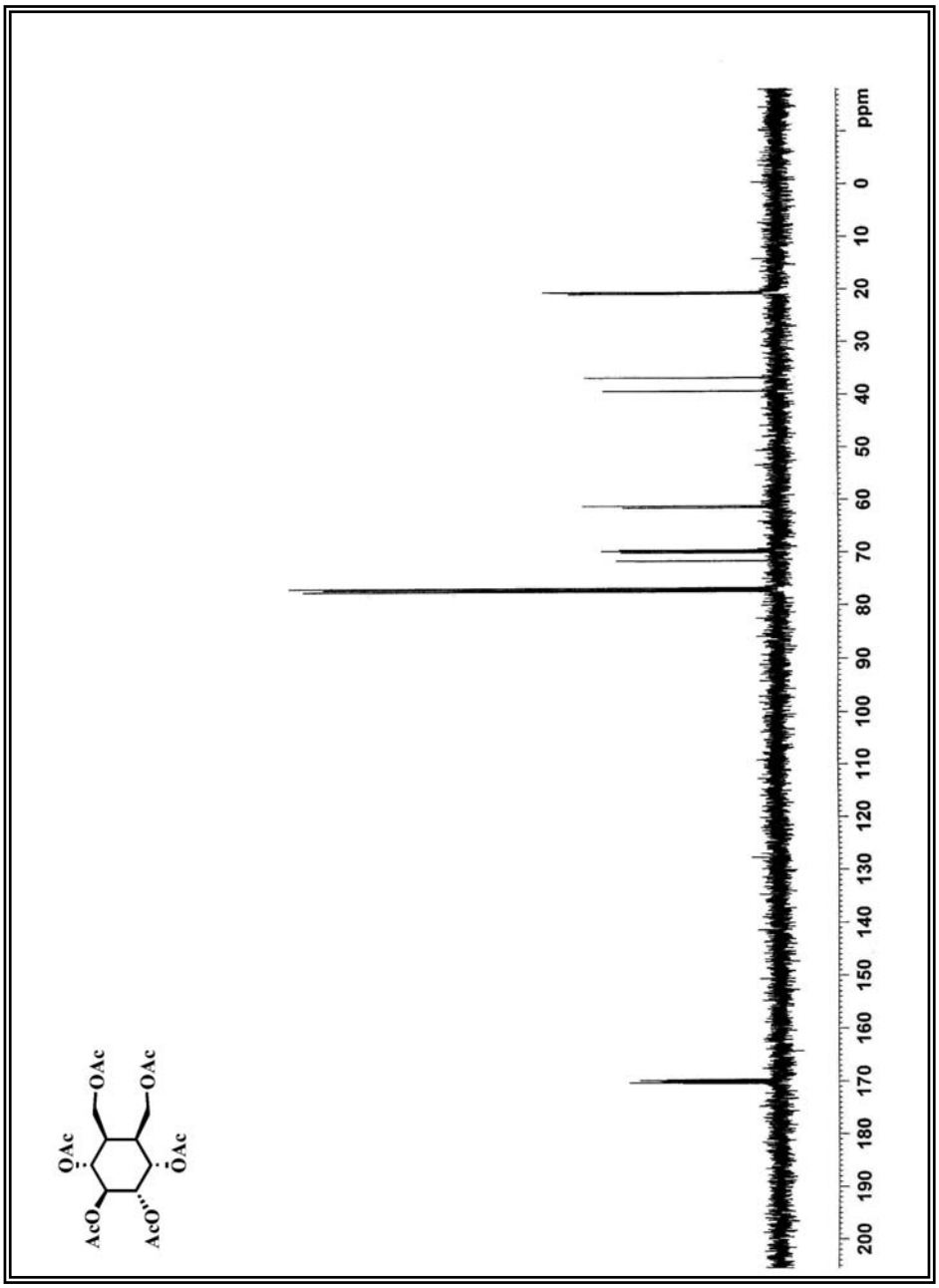

Figure 45. ^{13}C-NMR spectrum of compound **156**

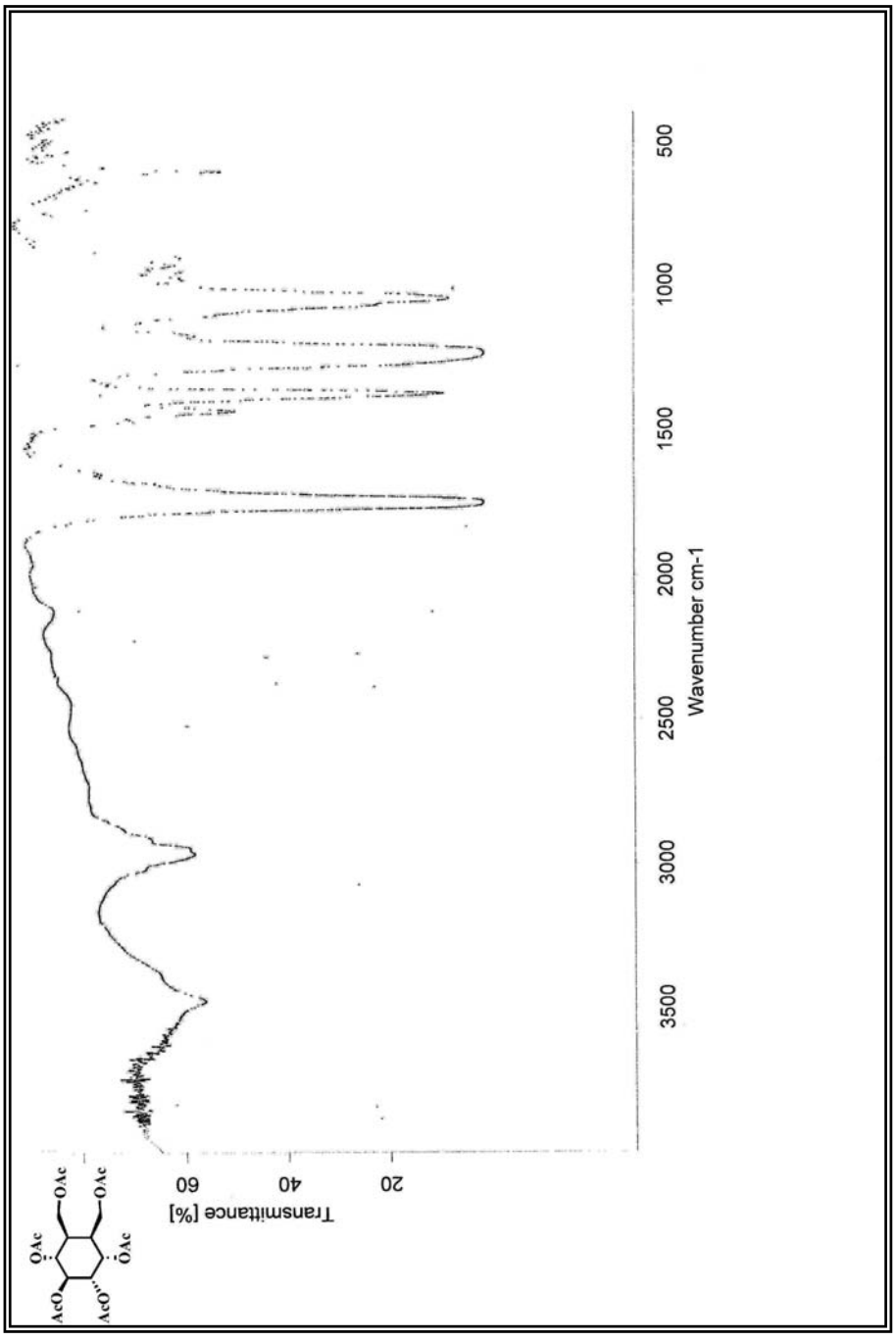

Figure 46. IR spectrum of compound **156**

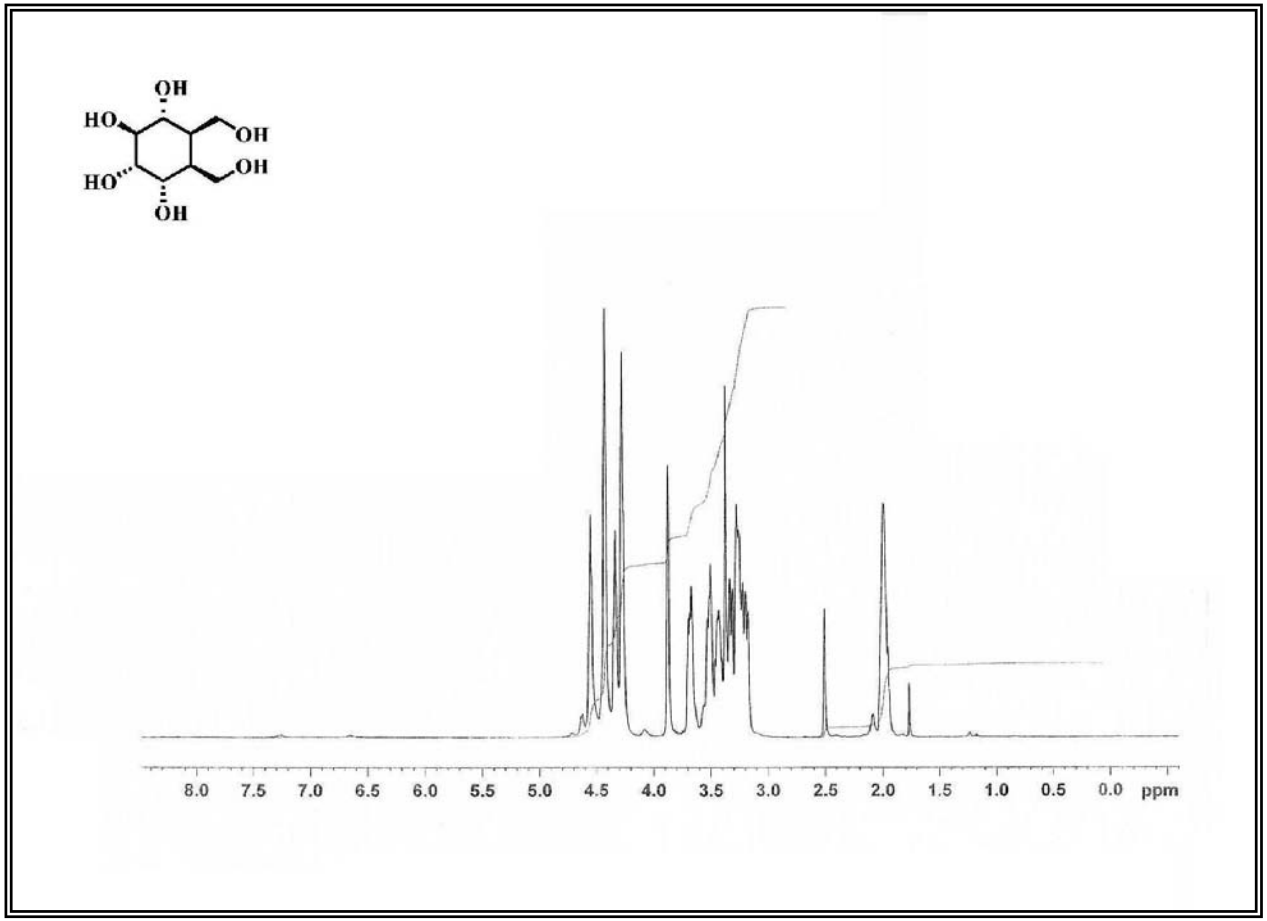

Figure 47. ^{1}H-NMR of spectrum of compound **127**

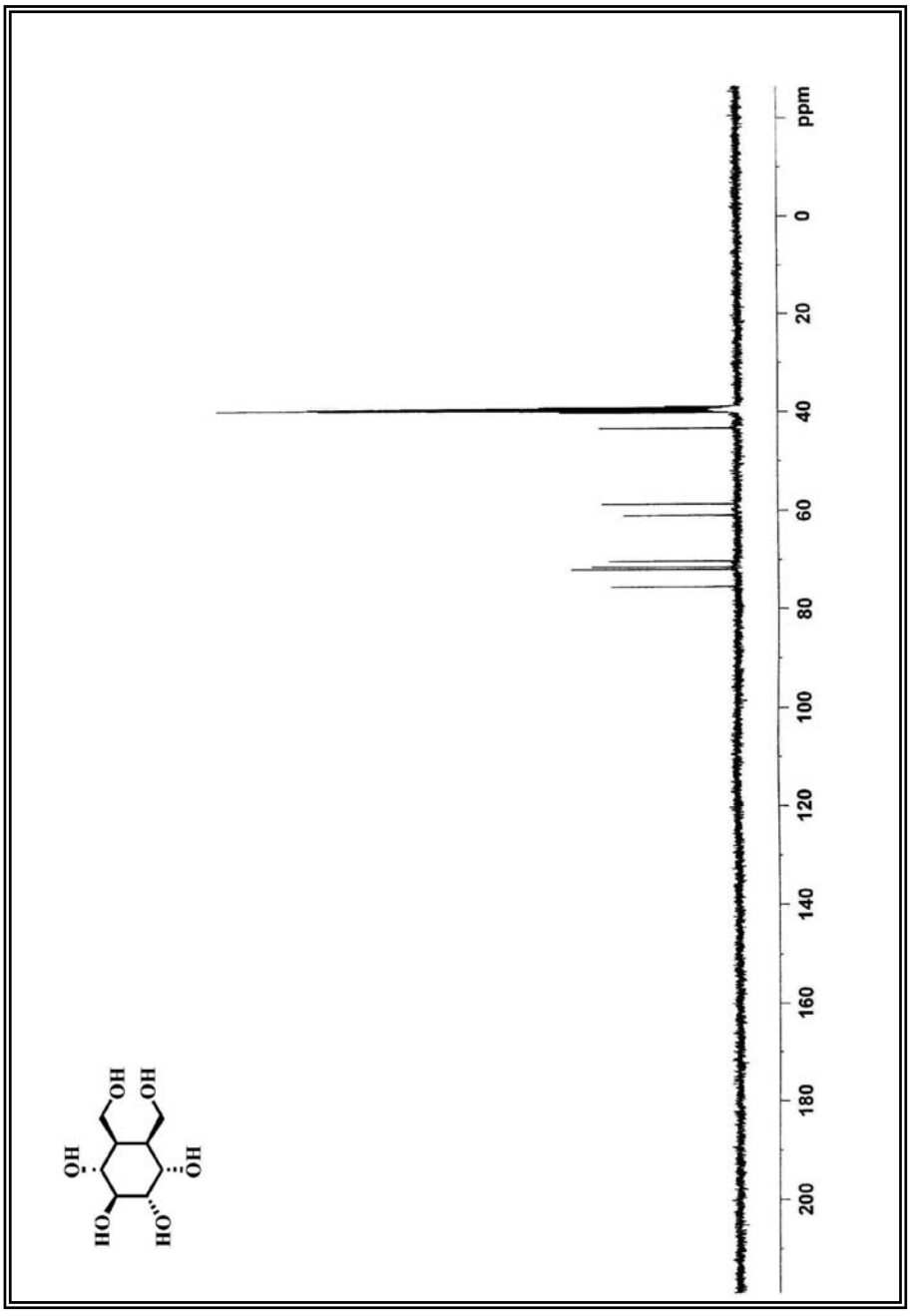

Figure 48. ^{13}C-NMR spectrum of compound **127**

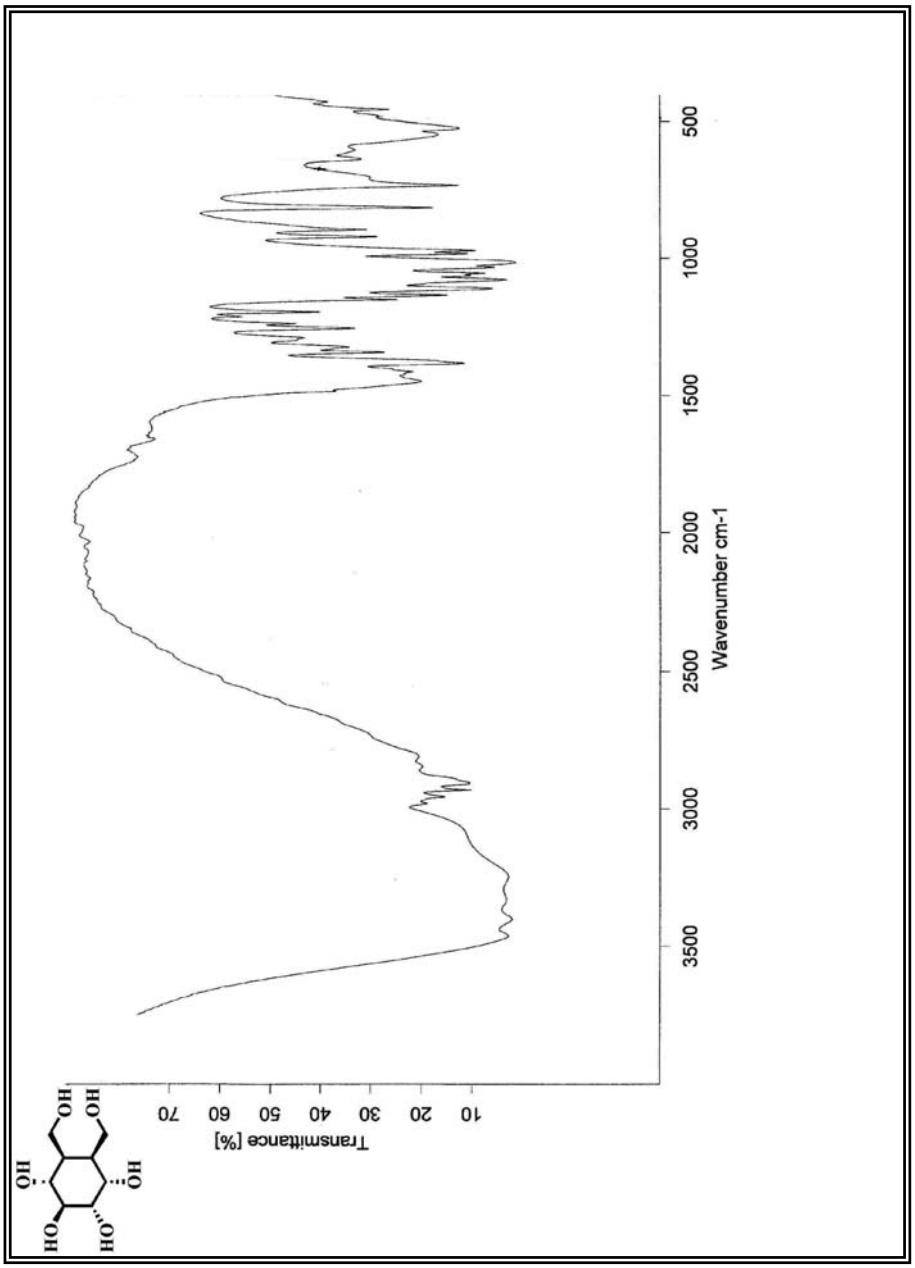

Figure 49. IR spectrum of compound **127**

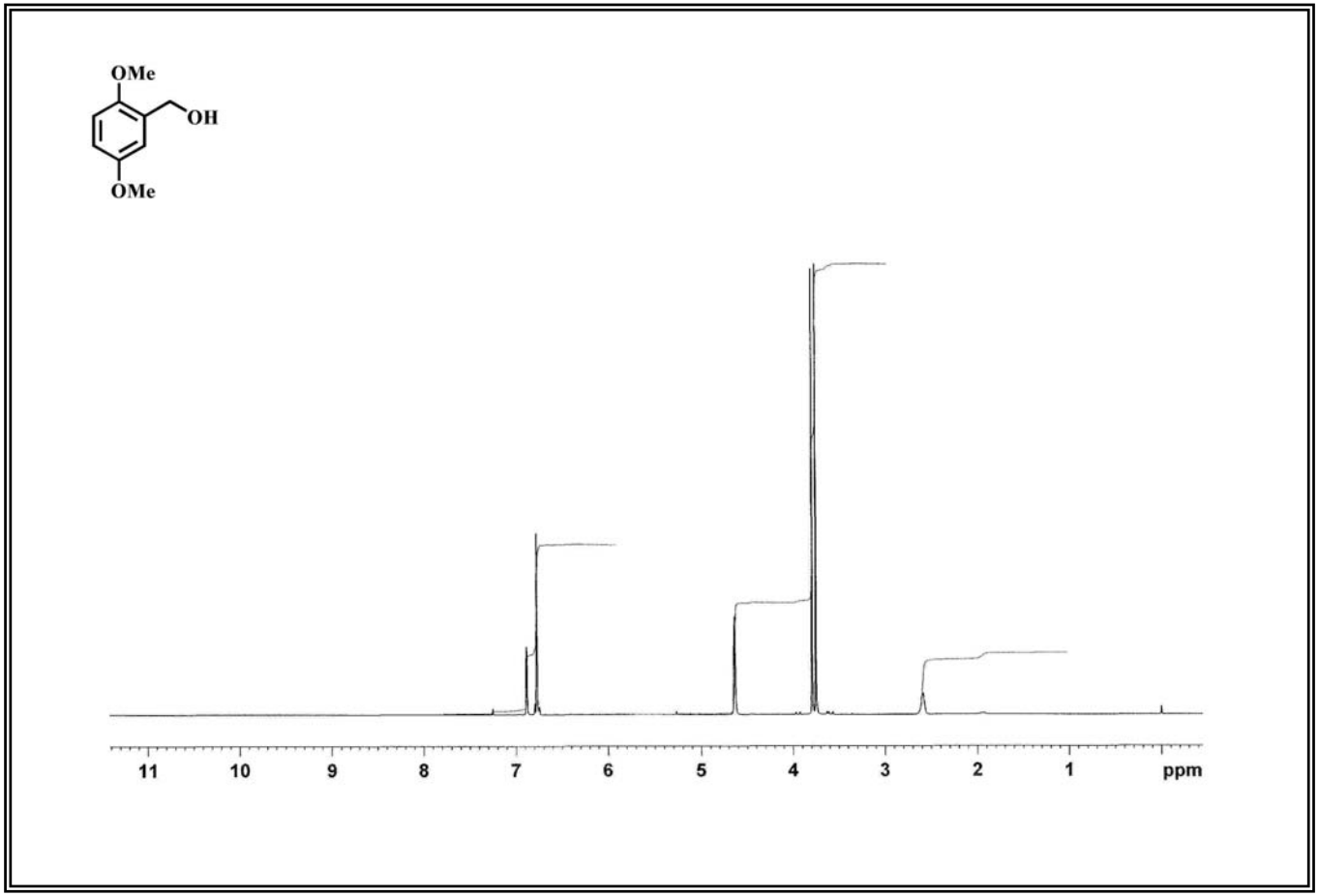

