REGIOSELECTIVITY IN THE ENE REACTION OF SINGLET OXYGEN WITH CYCLIC ALKENES AND APPLICATION OF ENE REACTION TO STEREOSELECTIVE SYNTHESIS OF CARBAHEPTOPYRANOSE DERIVATIVES

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ABSTRACT

REGIOSELECTIVITY IN THE ENE REACTION OF SINGLET OXYGEN WITH CYCLIC ALKENES AND APPLICATION OF ENE REACTION TO STEREOSELECTIVE SYNTHESIS OF CARBAHEPTOPYRANOSE DERIVATIVES

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In the first part of this thesis is related to the regioselectivity in ene reaction of singlet oxygen with cyclic alkenes. The photooxygenation of 1-methyl-, 2,3-dimethyl-, 1,4-dimethylcyclohexa-1,4-dienes, 1,2,3,4,5,8-hexahydronaphthalene (**16**) and 2,3,4,7-tetrahydro-*1H*-indene (**17**) which are readily available through Birch reduction, yielded the ene products. The formed endocyclic dienes were trapped by the addition of singlet oxygen to give corresponding bicyclic endoperoxy-hydroperoxides. In the case of 1-methylcyclohexa-1,4-diene (**13**) and 1,4-dimethyl-cyclohexa-1,4-diene (**15**), *cis*-effect determined the product distribution. Photooxygenation of 2,3-dimethylcyclohexa-1,4-dienes (**14**) gave mainly exocyclic olefin, which was attributed to the lowered rotational barrier of the methyl group and increased reactivity of the methyl groups. Photooxygeneation of 1,2,3,4,5,8-hexahydronaphthalene (**16**) and 2,3,4,7-tetrahydro-*1H*-indene (**17**) shows importance of the geometry of the allylic hydrogen in the ground state.

In the second part of this thesis is related to the stereoselective synthesis of carbaheptopyranose derivatives. Two new carbaheptopyranoses, 5a-carba-6-deoxy-α-DL-galacto-heptopyranose (**184**) and 5a-carba-6-deoxy-α-DL-gulo-heptopyranose (**185**) have been prepared starting from cyclohexa-1,4-diene. The addition of dichloroketene to cyclohexa-1,4-diene followed by subsequent reductive elimination and Baeyer-Villiger oxidation formed the bicyclic lactone **188**. Reduction of the lactone moiety followed by acetylation gave the diacetate **182b** with *cis*-configuration. Introduction of additional acetate functionality into the molecule was achieved by singlet oxygen ene-reaction. The formed hydroperoxide **189** was reduced and then acetylated. The double bond in triacetate was further functionalized either by direct *cis*-hydroxylation using OsO_4 or epoxidation followed by ring-opening reaction to give the hepto-pyranose derivatives **184** and **185**.

Keywords: Cyclitols, Singlet Oxygen, Endoperoxide, Hydroperoxide, Photooxygenation, Ene reaction, Hydrocarbons, Carbasugar, Carbaheptopyranose, *Cis*-hydroxylation.

ÖZ

SİNGLET OKSİJENİN SİKLİK ALKENLERLE OLUŞTURDUĞU EN TEPKİMESİNDE GÖZLENEN REGİOSELEKTİVİTE VE EN TEPKİMESİNİN STEREOSELEKTİV KARBAHEPTOPİRONOS TÜREVLERİNİN SENTEZİ İÇİN UYGULANMASI

Doğan, Şengül Dilem

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Ekim 2010, 199 sayfa

Bu tezin birinci kısmı singlet oksijenin siklik alkenlerle oluşturduğu en tepkimesinde gözlenen regioselektivite ile ilgilidir. Birch indirgenmesi sonucu elde edilen 1-metil-, 2,3-dimetil-, 1,4-dimetilsikloheksan-1,4-dien, 1,2,3,4,5,8-heksahidronaftalin (**16**) ve 2,3,4,7-tetrahidro-*1H*-inden (**17**) fotooksijenasyon reaksiyonu sonucunda en ürünlerine dönüşmektedirler. 1-methyl- ve 1,4-dimetilsiklohexa-1,4-dienlerin fotooksijenasyon reaksiyonunda *cis*-etki, ürün dağılımını belirlemektedir. 1,2-Dimetilsiklohexa-1,4-dien'in fotooksijenasyon reaksiyonunda ana ürün olarak eksosiklik olefin oluşmaktadır. Bu oluşum, metil grubunun serbest dönme hareketinin engellenmesine ve metil gruplarının yüksek reaktivitesine dayandırılmaktadır.

Bu tezin ikinci kısmı stereoselektiv karbaheptopironos türevlerinin sentezi ile ilgilidir. 1,4-sikloheksadienden çıkılarak iki yeni karbaheptopironos türevi, 5a-karba-6-deoxy-α-DL-galakto-heptopironos (**184**) and 5a-karba-6-deoxy-α-DL-gulo-

heptopironos (**185**), sentezlendi. Bisiklik lakton bileşiği (**188**), 1,4-sikloheksadiene diklorketen katılması ile oluşan bileşikte klor atomlarının indirgenmesi ve Baeyer-Villeger yükseltgenmesi reaksiyonları sonucunda elde edildi. Lakton grubunun indirgenmesi ve oluşan diolün asetatlanması ile cis-diacetat (**182b**) elde edilmiştir. Bu sisteme diğer bir asetat fonksiyonel grubu ilave etmek için singlet oksijen en-reaksiyonu uygulandı. Oluşan hidroperoksit, indirgendikten sonra asetillendi. Heptopironos türevleri **184** ve **185** triasetat yapısındaki çift bağın doğrudan OsO_4 kullanılarak cis hidroksilasyonu veya epoksidasyon reaksiyonu sonucu oluşan ürünün halka açılması sonucu fonksiyonel hale getirilmesiyle sentezlendi.

Anahtar Kelimeler: Siklitoller, Singlet Oksijen, Endoperoksit, Hidroperoksit, Fotooksijenasyon, En reaksiyon, Karbaşeker, Karbaheptopironos, Cis-Hidroksilasyon.

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CHAPTER 1

INTRODUCTION

I. 1 SINGLET OXYGEN

Singlet molecular oxygen which is important and reactive species in oxidation reactions was first observed in 1924 [1]. It has received remarkable attention by chemists and other scientists such as biologists and biochemists because of its large environmental and biomedical significance [2-4]. The interest to singlet oxygen 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. Besides to searching the role of singlet oxygen in this phenomena and the mechanism of its reactions, its synthetic applications have also been explored and their utility has been demonstrated [3].

The reactivity of a molecule is closely related to its electronic structure so MO-theory and excitation spectroscopy is greatly utilized to understand the reactivity behavior of oxygen (Figure I.1) [5,6]. It is known that molecular oxygen in its ground state has two unpaired electrons with parallel spin and these electrons occupy π^*2p orbital. This electronic configuration is indicated by $^3\Sigma^-g$ so molecular oxygen, at ground state, is symbolized by $^3O_2$ [5,6,7].

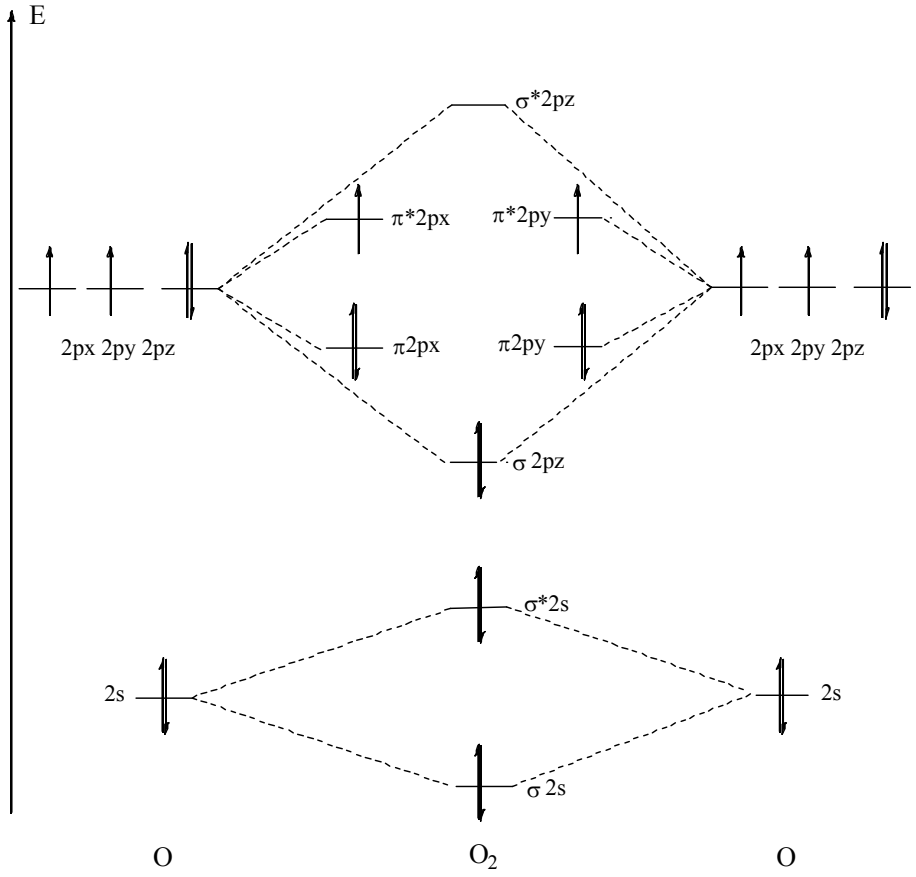


Figure I. 1 The Molecular Orbital of Diatomic Oxygen Molecule

The unpaired electrons in parallel spins in the ground state of the oxygen cause the diatomic molecule to be paramagnetic and biradical [5,6]. Triplet configuration of oxygen lets to form reaction which involves single-electron step. As a result, the oxygen reactions are usually exothermic and the barrier of spin prevents the reaction between triplet oxygen and molecule ground state singlet [5,6,7].

The lowest electronic states of molecular oxygen are known as singlet oxygen and the high energy electrons are antiparallel in π^*2p orbitals. There are two electronically excited singlet states of oxygen. The first shown $^1\Delta_g$ locates 22.4 kcal above ground state. It is not a radical because there are no unpaired electrons. The second singlet state shown $^1\Sigma_g$ is 37.0 kcal above ground state and is relatively short lived (Figure I.2). In both forms of singlet oxygen the spin restrictions are removed and so singlet oxygen can react with any kinds of organic substrates [8,9].

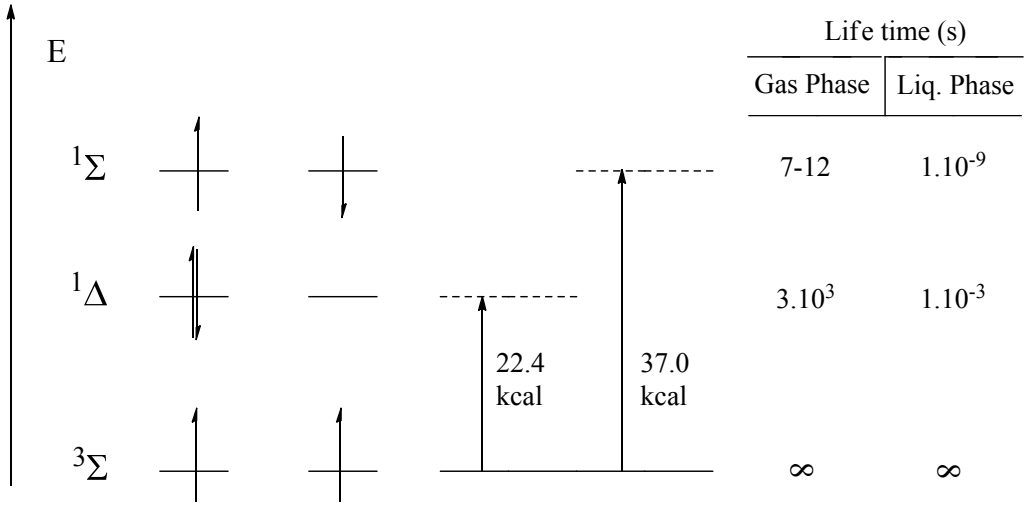


Figure I. 2 Energy Diagrams and Life Time of Singlet and Triplet Oxygen States

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 become 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 [8a] 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 [5,10].

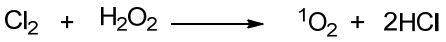
Two excited states of singlet oxygen are $^1\Sigma_g^+$ and $^1\Delta_g$. The lower energy state, $^1\Delta_g$ is much longer lived and is now believed to be the only singlet oxygen species, which leads to reaction in solution [5].

I.1.1 GENERATION OF SINGLET OXYGEN

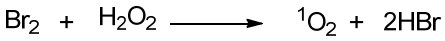
A. Chemical Methods

Several laboratory methods for the preparation of singlet oxygen in simple chemical reactions have been described [11]. By the;

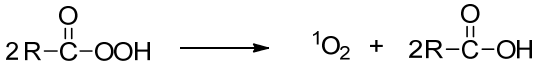
i) Reaction of active chlorine from the decomposition of sodium or calcium hypochlorites with hydrogen peroxide [10,11,12] .

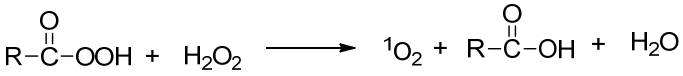


ii) Reaction of bromine with hydrogen peroxide [11].

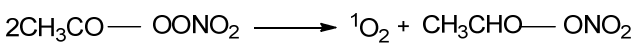


iii) Decomposition of peracids in alkaline medium or reaction of peracids with hydrogen peroxide [11].

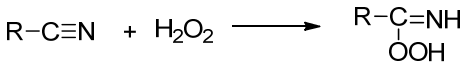


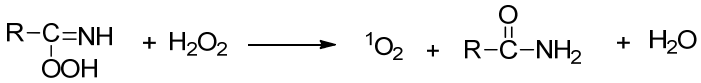


iv) Decomposition of peroxyacetyl nitrate in alkaline medium [11].

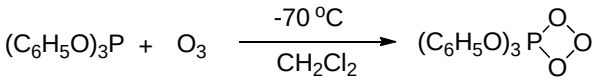


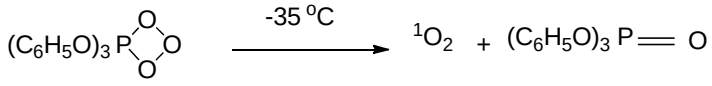
v) Reaction of nitriles with hydrogen peroxide in an alkaline medium [11].



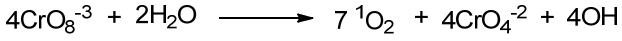


vi) Thermal decomposition of an adduct of triphenylphosphite with ozone at -35 ^{o}C. The adduct can be prepared and stored at -70 ^{o}C [11].

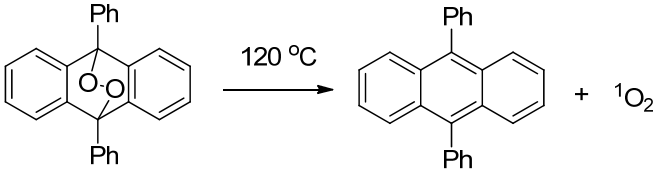




vii) Decomposition of potassium perchromate with water [11].



vii) Decomposition of 9,10- diphenylanthracene endoperoxide.



B. Physical Methods

Generation of singlet oxygen in the gas phase can be achieved by high frequency electric discharge in oxygen atmosphere using a microwave apparatus [11,12].

C. Photosensitizing Methods

A widely applied method for the preparation of singlet oxygen on a laboratory scale involves the use of different photosensitizers [11]. The mechanism for the generation of singlet oxygen was proposed by Kautsky. This mechanism involves the excitation of an appropriate sensitizer with visible light to form corresponding excited single state. Rapid intersystem crossing generates the excited triplet state of the sensitizer, which undergoes an energy transfer with triplet oxygen to form singlet oxygen, regenerating the ground state sensitizer (Figure I.3) [9,11]

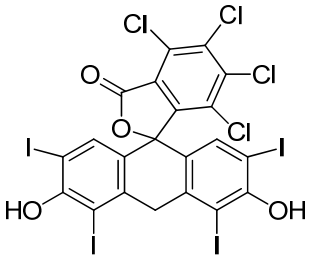
$$^1\text{Sensitizer} \xrightarrow{h\upsilon} {}^1\text{Sensitizer}^*$$

$$^1\text{Sensitizer}^* \xrightarrow{\text{ISC}} {}^3\text{Sensitizer}^*$$

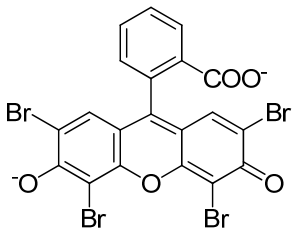
$$^3\text{Sensitizer}^* \xrightarrow{^3O_2} {}^1\text{Sensitizer} + {}^1O_2$$

Figure I. 3 Formation of Singlet Oxygen with Sensitizer

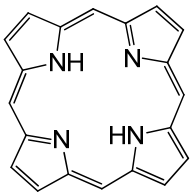
Popular sensitizers of singlet oxygen generation include the dyes *acridine orange, methylene blue, rose bengal, eosin y, meso-tetraphenlyporphin, and toluidine blue.*



Rose Bengal



Eosin Y



Porphyrin

Theoretical investigation and experimental results show that in the case of sensitizers having high energy in the triplet state (E_T>40 kcal/mol), singlet oxygen $^1O_2$ ($^1\Sigma_g^+$) is the main product in the energy transfer reaction. The amount of singlet oxygen $^1O_2$ ($^1\Delta_g$) formed in this reaction is ten-times lower. In the case of sensitizers with triplet energy (E_T) between 22 and 37 kcal/mol, only singlet oxygen $^1O_2$ ($^1\Delta_g$) is formed. Both forms of singlet oxygen are formed when the triplet energy of a sensitizer E_T exceeds 37 kcal/mol. These results indicate that the form of singlet oxygen is dependent on the excitation energy of the sensitizer [11,12].

I. 1.2 REACTIONS OF SINGLET OXYGEN

[4+2] Diels-Alder cycloaddition, [2+2] cycloaddition and ene reaction are the most common type of singlet oxygen. Diels-Alder type reaction of singlet oxygen gives endoperoxides, direct addition of singlet oxygen to an activated double bond leading to 1,2-dioxetane, and ene reaction leading to hydroperoxide. All types of singlet oxygen reactions have been used for the regiospecific and stereospecific oxidation of olefins [9].

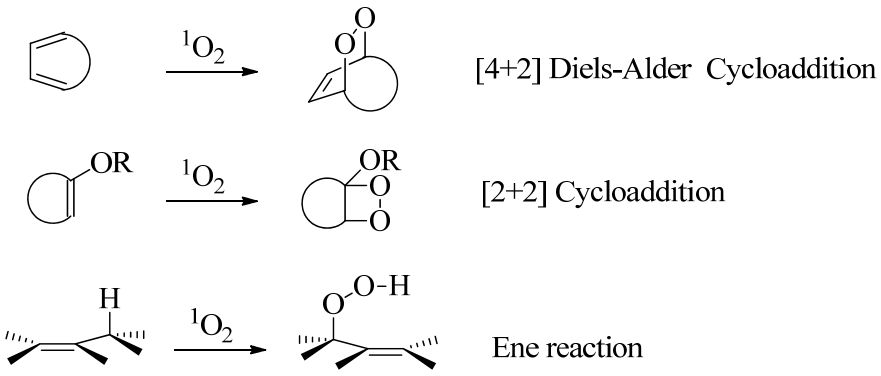


Figure I. 4 The Types of Singlet Oxygen Reactions

I. 1.2.1 [4+2] Diels-Alder Cycloaddition

The [4+2] cycloaddition reaction of singlet oxygen is an important reaction for the 1,4-functionalization of versatile compounds and is an elegant method for synthesis of cyclic and bicylic endoperoxides (Fig I.5) [12,13].

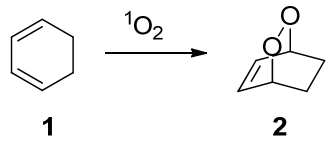


Figure I. 5 [4+2] Cycloaddition reaction of singlet oxygen

If the rate constant of [4+2] cycloaddition reaction of singlet oxygen compared with normal Diels-Alder reactions, cycloaddition reaction of singlet oxygen is faster than normal Diels-Alder reactions [14]. The effect of substituents on the diene is similar to the normal Diels-Alder reactions. The cycloaddition of singlet oxygen proceed via a 6-centered concerted transition state. Orbital symmetry considerations show that 1,4-cyloaddition is a ground state thermally allowed process [5,12,15,16].

I. 1.2.2 [2+2] Cycloaddition Reaction

1,2-Cyloaddition reaction of singlet oxygen leads to 1,2-dioxetanes. Only highly strained or electron rich olefins such as vinyl sulfides, enol ethers or enamines give this type of reaction. Unstable peroxides decompose on warming to form carbonyl products as a result of oxidative cleavage of the original carbon-carbon double bond. Applications of this type of singlet oxygen reaction in the synthesis have been limited, as a result of the restriction of this type of oxygenation to specific types of olefinic systems [9].

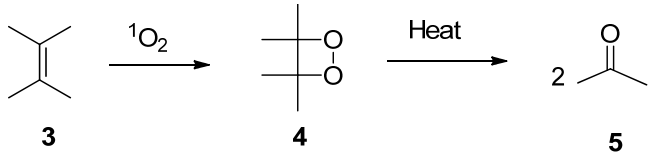


Figure I. 6 [2+2] Cycloaddition reaction of singlet oxygen

I.1.2.3 Ene Reaction

Interaction of singlet oxygen with alkenes containing allylic hydrogens results in the formation of allylic hydroperoxide with a shifted double bond as required by an ene-type reaction [7,17]. Allylic hydroperoxides are very important building blocks for synthetic organic chemistry so this type of reaction of singlet oxygen has attracted much attention.

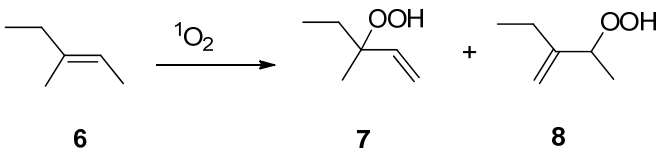
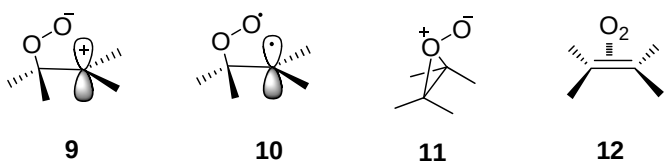


Figure I. 7 Ene reaction of singlet oxygen

The ene reaction was discovered by Schenck in 1943 and named the ‘‘Schenck reaction’’ or ‘‘ene reaction’’ by Schönberg [17,18]. A large number of experimental and theoretical studies have been focused on whether the ene reaction occurs through a concerted or stepwise mechanism. The stepwise mechanism have included zwitterionic (**9)**, biradical (**10),** peroxide (**11**), and exciplex (**12**) intermediates [17, 19].



Irreversible formation of intermediate peroxide is supported by kinetic isotope effects in the photooxygenation of tetrasubstituted [20], trisubstituted [21] and cis alkenes [22,4]. Consistent with the perepoxide intermediate, the singlet oxygen ene reaction is a suprafacial process, in which the conformational arrangement of the allylic hydrogen controls the stereochemistry of the allylic hydroperoxide produced [4,19,23].

Perepoxide is the most possible intermediate, which is supported by the trapping of the intermediate with sulfoxides [24], phosphites [25], and sulfenates or sulfinate esters [26] in the photooxygenation of adamandylidenoadamantane, and theoretical calculations [27]. Many authors consider an intermediate exciplex [28] instead of the polar peroxide. Since the geometry of the intermediate is well defined from isotope effects and stereochemical studies, if an intermediate exciplex is formed, its geometry features must resemble those of a perepoxide [4].

In the photooxygenation of electron rich alkenes like enamines [29], enol ethers [30], enol esters [31], and dienes [32], there is a partitioning between perepoxide and zwitterionic intermediates, affording mixtures of ene and cycloaddition products, whose relative abundance depends on solvent polarity and temperature.

I. 1.2.3.1 Regioselectivity of Ene Reaction

The detailed information is given about the most observed factors that affect the regioselectivity of ene reaction.

i) 'Cis Effect' with trisubstituted alkenes

In the reaction of singlet oxygen with trisubstituted alkenes [33], the more reactive side of double bond is the highly substituted side. This surprising selectivity is referred to as '*cis effect'* (Fig I.8). Both experimental and theoretical chemists have offered explanations for the '*cis effect'* [2,4].

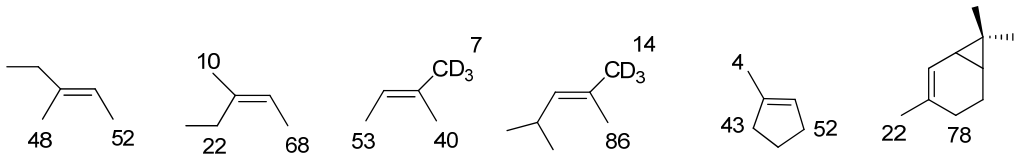


Figure I. 8 Product distribution of the ene reaction of various olefins**.**

Stephenson and co-workers suggested that interaction between HOMO orbital of the olefin and LUMO orbital of the oxygen stabilizes the perepoxide formation in the transition state [34]. For example in the case of *cis*-2-butene, the bonded orbitals of the allylic hydrogen contribute to the HOMO orbital of the olefin, so generating a system similar to the Ψ_3 state of butadiene. The interaction of this system with π^* LUMO orbital of the oxygen is favourable. For the *trans*-isomer the contribution of the bonded orbitals of the allylic C-H bonds to the HOMO orbital of the olefin approximately half, so making the interaction with the oxygen LUMO less favourable [34,4].

For a cycloalkene, there is a correlation between the orientation of allylic hydrogen in the ground state and its reactivity. The allylic hydrogen at the axial position is more rective than equatorial position. In such conformation the orbital overlap between oxygen and allylic hydrogen is optimum [35,4].

The STO-EG semiempirical calculations shows that for acyclic alkenes differences in regioselectivity are related to the different energy requires for an allylic hydrogen to adopt to perpendicular arrangement to the olefinic plane. For example *cis*-2-butene the rotational barrier of allylic hydrogen to adopt a perpendicular alignment to the double bond plane from an eclipsed conformation was calculated to be 1.06 kcal/mol while for *trans* isomer it is higher by 1 kcal/mol. This theoretical result accordance with experimental observations showed that cis alkenes react about 10-20 times faster than their *trans* isomers [36,37].

Schuster *et al*. suggest that there is a type of hydrogen bonding interaction in the rate limiting step of perepoxide formation between the allylic hydrogen and intermediate according to measurement of the activation parameters ΔH and ΔS in the ene reaction of singlet oxygen with series of alkenes. For example, in the reaction of *cis*-2-butene activation entropy ΔS is less negative by 10 e.u. than corresponding *trans* isomer, while the activation enthalpies ΔH are very similar. These differences arise from the in the case of *cis* olefins requiring more organization because of the simultaneous interaction of the incoming oxygen with two allylic hydrogen (Figure I.9). For the *trans* alkenes this interaction occurs with only one allylic hydrogen [38,39].

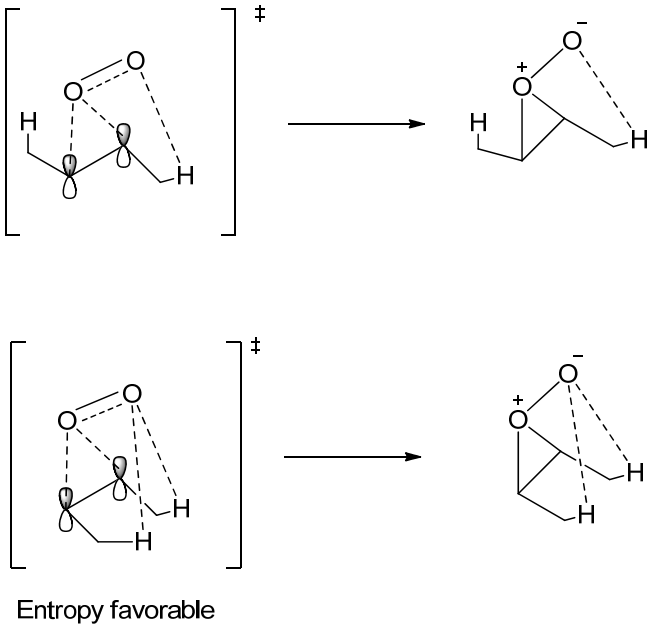


Figure I. 9 Interaction of singlet oxygen with *trans* and *cis* alkenes via transition state.

As a result interaction between incoming oxygen and two allylic hydrogen that highly stabilizes the transition state of perepoxide formation [2,4,19].

ii) Anti 'Cis Effect' Selectivity

Anti '*cis* effect' selectivity has been observed in the photooxygenation of the series of trisubstituted alkenes (Fig I.10) [40]. According to the anti '*cis* effect' selectivity the less substituted side of olefin double bond is the more reactive. Formation of the perepoxide on the more substituted side of the olefin is not favourable because of steric repulsion between the oxygen and two alkyl groups. During the formation of the intermediate, oxygen interacts with only one allylic hydrogen on the both sides of the double bond.

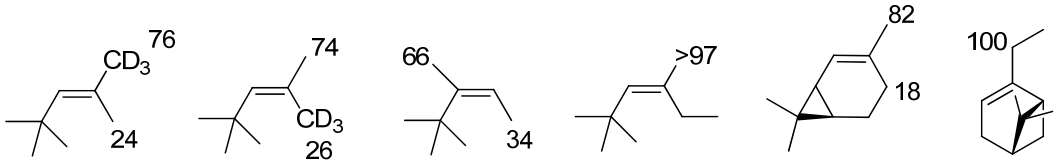


Figure I. 10 Product distribution of the ene reaction of various olefins.

In general, the anti '*cis* effect' selectivity is related to the degree of crowdedness on the more substituted side of the olefin, the non-bonded interaction during the formation of the new double bond and the lack of simultaneous interaction of the incoming oxygen with two allylic hydrogens [4].

iii) The Large Group Non-Bonded Effect with cis and trans Disubstituted Alkenes.

In the reaction of singlet oxygen with non-symmetrical *cis* disubstituted alkenes, an unexpected regioselectivity was found. The allylic hydrogen next to the large alkyl substituent are more reactive then those next to the small groups.

The regioselectivity was explained by examing the possible transition states leading to the allylic hydroperoxides. In transition state which leads to the minor products, there is the repulsive 1,3-non-bonded interaction between the oxygen atom and the

large group. This transition state is expected to be higher in energy than transition state leading to the major products [41].

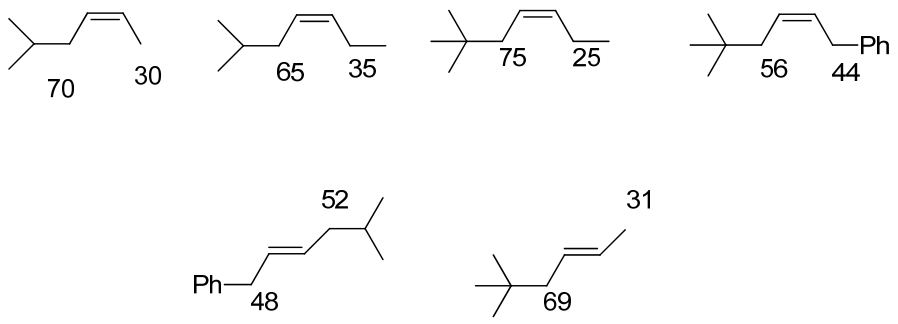


Figure I. 11 *Cis* and *Trans* disubstituted alkenes

The photooxygenation of the *trans* alkenes proceed approximately 20 times more slowly than those of the corresponding *cis* isomer [42]. Considering that the formation of perepoxide in the photooxygenation of *trans* alkenes is reversible, 1,3-non-bonded interactions in the product forming transition state between oxygen and alkyl substituent appear to control the regioselectivity [42,43,44].

I. 1.2.3.2 Solvent Effects In the Ene Regioselectivity

Earlier and recent studies have shown that the rate and the product distribution of the ene reaction of singlet oxygen with alkenes is almost independent of solvent polarity [45,46]. A small variation in the ratio of the ene photooxygenation products of some non-functionalized olefins by changing the solvent has been reported earlier [47,48]. However, no mechanistic explanation was offered to account for the observed solvent effects. The product distribution depends substantially on solvent polarity and reaction temperature, only in substrates where both ene and dioxetane products are formed [49,50].

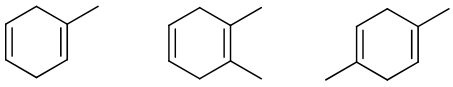
I. 1. 3. AIM OF THE STUDY

The main reactions of singlet oxygen are cycloaddition and ene reaction. The 1,4-cycloaddition of singlet oxygen to a cyclic diene give bicyclic endoperoxide. The ene reaction of singlet oxygen with olefins containing allylic hydrogen gives unsaturated hydroperoxide [1].

The ene reaction of singlet oxygen with olefins has synthetic, environmental and biochemical significance [51]. The mechanism of ene reaction of singlet oxygen with alkenes has attracted the interest of many organic chemists because of its unusual regio- and stereoselectivity [52].

In the past, a great deal of work has been focused on whether the ene reaction proceeds through a concerted or a stepwise mechanism [4].

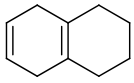
In the first part of our study, we investigated the singlet oxygen ene reaction of the methyl substituted 1,4-cyclohexadiene derivatives **13**, **14** and **15**. Compounds **13** and **14** have two different double bonds. Therefore, we also were interested in searching the regioselectivity of two different double bonds. Our starting material was synthesized by the Birch reduction reaction [53].



13 **14** **15**

In the second part of our study we investigated the photooxygenation reaction of bicyclic system of **16** and **17**. Those systems **16** and **17** were choosen as model compounds. In the case of bicyclic system, the conformation of allylic hydrogens will not be as flexible as in the case of acyclic systems. Therefore, the study of these

systems would release further knowledge to understand the mechanism of ene reaction.



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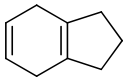


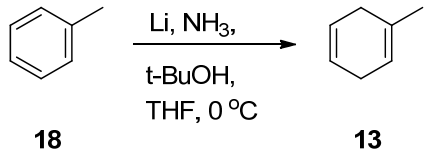
17

CHAPTER 2

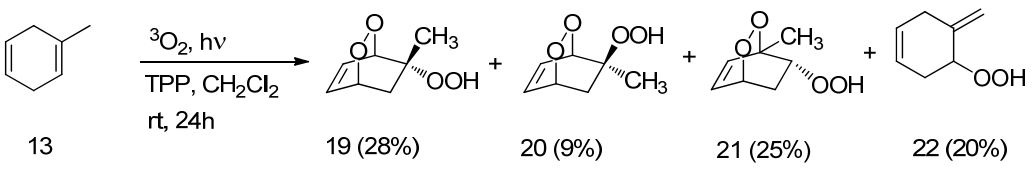
RESULTS AND DISCUSSION

I.2.1 PHOTOOXYGENATION OF 1-METHYLCYCLOHEXA-1,4-DIENE

The compound **13** was synthesized by using Birch reduction [95,53a]. The reduction was applied to toluene with NH_3 and lithium in presence of *tert*-butanol and THF at 0 ^oC.



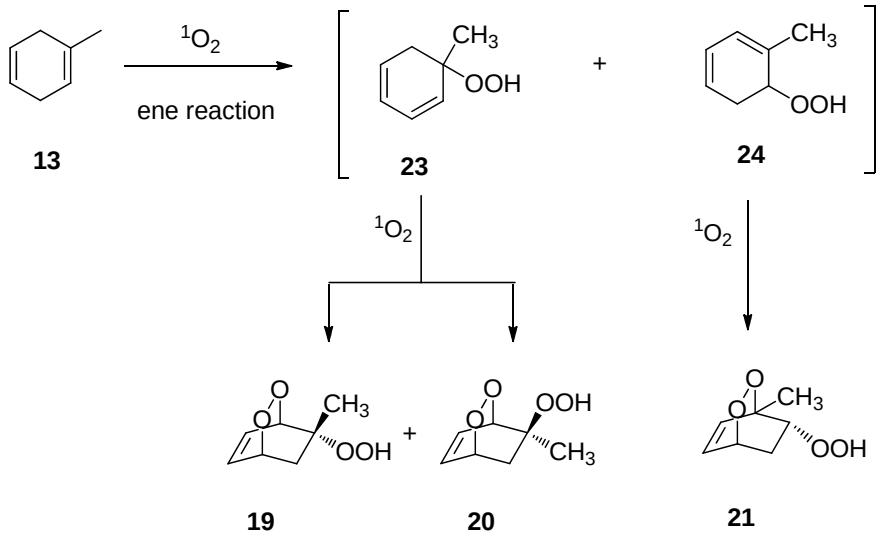
Tetraphenylporphyrin sensitized photooxygenation of 1,4-cyclohexadiene-1-methyl (**13**) in methylene chloride at room temperature produced three bicyclic endoperoxides **19-21** and a monocyclic hydroperoxide **22** in a ratio of 3:1:2.5:2. The isolated endoperoxides are quite stable at room temperature for many days.



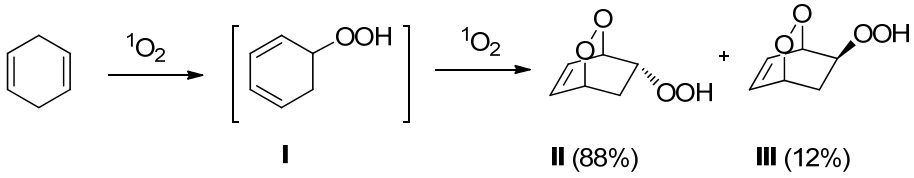
The structures of **19** and **20** were assigned by ^{1}H and ^{13}C NMR spectra. The most conspicuous features in the ^{1}H NMR spectra of the endoperoxide **19** and **20** are the presence of double bond protons and two bridgehead protons along with one AB system that corresponds to methylenic protons. This clearly indicates that the methyl group is attached to the carbon-atom bearing the hydroperoxide. In the ^{1}H-NMR spectrum of **19** methylenic protons resonate as AB-system. A-part resonate at 2.1 ppm as doublet of doublets (J=14.1 and 3.7 Hz). The large splitting originates from the geminal coupling and second doublet splitting (3.7 Hz) arises from the H_{6endo} and bridgehead proton (*exo*/*endo* referred to the double bond). B-part resonate at 1.70 ppm as doublet of doublets (J=14.1 and 1.9 Hz). The large coupling constant arises from the germinal coupling and small coupling (1.9 Hz) arises from the H_{6exo} and bridgehead. In the ^{1}H-NMR spectrum of **20**, methylenic protons resonate as AB-system. A-part resonate at 2.1 ppm as doublet of doublets with coupling constant J=14.2 and 4.1 Hz and B-part resonates at 1.45 ppm as doublet of doublets with coupling constant J=14.1 and 1.8 Hz.

The presence of two olefinic protons and one bridgehead proton in the ^{1}H-NMR spectrum of **21** showed that the methyl group is attached to the bridgehead carbon atom. The structure of **22** was established based on the presence of four olefinic protons (two of them are methylenic) and two methylene groups with large geminal couplings ($J_{5a,5e}$ = 21.0 Hz, $J_{2a,2e}$= 20.1 Hz) that indicate the location of these methylene groups between the double bonds.

For the mechanism of the formation of endoperoxide containing hydroperoxide groups, 1,4-cyclohexadiene unit in **13** first undergoes an ene reaction to give hydroperoxide **23** and **24**. The proposed intermediates **23** and **24** were not detected. The conjugated diene system in **23** and **24** is then easily trapped by a second mole of singlet oxygen to give endoperoxides **19**-**21**. Probably, the rate of the cycloaddition of singlet oxygen to the diene unit in **23** and **24** is most likely too much faster than the rate of the ene reaction with **13**.



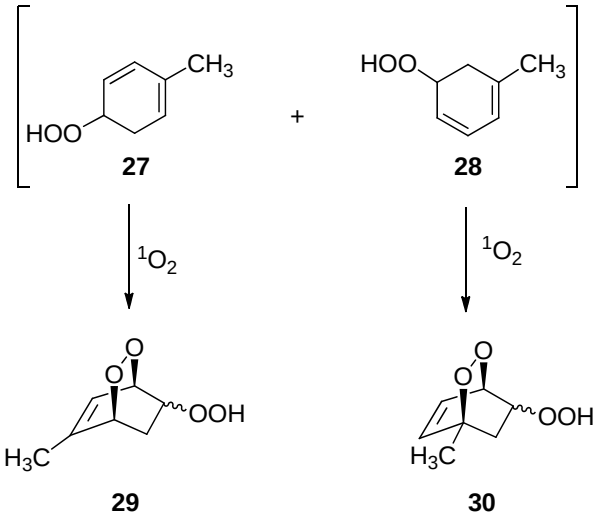
Hydroperoxide **23** has no plane symmetry so singlet oxygen approached the diene unit in **23** from the face of methyl substituted side or face of hydroperoxide side. Product distribution shows that singlet oxygen exclusively attacks hydroperoxide **23** from the methyl substituted side. As a consequences of interaction between incoming singlet oxygen and oxygen atom in hydroperoxide give rise to major isomer **(19)** formation. Previous study of Balcı et *al.* examined the photooxygenation reaction of 1,4-cyclohexadiene. In this study, photooxygenation of cyclohexadine gave two isomeric bicyclic endoperoxide **II** and **III** in ratio of 88:12. The product distribution shows that singlet oxygen approaches the diene unit **(I)** from the back side of the hydroperoxide. This result supports our product distribution of **19** and **20** [63].



Because of the unsymmetrical arrangement of the double bonds in **13**, singlet oxygen can attack two double bonds and form perepoxide **25** and **26**.

25 **26**

If the singlet oxygen would attack the sterically less crowded double bond, the perepoxide **25** can be formed, which would then rearrange to the hydroperoxides **27** and **28**. Trapping of the diene units in **27** and **28** would end up with the formation of the bicyclic endoperoxides **29** and **30**. However, careful analysis of the different fractions did not reveal the formation of any trace of the endoperoxides **29** and **30**. The structures of the isolated products clearly show that singlet oxygen exclusively attacks the higher substituted double bond in **13** [2,18].

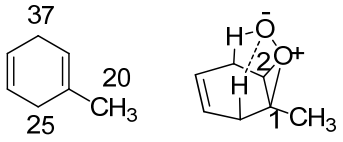


27 **28** **29** **30**

The site selection of singlet oxygen for the higher substituted double bond in **13** can be rationalized in terms of the electrophilic character of this species. The product distribution shows that the ratio of the products **(19, 20**, and **21),** which were derived

from the *cis*-effect to the product from the *anti*-side is 62:20, and in turn indicates that the more substituted side of the double bond is more reactive. The formation of the perepoxide on the more-substituted side is favored. Thus, the stabilizing interaction of oxygen with two allylic hydrogens in the same side of the double bond determines the mode of singlet oxygen attack to the double bond. Once the singlet oxygen has selected the favored side of the double bond by hydrogen bonding, it still has the choice for hydrogen abstraction between the two sides of two different allylic hydrogens.

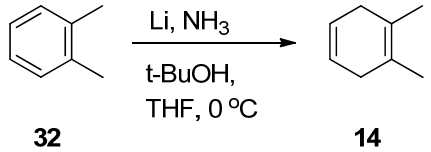
Geminal selectivity was also observed in this case. The product distribution ratio was 37:25. The factors affecting the geminal regioselectivity has been studied by several groups [4,19,54]. A methyl group can interact with the perepoxide ring system (1,3-repulsion between the oxygen atom and methyl group) and lengthen the $^{+}O–C_1$ bond length. As a consequence of this interaction, the hydrogen abstraction from the end of the double bond bearing the methyl group will take place as shown in **31**.



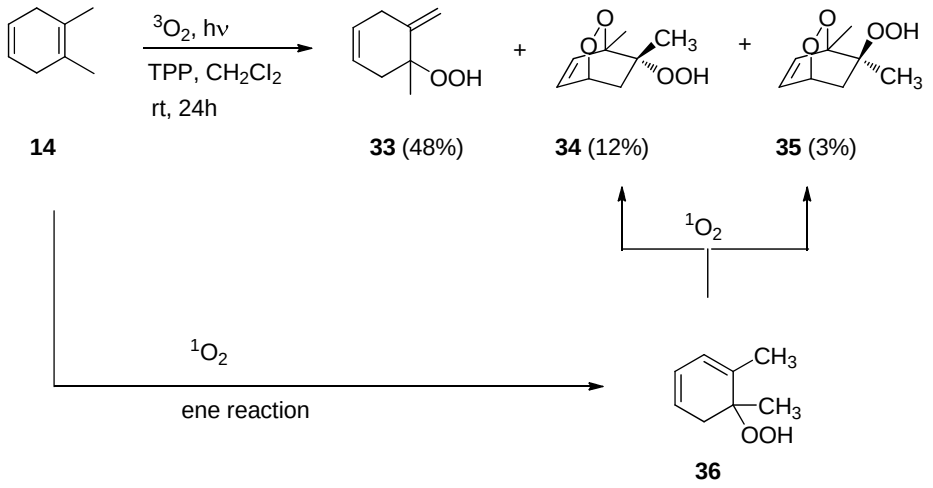
13 **31**

I.2.2 PHOTOOXYGENATION OF 1,2-DIMETHYLCYCLOHEXA-1,4-DIENE

The compound **14** was synthesized by using Birch reduction [53c]. The reduction was applied to o-xylene with NH_3 and lithium in presence of *tert*-butanol and THF at 0^oC.



Tetraphenylporphyrin-sensitized photooxygenation of 1,2-dimethylcyclohexa-1,4-diene resulted in the formation of the three peroxides **33**, **34** and **35**. The major product was identified as the exocyclic ene product **33**. The minor product **34** and **35** were formed by the ene reaction of singlet oxygen with the primarily formed conjugated diene **36**.



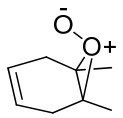
Three isomers were separated by using column chromatography eluting with ether-hexane mixture giving as the first fraction hydroperoxide **33**, as the second fraction endoperoxide **34**, and as the third fraction **35**. Pure samples were obtained by repeated column chromatography.

The structure of **33**, **34** and **35** were determined by NMR spectral data. Major product exo-cyclic alkene is easly distinguishable other isomer endoperoxide **34** and **35**.

In the ^{1}H-NMR spectra of major product **33** there are four olefinic protons (two of them are methlenic) and two methylene groups with large geminal couplings ($J_{3a,3e}$=18.4 Hz, $J_{6a,6e}$=21.3 Hz). In ^{13}C-NMR spectrum of **33** olefinic carbons give signal at 145.9, 126.0, 123.2, 110.1 ppm. The carbon next to the oxygen appears at 82.9 ppm. Other signals are consistent with the structure.

In the ^{1}H-NMR spectra of endoperoxide **34** and **35** only one bridgehead proton was observed, resonating at 4.59 and 4.76 ppm, and it indicates that the one methyl group attached to the bridgehead carbon atom. In the ^{1}H-NMR spectra of **34** and **35**, the lacking of any protons signal at low field area apart from the double bond protons and one bridgehead proton showed that the second methyl group attached to the carbon bearing to the –OOH group. In the ^{1}H-NMR spectra of **34** and **35**, there are two distinct AB-systems, which are two olefinic and two methylenic protons. In the ^{13}C-NMR spectrum of compound **34** and **35**, we observed eight carbon signals with the expected chemical shift.

The structures of the products show that singlet oxygen exclusively attacks the more substituted double bond. Any product derived from the attack of the less-substituted double bond was not detected. Singlet oxygen reacts with the tetrasubstituted double bond in **14** and forms two diastereomeric perepoxides **37** and **38.**



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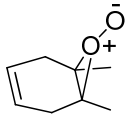


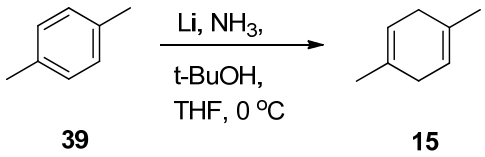
38

Because of the symmetrical environment in **37** as well as in **38**, the pendant oxygen can abstract the allylic hydrogen from one of the neighboring allylic hydrogens and form the corresponding products **34** and **35**. Stereoselective formation of two compounds (**34** and **35**) was explained in I.2.1. The product distribution showed that the diastereoisomer **38** was formed as the major intermediate. Houk et al. [42] suggested that the barrier to rotate the allylic hydrogen to the perpendicular geometry

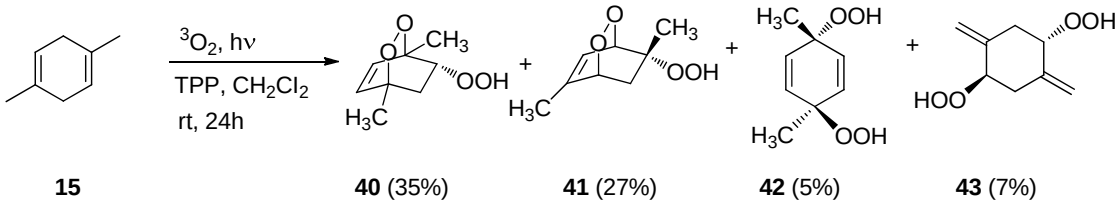
desired for hydrogen abstraction determines the mode of singlet oxygen attack. Thus, the greater reactivity of the methyl groups of this molecule may arise from the relative ease of the rotating of one C-H bond on one of these methyls to the perpendicular conformation in the transition state. The presence of a second methyl group at the C-2 position in **14** most likely decreases the rotational barrier of the methyl group and increases their reactivity.

I.2.3 PHOTOOXYGENATION OF 1,4-DIMETHYLCYCLOHEXA-1,4-DIENE

The compound **15** was synthesized by using Birch reduction [53a]. The reduction was applied to *p*-xylene with NH_3 and lithium in presence of *tert*-butanol and THF at 0^oC.



Photooxygenation of 1,4-dimethylcyclohexa-1,4-diene in methylene chloride at room temperature the products **40**, **41**, **42** and **43** were formed in a ratio of 1.5: 1.0: 0.3:0.2.

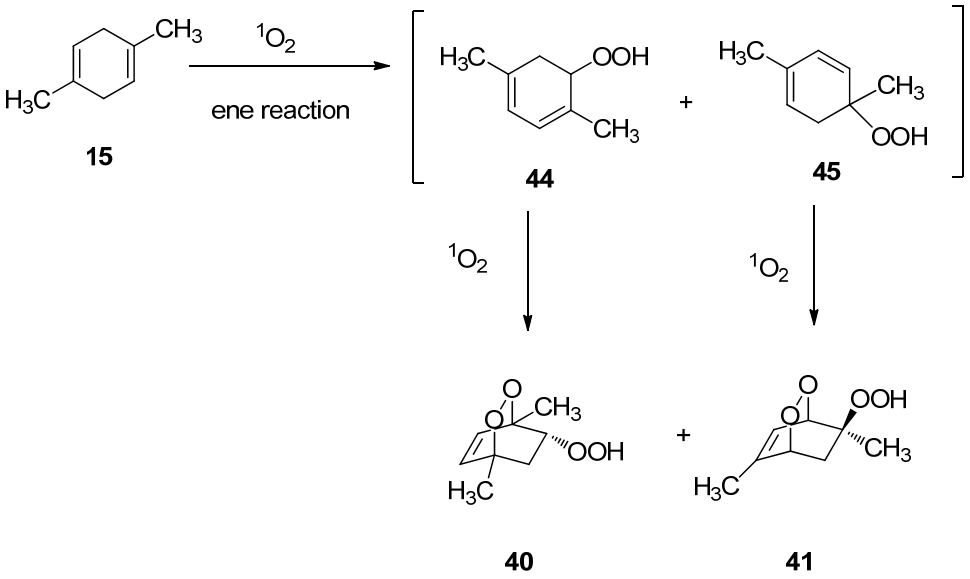


Four isomers were separated by using column chromatography eluting with ether-hexane gave as the first fraction endoperoxide **40**, the second fraction endoperoxide **41**, the third fraction **43**, and as the last fraction **42**.

The structure of **40**, **41**, **42** and **43** were assigned by ^{1}H- and ^{13}C-NMR spectra. The most conspicuous feature in ^{1}H-NMR spectra of the endoperoxides **40** and **41** is the number of the double bond protons. In the ^{1}H-NMR spectrum of endoperoxide **40** there are two olefinic protons and they resonate at 6.49 and 6.26 ppm. Whereas, in the ^{1}H-NMR spectrum of endoperoxide **41** there is one olefinic proton resonate at 6.25 ppm appearing as a doublet of quartets. According to the ^{1}H-NMR spectrum, endoperoxide **40** and **41** can easily differentiate from the other isomers **42** and **43** because both of them contain two hydroperoxide signals at low field. In the ^{1}H-NMR spectrum of hydroperoxide **42** four olefinic protons (-CH=CH-) resonate at 5.89 ppm as a singlet. In the ^{1}H-NMR spectrum of hydroperoxide **43** olefinic protons (-C=CH_2) resonate at 5.04 and 4.99 ppm as a singlet.

The ^{13}C-NMR spectra were also consistent with the all isomers. In the ^{13}C-NMR spectra of **40** and **41** there are eight different carbon resonances. In the spectra of **42** there are three carbon resonances and in the spectra of **43** there are four carbon resonances.

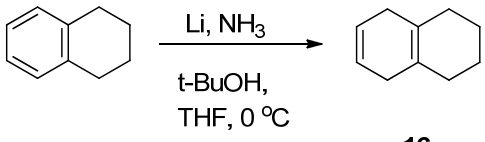
The singlet oxygen first undergoes an ene reaction to give conjugated diene systems **44** and **45**. These diene systems are easily trapped by a second mole of singlet oxygen to give bicylic endoperoxides **40** and **41**.



The diene **45** also undergoes an ene-reaction besides for the cycloaddition reaction to form **42**. Singlet oxygen attacks the trisubstituted double bond in **45** and forms a *syn*-perepoxide, which is responsible for the formation of **42**. The hydroperoxide **43** derives from the formation of an *exo*-perepoxide formed by the reaction of singlet oxygen with one of the double bonds in **15**. Based on the product distribution it can be easily rationalized that the major products are derived from the *endo*-perepoxide (10:1). The reaction of singlet oxygen with dienes **14** and **15** clearly demonstrates that the position of the second methyl group in 1,4-cyclohexadiene unit has a dramatic effect on product distribution. In the case of **14** the products derived from the *exo*-perepoxide were the major products (1:4); however, in the case of **15**, the major products are derived from the *endo*-peroxide (10:1). The product distribution is completely reversed. On the other hand, the product distribution of **15** resembles the product distribution from **13** as expected.

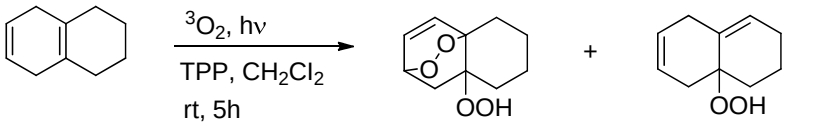
I.2.4 PHOTOOXYGENATION OF 1,2,3,4,5,8-HEXAHYDRONAPHTHALENE

The compound **16** was synthesized by using Birch reduction [95]. The reduction was applied to 1,2,3,4-tetrahydronaphthalene with NH_3 and lithium in presence of *tert*-butanol and THF at 0^oC.



46 **16**

1,2,3,4,5,8-hexahydronaphthalene was submitted to the photooxygenation reaction under the same conditions as described above I.2.3.2 and produced endoperoxide **47** and hydroperoxide **48**.



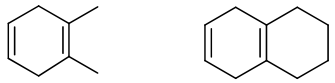
16 **47** (88.9%) **48** (11.1%)

The structures of products show that singlet oxygen attacks the tetrasubstituted double bond. Any product derived from the attack of the disubstituted double bond was not detected. Singlet oxygen reacts with the tetrasubstituted double bond in **16** and form two diastereomeric perepoxides **49** and **50**.

49 **50**

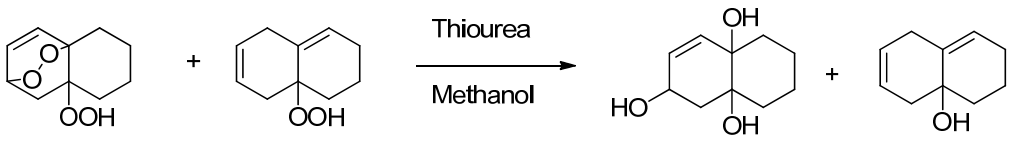
The product distribution shows that diastereoisomer **49** was formed as the major intermediate. If we compare the singlet oxygen reactions of tetrasubstituted diene **14**

and **16,** one would expect the formation of the perepoxide **50** as the major intermediate. Howewer, **50** was formed as the minor intermediate. It is concluded that the geometry of two allylic hydrogens in intermediate **50** is not suitable to stabilize the perepoxide due to the cyclic system which prevents free rotation.



14 **16**

Products distribution was made according to crude ^{1}H-NMR result. Separation and purification of these two isomers were failed due to unstability of the endoperoxide at room temperature. Therefore, the reaction mixture of **47** and **48** was submitted to the reduction of the endoperoxide moities and hydroperoxide functionalities were achieved by using thiourea as reductant.



47 **48** **51** **52**

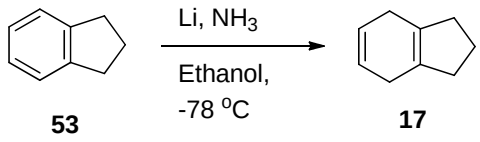
Triol **51** was easily separated from the reaction mixture by using the solubility differences, whereas, isomer **52** was not isolated but rearrangement products was observed due to the presence of allylic alcohol group.

Triol **51** was characterized on the basis of the ^{1}H- and ^{13}C-NMR spectra, which were consistent with the proposed structure. In the ^{1}H-NMR spectrum, there is an AB-system at 5.65 and 5.5 ppm arising from the olefinic protons. The proton next to the hydroxyl group resonate 4.36 ppm as multiplet. Remaining protons resonates between 1.25-1.83 ppm as multiplet.

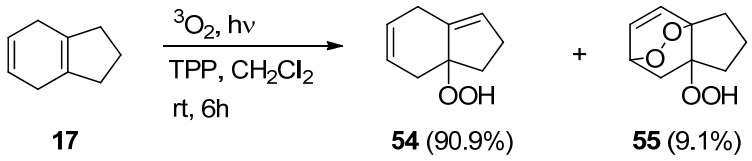
In the ^{13}C-NMR spectrum, the signal at 132.79 and 132.24 ppm belong to the olefinic carbons. The carbons next to the oxygen appear at 73.70, 69.25 and 65.59 ppm. Other signals are consistent with the structure.

I.2.5 PHOTOOXYGENATION OF 2,3,4,7-TETRAHYDRO-*1H*-INDENE

The compound **17** was synthesized by using Birch reduction [53]. The reduction was applied to 2,3-dihydro-*1H*-indene with liquid NH_3 and lithium in presence of ethanol at -78^{o}C.



Tetraphenylporphyrin-sensitized photooxygenation of **17** in methylene chloride at room temperature produced hydroperoxide **54** and bicyclic endoperoxide **55** in a ratio of 1:0.1.



Isomers **54** and **55** were tried to separation and purification by coloumn chromatography. Only isomer **54** was separated. Endoperoxide **55** was not isolated because of the not stable at room temperature.

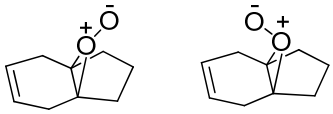
The characterization of isomer **54** was done on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, olefinic proton in the five member ring resonates

at 5.68 ppm as triplet. Other olefinic protons appear as an AB-system. The A part of this system resonates at 5.65-5.58 ppm as multiplet. The B part of the system resonates at 5.49-5.55 ppm as multiplet. Other signals resonate between 2.84 and 1.58 ppm as multiplet.

In the ^{13}C-NMR spectrum of isomer **54** we observe four olefinic carbon signals resonating 137.6, 129.0, 125.1 and 124.1. The carbon atom next to the oxygen resonates at 93.4 ppm. Other carbon signals are also consistent with the structure.

The characterization of isomer **55** was done according to the crude ^{1}H-NMR spectra. In the ^{1}H-NMR spectrum olefinic protons resonate at 6.65 ppm as a doublet of doublets and the B part of the system resonates at 6.41 ppm as a doublet. Other specific signal of the endoperoxide bridgehead proton resonates at 4.79 ppm as a multiplet.

Major product hydroperoxide **54** was formed by ene reaction of singlet oxygen. The minor product **55** was formed by the ene reaction of singlet oxygen **17** followed by the [4+2] cycloaddition reaction of singlet oxygen.

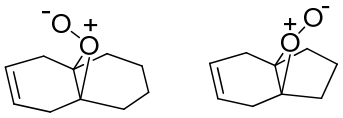


56 **57**

Any product derived from the attack of the less substituted double bond was not detected. Singlet oxygen reacts with tetrasubstituted double bond in **17** and forms two diastereomeric perepoxides **56** and **57**. The product distribution shows that intermediate **56** is the major.

The product distribution **16** and **17** show that perepoxide **49** and **56** as the major intermediate. These two examples show that geometry of allylic hydrogens is very important for the regioselectivity of ene reaction. In the five membered ring allylic hydrogen geometry is suitable to stabilize perepoxide however in six membered ring

is not suitable. This differences arising from the ring strain in the five membered ring.



49 **56**

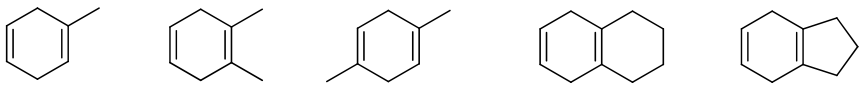
As a result, in the case of bicylic systems (**16** and **17**) the allylic hydrogen is not flexible as in the case of acyclic systems. But ring strain in the five membered ring comes to allylic hydrogens suitable geometry to stabilize the perepoxide **56.** Otherwise we expect **57** as the major intermediate.

CHAPTER 3

CONCLUSION

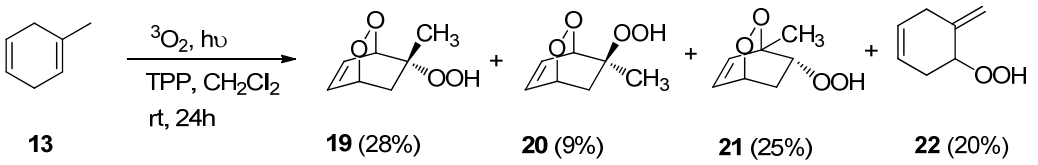
The ene reaction has attracted major interest due to its controversial reaction mechanism and fascinating regiochemistry and stereochemistry. Various reaction mechanisms have been proposed, which vary from the concerted to nonconcerted and include diradical, open-chain zwitterionic, and perepoxide intermediates. Perepoxide or exciplex intermediates have been proposed in most cases. The reaction of trisubstituted olefins with singlet oxygen gave products derived from the most substituted side of the olefin. This selectivity is referred to as the *cis*-effect. For the singlet oxygen reaction of cyclic alkenes; it was proposed that the geometry of the allylic hydrogen in the ground state determines the regioselectivity [2,4].

In this study, we searched the photoxygenation of three different methyl substituted cyclohexa-1,4-dienes **13**, **14**, and **15** and bicyclic dien system **16** and **17**.

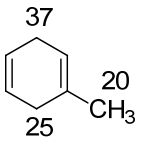


13 **14** **15** **16** **17**

In the photoxygenation of **13** we isolated three bicyclic endoperoxides (**19**-**2**1) and a monocyclic hydroperoxide **22** in a ratio of 3:1:2.5:2.



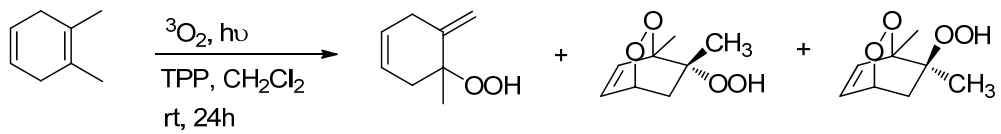
The ratio of products **19**, **20** and **21** show that the reaction of trisubstituted olefins with singlet oxygen gave products derived from the most substituted side of olefin which referred to as the cis-effect. Any product derived from the disubstituted double bond was not observed. The ratio of products derived from the cis effect to the product derived from the anti side is 62:20.



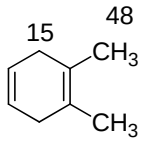
13

The ratio of 37:25 shows germinal selectivity. Hydrogen abstraction can take place end of the double bond bearing the methyl group because of the interaction of methyl group with peropoxide ring system this interaction leads to 1,3-repulsion between oxygen atom and methyl group.

In the photoxygenation of **14** we isolated three products. The major product is exo-cyclic ene products. The minor products are bicyclic endoperoxides.



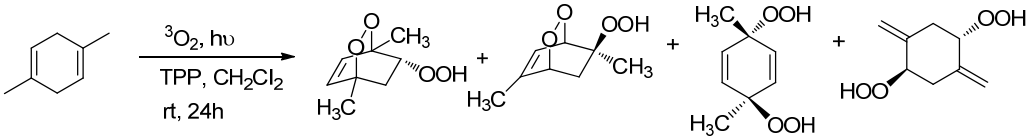
The structure of products show that singlet oxygen attacks the more substituted double bond and any product derived from the less substituted double bond was not detected.