Figure 50. ^{1}H-NMR of spectrum of compound **163**

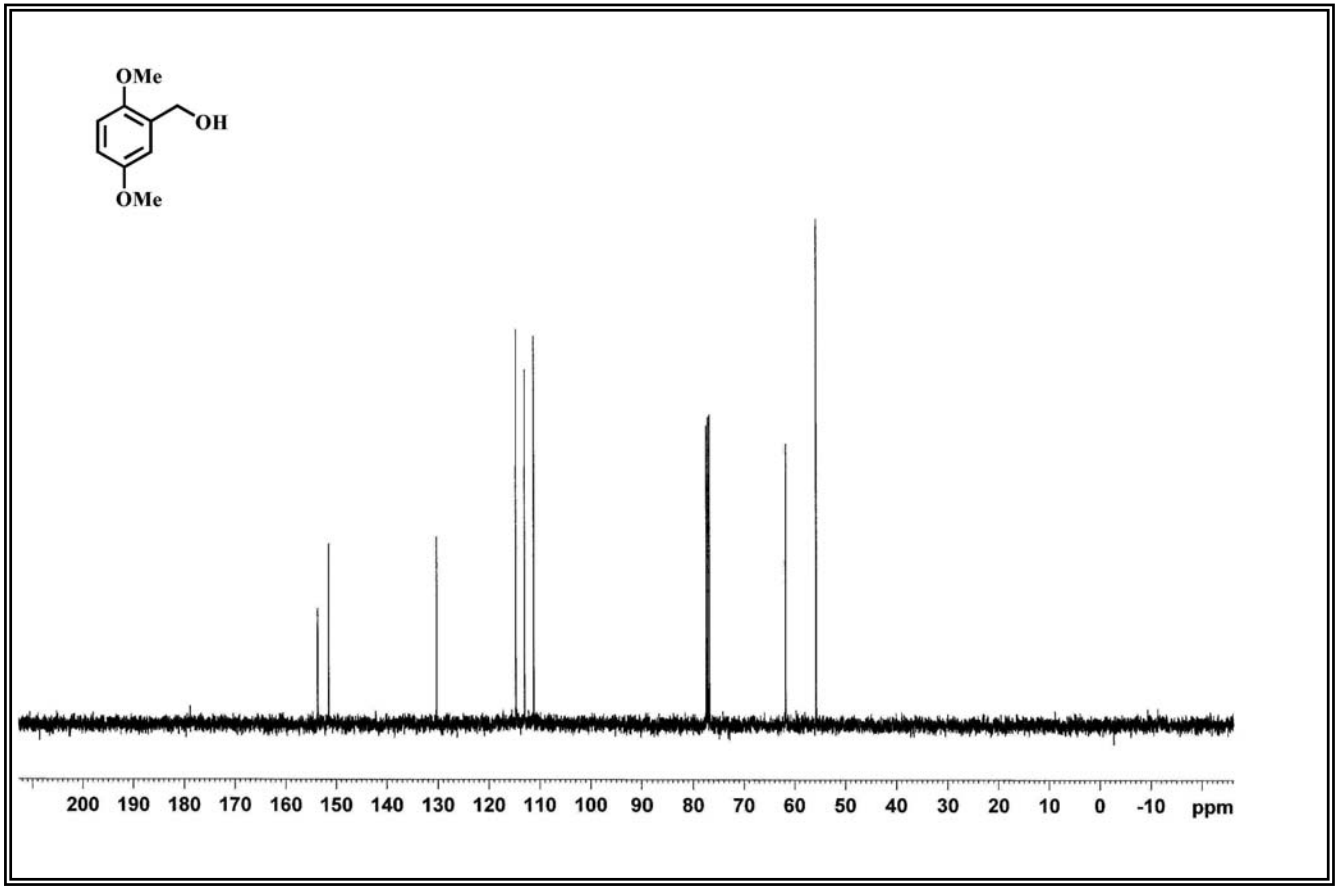

Figure 51. ^{13}C-NMR spectrum of compound **163**

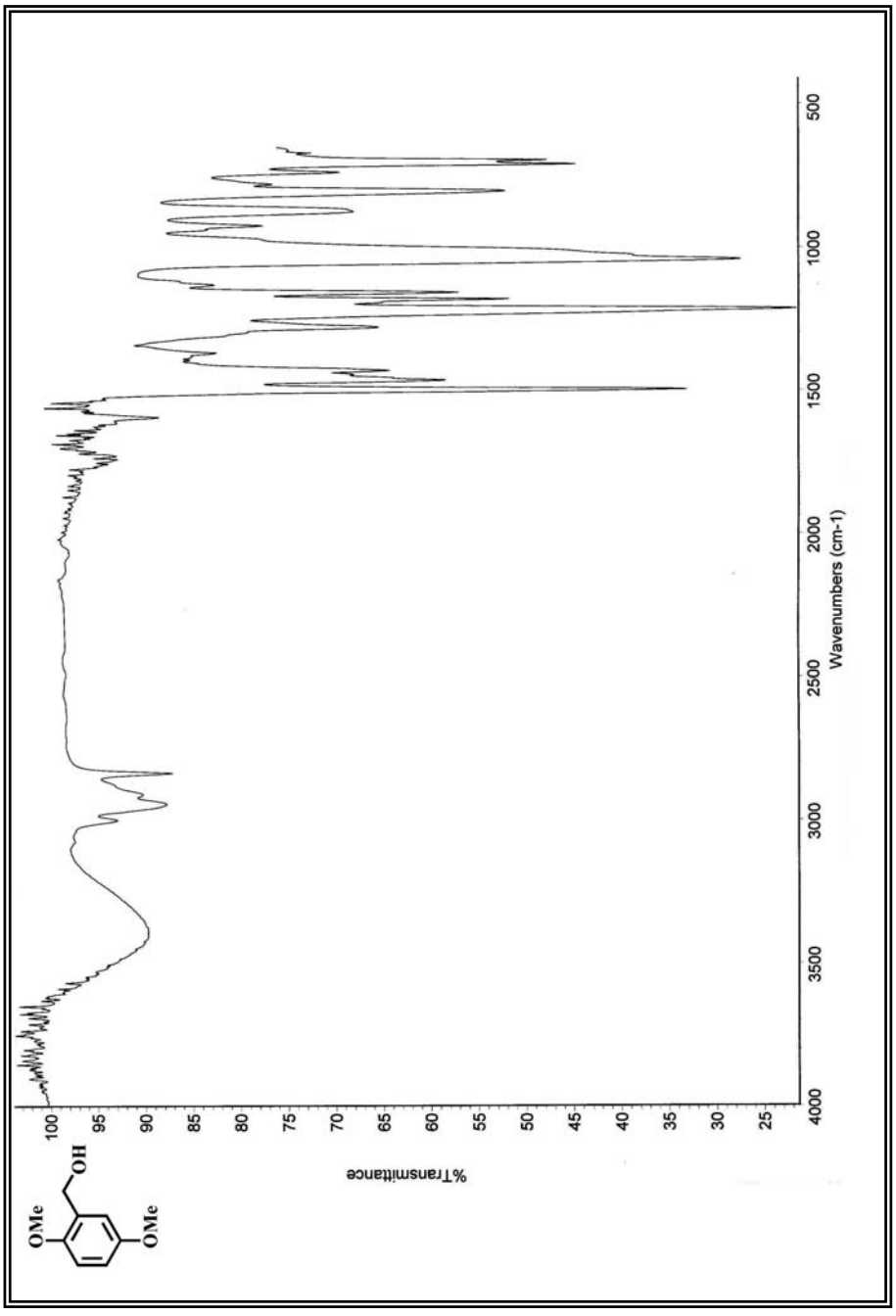

Figure 52. IR spectrum of compound **163**

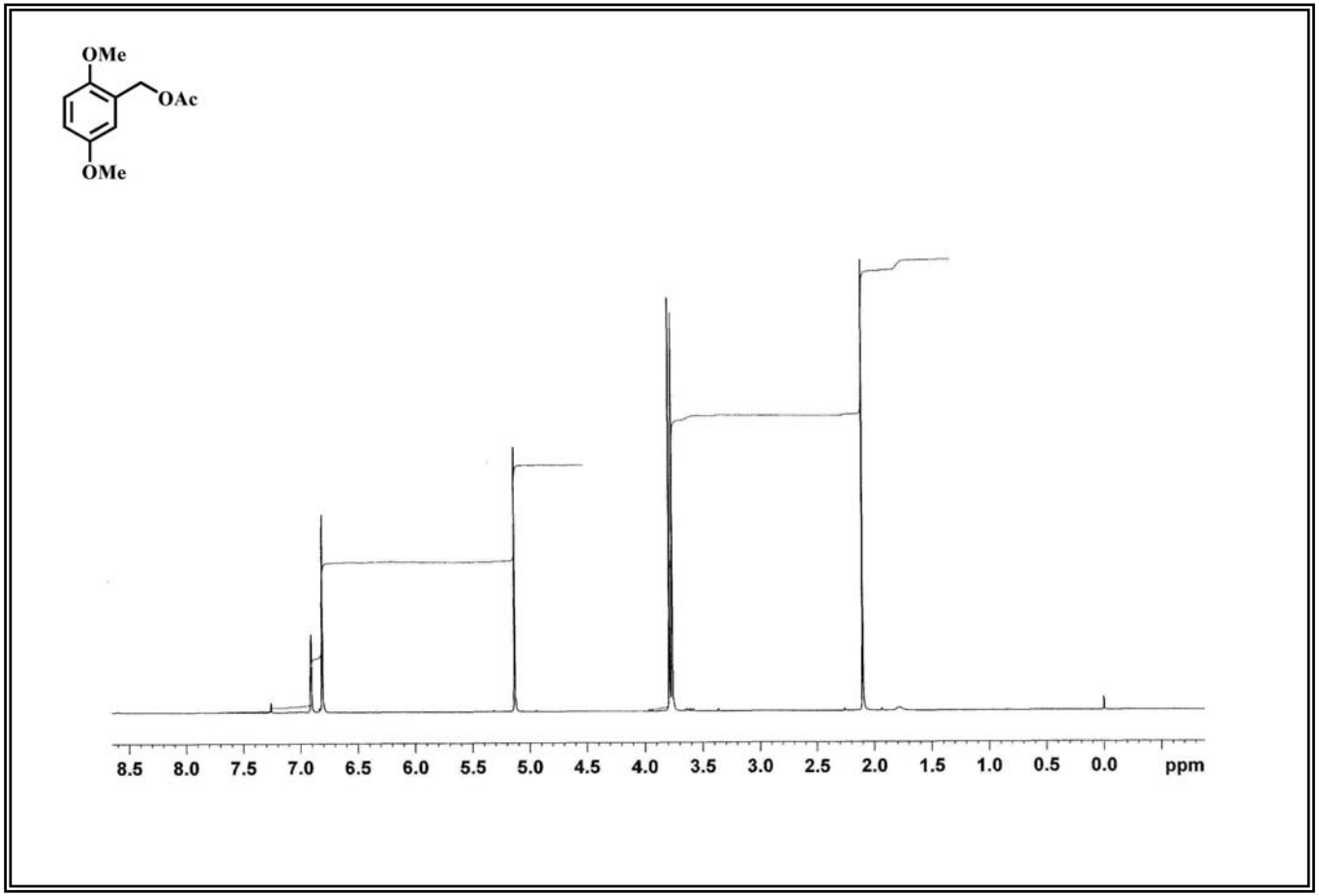

Figure 53. ^{1}H-NMR of spectrum of compound **164**

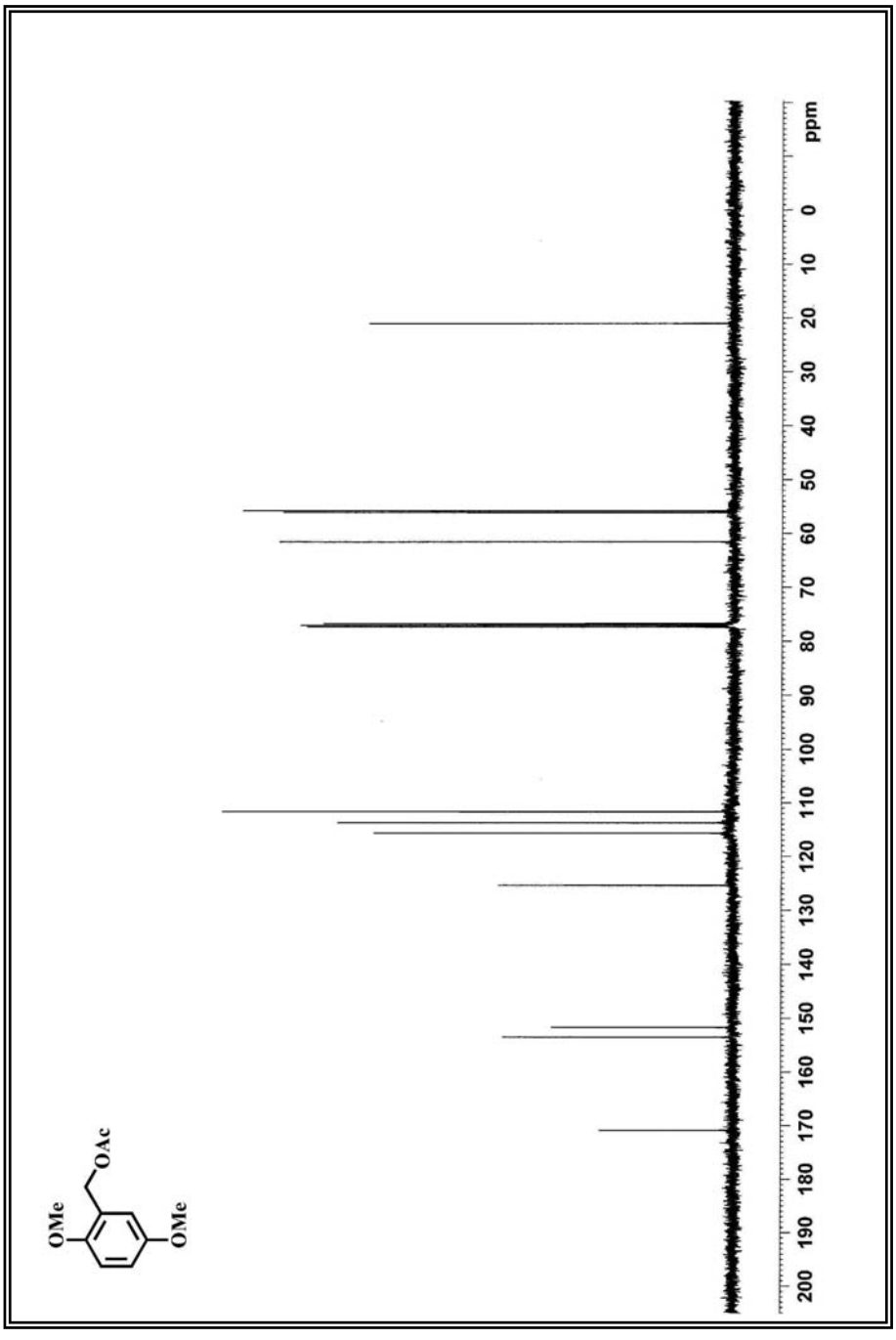

Figure 54. ^{13}C-NMR spectrum of compound **164**

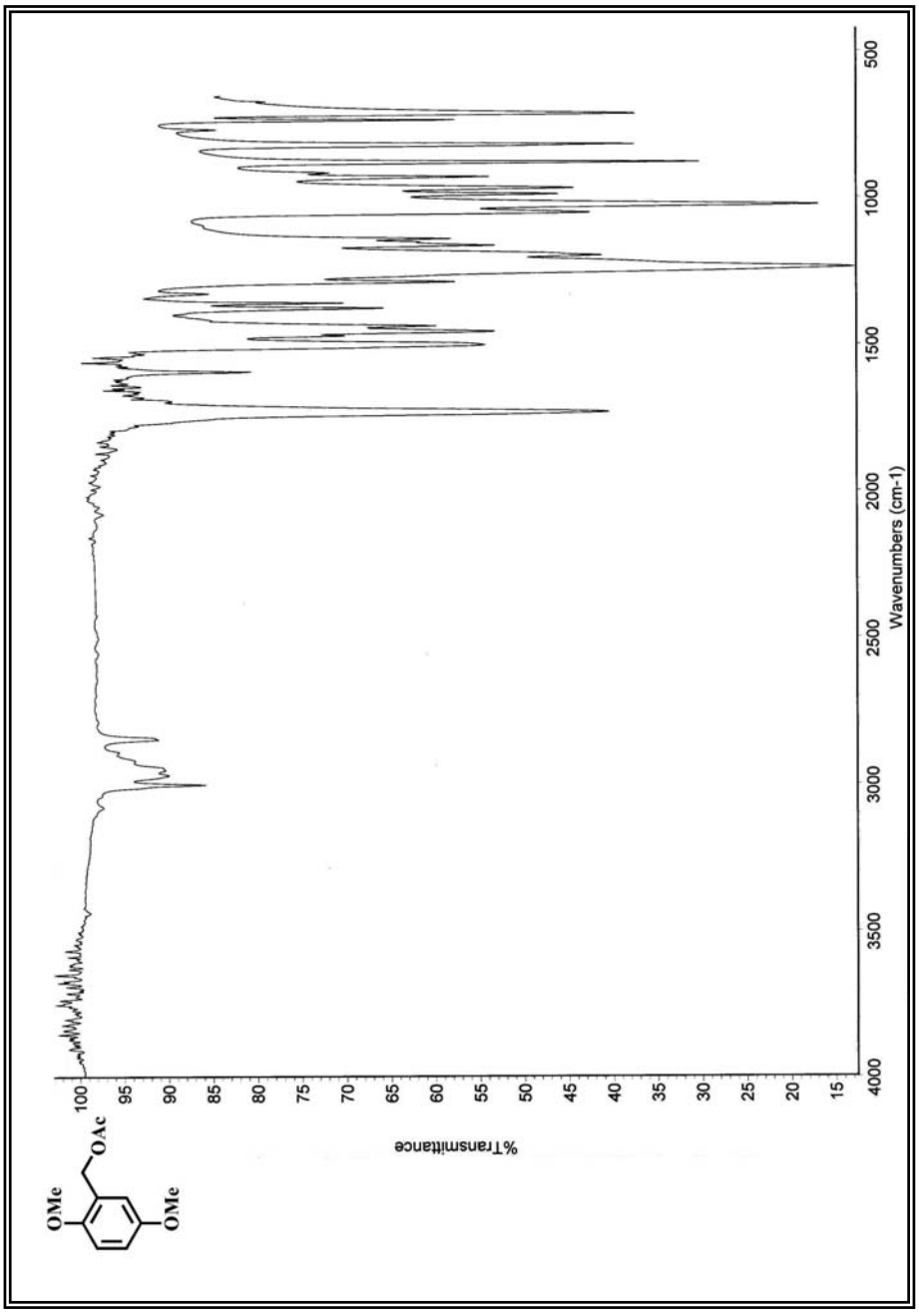

Figure 55. IR spectrum of compound **164**

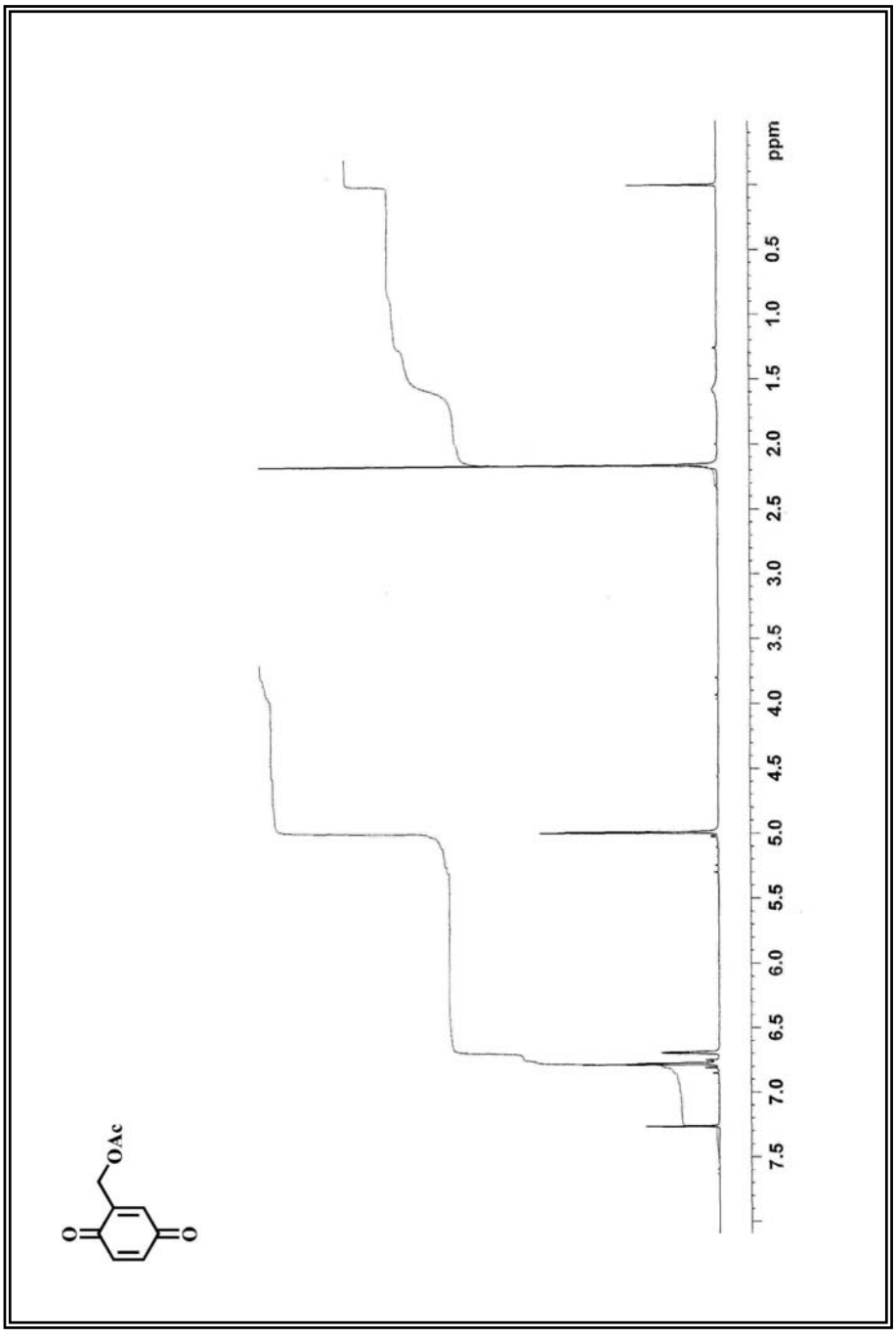

Figure 56. ^{1}H-NMR of spectrum of compound **136**

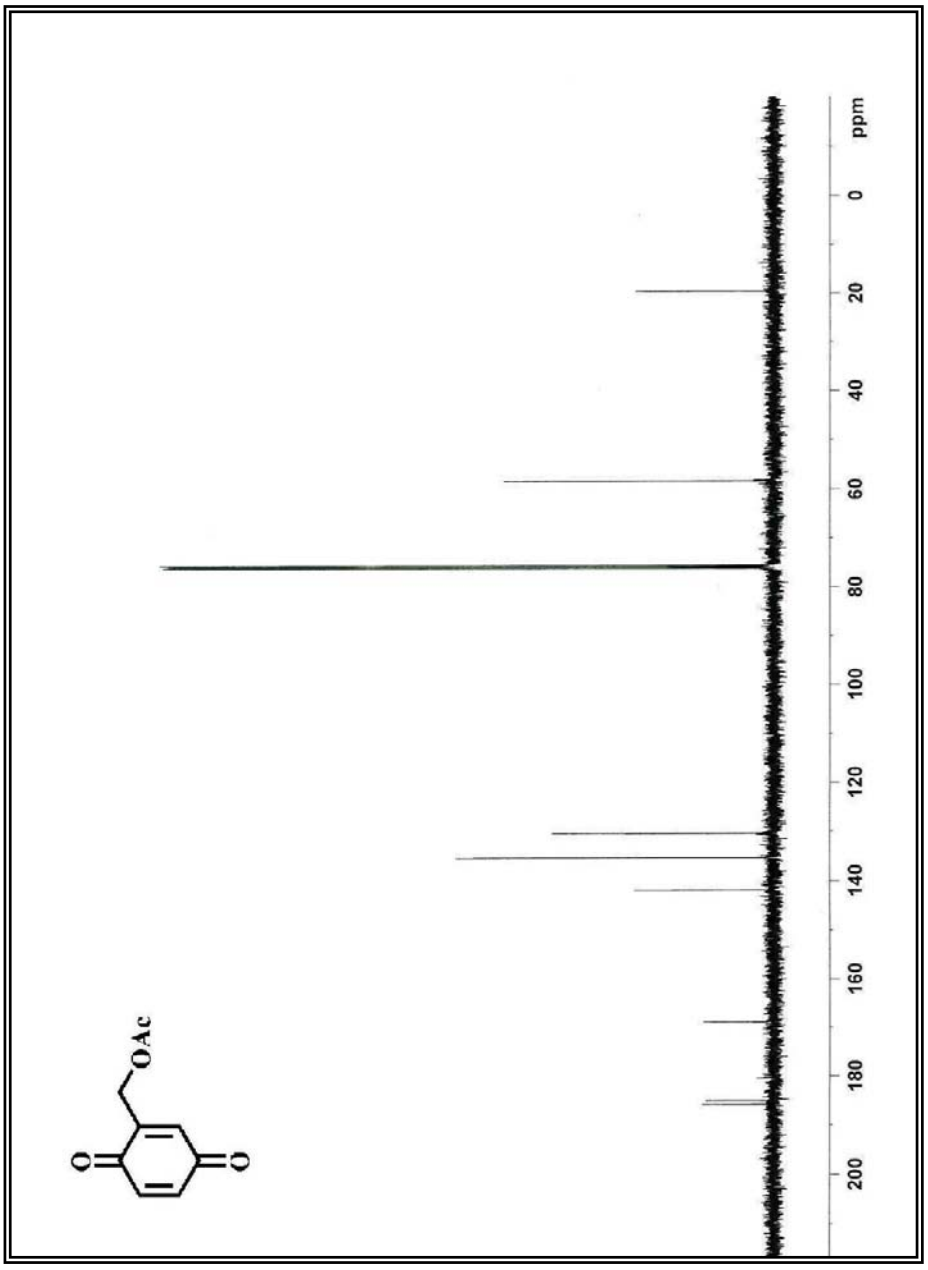

Figure 57. ^{13}C-NMR spectrum of compound **136**

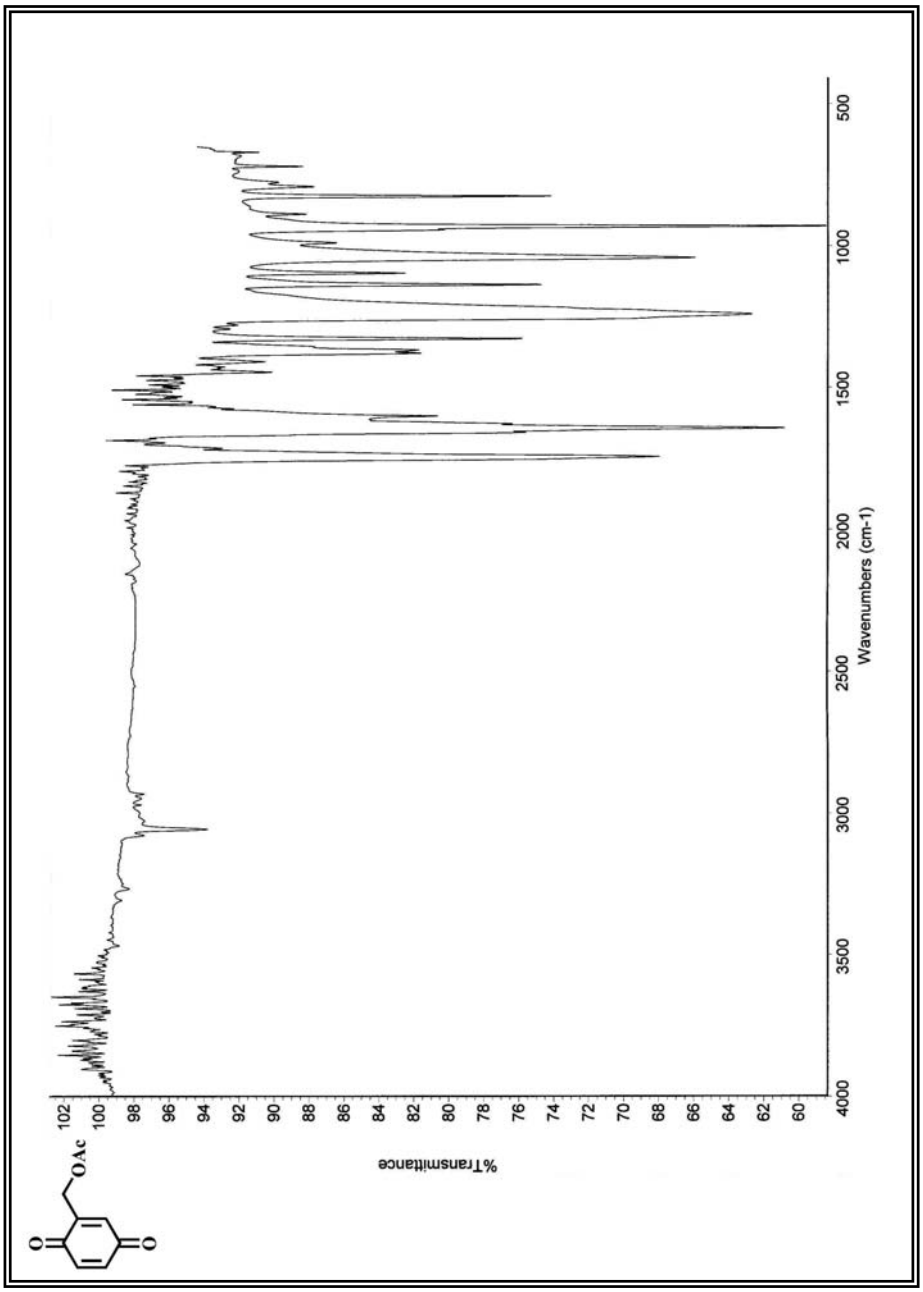

Figure 58. IR spectrum of compound **136**

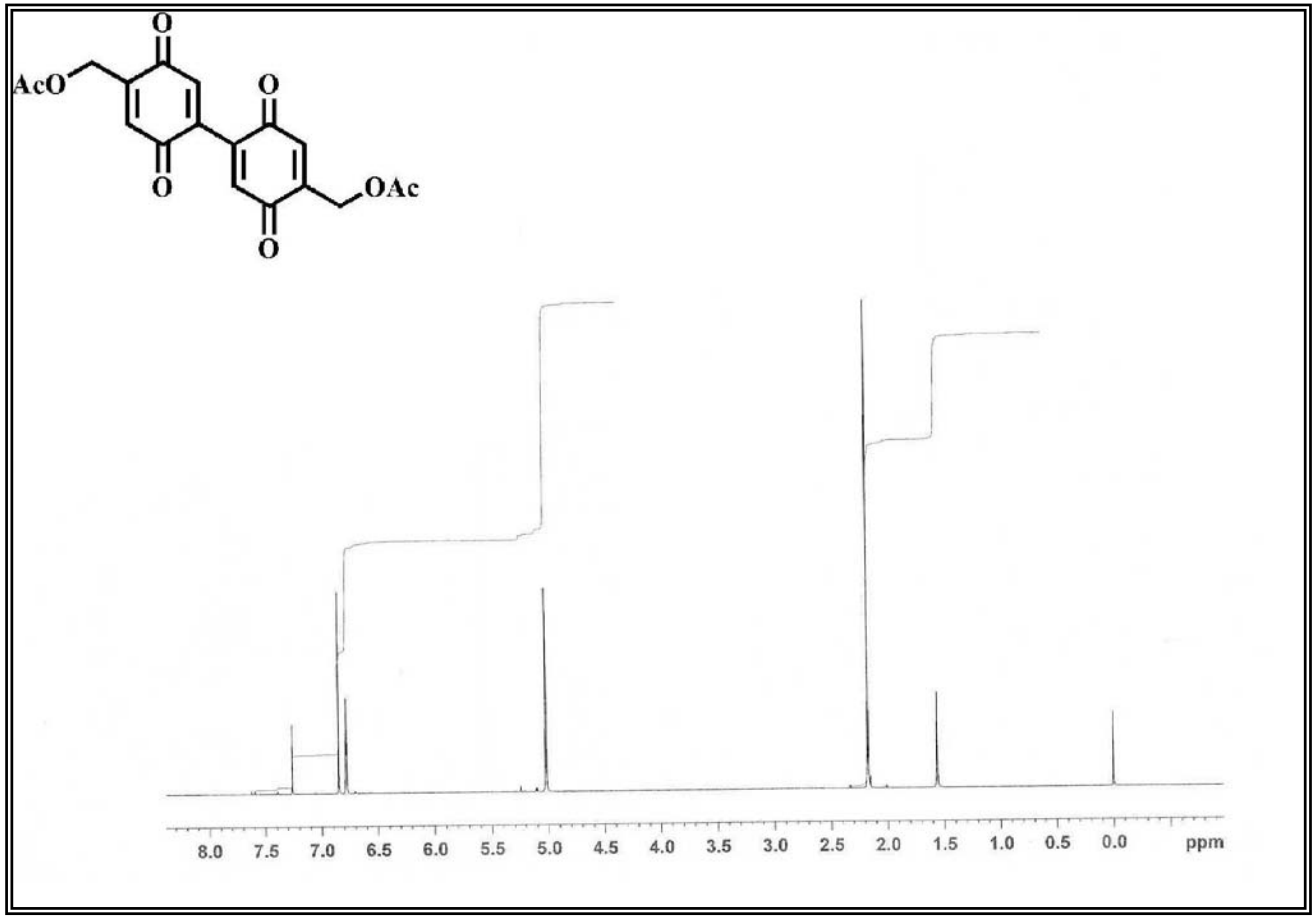

Figure 59. ^{1}H-NMR of spectrum of compound **165**

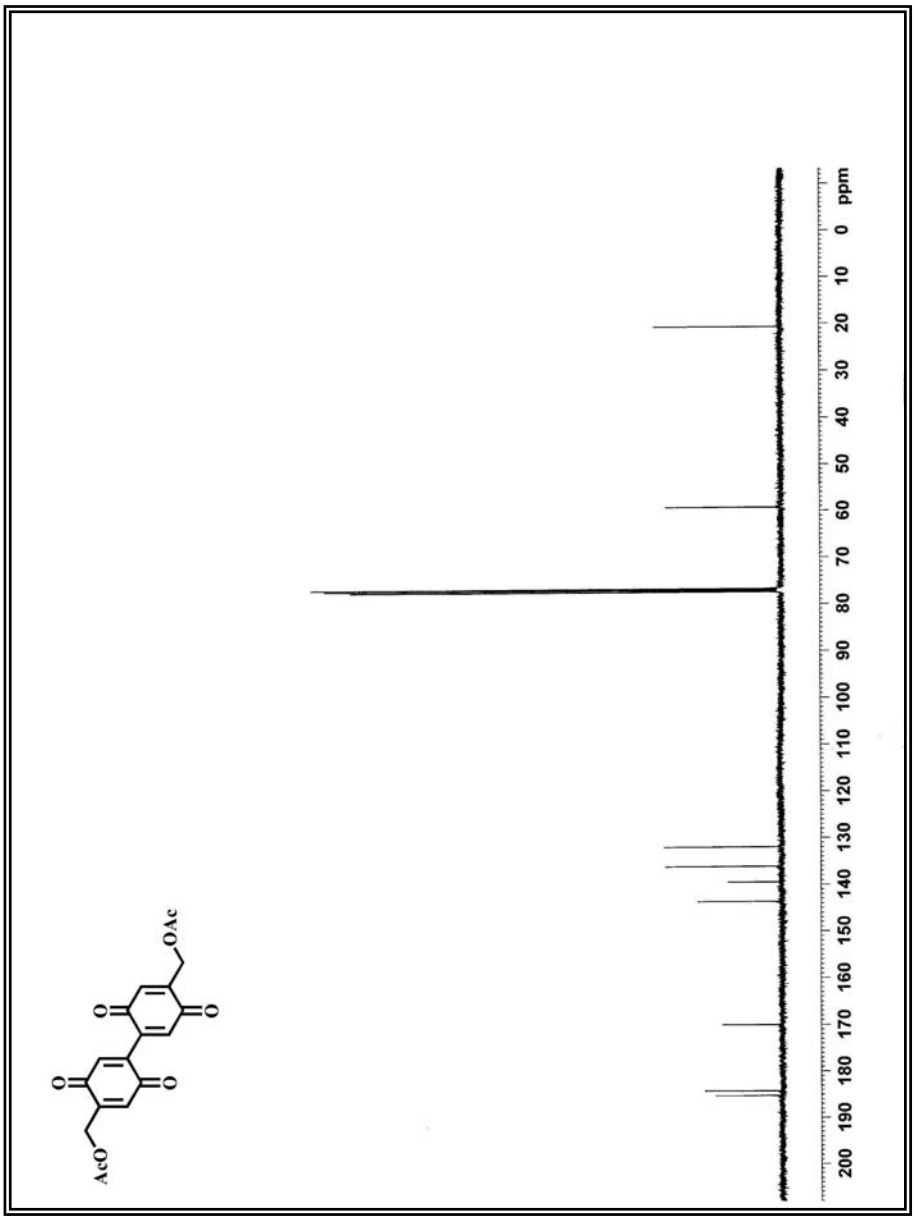

Figure 60. ^{13}C-NMR spectrum of compound **165**