14

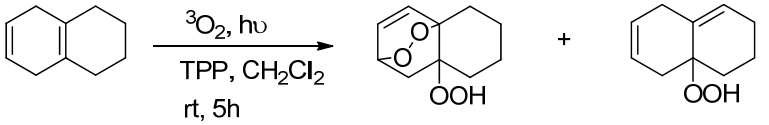
The ratio of 48:15 shows that reactivity of methyl group is higher than other allylic hydrogens. It has attributed the the lower rotational barrier of the methyl groups that in turn increases their reactivitiy.

In the photoxygenation of **15** we isolated four products. Two of them are bicyclic endoperoxides. The products distribution show that the major products derived from the endo-perepoxide (10:1). As a result second methyl group in 1,4-cyclohexadiene unit has a dramatic effect on product distribution. The product distribution is completely reserved the product distribution of **14**. On the other hand the product distribution of **15** resemles the product distribution of **13** as expected.



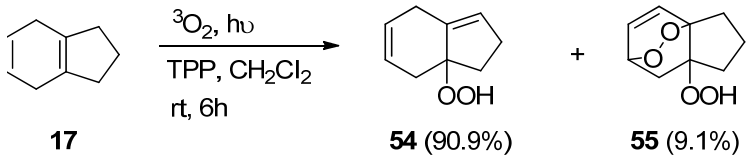
15 **40** (35%) **41** (27%) **42** (5%) **43** (7%)

In the photooxygenation of **16** we observed two products. Major product is bicyclic endoperoxide. The products distribution of **16** is completely reserved the product distribution of **14**. Because of the bicyclic system is not flexible as the acyclic system.



16 **47** (88.9%) **48** (11.1%)

In the photoxygenation of **17** we observed two products. Major product is hydroperoxide **54**. Proton abstraction took place from the allylic protons located in five membered ring. The product distribution of **17** resembles the product distribution of **14** as expected.



17 **54** (90.9%) **55** (9.1%)

As a result, photoxygenation of bicyclic system **16** and **17** show that the geometry of allylic hydrogens plays an important role in determining the regioselectivity.

PART II

APPLICATION OF ENE REACTION TO STEREOSELECTIVE SYNTHESIS OF CARBAHEPTOPYRANOSE DERIVATIVES

CHAPTER 1

INTRODUCTION

II.1.1 CYCLITOLS

Polyhydroxylated cylohexanes are called cyclitols [55,56]. They have attracted a great deal of attention from the synthetic community because of the glycosidase inhibition activities. They are potential therapeutic agents for the treatments of diseases related to metabolic disorders of carbohydrates for example diabetes, cancer, AIDS and viral infections [57]. Better known examples of cyclitols are conduritols (**58**), quercitols (**59**), inositols (**60**) and carbasugars (**61**) [55].

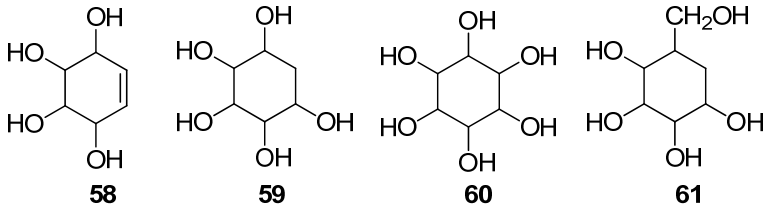


Figure II. 1 Cyclitol derivatives

II.1. 2 CONDURITOLS

Conduritols (**58**), **(**5-cylohexen-1,2,3,4-tetrols) have six diastereomers, theoretically. Two of these diastereoisomers are symmetrical pairs [58]. To prevent confusion, conduritols are named by letters A, B, C, D, E and F in the order of their discovery. Only conduritol A and F occur in nature [59]. All possible conduritol isomers have been synthesized and their biological importance has been studied [59].

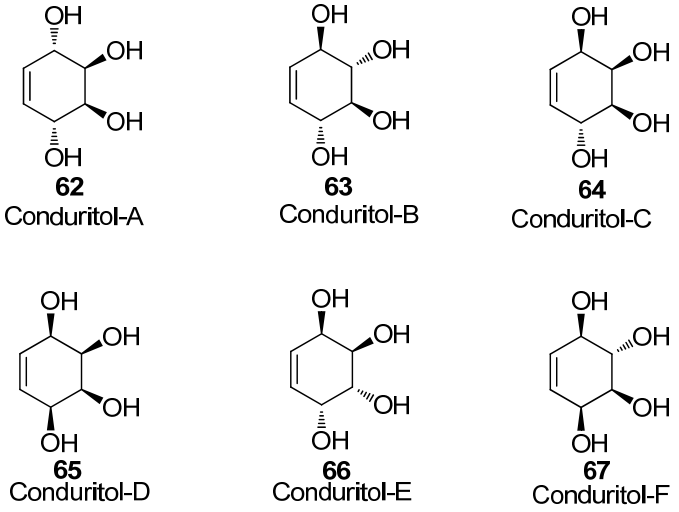


Figure II. 2 Conduritol isomers

From the bark of the vine *Marsdenia condurango* new alcohol was isolated by Kübler in 1908 and he named this alcohol as a ‘‘conduritol’’. Dangschat and Fischer determined the constitution and configuration of conduritol 30 years later [60,61].

For the first time, Nakajima *et al*. synthesized conduritol A, B and E starting from *trans*-benzenediol. Oxidation of diacetate **68** with perbenzoic acid gave a mixture of **69** and **70**. This mixture was hydrolysed with H_2SO_4 and conduritol isomers (A, B and E) formed [60].

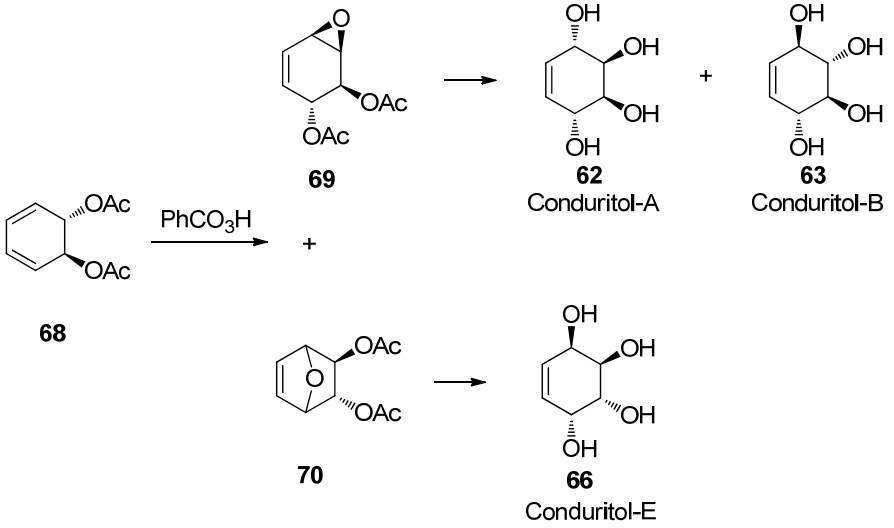


Figure II. 3 Synthesis of Conduritol-A

Conduritols and their derivatives have interesting biological properties. For example, conduritol epoxides and amino conduritols have been proved to be glycosidases inhibitors, cylophellitols act as inhibitors of human immunodeficiency virus (HIV) and glycosidases [62].

Besides, conduritols have been used as intermediates to synthesize important chemical compounds for example, the synthesis of inositols, conduritol epoxides, pseudosugars, aminosugar anologues, and etc. [60,62].

II.1. 3 QUERCITOLS

Cyclohexapentols are called as quercitols. They are basically deoxyinositols which have 16 stereoisomeric forms. Four of them are symmetric, the rest of them are being grouped in six pairs of optical mirror images. Only viz. (+)-*proto*, (-)-*proto*, (-)-*vibo* stereoisomers occur in nature and only in plants [56,63].

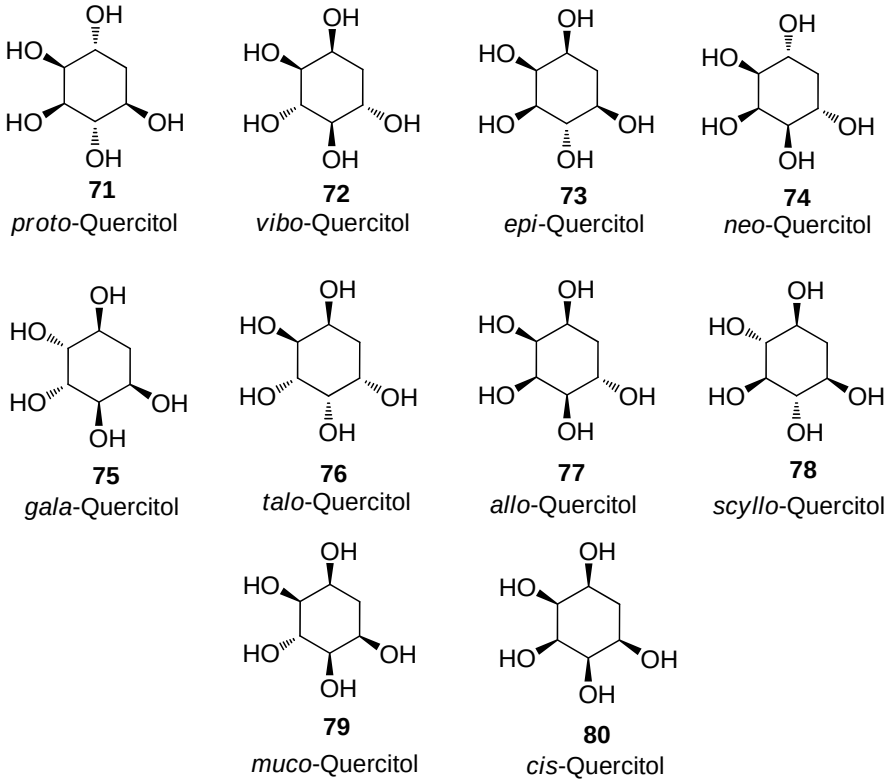


Figure II. 4 Quercitol stereoisomers

In 1849, Braconnot isolated the (+)-protoquercitol from the acorns of an oak tree (genus *Quercus*) as a colorless, crystalline compound. Cyclohexapentanol structure was not known until the 1885, and its configuration was established in 1932, no synthesis has been reported until the 1960s. [64].

So far ten possible diasteroisomers *proto*-, *allo*-, *talo*-, *epi*-, *vibo*-, *gala*-, *scyllo*-, *neo*-, *cis*- and *muco*-quercitols have been synthesized by different methods [63, 65]. In

1968, McCasland synthesized (-)-*proto* quercitol from (-)-inositol in many steps [55]. For the synthesis of *proto*-quercitol, DL-1,2-anhydro-5,6-*O*-cylohexylidene-*chiro*-inositol, conduritol A and natural products were used as a starting materials which required many steps to synthesize [55].

Balcı *et al*. synthesized *proto*-quercitol and *gala*-quercitol starting from 1,4-cylohexadiene by a concise and convenient three step. Photooxygenation of 1,4-cylohexadiene gave endoperoxide **82** and **83**. Reduction of **82** with $LiAlH_4$ or thiourea followed by the acetylation of the hydroxyl group and OsO_4 oxidation of the double bond and acetylation gave pentaacetate form of **71**. Same reaction sequences to **83** gave pentaacetate form of **75**. Proto-quercitol (**71**) and gala-quercitol (**75**) were obtained by ammonolysis of pentaacetate derivatives in MeOH [63].

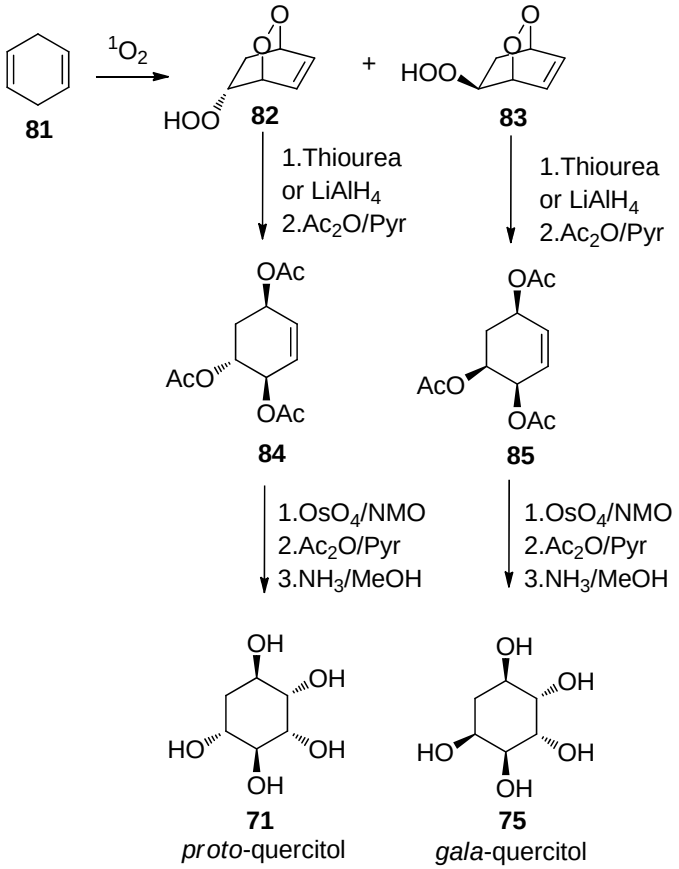


Figure II. 5 Synthesis of *proto*- and *gala*-quercitols

II.1. 4 INOSITOLS

In 1850, the first cyclohexanehexol was isolated from meat by Scherer, which was an optically inactive *myo*-inositol **(89)** isomer [66]. 'Inositol' has been used as a generic term for cyclohexanehexols [64].

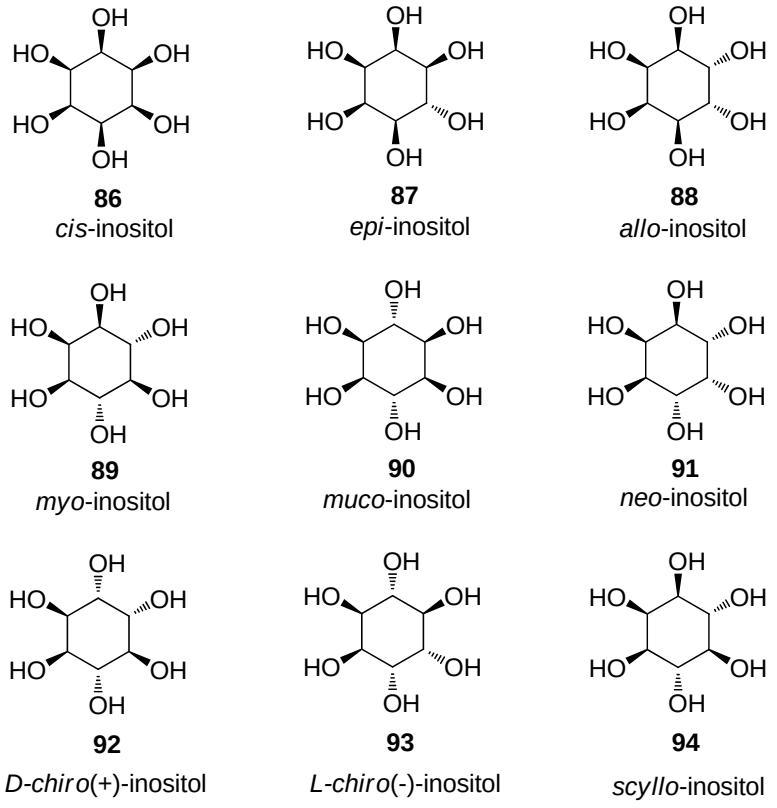
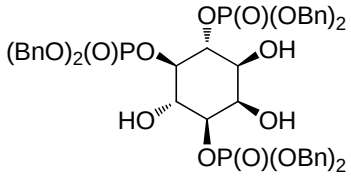


Figure II. 6 Inositol stereoisomers

There exist nine stereoisomers of inositols: *myo, scyllo, cis, D-chiro-(+), L-chiro-(-), epi, allo, muco,* and *neo*. Five stereoisomers (*myo*, scyllo, *D-chiro-(+), L-chiro-(-),* and *neo*) have been found in nature, and their other four stereoisomers (*cis, epi, allo,* and *muco)* are unnatural synthetic products [67,68]. *Myo*-Inositol (**89**) occurs widely in nature in both free and combined forms [68].

cis- Inositol, has three syn-axial hydroxy group in its chair conformations, which easily create strong complexes with metal cations with oxyacid anions. *scyllo*-Inositol with all equatorial hydroxyl groups has been found in animals and plants [67].

Inositols (cylohexanehexols), can be synthesized using the halobenzenes, hexahydrobenzene, sugars and tetrahydroxyquinone as a starting materials [66,67,69]. Particularly, the cylohexa-3,5-diene-1,2- diol have been widely used in the synthesis of inositols [66].



1,4,5-IP_3

Inositol phosphates have attracted a great deal of attention because of their biological roles. Firt observation of Inositol 1,4,5-triphosphate (IP_3) was made by the Berridge in 1984. Inositol 1,4,5-triphosphate is a second messenger molecules used in signal transduction in biological cells. *myo*- Inositol 1,4,5-triphosphate acts as a Ca^{+2} mobilizing intracellular second messenger [70,71].

II.1. 5 CARBASUGARS

Highly oxygenated cyclohexanes are often referred to as pseudosugars or as carbasugars due to resemblence of their structure to the true sugars. In carbasugars the endocylic oxygen atom is replaced by a methylene group [72,73,74].

The term ‘‘pseudo-sugar’’ was first proposed by McCasland, who synthesized pseudo-α-DL-talose as a first pseudo-sugar in 1966. In 1973, a first naturally occurred pseudo-sugar: pseudo-α-D-galactose was discovered as a fermentation

product of *Streptomyces sp*. MA-4145 and had antibiotic activity against *Klebsiella pneumonia* MB-1264 [75].

Pseudo-sugar family consist of 32 possible stereoisomers, including anomer like compounds [76].

II. 1.5.1 Natural Occurance of Carbasugars

Carbapyranoses have been barely found in nature. But they are plenty of as subunits of other natural products.

Carba-α-D-talopyranose (**95**) which is only ‘‘genuine’’ carbasugar isolated from natural sources is isolated from *Streptomyces sp*. MA-4145 [73]. Cylophellitol (**96**) isolated from culture filtrates of a mushroom, *phellinus sp.* [77]. MK7607 (**97**) is isolated directly from natural sources [73].

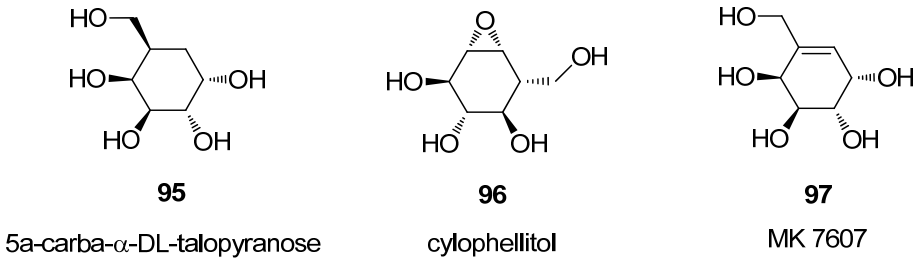


Figure II. 7 Naturally occurring carbapyranose derivatives

Aminosugar derivatives are secondary metabolites mainly produced by microorganism [73]. Better known examples of naturally occurring aminocarbasugars are valienamine (**98**), validamine (**99**), hydroxyvalidamine (**100**), and valiolamine (**101**). Some of these and their derivatives have been found commercial use [73,78].

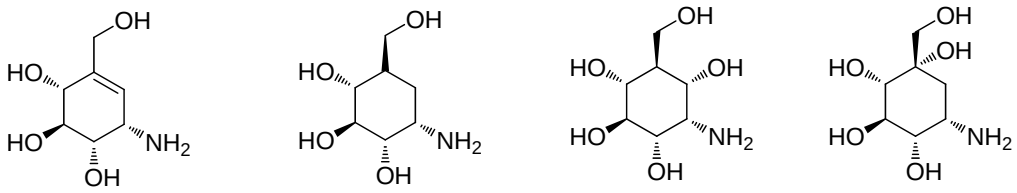


Figure II. 8 Naturally occurring aminocarbapyranoses

Carbafuranoses have not been encountered free in nature but they are subunits of products isolated from natural sources [71]. However, there are two five-membered cyclitol derivatives; caryose (**102**) [79] and calditol (**103**) [80] have been isolated as natural products [73].

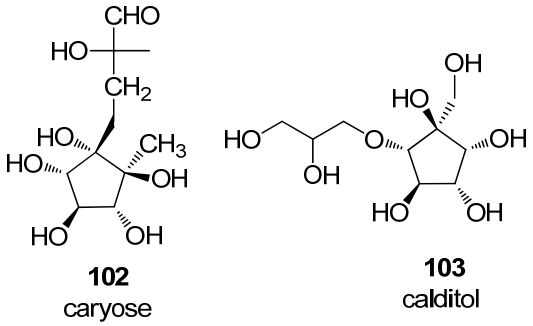
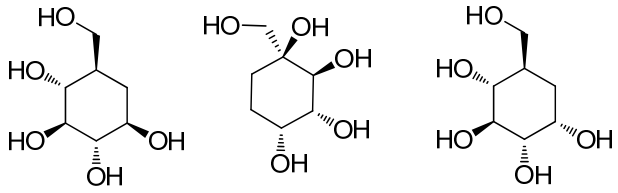


Figure II. 9 Naturally occurring carbafuranoses

II.1.5.2 Biological Activity of Carbasugars

Ring-oxygen of pyranoid sugar is not important for sweetness and the ring oxygen can be changed by a methylene group without any lossful effect on the sweetness of glucose and galactose [75]. Suami *et al.* found that there was no differences between synthetic carba-β-DL-glucopyranose **104** and D-glucose by taste and synthetic 6a-carba-β-DL-fructopyranose **105** was as sweet as D-fructose [73,75].

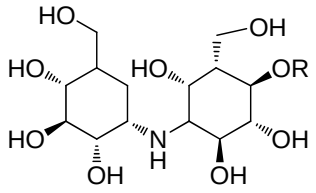


104 **105** **106**

Figure II. 10 Racemic carbasugars

Carbapyranose derivatives of (+)-cylophellitol (**96**) and MK7067 (**97**) have showed biological activities. Cylophellitol (**96**) is a potent inhibitor of β-glucosidases with potential inhibition of the human immunodeficiency virus (HIV) and with possible antimetastatic therapeutic activity [81]. (1R,6S)-cylophellitol, inhibits α-glucosidases [82]. The unsaturated carbapyranose MK7067 **97** was found to have an effective herbicidal activity [83].

α-D-galactopyranose exhibited a low antibiotic activity against *Klebsiella pneumonia* MB-1264 [84]. Carbasugar **106** inhibited both glucose-stimulated insulin release and small glucokinase activity whereas β-anomer **104** showed no activity. Carba-β-DL-glucopyranose **104** is a substrate of the cellobioside phosphorilase of *cellvibrio gilvuse* [85].



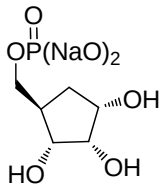
107

R= D-Glc

Validamycin A

Figure II. 11 Validamycins-type compound

Most of the aminocarbapyronoses have become clinically successful to fight diseases in humans and plants. Some aminocabapyronoses derivatives have been reported to be mechanistically unique antifungal agents. Validamycin A (**107**) is the most active compound of the complex and is widely used in Japan and in other rice producing countries in Asia to control sheath blight disease of the rice plants [86].



108

Figure II. 12 Carbocyclic analogue of 5- phosphoribosyl-1-pyrophosphate (cPRPP)

The only information about the biological activity of carbafuranoses was that carboxylic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP) (**108**) against the enzyme 5-phosphoribosyl-α-1-pyrophosphate (PRPP) synthetase. This enzyme reacts with ATP in the presence of Mg ion to give PRPP, a compound involved in the biosynthesis of histidine and tryptophan [87].

II.1.5.3 Synthesis of Carbapyranoses

Syntheses of carbapyranoses have been classified according to the type of compounds using as starting materials: from 7-oxanorbornene derivatives, from other bicyclic compounds, from aromatic derivatives, from carbahydrate derivatives, and other natural sources.

First pseudosugar, 5a-carba-α-DL-talopyranose (**95**), was synthesized in 1966 by McCasland using ketoacid (**113**) as the key intermediate [88]. The synthesis of **113** was carried out using a route previously used by Daniels and co-workers [89] in their synthesis of shikimic acid and based on a Diels-Alder reaction of 2-acetoxy furan

(**109**) and maleic anhydride (**110**) [88]. Hydroxylation and hydrolysis of Diels-Alder adduct, **111**, gave diol diacid **112**. Diol diacid undergoes a series of transformations (acetyl migration, opening of the 1,4-oxacyclic ring, carbonyl liberation, and decarboxylation) leading to **113**. Sodium borohydride reduction of **113**, and subsequent esterification with methanol and trifluoracetic acid, followed by acetylation gave tetraacetate **114**. Tetraacetate was converted into the target carbasugar **95**, by reduction with lithium aliminum hydride followed by hydrolysis [73].

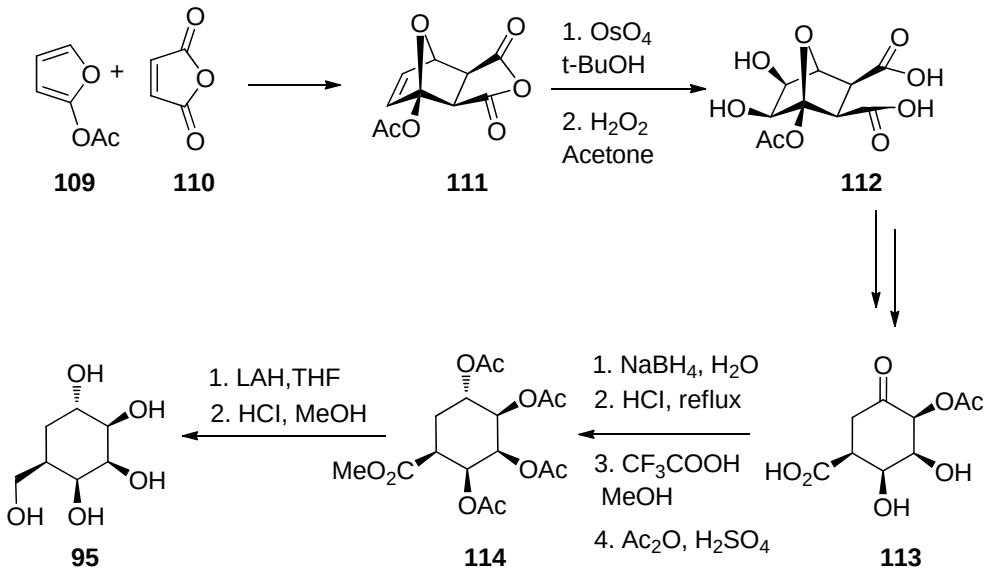


Figure II. 13 Synthesis of 5a-carba-α-DL-talopyranose **(95)**

7-Oxanorbornene derivatives have been extensively used as starting materials for the synthesis of carbapyranoses and derivatives. Ogawa and co-workers used 7-oxabiccylo[2.2.1]hepten-5-ene-2-carboxylic acid (**117**) is the key intermediate for the synthesis of different pseudosugar derivatives [90].

7-Oxabiccylo[2.2.1]hepten-5-ene-2-carboxylic acid (**117**) was prepared by Diels-Alder cyloaddition of furan (**115**) and acrylic acid (**116**). Adduct **117** was treated

with hydrogen peroxide and formic acid, and the hydroxylactone **118** was formed. Treatment of **117** with hydrobromous acid gave lactone **119**.

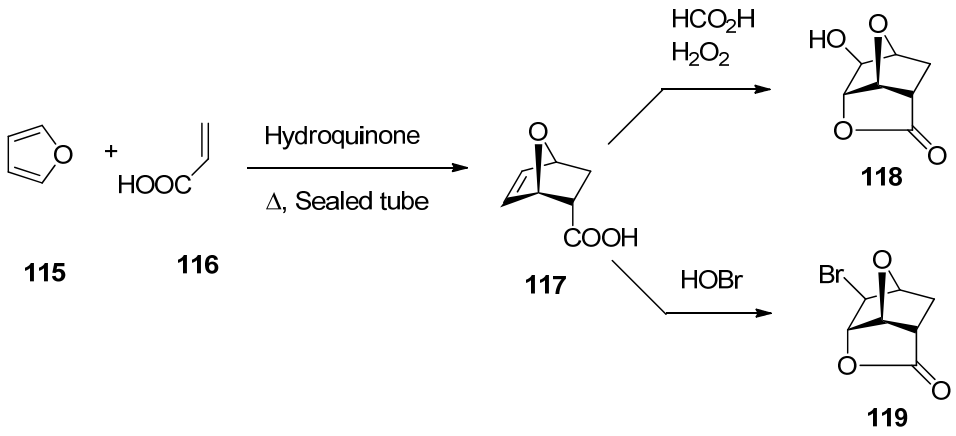


Figure II. 14 Synthesis of hydroxylactone **118** and lactone **119**

Reduction and peracetylation of hydroxylactone **118** under acidic conditions, regioselective cleavage of 1,4-oxa-bridge occured and gave 5a-carba-β-DL-glucopyranose pentaacetate (**121**) and 5a-carba-α-DL-galactopyranose (**123**) [90].

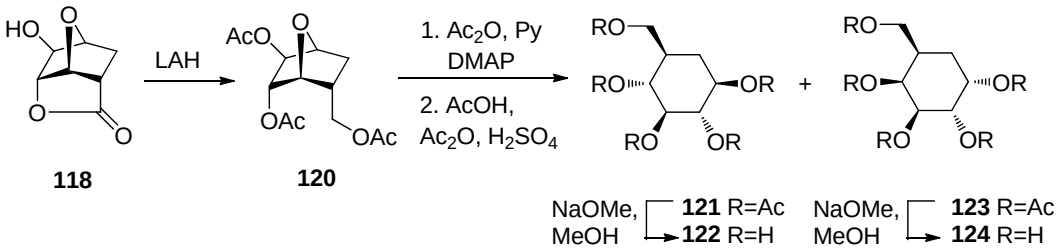


Figure II. 15 Synthesis of 5a-carba-β-DL-glucopyranose (**122**) and 5a-carba-α-DL-galactopyranose (**124**)

Bromo derivatives **125** and **126** were obtained from the reduction, acetylation and acetolysis reaction of **119**. Substitution reaction of **125** and **126** with acetate ion gave 5a-carba-α-DL-galactopyranose pentaacetate (**123**), 5a-carba-α-DL-idopyranose (**128**), 5a-carba-α-DL-mannopyranose pentaacetate (**130**), and 5a-carba-β-DL-altropyranose (**132**). Acetoxonium cations are intermediates for the substitution reactions [90].

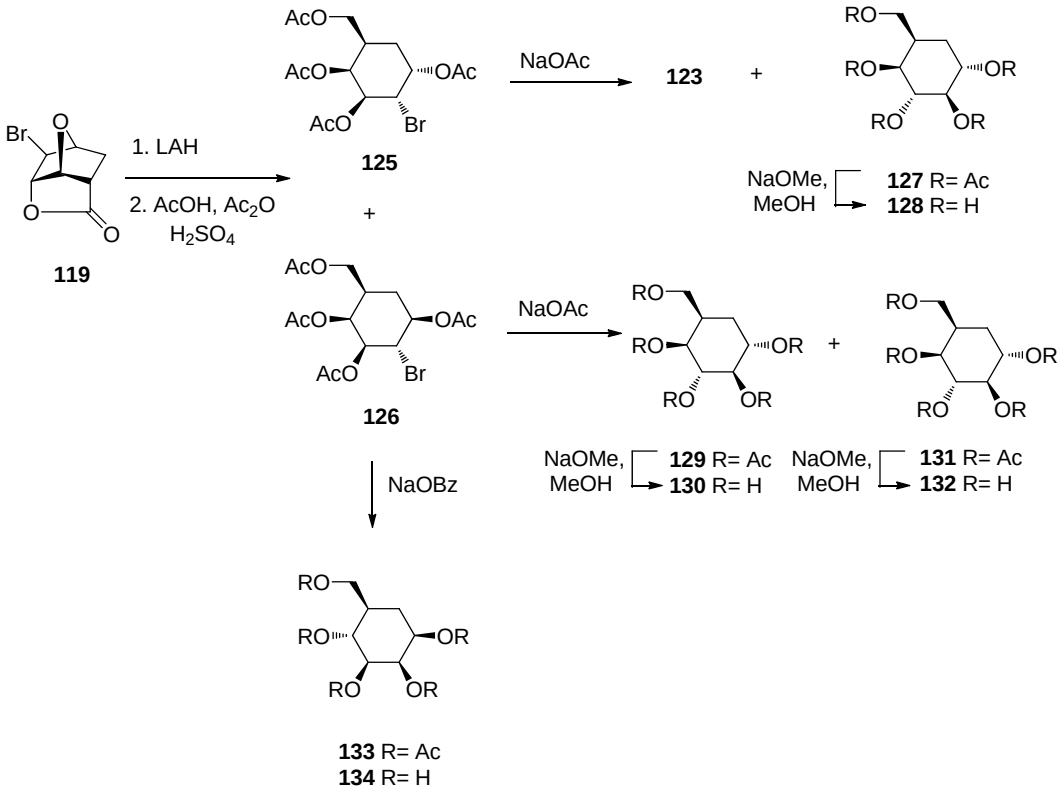


Figure II. 16 The synthesis of **123**, **128**, **130**, **132**, and **134** from bromo derivatives **125** and **126**

5a-carba-β-DL-mannopyranose (**134**) was obtained when sodium benzoate was used instead of sodium acetate. Direct S_N2 reaction occurred [90].

Bicylo[2.2.1]heptane system has been used as a starting material for the synthesis of carbasugars. Mehta and co-workers has used [2.2.1]heptane systems to obtain

carbasugars and ‘‘confused’’ carbasugars. According to the Mehta *et al*. ‘‘confused’’ carbasugars have the same oxygenation level as carbasugars but differ in the location of the hydroxymethyl group and the ‘‘para’’ hydroxy groups [91].

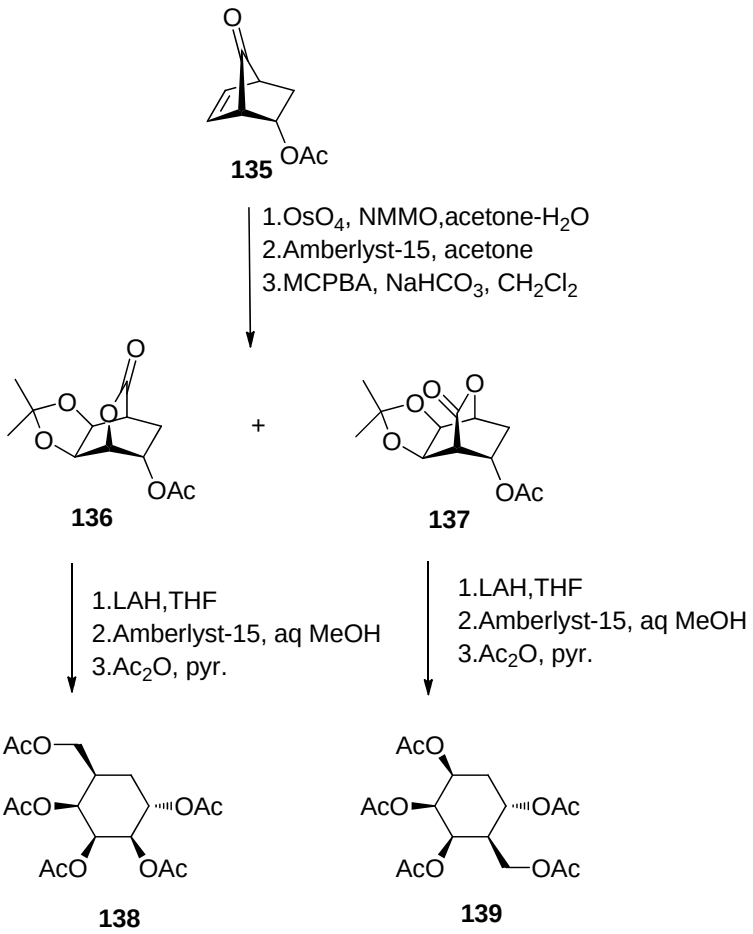


Figure II. 17 Synthesis of 5a-carba-α-DL-talopyranose and ‘‘confused’’ carbasugars from bicylo[2.2.1]heptanes **135**

Landais and co-workers synthesized carbasugar derivatives using aromatic compound as a starting material. Desymmetrization of cylohexadienylsilane (**141**) was used to synthesize carbasugars. Birch reduction of (*tert*-butyldimethylsilyl) benzene (**140**) gave cylohexadienyl silane (**141**). Sharpless asymmetric dihyroxylation of enantiotopic double bonds of **141** resulted diol (71% ee) which was

protected as its bis-benzylether (**142**). As a result of silicon group cyclopropanation of ally silanes (**142**) gave anti product (**143**). For the electrophile- mediated cyclopropane ring opening reaction of **143** with N-iodo and N- bromosuccinimide **144** and **145** were formed. Iodide **144** was converted to (phenyl dimethyl) sillyl derivative **146**. Catalytic osmylation, oxidation of sillyl group, acetylation, debenzylation, and complete acetylation reaction of **146** gave the 5a-carba-β L-altropyranose pentaacetate (**148**) [92].

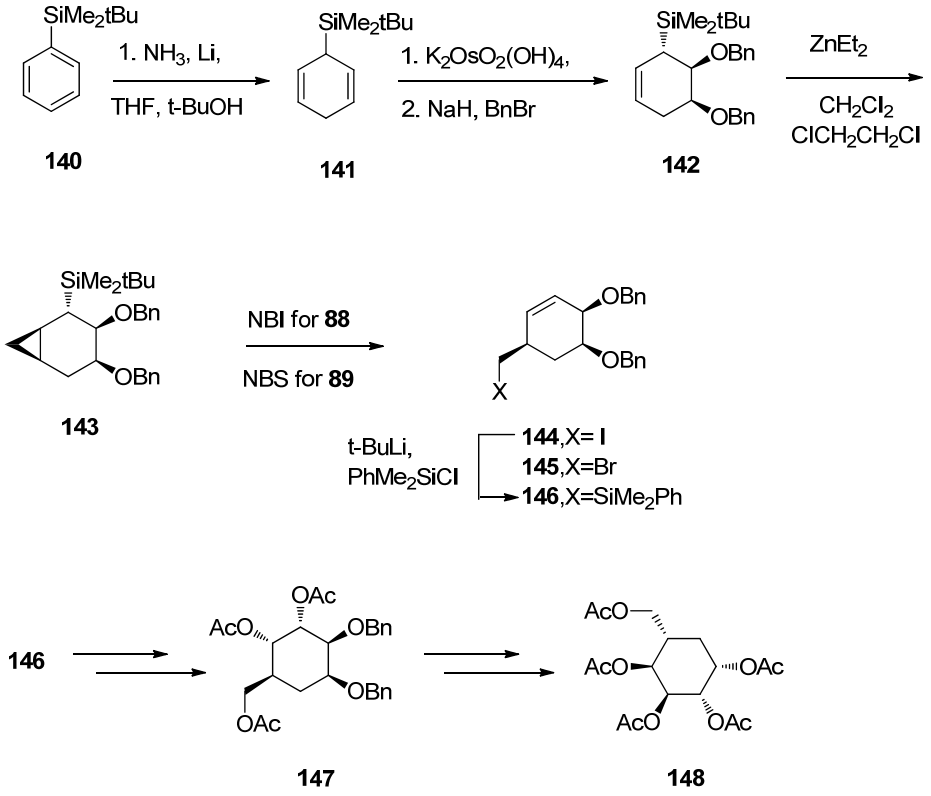


Figure II. 18 Synthesis of 5a-carba-β-DL-altropyranose pentaacetate (**148**) by desymmetrization of dienylsilanes (**141**)

Use of carbohydrates as a starting materials provide important advantages to the preparation of their carbocylic analogues. On the other hand, the hydroxyl groups have been preserved thorough the synthetic sequence, with no need for ‘‘hydroxylation’’ reaction, and enantiomeric purity of the target carbasugars will be

guaranteed. The key step for the synthesis of carbasugars from carbohydrates is ring-closing. Generally, preparations of carbasugars have been classified according to the type of ring-closing rection. These are nucleophilic cyclization, electrophilic cyclizatio, radical cyclization and ring-closing olefin metathesis [73].

Suami and Tadano synthesized 5a-carba-α-L- mannopyranose pentaacetate starting from D-ribose. Compound **150** was obtained from D-arabinosediethyl dithioacetal (**149**) by serially tritylation, benzylation, detritylation, O-sillylation, and regeneration of the parent aldehyde group. Knoevenagel reaction of **150** with dimethyl malonate and pyridine gave compound **151** after catalytic hydrogenation and desilylation. The crucial cyclization of **151** was made by using pyridinium chlorochromate (PCC), gave two cylohexane derivatives **152** and **153** in the ratio of 10:1. Thermal demothoxycarbonylation of **152** followed by β-elimination of the acetoxy group gave protected shikimate **154**. Lithium aluminium hydride reduction followed by hydroboration, O-debenzylation and acetylation gave 5a-carba-α-L- mannopyranose pentaacetate (**155**) [93].

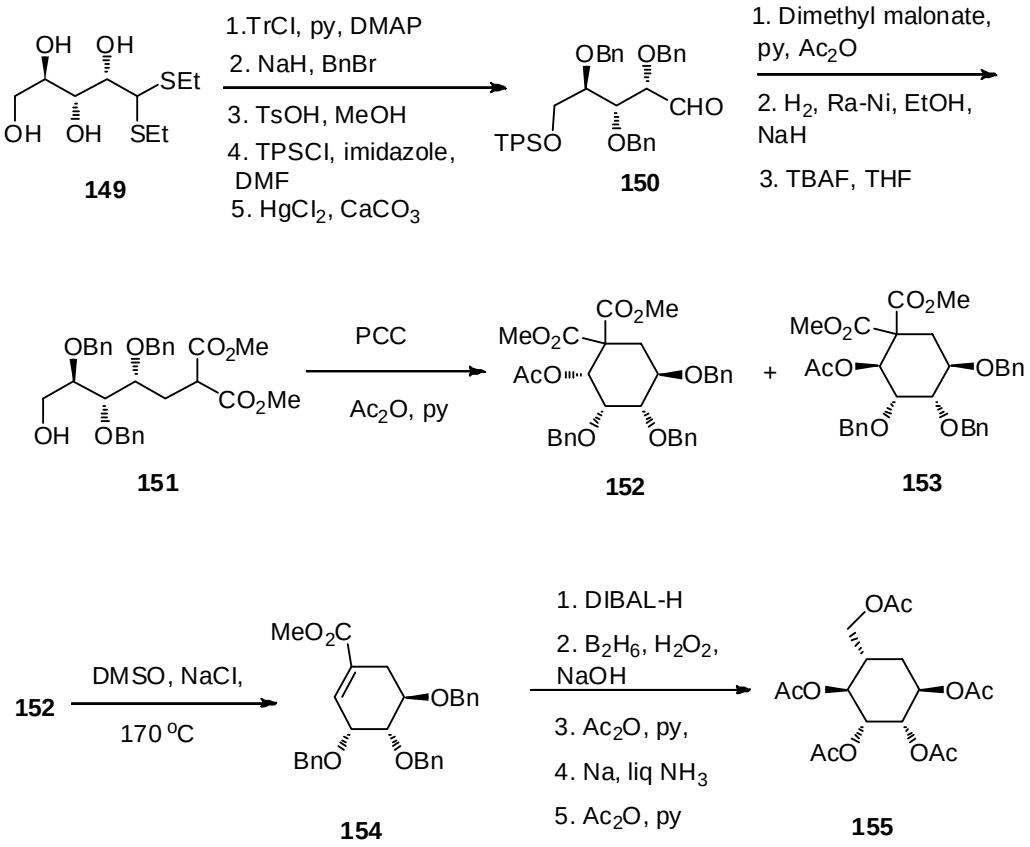


Figure II. 19 Suami and Tadano's work for obtaining 5a-carba-α-L- mannopyranose pentaacetate (**155**)

Wagner and Lunft have synthesized the first carbaheptopyranose **161** starting from tartaric acid (**156**). The key step was radical induced carbocylization of bromo derivative **159**. L-tartaric acid was converted into compound **157** by sequential isopropylidation, esterification, reduction, monobenzylation and finally by Swern oxidation. Condensation reaction of aldehyde (**157**) with 2-(trimethylsiloxy) furan gave octono-1,4-lactone (**158**) which was converted to bromo derivative **159**. Radical cyclization of bromo derivative in the presence of Bu_3SnH gave bicylic compound **160**. 5a-carba-6-deoxy-β-L-guloheptopyranose (**161**) was obtained by reduction of lactone with $Ca(BH_4)_2$ [94].

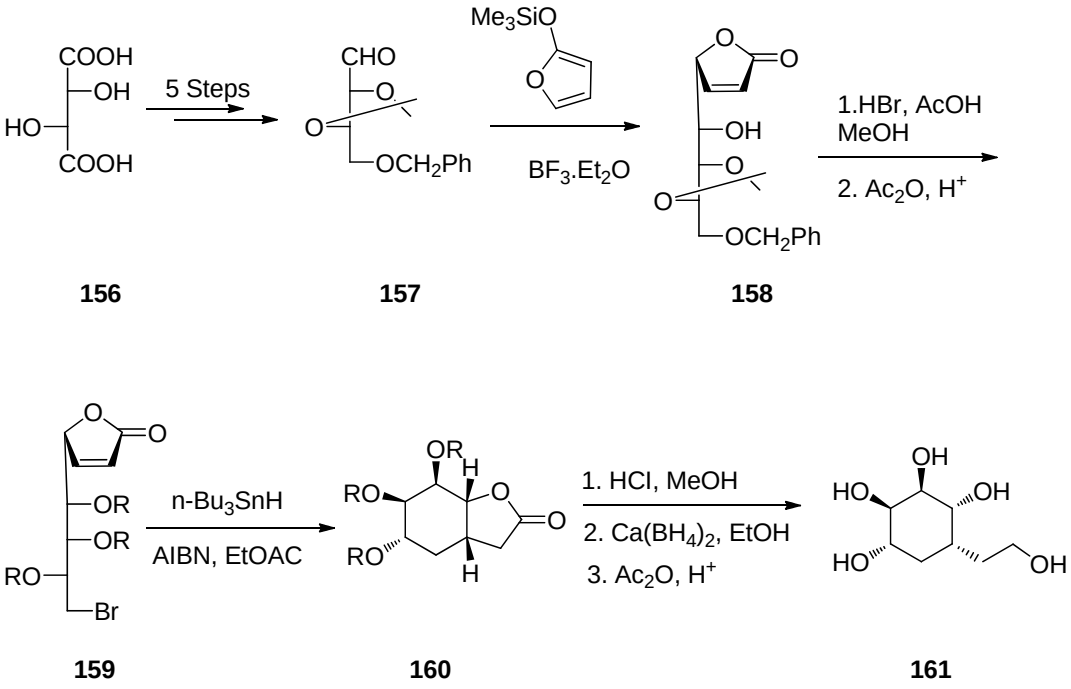


Figure II. 20 Synthesis of 5a-carba-6-deoxy-β-L-guloheptopyranose (**161**)

II. 1. 7 KETENES

Dichloroketene is a reactive and unstable molecule [96]. α,α-Dichlorocyclobutanone can be obtained from the reaction of dichloroketene with conjugated dienes [97]. 1,4-Cycloadducts were not observed. Other activated olefins for example indene or dihydropyran also give good yields of cycloadducts. Methyl methacrylate or methyl fumarate, electrophilic olefins, is completely inert towards dichloroketene. Less reactive ketenes are not reacting at room temperature with unactivated olefins such as cyclopentene and cyclohexene, but dichloroketene reacts. However bicyclic olefins for example norbornene or norbornadiene are shown to be poor ketenophiles. These results indicate that concerted cycloaddition involving an orthogonal approach of the ketene and olefin is in agreement with Woodward and Hoffmann's suggestions [96].

II. 1. 7.1 Preparation of Halogenated Ketenes

There are two methods widely used for the preparation of ketenes. The first one is the dehalogenation of an appropriately substituted α-haloacid halide with activated zinc. Second way is the triethylamine dehydrohalogenation of an acid halide [98].

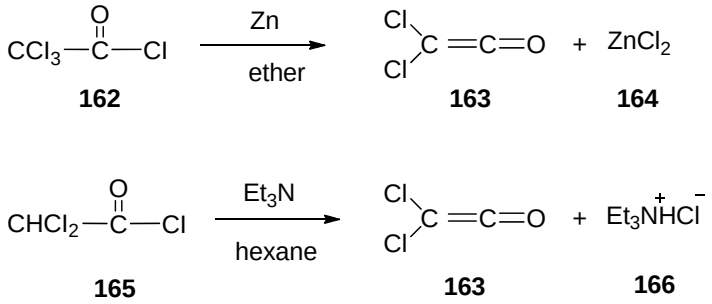


Figure II. 21 Preparation of halogenated ketenes

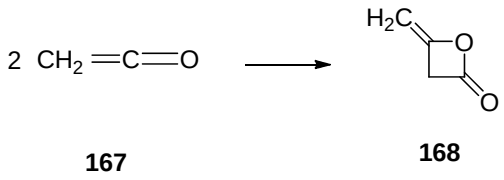
The majority of the halogenated ketenes are generated by using one of these two methods and both methods have been used in situ generation of dichloroketene. However, these two methods have certain disadvantages. [97]. Tertiary amines and/or ammonium salts catalyzed both the polymerization of especially low molecular weight ketenes and the decomposition of dichloroketene. The zinc dehalogenation method catalyzed the polymerization of olefins such as ethyl vinyl ether, styrene, furan, enol ethers, cyclopentadiene and other conjugated dienes [97,98].

The addition of phosphorus oxychloride decreases the limitations of zinc dehalogenation method. The addition of phosphorus oxychloride leads to improved yields of dichloroketene cycloaddition products and olefin facilitates product isolation [98].

II. 1. 7. 2 General Reaction Types of Ketenes

Ketenes undergo dimerization, trimerization, polymerization and cyloaddition reactions.

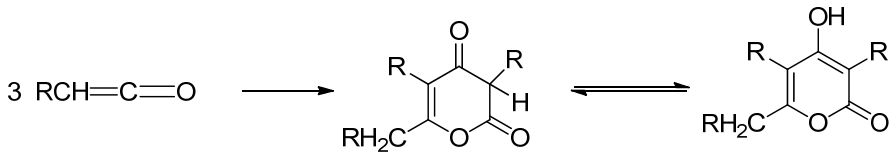
i) Dimerization: The dimerization of the ketene can be effected by heat [99,100], an acid or base catalysis, and often diketene is formed as a by-product in ketene reactions. [101].



167 **168**

Figure II. 22 Dimerization of ketene.

ii) Trimerization: Trimerization of the ketenes has received little attention, most likely because the dimerization is so pronounced [101]. In the early century, however, some study has been done conducted by Wedekind [102].



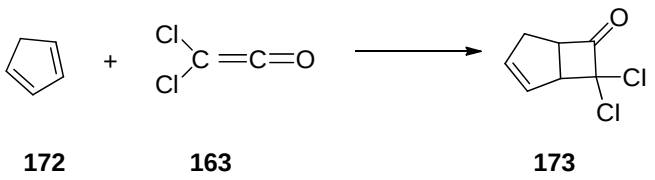
169 **170** **171**

Figure II. 23 Trimerization of ketene

The reaction proceeds via the symmetrical dimer, as evidenced by the cyclobutenone structure of the isolated trimer [101].

iii) Polymerization: Ketenes can be polymerized in the presence of a base catalyst such as triethylamine or some aluminium compounds like trialkylaluminum. Also thermal conditions affect the polymerization of ketenes, which may appear as side products in the ketene reactions [101].

iv) Cyloaddition Reaction of Ketenes: Ketenes undergo cyloaddition to double bonds to give cylobutanones [103,104].



172 **163** **173**

Figure II. 24 Ketene cycloaddition to double bond

When the ketene has electron-withdrawing groups on it (like C1) and when olefin is electron rich, the cycloaddition reaction can take place very easily. The electron-withdrawing groups lower the energy of the LUMO of the ketene, and electron-rich olefins have a high-energy HOMO. The important interaction occurs between HOMO (ketenophile) and LUMO (ketene). However, if we examine this reaction very closely, at first glance this interaction is not possible according to the Woodward-Hoffmann rules. However there is a lot of evidence that it is concerted reaction: it is an allowed pathway in which a [π2s + π2a] process occurs [105]. One end of the π-bond of the olefin overlaps to the p_z orbital at the terminal carbon atom of the ketene, while the other end of the π-bond of the olefin overlaps to the p_y orbital of the central carbon atom of the ketene (Figure II.25).

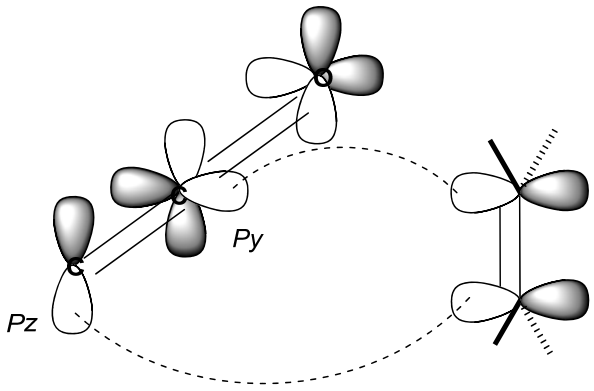


Figure II. 25 Overlap in a cycloaddition of an olefin to a ketene

Regioselectivity is determined by the fact that tle larger lobe of the HOMO of the olefin overlaps with the larger lobe of the LUMO of the ketene. The energies and coefficients of the frontier orbitals of ketenes [106] are shown in Figure II.26.

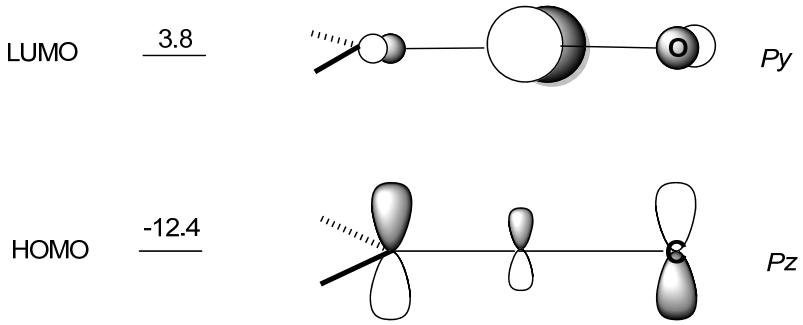
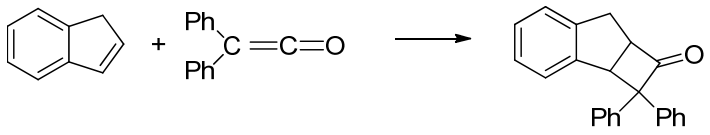


Figure II. 26 Energies and coefficients of the frontier orbitals of ketene

These may be compared with a simple carbonyl group. Clearly the major interaction is that from the large LUMO coefficient on the central atom to the carbon atom having the larger coefficient in the HOMO of the olefin. This is exactly what has been observed with C-, Z- and X- substituted olefins, as the following examples show.

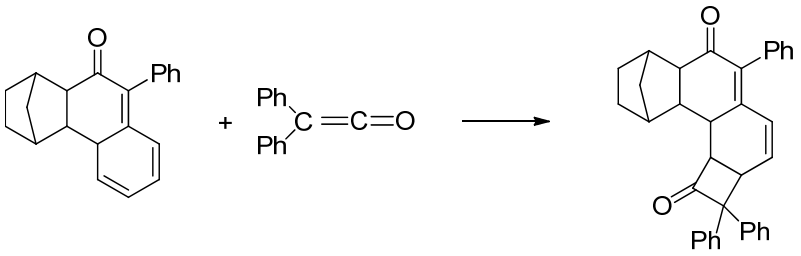
C-substituted ketenophiles [107]:



174 **175** **176**

(C-substitution: simple conjugated systems like vinyl or phenyl etc.)

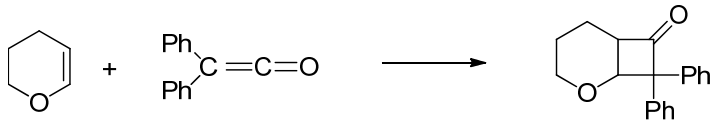
Z-Substituted Ketenophile [108]:



177 **175** **178**

(Z-subtitution: conjugated systems which are also electron-withdrawing like formyl, cyano,nitro etc.)

X-Substituted Ketenophile [109,110]:



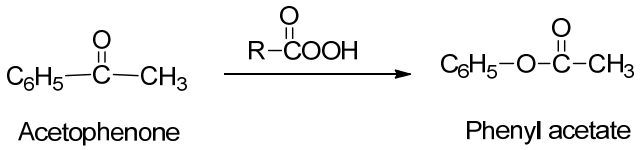
179 **175** **180**

(X-substitution: Heteroatoms having lone pairs of electrons capable of overlap with benzene ring etc.)

II. 1. 8 THE BAEYER VILLEGER OXIDATION

Peroxyacids and hydrogen peroxide oxidize the aldehyde and ketones. This reaction is called as the *Baeyer–Villeger* oxidation and is very useful method, especially for

converting to ketones to esters. For example the ester phenyl acetate is obtained by the reaction of acetophenone with peroxy acids [113].



The mechanism proposed for this reaction involves the following steps [113].

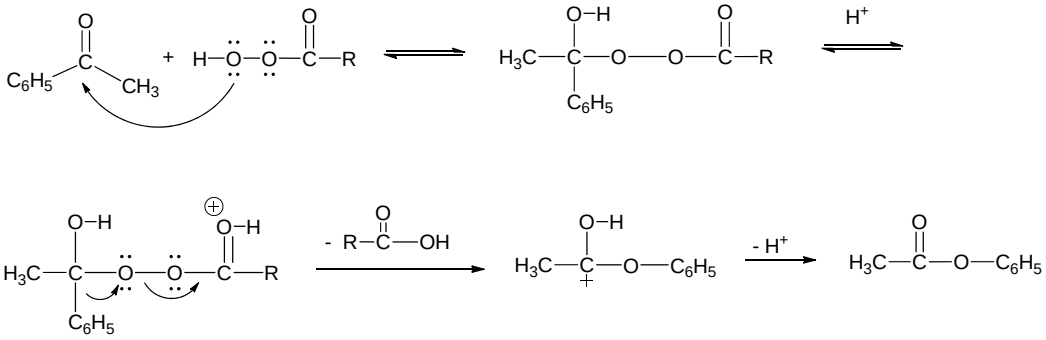


Figure II. 27 The mechanism for the Baeyer-Villeger oxidation

The reaction mechanism of this oxidative cleavage involves first addition of the peroxy acid to the carbonyl group of ketone. The peroxy acid carbonyl group is protonated, preparing the RCO_2H portion to be a leaving group. Next the phenyl group migrates with an electron pair to the adjacent oxygen with loss of carboxylic acid. After that, the loss of a proton produces the ester.

The products of this reaction indicate that a phenyl group has a greater tendency to migrate than a methyl group. This tendency of a group to migrate is called its *migratory aptitude*. Studies of the Baeyer-Villeger oxidation indicate that the migratory aptitude of groups is

H > phenyl > 3^o alkyl > 2^o alkyl > 1^o alkyl > methyl

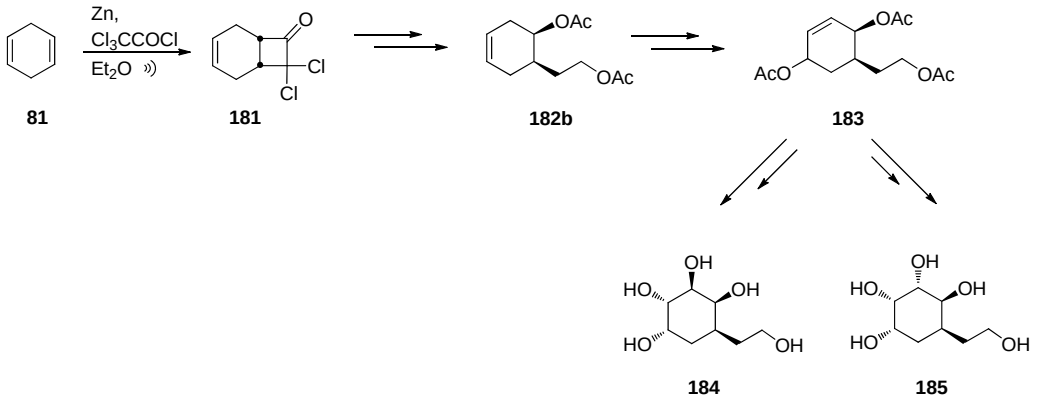
In all cases, this order is for groups migrating with their electron pairs, that is, as anions [113].

II.1. 9 AIM OF THE STUDY

Cyclitols have attracted a great deal of attention because of their glycosidase inhibition activities and their versatility as synthetic intermediates. Carba-sugars are cyclic monosaccharide analogues in which the endocyclic oxygen atom is replaced by a methylene group [72].

Preparation of carba-sugars is of interest and since the discovery of the first carba sugars a number of methods have been developed for the synthesis of carbapyranoses [94].

The aim of our study is to develop a new and efficient strategy for the synthesis of carbapyranose derivatives. Our study consists of two main parts. First part is the dichloroketene addition which is the key step to introduce the alkyl group to the cyclohexane molecule. Second part is the singlet oxygen reaction (specifically *ene* reaction) to provide additional oxygen functionality. Following steps are afforded the one-carbon-inserted-carba-sugar derivatives **184** and **185**.



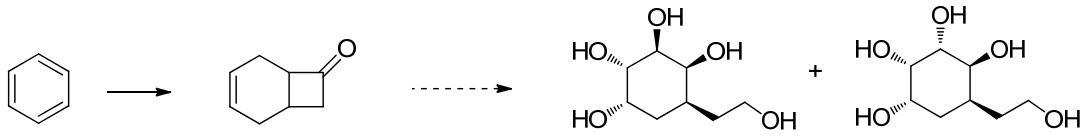
Carbapyranoses have potential biological activity as antibiotics, inhibitors of glucose stimulated insulin release and more recently as inhibitors of glycosidases [92]. So we also aimed to investigate biological activities of **184** and **185**.

CHAPTER 2

RESULTS AND DISCUSSION

In order to able to synthesize the target compounds (**184** and **185**) commercially available 1,4-cylohexadiene, which can also be synthesized from benzene, was used as a starting material.

Synthetic strategy of this study consists of two main key steps. First one is the dichloroketene addition to 1,4-cylohexadiene to introduce the alkyl chain. Second one is the singlet oxygen to introduce another functional hydroxyl group into the molecule. As a result, the following synthetic route was developed.

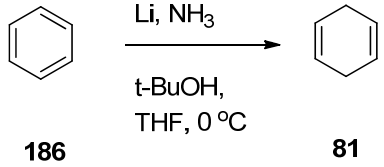


186 **187** **184** **185**

II.2.1 SYNTHESIS OF 5a-CARBA-6-DEOXY-α-DL-GALACTO-HEPTOPYRANOSE (184) AND 5a-CARBA-6-DEOXY-α-DL-GULO-HEPTOPYRANOSE (185)

II.2.1.1 Synthesis of 1,4-Cyclohexadiene (81), as the Starting Material

1, 4-Cyclohexadiene was synthesized from benzene by using Birch reduction. The reduction was applied to benzene with NH_3 and lithium in the presence of *tert*-butanol and THF at 0 °C [95].

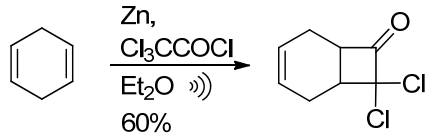


II.2.1.2 Dichloroketene Addition to 1,4-Cyclohexadiene

In this study, one of the dehydrohalogenation method in which trichloroacetylchloride is subjected to metallic zinc [98] was applied for the generation of dichloroketene *in situ*.

Ultrasound is used for the promotion of the reaction by applying high pressure in the unit cell of the substances during the dichloroketene addition [111].

The reaction was performed under ultrasound and etheral solution of trichloroacetyl chloride was added to an etheral solution of 1,4-cylohexadiene and zinc dust. During the reaction temperature did not exceed 15-20 ^{o}C. After the work up, 8,8-dichlorobicyclo[4.2.0]oct-3-en-7-one (**181**) was obtained in 60% yield [112].

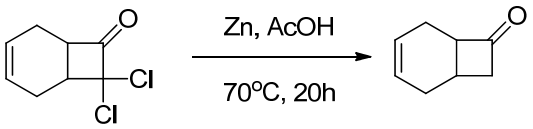


81 **181**

NMR data was good in agreement with the structure of **181** and data was also consistent with the literature data [112].

II.2.1.3 Dechlorination of the Ketene Cycloadduct: Reductive Elimination

After the compound 8,8-dichlorobicyclo[4.2.0]oct-3-en-7-one (**181**) was prepared the next step was reductive elimination of chlorine atoms in **181**. For this step, the metal dehalogenation method, Zn in the presence of acid, was used.