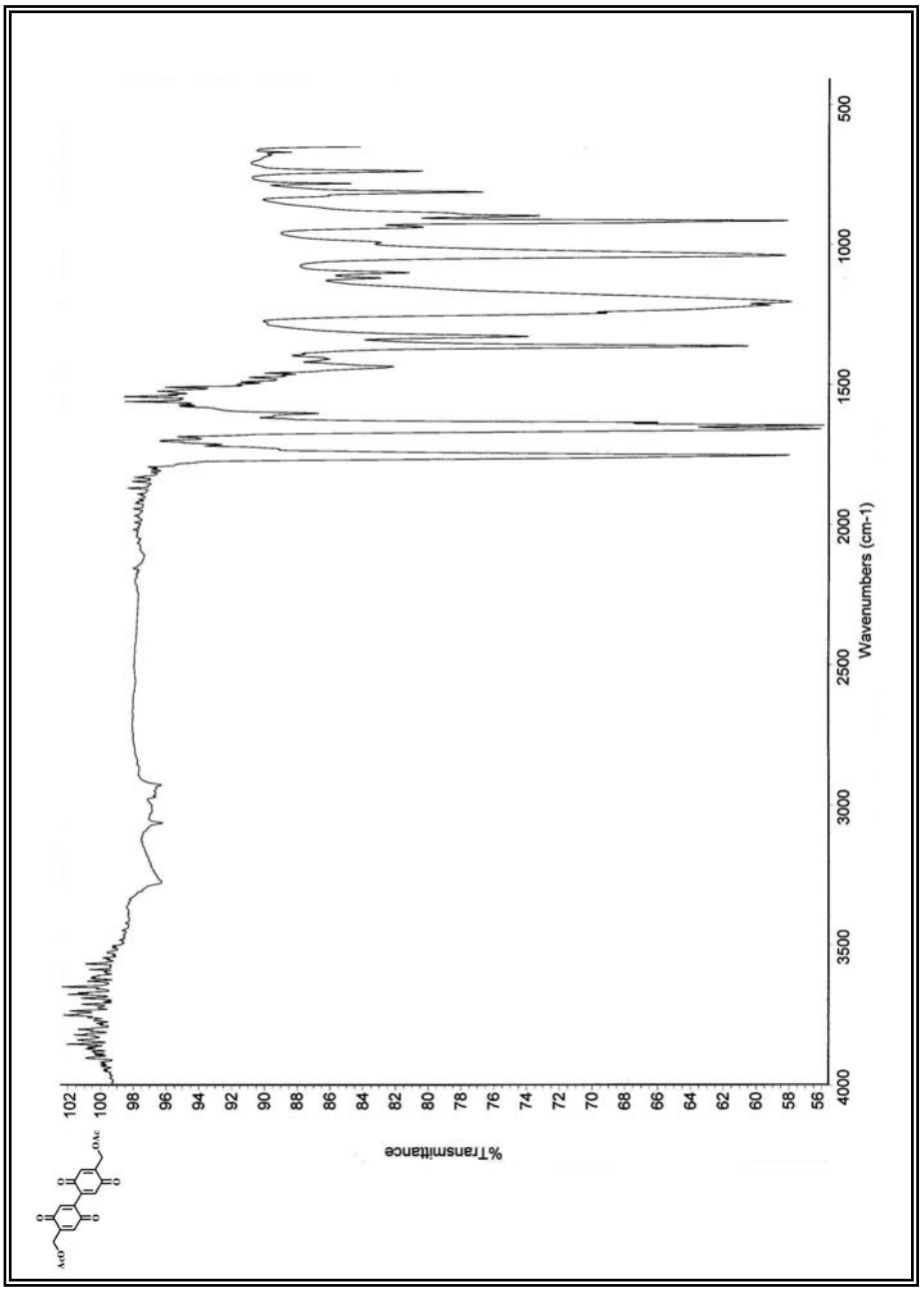

Figure 61. IR spectrum of compound **165**

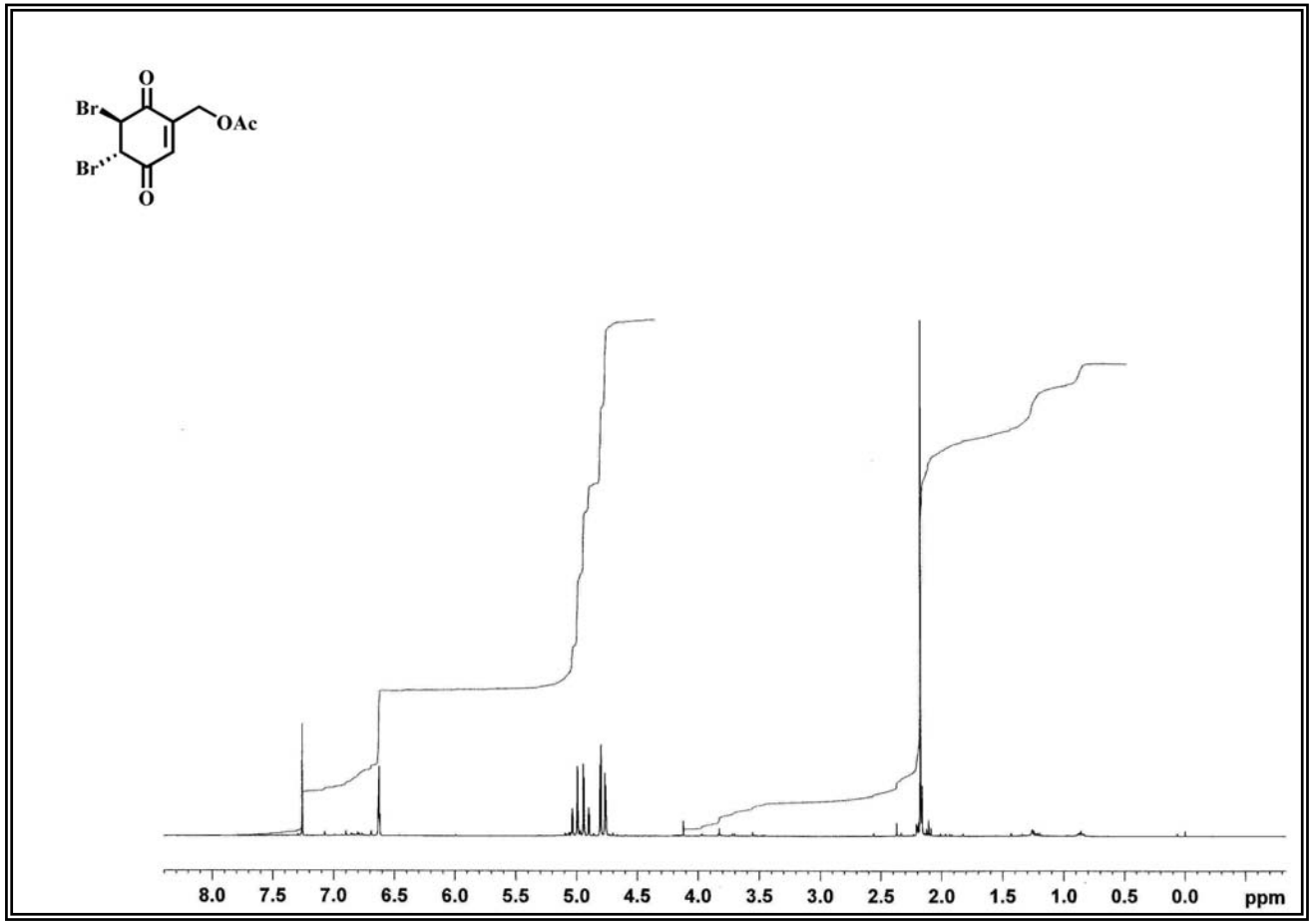

Figure 62. ^{1}H-NMR of spectrum of compound **166**

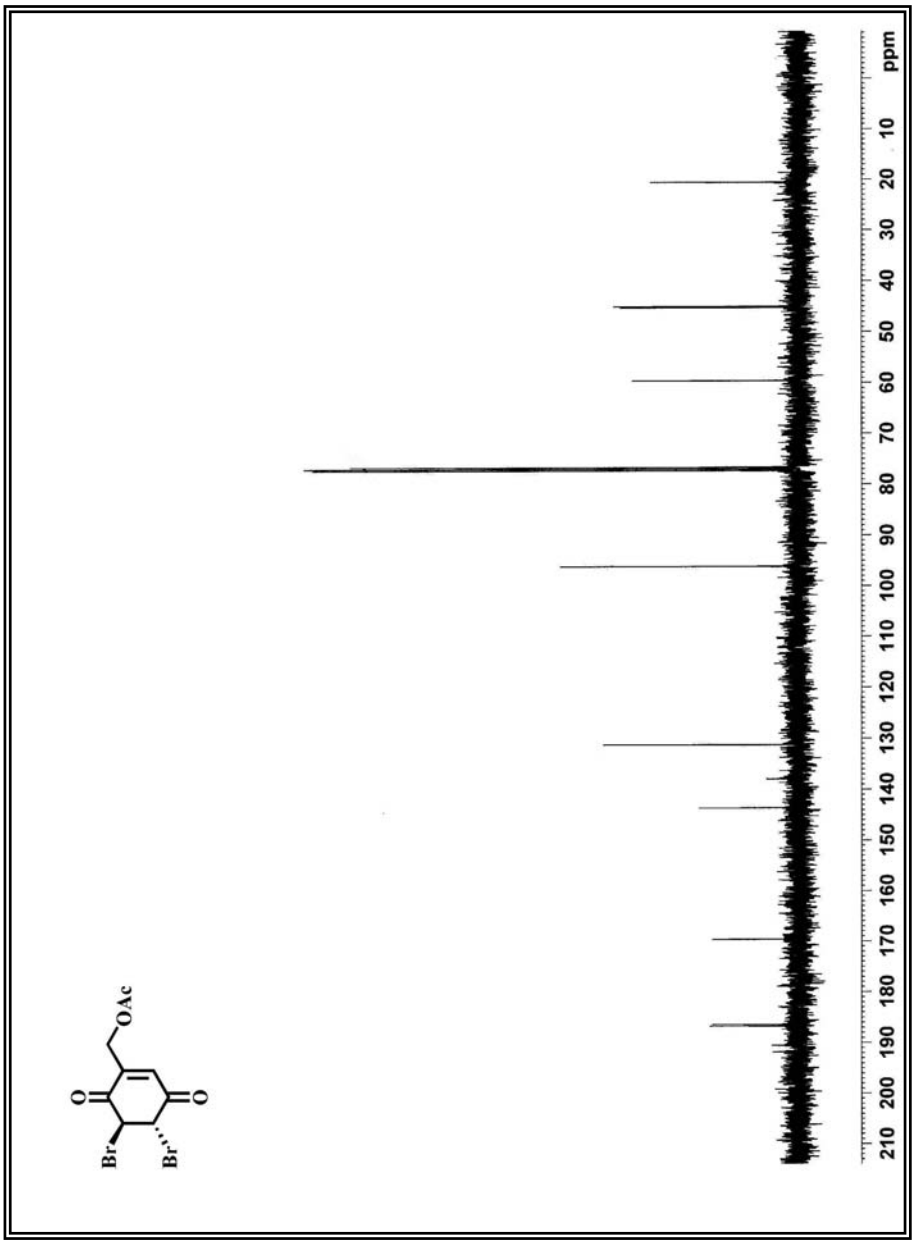

Figure 63. ^{13}C-NMR spectrum of compound **166**

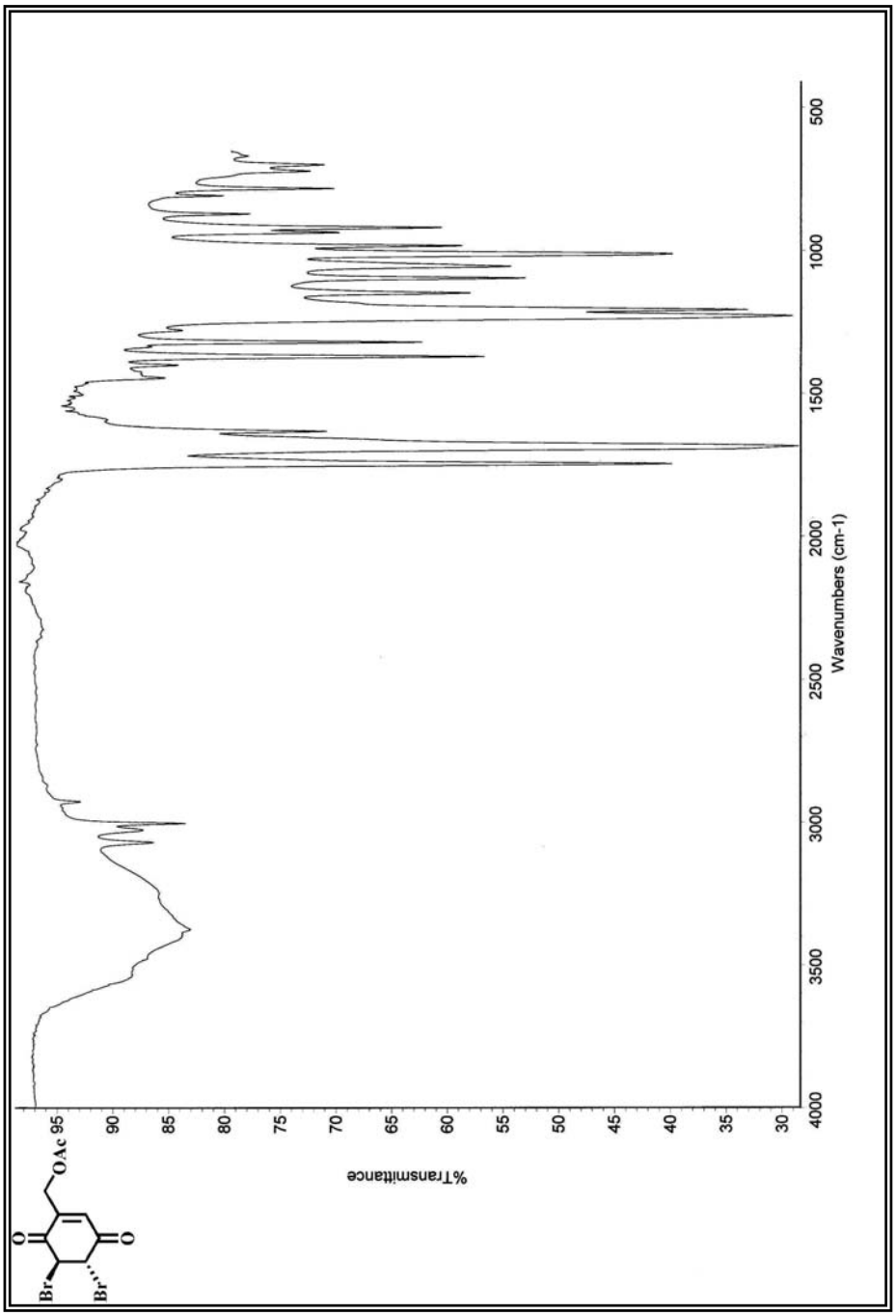

Figure 64. IR spectrum of compound **166**

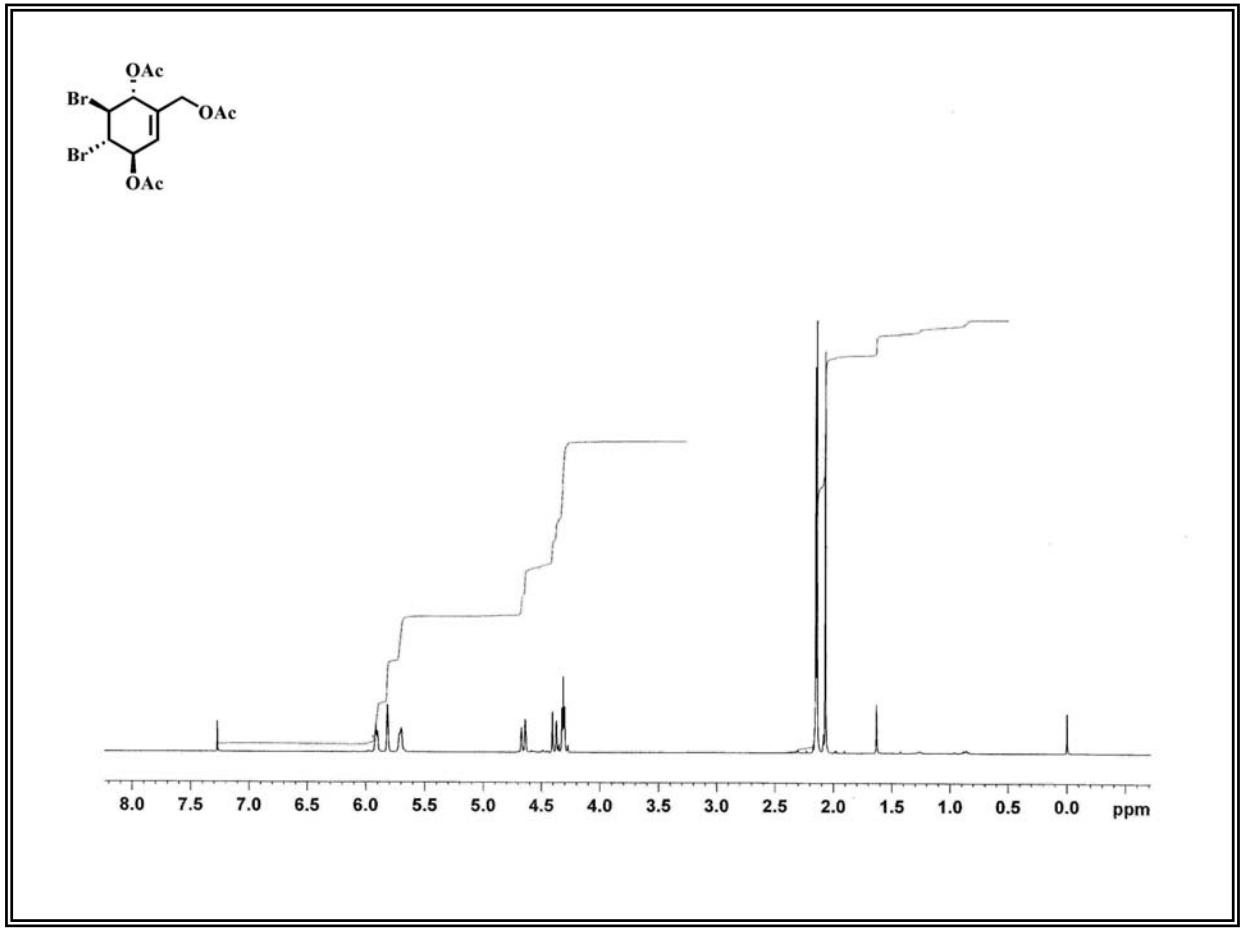

Figure 65. ^{1}H-NMR of spectrum of compound **170**

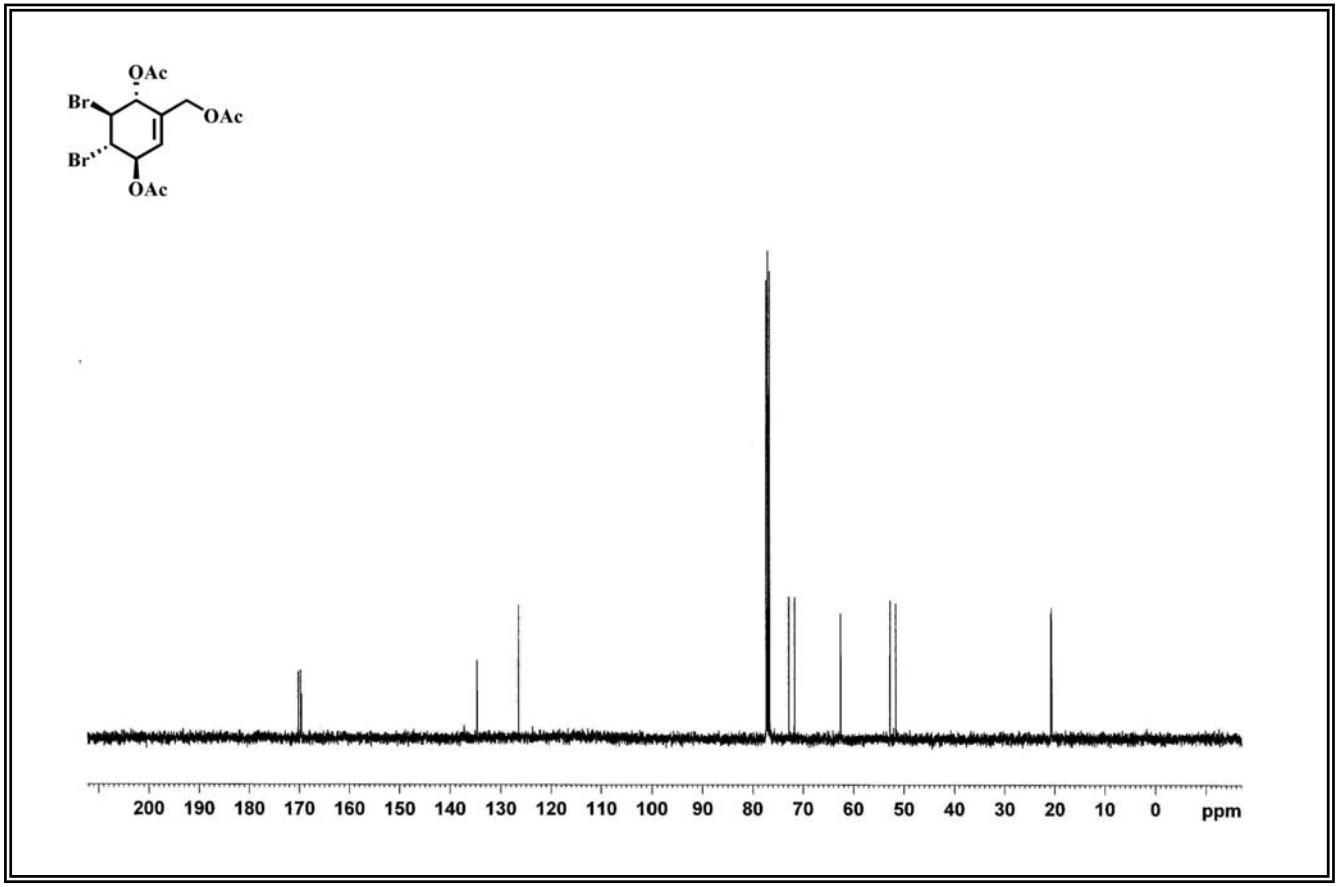

Figure 66. ^{13}C-NMR spectrum of compound **170**

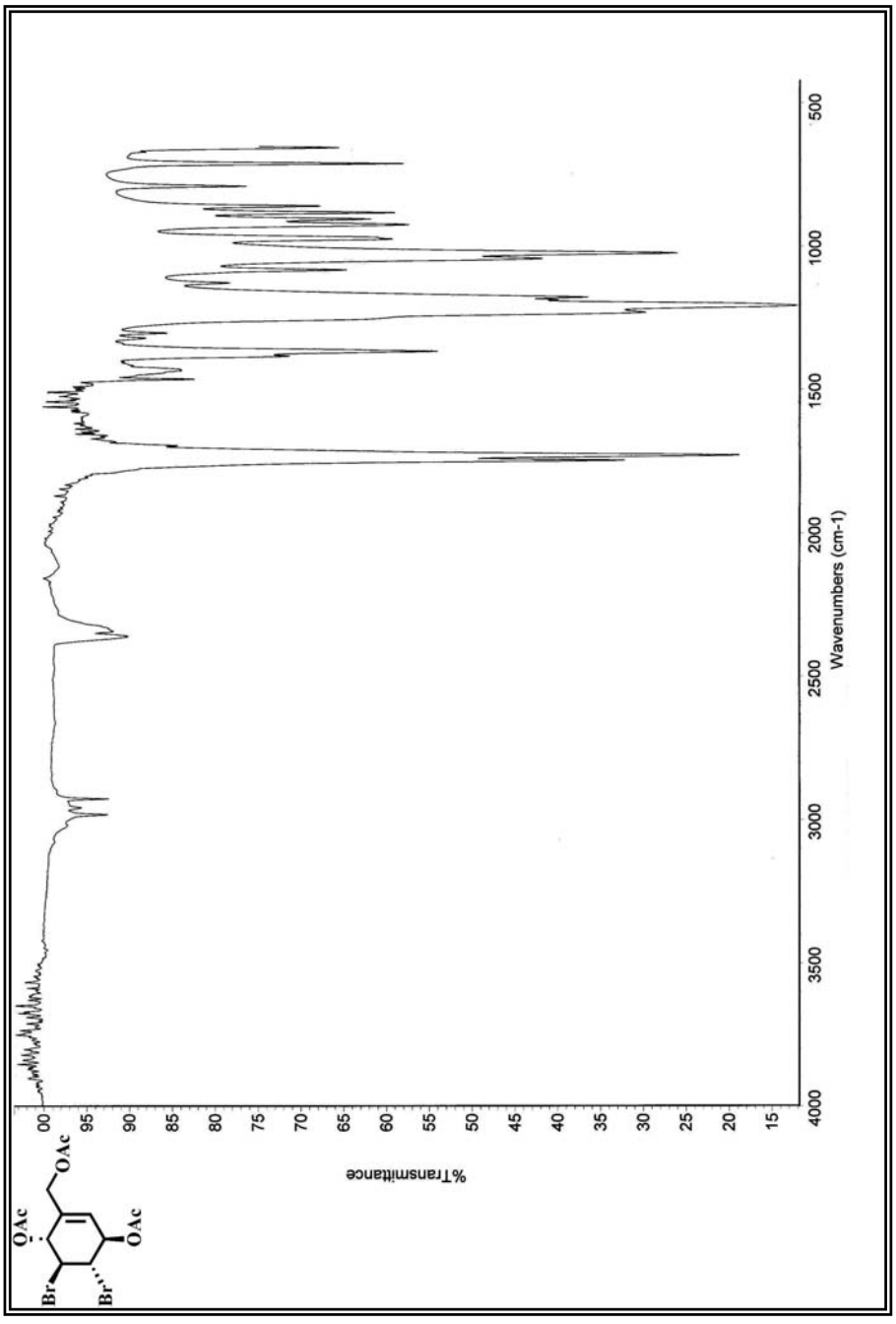

Figure 67. IR spectrum of compound **170**

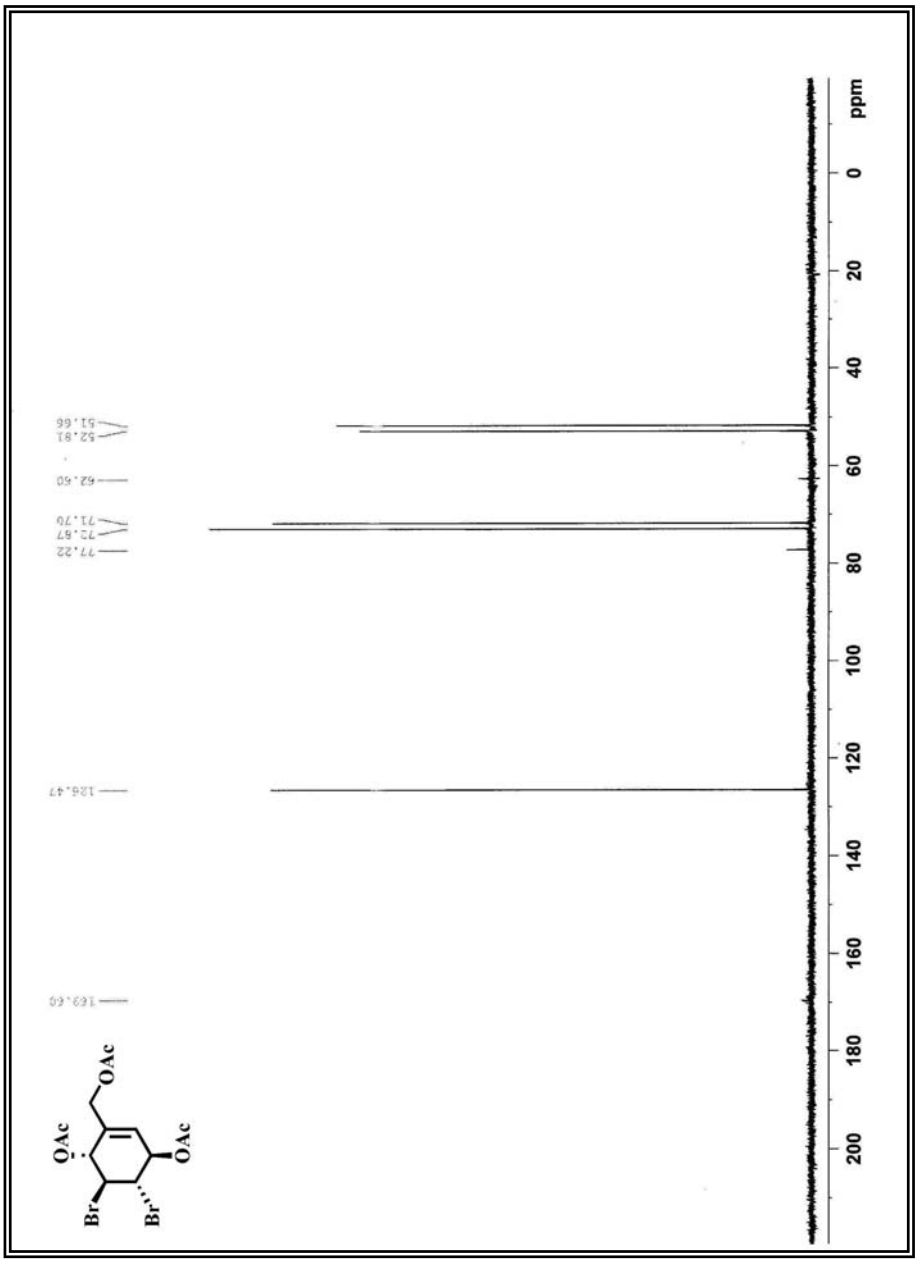

Figure 68. DEPT-90 spectrum of compound **170**

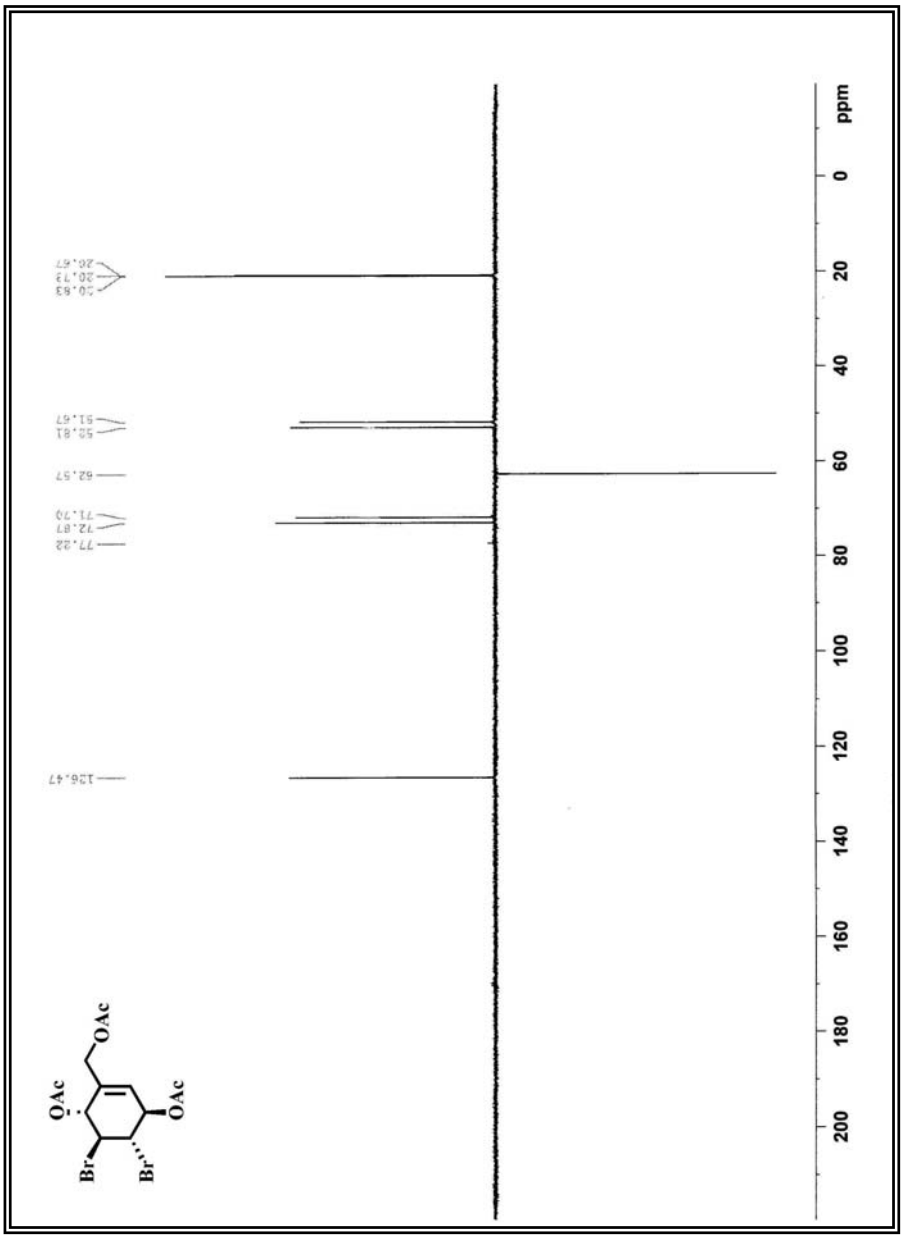

Figure 69. DEPT-135 spectrum of compound **170**

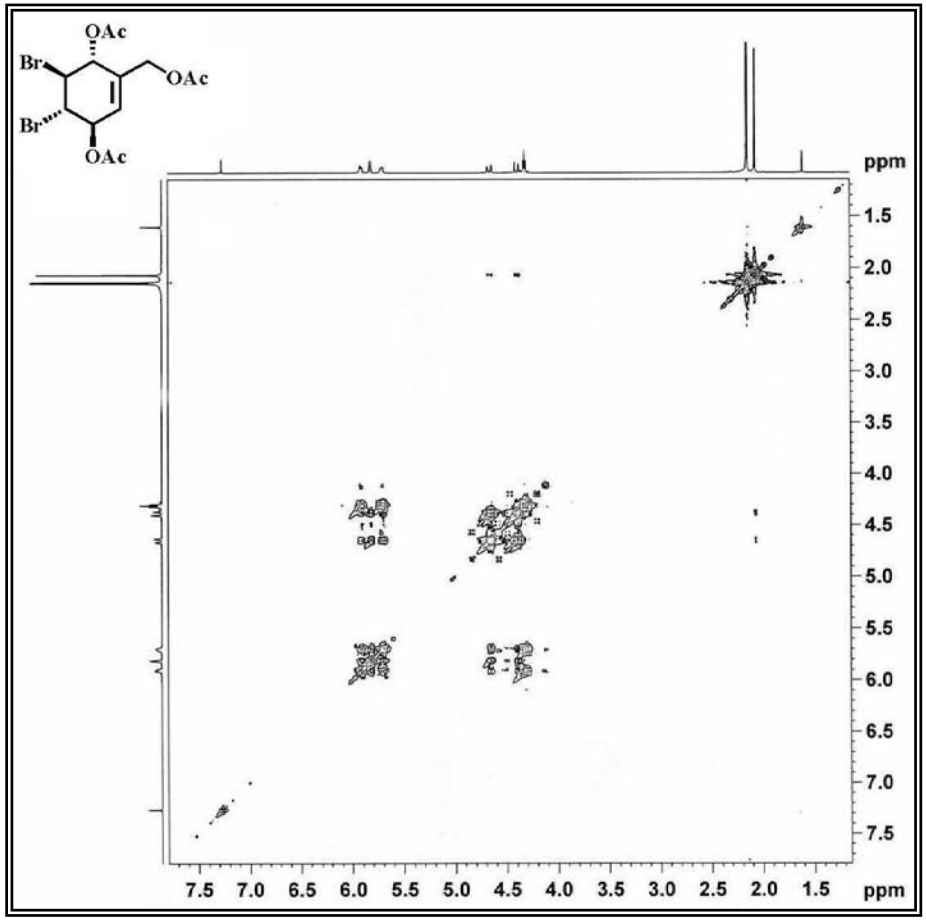

Figure 70. COSY spectrum of compound **170**

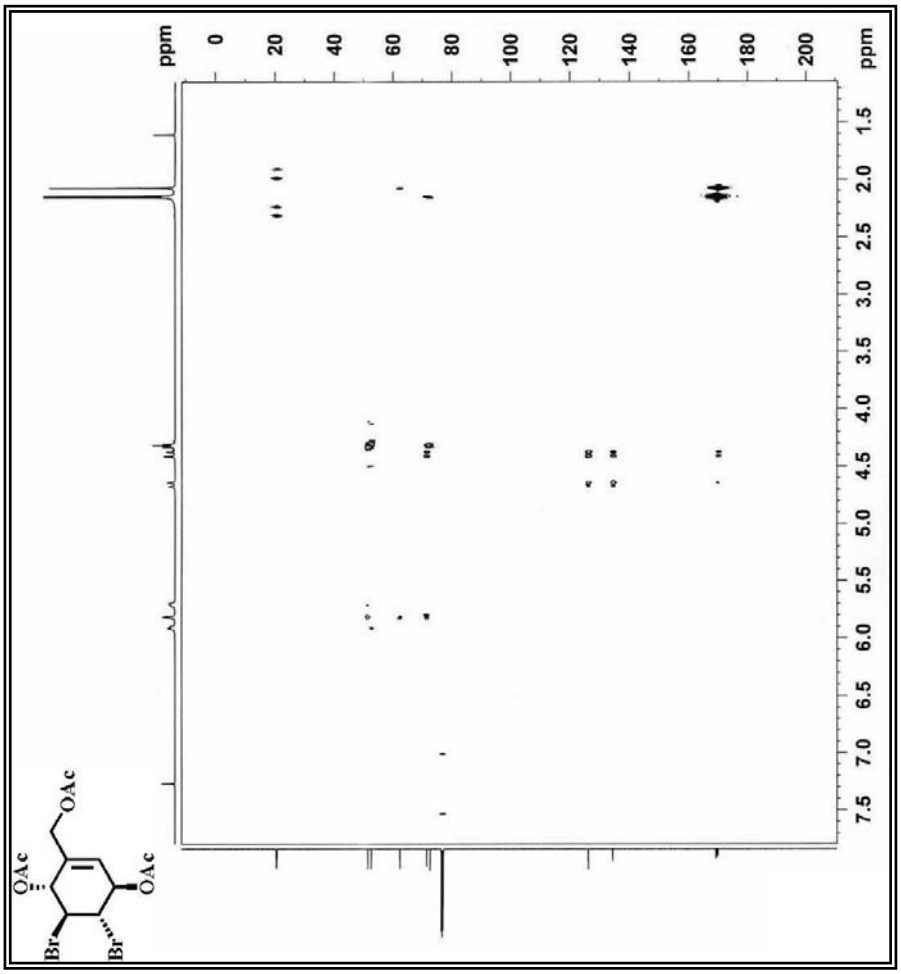