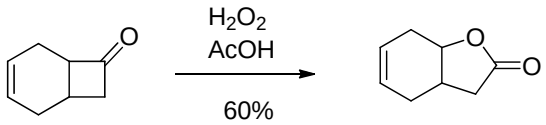
181 **187**

A solution of dichloroketene in acetic acid was added dropwise to stirring suspension of Zn in acetic acid at room temperature. After the addition was complete, the temperature was raised to and maintained at 70 ^{o}C for 20 hours. The reaction mixture was cooled to room temperature stirred for additional 8 hours, to yield ketone **187** in 57.5% yield.

The structure of **187** was assigned by the ^{1}H and ^{13}C NMR spectra and they are consistent with literature [112].

II.2.1.4 Oxidation of the Bicylic Ketone to Lactone (188): The Baeyer Villeger Oxidation

The Baeyer-Villeger oxidation reaction was applied to bicyclo[4.2.0]oct-3-en-7-one(**187**), for the purpose of introducing an oxygen atom to the cyclobutanone structure, to synthesize the lactone **188**. To prevent the epoxidation of the double bond in **187**, the Baeyer-Villeger oxidation was preferred with H_2O_2 instead of *m*-chloroperbenzoic acid.



187 **188**

A solution of H_2O_2 in acetic acid was added to a solution of bicyclo[4.2.0]oct-3-en-7-one (**187**) in methylene chloride and the resulting mixture was stirred for 6 hours at room temperature. The expected lactone (**188**) was formed as a colorless liquid in 60 % yield [112].

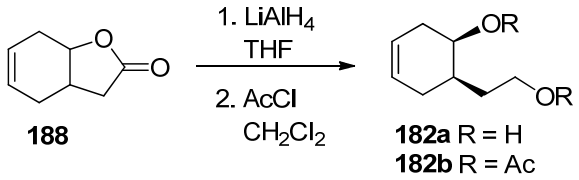
In ^{1}H-NMR spectra, there is a multiplet at 5.88-5.81 ppm arising from the olefinic protons. One of the protons next to the oxygen resonates at 4.74 ppm as doublet of doublets of doublets.

In ^{13}C-NMR spectrum, carbonyl carbon resonates at 177.0 ppm at the lower field of spectrum. The olefinic carbons give signals at 125.8 and 124.0 ppm. The tertiary carbon next to oxygen appears at 77.7 ppm.

II.2.1.5 Reduction of the Lactone and Acetylation of the Formed Diol

After the successful synthesis of lactone **188**, the next step was the reduction of the lactone to the corresponding diol by using the strong reducing agent, lithium

aluminium hydride. The reduction gave the diol **182a** in 90% yield, which was converted into diacetate **182b** with acetyl chloride almost in quantitative yield. Since the reduction reaction took place at the carbonyl group, the configuration of the substituents attached to the cyclohexene ring was retained.

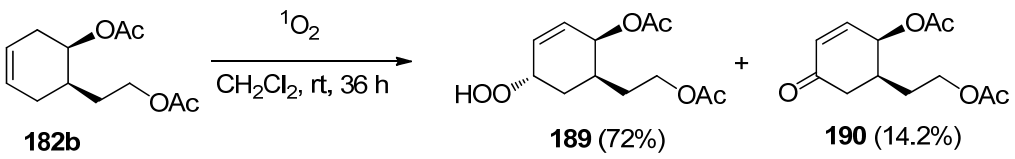


In ^{1}H-NMR spectrum of **182b**, the olefinic protons give an AB system. A part of the system resonates at 5.69 ppm as a broad doublet with coupling constant of J= 9.9 Hz. B part of the system resonates at 5.56 ppm and doublet of multiplet with coupling constant J= 9.9 Hz. Tertiary protons next to the acetates resonate as a multiplet between 5.10-5.14 ppm.

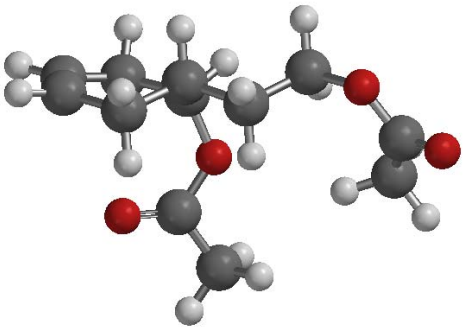
^{13}C-NMR spectrum of **182b** shows two different carbonyl carbon signals at 170.5, 170.3 ppm. The olefinic carbon resonances appear at 125.3 and 122.7 ppm. Two acetoxy carbons give signal at 69.9 and 61.9 ppm. Other signals are also consistent with the structure.

II.2.1.6 Reaction of Singlet Oxygen with Diacetate (182b)

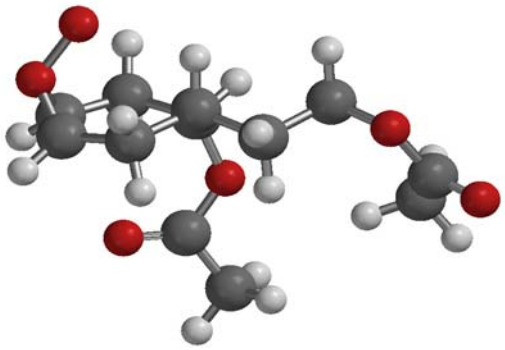
For introduction of an additional hydroxyl group into the molecule, cyclohexene derivative **182b** was submitted to singlet oxygen ene reaction. Tetraphenylporphyrin sensitized photooxygenation of **182b** in methylene chloride at room temperature produced two compounds **189** and **190** in a ratio of 5.1:1.



The structures of **189** and **190** were assigned by ^{1}H and ^{13}C NMR spectra. The compound **189** showed the presence of a hydroperoxide group whereas the other compound **190** did not. The most conspicuous features in the ^{1}H NMR spectrum of the hydroperoxide **189** were the presence of the double bond protons and incorporation of the hydroperoxide functionality in the molecule. Furthermore, ^{1}H-NMR analysis of the crude product suggested that the hydroperoxide was a single stereoisomer, although two stereoisomers would be formed. The exact stereochemistry of the hydroperoxide functionality in **189** was later confirmed by a single crystal X-ray analysis of the pentaacetate **194**. The regio- and stereoselective formation of the product **189** is remarkable. It is well established that singlet oxygen attacks first the C=C double bond to form perepoxide which would then rearrange to hydroperoxide [114]. Two faces of the double bond in **182b** is not symmetric, therefore the double bond can be attacked from both sides. The configuration of the hydroperoxide in **189** shows exclusively *anti*-attack. We assume that the repulsive interaction between the nonbonded electron pairs on acetyl oxygen and singlet oxygen is responsible for the exclusively *anti*-attack [115]. In order to understand the regioselective formation of **189** we performed a restricted hybrid HF-DFT SCF calculation using basis set, 6-31G(d) as implemented in the Spartan08V111 package program. First we determined the most stable conformation of **189** shown in Figure II.28.

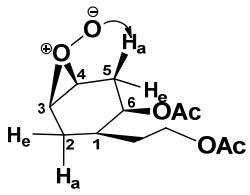


	C2-C3-C4-H5a	C5-C4-C3-H2e
Dihedral angle	58º	34º



	C2-C3-C4-H5a	C5-C4-C3-H2e
Dihedral angle	72.1º	42.3º

Figure II. 28 a) Optimized geometry of the most stable conformation of **182b** b) the formed perepoxide **191**.



191

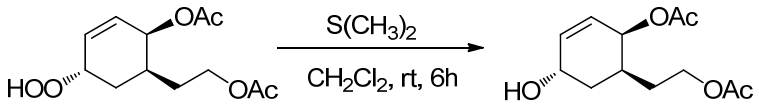
The initially formed perepoxide **191** can abstract two different hydrogen atoms. The product **189** shows that the pendant oxygen exclusively abstract the hydrogen atom connected to C-5 carbon atom. For a cycloalkene [116] it was proposed that there is a correlation between the orientation of the allylic hydrogen in the ground state and its reactivity. The allylic hydrogens at the axial position are more reactive, because the orbital overlap between oxygen and allylic hydrogens is optimum in such a conformation. Calculations clearly show that the H-5a has axial orientation (Dihedral angle C2-C3-C4-H5a = 72.1°) whereas the other allylic proton H-2e has equatorial

orientation (Figure II.28). Thus findings support the regio- and stereoselectivity of this ene-reaction.

The exact position of enone functionality in **190** was easily determined. This compound is a secondary product formed by decomposition of **189**. It is well known that the hydroperoxides can undergo decomposition in the presence of bases and acids to give hydroxy ketones [117].

II.2.1.7 Reduction of the Hydroperoxide and Conversion of the Formed Alcohol to Triacetate

There are various methods for reduction of the hydroperoxide to hydroxide. Triphenylphosphine, thiourea, sodium carbonate, sodium thiosulfate, dimethyl sulfide, and lithium aluminium hydride are used for this aim.



189 **192**

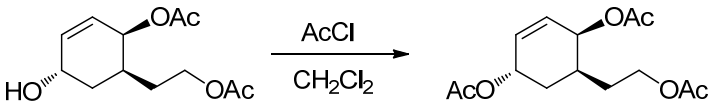
The selective reduction of the peroxide functionality in **189** was achieved by using dimethyl sulfide [118] as reductant, to give the desired hydroxy diacetate **192.**

Hydroperoxide **189** was dissolved in methylene chloride and given to solution of dimethyl sulfide in methylene chloride. This mixture was stirred at room temperature 6 hours. Evaporation of solvent and excess dimethyl sulfide gave pure **192** in 98% yields.

The structure of compound **192** was elucidated on the basis of ^{1}H- and ^{13}C-NMR spectra. In ^{1}H-NMR spectrum hydroperoxide hydrogen disappears and hydroxyl

group resonate at 2.58 ppm as a broad singlet. Other signals are consistent with the structure.

As the compound **192** was synthesized, next step was acetylation. The product **192** was acetylated with acetyl chloride to give triacetate **183**.



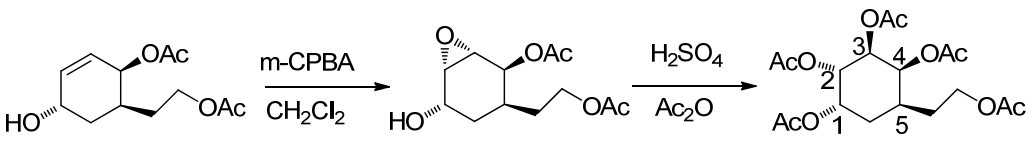
192 **183**

The resulting product was characterized on the basis of ^{1}H- and ^{13}C-NMR spectra. In ^{1}H-NMR, there is an AB-system at 6.10 and 6.00 ppm arising from the olefinic protons. The protons attached to the carbon bearing acetoxy group resonate between 5.30-5.27 ppm as multiplet. The other one resonates at 5.22 ppm as triplet. Methylene protons attached to the acetoxy group have AB-system between 4.16 and 4.13 ppm and both parts resonate as doublet of triplets.

The ^{13}C-NMR spectrum reveals carbonyl carbons at 171.0, 170.5, 170.5 ppm, the olefinic carbons at 129.8, 129.2 ppm, the acetoxy carbons at 67.3, 66.1, 62.3 ppm and the saturated carbons at 30.5, 29.5, 29.4, 21.1, 20.9, 20.9 ppm.

II.2.1.8 Epoxidation Reaction of 192 with *m*-CPBA

For further functionalization of double bond, allylic alcohol **192** was reacted with *m*-chloroperbenzoic acid.



192 **193** **194**

Only a single epoxide isomer **193** was obtained according to the ^{1}H-NMR spectrum of the crude product. It is well established that upon treatment of cyclic allylic alcohols with *m*-CPBA the formation of epoxides occurs on the same side as the hydroxyl group [119]. The fact, that a single isomer is formed during epoxidation reaction, strongly supports the participation of the hydroxyl group. Again, attempted purification of the crude product failed due to the partial epoxide-ring opening during column chromatography. Therefore, the crude product **193** was submitted to acid-catalyzed ring-opening followed by acetylation to give **194** in 70 % yield. The structure of **194** was found to be 5a-carba-6-deoxy-α-DL-galacto-heptopyranose based on the analysis of NMR spectral data (COSY, HSQC, HMBC). First, we assigned the acetoxyl proton resonances using the COSY spectrum and then the coupling constants between the acetoxyl protons were determined. The large coupling constant, J = 11 Hz between the axial protons H_2 and H_3 confirmed the *trans*-configuration at the new stereogenic centers. *Cis*-configuration of the adjacent protons H-1/H-2 and H-3/H-4 was supported by the extracted small coupling constants J_{12} = 2.7 and J_{34} = 2.9 Hz. Finally, the structure **194** was further confirmed by single crystal analysis.

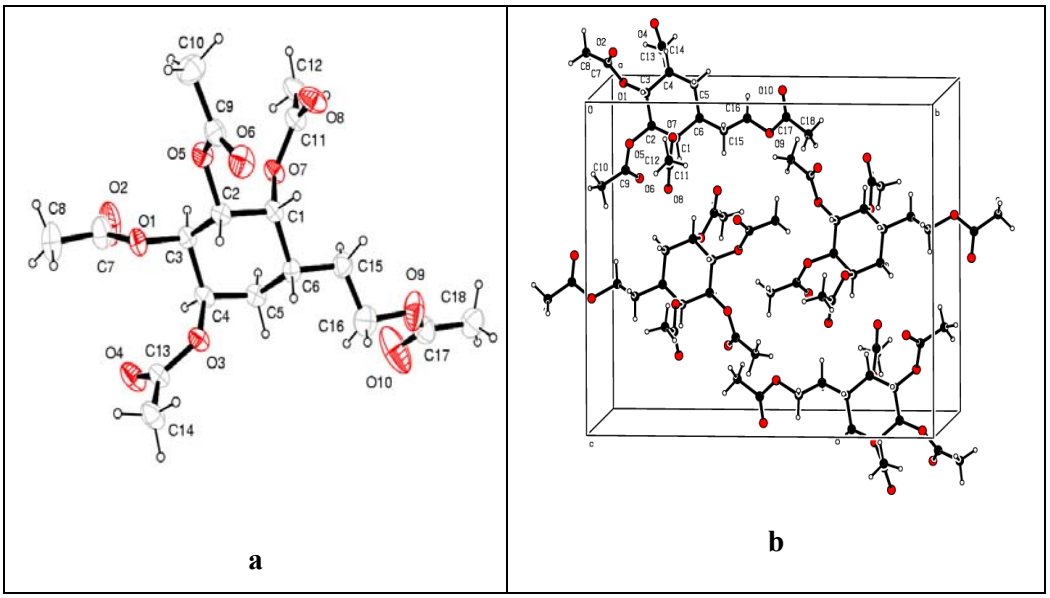
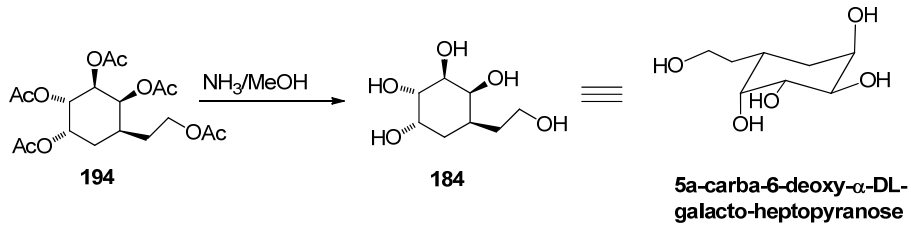


Figure II. 29 a) The molecular structure of compound **194** showing the atom numbering scheme, Thermal ellipsoids are drawn at the 40% probability level. b) A packing diagram for (**194**), viewed down the c-axis.

The results of this study confirmed unambiguously the proposed structure (Figure II.29a). The compound crystallizes in the monoclinic space group P21/c, with four molecules in the unit cell (Figure II.29b). Single crystal analysis, furthermore support the *trans*-ring opening reaction as well as the stereochemistry of the singlet oxygen ene-reaction.

II.2.1.9 Deacetylation of Pentaacetate 194

For the first target compound **184**, the final step was the conversion of acetoxy group into hydroxyl group by deacetylation reaction. The acetate groups were removed by treatment of pentaacetate **194** with ammonia in methanol to give 5a–carba-6-deoxy-α-DL-galacto-heptopyranose (**184**) in high yield.

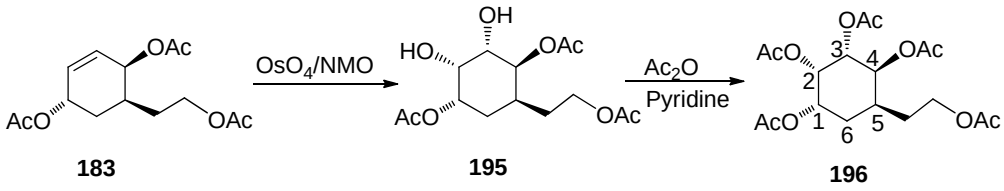


The structure of compound **184** was determined on the basis of ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrums there are six proton resonances at the lower field of the spectrum due to the inductive effect of oxygen. All of them give multiplet. In the higher parts of the spectrum there are five proton signals appearing as a multiplet.

In the ^{13}C-NMR spectrum there are eight lines. The alkoxy carbon atoms give signals at 72.2, 71.8, 71.3, 69.4 and 59.2 ppm. Other saturated carbons give signals at 34.1, 31.2 and 30.7 ppm.

II.2.1.10 *Cis* Hydroxylation of the Triacetate 183 with Osmium Tetraoxide

In order to synthesize second target molecule heptopyranose derivative **185** the triacetate **183** is an ideal compound. For that reason the double bond in the triacetate **183** was *cis*-hydroxylated with OsO_4-NMO system to give **195**. After acetylation of the reaction mixture, only a single isomer **196** was isolated in 67% yield.

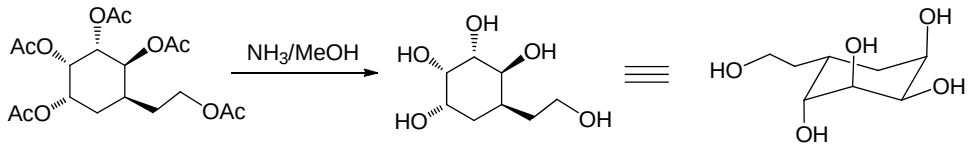


Two faces of the double bond in **183** are not symmetric and the double bond can be attacked both sides. We assume that OsO_4 approaches the double bond from the less congested side to form the diol **195**. It is likely that the nonbonded interactions between the substituents and OsO_4 are responsible for the exclusively *anti*-addition. The configuration of the pentaacetate **196** was confirmed by ^{1}H NMR spectroscopy.

The most conspicuous feature in the ^{1}H NMR spectrum is doublet of triplets arising from the alkoxy proton H-1 resonance at 5.24 ppm. The measured coupling constants J = 4.5 and 3.7 Hz clearly indicated that the H-1 proton has equatorial conformation and the acetate group attached to the carbon atom C-1 has an axial conformation. Otherwise, an axial proton attached to C1 would give a large coupling with the axial proton attached to the carbon atom C-6. Furthermore, the adjacent proton H-2 resonates as a broad triplet with a coupling constant of $J_{1,2} = J_{2,3}$ = 3.7 Hz. This small coupling indicates that the acetoxyl group attached to C-2 carbon atom has axial conformation. The fact that the acetate groups attached to C1 and C-2 carbon atoms have *cis*-configuration, strongly support that the OsO_4 approaches the molecule **183** from the *anti*-side of the double bond.

II.2.1.11 Deacetylation of Pentaacetate 196

After characterization of compound **196**, the acetate groups were hydrolyzed to obtain pure pentol, 5a-carba-6-deoxy-α-DL-galacto-heptopyranose (**185**). The hydrolysis was performed with NH_3 gas in methanol.



196 **185** **5a-carba-6-deoxy-α-DL-galacto-heptopyranose**

Compound **185** was characterized on the basis ^{1}H- and ^{13}C-NMR spectra. Tertiary protons next to hydroxyl groups resonate between 3.96 and 3.74 ppm as multiplet. Methylene protons next to the hydroxyl group resonate between 3.1-3.51 ppm as multiplet. In the higher parts of spectrum, there is a multiplet between 1.71 and 1.59 ppm, quintet at 1.48 ppm, and doublet of triplet at 1.41 ppm.

In ^{13}C-NMR spectrum there are five carbons resonances at the lower field of the spectrum. In the higher parts of the spectrum there are three carbon signals.

II.2.1.12 The Inhibitory Activity of 5a-Carba-6-Deoxy-α-DL-Galacto-Heptopyranose (184) and 5a-Carba-6-Deoxy-α-DL-Gulo-Heptopyranose (185) Against α-Glucosidase and α-Amylase

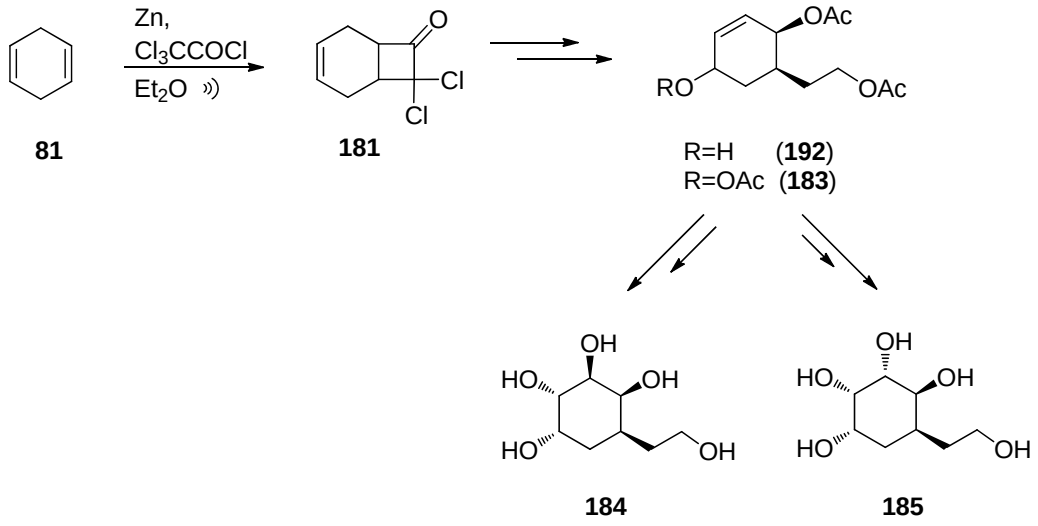
α-Glucosidase inhibition was performed with compounds **184** and **185**. Compound **184** shows inhibition for α-glucosidase, inhibition rate measured as 43.64%. Compound **185** did not show any inhibition for α-glucosidase [121].

Both compounds (**184** and **185**) did not show inhibition for α-amylase but both compounds increased activation of α-amylase. α-Amylase inhibition activity was carried out between 10-1000 μM range. Absorbance of 10-50 μM compounds same as control reactions whereas both **184** and **185** containing mixtures were exhibited higher absorbances than that of control meaning that the α-amylase activity increased with increasing concentrations of these compounds [121].

CHAPTER 3

CONCLUSION

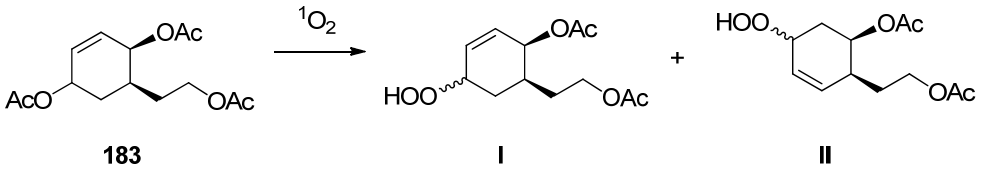
In this study, we had two target molecules, **183** and **185**. Whole synthetic schema includes available reagent and feasible steps.



81 **181** **184** **185**

Synthesis of the heptopyranose derivatives **184** and **185** were achieved successfully. We began to this study with the commercially available 1,4-cyclohexadiene. Following keten addition step was the key in order to insert an alkyl group and hydroxide to the cyclohexane. The addition of dichloroketen followed by reductive elimination and Baeyer Villeger oxidation gave bicyclic lactone. Reduction of the lactone followed by acetylation gave diacetate **182b** with *cis*-configuration

Introduction of additional oxygen functionality into the molecule was achieved by singlet oxygen ene reaction.



183 **I** **II**

We actually expected isomers of **I** and **II** formation in the ene reaction of **183**. Detailed examination of reaction mixture show that the product **II** was not formed. Double resonance experiments show that CH=CH double bond was located between the carbon atoms bearing acetoxy and hydroperoxyde group.

Triacetate **183** was obtained by reduction of hydroperoxide and then acetylation reaction. The triacetate is the key compound for the synthesis of target compounds heptopyranose derivatives.

The double bond in the **192** was functionalized by epoxidation followed by ring-opening reaction to give pentaacetate **194**. The structure of **194** was found using the NMR spectral data (COSY, HSQC, HMBC). The structure **194** was confirmed by single crystal analysis.

Other method for the functionalized the double bond in **183** was made by directs *cis*-hydroxylation using OsO_4-NMO. After acetylation reaction gave pentaacetate **196**. The structure of **196** supports the result that OsO_4 approaches the molecule **183** from the anti side of the double bond.

Deactylation of **194** and **196** with ammonia give target compounds 5a–carba-6-deoxy-α-DL-galacto-heptopyranose (**184**) 5a-carba-6-deoxy-α-DL-gulo-heptopyranose (**185**).

The inhibitory activity of **184** and **185** were screened against α-Glucosidase and α-Amylase. Carboheptopyranose derivative **184** show α-Glocosidase inhibition the other derivative **185** did not show inhibition. Both carbopyranoses derivatives **184** and **185** did not show inhibition for α-Amylase. But both compounds increased activation of α-Amylase.

As a conclusion, we performed a very useful and versatile synthetic way from cylohexadiene to carboheptapyranoseses **184** and **185**.

EXPERIMENTAL

PART I

I.1 GENERAL CONSIDERATIONS

Melting points are uncorrected. Infrared spectra were obtained from a solution in 0.1 mm cells or KBr pellets on a regular instrument. The ^{1}H- and ^{13}C-NMR spectra were recorded on 400 (100) MHz spectrometers. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates. All of the substances reported in this paper are in their racemic form.

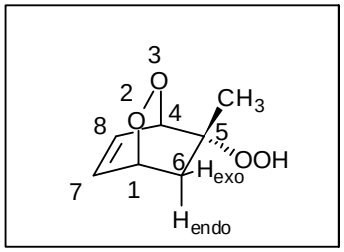
I.2. PHOTOOXYGENATION OF 1-METHYLCYCLOHEXA-1,4-DIENE (13)

To a stirred solution of 1-methylcyclohexa-1,4,-diene (**13**) [53a,95] (5.0 g, 53.14 mmol) in 500 mL of CH_2Cl_2 was added 85 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through solution, in which the mixture was stirred for 24 h at room temperature. The ^{1}H-NMR spectrum of the mixture showed that the conversion was approximately 80% and the products **19**, **20**, **21** and **22** were formed in a ratio of 3:1:2.5:2, respectively (6.5 g). Evaporation of the solvent (30°C, 20 mmHg) and chromatography of the residue on a silica gel column (200 g) eluting with hexane/ether (3:2) gave as the first fraction hydroperoxide **22,** the second fraction a mixture of the endoperoxide **19** and **21,** and as the third fraction **20**, **19** and **21** were

separated by crystallization from hexane/ether mixture. Pure samples were obtained by repeated column chromatography.

I.2.1 (1*R*(*S*),4*S*(*R*),5*R*(*S*))-5-methyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (19).

19: Colorless solid, mp 108-109 ^{o}C from ether/hexane (28%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (b.s, 1H, -OOH), 6.68 (quasi t, 2H, H_7 and H_8), 4.70 (m, 2H, H_1 and H_4), 2.10 (dd, A-part of AB system, $^{2}J_{gem}$ = 14.1 Hz, $^{3}J_{1,6endo}$ = 3.7 Hz, 1H, H_{6endo}), 1.70 (s, 3H, -CH_3), 1.42 (dd, B-part of AB system, $^{2}J_{gem}$ = 14.1 Hz, $^{3}J_{1,6exo}$ = 1.9 Hz, 1H, H_{6exo}). (*Exo*/*endo* referred to the double bond)

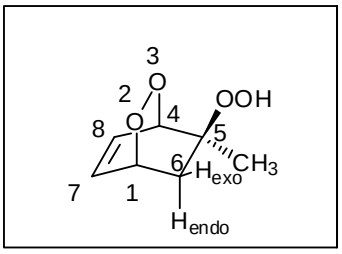
^{13}C-NMR (100 MHz, $CDCl_3$) δ 131.8, 130.7, 78.6, 75.7, 71.0, 36.5, 21.8.

IR (KBr, cm^{-1}) 3339, 2979, 2935, 1368, 1105, 925, 707.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37; Found: C, 53.01; H, 6.51.

I.2.2 (1*R*(*S*),4*S*(*R*),5*S*(*R*))-5-methyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (20).

20: Colorless liquid, purity 95% (9%);



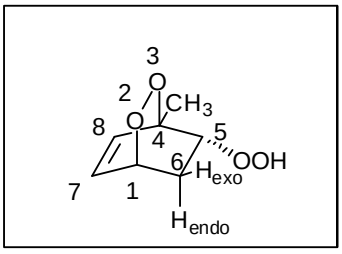
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (b.s, 1H, -OOH), 6.60 (m, 2H, H_7 and H_8), 4.75(m, 1H, H_4), 4.64 (m, 1H, H_1), 2.1 (dd, A-part of AB-system, $^2J_{gem}$ = 14.2 Hz, $^3J_{1,6endo}$ = 4.1 Hz, 1H, H_{6endo}), 1.45 (dd, B-part of AB system, $^2J_{gem}$ = 14.1 Hz, $^3J_{1,6exo}$ = 1.8 Hz, 1H, H_{6exo}). 1.25 (s, 3H, CH_3). (*Exo*/*endo* referred to the double bond)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.0, 130.9, 80.2, 74.9, 70.9, 35.2, 23.3.

IR (**Anal. Calcd** for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.90; H, 6.49.

I.2.3 (1*R*(*S*),4*S*(*R*),5*R*(*S*))-4-methyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (21) :

21: Viscous liquid (25%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.1 (b.s, 1H), 6.66 (dd, A-part of AB system, $J_{7,8}$ = 8.3 Hz, $J_{7,6}$ = 6.1 Hz, 1H, H_7), 6.21 (br.d, B-Part of AB-system, $J_{7,8}$ = 8.3 Hz, 1H, H_8), 4.65 (m, 1H, H_1), 4.32 (dd, $J_{5,6endo}$= 8.1 Hz, $J_{5,6exo}$= 2.3 Hz, 1H_5), 2.55 (ddd, A-part of AB-system, $^2J_{gem}$= 14.8, $J_{5,6endo}$= 8.1 and $J_{1,6endo}$= 3.7 Hz, 1H, H_{6endo}), 1.50 (s, 3H, -CH_3), 1.41 (dt, B-part of AB-system, $^2J_{gem}$= 14.8, $J_{5,6exo}$= $J_{1,6exo}$= 2.2 Hz, 1H, H_{6exo}). (*Exo*/*endo* referred to the double bond)

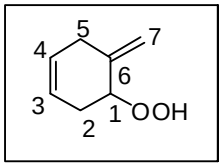
^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.6, 133.1, 80.9, 76.0, 70.9, 31.6, 19.8.

IR (KBr, cm^{-1}) 3403, 2979, 2940, 1432, 1381, 1105.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.45; H, 6.56.

I.2.4 (1*R*(S))-6-methylenecyclohex-3-en-1-yl hydroperoxide (22).

22: Colorless liquid, (20%), purity 95%;



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, -OOH), 5.62 (d, AB-system, $J_{3,4}$= 9.71, 1H, H_3 or H_4), 5.54 (br. d, B-part of AB-system, J= 9.93, 1H, H_3 or H_4), 5.04 (s, 1H, C=CH_2), 5.0 (s, 1H, C=CH_2), 4.60 (t, $J_{1,2a}$= $J_{1,2}$ = 4.6, 1H, H_1), 2.96-2.75 (br. AB-system, $J_{5a,5e}$ = 21.0 Hz, 2H, H_5), 2.5-2.42 (m, AB- system, $J_{2a,2}$= 20.1 Hz, 1H, H_2).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.6, 128.5, 126.6, 111.3, 83.3, 30.8, 21.6.

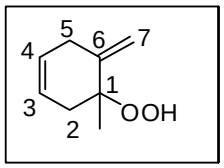
IR (KBr, cm^{-1}) 3340, 2936, 1598, 1452, 1400, 1178, 1076.

I.3. PHOTOOXYGENATION OF 1,2-DIMETHYLCYCLOHEXA-1,4-DIENE (14)

To a stirred solution of 1,2-dimethylcyclohexa-1,4-diene [53c] (5.0 g, 46.25 mmol) in 500 mL of CH_2Cl_2 was added 75 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through solution, in which the mixture was stirred for 24 h at room temperature. The ^{1}HNMR spectrum of the mixture showed that the conversion was about 60% and the products **33** and **34/35** were formed in a ratio of 4:1 (4.06 g). Evaporation of the solvent (30°C, 20 mmHg) and chromatography of the residue on a silica gel column (200 g) eluting with hexane/ether (3:2) gave as the first fraction hydroperoxide **33,** and as the second fraction endoperoxide **34** and as the third fraction **35**. Pure samples were obtained by repeated column chromatography.

I.3.1 1*R*(*S*)-1-Methyl-6-methylenecyclohex-3-en-1-yl hydroperoxide (33).

33: Viscous liquid (48%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, -OOH), 5.69 (br. d, A-part of AB-system, J = 9.8 Hz, 1H, C_3 or C_4), 5.45 (br. d, B-part of AB-system, J = 9.8 Hz, 1H, H_3 or H_4), 5.06 (s, 1H, -C=CH_2), 5.03 (s, 1H, -C=CH_2), 3.08 (br. d, A-part of AB-system, J = 18.4 Hz, 1H, H_5), 2.81 (br. d, B-part of AB-system, J = 18.4 Hz, 1H, $H_{5'}$), 2.44 (br. d, A-part of AB-system, J = 21. 3 Hz, 1H, H_2), 2.23 (br. d, B-part of AB-system, J = 21,3 Hz, 1H, $H_{2'}$), 1.49 (s, 3H, -CH_3).

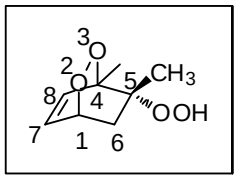
^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.9, 126.0, 123.2, 110.1, 82.9, 37.4, 33.1, 21.5.

IR (KBr, cm^{-1}) 3400, 3089, 3030, 2979, 2934, 1423,1370, 912,744.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.01; H, 8.44.

I.3.2 (1R(S),4S(R),5R(S))-4,5-dimethyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (34).

34: Viscous liquid (9%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.5 (s, 1H, -OOH), 6.59 (dd, A-part of AB-system, $J_{7,8}$ = 8.3 Hz, $J_{1,7}$ = 6.1 Hz, 1H, H_7), 6.25 (dd, B-part of AB-system, $J_{7,8}$ = 8.31 Hz and $J_{1,8}$ = 1,4 Hz, 1H, H_8), 4.59 (m, 1H, H_1), 2.08 (dd, A-part of AB-system, $J_{6,6'}$ = 14,1 Hz and $J_{1,6}$ = 3,6 Hz, 1H, H_6), 1.74 (dd, B-part of AB-system, $J_{6,6'}$ = 14.1 and $J_{1,6}$ = 2.1 Hz, 1H, $H_{6'}$), 1.52 (s, 3H, -CH_3), 1.37 (s, 3H, -CH_3).

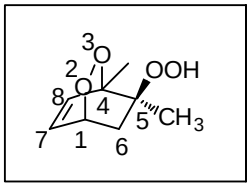
^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.8, 131.8, 81.7, 78.3, 71.4, 37.8, 18.9, 16.6.

IR (KBr, cm^{-1}) 3421, 2988, 1452, 1380, 1124, 1082, 1059, 835, 748.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C,55.35; H, 7.01.

I.3.3 (1*R*(*S*),4*S*(*R*),5*S*(*R*))-4,5-dimethyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (35).

35: Viscous liquid (3%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H, -OOH), 6.70 (dd, A-part of AB-system, J_{78} = 8.2 Hz, $J_{1,7}$ = 5.8 Hz, 1H, H_7), 6.25 (br. d, B-part of AB-system, J_{78} = 8.2 Hz,b1H, H_8), 4.76 (m, 1H, H_1), 2.97 (br.d, A-part of AB-system, $J_{66'}$ = 14,2 Hz, 1H, H_6), 1.50 (d, B-part of AB-system, $J_{66'}$ = 14.2 Hz, 1H, $H_{6'}$), 1.45 (s, 3H, -CH_3), 1.19 (s, 3H, -CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.1, 133.3, 82.9, 81.1, 71.9, 33.1, 24.1, 15.0.

IR (KBr, cm^{-1}) 3392, 2984, 2940, 1371, 913, 745.

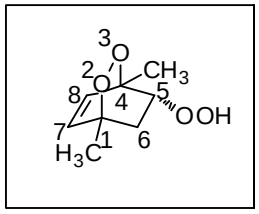
Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.51; H, 7.23.

I.4 PHOTOOXYGENATION OF 1,4-DIMETHYLCYCLOHEXA-1,4-DIENE (15)

To a stirred solution of 1,4-dimethylcyclohexa-1,4-diene **15** [53a] (5.0 g, 46.25 mmol) in 500 mL of CH_2Cl_2 was added 75 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through solution, in which the mixture was stirred for 24 h at room temperature. The ^{1}H-NMR spectrum of the mixture showed that the conversion was 70% and the products **40, 41, 42,** and **43** were formed were in a ratio of 1.5:1.0:0.3:0.2, respectively (5.60 g). Evaporation of the solvent (30 ^{o}C, 20 mmHg) and chromatography of the residue on a silica gel column (200 g) eluting with hexane/ether (3:2) gave as the first fraction hydroperoxide **40,** the second fraction the endoperoxide **41,** the third fraction **43** and as the last fraction **42**.

I.4.1 (1*R*(*S*),4*S*(*R*),5*R*(*S*))-1,4-dimethyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (40).

40: Colorless solid, mp 105-106 ^{o}C from ether/hexane (35%);



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.1 (br. s, 1H, -OOH), 6.49 (d, A-part of AB-system, $J_{8,7}$ = 8.3, 1H, H_7 or H_8), 6.26 (d, B-part of AB-system, $J_{8,7}$ = 8.3, 1H, H_8 or H_7) 4.42 (dd, $J_{5,6}$ = 8.1 Hz and $J_{5,6'}$ = 2.5 Hz, 1H, H_5), 2.40 (dd, A-part of AB-system, J_{gem} = 14.0 and $J_{5,6}$ = 8.1 Hz, 1H, H_6), 1.59 (s, 3H, CH_3), 1.58 (dd, B-part of AB-system, J_{gem} = 14.0 and $J_{5,6'}$ = 2.5 Hz, 1H), 1.42 (s, 3H, CH_3).

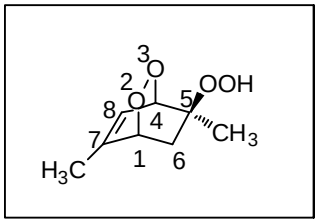
^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.8, 132.4, 82.0, 75.5, 74.8, 37.3, 20.3, 18.9.

IR (KBr, cm^{-1}) 3429, 2988, 2940, 2916, 1452, 1308, 1124, 1082, 1059, 835, 748.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.42; H, 7.08.

I.4.2 (1*R*(*S*),4*S*(*R*),5*R*(*S*))-5,7-Dimethyl-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (41).

41: Viscous liquid, (20%);



^{1}H-NMR (400 MHz, $CDCl_3$, acetone-d_6) δ 8,71 (s, 1H, -OOH), 6.25 (dq, $J_{4,8}$ = 6.7 Hz and $^4J_{8,Me}$ = 1,6 Hz, 1H, H_8), 4.72 (dd, $J_{4,8}$ = 6.7 Hz and $J_{1,4}$ = 0.8 Hz, 1H, H_4), 4.45 (br. dd, $J_{1,6}$ = 4.0 Hz and $J_{1,6'}$ = 1,7 Hz, 1H, H_1), 2.10 (dd, A-part of AB-system, J_{gem} = 14.1 Hz and $J_{1,6}$ = 4.0 Hz, 1H, H_6), 1.93 (d, $J_{1.6}$ = 1,6 Hz, 3H, -CH_3), 1.49 (dd, B-part of AB-system, J_{gem} = 14.1 Hz and $J_{1,6'}$ = 1.7 Hz, 1H, $H_{6'}$), 1.27 (s, 3H, -CH_3).

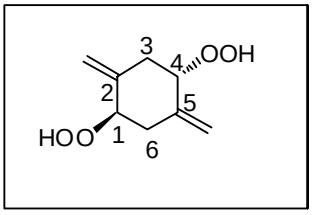
^{13}C-NMR (100 MHz, acetone-d_6) δ 138.3, 119.0, 76.2, 71.2, 71.0, 19.1, 19.0, 14.1.

IR (KBr, cm^{-1}) 3384, 2981, 2935, 1323, 1124, 913, 744.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.47; H, 6.79.

I.4.3 4-Hydroperoxy-2,5-dimethylenecyclohexyl hydroperoxide (43).

43: Colorles solid, mp 123-124 ^oC from ether/hexane (7%);



^{1}H-NMR (400 MHz, $CDCl_3$, acetone-d_6) 9.35 (s, 2H, -OOH), 5.04 (s, 2H, -C=CH_2), 4.99 (s, 2H, -C=CH_2), 4.4 (t, $J_{1,2}$ = $J_{1,2'}$ = 3.1 Hz, 2H, H_1 and H_4), 2.61 (dd, A-part

AB-system, J_{gem} = 14.6 Hz and $J_{1,2}$ = 3.1 Hz, 2H, H_3 and H_6 or ($H_{3'}$ and $H_{6'}$)), 2.15 (dd, B-part AB-system, J_{gem} = 14.6 Hz and $J_{1,2'}$ = 3.1 Hz, 2H, $H_{3'}$ and $H_{6'}$ (or H_3 and H_6)).

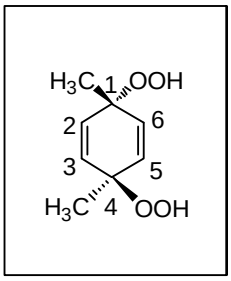
^{13}C-NMR (100 MHz, acetone-d_6) δ 136.1, 111.7, 80.3, 30.3.

IR (KBr, cm^{-1}) 3342, 3028, 2990, 1404, 1061, 847, 787.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.50; H, 6.70.

I.4.4 4-Hydroperoxy-1,4-dimethylcyclohexa-2,5-dien-1-yl hydroperoxide (42).

42: Colorless solid, mp 147-148 ^{o}C from ether/hexane (5%);



^{1}H-NMR (400 MHz, acetone-d_6, $CDCI_3$) δ 9.9 (s, 2H, -OOH), 5.89 (s, 4H, -CH=CH-), 1.24 (s, 6H, $-CH_3$).

^{13}C-NMR (100 MHz, acetone-d_6) δ 133.9, 77.9, 23.8.

IR (KBr, cm^{-1}) 3331, 2930, 1429, 1057, 995, 931, 744.

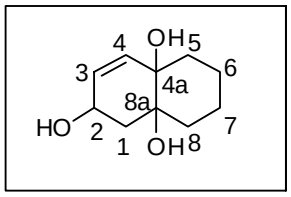
Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.17; H, 6.81

I.5 PHOTOOXYGENATION OF 1,2,3,4,5,8-HEXAHYDRONAPHTHALENE AND REDUCTION REACTION WITH THIOUREA

To a stirred solution of 1,2,3,4,5,8-hexahydronaphthalene **16** [95] (5.0 g, 37.25 mmol) in 500 mL of CH_2Cl_2 was added 75 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was

passed through solution, in which the mixture was stirred for 5 h at room temperature. The ^{1}H-NMR spectrum of the mixture showed that the conversion was 60% and the products **47** and **48** were formed were in a ratio of 1:0.1. After evaporation of the solvent (30 °C, 20 mmHg), reaction mixture was dissolved in methanol and 6.1 g (40 mmols) thiourea was added. The reaction mixture was stirred magnetically for 2 hours at room temperature. The mixture was filtered and solvent was removed by rotary evaporator. $CHCI_3$ (100 ml) and water (100 ml) were added this mixture. Water phase wash with $CHCI_3$ (3x50ml). Removal of the water under reduced pressure gave triol **51** (3.7 g, 78%) as colorless liquid. Compound **52** was not isolated.

51: Viscous liquid (78%);



^{1}H-NMR (400 MHz, D_2O) δ 5.65 (d, A-part of AB system, 1H, J= 10 Hz), 5.5 (d, B-part of AB system, 1H, J=10 Hz), 1.25-1.83 (m, 10 H)

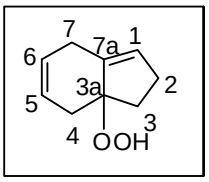
^{13}C-NMR (100 MHz, D_2O) δ 132.79, 132.24, 73.70, 69.25, 65.59, 38.77, 32.49, 30.86, 19.59, 19.09.

I.6 PHOTOOXYGENATION OF 2,3,4,7-TETRAHYDRO-*1H*-INDENE (17)

To a stirred solution of 2,3,4,7-tetrahydro-*1H*-indene (**17**) [53] (2 g, 16.64 mmol) in 250 mL of CH_2Cl_2 was added 40 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through solution, in which the mixture was stirred for 6 h at room temperature. The ^{1}H-NMR spectrum of the mixture showed that the conversion was approximately 80% and the products **54** and **55** were formed in a ratio of 1:0.1. Evaporation of the solvent (30°C, 20 mmHg) and chromatography of the residue on a basic aluminium

oxide column (100 g) eluting with hexane/EtOAc (3:2) gave hydroperoxide **54**. Endoperoxide **55** was not isolated because of the not stable at room temperature. Compound **55** characterized only according to the crude ^{1}H-NMR spectra.

54: Viscous liquid;



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, -OOH), 5.68 (t, 1H, J=1.6 Hz), 5.65-5.58 (m, A-part of AB system, 1H), 5.49-5.55 (m, B-part of AB system, 1H), 2.84-1.58 (m, 8H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.6, 129.0, 125.1, 124.1, 93.4, 35.6, 33.3, 29.8, 26.2.

PART II

II.1 GENERAL CONSIDERATIONS

Nuclear Magnetic Resonance (^{1}H, ^{13}C and 2D) spectra were recorded on a Bruker Instruments Avance Series-Spectrocpin DPX, Ultra Sield (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 ($CDCl_3$), deuterowater (D_2O) 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, dd:doublet of doublet, ddd:doublet of doublet of doublet.

Infrared spectra were obtained from solution in 0.1 mm cells or KBr pellets on an FT-IR Bruker Vertex 70 instrument. Elemental analyses were carried out on a Leco-932 model CHNS analyzer.

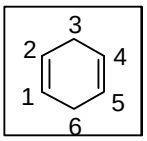
Column chromatographic separations were performed by using Fluka Silicagel 60 with 0.063-0.170 mm particle size. The relative proportions of solvents refer to volume:volume ratio. Thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Fuluka.

All the solvent purifications were done as stated in the literature [120].

II.2 THE REACTION PATH FOR THE SYNTHESIS OF 5a-CARBA-6-DEOXY-α-DL-GALACTO-HEPTOPYRANOSE (184) AND 5a-CARBA-6-DEOXY-α-DL-GULO-HEPTOPYRANOSE (185)

II.2.1 Synthesis of 1,4-cyclohexadiene (81)

In a three necked flask 27.3 g dry benzene, 72 g *tert*-buthanol, 120 mL THF was added and the medium was saturated with NH_3 gas at 0 ^oC. 7.35 g lithium was added to the reaction mixture with very small portions in 5 minutes. The reaction was refluxed for one night. Then small portions of ice wad added until there was no more lithium left. The mixture was washed with saturated NH_4Cl solution and water. After washing, it was dried over $CaCl_2$ and filtered. 17.75 g diene **81** was obtained.



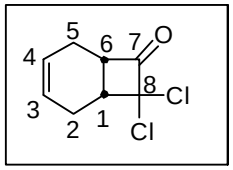
^{1}H NMR (400 MHz, $CDCl_3$) 5.71 (s, 4H), 2.69 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 124.5, 25.7.

II. 2.2 The Synthesis of 8,8-Dichlorobicyclo[4.2.0]oct-3-en-7-one (181)

A 500 mL two-neck round bottom flask was equipped with a nitrogen inlet and pressure-regulated dropping funnel. A solution of 1,4-cylohexadiene (5.0 g, 62.5 mmol) and Zn powder (8.15 g, 125 mmol) in 100 mL dry ether was immersed into an ultrasound bath where sonication was most to acquire maximum agitation. The water bath was cooled to 15 °C by adding pieces of ice periodically. A solution of trichloroacetyl chloride (22.7 g, 125 mmol) in 100 mL dry ether was added drop wise within 2 h under sonication. The reaction was continued to stir an additional hour while maintaining the water bath temperature at 15 °C. When the reaction was complete, the solids were removed by simple filtration. Then filtrate was extracted first with H_2O (2 x 100 mL) and then with saturated $NaHCO_3$ (2 x 100 mL). The organic solution was dried over Na_2SO_4 and solvent was evaporated. The resulting

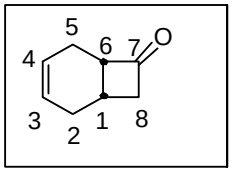
mixture was purified by vacuum distillation at reduced pressure (7 mm-Hg). The first fraction (collected at 76 °C) was identified as the desired addition product **181**. Yellow liquid (7.164 g, 60 %) [112].



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.81 (m, 2H), 4.03 (ddd, *J* = 10.6, 7.6 and 2.4 Hz, 1H), 3.32 (dt, *J* = 7.6 and 1.8 Hz, 1H), 2.64-2.08 (m, 4H).

II.2.3 The Synthesis of Bicyclo[4.2.0]oct-3-en-7-one (187)

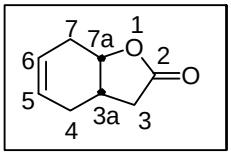
A solution of dichloroketone **181** (7.5 g, 39.3 mmol) in 25 mL of acetic acid was added dropwise to a vigorously stirring suspension of Zn (5.0 g, 76.9 mmol) in 50 mL of glacial acetic acid at room temperature, After addition was complete, the temperature was raised to and maintained at 70 °C for 20 h. The reaction mixture was cooled to room temperature stirred for additional 8 h. To dissolve the formed Zn salts water was added.The resulting mixture was treated with diethyl ether, and the zinc residue was filtered. The ethereal layer was washed three times with water and a saturated solution of sodium carbonate to remove acetic acid and dried over MgSO4. The solvent was removed under vacuum. Chromatographyof the residue on 30 g of silica gel eluting with ethyl acetate/hexane (1:9) afforded ketone **187** (2.75 g, 0.07 mol, 57.5%) as a colorless liquid [112].



^{1}H-NMR (400 MHz, $CDCI_3$) δ 5.90-5.81 (m, 2H), 3.48-3.41 (m, 1H), 3.22 (ddd, *J* =17.8, 9.2, and 3.8 Hz, 1H), 2.83-2.77 (m, 1H), 2.55 (ddd, *J* = 17.8, 5.1, 3.1, and Hz,1H), 2.42-2.01 (m, 4H).

II.2.4 The Synthesis of 3a,4,7,7a-Tetrahydro-1-benzofuran-2(3*H*)-one (188)

A solution of H_2O_2 (4.65 g, 30%) in 2 mL acetic acid was added to a solution of bicyclo[4.2.0]oct-3-en-7-one (**187**) (5.0 g, 40.98 mmol) in CH_2CI_2 (25 mL) and the resulting mixture was stirred for 6 h at room temperature. After completion of the reaction, the mixture was washed with water, saturated $NaHCO_3$ and then with brine. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give the known lacton **188** [112] as colorless liquid (3.4 g, 60%).



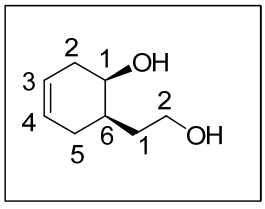
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.81 (m, 2H), 4.74 (ddd, *J* = 11.7, 6.0 and 3.9 Hz, 1H) 2.74-1.91 (m, 7H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.0, 125.8, 124.0, 77.7, 36.8, 32.1, 27.4, 26.2.

IR ($CHCl_3$, cm^{-1}): 3034, 2917, 2838, 1772, 1236, 1016.

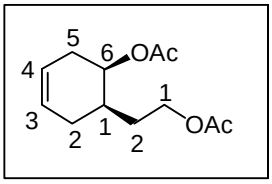
II.2.5 The Synthesis of 2-[rel-(1*S*,6*R*)-6-(acetyloxy)cyclohex-3-en-1-yl]ethyl acetate 182b

To a magnetically stirred slurry of $LiAlH_4$ (1.0 g, 26.3 mmol) in ether (180 mL) was added a solution of lactone **188** (3.0 g, 22 mmol) in ether (90 mL) dropwise at 0 ºC over a period of 3 h. The resulting mixture was then stirred at room temperature for additional 3 h. The reaction mixture was cooled to 0 ºC and cold water was added to destroy the unreacted $LiAlH_4$. The formed aluminium salt was filtered through silica gel (5 g). The organic layer was dried ($MgSO_4$). Removel of the solvent gave the diol **182a** (2.8 g, 89.7%).



^{1}H-NMR (400 MHz, $CDCI_3$) δ 5.68-5.55 (m, 2H), 4.02-3.98 (m, 1H), 3.78-3.61 (m, 2H), 3.34-3.2 (bs, 2OH), 2.33-1.46 (m, 2H).

The above formed crude product **182a** was submitted without further purification to acetylation. To a magnetically stirred solution of diol **182a** (2.8 g, 19.7 mmol) in 100 mL of CH_2Cl_2 was added acetylchloride (8.25 g, 105 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 ºC and then water (100 mL) was added. Organic phase was separated, washed with water, saturated $NaHCO_3$ and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave diacetate **182b** (4.28, 96%) as colorless liquid.



^{1}H-NMR (400 MHz, $CDCI_3$) δ 5.69 (bd, A-part of AB-system, *J* = 9.9 Hz, 1H), 5.56 (dm, B-part of AB-system, *J* = 9.9 Hz, 1H), 5.10-5.14 (m, 1H), 4.15 (dt, A-part of AB-system, *J* = 11.1 and 6.5 Hz, 1H),4.12 (dt, B-part of AB-system, *J* = 11.1, and 6.6 Hz, 1H), 2.39-2.10 (m, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.05-1.51 (m, 4H).

^{13}C-NMR (100 MHz, $CDCI_3$, ppm) δ 170.5, 170.3, 125.3, 122.7, 69.9, 61.9, 32.6, 29.6, 29.5, 27.1, 20.7, 20.4.

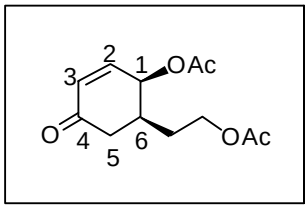
IR (KBr, cm^{-1}) 3029, 2933, 2856, 1739, 1443, 1374, 1247, 1042, 992, 846, 674, 673.

Anal. Calcd for. $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.70; H, 8.24.

II.2.6 Photooxygenation of diacetate 182b

A stirred solution of diacetate **182b** (1.0 g, 4.4 mmol) and 50 mg of tetraphenylporphyrine (TPP) in 150 ml of CH_2CI_2 was added 20 mg of tetraphenylporphyrin (TPP). The resulting mixture was irradiated with a projection lamp (500 W) while oxygen was passed through solution. The reaction mixture was irradiated for 36 h at room temperature. Removal of solvent (30 ^{o}C, 20 mmHg) and ^{1}H-NMR spectral analysis of oily residue revealed that the conversion was approximately 95% and two products **189** and **190** were formed in a ratio of 5.1:1. Chromatography of the residue on silica gel (100 g) eluting with hexane/ethylacetate

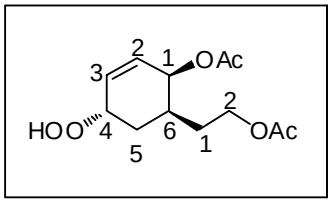
(70:30) gave as the first fraction ***rel*-(1S,6*R*)-6-[2-(acetyloxy)ethyl]-4-oxocyclohex-2-en-1-yl acetate (190)**: Pale yellow liquid, (142 mg, 14.2%)**.**



^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 6.91 (dd, A-part of AB-system, *J* =10.0 Hz, 4.7 Hz, 1H), 6.02 (d, B-part of AB-system, *J* =10.0 Hz, 1H), 5.42 (t, *J* = 3.9 Hz, 1H), 4.13-4.03 (m, 2H), 2.57 (dd, A-part of AB-system, *J* = 16.8 and 10.9 Hz, 1H), 2.49 bd, B-part of AB-system, *J* = 16.8 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 3H), 1.96 (dq, *J* = 14.4 and 6.6 Hz, 1H), 148 (dq, *J* = 14.4 and 6.4 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.6, 170.7, 170.1, 144.1, 131.6, 67.4, 61.6, 39.4, 35.1, 29.1, 20.7, 20.6.

As the second fraction, the major product ***rel*-(1S,6*S*)-*6*-[2-(acetyloxy)ethyl]-4-hydroperoxycyclohex-2-en-1-yl acetate (189)** was isolated as viscous liquid (776 mg, 72%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H, -OOH), 6.13 (dd, A-part of AB-system, *J* = 9.9, 5.2 Hz, 1H), 5.99 (dd, B-part of AB-system, *J* =9.9, 4.7 Hz, 1H), 5.15 (t, *J* =4.3 Hz, 1H), 4.55-4.51 (m, 2H), 4.0 (dt, *J* = *J* = 11.3 and 5.2 Hz, 1H), 2.75 (bd, J=14.3 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.0-2.08 (m, 1H), 1.79 (ddt, A-part of AB-system, *J* = 14.5, 9.2 and 4.5 Hz, 1H), 1.66 (ddd, *J* = 14.4, 12.8 and 3.9 Hz, 1H), 1.57 (ddt, *J* = 14.4, 9.4 and 4.8 Hz, 1H,).

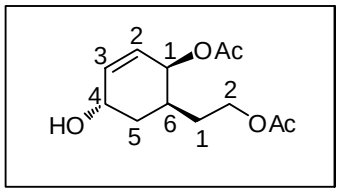
^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.1, 170.6, 131.6, 127.9, 77.0, 68.1, 61.6, 30.4, 29.2, 26.0, 21.0, 20.09.

IR (KBr, cm-1) 3403, 3029, 2960, 2933, 1736, 1439, 1381, 1254, 1035, 985, 765.

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.71; H, 7.08.

II.2.7 The Synthesis of *rel*-(1*S*,4*S*,6*S*)-6-[2-(Acetyloxy)ethyl]-4-hydroxycyclohex-2-en-1-yl acetate (192)

A solution of hydroperoxide **189** (500 mg, 1.94 mmol) in 25 ml of CH_2CI_2 was added to magnetically stirred solution of Me_2S (309 mg, 5 mmol) in 25 ml of CH_2CI_2 at room temperature. After the addition was complete (ca. 10 min), the mixture was stirred for 6h and the 25 mL of water was added. The organic phase was separataed and dried over Na_2SO_4. Evaporation of solvent in vacuo and gave pure **192** (460 mg, 98%) as pale yellow liquid).



^{1}H-NMR (400 MHz, $CDCI_3$) δ 6.02 (dd, A-part of AB-system, *J* = 9.9, 4.2 Hz, 1H), 5.96 (dd, B-part of AB-system, *J* = 9.9, 4.6 Hz, 1H), 5.18 (t, *J* = 4.2 Hz, 1H), 4.25 (q, *J* = 3.9 Hz, 1H), 4.17-4.11 (m, 2H), 2.58 (bs, -OH, 1H,), 2.25-2.17 (m, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.88 (dt, *J* = 13.9 and 6.5 Hz, 1H), 1.82-1.71 (m, 2H), 1.59 (ddt, *J* = 13.9, 7.1 and 6.5 Hz, 1H).

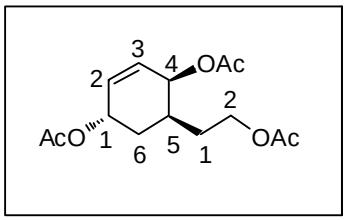
^{13}C-NMR (100 MHz, $CDCI_3$) δ 171.2, 170.7, 133.1, 127.5, 67.9, 63.3, 62.4, 32.6, 29.8, 29.5, 20.9 (2C).

IR (KBr, cm^{-1}) 3391, 3037, 29.41, 2255, 1736, 1439, 1374, 1247, 1027, 977.

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.23; H, 7.39.

II.2.8 The Synthesis of *rel*-(1*S*,4*S*,5*S*)-4-(acetyloxy)-5-[2-(acetyloxy)ethyl]cyclohex-2-en-1-yl acetate 183

To a magnetically stirred solution of alcohol **192** (500 mg, 2.06 mmol) in 25 mL CH_2CI_2 was added acethyl chlorid (400 mg, 5.1 mmol). The reaction mixture was stirred at room temperature for 6 h and then cooled to 0 ^oC. After addition of 100 mL of water, the water phase was extracted with ether (3x30 mL). The combined organic extracts was washed with $NaHCO_3$ solution (2x10 ml) and water (2x5 ml) and then dried over Na_2SO_4. Removal of the solvent under reduced pressure gave triacetate **183** (550 mg, 94%) as colorless liquid).



^{1}H-NMR (400 MHz, $CDCI_3$, ppm): δ 6.10 (dd, A-part of AB-system, *J* = 9.9, 4.9 Hz, 1H), 6.00 (dd, B-part of AB-system, *J* = 9.9, 4.6 Hz,1H), 5.30-5.27 (m, 1H), 5.22 (t, *J* = 4.3 Hz, 1H), 4.16 (dt, A-part of AB-system, *J* = 11.1 and 6.8 Hz, 1H), 4.13 (dt, B-part of AB-system, *J* = 11.1 and 6.5 Hz, 1H), 2.19-2.13 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.95-1.88 (m, 1H), 1.84-1.75 (m, 1H), 1.62 (dq *J* = 11.9 and 5.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCI_3$) δ 171.0, 170.5, 170.5, 129.8, 129.2, 67.3, 66.1, 62.3, 30.5, 29.5, 29.4, 21.1, 20.9, 20.9.

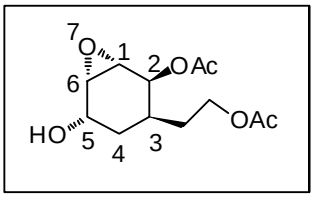
IR (KBr, cm-1): 3029, 2952, 1739, 1447, 1374, 1247, 1027, 985, 919.

Anal. Calcd for. $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.19; H, 7.34.

II.2.9 Epoxidation of 192 with *m*-CPBA

To a stirred solution of **192** (200 mg, 0.83 mmol) in 8 mL of CH_2CI_2 was added *m*-CPBA 60% (310 mg, 1.66 mmol). The reaction mixture was stirred overnight, the

solid matter was removed by filtration, and the filtrate was washed with saturated $NaHCO_3$ (2x50 mL), and water (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave epoxide **193** (148 mg, 69%, yellow liquid).



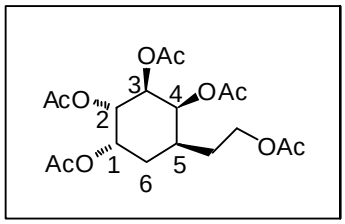
^{1}H-NMR (400 MHz, $CDCI_3$) δ 5.34 (bs, 1H), 4.2 (bs, 1H), 4.16-4.05 (m, 4H), 3.45-3.38 (m, 2H), 2.17 (s, 3H), 2.04 (s, 3H), 2.08-2.02 (m, 4H).

^{13}C-NMR (100 MHz, $CDCI_3$) 171.0, 170.3, 68.9, 63.1, 62.0, 54.7, 54.2, 31.5, 30.9, 26.6, 20.9, 20.8.

IR (KBr, cm^{-1}) 3469, 2938, 1734, 1438, 1359, 1250, 1047.

II.2.10 The Synthesis of 1,2,3,4,7-Penta-*O*-acetyl-6-deoxy-5a–carba-α-DL-galacto-heptopyranose 194

To stirred solution of **193** (200 mg, 0.77 mmol) in 2 mL of Ac_2O was added catalytic amount of concentrated H_2SO_4. The reaction mixture was stirred for 3 h at room temperature. The mixture was cooled to 0 ^oC and 20 mL of water was added and then stirred for 1 h. The reaction mixture was extracted with ether (3x50 ml). The combined organic extracts were washed with $NaHCO_3$ solution (15 mL) and water (15 mL) then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the pentaacetate **194** (220 mg, 82.1%) as white crystalline solid. Mp 116.7-117.5 ^oC from Et_2O-Hexane).



^{1}H-NMR (400 MHz, $CDCI_3$) δ 5.48-5.46 (m, 2H), 5.22 (dd, A-part of AB-system, J = 10.9 and 2.7 Hz, 1H), 5.18 (dd, B-part of AB-system, J = 10.9 and 2.9 Hz, 1H), 4.09-4.05 (m, 2H), 2.24-2.13 (m, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.98

(3H), 1.8-1.77 (m, 2H), 1.64 (dq, *J* = 14.2 and 7.0 Hz, 1H), 1.51 (dq, *J* = 14.2, 6.8 Hz, 1H).

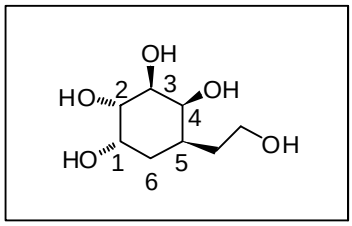
^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.1, 170.8, 170.2 (2C), 170.0, 71.0, 69.9, 69.3, 68.6, 61.8, 30.9, 30.0, 29.8, 21.0, 20.9, 20.7(3C).