Figure 71. HMBC spectrum of compound **170**

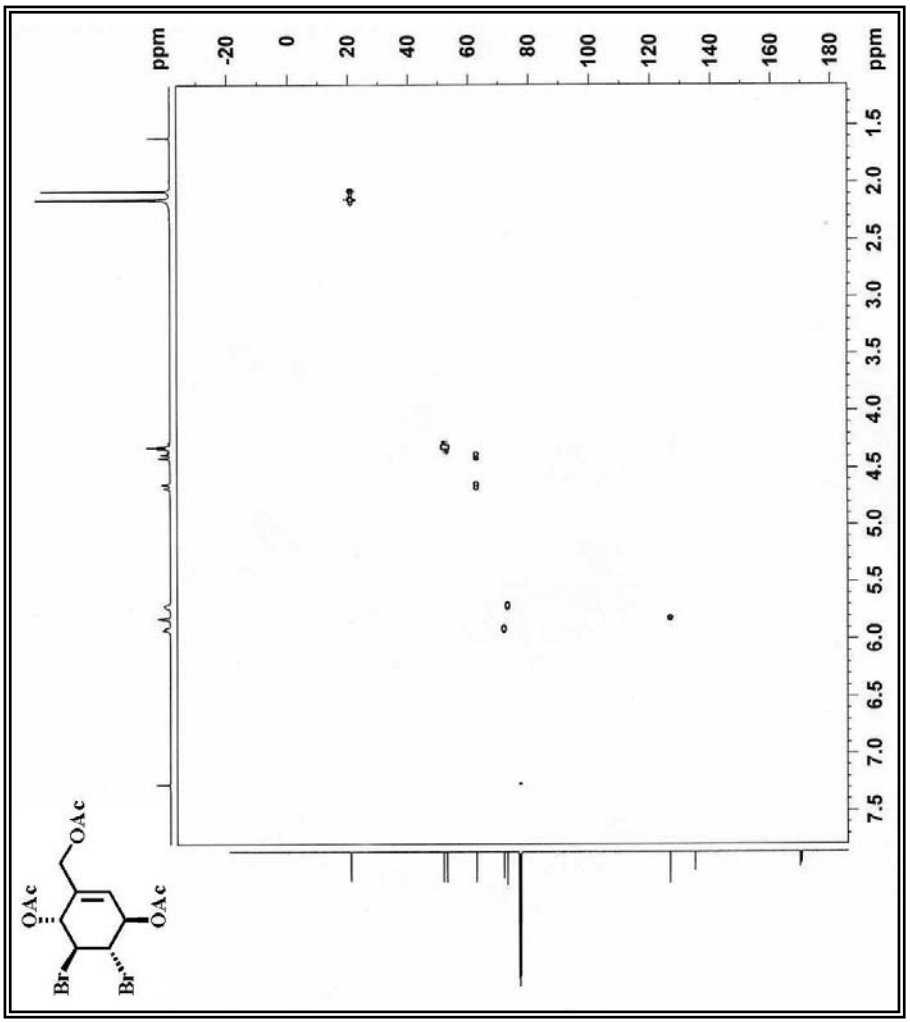

Figure 72. HSQC spectrum of compound **170**

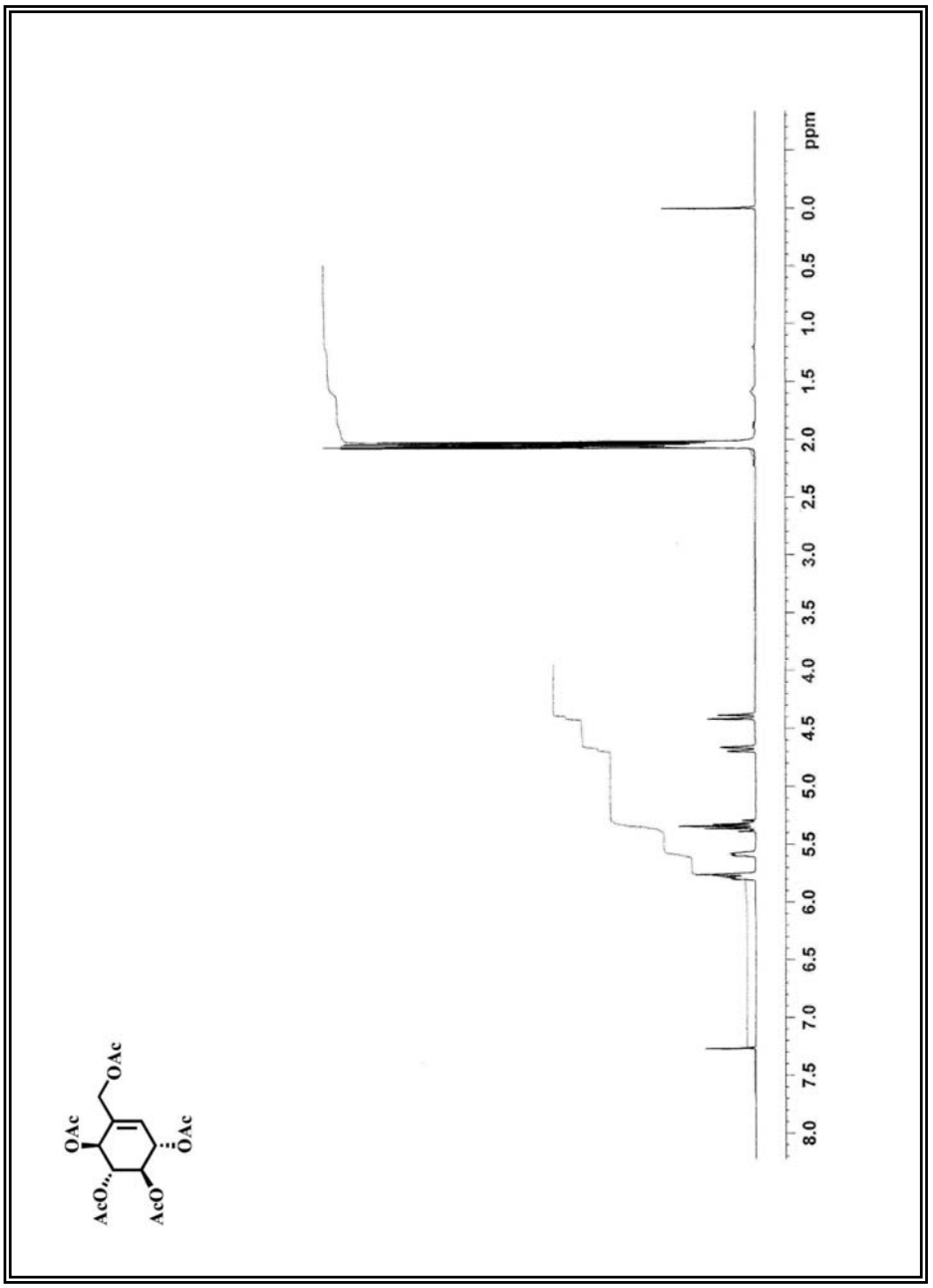

Figure 73. ^{1}H-NMR of spectrum of compound **173**

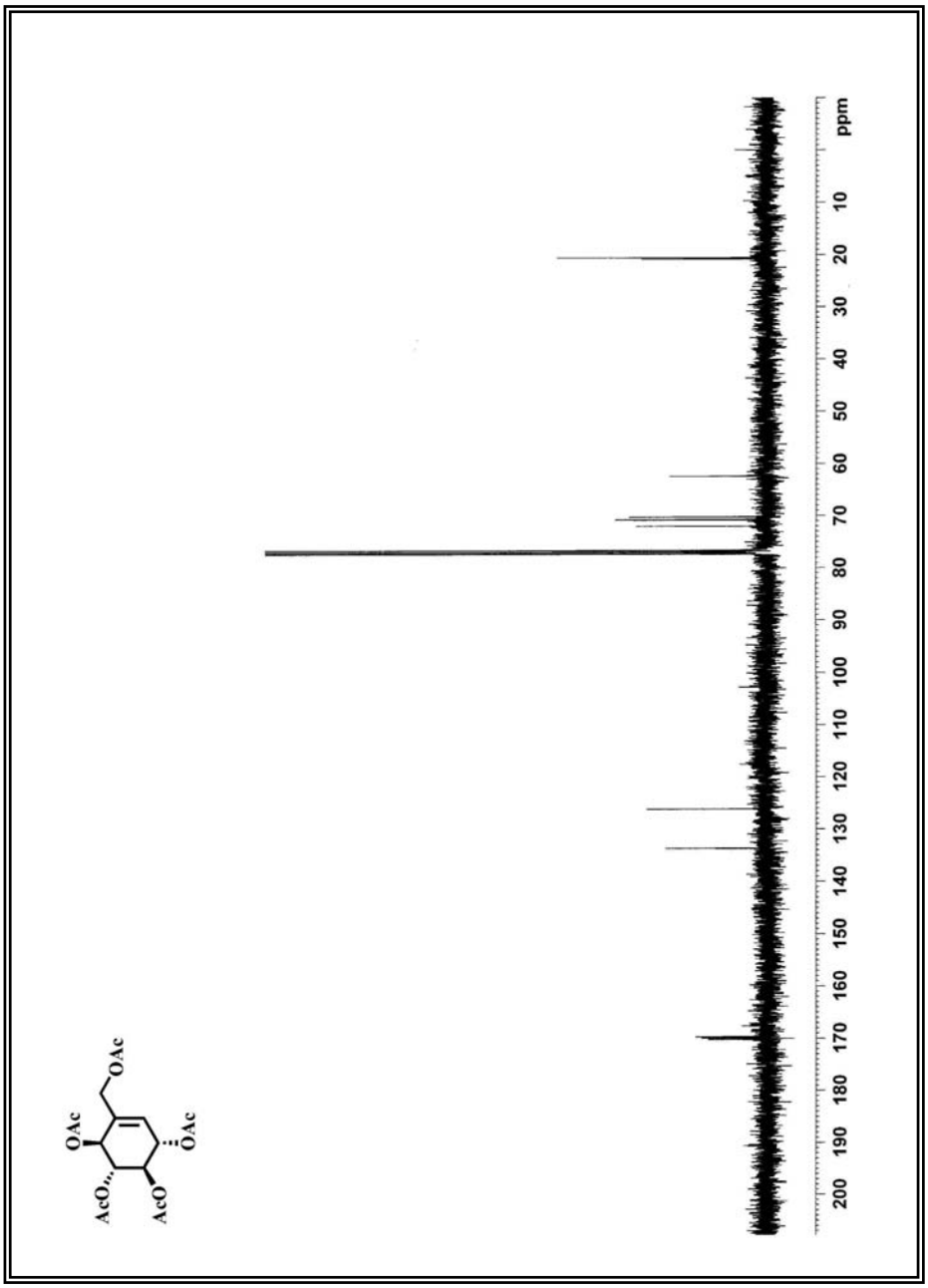

Figure 74. ^{13}C-NMR spectrum of compound **173**

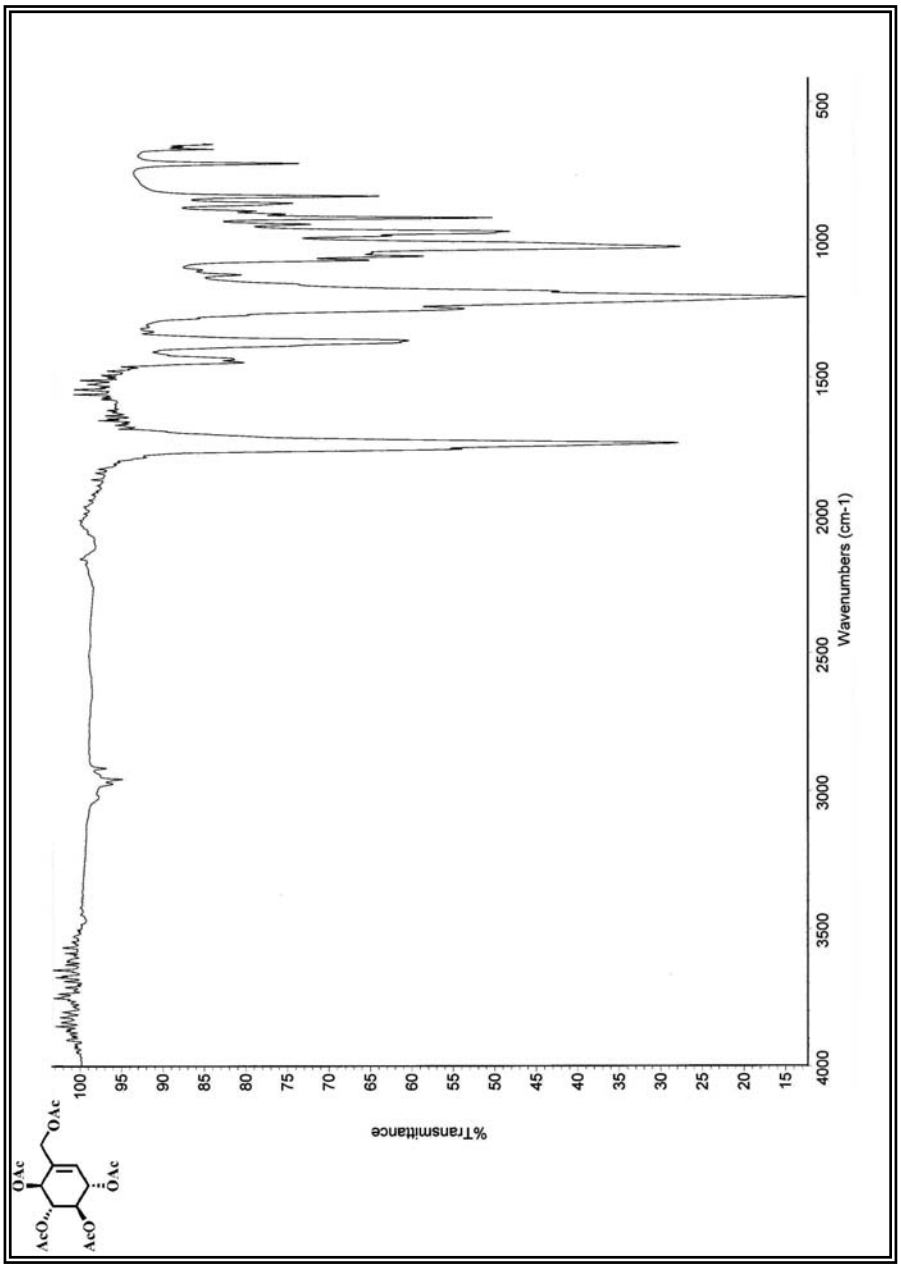

Figure 75. IR spectrum of compound **173**

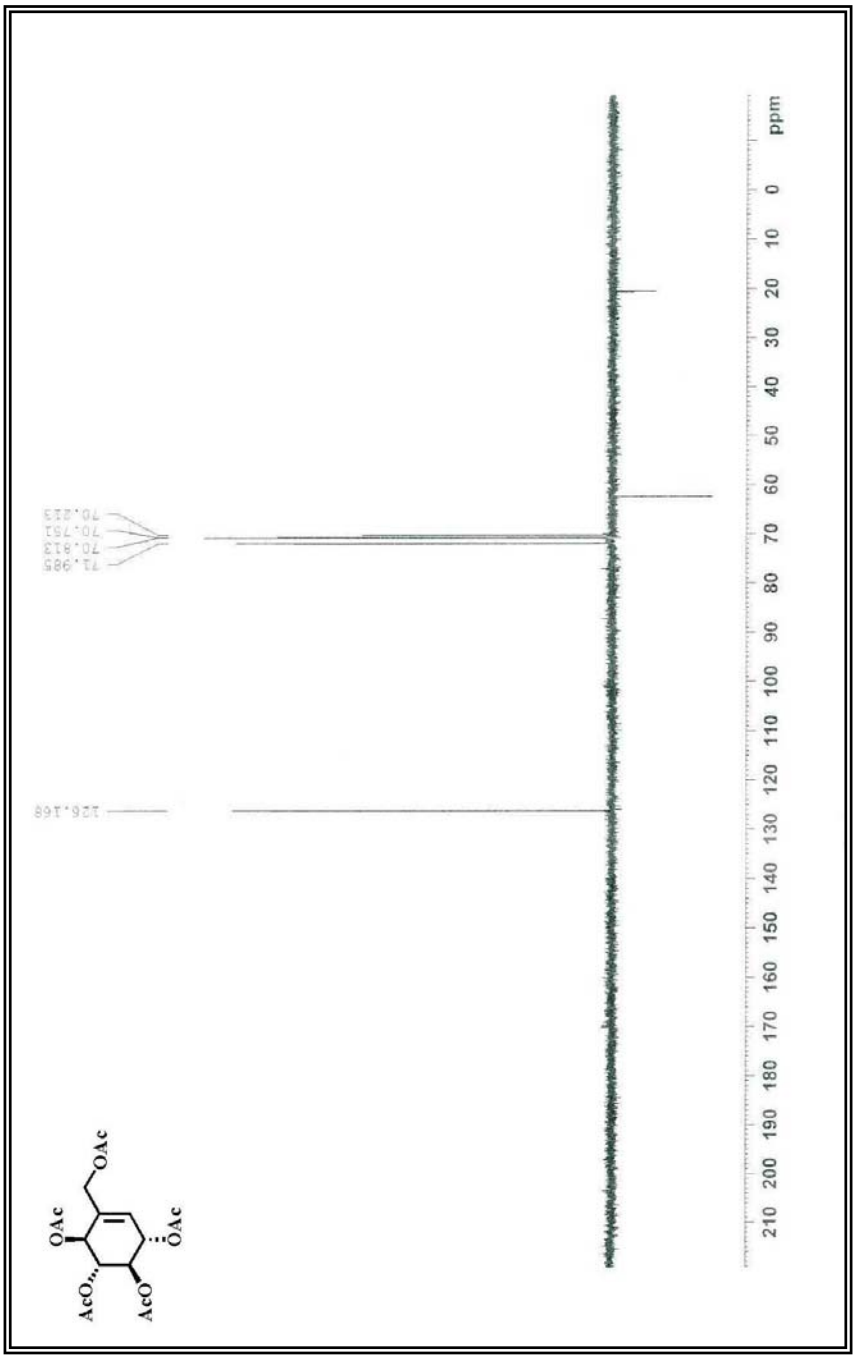

Figure 76. DEPT-90 spectrum of compound **173**