IR (KBr, cm^{-1}): 2974, 2948, 1751, 1455, 1391, 1249, 1172, 1069, 1017, 940, 863.

Anal. Calcd for. $C_{18}H_{26}O_{10}$: C, 53.73; H, 6.51. Found: C, 53.50; H, 6.67.

II.2.11 The Synthesis of 5a–Carba-6-deoxy-α-DL-galacto-heptopyranose 184

Pentaacetate **194** (100 mg, 0.25 mmol) was dissolved in 20 mL of absolute methanol. While dry NH_3 gas was passed through solution, the mixture was stirred for 4 h at room temperature. Evaporation of the solvent and formed acetamide gave the pentol **184** (46 mg) in a yield of 96% (viscous liquid).



^{1}H-NMR (400 MHz, D_2O) δ 4.21-4.14 (m, 1H), 4.07-4.06 (m, 1H), 3.95-3.91 (m 1H), 3.73-3.61 (m, 3H), 2.17-1.6 (m, 5H).

^{13}C-NMR (100 MHz, D_2O) δ 72.2, 71.8, 71.3, 69.4, 59.2, 34.1, 31.2, 30.7.

IR (KBr, cm^{-1}): 3391, 2953, 1734, 1688, 1494.

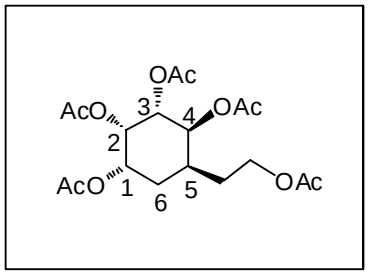
Anal. Calcd for. $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.40; H, 8.57.

HRMS Spectrum: Found: 215.0895; Calculated: 215.0887

II.2.12 The Synthesis of 1,2,3,4,7-penta-*O*-acetyl-6-deoxy-5a–carba-α-gulo-heptopyranose 196

To a stirred solution of triacetate **183** (171.6 mg, 0 .61 mmol) in 2 mL of acetone/H_2O (1:1) were added NMO (91 mg, 0.77 mmol) and OsO_4 (2.0 mg, 0.008 mmol) at 0 ^oC. The resulting mixture was stirred vigorously under nitrogen at room temperature for 24 h. During the stirring the reaction mixture became homogeneous. Sodium hydrogensulfite (0.01 g) and 0.5 g of florisil slurried in 2 mL of water were added, the slurry was stirred for 10 min and the mixture was filtered through a pad of 0.5 g of celite in a 50 mL sintered-glass funnel. The celite cake was washed with acetone (3x10 mL). The filtrate was neutralized to pH 7 with H_2SO_4. The organic layer was removed in vacuo. The pH of the resulting aqueous solution was adjusted to pH 5 with sulfuric acid, and the diol was separated from N-methylmorpholine hydrosulfate by extraction with ethyl acetate (4x20 mL). The combined ethyl acetate extracts were washed with 5 mL of 25% NaCI solution and three times with water and dried (Na_2SO_4). Evaporation of solvent gave **195**, which was submitted to acetylation.

To a magnetically stirred solution of diol **195** (120 mg, 0.38 mmol) in 1 mL of pyridine was added Ac_2O (0.16 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 ^oC and 25 mL of 1 N HCI solution added, and the mixture was extracted with ether (3x25 mL). The combined organic extracts were washed with $NaHCO_3$ solution (25 mL) and water (10 mL) and then dried (Na_2SO_4). Removing of the solvent under reduced pressure and crystallization from ethyl acetate/n-hexane gave **196** (112.6 mg, 66.6%, as colorless solid, mp 138.0-138.7 ^oC).



^{1}H-NMR (400 MHz, $CDCI_3$, ppm): 5.24 (t, *J* = 3.0 Hz 1H), 5.14 (t, *J* = 3.4 Hz, 1H), 5.08 (t, *J* = 3.7 Hz, 1H) 5.02 (dt *J* = 4.5 and 3.0 Hz), 4.05 (dt, A-part of AB-system, *J* = 12.6 and 6.2 Hz, 1H), 4.01) dt, B-part of AB-system, *J* = 12.6 and 6.4 Hz), 2.20

(s, 6H), 2.0 (s, 3H), 2.11-2.05 (m, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.91-1.83 (m, 1H), 1.78-1.49 (m, 3H).

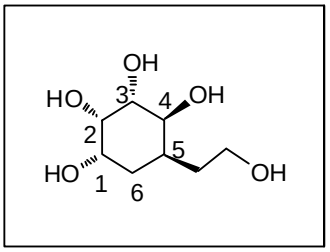
^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 170.1, 169.8, 169.5, 169.4, 69.7, 68.9, 68.7, 68.4, 62.0, 31.2, 29.8, 26.8, 21.0, 20.9, 20.8, 20.7, 20.6.

IR (KBr, cm^{-1}) 2960, 1747, 1439, 1374, 1239, 1042, 611.

Anal. Calcd for $C_8H_{26}O_{10}$: C, 53.73; H, 6.51. Found: C, 53.48; H, 6.34.

II.2.13 The Synthesis of 5a-carba-6-deoxy-α-L-talo-heptopyranose 185

Pentaacetate **196** (80 mg, 0.2 mmol) was dissolved in 25 mL absolute methanol. While dry NH_3 gas was passed through solution, the mixture was stirred for 4 days at room temperature. When the reaction was complete the solvent was removed by rotary evaporator to give the pentol **185** in quantitative yield. (Viscous liquid).



^{1}H-NMR (400 MHz, D_2O) δ 3.96-3.91 (m, 1H), 3.81-3.78 (m, 1H), 3.74-3.70 (m, 2H), 3.1-3.51 (m, 2H), 1.88-1.80 (m, 1H), 1.71-1.59 (2H), 1.48 (qui, *J* = 7.2 Hz, 1H), 1.41 (dt, *J* = 14.4 and 4.0 Hz, 1H).

^{13}C-NMR (100 MHz, D_2O, ppm): 73.4, 72.9, 69.3, 68.4, 59.4, 33.1, 31.2, 26.9.

IR (KBr, cm-1): 3354, 2932, 1665, 1561**.**

HRMS Spectrum: Found: 215.0895; Calculated: 215.0889

II.2.14 α-Glucosidase Inhibition Test

α-Glucosidase inhibition assay was performed for **184** and **185** compounds. 50 µL of sample solution (10-1000 µM) and 100 µL of 100 mM phosphate buffer pH 6.9 containing α-glucosidase solution (1.0 U/mL) were incubated at 25^{o}C for 10 min. After incubation of enzyme and compounds, 50 µL 5-mM p-nitrophenyl-α-D-glucopyranoside was added to mixture and incubated at 25^{o}C for 5 min. Absorbance of the liberated *p*-nitrophenol was measured at 405 nm. 50 µL Phosphate buffer was used instead of compound for control [67].

II.2.15 α- Amylase Inhibition Test

500 µL of compound **184** and **185** mixed with 500 µL of 20 Mm phosphate buffer pH 6.9 containing 6.7 mM sodium chloride containing α-amylase solution (0.5 mg/mL) were incubated at 25^{o}C for 10 min. After preincubation, 500 µL of 1% starch solution in 20 mM phosphate buffer pH 6.9 with 6.7 mM sodium chloride was added to each tube The reaction mixtures were then incubated at 25^{o}C for 10 min. The reaction was stopped with 1.0 mL of dinitrosalicylic acid reagent (1% 3,5 dinitro salysilic acid in 0.5M sodium hydroxide/2 M potassium hydroxide, 30% $NaKC_4H_4O_6$). The test tubes were then incubated at 85 ^{o}C water bath for 5 min, then cooled to room temperature. The reaction mixture was then diluted after adding 10-mL distilled water; the absorbance was measured at 540 nm. 500 µL Phosphate buffer was used instead of compound for control [67].

II.2.16 Crystallograpy

For the crystal structure determination, the single-crystal of the compound **194** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer

(equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo K_α radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega$=5˚ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software. The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97. H atoms were positioned geometrically and refined using a riding model**.** The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **194**: $C_{18}H_{26}O_{10}$, crystal system, space group: monoclinic, *P*21/c; unit cell dimensions: *a*= 7.9834(5), *b*=18.1820(8), *c*=14.4307(8)Å, α=90 β=95.053(3), γ=90 ; volume: 2086.5(2) $Å^3$; *Z*=4; calculated density: 1.28 mg/m^3; absorption coefficient: 0.105 mm^{-1}; F(000): 856; θ range for data collection 2.2 –30.4˚; refinement method: full-matrix least-square on F^2; data/parameters: 2257/258; goodness-of-fit on F^2: 1.055; final R indices [$I>2\sigma(I)$]: R_1= 0.089, wR_2=0.142; R indices (all data): R_1=0.140, wR_2=0.240; largest diff. peak and hole: 0.842 and -0.269 e $Å^{-3}$; Crystallographic data were deposited in CSD under CCDC registration number 768082.

REFERENCES

[1] Kishali, N. H., Şahin, E., Kara, Y., *Org. Lett.*, **2006**, *8*, 1791-1793.

[2] Yardımcı, Ş. D., Kaya, N., Balci, M., *Tetrahedron*, **2006**, *62*, 10633-10638.

[3] Balci, M., *Chem. Rev*., **1981**, 81, *91*-108.

[4] Stratakis, M., Orfanopoulos, M., *Tetrahedron*, **2000**, *56*, 1595-1615.

[5] Kaya, N., Ph.D. Thesis, METU, Ankara, '*The Synthesis of Hydroxymethyl Containing Cyclitol Derivatives*', **2009**.

[6] Ertaş, M., Ms Thesis, METU, Ankara, '*A Novel Synthesis of Polyhydroxycyclohexane Derivatives*', **2000**.

[7] Wasserman, H. H., Murray, R. W., *Organic Chemistry*, Vol: 70, Academic Press, New York, **1979**.

[8] (a) Arnold, S. J., Kubo, M., Ogryzlo, E. A., *Adv. Chem. Ser*., **1968**, *77*, 133-142. (b) Merkel, P. D., Kearnes, D. R., *J. Am. Chem. Soc*., **1972**, *94*, 1029-1030.

[9] Wasserman, H. W., Ives, J. L., *Tetrahedron*, **1981**, *37*, 1825-1852.

[10] Gorman, A. A., *Chem. Soc. Rev*., **1981**, *10*, 205-231.

[11] Ranby, B., Rabek, J. F., *Photodegradation, Photo oxidation and Photostabilization of Polymers*, John Wiley and Sons Ltd, **1975**.

[12] Adam, W., *Chem. Ztg.*, **1975**, *3*, 142-155.

[13] Akbulut, N., Menzek, A., Balcı, M., *Doğa- Turk. J. Chem.*, **1991**, *15*, 232-245.

[14] Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*, New York, John Wiley and Sons Ltd, **1976**.

[15] Wasserman, A., *Diels-Alder Reactions*, Elsevier, Amsterdam, **1965**.

[16] Paquette, L. A., Carr, R. V. C., Arnold, E., Clardy, J., *J. Org. Chem*., **1980**, *45*, 4907-4913.

[17] Chen, Y., Wu, L., Zhang, L., Tung, C., *J. Org. Chem*., **2005**, *70*, 4676-4681.

[18] Linker, T., Fröhlich, L., *J. Am. Chem. Soc*., **1995**, *117*, 2694-2697.

[19] Clennan, E.L., *Tetrahedron*, **2000**, *56*, 9151-9176.

[20] Grdina, M. B., Orfanopoulos, M., Stephenson, L.M., *J. Am. Chem. Soc*., **1979**, *101*, 3111-3112.

[21] Stratakis, M., Orfanopoulos, M., Chen, J., Foote, C. S., *Tetrahedron Lett.,* **1996**, *37*, 4105-4108.

[22] Orfanopoulos, M., Foote, C. S., *J. Am. Chem. Soc*., **1988**, *110*, 6583-6584.

[23] Orfanopoulos, M., Stephenson, L.M., *J. Am. Chem. Soc*., **1980**, *102*, 1417-1418.

[24] Schaap, A.P., Recher, S.G., Faler, G.R., Villasenor, S.R., *J. Am. Chem. Soc*., **1983**, *105*, 1691-1693.

[25] Stratakis, M., Orfanopoulos, M., Foote, C. S., *Tetrahedron Lett.,* 1991, *32*, 863-866.

[26] Clennan, E.L., Chen, M., Xu, G., *Tetrahedron Lett.,* **1999**, *37*, 2911-2914.

[27] Inagaki, S., Fukui, K., *J. Am. Chem. Soc*., **1975**, *97*, 7480-7484.

[28] Clennan, E.L., Nagraba, K., *J. Am. Chem. Soc*., **1983**, *105*, 5932-5933.

[29] Saito, I., Matsugo, S., Matsuura, T., *J. Am. Chem. Soc*., **1979**, *101*, 7332-7338.

[30] Asveld, E. W. H., Kellogg, R.M., *J. Am. Chem. Soc*., **1980**, *102*, 3644-3646.

[31] Wilson, S.L., Schuster, G. B., *J. Am. Chem. Soc*., **1983**, *105*, 679-681.

[32] Clennan, E. L., *Tetrahedron*, **1991**, *47*, 1343-1382.

[33] Schulte-Elte, K. H., Muller, B. L., Rautesrauch, V., *Helv. Chim. Acta*., **1978**, *61*, 2777-2783.

[34] Stephenson, L. M., *Tetrahedron Lett.,* 1980, *21*, 1005-1008.

[35] Schulte-Elte, K. H., Rautesrauch, V., *J. Am. Chem. Soc*., **1980**, *102*, 1738-1740.

[36] Vassilikogiannakis, G., Stratakis, M., Orfanopoulos, M., *J. Org. Chem*., **1998**, *63*, 6390-6393.

[37] Foote, C. S., *Chem. Res*., **1968**, *1*, 104-109.

[38] Hurst, J. R., McDonald, J. D., Schuster, G. B., *J. Am. Chem. Soc*., **1982**, *104*, 2065-2067.

[39] Hurst, J. R., Wilson, S. L., Schuster, G. B., *Tetrahedron*, **1985**, *41*, 2191-2195.

[40] Stratakis, M., Orfanopoulos, M., *Tetrahedron Lett.,* **1995**, *36*, 4875-4879.

[41] Orfanopoulos, M., Stratakis, M., Elemens, Y., *Tetrahedron Lett.,* **1989**, *30*, 4755-4758.

[42] Houk, K. N., Williams, P. A., Mitchell, P. A., Yamaguchi, K., *J. Am. Chem. Soc*., **1981**, *103*, 949-950.

[43] Stratakis, M., Orfanopoulos, M., *Tetrahedron*, **2000**, *56*, 1595-1615.

[44] Orfanopoulos, M., Smonou, I., Foote, C. S., *J. Am. Chem. Soc*., **1990**, *112*, 3607-3610.

[45] Foote, C. S., Denny, R. W., *J. Am. Chem. Soc*., **1971**, *93*, 5168-5171.

[46] Gollnick, K., Griesbeck, A., *Tetrahedron Lett.,* **1984**, *25*, 725-728.

[47] Manring, L. E., Foote, C. S., *J. Am. Chem. Soc*., **1983**, *105*, 4710-4717.

[48] Rautenstrauch, V., Thommen, W., Schulte-Elte, K. H*., Helv. Chim. Acta*, **1986**, *69*, 1638-1642.

[49] Asveld, E. W. H., Kellogg, R. M., *J. Am. Chem. Soc*., **1980**, *102*, 3644-3646.

[50] Matsumoto, M., Suganuma, H., *Chem. Commun*., **1994**, *21*, 2449-2450.

[51] Harding, L. B., Goddard, W. A., *J. Am. Chem. Soc*., **1980**, *102*, 439-449.

[52] Stratakis, M., Orfanopoulos, M., Chen, J. S., Foote, C. S., *Tetrahedron Lett.,* **1996**, *37*, 4105-4108.

[53] (a) Banwell, M. G., Halton, B., *Austr. J. Chem.,* **1980**, *33*, 2673-2683. (b) Huckel, W., Worffel, U., *Chem. Ber.,* **1955**, *88***,** 338-345.

[54] (a) Clennan, E. L., Chen, X., Koola, J. J., *J. Am. Chem. Soc.*, **1990**, *112*, 5193-5199. (b) Orfanopoulus, M., Stratakis, M., Elemes, Y. *J., Am. Chem. Soc.,* **1990**, *112,* 6417-6418. (c) Adam, W., Bottke, N., Krebs, O., Lykakis, I., Orfanopoulus, M., Stratakis, M., *J. Am. Chem. Soc.,* **2002**, *124,* 14403-14409 (d) H.E. Ensley. In: A.L. Baumstark, Editor, *Reactions of Singlet Oxygen with*

α,β-Unsaturated Carbonyl Compounds **2**, JAI, Greenwich, Connecticut (**1990**), 181–202.

[55] Mehta, G., Mohal, N., Lakshminath, S., *Tetrahedron Lett.,* **2000**, *41*, 3505-3508.

[56] Doddi, R. V., Kumar, A., Vankar, Y. D., *Tetrahedron*, **2008**, *64*, 9117-9122.

[57] Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem*., **1990**, *48*, 21-90.

[58] Patti, A., Sanfilippo, C., Plattelli, M., Nicolosi, G., *Tetrahedron Asymmetry*, **1996**, *7*, 2665-2670.

[59] Mereyala, H. B., Gaddam, B. R., J. *Chem. Soc. Perkin Trans I*, **1994**, *1*, 2187-2190.

[60] Balcı, M., Seçen, H., Sütbeyaz, Y., *Tetrahedron*, **1990**, *46*, 3715-3742.

[61] Honzumi, M., Hiroya, K., Taniguchi, T., Ogasawara, K., *Chem. Commun*., **1999**, *19*, 1985-1986.

[62] Kwon, Y., Chung, S., *Org. Lett.,* **2001**, *3*, 3013-3016.

[63] Salamcı, E., Seçen, H., Sütbeyaz, Y., Balcı, M., *J. Org. Chem.,* **1997**, *62*, 2453-2457.

[64] McCasland, G. E., Furuta,S., Durham, L. J., *J. Org. Chem.,* **1968**, *33*, 4220-4227.

[65] Shih, T., Lin, Y., Kuo, W., *Tetrahedron*, **2005,** *61*, 1919-11924.

[66] Kara, Y., Balcı, M., *Tetrahedron*, **2003**, *59*, 2063-2066.

[67] Kwon, Y., Lee, C., Chung, S., *J. Org. Chem*., **2002**, *67*, 3327-3338.

[68] Sureshan, K. M., Shashidhar, M. S., Praveen, T., Das, T., *Chem. Rev*., **2003**, *103*, 4477-4503.

[69] Chung, S., Kwon, Y., *Bioorg. Med. Chem. Lett.,* **1999**, *9*, 2135-2140.

[70] Baran, A., Balcı, M., *J. Org. Chem.,* **2009**, *74*, 88-95.

[71] Ley, S., *Pure Appl. Chem*., **1990**, *62*, 2031-2034.

[72] Murugan, A., Yadav, A., Gurjar, M. K., *Tetrahedron Lett.,* **2005**, *46*, 6235-6238.

[73] Arjona, O., Gomez, A. M., Lopez, J. C., Plumet, J., *Chem. Rev*., **2007**, *107*, *1919*-2036.

[74] Baran, A., Günel, A., Balcı, M., *J. Org. Chem.,* **2008**, *73*, 4370-4375.

[75] Suami, T., Ogawa, S., Toyokuni, T., *Chem. Lett.,* **1983**, *23*, 611-612.

[76] Suami, T., *Pure Appl. Chem*., **1987**, *59*, 1509-1520.

[77] Tatsuta, K., *Pure Appl. Chem*., **1996**, *68*, 1341-1346.

[78] Mehta, G., Lakshminath, S., Talukdar, P., *Tetrahedron Lett.,* **2002**, *43*, 335-338.

[79] Adinolfi, M.; Corsaro, M. M.; De Castro, C., Evidente, A., Lanzetta, R., Molinaro, A.; Parrilli, M. *Carbohydr. Res.,* **1996**, *284*, 111-118.

[80] Bleriot, Y., Untersteller, E., Fritz, B., Sinay, P., *Chem. Eur. J*., **2002**, *8*, 240-246.

[81] Atsumi, S., Linuma, H., Nosaka, C., Umezawa, K., *J. Antibiot*., **1990**, *43*, 1579-1585.

[82] Tatsuta, K., Niwata, Y., Umezawa, K., Toshima, K., Nakata, M. J., *J. Antibiot*., **1991**, *44*, 456-458.

[83] Lim, C., Baek, D. J., Kim, D., Youn, S. W., Kim, S., *Org. Lett*., **2009**, *11*, 2583-2586.

[84] Miller, T. W., Arison, B. H., Albers-Schonberg, G., *Biotechnol. Bioeng*. **1973**, *15*, 1075-1080.

[85] Kitaoka, M. Ogawa, S., Taniguchi, H., *Carbohydr. Res.,* **1993**, *247*, 355-359.

[86] a) Nioh, T., Mizushima, S., *J. Gen. Appl. Microbiol*., **1974**, *20*, 373-383.

b) Uyeda, M., Ikeda, A., Machimoto, T., Shibata, M., *Agric. Biol. Chem*., **1985**, *49*, 3485-3491.

[87] Parry, R. J., Burns, M. R., Skae, P. N., Hoyt, J. C., Pal, B., *Bioorg. Med. Chem*., **1996**, *4*, 1077-1088.

[88] McCasland, G. E., Furuta,S., Durham, L. J., *J. Org. Chem.,* **1966**, *31*, 1516-1521.

[89] a) Smissman, E. E., Suh, J. T., Oxman, M.; Daniels, R. *J. Am. Chem. Soc*., **1962**, *84*, 1040-1041. b) Hudlicky, T., Enwistle, D. A., Pitzer, K. K., Thorpe, A., *J. Chem. Rev.,* **1996**, *96*, 1195-1220.

[90] Suami, T., Ogawa, S., Toyokuni , Nakamoto, K., Kasahara, I., *Carbohydr. Res.,* **1977**, *58*, 240-244.

[91] Mehta, G., Talukdar, P., Mohal, N., *Tetrahedron Lett.,* **2001**, *42*, 7663-7666.

[92] Angelaud, R., Landais, Y., *Tetrahedron Lett.,* **1997**, *38*, 8841-8844.

[93] Tadano, K., Maeda, H., Hoshino, M., Iimura, Y., Suami, T., *J. Org. Chem*., **1987**, *52*, 1946-1956.

[94] Wagner, H., Lunft, Inge., *J. Chem. Soc., Perkin Trans. 1*, **2001**, *8,*780-788.

[95] Altundas, A., Menzek, A., Demirci-Gultekin, D., Karakaya, M., *Turk. J. Chem.,* **2005**, *29*, 513-518.

[96] Ghosez, L., Montaigne, R., Roussel, A., Vanlierde, H., Mollet, P., *Tetrahedron*, **1971**, *27*, 615-633.

[97] Ramnauth, J., Lee-Ruff, E., *Can. J. Chem*., **1999**, *77*, 1245-1248.

[98] Brady, W. T., *Tetrahedron*, **1981**, *37*, 2949-2966.

[99] Rice, F. O., Roberts, R., *J. Am. Chem. Soc.*, **1943**, *65*, 1677-1681.

[100] Rice, F. O., Greenberg, J., *J. Am. Chem. Soc.*, **1934**, *56*, 2132-2134.

[101] Ulrich, H., *Cycloaddition Reactions of Heterocumulens*, **1967**, Academic Press, New York, London.

[102] Wedekind, E., *Ann*, **1910**, 378, 261.

[103] Stevens, H. C., Reich, D. A., Brandt, D. R., Fountain, K. R., Gaughan, E. J., *J. Am. Chem. Soc.*, **1965**, *87*, 5257-5259.

[104] Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*, **1976**, Wiley and Sons Press, London, New York, Sydney, Toronto.

[105] a) Brady, W. T., O'Neal, H. R., *J. Org. Chem.,* **1967**, *32*, 612-614.

b) Wagner, H. U., Gompper, R., *Tetrahedron Lett*., **1970**, *11*, 2819-2822.

[106] a) Houk, K. N., Strozier, R. W., Hall, J. A., *Tetrahedron Lett*., **1974**, *15*, 897-900.

b) Sustmann, R., Ansmann, A., Vahrenholt, F., *J. Am. Chem. Soc.*, **1972**, *94*, 8099-8105.

c) Inagaki, S., Minato, T., Yamabe, S., Fujitomo, H., Fukui, K., *Tetrahedron*, **1974**, *30*, 2151-2157.

[107] Campbell, N., Heller, H. G., *J. Chem. Soc*., **1965**, 5473-5475.

[108] Fish, R. H., *J. Org. Chem*., **1969**, *34*, 1127-1128.

[109] Hurd, C. D., Kimbrough, R. D., *J. Am. Chem. Soc.* **1960**, *82*, 1373-1376.

[110] Arens, J. F., *Angew. Chem*., **1958**, *70*, 631-636.

[111] Mehta, G., Rao, P. S. H., *Synth. Commun*., **1985**, *15*, 991-1000.

[112] a) Davis, K. M., Carpenter, B. K., J. *Org. Chem.,* **1996**, *61*, 4617-4622.

b) Liotta, F. J., Duyne, G. V., Carpenter, B. K., *Organometallics,* **1987**, *6*, 1010-1023.

[113] Solomons, T. W. G., *Organic Chemistry*, **1996**, Seventh Edition, Wiley and Sons Press, New York, Chichester, Brisbane, Toronto, Singapore.

[114] (a) Griesbeck, A. G., El-Idreesy, T. T., Adam, W., Krebs, O., *Ene-reactions with Singlet Oxygen. CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; W. M. Horspool, P. S. Song, Eds.; CRC: Boca Raton, FL, **2004**.

(b) Clennan, E. L., *Tetrahedron,* **2000**, *56*, 9151–9179.

(c) Stratakis, M., Orfanopoulos, M., *Tetrahedron,* **2000**, *56,* 1595-1615.

[115] (a) Gillard, J. R., Burnell, D. J., *J. Chem. Soc.* Commun., **1989**, 1439-1440.

(b) Paquette, L. A., Branan, B. M., Rogers, R. D., Bond, A. H. Lange, H.

Gleiter, R. *J. Am. Chem. Soc*., **1995**, *117,* 5992-6001.

[116] Schulte-Elte, K. H., Rautestrauch, V., *J. Am. Chem. Soc.,* **1980**, *102*, 1738–1740.

[117] (a) Kornblum, N., La Mare, H. E., *J. Am. Chem. Soc.,* **1951**, *73***,** 880-881.
(b) M. Balci, *Chem. Rev.* **1981**, *81*, 91–108.

(c) Mete, E., Altundaş, R., Seçen, H., Balci, M., *Turk. J. Chem.,* **2003**, *27,* 145-153.

[118] Kishali, N. H., Kara, Y., *Tetrahedron*, **2008**, *64*, 7956-7959.

[119] (a) Hoveyda, A. H. Evans, D. A.,Fu, G. C., *Chem. Rev.,* **1993**, *93*, 1307-1370.

(b) Robert, D. B. Carlos, M. E. Julia, E. W., Mikhail N. G., *J. Am. Chem. Soc.,* **1998**, *120,* 680-685.

(c) Itoh, T. Jitsukawa, K., Kaneda, K., Teranishi, S., *J. Am. Chem. Soc.,* **1979**, *101*, 159-160.

[120] Furniss, B.S., Hannaford, A.C., Smith G.S.W., Tatchell, A.R., Vogel's Textbook of Practical Organic Chemistry, 5th Edition, Wiley and Sons, **1991-1994**.

[121] Biological activitiy tests were performed by Assist. Prof. Aslıhan Günel; *Plant Functional Genomics Labaratory*, METU, Ankara.

APPENDIX

PART I

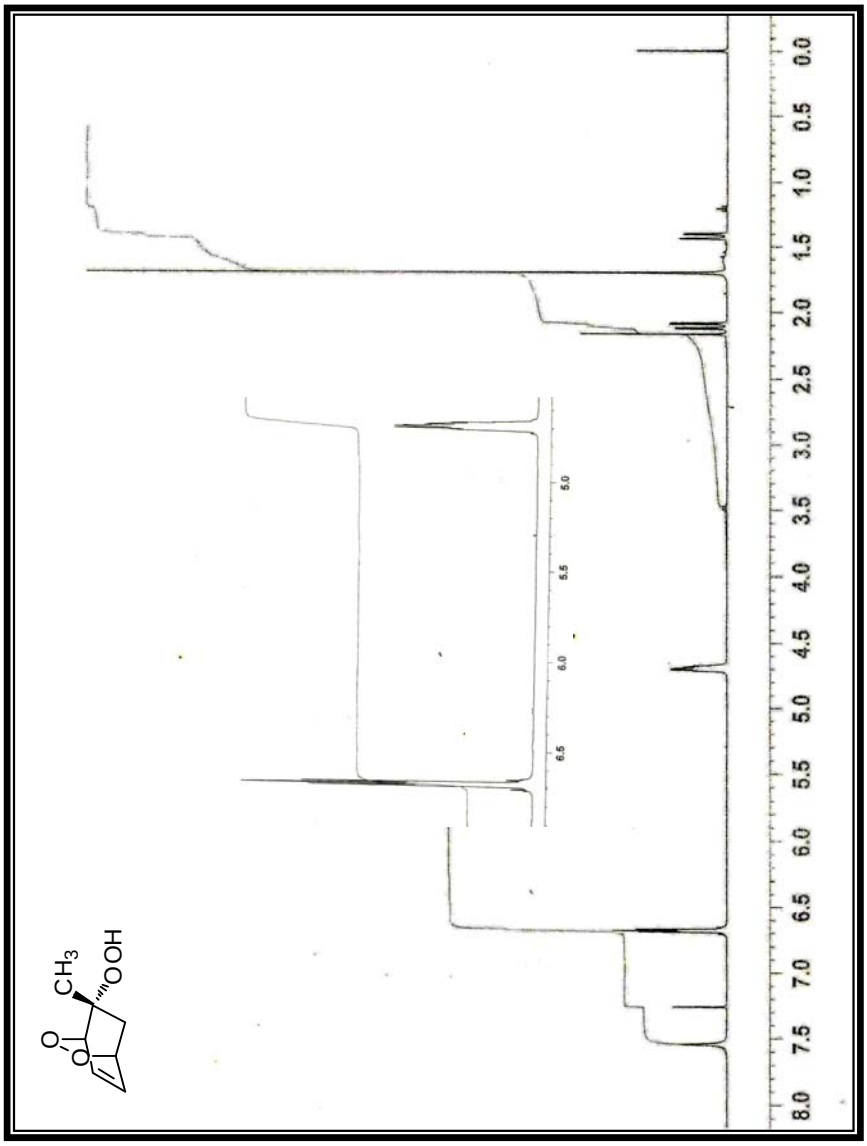


Figure I. 12 ^{1}H-NMR spectrum of compound **19**

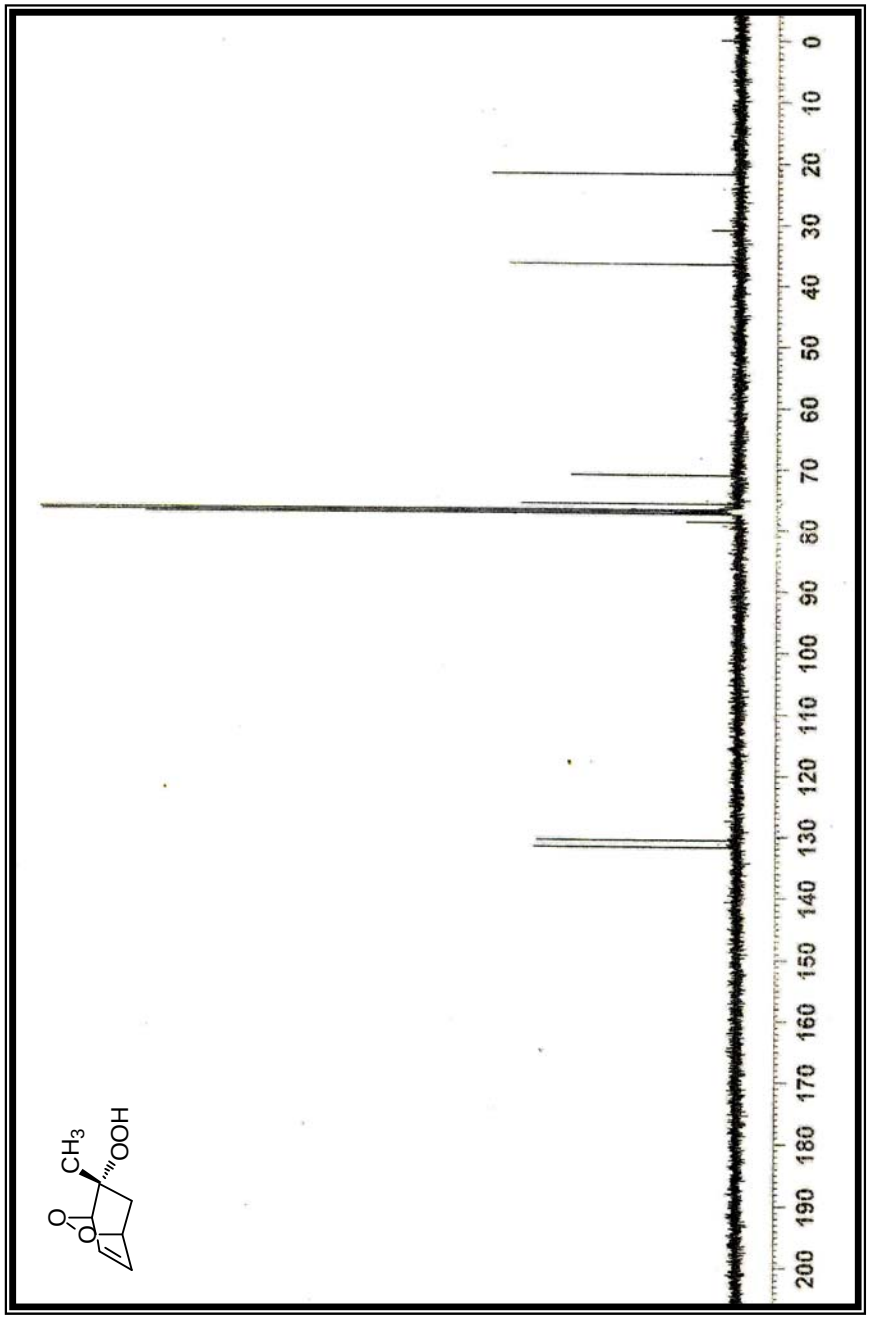


Figure I. 13. ^{13}C-NMR spectrum of compound **19**

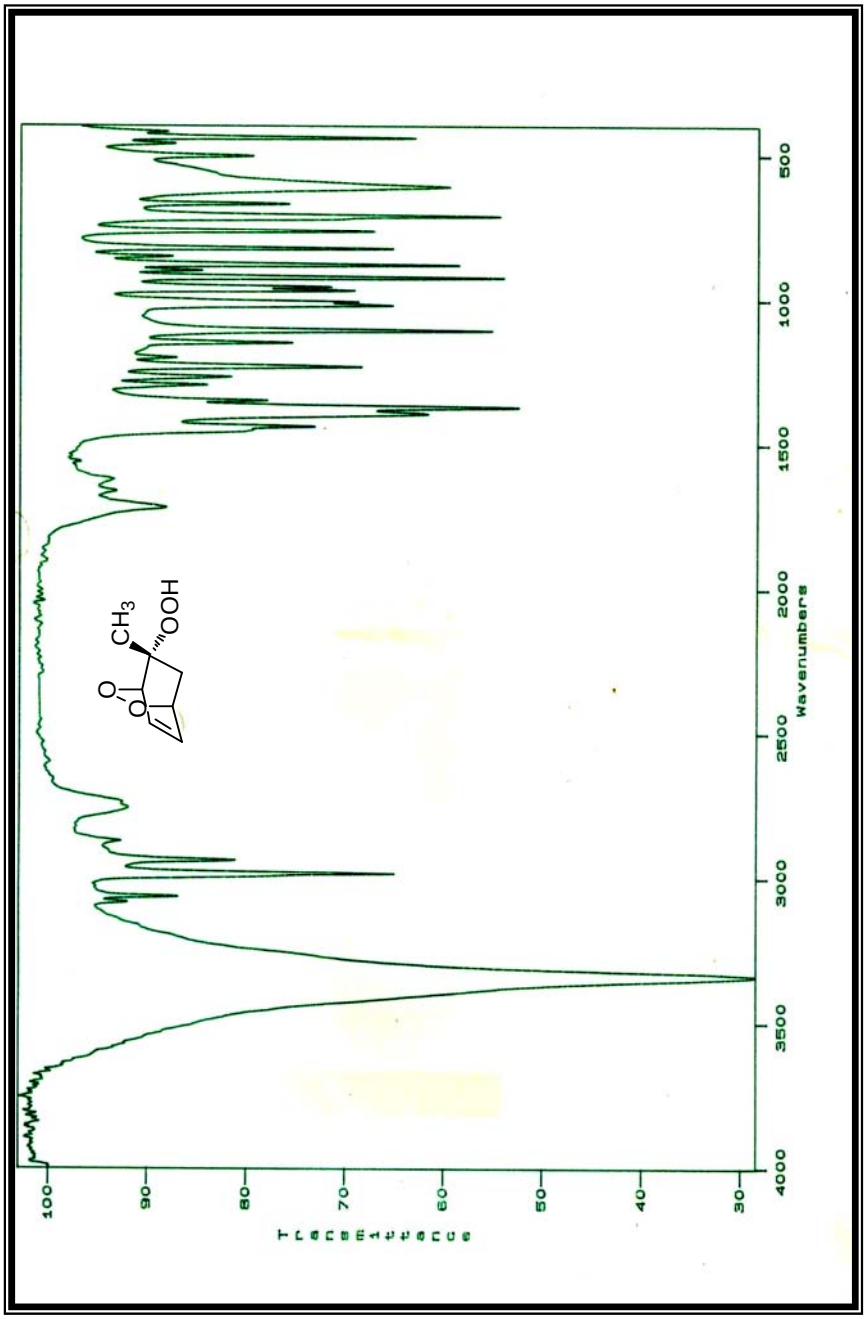


Figure I. 14 IR spectrum of compound **19**

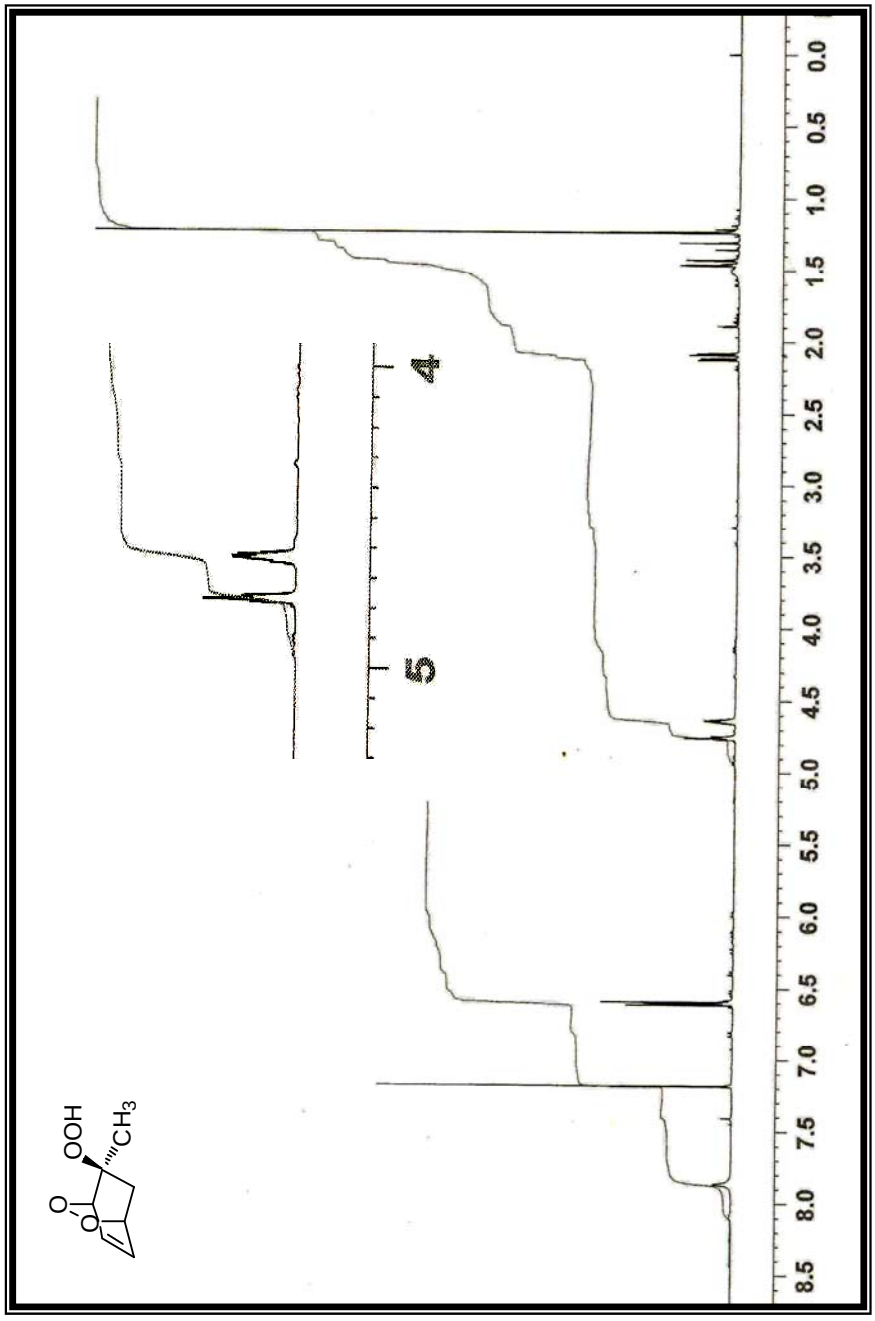


Figure I. 15 ^{1}H-NMR spectrum of compound **20**

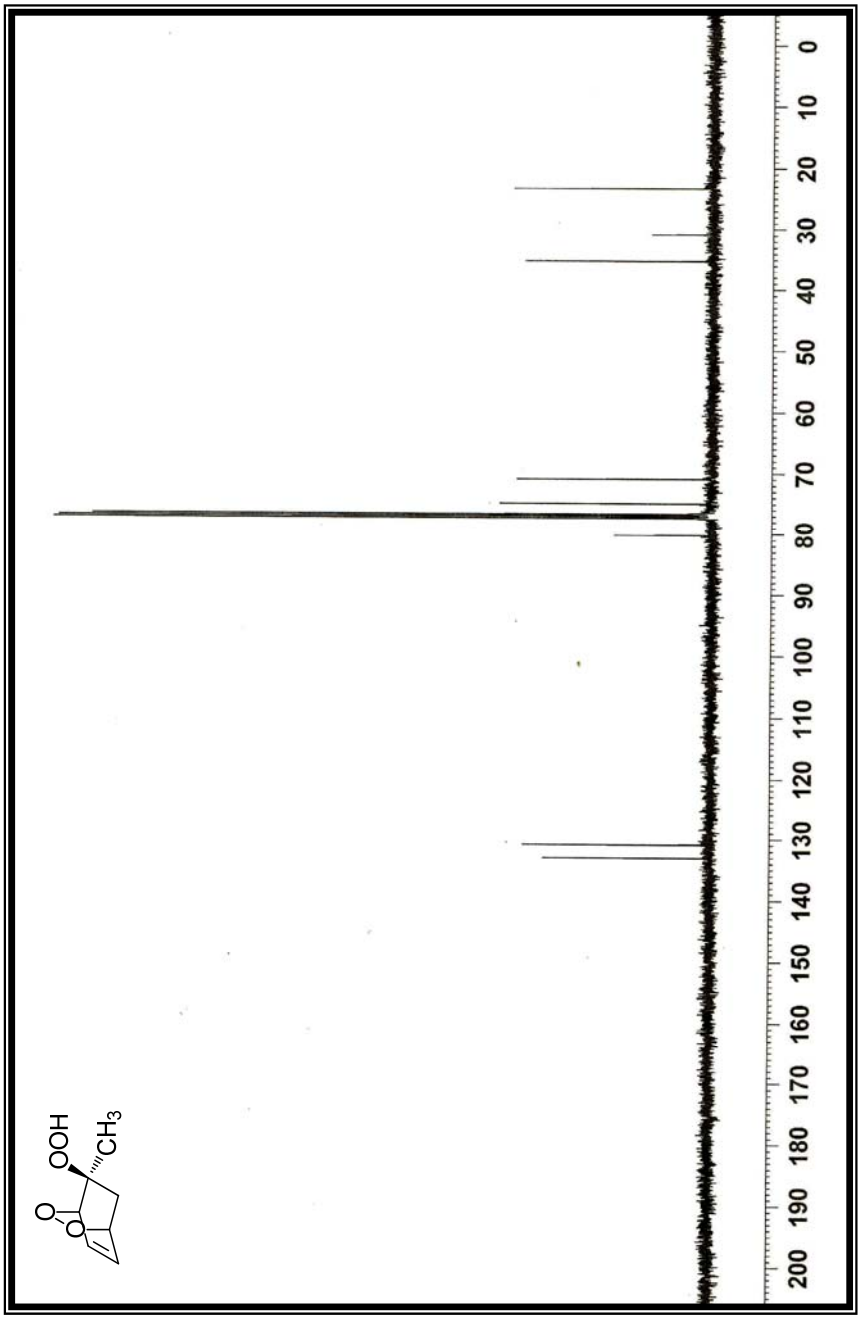


Figure I. 16 ^{13}C-NMR spectrum of compound **20**

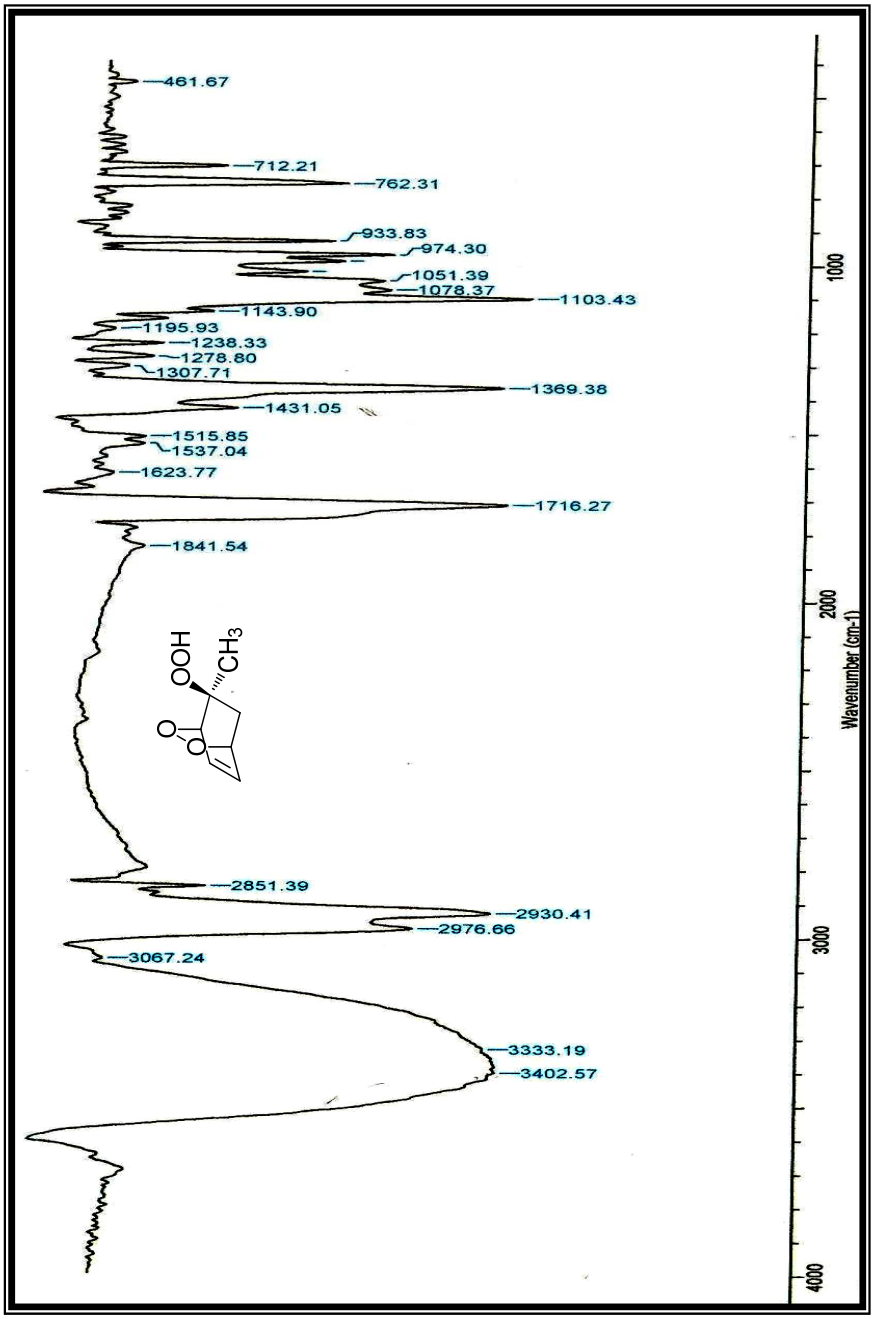


Figure I. 17 IR spectrum of compound 20

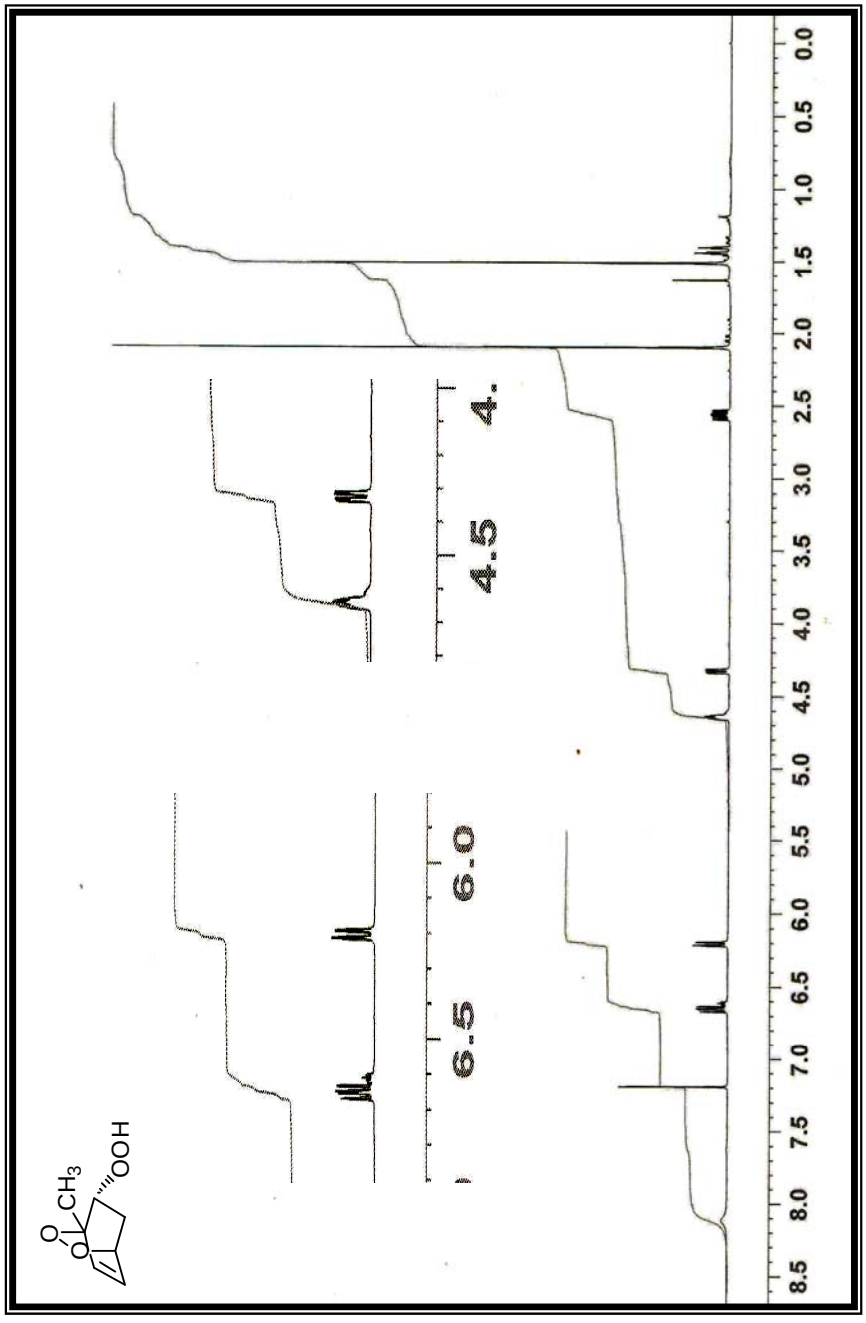


Figure I. 18 ^{1}H-NMR spectrum of compound **21**

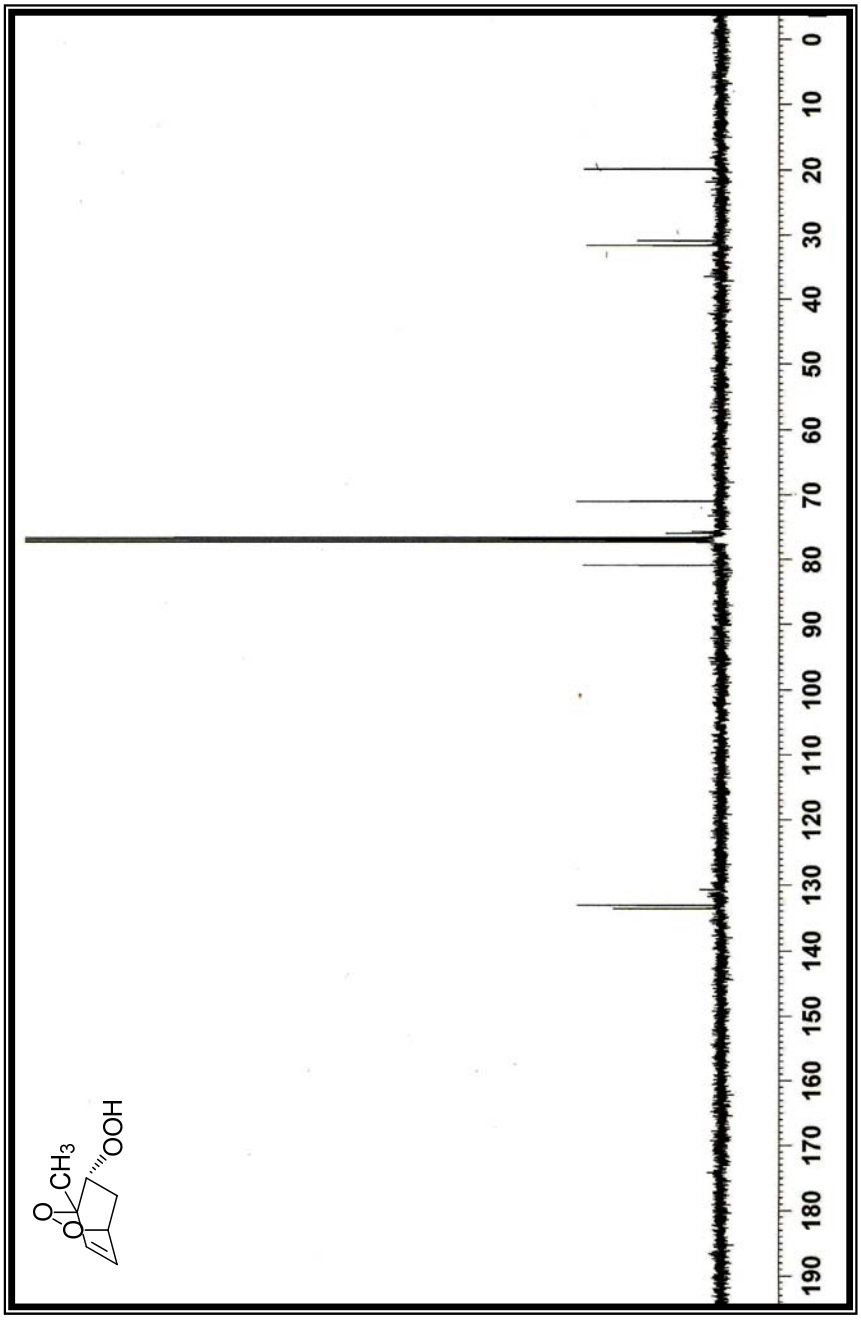


Figure I. 19 ^{13}C-NMR spectrum of compound **21**

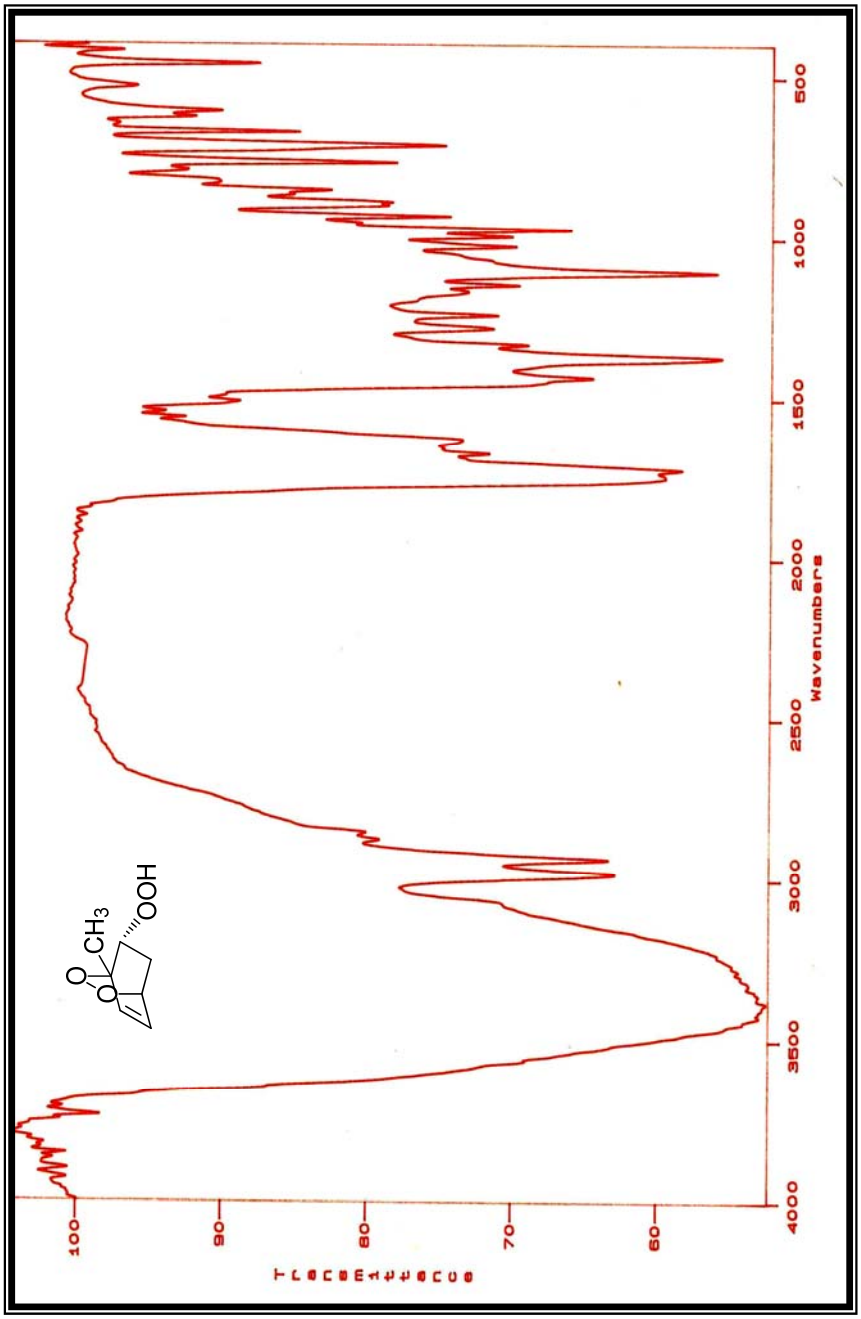


Figure I. 20 IR spectrum of compound **21**

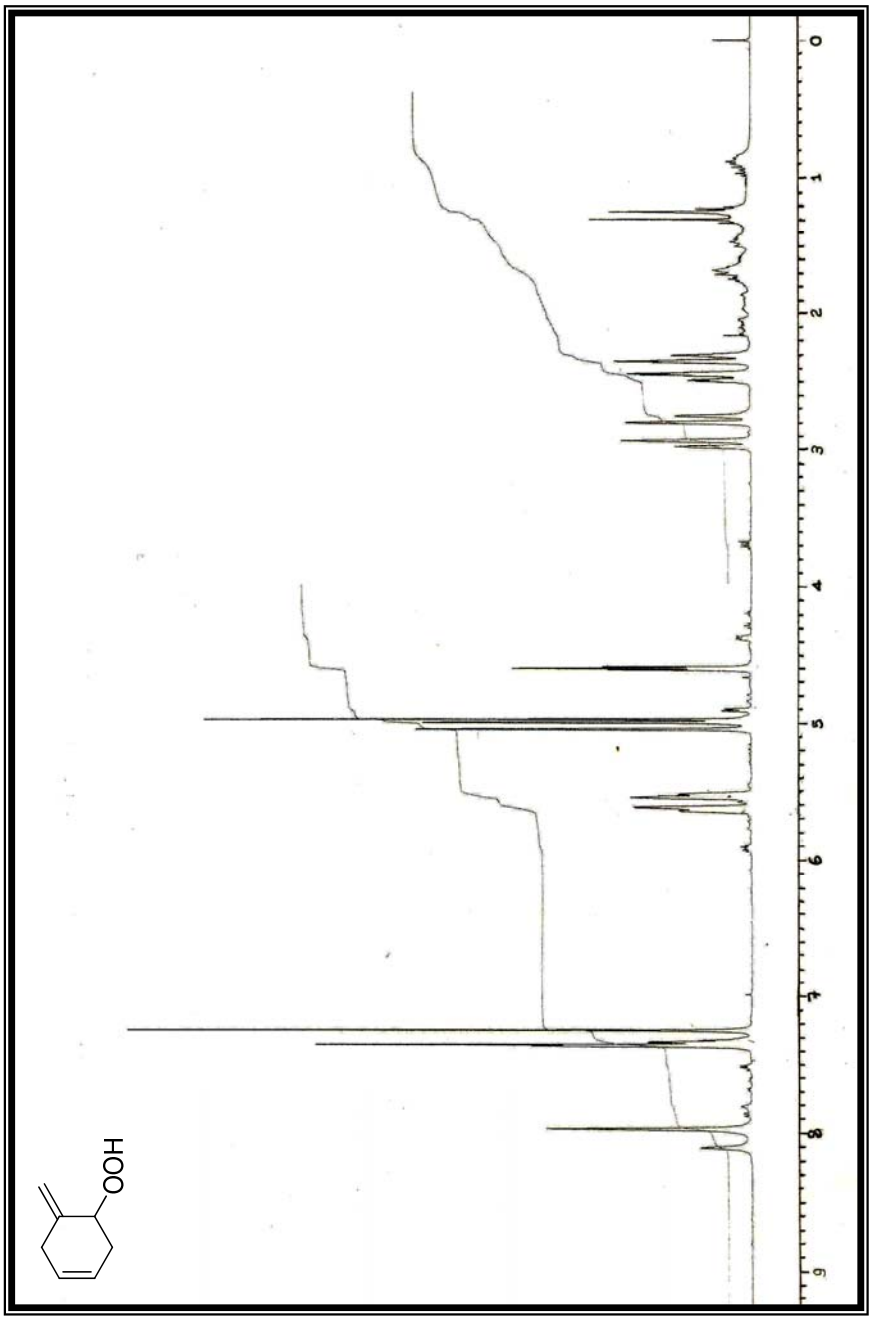


Figure I. 21 ^{1}H-NMR spectrum of compound **22**

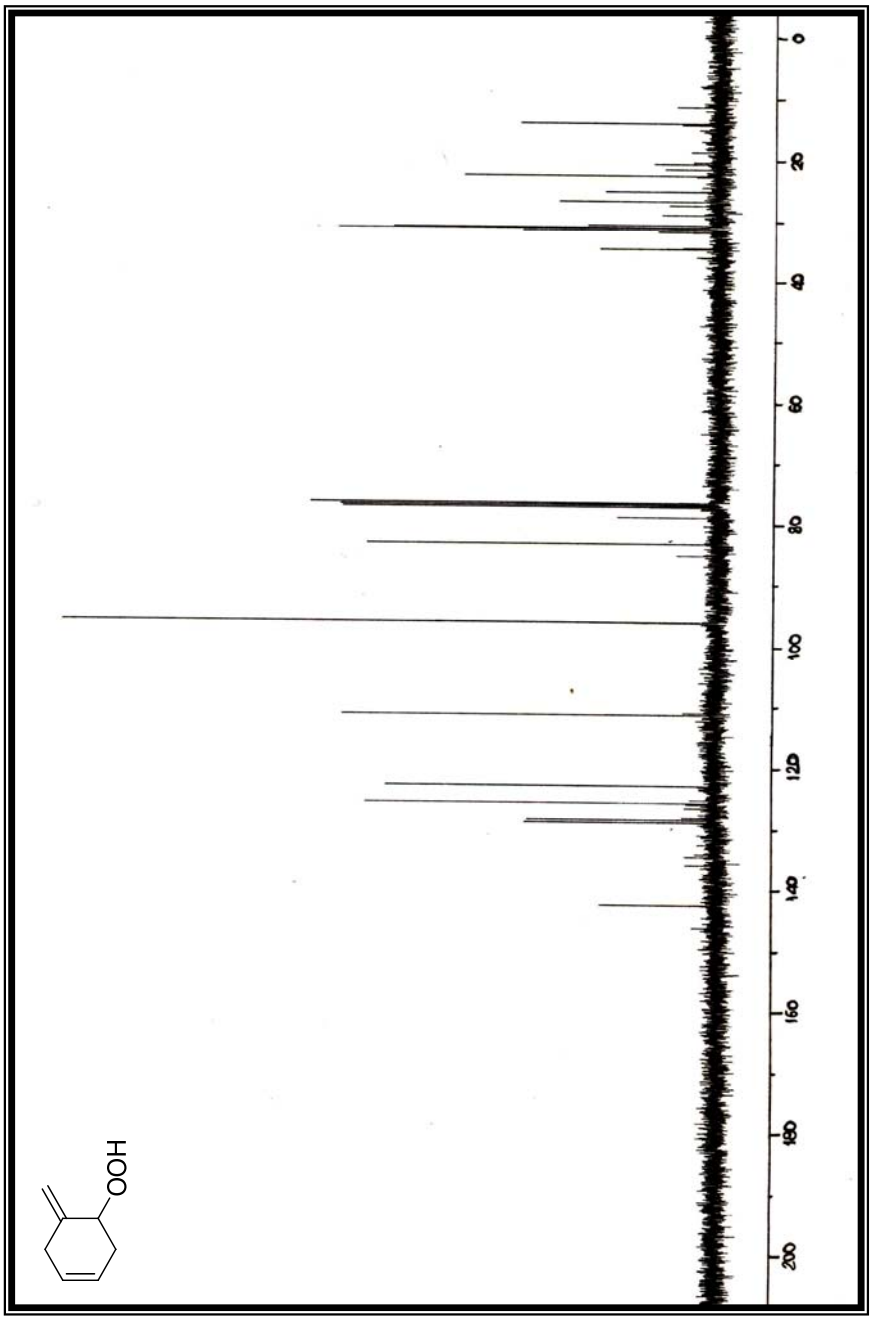


Figure I. 22 ^{13}C-NMR spectrum of compound **22**

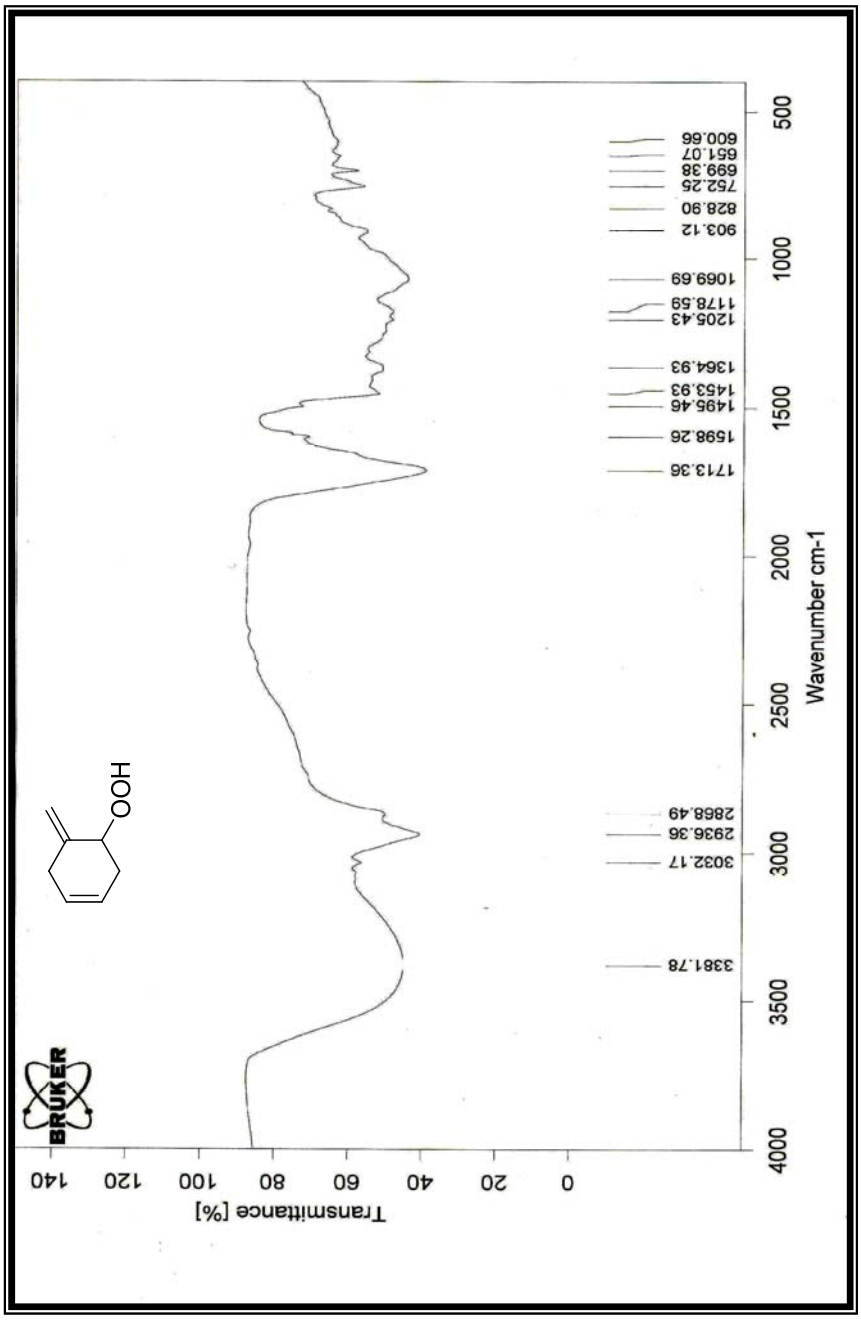


Figure I. 23 IR spectrum of compound **22**

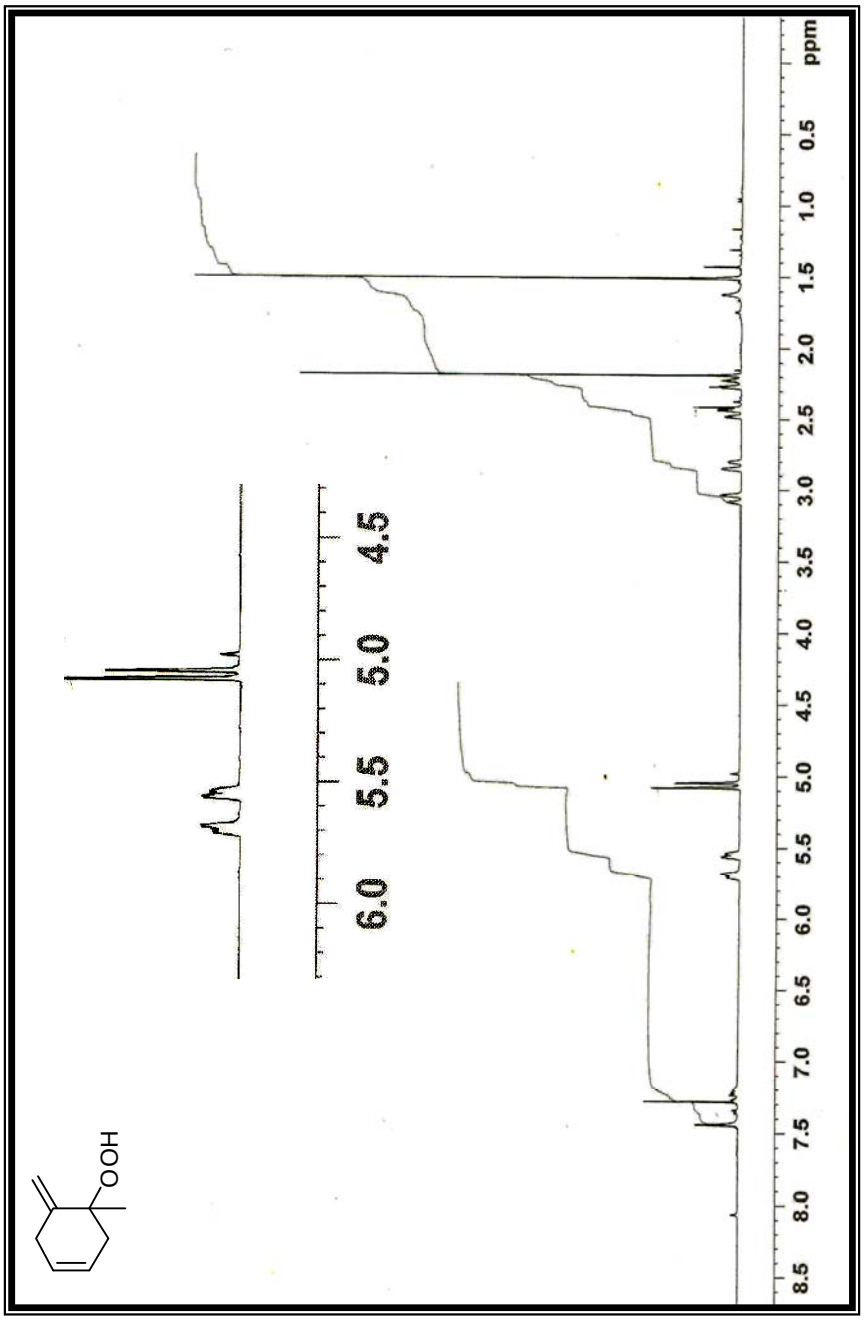


Figure I. 24 ^{1}H-NMR spectrum of compound **33**

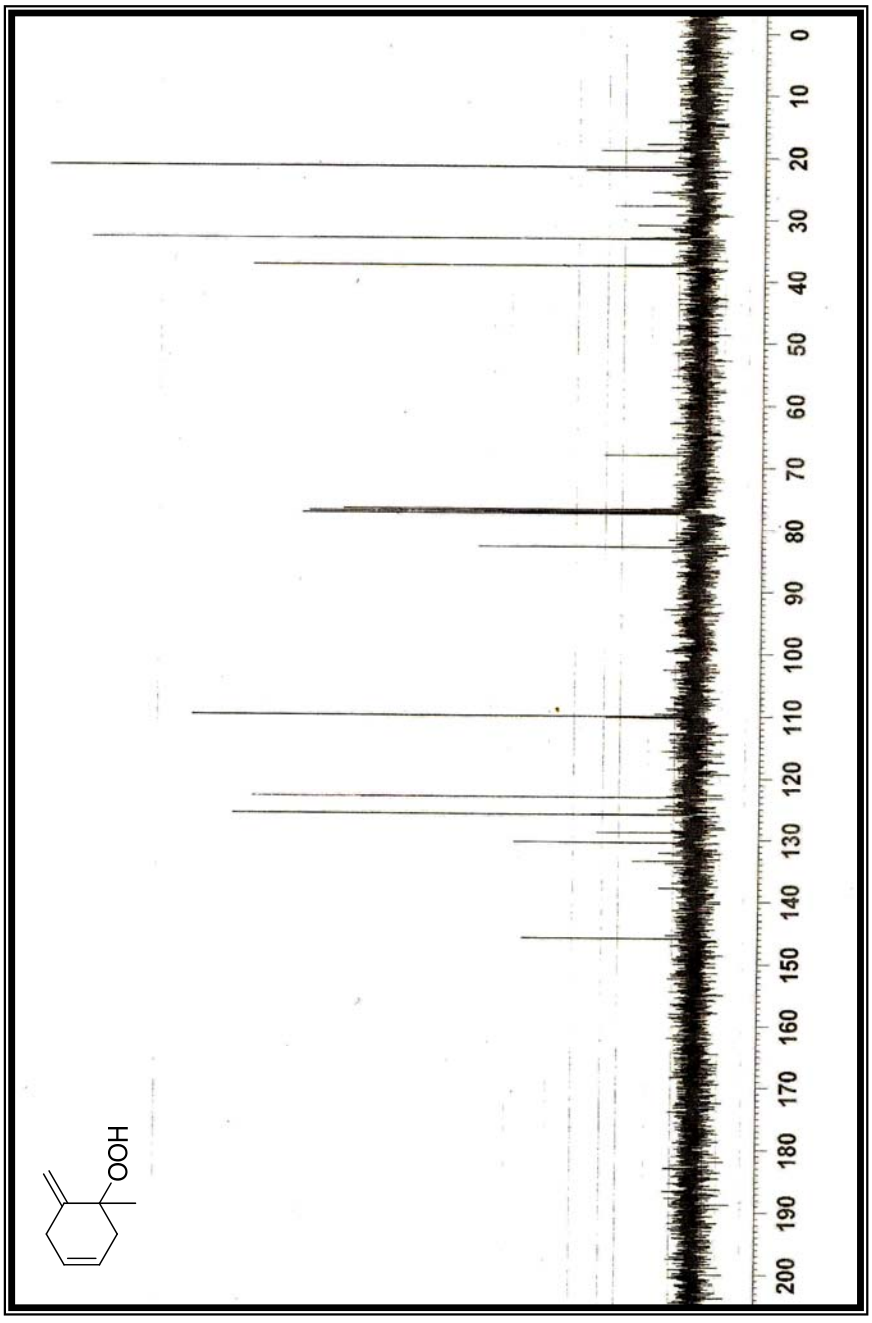


Figure I. 25 ^{13}C-NMR spectrum of compound **33**

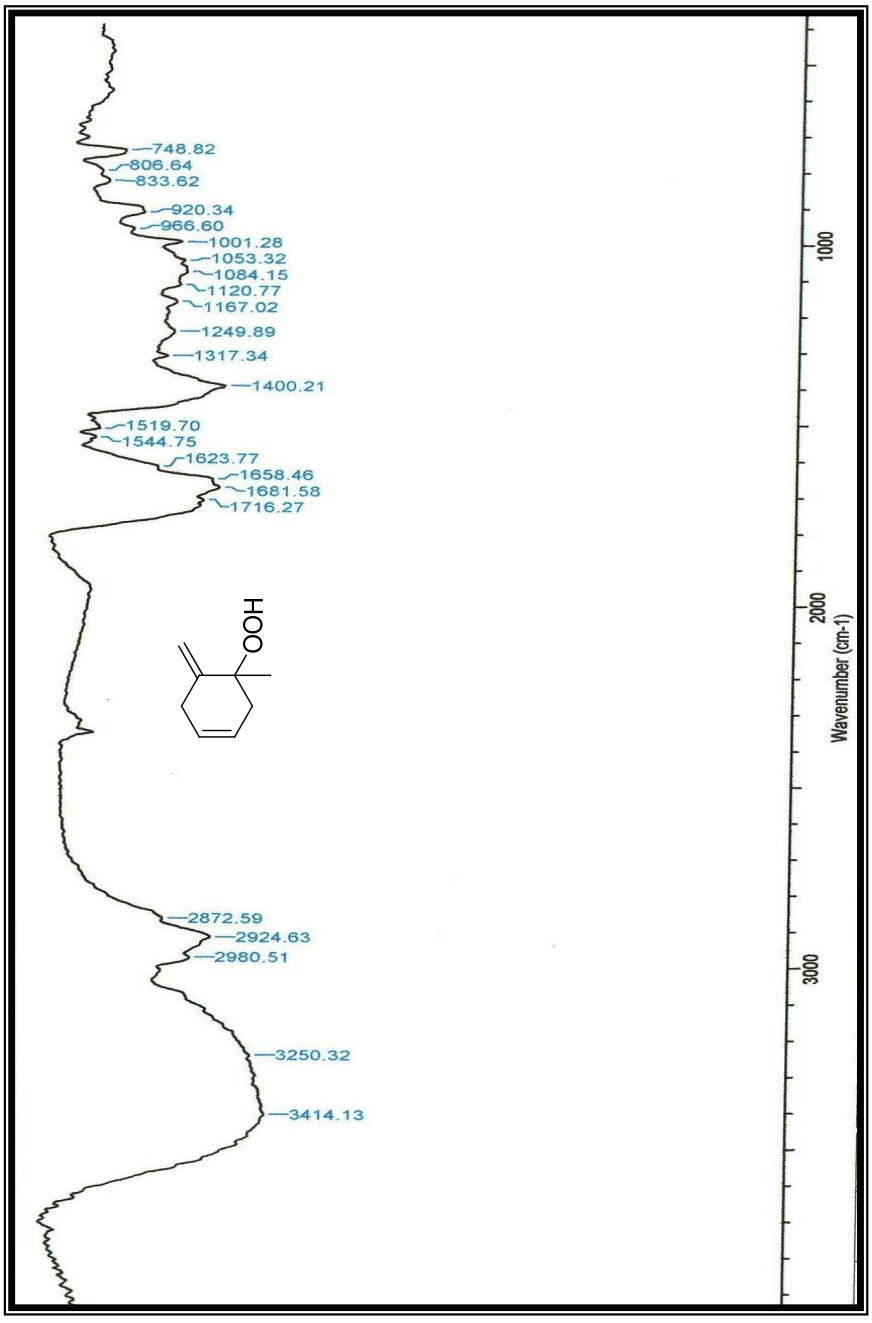


Figure I. 26 IR spectrum of compound **33**

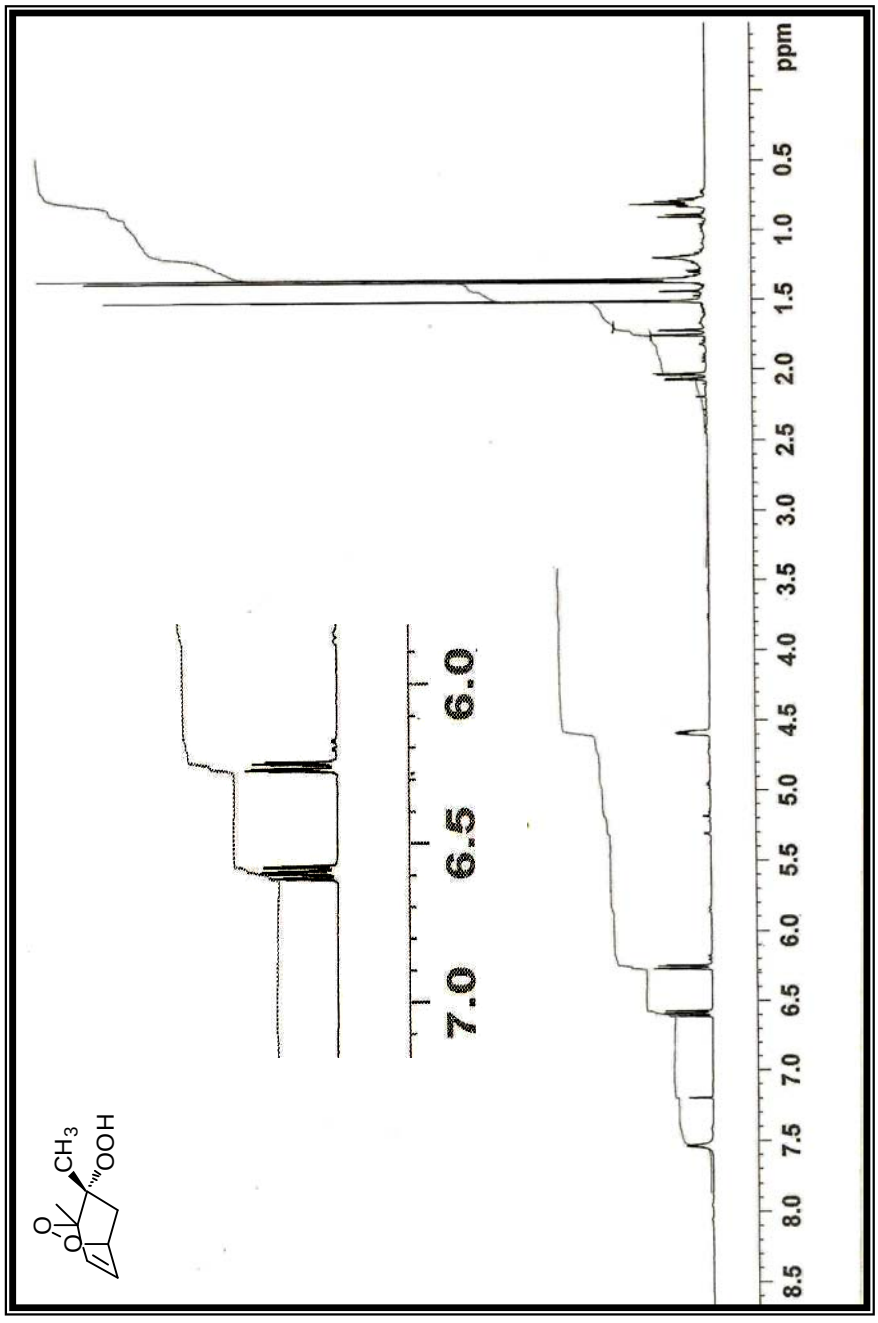


Figure I. 27 ^{1}H-NMR spectrum of compound **34**

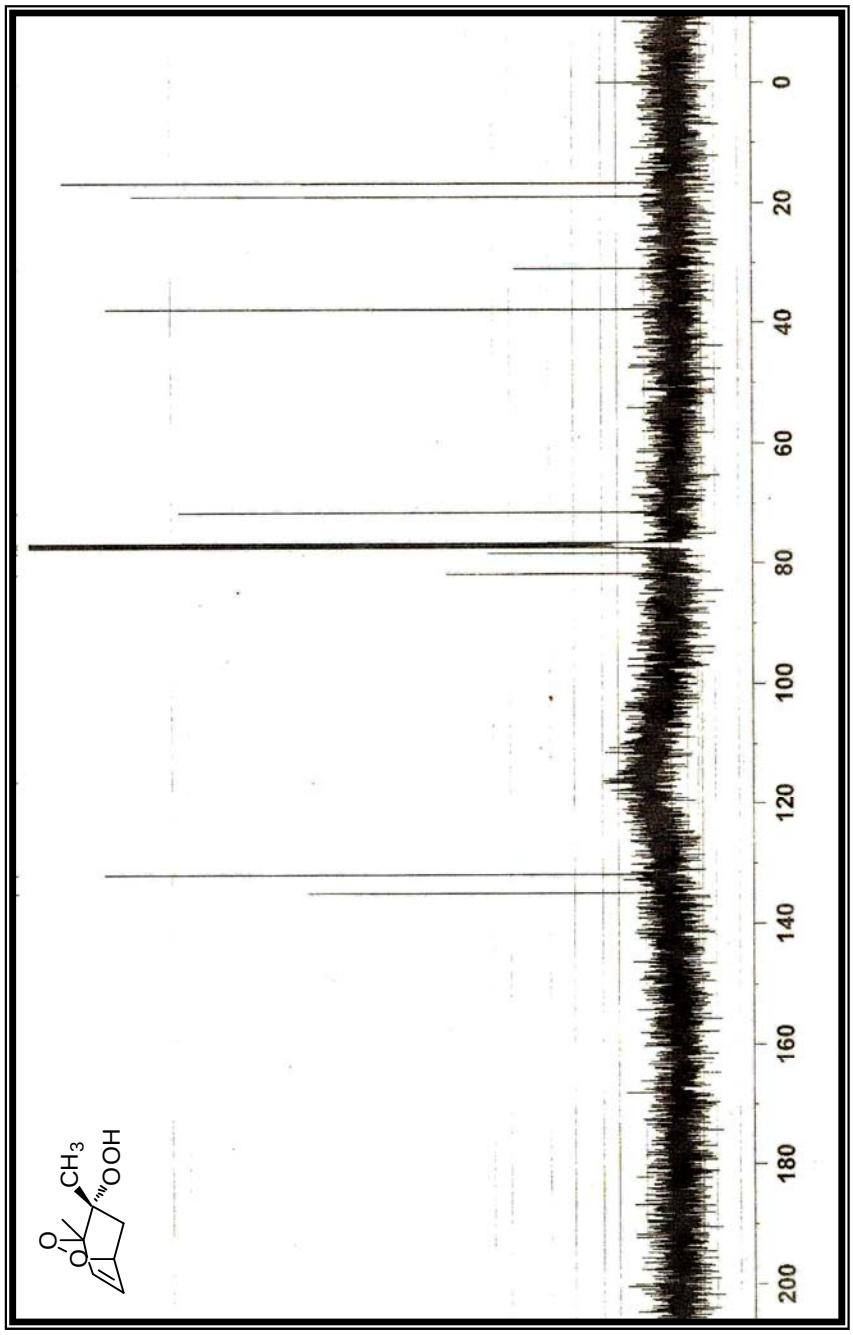


Figure I. 28 ^{13}C-NMR spectrum of compound **34**

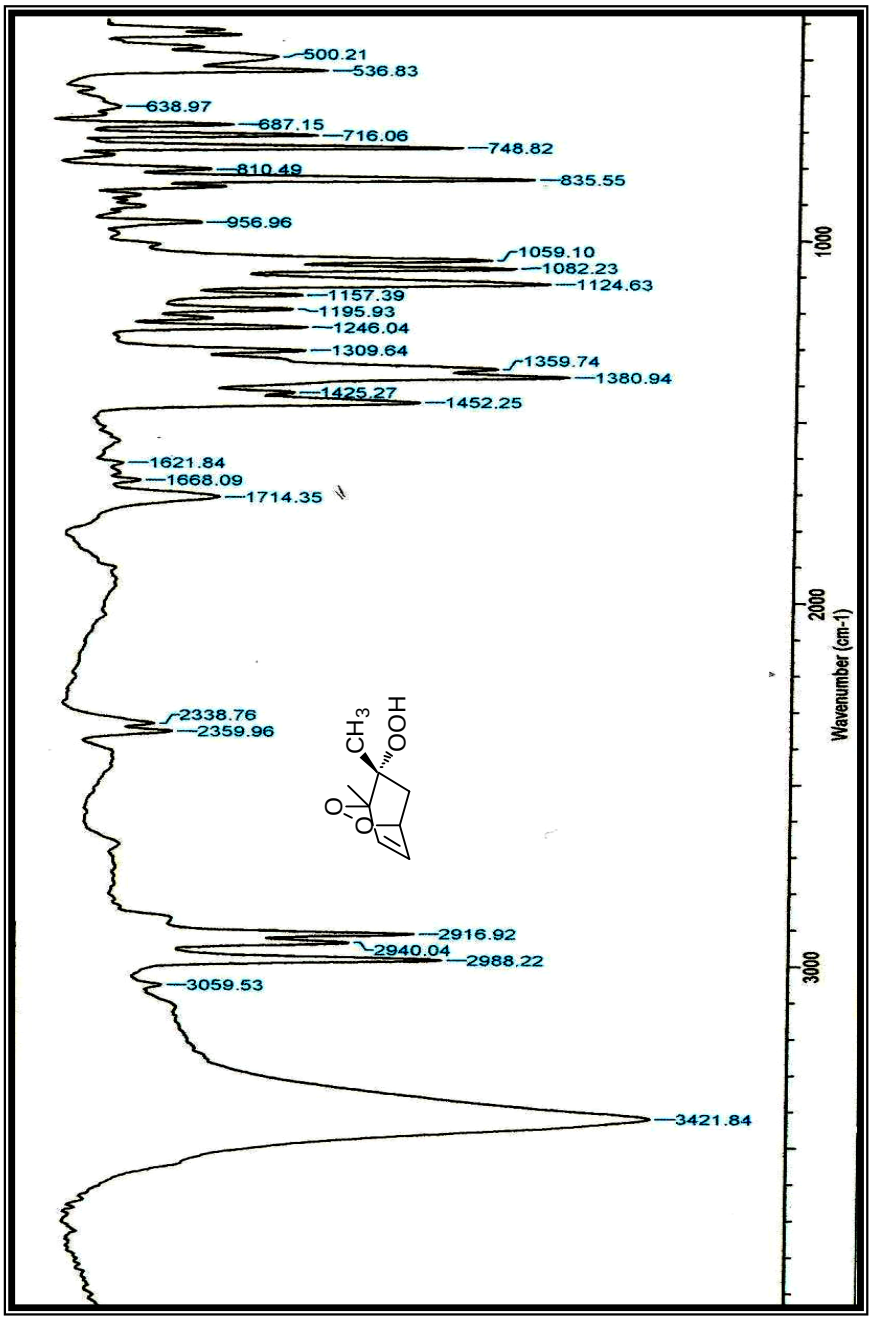


Figure I. 29 IR spectrum of compound **34**

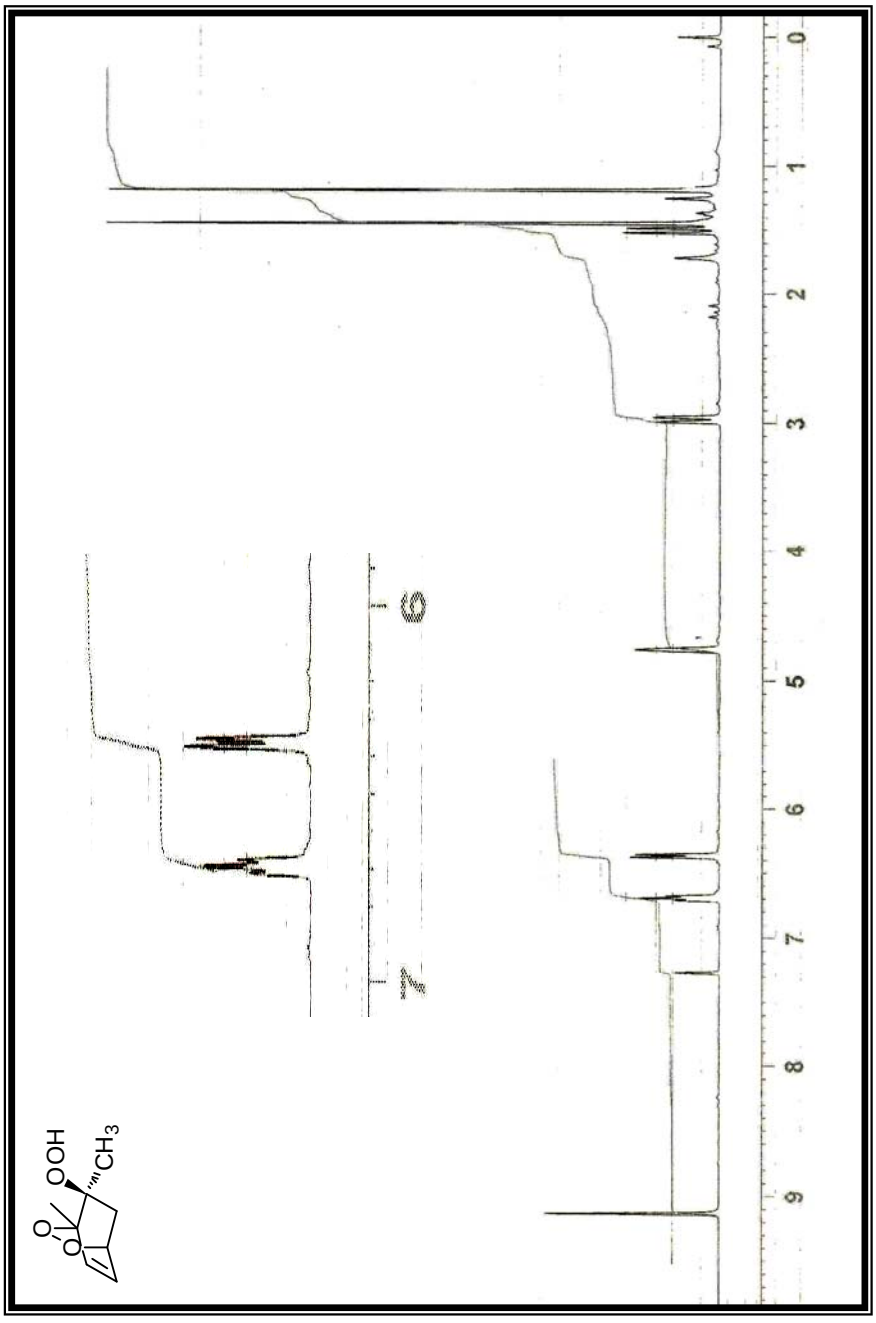


Figure I. 30 ^{1}H-NMR spectrum of compound **35**

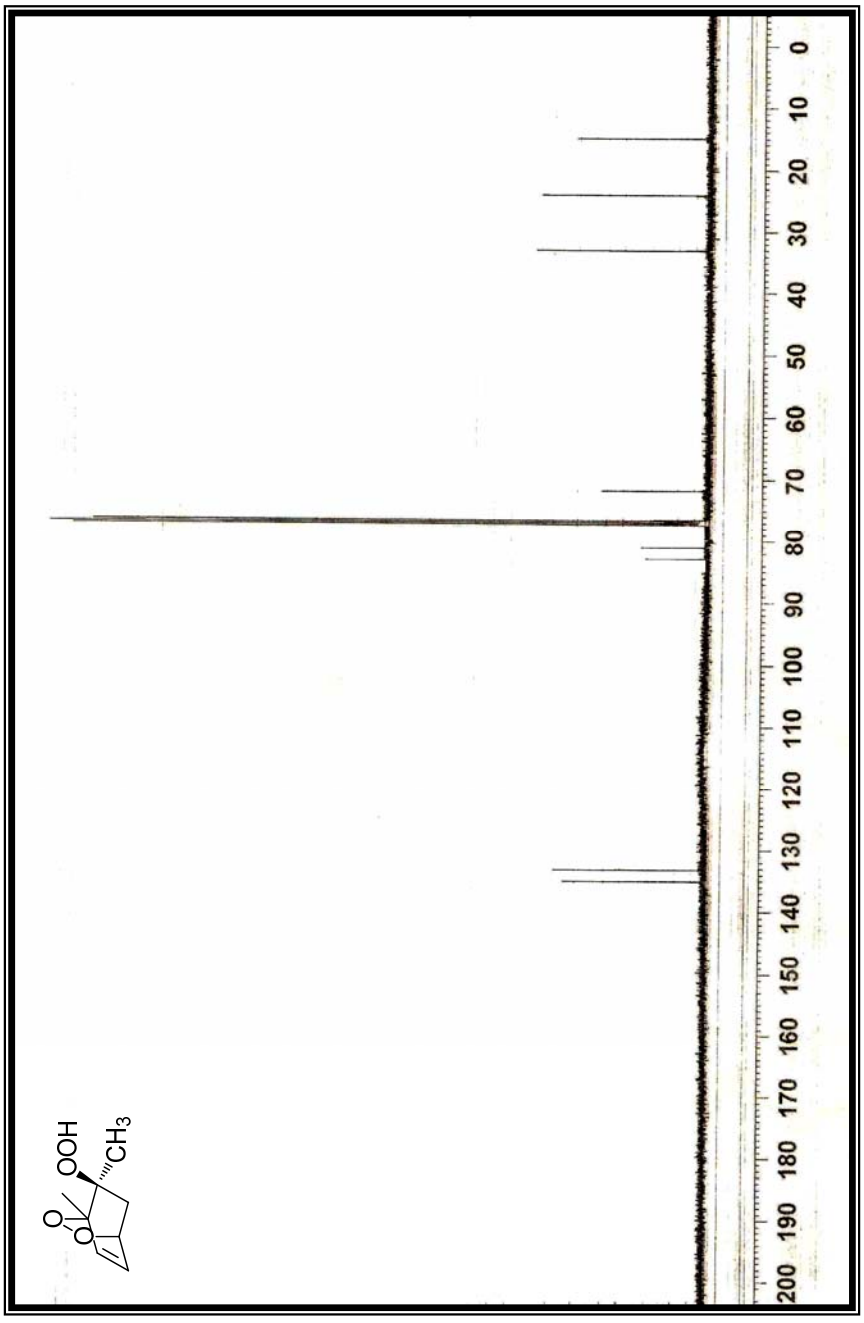


Figure I. 31 ^{13}C-NMR spectrum of compound **35**

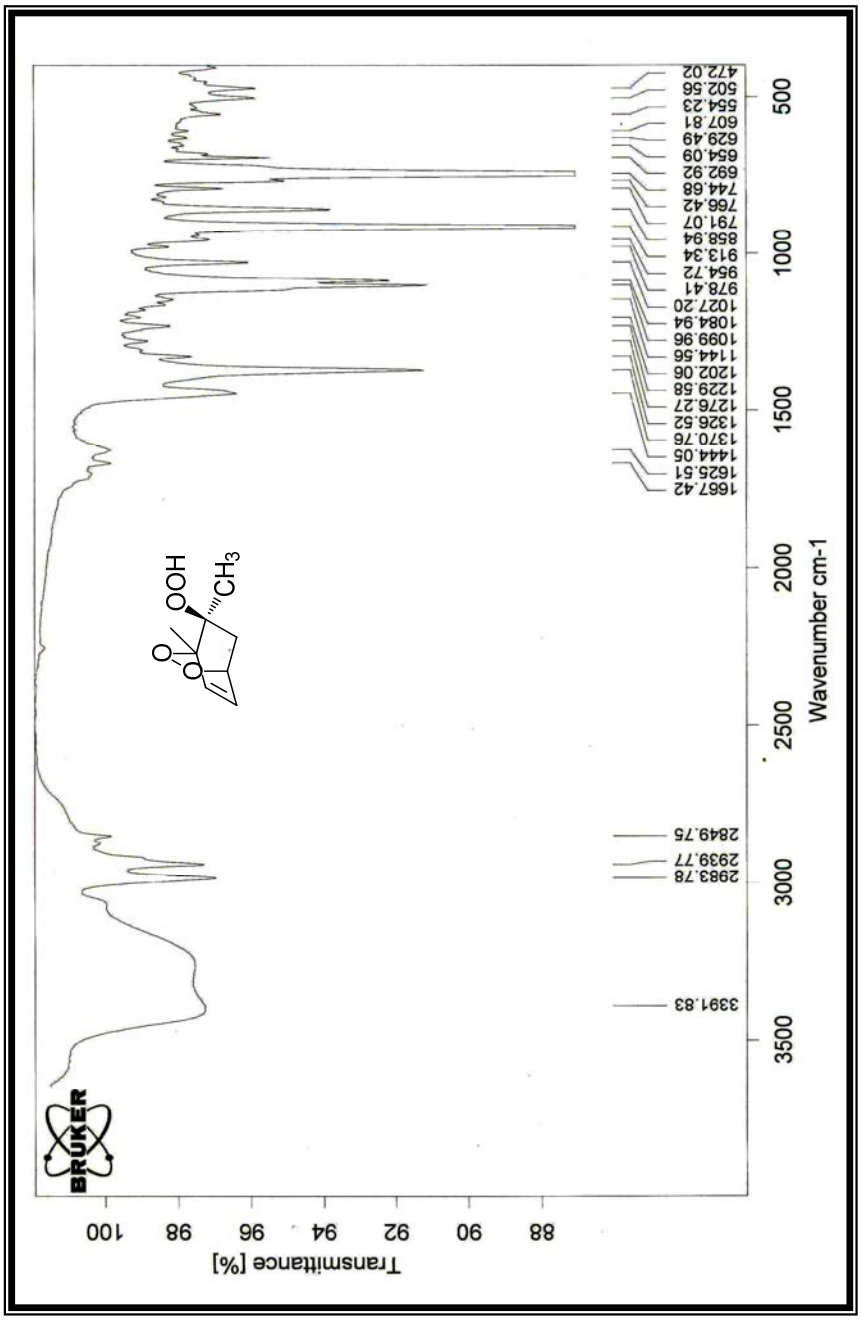


Figure I. 32 IR spectrum of compound **35**

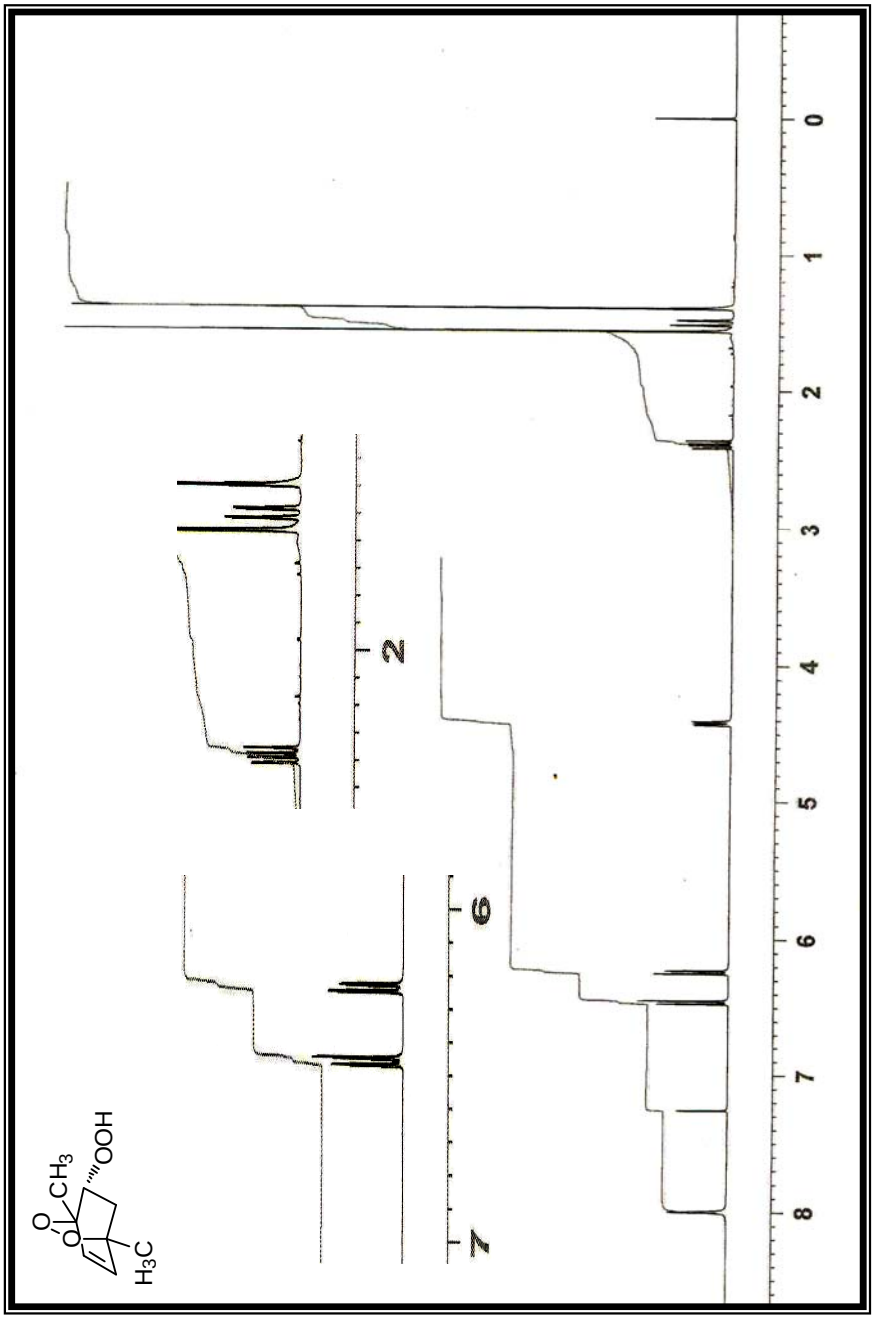