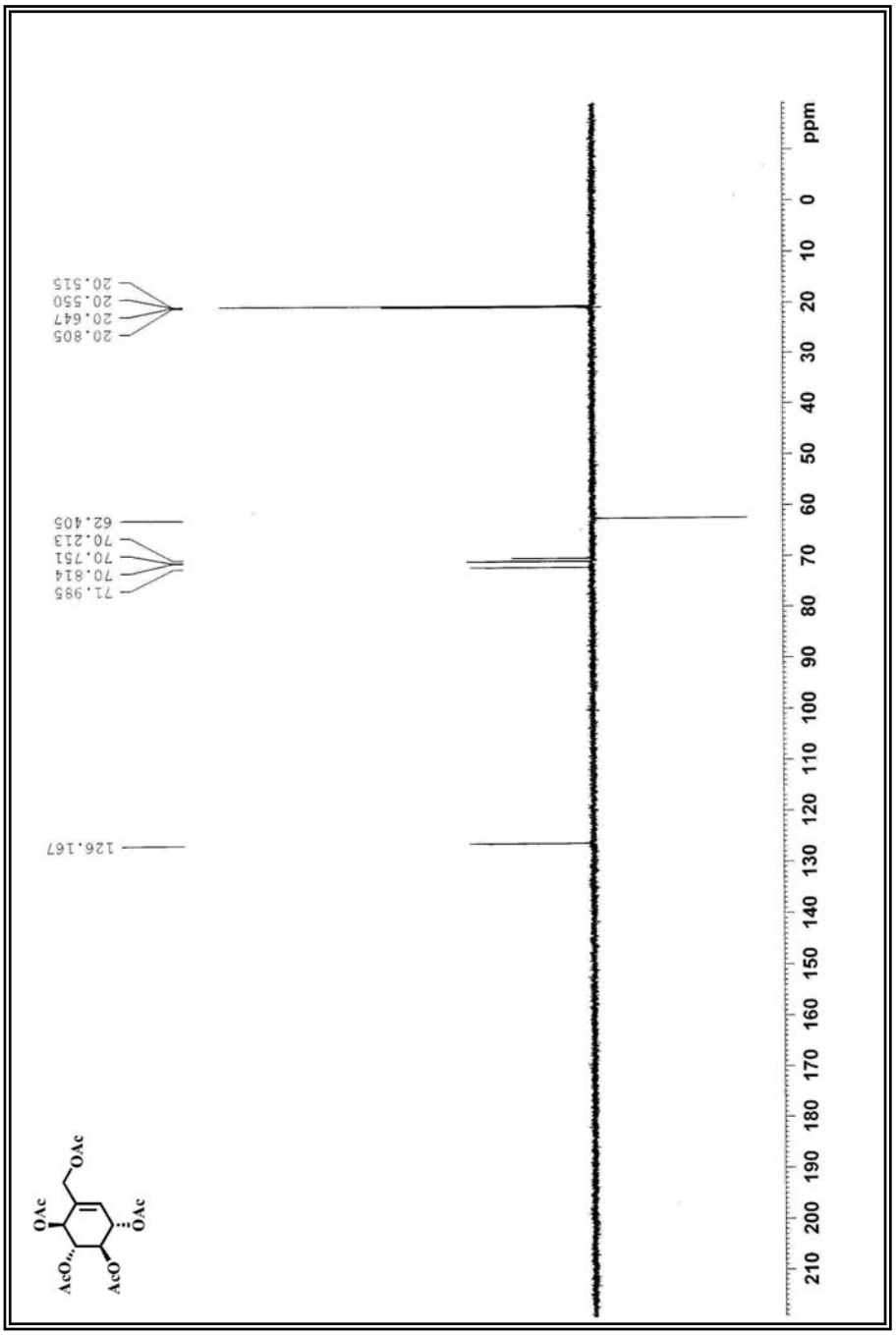

Figure 77. DEPT-135 spectrum of compound **173**

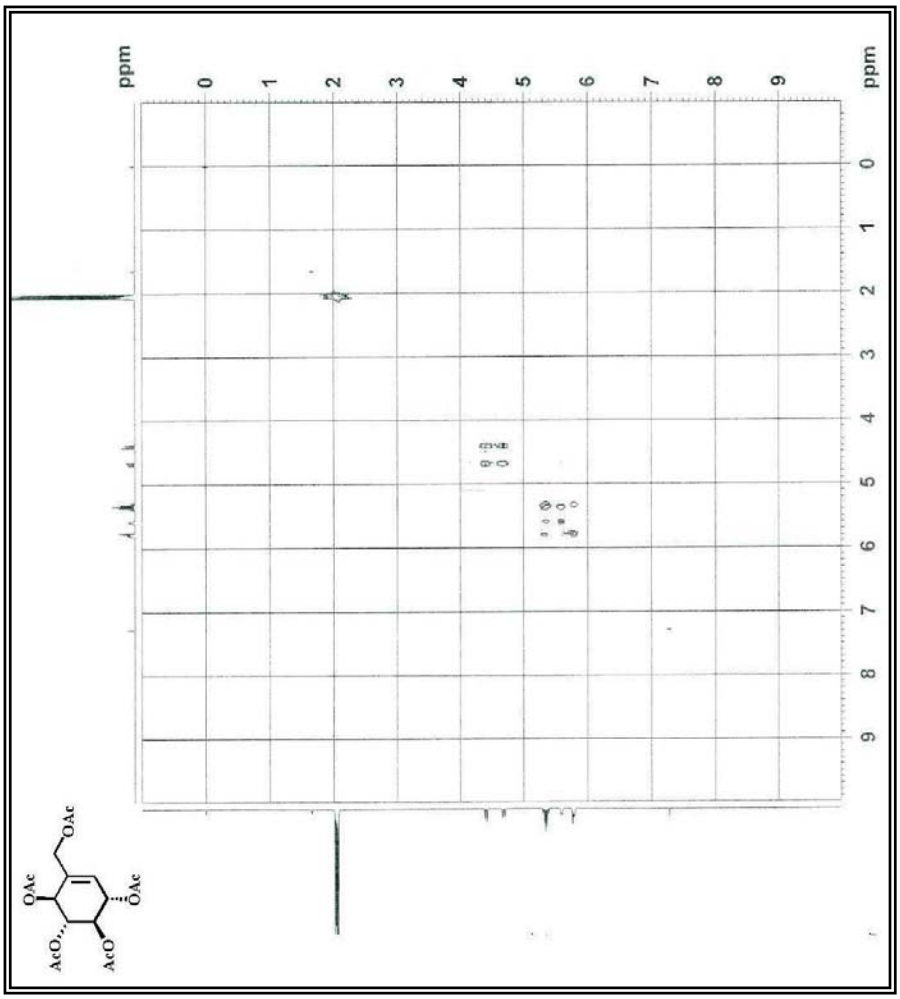

Figure 78. COSY spectrum of compound **173**

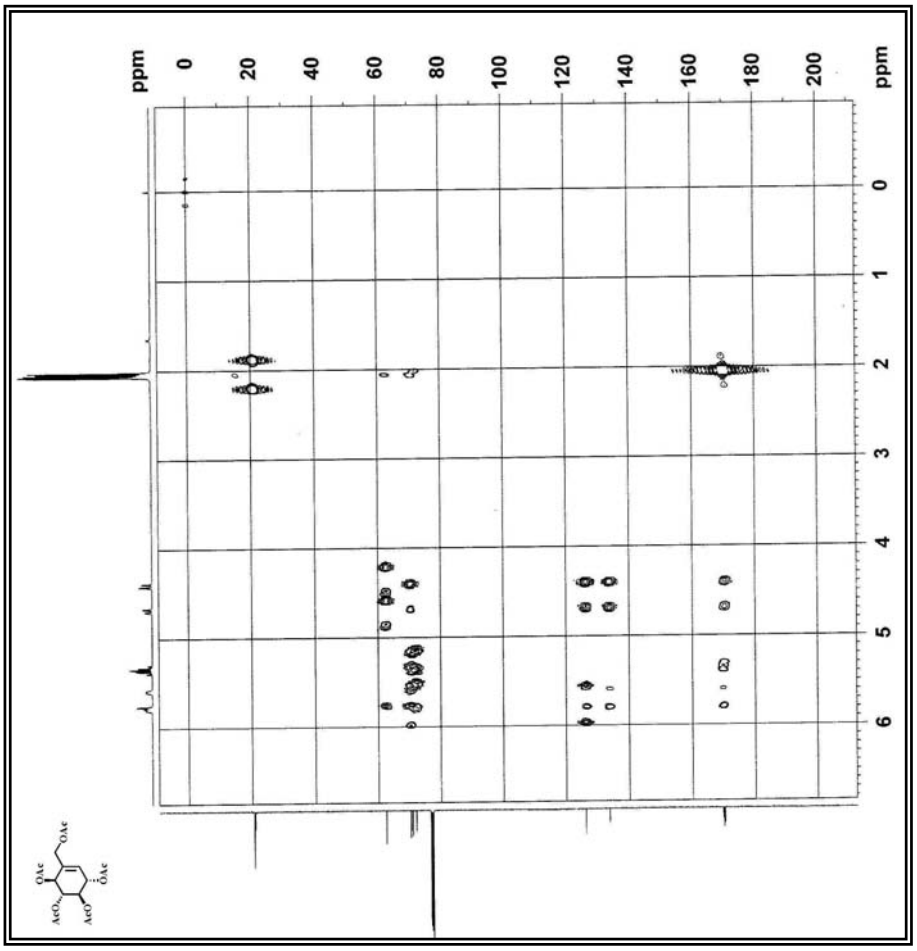

Figure 79. HMBC spectrum of compound **173**

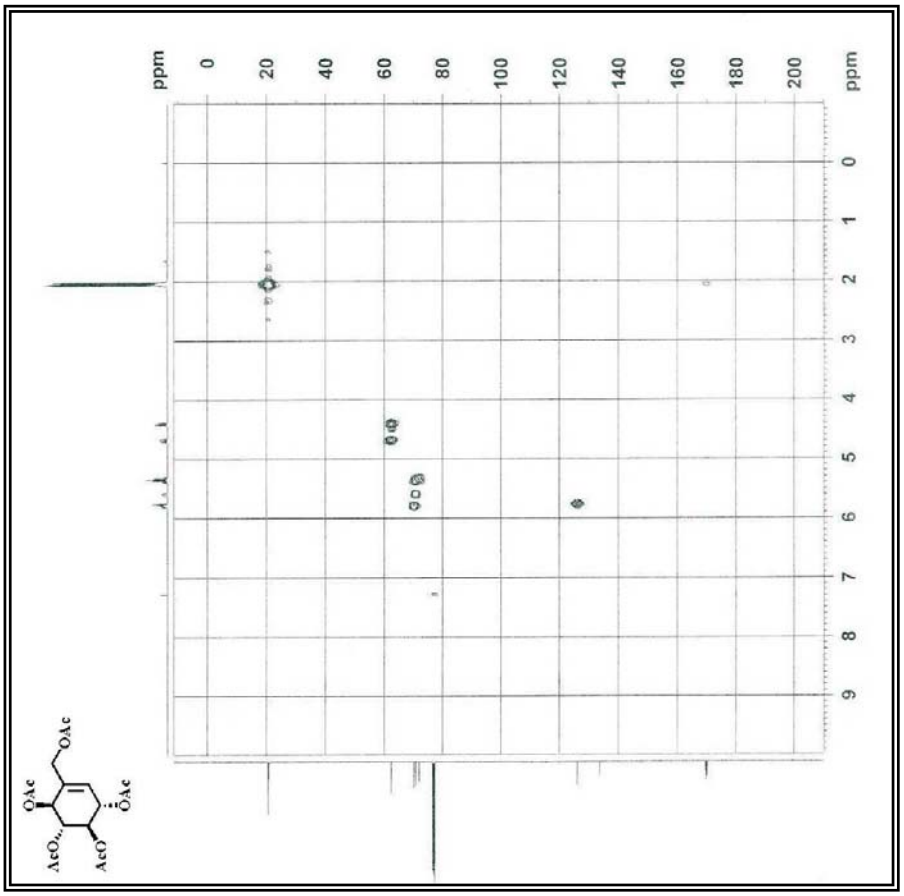

Figure 80. HMQC spectrum of compound **173**

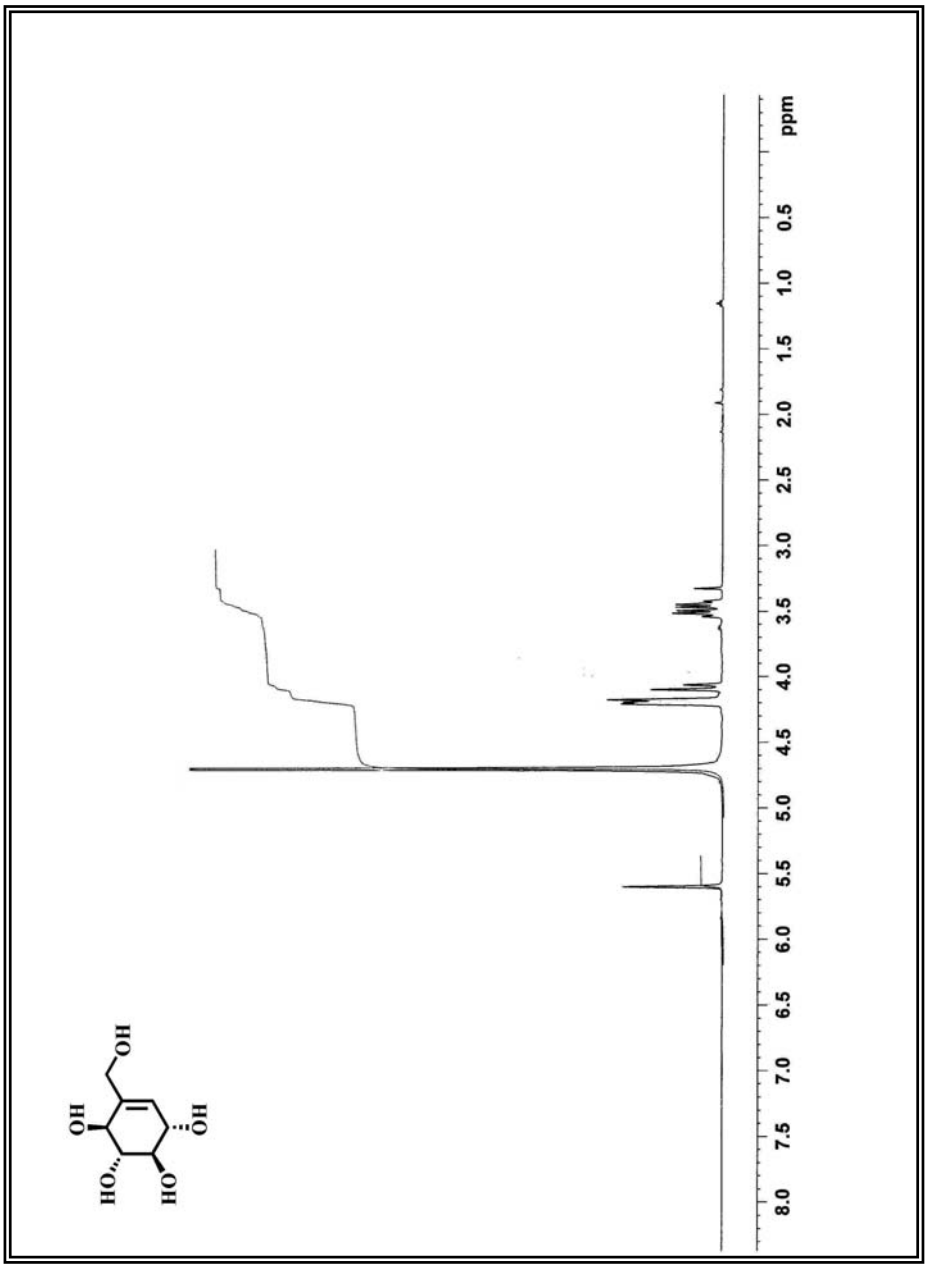

Figure 81. ^{1}H-NMR of spectrum of compound **137**