Figure I. 33 ^{1}H-NMR spectrum of compound **40**

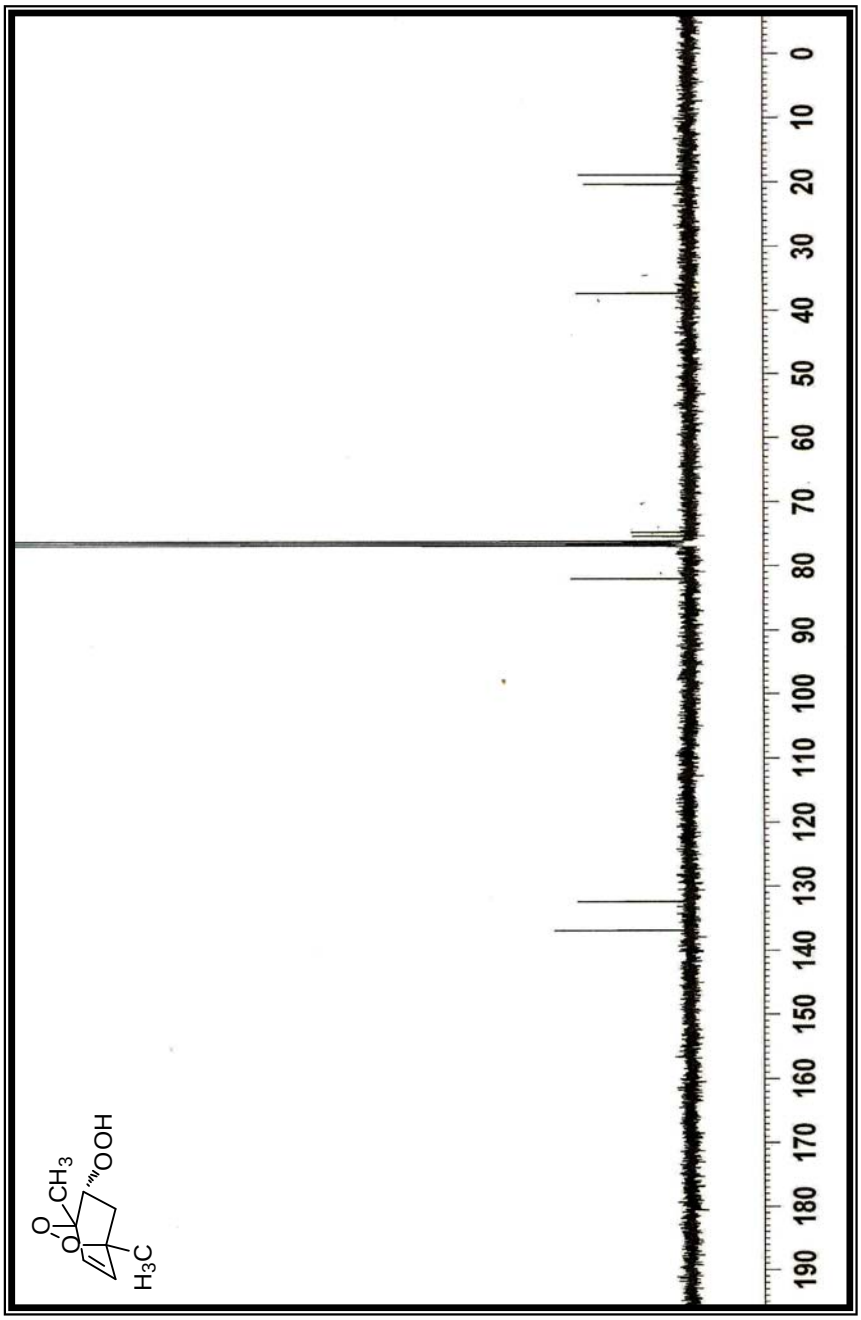


Figure I. 34 ^{13}C-NMR spectrum of compound **40**

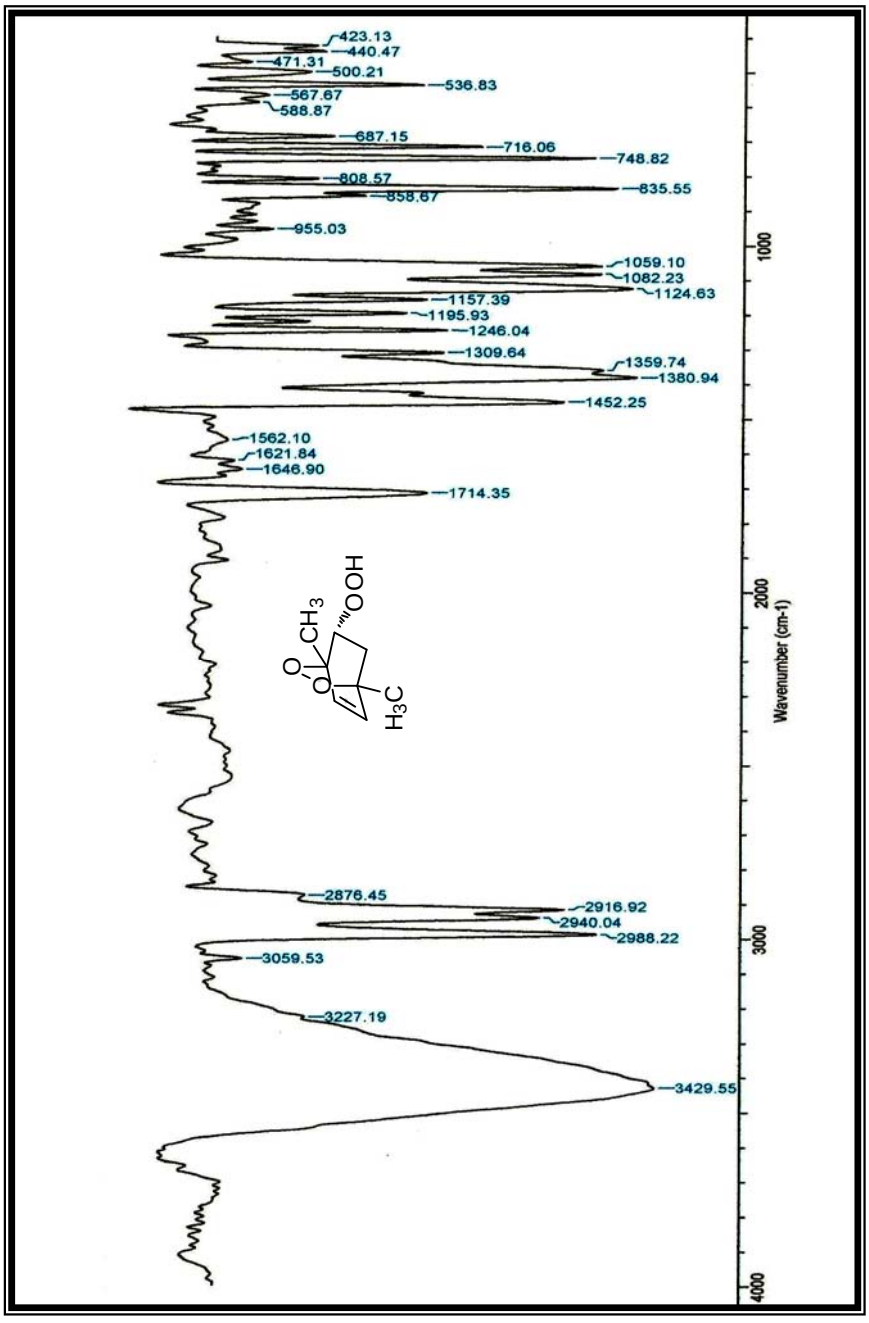


Figure I. 35 IR spectrum of compound **40**

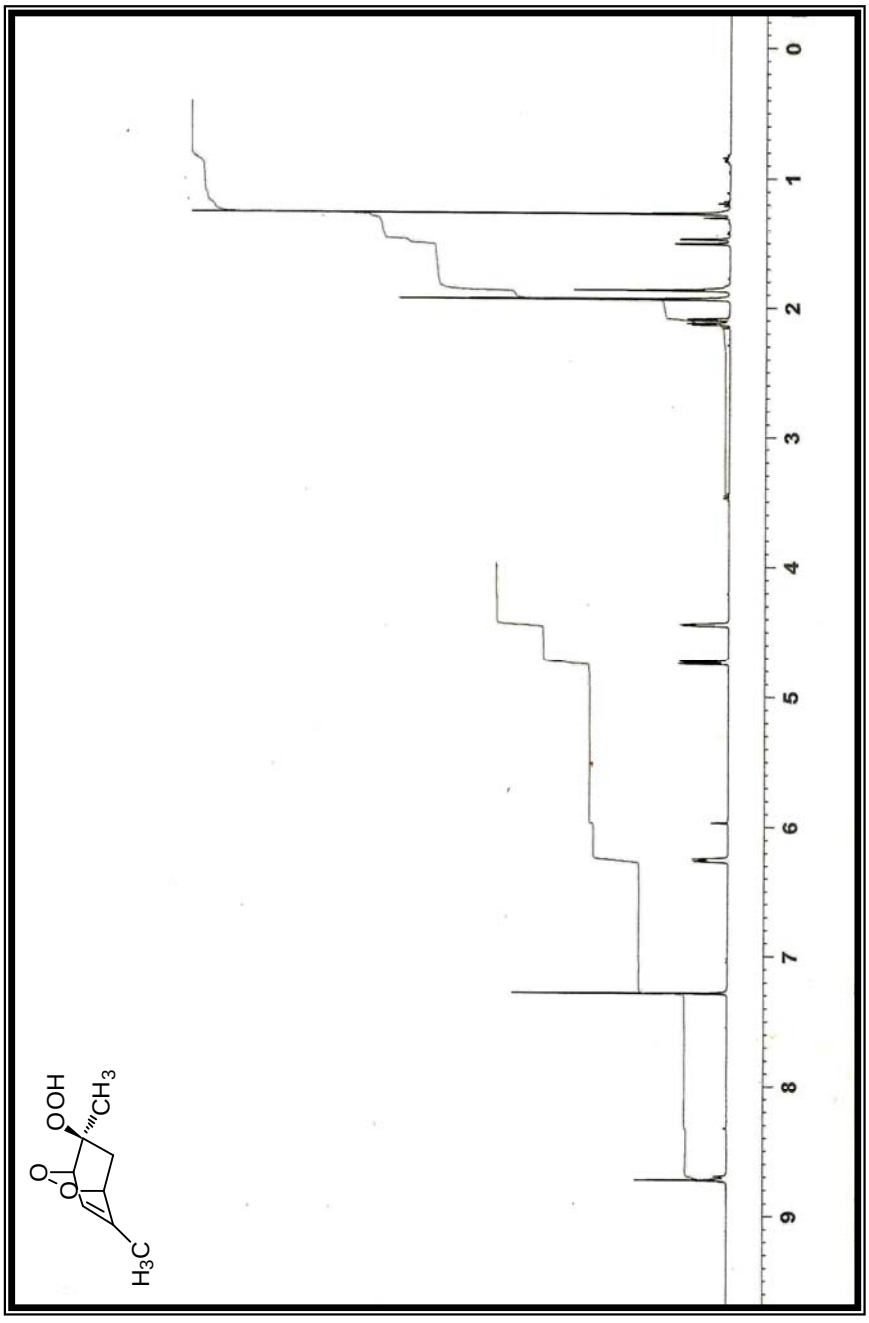


Figure I. 36 ^{1}H-NMR spectrum of compound **41**

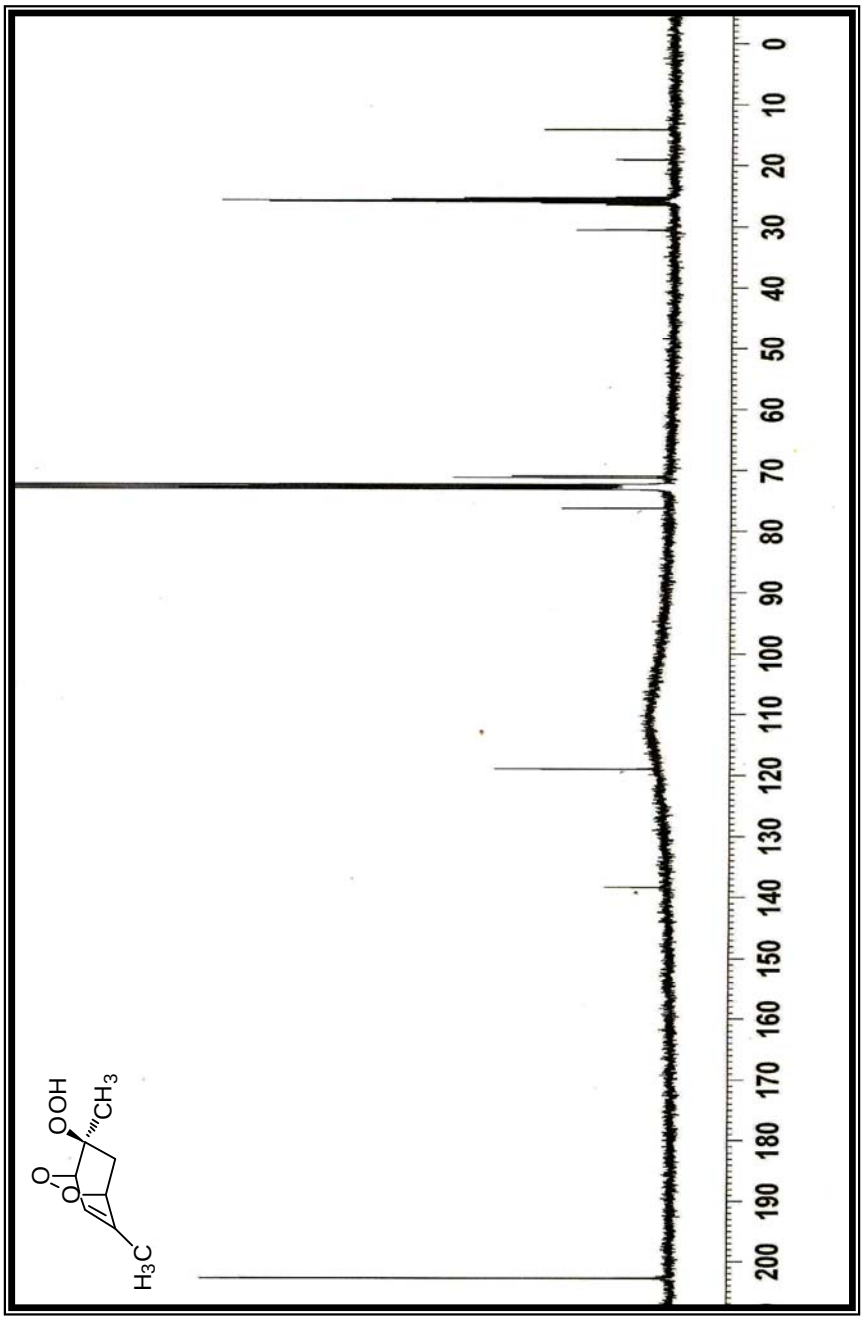


Figure I. 37 ^{13}C-NMR spectrum of compound **41**

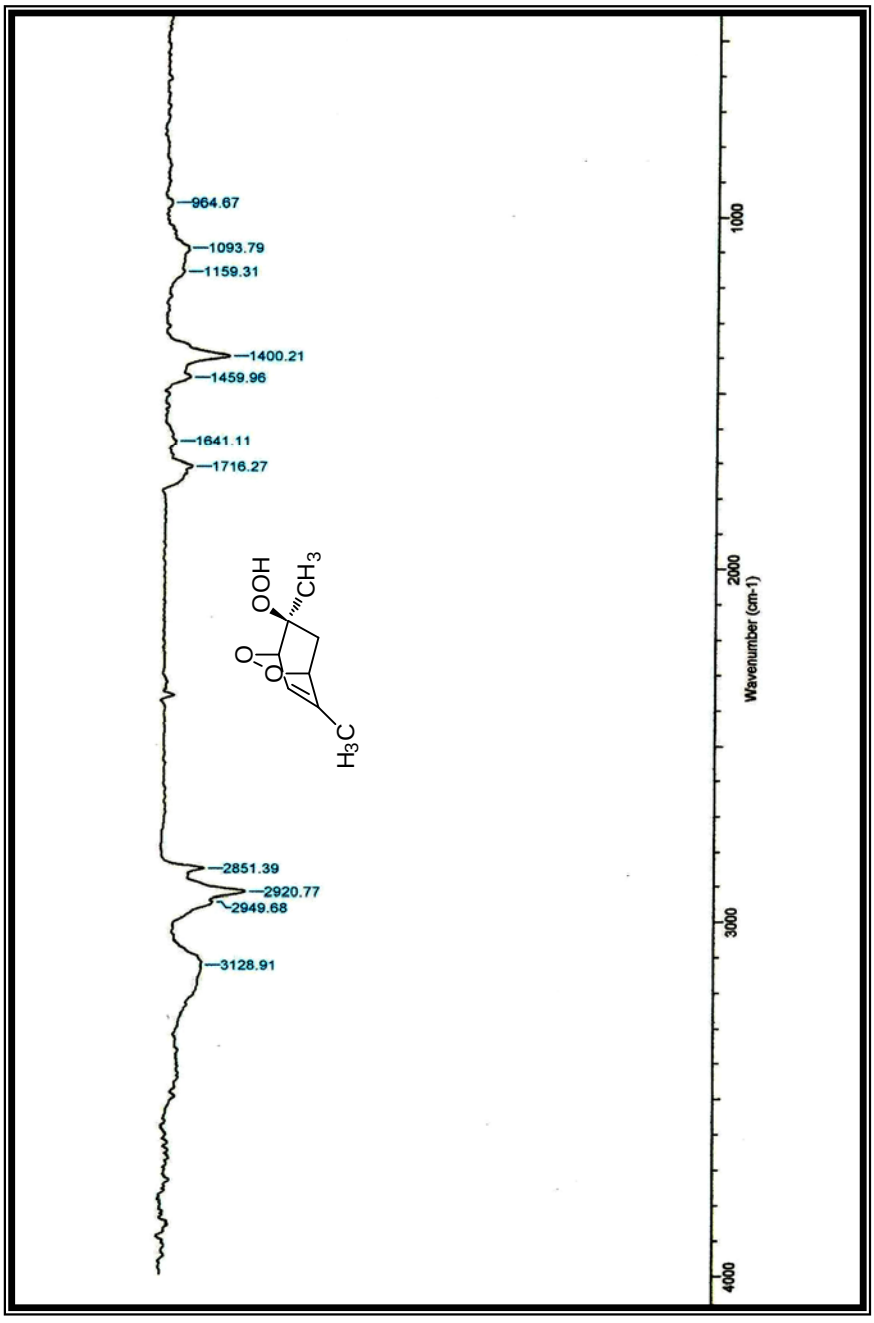


Figure I. 38 IR spectrum of compound **40**

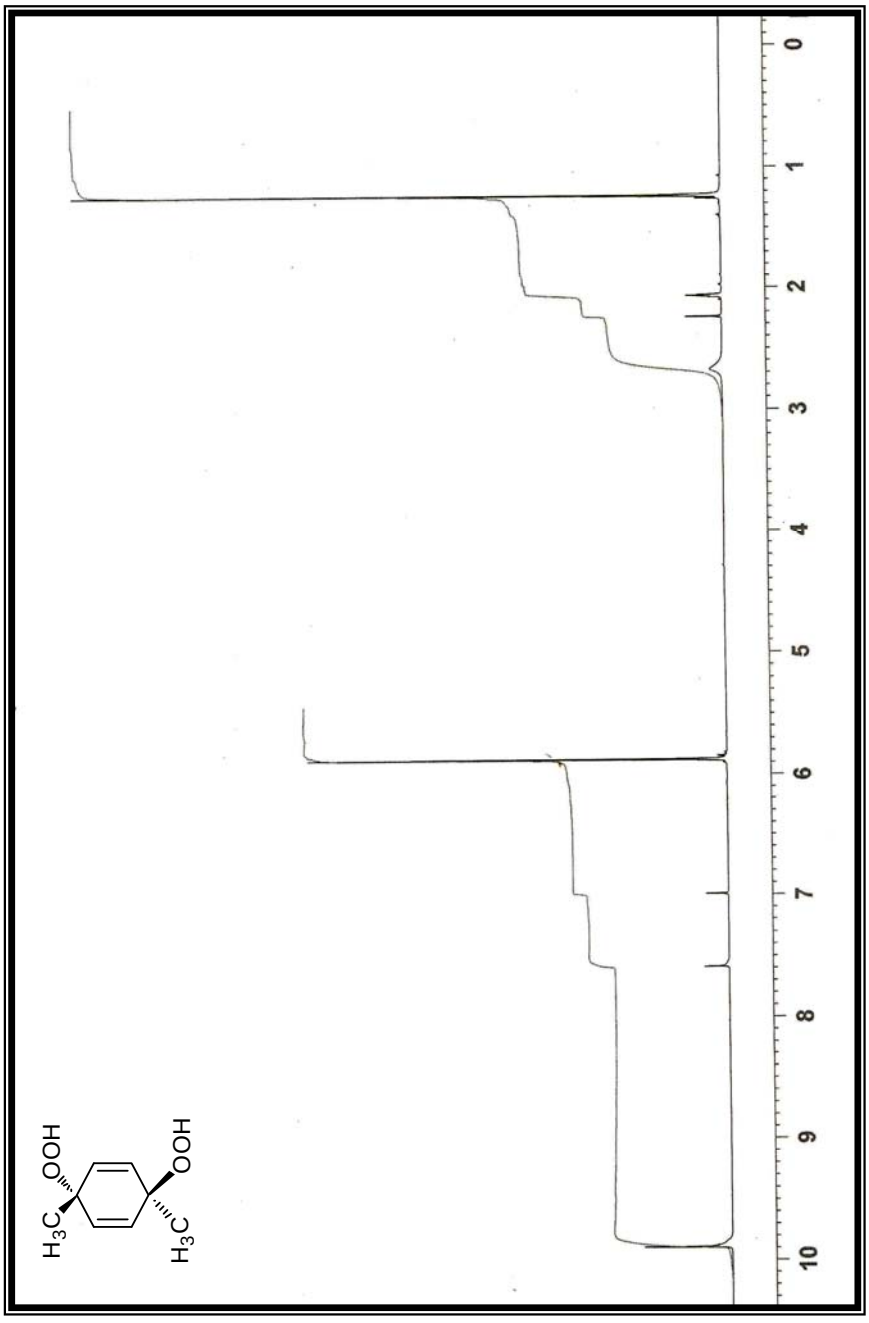


Figure I. 39 ^{1}H-NMR spectrum of compound **42**

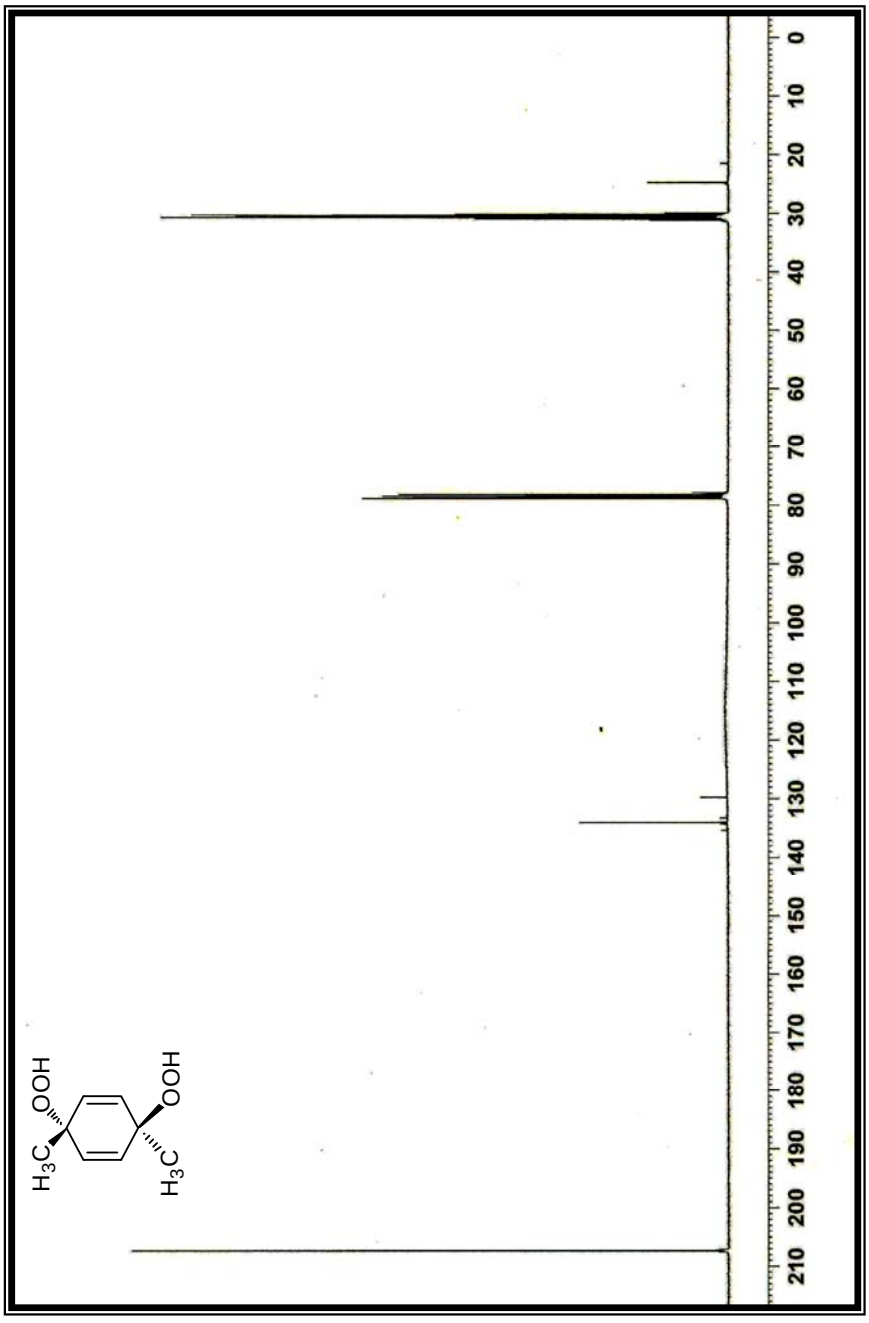


Figure I. 40 ^{13}C-NMR spectrum of compound **42**

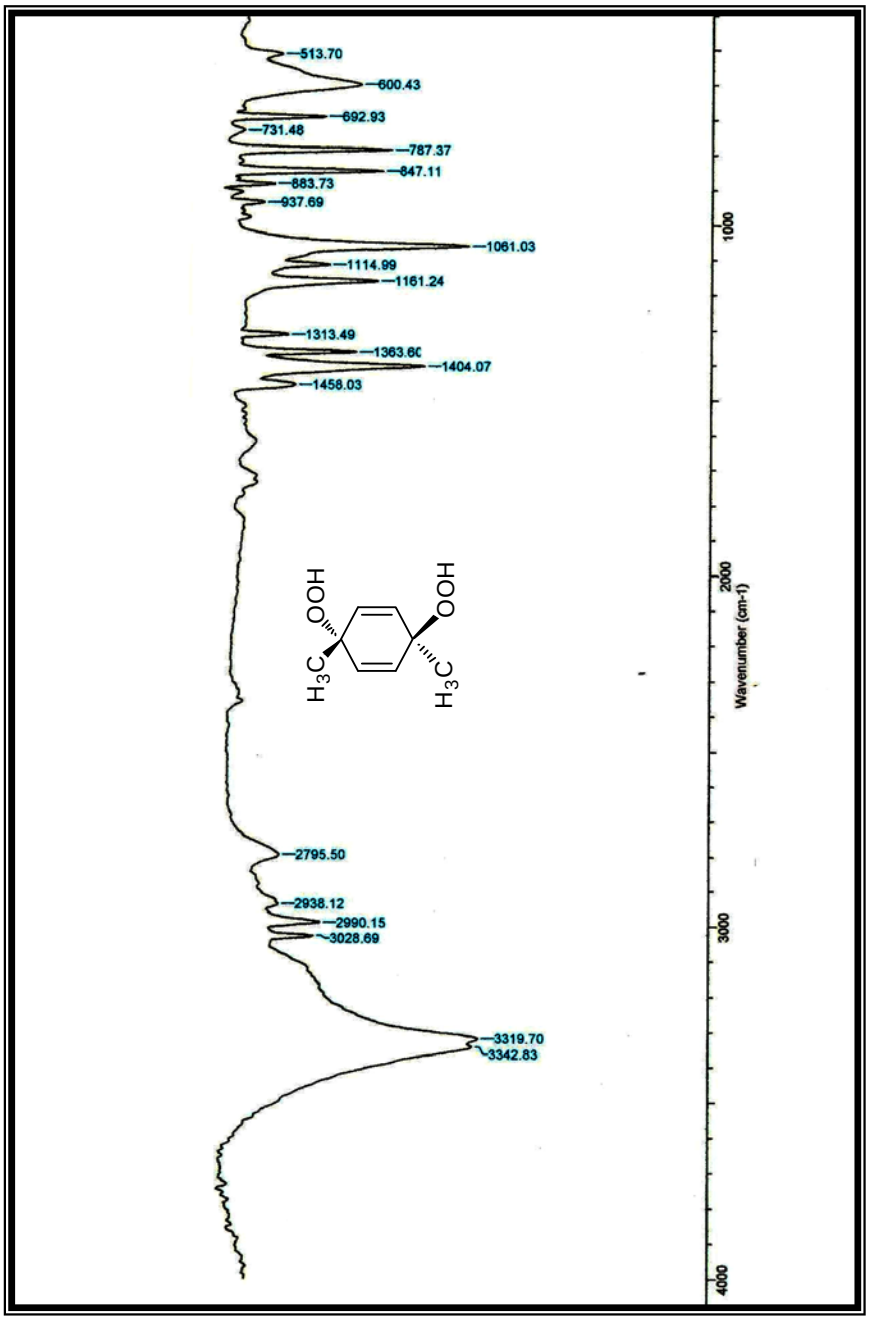


Figure I. 41 IR spectrum of compound **42**

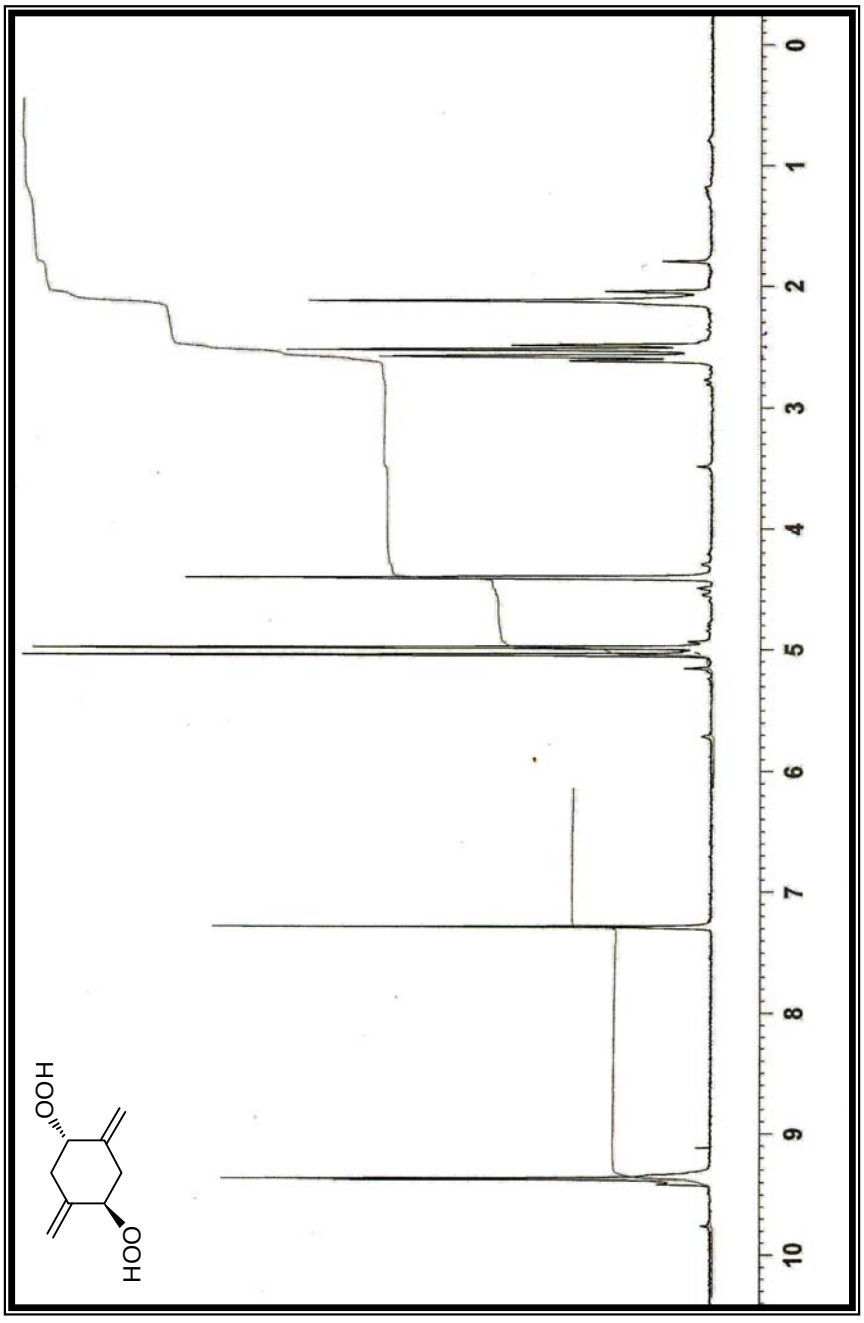


Figure I. 42 ^{1}H-NMR spectrum of compound **43**

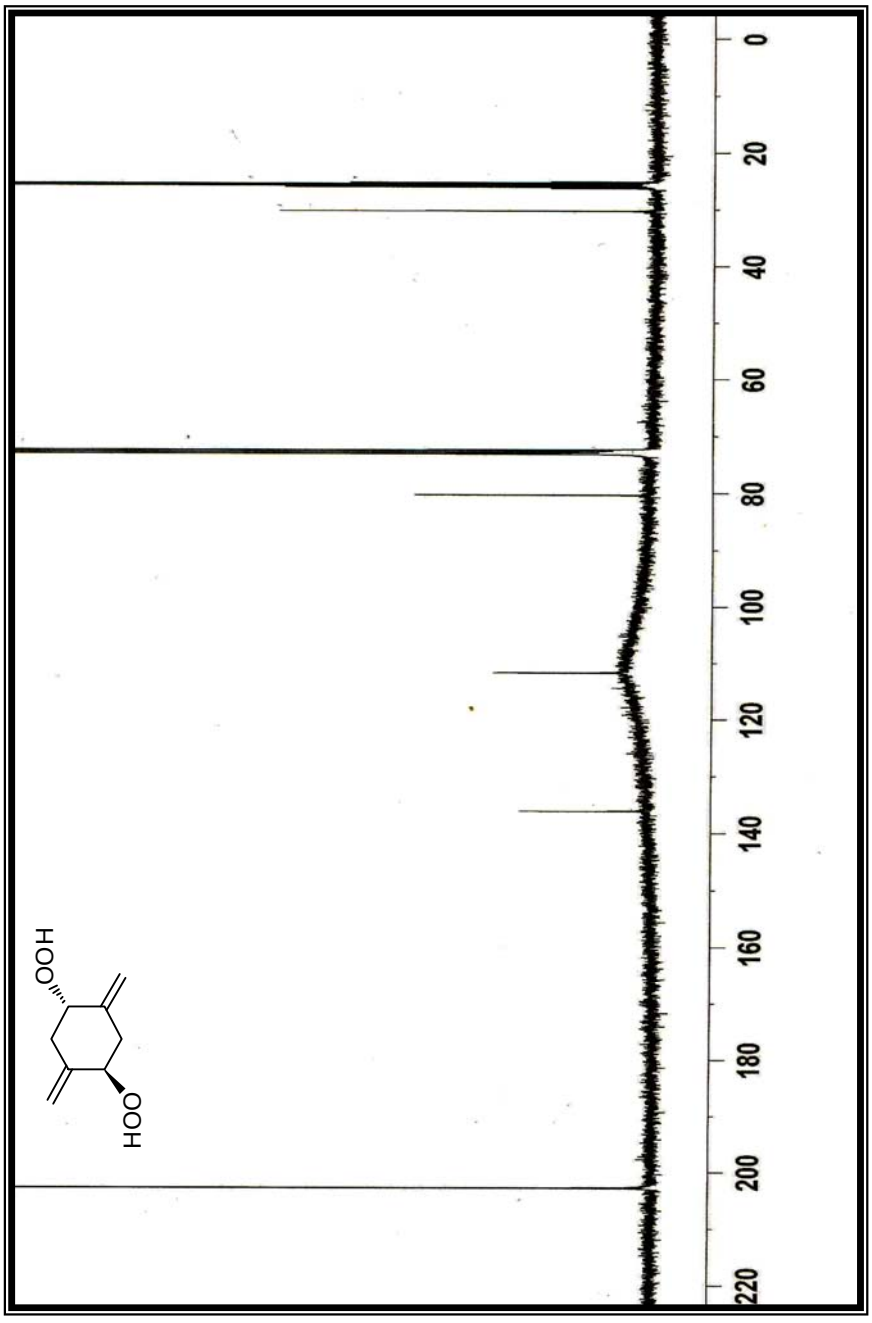


Figure I. 43 ^{13}C-NMR spectrum of compound **43**

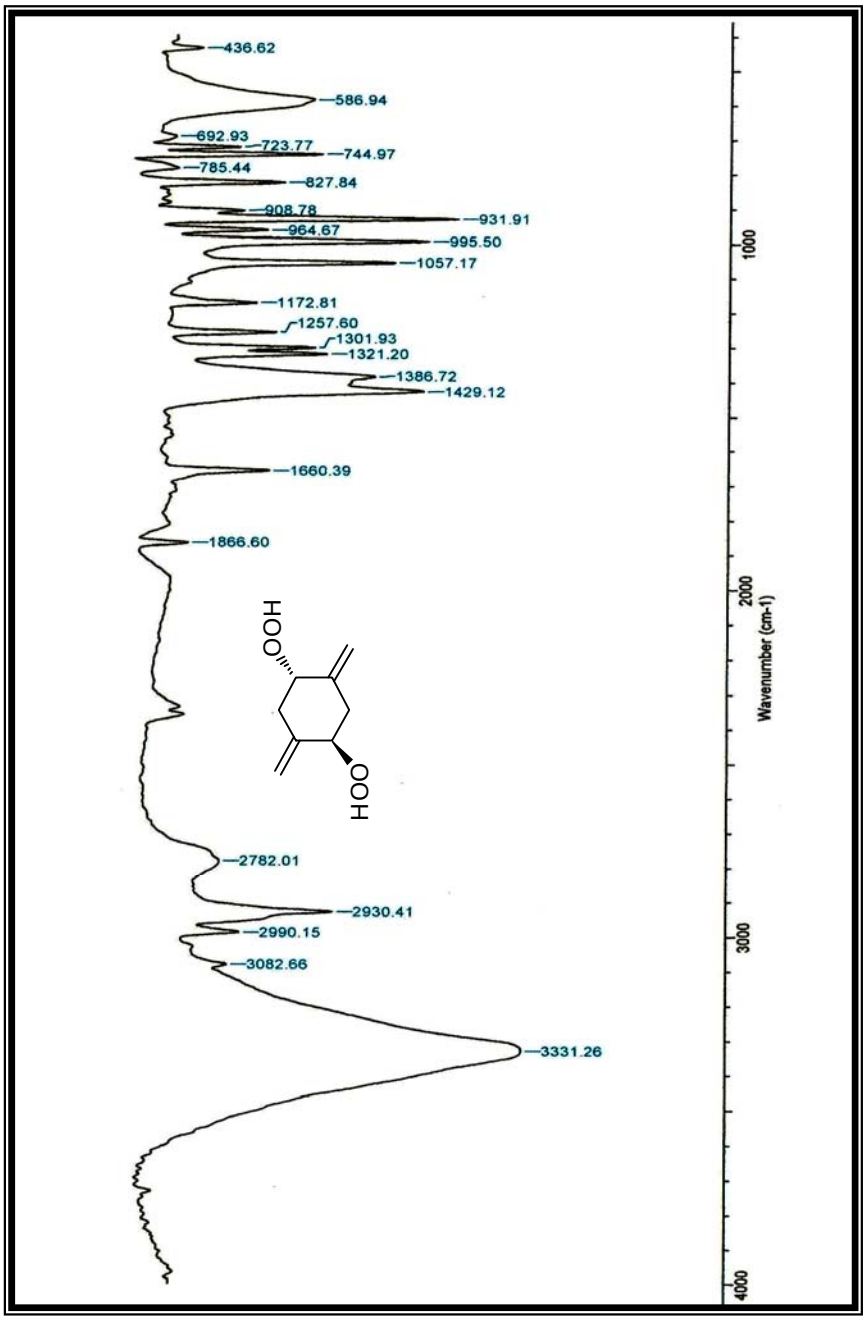


Figure I. 44 IR spectrum of compound **43**

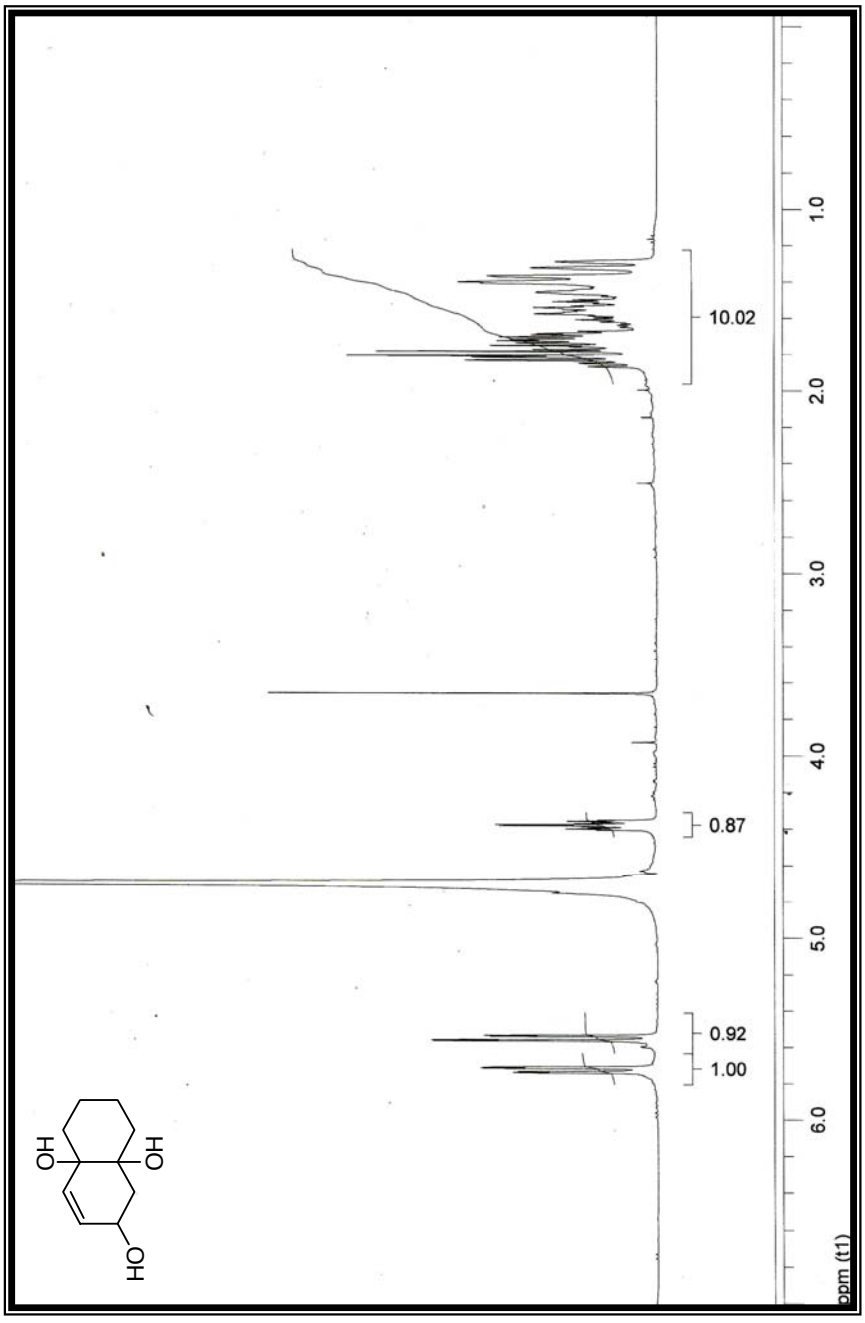


Figure I. 45 ^{1}H-NMR spectrum of compound **51**

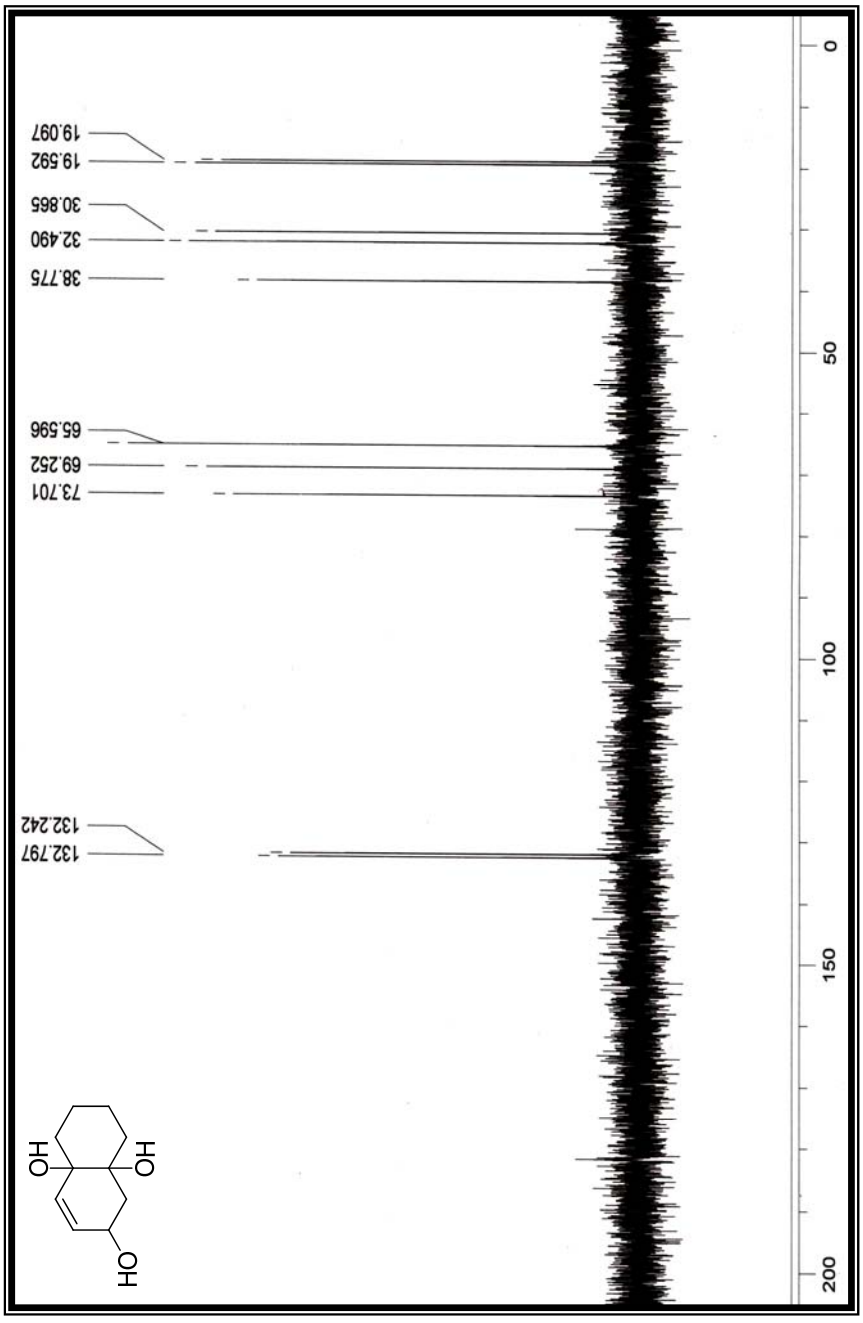


Figure I. 46 ^{13}C-NMR spectrum of compound **51**

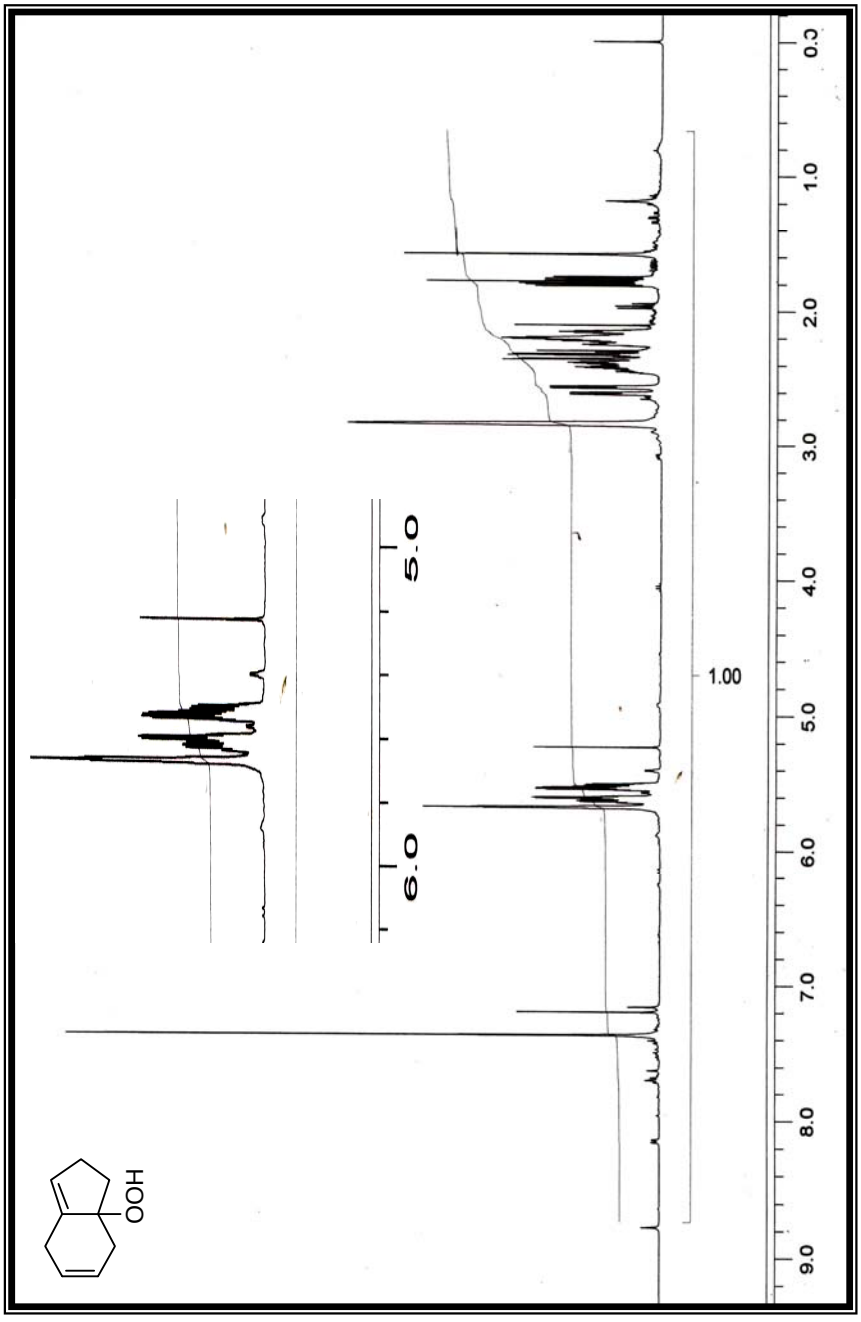


Figure I. 47 ^{1}H-NMR spectrum of compound **54**

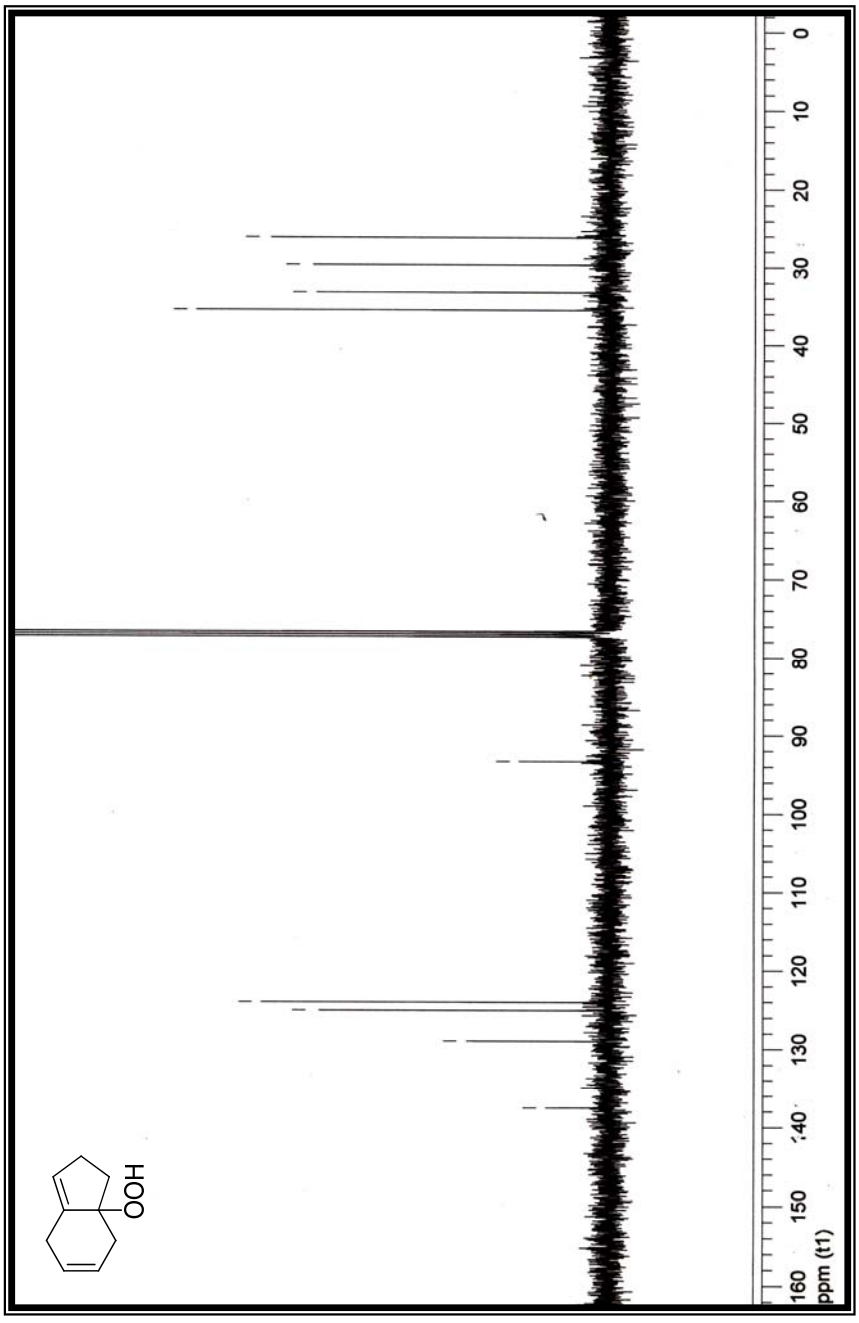


Figure I. 48 ^{13}C-NMR spectrum of compound **54**

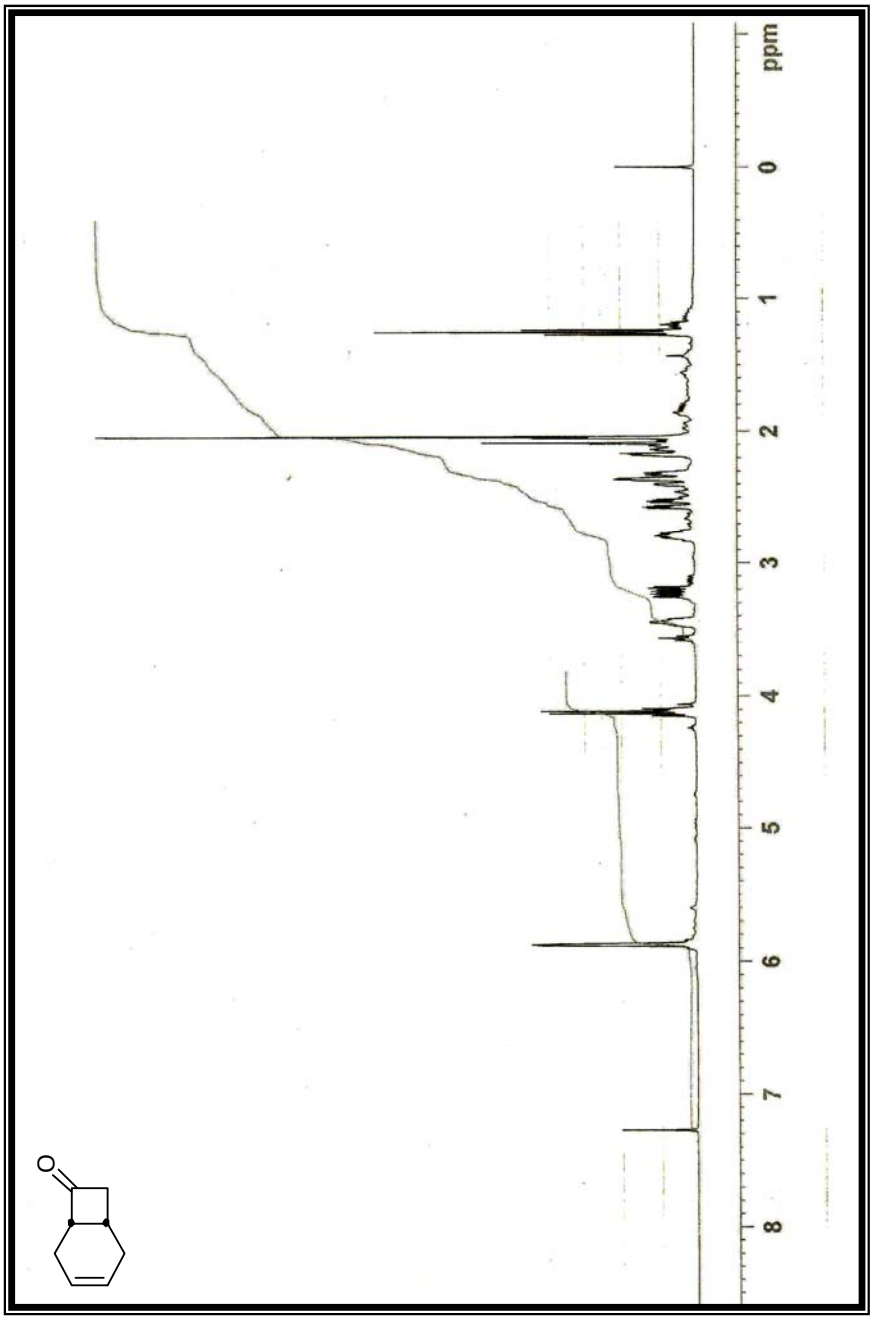


Figure II. 30 ^{1}H-NMR spectrum of compound **187**

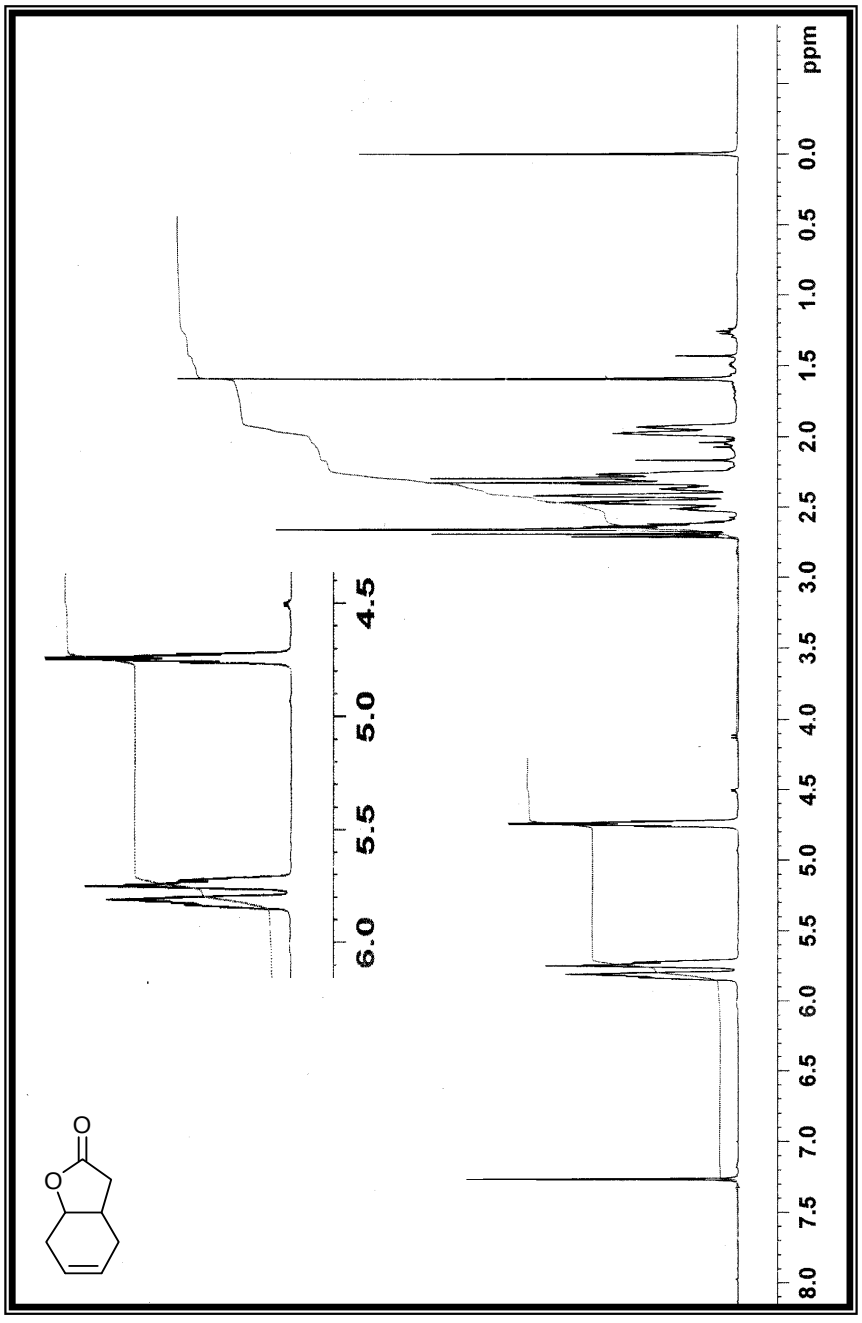


Figure II. 31 ^{1}H-NMR spectrum of compound **188**

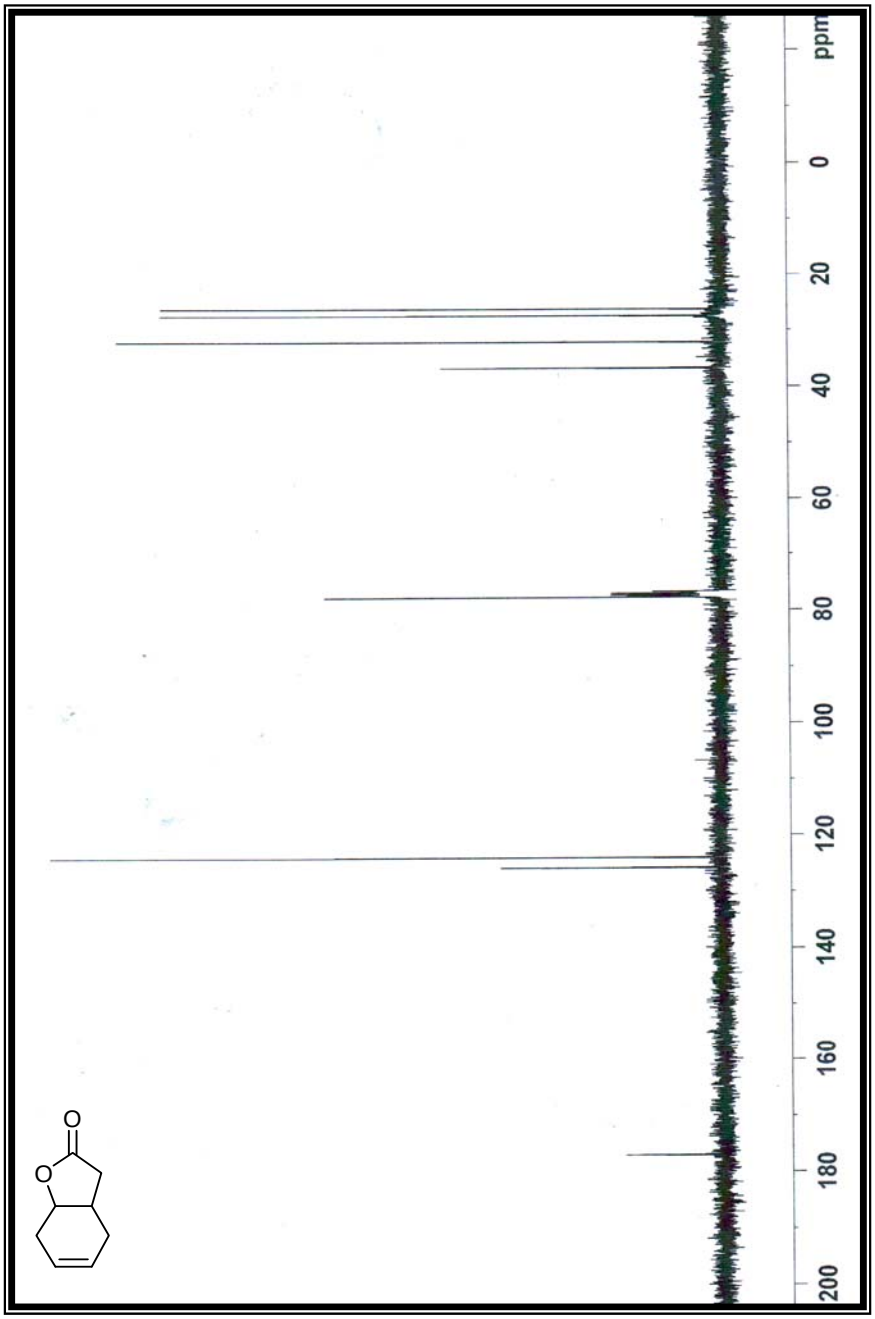


Figure II. 32 ^{13}C-NMR spectrum of compound **188**

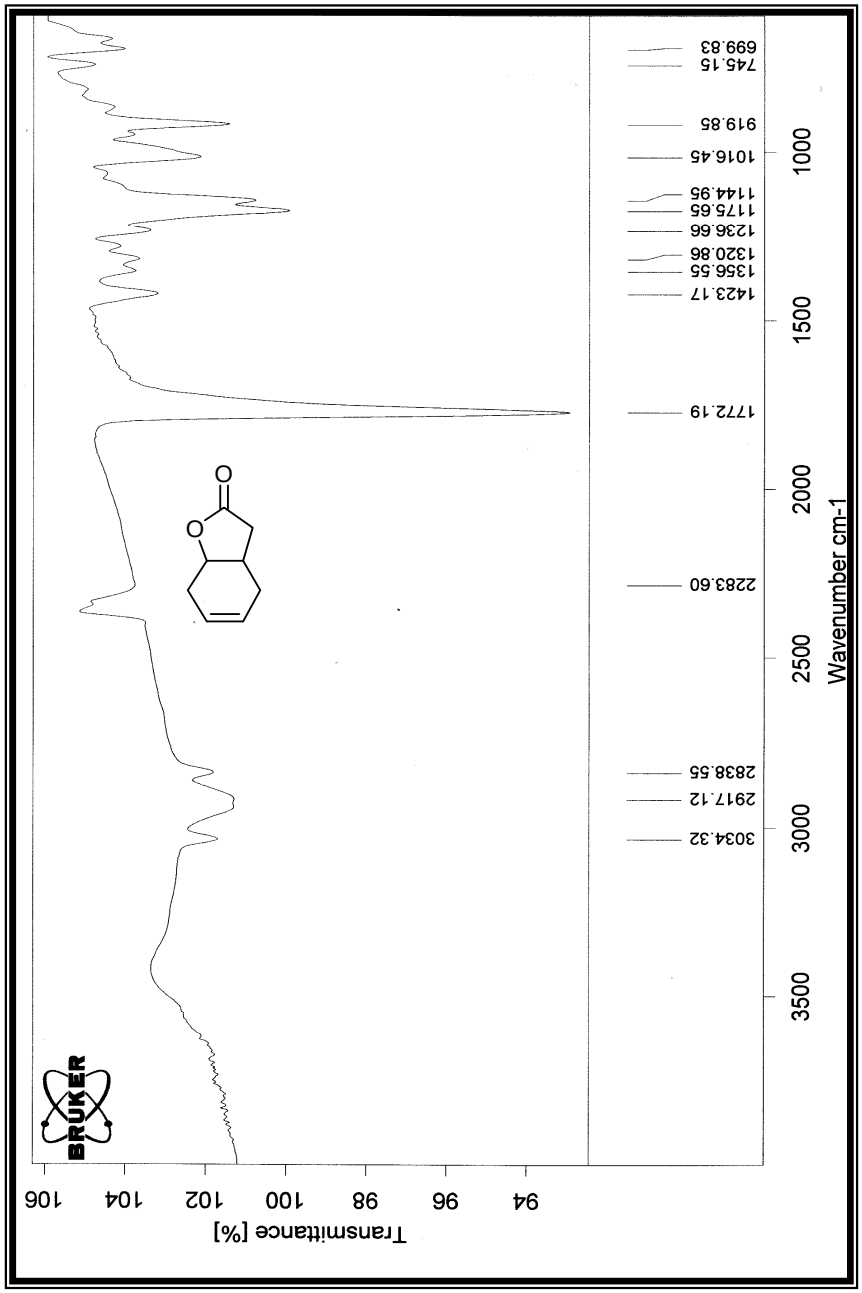


Figure II. 33 IR spectrum of compound **188**

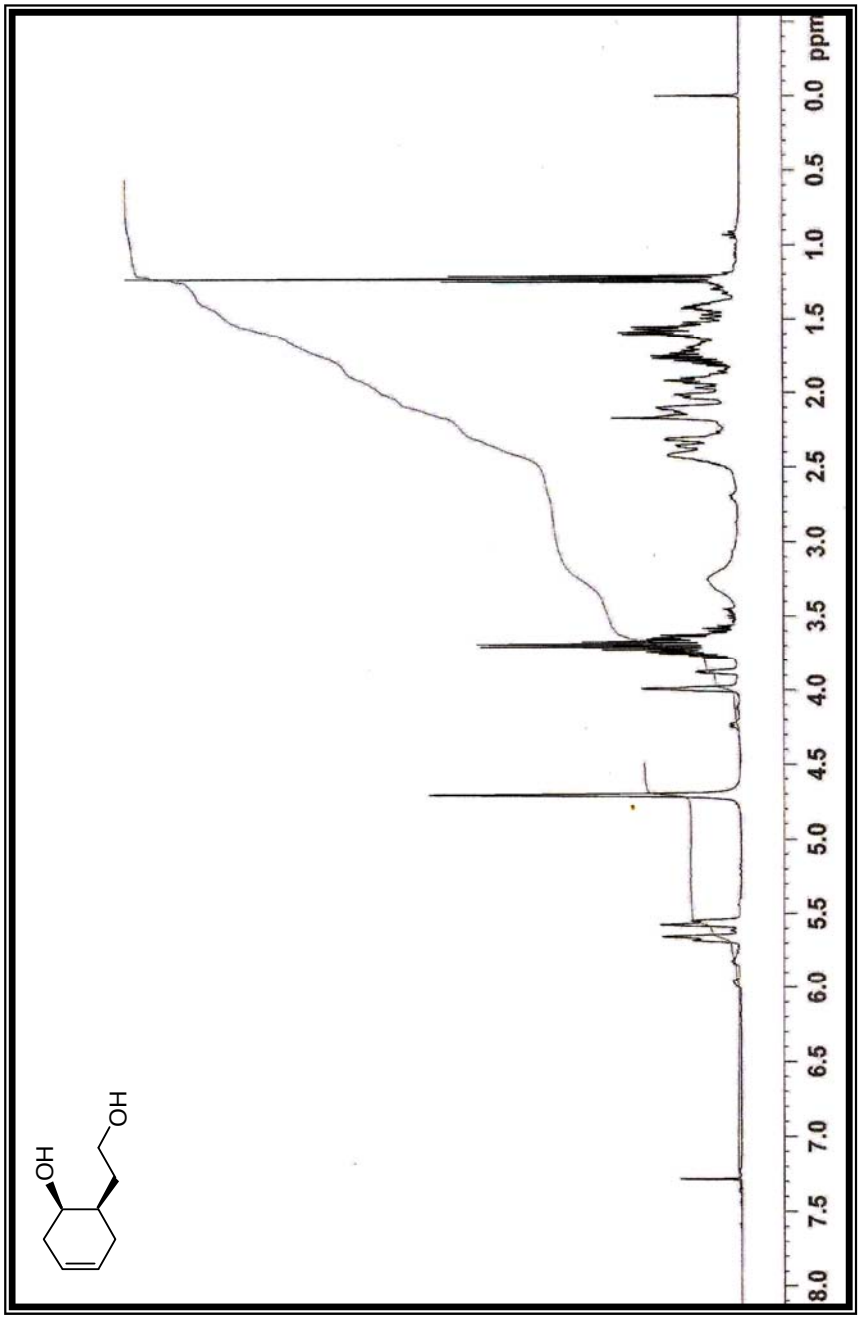


Figure II. 34 ^{1}H-NMR spectrum of compound **182a**

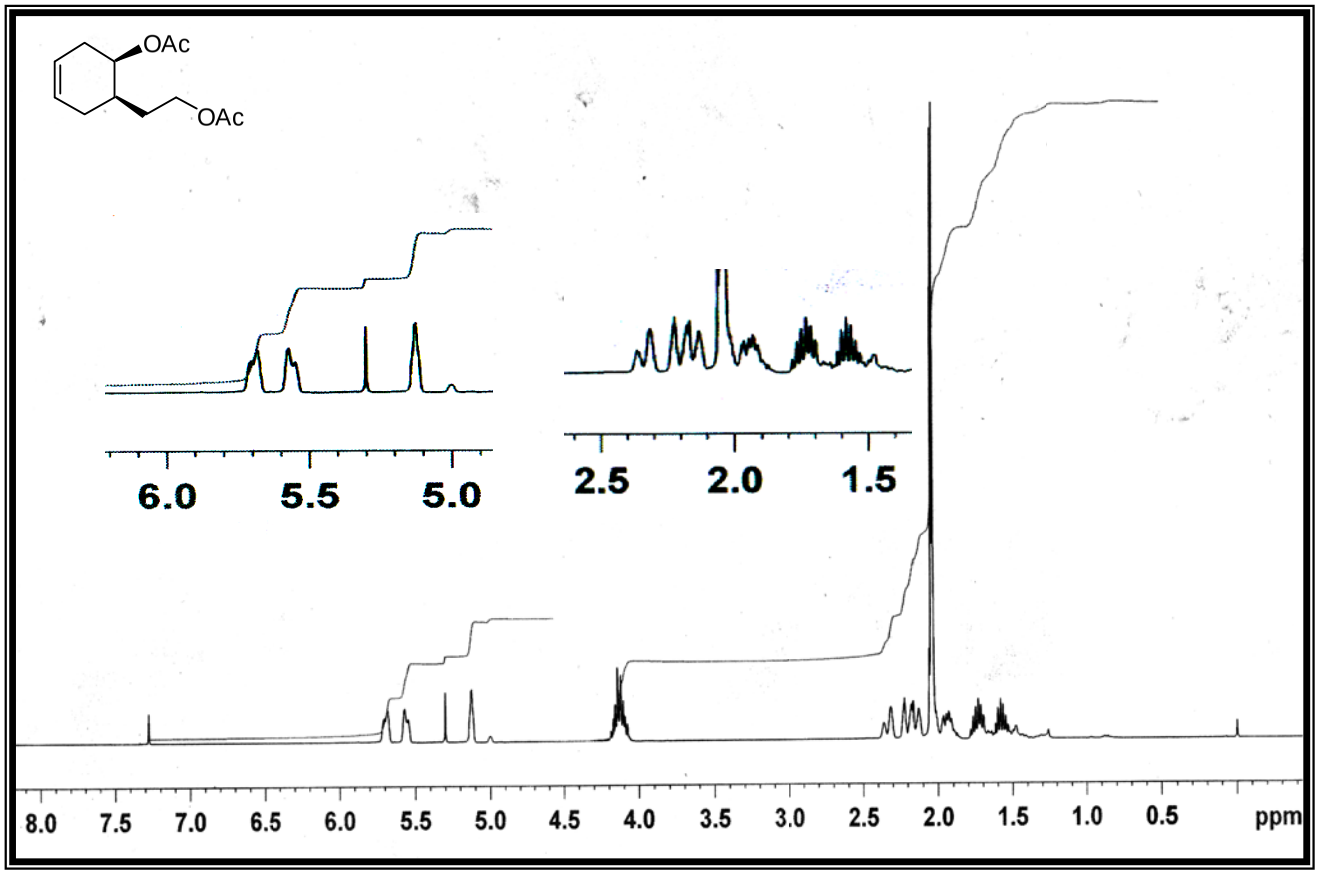


Figure II. 35 ^{1}H-NMR spectrum of compound **182b**

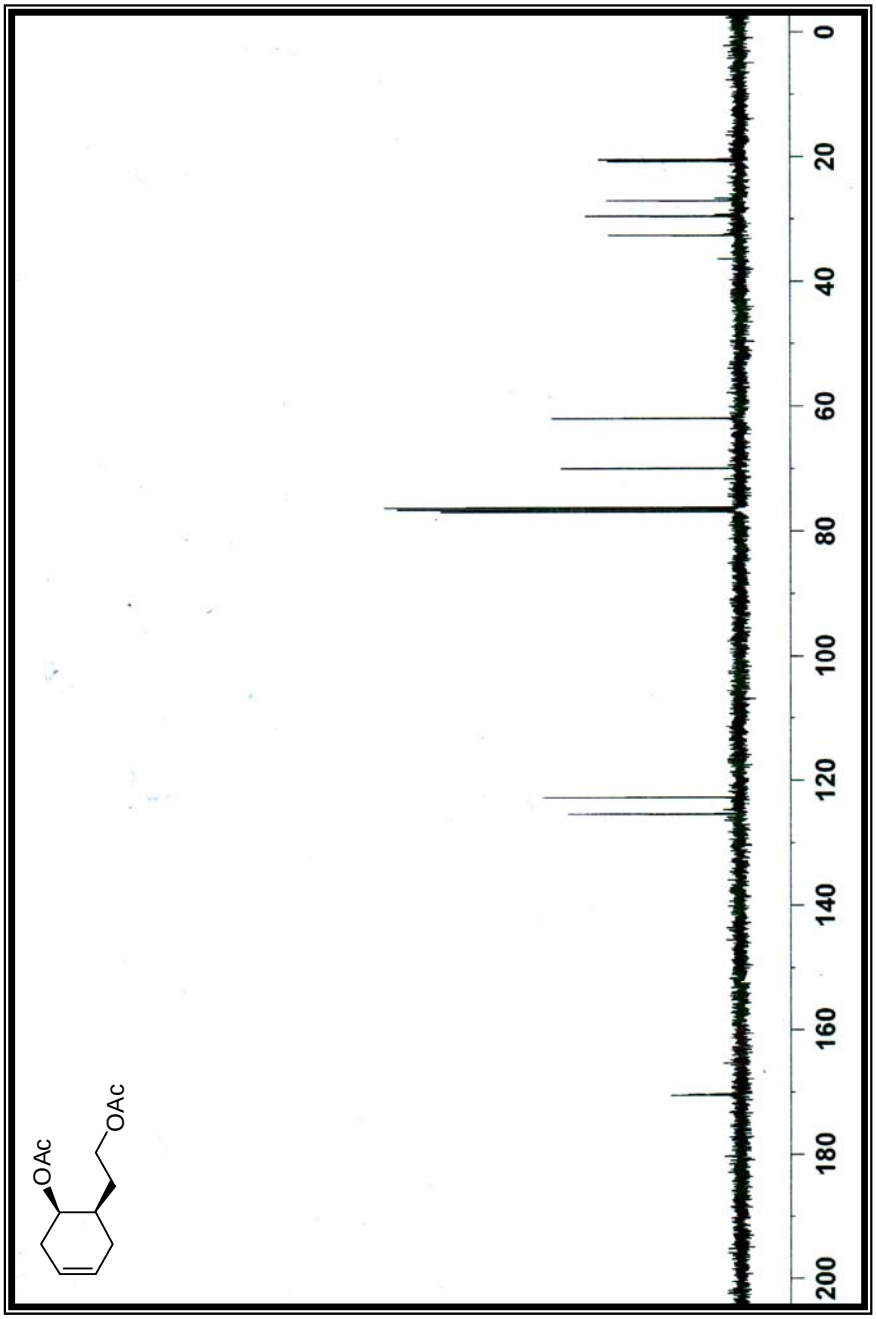


Figure II. 36 ^{13}C-NMR spectrum of compound **182b**

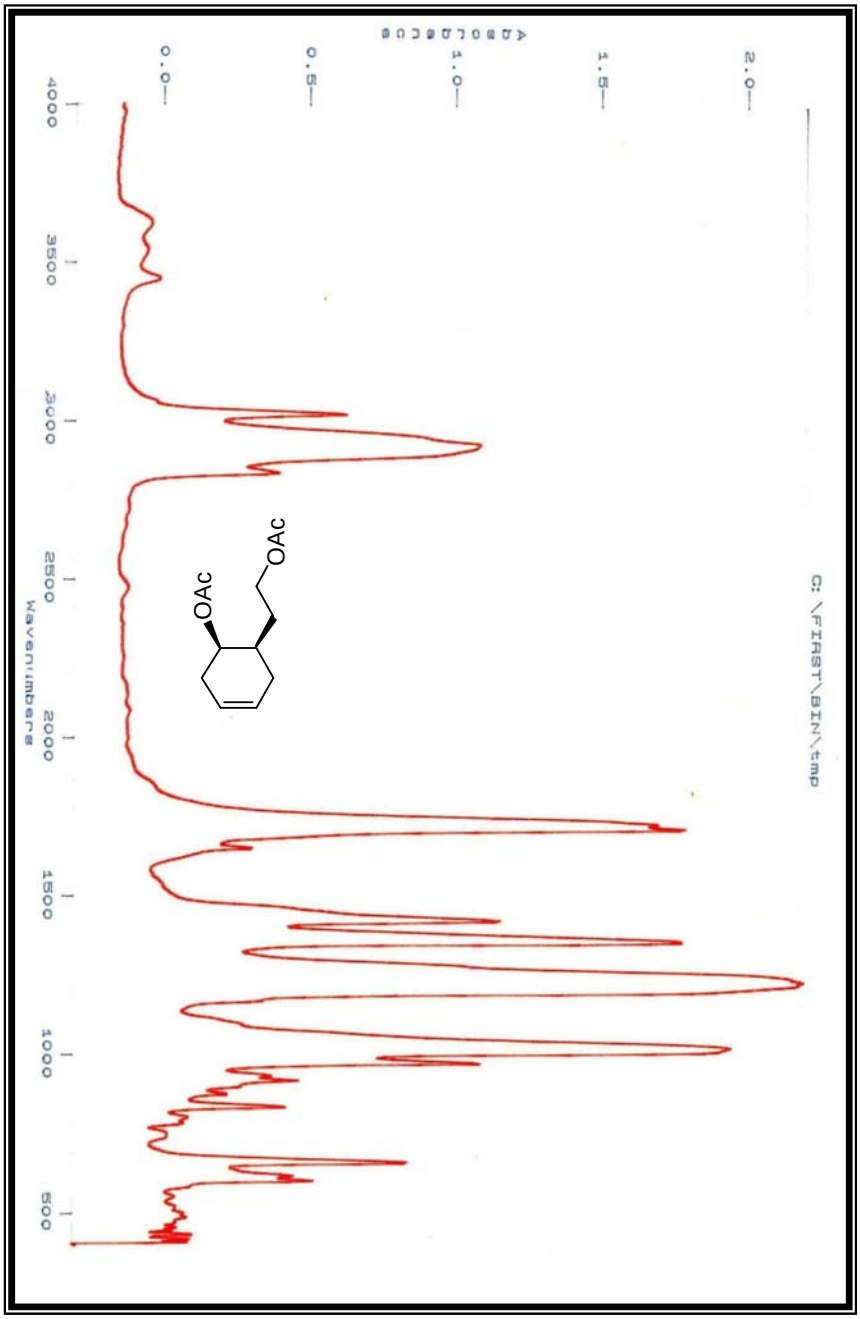


Figure II. 37 IR spectrum of compound **182b**

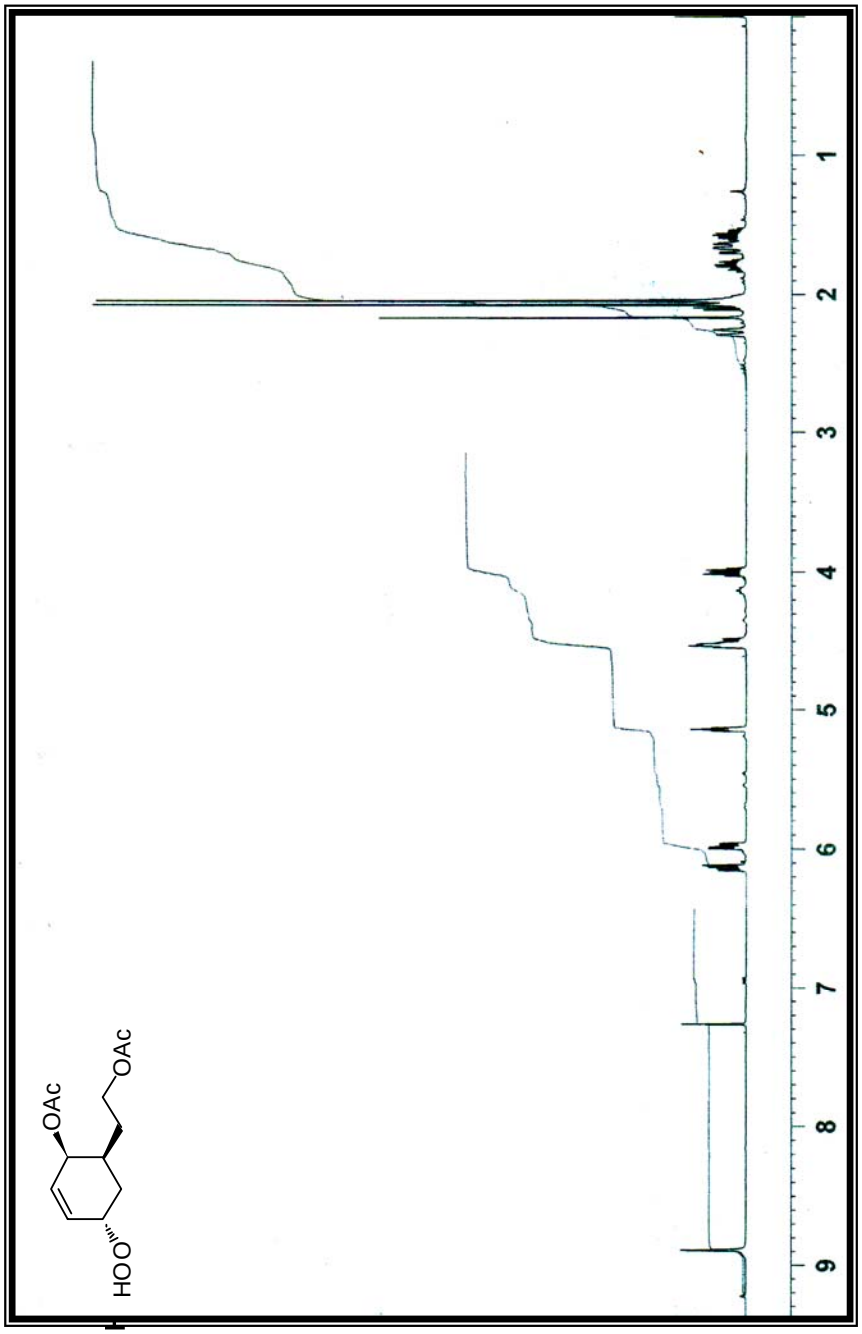


Figure II. 38 ^{1}H-NMR spectrum of compound **189**

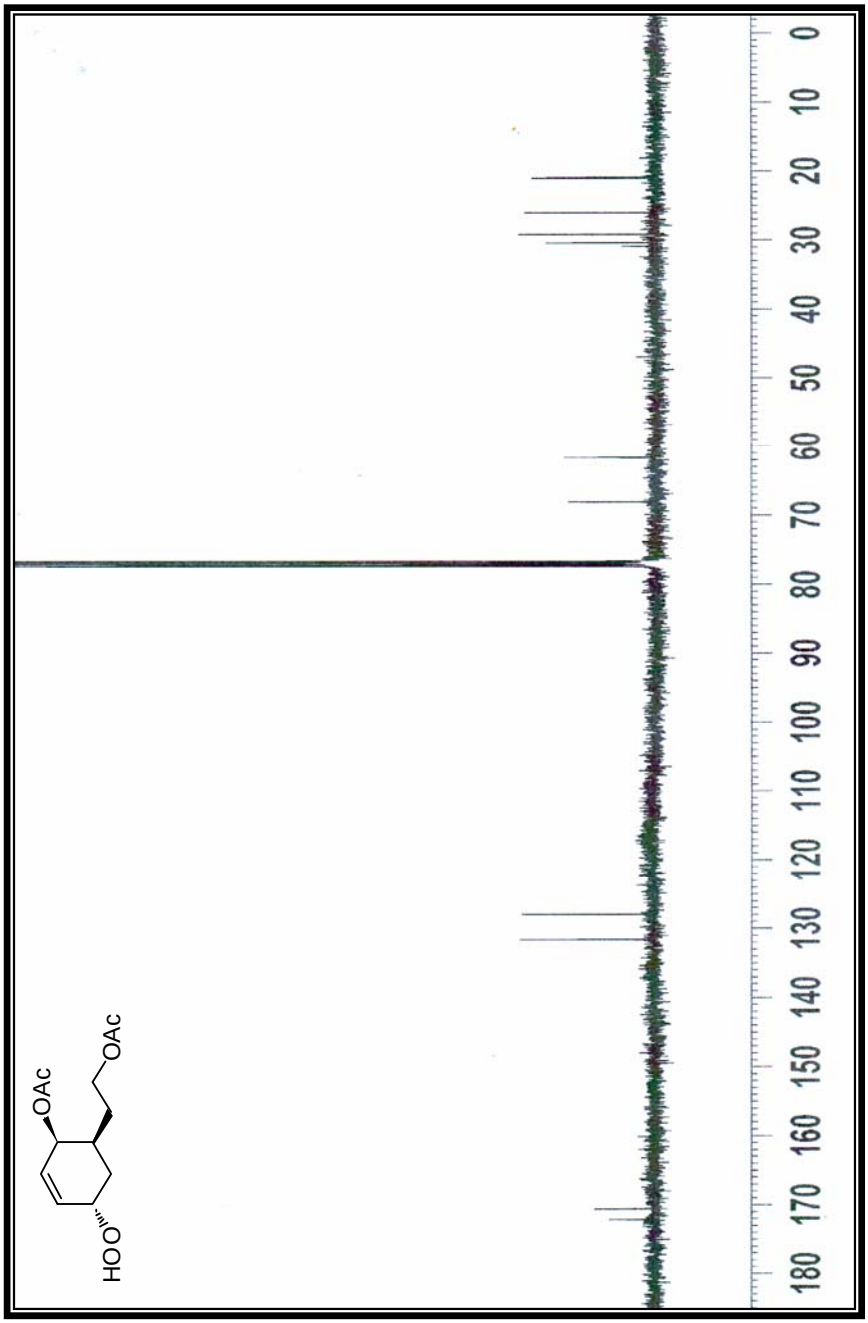


Figure II. 39 ^{13}C-NMR spectrum of compound **189**

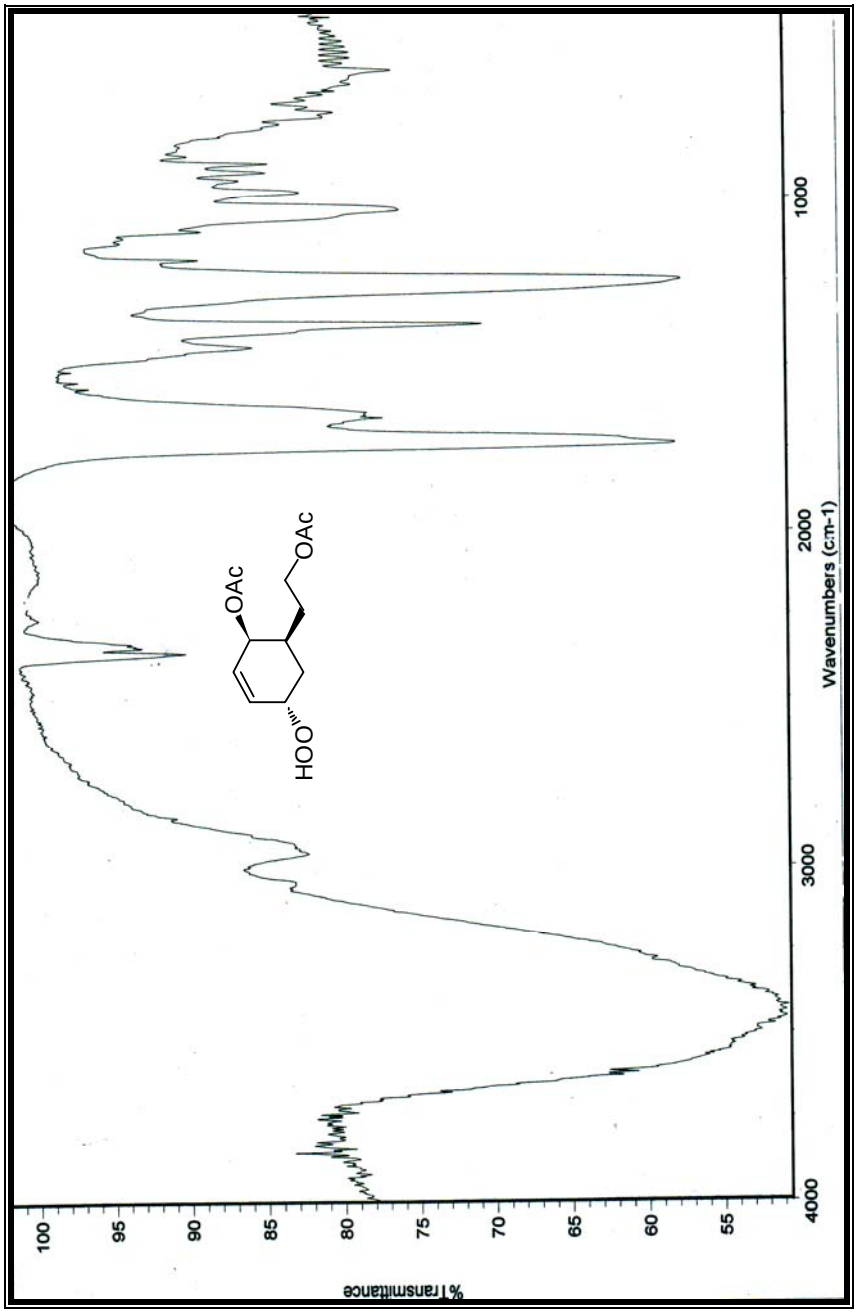


Figure II. 40 IR spectrum of compound **189**

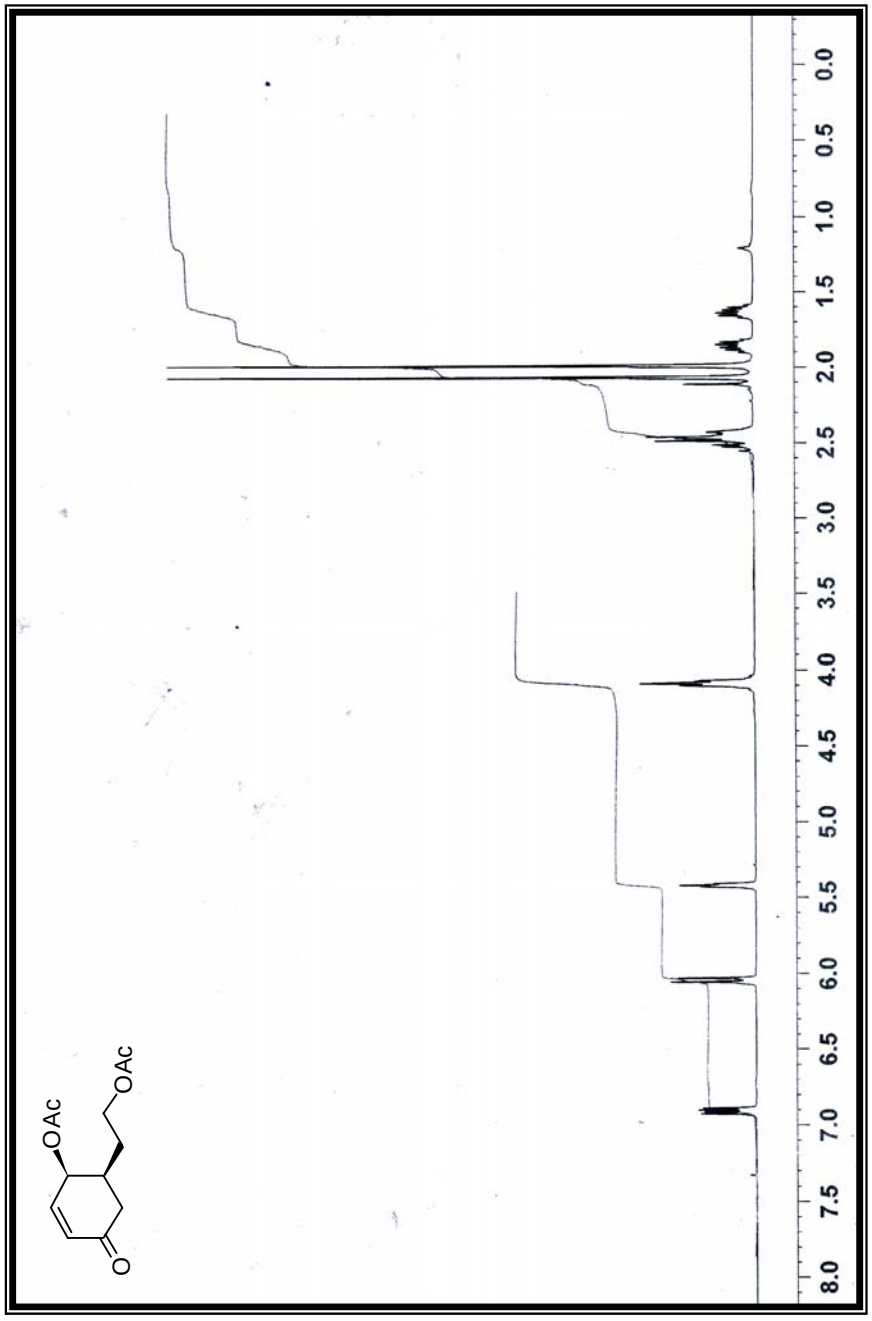


Figure II. 41 ^{1}H-NMR spectrum of compound **190**

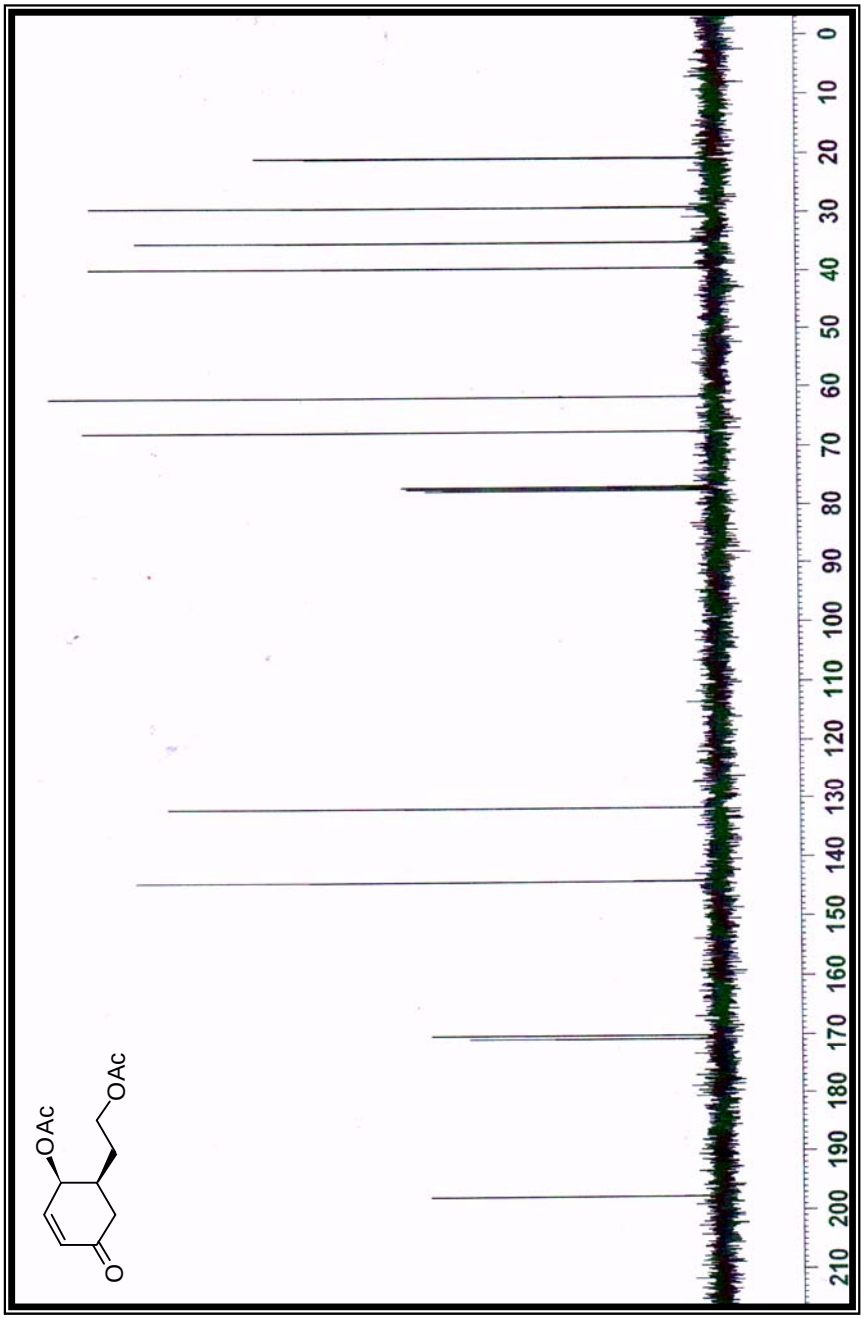


Figure II. 42 ^{13}C-NMR spectrum of compound **190**

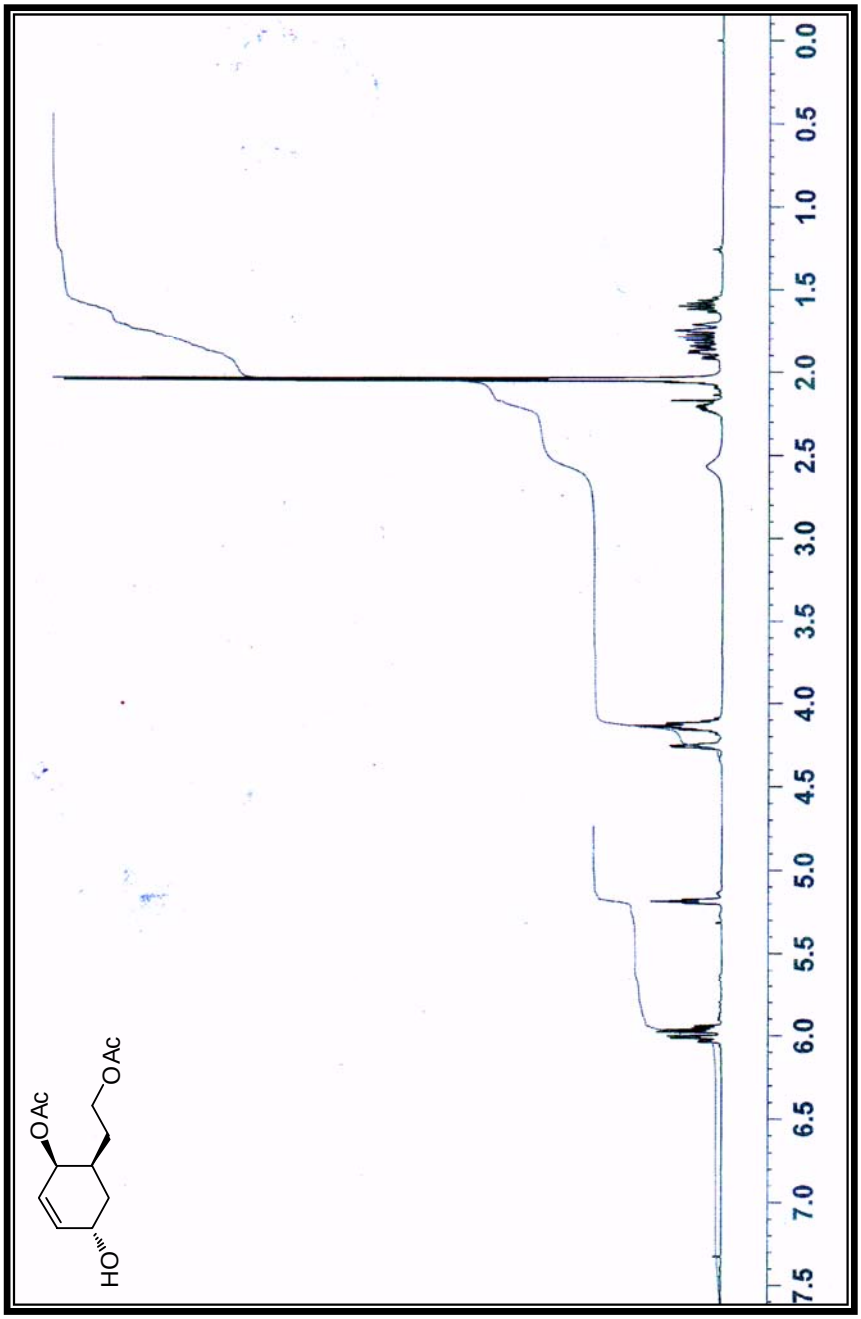


Figure II. 43 ^{1}H-NMR spectrum of compound **192**

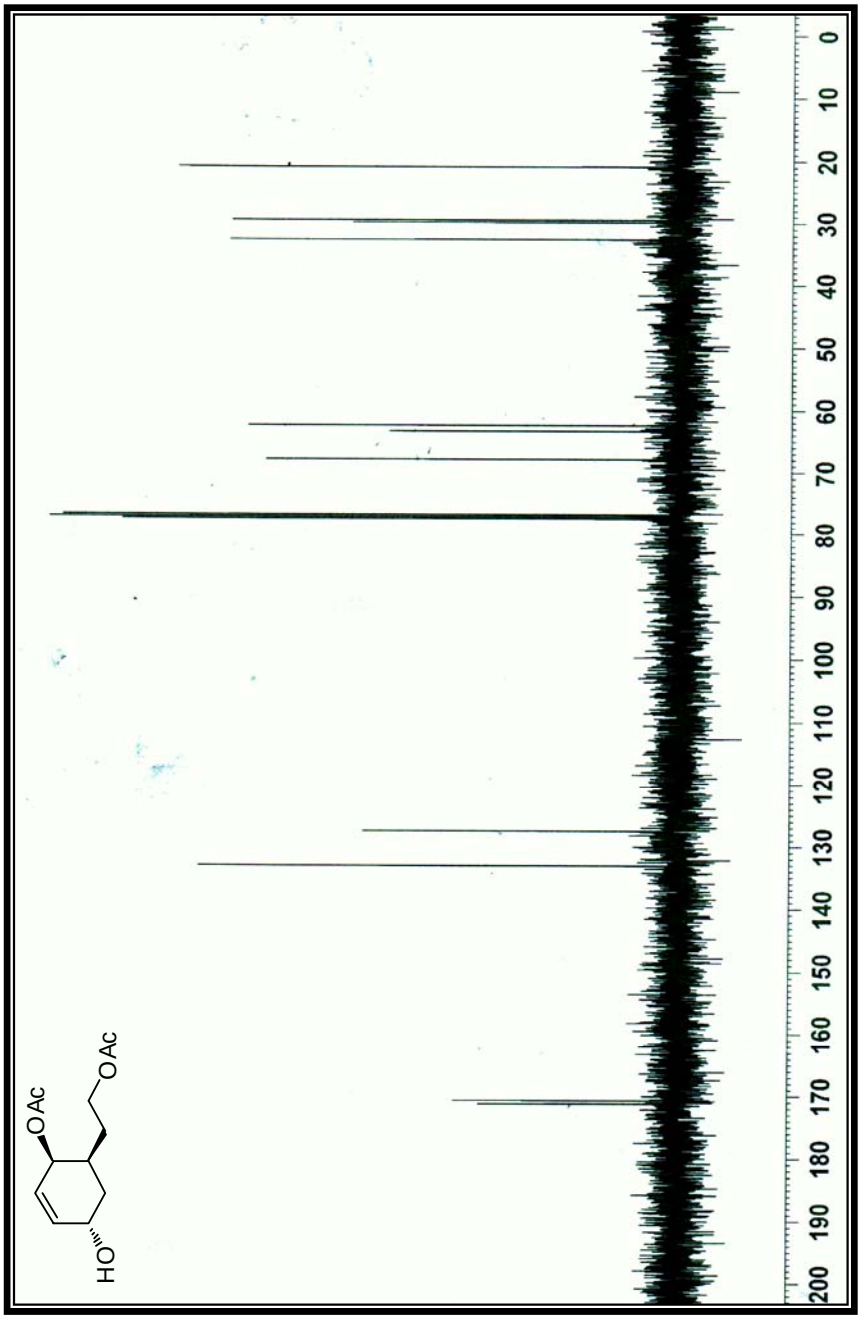


Figure II. 44 ^{13}C-NMR spectrum of compound **192**

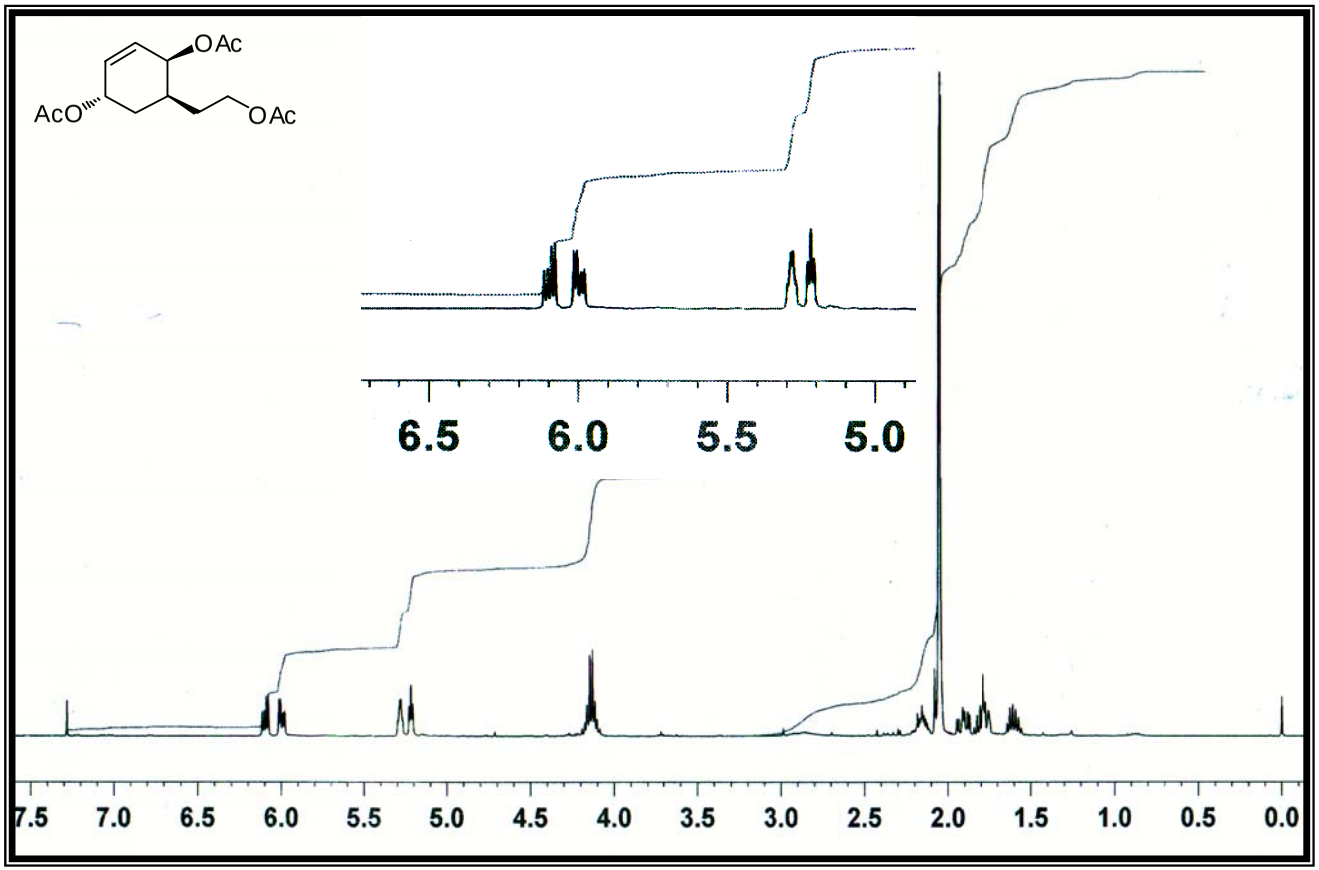


Figure II. 45 ^{1}H-NMR spectrum of compound **183**

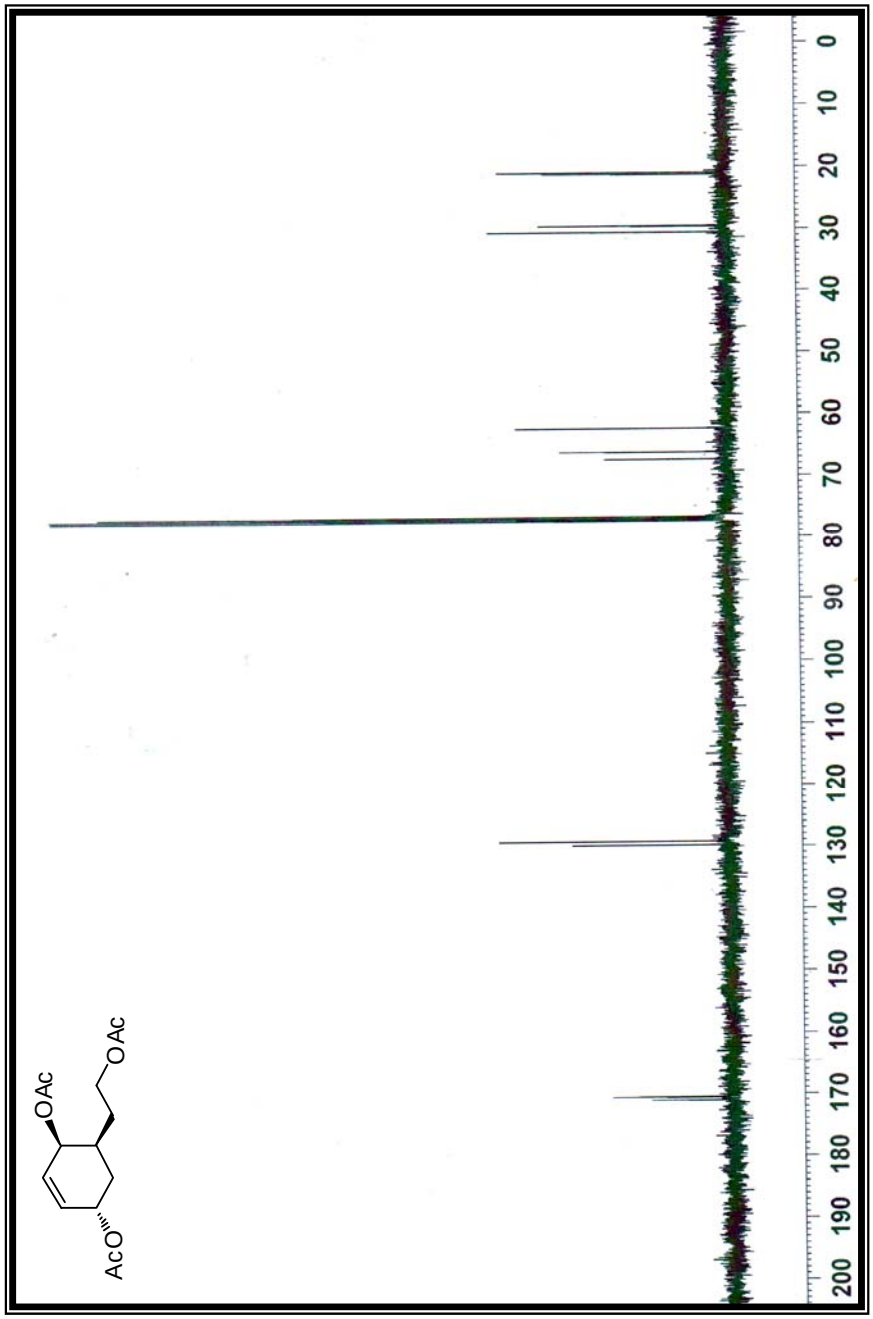


Figure II. 46 ^{13}C-NMR spectrum of compound **183**

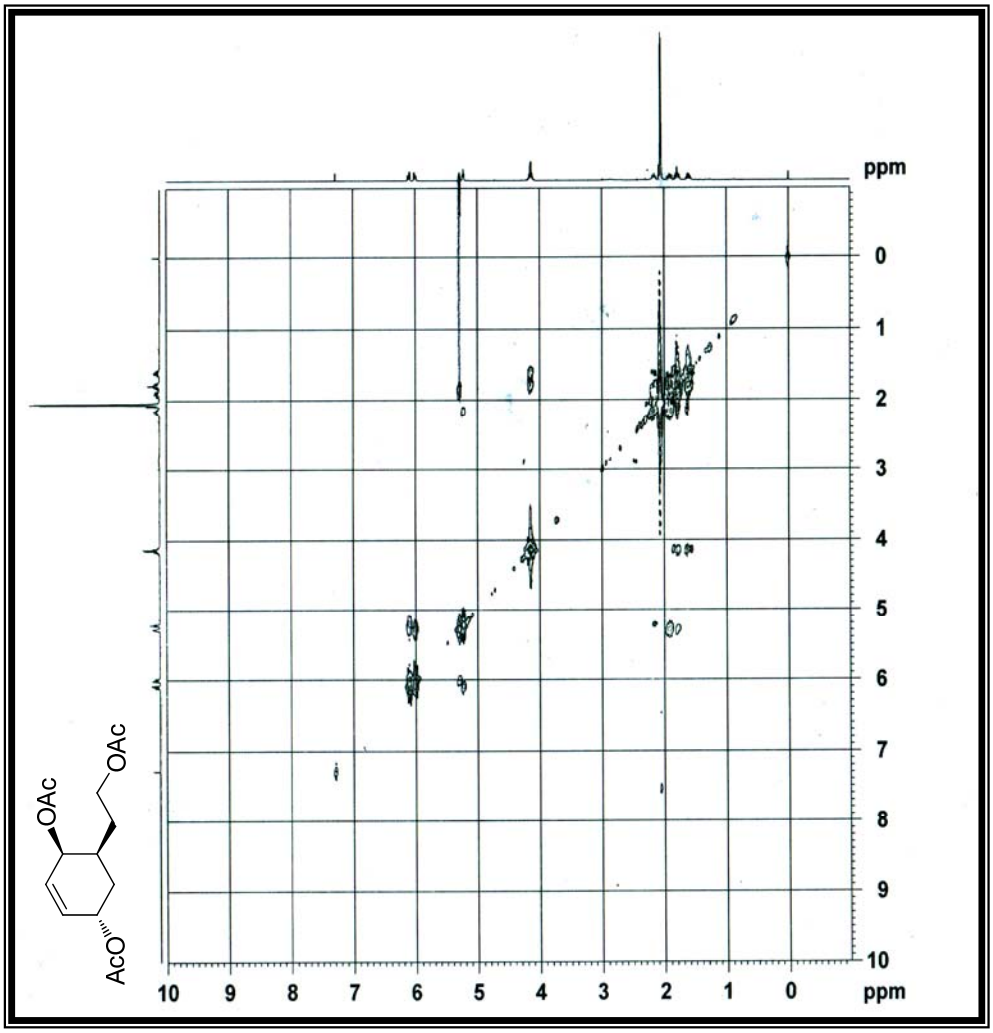


Figure II. 47 COSY spectrum of compound **183**

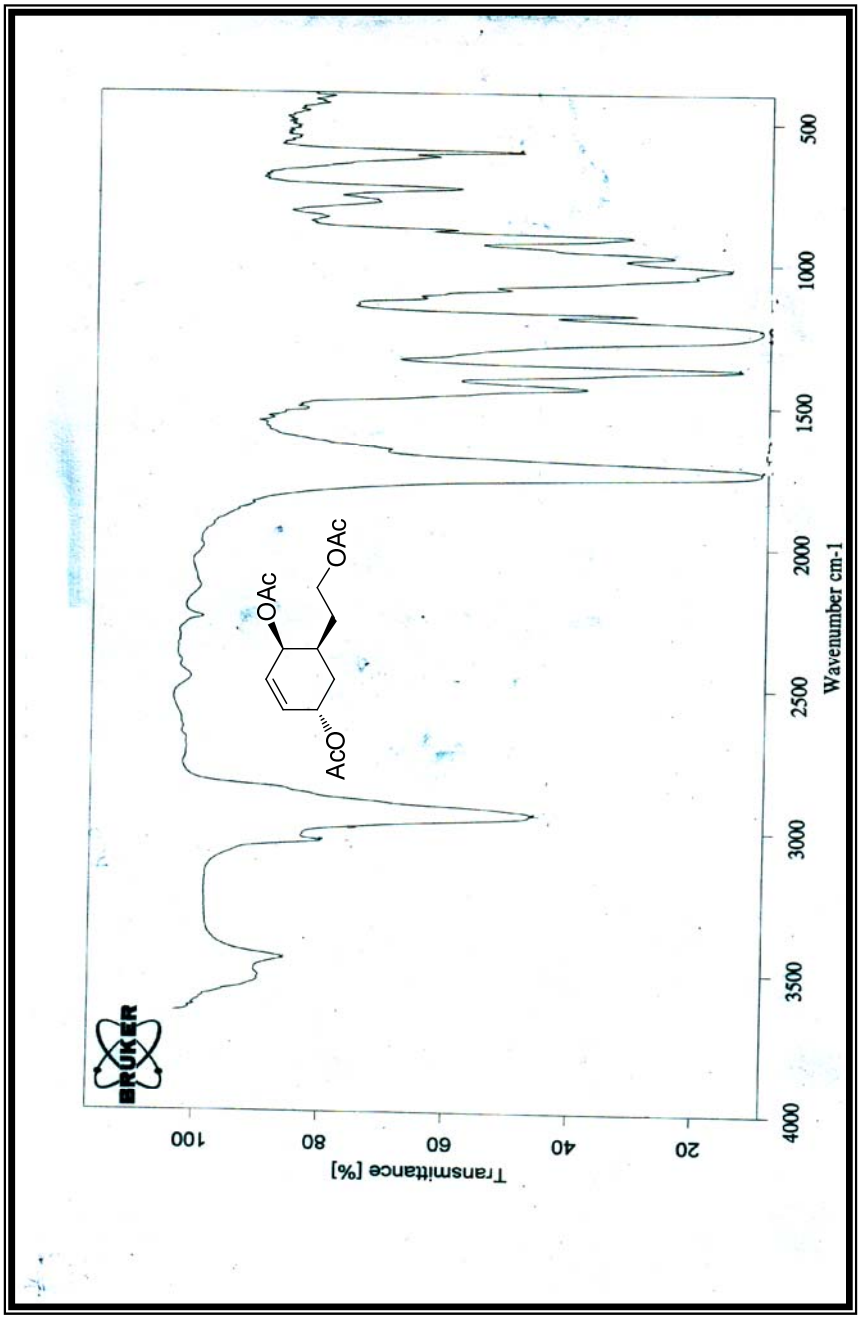


Figure II. 48 IR spectrum of compound **183**

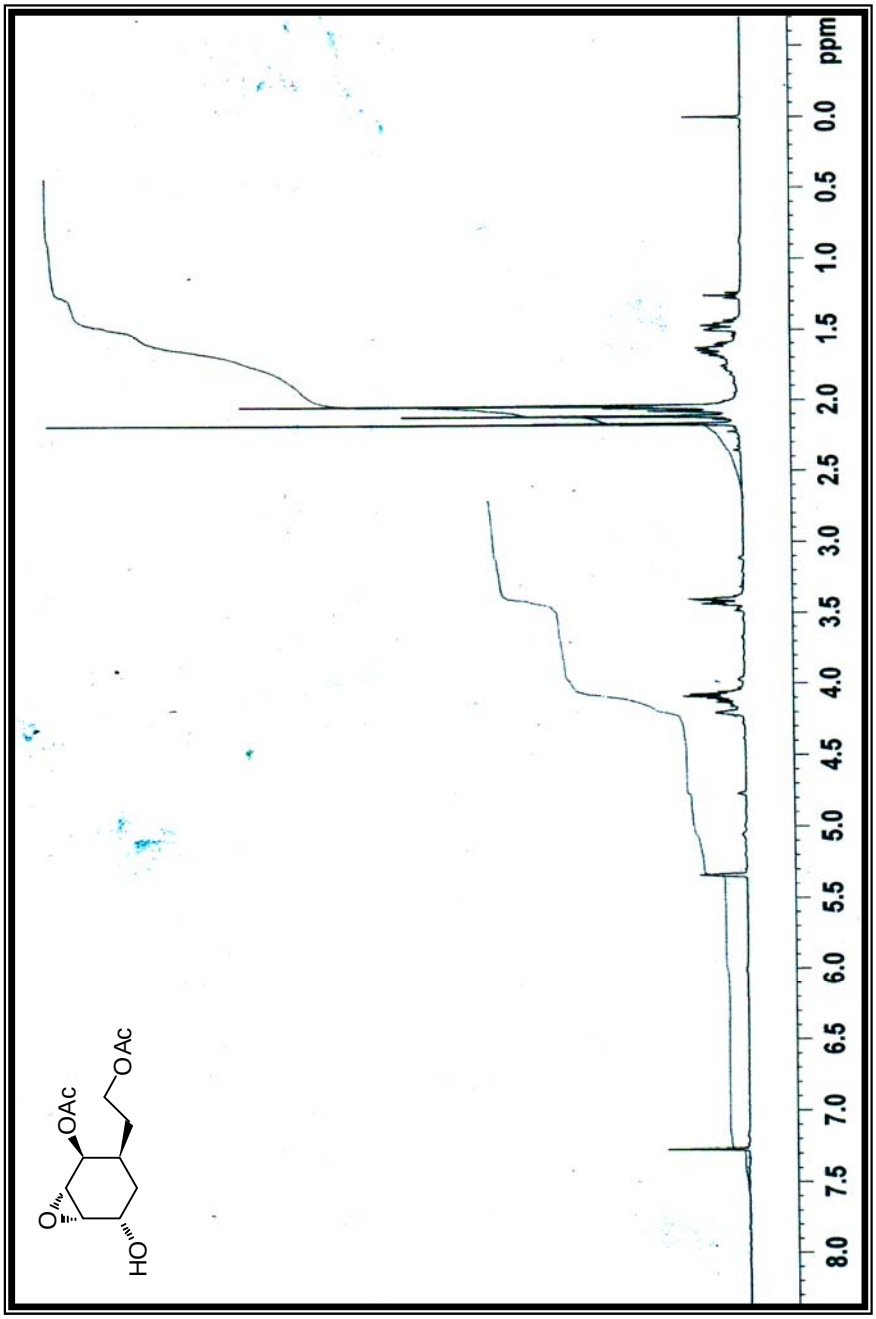


Figure II. 49 ^{1}H-NMR spectrum of compound **193**

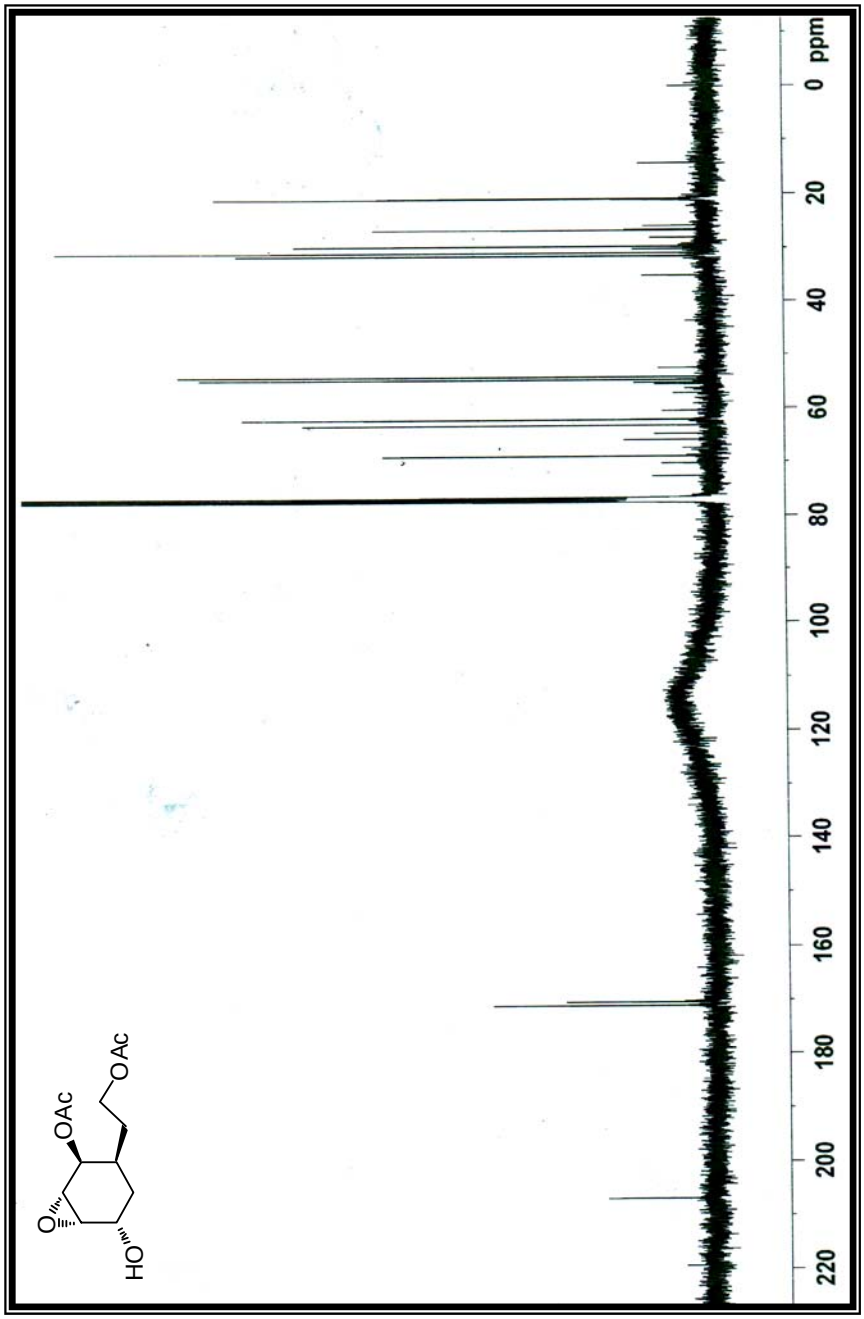


Figure II. 50 ^{13}C-NMR spectrum of compound **193**

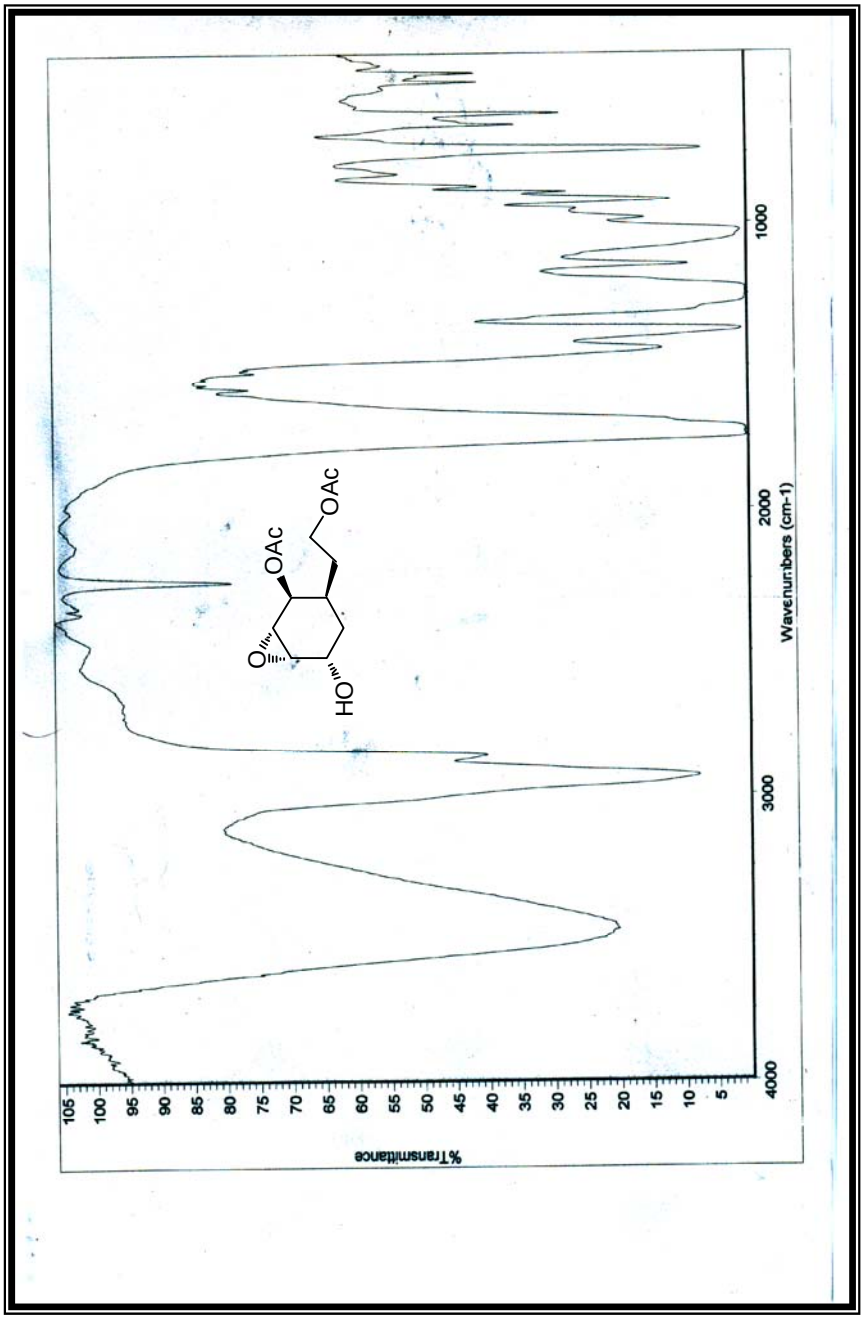


Figure II. 51 IR spectrum of compound **193**

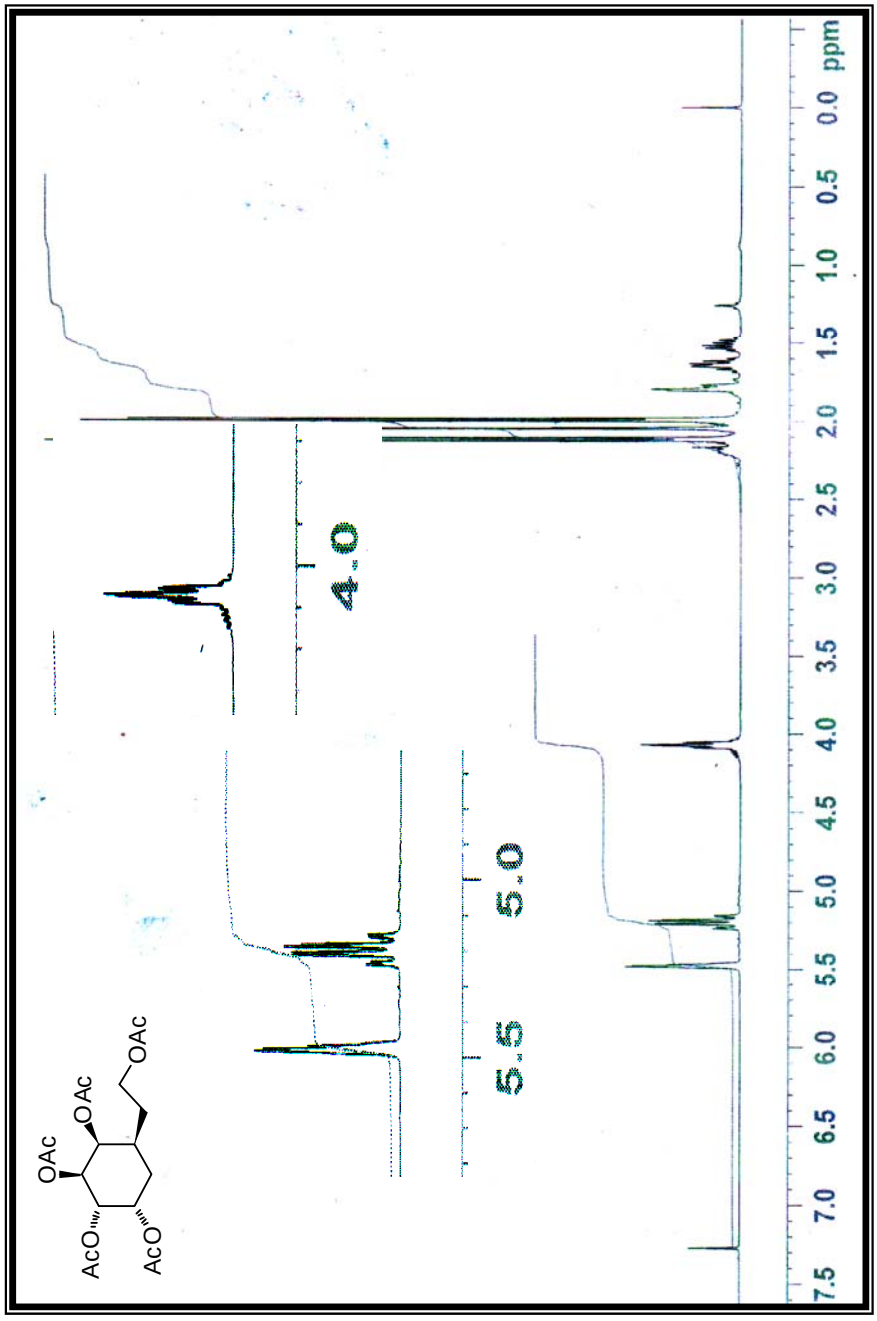


Figure II. 52 ^{1}H-NMR spectrum of compound **194**

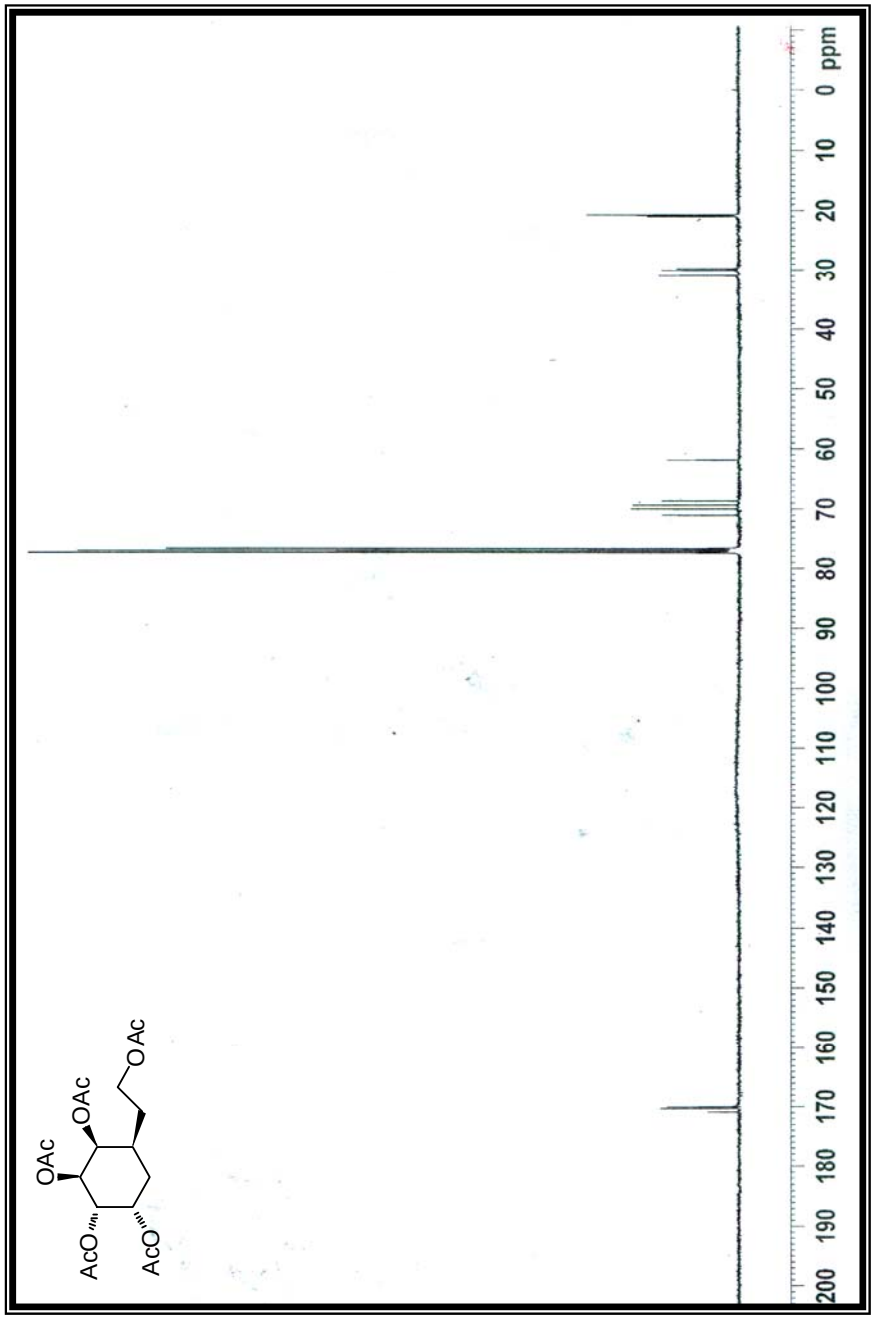


Figure II. 53 ^{13}C-NMR spectrum of compound **194**

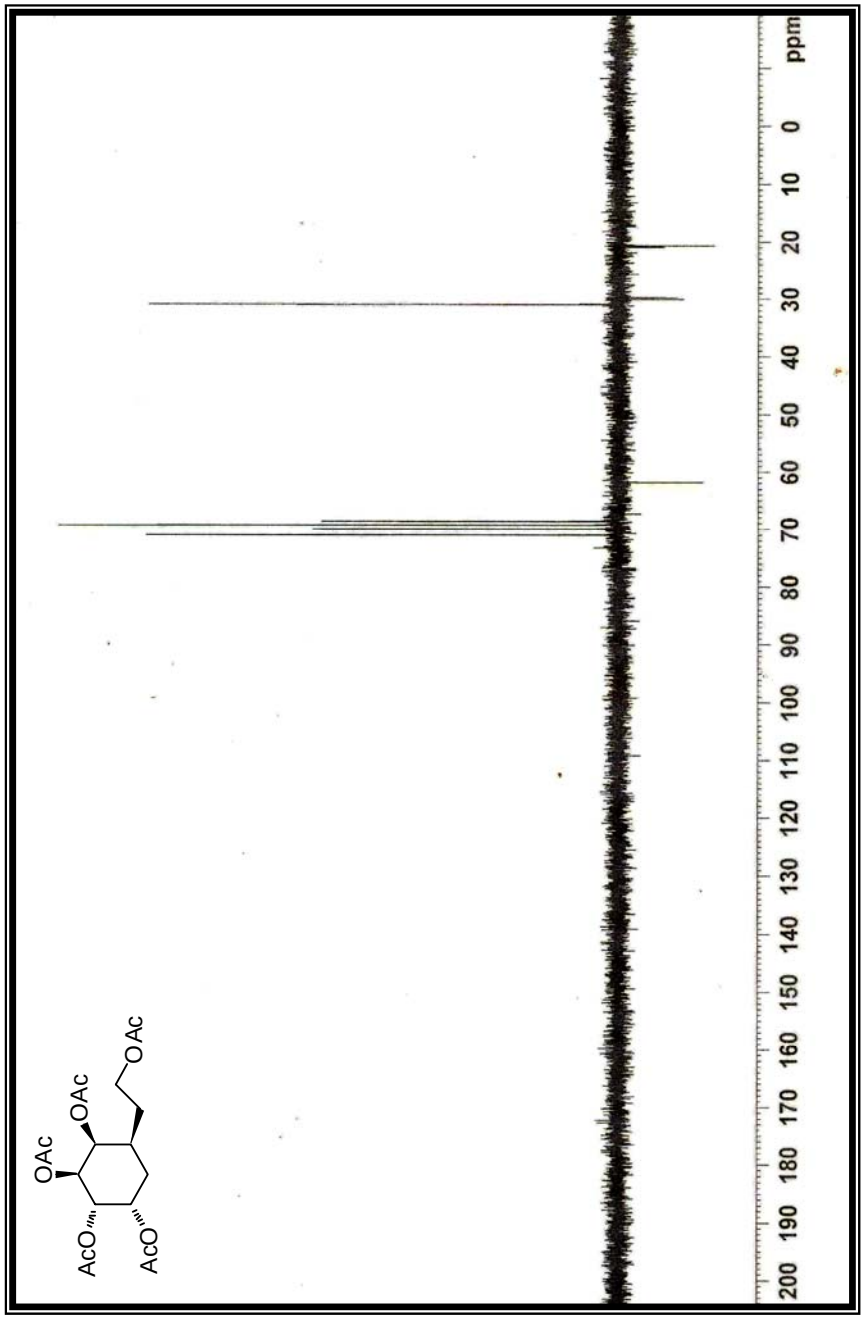


Figure II. 54 DEPT-90 spectrum of compound **194**

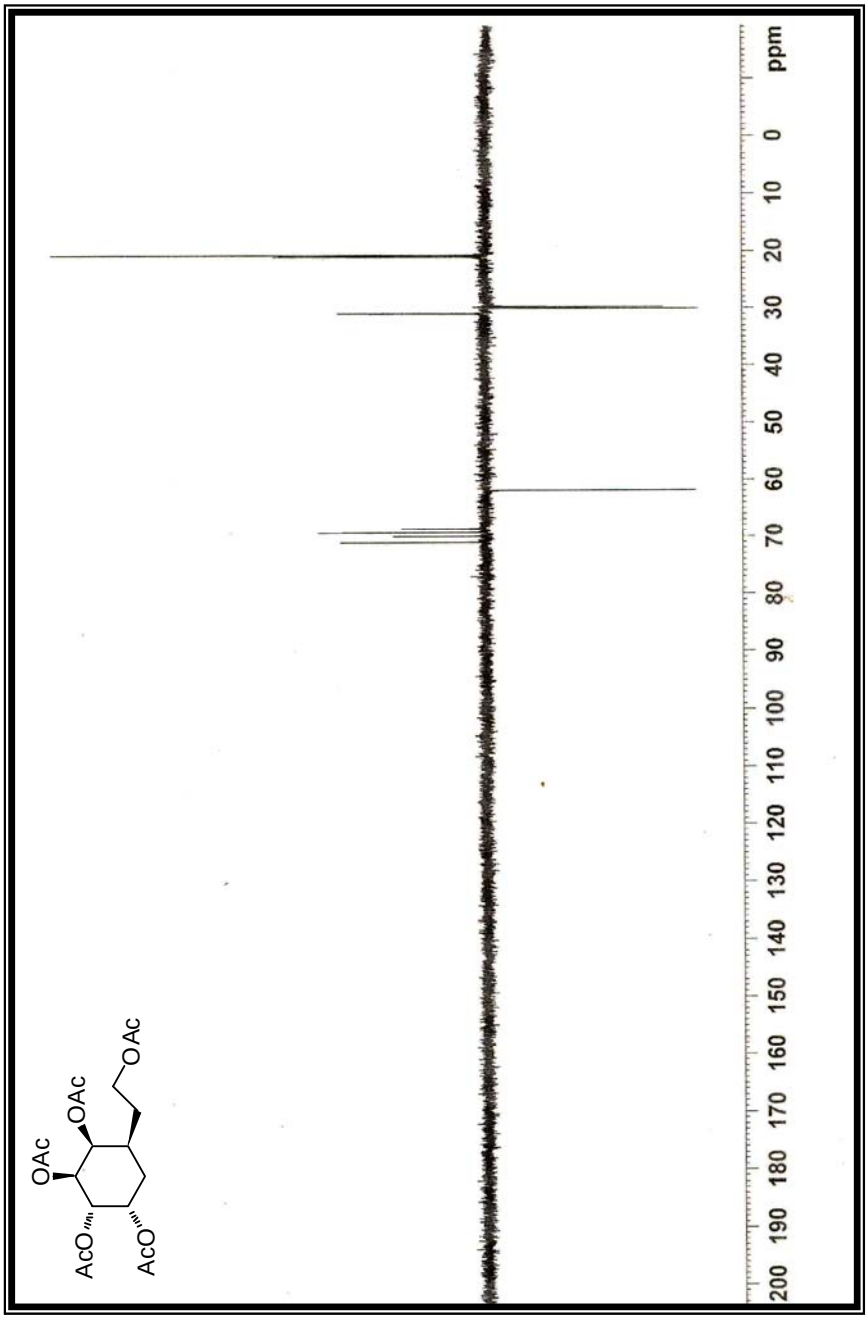


Figure II. 55 DEPT-135 spectrum of compound **194**

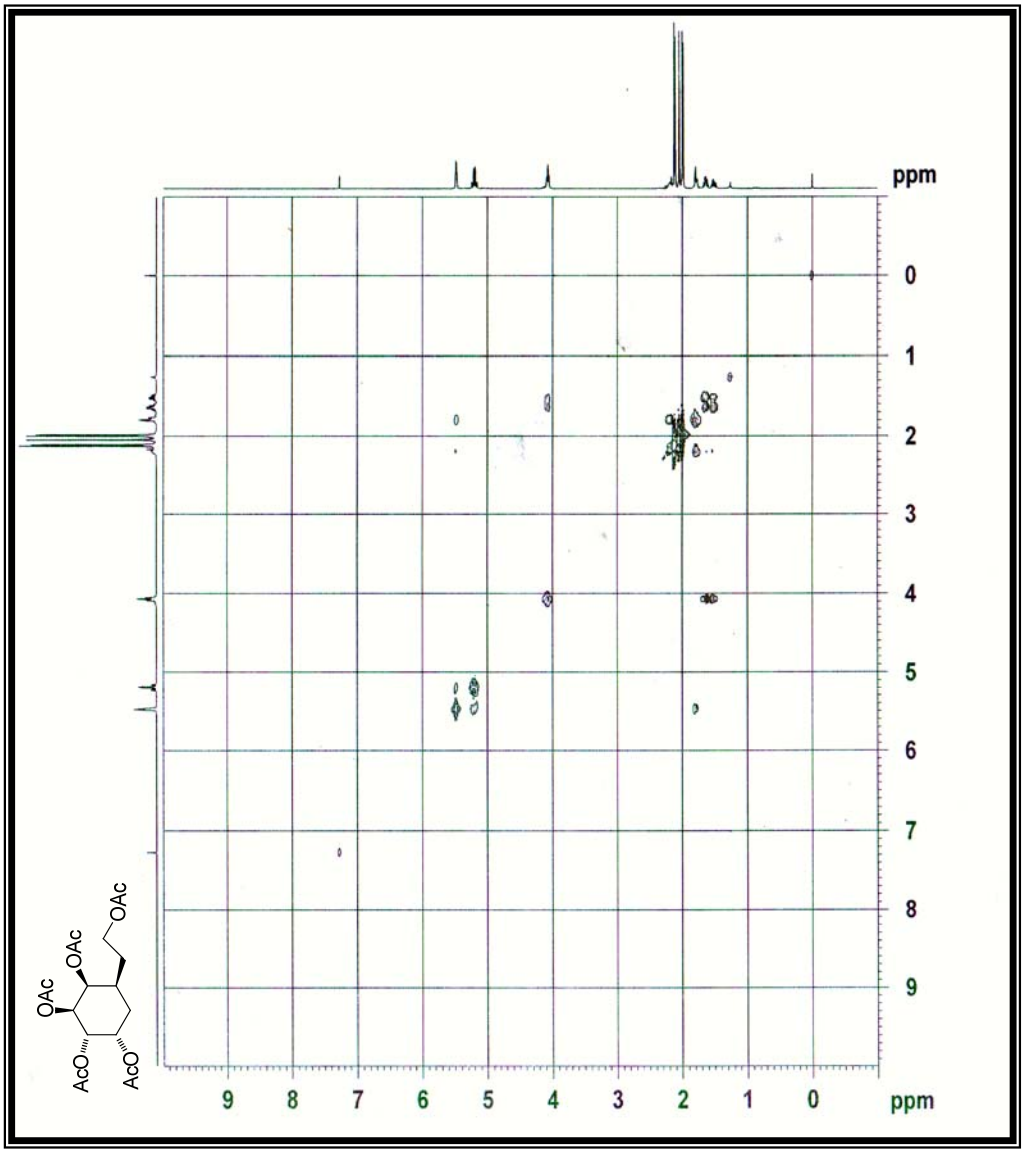


Figure II. 56 COSY- spectrum of compound **194**

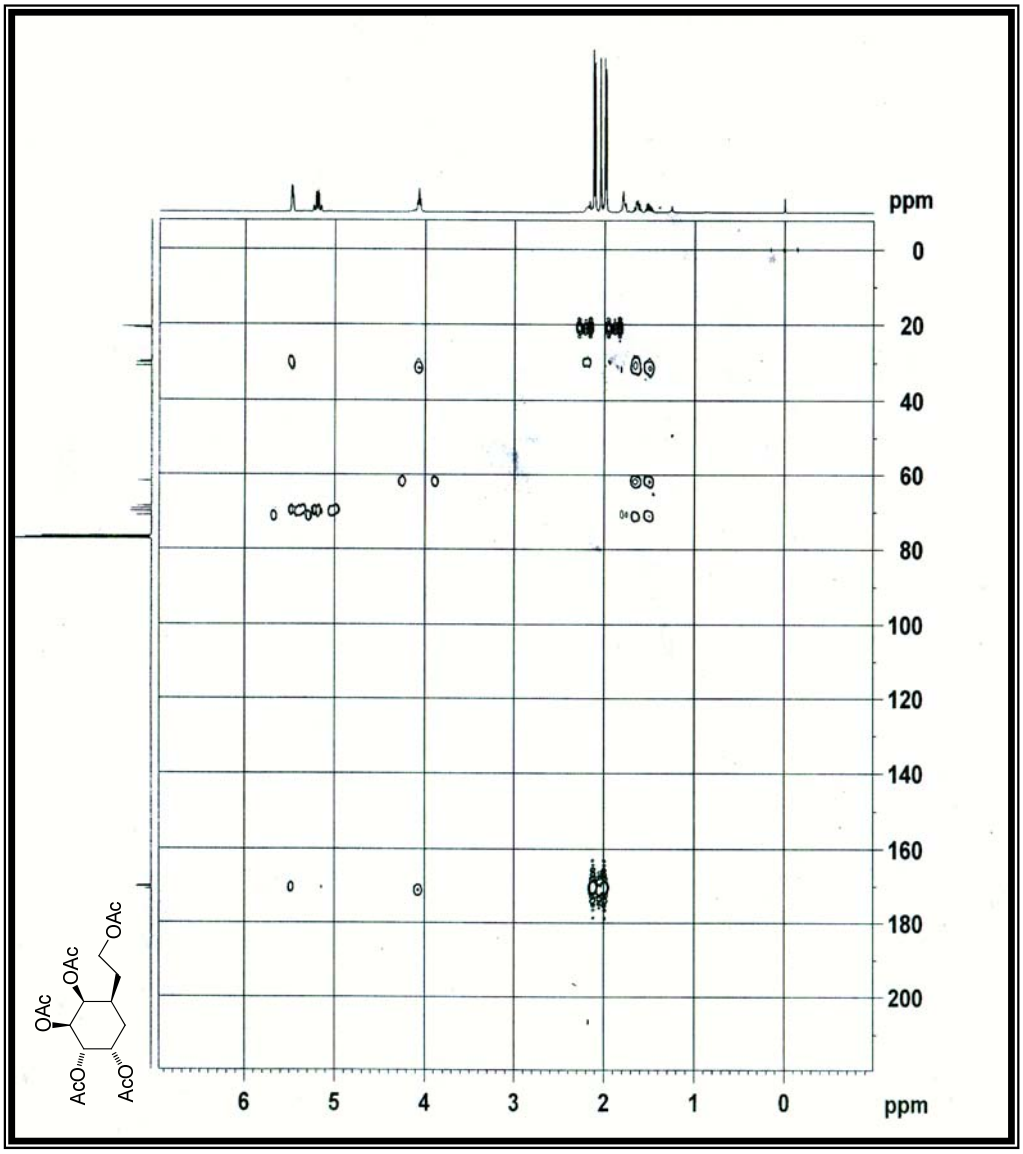