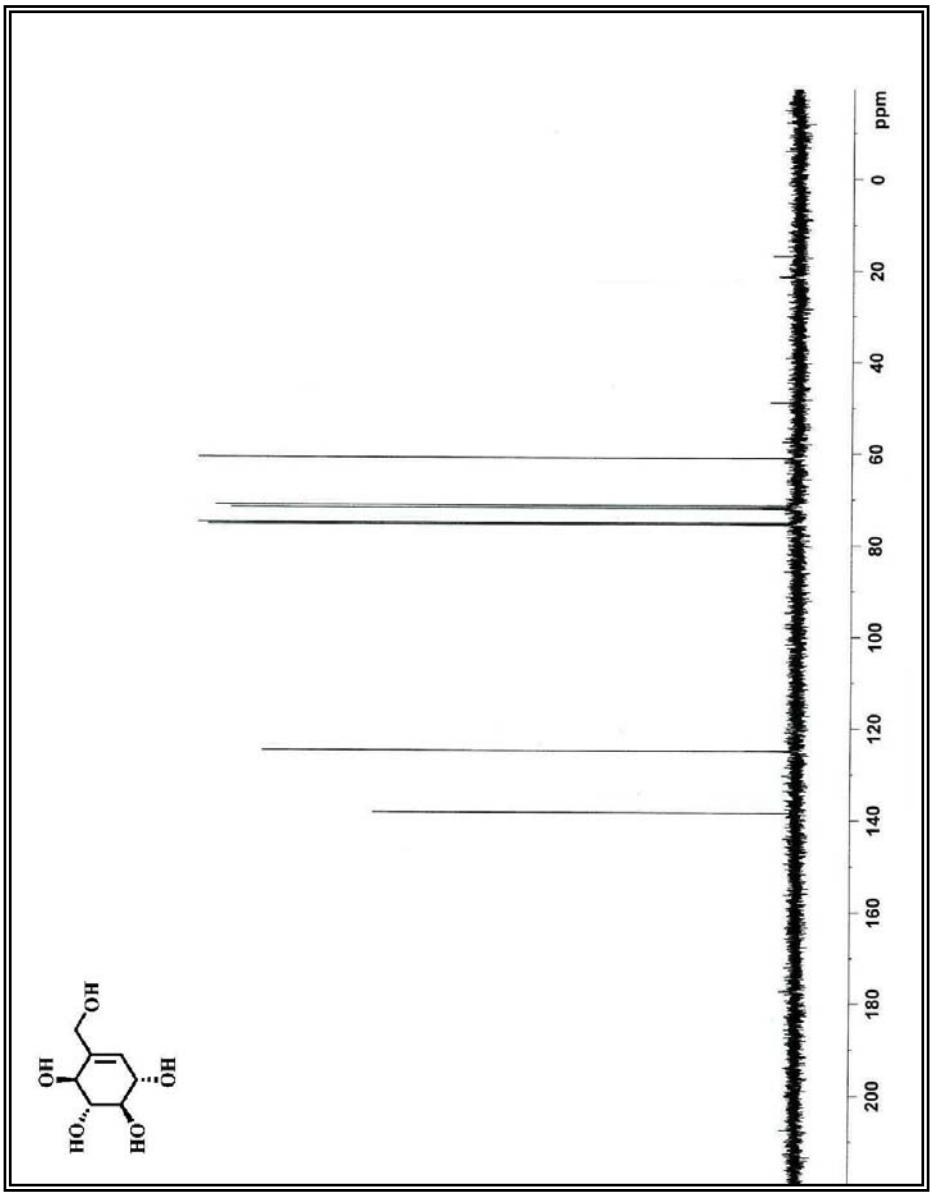

Figure 82. ^{13}C-NMR spectrum of compound **137**

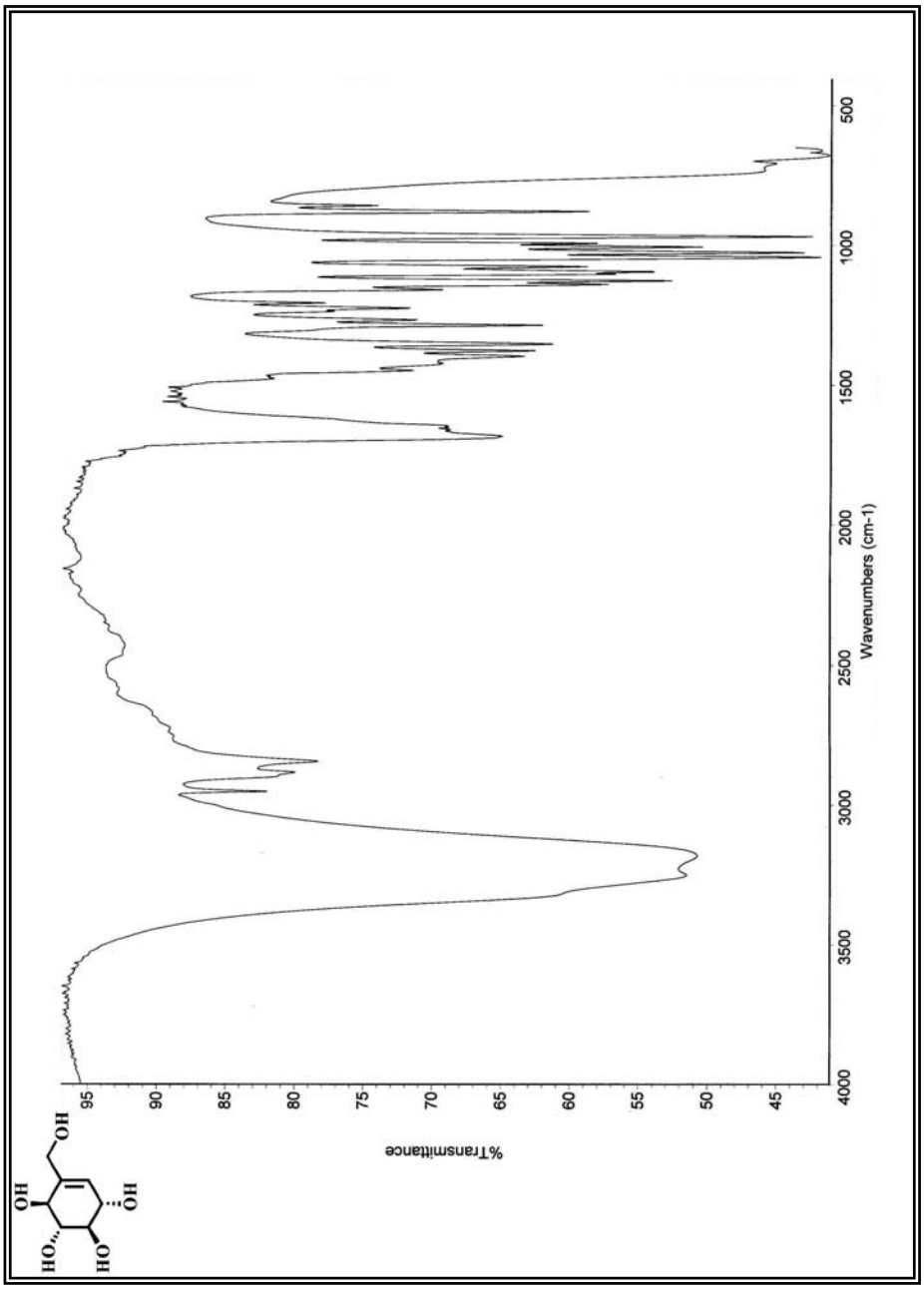

Figure 83. IR spectrum of compound **137**

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PUBLICATIONS

1) Balcı, M., **Kaya, N.**, Yardımcı, D. Ş., *Tetrahedron*, 2006, Vol. 62, 10633-10638

2) Balcı, M., **Öztürk, N**., Çelik, M., Demir, E., Ertaş, M., Gültekin, S. M., Kara, Y., Horasan, N., *Frontiers in Natural Products Chem.*, 2005, Vol. 1. 169-175