Figure II. 57 HMBC-spectrum of compound **194**

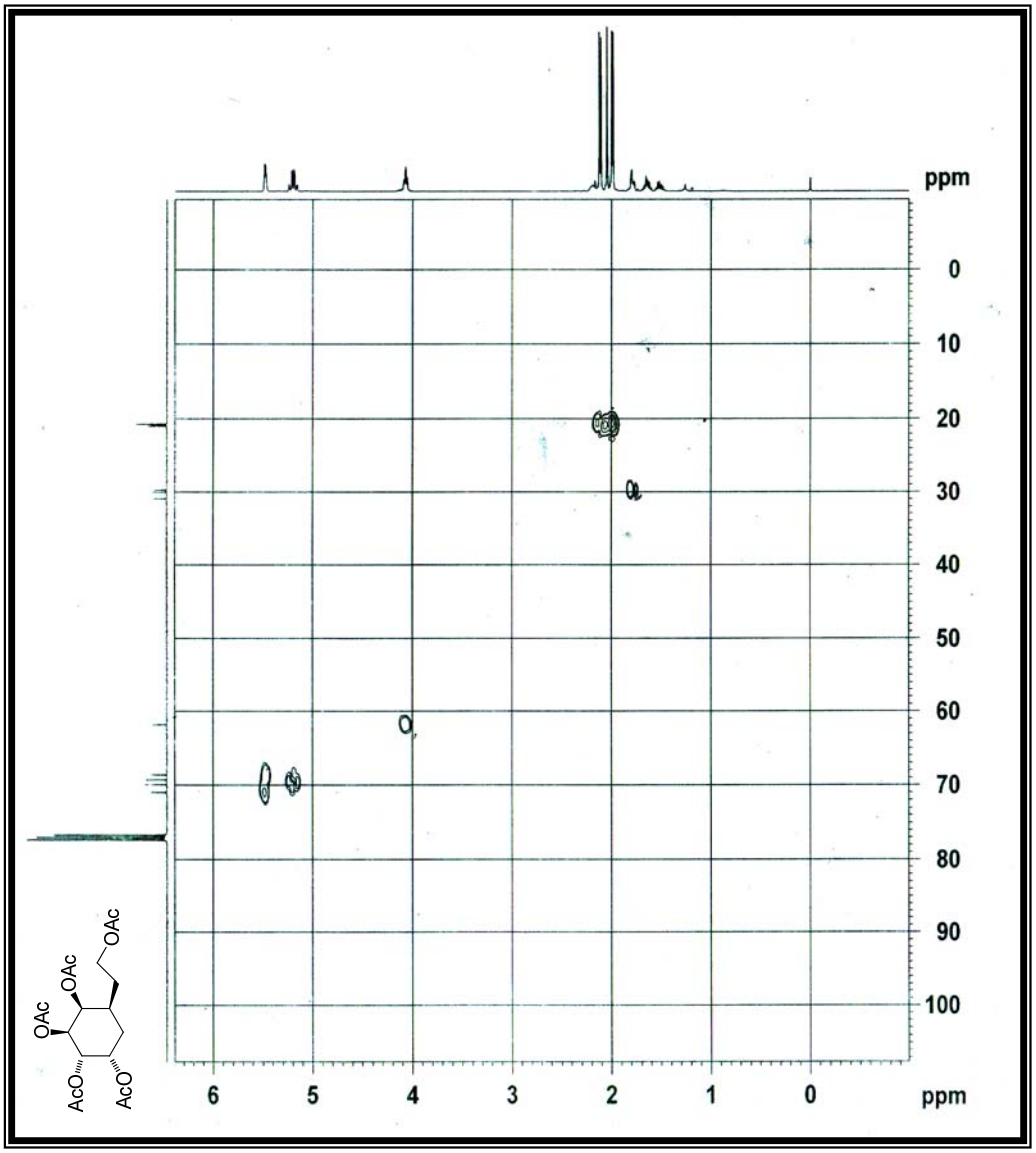


Figure II. 58 HMQC-spectrum of compound **194**

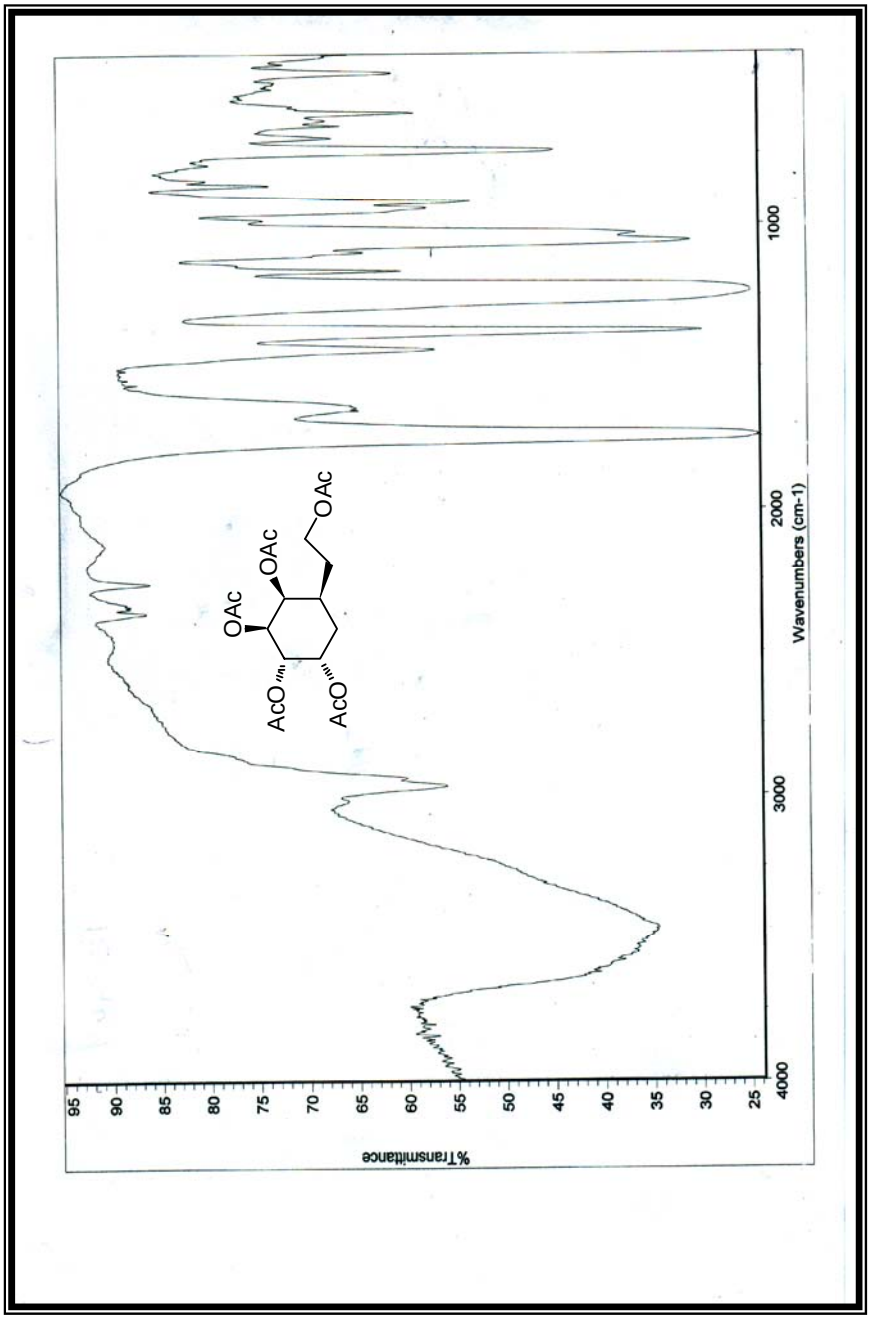


Figure II. 59 IR spectrum of compound **194**

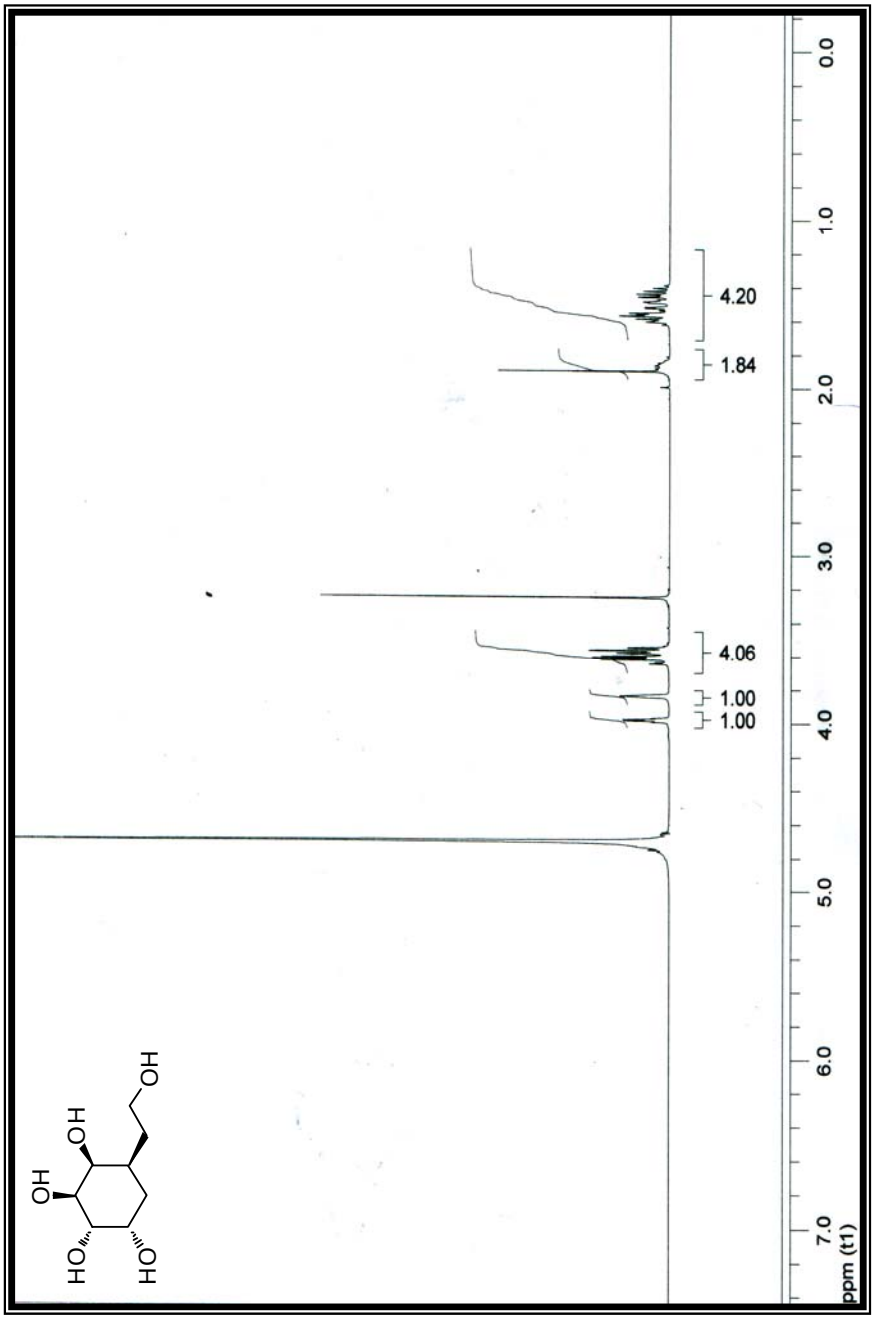


Figure II. 60 ^{1}H-NMR spectrum of compound **184**

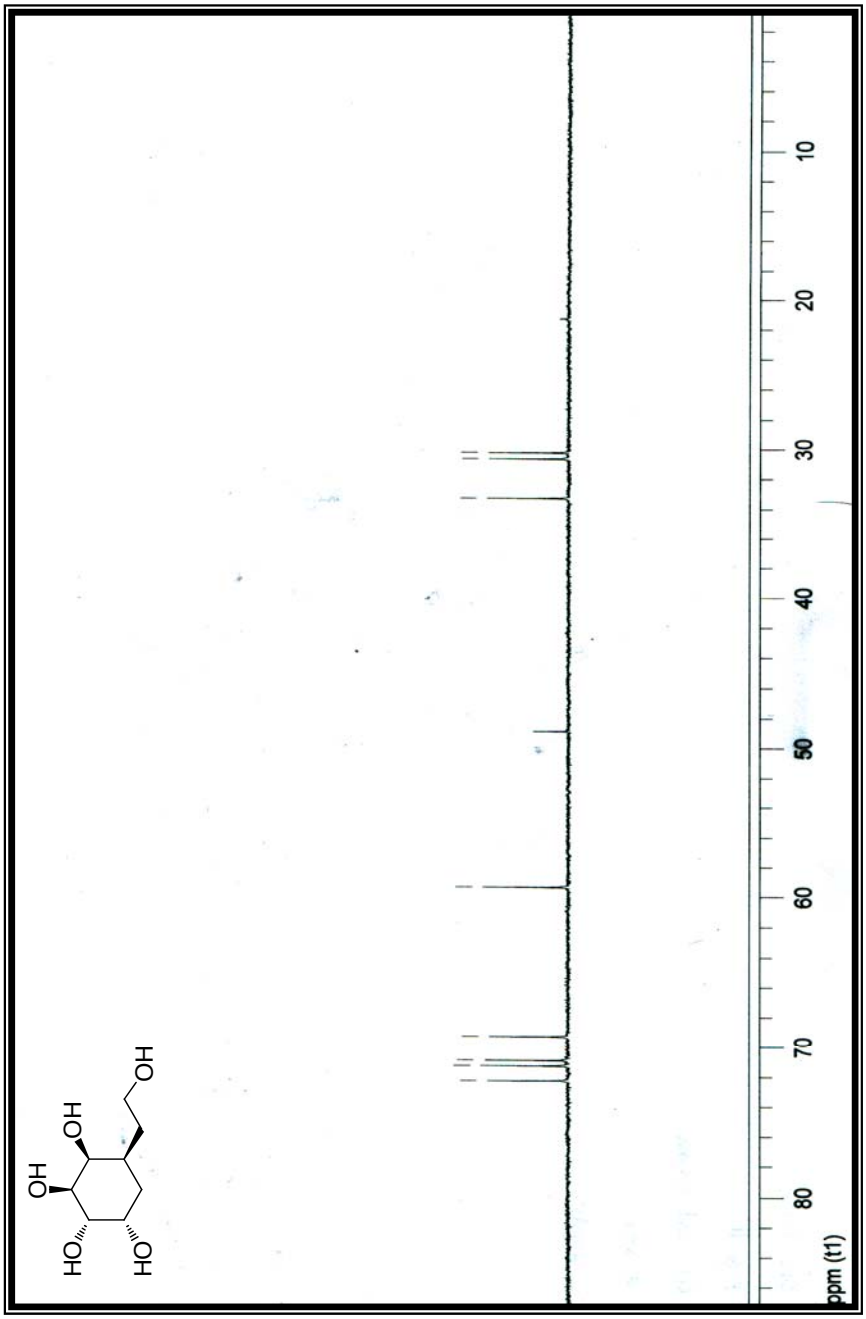


Figure II. 61 ^{13}C-NMR spectrum of compound **184**

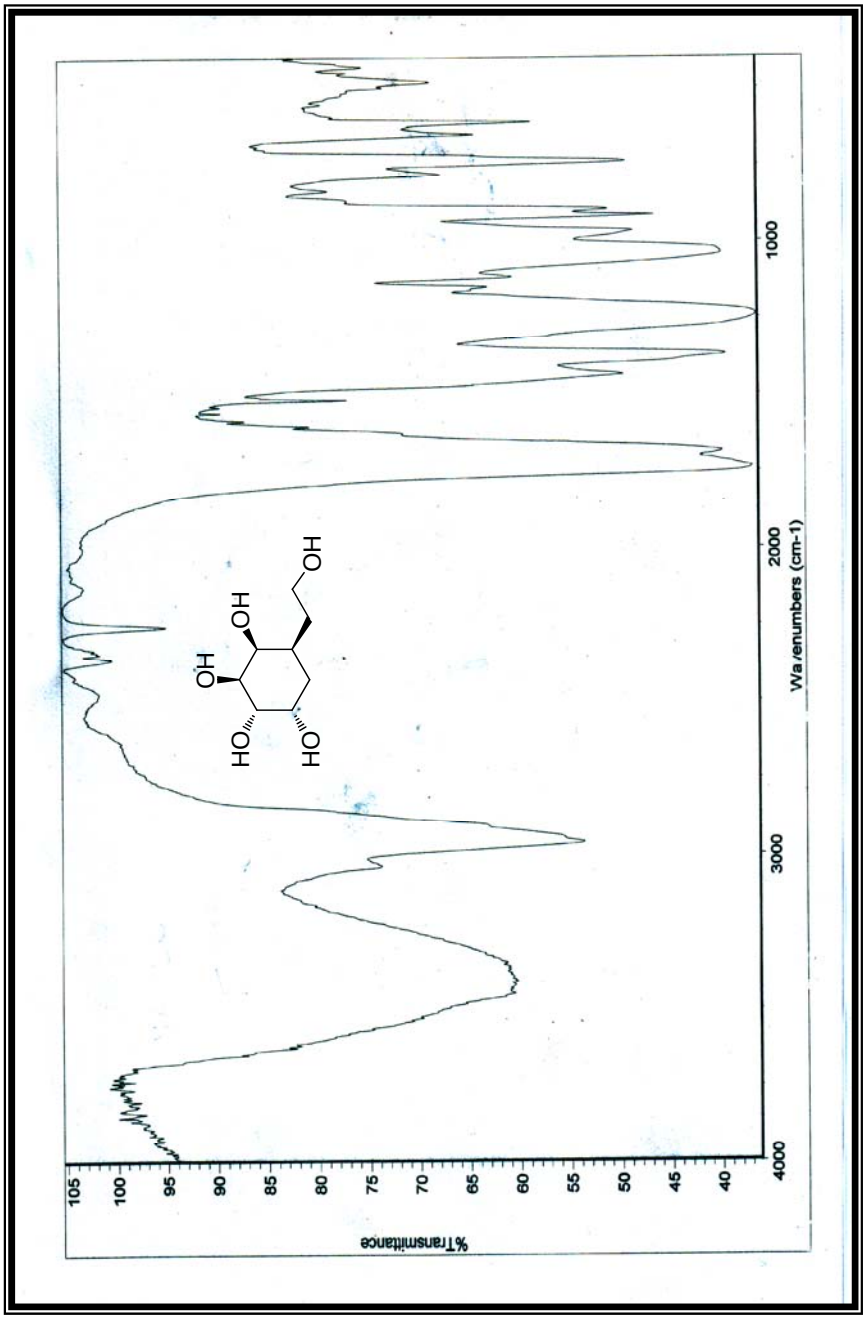


Figure II. 62 IR spectrum of compound **184**

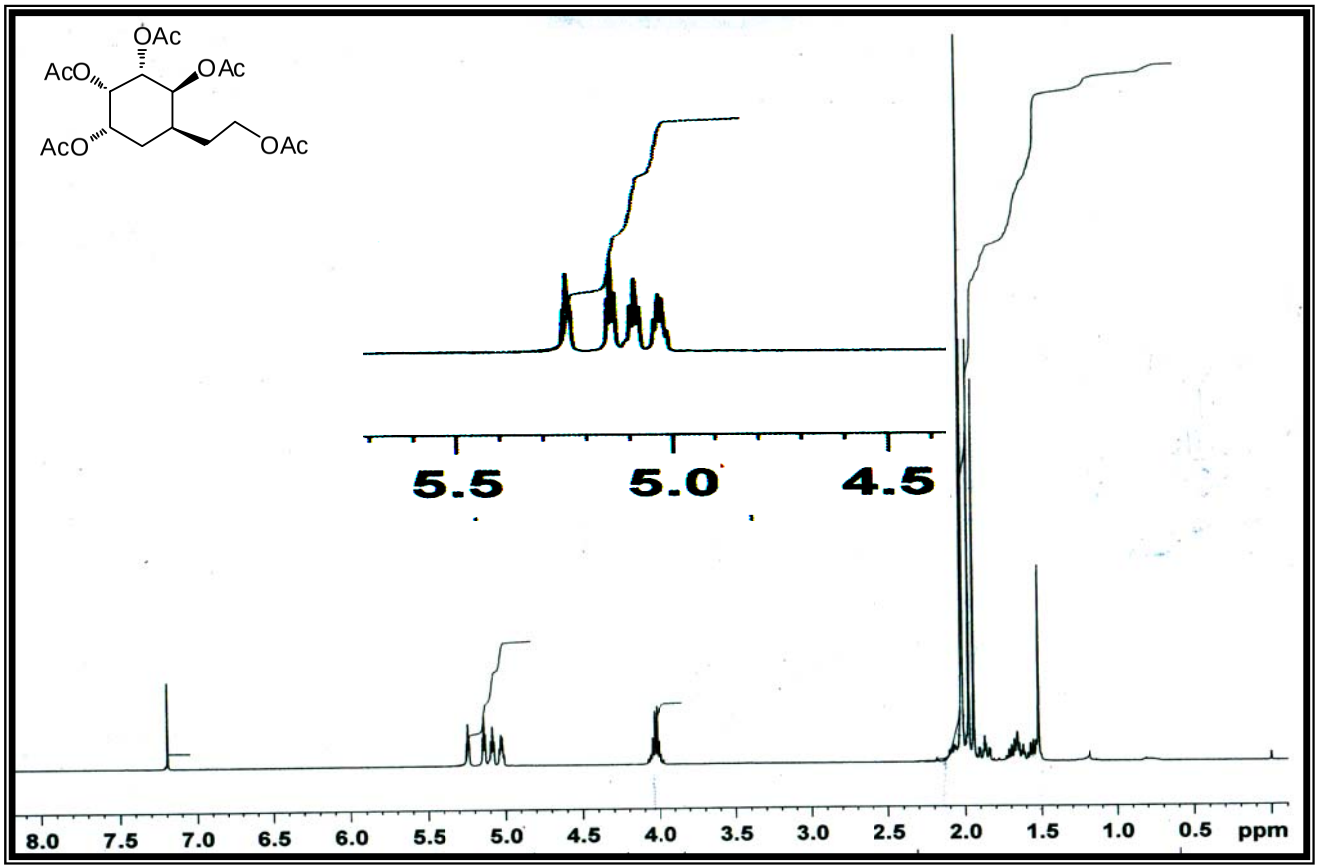


Figure II. 63 ^{1}H-NMR spectrum of compound **196**

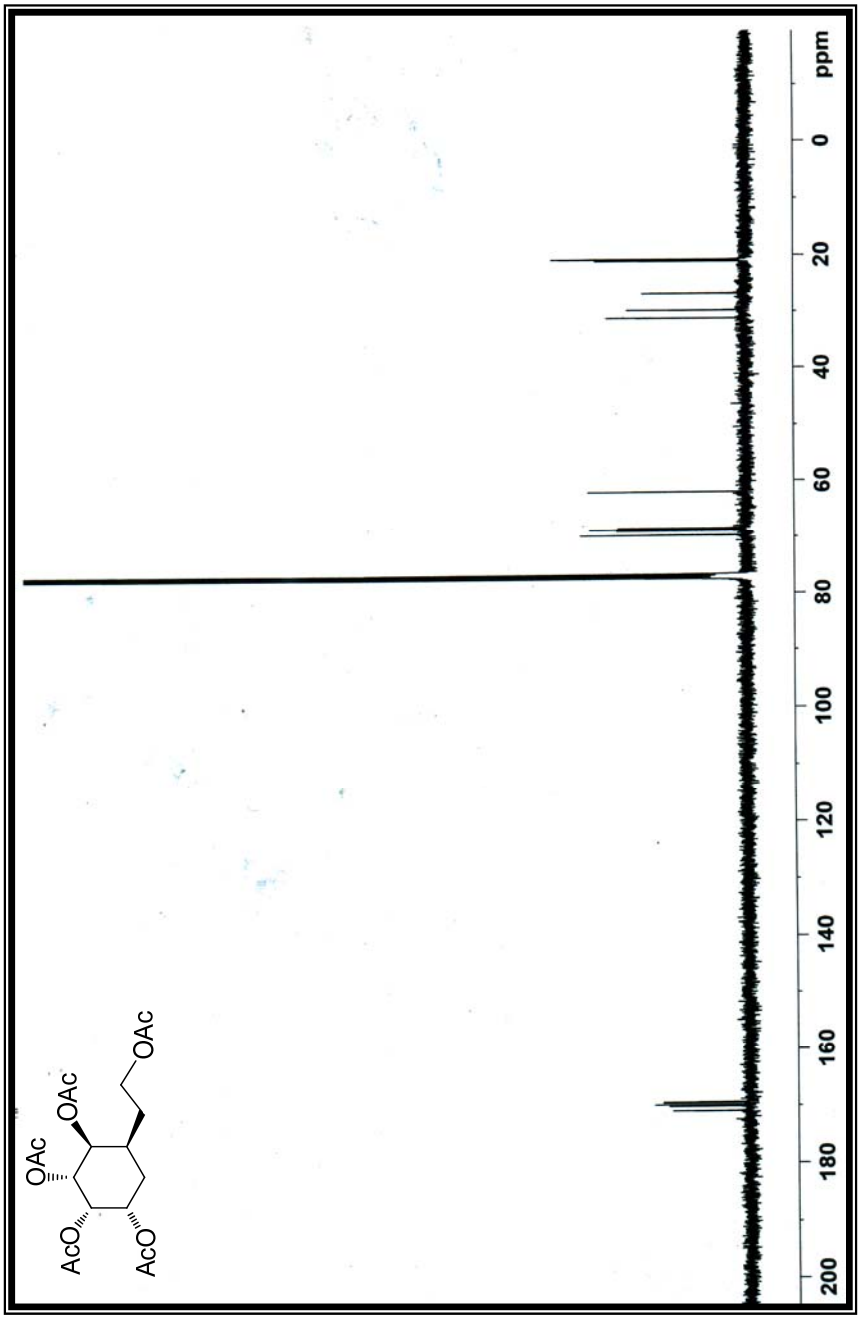


Figure II. 64 ^{13}C-NMR spectrum of compound **196**

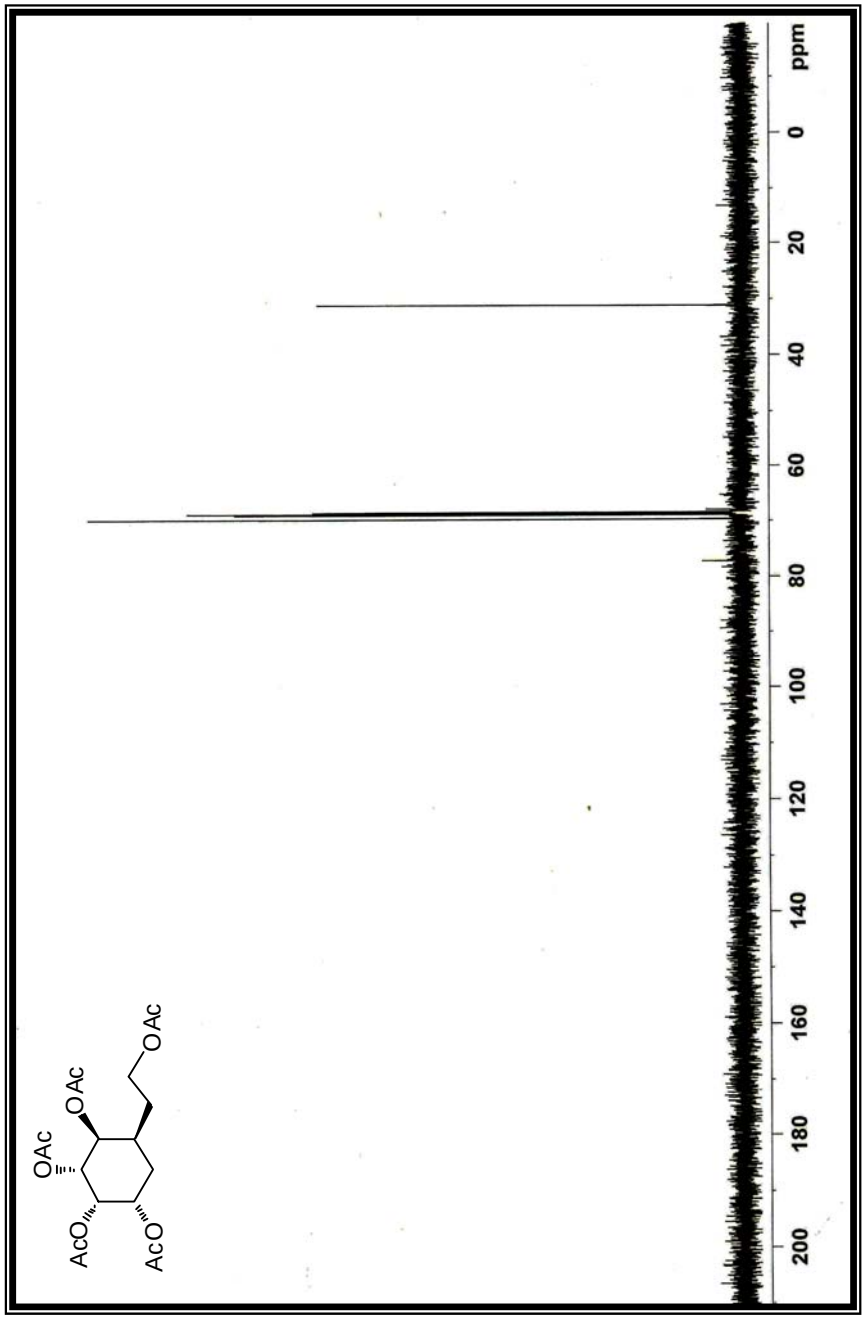


Figure II. 65 DEPT-90 spectrum of compound **196**

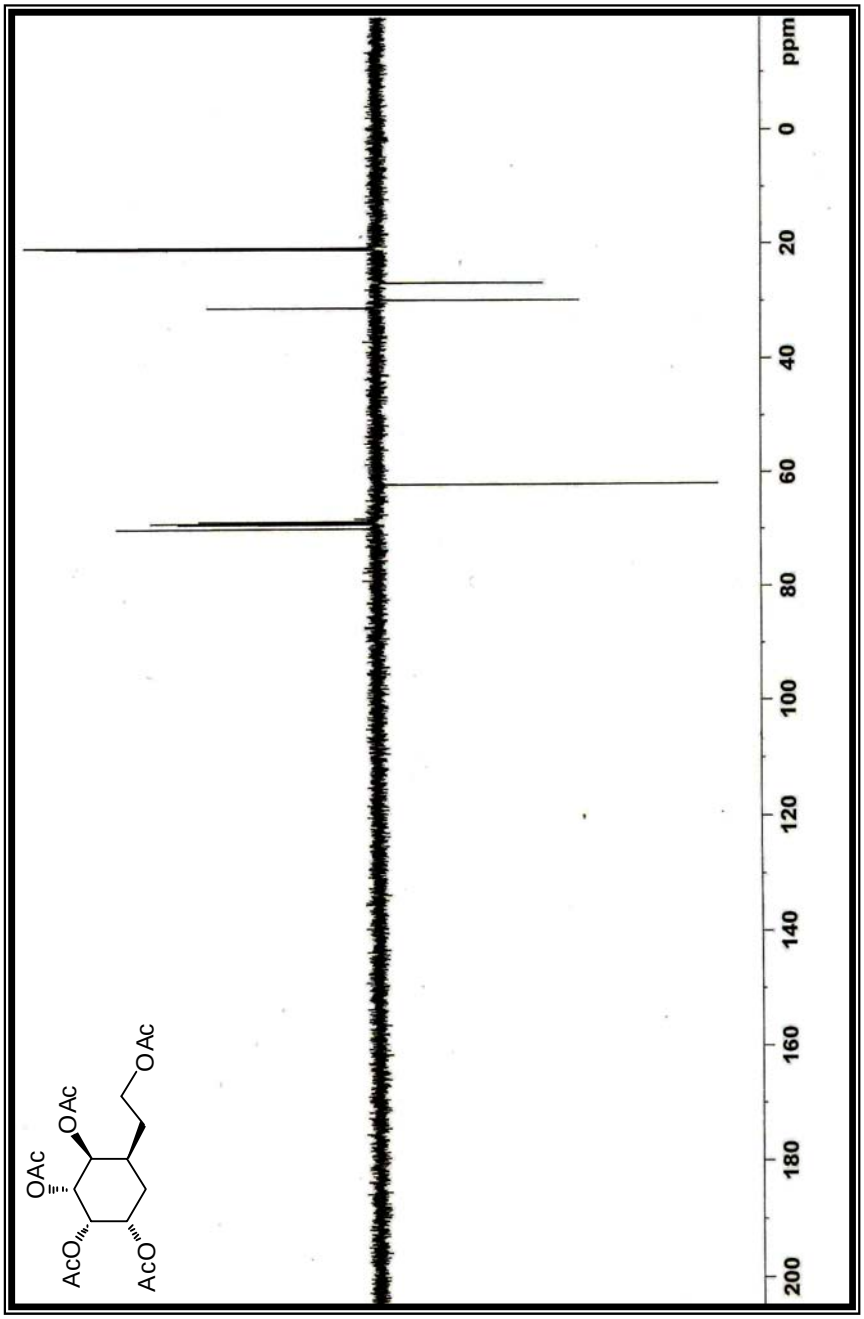


Figure II. 66 DEPT-135 spectrum of compound **196**

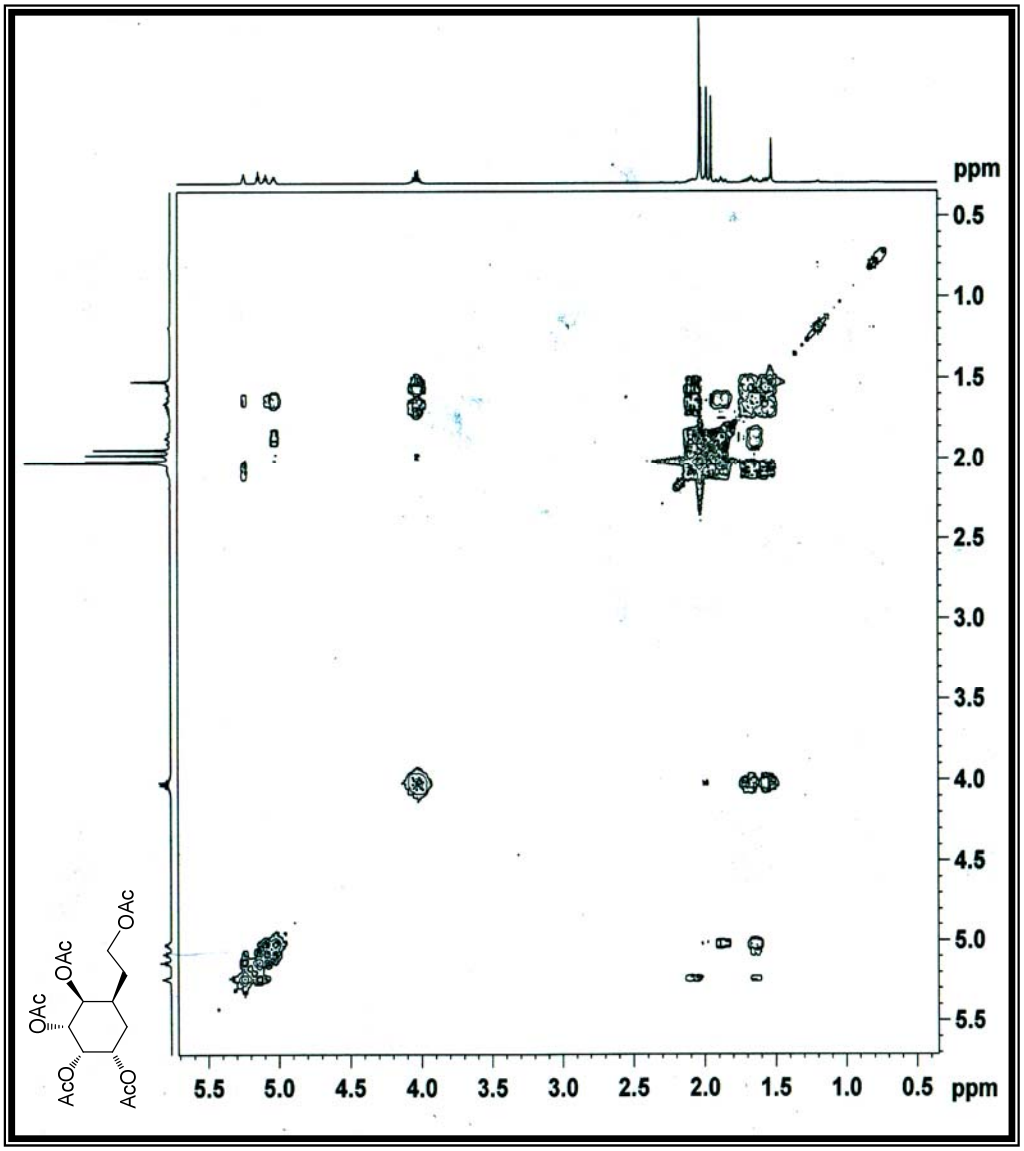


Figure II. 67 COSY- spectrum of compound **196**

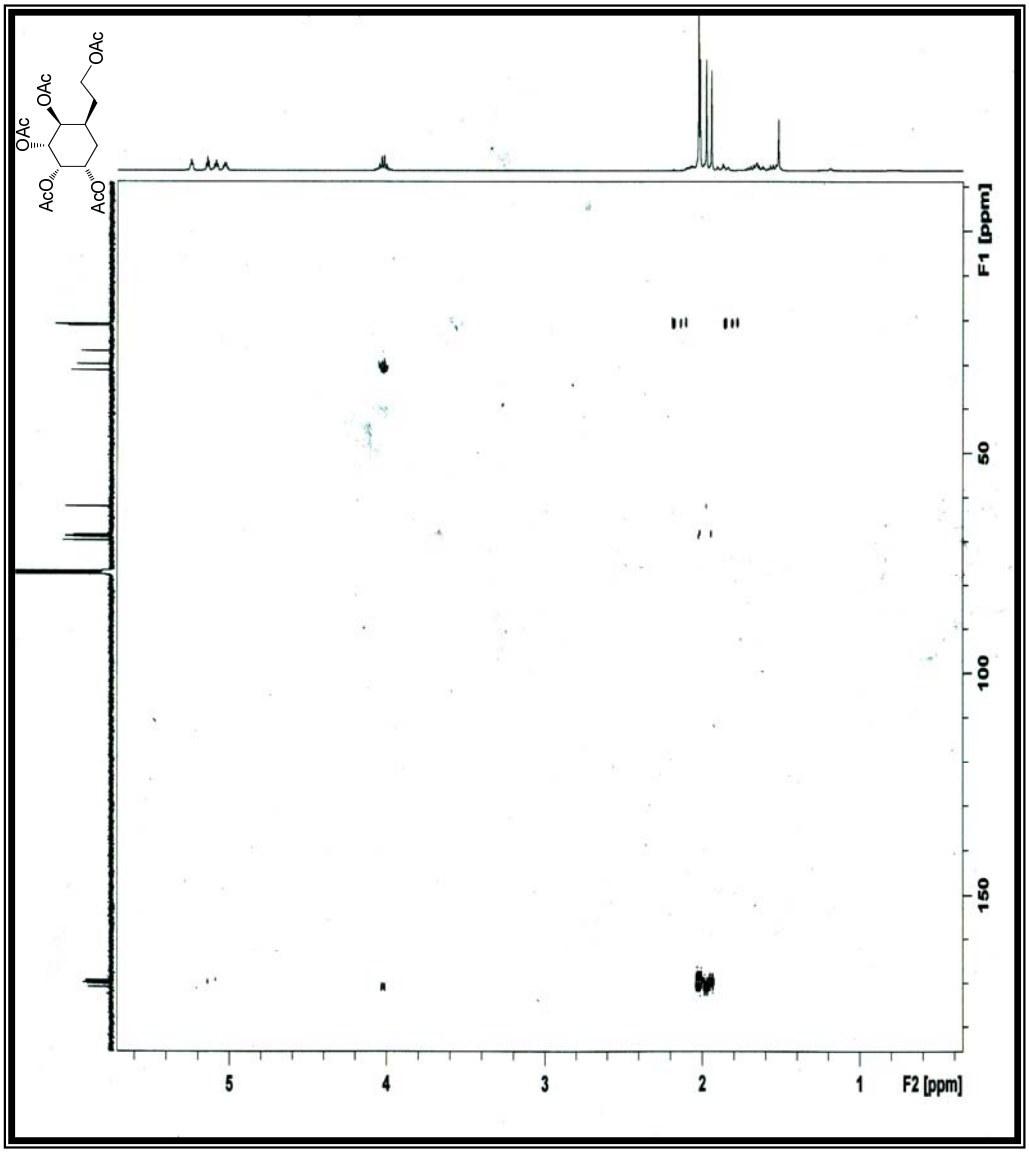


Figure II. 68 HMBC-spectrum of compound **196**

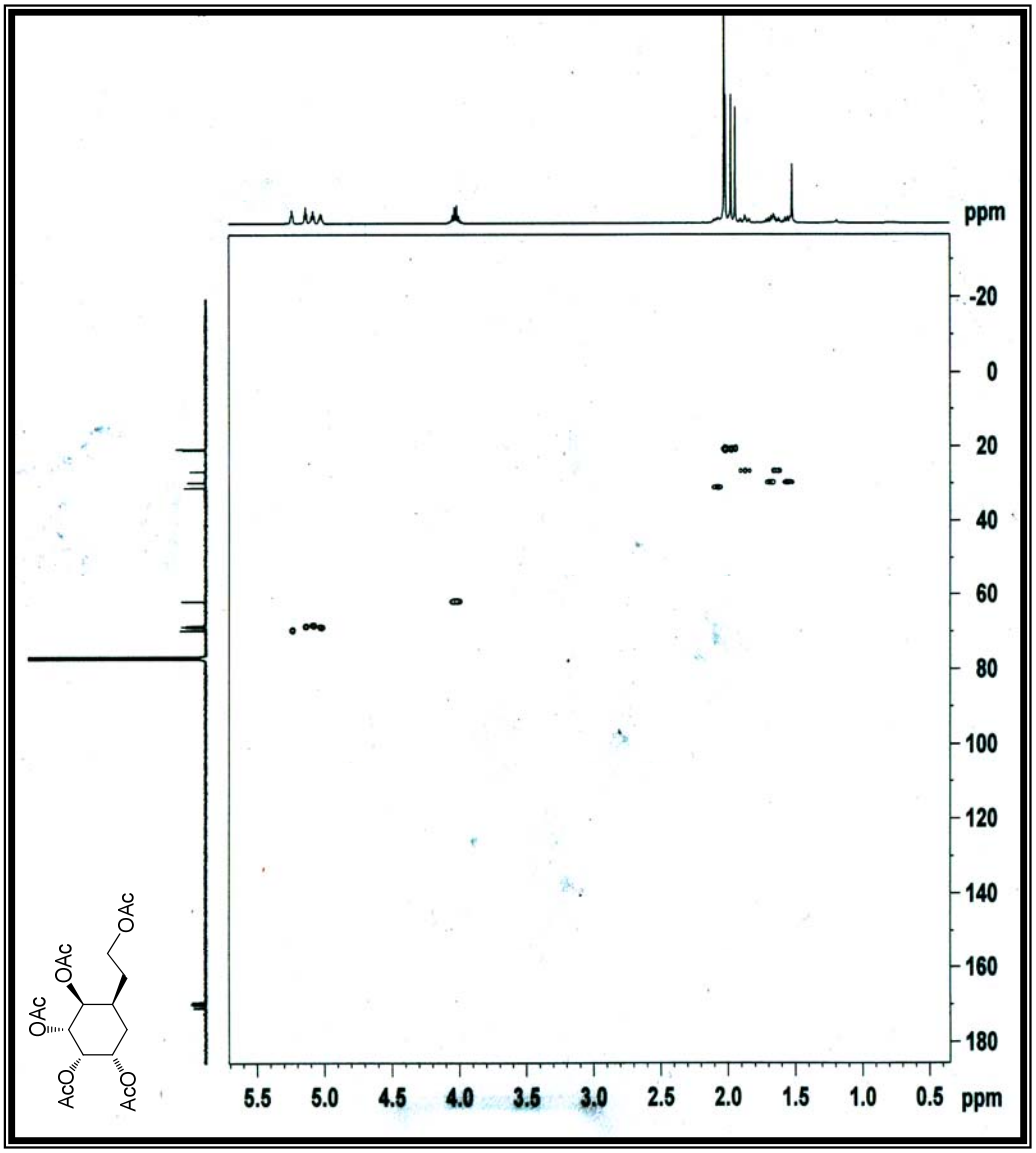


Figure II. 69 HMBQ-spectrum of compound **196**

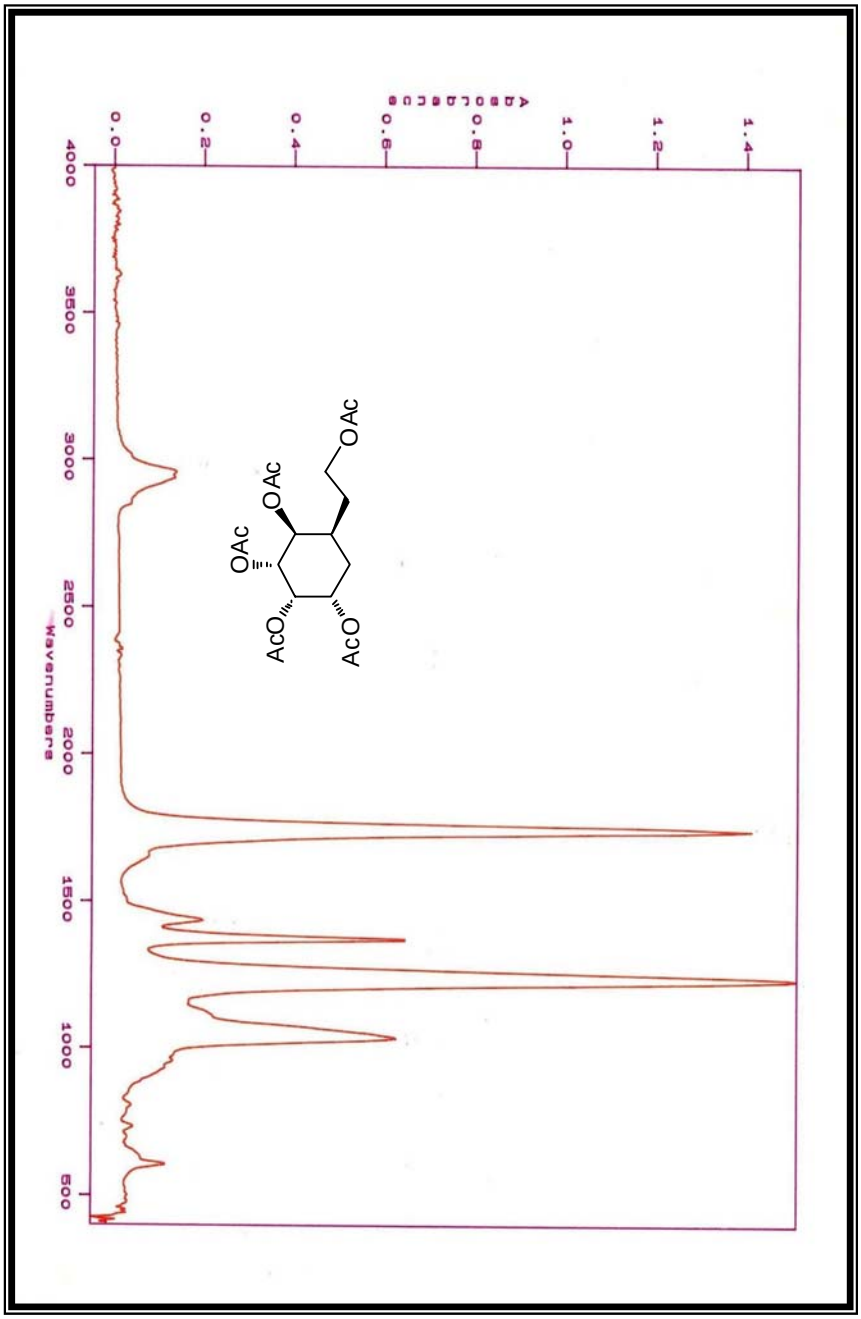


Figure II. 70 IR spectrum of compound **196**

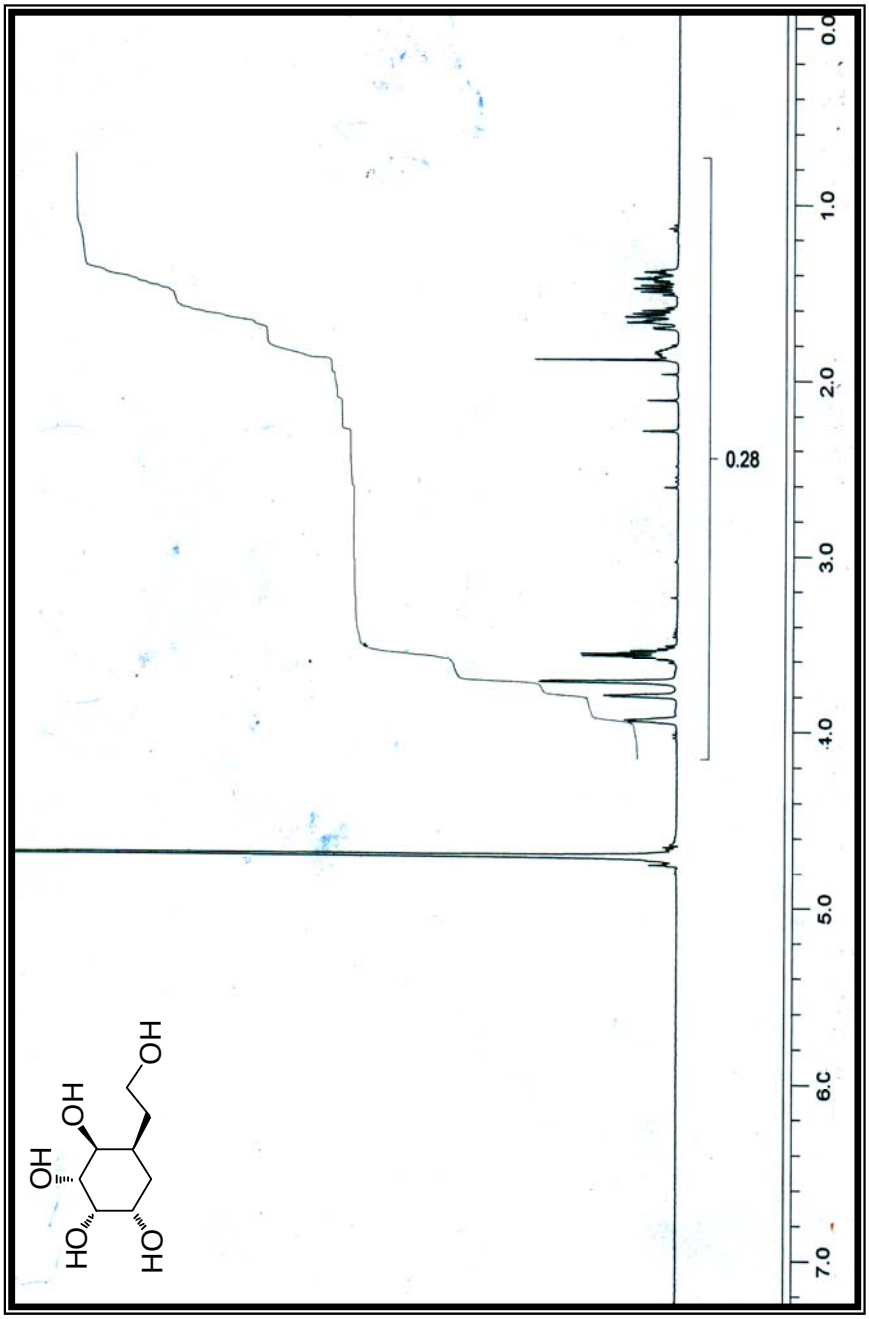


Figure II. 71 ^{1}H-NMR spectrum of compound **185**

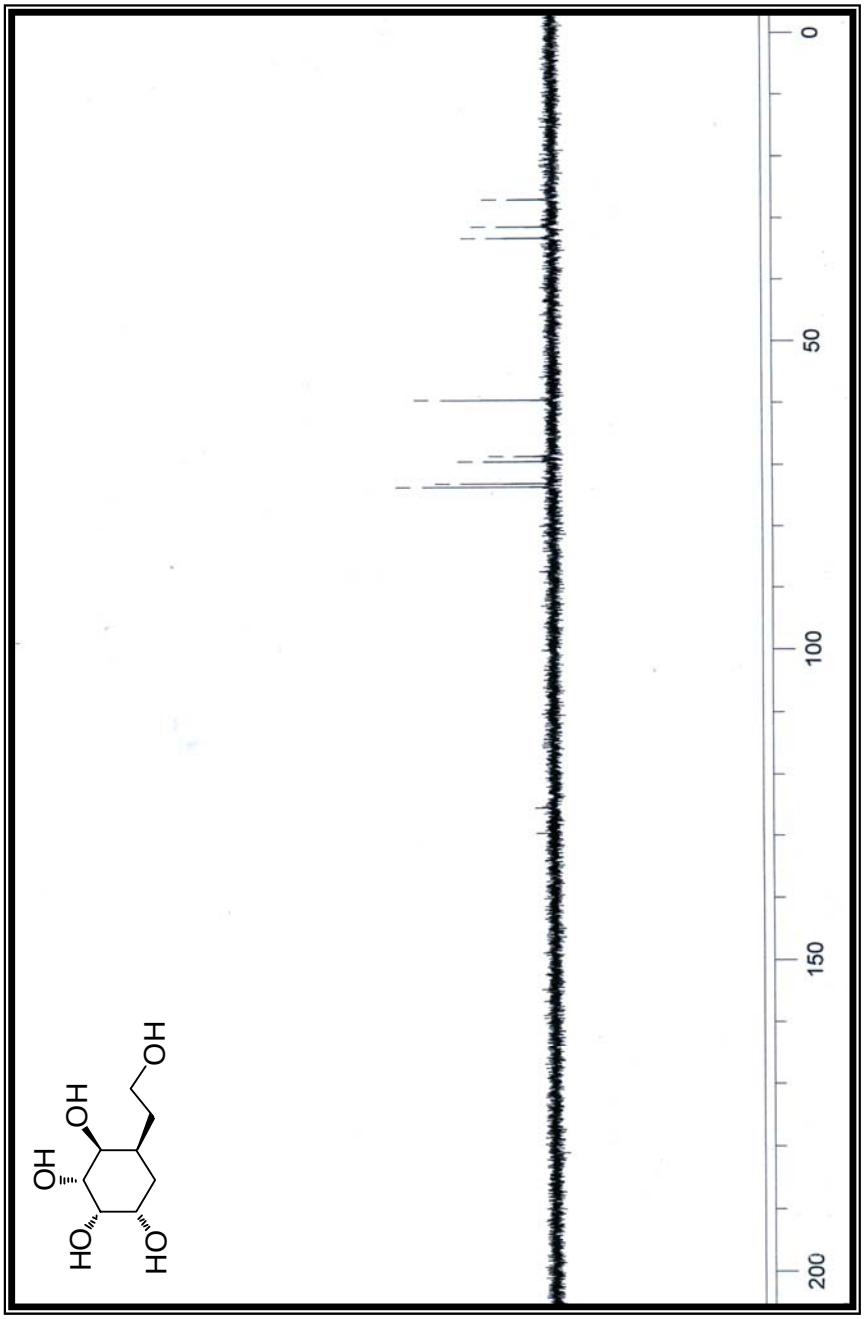


Figure II. 72 ^{13}C-NMR spectrum of compound **185**

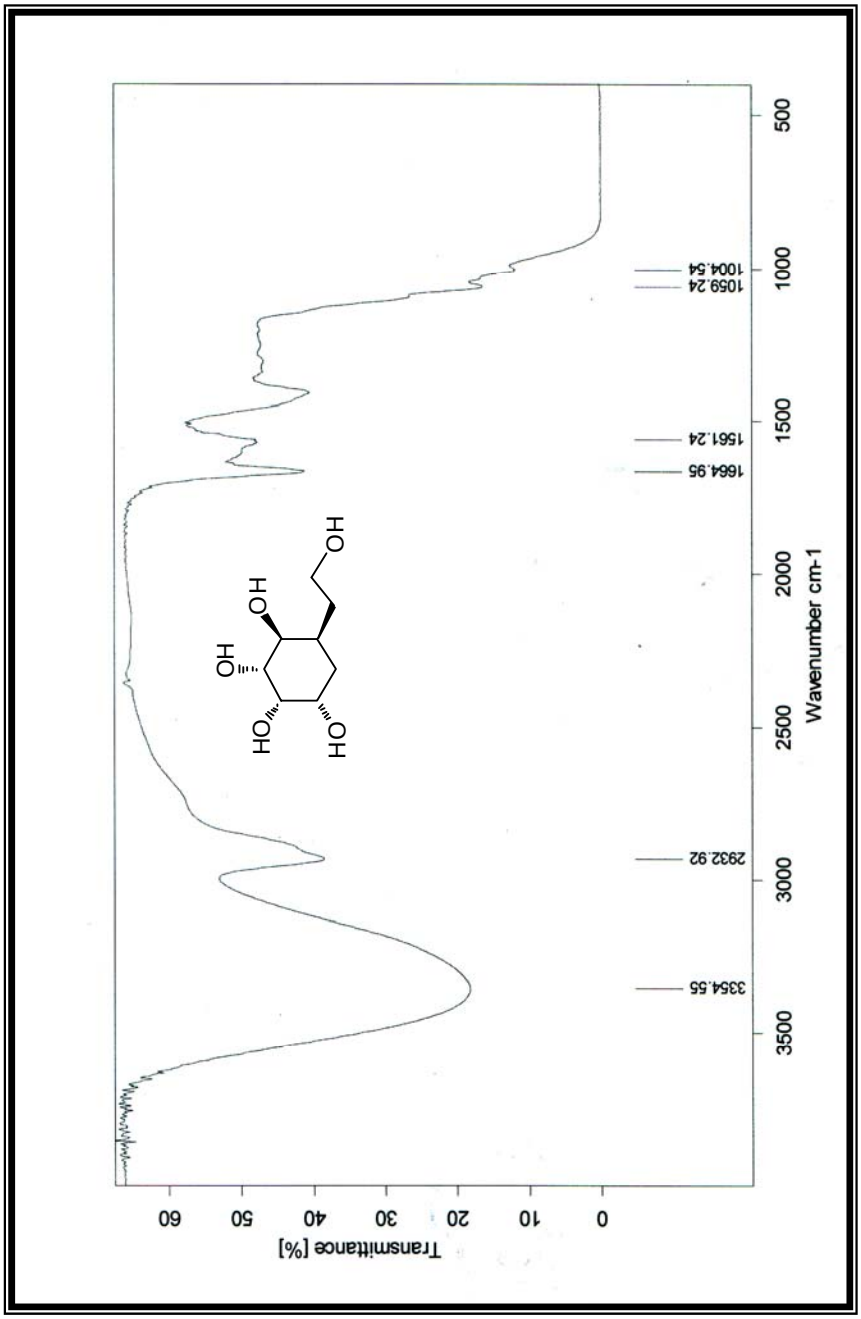


Figure II. 73 IR spectrum of compound **185**

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FOREIGN LANGUAGES

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PUBLICATIONS

1) Balcı, M., Yardimci, Ş. D., Kaya, N., *Tetrahedron*, **2006**, *62*, 1063-10638.

2) Stereoselective Synthesis of Carbaheptopyranose Derivatives: 5a-Carba-6-deoxy-DL-galacto-heptopyranose and 5a-Carba-6-deoxy-DL-gulo-heptopyranose. Nurhan Horasanlı, Ş. Dilem Doğan, Ertan Şahin, Yunus Kara, Metin Balci. (Prepared for publication).